JMIR Research Protocols

Impact Factor (2022): 1.7
Volume 13 (2024) ISSN: 1929-0748 Editor in Chief: Gunther Eysenbach, MD, MPH, FACMI; Xiaomeng (Simone) Ma, PhDc, MS, BS

Contents

Protocols

Proposals

Original Papers

Corrigenda and Addendas

Protocol

Impact of a Mobile App (LoAD Calc) on the Calculation of Maximum Safe Doses of Local Anesthetics: Protocol for a Randomized Controlled Trial

Pietro Elias Fubini[1], MD; Georges Louis Savoldelli[1], MEd, MD; Tal Sara Beckmann[1], MD; Caroline Flora Samer[2], MAS, MD; Mélanie Suppan[1], MSc, MD

[1]Division of Anesthesiology, Department of Anesthesiology, Clinical Pharmacology, Intensive Care and Emergency Medicine, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland

[2]Clinical Pharmacology and Toxicology Division, Department of Anesthesiology, Clinical Pharmacology, Intensive Care and Emergency Medicine, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland

Corresponding Author:
Mélanie Suppan, MSc, MD
Division of Anesthesiology
Department of Anesthesiology, Clinical Pharmacology, Intensive Care and Emergency Medicine
Geneva University Hospitals and Faculty of Medicine
Rue Gabrielle-Perret-Gentil 4
Geneva, 1211
Switzerland
Phone: 41 223723311
Email: melanie.suppan@hcuge.ch

Abstract

Background: Local anesthetics (LAs) are regularly used to alleviate pain during medical or surgical procedures. Their use is generally considered safe, but exceeding the maximum recommended doses can lead to LA systemic toxicity, a rare but potentially lethal complication. Determining maximum safe doses is therefore mandatory before performing local anesthesia, but rules are often unclear and the factors affecting dose calculation are numerous. Mobile health apps have been shown to help clinical decision-making, but most currently available apps present significant limitations. The Local Anesthetics Dose Calculator (LoAD Calc) app was designed to overcome these limitations by taking all relevant parameters into account. Before deploying this app in a clinical setting, it should be tested to determine its effectiveness and whether clinicians would be willing to use it.

Objective: The primary objective will be to evaluate the effectiveness of the LoAD Calc app through written simulated cases. The secondary objective will be to determine whether physicians find this app easier, faster, and safer than the methods they generally use.

Methods: We describe a parallel-group randomized controlled trial protocol. Anesthesiologists working at the Geneva University Hospitals will be invited to participate. Participants will be asked to compute the maximum dose of LA in 10 simulated clinical cases using 3 different LAs. The maximum safe dose will be determined manually using the same calculation rules that were used to develop LoAD Calc, without using the app itself. An overdose will be considered any dose higher than the correct dose, rounded to the superior integer, while an underdose will be defined as the optimal calculated dose minus 20%, rounded to the inferior integer. Randomization will be stratified according to current position (resident vs registrar). The participants allocated to the LoAD Calc (experimental) group will use the LoAD Calc app to compute the maximum safe LA doses. Those allocated to the control group will be asked to use the method they generally use. The primary outcome will be the overall overdose rate. Secondary outcomes will include the overdose rate according to ideal and actual body weight and to each specific LA, the overall underdose rate, and the time taken to complete these calculations. The app's usability will also be assessed.

Results: A sample size of 46 participants will be needed to detect a difference of 10% with a power of 90%. Thus, a target of 50 participants was set to allow for attrition and exclusion criteria. We expect recruitment to begin during the winter of 2023, data analysis in the spring of 2024, and results by the end of 2024.

Conclusions: This study should determine whether LoAD Calc, a mobile health app designed to compute maximum safe LA doses, is safer and more efficient than traditional LA calculation methods.

International Registered Report Identifier (IRRID): PRR1-10.2196/53679

(JMIR Res Protoc 2024;13:e53679) doi:10.2196/53679

KEYWORDS

dose calculation; drug safety; information systems research; local anesthetic systemic toxicity; local anesthetics; mobile health app; study protocol; toxicity

Introduction

Background

Local anesthetics (LAs) are used daily by physicians to perform minor procedures. While the doses they use are generally limited, anesthesiologists often use higher doses to perform regional anesthesia techniques [1]. While the advantages of such techniques are undeniable, using high LA doses increases the risk of local anesthetic systemic toxicity (LAST), a potentially lethal complication associated with the use of these agents [2]. The actual incidence of LAST is unknown since most minor symptoms are not specific and because LAST awareness varies considerably between practitioners [3,4]. The incidence reported in scientific studies varies from 0.04 to 1.8 per 1000 regional anesthesia procedures but is probably underestimated [5,6]. The main risk factors seem to be inadvertent intravascular injections and inappropriately large doses [7,8].

Prevention of intravascular injection can be achieved by ultrasound guidance and careful aspiration during the procedure, while adequate calculation of the maximum dose of LA before administration is the best way to avoid incorrect doses.

Although different guidelines have been created to help clinicians calculate the maximum safe LA doses, quickly and reliably determining such doses often proves difficult in clinical practice [9]. Many anesthesiologists rely on mental calculation (with or without a pen and paper aid), and some use calculators. These methods are, however, often challenging and inaccurate, especially if LA mixtures are used or when patients present multiple comorbidities [10]. More advanced solutions have been developed to support LA dosage calculation, such as the nomogram created by Williams and Walker [11]. The main limitation of this solution is that the nomogram must always be at hand. Moreover, specificities such as ideal body weight (IBW) calculation and adaptation in the case of relevant comorbidities are indicated but not directly integrated into dose determination.

To facilitate the calculation of safe maximum LA doses, a mobile health (mHealth) app, Local Anesthetics Dose Calculator (LoAD Calc), was developed at the Geneva University Hospitals [12]. This app takes all relevant parameters (IBW and actual weight, height, age, medications, and comorbidities) into account and allows the use of a mixture of 2 different LAs. Since smartphones have widely replaced older paging systems and are therefore always at hand, this mHealth app could be an appropriate solution to enable anesthesiologists to efficiently compute safe maximum LA doses.

Objectives

This study protocol follows the hypothesis that LoAD Calc, an mHealth app designed to help clinicians calculate maximum safe LA doses, is safer and more effective than traditional methods. Thus, the primary objective will be to evaluate the effectiveness of the LoAD Calc app by using it to compute the maximum single doses of LA in written simulated cases. The secondary objective will be to determine whether physicians find this app easier, faster, and safer than the methods they generally use.

Methods

Ethical Considerations

A synopsis of the study protocol was presented to the regional ethics committee (Commission Cantonale d'Ethique de la Recherche [CCER]). This committee confirmed that this project does not fall within the scope of the Swiss Federal Act on Research involving Human Beings and issued a "declaration of no objection" (CCER 2022-01577) [13]. This study protocol does not fall within the scope of the Swiss Federal Act on Research involving Human Beings [13]. It will nevertheless be presented to the regional ethics committee to ascertain that no important or relevant ethical consideration was omitted.

Participants will be told that participation is entirely voluntary, that there will be no consequence if they refuse to participate, and that they will be able to withdraw at any time without explanation. All participants will be asked to sign an electronic consent form immediately after logging in. There is no compensation for participation in the study.

Study Design

This will be a monocentric, parallel-group, randomized controlled trial based on clinical vignettes. The protocol was developed according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement (Multimedia Appendix 1) [14]. Given its design, the investigators will not be blinded as to the intervention. Nevertheless, participants will not be informed that there are 2 different arms and will not be told the exact outcomes studied, even though they will be provided with general information regarding the study. In addition, the data analyst will be blinded as to participant allocation by renaming the groups before sending data for statistical analysis. Randomization will be stratified according to current position (resident vs registrar).

Results will be reported according to the CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile HEalth Applications and onLine TeleHealth) guidelines [15]. Relevant elements of the CHERRIES (Checklist for Reporting Results of Internet E-Surveys) will be included since web-based questionnaires will be used in the course of this study [16].

Clinical Vignettes

A total of 10 clinical vignettes will be developed for the purpose of this study. These vignettes will describe clinical cases

requiring the use of LAs for regional anesthesia. We will include 3 of the most commonly used LAs in these vignettes: lidocaine, levobupivacaine, and ropivacaine. Some vignettes will ask the participant to use LA mixtures, and several will include comorbidities or medications requiring dose adaptations.

For each vignette, 3 authors will be required to determine the maximum dose of LA the simulated patient should receive according to the rules used to develop the LoAD Calc app [12], without using the app. These rules, which are derived from the scientific literature, are summarized in Textbox 1. They were reviewed and approved by clinical pharmacologists and toxicologists [12]. Any disagreement will prompt a review of the vignette. Final vignette approval will only be possible if a consensus can be reached.

Textbox 1. Dosage elements and app rules used to calculate the maximum safe dose of local anesthetics, adapted from Suppan et al [12].

Dose limit for a single LA (local anesthetic)

- Levobupivacaine: 2 mg/kg (maximum 150 mg/dose)
- Lidocaine: 3 mg/kg (maximum 300 mg/dose)
- Ropivacaine: 3 mg/kg (maximum 225 mg/dose)

Influence of epinephrine on dose limit

- Levobupivacaine: 3 mg/kg (maximum 150 mg/dose)
- Lidocaine: 7 mg/kg (maximum 400 mg/dose)
- Ropivacaine: 3 mg/kg (maximum 225 mg/dose)

Determination of calculation weight (CW)

- Calculation of BMI
- Calculation of ideal body weight (IBW; Devine formula)
- Application of the following algorithm to define CW:
  - weight≤70 kg and BMI<30 and IBW >weight → CW=weight
  - weight≤70 kg and BMI<30 and IBW ≤weight → CW=IBW
  - weight≤70 kg and BMI≥30 → CW=IBW
  - weight>70 kg and IBW>70 → CW=70
  - weight>70 kg and IBW≤70 → CW=IBW

Dose adaptation depending on health conditions and drugs

- Conditions
  - Old age (70 years or older)
  - Renal dysfunction (glomerular filtration rate [GFR]<50 mL/minute)
  - Hepatic insufficiency (prothrombin time <50%)
  - Heart failure (left ventricular ejection fraction≤30%)
  - Pregnancy
  - Drugs decreasing LA metabolism
- List of drugs decreasing LA metabolism
  - Major CYP1A2 inhibitors: ciprofloxacin, norfloxacin, and fluvoxamine
  - Major CYP3A inhibitors: azole antifungals, macrolides, calcium channel blockers, HIV antiretroviral therapy, and tyrosine kinase inhibitors
- If 1 condition is present, the calculator reduces the total maximum dose by 20%
- If 2 or more conditions are present, the calculator reduces the total maximum dose by 30%.

Calculation rule for LA mixtures

- The app performs the following steps
  - Calculation of maximum safe volume for first LA
  - The user enters which volume of first LA is to be used (0–maximum volume)
  - Calculation of corresponding maximum dose of first LA and determination of percentage of total maximum dose
  - Calculation of maximum dose of second LA based on remaining percentage of total maximum dose
  - Calculation of maximum volume of second LA

Groups and Randomization

There will be 2 study groups: in the control group, participants will be asked to use the method they usually use in their clinical practice to calculate the maximum safe dose of LA; in the LoAD Calc (experiment) group, participants will be required to use the LoAD Calc app, which will be preinstalled on a standard Geneva University Hospitals (HUG) smartphone (Galaxy XCover 4s; Samsung) running on Android 11.

Stata's (StataCorp LLC) replicable balanced randomization mechanism will be used to allocate participants to their study group. Textbox 2 contains the code that will be used.

Textbox 2. Randomization code.

```
set obs #N
egen arm = seq(), to(2)
set seed #S
gen random = uniform()
sort random
```

Wherein "1" will be the control group, and "2" will be the LoAD Calc group.

Since randomization will be stratified according to participant position (either resident or registrar), 2 seeds (#S) will be used (07022023 and 20230207).

A sample size calculation will be used to determine the total number of observations. It will be rounded up to the nearest ten to enhance the study power and take into account attrition and potential exclusions. The stratified number of observations (#N) will be computed according to the proportion of potential participants belonging to both eligible positions (residents vs registrars).

The method used by the participants allocated to the control group to calculate the maximum safe dose of LA will be recorded. There will be no teaching or introductory intervention for any of the participants before the study, and the participants allocated to the LoAD Calc group will therefore discover the app while answering the first vignette.

Web-Based Study Platform

A specific web-based platform will be developed using the Joomla! 4.3 content management system (Open Source Matters). It will be hosted on a Swiss server (Kreativmedia GmbH) and secured by the RSFirewall 3 (RSJoomla) and AdminTools 7 (Akeeba Ltd) components. To ensure participant anonymity, unique usernames and passwords will be created using Manytools' web-based password generator [17]. These credentials will then be imported into Stata and allocated to either study group according to the randomization process described above. Finally, this data will be exported to a CSV file, which will be imported into the web-based study platform using the Import Joomla Users component (version 3.4; Lerus Ltd).

Consents, questionnaires, and vignettes will be managed using Shondalai's Community Surveys 6 and Community Quiz 6 components (Bulasikku Technologies Pvt Ltd). All data will be stored on an encrypted MySQL-compatible database (MariaDB 10, MariaDB Foundation).

Inclusion and Exclusion Criteria

All resident physicians and registrars working in the HUG anesthesiology department will be eligible for inclusion. The only exclusion criteria will be current or previous use of the LoAD Calc app. This criterion will be assessed by a screening question asked after the completion of all study vignettes.

Recruitment

The project will first be presented to the head of the anesthesiology department and then to all consultants. After obtaining their agreement, investigators will recruit potential participants directly in the operating room. These residents and fellows in anesthesiology will be informed that the study will last at most 1 hour and that an investigator will replace them in the operating room while they participate. They will be told that participation is entirely voluntary, that there will be no consequence if they refuse to participate, and that they will be able to withdraw at any time without explanation. No incentive other than advancing scientific knowledge will be given to promote participation. They will be given a paper sheet summarizing the information regarding the study and data protection (Multimedia Appendix 2). Those who agree will be scheduled for participation on the same day. Together with the anesthesiology consultant overseeing the operating room, an investigator will organize replacements to avoid any disruption in the operating program. There will be only 1 slot, and therefore, only 1 participant per hour.

Consent and Study Sequence

Participants will be asked to set their phones to flight mode. This will enable them to access any note, calculator, or app they use to calculate LA doses while avoiding potentially disruptive interruptions. The study itself will take place in a separate, quiet room. There, an investigator will prompt them to pick up a sealed, opaque envelope containing the credentials necessary to log in.

All participants will be asked to sign an electronic consent form immediately after logging in. Those who agree will proceed to a first questionnaire designed to gather demographical data (Textbox 3) and determine whether these participants are currently using LoAD Calc or if they have used this app before (exclusion criterion). After completing this questionnaire, an introductory screen giving information regarding the vignettes they are about to see and specifying the calculation method they are to use (LoAD Calc for the experimental group vs left at the participant's will for the control group) will be displayed. At

this stage, those allocated to the LoAD Calc group will be given the smartphone preinstalled with the LoAD Calc app.

Textbox 3. First questionnaire.

Page 1: consent

- Consent to participate and to data reuse (multiple-choice questions with only 1 acceptable answer)

Page 2: exclusion criterion

- Has heard of LoAD Calc (multiple-choice questions with only 1 acceptable answer)[a]
- Has installed LoAD Calc (multiple-choice questions with only 1 acceptable answer; branching logic will be used to avoid displaying irrelevant questions)
- Has used LoAD Calc (multiple-choice questions with only 1 acceptable answer; branching logic will be used to avoid displaying irrelevant questions; answering "yes" to either of those questions will lead to participant exclusion)
- Context of LoAD Calc use (multiple-choice question with only 1 acceptable answer; branching logic will be used to avoid displaying irrelevant questions)
- Has LoAD Calc still installed (multiple-choice question with only 1 acceptable answer; branching logic will be used to avoid displaying irrelevant questions)
- Still uses LoAD Calc (multiple-choice questions with only 1 acceptable answer; branching logic will be used to avoid displaying irrelevant questions; answering "yes" to either of those questions will lead to participant exclusion)

Page 3: demographics

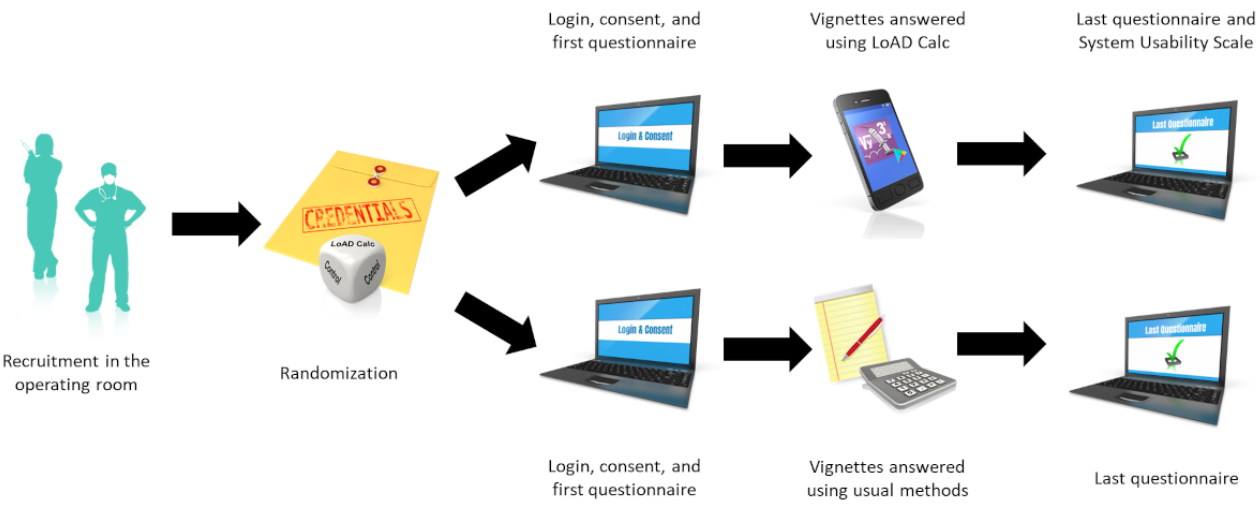
- Gender (multiple-choice questions with only 1 acceptable answer)
- Age (free text with regular expression [regex] validation rule)
- Position (multiple-choice questions with only 1 acceptable answer; custom answer accepted)
- Years since graduation (free text with regular expression [regex] validation rule)
- Years of practice in anesthesiology (free text with regular expression [regex] validation rule)
- Specialist diplomas (custom answer accepted; multiple-answer question with more than 1 answer accepted)

After completing the vignettes, the participants allocated to the LoAD Calc group will be asked to complete the French version of the System Usability Scale [18], the translation of which has been validated [19]. Participants allocated to the control group will then be asked which methods they used to calculate LA doses.

Finally, both groups will have to answer a question based on a 10-point Likert scale to assess their confidence as to the method they used to carry out the maximum safe LA dose calculations, from score 1 (absolutely not confident) to score 10 (perfectly confident).

The whole study sequence is summarized in Figure 1.

Figure 1. Study sequence. LoAD Calc: Local Anesthetics Dose Calculator.



Outcomes

The primary outcome will be the overall overdose rate, according to the method used. To assess this outcome, the maximum acceptable dose in milligrams, or milliliters, must therefore be established. While this might seem straightforward at first sight, it is actually rather complex. Indeed, although maximum safe doses are calculated in milligrams, anesthetists administer a volume of LA (the concentration of which can vary) rather than a quantity of LA. Therefore, even though toxicity is related to the quantity (in milligrams) of LA administered, it is clinically more relevant to determine the maximum volume (in milliliters) of LA that can be used for a particular patient. Consequently, after applying the rules described in Textbox 1, a quantity in milligrams will be obtained. It will then be converted in milliliters according to the concentration of the LA used in the vignette. This volume will then be rounded to the inferior integer. To be less conservative, 1 mm will be added to this calculated volume, and the total will represent the maximum acceptable volume. An overdose will be considered any dose higher than this maximum acceptable volume or than its corresponding LA quantity in milligrams.

The secondary outcomes will be the overall overdose rate, considering the simulated patient's ideal weight and the simulated patient's actual weight, the overdose rate according to each LA studied, and the overall underdose rate. An underdose will be defined as the maximum acceptable volume minus 20% (or its corresponding LA quantity in milligrams), rounded to the inferior integer. This is an empirical choice since anesthetic underdose can only be determined clinically [20,21].

Other secondary outcomes will be the time taken to complete these calculations, the app's usability, and the physicians' confidence in using the method they were allocated to. The app's usability will be evaluated using the System Usability Scale [18]. Provided that the statistical assumptions are met, factors associated with a higher probability of overdose or underdose will also be assessed.

Statistical Analysis

The sample size calculation and all other statistical analyses will be carried out using Stata (version 17.0 or above). The complete data set will be exported by the webmaster, who will give the study groups codenames before sending the curated data set for statistical analysis. Descriptive statistics will be used to present demographical data. Normality will be assessed graphically, and the Kolmogorov-Smirnov test will be used in cases of doubt. Accordingly, all outcomes will then be computed using either parametric or nonparametric tests. The data acquisition mechanisms will ensure that all data are recorded after each stage. Thus, there should not be any missing data, and there shall be no need for imputation. When LA mixtures are used, participants will be told that 1 anesthetic has already been injected and the dose used has been clearly reported. Thus, they will be asked to determine the maximum safe dose for the second local anesthetic. Multivariable regression will be used to determine an association between specific clinical parameters and the probability of overdose or underdose, provided that all required assumptions are met and that the risk of overfitting is adequately limited. Double-sided P values ($P<.05$) will be considered significant.

Results

The 10 vignettes necessary to carry out the study were successfully created, and the maximum safe doses were determined. These vignettes and the doses were checked and approved by all authors. The 10 vignettes, as well as their English translation, were presented to peer reviewers but are not publicly available to avoid any potential bias. They will nevertheless be published along with the results paper.

The sample size calculation was performed using Stata (version 17.0). It showed that 46 participants (23 in each group) would be needed to detect a 10% difference with a power of 90%, taking into account an SD of 10%. In line with the above methods, a total of 50 anesthesiologists should therefore be recruited. Since there are 62 residents and 52 registrars in the HUG Anesthesiology Department, a participation rate of 44% (50/114) will be necessary. This participation rate seems achievable with the aforementioned recruitment procedure. If this rate cannot be achieved, other Swiss University hospitals will be contacted, and similar recruitment procedures will be carried out to obtain the required sample size.

The study platform has been successfully created and tested by all coauthors [22]. The data extraction mechanisms have also been successfully checked.

The recruitment will take place once this study protocol has been reviewed and accepted for publication to allow for any necessary adjustments before study inception. The current version of the protocol is 0.9 (October 10, 2023). The published version will be 1.0.

It should be possible to start recruitment during the winter of 2023. This would allow data analysis to take place in spring 2024, and results should be submitted for publication in an international peer-reviewed journal by the end of the same year.

Discussion

Overview

This study should allow us to determine whether LoAD Calc, an mHealth app designed to calculate maximum safe LA doses, is safer and more effective than current clinical practice. Previous studies have shown that mHealth apps can enhance dose calculation and potentially improve safety [23], decrease time to drug delivery [23], and lessen stress [24]. Assessing this latter parameter would not make much sense given the design of this study but could prove interesting in future high-fidelity or field trials.

Other solutions have already been proposed for the calculation of the maximum safe LA dose but present significant drawbacks. Some of them, such as the nomogram created by Williams and Walker [11], do not depend on technological devices. This nomogram, which represents a rapid and calculation-free way, must, however, always be within reach. In addition, IBW must first be determined, and there is no dose adaptation based on health conditions or drug interactions. Computer-based solutions

and mobile apps have also been created, such as MDCalc Local Anesthetic Dosing Calculator [25], The Podiatry Institute's LA Toxic Dose Calculator [26], and SafeLocal by Johns Hopkins Digital [27]. All these solutions lack key elements and do not consider either IBW, comorbidities, or medications. Most allow invalid data to be entered or suggest doses exceeding the maximum safe dose, thereby presenting potential safety issues.

No study can be devoid of limitations, and the one planned according to this protocol is no exception. The first foreseeable limitation is that the LoAD Calc app will be compared to many different methods of LA dose calculation, thereby preventing us from directly comparing this app to a specific method. However, there is no gold standard to calculate the maximum safe LA doses, and the design of the proposed study can be considered pragmatic. Another limitation is that the maximum safe doses will be calculated using the same scientifically grounded rules that were used to develop LoAD Calc [12]. However, some of the calculation rules used by the app are not supported by strong scientific evidence, and there is no gold standard for comprehensive, safe calculation of maximum LA doses. Finally, the results obtained through this study will only apply to the single-dose administration of a limited number of LAs or of LA mixtures. This will not affect the validity of the study's results nor compromise the use of the app since the 3 LAs selected (levobupivacaine, lidocaine, and ropivacaine) are commonly used in clinical practice. Nevertheless, further app developments will be needed to take other LAs and repeated doses into account. Since some LAs, such as lidocaine, are also safe for intravenous use, future versions of the app should enable practitioners to select different injection sites and routes.

Conclusions

Following this protocol should enable us to determine whether LoAD Calc, a mHealth app designed to calculate the maximum safe doses of LA, is both safe and effective. If this hypothesis proves to be true, clinical trials could be considered, and further outcomes, such as the impact of LoAD Calc on cognitive load and physiologic stress, could be considered.

Acknowledgments

The authors of this protocol would like to thank all members of the original LoAD Calc development team for their support throughout its development.

Data Availability

The data sets generated during and/or analyzed during this study will be available in an open access repository.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT checklist.
[PDF File (Adobe PDF File), 555 KB - resprot_v13i1e53679_app1.pdf]

Multimedia Appendix 2
Study information sheet.
[PDF File (Adobe PDF File), 84 KB - resprot_v13i1e53679_app2.pdf]

References

1. Altman RS, Smith-Coggins R, Ampel LL. Local anesthetics. Ann Emerg Med 1985;14(12):1209-1217 [FREE Full text] [doi: 10.1016/s0196-0644(85)81031-3] [Medline: 4061995]
2. Macfarlane AJR, Gitman M, Bornstein KJ, El-Boghdadly K, Weinberg G. Updates in our understanding of local anaesthetic systemic toxicity: a narrative review. Anaesthesia 2021;76(Suppl 1):27-39 [FREE Full text] [doi: 10.1111/anae.15282] [Medline: 33426662]
3. Edwards AE, Bowsher GM, Deepak S, Ali M. Improving Local Anaesthetic Systemic Toxicity (LAST) awareness in maternity care using tailored educational tools. BMJ Open Qual 2018;7(2):e000070 [FREE Full text] [doi: 10.1136/bmjoq-2017-000070] [Medline: 29682617]
4. Collins J. Awareness of local anaesthetic toxicity issues among hospital staff. Anaesthesia 2010;65(9):960-961 [FREE Full text] [doi: 10.1111/j.1365-2044.2010.06472.x] [Medline: 21198500]
5. Mörwald EE, Zubizarreta N, Cozowicz C, Poeran J, Memtsoudis SG. Incidence of local anesthetic systemic toxicity in orthopedic patients receiving peripheral nerve blocks. Reg Anesth Pain Med 2017;42(4):442-445 [FREE Full text] [doi: 10.1097/AAP.0000000000000544] [Medline: 28079735]
6. Liu SS, Ortolan S, Sandoval MV, Curren J, Fields KG, Memtsoudis SG, et al. Cardiac arrest and seizures caused by local anesthetic systemic toxicity after peripheral nerve blocks: should we still fear the reaper? Reg Anesth Pain Med 2016;41(1):5-21 [FREE Full text] [doi: 10.1097/AAP.0000000000000329] [Medline: 26650424]

7. Mulroy MF. Systemic toxicity and cardiotoxicity from local anesthetics: incidence and preventive measures. Reg Anesth Pain Med 2002;27(6):556-561 [FREE Full text] [doi: 10.1053/rapm.2002.37127] [Medline: 12430104]
8. Dickerson DM, Apfelbaum JL. Local anesthetic systemic toxicity. Aesthet Surg J 2014;34(7):1111-1119 [FREE Full text] [doi: 10.1177/1090820X14543102] [Medline: 25028740]
9. Gadsen J. Local anesthetics: clinical pharmacology and rational selection. In: Hadzic's Peripheral Nerve Blocks and Anatomy for Ultrasound-Guided Regional Anesthesia 2nd Edition. New York: McGraw Hill LLC; 2012.
10. Rosenberg PH, Veering BT, Urmey WF. Maximum recommended doses of local anesthetics: a multifactorial concept. Reg Anesth Pain Med 2004;29(6):564-575 [FREE Full text] [doi: 10.1016/j.rapm.2004.08.003] [Medline: 15635516]
11. Williams DJ, Walker JD. A nomogram for calculating the maximum dose of local anaesthetic. Anaesthesia 2014;69(8):847-853 [FREE Full text] [doi: 10.1111/anae.12679] [Medline: 24820093]
12. Suppan M, Beckmann TS, Gercekci C, Sigrist T, Savoldelli GL, Fournier R, et al. Development and preliminary validation of load calc, a mobile app for calculating the maximum safe single dose of local anesthetics. Healthcare (Basel) 2021;9(7):799 [FREE Full text] [doi: 10.3390/healthcare9070799] [Medline: 34202140]
13. CC 810.30 Federal Act of 30 September 2011 on Research involving Human Beings (Human Research Act, HRA). The Federal Assembly of the Swiss Confederation. 2020. URL: https://www.fedlex.admin.ch/eli/cc/2013/617/en#cha [accessed 2023-12-13]
14. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med 2013;158(3):200-207 [FREE Full text] [doi: 10.7326/0003-4819-158-3-201302050-00583] [Medline: 23295957]
15. Eysenbach G, CONSORT-EHEALTH Group. CONSORT-EHEALTH: improving and standardizing evaluation reports of Web-based and mobile health interventions. J Med Internet Res 2011;13(4):e126 [FREE Full text] [doi: 10.2196/jmir.1923] [Medline: 22209829]
16. Eysenbach G. Improving the quality of Web surveys: the Checklist for Reporting Results of Internet E-Surveys (CHERRIES). J Med Internet Res 2004;6(3):e34 [FREE Full text] [doi: 10.2196/jmir.6.3.e34] [Medline: 15471760]
17. Password generator. Manytools. URL: https://manytools.org/network/password-generator/ [accessed 2023-12-13]
18. Brooke J. SUS: a 'quick and dirty' usability scale. In: Usability Evaluation In Industry. London, Bristol, PA: CRC Press; 2020:207-212.
19. Gronier G, Baudet A. Psychometric evaluation of the F-SUS: creation and validation of the French version of the system usability scale. Int J Human–Computer Interact 2021;37(16):1571-1582 [FREE Full text] [doi: 10.1080/10447318.2021.1898828]
20. Visavakul O, Leurcharusmee P, Pipanmekaporn T, Khorana J, Patumanond J, Phinyo P. Effective dose range of intrathecal isobaric bupivacaine to achieve T5-T10 sensory block heights for elderly and overweight patients: an observational study. Medicina (Kaunas) 2023;59(3):484 [FREE Full text] [doi: 10.3390/medicina59030484] [Medline: 36984485]
21. Andreae M. Underdosing the epidural invalidates a good clinical trial. Anesthesiology 2002;97(4):1026-1027 [FREE Full text] [doi: 10.1097/00000542-200210000-00047] [Medline: 12357181]
22. Suppan M. Local Anesthetics Study. URL: https://local.anesth.ch/ [accessed 2023-12-13]
23. Siebert JN, Bloudeau L, Combescure C, Haddad K, Hugon F, Suppan L, et al. Effect of a mobile app on prehospital medication errors during simulated pediatric resuscitation: a randomized clinical trial. JAMA Netw Open 2021;4(8):e2123007 [FREE Full text] [doi: 10.1001/jamanetworkopen.2021.23007] [Medline: 34459905]
24. Lacour M, Bloudeau L, Combescure C, Haddad K, Hugon F, Suppan L, et al. Impact of a mobile app on paramedics' perceived and physiologic stress response during simulated prehospital pediatric cardiopulmonary resuscitation: study nested within a multicenter randomized controlled trial. JMIR Mhealth Uhealth 2021;9(10):e31748 [FREE Full text] [doi: 10.2196/31748] [Medline: 34617916]
25. Local anesthetic dosing calculator. MDCalc. URL: https://www.mdcalc.com/calc/10205/local-anesthetic-dosing-calculator [accessed 2023-12-13]
26. LA toxic dose calculator. The Podiatry Institute. URL: http://www.podiatryinstitute.com/Local_Anesthetic_Toxic_Dose_Calculator.xls [accessed 2023-12-13]
27. SafeLocal. Johns Hopkins Digital. URL: https://apps.apple.com/us/app/safelocal/id1440999841 [accessed 2023-12-13]

Abbreviations

CCER: Commission Cantonale d'Ethique de la Recherche
CHERRIES: Checklist for Reporting Results of Internet E-Surveys
CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile HEalth Applications and onLine TeleHealth
HUG: Geneva University Hospitals
IBW: ideal body weight
LA: local anesthetic
LAST: local anesthetic systemic toxicity

LoAD Calc: Local Anesthetics Dose Calculator
mHealth: mobile health
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

Edited by G Eysenbach; submitted 15.10.23; peer-reviewed by N Buckley, T Girard; comments to author 02.11.23; revised version received 04.11.23; accepted 21.11.23; published 03.01.24.

Please cite as:
Fubini PE, Savoldelli GL, Beckmann TS, Samer CF, Suppan M
Impact of a Mobile App (LoAD Calc) on the Calculation of Maximum Safe Doses of Local Anesthetics: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2024;13:e53679
URL: https://www.researchprotocols.org/2024/1/e53679
doi:10.2196/53679
PMID:38170571

Protocol

Professional Development to Improve Responsible Beverage Service Training: Formative Research Results and Protocol for a Randomized Controlled Trial

W Gill Woodall[1*], PhD; David Buller[1*], PhD; Robert Saltz[2*], PhD; Lila Martinez[1*], BA

[1]Klein Buendel, Inc, Golden, CO, United States

[2]Prevention Research Center, Pacific Institute for Research and Evaluation, Berkeley, CA, United States

[*]all authors contributed equally

Corresponding Author:
David Buller, PhD
Klein Buendel, Inc
1667 Cole Blvd
Ste 220
Golden, CO, 80401
United States
Phone: 1 303 565 4321
Email: dbuller@kleinbuendel.com

Abstract

Background: Improved interventions are needed to reduce the rate of driving while intoxicated. Responsible beverage service (RBS) training has reduced service to intoxicated patrons in licensed premises in several studies. Its efficacy might be improved by increasing the proper application and continued use of RBS with a professional development program in the 3 to 5 years between the required RBS retraining.

Objective: This study aims to develop and evaluate a professional development component for an RBS training that aims to improve the effectiveness of the web-based training alone.

Methods: In a 2-phase project, we are creating a professional development component for alcohol servers after completing an RBS training. The first phase involved formative research on the feasibility, acceptability, and potential effectiveness of components. Semistructured interviews with owners and managers of licensed establishments and focus groups and a survey with alcohol servers in New Mexico and Washington State examined support for RBS and the need for ongoing professional development to support RBS. A prototype of a professional development component, *WayToServe Plus*, was produced for delivery in social media posts on advanced RBS skills, support from experienced servers, professionalism, and basic management training. The prototype was evaluated in a usability survey and a field pilot study with alcohol servers in California, New Mexico, and Washington State. The second phase of the project will include full production of the professional development component. It will be delivered in Facebook private groups over 12 months and evaluated with a sample of licensed premises (ie, bars and restaurants) in California, New Mexico, and Washington State (n=180) in a 2-group randomized field trial (*WayToServe* training only vs *WayToServe* training and *WayToServe Plus*). Licensed establishments will be assessed for refusal of sales to apparently intoxicated pseudopatrons at baseline and 12 months after the intervention commences.

Results: Although owners and managers (n=10) and alcohol servers (n=43) were favorable toward RBS, they endorsed the need for ongoing support for RBS for servers and identified topics of interest. A prototype with 50 posts was successfully created. Servers felt that it was highly usable and appropriate for themselves and the premises in the usability survey (n=20) and field pilot test (n=110), with 85% (17/20) and 78% (46/59), respectively, saying they would use it. Servers receiving the professional development component had higher self-efficacy (d=0.30) and response efficacy (d=0.38) for RBS compared with untreated controls.

Conclusions: Owners, managers, and servers believed that an ongoing professional development component on RBS would benefit servers and licensed premises. Servers were interested in using such a program, a large majority engaged with the prototype, and servers receiving it improved on theoretic mediators of RBS. Thus, the professional development component may improve RBS training.

Trial Registration: ClinicalTrials.gov NCT05779774; http://tinyurl.com/4mw6d2vk

International Registered Report Identifier (IRRID): DERR1-10.2196/49680

(JMIR Res Protoc 2024;13:e49680) doi:10.2196/49680

KEYWORDS

alcohol; driving while intoxicated; responsible beverage service; training; prevention; professional development; social media

Introduction

Background

Driving while intoxicated (DWI) is one of the most preventable public health risks in the United States. However, from 2019 to 2020, there was an increase of 14.3% in DWI deaths, after remaining largely stable from 2015 to 2019 [1]. Although new policies and interventions are needed to reduce the consequences of DWI, gains are possible by increasing the efficacy of existing interventions. Responsible beverage service (RBS) training [2-4] has been effective in some cases [5], but methods of boosting its efficacy are needed. The goal of this research is to develop and evaluate a professional development component for a web-based RBS training program that aims to improve the effectiveness of web-based training. The professional development component will provide ongoing information and instruction in advanced RBS techniques and emphasize professionalism in the hospitality industry. It will be continuously available and easily accessible to alcohol servers via social media after completing the web-based training.

Marketplace approaches to prevent alcohol service that results in intoxication or restrict access to alcohol by persons already intoxicated are an alternative policy approach to deterrence of driving by drinkers considered impaired to decrease DWI [6]. Most US states have laws prohibiting sales of alcohol to visibly intoxicated customers [7]. A complementary intervention is RBS training, which aims to instruct servers on how to prevent intoxication by teaching drink counting techniques, ways to recognize signs of intoxication, and strategies to refuse alcohol sales. This environmental intervention aims to decrease opportunities for risky behavior [8], consistent with harm reduction in a nurturing environment perspective [9]. It is a targeted restriction on alcohol accessibility at the times and places where risk is greatest that does not depend on decision-making by persons considered alcohol impaired, can be applied to all alcohol sales premises, does not depend on house policies of licensees to refuse sales, and reduces intoxicated customers' ability to *shop around* to find premises that will serve.

Research on RBS training presents a mixed picture [5]. Although some studies have failed to show effectiveness [10], reviews in 2000 and 2001 concluded that RBS training can prevent alcohol overservice [11] with strong management support [12]. Recent studies have found RBS training to be associated with increases in refusals of service to apparently intoxicated customers. In addition it was related to decreases in blood alcohol concentration and calls to emergency services [13]. RBS training combined with enforcement reduced alcohol overservice and violent assaults in a trial in Sweden [14-16] but not in Norway [17]. In addition, lower levels of motor vehicle crashes with a high percentage of alcohol involvement were observed in a mandatory RBS training state [18], and another analysis found that states with RBS laws had a reduced number of underage drinking driver fatality crash ratios [19]. Data on self-reported DWI have been mixed, with one study showing no association [20] and another finding a decrease in reported DWI with RBS training [13]. Continued research on RBS training [21] is warranted because (1) positive outcomes have been reported [5,16,22,23]; (2) methodological problems limit existing evidence (eg, lack of randomized trials, clear outcome variables, training fidelity data, and effect size reporting) [5,11,12]; and (3) data are limited on web-based training that can improve training engagement, fidelity, and quality, compared with in-person training [5]. Our team showed that a web-based RBS training program, named *WayToServe*, was effective in premises serving alcohol for onsite consumption (ie, bars and restaurants) [24].

RBS training laws are highly variable across US states [25]. It is legally mandated in 25 US states and incentivized in some fashion in a number of other states [26]. Most states that require training have long periods of 3 to 5 years between required retraining. Consequently, the proper application, monitoring, and continued use of the RBS techniques falls on the shoulders of premises management, so it is not surprising that management commitment to RBS can affect servers' adherence to RBS methods [5,12]. Developing ways to support RBS techniques after training may counter the management's ineffective or limited support for, disinterest in, or outright resistance to RBS.

Objectives

The goal of this study is to develop and evaluate a follow-on professional development component to increase the efficacy of our web-based RBS training, *WayToServe*. Continuing professional development is a widespread practice across a variety of fields including accounting, social work, and medicine [27]. Typically, it focuses on improving knowledge, skills, and performance to help employees stay up-to-date on industry developments, develop and maintain job capabilities, convey professional values and norms, and create communities of practice [27-32]. Although often focused on *high-skill* professional workers (eg, nurses, physicians, lawyers, and architects) [27], the training and certification of community members has improved professionalism [33] and, along with in-service contact, has boosted the success of community prevention programs [34,35]. Vocational education and lifelong learning play essential roles in the hospitality industry. They offer both general knowledge and skills such as communication and customer service as well as job-related knowledge such as understanding laws related to serving alcohol and the ability to recognize signs of intoxication [32,36,37]. Alcohol servers trained in RBS practices should benefit from ongoing professional development by (1) motivating them to implement RBS skills in the face of common barriers, such as pressure to

sell, low management support, and customers' attempts to continue being served; (2) receiving support for RBS from a *community* of alcohol servers, especially for servers who work in small or unsupportive premises; and (3) preventing the degradation of RBS skills over time.

Methods

Overview

This study is being conducted in 2 phases to create an effective professional development component for alcohol servers who completed state-approved RBS training. The first phase aimed to determine whether a professional development component delivered over social media was feasible, acceptable, and potentially effective for alcohol premises management and servers. The second phase will involve production of the professional development component and testing its efficacy in a randomized controlled trial (RCT).

Phase 1: Formative Research

Overview

A formative research phase in 2022 used both qualitative and quantitative techniques to provide a detailed picture of RBS training and its gaps as well as the feasibility and potential effectiveness of adding a professional development component. It included semistructured interviews with premises managers, focus groups and a survey with alcohol servers, development of a prototype of the professional development component, and usability testing and a field pilot study evaluating the prototype.

Semistructured Interviews With Alcohol Premises Owners and Managers

Owners and managers (n=10) of onsite alcohol premises in New Mexico and Washington State participated in semistructured interviews. Premises had to hold an active state alcohol license and be a bar or restaurant that served alcohol. Managers discussed RBS policies at their premises, support for RBS methods, perceived importance of RBS, quality of RBS methods implemented by their servers, and need for ongoing training and support for RBS among their servers. They also suggested content for a professional development component. The transcripts were coded to identify themes.

Focus Groups and Survey With Alcohol Servers

Alcohol servers working in onsite alcohol sales premises in New Mexico and Washington State were recruited from the roster of *WayToServe* trainees to provide input on experience with RBS methods and interest in ongoing professional development related to RBS methods. To be included, servers had to be aged ≥19 years (by state regulation), serve alcoholic beverages at a licensed premises, have completed the *WayToServe* RBS training, and be proficient in English. Initially, alcohol servers (n=19) were recruited to web-based focus groups; however, when participation lagged, servers (n=24) were recruited instead to complete a web survey. In both the focus groups and survey, servers were asked about their experience with, confidence in, and barriers to RBS methods; support from management and other alcohol servers for RBS; and experience refusing service to customers. They also indicated their interest in and potential utility of receiving ongoing information and activities from *WayToServe* to keep up-to-date and be capable of using RBS methods via a Facebook group. Servers reported whether they were willing to share their RBS experiences or provide feedback on RBS actions with other servers. Focus group transcripts were coded for themes for each question. The survey responses were summarized using descriptive statistics.

Production of a Prototype Professional Development Component

A prototype of the professional development component was produced by the project staff and media developers. Named *WayToServe Plus*, it comprised a series of 50 social media posts. The goal of the messages was to improve servers' professionalism by (1) increasing the confidence and motivation of RBS-trained servers to implement RBS methods, with attention to ways of overcoming common barriers; (2) creating a professional community of servers that supports one another in implementing RBS actions and serves as a resource for advice and strategies to implement RBS (eg, tips and tricks) by encouraging servers to share their personal experiences through comments and posts; and (3) preventing the deterioration of RBS skills and motivation over time by providing refresher instruction. Posts contained text, graphics, web-based learning activities, and videos demonstrating RBS techniques in 4 topic areas derived from the results of the manager interviews and alcohol server focus groups and surveys: advanced RBS skills training (ID checking, cannabis and alcohol, drink counting, and home delivery), experienced servers supporting new servers (eg, tips and tricks to apply RBS and sharing stories on RBS experiences), professionalism (safety and security, security personnel, and handling disruptive customers), and basic management training (content and development of house RBS policies and best practices for RBS). Instructional goals included improving the application of RBS information and skills in realistic settings and circumstances that servers have encountered in their jobs. *WayToServe Plus* was consistent with the transformative approach to continuing professional development by Kennedy [38], combining the transmission of information, skills, and norms and providing coaching or mentoring by striving to create a community of practice among servers with varying levels of experience. Messages in the posts were guided by principles of diffusion of innovation theory (eg, compatibility, simplicity, trialability, and observability) [39] and social cognitive theory (ie, modeling) [40] and written to be relatable, positive, and entertaining. A total of 14 short videos were produced using the TikTok video authoring platform. An interactive quiz activity was taken from the *WayToServe* training and linked to a social media post. *WayToServe Plus* was authored in English because most servers had elected to complete *WayToServe* training in English.

Evaluation of Prototype Professional Development Component

The prototype *WayToServe Plus* component was evaluated for usability, feasibility, acceptability, and engagement through a survey and a field pilot test with alcohol servers recruited from the roster of *WayToServe* trainees.

Usability Testing

Alcohol servers (n=20) who met the aforementioned inclusion criteria (refer to the *Focus Groups and Survey With Alcohol Servers* section) completed a web survey on prototype acceptability, feasibility, and utility (10 in New Mexico and 10 in Washington State). Ten usability testers can identify 95% of problems [41-43]. In the survey, servers were provided with a description of the *WayToServe Plus* component. Each server was presented with 3 posts and 1 video randomly selected from posts in the prototype. They were then asked to evaluate these items based on their appropriateness for themselves and licensed establishments, their acceptability, and usefulness, using 5-point Likert scales. Servers indicated if they would read or view the post or video, react to it (eg, like, sad, and angry), comment on it, and share it. A description of the interactive activities was provided and rated based on these measures. Next, servers evaluated the *WayToServe Plus* concept on the validated System Usability Scale (SUS) [44-46]. The 10 items were combined using standard techniques, with a score of ≥68 indicating adequate usability. In addition, a single item assessed user-friendliness (1=worst imaginable and 7=best imaginable). Finally, servers indicated whether they would be interested in getting the ongoing information and activities from *WayToServe Plus*, topics that would be of interest to them, and potential reasons for not using it.

Field Pilot Test

A sample of 59 alcohol servers (5 in California, 21 in New Mexico, and 33 in Washington State) participated in a 1-month field pilot test of the prototype, meeting the same inclusion criteria as the focus group and usability testing participants. The study involved a nonrandomized posttest-only 2-group design, in which the treatment group had 2 levels: prototype *WayToServe Plus* program versus no treatment. In the intervention group, 59 servers were recruited and joined a Facebook private group on a rolling basis over 8 weeks. Staff posted prototype *WayToServe Plus* posts (1 per day, Monday to Friday) for the 8-week period. Approximately 24 posts were posted to the private group during any 4-week period in the intervention period. The posts were only viewable to members of the private group and could not be shared outside the private group. Outcomes were assessed in 2 ways at 4 weeks after enrollment. First, servers' engagement with *WayToServe Plus* was measured by recording the number of times posts were viewed, reacted to (eg, liked), and commented on by servers. Second, servers completed a web-based posttest, assessing the prototype on appropriateness, acceptability, and utility for servers and premises and usability on the SUS [44-46] and whether the tone of the prototype aligned with their licensed establishment's atmosphere, using scales similar to those used in the usability survey. Perceived self-efficacy and response efficacy for maintaining community safety by using RBS methods (5-point Likert scales) were measured as proxy outcomes of the effectiveness of the prototype program (ie, dependent variables). Willingness to use the *WayToServe Plus* program in the future and job and demographic characteristics were also measured. The respondents suggested ways to improve the prototype and make it more engaging. A second group of 51 servers was recruited to serve as an untreated control group and completed only a posttest web survey, with the primary purpose being to assess their perceived self-efficacy and response efficacy of RBS methods and compare them with ratings provided by servers who received the prototype.

Phase 2: RCT Protocol for Evaluating the Professional Development Component

The *WayToServe Plus* professional development component will be fully produced and evaluated for effectiveness in an RCT.

Production and Implementation of WayToServe Plus Component

A 12-month version of the *WayToServe Plus* professional development component will be created for evaluation in the trial. Content and format will be developed according to instructional goals, principles from diffusion of innovation theory and social cognitive theory, and insights derived from the formative research findings in phase 1. Posts will contain text, infographics, short videos, and interactive activities based on the *WayToServe* RBS training. Features to elicit user-generated content will be included in posts, such as posing a common situation and asking, for example, RBS strategies; providing polls about RBS methods; and soliciting stories, tips, and tricks from experienced servers for applying RBS. These posts are intended to create sense of community among alcohol servers. An agile iterative production process will be used to author the posts [47]. Approximately 2 months of posts will be prepared before launching the intervention; additional posts will be developed during the intervention, adjusting them for season, current events, and reactions and comments from servers to prior posts.

WayToServe Plus will be administered by a staff member who serves as a community manager. The manager will post 4 posts per week, Monday through Friday, for 12 months (approximately 208 posts in total). In addition, posts selected from the usual-and-customary *WayToServe* Facebook page will be posted once per week. Alcohol servers can comment on and react to posts but cannot share them on their own feed. Orientation to private groups will be self-explanatory. The community manager will stress respect for others; monitor comments; and correct inappropriate, unfavorable, or bullying comments or misinformation [48]. Servers will be compensated US $50 for joining the *WayToServe Plus* Facebook private group.

Randomized Trial Design

The *WayToServe Plus* professional development component will be evaluated with a sample of 180 establishments licensed for sale of alcohol for onsite consumption (ie, liquor by the drink) and their alcohol servers. Premises will be enrolled in a 2-group randomized field trial (*WayToServe* training only [comparison control] vs *WayToServe* training plus *WayToServe Plus* [intervention]) with 2 assessment rounds (baseline and posttest [12 months after intervention commences]), yielding a 2 (treatment)×2 (assessment time) factorial design. Using a custom-written program, the project biostatistician will randomly assign half of the premises (90/180, 50%) to *WayToServe* training plus *WayToServe Plus*, stratified by state (ie,

independent variables). The remaining half of the premises (90/180, 50%) will receive *WayToServe* training only. All premises will be recruited to have servers complete the *WayToServe* training. Servers in the intervention group will be joined to a *WayToServe Plus* Facebook private group after training to receive the professional development component. To be added to the group, servers will friend the community manager, the manager will invite them to join the group, and servers will accept this invitation. Servers in the control group will be invited to join the usual-and-customary *WayToServe* Facebook page, which is administered by the training company. Premises will be assessed for refusal of alcohol service to visibly intoxicated patrons, the primary outcome or dependent variable and a measure of the impact of *WayToServe Plus* on actual practice [29], using a pseudointoxicated patron (PiP) protocol at baseline and at posttest. The PiP protocol presents a server with the most overt situation in which alcohol service should be refused (ie, when a patron shows clear signs of intoxication), models the behavior of patrons most at risk, and is relatively low cost. The PiP protocol has been used in thousands of alcohol premises [49], including by the research team [50-52]. PiP teams will be blinded to experimental conditions, and premises owners, managers, and alcohol servers will be blinded to PiP assessments.

Selection and Recruitment of Licensed Alcohol Premises

State-licensed onsite alcohol establishments (n=180) in California (n=60), New Mexico (n=60), and Washington State (n=60) were randomly selected from publicly available lists from state alcohol regulation agencies, stratified by location (metro areas [Albuquerque, San Francisco {including Oakland and San Jose}, and Seattle; n=148 premises] vs suburban towns [n=7 towns and 32 premises]). As in the formative research, they had to hold an active state license to sell alcohol and be a bar or restaurant that sold alcoholic beverages. To control travel costs in the large San Francisco and Seattle metropolitan areas, *clusters* of establishments were constructed by randomly selecting seed premises. Next, 14 additional establishments were randomly selected from within the same zip codes of the seed premises. Within each seed area, 5 to 7 establishments were selected at random for PiP visits, with the remaining premises serving as replacements for any deemed ineligible (eg, do not sell alcohol for onsite consumption) or that were closed (either permanently or during evening hours) when visited by PiP teams. In New Mexico, the Albuquerque metropolitan area was much smaller geographically, so we selected premises at random from the state lists.

After the baseline PiP assessment, project staff will contact premises management, describe participation, record the number of alcohol servers, and obtain agreement to participate in the study. Premises will be given a voucher to provide to their servers to access the *WayToServe* training and complete it within 4 weeks from registration. Severs will complete a consent form. For completing the training, servers will receive US $35 and a new server training certificate for their state. *WayToServe* will remain available to the participating premises throughout the trial, and managers will be asked to have newly hired alcohol servers complete it.

PiP Assessment Protocol

The primary outcome (ie, dependent variable) will be refusal of sale of alcoholic beverages to visibly intoxicated patrons assessed using a PiP protocol. Ethnically diverse male and female legal-age individuals (aged ≥ 21 years) will be hired as confederates, chosen for prior acting experience, and trained to feign intoxication when acting as buyers [50-52]. Signs of intoxication (ie, fumbling with keys or cash, swaying, slurred speech, and stumbling) indicate a high level of alcohol intoxication [53], provide a clear unambiguous choice whether to serve, and are signs that alcohol servers are trained to recognize in the *WayToServe* training and *WayToServe Plus* component. In each round (baseline and posttest), assessment will involve 2 PiP buyer visits per premises by the PiP team comprising a buyer and an observer, separated by at least 6 weeks. At each visit, observers will enter the premises before the buyer and position themselves to be able to see the buyer-server interactions. Buyers will enter the premises displaying intoxication signs and order an inexpensive beer. Both buyers and observers will record if alcohol servers agree to serve the buyers the requested alcoholic beverage. Buyers will also record if the drink was served either as requested, with reluctance, with a joke or similar remark, or with a warning that no future drinks will be served.

In addition, buyers will note the type of beverages requested, if their ID was requested, and other responses by the alcohol servers (made statements of risk, enlisted other patrons to support nonsale, offered a nonalcoholic beverage instead, offered food, provided other information [offer of taxi or safe ride, drinking facts, etc], or delayed or ignored service). Observers will record the characteristics of the establishments (state, type, number of staff and patrons, warning signs posted, and cleanliness), rate how busy the establishment is and speed of service, note if staff appear overly familiar with customers, and record the behavior of buyers (type of drink ordered, signs of intoxication displayed, and rating of obviousness of signs of intoxication). Both buyers and observers will record the servers' job at the establishment (bartender, server, manager, bouncer, or other) and apparent sex (male, female, or do not know), Hispanic ethnicity, and race.

Outcome Analysis

The analysis of study outcomes will test the following hypothesis that compared with premises in *WayToServe* RBS training only group, premises assigned to receive *WayToServe* RBS training and *WayToServe Plus* will have higher rates of refusing PiP at posttest.

In our prior research, the uptake of training in alcohol establishments affected refusal rates [54], so we will test whether improvements in refusal rates are associated with uptake of the *WayToServe* training and engagement with the *WayToServe Plus* component. Training uptake will be obtained from the *WayToServe* web-based program database (ie, the number of servers registered, training modules completed, and completion of the training). Engagement with *WayToServe Plus* will be assessed by counting the number of reactions and comments on posts by servers within each premise [55]. We will not be able to count the views of posts because our sample size exceeds

250 participants; Facebook does not report views of posts in private groups with >250 users. Characteristics of alcohol establishments (type of license, type of business [bar or restaurant], how busy the premises was, and number of staff present during visit), alcohol servers interacting with PiP buyers (sex and ethnicity observed by PiP observers), and PiP buyers (sex and ethnicity) will be analyzed initially as control variables and then in subsequent models as effect modifiers of *WayToServe Plus*.

Interviews of Owners and Managers on WayToServe Plus Feasibility

After posttesting of establishments is completed, 18 owners and managers (6 per state) from premises in the *WayToServe* training and *WayToServe Plus* groups will be selected at random for interviews about *WayToServe Plus*, its compatibility with premises' RBS policies and practices, helpful features, server engagement, suggested improvements, and problems or barriers (compensation=US $75). In addition, alcohol servers in these premises will be surveyed about the same issues and report their engagement with *WayToServe Plus*, whereas servers in the control premises will be surveyed about the *WayToServe* web-based training.

Ethical Considerations

The protocols used in the formative research and randomized trial were reviewed and approved by the WCG institutional review board (#20211770). Participants read and signed an informed consent form (interviews, focus groups, and pilot field trial) or read and acknowledged a consent statement (surveys) approved by the institutional review board that described the purpose of the research, the research procedures, known risks and benefits, and the use and security of the data. Participants were informed that their participation was voluntary and that they could withdraw at any time without penalty. Participants were informed that the data collected from them in the study would be confidential and that their identity would not be disclosed in any public presentation. The participants were compensated as follows: interviews (US $75), focus group discussion (US $50), survey (US $25), usability test (US $50), and field pilot study (US $100).

Results

Phase 1

Owner and Manager Interviews About Professional Development

All owners and managers (n=10; 4 female individuals; 1 African American and 5 Hispanic White individuals) indicated that they supported RBS methods to maintain their establishment's reputation in the community; keep the community safe; and avoid fines, disruptions, and other problems. They supported alcohol servers by addressing RBS methods in mandatory staff meetings and trainings and manager logs. They said that support for RBS was provided by experienced staff. Although most felt the RBS methods were effective at their premises, they did indicate that bartenders have many job tasks and need more help, and some establishments had more difficulty with RBS methods during summers when patrons drank longer and larger quantities of alcohol.

All owners and managers endorsed the need for ongoing training and support for RBS methods and felt that a program could help them support RBS practices. They desired topics such as checking IDs, new recreational marijuana laws, special venues (eg, music venues, wineries, and events), and communication and conflict resolution. They preferred formats such as educational memes, videos, shared experiences and tips and tricks from experienced servers, resource pages, reminders, and work group chats. Owners and managers felt that a variety of staff would benefit from ongoing training. Some of them did not feel confident addressing topics such as marijuana laws, how to handle patrons with children, and how to manage servers' desires to sell alcoholic beverages and make money. All owners and managers would be interested in a program that provided ongoing training and support for RBS if it provided new, relevant content in engaging, easily digestible formats without a large time commitment. They were mostly or very likely to use such a program with their alcohol service staff.

Focus Groups and Survey of Alcohol Servers About Professional Development

Focus Groups

Alcohol servers participating in the focus groups (n=19) were employed in bars, restaurants, and other premises (eg, ski resort, theatre, and market) as bartenders, servers, and other staff. They had worked as servers for 2 months to 6 years.

Most servers had positive experiences applying RBS methods. They reported that owners and managers at their establishment considered RBS methods to be positive, took them seriously, and supported using them. A few servers said that they received very little support, support only from direct supervisors, and support only when they did something incorrectly. They cited management turnover and very large venues as situations that reduced support for RBS. Obstacles to RBS included customers drinking before arriving; pressure to not check IDs or provide heavier pours to regular customers or members of clubs; customers not wanting to hand over ID during COVID-19 social distancing rules; ability to check IDs from different states or military IDs; fake IDs; pressure to sell and fear of losing tips; large, busy events; and potential for negative reactions when refusing sales to intoxicated patrons. Methods to overcome obstacles included observing customers when they arrive; relying on managers, bartenders, and other servers for help; slowing down activities during busy times or slowing service to intoxicated customers; eliminating tips; having support from management; dividing RBS tasks among different staff; serving water to intoxicated customers; and setting limits on the number of drinks served.

All servers saw benefits of continued information, training, and support for RBS methods. The servers also described topics that would be helpful. The perceived benefits of a continuing professional development program included peer support, sense of community, networking among servers, keeping updated on new information, and helping new servers. These included interactive learning activities, prompts, refreshers on laws, IDs,

recognizing intoxication, drink counting, and refusing service, instruction on how to deal with minors, forums for sharing stories and tips with other servers, help for newer servers, ways of managing difficult customers and de-escalating conflict, polls, infographics, and reminders. Almost all servers indicated that they would be willing to share their experiences and provide feedback on RBS methods in the *WayToServe Plus* Facebook group.

Survey

Table 1 presents the profile of the sample of alcohol servers (n=24) who completed the web survey. Alcohol servers ranged in age from 20 to 40 (mean 28.8, SD 5.4) years; a majority were non-Hispanic White (7/24, 29% Hispanic), and there were slightly more female individuals than male individuals. Most servers worked in restaurants and bars as alcohol servers and bartenders and were a mix of new (7/24, 29% had worked less than 1 year) and experienced (15/24, 63% had worked 3 years or more) servers.

Although most servers were very sure of their ability to apply RBS methods, some encountered problems. A sizable minority were only somewhat sure or unsure that they could verify the validity of IDs (3/24, 12%; mean 4.79 out of 5, SD 0.66), check IDs for age of patron (2/24, 8%; mean 4.83, SD 0.64), count number of drinks to prevent intoxication (6/24, 25%; mean 4.63, SD 0.77), recognize if a patron is intoxicated (6/24, 25%; mean 4.63, SD 0.88), or refuse alcohol service to an intoxicated patron (5/24, 21%; mean 4.75, SD 0.53). The obstacles to RBS methods cited included busy serving environments (10/24, 42%), customer intoxicated before arriving (10/24, 42%), regular customers expecting heavier pours (6/24, 25%), coworker or management pressure to not follow RBS regulations (5/24, 21%), fear of sacrificing tips (3/24, 12%), and checking IDs in a group of customers (2/24, 8%). Servers suggested several ways to overcome these obstacles, such as checking everyone's ID (11/24, 46%), getting support from management to follow rules (5/24, 21%), taking a moment to breathe in busy environments (9/24, 38%), serving water (6/24, 25%) or food (5/24, 21%) to patrons that need to sober up, monitoring patrons for signs of intoxication (13/24, 54%), and involving a manager in handling difficult customers (13/24, 54%).

Almost all servers felt that the management of their establishment was supportive of RBS methods, agreeing that management believes RBS methods are beneficial (22/24, 92%; mean 4.54 out of 5, SD 0.66) and management takes RBS methods seriously (22/24, 92%; mean 4.67, SD 0.64). However, 21% (5/24) reported that management at their establishment provided support for RBS methods only sometimes, rarely, or never. The most common support was help serving when the establishment gets busy (16/20, 80%), answering questions about RBS methods (17/21, 81%), helping servers refuse service to a customer (14/20, 70%), helping check IDs during busy periods (9/20, 45%), and highlighting things to be on alert for before a shift (9/19, 47%).

Servers favorably evaluated the idea of professional development. Overall, 71% (17/24) of servers expressed interest in receiving ongoing information and activities from *WayToServe* to help keep them up-to-date and be able to use the RBS methods. The benefits servers saw from this professional development for themselves would be receiving tips and tricks from other servers, getting refreshers on everyday work practices, helping other servers who need it, and providing a place to vent about poor experiences while serving alcohol (Table 2). Benefits for the establishment included having servers be on the same page when it comes to serving alcohol and remaining in good standing with the state's alcohol licensing agency. Finally, 46% (11/24) of the servers said they were somewhat or very likely to join a Facebook group with the professional development content, and 21% (5/24) might join it. The topics of most interest to servers included refreshers on signs of intoxication, unusual or humorous experiences by another server, quizzes that test knowledge of alcohol serving laws, servers sharing positive or negative on-the-job experiences, stories from other servers about how they used an RBS method, and polls on what the servers believe the community thinks about alcohol serving topics (Table 2). Less popular topics were servers sharing experiences via Facebook Live, refreshers on laws and penalties, information on new state laws, refreshers on ID checking, interactive learning activities, and instruction on using RBS methods.

Table 1. Profile of alcohol server samples in formative research.

Profile	Server survey (n=24)	Usability testing (n=20)	Field pilot study	
			Prototype group (n=59)	Control group (n=51)
Type of licensed sales, n/N (%)				
On site (by the drink)	—[a]	13/20 (65)	38/59 (64)	39/51 (77)
Off site (package)	—	1/20 (5)	7/59 (12)	8/51 (16)
Both	—	6/20 (30)	13/59 (22)	4/51 (8)
Type of establishment, n/N (%)				
Bar	4/24 (17)	1/20 (5)	—	—
Restaurant	12/24 (50)	14/20 (70)	—	—
Nightclub	0/24 (0)	2/20 (10)	—	—
Brewery	3/24 (12)	2/20 (10)	—	—
Distillery or winery tasting room	0/24 (0)	1/20 (5)	—	—
Other	5/24 (21)	1/20 (5)	—	—
Job type, n/N (%)				
Bartender	8/24 (33)	7/20 (35)	15/59 (25)	13/51 (26)
Server	12/24 (50)	9/20 (45)	27/59 (46)	24/51 (47)
Manager	2/24 (8)	1/20 (5)	7/59 (12)	7/51 (14)
Other	2/24 (8)	3/20 (15)	9/59 (15)	6/51 (12)
Years of experience, n/N (%)				
<1	7/24 (29)	1/20 (5)	14/59 (24)	6/51 (12)
1-2	1/24 (4)	1/20 (5)	14/59 (24)	9/51 (18)
2-5	8/24 (33)	5/20 (25)	10/59 (17)	14/51 (27)
>5	8/24 (33)	13/20 (65)	20/59 (34)	22/51 (43)
Age (y), mean (SD)	28.8 (5.3)	32.2 (4.7)	33.1 (11.5)	34.5 (11.7)
Race or ethnicity, n/N (%)				
African American	0/24 (0)	0/20 (0)	1/51 (2)	0/51 (0)
American Indian or Alaska Native	1/24 (4)	2/20 (10)	2/51 (4)	3/51 (6)
Asian	0/24 (0)	0/20 (0)	1/51 (2)	4/51 (8)
Hispanic	7/24 (29)	8/20 (40)	13/59 (22)	17/51 (33)
Native Hawaiian or other Pacific Islander	2/24 (8)	0/20 (0)	4/51 (8)	0/51 (0)
Non-Hispanic White	11/18 (61)	9/20 (45)	27/48 (56)	30/51 (59)
Sex, n/N (%)				
Male	13/24 (54)	12/19 (63)	41/59 (70)	18/48 (38)
Female	10/24 (42)	7/19 ((37)	17/59 (30)	29/48 (60)
Other	1/24 (4)	0/19 (0)	0/59 (0)	1/48 (2)

[a]Not available.

Table 2. Topics of interest in continuing professional development identified by alcohol servers (n=23).

Topic	Participants, n (%)
Benefits to servers	
Tips and tricks from other servers	18 (78)
Refreshers on everyday work practices	13 (56)
Providing help to other servers who need it	12 (52)
Having a place to vent about poor experiences while serving alcohol	11 (48)
Benefits to establishments	
Having servers on the same page when it comes to serving alcohol	21 (91)
Remaining in good standing with the state's licensing body	13 (56)
Professional development topics of interest	
Stories from other servers about how they used an RBS[a] method	8 (35)
Unusual or humorous experience by another server	11 (48)
Refreshers on signs of intoxication	12 (52)
Quizzes that test knowledge of alcohol serving laws with prizes	9 (39)
Servers sharing positive or negative on-the-job experiences	9 (39)
Polls on what the server community thinks about alcohol serving topics	8 (35)
Interactive activities that help maintain a skill	7 (30)
Information on new state laws	7 (30)
Question and answer posts	9 (39)
Interactive learning activity for applying an RBS method with feedback	6 (26)
How to use an RBS method	5 (22)
Refreshers on ID checking	5 (22)
Refreshers on laws and penalties pertinent to servers	5 (22)
Servers sharing their experiences via Facebook Live segments	4 (17)

[a]RBS: responsible beverage service.

Survey on Acceptability, Feasibility, and Usability of WayToServe Plus Prototype

Table 1 presents the profile of the sample of alcohol servers in the usability test of the *WayToServe Plus* prototype (n=20). They were aged 25 to 42 (mean 32.2, SD 4.7) years, and the majority were non-Hispanic White (8/20, 40% were Hispanic) and predominately female individuals. Most worked in on-premises alcohol sales establishments, especially restaurants; however, several worked in nightclubs, breweries, and distillery or winery tasting rooms. The main job types were bartender and alcohol server. Most were experienced alcohol servers, with 90% (18/20) working for >2 years as a server.

Alcohol servers rated the posts in *WayToServe Plus* prototype as highly appropriate for themselves and their establishment, very acceptable, and useful (with average ratings of all social media posts and the video being above the scale midpoint; Table 3). They evaluated posts on management and house policy most favorably (means ranged from 3.80 to 4.30), compared with posts on additional training (means ranged from 3.30 to 3.85) and disruptive customers (means ranged from 3.58 to 4.05). The prototype videos were very favorably evaluated in terms of appropriateness, acceptability, and usefulness (means 3.80-4.25). Of the 20 servers, 8 (40%) rated the prototype as usable on the SUS, and 90% (18/20) evaluated it as user-friendly (good, excellent, or best imaginable).

Most servers indicated that they would use *WayToServe Plus* if it was available. Specifically, 60% (12/20) felt that they would like to use it in the future, and 85% (17/20) were interested in getting ongoing information and activities from *WayToServe Plus* to help keep up-to-date and be able to use RBS methods. When considering specific posts, most servers said they would engage with the posts (view, react to, comment, and share), with the number who would read and react to them being especially high. Slightly fewer servers said they would comment on or share their own posts, but ≥45% (9/20) said they would do so. Videos were the most engaging, with >70% (14/20) saying they would read, react, comment on, and share them (Table 3). In addition, 85% (17/20) of the servers would use an interactive learning activity if posted in the *WayToServe Plus* component.

Table 3. Acceptability and potential engagement with messages in the *WayToServe Plus* prototype usability survey (N=20).

	Social media posts by topic			Videos
	Professionalism	Premises management	Advanced responsible beverage service skills	
Acceptability of posts, mean (SD)				
Appropriate for me	3.70 (1.45)	4.20 (0.83)	3.90 (0.85)	4.15 (1.27)
Appropriate for establishment	3.85 (1.35)	4.25 (0.91)	3.58 (1.17)	3.80 (1.61)
Acceptable to me	3.80 (1.40)	4.30 (0.66)	3.95 (0.89)	4.25 (1.02)
Useful to me	3.30 (1.45)	3.80 (0.95)	4.05 (1.05)	4.05 (1.32)
Potential engagement with posts, n (%)				
Would read post	12 (60)	16 (80)	16 (80)	18 (90)
Would react to post	10 (50)	13 (65)	15 (75)	15 (75)
Would comment on post	12 (60)	10 (50)	10 (50)	15 (75)
Would share post	11 (55)	9 (45)	11 (55)	14 (70)

Field Pilot Test of WayToServe Plus

The profile of the alcohol servers participating in the intervention group (n=59) and control group (n=51) in the pilot test is presented in Table 1. Intervention group participants ranged in age from 18 to 65 (mean 33.1, SD 11.5) years, were mostly non-Hispanic White (13/59, 22% Hispanic), and were predominately female individuals. By job type, most worked in on-premises sales establishments as bartenders or alcohol servers. They were a mix of new and experienced servers (14/59, 24% had worked less than 1 year and 20/59, 34% had worked 5 years or more).

Alcohol servers had high engagement with the *WayToServe Plus* professional development component. Overall, 83% (50/60) viewed at least 1 post, and they viewed an average of 14.85 (SD 12.41) posts over 4 weeks (approximately 24 posts were displayed in any 4-week period). Just under half of the servers (28/60, 47%) reacted (eg, liked) or commented on a post in the *WayToServe Plus* group. Servers on average reacted to 4.17 posts (SD 7.08).

Alcohol servers evaluated the *WayToServe Plus* component as highly usable and its content as appropriate. The mean rating on the SUS scale was 81.10 out of 100, with 88% (52/59) giving it a score of ≥68, a common threshold for usability on this scale. They also gave it high marks on user-friendliness (mean 5.81 out of 7). Many felt that the component (52/59, 88% agreed or strongly agreed; mean 4.42 out of 5, SD 1.19) and its content (50/59, 84%; mean 4.31, SD 1.25) were appropriate for them as alcohol servers and aligned with their establishment's atmosphere (48/59, 81%; mean 4.12, SD 0.79). Most found the posts (49/59, 83%; mean 4.08, SD 0.75) and other servers' comments on the posts (47/59, 80%; mean 4.05, SD 0.78) to be useful. A large majority of the alcohol servers said that they were likely to use *WayToServe Plus* in the future (46/59, 78% somewhat likely or very likely; mean 3.95 out of 5, SD 0.99).

Servers in the control group were similar in characteristics to those in the intervention group (Table 1), although control servers had more years of experience on average. Alcohol servers who received the *WayToServe Plus* prototype were compared with those in the control group in their reported self-efficacy and response efficacy for implementing RBS methods as an indicator of the potential impact of the *WayToServe Plus* program. Given the small sample size, we planned a priori to calculate the effect size estimate, *d*, rather than perform a standard statistical significance test. Ratings on self-efficacy were higher among servers in the prototype group (mean 4.53, SD 0.57) than servers in the control group (mean 4.33, SD 0.77; *d*=0.30). Likewise, ratings on response efficacy were greater in the prototype group (mean 4.68, SD 0.68) than in the control group (mean 4.39; *SD* 0.83; *d*=0.38).

Phase 2

Phase 2 was funded in September 2022. Baseline assessment of licensed alcohol premises (n=179) in California (n=59), New Mexico (n=60), and Washington (n=60) was conducted in 2022-2023 using the pseudopatron protocol, and results are available elsewhere [56]. The recruitment of premises to have servers trained and join the Facebook private group containing the professional development posts is ongoing. Posttest assessment is planned for summer and fall, 2024 with results expected to be published in 2025.

Discussion

Principal Findings

The development of a professional development extension of our RBS training course aims to improve the efficacy of RBS training in the field. The formative research confirmed that owners, managers, and alcohol servers considered a professional development component for RBS to be beneficial, and a large majority would be interested in using such a program. Many owners and managers have already taken steps to help servers implement and maintain their RBS skills, and several of them felt that *WayToServe Plus* would complement and aid in these efforts. A previous study found that managers trained in RBS also trained their staff in cutting off intoxicated patrons and handling fake IDs [57]. Alcohol servers considered the *WayToServe Plus* prototype to be highly appropriate, acceptable, usable, and useful. Many servers followed (ie, viewed a post) and engaged (ie, reacted to or commented on a post) with the

prototype. These results are consistent with the literature citing education and lifelong learning as essential in the hospitality industry to maintain job competence, be productive, and be valued employees [37]. A formal professional development program, such as *WayToServe Plus*, might help employees improve RBS practice faster than informal training by owners and managers [32]. Continued professional development might also increase employee retention and reduce absenteeism by improving confidence in role, clarifying job expectations, helping to manage stressful situations, and increasing job satisfaction and commitment [29,58].

Formative research identifying the topics of interest to servers likely contributed to creating highly engaging posts in the *WayToServe Plus* prototype. Most servers said that they would be interested in receiving ongoing information and support for RBS methods, and many would enroll in the *WayToServe Plus* component in the future. Moreover, the *WayToServe Plus* prototype appeared to improve theoretic mediators of effective RBS training. Continuing professional development programs should be more effective when personally meaningful to learners [30,59]. Together, these findings suggest that the ongoing professional development in *WayToServe Plus* is likely to improve RBS practices in the upcoming RCT and when disseminated with the *WayToServe* RBS training.

Owners, managers, and servers felt that the professional development content fit with the atmosphere of their licensed establishments. Fit might be further enhanced by providing the information in easily digestible and relatable formats that do not require a large time commitment. Fit is an important innovation characteristic that predicts adoption [39], and continuing professional development programs may be most effective when reflecting the context and experiences of learners [30].

The formative research provided insights into the potentially effective content of a professional development component. Servers and managers wanted skills training on refusing service, handling intoxicated and difficult customers, conflict resolution, communication, drink counting, and recognizing intoxication; serving at special events; ID checking; serving laws and penalties; and prohibited conduct (eg, recreational cannabis, drinking on the job, and firearms). These represent a combination of generic as well as job-specific information and skills for alcohol service, a common combination of skills in the hospitality industry [36,37]. Servers suggested several message features that would promote engagement with the professional development content, including positive messages; relaxed, conversational tone; humor; infographics or charts; articles; videos; questions and answers; resources; reminders; interactive activities; badges or rewards; polls; quizzes; games; weekly discussion topics; tips, stories, and comments from experienced servers; and opportunities to share experiences. Sharing ideas and experiences among servers and creating learning communities where they can work collaboratively should facilitate the success of continuing professional development [59,60]. User-generated content stands out as a key feature of social media platforms and holds significant sway in shaping social norms, particularly through the process of opinion leadership [39]. Managers and servers were interested in developing professionalism, such as understanding the roles of management, building a community in the hospitality environment, and enhancing hospitality careers. Cultivating or enhancing a sense of professionalism among servers could potentially elevate their regard for customer and community safety (ie, fostering professional norms [29]), strengthen their commitment to their roles, and motivate the consistent use of RBS methods.

The findings supported the use of a social media platform to deliver the professional development content. In 2021, most adults used social media (72%), including >80% of those aged 18 to 49 years [61], for information and peer connections that can be influential [62,63]. Web-based learning is common in vocational education and continuing professional development, providing advantages in terms of low cost, time efficiency, media-rich presentations, and interactivity [31,59,60]. Our plan to deliver the professional development content on an ongoing basis should help confer mastery of RBS techniques taught initially in the single, intensive *WayToServe* course by providing time for servers to set goals to improve behavior, assess current performance, and receive timely feedback to make improvements [60]; however, to be effective, servers will need to be self-directed learners with sufficient motivation to engage with the post. Effectiveness and motivation may increase when coupled with in-person instruction and mentoring from managers and experienced servers [31,59,60], rather than replacing this on-the-job support.

We chose to deliver the *WayToServe Plus* over Facebook because (1) the *WayToServe* training had an existing Facebook page with approximately 20,000 followers; (2) despite some decline in its user base [64-66], Facebook still reaches a large majority of adults including more than 70% adults aged 18-49 years by one estimate in 2021 [61]; and (3) Facebook's private group feature will control treatment presentation to prevent contamination when testing the effectiveness of *WayToServe Plus*. Video content appeared to be especially popular, which was not surprising given the popularity of video-dominated social media such as YouTube and TikTok [61,67]. Theoretically, visual depictions should be effective at teaching skills through observational learning [40]. To broaden the appeal of the *WayToServe Plus* component, some posts should be linked to relevant content posted on Instagram, YouTube, and other highly popular social media. Once disseminated, it may be most effective to deliver *WayToServe Plus* messaging through multiple social media platforms.

Limitations

The formative research and upcoming RCT evaluating the *WayToServe Plus* professional development component will be limited by conducting them with servers in only 3 states in the western United States, California, New Mexico, and Washington State, where the *WayToServe* is an approved RBS training provider. However, these states are diverse in population size, history of RBS training requirements (ie, New Mexico and Washington State have required RBS for over 2 decades, whereas California's requirement was new in 2022), and content requirement for RBS training (eg, California requires more content for managers than New Mexico and Washington State).

The selection method using clustering of establishments in California and Washington State could introduce a design effect, but it was balanced against cost controls and project feasibility. The findings pertain to web-based professional development content, not other forms of support delivered in person or in print, but web delivery creates a high-quality, high-fidelity, engaging learning environment [68]. Uptake of *WayToServe Plus* will undoubtedly vary among servers and across establishments, which could diminish its effectiveness. However, the formative research suggests that many servers will engage with the professional development posts. The upcoming evaluation of *WayToServe Plus* will be strengthened by random selection of the licensed establishments; random assignment to experimental conditions; observational measures of refusal rates; and blinding of PiP teams, establishment management, and alcohol servers.

Conclusions

If successful, this study has the potential to improve the effectiveness of evidence-based RBS training and reduce the negative consequences of DWI. The results will also provide evidence that personnel in regulated industries that affect public health and safety, such as hospitality, can be trained to improve compliance with state policies and regulations. Furthermore, it will show whether professional development can be effective for individuals without specialized professional education. Far from *low-skilled*, alcohol service requires key skills in managing emotions, communication, problem-solving, and flexibility [36] as well as learning and applying the regulations and best practices surrounding responsible alcohol service. It should be amenable to improvement through ongoing professional development between state-required retraining in RBS techniques. The market for RBS training is large; therefore, improvements in this common intervention could have a substantial impact on DWI rates. No RBS training provider currently provides ongoing professional development as extensive as is planned for *WayToServe Plus*, so it should be seen as a value-added component for many licensed establishments, improving its dissemination potential.

Acknowledgments

This study is supported by a grant from the National Institute on Alcohol Abuse and Alcoholism (R44 AA029364). The opinions are those of the authors. The funding agency had no input on the contents of this paper.

Data Availability

The data set generated and analyzed during the pilot study is available in the Inter-university Consortium for Political and Social Research (ICPSR) repository [69].

Authors' Contributions

WGW, DB, and RS conceptualized the study, designed the methods, and secured extramural funding. WGW and DB are supervising project activities. LM is managing day-to-day study activities. All authors reviewed and approved the manuscript before submission.

Conflicts of Interest

WGW, DB, and LM receive a salary from Klein Buendel, Inc. DB’s spouse is an owner of Klein Buendel, Inc. WGW and DB are owners of Wedge Communications LLC, the distributor of the *WayToServe* web-based training. An active management plan is in place at Klein Buendel to manage this conflict of interest. RS has no conflicts of interest.

References

1. National Highway Traffic Safety Administration. Alcohol-impaired driving data (Traffic Safety Facts). National Center for Statistics and Analysis web site. Washington, D.C: National Center for Statistics and Analysis; 2022. URL: https://crashstats.nhtsa.dot.gov/Api/Public/Publication/813294#:~:text=In%202020%20there%20were%2011%2C654%20people%20killed%20in%20alcohol%2Dimpaired,the%20United%20States%20in%202020 [accessed 2024-01-05]
2. Chang I, Lapham SC, Barton KJ. Drinking environment and sociodemographic factors among DWI offenders. J Stud Alcohol 1996 Nov;57(6):659-669. [doi: 10.15288/jsa.1996.57.659] [Medline: 8913998]
3. Gruenewald PJ, Stockwell T, Beel A, Dyskin EV. Beverage sales and drinking and driving: the role of on-premise drinking places. J Stud Alcohol 1999 Jan;60(1):47-53. [doi: 10.15288/jsa.1999.60.47] [Medline: 10096308]
4. Stockwell T, Lang E, Rydon P. High risk drinking settings: the association of serving and promotional practices with harmful drinking. Addiction 1993 Nov;88(11):1519-1526. [doi: 10.1111/j.1360-0443.1993.tb03137.x] [Medline: 8286997]
5. Ker K, Chinnock P. Interventions in the alcohol server setting for preventing injuries. Cochrane Database Syst Rev 2006 Apr 19(2):CD005244. [doi: 10.1002/14651858.CD005244.pub2] [Medline: 16625630]
6. Fell JC, McKnight AS, Auld-Owens A. Increasing impaired-driving enforcement visibility: six case studies. National Highway Traffic Safety Administration web site. Washington, D.C: National Highway Traffic Safety Administration; 2013. URL: https://www.nhtsa.gov/sites/nhtsa.gov/files/811716.pdf [accessed 2023-12-27]

7. Lenk KM, Toomey TL, Nelson TF, Jones-Webb R, Erickson DJ. State and local law enforcement agency efforts to prevent sales to obviously intoxicated patrons. J Community Health 2014 Apr 26;39(2):339-348 [FREE Full text] [doi: 10.1007/s10900-013-9767-9] [Medline: 24068596]
8. Foxcroft DR. Can prevention classification be improved by considering the function of prevention? Prev Sci 2014 Dec;15(6):818-822. [doi: 10.1007/s11121-013-0435-1] [Medline: 24052320]
9. Biglan A, Flay BR, Embry DD, Sandler IN. The critical role of nurturing environments for promoting human well-being. Am Psychol 2012;67(4):257-271 [FREE Full text] [doi: 10.1037/a0026796] [Medline: 22583340]
10. Toomey TL, Lenk KM, Erickson DJ, Horvath KJ, Ecklund AM, Nederhoff DM, et al. Effects of a hybrid online and in-person training program designed to reduce alcohol sales to obviously intoxicated patrons. J Stud Alcohol Drugs 2017 Mar;78(2):268-275 [FREE Full text] [doi: 10.15288/jsad.2017.78.268] [Medline: 28317507]
11. Graham K. Preventive interventions for on-premise drinking: a promising but underresearched area of prevention. Contemp Drug Probl 2016 May 18;27(3):593-668 [FREE Full text] [doi: 10.1177/009145090002700307]
12. Shults RA, Elder RW, Sleet DA, Nichols JL, Alao MO, Carande-Kulis VG, et al. Reviews of evidence regarding interventions to reduce alcohol-impaired driving. Am J Prev Med 2001 Nov;21(4 Suppl):66-88. [doi: 10.1016/s0749-3797(01)00381-6] [Medline: 11691562]
13. Fell JC, Fisher DA, Yao J, McKnight AS. Evaluation of a responsible beverage service and enforcement program: effects on bar patron intoxication and potential impaired driving by young adults. Traffic Inj Prev 2017 Aug 18;18(6):557-565. [doi: 10.1080/15389588.2017.1285401] [Medline: 28107050]
14. Wallin E, Gripenberg J, Andréasson S. Too drunk for a beer? a study of overserving in Stockholm. Addiction 2002 Jul;97(7):901-907. [doi: 10.1046/j.1360-0443.2002.00160.x] [Medline: 12133129]
15. Trolldal B, Brännström L, Paschall MJ, Leifman H. Effects of a multi-component responsible beverage service programme on violent assaults in Sweden. Addiction 2013 Jan;108(1):89-96. [doi: 10.1111/j.1360-0443.2012.04004.x] [Medline: 22775309]
16. Wallin E, Gripenberg J, Andréasson S. Overserving at licensed premises in Stockholm: effects of a community action program. J Stud Alcohol 2005 Nov;66(6):806-814. [doi: 10.15288/jsa.2005.66.806] [Medline: 16459942]
17. Skardhamar T, Fekjær SB, Pedersen W. If it works there, will it work here? the effect of a multi-component responsible beverage service (RBS) programme on violence in Oslo. Drug Alcohol Depend 2016 Dec 01;169:128-133. [doi: 10.1016/j.drugalcdep.2016.10.019] [Medline: 27810655]
18. Holder HD, Wagenaar AC. Mandated server training and reduced alcohol-involved traffic crashes: a time series analysis of the Oregon experience. Accid Anal Prev 1994 Feb;26(1):89-97. [doi: 10.1016/0001-4575(94)90071-x] [Medline: 8110360]
19. Scherer M, Fell JC, Thomas S, Voas RB. Effects of dram shop, responsible beverage service training, and state alcohol control laws on underage drinking driver fatal crash ratios. Traffic Inj Prev 2015;16 Suppl 2(0 2):S59-S65 [FREE Full text] [doi: 10.1080/15389588.2015.1064909] [Medline: 26436244]
20. Linde AC, Toomey TL, Wolfson J, Lenk KM, Jones-Webb R, Erickson DJ. Associations between responsible beverage service laws and binge drinking and alcohol-impaired driving. J Alcohol Drug Educ 2016 Aug;60(2):35-54 [FREE Full text] [Medline: 29225382]
21. Buvik K, Rossow I. Server training at drinking establishments: a Sisyphean task? a commentary on Toomey et al. (2017). J Stud Alcohol Drugs 2017 Mar;78(2):276-277. [doi: 10.15288/jsad.2017.78.276] [Medline: 28317508]
22. Gripenberg J, Wallin E, Andréasson S. Effects of a community-based drug use prevention program targeting licensed premises. Subst Use Misuse 2007 Jul 03;42(12-13):1883-1898. [doi: 10.1080/10826080701532916] [Medline: 18075915]
23. Gripenberg Abdon J, Wallin E, Andréasson S. Long-term effects of a community-based intervention: 5-year follow-up of 'Clubs against Drugs'. Addiction 2011 Nov;106(11):1997-2004. [doi: 10.1111/j.1360-0443.2011.03573.x] [Medline: 21749523]
24. Woodall WG, Starling R, Saltz RF, Buller DB, Stanghetta P. Results of a randomized trial of web-based retail onsite responsible beverage service training: WayToServe. J Stud Alcohol Drugs 2018 Sep;79(5):672-679 [FREE Full text] [doi: 10.15288/jsad.2018.79.672] [Medline: 30422777]
25. TED: The Economics Daily: sports and exercise among Americans. U.S. Bureau of Labor Statistics web site. URL: https://www.bls.gov/opub/ted/2016/sports-and-exercise-among-americans.htm [accessed 2023-05-25]
26. Alcohol policy information system: beverage service training and related practices. National Insitute on Alchohol Abuse and Alcoholism. 2022. URL: https://alcoholpolicy.niaaa.nih.gov/apis-policy-topics/beverage-service-training-and-related-practices/26 [accessed 2023-05-07]
27. Dymock D, Tyler M. Towards a more systematic approach to continuing professional development in vocational education and training. Stud Contin Educ 2018 Mar 14;40(2):198-211. [doi: 10.1080/0158037x.2018.1449102]
28. Konnyu KJ, McCleary N, Presseau J, Ivers NM, Grimshaw JM. Behavior change techniques in continuing professional development. J Contin Educ Health Prof 2020;40(4):268-273. [doi: 10.1097/CEH.0000000000000319] [Medline: 33284178]
29. Harland J, Kinder K. Teachers' continuing professional development: framing a model of outcomes. J In Serv Educ 2006 Dec 20;23(1):71-84. [doi: 10.1080/13674589700200005]
30. Mansour N, EL-Deghaidy H, Alshamrani S, Aldahmash A. Rethinking the theory and practice of continuing professional development: science teachers' perspectives. Res Sci Educ 2014 Apr 25;44(6):949-973. [doi: 10.1007/s11165-014-9409-y]

31. Klein D, Ware M. E‐learning: new opportunities in continuing professional development. Learn Publ 2003 Jan;16(1):34-46 [FREE Full text] [doi: 10.1087/095315103320995078]
32. Lashley C. Investing in people: training is not a cost!. In: Oskam JA, Dekker DM, Wiegerink K, editors. Innovation in Hospitality Education: Anticipating the Educational Needs of a Changing Profession. Cham, Switzerland: Springer; 2018:197-213.
33. Ingram M, Reinschmidt KM, Schachter KA, Davidson CL, Sabo SJ, de Zapien JG, et al. Establishing a professional profile of community health workers: results from a national study of roles, activities and training. J Community Health 2012 Apr;37(2):529-537 [FREE Full text] [doi: 10.1007/s10900-011-9475-2] [Medline: 21964912]
34. Woodruff SI, Candelaria JI, Elder JP. Recruitment, training outcomes, retention, and performance of community health advisors in two tobacco control interventions for Latinos. J Community Health 2010 Apr 11;35(2):124-134. [doi: 10.1007/s10900-009-9207-z] [Medline: 20012475]
35. Horwood C, Butler L, Barker P, Phakathi S, Haskins L, Grant M, et al. A continuous quality improvement intervention to improve the effectiveness of community health workers providing care to mothers and children: a cluster randomised controlled trial in South Africa. Hum Resour Health 2017 Jun 13;15(1):39 [FREE Full text] [doi: 10.1186/s12960-017-0210-7] [Medline: 28610590]
36. Baum T. Skills and training for the hospitality sector: a review of issues. J Vocat Educ Train 2002 Sep;54(3):343-364. [doi: 10.1080/13636820200200204]
37. Trivun V, Kenjic V, Mahmutcehajic F. Life-long learning strategies in tourism and hotel industry. Tour Hosp Manag 2017;14(1):171-184. [doi: 10.20867/thm.14.1.15]
38. Kennedy A. Models of continuing professional development: a framework for analysis. J In Serv Educ 2005 Jun 1;31(2):235-250 [FREE Full text] [doi: 10.1080/13674580500200277]
39. Rogers EM. Diffusion of Innovations. 5th edition. New York, NY: Free Press; 2003.
40. Bandura A. Social Foundations of Thought and Action: A Social Cognitive Theory. Englewood Cliffs, NJ: Prentice-Hall, Inc; 1986.
41. Faulkner L. Beyond the five-user assumption: benefits of increased sample sizes in usability testing. Behav Res Meth Instrum Comput 2003 Aug;35(3):379-383. [doi: 10.3758/BF03195514]
42. Macefield R. How to specify the participant group size for usability studies: a practitioner's guide. J Usability Stud 2009;5(1):34-45 [FREE Full text]
43. Turner CW, Lewis JR, Nielsen J. Determining usability test sample size. In: Karwowski W, editor. International Encyclopedia of Ergonomics and Human Factors. Boca Raton, FL: CRC Press; 2006:3084-3088.
44. Brooke J. SUS - A quick and dirty usability scale. In: Jordan PW, Thomas B, Weerdmeester BA, McClelland IL, editors. Usability Evaluation in Industry. London, UK: Taylor & Francis; 1996:189-194.
45. Bangor A, Kortum P, Miller J. Determining what individual SUS scores mean: adding an adjective rating scale. J Usability Stud 2009;4(3):114-123 [FREE Full text]
46. Bangor A, Kortum PT, Miller JT. An empirical evaluation of the system usability scale. Int J Hum Comput Interact 2008 Jul 30;24(6):574-594. [doi: 10.1080/10447310802205776]
47. Buller DB, Walkosz B, Henry K, Woodall WG, Pagoto S, Berteletti J, et al. Promoting social distancing and COVID-19 vaccine intentions to mothers: randomized comparison of information sources in social media messages. JMIR Infodemiol 2022 Aug 23;2(2):e36210 [FREE Full text] [doi: 10.2196/36210] [Medline: 36039372]
48. Buller DB, Pagoto S, Walkosz BJ, Woodall WG, Berteletti J, Kinsey A, et al. The process of responding to COVID-19 misinformation in a social media feed. J Public Health Manag Pract 2023;29(4):E124-E127. [doi: 10.1097/PHH.0000000000001679] [Medline: 36383086]
49. McKnight AJ. Server intervention: accomplishments and needs. Alcohol Health Res World 1993;17(1):76-83 [FREE Full text]
50. Saltz R, Buller DB, Woodall WG, Buller MK, Grayson A. Refusal of pseudo-intoxicated customers by retail marijuana outlets in three states. In: Proceedings of the 27th Annual Meeting of the Society for Prevention Research. 2021 May 29 Presented at: SPR '19; May 29-31, 2019; San Francisco, CA.
51. Buller DB, Woodall WG, Saltz R, Starling R. Pseudo-underage assessment of compliance with identification regulations at retail marijuana outlets in Colorado. J Stud Alcohol Drugs 2016 Nov;77(6):868-872 [FREE Full text] [doi: 10.15288/jsad.2016.77.868] [Medline: 27797687]
52. Buller DB, Woodall WG, Saltz R, Buller MK. Compliance with personal ID regulations by recreational marijuana stores in two U.S. states. J Stud Alcohol Drugs 2017 Nov;80(6):679-686 [FREE Full text] [doi: 10.15288/jsad.2019.80.679] [Medline: 31790358]
53. McKnight AJ, Langston EA, Marques PR, Tippetts AS. Estimating blood alcohol level from observable signs. Accid Anal Prev 1997 Mar;29(2):247-255. [doi: 10.1016/s0001-4575(96)00079-6] [Medline: 9088364]
54. Woodall WG, Buller DB, Saltz RF, Starling R, Stanghetta P. Uptake of web-based RBS training to prevent alcohol over-service. In: Proceedings of the 43rd Annual Alcohol Epidemiology Symposium of the Kettil Bruun Society. 2017 Jun 05 Presented at: AESKBS '17; June 5-9, 2017; Sheffield, UK.

55. Buller DB, Walkosz BJ, Berteletti J, Pagoto SL, Bibeau J, Baker K, et al. Insights on HPV vaccination in the United States from mothers' comments on Facebook posts in a randomized trial. Hum Vaccin Immunother 2019 Jul 11;15(7-8):1479-1487 [FREE Full text] [doi: 10.1080/21645515.2019.1581555] [Medline: 30785361]
56. Buller DB, Woodall WG, Saltz R, Martinez L, Small A, Chirico N, et al. Sales to apparently intoxicated customers in three states with different histories of responsible beverage service training. J Stud Alcohol Drugs (Forthcoming) 2024 Jan 16. [doi: 10.15288/jsad.23-00258] [Medline: 38227392]
57. Lenk KM, Erickson DJ, Nelson TF, Horvath KJ, Nederhoff DM, Hunt SL, et al. Changes in alcohol policies and practices in bars and restaurants after completion of manager-focused responsible service training. Drug Alcohol Rev 2018 Mar;37(3):356-364 [FREE Full text] [doi: 10.1111/dar.12629] [Medline: 29151272]
58. Ko WH. The relationships among professional competence, job satisfaction and career development confidence for chefs in Taiwan. Int J Hosp Manag 2012 Sep;31(3):1004-1011 [FREE Full text] [doi: 10.1016/j.ijhm.2011.12.004]
59. Micallef R, Kayyali R. A systematic review of models used and preferences for continuing education and continuing professional development of pharmacists. Pharmacy (Basel) 2019 Nov 16;7(4):154 [FREE Full text] [doi: 10.3390/pharmacy7040154] [Medline: 31744140]
60. Sachdeva AK. Continuing professional development in the twenty-first century. J Contin Educ Health Prof 2016;36 Suppl 1:S8-13. [doi: 10.1097/CEH.0000000000000107] [Medline: 27584081]
61. Auxier B, Anderson M. Social media use in 2021. Pew Research Center. 2021. URL: https://www.pewresearch.org/internet/2021/04/07/social-media-use-in-2021/ [accessed 2023-05-25]
62. Walther JB, Pingree S, Hawkins RP, Buller DB. Attributes of interactive online health information systems. J Med Internet Res 2005 Jul 01;7(3):e33 [FREE Full text] [doi: 10.2196/jmir.7.3.e33] [Medline: 15998624]
63. Walther JB, Tong ST, DeAndrea DC, Carr CT, Van DH. A juxtaposition of social influences: web 2.0 and the interaction of mass, interpersonal, and peer sources online. In: Birchmeier Z, Dietz-Uhler B, Stasser G, editors. Strategic Uses of Social Technology: An Interactive Perspective of Social Psychology. Cambridge, UK: Cambridge University Press; 2011:172-194.
64. Romm T. Facebook's Zuckerberg just survived 10 hours of questioning by Congress. The Washington Post. 2018. URL: https://www.washingtonpost.com/news/the-switch/wp/2018/04/11/zuckerberg-facebook-hearing-congress-house-testimony/?noredirect=on&utm_term=.fd98bc76ea38 [accessed 2023-05-25]
65. Confessore N. Cambridge Analytica and Facebook: the scandal and the fallout so far. The New York Times. 2018. URL: https://www.nytimes.com/2018/04/04/us/politics/cambridge-analytica-scandal-fallout.html [accessed 2023-05-25]
66. Wagner K, Molla R. Facebook lost around 2.8 million U.S. users under 25 last year. 2018 won't be much better. Vox Media. 2018. URL: https://www.vox.com/2018/2/12/16998750/facebooks-teen-users-decline-instagram-snap-emarketer [accessed 2023-05-26]
67. Ceci L. Tiktok user ratio in the U.S. 2022, by age group. Statista. 2022. URL: https://www.statista.com/statistics/1095186/tiktok-us-users-age/ [accessed 2023-05-25]
68. Buller DB, Woodall WG, Saltz R, Grayson A, Buller MK. Implementation and effectiveness of an online responsible vendor training program for recreational marijuana stores in Colorado, Oregon, and Washington state. J Public Health Manag Pract 2019;25(3):238-244 [FREE Full text] [doi: 10.1097/PHH.0000000000000843] [Medline: 30180110]
69. Accessibility. Institute for Social Research, University of Michigan. 2023. URL: https://www.icpsr.umich.edu/web/pages/datamanagement/policies/access.html?utm_source=web&utm_medium=web&utm_campaign=webfooter&utm_id=webfooter [accessed 2023-11-06]

Abbreviations

DWI: driving while intoxicated
PiP: pseudointoxicated patron
RBS: responsible beverage service
RCT: randomized controlled trial
SUS: System Usability Scale

Edited by A Mavragani; submitted 05.06.23; peer-reviewed by Y Shehawy; comments to author 13.10.23; revised version received 15.11.23; accepted 23.11.23; published 24.01.24.

Please cite as:
Woodall WG, Buller D, Saltz R, Martinez L
Professional Development to Improve Responsible Beverage Service Training: Formative Research Results and Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2024;13:e49680
URL: https://www.researchprotocols.org/2024/1/e49680
doi:10.2196/49680
PMID:38265847

Protocol

Effectiveness of the Wellness Together Canada Portal as a Digital Mental Health Intervention in Canada: Protocol for a Randomized Controlled Trial

Syaron Basnet[1*], PhD; Michael Chaiton[1,2*], PhD

[1]Centre For Addiction and Mental Health, University of Toronto, Toronto, ON, Canada

[2]Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada

[*]all authors contributed equally

Corresponding Author:
Syaron Basnet, PhD
Centre For Addiction and Mental Health
University of Toronto
250 College Street
Toronto, ON, M5T 1R8
Canada
Phone: 1 416 6052464
Email: syaronbasnet@gmail.com

Abstract

Background: The Wellness Together Canada (WTC) portal is a digital mental health intervention that was developed in response to an unprecedented rise in mental health and substance use concerns due to the COVID-19 pandemic, with funding from the Government of Canada. It is a mental health and substance use website to support people across Canada providing digital interventions and services at no cost. Two million people have visited the WTC portal over the course of 1 year since launching; however, rigorous evaluation of this potential solution to access to mental health care during and after the COVID-19 pandemic is urgently required.

Objective: This study aims to better understand the effectiveness of the existing digital interventions in improving population mental health in Canada.

Methods: The Let's Act on Mental Health study is designed as a longitudinal fully remote, equally randomized (1:1), double-blind, alternative intervention–controlled, parallel-group randomized controlled trial to be conducted between October 2023 and April 2024 with a prospective follow-up study period of 26 weeks. This trial will evaluate whether a digital intervention such as the WTC improves population mental health trajectories over time.

Results: The study was approved by the research ethics board of CAMH (Centre for Addiction and Mental Health, Toronto, Ontario, Canada). It is ongoing and participant recruitment is underway. As of August 2023, a total of 453 participants in the age group of 18-72 years have participated, of whom 70% (n=359) are female.

Conclusions: This initiative provides a unique opportunity to match people's specific unmet mental health and substance use needs to evidence-based digital interventions.

(JMIR Res Protoc 2024;13:e48703) doi:10.2196/48703

KEYWORDS

Wellness Together Portal; randomized trial; COVID-19; mental health; digital health; digital intervention; substance use; portal; effectiveness; well-being

Introduction

Mental health problems are the leading cause of global disability affecting worldwide populations including Canadians. The Bell Let's Talk campaign promotes mental health awareness by engaging Canadians in encouraging people to speak up about mental health. Yet, many Canadians lack access to mental health care services, with equity in access being a key concern for specific groups (eg, gender, race and ethnicity, socioeconomic status, geographic isolation, and immigration status). As a result of the COVID-19 pandemic and preventive measures such as

social distancing, an "echo pandemic" of declining mental health in the Canadian population has emerged [1]. The COVID-19 pandemic is exacerbating mental health challenges and widening service gaps, especially among those in marginalized groups and those with preexisting mental health issues [2,3]. Research on mental health during the pandemic has found that 40% of Canadians stated that their mental health has declined due to the COVID-19 pandemic, and 48% of individuals felt anxious or worried [4,5]. Even prior to the pandemic, the burden of mental illness was widespread in the population. Worldwide, an estimated 264 million people are affected by depression alone [6]. Mood and anxiety disorders are the most prevalent mental health issues in Canada, occurring among 11.6% of Canadian adults [7]. Our mental health care system is overwhelmed and too underfunded to address the pervasiveness of mental health challenges [8]. At the same time, many people are reluctant to maintain or improve their mental health, with a stigma-based perception that mental health is only an issue for people with a diagnosed mental disorder, rather than being a concern for everyone [9]. The experience of the COVID-19 pandemic demonstrates that it is critical to provide tools to all Canadians, which will improve mental health and provide self-assessment and self-help aids at the population level [10].

The digital intervention for mental health, the Wellness Together Canada (WTC) portal [11], was developed in response to an unprecedented rise in mental health and substance use concerns due to the COVID-19 pandemic, with funding from the Government of Canada. It is a mental health and substance use website to support people across Canada, providing digital interventions and services at no cost. It partners with other digital interventions to be the home portal for access to digital interventions from 1:1 support, peer groups, and self-help tools. WTC is a one-stop, web-based portal, available nationally, which provides all people in Canada with 24/7 free and confidential access to a web-based network of information and psychosocial support services, which comprise triage and self-monitoring tools, mental health promotion information, self-guided apps, coached and peer support programs, mental health counseling, and crisis intervention. Services are readily accessible, available in French and English, and are made available through a variety of digital media (eg, computer and phone) and web-based services (eg, voice, text, web-based chat, and responsive web design). The portal is stigma-free and recovery-oriented, providing a wide range of intervention options, and follows a continuous improvement process based on stakeholder engagement, program data, and user feedback. Two million people have visited the WTC portal over the course of 1 year since launching; however, rigorous evaluation of this potential solution to access to mental health care during and after the COVID-19 pandemic is urgently required.

This initiative provides a unique opportunity to match people's specific unmet mental health and substance use needs to evidence-based digital interventions. Canadians will have a tool that provides valuable information, self-assessment on mental health, access to personalized digital interventions, and an avenue for everyone to participate in better understanding and improving mental health in Canada.

This study aims to evaluate the effectiveness and cost-effectiveness of the WTC portal by conducting a randomized controlled trial. The control group will be referred to the usual care tools available on the CAMH (Centre for Addiction and Mental Health) website. CAMH provides a range of self-care interventions, particularly different mental health programs and resources such as "Game Changers: Self-care information," which is a hub of resources to help start a conversation about health, including a self-help booklet series, a relaxation guide, and free web-based education with a personalized dashboard, which provides an opportunity for the client to self-monitor (symptoms or physiological processes), build awareness, and improve self-efficacy and visualization. Usual care tools such as digital interventions have a self-care and self-help component. Many studies have shown positive outcomes deemed acceptable and feasible with >95% completion rates and a high degree of participation with self-care interventions; some offer significant early benefits of tailored self-care programs [12,13]. A meta-analysis indicates that these interventions can be effective and potentially be future home-based interventions, especially in mental health care such as digital interventions; hence, it has been chosen as a control intervention in this study.

Methods

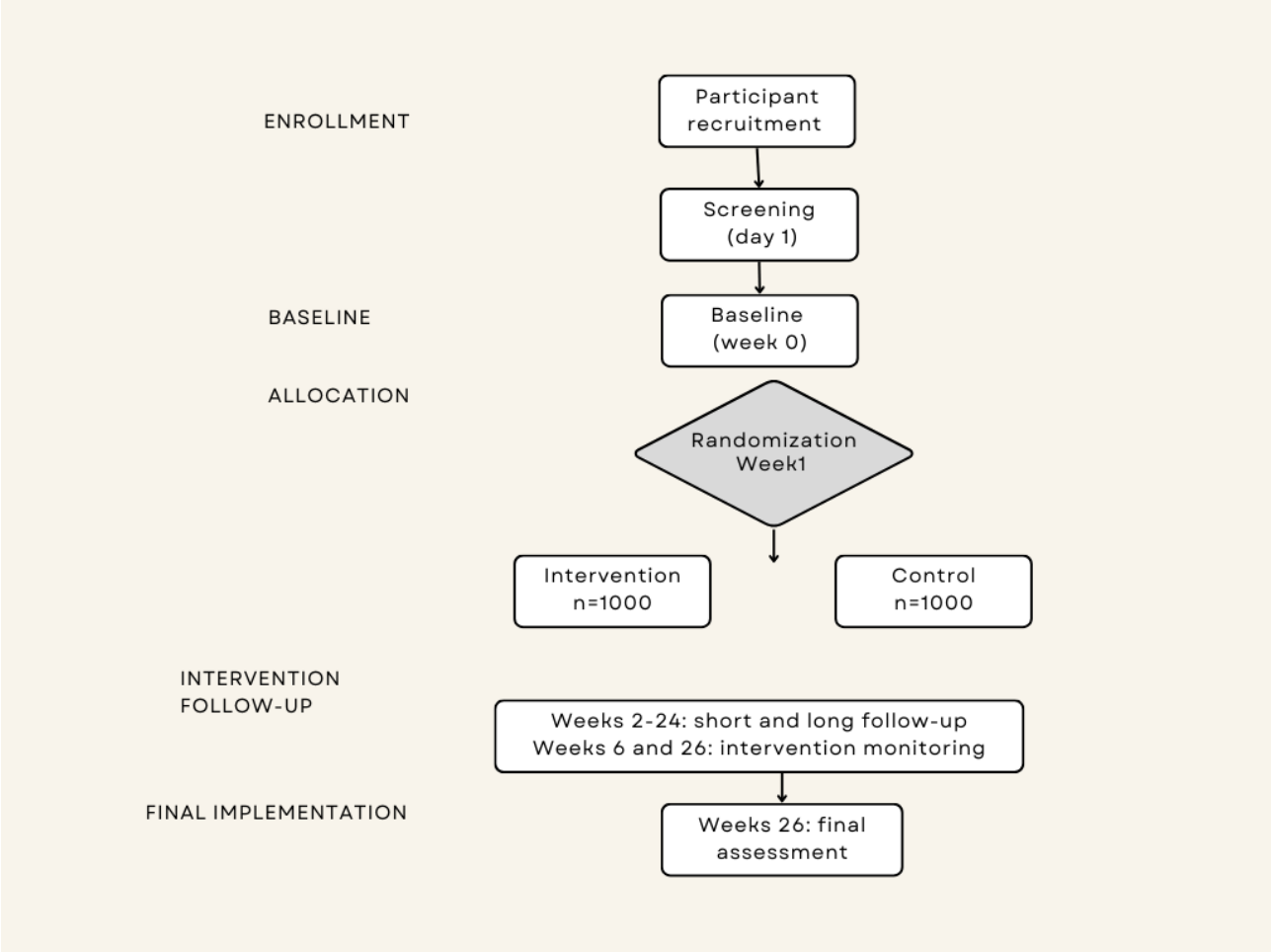
Trial Design

The Let's Act on Mental Health study is a longitudinal, fully remote, equally randomized (1:1), double-blind, alternative intervention–controlled, parallel-group randomized controlled trial to be conducted between October 2023 and April 2024 with a prospective follow-up for 26 weeks. This trial will evaluate whether digital interventions such as WTC improve population mental health trajectories over time. The trial will consist of 1 baseline assessment at week 0, 13 biweekly short and long follow-ups from week 24, intervention monitoring twice at weeks 6 and 26, and 1 final assessment at the end of the 26-week follow-up period. An overview of the trial process is shown in Figure 1.

The study's overall objective is to evaluate the effectiveness and cost-effectiveness of the WTC portal by conducting a randomized controlled trial. We will use a "Knowledge-to-Action Framework" [14] with extensive stakeholder and cross-sectoral engagement and will incorporate program elements with people with lived experience.

The research questions we seek to answer with this study are the following: (1) how effective is the WTC portal in altering the trajectories of mental health and substance use, primarily anxiety, compared to usual care? (2) What is the benefit of WTC versus usual care in terms of incremental costs, health outcomes, ongoing recruitment, and maintenance costs compared to the cost per quality-adjusted life year (QALY) gained using these interventions? (3) What is the differential impact of WTC by age, sex or gender, race, and socioeconomic status?

Figure 1. Flow chart showing participation stages and assessments in the Let's Act on Mental Health Survey of 2022.



Participants and Recruitment

Adults (N=2000) will be recruited using both paid and free web-based advertisements (social networking sites, Google advertisements, Facebook, Instagram stories, Twitter, etc). The Facebook business account of CAMH will be used to advertise the study and recruit participants. In the case of web-based advertisements, participants will click on a link in the advertisement that will direct them to a REDCap (Research Electronic Data Capture) survey, which will screen them for eligibility (see Textbox 1 for inclusion and exclusion criteria).

The project's social media pages and CAMH's page will be used for advertisements. Further, we will also approach the participants from other ongoing studies at CAMH including the Vaping Research Panel, Smoking Panel, and those who had agreed to be contacted for future studies. We will not cold contact previous participants; we will ensure that initial contact with the participants is made by the research staff who had previously contacted and are known to them. This will help establish trust and compliance for the Let's Act on Mental Health study.

Textbox 1. Inclusion and exclusion criteria for the study.

Inclusion criteria:

- Adults (≥18 years of age) residing in Canada and speaking English or French
- Ability to complete study assessments in English
- Interest in the use of digital interventions to improve their mental health
- Having internet access

Exclusion criteria:

- People who are at risk for suicide (based on the 9-item Patient Health Questionnaire scores)

Inclusion Criteria

Inclusion criteria are (1) being aged 18 years or older, (2) residing in Canada and speaking either English or French, (3) able to complete study measures in English, (4) willing or interested to use the digital interventions to improve their mental health, and (5) having internet access. Furthermore, concomitant psychotropic medication use will be allowed.

Exclusion Criteria

The main exclusion criterion was being at risk for suicide (based on the 9-item Patient Health Questionnaire [PHQ-9] score).

Participants who are not eligible for this study after screening will be redirected to a different page, informing them that they are not eligible and thanking them for their time.

Participant Withdrawal Criteria

Participants will not be withdrawn from the study for not wanting to receive the WTC or control intervention. Participants' intention to use and the reason to not use the intervention will be identified through self-assessments. However, they will be withdrawn from the study if suicidal thoughts occur in any of the long-term follow-up assessments at weeks 4, 8, 12, 16, 20, and 24.

Sample Size

The target sample size for the population survey and learning systems sample is 2000. This sample size will also allow for the estimation of the impact of the dashboard and app recommendations on score trajectories of the PHQ-9 and 7-item Generalized Anxiety Disorder Scale (GAD-7). Based on an estimated effect size of Cohen *d*=0.17 for changes in the PHQ-9 score and Cohen *d*=0.13 for changes in the GAD-7 score (based on the expected effects of the dashboard) [15], an expected dropout rate of no more than 35% [16], and population mean and SD estimates of PHQ-9 and GAD-7 scores [17,18], we estimate having a power of 0.90 and a type I error rate of 0.05 for detecting improvements in PHQ-9 and GAD-7 scores for subsamples with at least 1000 participants. Therefore, in this study, we will have a sample size of a total 2000 participants, with 1000 randomized to each group.

Randomization

At week 1, after baseline assessments, participants will be randomly allocated through email invitation to intervention or control groups using a simple randomization method equivalent of tossing a coin to ensure double-blinding. Participants deemed eligible after a manual-fraud check will be emailed a personalized URL invitation based on the groups in the study by the research personnel within the study, using the email template attached.

Blinding

Both participants and the research team involved in the trial will be blinded about the groups. The groups will be observed in an identical manner by the study team to ensure randomization. Further, to ensure that the study team is double-blinded, the potential participant receiving the intervention or usual care will be contacted by a research assistant outside the research team. The 2 groups will be followed up for 26 weeks to determine whether there are any differences in outcomes between them. The results and subsequent analysis of the trial will be used to assess the effectiveness of the WTC portal, which is the extent to which the service benefits the patients rather than doing them any harm.

Intervention

The intervention group will be invited to the WTC portal, which provides options for digital interventions. A single-sign on system used by WTC will be used to facilitate ease of transfer.

Control

The control group will be referred to the usual care tools available on the CAMH website, particularly (different mental health programs and resources such as "Game Changers: Self-care information," which is a hub of resources to help start conversations about health, self-help booklet series, relaxation guides, and free web-based education with a personalized dashboard), which provides an opportunity to clients for self-monitoring (symptoms or physiological processes), build awareness, improve self-efficacy, and visualization. The control group will not receive process monitoring assessments at week 6 or 26. Service usage and contamination in the control group will not be monitored.

Duration and Assessments

The expected duration of each participant's involvement in the study is for 6 months with baseline, weekly short follow-ups, intervention monitoring, and final assessments. Participants from the intervention and control groups will be asked to fill 1 baseline assessment at week 0 and 12 biweekly follow-ups from week 2 until week 24 including process monitoring of the intervention at weeks 6 and 26. Lastly, one final assessment will be carried out at week 26, for a total duration of 6 months. Hence, in total, a participant will complete 14 assessments. Participants will be sent weekly reminder emails to complete the assessments for compliance. The study team will track people who are lost to follow-up by communicating with them regularly through weekly emails and will continue to do so until the end of the study. They will be sent emails every week and will be provided an opportunity to complete the assessments when they show up until the end.

Ethical Considerations

This study is approved by the Research Ethics Board (REB) of CAMH (reference <REB#: 037-2022>, version 7.0). The protocol will be reapproved by the REB if it requires amendment. Participants will be screened and provided a unique ID number to protect their personal information. An electronic informed consent form has been prepared in REDCap to remotely obtain consent from the participants prior to enrolling them in the trial. A REDCap survey has also been designed separately for participants' eligibility screening at baseline, biweekly follow-ups, intervention monitoring, and final assessment over the 26-week period. Participants will be allowed to withdraw at any time without penalty.

Participants who meet the eligibility requirements of the initial screening form will be prompted to fill out a contact form with

their first name and email address. Participants deemed eligible after a manual fraud check will be emailed a personalized URL to the baseline questionnaire by the research staff and those who are deemed ineligible by the fraud check will be sent a notification from REDCap about their ineligibility. The baseline questionnaire is largely composed of questions about age, sex, gender, race and ethnicity, education, and 3 digits of the participants' postal code to later connect it with census data and community-level equity data. Lifetime history of substance use and mental health will be ascertained, including problematic alcohol use (assessed using Alcohol Use Disorders Identification Test item 3 about how often they had 6 or more drinks on 1 occasion in the past year) and drug use (assessed using the modified Drug Use Disorders Identification Test). Finally, we will measure time to completion for data quality reasons, but this variable will not be visible to participants.

This randomized population trial will be compensating thousands of participants (N=2000). We will compensate participants at a rate sufficient to motivate them to comply with the study protocol and to complete all surveys and measures. This will include a CAD $10 (US $7.24) Giftbit [19] e-card after completing the initial baseline survey at week 0, and then CAD $24 (US $17.38) for completing the 12 assessments during biweekly follow-up in weeks 2-24, and finally CAD $10 (US $7.24) for final assessments at week 26. The follow-up payment will be based on completion rate, which, in turn, is based on the number of assessments completed at a rate of CAD $2 (US $1.45) biweekly. Hence, a participant completing 100% of the assessments (N=14) will receive CAD $44 (US $31.87) in total.

Privacy and Confidentiality

The master linking log will be stored in a separate folder than the other data files on the CAMH server. The master linking log will be used to identify contact information in order to send the baseline questionnaire link, follow-up questionnaire, and gift cards; to store status of interest in the qualitative study and future research studies; and to monitor completion of baseline and follow-up surveys. A numerical participant ID number will be used to differentiate participants in an anonymous manner across measures and follow-up questionnaires.

Participants who complete surveys will receive e-gift cards through Giftbit, which allows one to select a gift card of one's choice. Giftbit Incentives is a secure platform that allows bulk and automated sending of e-gift cards, and has been used by the principal investigator (MC) in previous studies at CAMH. Participant information shared with Giftbit will be limited to their first name and email address, in order to allow personalized e-gift card emails.

Safety and Adverse Events

Since the study procedures are not at higher than minimal risk, adverse events (AEs) and serious AEs (SAEs) are not expected. If any unanticipated problems related to the research involving risks to participants or others occur during this study, they will be reported to applicable stakeholders in alignment with institutional policies. AEs that are not serious but are notable and could involve risks to participants will be documented in accordance with institutional documentation requirements.

Outcome Measures

Primary Outcomes

The primary outcomes are the changes in trajectories of mental health, primarily anxiety at baseline (week 0) until final assessments (week 26) between 6 months after invitation to the WTC intervention or usual care. The trajectories are also measured biweekly with short follow-ups at different time points from week 2 until week 26. We will use multilevel modeling to describe within-person differences in anxiety and depression at different time points. We will compare the observed trajectory with those of the control group. Interactions by demographic subgroups (primarily age, gender, race, and socioeconomic status) will be assessed for identification of potential effect modifications.

Secondary Outcomes

An economic analysis will be conducted by comparing incremental costs and health outcomes for the Wellbeing Tracker and WTC compared to within-person expected trajectories using a cost-effectiveness acceptability curve. These costs will be based on the costs associated with the ongoing recruitment and maintenance costs of WTC compared to the cost per QALY gained through the use of these interventions [20]. To be somewhat comparable with World Health Organization's standards for ranking public health interventions, the determination of whether the WTC overall is highly cost-effective will be based on a threshold of CAD $124 (~US $100) per QALY gained [21]. QALYs will be estimated using the SF-6D (Short-Form Six-Dimension), calculated on the basis of the SF-12 (12-item Short Form Survey) [21]. This analysis will provide an empirical basis for the effect of allocation of health care resources in Canada. To aid other countries, we will also base cost-effectiveness calculations based on estimations that incorporate implementation costs of the Wellbeing Tracker and WTC. We will also estimate cost-effectiveness based on clinically Reliable Change Index scores (ie, 5 points on the PHQ-9 [22] and a 6-point change on the GAD-7 [23], as well as employment status. The schedule of the Let's Act on Mental Health study is outlined in Table 1.

Table 1. Schedule of the Let's Act on Mental Health Survey of 2022.

Procedures	Study period (day 1 to week 26)						
Enrollment	Day 1	Week 0	Week 1	Weeks 2 and 4	Week 6	Weeks 8-24	Week 26
Eligibility screening	✓						
Informed consent	✓						
Screening assessments (PHQ-9[a] item 9)	✓						
Drug use (DUDIT-C modified[b])	✓						✓
Problematic alcohol use (AUDIT-C[c])	✓						✓
Enrollment							
Demographics		✓					
3-Digit postal codes		✓					
Baseline with self-reported questionnaires (GAD-7[d], PHQ-4[e], Current Substance Use, SF-12[f], and WSAS[g])		✓					
Randomization to the WTC[h] intervention or usual care group through an email invitation			✓				
Biweekly short and long follow-up (GAD-7, PHQ-4, Current Substance Use, SF-12, and WSAS)				✓		✓	
WTC and usual care monitoring for contamination and compliance checks					✓		✓
Final assessment (GAD-7, PHQ-4, current substance use, SF-12, and WSAS)							✓

[a]PHQ-9: 9-item Patient Health Questionnaire.

[b]DUDIT-C modified: modified Drug Use Disorders Identification Test.

[c]AUDIT-C: Alcohol Use Disorders Identification Test.

[d]GAD-7: 7-item Generalized Anxiety Disorder Scale.

[e]PHQ-4: 4-item Patient Health Questionnaire.

[f]SF-12: 12-item Short Form Survey.

[g]WSAS: Work and Social Adjustment Scale.

[h]WTC: Wellness Together Canada.

Data Management and Availability

All data will be collected and managed in the REDCap electronic case report forms. This system is maintained on central CAMH servers, with data backed up daily, and is supported by the Research Informatics department. This will strengthen the data's accuracy and maintain data quality. Only authorized personnel will monitor the completion of surveys, sending up to 3 reminder emails to participants who have not completed baseline surveys, up to 3 reminder emails to participants who have not completed follow-up surveys, and up to 3 reminder emails to participants who have not completed 6-month surveys.

The data sets will be stored on the secure CAMH server, and only for the minimum amount of time needed for fraud screening. Only trained research staff will have access to the data sets, and they will only use the merged data set for fraud screening purposes. As participants are screened, they will be entered into the screening log. Those deemed eligible will have their contact information, study ID number, and first name copied by research staff into the master linking log (a separate Excel [Microsoft Corp] file stored in a separate location from the fraud screening data). Once each round of fraud screening is completed, the merged data file will be securely destroyed. The original contact files may remain on the CAMH server to cross-check study IDs with the screening log, in the event that an ineligible individual contacts staff and inquiries about their eligibility.

Statistical Analysis

A statistician who is not affiliated with this study will perform the statistical analyses for Linear random effects modeling—which accounts for repeated measures over time—that will be used to study the intervention's effect [24]. We will also use multilevel modeling to describe within-person differences in anxiety and depression. We will then compare this observed trajectory with the control group's trajectories.

The level of change in anxiety from weeks 0-26 (baseline to final assessment) over the 6 months' time period is the primary trajectory of concern for mental health in this study. We will test the hypothesis that the trajectories are changing over time and the intervention's effects are expected to be observed as

changes in self-reported mood, which will be measured with the mood scores, cutoff scores, sensitivity, etc, obtained at various time points. Interactions by demographic subgroups (primarily age, gender, race, and socioeconomic status) will be assessed for identifying potential effect modifications.

Analysis will be based on the intention-to-treat principle, as this method allows to draw an unbiased conclusion regarding the effectiveness of an intervention. It also preserves the benefits of randomization, which cannot be assumed when using other methods of analysis [25]. Further, this method is also more effective in accommodating missing data, as missingness is assumed at random.

Results

The study is ongoing and the first wave data collection is complete; we are analyzing data from the baseline and weeks 2-26. The study is ongoing at week 26, we have analyzed the preliminary baseline data and weeks 2 and 4 short and long follow-ups to understand the ongoing trajectory of depression. Until now, 453 individuals in the age group of 18-72 years have responded to the study invitation emails.

The trial is currently in the ethics approval process. Thus far, ethics approval has been granted by the REB of CAMH, and participant recruitment is ongoing. The study will be conducted in accordance with the REB-approved study documents and the determinations (including any limitations) of the REB, and in compliance with the REB's requirements.

Discussion

Anticipated Findings

At baseline, with regard to gender and race, a greater proportion of participants are female (n=359, 75.57%) and White (n=335, 67.95%). We aim to generalize this study to the Canadian population; hence, we have been weighting samples at the census level based on gender and province to make this study representative. Weighing of the sample will help us understand how generalizable the sample and advertisements are and whether they are adequately representative. The SF-12, measuring mental and physical health, has revealed a significant decline in mental health from baseline to short and long follow-ups in this study. It is too early to discuss how this will develop longitudinally, but the preliminary results suggest a larger decline in mental health than in physical health in the Canadian population.

Limitations

The foreseeable factors that could compromise the outcome of this study is the monitoring of WTC usage, which is based on self-reports. However, to mitigate the challenge, the study team will ensure detailed monitoring and contamination of intervention at 1 and 6 months. The study team will continuously explore its potential partners for incorporating artificial intelligence within the digital interventions, such as the WTC, for real-time monitoring of service usage. Service usage and contamination in the control group will not be evaluated.

Digital health interventions for delivering mental health care were relevant even before the COVID-19 pandemic. After the pandemic, it has proven to be a safer alternative to face-to-face treatment [26]. It offers great potential, and there is an urgent need for up-to-date information on the mental health impacts post the COVID-19 pandemic. Especially after pandemic, there is a dire need of population-level mental health interventions to improve access to and the quality of mental health care. The challenges of mental health care are its reach at the population level. Interventions such as WTC have shown great potential in developing interest toward mental health interventions in any population; however, the challenge of consistency remains to be studied.

Acknowledgments

This study is funded through a grant from the Canadian Institutes of Health Research (179471).

Conflicts of Interest

None declared.

References

1. COVID-19 National Survey Dashboard. Centre for Addiction and Mental Health. URL: https://www.camh.ca/en/health-info/mental-health-and-covid-19/covid-19-national-survey [accessed 2020-10-13]
2. Hawke LD, Hayes E, Darnay K, Henderson J. Mental health among transgender and gender diverse youth: an exploration of effects during the COVID-19 pandemic. Psychol Sex Orientat Gend Divers 2021 Jun;8(2):180-187. [doi: 10.1037/sgd0000467]
3. Elton-Marshall T, Wells S, Jankowicz D, Nigatu YT, Wickens CM, Rehm J, et al. Multiple COVID-19 risk factors increase the likelihood of experiencing anxiety symptoms in Canada. Can J Psychiatry 2021 Jan 13;66(1):56-58 [FREE Full text] [doi: 10.1177/0706743720949356] [Medline: 32787572]
4. Moreno C, Wykes T, Galderisi S, Nordentoft M, Crossley N, Jones N, et al. How mental health care should change as a consequence of the COVID-19 pandemic. Lancet Psychiatry 2020 Sep;7(9):813-824 [FREE Full text] [doi: 10.1016/S2215-0366(20)30307-2] [Medline: 32682460]

5. Robillard R, Daros AR, Phillips JL, Porteous M, Saad M, Pennestri M, et al. Emerging new psychiatric symptoms and the worsening of pre-existing mental disorders during the COVID-19 Pandemic: A Canadian Multisite Study: Nouveaux symptômes psychiatriques émergents et détérioration des troubles mentaux préexistants durant la pandémie de la COVID-19: une étude canadienne multisite. Can J Psychiatry 2021 Sep 19;66(9):815-826 [FREE Full text] [doi: 10.1177/0706743720986786] [Medline: 33464115]
6. Foley T, Fairmichael F. The Potential of Learning Healthcare Systems. The Learning Healthcare Project. 2015. URL: https://learninghealthcareproject.org/wp-content/uploads/2015/11/LHS_Report_2015.pdf [accessed 2023-11-09]
7. Mood and anxiety disorders in Canada. Government of Canada. URL: https://www.canada.ca/en/publichealth/services/publications/diseases-conditions/mood-anxiety-disorders-canada.html [accessed 2021-06-30]
8. Daly M, Robinson E. Psychological distress and adaptation to the COVID-19 crisis in the United States. J Psychiatr Res 2021 Apr;136:603-609 [FREE Full text] [doi: 10.1016/j.jpsychires.2020.10.035] [Medline: 33138985]
9. Urbanoski KA, Cairney J, Bassani DG, Rush BR. Perceived unmet need for mental health care for Canadians with co-occurring mental and substance use disorders. Psychiatr Serv 2008 Mar;59(3):283-289. [doi: 10.1176/ps.2008.59.3.283] [Medline: 18308909]
10. Strudwick G, Sockalingam S, Kassam I, Sequeira L, Bonato S, Youssef A, et al. Digital interventions to support population mental health in Canada during the COVID-19 pandemic: rapid review. JMIR Ment Health 2021 Mar 02;8(3):e26550 [FREE Full text] [doi: 10.2196/26550] [Medline: 33650985]
11. Humanitarian Emergencies Around the World: Coping Together. Wellness Together Canada. URL: https://www.wellnesstogether.ca/en-ca/ [accessed 2023-11-09]
12. Bugajski AA, Frazier SK, Cousin L, Rechenberg K, Brown J, Lengerich AJ, et al. Effects of a digital self-care intervention in adults with COPD: a pilot study. West J Nurs Res 2020 Sep;42(9):736-746. [doi: 10.1177/0193945919892282] [Medline: 31854271]
13. Collins MH, Cassill CK. Psychological wellness and self-care: an ethical and professional imperative. Ethics Behav 2021 Oct 21;32(7):634-646 [FREE Full text] [doi: 10.1080/10508422.2021.1971526]
14. Davison CM, Ndumbe-Eyoh S, Clement C. Critical examination of knowledge to action models and implications for promoting health equity. Int J Equity Health 2015 May 29;14(1):49 [FREE Full text] [doi: 10.1186/s12939-015-0178-7] [Medline: 26022369]
15. Delgadillo J, de Jong K, Lucock M, Lutz W, Rubel J, Gilbody S, et al. Feedback-informed treatment versus usual psychological treatment for depression and anxiety: a multisite, open-label, cluster randomised controlled trial. Lancet Psychiatry 2018 Jul;5(7):564-572. [doi: 10.1016/s2215-0366(18)30162-7]
16. Wood AM, White IR, Thompson SG. Are missing outcome data adequately handled? A review of published randomized controlled trials in major medical journals. Clin Trials 2004 Sep 03;1(4):368-376. [doi: 10.1191/1740774504cn032oa] [Medline: 16279275]
17. Kocalevent R, Hinz A, Brähler E. Standardization of the depression screener patient health questionnaire (PHQ-9) in the general population. Gen Hosp Psychiatry 2013 Sep;35(5):551-555. [doi: 10.1016/j.genhosppsych.2013.04.006] [Medline: 23664569]
18. Löwe B, Decker O, Müller S, Brähler E, Schellberg D, Herzog W, et al. Validation and standardization of the Generalized Anxiety Disorder Screener (GAD-7) in the general population. Med Care 2008 Mar;46(3):266-274. [doi: 10.1097/MLR.0b013e318160d093] [Medline: 18388841]
19. Giftbit. URL: https://www.giftbit.com/ [accessed 2023-11-09]
20. Rocchi A, Miller E, Hopkins RB, Goeree R. Common Drug Review recommendations: an evidence base for expectations? Pharmacoeconomics 2012 Mar;30(3):229-246. [doi: 10.2165/11593030-000000000-00000] [Medline: 22283689]
21. "Best-buys" and other recommended interventions for the prevention and control of noncommunicable diseases. Pan American Health Organization. URL: https://www3.paho.org/hq/index.php?option=com_content&view=article&id=14418:ncds-graphic-materials-best-buys&Itemid=0&lang=en#gsc.tab=0 [accessed 2023-11-09]
22. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001 Sep;16(9):606-613 [FREE Full text] [doi: 10.1046/j.1525-1497.2001.016009606.x] [Medline: 11556941]
23. Bischoff T, Anderson SR, Heafner J, Tambling R. Establishment of a reliable change index for the GAD-7. Psychol Community Health 2020 Apr 08;8(1):176-187. [doi: 10.5964/pch.v8i1.309]
24. Laird N, Ware J. Random-Effects Models for Longitudinal Data. Biometrics 1982 Dec;38(4):963 [FREE Full text] [doi: 10.2307/2529876]
25. McCoy E. Understanding the intention-to-treat principle in randomized controlled trials. West J Emerg Med 2017 Oct 18;18(6):1075-1078 [FREE Full text] [doi: 10.5811/westjem.2017.8.35985] [Medline: 29085540]
26. Philippe TJ, Sikder N, Jackson A, Koblanski ME, Liow E, Pilarinos A, et al. Digital health interventions for delivery of mental health care: systematic and comprehensive meta-review. JMIR Ment Health 2022 May 12;9(5):e35159 [FREE Full text] [doi: 10.2196/35159] [Medline: 35551058]

Abbreviations

AE: adverse event
CAMH: Centre for Addiction and Mental Health
GAD-7: 7-item Generalized Anxiety Disorder Scale
PHQ-9: 9-item Patient Health Questionnaire
QALY: quality-adjusted life year
REB: Research Ethics Board
REDCap: Research Electronic Data Capture
SAE: serious adverse event
SF-6D: Short-Form Six-Dimension
SF-12: 12-item Short Form Survey
WTC: Wellness Together Canada

Edited by A Mavragani; submitted 03.05.23; peer-reviewed by L Southwick, D Alfarra; comments to author 19.05.23; revised version received 29.08.23; accepted 30.08.23; published 30.01.24.

Please cite as:
Basnet S, Chaiton M
Effectiveness of the Wellness Together Canada Portal as a Digital Mental Health Intervention in Canada: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2024;13:e48703
URL: https://www.researchprotocols.org/2024/1/e48703
doi:10.2196/48703
PMID:38289642

Protocol

Role of Chinese Acupuncture in the Treatment for Chemotherapy-Induced Cognitive Impairment in Older Patients With Cancer: Protocol for a Randomized Controlled Trial

Sunyan Zhao[1*], BS; Jing Zhang[1*], BS; Haijun Wan[2*], MS; Chenjie Tao[3], MS; Meng Hu[4], MS; Wei Liang[1], MD; Zhi Xu[5], MD; Bingguo Xu[6], MS; Jiaying Zhang[6], MS; Guoxin Wang[6], MS; Ping Li[7*], MD; Guangmei Lyu[8*], BS; Yongling Gong[1*], MD

[1]Department of Oncology, Nanjing First Hospital, Nanjing Medical University, Nanjing, China

[2]Department of Gastroenterology, Jinling Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing, China

[3]Department of Oncology, Eastern Hepatobiliary Hospital, Naval Medical University, Shanghai, China

[4]Department of Medical Oncology, Liyang People's Hospital, Liyang, China

[5]Medical Affairs, ICON Public Limited Company (ICON Plc), Beijing, China

[6]Division of Chinese Medicine, Nanjing First Hospital, Nanjing Medical University, Nanjing, China

[7]Department of Gastroenterology, Changhai Hospital, Naval Medical University, Shanghai, China

[8]Information Centre, Jiangsu Health Vocational College, Nanjing, China

[*]these authors contributed equally

Corresponding Author:
Yongling Gong, MD
Department of Oncology
Nanjing First Hospital
Nanjing Medical University
Changle Road 68
Nanjing, 210006
China
Phone: 86 25 52271000 ext 66243
Fax: 86 25 52271000
Email: gongyongling26@163.com

Abstract

Background: Older patients with cancer experience cognitive impairment and a series of neurocognitive symptoms known as chemobrain due to chemotherapy. Moreover, older populations are disproportionately affected by chemobrain and heightened negative mental health outcomes after cytotoxic chemical drug therapy. Chinese acupuncture is an emerging therapeutic option for chemotherapy-induced cognitive impairment in older patients with cancer, despite limited supporting evidence.

Objective: Our study aims to directly contribute to the existing knowledge of this novel Chinese medicine mode in older patients with cancer enrolled at the Department of Oncology/Chinese Medicine, Nanjing First Hospital, China, thereby establishing the basis for further research.

Methods: This study involves a 2-arm, prospective, randomized, assessor-blinded clinical trial in older patients with cancer experiencing chemobrain-related stress and treated with Chinese acupuncture from September 30, 2023, to December 31, 2025. We will enroll 168 older patients with cancer with clinically confirmed chemobrain. These participants will be recruited through screening by oncologists for Chinese acupuncture therapy and evaluation. Electroacupuncture will be performed by a registered practitioner of Chinese medicine. The electroacupuncture intervention will take about 30 minutes every session (2 sessions per week over 8 weeks). For the experimental group, the acupuncture points are mainly on the head, limbs, and abdomen, with a total of 6 pairs of electrically charged needles on the head, while for the control group, the acupuncture points are mainly on the head and limbs, with only 1 pair of electrically charged needles on the head.

Results: Eligible participants will be randomized to the control group or the experimental group in 1:1 ratio. The primary outcome of this intervention will be the scores of the Montreal Cognitive Assessment. The secondary outcomes, that is, attentional

function and working memory will be determined by the Digit Span Test scores. The quality of life of the patients and multiple functional assessments will also be evaluated. These outcomes will be measured at 2, 4, 6, and 8 weeks after the randomization.

Conclusions: This efficacy trial will explore whether Chinese electroacupuncture can prevent chemobrain, alleviate the related symptoms, and improve the quality of life of older patients with cancer who are undergoing or are just going to begin chemotherapy. The safety of this electroacupuncture intervention for such patients will also be evaluated. Data from this study will be used to promote electroacupuncture application in patients undergoing chemotherapy and support the design of further real-world studies.

Trial Registration: ClinicalTrials.gov NCT05876988; https://clinicaltrials.gov/ct2/show/NCT05876988

International Registered Report Identifier (IRRID): DERR1-10.2196/53853

(JMIR Res Protoc 2024;13:e53853) doi:10.2196/53853

KEYWORDS

older patients with cancer; cognitive impairment; chemobrain; Chinese medicine; electroacupuncture

Introduction

With the development of new cytotoxic drugs for clinical practice, the clinical curative effects and survival rates of patients with cancer have improved greatly [1]. However, these drugs have considerable adverse side effects that are pernicious, unexpected, and occur at standard doses when administered to older patients with cancer [2]. Studies have shown that older patients with cancer undergoing chemotherapy develop chemotherapy-induced cognitive impairment, known as chemobrain, including a series of neurocognitive symptoms (forgetfulness, trouble concentrating and remembering details, difficulty with multitasking word finding, and taking longer to finish tasks), hospitalizations, and poor quality of life (QoL) [3,4]. In fact, chemobrain-related stress has been reported disproportionately among older individuals with cancer who have undergone chemotherapy [5].

With advances in cancer treatment over the decades, the survival time of older patients with cancer has been gradually extended, and the accompanying symptoms of chemobrain have gradually drawn increasing attention [5]. Recent data have shown that chemobrain-related stress could persist for a long-term period after a systemic therapy, which is particularly relevant to older patients with cancer [6]. These individuals report chemobrain symptoms of anxiety and depressive disorder, and the number of older patients with cancer will increase dramatically in the coming future. Although data on cognitive impairment onset after chemotherapy are lacking for older patients with cancer in China, clinical practitioners have paid constant attention to the health of their constituents, given their propensity for worse physical and mental health outcomes related to chemotherapy [7]. Data suggest that up to two-thirds of older patients with cancer develop chemobrain during or after chemotherapy [8]. Most of these patients experience cognitive impairments for months, but 10%-20% of these individuals experience persistent chemobrain-related stress even after many years of completing chemotherapy. In recent years, the incidence rate of cancer in senile patients has been rising in China [9]. The problem of chemotherapy-induced cognitive dysfunction is becoming increasingly common, and there are growing concerns that chemobrain could become a threat. Therefore, it is crucial to explore an intervention that can effectively prevent and treat chemotherapy-induced cognitive impairment in older patients with tumors.

Pre-existing studies [10] have shown that some neuroprotective factors such as methylphenidate and modafinil are effective for treating chemotherapy-related cognitive impairment; however, most clinical trials on interventions for chemobrain report less access to control groups and less treatment engagement. Combo acupoint stimulation therapy is a new technique based on the theory of traditional Chinese medicine and modern biological principles. With the help of invasive or noninvasive interventions, different stimuli or drug intakes would be administered at acupuncture points, meridians, or related specific body surface sites [11].

Acupuncture has been used for thousands of years in China and other Asian countries to treat various diseases, including sleep disturbance [12]. It is a nonpharmacological therapy that involves inserting needles into acupuncture points and sometimes applying minielectrical current stimulation on acupuncture points via needles or applying acupressure on the surface of points in different parts of the body, including ear and scalp [12]. Electroacupuncture (EA) is an effective family member of combo acupoint stimulation [13]. Lyu et al [14] reported that EA could be effective in alleviating various side effects caused by anticancer drugs, such as pain, vomiting, fever, fatigue, dry mouth, anxiety, depression, and insomnia. In addition, EA could promote the rehabilitation of pathological microstructures in the brain and improve the cognitive ability of patients with cognitive impairment. Clinical trials [14,15] of acupuncture for preventing and managing mild cognitive impairment in older adults show that it can improve the clinical efficacy rate, Mini-Mental State Examination Scale score, Montreal Cognitive Assessment (MoCA) test score, and clock drawing task scores, suggesting that acupuncture can be an effective approach complementary to existing therapies. Evidences [14] from acupuncture in patients after an ischemic stroke support its role in the treatment of neurological deficits through modulation of neuroplasticity. Chemobrain affects cognitive function, in particular, think and memory functions through various mechanisms, including inflammation and oxidative stress, which may lead to neurogenesis and glycogenesis reduction. This pathological process shares some similarities with brain damage after an ischemic stroke [3,16]. Therefore, it is important to investigate if EA is effective in preventing and treating chemobrain in older patients with cancer and for improving the QoL of cancer survivors.

Emerging chemotherapy-induced cognitive impairments in older patients with cancer are likely to widen without proper early intervention tactics. In this protocol, we propose a 2-arm, prospective, randomized, assessor-blinded trial to examine the efficacy and safety of EA for chemobrain among older patients with cancer who are on or about to receive chemotherapy. The aim of this study directly contributes to the existing knowledge in this area, thereby establishing a basis for further research. Changes in the scores on MoCA [17] and the incidence of adverse events serve as the primary outcome. Scores on the Digit Span Test will be the secondary outcome for attentional function and working memory [18]. The QoL and multiple functional assessments will also be evaluated [19]. Outcomes include the MoCA, Digit Span Test, QoL, and multiple functional assessments at 2, 4, 6, and 8 weeks after randomization. Data from this efficacy trial will determine whether Chinese EA successfully improves the symptoms of chemobrain and whether these improvements could markedly reduce the various side effects caused by cytotoxic chemotherapy drugs. If successful, findings from this study might have benefits in reducing chemotherapy-induced working memory impairment. Data from this study may be used to support an implementation and dissemination trial of Chinese EA within real-world behavioral health and social service settings.

Methods

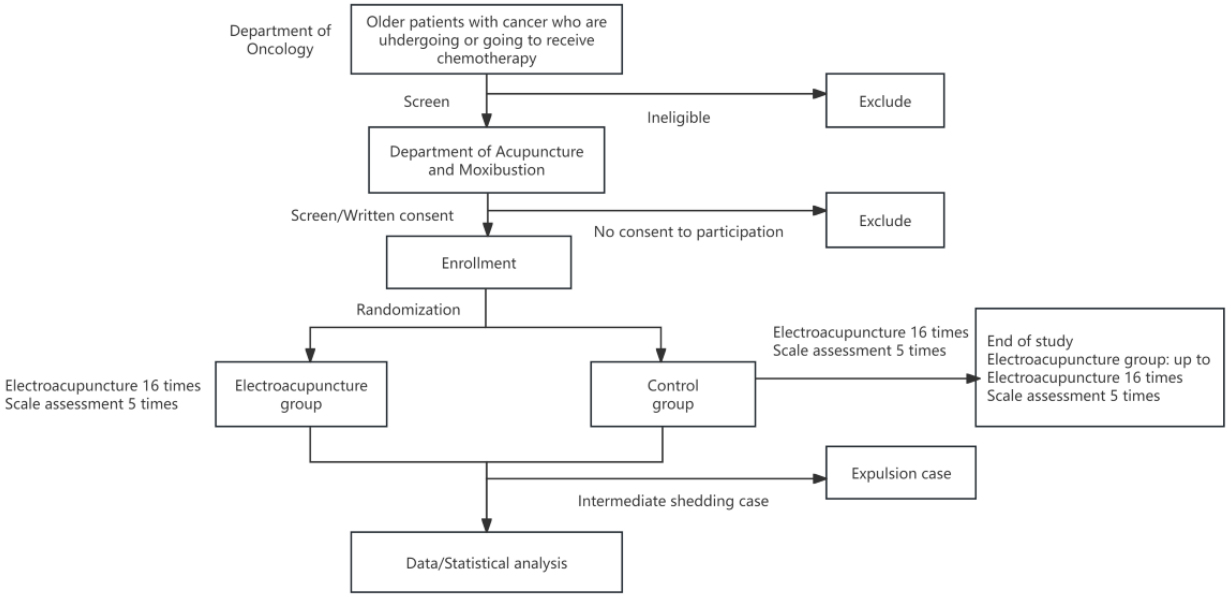
Ethics Approval

Eligible participants should provide written informed consent after reviewing consent documents with medical staff. To protect participant privacy and confidentiality, questionnaire surveys for the evaluation of cognitive function should be completed by research staff in a secure office in the inpatient ward. Only trained research staff have access to the key that can match participant data to the participant's name. This trial has been approved by the ethics committee of Nanjing First Hospital (approval KY20230310-05-KS-0I), and the collaborator of Jiangsu Health Vocational College provides ongoing oversight. This study was registered in ClinicalTrials.gov (NCT05876988) on April 13, 2023, before the first participant was recruited.

Study Design

We present a protocol for a 2-arm, prospective, randomized, assessor-blinded trial to examine the efficacy and safety of EA for chemobrain among older patients with cancer who are undergoing chemotherapy or those are going to just begin chemotherapy. This study refers to a double-blinded trial in which neither the investigator nor the participant knows the group to which the participant belongs (experimental group or control group), and the analyst usually does not know which group the data being analyzed belong to. This study is designed to eliminate subjective biases and personal preferences that may arise in the consciousness of investigators and participants. Those who report clinically significant cognitive impairment are being recruited and enrolled to participate in a trial on the effects of a novel EA intervention to address negative mood symptoms and reduce chemotherapy-induced adverse reactions. Participants are recruited via community organizations, social media, and internet outlets (eg, hospital classified ads, WeChat). Interested older patients with cancer complete a screener assessment by the medical staff of the Oncology department or a Chinese medicine doctor, and they report the levels of cognitive dysfunction they are experiencing through the Overall Anxiety Severity and Impairment Scale [20] and the Overall Depression Severity and Impairment Scale [21]. Those eligible at the screener complete an enrollment for full eligibility and receive instructions on how to accept EA therapy to complete the baseline assessment. Additionally, eligible participants will be randomly assigned to either an experimental group or a control group at 1:1 ratio. Participants then engage with the assigned intervention for 8 weeks following randomization. Participants complete follow-up assessments at baseline, 2, 4, 6, and 8 weeks after randomization, which include the MoCA, Digit Span Test, QoL, and multiple functional assessments. Additionally, participants are prompted to complete ecological momentary assessments [22] twice weekly throughout the 2-month postrandomization period. The study flow diagram is shown in Figure 1.

Figure 1. Participant flow diagram in the clinical trial.



Specific Aims and Hypotheses

Chinese acupuncture is an emerging therapeutic option for chemotherapy-induced cognitive impairment in older patients with cancer, despite limited supporting evidence [23]. This study has 2 specific aims.

1. First, to evaluate the clinical therapeutic response of EA intervention for the treatment of chemobrain in older patients with cancer, a randomized controlled trial is designed to study the effects of EA on chemobrain at baseline, 2, 4, 6, and 8 weeks follow-up. We hypothesize that those assigned to EA will show greater reductions from baseline to follow-ups in MoCA Overall Anxiety Severity and Impairment Scale and Digit Span Test scores and greater reductions in cognitive impairment in daily responsibilities relative to the control group. We also hypothesize that the effectiveness of EA on QoL and multiple functional assessments will be similar across experimental or control groups.
2. Second, our aim is to elucidate the modern biomedical mechanism of EA in the treatment of chemobrain in older patients with cancer. In testing the putative mechanisms of action, we hypothesize that the intervention effects on study outcomes will be mediated by reductions in chemotherapy-induced working memory impairment and the incidence of certain digestive, neurological, and distress-related symptoms.

Participants and Recruitment

This 2-arm, prospective, randomized, assessor-blinded trial will be conducted from September 2023 to December 2025 in the Department of Oncology/Chinese Medicine, Nanjing First Hospital, China. Potentially eligible participants would be screened and recruited through clinical oncologists/Chinese medicine acupuncturists' referral from local hospitals and advertisements. Enrollment to this study began in September 2023 and, as of writing this paper, is in the recruitment phase. Enrollment, randomization, intervention delivery, and assessments are completed by trained research staff. Both study conditions receive the same set of questionnaires at each assessment (see Figure 2) or the full list and timeline of study measures. These questionnaires assess chemobrain symptoms, functional impairment, general and chemotherapy-specific affect constructs, and sociocultural factors. Interested individuals complete an initial screener to assess age, racial/ethnic identity, clinical confirmation of chemobrain, state of residence, and willingness to complete study assessments. During the enrollment, volunteer participants will be asked to sign written informed consent forms and are informed of the purpose, goals, and procedures of the study. All participants will give voluntary, written, and informed consent before entering the trial.

Figure 2. Schedule of enrollment, interventions, and assessments. T0: baseline; T1-T3: midpoint of main treatment once every 2 weeks; T4: end of the 8-week main treatment.

	Study period					
	Enrollment	Baseline	Main treatment			End of treatment
		T0	T1	T2	T3	T4
Timepoint		0 weeks	2 weeks	4 weeks	6 weeks	8 weeks
Enrollment						
Eligibility screen	✓					
Informed consent	✓					
Allocation groups		✓				
Experiment (electroacupuncture) group		◄	—	—	—	►
Control group		◄	—	—	—	►
Assessments						
Montreal Cognitive Assessment	✓	✓	✓	✓	✓	✓
Functional Assessment of Cancer Therapy-Cognitive function	✓	✓	✓	✓	✓	✓
Functional Assessment of Cancer Therapy	✓	✓	✓	✓	✓	✓
Functional Assessment of Chronic Illness Therapy-Fatigue	✓	✓	✓	✓	✓	✓
Functional Assessment of Anorexia-Cachexia Therapy	✓	✓	✓	✓	✓	✓
Functional Assessment of Cancer Therapy-Biologic Response Modifier	✓	✓	✓	✓	✓	✓
European Organization for Research and Treatment of Cancer Quality of Life questionnaire-Core 30	✓	✓	✓	✓	✓	✓

Inclusion and Exclusion Criteria

The participants in this study are 168 older patients with cancer who are further assessed for eligibility and meet the following eligibility criteria: (1) have clinically pathological diagnosis of malignant tumor, (2) aged 60 years or older, and (3) are currently undergoing or just about to commence a comprehensive treatment of chemotherapy. The exclusion criteria are as follows: (1) undergone chemotherapy within the last 2 years; (2) metal device or pacemaker planted in the body, developed epilepsy, and experienced instability; (3) participated in a drug trial within the last 6 months; (4) alcohol or drug abuse history in the past year; and (5) those who are afraid of acupuncture.

Study Procedures

After screening, eligible participants will be enrolled and they will complete baseline assessments. Thereafter, participants will be randomly assigned to either an EA experimental group or a sham control group. EA or sham treatments will be given twice weekly for 8 weeks—a total of 16 sessions. Participants in both groups will receive routine chemotherapy provided by their oncologists, which will include the use of cytotoxic drugs. Participants will be assessed at the following timepoints (see Figure 2): baseline (T0), midpoint of main treatment (T1-T3) once every 2 weeks, and end of the 8-week main treatment (T4). Assessments include MoCA [24] + Functional Assessment of Cancer Therapy-Cognitive function (FACT-Cog) [25] for cognitive performance, FACT/Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) [26] for fatigue, European Organization for Research and Treatment of Cancer QoL Questionnaire-Core 30 (EORTC QLQ-C30) [27] for QoL, and Functional Assessment of Anorexia-Cachexia Therapy (FAACT)/FACT-Biologic Response Modifier (FACT-BRM) [28] for chemotherapy-related side effects. Assessments will be done prior to any procedures in that visit, including disease assessment and physician consultation.

Randomization and Allocation Concealment

Older patients with tumors will be screened for eligibility, and enrollment and baseline assessments should be completed thereafter. A random code of simple, complete, and nonsequential numbers could be produced in advance from a computer-generated block randomization with random block sizes. Participants will be randomly assigned to experimental or control groups in a 1:1 ratio. Random information will be sealed in sequentially numbered opaque envelopes.

Blinding

Only the acupuncturist can open the envelope after the participant's completion of baseline assessments. Participants and all other researchers will be blinded to group assignments. Participants are informed that they have a similar chance of allocation to any group and will be blinded to group assignments. A clinical assessor will be arranged to conduct assessments on a day different from the day of acupuncture treatment to avoid cross communications among the assessors,

acupuncturists, and participants. An eye mask will be used to avoid communications among participants during EA treatment.

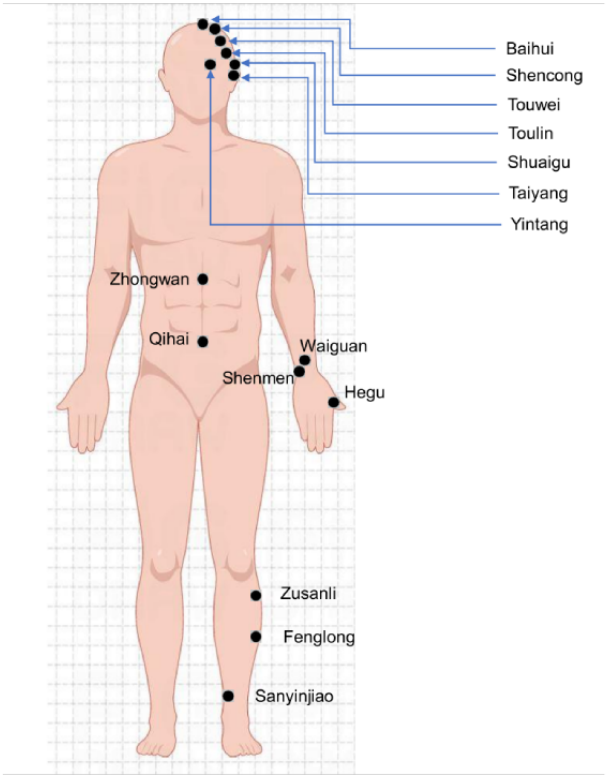
Interventions

Potentially eligible patients will be recruited through clinical oncologists' referral from local hospitals and advertisements. Research staff are notified once a participant completes the baseline assessment. The interventions of the experimental and control groups will be performed in the Department of Medical Oncology, Nanjing First Hospital, Nanjing Medical University, Nanjing, Jiangsu, China. Registered Chinese medicine acupuncturists at the Division of Chinese Medicine will be recruited who will be responsible for delivering treatment according to STRICTA (Standards for Reporting Interventions in Clinical Trials of Acupuncture) [29].

Acupuncture Group

Participants in the experimental group will receive EA treatment. Acupuncture intervention will be conducted for 2 sessions per week over 8 consecutive weeks. Assessments will be conducted at baseline and once biweekly thereafter. For the experimental group, acupuncture points are mainly on the head, limbs, and abdomen, with a total of 6 pairs of electrically charged needles on the head, while for the control group, acupuncture points are mainly on the head and limbs, with only a pair of electrically charged needles on the head. The acupuncture points are as follows: Baihui point, left Shencong point, right Shencong point, bilateral Shuaigu point, bilateral Touwei point, bilateral Toulin point, bilateral Taiyang point, Yintang point, Zhongwan point, Qihai point, bilateral Waiguan point, bilateral Shenmen point, bilateral Hegu point, bilateral Zusanli point, bilateral Fenglong point and bilateral Sanyinjiao point. A total of 6 pairs of electrodes from the electric stimulator (CMNS6-3; 2-5 Hz, continuous wave) will be connected to the end of the needles. The 6 fixed points are Baihui and Yintang, left Shencong and left Toulin, right Shencong and right Toulin, left Shuaigu and right Shuaigu point, left Touwei and right Touwei points, and left Taiyang and right Taiyang (see Figure 3).

Figure 3. Acupoints for electroacupuncture stimulation.



Disposable acupuncture needles (0.30 mm in diameter and 25-40 mm in length) will be inserted at a depth of 10-30 mm perpendicularly or obliquely into the acupoints. Manual manipulation will be performed for all acupoints to evoke needling sensation. Electrical stimulation will be additionally delivered on the 6 pairs of the frontal acupoints. The output peak current and voltage of the machine would be 6 V and 48 mA, respectively, with constant waves at frequencies of 2 Hz and phase duration of 100 μs for 30 minutes. Electrical stimulation will last for 30 minutes. The needles on body acupoints will also be retained for 30 minutes. Upon needle withdrawal, the points will be compressed with iodine volts swabs to prevent bleeding [30].

Control Group

The control treatment procedure is the same as that in the experimental group, except that only a pair of electric needles will be selected for the electrical stimulation on the head. After completing the 8-week acupuncture intervention, patients in the control group will be administered follow-up EA acupuncture free of charge. The same 16 sessions or a total of no more than 8 weeks of acupuncture will be performed as compensation.

Assessments

In this study, therapeutic efficiency will be assessed in terms of the following aspects: cognitive performance, fatigue, QoL, and chemotherapy-induced side effects. The primary outcome

of this study is to verify whether EA is therapeutically useful for preventing chemobrain and alleviating the related symptoms and the safety of intervention. Cognitive performance will be assessed using MoCA + FACT-Cog. The secondary outcomes are as follows: QoL will be measured using EORTC QLQ-C30, fatigue will be assessed using the FACIT-Fatigue scale, and the manifestation of chemotherapy-induced side effects will be assessed using the Chemotherapy Symptom Rating Scale FAACT + FACT-BRM. All assessment scales will be evaluated by previously trained researchers at the following timepoints (see Figure 2): baseline (T0), midpoint of main treatment (T1-T3) once every 2 weeks, and end of the 8-week main treatment (T4) (a total of 5 timepoints). We will also keep a record of all the shedding cases. This study is a multidisciplinary clinical trial (across oncology and Chinese medicine disciplines) on the role of Chinese acupuncture as therapy for chemotherapy-induced cognitive impairment in older patients with cancer. If successful, findings from this study might have benefits in reducing chemotherapy-induced working memory impairment. Data from this study may be used to support an implementation and dissemination trial of Chinese EA in real-world behavioral health and social service settings.

Questionnaires/Instruments

MoCA Self-Reported Questionnaire

The MoCA self-reported questionnaire is the main method used for assessing cognitive function. To objectively measure the cognitive impairment patterns of the participants, MoCA, a sensitive, time-sparing tool with high diagnostic validity, will be used to measure the degree of chemobrain. We evaluate the utility of MoCA as a chemobrain screening test for older patients with cancer who are undergoing or about to receive chemotherapy. Participants will be instructed to self-report their cognitive functions through MoCA for 5 consecutive timepoints from baseline to the end of the 8-week treatment. Statistical software will be used to analyze participants' cognitive function information recorded in case report forms.

FACT-Cog Questionnaire

FACT-Cog is a subjective measure of chemobrain. The FACT-Cog is a 37-item member of the FACIT suite of questionnaires, which is made up of 4 subscales: perceived cognitive impairments (18 items), perceived cognitive abilities (7 items), impact of perceived cognitive impairment on QoL (4 items), and comments from others on cognitive function (4 items) [24]. FACT-Cog is considered a reliable and valid patient report of chemotherapy-induced cognitive symptoms. Participants are required to report their responses in FACT-Cog just the same as MoCA.

FACT Instrument

FACT is a 37-item self-reported instrument devised to assess the multidimensional health-related QoL in patients with cancer. It consists of 5 subscales, namely, physical, social/family, emotional, functional well-being, and additional concerns for cancer. Each item is scored on a 0 to 4 scale, and the sum of all 5 subscales ranges from 0 to 144. A higher score indicates a better QoL [12].

FACIT-Fatigue Self-Report Questionnaire

The FACIT-Fatigue is a valid self-reported questionnaire for assessing anemia-related fatigue in patients with cancer. This 13-item questionnaire comprises concepts related to the severity and impact of fatigue over the last 7 days, including varied fatigue-related concepts across its 13 items, allowing for a nuanced assessment.

EORTC QLQ-C30 Questionnaire

The EORTC QLQ-C30 will be used as a self-reported questionnaire for interpreting group-level results in older patients with cancer. The current estimates can be used to better interpret the results of clinical trials in older patients with cancer using the EORTC QLQ-C30 questionnaire.

FAACT Self-Administered Questionnaire

The FAACT is a self-administered questionnaire developed to assess symptoms in patients with cancer with limited food intake and decreased QoL. For FAACT, a cutoff value of ≤24 has been advised to assess anorexia based on the fact that it is the half of the maximum score than can be obtained [31].

FACT-BRM Screening Tool

The FACT-BRM is a brief screening tool designed to assess the QoL in patients treated with BRMs. The FACT-BRM scale will be useful for measuring QoL in older patients with cancer who are receiving treatment with BRMs.

Safety Assessment

Except for the sensation of soreness, numbness, swelling, and heaviness, the EA intervention will not usually cause significant discomfort or serious adverse effects, but some participants may experience pain or subcutaneous ecchymosis. Patients who have acupuncture on an empty stomach are more likely to experience dizziness. Subcutaneous ecchymosis will disappear spontaneously if the participant's blood coagulation is normal. Patients will be reminded to avoid acupuncture on an empty stomach. The condition of each participant will be closely monitored, and if other symptoms or adverse effects occur, the investigator will ensure that the participant is receiving the appropriate treatment and is suitable to continue receiving EA. All participants in the clinical trial will be asked to evaluate the safety of the intervention, and any adverse events experienced during acupuncture treatment will be reported at each visit. The severity of adverse events will be assessed according to the Common Terminology Standard for Adverse Events v5.0 criteria [32], which are useful for determining the causal relationship between acupuncture and adverse reactions. Serious adverse events will be immediately reported to the project investigator and ethics committee. The investigator will also discuss the situation with the participant to plan any temporary discontinuation or withdrawal. The costs will be reimbursed by the investigator's organization.

Sample Size Estimation

A total of 168 older patients with cancer will be recruited, of which 84 will be in the experimental group (EA) and 84 will be in the control group. Sample size calculation:

$$n = [p1 (1 – p1) + p2 (1 – p2)]/(p1 – p2)] \times Cp.power$$

Cp refers to the process capability index. In the 2-sided test, Cp.power = 10.5 when $P<.05$ is met. n is the number of patients to be recruited in each group, p1 and p2 represent the incidence in each group, and a mean difference with 95% level of significance (α) and 80% power ($1 - \beta$) is set. In older patients with cancer, the incidence of chemobrain after chemotherapy is 30%, and the reduction of chemobrain could be 10%-20% with acupuncture intervention. The sample size for each group is 84 participants, considering a 20% dropout. Therefore, the overall target sample size of 168 will be included.

Statistical Analyses

Cognitive impairment is defined as those with SD>1.5 in the mean scores of MoCA and the QLQ-C30 at baseline for all participants at different timepoints. A time-series test in the Kaplan-Meier survival analysis will be used to compare the incidence of cognitive deficits accumulated after 8 weeks of acupuncture intervention between the 2 groups. Linear mixed-effects modeling will be used to compare participants' cognitive impairment, fatigue, and depression at baseline, during, and after acupuncture intervention, where only those who have completed at least one assessment at baseline and during treatment will be compared. This model will use time and group as categorical fixed factors and random intercepts and use random intercepts in conjunction with a measurement covariance matrix. Participants' age, chemotherapeutic drug dosage, fatigue at baseline, depression, and additional treatments will be considered as covariates in the statistical analyses. A 2-sided *t* test will be used to compare the covariates at each timepoint between the 2 groups. The chi-square test will be used for qualitative information and the *t* test will be used for continuous information at baseline. Statistical significance will be considered at $P<.05$. The study data used will be statistically analyzed using SPSS software (IBM Corp) under the supervision of a statistician. To ensure the privacy of the patients, all relevant study data and personal data will be kept in a locked file cabinet. Electronic data will be stored on an encrypted computer and will not be stored on any external storage device. Each participant will be assigned his or her own ID in the study record, which will be used in lieu of his or her name and personal identifying information. Clinical data from the study will be kept in a separate file from the participant's personal data. The principal investigator will be responsible for all the clinical trial data. During and after the clinical trial, the principal investigator, researchers, and the ethical review committee have the right to view the study data. Participants will have the right to access their personal data and the results of the study. All study data will be stored for a minimum of 3 years after the completion of the trial, after which they will be destroyed in accordance with the rules of the ethics review committee.

Results

This clinical trial was funded by the Jiangsu Health Vocational College and Nanjing First Hospital in January 2023. The ethics review committee approval was finalized in April 2023, and data collection began on September 1, 2023. Investigators have since been engaged in activities associated with study enrollment and data collection, including recruitment, screening, consenting, and enrolling participants; administering EA intervention; timepoint assessing; and monitoring adverse events and resolving problems early. As of October 21, 2023, 11 participants have been recruited into the clinical trial. A total of 168 older patients with cancer who are undergoing or are just about to commence chemotherapy will be enrolled in this clinical trial, and they will be randomly assigned into either the experimental group or the control group of 84 participants each. A total of 16 EA treatments (twice per week) will be administered to each participant for 8 weeks, and the participants will be assessed for cognitive performance, fatigue, and QoL. Concurrently, they will receive conventional chemotherapy. Improvement or even relief of chemobrain symptoms in older patients with cancer undergoing chemotherapy will be expected if the results of the EA intervention are satisfactory.

Discussion

Patients with cancer may have concerns of psychiatric and digestive symptoms while undergoing or just after having recently undergone chemotherapy [3]. The most common clinical manifestations are fatigue, nausea, vomiting, dry mouth, anxiety, depression, and insomnia. More seriously, cognitive impairments with a range of neurocognitive symptoms occur frequently, including visual and verbal memory impairment, forgetfulness, difficulty concentrating, learning difficulties, and organizational and coordination dysfunction [3,4]. Since the 1980s, researchers have been studying chemotherapy-induced cognitive impairment and have given several definitions to this condition, such as postchemotherapy cognitive impairment and chemotherapy-induced cognitive dysfunction. Recently, this condition was termed as chemobrain [3-5].

Chemobrain is a frequent side effect experienced by an increasing number of older patients with cancer, and it has significantly impacted their QoL [4]. Chemobrain can be described as cognitive symptoms reported by patients with cancer in self-reported questionnaires or as cognitive changes evaluated by formal neuropsychological tests [5]. Older patients with cancer will experience cognitive impairment due to chemoradiotherapy, which will lead to a series of neurocognitive symptoms called chemobrain. Older populations have been disproportionately affected by chemobrain and have heightened negative mental health outcomes after cytotoxic chemical drug therapy [3,5,7].

According to available literature [3,14], more than 75% of patients with cancer experience cognitive impairment while undergoing chemotherapy or just after completing chemotherapy, with 15%-30% of these patients experiencing persistent symptoms for up to decades. The prevalence of postchemotherapy cognitive impairment is as high as 50%-75% among older cancer survivors [33]. In some circumstances, the cognitive impairment can be lifelong, affecting the patient's mood, relationships, QoL, career, social activity, and family life. Considering the increasing incidence of cancer, chemobrain is quite complicated, increasingly important, and has far-reaching consequences. As the incidence of cancer survivors rises, the adverse effects of chemobrain will become more

frequent, thus necessitating the need to effectively prevent and treat chemobrain.

At present, there is no responsive therapy for chemobrain. The current clinical medications are not effective for chemobrain prevention and therapy. Study and research literatures [14,15] suggest that Chinese acupuncture might be effective for relieving various discomforts caused by anticancer drugs, such as pain, vomiting, fever, fatigue, dry mouth, anxiety, depression, and sleep disorders. Several studies [11,13-16,30] have shown the efficacy of EA intervention in various neurological diseases. Compared with acupuncture, EA has reported to produce a higher intensity of stimulation on acupoints and is progressively being widely used for its adjustable strength, frequency, and easy quantification in clinical practice [14]. In addition, EA can promote the rehabilitation of pathological microstructures in the brain and improve the cognitive function of patients with cognitive impairment [16].

Our study aims to explore the feasibility, efficacy, and safety of using EA by involving multiple disciplines (oncology and Chinese Medicine) to treat chemobrain in older patients with cancer. Acupuncture itself has been demonstrated as a safe and effective treatment, and EA is a widely accepted and cost-effective alternative therapy option with low adverse effects for older patients with cancer. The findings of this study will provide useful information on determining a suitable therapy for chemobrain in older patients with cancer. EA may be ready for implementation and dissemination in real-world cognitive function settings consistent with the objectives outlined in this clinical trial's strategic plan. Overall, this proposal has the potential to decrease neurocognitive symptoms among older patients with cancer—populations determined to be most at risk of exacerbated, long-lasting negative health sequelae. EA, if proven to be effective, can be implemented into routine settings to benefit older patients with cancer experiencing chemobrain. We believe that data from this efficacy trial will determine whether Chinese EA successfully alleviates the symptoms of chemobrain and whether these improvements could markedly reduce the various side effects due to cytotoxic chemical drugs.

In conclusion, the goal of this clinical trial is to target and reduce emerging and likely exacerbated cognitive impairments caused by chemotherapy among older patients with cancer. We aim to evaluate this novel Chinese medicine mode of EA in older patients with cancer by developing a therapeutic responsive treatment for chemobrain. By addressing neurocognitive symptoms through an EA intervention that targets underlying pathophysiological and psychological factors, we hope that this EA intervention will reduce the symptoms of chemobrain in older patients with cancer. If successful, findings from this study might have benefits in reducing chemotherapy-induced working memory impairment. Data from this study may be used to support an implementation and dissemination trial of Chinese EA within real-world behavioral health and social service settings.

Acknowledgments

The study is funded by the Jiangsu Provincial Health Commission of China on senile health (LKM2023026) grant to GL and is registered at Clinical Trials (ID: NCT05876988) by YG. This work is also partially supported by the Clinical Science and Technology Development Fund of Jiangsu University, China (JYL2021142) granted to MH.

Data Availability

The data sets generated and analyzed during this study will be available from the corresponding author on reasonable request following the completion of the trial and publication of the main outcomes paper. Deidentified data also will be made available via the Jiangsu Health Vocational College and Nanjing First Hospital.

Authors' Contributions

SZ, JZ, and HW contributed to data curation, formal analysis, investigation, writing the original draft, review, and editing. CT, MH, and WL contributed to conceptualization, data curation, formal analysis, investigation, and methodology. ZX contributed to data curation, formal analysis, writing the review, and editing. BX, JZ, and GW contributed to the electroacupuncture intervention, methodology, and investigation. PL contributed to project administration, writing the review, editing, and supervision. YG contributed to funding acquisition, project administration, writing the review, editing, and supervision. GL contributed to conceptualization, project administration, resources, supervision, writing the original draft, review, and editing. Correspondence may also be sent to Guangmei Lyu 939146961@qq.com and Ping Li Pingli1965@163.com.

Conflicts of Interest

None declared.

References

1. Luo Z, He Y, Ma G, Deng Y, Chen Y, Zhou Y, et al. Years of life lost due to premature death and their trends in people with malignant neoplasm of female genital organs in Shanghai, China during 1995-2018: a population based study. BMC Public Health 2020 Oct 01;20(1):1489 [FREE Full text] [doi: 10.1186/s12889-020-09593-6] [Medline: 33004024]

2. Sienkiewicz K, Burzyńska M, Rydlewska-Liszkowska I, Sienkiewicz J, Gaszyńska E. The importance of direct patient reporting of adverse drug reactions in the safety monitoring process. Int J Environ Res Public Health 2021 Dec 31;19(1):413 [FREE Full text] [doi: 10.3390/ijerph19010413] [Medline: 35010673]
3. Lv L, Mao S, Dong H, Hu P, Dong R. Pathogenesis, assessments, and management of chemotherapy-related cognitive impairment (CRCI): an updated literature review. J Oncol 2020;2020:3942439 [FREE Full text] [doi: 10.1155/2020/3942439] [Medline: 32684930]
4. Vega JN, Dumas J, Newhouse PA. Cognitive effects of chemotherapy and cancer-related treatments in older adults. Am J Geriatr Psychiatry 2017 Dec;25(12):1415-1426 [FREE Full text] [doi: 10.1016/j.jagp.2017.04.001] [Medline: 28495470]
5. Walczak P, Janowski M. Chemobrain as a product of growing success in chemotherapy - focus on glia as both a victim and a cure. Neuropsychiatry (London) 2019;9(1):2207-2216 [FREE Full text] [doi: 10.4172/Neuropsychiatry.1000565] [Medline: 31316584]
6. Was H, Borkowska A, Bagues A, Tu L, Liu JYH, Lu Z, et al. Mechanisms of chemotherapy-induced neurotoxicity. Front Pharmacol 2022;13:750507 [FREE Full text] [doi: 10.3389/fphar.2022.750507] [Medline: 35418856]
7. Piechotta V, Adams A, Haque M, Scheckel B, Kreuzberger N, Monsef I, et al. Antiemetics for adults for prevention of nausea and vomiting caused by moderately or highly emetogenic chemotherapy: a network meta-analysis. Cochrane Database Syst Rev 2021 Nov 16;11(11):CD012775 [FREE Full text] [doi: 10.1002/14651858.CD012775.pub2] [Medline: 34784425]
8. Sekeres MJ, Bradley-Garcia M, Martinez-Canabal A, Winocur G. Chemotherapy-induced cognitive impairment and hippocampal neurogenesis: a review of physiological mechanisms and interventions. Int J Mol Sci 2021 Nov 24;22(23):12697 [FREE Full text] [doi: 10.3390/ijms222312697] [Medline: 34884513]
9. Duan W, Zheng A, Mu X, Li M, Liu C, Huang W, et al. How great is the medical burden of disease on the aged? Research based on "System of Health Account 2011". Health Qual Life Outcomes 2017 Jul 03;15(1):134 [FREE Full text] [doi: 10.1186/s12955-017-0709-6] [Medline: 28673360]
10. Balasubramanian P, Kiss T, Tarantini S, Nyúl-Tóth Á, Ahire C, Yabluchanskiy A, et al. Obesity-induced cognitive impairment in older adults: a microvascular perspective. Am J Physiol Heart Circ Physiol 2021 Feb 01;320(2):H740-H761 [FREE Full text] [doi: 10.1152/ajpheart.00736.2020] [Medline: 33337961]
11. Ni X, Dong L, Tian T, Liu L, Li X, Li F, et al. Acupuncture versus various control treatments in the treatment of migraine: a review of randomized controlled trials from the past 10 years. J Pain Res 2020;13:2033-2064 [FREE Full text] [doi: 10.2147/JPR.S259390] [Medline: 32884332]
12. Zhang J, Yang M, So TH, Chang TY, Qin Z, Chen H, et al. Electroacupuncture plus auricular acupressure on chemotherapy-related insomnia in patients with breast cancer (EACRI): study protocol for a randomized, sham-controlled trial. Integr Cancer Ther 2021 Dec;20:15347354211058695 [FREE Full text] [doi: 10.1177/15347354211058695] [Medline: 34802291]
13. Jiang X, Tian Y, Xu L, Zhang Q, Wan Y, Qi X, et al. Inhibition of triple-negative breast cancer tumor growth by electroacupuncture with encircled needling and its mechanisms in a mice xenograft model. Int J Med Sci 2019;16(12):1642-1651 [FREE Full text] [doi: 10.7150/ijms.38521] [Medline: 31839752]
14. Lyu YR, Lee H, Park H, Kwon O, Kim A, Jung IC, et al. Electroacupuncture for cancer-related cognitive impairment: a clinical feasibility study. Integr Cancer Ther 2022;21:15347354221098983 [FREE Full text] [doi: 10.1177/15347354221098983] [Medline: 35608027]
15. Zhang ZJ, Man SC, Yam LL, Yiu CY, Leung RCY, Qin ZS, et al. Electroacupuncture trigeminal nerve stimulation plus body acupuncture for chemotherapy-induced cognitive impairment in breast cancer patients: An assessor-participant blinded, randomized controlled trial. Brain Behav Immun 2020 Aug;88:88-96. [doi: 10.1016/j.bbi.2020.04.035] [Medline: 32305573]
16. Chang QY, Lin YW, Hsieh CL. Acupuncture and neuroregeneration in ischemic stroke. Neural Regen Res 2018 Apr;13(4):573-583 [FREE Full text] [doi: 10.4103/1673-5374.230272] [Medline: 29722298]
17. Pirani A, Nasreddine Z, Neviani F, Fabbo A, Rocchi MB, Bertolotti M, et al. MoCA 7.1: Multicenter validation of the first Italian version of Montreal Cognitive Assessment. J Alzheimers Dis Rep 2022;6(1):509-520 [FREE Full text] [doi: 10.3233/ADR-210053] [Medline: 36186724]
18. On AK, Hwang K, Jang S, Lee H, Soh M, Yang C, et al. Detection of malingering using Wechsler Adult Intelligence Scale-IV for psychiatric patients. Psychiatry Investig 2020 Jun;17(6):526-532 [FREE Full text] [doi: 10.30773/pi.2019.0330] [Medline: 32450624]
19. Suica Z, Behrendt F, Gäumann S, Gerth U, Schmidt-Trucksäss A, Ettlin T, et al. Imagery ability assessments: a cross-disciplinary systematic review and quality evaluation of psychometric properties. BMC Med 2022 May 02;20(1):166 [FREE Full text] [doi: 10.1186/s12916-022-02295-3] [Medline: 35491422]
20. Hiller TS, Hoffmann S, Teismann T, Lukaschek K, Gensichen J. Psychometric evaluation and Rasch analyses of the German Overall Anxiety Severity and Impairment Scale (OASIS-D). Sci Rep 2023 Apr 26;13(1):6840 [FREE Full text] [doi: 10.1038/s41598-023-33355-0] [Medline: 37100805]
21. Health Quality Ontario. Psychotherapy for major depressive disorder and generalized anxiety disorder: a health technology assessment. Ont Health Technol Assess Ser 2017;17(15):1-167 [FREE Full text] [Medline: 29213344]

22. Bittel KM, O'Briant KY, Ragaglia RM, Buseth L, Murtha C, Yu J, et al. Associations between social cognitive determinants and movement-related behaviors in studies using ecological momentary assessment methods: systematic review. JMIR Mhealth Uhealth 2023 Apr 07;11:e44104 [FREE Full text] [doi: 10.2196/44104] [Medline: 37027185]
23. Wang S, Lin H, Cong W. Chinese medicines improve perimenopausal symptoms induced by surgery, chemoradiotherapy, or endocrine treatment for breast cancer. Front Pharmacol 2019;10:174 [FREE Full text] [doi: 10.3389/fphar.2019.00174] [Medline: 30930771]
24. Khan G, Mirza N, Waheed W. Developing guidelines for the translation and cultural adaptation of the Montreal Cognitive Assessment: scoping review and qualitative synthesis. BJPsych Open 2022 Jan 07;8(1):e21 [FREE Full text] [doi: 10.1192/bjo.2021.1067] [Medline: 34991771]
25. Bell ML, Dhillon HM, Bray VJ, Vardy JL. Important differences and meaningful changes for the Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog). J Patient Rep Outcomes 2018 Oct 12;2(1):48. [doi: 10.1186/s41687-018-0071-4]
26. Cai T, Chen J, Ni F, Zhu R, Wu F, Huang Q, et al. Psychometric properties of the Chinese version of the functional assessment of chronic illness therapy-fatigue (FACIT-F) among patients with breast cancer. Health Qual Life Outcomes 2023 Aug 15;21(1):91 [FREE Full text] [doi: 10.1186/s12955-023-02164-4] [Medline: 37582752]
27. Imran M, Al-Wassia R, Alkhayyat SS, Baig M, Al-Saati BA. Assessment of quality of life (QoL) in breast cancer patients by using EORTC QLQ-C30 and BR-23 questionnaires: A tertiary care center survey in the western region of Saudi Arabia. PLoS One 2019;14(7):e0219093 [FREE Full text] [doi: 10.1371/journal.pone.0219093] [Medline: 31291302]
28. Blauwhoff-Buskermolen S, Ruijgrok C, Ostelo RW, de Vet HCW, Verheul HMW, de van der Schueren MAE, et al. The assessment of anorexia in patients with cancer: cut-off values for the FAACT-A/CS and the VAS for appetite. Support Care Cancer 2016 Feb;24(2):661-666 [FREE Full text] [doi: 10.1007/s00520-015-2826-2] [Medline: 26160463]
29. MacPherson H, Altman DG, Hammerschlag R, Youping L, Taixiang W, White A, STRICTA Revision Group. Revised STandards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA): extending the CONSORT statement. PLoS Med 2010 Jun 08;7(6):e1000261 [FREE Full text] [doi: 10.1371/journal.pmed.1000261] [Medline: 20543992]
30. Zhang J, Qin Z, So TH, Chang TY, Yang S, Chen H, et al. Acupuncture for chemotherapy-associated insomnia in breast cancer patients: an assessor-participant blinded, randomized, sham-controlled trial. Breast Cancer Res 2023 Apr 26;25(1):49 [FREE Full text] [doi: 10.1186/s13058-023-01645-0] [Medline: 37101228]
31. Muscaritoli M, Anker S, Argilés J, Aversa Z, Bauer J, Biolo G, et al. Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics". Clin Nutr 2010 Apr;29(2):154-159. [doi: 10.1016/j.clnu.2009.12.004] [Medline: 20060626]
32. U.S. DOHS. Common terminology criteria for adverse events (CTCAE) v5. 0 Nov 2017:103. [doi: 10.1016/b978-0-12-373695-6.00022-3]
33. Országhová Z, Mego M, Chovanec M. Long-term cognitive dysfunction in cancer survivors. Front Mol Biosci 2021;8:770413 [FREE Full text] [doi: 10.3389/fmolb.2021.770413] [Medline: 34970595]

Abbreviations

EA: electroacupuncture
EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
FAACT: Functional Assessment of Anorexia-Cachexia Therapy
FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue
FACT: Functional Assessment of Cancer Therapy
FACT-BRM: Functional Assessment of Cancer Therapy-Biologic Response Modifier
FACT-Cog: Functional Assessment of Cancer Therapy-Cognitive function
MoCA: Montreal Cognitive Assessment
QoL: quality of life
STRICTA: Standards for Reporting Interventions in Clinical Trials of Acupuncture

Edited by A Mavragani; submitted 21.10.23; peer-reviewed by L Yongping, Z Chen, Y You; comments to author 02.01.24; revised version received 06.01.24; accepted 11.01.24; published 08.02.24.

Please cite as:
Zhao S, Zhang J, Wan H, Tao C, Hu M, Liang W, Xu Z, Xu B, Zhang J, Wang G, Li P, Lyu G, Gong Y
Role of Chinese Acupuncture in the Treatment for Chemotherapy-Induced Cognitive Impairment in Older Patients With Cancer: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2024;13:e53853
URL: https://www.researchprotocols.org/2024/1/e53853
doi:10.2196/53853
PMID:38329790

Protocol

Mobile Mindfulness Meditation for Cancer-Related Anxiety and Neuropathy: Protocol for a Randomized Controlled Trial

Ariel Siritorn Orasud[1], BSN; Mai Uchiyama[1†], MPH, MSW; Ian Pagano[1], PhD; Erin Bantum[1], PhD

Cancer Prevention in the Pacific, University of Hawai'i Cancer Center, Honolulu, HI, United States

[†]deceased

Corresponding Author:
Erin Bantum, PhD
Cancer Prevention in the Pacific
University of Hawai'i Cancer Center
701 Ilalo St, B4
Honolulu, HI, 96813
United States
Phone: 1 8083493621
Email: ebantum@cc.hawaii.edu

Abstract

Background: Anxiety- and cancer-related neuropathy are two persistent effects related to treatment for cancer. Mindfulness meditation has been used with substantial impact as a nonpharmacologic intervention to mitigate side and late effects of treatment. Mobile apps are ubiquitous for most of the general population, yet have a particular relevance for cancer survivors, given that physical and geographic limitations can be present.

Objective: This study aims to describe an ongoing trial of the Mindfulness Coach mobile app for cancer survivors.

Methods: In this randomized waitlist controlled trial, cancer survivors experiencing anxiety- or cancer-related neuropathy (200 for neuropathy and 200 for anxiety) and who had finished primary cancer treatment were invited to participate. Data were collected at 3 time points regardless of randomization condition: baseline, 8 weeks, and 16 weeks. Both face-to-face and web-based recruitment strategies were used. The trial was opened for 2 separate primary outcomes (anxiety- or cancer-related neuropathy). The goal was not to compare these groups but to compare treatment and waitlist groups for each condition. In addition to evaluating the impact of mobile mindfulness on reported anxiety- or cancer-related neuropathy, other pain, fatigue, trauma, sleep, and satisfaction with the Mindfulness Coach app will also be assessed.

Results: Outcomes of the study are expected in early 2024.

Conclusions: Mindfulness meditation has become widely practiced, and the use of mobile technology has become ubiquitous. Finding ways to deliver mindfulness meditation to people who have been treated for cancer allows for the intervention to be accessible to a larger number of survivors. The results of this intervention could have implications for further understanding the impact of mindfulness meditation on 2 persistent side and late effects of treatment of cancer, namely anxiety- and cancer-related neuropathy.

Trial Registration: ClinicalTrials.gov NCT03581357; https://ClinicalTrials.gov/study/NCT03581357

International Registered Report Identifier (IRRID): DERR1-10.2196/47745

(JMIR Res Protoc 2024;13:e47745) doi:10.2196/47745

KEYWORDS

cancer; cancer survivorship; mindfulness meditation; mHealth; well-being; quality of life; mobile health; coaching; coach; mindfulness; meditation; survivor; survivorship; oncology; mental health; anxiety; neuropathy; survivors; RCT; randomized; clinical trial; clinical trials

Introduction

Background

The latest report from the American Cancer Society estimates that there are 16.9 million cancer survivors in the United States [1]. A diagnosis of cancer or recurrence of cancer can cause psychological distress, including symptoms of anxiety and depression [2]. For patients receiving treatment for cancer, 10.3% meet the clinical criteria for an anxiety disorder [3], compared with 7% of those in the general population [4]. The prevalence of anxiety disorders is reported to be even higher for those who have been living with cancer for more than 2 years, with 17.9% of survivors meeting diagnostic criteria for anxiety [5]. As cancer treatments have become more effective than in previous decades, there are more cancer survivors living longer with cancer [6], yet also living with side and late effects of treatment.

Anxiety can manifest in both physical and psychological symptoms that negatively impact quality of life and are associated with a substantially increased risk of cancer incidence and cancer-specific mortality [7]. Psychological distress can affect a number of cancer outcomes, including quality of life, adherence to treatment, health behaviors, and potentially disease progression and survival, as well as increased use of health care resources [2].

Neuropathy is another common symptom of either cancer treatment or, less frequently, cancer itself and can be acute or chronic in nature [6]. There are a wide range of ways in which patients describe this experience, although peripheral neuropathy is often described as the sensation of shooting or stabbing pain and tingling or loss of feeling in the affected areas. This can impact many activities, such as walking, balance, and mood [6]. In patients receiving neurotoxic chemotherapy, such as platinum drugs, taxanes, vinca alkaloids, proteasome inhibitors, and immunomodulatory drugs, approximately 30%-40% of patients will develop chemotherapy-induced peripheral neuropathy (CIPN) [8]. CIPN is a common cause of pain and decreased quality of life for patients with cancer undergoing treatment as well as cancer survivors [9]. In approximately 50% of people who experience CIPN, this condition will become chronic [10].

Mindfulness and Mindfulness Meditation

Historically conceptualized in Buddhist spiritual practice with the purpose of cultivating compassion and alleviating suffering, mindfulness meditation has been practiced for thousands of years [11,12]. Mindfulness can be described as bringing nonjudgmental attention or awareness to one's moment-to-moment experience [12]. Mindfulness meditation is the setting aside of time to specifically engage in what is often a seated meditation practice where participants are instructed to close their eyes and are guided through a breathing and focused attention process [13].

The practice of mindfulness with the goal of improving well-being has been described as a universal human capacity that does not involve a particular cultural or religious belief system [11,12]. In recent decades, mindfulness has gained popularity in the United States and has been found to have numerous psychological and physical benefits, with a growing body of research on clinical applications of mindfulness to treat various conditions [2,11,14-20]. Mindfulness has been studied as a therapy to reduce symptoms of depression and anxiety [2], improve outcomes for chronic pain [14], reduce stress and improve attention [15], improve brain function and connectivity [16], and improve immune function [17].

The practice of mindfulness has been shown to improve quality of life and be related to more positive mental health in cancer survivors [18]. Recent studies indicate that mindfulness-based interventions have a positive impact on depression, anxiety, and quality of life in patients with ovarian cancer [2], men living with cancer [19], and patients with metastatic non–small cell lung cancer and their caregivers [20], to name just a few.

Web-Based Behavioral Therapy for Anxiety- and Cancer-Related Neuropathy

While mindfulness is gaining a larger evidence base for applications in the clinical setting, lack of trained personnel, time constraints, reimbursement issues, and patient and provider availability are barriers to delivery and participation in a traditional, face-to-face mindfulness course [21]. Researchers in a recent face-to-face mindfulness-based stress reduction (MBSR) intervention for young adult cancer survivors identified barriers to participation reported by eligible patients who declined to participate in the intervention [22]. Out of the 446 eligible people who declined to participate, the majority reported distance to the intervention site as the main factor (41.5%), followed by time constraints (21.7%). A subset of individuals who declined were asked if they would participate in the course if it were offered in a different location or format. Of those asked, 73.8% stated that they would enroll in an MBSR course offered closer to their home, and 70.8% stated that they would enroll in a online MBSR course. Of the individuals who stated interest in a online MBSR course, 70.9% stated that they would enroll in a self-directed course delivered through educational modules [22]. These barriers to face-to-face mindfulness interventions limit access to care and therefore make face-to-face interventions less likely to be a realistic treatment model [21], but online interventions for mindfulness provide a potential avenue to overcome these barriers and increase accessibility to effective mindfulness interventions.

Advances in technology have allowed for the delivery of effective interventions in the patient's home through a mobile app [23]. When used to effectively disseminate evidence-based interventions, apps have the potential to increase access to evidence-based health care and the use of evidence-based practices by the general population [21,23]. Previous studies have shown that mindfulness-based interventions via the web involving guided meditation audios are feasible and acceptable for cancer survivors [24], who may be too ill or lack the resources to travel to a face-to-face mindfulness intervention. A recent study using the Calm mobile app for mindfulness meditation found that the use of the app for 10 minutes daily for 4 weeks was substantially effective in reducing symptoms of depression and anxiety in patients with myeloproliferative

neoplasm but did not substantially impact sleep disturbance [25].

The current American Society of Clinical Oncology clinical practice guideline does not recommend any pharmacologic agents in preventing CIPN, and there is limited evidence for the treatment of existing CIPN with pharmacologic agents, with a moderate recommendation for the use of duloxetine [26]. Previous studies suggest that online interventions may have the potential to improve conditions involving chronic pain. A study involving an online, self-guided cognitive- and behaviorally-based pain management intervention for cancer survivors experiencing CIPN had substantially greater improvements in "worst pain" compared with individuals receiving usual care [27].

Mindfulness Coach, an iOS- and Android-based mobile app, is designed to deliver a mobile mindfulness training course designed by researchers from the US Department of Veterans Affairs [21,28]. The senior author of this paper, ER, was part of the team that developed the most recent version of the app. Initially developed among other mobile apps in collaboration with the US Department of Defense [28], Mindfulness Coach is freely available to the general public for both iOS and Android operating systems. A recent study exploring the effects of the app among the general population found that use of the Mindfulness Coach app was feasible, and increased use was strongly correlated with an increase in scores measuring mindfulness characteristics including observing, describing, acting with awareness, nonreactivity to inner experience, and nonjudging of inner experience, as measured by the Five-Facet Mindfulness Questionnaire Short Form (FFMQ-SF) [21,29]. Although mobile health is increasingly being used in research and clinical settings, a recent systematic review and meta-analysis concluded that there is still inconclusive evidence due to small nonsubstantial effects of interventions, as well as concerns regarding study quality [30].

Given the persistent effects of diagnosis and treatment and the limitations of in-person offerings in most places, the Mobile Mindfulness Study was conducted to test the impact on anxiety- and cancer-related neuropathy after 8 weeks of use of the Mindfulness Coach mobile app. The study contains the following secondary aims: evaluate the impact of mobile mindfulness on general pain, fatigue, trauma, and sleep, in addition to evaluating the satisfaction with the Mindfulness Coach mobile app. The goal of this paper is to describe the study design.

Methods

Study Design

The study is being conducted with a randomized waitlist control design, such that participants were randomized through Qualtrics to either begin the intervention immediately or after 8 weeks. In addition, participants were invited to participate with the goal of impacting anxiety- or cancer-related neuropathy as a primary outcome (additional discussion on this below). The goal was to have 200 people complete the 8-week survey measures in each group. Funding was originally garnered to examine anxiety as a primary outcome, with additional seed funding received through the University of Hawai'i Cancer Center to test the same design for cancer-related neuropathy. These groups will not be compared with each other, rather, each treatment group (anxiety- and cancer-related neuropathy, respectively) will be compared with each waitlist control group (anxiety- and cancer-related neuropathy).

Procedure

Recruitment

Recruitment closed for the study in July 2023. The University of Hawai'i (UH) Cancer Center is recognized by the National Cancer Institute as one of their designated cancer centers. The Hawai'i Cancer Consortium, to which all major medical centers on Oahu belong, is led by the UH Cancer Center. Recruitment efforts took place in oncology clinics, via the web, and through organized community events [31]. These included local medical centers and clinical offices, public events (eg, senior fair), and cancer organizations, such as the American Cancer Society and Stupid Cancer, via social media and newsletter unpaid advertisements.

Participants

Cancer survivors experiencing anxiety- or cancer-related neuropathy who had finished primary treatment for cancer were invited to participate in the study. They were first screened and then consented via Qualtrics, where all data were collected, as well. Inclusion criteria were the same for both groups, aside from the different scales used to measure levels of anxiety or neuropathy. Inclusion criteria for both groups include a previous diagnosis of cancer, other than nonmelanoma skin cancer; completion of primary treatment for cancer; not currently practicing meditation for more than 1 hour per week; age older than 21 years; comfortable reading and writing in English; routine access to the internet; and own a smartphone or tablet. There are no exclusion criteria.

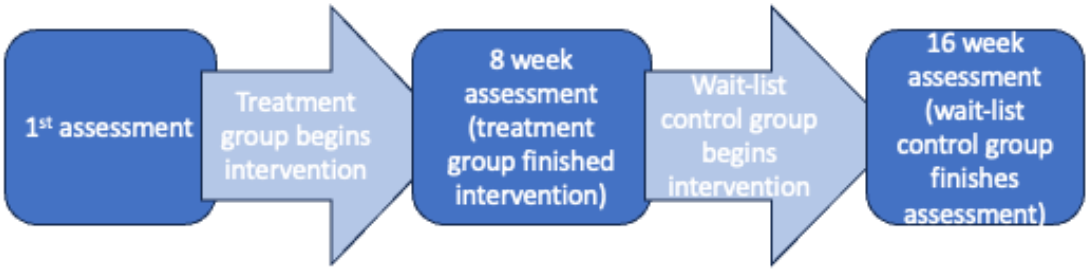
For the anxiety group, participants needed to be experiencing cancer-related anxiety, per self-report, as indicated by a score of 22 or higher on the PROMIS (Patient Reported Outcomes Measurement Information System) anxiety short form measure [32]. For the neuropathy group, participants needed to be experiencing CIPN, per self-report, as indicated by a score of 22 points or higher on the Functional Assessment of Cancer Therapy-Cognitive subscale (FACT-GOG-Ntx) CIPN items [33]. The study was powered to examine differences between groups with 200 people in each group (200 total for anxiety, 200 total for neuropathy).

Baseline and Follow-Up Assessments

Figure 1 summarizes the overall timeline for baseline and follow-up data collection. For both the anxiety and neuropathy groups, data on demographics and medical history were collected at baseline. Baseline data collected included cancer status and treatment, past medical conditions, gender, ethnicity, and previous experience with mindfulness. For both the anxiety and neuropathy groups, all 3 surveys include questions about the quality of life (physical well-being, social or family well-being, emotional well-being, and functional well-being),

anxiety (symptoms of anxiety and whether help was needed due to anxiety symptoms), fatigue (severity of fatigue and the impact of fatigue on daily functioning), pain (sensory, affective or emotional impact, and cognitive evaluation of pain), and mood (anxiety). The anxiety group received additional assessment questions: depression, mindfulness, and posttraumatic stress disorder (PTSD). The neuropathy group received questions about neuropathy: severity and impact of CIPN. Specific measures are listed below for each group.

Figure 1. Timeline for baseline and follow-up data collection.



Anxiety Group

Potential participants were screened with the PROMIS anxiety short form measure, an 8-item measure assessing anxiety on a Likert-type scale, with options ranging from "never" to "always" [32]. Pain is measured with the Pain Intensity Enjoyment of Life General Activity Scale, a 3-item measure assessing pain intensity, interference with general activity, and interference with enjoyment of life, with response options ranging from a 0-10 scale, with 0 being "no pain" or "does not interfere" and 10 being "pain as bad as you can imagine" or "completely interferes" [34]. Sleep-related impairment is measured using the PROMIS sleep-related impairment short form, an 8-item measure assessing sleep disturbance and sleep-related impairment [35]. Fatigue is measured with the brief fatigue inventory, a 9-item measure to rate fatigue on a 0-10 scale, with 0 being "no fatigue" or "does not interfere" and 10 being "as bad as you can imagine" or "completely interferes" [36]. Anxiety is measured with the General Anxiety Disorder 7-item measure of anxiety on a 5-point Likert-type scale [37]. Depression is measured with the Patient Health Questionnaire-9, a 9-item measure using 4 response options to assess depressive symptoms and behaviors [38]. PTSD is measured using the PTSD Checklist for DSM-5, a 20-item measure that assesses the 20 *Diagnostic and Statistical Manual of Mental Disorder* symptoms of PTSD [39]. Mindfulness is measured with the FFMQ, a 39-item measure of the 5 facets of mindfulness (observing, describing, acting with awareness, nonjudging of inner experience, and nonreactivity to inner experience), with answer options on a 1-5 scale ranging from "never or rarely true" to "very often or always true" [29]. For the follow-up assessments, the demographic questions are removed. A question regarding how much they have been practicing mindfulness (all groups), and a question about satisfaction with the intervention (for the intervention groups) are added.

Neuropathy Group

Potential participants were screened with the 11-item CIPN measure included in the FACT-GOG-Ntx [33]. The Functional Assessment of Cancer Therapy (FACT) scale is a well-validated quality of life measure with 27 items measuring physical, social or family, emotional, and functional well-being, with the FACT-GOC-Ntx scale including 11 additional items to measure the severity and impact of CIPN [33]. The 11-item FACT-GOG-Ntx data serves as both a screening tool and a baseline measure of CIPN. The rest of the FACT items (27 questions) are included in the baseline questionnaire, with the total measure being included at the 8- and 16-week assessment time points. At each assessment time point, participants are asked about any additional support services (such as support groups or clinical trials that they have been enrolled in, including anything they have done to treat CIPN. In order to assess anxiety, the 8-item PROMIS anxiety short form measure is used [32]. Fatigue is measured using the brief fatigue inventory [36]. The short-form McGill Pain Questionnaire (MPQ) is used as a brief measure of pain [40]. The original MPQ is a self-report questionnaire, consisting of 3 major classes of word descriptors of pain: sensory, affective or emotional impact, and cognitive evaluation of pain. The short-form MPQ was developed to provide an instrument that could be completed in less time than the MPQ but would still reflect both the sensory and affective dimensions of pain and has been shown to have high correlations with the original MPQ [40]. For the follow-up assessments, the demographic questions are removed. For the follow-up assessments, a question regarding how much they have been practicing mindfulness (all groups), and a question about satisfaction with the intervention (for the intervention groups) are added.

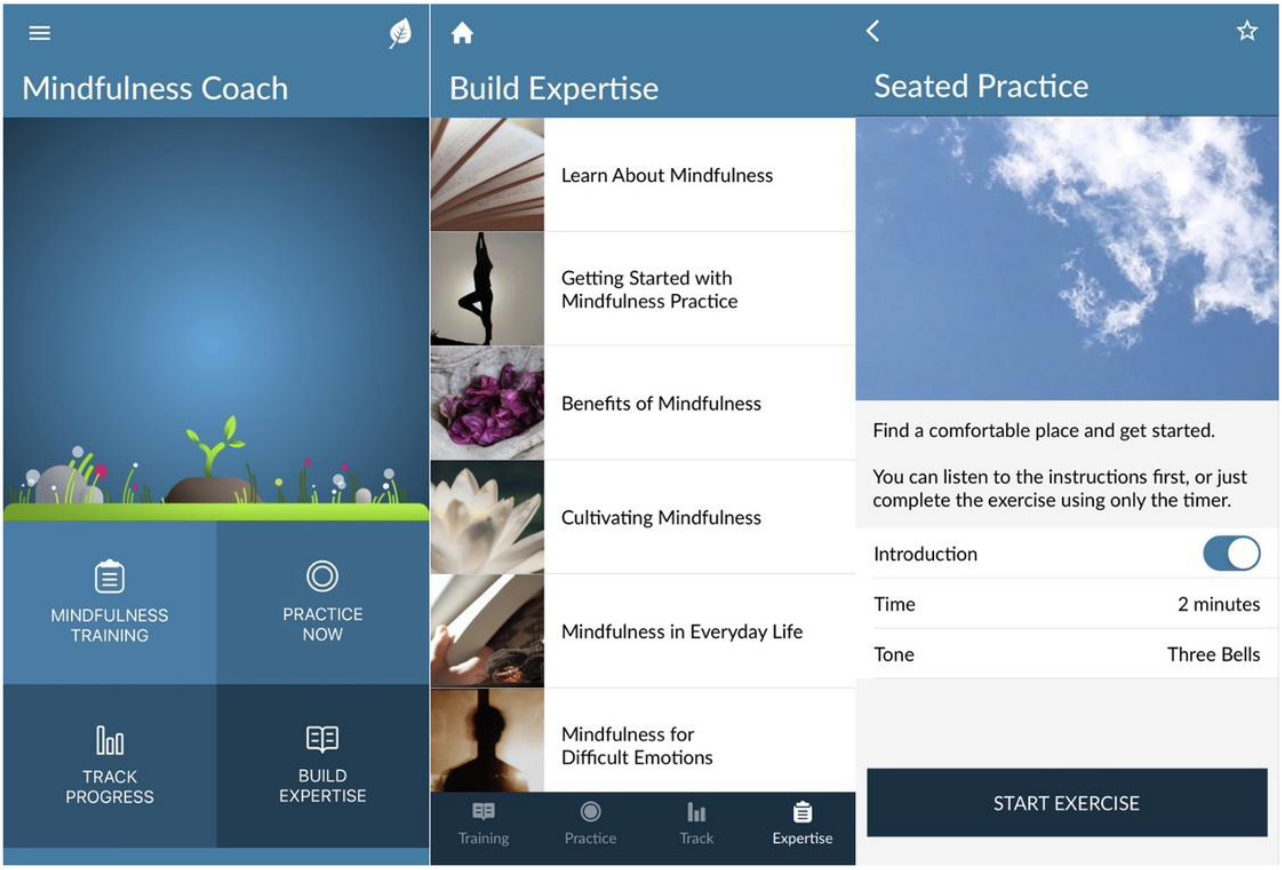
Intervention

Mindfulness Coach provides simple written instructions and a brief tutorial that introduces the major features, including a training plan, practice exercises, learning topics, and tracking via the app. Mindfulness exercises are delivered via brief, guided audio mindfulness exercises. This information has been arranged in such an order that it is helpful to have learned the material prior to any given session, although not necessary. The core meditation centers around the seated mindfulness practice, and as the sessions go on, users are asked to sit for longer periods of time, building physical and mental capabilities for meditation. Through this process, participants are instructed to bring nonjudgmental awareness to what they are experiencing in a basic sensorial way (eg, what they are feeling on their skin, hearing in the environment, and experiencing inside their body in regard to physical or emotional sensations or thoughts), with a primary aspect of this involving paying attention to and

deepening one's breathing. The app delivers 14 sessions (levels) that each include a prerecorded guided audio meditation exercise. The app also provides a mindfulness self-assessment tool through the FFMQ-SF [29], which users are reminded, but not required, to complete at levels 1, 7, and 14. Assessment feedback "quick tips" are provided based on the results of the FFMQ-SF.

The intervention includes 8 weeks of Mindfulness Coach. (see Figure 2 for examples of features included in Mindfulness Coach). This practice is encouraged daily through the app and participants are asked to build the amount of time they are spending daily. There are many other audio recordings that are placed throughout the sessions, including meditations around scanning the body for sensations, awareness, and processing of difficult emotions, eating mindfully, and loving kindness. Participants are asked to use Mindfulness Coach for 8 weeks, either immediately (treatment group) or 8 weeks after the baseline assessment (waitlist control group).

Figure 2. Screenshots of the Mindfulness Coach mobile app.



Ethical Considerations

The study was approved by the Western Internal Review Board (20131065). Informed consent was obtained from all participants included in the study. Study data were collected in Qualtrics and only relevant study personnel have access to the data. Participants receive a US $20 gift card after completing each of the 3 surveys, with a total incentive of US $60 for completing all 3 surveys. Reminder emails are sent to participants by a member of the study team.

Results

Overview

We will conduct the primary evaluation of the intervention, comparing changes in multiple outcomes between the treatment and waitlist control groups. Participants were randomized using a simple, open-label (nonblinded) randomization procedure. The intervention was individually guided and conducted electronically. We will follow an intent-to-treat approach, in which individuals are analyzed based on their randomization groups, regardless of adherence. Adherence effects will be examined in a subsequent analysis.

To account for repeated measures, we will run a mixed (both between- and within-subjects variables) linear or logistic model for each outcome. The independent variables are the randomization group (treatment vs waitlist control), time (baseline, 8 weeks, or 16 weeks), and the group by time interaction. The interaction term tests the intervention effect. For all analyses, the assumptions of the models will be checked and remedial measures (eg, transformations and nonparametric tests) will be taken as needed. Logistic models will assess dichotomous outcomes and linear models will assess continuous outcomes. Potential confounders (adherence, age, sex, and race or ethnicity) will be included. Where possible we will run the analyses within subgroups defined by these covariates, providing information on whether the intervention was more effective in certain groups (moderator effects). If there is evidence of nonrandom missing data, such as by differential dropout between groups, we will apply multiple imputation procedures. SAS

(version 9.4; SAS Institute Inc) will be used to perform all analyses.

Data collection began in 2019 and was completed in 2023. We had very differential rates of recruitment for the differing arms with reaching near the target for the anxiety arm yet not for the cancer related neuropathy arm. This, along with other outcomes of the study will be reported in a separate manuscript.

Power

Assuming a Bonferroni corrected (for 10 outcome measures) 2-tailed type I error rate (α) equal to .005 (0.05/10), 80% power, and 200 participants per group (400 total), a standardized difference (Cohen *d* effect size) of 0.37 will be detectable. Cohen *d* is the standardized difference and can be converted to the original units by multiplying the SD of the original variable.

Discussion

We hope that this study will result in findings that are useful to improving the well-being of cancer survivors experiencing anxiety- and cancer-related neuropathy. If the study shows improvement in symptoms of anxiety or neuropathy in cancer survivors, it will allow for greater accessibility to mindfulness meditation via Mindfulness Coach, which is free, publicly available, and easily accessible through a mobile app. This will allow patients with cancer to access guided mindfulness meditation exercises in the comfort of their own homes and on their own time. This can be helpful for patients who may be too ill, lack resources, or live in a rural area where accessing a face-to-face mindfulness meditation intervention would be difficult or impossible. Results of the study may also be useful for clinicians working alongside patients with cancer or survivors searching for evidence-based, nonpharmacologic interventions to improve anxiety or neuropathy, with mindfulness meditation used alone or along with pharmacologic interventions.

Nonpharmacologic interventions, including exercise, yoga, and mindfulness meditation, have been studied for the treatment of psychological disorders, including anxiety, as a monotherapy or adjunctive therapy [41]. Current evidence supports the use of mindfulness meditation as an adjunctive therapy for people with an anxiety disorder, as there is limited evidence for mindfulness being used as a monotherapy for anxiety [41]. The general health benefits and low risk for harm justify the use of mindfulness as adjunctive therapy for patients with anxiety disorders and other mental health conditions such as depression [41]. At the current time, pharmacologic interventions for neuropathy are not highly effective and are not well tolerated by many patients due to various side effects [42,43]. First-line drugs used to treat neuropathy include antidepressants and anticonvulsants acting at voltage-gated calcium channels, which can have side effects including risk for cardiotoxicity, orthostatic hypotension, dry mouth, nausea, and confusion, among others [43]. In a randomized controlled trial involving 402 patients with neuropathy, 4 drugs commonly used for neuropathy of different drug classes (pregabalin, duloxetine, nortriptyline, and mexiletine) were tested for tolerance and treatment of neuropathic pain. The results of the study found that none of the drugs tested was clearly superior in performance or highly effective for treating neuropathic pain [42]. If results from this study show potential for mindfulness to be used as an alternative intervention to treat neuropathy, a larger number of people, including cancer survivors affected by CIPN, can access effective treatment without the side effects associated with medications commonly used to treat neuropathy.

Mobile apps have large dissemination potential and identifying apps that are found to be related to outcomes of interest is important given the ubiquitous nature of apps. Without identifying apps that are effective, apps that are available yet not effective can easily be reached. Findings from the currently described study will be published as soon as available.

Acknowledgments

The authors would like to thank all of the participants who have consented and participated in this study. The authors would also like to thank everyone who has helped inform potential participants of the study and would like to thank Dr Jami Fukui, Celine Arnobit, and Dr Jason Owen for their help with the study, as well. A special thank you to Dr. Thanh Huynh who was instrumental in the creation of the original design of the study. The study is funded by a donation to the University of Hawai'i (UH) Cancer Center from the Women's Veterans Fund and through seed funding through a Strategic Investment in Translational Science from the UH Cancer Center. The first author is supported in part by a grant from the National Cancer Institute (R25 CA244073), an endowment from the Meiji Yasuda Life Insurance Company, donations from The Friends of the UH Cancer Center, and support from the UH Cancer Center.

Data Availability

The data sets generated or analyzed during this study are not publicly available because it is ongoing. Findings from the currently described study will be published as soon as available.

Authors' Contributions

EB created the design for the study and wrote the proposal to receive funding for the project. ASO and EB conducted the literature review and wrote the main manuscript text. MU edited the manuscript. IP has provided statistical guidance and run power calculations and any relevant statistics for these studies. All authors are team members involved in the research study and reviewed the manuscript.

Conflicts of Interest

None declared.

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin 2022;72(1):7-33 [FREE Full text] [doi: 10.3322/caac.21708] [Medline: 35020204]
2. Arden-Close E, Mitchell F, Davies G, Bell L, Fogg C, Tarrant R, et al. Mindfulness-based interventions in recurrent ovarian cancer: a mixed-methods feasibility study. Integr Cancer Ther 2020;19:1534735420908341 [FREE Full text] [doi: 10.1177/1534735420908341] [Medline: 32174190]
3. Curran L, Sharpe L, Butow P. Anxiety in the context of cancer: a systematic review and development of an integrated model. Clin Psychol Rev 2017;56:40-54 [FREE Full text] [doi: 10.1016/j.cpr.2017.06.003] [Medline: 28686905]
4. Pitman A, Suleman S, Hyde N, Hodgkiss A. Depression and anxiety in patients with cancer. BMJ 2018;361:k1415 [FREE Full text] [doi: 10.1136/bmj.k1415] [Medline: 29695476]
5. Mitchell AJ, Chan M, Bhatti H, Halton M, Grassi L, Johansen C, et al. Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: a meta-analysis of 94 interview-based studies. Lancet Oncol 2011;12(2):160-174 [FREE Full text] [doi: 10.1016/S1470-2045(11)70002-X] [Medline: 21251875]
6. Fallon MT. Neuropathic pain in cancer. Br J Anaesth 2013;111(1):105-111 [FREE Full text] [doi: 10.1093/bja/aet208] [Medline: 23794652]
7. Wang YH, Li JQ, Shi JF, Que JY, Liu JJ, Lappin JM, et al. Depression and anxiety in relation to cancer incidence and mortality: a systematic review and meta-analysis of cohort studies. Mol Psychiatry 2020;25(7):1487-1499 [FREE Full text] [doi: 10.1038/s41380-019-0595-x] [Medline: 31745237]
8. Staff NP, Grisold A, Grisold W, Windebank AJ. Chemotherapy-induced peripheral neuropathy: a current review. Ann Neurol 2017;81(6):772-781 [FREE Full text] [doi: 10.1002/ana.24951] [Medline: 28486769]
9. Gordon-Williams R, Farquhar-Smith P. Recent advances in understanding chemotherapy-induced peripheral neuropathy. F1000Res 2020;9:F1000 [FREE Full text] [doi: 10.12688/f1000research.21625.1] [Medline: 32201575]
10. Seretny M, Currie GL, Sena ES, Ramnarine S, Grant R, MacLeod MR, et al. Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: a systematic review and meta-analysis. Pain 2014;155(12):2461-2470 [FREE Full text] [doi: 10.1016/j.pain.2014.09.020] [Medline: 25261162]
11. Ludwig DS, Kabat-Zinn J. Mindfulness in medicine. JAMA 2008;300(11):1350-1352. [doi: 10.1001/jama.300.11.1350] [Medline: 18799450]
12. Keng SL, Smoski MJ, Robins CJ. Effects of mindfulness on psychological health: a review of empirical studies. Clin Psychol Rev 2011;31(6):1041-1056 [FREE Full text] [doi: 10.1016/j.cpr.2011.04.006] [Medline: 21802619]
13. Bishop SR, Lau M, Shapiro S, Carlson L, Anderson ND, Carmody J, et al. Mindfulness: A proposed operational definition. Clin Psychol 2004;11(3):230-241. [doi: 10.1093/clipsy.bph077]
14. Chiesa A, Serretti A. Mindfulness-based interventions for chronic pain: a systematic review of the evidence. J Altern Complement Med 2011;17(1):83-93 [FREE Full text] [doi: 10.1089/acm.2009.0546] [Medline: 21265650]
15. Anderson ND, Lau MA, Segal ZV, Bishop SR. Mindfulness ‐ based stress reduction and attentional control. Clin Psychology and Psychoth 2007;14(6):449-463 [FREE Full text] [doi: 10.1002/cpp.544]
16. Kilpatrick LA, Suyenobu BY, Smith SR, Bueller JA, Goodman T, Creswell JD, et al. Impact of mindfulness-based stress reduction training on intrinsic brain connectivity. Neuroimage 2011;56(1):290-298 [FREE Full text] [doi: 10.1016/j.neuroimage.2011.02.034] [Medline: 21334442]
17. Davidson RJ, Kabat-Zinn J, Schumacher J, Rosenkranz M, Muller D, Santorelli SF, et al. Alterations in brain and immune function produced by mindfulness meditation. Psychosom Med 2003;65(4):564-570 [FREE Full text] [doi: 10.1097/01.psy.0000077505.67574.e3] [Medline: 12883106]
18. Speca M, Carlson LE, Goodey E, Angen M. A randomized, wait-list controlled clinical trial: the effect of a mindfulness meditation-based stress reduction program on mood and symptoms of stress in cancer outpatients. Psychosom Med 2000;62(5):613-622 [FREE Full text] [doi: 10.1097/00006842-200009000-00004] [Medline: 11020090]
19. Ford CG, Vowles KE, Smith BW, Kinney AY. Mindfulness and meditative movement interventions for men living with cancer: a meta-analysis. Ann Behav Med 2020;54(5):360-373 [FREE Full text] [doi: 10.1093/abm/kaz053] [Medline: 31773148]
20. Milbury K, Li Y, Durrani S, Liao Z, Tsao AS, Carmack C, et al. A mindfulness-based intervention as a supportive care strategy for patients with metastatic non-small cell lung cancer and their spouses: results of a three-arm pilot randomized controlled trial. Oncologist 2020;25(11):e1794-e1802 [FREE Full text] [doi: 10.1634/theoncologist.2020-0125] [Medline: 32621630]
21. Kozlov E, Bantum E, Pagano I, Walser R, Ramsey K, Taylor K, et al. The reach, use, and impact of a free mHealth mindfulness app in the general population: mobile data analysis. JMIR Ment Health 2020;7(11):e23377 [FREE Full text] [doi: 10.2196/23377] [Medline: 33245289]

22. Victorson D, Murphy K, Benedict C, Horowitz B, Maletich C, Cordero E, et al. A randomized pilot study of mindfulness-based stress reduction in a young adult cancer sample: feasibility, acceptability, and changes in patient reported outcomes. Psychooncology 2020;29(5):841-850 [FREE Full text] [doi: 10.1002/pon.5355] [Medline: 32040222]
23. Price M, Yuen EK, Goetter EM, Herbert JD, Forman EM, Acierno R, et al. mHealth: a mechanism to deliver more accessible, more effective mental health care. Clin Psychol Psychother 2014;21(5):427-436 [FREE Full text] [doi: 10.1002/cpp.1855] [Medline: 23918764]
24. Price-Blackshear MA, Pratscher SD, Oyler DL, Armer JM, Cheng AL, Cheng MX, et al. Online couples mindfulness-based intervention for young breast cancer survivors and their partners: a randomized-control trial. J Psychosoc Oncol 2020;38(5):592-611 [FREE Full text] [doi: 10.1080/07347332.2020.1778150] [Medline: 32552446]
25. Puzia ME, Huberty J, Eckert R, Larkey L, Mesa R. Associations between global mental health and response to an app-based meditation intervention in myeloproliferative neoplasm patients. Integr Cancer Ther 2020;19:1534735420927780 [FREE Full text] [doi: 10.1177/1534735420927780] [Medline: 32564631]
26. Loprinzi CL, Lacchetti C, Bleeker J, Cavaletti G, Chauhan C, Hertz DL, et al. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: ASCO guideline update. J Clin Oncol 2020;38(28):3325-3348 [FREE Full text] [doi: 10.1200/JCO.20.01399] [Medline: 32663120]
27. Knoerl R, Smith EML, Barton DL, Williams DA, Holden JE, Krauss JC, et al. Self-guided online cognitive behavioral strategies for chemotherapy-induced peripheral neuropathy: a multicenter, pilot, randomized, wait-list controlled trial. J Pain 2018;19(4):382-394 [FREE Full text] [doi: 10.1016/j.jpain.2017.11.009] [Medline: 29229430]
28. Owen JE, Kuhn E, Jaworski BK, McGee-Vincent P, Juhasz K, Hoffman JE, et al. VA mobile apps for PTSD and related problems: public health resources for veterans and those who care for them. Mhealth 2018;4:28 [FREE Full text] [doi: 10.21037/mhealth.2018.05.07] [Medline: 30148141]
29. Baer RA, Smith GT, Hopkins J, Krietemeyer J, Toney L. Using self-report assessment methods to explore facets of mindfulness. Assessment 2006;13(1):27-45 [FREE Full text] [doi: 10.1177/1073191105283504] [Medline: 16443717]
30. Lu J, Chen XM, Xie KH. Effectiveness of nursing interventions on the sexual quality of life of patients with breast cancer: a systematic review and meta-analysis. PLoS One 2022;17(11):e0277221 [FREE Full text] [doi: 10.1371/journal.pone.0277221] [Medline: 36327334]
31. Arnobit CI, Loo K, Pagano I, Uchiyama M, Fukui J, Braun-Inglis C, et al. Recruiting cancer survivors to a mobile mindfulness intervention in the United States: exploring online and face-to-face recruitment strategies. Int J Environ Res Public Health 2021;18(19):10136 [FREE Full text] [doi: 10.3390/ijerph181910136] [Medline: 34639439]
32. Pilkonis PA, Choi SW, Reise SP, Stover AM, Riley WT, Cella D, PROMIS Cooperative Group. Item banks for measuring emotional distress from the Patient-Reported Outcomes Measurement Information System (PROMIS®): depression, anxiety, and anger. Assessment 2011;18(3):263-283 [FREE Full text] [doi: 10.1177/1073191111411667] [Medline: 21697139]
33. Calhoun EA, Welshman EE, Chang CH, Lurain JR, Fishman DA, Hunt TL, et al. Psychometric evaluation of the functional assessment of cancer therapy/gynecologic oncology group-neurotoxicity (Fact/GOG-Ntx) questionnaire for patients receiving systemic chemotherapy. Int J Gynecol Cancer 2003;13(6):741-748. [doi: 10.1111/j.1525-1438.2003.13603.x] [Medline: 14675309]
34. Krebs EE, Lorenz KA, Bair MJ, Damush TM, Wu J, Sutherland JM, et al. Development and initial validation of the PEG, a three-item scale assessing pain intensity and interference. J Gen Intern Med 2009;24(6):733-738 [FREE Full text] [doi: 10.1007/s11606-009-0981-1] [Medline: 19418100]
35. Yu L, Buysse DJ, Germain A, Moul DE, Stover A, Dodds NE, et al. Development of short forms from the PROMIS™ sleep disturbance and sleep-related impairment item banks. Behav Sleep Med 2011;10(1):6-24 [FREE Full text] [doi: 10.1080/15402002.2012.636266] [Medline: 22250775]
36. Mendoza TR, Wang XS, Cleeland CS, Morrissey M, Johnson BA, Wendt JK, et al. The rapid assessment of fatigue severity in cancer patients: use of the brief fatigue inventory. Cancer 1999;85(5):1186-1196 [FREE Full text] [doi: 10.1002/(sici)1097-0142(19990301)85:5<1186::aid-cncr24>3.0.co;2-n] [Medline: 10091805]
37. Esser P, Hartung TJ, Friedrich M, Johansen C, Wittchen HU, Faller H, et al. The Generalized Anxiety Disorder Screener (GAD-7) and the anxiety module of the Hospital and Depression Scale (HADS-A) as screening tools for generalized anxiety disorder among cancer patients. Psychooncology 2018;27(6):1509-1516 [FREE Full text] [doi: 10.1002/pon.4681] [Medline: 29473255]
38. Randall JM, Voth R, Burnett E, Bazhenova L, Bardwell WA. Clinic-based depression screening in lung cancer patients using the PHQ-2 and PHQ-9 depression questionnaires: a pilot study. Support Care Cancer 2013;21(5):1503-1507 [FREE Full text] [doi: 10.1007/s00520-012-1712-4] [Medline: 23325092]
39. Blevins CA, Weathers FW, Davis MT, Witte TK, Domino JL. The posttraumatic stress disorder checklist for DSM-5 (PCL-5): development and initial psychometric evaluation. J Trauma Stress 2015;28(6):489-498 [FREE Full text] [doi: 10.1002/jts.22059] [Medline: 26606250]
40. Melzack R. The short-form McGill pain questionnaire. Pain 1987;30(2):191-197. [doi: 10.1016/0304-3959(87)91074-8] [Medline: 3670870]
41. Saeed SA, Cunningham K, Bloch RM. Depression and anxiety disorders: benefits of exercise, yoga, and meditation. Am Fam Physician 2019;99(10):620-627 [FREE Full text] [Medline: 31083878]

42. Barohn RJ, Gajewski B, Pasnoor M, Brown A, Herbelin LL, Kimminau KS, et al. Patient Assisted Intervention for Neuropathy: Comparison of Treatment in Real Life Situations (PAIN-CONTRoLS): bayesian adaptive comparative effectiveness randomized trial. JAMA Neurol 2021;78(1):68-76 [FREE Full text] [doi: 10.1001/jamaneurol.2020.2590] [Medline: 32809014]
43. Fornasari D. Pharmacotherapy for neuropathic pain: a review. Pain Ther 2017;6(Suppl 1):25-33 [FREE Full text] [doi: 10.1007/s40122-017-0091-4] [Medline: 29178034]

Abbreviations

CIPN: chemotherapy-induced peripheral neuropathy
FACT: Functional Assessment of Cancer Therapy
FACT-GOG-Ntx: Functional Assessment of Cancer Therapy-Cognitive subscale
FFMQ-SF: Five-Facet Mindfulness Questionnaire Short Form
MBSR: mindfulness-based stress reduction
MPQ: McGill Pain Questionnaire
PROMIS: Patient Reported Outcomes Measurement Information System
PTSD: posttraumatic stress disorder
UH: University of Hawai'i

Edited by A Mavragani; submitted 14.04.23; peer-reviewed by C Baxter, N Badaghi; comments to author 08.10.23; revised version received 20.11.23; accepted 14.12.23; published 12.02.24.

Please cite as:
Orasud AS, Uchiyama M, Pagano I, Bantum E
Mobile Mindfulness Meditation for Cancer-Related Anxiety and Neuropathy: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2024;13:e47745
URL: https://www.researchprotocols.org/2024/1/e47745
doi:10.2196/47745
PMID:38345843

Protocol

Supporting Life Adjustment in Patients With Lung Cancer Through a Comprehensive Care Program: Protocol for a Controlled Before-and-After Trial

Wonyoung Jung[1,2*], MD, PhD; Alice Ahn[3,4*], BS; Genehee Lee[3], PhD; Sunga Kong[3,5], PhD; Danbee Kang[3,5,6], PhD; Dongok Lee[3], RN, APN, MSN; Tae Eun Kim[3], RN; Young Mog Shim[7], MD, PhD; Hong Kwan Kim[7], MD, PhD; Jongho Cho[7], MD, PhD; Juhee Cho[3,5*], PhD; Dong Wook Shin[1,5], MBA, MD, DrPH

[1]Department of Family Medicine and Supportive Care Center, Samsung Medical Center, Sungkyunkwan University, Seoul, Republic of Korea

[2]Department of Medicine, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

[3]Patient-Centered Outcomes Research Institute, Samsung Medical Center, Seoul, Republic of Korea

[4]Department of Psychology and Philosophy, Sam Houston State University, Huntsville, TX, United States

[5]Department of Clinical Research Design and Evaluation, Samsung Advanced Institute for Health Science & Technology, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

[6]Center for Clinical Epidemiology, Samsung Medical Center, Seoul, Republic of Korea

[7]Department of Thoracic and Cardiovascular Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

[*]these authors contributed equally

Corresponding Author:
Dong Wook Shin, MBA, MD, DrPH
Department of Family Medicine and Supportive Care Center
Samsung Medical Center
Sungkyunkwan University
81 Irwon-ro, Gangnam-gu
Seoul, 06351
Republic of Korea
Phone: 82 2 3410 5252
Email: dwshin.md@gmail.com

Abstract

Background: Lung cancer diagnosis affects an individual's quality of life as well as physical and emotional functioning. Information on survivorship care tends to be introduced at the end of treatment, but early intervention may affect posttreatment adjustment. However, to the best of our knowledge, no study has explored the effect of early information intervention on the return to work, family, and societal roles of lung cancer survivors.

Objective: We report the study protocol of a comprehensive care prehabilitation intervention designed to facilitate lung cancer survivors' psychological adjustment after treatment.

Methods: A comprehensive care program was developed based on a literature review and a qualitative study of patients with lung cancer and health professionals. The Lung Cancer Comprehensive Care Program consists of educational videos and follow-up visits by a family medicine physician. To prevent contamination, the control group received routine education, whereas the intervention group received routine care and intervention. Both groups completed questionnaires before surgery (T0) and at 1-month (T1), 6-month (T2), and 1-year (T3) follow-up visits after surgery. The primary outcome was survivors' psychological adjustment to cancer 6 months after pulmonary resection.

Results: The historical control group (n=441) was recruited from September 8, 2021, to April 20, 2022, and the intervention group (n=350) was recruited from April 22, 2022, to October 17, 2022. All statistical analyses will be performed upon completion of the study.

Conclusions: This study examined the effectiveness of an intervention that provided general and tailored informational support to lung cancer survivors, ranging from before to the end of treatment.

Trial Registration: ClinicalTrials.gov NCT05078918; https://clinicaltrials.gov/ct2/show/NCT05078918

International Registered Report Identifier (IRRID): DERR1-10.2196/54707

(JMIR Res Protoc 2024;13:e54707) doi:10.2196/54707

KEYWORDS

comprehensive care; early intervention; adjustment to cancer; return to work; lung cancer; unmet needs; lung; lungs; pulmonary; respiratory; cancer; oncology; prehabilitation; survivor; survivors; survivorship; education; educational

Introduction

Lung cancer remains the leading cause of cancer-related mortality worldwide and is prevalent in Korea [1,2]. However, advancements in screening and treatment have notably improved lung cancer outcomes. For example, the 5-year conditional recurrence-free survival rate of patients with surgically resected non–small cell lung cancer (NSCLC) in Korea increased from 51.5% to 68.5% in those diagnosed in the 1990s and the 2010s, respectively [3]. Consequently, the growing number of lung cancer survivors underscores the urgent need to address posttreatment needs.

Surviving lung cancer can substantially impact the quality of life and emotional health [4-6]. Many survivors adjust over time; however, persistent fear and the expectation of a rapid return to normal posttreatment life are common [7,8]. While initial postdiagnosis support is robust, survivors often encounter a new spectrum of concerns as they transition to life after cancer, including managing lingering symptoms and comorbidities that can affect overall well-being [8-10]. The commonly reported symptoms among lung cancer survivors include fatigue, pain, dyspnea, and impaired pulmonary function [11-13]. They also experience psychological distress and a fear of cancer recurrence [14,15]. Studies have shown that interventions focusing on physical rehabilitation and psychological adaptations can be effective for cancer survivors [16,17]. These interventions address both the physical and emotional challenges faced during the recovery process.

Despite the abundant information and support available after diagnosis, survivors later find themselves having a different set of questions and concerns related to life after cancer [18]. Our prior qualitative study of patients with lung cancer revealed the need for information on the expected trajectories after treatment. The patients expressed a desire for guidance in managing symptoms, stress, exercise, and nutrition to ease their “new normal” lives [19]. Recently, the importance of integrating oncological and supportive care has been increasing [20], as early interventions designed to provide supportive care for patients with cancer are in demand. Based on the findings of our qualitative interview, we hypothesized that an intervention introduced in the early stages of lung cancer treatment can help survivors return to their new normal lives.

Recognizing the critical need for early supportive interventions, we developed the Lung Cancer Comprehensive Care Program (LC^3P). This program aims to support patients from diagnosis through their adjustment to posttreatment life, encompassing their return to work, family, and societal roles. This study aimed to evaluate the effectiveness of LC^3P in enhancing psychological adjustment to cancer, with the hypothesis that participants receiving the intervention would demonstrate improved adjustment 6 months after surgery.

Methods

Study Setting

We designed a controlled before-and-after trial at the Samsung Comprehensive Cancer Center of the Samsung Medical Center (SMC), a university-affiliated hospital in Seoul, Republic of Korea, to evaluate the impact of LC^3P compared to routine care. This design was selected to minimize the risk of information contamination between the control and intervention groups. This risk is particularly pertinent to educational interventions, in which the exchange of information between participants can confound outcomes.

Eligibility Criteria

The inclusion criteria for the study are (1) age 18 years or older at enrollment, (2) diagnosis of stage I, II, or III NSCLC, and (3) a plan to undergo pulmonary resection. Patients with (1) recurrent lung cancer, (2) multiple sites of primary cancer, and (3) a history of other cancers or those who had received active cancer treatment within the past 3 years were excluded. Participants who canceled their pulmonary resection, received a confirmed diagnosis of stage IV lung cancer, or wished to withdraw from the study were excluded. All participants will be required to provide written informed consent before undergoing baseline assessment.

Intervention

Developing the Intervention

The LC^3P was developed following an extensive literature review [17,21,22], qualitative interviews [19], and cross-sectional studies [15]. These studies aimed to define the informational necessities and challenges faced by lung cancer survivors during their treatment journey. We discovered that the survivors adjusted their postcancer lives by reconciling their expectations with reality [19]. Physical symptoms, psychological challenges, and concerns regarding exercise and nutrition were also examined. Therefore, our intervention delivered timely and stage-specific information from the onset of treatment, primarily through educational videos. This format was selected due to its accessibility, patient friendliness, and potential to alleviate the workload of clinicians.

Content of the Intervention

The LC^3P is a 2-part intervention. The first part of the program comprised 7 educational videos, 4 of which were designed to meet the specific needs of lung cancer survivors. The first video provided general information regarding lung cancer, treatment

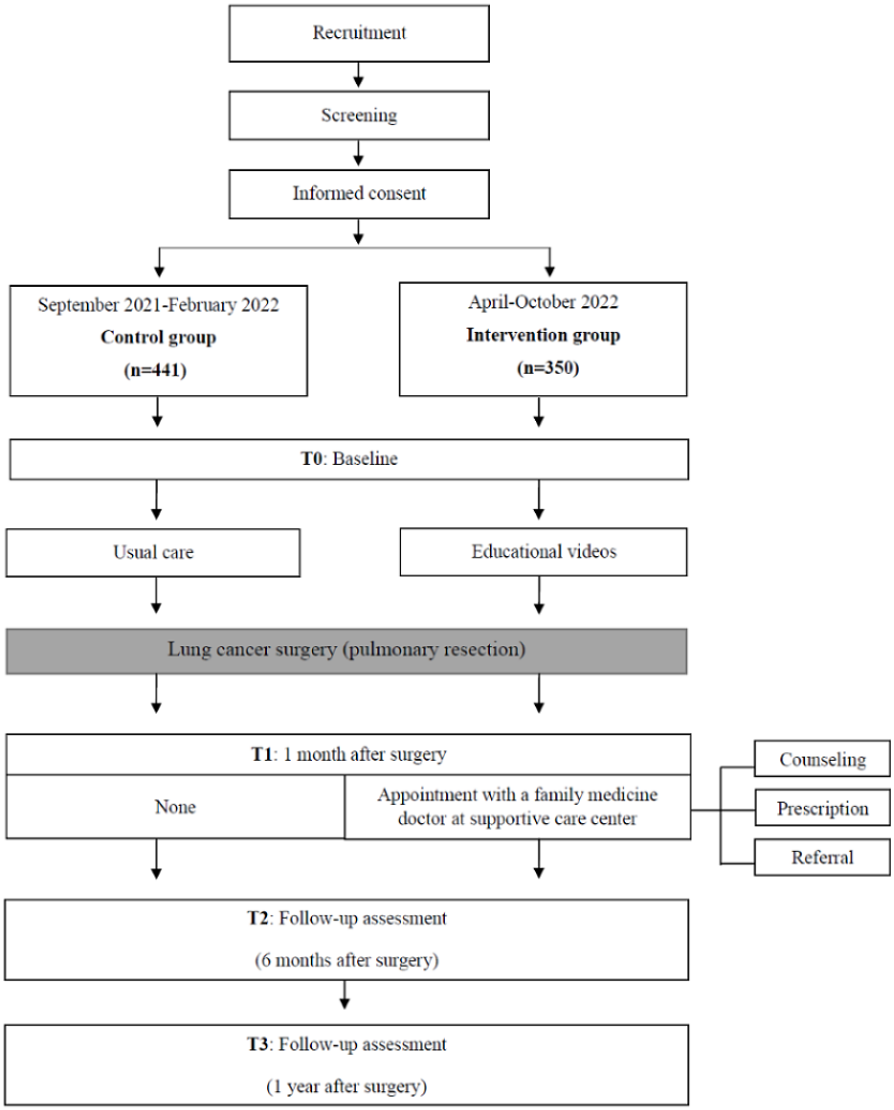
options, and postsurgery challenges such as pain, emphasizing the importance of smoking cessation and exercise. The second video covered postoperative recovery, addressed symptoms such as reduced lung function and fatigue and offered management strategies. The third video was an exercise tutorial for patients, and the fourth video offered nutritional guidance through a sample meal plan. The latter 3 videos provided general information regarding distress management, return to work [23], and fear of cancer recurrence. The second part of the program was the first postsurgical follow-up with a family medicine physician who assessed the patient's unique needs using a study-specific checklist (Figure S1 in Multimedia Appendix 1). This visit focused on personalized care through counseling, medication management, and referrals to specialists as needed.

Delivery of the Intervention

Eligible participants received a brochure containing QR codes linked to educational videos (Figure S2 in Multimedia Appendix 1). We added QR codes for all the videos in a brochure and gave it to participants before surgery so they could preview the videos if they were curious about what to expect and what to work on after surgery. Participants were strongly encouraged to view the first video before surgery. The link to the first video was sent via SMS text message at the time of enrollment to increase patient accessibility. Around the time of discharge, a research assistant visited the intervention group participants to offer them a second copy of the brochure and sent links to each of the 3 videos, reminding them to watch the videos at their convenience. Data on compliance, satisfaction, and feedback on the educational videos were collected during follow-up visits. Measures were taken until the survivors reported watching all 4 videos or at their 1-year follow-up visit.

During the first follow-up visit after discharge, participants in the intervention group were scheduled to visit a family medicine doctor in addition to regular oncology appointments. During their appointment, the participants discussed any physical or psychological difficulties they had experienced after surgery, and the family medicine doctor provided tailored assistance based on the type and depth of their needs. As our intervention was educational, the participants in the intervention group were qualified to receive other concomitant care or additional necessary measures during the study. A flowchart of the study procedure and intervention is shown in Figure 1.

Figure 1. Flowchart of the Lung Cancer Comprehensive Care Program.



Control Group

Participants in the control group received routine preoperative and discharge information regarding hospital stay, costs, and postoperative care. They did not have access to educational programs or postoperative educational support.

Outcomes

Primary Outcome Measures

The primary outcome of the study was psychological adjustment for cancer, measured 6 months after pulmonary resection. The Korean version of the Mini-Mental Adjustment to Cancer (Mini-MAC) was used to assess survivors' psychological adjustments to cancer. The Mini-MAC is a 29-item scale scored on a 4-point Likert scale (1=definitely does not apply to me and 4=definitely applies to me) previously validated in Korea [24,25]. The Korean-validated scale consists of the following 4 dimensions: helpless-hopeless (8 items), anxious preoccupation (8 items), cognitive avoidance (4 items), and positive attitude (9 items). The positive attitude dimension contained items identical to those of fighting spirit and fatality from the original Mini-MAC. The total score is the sum of all dimension scores, with higher scores indicating a stronger use of coping strategies. Permission to use the Mini-MAC was obtained from the International Psycho-Oncology Society on May 19, 2021.

Secondary Outcome Measures

The secondary outcomes were unmet informational needs, quality of life, distress, and symptoms. Unmet informational needs were assessed using the information needs scale (3 items) from the Korean version of the Cancer Survivors' Unmet Needs scale [26,27]. Health-related quality of life is measured using the Korean version of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire—Core 30 [28]. Distress was assessed using the National Comprehensive Cancer Network Guidelines for Distress Management (version 2.2021) [29]. The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire—Lung Cancer 13 [30], the Chronic Obstructive Pulmonary Disease Assessment Test [31,32], and the modified Medical Research Council dyspnea scale [33] are used to assess the presence and severity of symptoms related to lung cancer.

The Korean version of the International Physical Activity Questionnaire-Short Form is used to identify participants' levels of physical activity [34]. Depending on the level of activity derived from the questionnaire, patients were categorized into high, moderate, or low groups. The Hospital Anxiety and Depression Scale is a measure of depressive mood [35]. The components of each intervention and the hypothesized effects on the primary and secondary outcomes are shown in Figure S3 in Multimedia Appendix 1.

Sociodemographic variables such as age, sex, and level of education were acquired directly from the participants via self-reported questionnaires. Clinical characteristics, such as cancer stage, type of treatment, and postsurgical complications, were obtained from electronic medical records.

Sample Size Calculation

Based on the primary hypothesis that the intervention group would demonstrate a 25% better psychological adjustment to cancer at 6 months after surgery than the control group, initial calculations with an effect size of 0.25 indicated that 252 participants per group would be required. We aimed for a sample size of approximately 300 per group to account for a dropout rate of 16%. However, to increase the robustness of our findings, allow for potential subgroup analyses, and ensure that the study had sufficient power to detect smaller effect sizes, we enrolled 400 participants per group. The sample size significantly exceeded the required number based on our initial estimates, thereby enhancing the statistical power and potential impact on the study's outcomes.

Recruitment

Patients scheduled for pulmonary resection were recruited as controls to prevent contamination. The recruitment and study period for the control group were completed before the start of the intervention to ensure no overlap. Subsequently, recruitment to the intervention group began.

Data Collection

The clinical trial procedure and intervention are outlined in Figure 1, with the outcomes assessed at baseline (T0), 1 month (T1), 6 months (T2), and 1 year (T3) postoperatively. Baseline data will be collected before surgery and immediately after enrollment. To enhance participant retention and adherence, individuals in both groups received a small token of appreciation upon completion of each of the 3 postoperative follow-up assessments (T1-T3). For participants who discontinued or deviated from the intervention protocols, the data collected up to the point of departure were included in the intention-to-treat analysis to maintain the robustness of the trial results and minimize the impact of attrition bias. The data obtained from self-administered questionnaires were coded and stored in password-encrypted Microsoft Excel (Microsoft Corp) files on a secure computer server. The specific variables measured at each time point are listed in Figure 2.

Figure 2. Schedule of enrollment, intervention, allocation, and assessments. CaSUN-Info: Cancer Survivors' Unmet Needs Measure—Information domain; CAT: Chronic Obstructive Pulmonary Disease Assessment Test; EORTC QLQ C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire—Core 30; EORTC QLQ LC13: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire—Lung Cancer 13; HADS: Hospital Anxiety and Depression Scale; IPAQ-7: International Physical Activity Questionnaire-Short Form; Mini-MAC: Mini-Mental Adjustment to Cancer; mMRC: Modified Medical Research Council; T0 is baseline (before surgery); T1 is 1 month after surgery; T2 is 6 months after surgery; T3 is 1 year after surgery. *Primary outcome.

		Study period		
	Enrollment or allocation	Postallocation		Closeout
Time point	T0	T1	T2	T3
Enrollment	O			
Eligibility screen	O			
Informed consent	O			
Allocation	O			
Interventions				
Educational videos	←	→		
Appointment with a family medicine doctor		O		
Outcomes				
Mini-MAC	O	—	O*	O
CaSUN-Info	O	O	O	O
EORTC QLQ C30	O	O	O	O
EORTC QLQ LC13	O	O	O	O
HADS	O	—	O	O
mMRC	O	O	O	O
CAT	O	O	O	O
Distress thermometer and problem list	O	O	O	O
IPAQ-7	O	O	O	O
Smoking and alcohol consumption	O	—	O	O
Sociodemographic characteristics	O	—	—	—
Clinical characteristics	O	—	—	—
Compliance and satisfaction (videos)		O	O	O

Data Monitoring

Although the intervention primarily comprised educational videos and consultations with a family medicine physician, the associated risk to the participants was anticipated to be minimal. Accordingly, the establishment of a formal data-monitoring committee was considered unnecessary. However, procedures for monitoring adverse events and their unintended effects remain in place. The research team regularly reviewed participants' feedback and outcomes to identify potential concerns. Should any adverse events or unintended consequences arise, they will be addressed promptly, with details reported to the overseeing institutional review board (IRB) at the SMC, as per the standard protocol.

Statistical Analysis

To assess the effectiveness of LC^{3}P, we compared the outcomes between the intervention and control groups at multiple time points. The primary analyses involved independent sample 2-tailed *t* tests for continuous variables and chi-square tests for categorical variables to compare baseline characteristics and outcomes between the 2 groups at each follow-up. To account for repeated measures within participants over time and potential within-subject correlations, a mixed-model repeated-measures analysis was used.

In addition to primary analyses, sensitivity analyses probed the robustness of the trial findings under different assumptions regarding missing data and the effects of protocol adherence on treatment outcomes. This included intention-to-treat and per-protocol analyses. Moreover, subgroup analyses were conducted to examine the variability in treatment effects across different patient characteristics such as age, cancer stage, and the presence of comorbid conditions. All tests were 2-tailed, with a significance level of $P<.05$. To address multiple testing concerns, particularly with numerous secondary outcomes, we used Bonferroni correction or other suitable adjustments to preserve the overall type I error rate. All statistical analyses were conducted using STATA/MP (version 16.0; StataCorp).

Ethical Considerations

This study was approved by the IRB of the SMC (SMC 2021-08-071). If any critical amendments, including but not limited to the eligibility criteria, outcomes, and analyses, become necessary in the future, modifications to the protocol will be shared with all relevant parties, including all investigators, the IRB committee, and the trial registry. A trained research assistant initiated contact with potential participants after screening for eligibility. Written informed consent forms were obtained after the purpose, procedure, and potential harm of participating in the study were explained. Informed consent was obtained from each patient before enrollment in the study. Personal data such as sociodemographic information, clinical characteristics, and outcomes measured at each visit were coded with a unique study identification number in password-encrypted Microsoft Excel files stored on a secure computer server to prevent unauthorized access. Hard copies of the questionnaire were retained for a decade after the completion of the study. Both the primary investigator and coinvestigators had access to the final data set without any contractual regulations.

Results

The historical control group (n=441) was recruited from September 8, 2021, to April 20, 2022, and the intervention group (n=350) was recruited from April 22, 2022, to October 17, 2022. All statistical analyses will be performed upon completion of the study.

As part of a nationally funded study, the results and details of the procedures will be made publicly available upon completion. The findings of this study will be actively shared through publications in peer-reviewed academic journals and at national and international scientific conferences. Regarding the intervention, the content and access to the educational videos will be refined based on the feedback patients provide on their first follow-up visit and will be made available on YouTube and to other health care professionals within the same health care institution, including oncologists and oncology nurses. The full protocol for this study is currently available at the ClinicalTrials.gov (NCT05078918). The raw data for this study will be shared upon request.

Discussion

Principal Findings

In this controlled before-and-after trial, the effectiveness of LC^3P in enhancing psychological adjustment to lung cancer treatment was examined. The LC^3P distinguishes itself by offering informational and personalized support from the initial phases of treatment.

Comparison to Prior Work

Lung cancer is often diagnosed during screening examinations or in the absence of a symptomatic presentation, resulting in a broad spectrum of patient effects upon diagnosis. Unlike previous interventions that typically introduced posttreatment survivorship care, our approach provided support from the outset. The median time for lung cancer survivors to engage in OncoLife and the LIVESTRONG Care Plans, 2 web-based programs providing survivorship care plans, was 1 year after treatment [11]. Similar trends in delivering survivorship care plans at the end of treatment have been reported, with the earliest delivery being within a year [36]. While providing survivorship care at the end of treatment allows survivors to process information relevant to their cancer continuum, some findings suggest that patients want to receive survivorship care plans during earlier stages of treatment [37]. The early engagement of the LC^3P aligns with emerging preferences for immediate survivorship care, as evidenced by patients expressing a desire to receive such information at earlier stages of their treatment trajectory.

In addition to early education, the intervention included general and tailored support. The educational videos offered to patients prior to treatment consisted of general information about the disease and survivorship care and were therefore applicable to all patients with NSCLC who are at stage I to III and who are planning to undergo lung resection. The second half of the intervention is personalized for each patient, as patients discuss their individual needs with their primary care physicians to determine the appropriate intervention to address their concerns. By taking a holistic approach to addressing patients' general and individual concerns about their disease, we expect lung cancer survivors to have a better understanding of their disease and to better adjust by recognizing and accepting the differences between their lives before and after cancer. In addition, the relative simplicity of LC^3P allows for its easy dissemination in routine care. Translating empirical evidence into clinical practice is difficult for several reasons including feasibility and pragmatism [38]. The educational videos that are part of our intervention are available on a web-based, easily accessible platform (eg, YouTube), allowing patients to obtain the information they need at their convenience. Displaying a booklet of QR codes linked to educational videos in outpatient clinics or inpatient wards is another viable option that does not interfere with the primary responsibilities of health care professionals. Furthermore, primary care and family medicine physicians commonly manage the long-term care of cancer survivors [39,40]. Given these considerations, we believe integrating the LC^3P into the routine care of patients with cancer will have fewer barriers.

Limitations

Despite these advantages, this study has some limitations that must be addressed. First, the design of the intervention might be more appealing to participants who are actively seeking ways to adapt to life after cancer, as opposed to those who are less motivated or indifferent about making such adjustments. In addition, although the use of a historical comparison group was intended to minimize the impact of exposure to our intervention in patients with lung cancer, the limitations of using a nonparallel comparison group should not be ignored. Second, socioeconomic and geographic disparities among older patients with cancer could affect accessibility to web-based educational videos. Although disseminating educational videos through web-based platforms allows cancer survivors to access as much information as they need at their convenience, it can be difficult

for survivors with limited access to technology to access this information. If found to be promising, future studies should address the disparities in accessing web-based educational videos. Finally, the trial was registered after the recruitment commenced. However, there were no changes in the study design, measurement, or analysis methods after receiving the initial ethics approval.

In conclusion, the LC^{3}P represents a proactive, holistic prehabilitation intervention aimed at supporting lung cancer survivors, as they navigate the transition to life after treatment. Our findings highlight the impact of early informational support on patients' psychological adaptation and postdiagnosis stress management. This could potentially establish a new standard for the timing and delivery of survivorship care, emphasizing the benefits of early intervention.

Acknowledgments

This research was partially supported by grants from the National Research Foundation of Korea (NRF) funded by the Republic of Korea (grants MSIT-2019R1A2C2009751 and NRF-2020R1F1A1075388).

Data Availability

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

Authors' Contributions

DWS and Juhee Cho supervised the study as cocorresponding authors. All authors contributed to the study conception and design. The first draft of the paper was written by WJ and AA, and all authors commented on previous versions of the paper. GL, SK, DL, and TEK contributed to material preparation and data collection. DK, YMS, HKK, and Jongho Cho contributed to resources. All authors read and approved the final paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Supplementary Figures 1-3.
[DOCX File , 12477 KB - resprot_v13i1e54707_app1.docx]

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71(3):209-249 [FREE Full text] [doi: 10.3322/caac.21660] [Medline: 33538338]
2. Jung KW, Won YJ, Hong S, Kong HJ, Im JS, Seo HG. Prediction of cancer incidence and mortality in Korea, 2021. Cancer Res Treat 2021;53(2):316-322 [FREE Full text] [doi: 10.4143/crt.2021.290] [Medline: 33735558]
3. Shin DW, Cho JH, Yoo JE, Cho J, Yoon DW, Lee G, et al. Conditional survival of surgically treated patients with lung cancer: a comprehensive analyses of overall, recurrence-free, and relative survival. Cancer Res Treat 2021;53(4):1057-1071 [FREE Full text] [doi: 10.4143/crt.2020.1308] [Medline: 33705624]
4. Yang P, Cheville AL, Wampfler JA, Garces YI, Jatoi A, Clark MM, et al. Quality of life and symptom burden among long-term lung cancer survivors. J Thorac Oncol 2012;7(1):64-70 [FREE Full text] [doi: 10.1097/JTO.0b013e3182397b3e] [Medline: 22134070]
5. Yun YH, Kim YA, Min YH, Chang YJ, Lee J, Kim MS, et al. Health-related quality of life in disease-free survivors of surgically treated lung cancer compared with the general population. Ann Surg 2012;255(5):1000-1007. [doi: 10.1097/SLA.0b013e31824f1e9e] [Medline: 22470076]
6. Karczmarek-Borowska B, Pelc M, Rabiej E, Grądalska-Lampart M. The quality of life of non-small cell lung cancer patients treated with chemotherapy. Pneumonol Alergol Pol 2014;82(4):349-357 [FREE Full text] [doi: 10.5603/PiAP.2014.0044] [Medline: 24964238]
7. Boyes AW, Girgis A, D'Este CA, Zucca AC, Lecathelinais C, Carey ML. Prevalence and predictors of the short-term trajectory of anxiety and depression in the first year after a cancer diagnosis: a population-based longitudinal study. J Clin Oncol 2013;31(21):2724-2729 [FREE Full text] [doi: 10.1200/JCO.2012.44.7540] [Medline: 23775970]
8. Henselmans I, Helgeson VS, Seltman H, de Vries J, Sanderman R, Ranchor AV. Identification and prediction of distress trajectories in the first year after a breast cancer diagnosis. Health Psychol 2010;29(2):160-168. [doi: 10.1037/a0017806] [Medline: 20230089]

9. Presley CJ, Arrato NA, Shields PG, Carbone DP, Wong ML, Benedict J, et al. Functional trajectories and resilience among adults with advanced lung cancer. JTO Clin Res Rep 2022;3(6):100334 [FREE Full text] [doi: 10.1016/j.jtocrr.2022.100334] [Medline: 35719868]
10. Andersen BL, McElroy JP, Carbone DP, Presley CJ, Smith RM, Shields PG, et al. Psychological symptom trajectories and non-small cell lung cancer survival: a joint model analysis. Psychosom Med 2022;84(2):215-223 [FREE Full text] [doi: 10.1097/PSY.0000000000001027] [Medline: 34629425]
11. Berman AT, DeCesaris CM, Simone CB, Vachani C, DiLullo G, Hampshire MK, et al. Use of survivorship care plans and analysis of patient-reported outcomes in multinational patients with lung cancer. J Oncol Pract 2016;12(5):e527-e535 [FREE Full text] [doi: 10.1200/JOP.2015.008904] [Medline: 27048615]
12. Polanski J, Jankowska-Polanska B, Rosinczuk J, Chabowski M, Szymanska-Chabowska A. Quality of life of patients with lung cancer. Onco Targets Ther 2016;9:1023-1028 [FREE Full text] [doi: 10.2147/OTT.S100685] [Medline: 27013895]
13. Hung R, Krebs P, Coups EJ, Feinstein MB, Park BJ, Burkhalter J, et al. Fatigue and functional impairment in early-stage non-small cell lung cancer survivors. J Pain Symptom Manage 2011;41(2):426-435 [FREE Full text] [doi: 10.1016/j.jpainsymman.2010.05.017] [Medline: 21216563]
14. Eichler M, Hechtner M, Wehler B, Buhl R, Stratmann J, Sebastian M, et al. Psychological distress in lung cancer survivors at least 1 year after diagnosis—results of a German multicenter cross-sectional study. Psychooncology 2018;27(8):2002-2008. [doi: 10.1002/pon.4760] [Medline: 29761591]
15. Jung W, Park J, Jeong A, Cho JH, Jeon YJ, Shin DW. Fear of cancer recurrence and its predictors among patients with non-small cell lung cancer (NSCLC). J Cancer Surviv 2023:4-7. [doi: 10.1007/s11764-023-01419-9] [Medline: 37351732]
16. Hulbert-Williams NJ, Storey L, Wilson KG. Psychological interventions for patients with cancer: psychological flexibility and the potential utility of Acceptance and Commitment Therapy. Eur J Cancer Care (Engl) 2015;24(1):15-27. [doi: 10.1111/ecc.12223] [Medline: 25100576]
17. Li TC, Yang MC, Tseng AH, Lee HHC. Prehabilitation and rehabilitation for surgically treated lung cancer patients. J Cancer Res Pract 2017;4(3):89-94 [FREE Full text] [doi: 10.1016/j.jcrpr.2017.06.001]
18. Boyes AW, Girgis A, D'Este C, Zucca AC. Prevalence and correlates of cancer survivors' supportive care needs 6 months after diagnosis: a population-based cross-sectional study. BMC Cancer 2012;12:150 [FREE Full text] [doi: 10.1186/1471-2407-12-150] [Medline: 22510387]
19. Lee G, Kim SY, Ahn A, Kong S, Nam H, Kang D, et al. Adjustment to "new normal" after cancer among non-small cell lung cancer survivors: a qualitative study. Palliat Support Care 2023:1-6. [doi: 10.1017/S1478951523001815] [Medline: 38129966]
20. Berman R, Davies A, Cooksley T, Gralla R, Carter L, Darlington E, et al. Supportive care: an indispensable component of modern oncology. Clin Oncol (R Coll Radiol) 2020;32(11):781-788 [FREE Full text] [doi: 10.1016/j.clon.2020.07.020] [Medline: 32814649]
21. Burg MA, Adorno G, Lopez EDS, Loerzel V, Stein K, Wallace C, et al. Current unmet needs of cancer survivors: analysis of open-ended responses to the American Cancer Society Study of Cancer Survivors II. Cancer 2015;121(4):623-630 [FREE Full text] [doi: 10.1002/cncr.28951] [Medline: 25581252]
22. Butow PN, Turner J, Gilchrist J, Sharpe L, Smith AB, Fardell JE, et al. Randomized trial of ConquerFear: a novel, theoretically based psychosocial intervention for fear of cancer recurrence. J Clin Oncol 2017;35(36):4066-4077 [FREE Full text] [doi: 10.1200/JCO.2017.73.1257] [Medline: 29095681]
23. Kang D, Bae KR, Ahn Y, Kim N, Nam SJ, Lee JE, et al. Effectiveness of Self-Assessment, TAilored Information, and Lifestyle Management for Cancer Patients' Returning to Work (START): a multi-center, randomized controlled trial. Cancer Res Treat 2023;55(2):419-428 [FREE Full text] [doi: 10.4143/crt.2022.939] [Medline: 36397237]
24. Kang JI, Chung HC, Kim SJ, Choi HJ, Ahn JB, Jeung H, et al. Standardization of the Korean version of Mini-Mental Adjustment to Cancer (K-Mini-MAC) scale: factor structure, reliability and validity. Psychooncology 2008;17(6):592-597. [doi: 10.1002/pon.1277] [Medline: 17957732]
25. Watson M, Law MG, dos Santos M, Greer S, Baruch J, Bliss J. The Mini-MAC. J Psychosoc Oncol 1994;12(3):33-46. [doi: 10.1300/J077V12N03_03]
26. Kang D, Lee G, Kim S, Nam H, Kong S, Shim S, et al. Psychometric validation of the Korean version of the Cancer Survivors' Unmet Needs (CaSUN) scale among Korean non-small cell lung cancer (NSCLC) survivors. Cancer Res Treat 2023;55(1):61-72 [FREE Full text] [doi: 10.4143/crt.2021.1583] [Medline: 35209702]
27. Hodgkinson K, Butow P, Hunt GE, Pendlebury S, Hobbs KM, Lo SK, et al. The development and evaluation of a measure to assess cancer survivors' unmet supportive care needs: the CaSUN (Cancer Survivors' Unmet Needs measure). Psychooncology 2007;16(9):796-804. [doi: 10.1002/pon.1137] [Medline: 17177268]
28. Yun YH, Park YS, Lee ES, Bang SM, Heo DS, Park SY, et al. Validation of the Korean version of the EORTC QLQ-C30. Qual Life Res 2004;13(4):863-868. [doi: 10.1023/B:QURE.0000021692.81214.70] [Medline: 15129896]
29. Cutillo A, O'Hea E, Person S, Lessard D, Harralson T, Boudreaux E. The distress thermometer: cutoff points and clinical use. Oncol Nurs Forum 2017;44(3):329-336 [FREE Full text] [doi: 10.1188/17.ONF.329-336] [Medline: 29493167]

30. Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M. The EORTC QLQ-LC13: a modular supplement to the EORTC Core Quality of Life Questionnaire (QLQ-C30) for use in lung cancer clinical trials. EORTC Study Group on Quality of Life. Eur J Cancer 1994;30A(5):635-642. [doi: 10.1016/0959-8049(94)90535-5] [Medline: 8080679]
31. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Leidy NK. Development and first validation of the COPD Assessment Test. Eur Respir J 2009;34(3):648-654 [FREE Full text] [doi: 10.1183/09031936.00102509] [Medline: 19720809]
32. Hwang YI, Jung KS, Lim SY, Lee YS, Kwon NH. A validation study for the Korean version of Chronic Obstructive Pulmonary Disease Assessment Test (CAT). Tuberc Respir Dis (Seoul) 2013;74(6):256-263 [FREE Full text] [doi: 10.4046/trd.2013.74.6.256] [Medline: 23814597]
33. Fletcher CM. The clinical diagnosis of pulmonary emphysema; an experimental study. Proc R Soc Med 1952;45(9):577-584. [Medline: 13003946]
34. Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 2003;35(8):1381-1395 [FREE Full text] [doi: 10.1249/01.MSS.0000078924.61453.FB] [Medline: 12900694]
35. Härter M, Reuter K, Gross-Hardt K, Bengel J. Screening for anxiety, depressive and somatoform disorders in rehabilitation—validity of HADS and GHQ-12 in patients with musculoskeletal disease. Disabil Rehabil 2001;23(16):737-744. [doi: 10.1080/09638280110062176] [Medline: 11732563]
36. Jacobsen PB, DeRosa AP, Henderson TO, Mayer DK, Moskowitz CS, Paskett ED, et al. Systematic review of the impact of cancer survivorship care plans on health outcomes and health care delivery. J Clin Oncol 2018;36(20):2088-2100 [FREE Full text] [doi: 10.1200/JCO.2018.77.7482] [Medline: 29775389]
37. Daudt HML, van Mossel C, Dennis DL, Leitz L, Watson HC, Tanliao JJ. Survivorship care plans: a work in progress. Curr Oncol 2014;21(3):e466-e479 [FREE Full text] [doi: 10.3747/co.21.1781] [Medline: 24940107]
38. Ioannidis JPA. Why most clinical research is not useful. PLoS Med 2016;13(6):e1002049 [FREE Full text] [doi: 10.1371/journal.pmed.1002049] [Medline: 27328301]
39. Price ST, Berini C, Seehusen D, Mims LD. Cancer survivorship training in family medicine residency programs. J Cancer Surviv 2021;15(5):748-754. [doi: 10.1007/s11764-020-00966-9] [Medline: 33175993]
40. Kang J, Park EJ, Lee J. Cancer survivorship in primary care. Korean J Fam Med 2019;40(6):353-361 [FREE Full text] [doi: 10.4082/kjfm.19.0108] [Medline: 31779063]

Abbreviations

IRB: institutional review board
LC3P: Lung Cancer Comprehensive Care Program
Mini-MAC: Mini-Mental Adjustment to Cancer
NSCLC: non–small cell lung cancer
SMC: Samsung Medical Center

Edited by A Mavragani; submitted 20.11.23; peer-reviewed by C Paul; comments to author 18.12.23; revised version received 05.01.24; accepted 11.01.24; published 13.02.24.

Please cite as:
Jung W, Ahn A, Lee G, Kong S, Kang D, Lee D, Kim TE, Shim YM, Kim HK, Cho J, Cho J, Shin DW
Supporting Life Adjustment in Patients With Lung Cancer Through a Comprehensive Care Program: Protocol for a Controlled Before-and-After Trial
JMIR Res Protoc 2024;13:e54707
URL: https://www.researchprotocols.org/2024/1/e54707
doi:10.2196/54707
PMID:38349712

Protocol

Efficacy of a Digital Health Preventive Intervention for Adolescents With HIV or Sexually Transmitted Infections and Substance Use Disorder: Protocol for a Randomized Controlled Trial

David Cordova[1], PhD; José A Bauermeister[2], MPH, PhD; Sydni Warner[3], MSc; The Youth Leadership Council[4*]; Patricia Wells[4*], MD; Jennifer MacLeod[5], CADC, MSc; Torsten B Neilands[6], PhD; Frania Mendoza Lua[7], MSW; Jorge Delva[8], MSW, PhD; Kathryn Bondy Fessler[4], MD, PhD; Versell Smith Jr, BA; Sarah Khreizat[1]; Cherrie Boyer[6], PhD

[1]School of Social Work, University of Michigan, Ann Arbor, MI, United States

[2]School of Nursing, University of Pennsylvania, Philadelphia, PA, United States

[3]School of Public Health, University of Michigan, Ann Arbor, MI, United States

[4]The Corner Health Center, Ypsilanti, MI, United States

[5]Livingston Physician Organization, Livingston, MI, United States

[6]School of Medicine, University of California San Francisco, San Francisco, CA, United States

[7]Crown Family School of Social Work, Policy, and Practice, University of Chicago, Chicago, IL, United States

[8]School of Social Work, Boston University, Boston, MA, United States

[*]these authors contributed equally

Corresponding Author:
David Cordova, PhD
School of Social Work
University of Michigan
1080 South University Avenue
Ann Arbor, MI, 48109
United States
Phone: 1 734 763 6201
Email: cordovad@umich.edu

Abstract

Background: HIV or sexually transmitted infections remain a significant public health concern in the United States, with adolescents affected disproportionately. Adolescents engage in HIV/STI risk behaviors, including drug use and condomless sex, which increase the risk for HIV/STIs. At-risk adolescents, many of whom are racial minorities, experience HIV/STI disparities. Although at-risk adolescents are disproportionately affected by HIV/STI risk behaviors and infections and although the Centers for Disease Control and Prevention recommends routine HIV/STI testing for adolescents, relatively few adolescents report having ever been tested for HIV/STI. With expected increases in health clinic visits as a result of the Affordable Care Act combined with technological advances, health clinics and mobile health (mHealth), including apps, provide innovative contexts and tools to engage at-risk adolescents in HIV/STI prevention programs. Yet, there is a dearth of efficacious mHealth interventions in health clinics to prevent and reduce both condomless sex and drug use and increase HIV/STI testing for at-risk adolescents.

Objective: To address this gap in knowledge, we developed a theory-driven, culturally congruent mHealth intervention (hereon referred to as S4E [Storytelling 4 Empowerment]) that has demonstrated feasibility and acceptability in a clinical setting. The next step is to examine the preliminary efficacy of S4E on adolescent HIV/STI testing and risk behaviors. This goal will be accomplished by 2 aims: the first aim is to develop a cross-platform and universal version of S4E. The cross-platform and universal version of S4E will be compatible with both iOS and Android operating systems and multiple mobile devices, aimed at providing adolescents with ongoing access to the intervention once they leave the clinic, and the second aim is to evaluate the preliminary efficacy of S4E, relative to usual care control condition, in preventing or reducing drug use and condomless sex and increasing HIV/STI testing in a clinical sample of at-risk adolescents aged 14-21 years living in Southeast Michigan.

Methods: In this study, 100 adolescents recruited from a youth-centered community health clinic will be randomized via blocked randomization with random sequences of block sizes to one of the 2 conditions: S4E mHealth intervention or usual care.

Theory-driven and culturally congruent, S4E is an mHealth adaptation of face-to-face storytelling for empowerment, which is registered with the Substance Abuse and Mental Health Services Administration's National Registry of Evidence-Based Programs and Practices.

Results: This paper describes the protocol of our study. The recruitment began on May 1, 2018. This study was registered on December 11, 2017, in ClinicalTrials.gov. All participants have been recruited. Data analysis will be complete by the end of March 2024, with study findings available by December 2024.

Conclusions: This study has the potential to improve public health by preventing HIV/STI and substance use disorders.

Trial Registration: ClinicalTrials.gov NCT03368456; https://clinicaltrials.gov/study/NCT03368456

International Registered Report Identifier (IRRID): DERR1-10.2196/47216

(JMIR Res Protoc 2024;13:e47216) doi:10.2196/47216

KEYWORDS

youth; mHealth; HIV; STI; illicit drugs; primary care; prevention; public health; USA; teens; drugs; drug use; sex; racial minority; risk behavior; engagement; tool; substance use disorder

Introduction

Background

HIV infections or sexually transmitted infections (STIs) and drug abuse remain significant public health priorities in the United States, with youths being affected disproportionately. Youths aged 15-24 years constitute only 25% of the sexually experienced population, but account for 46% and 50% of HIV infections and new STIs, respectively [1,2]. National surveillance data indicate that youths disproportionately engage in HIV/STI risk behaviors, including condomless sex [3] and licit and illicit drug use [4], which increase their risk for HIV/STI. Despite the disproportionately high rates of HIV/STI and risk behaviors in youths, less than 14% report having ever been tested for HIV infection [3]. Further, many youths are not routinely screened for asymptomatic STIs as recommended by the Centers for Disease Control and Prevention [5]. In Southeast Michigan (the area targeted in this proposed research), HIV/STI cases are disproportionately high [6,7]. To address these significant public health concerns, we developed an innovative mobile health (mHealth) intervention—the practice and dissemination of public health through mobile devices—for health clinic settings. Using this AIDS-Science Track Award for Research Transition (A-START) mechanism, we propose to examine the preliminary efficacy of our mHealth intervention.

The efficacy rates of mHealth [8-10] and brief interventions delivered in health care settings [11-14] aimed at preventing or reducing condomless sex and drug use in youths have been mixed. We believe our intervention, Storytelling 4 Empowerment (S4E), shows promise for several reasons. First, we developed S4E through a community-university collaboration, integrating community-based participatory research principles [15] with the National Institute on Drug Abuse's prevention guidelines [16]. This process transformed the effective S4E program [17] into an mHealth app [18-22].

S4E is culturally congruent and was adapted in consultation with youths and clinicians from a targeted youth-centered community health clinic. This app is grounded in empowerment [23,24] and ecodevelopmental [22,25-27] theories. S4E uses innovative storytelling scenarios to address key aspects of our intervention's mechanisms of change, including self-efficacy for condom use and drug use refusal skills (hereon referred to as self-efficacy) and improving clinician-youth communication during the health care visit. These elements aim to increase HIV testing and prevent or reduce condomless sex and drug use behaviors among at-risk youths. Our formative research with youths (defined hereon as adolescents and young adults aged 14-21 years) and clinicians demonstrated that youths in the targeted health care clinic (1) routinely visit the clinic for reproductive and other health care, (2) are at increased risk of HIV/STIs, and (3) found S4E to be feasible and acceptable but also want access to S4E outside of the health clinic to continue participating in intervention activities [18-21,28-30].

Youth-centered community health clinics are an ideal setting for delivering and evaluating the efficacy of an mHealth HIV/STI and drug abuse preventive intervention. Many youths do not seek such services in public health clinics or AIDS service organizations [31]. Furthermore, many primary care pediatric practices do not routinely screen youths for HIV/STIs or drug use [32]. Thus, a gap in knowledge persists regarding efficacious mHealth interventions that improve HIV/STI testing and prevent or reduce condomless sex and drug use in at-risk youths in health care settings [10,18,33]. Since S4E has demonstrated feasibility or acceptability [20], the next important step is to develop a more accessible version of S4E and conduct a stage 1 randomized controlled trial (RCT) [34,35] to examine the preliminary efficacy of S4E in at-risk youths.

Aims

The proposed study seeks to accomplish the following 2 aims:

1. The first aim is to develop a cross-platform and universal version of S4E. The cross-platform and universal version of S4E will be compatible with both iOS and Android operating systems and multiple mobile devices aimed at providing adolescents with ongoing access to the intervention once they leave the clinic.
2. The second aim is to evaluate the preliminary efficacy of S4E, relative to usual care, to improve HIV/STI testing and reduce HIV/STI risk behaviors in a clinical sample (N=100) of at-risk youths aged 14-21 years living in Southeast Michigan. We will conduct a stage 1 RCT [34,35] to examine the preliminary efficacy of S4E, relative to usual

care, in a sample of 100 at-risk youths for 6 months. Our primary outcome is adolescent HIV and STI testing. Secondary outcomes include condomless sex and drug use at 3 months and 6 months postbaseline. As a secondary exploratory aim, we will examine the extent to which our theoretically guided mechanisms of change (ie, self-efficacy, clinician-youth communication) lead to increased HIV and STI testing and prevent or reduce HIV/STI risk behaviors.

The proposed study is innovative, as it is the first to combine mHealth and storytelling to facilitate clinician-youth communication, deliver prevention services, linkage to care, and treatment immediately [27,36,37]. This research program focuses on increasing HIV and STI testing and reducing key risk behaviors such as condomless sex and drug use among at-risk youths. This aligns with the National Institutes of Health HIV/AIDS research priorities [38]. By doing so, it addresses 2 critical goals: (1) preventing and reducing new HIV infections and (2) diminishing HIV-related health disparities. These objectives are among the top 4 priorities outlined in the United States National HIV/AIDS strategy [39].

Significance

HIV/STI risk behaviors among youths remain the major public health concerns. National surveillance data show that 40.9% of the youths reported condomless sex in the last sexual intercourse [3]. Beyond condomless sex, youths engage in drug use behaviors that increase their risk for HIV/STI. National surveillance data indicate that 66% and 49.1% of youths report lifetime licit and illicit drug use, respectively [4]. Alcohol is the most widely used licit drug, with 37.4% and 66% of youths reporting current and lifetime use, respectively [3,4]. Parallel data from Monitoring the Future study indicate that, from 2008 to 2011, youths' lifetime, annual, and 30-day prevalence of any illicit drug use have increased [4]. Marijuana remains the most widely used illicit drug with 21.2% and 44% of adolescents reporting current and lifetime marijuana use, respectively [4]. Although the Centers for Disease Control and Prevention recommends HIV/STI testing among youths as part of routine care, many are only being tested based on their perceived risk [5]. HIV/STI testing has important prevention implications, including linkage to both care (eg, preventing transmission of HIV/STI) and important preventive services to remain HIV/STI-free [5].

Racial or ethnic minority youths experience HIV/STI disparities. Youths aged 15-24 years represent 25% of the sexually experienced population and comprise nearly 46% and 50% of HIV infections and new STIs, respectively [1,2]. In 2014, an estimated 9731 youths were diagnosed with HIV in the United States; 78% of these diagnoses occurred in Black/Latino youths [40]. Although the majority of these infections are among young men who have sex with men [40], African American young women are disproportionately affected by STIs, which increases the risk of HIV infection [41]. Given their needs, our sample will consist of a predominantly racial or ethnic minority sample of adolescents in the age group of 14-21 years. This age group spans a time of limited HIV testing and increased HIV/STI risk-taking [3,4] and thereby permits us to intervene at a developmental moment of increased risk [42,43].

Youth in the targeted clinic, many of whom are racial or ethnic minorities, are at disproportionate risk of HIV/STI. Our research shows that, relative to the general US adolescent population, youths in the targeted clinic are more likely to report condomless sex in the last sexual intercourse (40.9% vs 57.9%) and lifetime alcohol (66.2% vs 71.4%) and marijuana (40.7% vs 46.7%) use, respectively [3,20]. Given that condomless sex and drug use are risk behaviors for HIV/STI, not surprisingly, youths in the targeted clinic experience HIV/STI disparities. In the first quarter of 2016 (January-March), 52% (33/63) of youths who received STI testing services tested positive for an STI compared to 25% of the sexually active US youth population [2].

Self-efficacy and clinician-youth communication are potential mechanisms by which change can occur. Researchers have identified a number of etiological factors that shape youth HIV/STI testing [44-46] and risk behaviors [47-49], including intrapersonal (eg, self-efficacy) and ecological (eg, clinician communication) [42,50]. At the intrapersonal level, for example, higher levels of refusal skills and knowledge of self-efficacy increase HIV/STI testing and prevent HIV risk behaviors in youths [42-45,51,52]. At the ecological level, effective sexual communication can ameliorate HIV/STI testing and risk behaviors. Indeed, higher levels of clinician-patient communication have been shown to yield better health outcomes [53-55]. Drawing from this basic science, the proposed study posits that interventions targeting these potential underlying mechanisms of change (ie, improving refusal skills, knowledge, and HIV communication, which in turn will improve self-efficacy and clinician-youth communication) may increase HIV/STI testing and prevent or reduce HIV and STI risk behaviors. Furthermore, understanding the role of etiological factors on youth HIV/STI testing and risk behaviors should be viewed through a cultural and developmental lens [26,56,57]. Therefore, integrating cultural and developmental perspective into theoretical frameworks is important to improve HIV/STI testing and reduce risk behaviors [26,56-58].

Empowerment and ecodevelopmental theories provide a framework for targeting the theoretical underpinnings of our intervention's mechanisms of change. The empowerment and ecodevelopmental frameworks guide the theoretically driven components of our intervention. The empowerment framework is concerned with linking youths' strengths and proactive behaviors to helping systems [24,25]. Thus, empowerment-informed interventions seek to enhance the knowledge of the risk factors, refusal communication skills, perceptions of self-efficacy, and engage health care clinicians as resources to accomplish these health goals [24,25]. Equally important is to consider ecological factors. The ecodevelopmental theory [59,60] posits that youths are embedded in integrated ecological systems (microsystem, mesosystem, exosystem, and macrosystem), including developmental and social interaction, which influence and are influenced by the youth [59,60]. In the proposed research, we focus on the health clinic microsystem and limit the conversation to that high-impact system. Microsystems are defined as systems in which the youths participate directly [59,60]. Researchers

have extensively applied the ecodevelopmental theory to the family microsystem aimed at improving parent-youth communication [61-63]. With the passing of the Affordable Care Act, we have an opportunity to apply the ecodevelopmental theory to the health clinic microsystem—a system that will only grow larger and increasingly important as a result of the Affordable Care Act—to understand clinician-youth communication [18-21]. Our formative research supports the use of empowerment and ecodevelopmental theories and provides a robust framework for the proposed research.

Health clinic HIV/STI preventive interventions are needed but limited in availability. A recent review of brief (<60 minutes) health clinic interventions examined 31 trials designed to increase HIV/STI testing and prevent HIV/STI risk behaviors. Of these, only 1 study focused on HIV/STI risk behavior outcomes through clinician-youth communication. Findings suggest that, relative to usual care, an audiotaped risk assessment and education intervention showed an increase in communication with providers on STIs and condom use [64]. Findings on the efficacy of brief interventions in health care settings on youth licit and illicit drug use have been mixed [11,14,65]. For example, a recent review of brief interventions in health care settings with clinician approaches was conducted, with 10 interventions designed to prevent or reduce youth alcohol use examined. Of these, only 3 studies were RCTs: 1 had a primarily racial minority sample and 1 was found to be efficacious in reducing alcohol use [11]. Our community-university approach aims to overcome the limitations of these studies. By engaging the community in the development of our mHealth intervention, we believe we will have a greater impact, given that community-university approaches increase uptake and optimize outcomes of prevention programs [66]. Although federal recommendations highlight the need for clinicians to provide youth HIV/STI and drug use preventive services [67,68], efficacious brief interventions designed to increase HIV/STI testing and prevent or reduce condomless sex and drug use are limited [18,33,64,69]. Our formative research suggests that youths in the targeted clinic routinely show for health care visits, with over 550 monthly visits by youths aged 12-21 years. This provides us with an exciting opportunity to impact HIV/STI testing and behaviors through an innovative and interactive mHealth app.

mHealth apps provide new opportunities for engaging youths in preventive interventions, but research is limited. Advances in technology and increased availability provide novel opportunities for prevention scientists [70,71]. Although mHealth interventions are efficacious for adolescent health behaviors [71-73], relatively few studies on HIV/STI testing and risk behaviors exist. A recent systematic review of mHealth apps aimed at addressing the HIV continuum of care identified only 4 published studies and 14 studies underway [10]. Of these, only 7 studies focused on primary prevention of HIV/STI and 6 studies on HIV/STI testing [10]. A limitation of these studies, however, is that they do not target at-risk youths in health care clinics. Our proposed research aims to harness the widespread use of mobile technology [74] and deliver and evaluate an mHealth HIV/STI intervention among at-risk youths, many of whom are racial minorities, in a health care clinic.

Storytelling for Empowerment (SFE) is an effective face-to-face intervention to translate and test a new mHealth preventive intervention. Registered with Substance Abuse and Mental Health Services Administration's National Registry of Evidence-Based Programs and Practices, SFE aims to increase self-efficacy and communication about HIV risk behaviors and has been shown to prevent or reduce HIV/STI risk behaviors and increase (1) HIV/STI and drug use prevention knowledge, (2) HIV/STI communication, and (3) perception of harm and self-efficacy in refusing drugs [17,75,76]. Adapting SFE into an mHealth version for health care clinics was ideal for several reasons, including SFE has already demonstrated efficacy with other youth populations and the use of storytelling makes it highly flexible and easily transportable into a brief mHealth modality. Based on empowerment [24,25] and ecodevelopmental [22,26,77] frameworks, the mHealth version of SFE, S4E, consists of 3 modules targeting youth: (1) HIV/STI risk assessment, (2) HIV/STI, and (3) alcohol/drugs. The risk assessment assesses youth HIV/STI risk behaviors. Both the HIV/STI and drug modules consist of videos (developed from focus group data on community-specific epidemiology) focused on HIV/STI testing and risk and promotive behaviors, knowledge development, interactive activities, and messaging aimed at increasing clinician-youth communication.

Despite federal guidelines urging clinicians to provide youth HIV and drug use preventative care [67,68], our research [19,20] and that of others [78-80] demonstrate that clinicians' limited HIV/STI communication training and embarrassment to discuss HIV/STI risk pose as challenges to engage youths in these conversations. With funding from the National Institute of Mental Health (R25MH067127), we developed a theory-driven and culturally congruent clinician component to overcome these barriers, which provides clinicians with (1) youth risk assessment scores, (2) tailored HIV/STI communication interviewing toolkits (eg, reflective questioning), and (3) tailored resources to link youths with care. We recognize that youths in health clinics represent one segment of the youth population, but nonetheless an important segment at disproportionate risk of HIV/STI [20,28].

Preliminary Studies

Study 1: Feasibility and Acceptability of S4E

Study Design

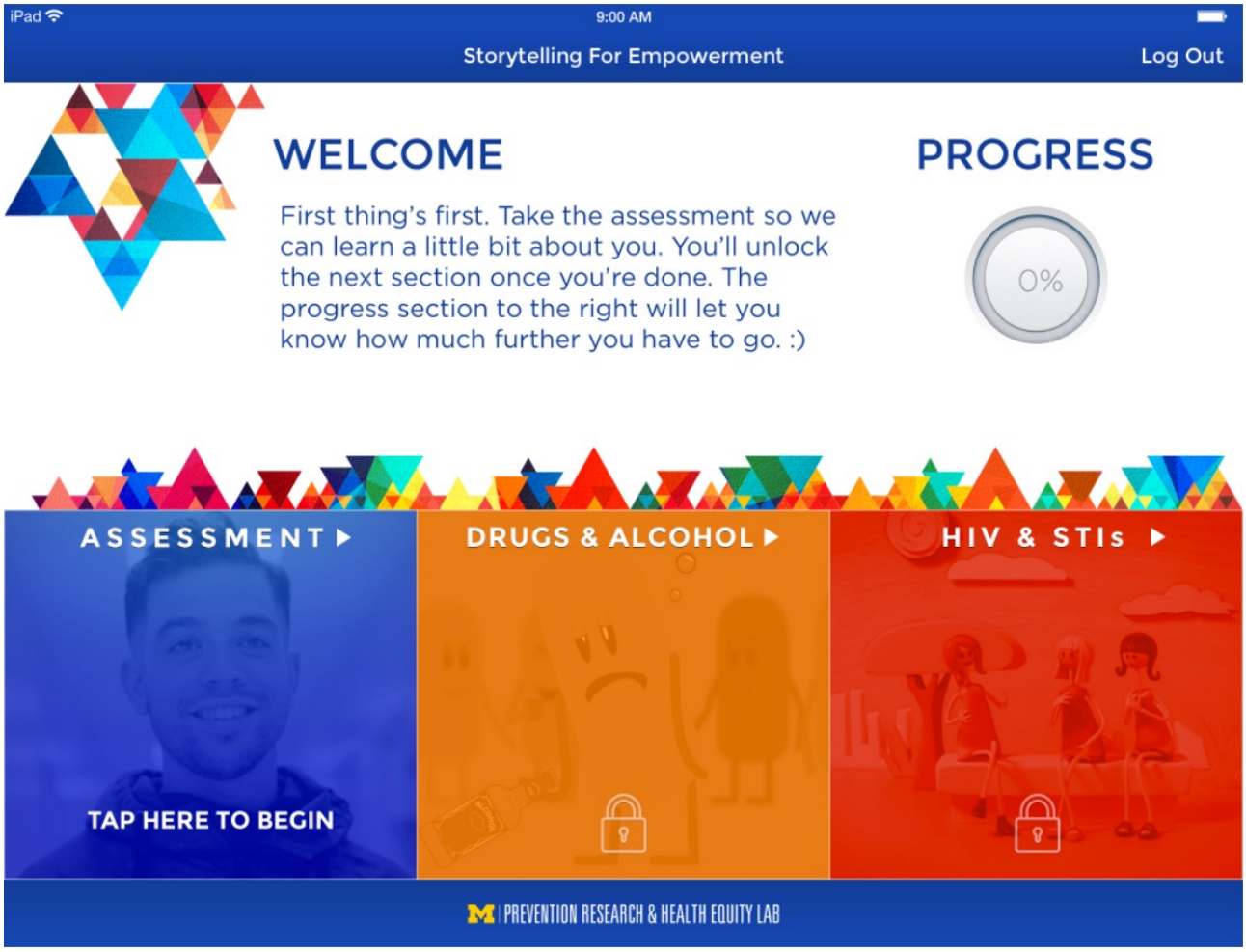
Youths (n=30) were recruited from Southeast Michigan and were primarily African Americans (20/30, 67%) and females (22/30, 73%) with a mean age of 16.23 (SD 2.09) years. We used a community-engaged research approach with 3 phases, that is, formative focus groups (n=29), app development, and feasibility testing (n=30). We used agile software development [81]. Formative focus group data collection and app development occurred simultaneously.

Results

We developed a theory-driven and culturally congruent mHealth version of SFE (Figure 1). Both qualitative and quantitative data from the Session Evaluation Form [82] (mean 1.42, SD 0.46) and Client Satisfaction Questionnaire [83] (mean 3.46, SD 0.47) indicate that S4E was acceptable to youths. Data also

showed that youths regularly visit the clinic (ie, 550 visits per month), visit the clinic multiple times (mean 3 visits), and are at increased risk of HIV/STI risk behaviors. Since we demonstrated the feasibility, the next important step was to conduct a stage 1 preliminary efficacy RCT of S4E on adolescent HIV/STI testing and risk behaviors [18-21].

Figure 1. A theory-driven and culturally congruent mobile health version of Storytelling for Empowerment.



Study 2: Development of S4E Clinician App

Employing Community-Based Participatory Action Research principles, we collaborated with clinicians from the targeted youth-centered community health clinic in Southeast Michigan (NIMH R25MH067127) to inform the development of the clinician components for the S4E app [84]. We used agile software development [81] for the creation of prototype models, obtained rapid feedback from clinicians regarding user interface/experience, and a feedback loop for revisions and to finalize the app. The S4E clinician app provides clinicians with (1) youths' risk assessment scores, (2) tailored HIV/STI communication interviewing toolkit (eg, reflective questioning, positive reinforcement), and (3) tailored resources to link youths with care. Feasibility or acceptability testing is underway and study findings will be incorporated into this proposed A-START research.

Methods

Study Design

The first aim is to develop a cross-platform and universal version of S4E. The purpose of developing a cross-platform and universal version of S4E is to create a more accessible app that is compatible with different operating systems (ie, Android and iOS) and multiple mobile devices, thereby providing youths with ongoing access to the intervention outside of the clinic. Finalizing the universal version of S4E will be streamlined because the app developer, The Annex Group, created S4E for the iOS operating system to use on iPads, which will serve as an existing framework (eg, code, design database). Similar to the methodology employed in our formative research, as part of the iterative process, we will hold weekly meetings with The Annex Group to discuss all aspects of finalizing the app, including framework and user interface or user experience. At the completion of the first aim, we will have finalized S4E, which will be used for our stage 1 preliminary efficacy RCT in the second aim. We will pilot test all study procedures prior to addressing the second aim.

The second aim is to evaluate the preliminary efficacy of S4E to improve HIV/STI testing and reduce HIV/STI risk behaviors in a clinical sample (N=100) of at-risk adolescents aged 14-21 years living in Southeast Michigan. To test the preliminary efficacy of S4E, we will conduct a stage 1 RCT and use a mixed between/within-subjects design with 2 levels of intervention

(S4E and usual care) as the between-subjects factor and 3 repeated measures assessments (baseline, 3-, and 6-months postbaseline) as the within-subjects factor.

Participants

A clinical sample of 100 youths and clinicians (n=6) will be recruited from Corner Health Center. In 2015, the clinic reported over 5600 visits from individuals aged 12-21 years; therefore, recruiting 100 youths will be feasible. With respect to participant race, ethnicity, and age, we will recruit a sample that is representative of the clinical population. As in our previous studies [28-30], we expect the majority of participants to be racial minority youths and be sexually active (50/70, 71% report past 90-day oral, vaginal, or anal sexual intercourse) [20,28].

Inclusion Criteria

Participants must be female or male youths aged 14-21 years, sexually active, live in Southeast Michigan, and have access to a smartphone or tablet (51/70, 73% report having access to smartphone [85]). Youths must see an enrolled clinician to participate in this study. Exclusion criteria include report of prior psychiatric hospitalization by the adolescent, visible cognitive impairment due to drug use, and adolescent reports (tentative or firm) plans to move out of the Southeast Michigan area during the study.

Recruitment

A multipronged recruitment strategy will be implemented: face-to-face interactions, flyer distribution, engagement in the clinic's waiting area, and informing youths with upcoming clinic appointments at the clinic about the study. Potential participants will be informed about the study by research staff, with details about its voluntary nature and the RCT design. Those interested will be sent a study web-based app link, where they can provide digital consent and screen for eligibility. Participants aged 13-17 years will be given a waiver of parental permission as per Michigan regulations. Following consent, participants will undergo baseline assessment and randomization through the study's web-based app. They will then be informed of their group allocation. Research staff will introduce participants to the app and ensure proper navigation. Participants will be incentivized, receiving a total of US $120: US $30 at baseline, US $40 at the 3-month follow-up, and US $50 at the 6-month follow-up.

Retention

To prevent attrition, we will ask youths to provide the names and contact information of 3 persons who will always know where they can be reached. These names will help maintain contact with the youths in case they move or their telephone lines become disconnected. Youths may choose to provide the names and contact information of individuals they trust, such as a primary caregiver, relative, or significant adult figure. Youths will be informed that if the research team cannot reach them and needs to contact these individuals, the team will only communicate their intention to contact the youths about a health study. Additionally, a sample of 6 clinicians will be recruited. Similar to our formative research, research staff will provide an overview of the study to all clinicians during a staff meeting, and they will be informed that participation is voluntary. To prevent coercion of clinician participation by clinic administration, potential participants will not need to go through nor inform the clinic administration for participation. An initial list of potential clinician participants will be developed, and research staff will follow up with those clinicians who express interest in this study.

Clinicians

Clinicians will be assigned to either S4E or control condition. In lieu of providing each clinician with an incentive for their participation in the study, the clinic will receive US $2000, which will benefit the entire clinic. Randomization will occur after baseline assessment. Three of the 6 clinicians will be assigned to the S4E condition and trained according to research criteria. Clinicians will receive a 1-hour training, encompassing content delivery, app navigation, risk assessment viewing, note-taking within the app, and effective communication strategies for discussing substance use and sexual behaviors. A review training will ensure adherence to the protocols. All clinicians who express interest in this study and do not report (tentative or firm) plans to move out of the region during this study will be eligible to participate.

Experimental and Control Conditions

Participants were assessed at baseline, randomized to intervention (n=50) or control (n=50) groups using block randomization [86], and then reassessed immediately postintervention, at 3 months, and at 6 months. Participants in the S4E condition will initially engage with the intervention by using iPads available in the waiting area. This includes iPads allocated for this study and an additional 10 from the principal investigator's pilot studies. They will also be instructed on how to download the intervention app onto their personal devices, enabling continued participation in intervention activities after leaving the clinic.

S4E Description

Informed by our formative research, the intervention lasts approximately 60 minutes and was found to be feasible and acceptable to youths. Content includes the theoretically driven components of SFE [17,75,76]: (1) storytelling scenarios, (2) drug use and HIV/STI knowledge development, (3) interactive activities, (4) increasing self-efficacy to prevent or reduce sexual risk and drug use behaviors and increase HIV/STI testing, (5) clinician-youth communication, and (6) highlighting prevention principles (Textbox 1 and Textbox 2).

Textbox 1. Experimental condition of S4E intervention.

Adolescent components

- Risk assessment: Youths complete an HIV/sexually transmitted infection (STI) risk behavior assessment, which include items from the CRAFFT (Car, Relax, Alone, Forget, Friends, Trouble) [87] measure, HIV testing, and sexual and drug use behaviors, and provide opportunity or receptivity to being counselled (1 min to complete).
- HIV/STI module: Youths are exposed to storytelling scenarios, including community-specific HIV/STI epidemiology (eg, risk, protective behaviors). Following the videos, youths operate an app aimed at increasing condom use self-efficacy, HIV/STI knowledge development, and interactive activities aimed at engaging youths and testing knowledge. Additionally, youths receive messaging aimed at facilitating clinician-youth communication and HIV/STI testing (30 min to complete).
- Alcohol/drugs module: Adolescents are exposed to storytelling scenarios, including community-specific alcohol/drug epidemiology (eg, prevalent licit and illicit drugs). Following the videos, adolescents operate an app aimed at increasing drug use refusal self-efficacy, drug use knowledge development, and interactive activities aimed at engaging youths and testing knowledge. Additionally, adolescents receive messaging aimed at facilitating clinician-adolescent communication (30 min to complete).

Clinician components

- Risk assessment scores: Clinicians are provided youth risk assessment scores, identifying at-risk youths, and provided opportunity to reinforce information provided to youths through the modules (above).
- Tailored HIV/STI communication toolkit: Based on empowerment and ecodevelopmental theories, clinicians are provided a communication toolkit, which includes examples of open-ended reflective questioning, positive reinforcement statements, HIV/STI risk probing, and empowerment messaging.
- Tailored resources and referrals: Clinicians are provided tailored community-identified local resources and referrals, including HIV/STI testing and linkage to care.

Textbox 2. Underlying mechanisms of change.

Consistent with empowerment and ecodevelopmental theories, Storytelling 4 Empowerment provides an opportunity to be counselled, which in turn:

- Increases clinician-youth communication
- Increases engagement of health care clinicians as collaborators to address HIV/sexually transmitted infection (STI) and drug use concerns
- Increases clinician-youth sexual risk communication
- Increases HIV/STI knowledge
- Increases condom use
- Increases condomless sex refusal skills
- Increases clinician-youth drug use communication
- Increases drug use knowledge
- Increases refusal skills
- Enables clinicians reinforce prevention strategies and link youths to HIV/STI testing and linkage to care

Control Condition

Participants in usual care (ie, control condition) will not receive the S4E intervention from the study staff. The clinic's usual care includes a standard risk behaviors intake form, pamphlets highlighting resources, and reproductive and health care services.

Measures

Youth HIV/STI Testing and Risk Behaviors

After the intervention, we will assess whether youths requested to receive HIV/STI testing at the clinic, and at 3 months, and 6-months postbaseline (yes/no). Adolescent unsafe sexual behavior will be measured (timepoints 1-3) by using items extracted from the Sexual Behavior Instrument [88]. This gated instrument will assess the adolescent's past 90-day condom use, number of sexual partners, and contraceptive use (not condoms). This measure also assesses the existence of an STI during their lifetime and in the past 90 days. Licit and illicit drug use behaviors will be assessed (timepoints 1-3) using items from the Monitoring the Future study [4]. Youths will be asked whether they have used licit or illicit drugs in their lifetime and in the past 90 days. Youths who report "Yes" to past 90-day sex will be asked to report frequency of drug use prior to sex. These measures have been used in our formative research [18-21].

Potential Mediators: Clinician-Youth Communication and Self-Efficacy

Completed by both the clinicians (α=.70) and youths (α=.69), clinician-youth communication will be assessed (timepoints 1-3) using items adapted from the Matched Pair Instrument (19 items) [89]. The Matched Pair Instrument assesses the process and content of communication, including verbal and

action-related behaviors performed by clinicians [89]. Responses range from "1=strongly disagree" to "5=strongly agree" on a 5-point Likert scale. A sample statement for clinicians and youths is, "Encouraged the patient/me to express his or her/my thoughts concerning drug use behaviors." Youths' self-efficacy will be assessed (timepoints 1-3) using 2 scales, namely, the Condom Self-Efficacy Scale (19 items, α=.85) [90] and Drug Use Resistance Self-Efficacy (24 items, α=.98) [91]. Responses range from "1=not sure at all" to "4=definitely sure" on a 4-point Likert scale. A sample question for the youth is, "How sure are you that you can refuse if a friend offers you marijuana at a party and you do not want it?" Additionally, youths and clinicians will respond to a demographic survey, wherein they will have to fill in the details of their date of birth, gender identity, sexual orientation, age, ethnicity or race, income, and education.

Intervention Dosage for Both Clinicians and Youths (Not Given to Participants)

S4E includes a login procedure. In addition to the login procedure serving as a mechanism by which the secure access and confidentiality of participants is ensured, it will facilitate the close monitoring of participants' dosage. The login procedure will be used to record whom (ie, participant), when (ie, day/time), how long (eg, dosage), and for what purpose (eg, module). We will assess participants' satisfaction with S4E across platforms (eg, mobile phone) and the use of the intervention once they leave the clinic. Higher frequencies of access and longer durations of app use will indicate higher levels of dosage and engagement with the intervention.

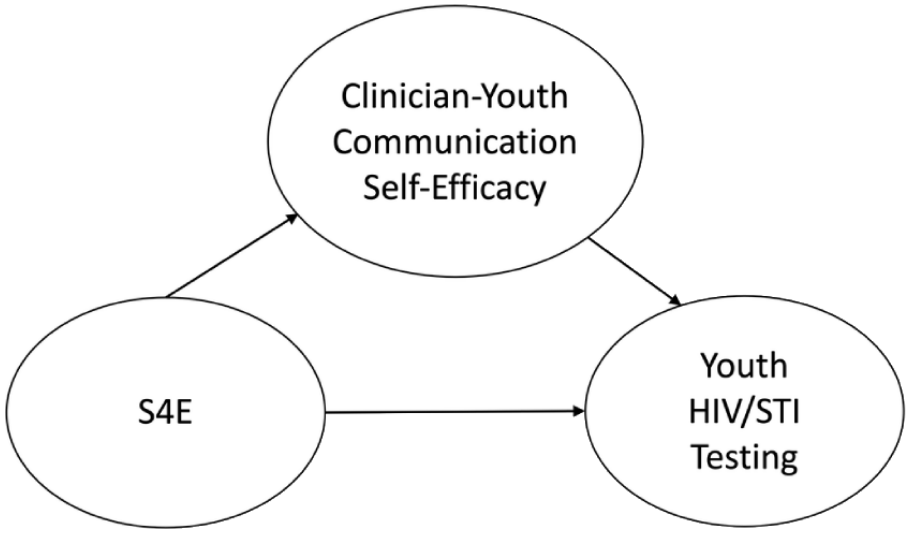
Statistical Analysis

Given the sample size and stage 1 RCT pilot nature of our study, we will not conduct a formal test of efficacy. Researchers affirm [92] that effect size estimates obtained using stage 1 RCT data may not be reliable, given their large variability. Therefore, our primary purpose was to estimate the critical parameters [92] required to inform the potential effects of S4E in a stage 2 RCT. As part of the preliminary efficacy process, we expect the following intervention exposure relative to usual care participants:

1. Hypothesis 1: S4E participants will have increased odds of repeat HIV/STI testing postintervention.
2. Hypothesis 2: S4E participants will have decreased odds of past 90-day condomless sex at 3 months and 6 months postbaseline.
3. Hypothesis 3: S4E participants will have decreased odds of past 90-day licit and illicit drug use at 3 months and 6 months postbaseline.

As a secondary exploratory aim to examine potential mechanisms of change (Figure 2), we also anticipate that S4E participants compared to usual care participants will report (1) higher mean levels of clinician-youth communication and (2) drug use and HIV/STI self-efficacy.

Figure 2. Potential mechanisms of change caused by Storytelling 4 Empowerment. S4E: Storytelling 4 Empowerment; STI: sexually transmitted infection.



To test differences between conditions postrandomization, we will plot means and proportions by condition over time for descriptive analysis of overall patterns of change across time in the outcomes for the S4E and usual care conditions. We will use linear mixed models (LMMs) for continuous outcomes (eg, clinician-adolescent communication scale scores measured to address exploratory aim) and generalized LMMs (GLMMs) for discrete data (eg, HIV/STI testing measured to address H1) to evaluate the proposed preliminary hypotheses. GLMMs fitted to discrete outcomes (eg, condomless sex) will employ a binomial distribution with a logit link; GLMMs fitted to count outcomes will use the best-fitting distribution from the Poisson family (eg, zero-inflated Poisson) with the log link function [93]. We will assess whether clustering effects associated with clinic physicians must be accounted for in these analyses. All mixed models will be estimated via maximum likelihood estimation and will be fitted to ensure that all requisite information is available in the survey and data to perform the types of analyses typically undertaken in a stage 2 RCT. Similarly, although the modest sample size precludes investigating mediation and moderation formally, we will employ the same LMM and GLMM approaches described above to examine potential mediators (ie, clinician-adolescent

communication, self-efficacy) and moderators (eg, gender, race) of the S4E intervention.

Power Analyses

Due to the modest sample size, significance testing will be de-emphasized. The purpose of stage 1 RCT is to determine preliminary efficacy rather than to conduct formal hypothesis tests; nevertheless, we conducted power analyses using nQuery Advisor version 7.0 [94] to estimate the magnitude of effect we could observe, given our pilot sample size. With 50 cases per group, we would have 80% power to detect an odds ratio of 3.7 in receiving HIV testing immediately postintervention between the 2 conditions. This would be considered a large effect size [95]. Using GLMM models to compare the 2 groups in terms of trends in the probability of binary outcomes over 6 months (eg, condomless sex), we performed a custom simulation study to estimate the size of the interaction between group × time that we could detect with 80% power when fitting our models (and assuming a within-subject correlation of 0.1 in the binary measures). We would be able to detect percentages of 70% in the intervention group at 3 months and 25% at 6 months as representing a significantly different reduction in the percentage with this outcome over time (ie, a significant group × time interaction) with approximately 80% power, which would again be considered a large effect.

Ethics Approval

The principal investigator (DC) received approval (HUM00158089) from the University of Michigan institutional review board to begin research in February 2017 and was awarded funding from the National Institute on Drug Abuse on February 01, 2017.

Results

This study has been designed to develop an mHealth intervention program (S4E) and evaluate its preliminary efficacy to improve HIV/STI testing and reduce HIV/STI risk behaviors among youth populations. Our study findings will contribute to reducing HIV/STIs and risk behaviors among youths. The development of the intervention has been completed, and recruitment for the preliminary efficacy trial began in May 2018. We completed the trial in August 2020. We recruited 100 participants, data analyses are underway, and the results are expected to be published by December 2024.

Discussion

The overarching goal of this program of research is to move a program of intervention research from efficacy to scale and to examine the extent to which these modules are generalizable to similar youth populations. If found to have preliminary efficacy, the next step in this program of research is to conduct a stage 2 RCT to examine the effects of S4E on youth HIV/STI testing and risk behaviors. We are aware that control group participants may unintentionally receive the experimental group content. Although it might not be possible for youths to see the same clinician at 3 months and 6 months postbaseline, we have the Corner Health's support that youths will only see clinicians in the condition to which they are assigned (ie, S4E or usual care). The proposed age range (14-21 years) may seem wide; however, this is an age group at increased risk for HIV/STI [1,2]. Further, this age range was established in consultation with Corner Health who, in considering both the strengths and limitations, preferred a universal app that was relevant to the clinical population. Our 2-arm, baseline, 3-month, and 6-month postbaseline design was chosen, given the scope of the R03 A-START mechanism.

Our protocol explores the behavioral change practice methods (ie, proposed mechanisms underlying the observed changes), namely, clinician-youth communication and self-efficacy. The use of storytelling scenarios, created by youths through a community-engaged research method grounded in community-based participatory research principles, could offer an innovative strategy for future studies. This approach highlights the importance of the relationship between clinicians and youths as well as the role of self-efficacy.

Our protocol may benefit the society by providing compelling evidence for the preliminary efficacy of an mHealth intervention in promoting HIV and STI testing and reducing sexual and substance use risks among adolescents and young adults. The promising intervention, combined with the proposed recruitment and retention strategies, may provide evidence for larger scale trials. Given the pressing demand for efficacious interventions in this domain, this protocol may have a significant societal impact. Further, this proposed research aligns well with the broader goals of the National Institutes of Health HIV/AIDS research priorities [38], the National HIV/AIDS strategy [4], and the recommendations issued by the US Preventive Services Task Force to reduce youth's HIV and drug use risks by linking them to screening and care services in community health clinic settings [67,68].

Acknowledgments

Financial support for the conduct of this research was provided by the National Institute of Mental Health grant R25MH067127, National Institute on Minority Health and Health Disparities Loan Repayment Program grant L60MD006269, Office of Vice President for Research at the University of Michigan and Vivian A and James L Curtis School of Social Work Research and Training Center grant 23665. These sponsors had no role in the study design, collection, analysis, or in the interpretation of the data, writing of this report, or the decision to submit this paper for publication.

Conflicts of Interest

None declared.

Authors' Contributions

The members of the Youth Leadership Council are: Ian Stewart, Erika Riano-Mojica, Bishop Warford, Franco Machado, Kiristen Hubbard, Maxine Abuelsamid, Sakinah Rahman, Zaki Rahman, Ziara Chestang, and Katheryne Messer.

References

1. Centers for Disease Control and Prevention. Diagnoses of HIV infection in the United States and dependent areas, 2014. HIV Surveillance Report, 2014. URL: https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-report-2014-vol-26.pdf [accessed 2015-03-12]
2. Sexually transmitted disease surveillance 2014. Centers for Disease Control and Prevention. 2015. URL: https://www.cdc.gov/std/stats/archive/surv-2014-print.PDF [accessed 2015-03-12]
3. Youth risk behavior surveillance — United States, 2013. Centers for Disease Control and Prevention. 2014. URL: http://www.cdc.gov/mmwr/pdf/ss/ss6304.pdf [accessed 2014-11-17]
4. Johnston L, O'Malley P, Bachman J, Schulenberg J. Monitoring the future national results on adolescent drug use: Overview of key findings, 2011. National Institutes of Health. 2012. URL: https://files.eric.ed.gov/fulltext/ED529133.pdf [accessed 2015-03-12]
5. Centers for Disease Control Prevention (CDC). Vital signs: HIV infection, testing, and risk behaviors among youths - United States. MMWR Morb Mortal Wkly Rep 2012 Nov 30;61(47):971-976 [FREE Full text] [Medline: 23190571]
6. Michigan Department of Health and Human Services. URL: https://www.michigan.gov/hivsti [accessed 2022-01-13]
7. Youth online. Centers for Disease Control and Prevention. URL: https://nccd.cdc.gov/youthonline/App/Default.aspx [accessed 2014-11-17]
8. Marsch LA, Carroll KM, Kiluk BD. Technology-based interventions for the treatment and recovery management of substance use disorders: a JSAT special issue. J Subst Abuse Treat 2014 Jan;46(1):1-4 [FREE Full text] [doi: 10.1016/j.jsat.2013.08.010] [Medline: 24041749]
9. Villarruel AM, Loveland-Cherry CJ, Ronis DL. Testing the efficacy of a computer-based parent-adolescent sexual communication intervention for Latino parents. Fam Relat 2010 Dec 01;59(5):533-543 [FREE Full text] [doi: 10.1111/j.1741-3729.2010.00621.x] [Medline: 21116466]
10. Muessig KE, Nekkanti M, Bauermeister J, Bull S, Hightow-Weidman LB. A systematic review of recent smartphone, Internet and Web 2.0 interventions to address the HIV continuum of care. Curr HIV/AIDS Rep 2015 Mar;12(1):173-190 [FREE Full text] [doi: 10.1007/s11904-014-0239-3] [Medline: 25626718]
11. Boekeloo B, Griffin M. Review of clinical trials testing the effectiveness of physician intervention approaches to prevention alcohol-related problems in adolescent outpatients. Curr Pediatr Rev 2007 Feb 01;3(1):93-101 [FREE Full text] [doi: 10.2174/157339607779941679] [Medline: 23513072]
12. Hosek SG, Lemos D, Harper GW, Telander K. Evaluating the acceptability and feasibility of Project ACCEPT: an intervention for youth newly diagnosed with HIV. AIDS Educ Prev 2011 Apr;23(2):128-144 [FREE Full text] [doi: 10.1521/aeap.2011.23.2.128] [Medline: 21517662]
13. Mason M, Pate P, Drapkin M, Sozinho K. Motivational interviewing integrated with social network counseling for female adolescents: a randomized pilot study in urban primary care. J Subst Abuse Treat 2011 Sep;41(2):148-155. [doi: 10.1016/j.jsat.2011.02.009] [Medline: 21489741]
14. Haller DM, Meynard A, Lefebvre D, Ukoumunne OC, Narring F, Broers B. Effectiveness of training family physicians to deliver a brief intervention to address excessive substance use among young patients: a cluster randomized controlled trial. CMAJ 2014 May 13;186(8):E263-E272 [FREE Full text] [doi: 10.1503/cmaj.131301] [Medline: 24616136]
15. Israel B, Eng E, Schulz A, Parker E. Introduction to methods for CBPR for health. In: Methods in Community-Based Participatory Research for Health. San Francisco: Jossey-Bass; 2005.
16. Principles of drug addiction treatment: a research-based guide (third edition). National Institute on Drug Abuse. 2014. URL: https://nida.nih.gov/sites/default/files/podat-3rdEd-508.pdf [accessed 2022-01-13]
17. Nelson A, Cordova D, Walters AS, Szecsy E. Storytelling for Empowerment for Latino teens: increasing HIV prevention knowledge and attitudes. Journal of Adolescent Research 2015 Jun 18;31(2):202-231. [doi: 10.1177/0743558415588350]
18. Cordova D, Bauermeister J, Delva J, Alers-Rojas F, Waller N, Youth LC. A community-engaged approach to developing a primary care substance abuse preventionsexual health promotion app. 2014 Presented at: Society for Prevention Research; May 27-30; Washington DC.
19. Cordova D, Bauermeister JA, Fessler K, Delva J, Nelson A, Nurenberg R, Youth Leadership Council. A community-engaged approach to developing an mHealth HIV/STI and drug abuse preventive intervention for primary care: a qualitative study. JMIR Mhealth Uhealth 2015 Dec 18;3(4):e106 [FREE Full text] [doi: 10.2196/mhealth.4620] [Medline: 26685288]

20. Cordova D, Alers-Rojas F, Lua FM, Bauermeister J, Nurenberg R, Ovadje L, et al. The usability and acceptability of an adolescent mHealth HIV/STI and drug abuse preventive intervention in primary care. Behav Med 2018;44(1):36-47 [FREE Full text] [doi: 10.1080/08964289.2016.1189396] [Medline: 27223646]
21. Cordova D, Bauermeister JA, Fessler K, Delva J, Nelson A, Nurenberg R, Youth Leadership Council. Developing and m-health primary care HIV/STI preventive intervention for urban adolescents: Methodological considerations in the context of policy and technological advances. 2015 Presented at: National Conference of the Society for Prevention Research; May 26-29; Washington DC.
22. Coatsworth J, Pantin H, Szapocznik J. Familias Unidas: a family-centered ecodevelopmental intervention to reduce risk for problem behavior among Hispanic adolescents. Clin Child Fam Psychol Rev 2002 Jun;5(2):113-132. [doi: 10.1023/a:1015420503275] [Medline: 12093012]
23. Perkins DD, Zimmerman MA. Empowerment theory, research, and application. American J of Comm Psychol 1995 Oct;23(5):569-579. [doi: 10.1007/bf02506982]
24. Zimmerman MA, Israel BA, Schulz A, Checkoway B. Further explorations in empowerment theory: An empirical analysis of psychological empowerment. Am J Commun Psychol 1992 Dec;20(6):707-727. [doi: 10.1007/bf00942234]
25. Szapocznik J, Coatsworth J. An ecodevelopmental framework for organizing the influences on drug abuse: a developmental model of risk and protection. Drug Abuse: Origins & Interventions 1999:331-366. [doi: 10.1037/10341-014]
26. Cordova D, Ciofu A, Park K, Parra-Cardona JR, Holtrop K, Cervantes R. The role of intrapersonal and ecodevelopmental factors in the lives of Latino alternative high school youth. J Ethn Cult Divers Soc Work 2014 Apr 01;23(2):148-167 [FREE Full text] [doi: 10.1080/15313204.2013.809510] [Medline: 25067923]
27. Tebb KP, Sedlander E, Bausch S, Brindis CD. Opportunities and challenges for adolescent health under the Affordable Care Act. Matern Child Health J 2015 Oct;19(10):2089-2093 [FREE Full text] [doi: 10.1007/s10995-015-1737-7] [Medline: 25724539]
28. Cordova D, Alers-Rojas F, Lua FM, Bauermeister J, Nurenberg R, Ovadje L, et al. The usability and acceptability of an adolescent mHealth HIV/STI and drug abuse preventive intervention in primary care. Behav Med 2018;44(1):36-47 [FREE Full text] [doi: 10.1080/08964289.2016.1189396] [Medline: 27223646]
29. Cordova D, Munoz-Velazquez J, Mendoza Lua F, Fessler K, Warner S, Delva J, Youth Leadership Council, et al. Pilot study of a multilevel mobile health app for substance use, sexual risk behaviors, and testing for sexually transmitted infections and hiv among youth: randomized controlled trial. JMIR Mhealth Uhealth 2020 Mar 17;8(3):e16251 [FREE Full text] [doi: 10.2196/16251] [Medline: 32181747]
30. Cordova D, Mendoza Lua F, Muñoz-Velázquez J, Street K, Bauermeister JA, Fessler K, Youth Leadership Council, et al. A multilevel mHealth drug abuse and STI/HIV preventive intervention for clinic settings in the United States: A feasibility and acceptability study. PLoS One 2019;14(8):e0221508 [FREE Full text] [doi: 10.1371/journal.pone.0221508] [Medline: 31437240]
31. Peralta L, Deeds BG, Hipszer S, Ghalib K. Barriers and facilitators to adolescent HIV testing. AIDS Patient Care STDS 2007 Jun;21(6):400-408. [doi: 10.1089/apc.2006.0112] [Medline: 17594249]
32. Goyal MK, Witt R, Hayes KL, Zaoutis TE, Gerber JS. Clinician adherence to recommendations for screening of adolescents for sexual activity and sexually transmitted infection/human immunodeficiency virus. J Pediatr 2014 Aug;165(2):343-347 [FREE Full text] [doi: 10.1016/j.jpeds.2014.04.009] [Medline: 24840761]
33. Kumar D, Arya M. mHealth is an innovative approach to address health literacy and improve patient-physician communication - An HIV testing exemplar. J Mob Technol Med 2015 Jan 01;4(1):25-30 [FREE Full text] [doi: 10.7309/jmtm.4.1.6] [Medline: 25729441]
34. Rounsaville BJ, Carroll KM, Onken LS. A stage model of behavioral therapies research: Getting started and moving on from stage I. Clinical Psychology: Science and Practice 2001 Feb;8(2):133-142. [doi: 10.1093/clipsy.8.2.133]
35. Gad S. Clinical Trials Handbook. Hoboken, NJ: Wiley; 2009.
36. Hofer A, Abraham J, Moscovice I. Expansion of coverage under the Patient Protection and Affordable Care Act and primary care utilization. Milbank Q 2011 Mar;89(1):69-89 [FREE Full text] [doi: 10.1111/j.1468-0009.2011.00620.x] [Medline: 21418313]
37. Swendeman D, Rotheram-Borus MJ. Innovation in sexually transmitted disease and HIV prevention: Internet and mobile phone delivery vehicles for global diffusion. Current Opinion in Psychiatry 2010;23(2):139-144. [doi: 10.1097/yco.0b013e328336656a]
38. NIH HIV/AIDS research priorities and guidelines for determining AIDS funding. National Institutes of Health. 2015. URL: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-137.html [accessed 2015-03-12]
39. Prior national HIV/AIDS strategies (2010-2021). HIV.gov. URL: https://www.hiv.gov/federal-response/national-hiv-aids-strategy/national-hiv-aids-strategies-2010-2021/ [accessed 2022-12-13]
40. HIV in the United States by age. Centers for Disease Control and Prevention. URL: https://www.cdc.gov/hiv/group/age/index.html [accessed 2022-12-13]
41. Reported STDs in the United States: 2013 national data for chlamydia, gonorrhea, and syphilis. Center for Disease Control and Prevention. URL: https://stacks.cdc.gov/view/cdc/26427 [accessed 2022-12-13]

42. Prado GJ, Schwartz SJ, Maldonado-Molina M, Huang S, Pantin HM, Lopez B, et al. Ecodevelopmental x intrapersonal risk: substance use and sexual behavior in Hispanic adolescents. Health Educ Behav 2009 Feb;36(1):45-61 [FREE Full text] [doi: 10.1177/1090198107311278] [Medline: 18326053]
43. Cordova D, Huang S, Arzon M, Freitas D, Malcolm S, Prado G. The role of attitudes, family, peer and school on alcohol use, rule breaking and aggressive behavior in Hispanic delinquent adolescents. Open Fam Stud J 2011;4(Suppl 1-M4):38-45 [FREE Full text] [doi: 10.2174/1874922401104010038] [Medline: 22473467]
44. Balaji AB, Eaton DK, Voetsch AC, Wiegand RE, Miller KS, Doshi SR. Association between HIV-related risk behaviors and HIV testing among high school students in the United States, 2009. Arch Pediatr Adolesc Med 2012 Apr;166(4):331-336. [doi: 10.1001/archpediatrics.2011.1131] [Medline: 22213606]
45. Decker MR, Rodney R, Chung S, Jennings JM, Ellen JM, Sherman SG. HIV testing among youth in a high-risk city: prevalence, predictors, and gender differences. AIDS Care 2015;27(5):555-560 [FREE Full text] [doi: 10.1080/09540121.2014.986048] [Medline: 25495522]
46. Uppal A, Chou KJ. Screening adolescents for sexually transmitted infections in the pediatric emergency department. Pediatric Emergency Care 2015;31(1):20-24. [doi: 10.1097/pec.0000000000000322]
47. Prado G, Pantin H, Huang S, Cordova D, Tapia MI, Velazquez MR, et al. Effects of a family intervention in reducing HIV risk behaviors among high-risk Hispanic adolescents: a randomized controlled trial. Arch Pediatr Adolesc Med 2012 Feb;166(2):127-133 [FREE Full text] [doi: 10.1001/archpediatrics.2011.189] [Medline: 21969363]
48. Reid RJ, Garcia-Reid P, Forenza B, Eckert C, Carrier M, Drag S. Let Our Voices Be Heard: urban minority adolescents share their perspectives regarding substance abuse and HIV/AIDS prevention messages. Am J Health Promot 2014 Nov 01;29(2):107-114. [doi: 10.4278/ajhp.130117-qual-34]
49. Hawkins JD, Catalano RF, Miller JY. Risk and protective factors for alcohol and other drug problems in adolescence and early adulthood: implications for substance abuse prevention. Psychol Bull 1992 Jul;112(1):64-105. [doi: 10.1037/0033-2909.112.1.64] [Medline: 1529040]
50. DiClemente R, Salazar L, Crosby R, Rosenthal S. Prevention and control of sexually transmitted infections among adolescents: the importance of a socio-ecological perspective--a commentary. Public Health 2005 Sep;119(9):825-836. [doi: 10.1016/j.puhe.2004.10.015] [Medline: 15913678]
51. Mahat G, Scoloveno MA, Scoloveno R. HIV/AIDS knowledge, self-efficacy for limiting sexual risk behavior and parental monitoring. J Pediatr Nurs 2016;31(1):e63-e69. [doi: 10.1016/j.pedn.2015.06.015] [Medline: 26216110]
52. Córdova D, Lua FM, Ovadje L, Fessler K, Bauermeister JA, Salas-Wright CP, et al. Adolescent experiences of clinician-patient HIV/STI communication in primary care. Health Commun 2018 Sep;33(9):1177-1183 [FREE Full text] [doi: 10.1080/10410236.2017.1339379] [Medline: 28686489]
53. Stewart MA. Effective physician-patient communication and health outcomes: a review. CMAJ 1995 May 01;152(9):1423-1433 [FREE Full text] [Medline: 7728691]
54. Coelho KR, Galan C. Physician cross-cultural nonverbal communication skills, patient satisfaction and health outcomes in the physician-patient relationship. Int J Family Med 2012;2012:376907 [FREE Full text] [doi: 10.1155/2012/376907] [Medline: 22792459]
55. Zolnierek KBH, Dimatteo MR. Physician communication and patient adherence to treatment: a meta-analysis. Med Care 2009 Aug;47(8):826-834 [FREE Full text] [doi: 10.1097/MLR.0b013e31819a5acc] [Medline: 19584762]
56. Nelson A. Multicultural model of HIV prevention for youth. In: International Journal of Learning. 2004 Presented at: Eleventh International Literacy and Education Research Network Conference on Learning; June 27-30; Havana, Cuba p. 1555-1564.
57. Szapocznik J, Prado G, Burlew AK, Williams RA, Santisteban DA. Drug abuse in African American and Hispanic adolescents: culture, development, and behavior. Annu Rev Clin Psychol 2007;3:77-105. [doi: 10.1146/annurev.clinpsy.3.022806.091408] [Medline: 17716049]
58. Cordova D, Estrada Y, Malcolm S, Huang S, Brown C, Pantin H, et al. Prevention science: an epidemiological approach. In: Defining Prevention Science. Boston, MA: Springer; 2014.
59. Ortega J, Huang S, Prado G. Applying ecodevelopmental theory and the theory of reasoned action to understand HIV risk behaviors among Hispanic adolescents. Hisp Health Care Int 2012 Jan 03;10(1):42-52 [FREE Full text] [doi: 10.1891/1540-4153.10.1.42] [Medline: 23152718]
60. Prado G, Huang S, Maldonado-Molina M, Bandiera F, Schwartz SJ, de la Vega P, et al. An empirical test of ecodevelopmental theory in predicting HIV risk behaviors among Hispanic youth. Health Educ Behav 2010 Feb;37(1):97-114 [FREE Full text] [doi: 10.1177/1090198109349218] [Medline: 20130302]
61. Perrino T, González-Soldevilla A, Pantin H, Szapocznik J. The role of families in adolescent HIV prevention: a review. Clin Child Fam Psychol Rev 2000 Jun;3(2):81-96. [doi: 10.1023/a:1009571518900] [Medline: 11227063]
62. Pantin H, Schwartz SJ, Sullivan S, Coatsworth JD, Szapocznik J. Preventing substance abuse in Hispanic immigrant adolescents: an ecodevelopmental, parent-centered approach. Hispanic Journal of Behavioral Sciences 2016 Jul 25;25(4):469-500. [doi: 10.1177/0739986303259355]

63. Prado G, Pantin H, Schwartz SJ, Lupei NS, Szapocznik J. Predictors of engagement and retention into a parent-centered, ecodevelopmental HIV preventive intervention for Hispanic adolescents and their families. J Pediatr Psychol 2006 Oct;31(9):874-890. [doi: 10.1093/jpepsy/jsj046] [Medline: 16049264]
64. Cooper B, Toskin I, Kulier R, Allen T, Hawkes S. Brief sexuality communication--a behavioural intervention to advance sexually transmitted infection/HIV prevention: a systematic review. BJOG 2014 Oct;121 Suppl 5:92-103. [doi: 10.1111/1471-0528.12877] [Medline: 25335846]
65. Sterling S, Kline-Simon AH, Satre DD, Jones A, Mertens J, Wong A, et al. Implementation of screening, brief intervention, and referral to treatment for adolescents in pediatric primary care: a cluster randomized trial. JAMA Pediatr 2015 Nov;169(11):e153145 [FREE Full text] [doi: 10.1001/jamapediatrics.2015.3145] [Medline: 26523821]
66. Naik AD, Lawrence B, Kiefer L, Ramos K, Utech A, Masozera N, et al. Building a primary care/research partnership: lessons learned from a telehealth intervention for diabetes and depression. Fam Pract 2015 Apr;32(2):216-223. [doi: 10.1093/fampra/cmu084] [Medline: 25552674]
67. US Preventive Services Task Force. The guide to clinical preventive services 2014. Agency for Healthcare Research and Quality. 2014. URL: https://www.ahrq.gov/sites/default/files/wysiwyg/professionals/clinicians-providers/guidelines-recommendations/guide/cpsguide.pdf [accessed 2022-01-13]
68. US Preventive Services Task Force. Recommendation topics. URL: http://www.uspreventiveservicestaskforce.org/Page/Name/recommendations [accessed 2022-01-13]
69. Levine D, McCright J, Dobkin L, Woodruff AJ, Klausner JD. SEXINFO: a sexual health text messaging service for San Francisco youth. Am J Public Health 2008 Mar;98(3):393-395. [doi: 10.2105/AJPH.2007.110767] [Medline: 18235068]
70. CDC's vision for public health surveillance in the 21st century. Centers for Disease Control and Prevention. URL: https://www.cdc.gov/mmwr/pdf/other/su6103.pdf [accessed 2022-01-13]
71. Lightfoot M. HIV prevention for adolescents: where do we go from here? Am Psychol 2012 Nov;67(8):661-671. [doi: 10.1037/a0029831] [Medline: 23163452]
72. Allison S, Bauermeister JA, Bull S, Lightfoot M, Mustanski B, Shegog R, et al. The intersection of youth, technology, and new media with sexual health: moving the research agenda forward. J Adolesc Health 2012 Sep;51(3):207-212 [FREE Full text] [doi: 10.1016/j.jadohealth.2012.06.012] [Medline: 22921129]
73. Civljak M, Stead LF, Hartmann-Boyce J, Sheikh A, Car J. Internet-based interventions for smoking cessation. Cochrane Database Syst Rev 2013 Jul 10(7):CD007078. [doi: 10.1002/14651858.CD007078.pub4] [Medline: 23839868]
74. Smith A. US smartphone use in 2015. Pew Research Center. 2015 Apr. URL: http://www.pewinternet.org/2015/04/01/us-smartphone-use-in-2015/ [accessed 2015-03-12]
75. Nelson A, Arthur B. Storytelling for empowerment: decreasing at-risk youth's alcohol and marijuana use. Journal of Primary Prevention 2003;24(2):169-180. [doi: 10.1023/A:1025944412465]
76. Nelson A. Final report submitted to the Virginia G. National Registry of Evidence-Based Programs and Practices. 2006. URL: http://ga-sps.org/public/resources/storytelling-for-empowerment1674120870.pdf [accessed 2015-03-01]
77. Bowen DJ, Kreuter M, Spring B, Cofta-Woerpel L, Linnan L, Weiner D, et al. How we design feasibility studies. Am J Prev Med 2009 May;36(5):452-457 [FREE Full text] [doi: 10.1016/j.amepre.2009.02.002] [Medline: 19362699]
78. Sterling S, Kline-Simon AH, Wibbelsman C, Wong A, Weisner C. Screening for adolescent alcohol and drug use in pediatric health-care settings: predictors and implications for practice and policy. Addict Sci Clin Pract 2012 Aug 16;7(1):13 [FREE Full text] [doi: 10.1186/1940-0640-7-13] [Medline: 23186254]
79. Schuster MA, Bell RM, Petersen LP, Kanouse DE. Communication between adolescents and physicians about sexual behavior and risk prevention. Arch Pediatr Adolesc Med 1996 Sep;150(9):906-913. [doi: 10.1001/archpedi.1996.02170340020004] [Medline: 8790119]
80. Epstein RM, Morse DS, Frankel RM, Frarey L, Anderson K, Beckman HB. Awkward moments in patient-physician communication about HIV risk. Ann Intern Med 1998 Mar 15;128(6):435-442. [doi: 10.7326/0003-4819-128-6-199803150-00003] [Medline: 9499326]
81. Dybå T, Dingsøyr T. Empirical studies of agile software development: A systematic review. Information and Software Technology 2008 Aug;50(9-10):833-859. [doi: 10.1016/j.infsof.2008.01.006]
82. Harper GW, Contreras R, Bangi A, Pedraza A. Collaborative process evaluation. Journal of Prevention & Intervention in the Community 2003 Nov 10;26(2):53-69. [doi: 10.1300/j005v26n02_05]
83. Attkisson CC, Greenfield TK. The use of psychological testing for treatment planning and outcomes assessment: Instruments for adults. The UCSF Client Satisfaction Scales: The Client Satisfaction Questionnaire-8. 2004. URL: https://psycnet.apa.org/record/2004-14941-027 [accessed 2024-01-22]
84. Cordova D, Guzman K, Martin C. A community engaged approach to working toward the implementation of mental health best practices in a primary care setting. 2014 Presented at: 7th annual conference on The Science of Dissemination Implementation; December 8-9; North Bethesda, MD, USA.
85. Lenhart A. Pew Research Center. 2015 Apr 9. URL: https://www.pewresearch.org/internet/2015/04/09/teens-social-media-technology-2015/ [accessed 2015-05-12]
86. Efird J. Blocked randomization with randomly selected block sizes. Int J Environ Res Public Health 2011 Jan;8(1):15-20 [FREE Full text] [doi: 10.3390/ijerph8010015] [Medline: 21318011]

87. Knight JR, Sherritt L, Shrier LA, Harris SK, Chang G. Validity of the CRAFFT substance abuse screening test among adolescent clinic patients. Arch Pediatr Adolesc Med 2002 Jun;156(6):607-614. [doi: 10.1001/archpedi.156.6.607] [Medline: 12038895]
88. Jemmott JB, Jemmott LS, Fong GT. Abstinence and safer sex HIV risk-reduction interventions for African American adolescents: a randomized controlled trial. JAMA 1998 May 20;279(19):1529-1536. [doi: 10.1001/jama.279.19.1529] [Medline: 9605896]
89. Campbell C, Lockyer J, Laidlaw T, Macleod H. Assessment of a matched-pair instrument to examine doctor-patient communication skills in practising doctors. Med Educ 2007 Feb;41(2):123-129. [doi: 10.1111/j.1365-2929.2006.02657.x] [Medline: 17269944]
90. Hanna KM. An adolescent and young adult condom perception scale. West J Nurs Res 1999 Oct;21(5):621-31; discussion 632. [doi: 10.1177/01939459922044081] [Medline: 11512183]
91. Carpenter C, Howard D. Development of a drug use resistance self-efficacy (DURSE) scale. Am J Health Behav 2009;33(2):147-157. [doi: 10.5993/ajhb.33.2.4] [Medline: 18844509]
92. Kraemer HC, Mintz J, Noda A, Tinklenberg J, Yesavage JA. Caution regarding the use of pilot studies to guide power calculations for study proposals. Arch Gen Psychiatry 2006 May;63(5):484-489. [doi: 10.1001/archpsyc.63.5.484] [Medline: 16651505]
93. Breslow NE, Clayton DG. Approximate inference in generalized linear mixed models. Journal of the American Statistical Association 1993 Mar;88(421):9. [doi: 10.2307/2290687]
94. Elashoff JD. nQuery Advisor® Version 7.0 User's Guide. 1997 Jan. URL: https://cdn2.hubspot.net/hubfs/488764/nQ70_Manual.pdf [accessed 2024-01-22]
95. Lachenbruch PA, Cohen J. Statistical Power Analysis for the Behavioral Sciences (2nd ed.). Journal of the American Statistical Association 1989 Dec;84(408):1096. [doi: 10.2307/2290095]

Abbreviations

A-START: AIDS-Science Track Award for Research Transition
GLMM: generalized linear mixed model
LMM: linear mixed model
mHealth: mobile health
RCT: randomized controlled trial
S4E: Storytelling 4 Empowerment
SFE: Storytelling for Empowerment
STI: sexually transmitted infection

Edited by A Mavragani; submitted 16.03.23; peer-reviewed by N Ilanchezhiyan, J Mitchell, C Baxter; comments to author 02.12.23; revised version received 21.12.23; accepted 24.12.23; published 19.02.24.

Please cite as:
Cordova D, Bauermeister JA, Warner S, The Youth Leadership Council, Wells P, MacLeod J, Neilands TB, Mendoza Lua F, Delva J, Fessler KB, Smith Jr V, Khreizat S, Boyer C
Efficacy of a Digital Health Preventive Intervention for Adolescents With HIV or Sexually Transmitted Infections and Substance Use Disorder: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2024;13:e47216
URL: https://www.researchprotocols.org/2024/1/e47216
doi:10.2196/47216
PMID:38373025

Protocol

Mobile Intervention to Address Cannabis Use Disorder Among Black Adults: Protocol for a Randomized Controlled Trial

Pamella Nizio[1], BS; Bryce Clausen[1], BS; Michael S Businelle[2], PhD; Natalia Ponton[1]; Ava A Jones[1], BA; Brooke Y Redmond[1], PhD; Julia D Buckner[3], PhD; Ezemenari M Obasi[1], PhD; Michael J Zvolensky[1], PhD; Lorra Garey[1], PhD

[1]University of Houston, Houston, TX, United States

[2]TSET Health Promotion Research Center, Stephenson Cancer Center, University of Oklahoma Health Sciences Center, Oklahoma City, OK, United States

[3]Louisiana State University, Baton Rouge, TX, United States

Corresponding Author:
Lorra Garey, PhD
University of Houston
3695 Cullen Blvd.
Room 104
Houston, TX, 77204
United States
Phone: 1 7137438056
Email: llgarey@uh.edu

Abstract

Background: African American or Black (hereafter referred to as Black) adults who use cannabis use it more frequently and are more likely to meet criteria for cannabis use disorder (CUD) than both White and Hispanic or Latin individuals. Black adults may be more apt to use cannabis to cope with distress, which constitutes a false safety behavior (FSB; a behavior designed to reduce psychological distress in the short term). Although FSB engagement can perpetuate the cycle of high rates of CUD among Black individuals, limited work has applied an FSB elimination treatment approach to Black adults with CUD, and no previous work has evaluated FSB reduction or elimination in the context of a culturally tailored and highly accessible treatment developed for Black individuals.

Objective: This study aims to develop and pilot-test a culturally tailored adaptive intervention that integrates FSB reduction or elimination skills for cannabis reduction or cessation among Black adults with probable CUD (Culturally Tailored-Mobile Integrated Cannabis and Anxiety Reduction Treatment [CT-MICART]).

Methods: Black adults with probable CUD (N=50) will complete a web-based screener, enrollment call, baseline assessment, 3 daily ecological momentary assessments (EMAs) for 6 weeks, and a follow-up self-report assessment and qualitative interview at 6 weeks after randomization. Participants will be randomized into 1 out of the 2 conditions after baseline assessment: (1) CT-MICART+EMAs for 6 weeks or (2) EMAs only for 6 weeks.

Results: The enrollment started in June 2023 and ended in November 2023. Data analysis will be completed in March 2024.

Conclusions: No culturally tailored, evidence-based treatment currently caters to the specific needs of Black individuals with CUD. This study will lay the foundation for a new approach to CUD treatment among Black adults that is easily accessible and has the potential to overcome barriers to treatment and reduce practitioner burden in order to support Black individuals who use cannabis with probable CUD.

Trial Registration: ClinicalTrials.gov NCT05566730; https://clinicaltrials.gov/study/NCT05566730

International Registered Report Identifier (IRRID): DERR1-10.2196/52776

(JMIR Res Protoc 2024;13:e52776) doi:10.2196/52776

KEYWORDS

cannabis use; false safety behaviors; mobile health, just-in-time adaptive interventions; Black or African American; mobile phone; African American; Black; cannabis; adults; adult; Hispanic; Latin; adaptive intervention; cannabis reduction; cessation; ecological momentary assessments

Introduction

Cannabis has been among the most widely used substances for 30 consecutive years in the United States [1], and rates of past-year use have consistently increased in the general population [2,3]. Among individuals who use cannabis, African American or Black (hereafter referred to as Black) individuals exhibit more severe use patterns, including weekly use, and are more likely to meet diagnostic criteria for current cannabis use disorder (CUD) than both White and Hispanic or Latin individuals who use cannabis [4-6]. These data are alarming as CUD is associated with more severe psychosocial risk profiles relative to cannabis users without CUD and nonusers, including poly-substance use, psychiatric problems, and legal trouble [7]. Additionally, although Black individuals who use cannabis are more likely to report being ready to quit and making a recent quit attempt than both Hispanic or Latin and White individuals who use cannabis [8,9], this population is less likely to seek in-person treatment relative to White individuals who use cannabis. Specific individual (eg, beliefs about use) [10], community (eg, neighborhood attitudes about use) [11], and institutional (eg, health care access) [12] factors, as well as institutionalized racism and discrimination (eg, more likely to not be listened to by practitioners) [13], likely contribute to the reluctancy to seek traditional treatments among Black individuals with CUD. Given that treatment involvement has been shown to assist with cannabis use reduction and prolonged abstinence [14], addressing the lack of treatment engagement among this population is imperative to reduce the potential negative health and psychological effects of cannabis use among this group.

Psycho-sociocultural models of substance use posit that Black individuals may use cannabis and continue using it despite cannabis-related problems to manage psychological distress associated with minority-related stress and daily stressors [15-18]. Using cannabis to cope with such distress reflects a false safety behavior (FSB), or a behavior designed to reduce psychological distress in the short term but paradoxically maintains or even exacerbates distress in the long term [19,20]. FSB is more frequent among Black individuals compared to non-Hispanic or Latin White individuals and it is associated with more anxiety, depression, and suicidal thoughts and behaviors among Black individuals [21]. Thus, FSB is an important behavioral vulnerability factor associated with mental health problems among Black individuals. These findings are concerning as problematic cannabis use is higher among those with mental health problems [22], and mental health problems interfere with changing cannabis use [23]. Moreover, the majority of individuals who use cannabis tend to engage in additional FSBs such as avoidance and avoiding social situations when cannabis is unavailable [24], and FSBs may contribute to cannabis-related problems due to tendencies to engage in maladaptive attempts to regulate negative affect [25]. As such, FSB engagement can perpetuate the cycle of high rates of CUD among Black individuals who use cannabis and increase the risk for poor psychosocial outcomes and cannabis-related disparities [24,26,27].

Importantly, transdiagnostic treatments have been developed to eliminate FSBs to improve behavioral health outcomes. Specifically, cognitive-behavioral approaches to FSB elimination treatment that target the identification and elimination of FSBs have been designed and successfully used for use across various anxiety disorders [20]. Furthermore, recent work has explored the potential of FSB elimination integrated with motivation enhancement therapy combined with cognitive behavioral therapy (MET-CBT) to address the co-occurrence among anxiety and CUDs, Integrated Cannabis and Anxiety Reduction Treatment (ICART) [28-30]. In a pilot test of ICART, individuals with CUD were randomized to either in-person ICART or MET-CBT for CUD [28]. Although participants in both study groups reported decreased cannabis use and related problems, patients in the ICART condition were more likely to be abstinent posttreatment than those in the MET-CBT condition. Patients with more severe baseline cannabis use and use-related problems were especially likely to benefit from ICART [31]. These findings suggest that integrating FSB elimination with MET-CBT is at least as efficacious, if not more efficacious, as a gold-standard psychosocial CUD treatment (MET-CBT), especially for patients with more severe cannabis-related pathology.

Despite the potential for FSB reduction or elimination treatments to assist with cannabis use reduction or cessation among individuals with problematic use, this work has been limited by its in-person design and lack of cultural tailoring to Black adults. Indeed, given the cannabis-related and FSB disparities experienced by Black adults [16,21], it may be beneficial to evaluate FSB reduction or elimination integrated with cognitive behavioral therapy (CBT) for CUD in the context of a culturally tailored and highly accessible treatment (ie, a mobile health [mHealth] intervention delivered via a smartphone app) developed for this underserved group.

Extant literature has highlighted existing mHealth work for cannabis use and CUD [32], including mHealth interventions that have been culturally tailored to treat specific populations such as individuals with psychosis [33], as well as individuals with comorbid CUD and cigarette smoking [34]. However, no mHealth interventions for cannabis use and CUD currently target specific psycho-sociocultural factors related to cannabis use and use-related problems among Black individuals who use cannabis with probable CUD. We have therefore developed and are currently pilot-testing a culturally tailored intervention for Black adults with probable CUD through integrated FSB reduction or elimination with CBT for CUD (Culturally Tailored-Mobile Integrated Cannabis and Anxiety Reduction Treatment [CT-MICART]) using an accessible, adaptable, and highly scalable smartphone app. The goal is to examine the effects of CT-MICART on cannabis use, coping motives for cannabis use, and FSB engagement. We hypothesize that participants who are randomized into the CT-MICART condition will report better cannabis outcomes and less FSB compared to those who are randomized into the control condition at the 6-week follow-up. Furthermore, we will examine app engagement indicators and review qualitative data for methods to improve app content.

Methods

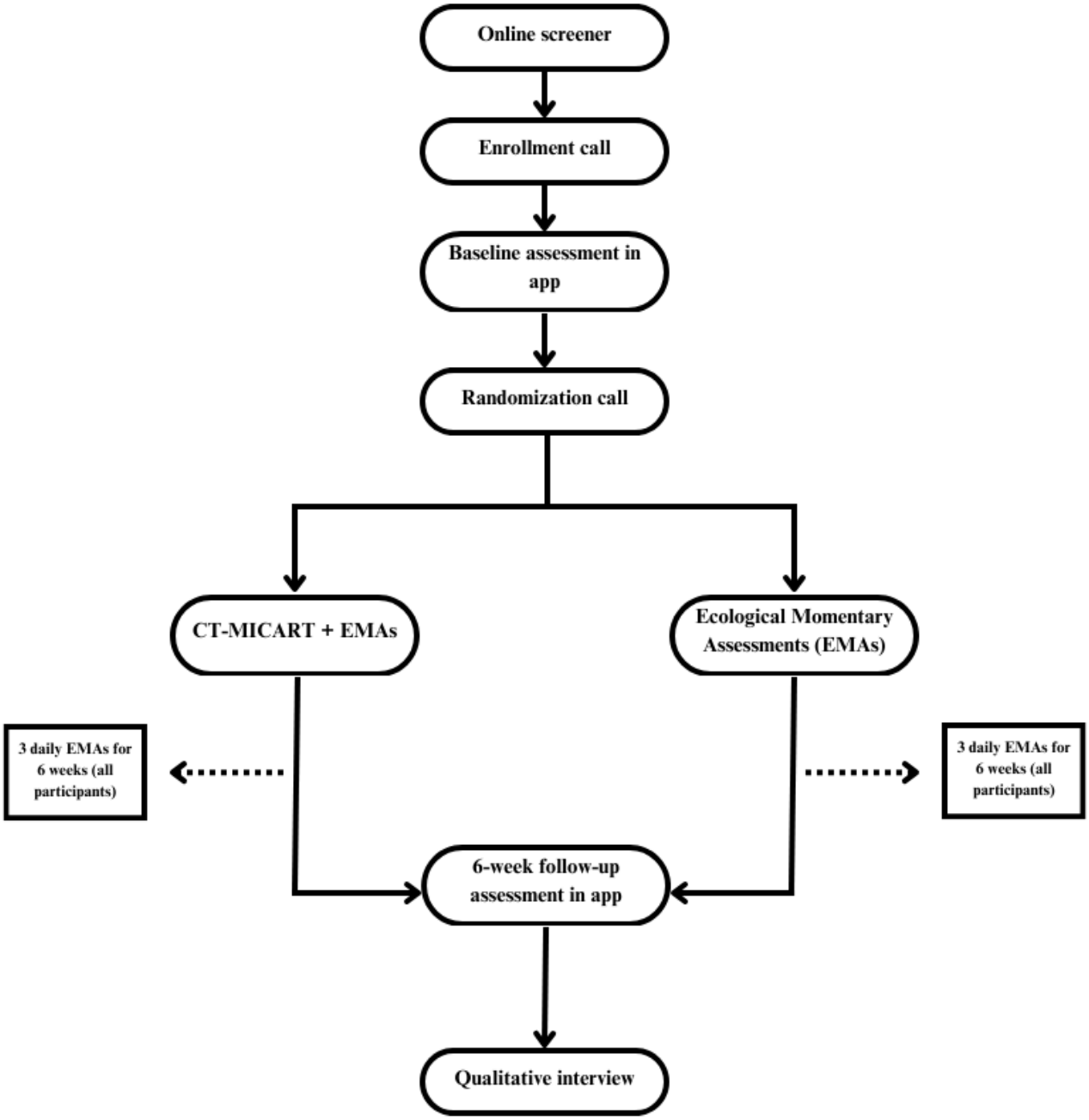
Ethical Considerations

All participants provided written informed consent signed electronically after reviewing consent documents with research staff. To protect participant privacy and confidentiality, all phone and Zoom (Zoom Video Communications) appointments are completed by trained research staff in a secure office. Additionally, participants are assigned an ID number that is used to identify their data throughout the study. Only trained research staff have access to the key that can match the participant data to the participant's name. The key is password-protected on a secure server housed at the University of Houston. Participants are compensated up to US $160 in Amazon electronic gift cards for participating in the study. The institutional review board (IRB) at the University of Houston approved the study (STUDY00003690).

Study Design

A total of 50 Black adults with probable CUD are being recruited through national advertisements across different social media and web-based platforms to participate in this study. Eligible participants are randomized into 1 out of the 2 conditions (ecological momentary assessment [EMA] only vs CT-MICART+EMA). All the participants who consented are asked to complete 3 prompted daily EMAs for 6 weeks. Only participants in the CT-MICART+EMA condition will receive intervention content. Participants are informed during the consent process that they have an equal chance of being assigned to each study condition. Moreover, participants are also informed that one of the study's treatment conditions consists of watching treatment videos and using CT-MICART app features, while the other condition consists only of completing daily EMAs. Following the 6-week intervention period, all participants will complete a follow-up assessment survey in the app and a qualitative interview phone call. See Figure 1 for the study flow.

Figure 1. Study flowchart. CT-MICART: Culturally Tailored-Mobile Integrated Cannabis and Anxiety Reduction Treatment; EMA: ecological momentary assessment.



Participants

Participants will include 50 individuals who identify as Black with probable CUD. Participants must meet the following eligibility criteria to participate: (1) at least 18 years of age, (2) self-identify as Black or African American, (3) meet criteria for probable CUD (assessed via the Cannabis Use Disorder Identification Test-Revised [CUDIT-R] with a score of >12) [35], (4) motivated to reduce cannabis (>5 on a 10-point scale), (5) score ≥4 on the Rapid Estimate of Adult Literacy in Medicine-Short Form (REALM-SF) indicating higher than sixth-grade English reading level [36], (6) own an Android smartphone for EMA completion, and (7) report cannabis use to manage anxiety or stress in the past month. Exclusion criteria include (1) legal mandate of substance misuse treatment; (2) report of current or intended participation in a concurrent substance use treatment, including pharmacotherapy or psychotherapy for CUD not provided by the researchers; (3) ongoing psychotherapy of any duration directed specifically toward the treatment of anxiety or depression; (4) not being fluent in English; (5) pregnant or planning to become pregnant within the next 6 months (assessed via self-report); and (6) inability to provide a photo ID and valid address to verify identity.

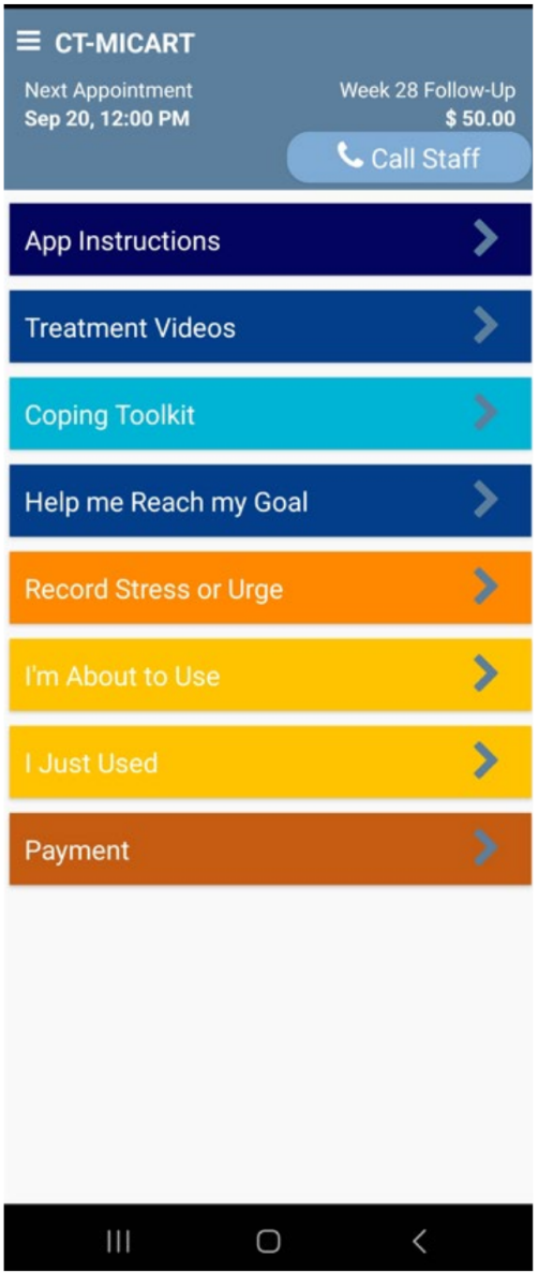
Procedures

This study is funded by the National Institute on Minority Health and Health Disparities (U54MD015946) and is registered on

ClinicalTrials.gov (NCT05566730). The IRB where the study takes place has reviewed and approved all procedures and study materials. Interested participants are asked to complete a web-based self-report screener survey via Qualtrics (Qualtrics International Inc). Those deemed eligible at the screener are then scheduled for an enrollment Zoom call of approximately 30 minutes. During the enrollment Zoom call, participants are given detailed information on the goals, purpose, and procedures of the study; provide informed consent; show their photo ID to the research team; and complete a literacy test to confirm they are at higher than sixth-grade English reading level [37]. Those found eligible during the enrollment Zoom call are asked to download the Insight smartphone app onto their personal smartphone and to complete the 30-minute baseline survey via the app. Eligible participants who complete the baseline survey are then contacted by research staff so they can be randomized into a study condition (ie, CT-MICART vs EMA only). During this randomization call, participants are oriented to app features for their assigned condition by the research team.

Following randomization, participants are prompted by the app to complete 3 EMAs daily. EMAs take approximately 2-3 minutes to complete. The research staff monitors the EMA completion rates of each participant on a weekly basis. When a participant's completion rate falls below 80%, a research staff member contacts the participant via text, phone, or email to remind them of the importance of completing their daily EMAs. Participants are informed that they can contact study staff at any point during the study by pressing the "Call Staff" button at the top of the app screen should they experience technical difficulties. Please see Figure 2 for a screenshot of the CT-MICART features available via the app home screen.

Figure 2. The main menu of CT-MICART features. CT-MICART: Culturally Tailored-Mobile Integrated Cannabis and Anxiety Reduction Treatment.



All participants are also asked to complete a 6-week postrandomization assessment and a qualitative interview. Specifically, at the end of the 6-week EMA period, the follow-up assessment becomes available on the app home screen and takes approximately 30 minutes to complete. The qualitative interview is scheduled with a trained research staff member and focuses on the participant's experiences using the CT-MICART+EMA or EMA-only app features. Participants can earn up to US $160 in Amazon electronic gift cards for their participation. Specifically, eligible participants are compensated with a US $20 gift card for completing the baseline assessment and a US $50 gift card for completing the 6-week follow-up, including the qualitative interview. Ineligible participants are not being compensated for completing the brief baseline Zoom call. In addition to baseline and follow-up compensation, participants are compensated for their EMA completion based on their completion rate. Those who complete 50% to 70% of all EMA assessments during the 6-week study period will receive a US $30 gift card, those who complete 71% to 79% will receive a US $60 gift card, and those who complete 80% or more will receive a US $90 gift card. Thus, if a participant completes 80% or more of the assessment across the entire 6-week trial, they can earn up to US $160 in electronic gift cards across all assessments.

Intervention Conditions

Overview

All participants have access to a "Call Staff" button that enables participants to easily call the study team. In addition, all participants have access to an "App Instructions" button that provides detailed descriptions of each of the app functions. Finally, all participants are informed that they can click the "Payment" button to view an up-to-the-moment accounting of all EMAs prompted and completed and the current compensation based on EMA and assessment completion.

All participants are instructed to complete all smartphone assessments through Insight (TSET Health Promotion Research Center), an encrypted mobile app through which participants receive all study content. Encrypted data will be automatically password protected and saved to the University of Houston's and the University of Oklahoma Health Science Center's institutional server and will only be accessible to the IRB-approved research team members. Moreover, participants are informed during the consent process that they are responsible for any phone service costs related to the study.

Active Condition (CT-MICART+EMAs)

Overview

The CT-MICART+EMA condition consists of access to the CT-MICART content in the Insight app and 3 prompted daily EMAs. The morning EMA is delivered 30 minutes after the preset waking time, the lunch EMA is delivered at 12:15 PM, and the evening EMA is delivered 1 hour and 15 minutes before the participant's preset sleep time. The core components of the CT-MICART condition include FSB elimination training and CBT for CUD with culturally tailored content. The CT-MICART+EMA content includes (1) treatment on a "schedule" that is culturally adapted (ie, 12 different 3- to 5-minute treatment video files); (2) participant-driven, automated, individually tailored treatment messages (eg, tailored to each participant's daily goal of reducing cannabis use, abstaining from cannabis, or no daily goal); (3) "on demand" features (ie, Coping Toolkit and Help Me Reach My Goal); and (4) end-of-day FSB elimination training exercises.

Process to Culturally Adapt Treatment

We followed the Cultural Adaptation Process [38] model of treatment adaption to culturally tailor CT-MICART. All treatment videos include depictions of Black adults and accompanying audio is voiced by Black voice actors who worked closely with our research team. Moreover, all app content was reviewed by a diverse Community Research Advisory Board (CRAB) at the Health Research Institute at the University of Houston. The CRAB was consulted: they provided feedback during the app development process, and appropriate modifications were made based on their feedback.

Treatment on a Schedule

To provide automated intervention content that is tailored to each participant's current goals and delivered in a manner that is best matched to their schedule, the app asks participants if they would like to watch 1 of the 12 different 3- to 5-minute treatment videos (ie, 2 videos per week) over the 6-week intervention period. Scheduled video sessions are cued (ie, the phone rings and vibrates) at the scheduled time and every 15 minutes (up to 2 times) after the scheduled time until the participant acknowledges the cue. Participants have the option to delay or reschedule videos or watch them after the scheduled day or time (ie, the next unwatched video populates [in order] in the app after the previous video is viewed). Videos can be watched as many times as desired. The phone records the date or time when each video is watched (ie, both initiation and completion). The 12 brief (3-5 minutes) CT-MICART videos provide psychoeducation on (1) the nature of cannabis use and negative affect (eg, anxiety and stress) and the FSB model; (2) the emotional processing model of negative affect (and how it relates to cannabis) and cannabis-related coping strategies (eg, avoiding people, places, and things); (3) relations between FSB and racial discrimination, negative affect, and cannabis use; (4) cannabis (and other substance) use as an FSB and understanding cannabis use patterns; (5) countering phobias (ie, exposure to anxiety- and stress-provoking stimuli without engagement in FSB, including cannabis) and coping with cravings; (6) fading other FSBs (eg, checking, reassurance seeking, companions, and avoidance of bodily sensations) and managing thoughts related to cannabis use; (7) fading other FSBs (avoidance) and managing negative moods; (8) fading other FSBs (cognitive avoidance) and seemingly irrelevant decisions; (9) problem-solving; (10) managing social influences (refusal skills and assertiveness); (11) planning for emergencies and coping with lapse; and (12) preventing relapse.

Tailored and Real-Time Treatment Messages

Participants receive personally tailored messages that are based upon each day's cannabis cessation or reduction goal (ie, reduce cannabis use today, abstinent from cannabis today, or no cannabis use goal today). Thus, the app "meets participants where they are" and provides messages that is in line with their

current goal. On days when the participant has no goal to reduce or abstain from cannabis, the app offers primarily "gain-framed" messages that aim to increase motivation for cannabis cessation or reduction. Importantly, the type of message that is delivered at the end of each EMA is recorded in the database so we may analyze the effect of messages on currently present cannabis use triggers.

On-Demand Features

Hundreds of unique messages were developed for this study to address various use risk triggers and to reduce repetition. Messages are consistent with MET-CBT approaches (including ICART) [31] and address identified cannabis use triggers. On-demand content is available through 2 buttons on the app home screen. First, the Coping Toolkit feature contains a menu of resources that become available once this button is pressed (see Figure 3), including Ways to Cope with Urges; Challenge Unhelpful Thoughts (see Figure 4 for a list of automatic thoughts that can be challenged via the app); I've Slipped, Now What?; How to Cope with Stress; Coping with Discrimination; Coping with others Using Marijuana; Motivate Me to Stay on Track; and Eliminate False Safety Behaviors (see Figure 5 for menu options). Second, the Help me Reach my Goal feature contains a menu of resources that also become available once this button is pressed (see Figure 6), including Benefits of Reducing or Quitting; Harms of Marijuana Use; Relaxation Exercises; Give Me Something to Do; and I'm Bored, Distract Me. Finally, all participants are instructed to click the "Record Stress or Urge," "I'm About to Use," and "I Just Used" buttons (see Figure 2) when appropriate. CT-MICART+EMA participants receive a tailored intervention message at the completion of each participant initiated EMAs.

Figure 3. Coping toolkit CT-MICART feature. CT-MICART: Culturally Tailored-Mobile Integrated Cannabis and Anxiety Reduction Treatment.

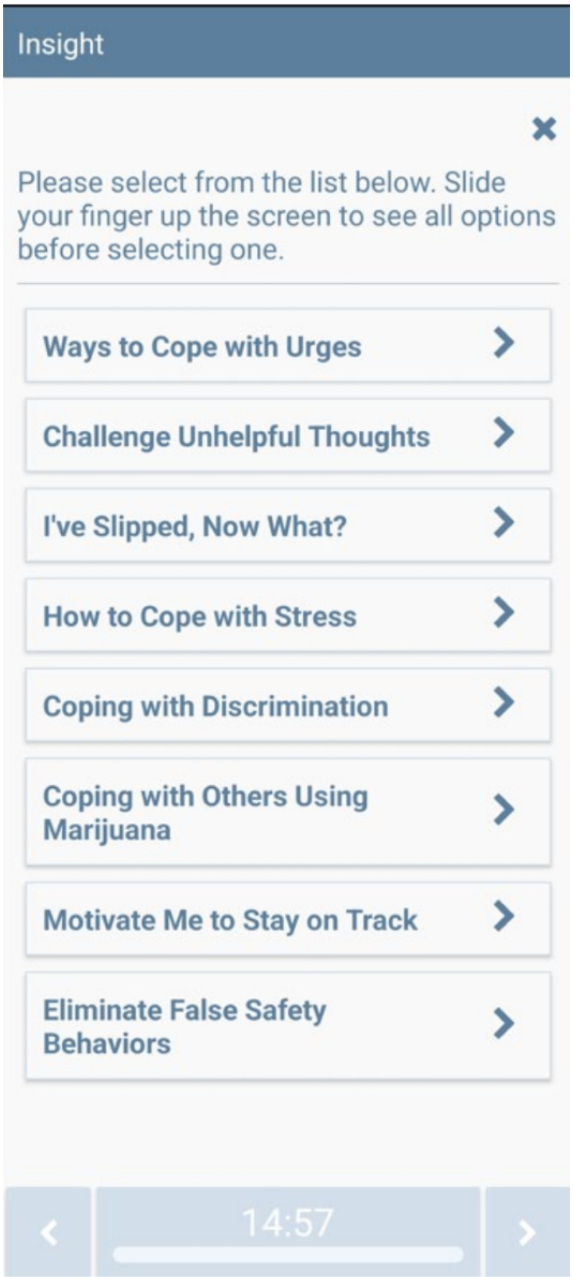


Figure 4. Challenging unhelpful thoughts CT-MICART feature. CT-MICART: Culturally Tailored-Mobile Integrated Cannabis and Anxiety Reduction Treatment.

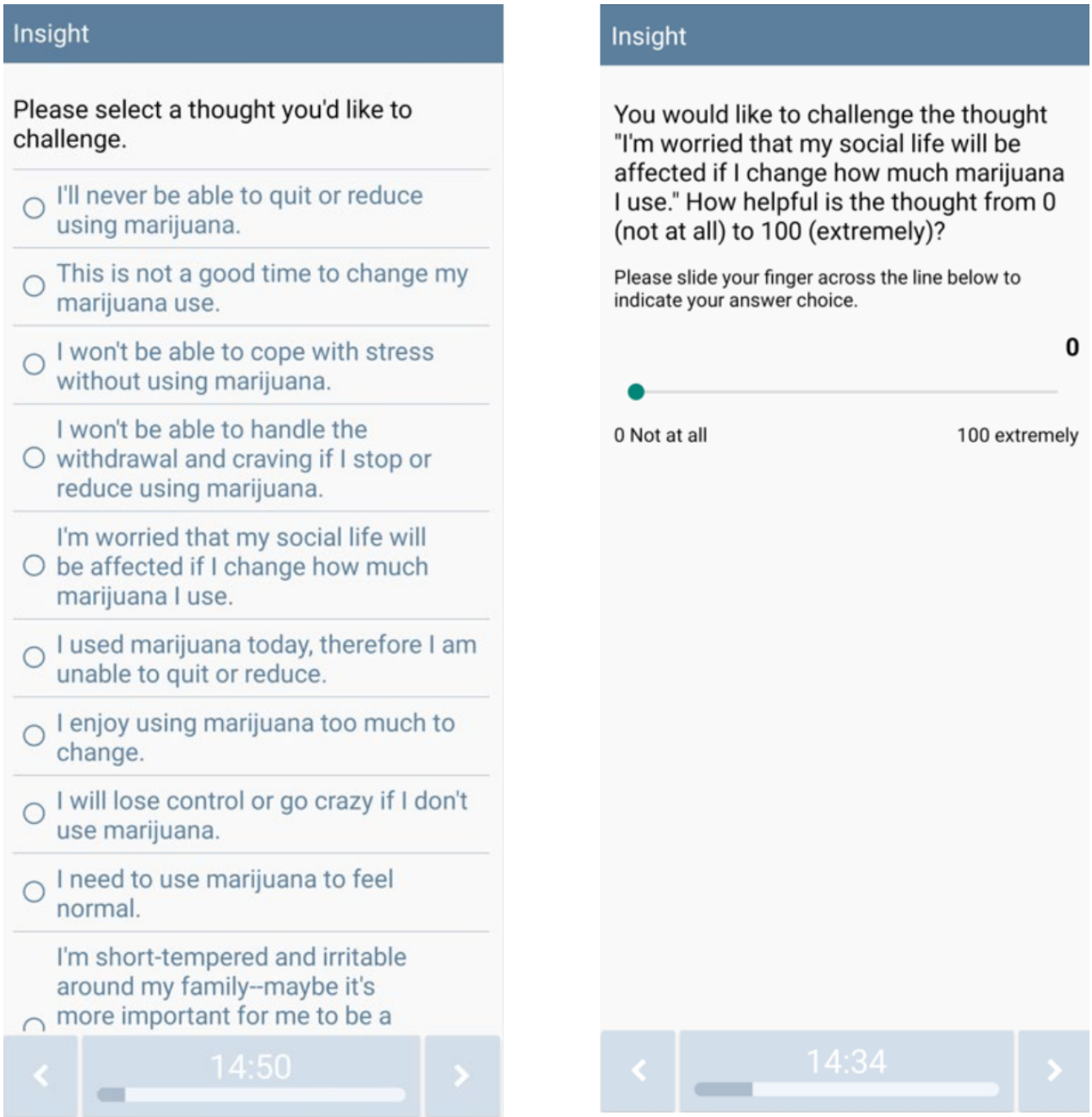


Figure 5. False safety behavior elimination CT-MICART feature. CT-MICART: Culturally Tailored-Mobile Integrated Cannabis and Anxiety Reduction Treatment.

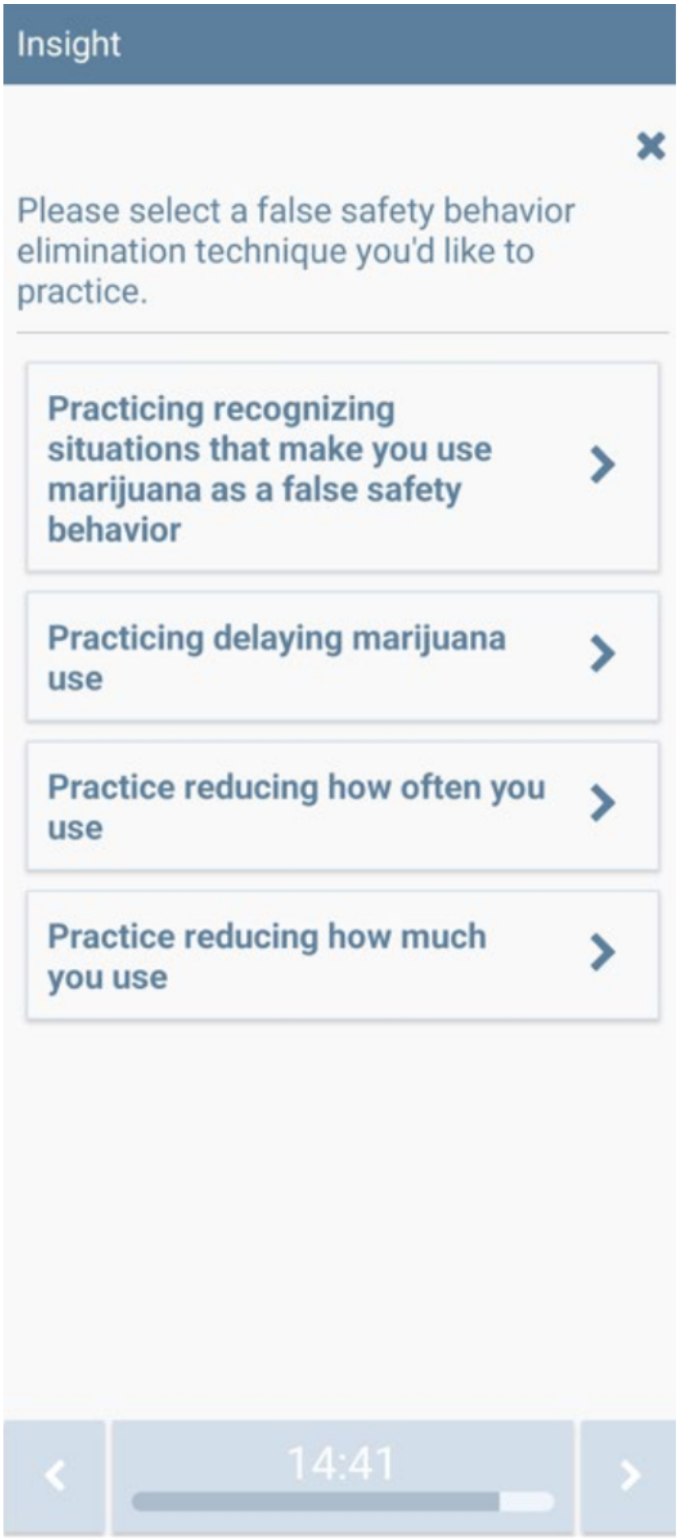
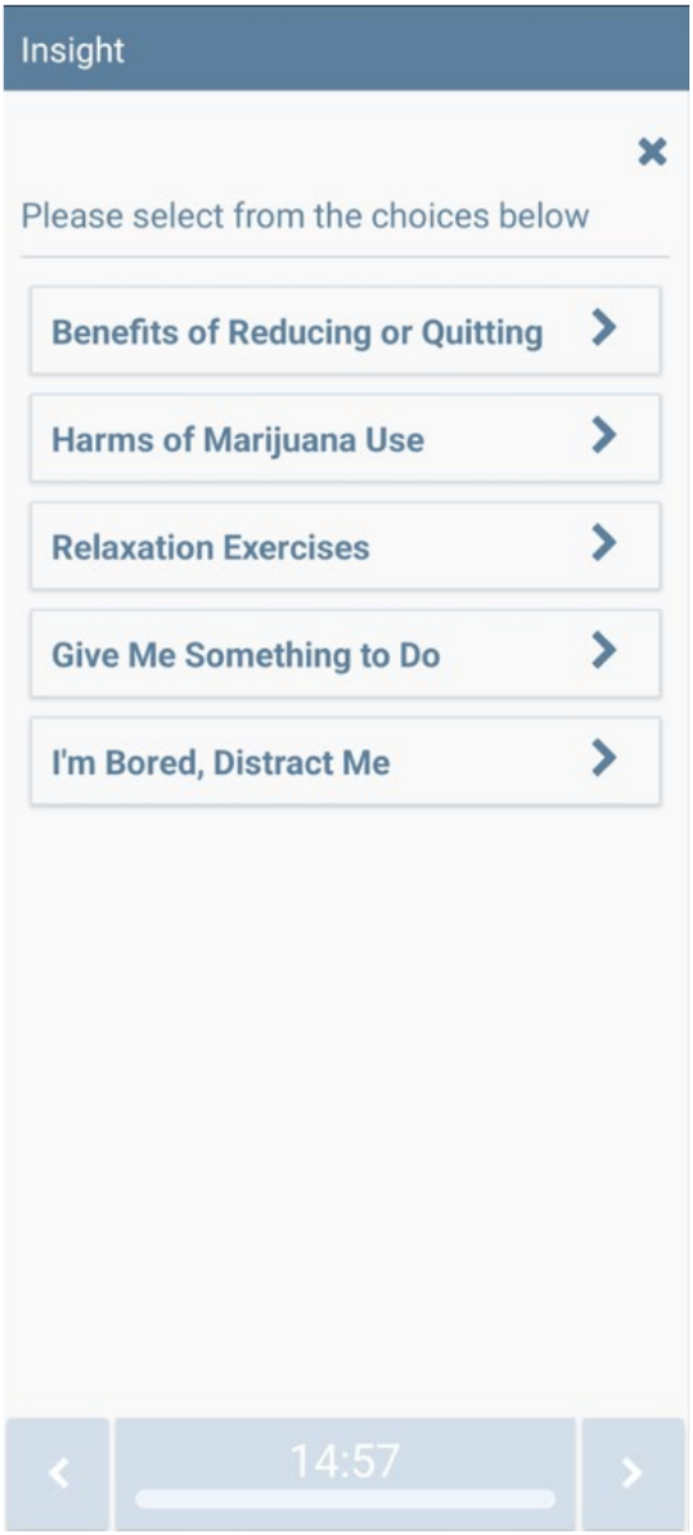


Figure 6. Help me reach my Goal CT-MICART feature. CT-MICART: Culturally Tailored-Mobile Integrated Cannabis and Anxiety Reduction Treatment.



Control Condition (EMAs Only)

Participants randomized to EMA only condition receive the baseline, follow-up, qualitative interview, 3 prompted daily EMAs for 6 weeks, and they have access to the participant-initiated "Record Stress or Urge," "I'm About to Use," and "I Just Used" buttons. However, they do not receive tailored messages or access to the CT-MICART intervention content.

Assessments

Overview

See Table 1 for a schedule of data collection and measures list. All measures have been used among samples of Black adults.

Table 1. Measures and schedule for data collection.

Measure name	Screener	Baseline	6-week follow-up	EMA[a] items
Demographics or background information	✓			Cannabis use assessment (outcomes)
Motivation to quit cannabis (eligibility)	✓			Alcohol consumption
REALM-SF[b] (eligibility)	✓			Motivation regarding cannabis use
CUDIT-R[c] (eligibility)	✓		✓	Watch treatment videos (CT-MICART[d] condition only)
Legal mandate status (eligibility)	✓			Cannabis use goal assessment (CT-MICART condition only)
Report of cannabis use to manage anxiety or stress in the past month (eligibility)	✓			Negative affect
Assessment of ongoing substance use treatment or anxiety and depression (eligibility)	✓			Confidence in reducing or quitting
Safety Aid Scale (outcome)		✓	✓	Urges or cravings
Qualitative interview (outcome)			✓	Social support and daily interactions
System Usability Scale (outcome)			✓	Coping motives for cannabis and consequences or benefits of using
Credibility or Expectancy questionnaire (outcome)		✓	✓	False safety behavior elimination engagement
Marijuana Motives Measure (outcome)		✓	✓	N/A[e]

[a]EMA: ecological momentary assessment.

[b]REALM-SF: Rapid Estimate of Adult Literacy in Medicine-Short Form.

[c]CUDIT-R: Cannabis Use Disorder Identification Test.

[d]CT-MICART: Culturally Tailored-Mobile Integrated Cannabis and Anxiety Reduction Treatment.

[e]N/A: not applicable.

Study Screening and Demographics Questionnaire

All participants are asked to answer questions related demographic characteristics during the Qualtrics screener (eg, race, ethnicity, age, sex, education, and marital status). In addition, participants answer questions related to previous substance use, discrimination experiences, acculturation, anxiety, depression, motivation to quit or reduce cannabis use (ie, “On a scale from 1 to 10 with 1 being ‘not at all motivated’ and 10 being ‘extremely motivated’ how motivated are you to reduce your marijuana use in the next month?”), legal status to engage in substance use treatment, use of cannabis in the past month to cope with anxiety or stress, and ongoing treatment of substance use, anxiety, or depression.

REALM-SF Assessment

The REALM-SF is designed to determine if participants have at least a sixth-grade literacy level through a 7-item assessment taken with the help of a research assistant [37]. The REALM-SF is used in this study by the research staff to determine if participants can read the EMA items and intervention content.

CUDIT-R Assessment

The CUDIT-R is an 8-item self-report measure designed to identify the likelihood of CUD [35]. The items are rated on a 5-point Likert-type scale where higher scores indicate a higher likelihood of CUD. Scores of 12 or greater indicate probable CUD and it is used as eligibility criteria for this study [35].

Safety Aid Scale

The Safety Aid Scale (SAS) is an 80-item measure that is designed to assess FSBs in participants [24]. Examples of items and FSBs include “Avoid being far from home” and “Fiddling with an object (eg, pen).” The items are rated based on how frequently participants endorse the behavior on a scale from 0 (never or rarely) to 4 (almost always). Items are summed to form a total score of FSB use. This measure has demonstrated excellent internal consistency among Black adults [21]. For this study, item reduction analysis was used to reduce the number of items to 22 [39].

Marijuana Motives Measure

The Marijuana Motives Measure (MMM) is a 25-item questionnaire that assesses 5 motives for cannabis use including enhancement, coping, social, conformity, and expansion regarding motives for, frequency of, and problems associated with cannabis use [40]. Items are rated on a 5-point Likert-type scale where 1=almost never or never, 2=some of the time, 3=half of the time, 4=most of the time, and 5=almost always or always.

System Usability Scale

The System Usability Scale (SUS) is a 10-item questionnaire that is used in this study to evaluate participants’ perceived usability of the app [41]. The SUS includes items related to app engagement, frequency of use, complexity of the app, and thoughts about using the app.

Credibility or Expectancy Questionnaire

The Credibility or Expectancy Questionnaire (CEQ) is a 6-item measure that assesses treatment expectancy and rationale credibility [42]. It derives 2 predicted factors including cognitively based credibility and affectively based expectancy. In this study, it is used to gauge participants' thoughts on the credibility of the intervention and assessment content assigned to them (CT-MICART+EMA or EMA only), and their expectations regarding the intervention (ie, "How successful do you think this intervention will be in helping you quit or reduce marijuana?").

Daily EMAs

Throughout the 6-week intervention period, participants complete 3 daily EMAs occurring at specific times (one 30 minutes after self-selected wake time, one 60 minutes before the self-selected sleep time, and one at 12:15 PM). Items include questions about cannabis use, duration of being high, urges or cravings, motivation, and confidence to reduce or quit cannabis, negative affect, social support, and other substance use. Each EMA also gauges the CT-MICART+EMA participants' cannabis goal for the day (ie, wanting to avoid using cannabis today, reduce use today, or no cannabis use goal today). All participants are also instructed to access the app's on-demand assessment features, including the "Record Stress or Urge," "I'm About to Use," and "I just used" buttons, when they experience increased stress or an urge to use cannabis as well as anytime they think they might use or after actual cannabis use. Each time participants click these buttons, they are asked to complete a brief set of questions pertaining to their current situation.

Qualitative Interview

After completing the 6-week follow-up assessment in the app, study staff are notified via an encrypted email to contact the participant to complete the qualitative interview phone call. Participants are asked to assess their satisfaction with their assigned app content and ways it could be improved via a semistructured interview. This 30-minute interview assesses participant engagement with the app, and specific thoughts about app features including EMA items, intervention content, and why they did or did not use certain features.

Data Analysis

General Overview

Given this pilot study is likely underpowered to detect statistical significance, conclusions will primarily be based on effect sizes and associated Cis, which will be used to guide future, larger, and fully powered trials of comparative efficacy. Prior to data analysis, we will assess the equivalence of groups on key baseline variables. Variables on which the groups differ will be used as covariates in the final analyses.

Hypothesis Testing

Overview

We will examine treatment effects on cannabis use (derived from EMA data) using multilevel models. We will focus on two cannabis use outcomes: (1) use on a given day and (2) frequency of use within a given day. We will account for baseline covariates and time since the start of the intervention. We will also use appropriate random effects and residual constraints. For coping motives for cannabis and FSB engagement, we will conduct a linear regression analysis wherein we will regress treatment condition on each outcome assessed at the 6-week follow-up while adjusting for baseline scores of the specific outcome and baseline covariates. Triangulation mixed methods quantitative or qualitative data analysis [43] will be used to evaluate quantitative and qualitative data.

Quantitative Data

The app's feasibility and use will be examined by quantifying the use of CT-MICART features (eg, the number of assigned videos that are watched) and by evaluating participant opinions about the helpfulness of CT-MICART features (eg, treatment videos, automated treatment messages that follow EMAs, and exercises). Quantitative data analysis will focus on (1) behavioral markers of engagement with the app; (2) overall evaluations of the app and evaluations of each app feature, including usefulness or helpfulness and likelihood to recommend the app to a friend; and (3) data from the CEQ and SUS [44-46]. Data will be compared across conditions.

Qualitative Data

The week 6 qualitative interviews will prompt information on what participants liked about CT-MICART, how it could be improved, and what barriers currently limit app engagement. Individual interviews will be transcribed following the completion of participant treatment and then reviewed by the research team to ensure data quality. Transcribed interviews will be coded using NVivo (version 12; Lumivero), and decisions regarding the appropriateness of suggested changes to potential future versions of CT-MICART will be evaluated using a team-based approach. Consistent with the systematic and reflexive interviewing and reporting method [47], this approach will help to systematically organize collected qualitative data and thus guide improvements to CT-MICART. Moreover, content analysis will be used to analyze collected qualitative data [48]. Participant responses will be integrated with quantitative usage data to identify inconsistencies in the participant's perceptions and actual engagement with the app [49,50].

Missing Data

Some participant attrition is anticipated to happen during this study. We will assume a missing-at-random mechanism if missing data occurs. This will allow us to increase statistical power and provide more accurate estimates of model parameters and standard errors, as they are the recommended intent-to-treat approach for clinical trials. We will compare this approach and the intent-to-treat approach as a sensitivity check of the influence of missing data on the statistical conclusion.

Results

This study's enrollment started in June 2023 and ended in November 2023. The estimated study completion date is March 2024.

Discussion

Principal Findings

Black adults evince significant cannabis-related health disparities compared with non-Black populations [13,15,51]. Thus, the primary goal of this study is to develop and pilot-test a culturally adapted mobile app for Black adults with probable CUD to help mitigate these disparities. We have culturally tailored this mobile intervention following the Cultural Accommodation Model [38], incorporating knowledge from the current research team, published literature, expert opinion, and feedback from the CRAB. As a next step, we seek to obtain data on the initial efficacy and qualitative evaluation of the app with the target population (ie, Black adults with probable CUD). To our knowledge, this is the first culturally tailored mHealth intervention to integrate FSB and CBT for CUD for Black adults with a probable CUD. We hypothesize that the culturally tailored mobile app CT-MICART will lead to reduced cannabis use and related problems and reduce the use of FSBs.

Though extant literature has highlighted existing mHealth work for cannabis use and CUD [32], including mHealth interventions tailored to treat specific populations (ie, individuals with psychosis and comorbid substance use) [33,34], this study is the first to target specific psycho-sociocultural factors related to cannabis use and use-related problems among Black cannabis users through a mobile intervention. Should the CT-MICART app prove efficacious in reducing cannabis use, it will provide health care officials and researchers a unique opportunity to further refine and provide low-cost and easily accessible treatment for a historically underrepresented and underserved population. The success of the CT-MICART app would also provide the foundation to further refine and culturally inform better implementation of the app through qualitative interviews of all participants. Overall, the CT-MICART app and its development provide the potential to address the dearth of literature that exists for mobile health development and Black individuals who use cannabis.

Limitations

This study has several limitations which warrant comment. First, this pilot randomized controlled trial (RCT) will only offer intervention content and collect data for 6 weeks. As such, future research should examine the efficacy of similar but longer-term interventions. Second, as the study will only enroll participants that are motivated to quit or reduce their cannabis use, future work should determine if participants who are not currently motivated to quit or reduce their cannabis use can benefit from this type of culturally tailored cannabis cessation or reduction app. Third, only Android smartphone users will be enrolled in this study due to the limitations of the Insight smartphone platform. Future studies will use the updated Insight platform that works on Apple and Android smartphones. Additionally, it is possible that the EMA-only condition will have potentially therapeutic benefits to participants due to self-monitoring of behaviors, although EMA studies on substance use have found such effects to be limited [52-54]. Thus, a waitlist control should be included in future study designs to isolate the effect of CT-MICART beyond the potential influence of behavior monitoring or tracking behavior. Finally, although the sample size will be adequate to achieve study aims or hypotheses, future fully powered studies will be needed to test intervention efficacy and effectiveness.

Conclusions

This study will address a significant gap in the literature. Specifically, this pilot RCT will offer initial insights on the use of an mHealth intervention that is tailored for Black individuals who use cannabis. Smartphone interventions similar to CT-MICART have incredible potential to provide low-cost, scalable treatments to diverse populations. Moreover, the CT-MICART app has the potential to help Black individuals who use cannabis achieve and maintain higher rates of cessation and reduction and help narrow health disparities that have negatively impacted this underserved population.

Acknowledgments

The research reported in this publication was supported by the National Institute on Minority Health and Health Disparities to the University of Houston (U54MD015946; Principal Investigator: EO) and specific U54 pilot funding to LG. Work on this paper was also supported by the National Institutes of Health (R25DA054015) and the National Cancer Institute (3R21CA263765-01A1S1; funding candidate: PN). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Programming and technological support was provided through the mobile health shared resource of the Stephenson Cancer Center via National Cancer Institute (NCI) Cancer Center Support Grant (P30CA225520) and through the Oklahoma Tobacco Settlement Endowment Trust grant (R21-02).

Data Availability

The data sets generated and analyzed during this study are not yet publicly available given that data analysis in currently in progress but will be available from the corresponding author on reasonable request.

Conflicts of Interest

MB is the primary inventor of the Insight mobile health platform, which was used in this study. He receives royalties related to its use. EO is the founder and sole owner of HEALTH Equity Empowerment, LLC.

References

1. Johnston LD, O'Malley PM, Bachman JG. Monitoring the future: national results on adolescent drug use: overview of key findings. Focus 2003;1(2):213-234 [FREE Full text] [doi: 10.1176/foc.1.2.213]
2. 2022 NSDUH annual national report. Substance Abuse and Mental Health Services Administration. 2022. URL: http://tinyurl.com/bddwh5h5 [accessed 2024-01-16]
3. Marijuana and hallucinogen use, binge drinking reached historic highs among adults 35 to 50. National Institute on Drug Abuse. 2023. URL: https://nida.nih.gov/news-events/news-releases/2023/08/marijuana-and-hallucinogen-use-binge-drinking-reached-historic-highs-among-adults-35-to-50 [accessed 2024-01-16]
4. Wu LT, Zhu H, Swartz MS. Trends in cannabis use disorders among racial/ethnic population groups in the United States. Drug Alcohol Depend 2016;165:181-190 [FREE Full text] [doi: 10.1016/j.drugalcdep.2016.06.002] [Medline: 27317045]
5. Mantey DS, Onyinye ON, Montgomery L. Prevalence and correlates of daily blunt use among U.S. African American, Hispanic, and White adults from 2014 to 2018. Psychol Addict Behav 2021;35(5):514-522 [FREE Full text] [doi: 10.1037/adb0000702] [Medline: 33914562]
6. Hasin DS, Saxon AJ, Malte C, Olfson M, Keyes KM, Gradus JL, et al. Trends in cannabis use disorder diagnoses in the U.S. Veterans Health Administration, 2005-2019. Am J Psychiatry 2022;179(10):748-757 [FREE Full text] [doi: 10.1176/appi.ajp.22010034] [Medline: 35899381]
7. Foster KT, Arterberry BJ, Iacono WG, McGue M, Hicks BM. Psychosocial functioning among regular cannabis users with and without cannabis use disorder. Psychol Med 2018;48(11):1853-1861 [FREE Full text] [doi: 10.1017/S0033291717003361] [Medline: 29173210]
8. Masters MN, Haardörfer R, Windle M, Berg C. Psychosocial and cessation-related differences between tobacco-marijuana co-users and single product users in a college student population. Addict Behav 2018;77:21-27 [FREE Full text] [doi: 10.1016/j.addbeh.2017.09.007] [Medline: 28941933]
9. McClure EA, Tomko RL, Salazar CA, Akbar SA, Squeglia LM, Herrmann E, et al. Tobacco and cannabis co-use: drug substitution, quit interest, and cessation preferences. Exp Clin Psychopharmacol 2019;27(3):265-275 [FREE Full text] [doi: 10.1037/pha0000244] [Medline: 30556733]
10. Copersino ML, Boyd SJ, Tashkin DP, Huestis MA, Heishman SJ, Dermand JC, et al. Sociodemographic characteristics of cannabis smokers and the experience of cannabis withdrawal. Am J Drug Alcohol Abuse 2010;36(6):311-319 [FREE Full text] [doi: 10.3109/00952990.2010.503825] [Medline: 20678028]
11. Warner TD. Up in smoke: neighborhood contexts of marijuana use from adolescence through young adulthood. J Youth Adolesc 2016;45(1):35-53. [doi: 10.1007/s10964-015-0370-5] [Medline: 26496730]
12. Kennedy BR, Mathis CC, Woods AK. African Americans and their distrust of the health care system: healthcare for diverse populations. J Cult Divers 2007;14(2):56-60. [Medline: 19175244]
13. Montgomery L, Dixon S, Mantey DS. Racial and ethnic differences in cannabis use and cannabis use disorder: implications for researchers. Curr Addict Rep 2022;9(1):14-22 [FREE Full text] [doi: 10.1007/s40429-021-00404-5] [Medline: 35251891]
14. Budney AJ, Roffman R, Stephens RS, Walker D. Marijuana dependence and its treatment. Addict Sci Clin Pract 2007;4(1):4-16 [FREE Full text] [doi: 10.1151/ascp07414] [Medline: 18292704]
15. Montgomery L, Robinson C, Seaman EL, Haeny AM. A scoping review and meta-analysis of psychosocial and pharmacological treatments for cannabis and tobacco use among African Americans. Psychol Addict Behav 2017;31(8):922-943 [FREE Full text] [doi: 10.1037/adb0000326] [Medline: 29199844]
16. Martins SS, Segura LE, Levy NS, Mauro PM, Mauro CM, Philbin MM, et al. Racial and ethnic differences in cannabis use following legalization in US States with medical cannabis laws. JAMA Netw Open 2021;4(9):e2127002 [FREE Full text] [doi: 10.1001/jamanetworkopen.2021.27002] [Medline: 34570205]
17. Solomon R. Racism and its effect on cannabis research. Cannabis Cannabinoid Res 2020;5(1):2-5 [FREE Full text] [doi: 10.1089/can.2019.0063] [Medline: 32322671]
18. Buckner JD, Zvolensky MJ, Scherzer CR. Microaggressions and cannabis-related problems among Black adults: the roles of negative affect and cannabis use motives. Cogn Ther Res 2023:1-10. [doi: 10.1007/s10608-023-10375-8]
19. Buckner JD, Zvolensky MJ, Lewis EM. Smoking and social anxiety: the role of false safety behaviors. Cogn Behav Ther 2020;49(5):374-384 [FREE Full text] [doi: 10.1080/16506073.2019.1696396] [Medline: 31847703]
20. Schmidt NB, Buckner JD, Pusser A, Woolaway-Bickel K, Preston JL, Norr A. Randomized controlled trial of false safety behavior elimination therapy: a unified cognitive behavioral treatment for anxiety psychopathology. Behav Ther 2012;43(3):518-532. [doi: 10.1016/j.beth.2012.02.004] [Medline: 22697441]
21. Buckner JD, Zvolensky MJ, Ferrie ML, Morris PE. False safety behavior use among Black adults. Cogn Behav Ther 2023;52(1):65-74. [doi: 10.1080/16506073.2022.2139291] [Medline: 36562142]
22. Lev-Ran S, Le Foll B, McKenzie K, George TP, Rehm J. Cannabis use and cannabis use disorders among individuals with mental illness. Compr Psychiatry 2013;54(6):589-598 [FREE Full text] [doi: 10.1016/j.comppsych.2012.12.021] [Medline: 23375264]
23. van Ours JC, Williams J. Cannabis use and mental health problems. J Applied Econometrics 2011;26(7):1137-1156. [doi: 10.1002/jae.1182]

24. Buckner JD, Zvolensky MJ, Ecker AH, Jeffries ER, Lemke AW, Dean KE, et al. Anxiety and cannabis-related problem severity among dually diagnosed outpatients: the impact of false safety behaviors. Addict Behav 2017;70:49-53 [FREE Full text] [doi: 10.1016/j.addbeh.2017.02.014] [Medline: 28214433]
25. Buckner JD, Zvolensky MJ, Businelle MS, Gallagher MW. Direct and indirect effects of false safety behaviors on cannabis use and related problems. Am J Addict 2018;27(1):29-34. [doi: 10.1111/ajad.12659] [Medline: 29280237]
26. Buckner JD, Zvolensky MJ, Scherzer CR. Alcohol-related problems among Black adults: the role of false safety behaviors. J Racial Ethn Health Disparities 2023;10(3):987-992. [doi: 10.1007/s40615-022-01286-7] [Medline: 35320510]
27. Peraza N, Smit T, Garey L, Manning K, Buckner JD, Zvolensky MJ. Distress tolerance and cessation-related cannabis processes: the role of cannabis use coping motives. Addict Behav 2019;90:164-170. [doi: 10.1016/j.addbeh.2018.10.047] [Medline: 30408699]
28. Buckner JD, Zvolensky MJ, Ecker AH, Schmidt NB, Lewis EM, Paulus DJ, et al. Integrated cognitive behavioral therapy for comorbid cannabis use and anxiety disorders: a pilot randomized controlled trial. Behav Res Ther 2019;115:38-45 [FREE Full text] [doi: 10.1016/j.brat.2018.10.014] [Medline: 30442329]
29. Buckner JD, Zvolensky MJ, Schmidt NB, Carroll KM, Schatschneider C, Crapanzano K. Integrated cognitive behavioral therapy for cannabis use and anxiety disorders: rationale and development. Addict Behav 2014;39(3):495-496 [FREE Full text] [doi: 10.1016/j.addbeh.2013.10.023] [Medline: 24290210]
30. Buckner JD, Ecker AH, Beighley JS, Zvolensky MJ, Schmidt NB, Shah SM, et al. Integrated cognitive behavioral therapy for comorbid cannabis use and anxiety disorders. Clin Case Stud 2016;15(1):68-83 [FREE Full text] [doi: 10.1177/1534650115590857] [Medline: 28603457]
31. Buckner JD, Morris PE, Zvolensky MJ. Integrated cognitive-behavioral therapy for comorbid cannabis use and anxiety disorders: the impact of severity of cannabis use. Exp Clin Psychopharmacol 2021;29(3):272-278. [doi: 10.1037/pha0000456] [Medline: 34264732]
32. Brezing CA, Levin FR. Applications of technology in the assessment and treatment of cannabis use disorder. Front Psychiatry 2022;13:1035345 [FREE Full text] [doi: 10.3389/fpsyt.2022.1035345] [Medline: 36339845]
33. Tatar O, Abdel-Baki A, Wittevrongel A, Lecomte T, Copeland J, Lachance-Touchette P, et al. Reducing cannabis use in young adults with psychosis using iCanChange, a mobile health app: protocol for a pilot randomized controlled trial (ReCAP-iCC). JMIR Res Protoc 2022;11(11):e40817 [FREE Full text] [doi: 10.2196/40817] [Medline: 36427227]
34. Beckham JC, Adkisson KA, Hertzberg J, Kimbrel NA, Budney AJ, Stephens RS, et al. Mobile contingency management as an adjunctive treatment for co-morbid cannabis use disorder and cigarette smoking. Addict Behav 2018;79:86-92 [FREE Full text] [doi: 10.1016/j.addbeh.2017.12.007] [Medline: 29268146]
35. Adamson SJ, Kay-Lambkin FJ, Baker AL, Lewin TJ, Thornton L, Kelly BJ, et al. An improved brief measure of cannabis misuse: the Cannabis Use Disorders Identification Test-Revised (CUDIT-R). Drug Alcohol Depend 2010;110(1-2):137-143. [doi: 10.1016/j.drugalcdep.2010.02.017] [Medline: 20347232]
36. Murphy PW, Davis TC, Long SW, Jackson RH, Decker BC. Rapid Estimate of Adult Literacy in Medicine (REALM): a quick reading test for patients. J Read 1993;37(2):124-130. [Medline: PMID: 8349060]
37. Arozullah AM, Yarnold PR, Bennett CL, Soltysik RC, Wolf MS, Ferreira RM, et al. Development and validation of a short-form, rapid estimate of adult literacy in medicine. Med Care 2007;45(11):1026-1033. [doi: 10.1097/MLR.0b013e3180616c1b] [Medline: 18049342]
38. Wieling E, Rastogi M. Voices of Color: First-Person Accounts of Ethnic Minority Therapists. Thousand Oaks, CA: Sage Publications, Inc; 2005.
39. Jin X, Liu GG, Gerstein HC, Levine MAH, Steeves K, Guan H, et al. Item reduction and validation of the Chinese version of Diabetes Quality-of-Life measure (DQOL). Health Qual Life Outcomes 2018;16(1):78 [FREE Full text] [doi: 10.1186/s12955-018-0905-z] [Medline: 29703205]
40. Simons J, Correia CJ, Carey KB, Borsari BE. Validating a five-factor marijuana motives measure: relations with use, problems, and alcohol motives. J Couns Psychol 1998;45(3):265-273. [doi: 10.1037//0022-0167.45.3.265]
41. Brooke J. SUS: a "quick and dirty' usability scale. In: Thomas B, Weerdmeester BA, McClelland IL, Jordan PW, editors. Usability Evaluation In Industry. London: CRC Press; 1996:189-194.
42. Devilly GJ, Borkovec TD. Psychometric properties of the credibility/expectancy questionnaire. J Behav Ther Exp Psychiatry 2000;31(2):73-86. [doi: 10.1016/s0005-7916(00)00012-4] [Medline: 11132119]
43. Wilson V. Research methods: triangulation. Evid Based Libr Inf Pract 2014;9(1):74-75 [FREE Full text] [doi: 10.18438/b8ww3x]
44. Rooke SE, Gates PJ, Norberg MM, Copeland J. Applying technology to the treatment of cannabis use disorder: comparing telephone versus internet delivery using data from two completed trials. J Subst Abuse Treat 2014;46(1):78-84 [FREE Full text] [doi: 10.1016/j.jsat.2013.08.007] [Medline: 24051076]
45. Hindson J, Hanstock T, Dunlop A, Kay-Lambkin F. Internet-delivered tobacco treatment for people using cannabis: a randomized trial in two Australian cannabis clinics. JMIR Form Res 2020;4(12):e14344 [FREE Full text] [doi: 10.2196/14344] [Medline: 33284121]

46. Macatee RJ, Albanese BJ, Okey SA, Afshar K, Carr M, Rosenthal MZ, et al. Impact of a computerized intervention for high distress intolerance on cannabis use outcomes: a randomized controlled trial. J Subst Abuse Treat 2021;121:108194 [FREE Full text] [doi: 10.1016/j.jsat.2020.108194] [Medline: 33357604]
47. Loubere N. Questioning transcription: the case for the Systematic and Reflexive Interviewing and Reporting (SRIR) method. Forum Qual Sozialforschung 2017:15 [FREE Full text]
48. Bengtsson M. How to plan and perform a qualitative study using content analysis. NursingPlus Open 2016;2:8-14 [FREE Full text] [doi: 10.1016/j.npls.2016.01.001]
49. Creswell JW, Clark VLP. Designing and Conducting Mixed Methods Research. Los Angeles: Sage Publications; 2017.
50. Cheney MK, Gowin M. Using Legal Documents for Public Health Research: An Innovative Application of Qualitative Methodology to Document the Experiences of Transgender Asylum Seekers. London: Sage Publications Limited; 2020.
51. Lanaway D, Burlew AK. The influence of distressed coping on the relationship between perceived racial discrimination and cannabis use among Black college students. J Psychoactive Drugs 2021;53(5):404-412. [doi: 10.1080/02791072.2021.1990443] [Medline: 34694206]
52. Litt MD, Cooney NL, Morse P. Ecological Momentary Assessment (EMA) with treated alcoholics: methodological problems and potential solutions. Health Psychol 1998;17(1):48-52. [doi: 10.1037//0278-6133.17.1.48] [Medline: 9459069]
53. Hufford MR, Shields AL, Shiffman S, Paty J, Balabanis M. Reactivity to ecological momentary assessment: an example using undergraduate problem drinkers. Psychol Addict Behav 2002;16(3):205-211. [Medline: 12236455]
54. Simpson TL, Kivlahan DR, Bush KR, McFall ME. Telephone self-monitoring among alcohol use disorder patients in early recovery: a randomized study of feasibility and measurement reactivity. Drug Alcohol Depend 2005;79(2):241-250. [doi: 10.1016/j.drugalcdep.2005.02.001] [Medline: 16002033]

Abbreviations

CBT: cognitive behavioral therapy
CEQ: Credibility or Expectancy Questionnaire
CRAB: Community Research Advisory Board
CT-MICART: Culturally Tailored-Mobile Integrated Cannabis and Anxiety Reduction Treatment
CUD: cannabis use disorder
CUDIT-R: Cannabis Use Disorder Identification Test-Revised
EMA: ecological momentary assessment
FSB: false safety behavior
ICART: Integrated Cannabis and Anxiety Reduction Treatment
IRB: institutional review board
MET-CBT: motivation enhancement therapy combined with cognitive behavioral therapy
mHealth: mobile health
MMM: Marijuana Motives Measure
RCT: randomized controlled trial
REALM-SF: Rapid Estimate of Adult Literacy in Medicine-Short Form
SAS: Safety Aid Scale
SUS: System Usability Scale

Edited by A Mavragani; submitted 14.09.23; peer-reviewed by C Doarn, F Muench; comments to author 04.12.23; revised version received 21.12.23; accepted 29.12.23; published 19.02.24.

Please cite as:
Nizio P, Clausen B, Businelle MS, Ponton N, Jones AA, Redmond BY, Buckner JD, Obasi EM, Zvolensky MJ, Garey L
Mobile Intervention to Address Cannabis Use Disorder Among Black Adults: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2024;13:e52776
URL: https://www.researchprotocols.org/2024/1/e52776
doi:10.2196/52776
PMID:38373037

Protocol

Family-Based WhatsApp Intervention to Promote Healthy Eating Behaviors Among Amazonian School Children: Protocol for a Randomized Controlled Trial

Ana Carolina de Andrade Hovadick[1], RDN; Marly Augusto Cardoso[1,2], PhD

[1]Department of Nutrition, School of Public Health, University of Sao Paulo, Sao Paulo, Brazil

[2]Global Health and Tropical Medicine (GHTM), Associate Laboratory in Translation and Innovation Towards Global Health (LA-REAL), Instituto de Higiene e Medicina Tropical (IHMT), Universidade NOVA de Lisboa (UNL), Lisbon, Portugal

Corresponding Author:
Marly Augusto Cardoso, PhD
Department of Nutrition, School of Public Health
University of Sao Paulo
Dr. Arnaldo Avenue, 715 - Cerqueira César
Sao Paulo, 01246-904
Brazil
Phone: 55 11 3061 7863
Fax: 55 11 3061 7863
Email: marlyac@usp.br

Abstract

Background: Stunting and micronutrient deficiencies have persistently affected children in the Brazilian Amazon for decades. However, in recent years, a notable increase in childhood overweight prevalence has been observed, particularly in the context of heightened food insecurity exacerbated by the COVID-19 pandemic. Despite the limited number of effective solutions proposed to tackle this problem, digital interventions have shown great promise worldwide in preventing obesity and promoting healthy diets.

Objective: This study aims to describe the protocol of a family-based WhatsApp intervention, specifically designed to investigate the efficacy of multimedia messaging in preventing excessive weight gain and improving healthy eating practices among school-aged children in the Amazon region.

Methods: This study protocol outlines a theory-driven randomized controlled trial based on the cognitive theory of multimedia learning and the social cognitive theory. A total of 240 parents or caregivers of children enrolled in the Maternal and Child Health and Nutrition Cohort Study in Acre (MINA-Brazil) will be recruited by phone and social media. The intervention group will receive persuasive multimedia messages through WhatsApp over 19 weeks, while the waitlist control group will remain in the usual care. The primary outcome is a change in children's BMI in *z* score. Secondary outcomes are changes in dietary intake and biochemical indicators of the children. Outcome measures will be assessed at baseline and 5 months after randomization in comparison to usual care. The analysis will use an intent-to-treat approach and will be conducted using the statistical package Stata (version 18.0), with a significance level set at $P<.05$. Paired and unpaired 2-tailed *t* tests will be applied to compare mean changes in the outcomes.

Results: Data collection started in June 2023, and final measurements are scheduled to be completed in December 2023. The results of the main analysis are expected to be available in 2024.

Conclusions: This innovative multimedia message intervention holds significant potential for fostering behavioral changes among Amazonian children.

Trial Registration: Brazilian Clinical Trials Registry RBR-5zdnw6t; https://ensaiosclinicos.gov.br/rg/RBR-5zdnw6t

International Registered Report Identifier (IRRID): DERR1-10.2196/54446

(JMIR Res Protoc 2024;13:e54446) doi:10.2196/54446

KEYWORDS

child health; Amazon; dietary intake; mHealth; mobile health; multimedia messaging service; WhatsApp

Introduction

In recent decades, childhood obesity has emerged as a global epidemic [1]. According to the World Health Organization (WHO), more than 340 million children were overweight or obese in 2016 [2]. In addition, with the emergence of the COVID-19 pandemic in 2019, the situation has been aggravated due to school closures, physical inactivity, dietary changes, and mental health disorders [3].

In Brazil, according to the latest national school anthropometric survey, in 2009, 1 out of 3 children were overweight [4]. However, it is expected that due to the COVID-19 crisis and the absence of national child anthropometric surveys for 15 years, the current prevalence of childhood overweight has likely worsened [5,6]. In this context, the Brazilian Amazon was one of the most affected regions in the country due to its remote location and lack of specialized health assistance [5,7]. Recent studies revealed that approximately 70% of the northern population experience food insecurity [8]. Additionally, 20% experience severe food insecurity, wherein individuals feel hungry but do not have funds to buy food, have only 1 meal a day, or endure entire days without any meals [8].

In this scenario, considering the Brazilian economic crisis paired with the neglected fast growth of the ultraprocessed food (UPF) industry, access to fresh food has become challenging, while UPF has become ubiquitous in most food markets [9,10]. UPF are formulations produced exclusively by the food industry through processing techniques that damage the food matrix (eg, extrusion, refining, and prefrying). Additionally, UPFs are frequently high in calories, harmful fats, sugar, and artificial additives [11]. Many studies in the literature have shown that the consumption of UPF may increase the risk of morbidity and early mortality [12]. Therefore, UPF's high availability and consumption are significantly endorsing a substantial change in Western Brazilian Amazon food patterns, which has placed overweight and obesity as an important public health problem due to the historical rates of stunting and micronutrient deficiencies in the region [13-15]. Although some studies have called attention to the urgent need for early interventions to prevent childhood obesity in the Amazon region, few effective solutions have been proposed to tackle this problem so far [16,17].

Along these lines, digital interventions focused on promoting weight loss and healthy eating behaviors have shown promising results, especially mobile phone interventions (mobile health [mHealth]) [18,19]. MHealth interventions are innovative and have countless advantages. First, it increases the contact between health care professionals and people living in remote areas, such as the Amazon region [20]. Second, it is a low-cost, easy-to-use, and alternative tool that is already widely incorporated into society. Lastly, these interventions can be developed on a large scale, benefiting people in a wide region. Although Amazon is considered a location of poverty and of great inaccessibility, about 80% of the population has access to the internet, and 8 out of 10 adults have a cell phone [21,22].

In this context, multimedia messages have spread rapidly in society in recent years. Since it includes both textual and visual resources, it provides efficient learning due to its greater ability to establish itself in the brain's long-term memory; therefore, it demonstrates great potential to generate changes in health behaviors, especially in populations with low educational levels [23-26]. As far as we know, no studies have evaluated the effects of multimedia messages on children's health behaviors; however, there is plenty of evidence indicating the extensive potential of multimedia resources. Randomized controlled trials based on soap operas, video games, and websites as multimedia components have reported a significant increase in fruit and vegetable consumption and a decrease in sugary drinks and sweets consumption [27-33].

Also, a recent systematic review and meta-analysis showed that childhood obesity risk is significantly influenced by parental weight status [34]. Thus, parent-focused interventions are an important key to promoting efficient and lasting changes in children's eating behaviors. Family-based interventions focusing on children who are overweight that used SMS text messaging lead to a significant reduction in children's adiposity and BMI [35]. Additionally, healthy eating patterns were improved among all family members [36]. These findings support the hypothesis that family-based multimedia messaging interventions have great potential to promote behavioral changes in children.

This study protocol will be the first to assess the effect of mHealth on dietary practices and anthropometric measurements of Amazonian children. We aim to develop a parenting-focused, mobile-based intervention through multimedia messaging to promote healthy eating habits and prevent obesity among Amazonian children. We also intend to support and provide high-quality evidence to guide future public policy regarding childhood obesity, food insecurity, and sustainable food systems.

Methods

Study Aim

The general aim of this study is to evaluate the efficacy of a parent-focused mHealth intervention to change dietary practices and prevent excessive weight gain among school-aged children from the Maternal and Child Health and Nutrition Cohort Study in Acre (MINA-Brazil). Therefore, we hypothesize that children whose parents or caregivers receive nutrition-related multimedia messages will have improvements in BMI in *z* score (BMIz), dietary food intake, and biochemical data.

Overview and Trial Design

This trial will be a parallel randomized controlled trial nested in MINA-Brazil, the first population-based birth cohort based in Cruzeiro do Sul, Acre State, in the Western Brazilian Amazon. The cohort was designed to investigate the determinants of maternal and child health and have as participants children born at the Hospital Estadual da Mulher e da Criança do Jurua, in Cruzeiro do Sul, in the period between July 2015 and June 2016. Participants have been followed up for 5 years, and the last evaluation of health status took place in 2021. This protocol was prospectively registered in the Brazilian Clinical Trials Registry (RBR-5zdnw6t; date of registration: March 30, 2023; UTN code: U1111-1289-0560) and has been described according to the CONSORT-EHEALTH

checklist (version 1.6.1; Multimedia Appendix 1 [37-47]) [48]. Table 1 shows the timeline of the study activities according to the intervention stage:

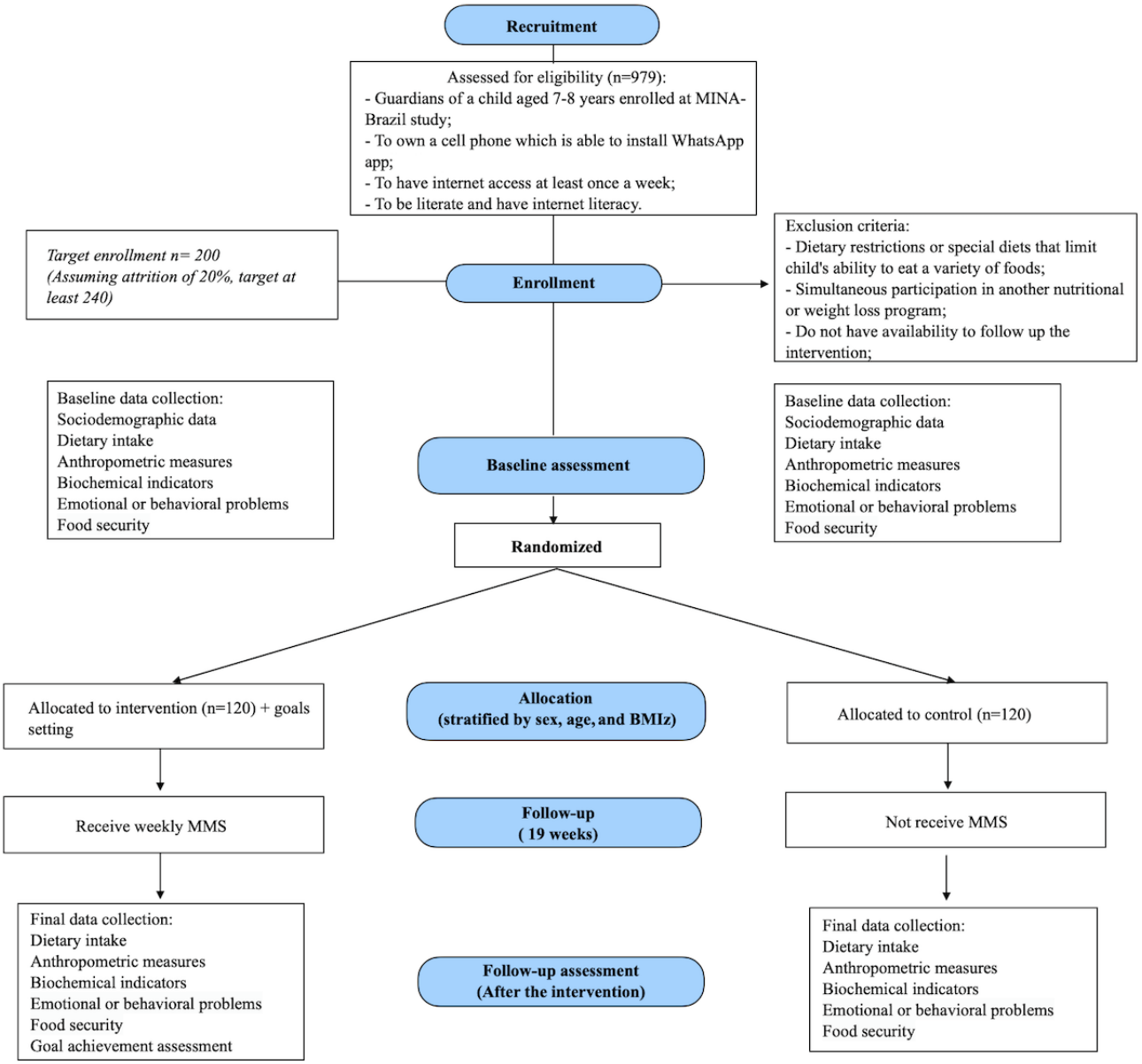
Table 1. Timeline of the study activities according to intervention stages.

Stage of intervention	Recruitment	Baseline	Intervention period	Postintervention
Verbal consent for screening	✓			
Eligibility screening verification	✓			
Study invitation	✓			
Face-to-face individual interview		✓		
Written consent from parents and written assent from children		✓		
Sociodemographic and participant information collection		✓		
Anthropometric measures		✓		✓
Food frequency questionnaire administration		✓		✓
Biochemical data collection		✓		✓
Strengths and Difficulties Questionnaire administration		✓		✓
Short version of the Brazilian Food Insecurity Scale administration		✓		✓
Delivery of an educational booklet		✓		
Goals setting for intervention group			✓	
Multimedia messaging for a 19-week follow-up			✓	
Phone call at 1 week to check if caregivers are properly receiving the messages			✓	
Goal achievement assessment for intervention group				✓
Delivery of same intervention to waitlist control group.				✓

Study Population and Setting

We will recruit 300 parents or caregivers of children enrolled in the MINA-Brazil birth cohort (Figure 1). They will be contacted by phone calls made from the Laboratory of Telephone Interviews of the Faculty of Public Health of the University of Sao Paulo. Family phone numbers will be assessed from the MINA-Brazil study database. Trained interviewers will make the calls at different times of the day to maximize the chance of contact with parents or caregivers. Additionally, MINA-Brazil's social media (ie, Facebook and Instagram) will be used to contact families who have changed their phone numbers but have not updated this information in their records. At this first contact, eligibility criteria will be assessed; then, the study's aim will be explained, and the parent or caregiver will be invited to be part of the study. Following this, a face-to-face meeting will be scheduled at a health care center in Cruzeiro do Sul with children and parents or caregivers to collect the consent forms and conduct the initial interview.

Figure 1. Study flowchart. BMIz: BMI in *z* score; MINA-Brazil: Maternal and Child Health and Nutrition Cohort Study in Acre; MMS: Multimedia Message Service.



Inclusion criteria for the study include (1) being a guardian of a child aged between 7 and 8 years enrolled in MINA-Brazil, (2) owning a cell phone that can install the WhatsApp app, (3) having internet access at least once a week, and (4) being literate and having internet literacy.

Exclusion criteria include (1) dietary restrictions or special diets that limit a child's ability to eat a variety of foods (eg, children on treatment for any disease that requires a specific diet), (2) simultaneous participation in another nutritional or weight loss program, and (3) not having the availability to follow up on the intervention for the whole period between baseline and final data collection (eg, intending to move out of town).

Power and Sample Size Calculation

The sample size estimation used the expected effect size (E) of at least 10% change for the mean value of BMIz as the main outcome (*z* score=1.5) and SD of 3.5 in a 2-tailed distribution, considering a *P* value of .05, statistical power of 80% (β=20%), and sample size ratio (group 1/group 2) of 1:1. Thus, for the expected E/SD ratio, the minimum sample required must be 100 participants per group [49]. However, assuming a dropout rate and potential losses of 20% during the intervention period, the sample size to be enrolled at baseline will be at least 120 children per study group [49].

Ethical Considerations

The MINA-Brazil birth cohort was approved by the Ethics Committee in Research with Human Beings of the School of Public Health of the University of São Paulo (protocols 872,613 of November 13, 2014, and 872,613 of October 30, 2017). For this trial, a new protocol was submitted and approved by the same Ethics Committee in Research with Human Beings (protocol 5,805,325 of December 9, 2022). Before taking part in the study, consent forms will be collected from parents or caregivers, and assent forms will be collected from children to guarantee the voluntary nature of participation. Additionally, participants will be informed of the minimal anticipated harms

of the intervention, such as the possibility of discomfort related to interviews with personal questions and venous blood collection, which will involve trained professionals and disposable materials. All participants will receive appropriate information on what to do if they wish to withdraw from the intervention at any time.

Baseline Information and Randomization

Face-to-face individual data collection meetings will take place before the beginning of the intervention to explain the study to parents or caregivers and schedule fasting blood collection at a local laboratory. After recruitment and data collection, participants will be randomly assigned to each experimental group using the R software (R Foundation for Statistical Computing), according to children's sex, age, and BMIz quartile intervals. Additionally, the stratified sortition will consider parents' or caregivers' schooling in years (≤9, 10-12, or ≥13) and wealth index quartiles.

Blinding

Given the nature of the intervention, we cannot guarantee participants will be blinded. However, study participants will not be aware of which group they will be assigned to. All participants will be informed that they will take part in a nutritional program; however, some children will receive the intervention before others. Furthermore, this strategy aims to minimize the chances of contamination bias due to information exchange between participants in the control and intervention groups. Researchers will be aware of participants' allocation, but all analyses will be blind to allocation.

Theoretical Basis

This intervention is grounded in the cognitive theory of multimedia learning (CTML) [50]. The CTML guides the development of efficient multimedia materials and how to implement effective cognitive strategies to amplify learning and promote deep understanding [50]. According to Mayer [50], the use of a dual learning channel activates the verbal and pictorial models of working memory. This activation allows readers to mentally connect visual and textual representations [50,51]. However, to promote effective learning, that is, to reach the individual's long-term memory, the information provided to the reader must be integrated into the working memory in a process called active processing (Figure 2 [50]). To trigger active processing, it is necessary for readers to form a mental representation connecting new knowledge to preexisting knowledge. In this way, readers will be able to make inferences regarding the combination of these contents to establish the understanding itself. Inferences are a central part of the understanding process, and the more inferences individuals make, the greater their active processing [52]. Furthermore, it is important to consider that working memory has a limited capacity. Thus, readers should not be overwhelmed with a large number of new concepts all at once. Therefore, for effective processing of information, the multimedia content should have as few words as possible and reinforce previously discussed concepts [50,52].

Also, social cognitive theory (SCT) was adopted as one of the foundations in the conception of the intervention. This theory claims that the behaviors of individuals are influenced by personal characteristics and the environment around them [53]. Thus, Bandura [53] argues that behavioral changes in health can be more effective if they strengthen individuals' knowledge on the subject, improve environmental factors such as social support, encourage self-efficacy, and, lastly, develop the use of self-regulatory behaviors through modeling of behaviors. Figure 3 shows the framework of the intervention, presenting how multimedia messages will operate to change children's behavior based on both CTML and SCT.

Figure 2. Multimedia information processing system according to the cognitive theory of multimedia learning.

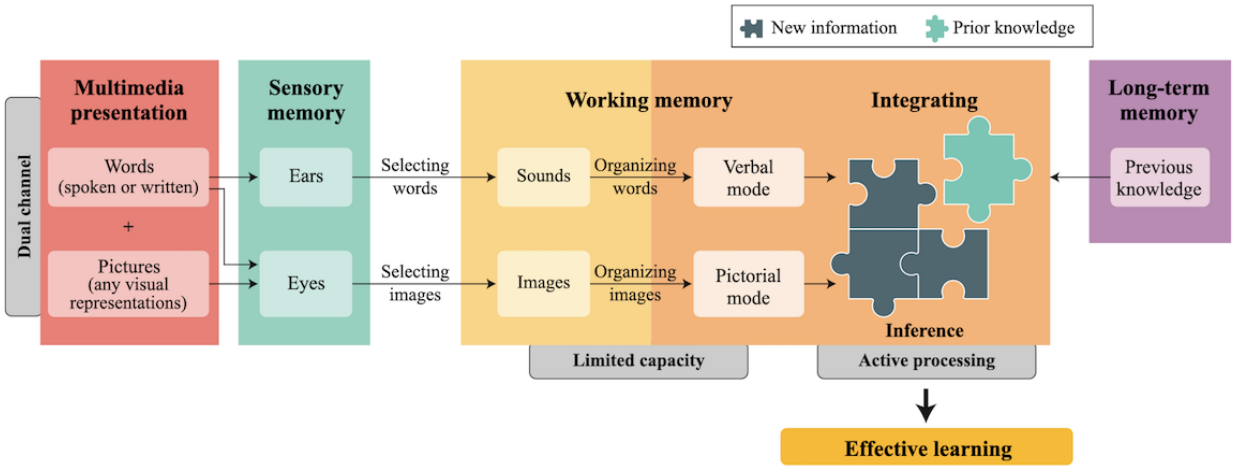
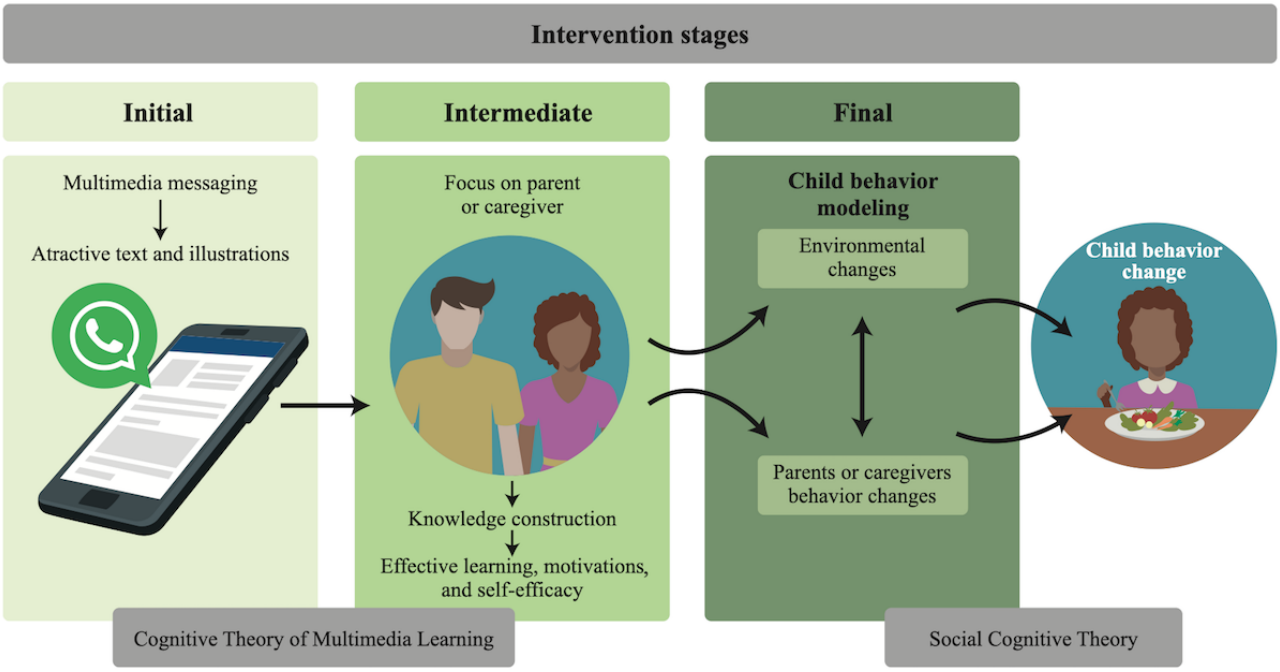


Figure 3. The framework of the intervention.



Intervention Plan

Participants allocated to the intervention group will receive individual multimedia messages 3 times a week for 19 weeks [54]. The message-sending system will be programmed using the Python programming language [55]. For individual goal-setting, parent-child or caregiver-child dyad will choose 2 specific, measurable, attainable, realistic, and timely (SMART) goals to focus on during the intervention according to their specific needs [56]. The goals will be chosen according to a preestablished list that will be defined by the topics of the messages that will be sent to parents or caregivers [56,57]. In addition, participants will receive an educational booklet about recommended dietary practices based on the food guide for the Brazilian population [58]. One week after the intervention commences, parents or caregivers will be contacted by phone calls to verify if they are appropriately receiving the messages.

Multimedia Message Content

To elaborate on the textual component of multimedia messages, the following 2 materials will be used as a guide: (1) the food guide for the Brazilian population [58] and (2) the protocol for the use of the food guide for the Brazilian population in the food guidance of children aged between 2 and 10 years [59]. Additionally, to assess the study population's dietary practices, previous results from a 24-hour Dietary Recall and Food Frequency Questionnaire applied to the target population were screened. While structuring the messages, behavior change techniques and persuasive writing strategies were used. Messages were structured according to 5 main topics related to the intervention objective: (1) increase fresh foods consumption, (2) reduce UPF consumption, (3) reduce culinary ingredients consumption (eg, excessive use of salt, sugar, and deep-frying practice), (4) encourage culinary practices, and (5) promote commensality and a healthy relationship with food. For the design of illustrations, we will adopt simple, precise, and easily recognizable images. In addition, persuasive techniques of color combination, typography, and cultural components, among others, will be applied [50,52].

Cross-Cultural Adaptation

To ensure the cultural appropriateness of the messages for the target population, the text component will undergo a 2-step cross-cultural adaptation [60]. The first step will include an expert committee of health professionals with experience in care or research in the Amazon region. In the second step, children's guardians will be invited to participate in formative research to assess the understanding and relevance of the elaborated messages. The formative research will be conducted through a telephone interview using a semistructured questionnaire with 4 exploratory questions for each SMS text message [61]. Then, the answers will be analyzed by 2 researchers, and the necessary adjustments will be made. Parents or caregivers involved in this phase will not be included in the intervention study.

Control Group

The control group will consist of children from the same population as the intervention group to ensure that both groups share similar characteristics, thereby guaranteeing accurate results for the intervention. In this context, the control group will not receive any messages during the intervention period. However, participants allocated to this group will be informed that they are on a waiting list and that the intervention will be carried out in stages, where children will receive the intervention at different times. After the end of the intervention period, the control group will receive the same treatment as the intervention group [35].

Outcome Measures

Participants in both groups will have the following data collected at baseline and immediately post intervention. The data obtained will be compiled onto tablets or computers with the Census and

Survey Processing System (CSPro) program (US Census Bureau and ICF Macro).

Primary Outcome (BMIz)

Children in both experimental groups will have their weight and height measured by trained study researchers according to the parameters established by the WHO [62]. BMIz and children's anthropometric indices, weight for age and height for age, will be assessed through WHO Anthro-Plus software and will be interpreted as recommended by the WHO [63]. In addition, children's waist circumference (WC) will be measured according to WHO recommendations [64]. Since no WC cutoff points were found in the literature for Brazilian children, to evaluate WC, we will consider that children with WC values above the 90th percentile of the sample have excessive abdominal fat [65,66]. The waist-to-height ratio will also be calculated, in which values above 0.5 will be considered to correspond to the presence of excessive abdominal fat [65,67].

Secondary Outcomes

Dietary Habits

In natural and minimally processed food (fruits, vegetables, grains, tubercles, and cereals) and UPF (chocolate powder, artificial and soft drinks, industrial bread, sweet-filled biscuits, salty crackers, deli products, pre-prepared frozen foods, instant noodles, sweets, and candies, among others), consumption will be assessed through a 1-month validated food frequency questionnaire for Amazonian schoolchildren [68]. Data will be collected by a trained nutritionist, and the frequency of food consumption will comprise the following 8 categories: rarely, 1-3 times a month, 1-3 times a week, 1 time a day, 2-3 times a day, 4-6 times a day, and more than 6 times a day.

Biochemical Indicators

Fasting blood collection will be performed by venipuncture to determine the lipid profile (total cholesterol, high-density lipoprotein [HDL], low-density lipoprotein [LDL], and very–low-density lipoprotein cholesterol), insulinemia, and blood glucose in a local clinical analysis laboratory with automated procedures. The lipid profile of the children will be interpreted according to the Brazilian Society of Cardiology, in which values <150 mg/dL for LDL and >45 mg/dL for HDL will be considered acceptable [69]. Blood glucose will be interpreted according to the Brazilian Society of Pediatrics, which establishes adequate values when <100 mg/dL [70]. Additionally, blood glucose and insulinemia will be used to assess peripheral insulin resistance through the Homeostasis Assessment Model-Insulin Resistance Index [71]. Results above the 90th percentile of the sample will indicate the presence of insulin resistance [71].

Other Measures

Sociodemographic and Participant Information

At baseline, only children's sex, age, and who is their primary caregiver will be assessed. For caregivers, the level of education and wealth index will be measured.

Emotional or Behavioral Problems

To screen 'children's mental health problems, the Strengths and Difficulties Questionnaire (SDQ) will be completed by the children's parents or caregivers [72]. SQD has 25 items divided between 5 scales: emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems, and prosocial behavior [72]. Total difficulty score will be calculated from the summary of the scale results (except prosocial behavior), and the final score will be classified into 3 categories: normal (0-13), borderline (14-16), and abnormal (17-40). For the assessment of prosocial behavior, a higher score will indicate better performance on this scale.

Food Security

To assess the food security of the study population, the short version of the Brazilian Food Insecurity Scale [73], with 5 questions, will be used. Study participants will be classified as food secure (0 points) or food insecure (>0 points) [73].

Data Analysis

The analysis will use an intent-to-treat approach to test the efficacy of the intervention. Tablets programmed with CSPro (US Census Bureau, ICF International) will be used for data entry. Descriptive statistics will be calculated for parents or caregivers and children. Paired and unpaired 2-tailed *t* tests will be applied when comparing mean changes of the outcome variables from pre- to post intervention when examining within-group changes in exploratory data analysis. For skewed distribution data, the Mann-Whitney test will be used to assess differences between groups. Multiple imputation methods will be used to deal with missing data. All analyses will be performed with the statistical package Stata 18.0 or higher (StataCorp), at a significant level of $P<.05$.

Results

Data collection started in June 2023, and 266 children were enrolled at baseline. Final measurements are scheduled to be completed in December 2023. The results of the main analysis will be conducted in 2024 and are expected to be available in 2024 and 2025.

Discussion

Overview

This is the first mHealth intervention focused on Amazonian children and also the first one, as far as we know, that investigates the efficacy of multimedia messages on children's dietary habits and excessive weight gain. Furthermore, it is novel because it translates policy-level recommendations from the food guide for the Brazilian population to a hard-to-reach and vulnerable population.

Furthermore, due to both food insecurity increases and large consumption of UPF, nutritionally adequate and environmentally sustainable food patterns from local Amazonian communities have been compromised, which may greatly influence global environmental changes [74,75]. Diets based on large consumption of UPF cause higher greenhouse gas emissions

through the need for large deforestation areas for monoculture farms and industrial processes. This contributes to biodiversity loss, land degradation, and intensification of climate change [74].

Conclusion

This trial is expected to better understand the efficacy, challenges, and limitations of the use of technologies in healthy eating promotion, particularly in regions characterized by high social vulnerability and limited access to health care, as is the case in the Western Amazon. We hypothesize that children whose parents or caregivers receive multimedia messages related to nutrition will demonstrate improvements in BMIz, dietary food intake, and biochemical data. Furthermore, we expect that the data produced by this trial will contribute to the development and strengthening of innovative public health policies aimed at preventing childhood obesity.

Acknowledgments

The authors thank the participants in the Maternal and Child Health and Nutrition Cohort Study in Acre birth cohort study in Cruzeiro do Sul, Acre, Brazil.

This work was supported by the Brazilian National Council of Technological and Scientific Development (CNPq; grants 407255/2013-3 and 404500/2021-8) and the São Paulo Research Foundation (FAPESP; grant 2016/00270-6). ACDAH is the recipient of the FAPESP PhD scholarship (grant 2022/03401-5). MAC is the recipient of the CNPq senior research scholarship (grant 303794/2021-6). The funders had no role in the design and analysis of the study or the writing of this study.

Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT-EHEALTH checklist (V 1.6.1).
[DOCX File , 50 KB - resprot_v13i1e54446_app1.docx]

References

1. Lee EY, Yoon KH. Epidemic obesity in children and adolescents: risk factors and prevention. Front Med 2018;12(6):658-666 [FREE Full text] [doi: 10.1007/s11684-018-0640-1] [Medline: 30280308]
2. Obesity and overweight. World Health Organization. 2017. URL: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight [accessed 2022-04-19]
3. Hauerslev M, Narang T, Gray N, Samuels TA, Bhutta ZA. Childhood obesity on the rise during COVID-19: a request for global leaders to change the trajectory. Obesity (Silver Spring) 2022;30(2):288-291 [FREE Full text] [doi: 10.1002/oby.23307] [Medline: 34570430]
4. [National school health survey]. Brazilian Institute of Geography and Statistics. 2009. URL: https://biblioteca.ibge.gov.br/visualizacao/livros/liv43063.pdf [accessed 2022-04-19]
5. Teixeira MT, Vitorino RS, da Silva JH, Raposo LM, de Aquino LA, Ribas SA. Eating habits of children and adolescents during the COVID-19 pandemic: the impact of social isolation. J Hum Nutr Diet 2021;34(4):670-678 [FREE Full text] [doi: 10.1111/jhn.12901] [Medline: 33811690]
6. Ferreira CM, Dos Reis ND, de Oliveira Castro A, Höfelmann DA, Kodaira K, Silva MT, et al. Prevalence of childhood obesity in Brazil: systematic review and meta-analysis. J Pediatr (Rio J) 2021;97(5):490-499 [FREE Full text] [doi: 10.1016/j.jped.2020.12.003] [Medline: 33577757]
7. Da Mata MM, Neves JA, de Medeiros MAT. Hunger and its associated factors in an urban cluster in the Western Brazilian Amazon: a population-based study. Research Square. Preprint posted online on July 13 2021 2021 [FREE Full text] [doi: 10.21203/rs.3.rs-634658/v1]
8. Food insecurity and COVID-19 in Brazil: II VIGISAN—national survey on food in the context of the COVID-19 pandemic in Brazil. The Brazilian Research Network on Food and Nutrition Sovereignty and Security. 2022. URL: https://olheparaafome.com.br/wp-content/uploads/2022/09/OLHESumExecutivoINGLES-Diagramacao-v2-R01-02-09-20224212.pdf [accessed 2024-01-17]
9. Dos Passos CM, Maia EG, Levy RB, Martins APB, Claro RM. Association between the price of ultra-processed foods and obesity in Brazil. Nutr Metab Cardiovasc Dis 2020;30(4):589-598 [FREE Full text] [doi: 10.1016/j.numecd.2019.12.011] [Medline: 32139251]

10. Mialon M, da Silva Gomes F. Public health and the ultra-processed food and drink products industry: corporate political activity of major transnationals in Latin America and the Caribbean. Public Health Nutr 2019;22(10):1898-1908 [FREE Full text] [doi: 10.1017/S1368980019000417] [Medline: 30859929]
11. Monteiro CA, Cannon G, Levy RB, Moubarac JC, Louzada ML, Rauber F, et al. Ultra-processed foods: what they are and how to identify them. Public Health Nutr 2019;22(5):936-941 [FREE Full text] [doi: 10.1017/S1368980018003762] [Medline: 30744710]
12. Nilson EAF, Ferrari G, Louzada MLC, Levy RB, Monteiro CA, Rezende LFM. Premature deaths attributable to the consumption of ultraprocessed foods in Brazil. Am J Prev Med 2023;64(1):129-136. [doi: 10.1016/j.amepre.2022.08.013] [Medline: 36528353]
13. Cobayashi F, Augusto RA, Lourenço BH, Muniz PT, Cardoso MA. Factors associated with stunting and overweight in Amazonian children: a population-based, cross-sectional study. Public Health Nutr 2014;17(3):551-560 [FREE Full text] [doi: 10.1017/S1368980013000190] [Medline: 23452910]
14. da Silva AP, Feilbelmann TCM, Silva DC, Palhares HMC, Scatena LM, de Resende EAMR, et al. Prevalence of overweight and obesity and associated factors in school children and adolescents in a medium-sized Brazilian city. Clinics (Sao Paulo) 2018;73:e438 [FREE Full text] [doi: 10.6061/clinics/2018/e438] [Medline: 30517282]
15. Mantovani SAS, Ramalho AA, Pereira TM, Branco FLCC, Oliart-Guzmán H, Delfino BM, et al. Stunting in children under five years old is still a health problem in the Western Brazilian Amazon: a population-based study in Assis Brasil, Acre, Brazil. Cien Saude Colet 2016;21(7):2257-2266 [FREE Full text] [doi: 10.1590/1413-81232015217.18602014] [Medline: 27383358]
16. de Morais Sato P, Ulian MD, da Silva Oliveira MS, Cardoso MA, Wells J, Devakumar D, et al. Signs and strategies to deal with food insecurity and consumption of ultra-processed foods among Amazonian mothers. Glob Public Health 2020;15(8):1130-1143. [doi: 10.1080/17441692.2020.1749694] [Medline: 32248738]
17. de Souza Almeida Aranha Camargo J, de Oliveira Zamarchi TB, da Silva Balieiro AA, Pessoaa FAC, Camargo LMA. Prevalence of obesity, high blood pressure, dyslipidemia and their associated factors in children and adolescents in a municipality in the Brazilian Amazon region. J Hum Growth Dev 2021;31(1):37-46 [FREE Full text] [doi: 10.36311/jhgd.v31.11209]
18. Ekambareshwar M, Ekambareshwar S, Mihrshahi S, Wen LM, Baur LA, Laws R, et al. Process evaluations of early childhood obesity prevention interventions delivered via telephone or text messages: a systematic review. Int J Behav Nutr Phys Act 2021;18(1):10 [FREE Full text] [doi: 10.1186/s12966-020-01074-8] [Medline: 33422066]
19. Azevedo LB, Stephenson J, Ells L, Adu-Ntiamoah S, DeSmet A, Giles EL, et al. The effectiveness of e-health interventions for the treatment of overweight or obesity in children and adolescents: a systematic review and meta-analysis. Obes Rev 2022;23(2):e13373. [doi: 10.1111/obr.13373] [Medline: 34747118]
20. Higgs ES, Goldberg AB, Labrique AB, Cook SH, Schmid C, Cole CF, et al. Understanding the role of mHealth and other media interventions for behavior change to enhance child survival and development in low- and middle-income countries: an evidence review. J Health Commun 2014;19(Suppl 1):164-189 [FREE Full text] [doi: 10.1080/10810730.2014.929763] [Medline: 25207452]
21. Research on the use of information and communication technologies in Brazilian households. Regional Center of Studies for the Development of the Information Society. 2021. URL: https://cetic.br/pt/tics/domicilios/2021/individuos/J2/ [accessed 2023-01-14]
22. Telecommunications sector monitoring report—mobile telephony 2nd half of 2020. National Telecommunications Agency. 2020. URL: https://www.gov.br/anatel/pt-br/dados/acompanhamento/relatorios-de-acompanhamento/2020#R2020_90 [accessed 2021-07-17]
23. Alshahrani A, Siddiqui A, Khalil S, Farag S, Alshahrani N, Alsabaani A, et al. WhatsApp-based intervention for promoting physical activity among female college students, Saudi Arabia: a randomized controlled trial. East Mediterr Health J 2021;27(8):782-789 [FREE Full text] [doi: 10.26719/emhj.21.012] [Medline: 34486714]
24. Trude ACB, Martins RC, Martins-Silva T, Blumenberg C, Carpena MX, Del-Ponte B, et al. A WhatsApp-based intervention to improve maternal social support and maternal-child health in Southern Brazil: the text-message intervention to enhance social support (TIES) feasibility study. Inquiry 2021;58:469580211048701 [FREE Full text] [doi: 10.1177/00469580211048701] [Medline: 34619999]
25. Pilus FM, Ahmad N, Zulkefli NAM, Shukri NHM. Effect of face-to-face and WhatsApp communication of a theory-based health education intervention on breastfeeding self-efficacy (SeBF intervention): cluster randomized controlled field trial. JMIR Mhealth Uhealth 2022;10(9):e31996 [FREE Full text] [doi: 10.2196/31996] [Medline: 36103244]
26. Patel SJ, Subbiah S, Jones R, Muigai F, Rothschild CW, Omwodo L, et al. Providing support to pregnant women and new mothers through moderated WhatsApp groups: a feasibility study. Mhealth 2018;4:14 [FREE Full text] [doi: 10.21037/mhealth.2018.04.05] [Medline: 29963559]
27. Kato-Lin YC, Kumar UB, Prakash BS, Prakash B, Varadan V, Agnihotri S, et al. Impact of pediatric mobile game play on healthy eating behavior: randomized controlled trial. JMIR Mhealth Uhealth 2020;8(11):e15717 [FREE Full text] [doi: 10.2196/15717] [Medline: 33206054]

28. Thompson D, Bhatt R, Vazquez I, Cullen KW, Baranowski J, Baranowski T, et al. Creating action plans in a serious video game increases and maintains child fruit-vegetable intake: a randomized controlled trial. Int J Behav Nutr Phys Act 2015;12:39 [FREE Full text] [doi: 10.1186/s12966-015-0199-z] [Medline: 25890060]
29. Arredondo EM, Ayala GX, Soto S, Slymen DJ, Horton LA, Parada H, et al. Latina mothers as agents of change in children's eating habits: findings from the randomized controlled trial Entre Familia: Reflejos de Salud. Int J Behav Nutr Phys Act 2018;15(1):95 [FREE Full text] [doi: 10.1186/s12966-018-0714-0] [Medline: 30285755]
30. Rangelov N, Bella SD, Marques-Vidal P, Suggs LS. Does additional support provided through e-mail or SMS in a web-based social marketing program improve children's food consumption? A randomized controlled trial. Nutr J 2018;17(1):24 [FREE Full text] [doi: 10.1186/s12937-018-0334-1] [Medline: 29452589]
31. Ahmad N, Shariff ZM, Mukhtar F, Lye MS. Effect of family-based REDUCE intervention program on children eating behavior and dietary intake: randomized controlled field trial. Nutrients 2020;12(10):3065 [FREE Full text] [doi: 10.3390/nu12103065] [Medline: 33049909]
32. Ragelienė T, Aschemann-Witzel J, Grønhøj A. Efficacy of a smartphone application-based intervention for encouraging children's healthy eating in Denmark. Health Promot Int 2022;37(1):daab081. [doi: 10.1093/heapro/daab081] [Medline: 34245283]
33. Cullen KW, Thompson D, Chen TA. Outcome evaluation of family eats: an eight-session web-based program promoting healthy home food environments and dietary behaviors for African American families. Health Educ Behav 2017;44(1):32-40. [doi: 10.1177/1090198116643917] [Medline: 27198535]
34. Lee JS, Jin MH, Lee HJ. Global relationship between parent and child obesity: a systematic review and meta-analysis. Clin Exp Pediatr 2022;65(1):35-46 [FREE Full text] [doi: 10.3345/cep.2020.01620] [Medline: 33781054]
35. Ahmad N, Shariff ZM, Mukhtar F, Lye MS. Family-based intervention using face-to-face sessions and social media to improve Malay primary school children's adiposity: a randomized controlled field trial of the Malaysian REDUCE programme. Nutr J 2018;17(1):74 [FREE Full text] [doi: 10.1186/s12937-018-0379-1] [Medline: 30071855]
36. Chai LK, Collins CE, May C, Brown LJ, Ashman A, Burrows TL. Fidelity and acceptability of a family-focused technology-based telehealth nutrition intervention for child weight management. J Telemed Telecare 2021;27(2):98-109. [doi: 10.1177/1357633X19864819] [Medline: 31390947]
37. Baker TB, Gustafson DH, Shaw B, Hawkins R, Pingree S, Roberts L, et al. Relevance of CONSORT reporting criteria for research on eHealth interventions. Patient Educ Couns 2010;81 Suppl:S77-S86 [FREE Full text] [doi: 10.1016/j.pec.2010.07.040] [Medline: 20843621]
38. Talmon J, Ammenwerth E, Brender J, de Keizer N, Nykänen P, Rigby M. STARE-HI--Statement on reporting of evaluation studies in Health Informatics. Int J Med Inform 2009;78(1):1-9. [doi: 10.1016/j.ijmedinf.2008.09.002] [Medline: 18930696]
39. Eysenbach G. Issues in evaluating health websites in an internet-based randomized controlled trial. J Med Internet Res 2002;4(3):E17 [FREE Full text] [doi: 10.2196/jmir.4.3.e17] [Medline: 12554548]
40. Blankers M, Koeter MWJ, Schippers GM. Missing data approaches in eHealth research: simulation study and a tutorial for nonmathematically inclined researchers. J Med Internet Res 2010;12(5):e54 [FREE Full text] [doi: 10.2196/jmir.1448] [Medline: 21169167]
41. Eysenbach G. The law of attrition. J Med Internet Res 2005;7(1):e11 [FREE Full text] [doi: 10.2196/jmir.7.1.e11] [Medline: 15829473]
42. Proudfoot J, Klein B, Barak A, Carlbring P, Cuijpers P, Lange A, et al. Establishing guidelines for executing and reporting Internet intervention research. Cogn Behav Ther 2011;40(2):82-97. [doi: 10.1080/16506073.2011.573807] [Medline: 25155812]
43. Webb TL, Joseph J, Yardley L, Michie S. Using the internet to promote health behavior change: a systematic review and meta-analysis of the impact of theoretical basis, use of behavior change techniques, and mode of delivery on efficacy. J Med Internet Res 2010;12(1):e4 [FREE Full text] [doi: 10.2196/jmir.1376] [Medline: 20164043]
44. Cugelman B, Thelwall M, Dawes P. Online interventions for social marketing health behavior change campaigns: a meta-analysis of psychological architectures and adherence factors. J Med Internet Res 2011;13(1):e17 [FREE Full text] [doi: 10.2196/jmir.1367] [Medline: 21320854]
45. Eysenbach G. Improving the quality of Web surveys: the Checklist for Reporting Results of Internet E-Surveys (CHERRIES). J Med Internet Res 2004;6(3):e34 [FREE Full text] [doi: 10.2196/jmir.6.3.e34] [Medline: 15471760]
46. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: Updated guidelines for reporting parallel group randomised trials. J Pharmacol Pharmacother 2010;1(2):100-107 [FREE Full text] [doi: 10.4103/0976-500X.72352] [Medline: 21350618]
47. Boutron I, Moher D, Altman DG, Schulz KF, Ravaud P, CONSORT Group. Extending the CONSORT statement to randomized trials of nonpharmacologic treatment: explanation and elaboration. Ann Intern Med 2008;148(4):295-309 [FREE Full text] [doi: 10.7326/0003-4819-148-4-200802190-00008] [Medline: 18283207]
48. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med 2013;158(3):200-207 [FREE Full text] [doi: 10.7326/0003-4819-158-3-201302050-00583] [Medline: 23295957]
49. Hulley SB, Cummings SR, Browner W, Grady D, Newman T. Designing Clinical Research. Philadelphia: Wolters Kluwer; 2013.

50. Mayer RE. Multimedia Learning, 2nd Edition. Cambridge: Cambridge University Press; 2009. URL: https://psycnet.apa.org/record/2009-01858-000
51. Sorden SD. The cognitive theory of multimedia learning. In: Irby BJ, Brown G, Lara-Alecio R, Jackson S, editors. The Handbook of Educational Theories. Charlotte, NC: Information Age Publishing, Inc; 2012:155-167 URL: https://psycnet.apa.org/record/2013-11995-014
52. Rudolph M. Cognitive theory of multimedia learning. J Online High Educ 2017;1(2) [FREE Full text]
53. Bandura A. Health promotion by social cognitive means. Health Educ Behav 2004;31(2):143-164. [doi: 10.1177/1090198104263660] [Medline: 15090118]
54. Armanasco AA, Miller YD, Fjeldsoe BS, Marshall AL. Preventive health behavior change text message interventions: a meta-analysis. Am J Prev Med 2017;52(3):391-402. [doi: 10.1016/j.amepre.2016.10.042] [Medline: 28073656]
55. Lutz M. Programming Python, 2nd Edition. Beijing: O'Reilly Media, Inc; 2001.
56. Eat well and be active educational toolkit—activity plan #3: setting SMART goals. Health Canada. 2010. URL: https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/fn-an/alt_formats/pdf/food-guide-aliment/educ-comm/toolkit-trousse/plan-3b-eng.pdf [accessed 2023-05-09]
57. Deslippe AL, Bains A, Loiselle SE, Kasvis P, Mak I, Weiler H, et al. SMART goals of children of 6-12 years enrolled in a family-centred lifestyle intervention for childhood obesity: secondary analysis of a randomized controlled trial. Pediatr Obes 2023;18(1):e12973. [doi: 10.1111/ijpo.12973] [Medline: 36066248]
58. Dietary guidelines for the Brazilian population. Ministry of Health of Brazil. 2015. URL: https://bvsms.saude.gov.br/bvs/publicacoes/dietary_guidelines_brazilian_population.pdf [accessed 2024-01-17]
59. Protocol for use of the food guide for the Brazilian population in dietary guidance for children aged 2 to 10 years. Ministry of Health of Brazil. URL: https://www.gov.br/saude/en [accessed 2024-01-17]
60. Castro FG, Barrera M, Steiker LKH. Issues and challenges in the design of culturally adapted evidence-based interventions. Annu Rev Clin Psychol 2010;6:213-239 [FREE Full text] [doi: 10.1146/annurev-clinpsy-033109-132032] [Medline: 20192800]
61. Diez-Canseco F, Zavala-Loayza JA, Beratarrechea A, Kanter R, Ramirez-Zea M, Rubinstein A, et al. Design and multi-country validation of text messages for an mHealth intervention for primary prevention of progression to hypertension in Latin America. JMIR Mhealth Uhealth 2015;3(1):e19 [FREE Full text] [doi: 10.2196/mhealth.3874] [Medline: 25693595]
62. WHO child growth standards: training course on child growth assessment. Measuring a child's growth. World Health Organization. 2008. URL: https://www.who.int/publications/i/item/9789241595070 [accessed 2024-01-17]
63. Recommendations for data collection, analysis and reporting on anthropometric indicators in children under 5 years old. World Health Organization. 2019. URL: https://www.who.int/publications/i/item/9789241515559 [accessed 2022-04-19]
64. Waist circumference and waist-hip ratio: report of a WHO expert consultation. World Health Organization. 2008. URL: https://www.who.int/publications/i/item/9789241501491 [accessed 2021-08-14]
65. Braunerová RT, Kunešová M, Heinen MM, Rutter H, Hassapidou M, Duleva V, et al. Waist circumference and waist-to-height ratio in 7-year-old children-WHO childhood obesity surveillance initiative. Obes Rev 2021;22(Suppl 6):e13208 [FREE Full text] [doi: 10.1111/obr.13208] [Medline: 34402567]
66. De Santis Filgueiras M, Vieira SA, de Almeida Fonseca PC, Pereira PF, Ribeiro AQ, Priore SE, et al. Waist circumference, waist-to-height ratio and conicity index to evaluate android fat excess in Brazilian children. Public Health Nutr 2019;22(1):140-146 [FREE Full text] [doi: 10.1017/S1368980018002483] [Medline: 30295220]
67. Fredriksen PM, Skår A, Mamen A. Waist circumference in 6-12-year-old children: the Health Oriented Pedagogical Project (HOPP). Scand J Public Health 2018;46(Suppl 21):12-20 [FREE Full text] [doi: 10.1177/1403494818767790] [Medline: 29754573]
68. Scagliusi FB, Garcia MT, Indiani ALC, Cardoso MA. Relative validity of a food-frequency questionnaire developed to assess food intake of schoolchildren living in the Brazilian Western Amazon. Cad Saude Publica 2011;27(11):2197-2206 [FREE Full text] [doi: 10.1590/s0102-311x2011001100013] [Medline: 22124497]
69. Giuliano ICB. I atherosclerosis prevention guideline in childhood and adolescence. Int J Atheroscler 2006;1(1):1-30 [FREE Full text]
70. Guidance manual for obesity in childhood and adolescence. Brazilian Society of Pediatrics. 2019. URL: https://www.sbp.com.br/reanimacao/braziliannrp/ [accessed 2024-01-17]
71. Cuartero BG, Lacalle CG, Lobo CJ, Vergaz AG, Rey CC, Villar MJA, et al. The HOMA and QUICKI indexes, and insulin and C-peptide levels in healthy children. Cut off points to identify metabolic syndrome in healthy children [Article in Spanish]. An Pediatr (Barc) 2007;66(5):481-490 [FREE Full text] [doi: 10.1157/13102513] [Medline: 17517203]
72. Fleitlich B, Cortázar PG, Robert G. Strengths and difficulties questionnaire (SDQ). Infanto Rev Neuropsiquiatr Infanc Adolesc 2000;8(1):44-50 [FREE Full text]
73. Maas NM, Mendoza-Sassi RA, Meucci RD, Cesar JA. Food insecurity in rural families in the extreme south of Brazil. Cien Saude Colet 2020;25(7):2605-2614 [FREE Full text] [doi: 10.1590/1413-81232020257.26402018] [Medline: 32667544]
74. Anastasiou K, Baker P, Hadjikakou M, Hendrie GA, Lawrence M. A conceptual framework for understanding the environmental impacts of ultra-processed foods and implications for sustainable food systems. J Clean Prod 2022;368:133155. [doi: 10.1016/j.jclepro.2022.133155]

75. da Silva JT, Garzillo JMF, Rauber F, Kluczkovski A, Rivera XS, da Cruz GL, et al. Greenhouse gas emissions, water footprint, and ecological footprint of food purchases according to their degree of processing in Brazilian metropolitan areas: a time-series study from 1987 to 2018. Lancet Planet Health 2021;5(11):e775-e785 [FREE Full text] [doi: 10.1016/S2542-5196(21)00254-0] [Medline: 34774121]

Abbreviations

BMIz: BMI in z score
CSPro: Census and Survey Processing System
CTML: cognitive theory of multimedia learning
E: effect size
HDL: high-density lipoprotein
LDL: low-density lipoprotein
mHealth: mobile health
MINA-Brazil: Maternal and Child Health and Nutrition Cohort Study in Acre
SCT: social cognitive theory
SDQ: Strengths and Difficulties Questionnaire
SMART: specific, measurable, attainable, realistic, and timely
UPF: ultraprocessed food
WC: waist circumference
WHO: World Health Organization

Edited by A Mavragani; submitted 09.11.23; peer-reviewed by FST Dewi, P Ebrahimi; comments to author 04.01.24; revised version received 10.01.24; accepted 11.01.24; published 19.02.24.

Please cite as:
Hovadick ACDA, Cardoso MA
Family-Based WhatsApp Intervention to Promote Healthy Eating Behaviors Among Amazonian School Children: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2024;13:e54446
URL: https://www.researchprotocols.org/2024/1/e54446
doi:10.2196/54446
PMID:38373039

Protocol

#4Corners4Health Social Media Cancer Prevention Campaign for Emerging Adults: Protocol for a Randomized Stepped-Wedge Trial

David B Buller[1*], PhD; Andrew L Sussman[2*], PhD; Cynthia A Thomson[3*], PhD; Deanna Kepka[4*], PhD; Douglas Taren[5*], PhD; Kimberly L Henry[6*], PhD; Echo L Warner[4*], PhD; Barbara J Walkosz[1*], PhD; W Gill Woodall[1*], PhD; Kayla Nuss[1*], PhD; Cindy K Blair[2*], PhD; Dolores D Guest[2*], PhD; Evelinn A Borrayo[7*], PhD; Judith S Gordon[8*], PhD; Jennifer Hatcher[9*], PhD; David W Wetter[10,11*], PhD; Alishia Kinsey[1*], BSc; Christopher F Jones[7*], MPH; Angela K Yung[12*], MBA; Kaila Christini[11*], MSPH, MS; Julia Berteletti[1*], MSW; John A Torres[2], BSc, BA; Emilia Yessenya Barraza Perez[13*], MPH; Annelise Small[1*], BA

[1]Klein Buendel, Golden, CO, United States

[2]University of New Mexico Comprehensive Cancer Care Center, Albuquerque, NM, United States

[3]Department of Health Promotion Sciences, Mel & Enid Zuckerman College of Public Health, University of Arizona, Tucson, AZ, United States

[4]College of Nursing and Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, United States

[5]Section of Nutrition, University of Colorado Denver, Aurora, CO, United States

[6]Department of Psychology, College of Natural Sciences, Colorado State University, Fort Collins, CO, United States

[7]University of Colorado Cancer Center, University of Colorado Denver, Aurora, CO, United States

[8]College of Nursing, University of Arizona, Tucson, AZ, United States

[9]Cancer Center, University of Arizona, Tucson, AZ, United States

[10]Department of Population Health Sciences, University of Utah, Salt Lake City, UT, United States

[11]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, United States

[12]College of Medicine, University of Arizona, Tucson, AZ, United States

[13]Department of Medicine, University of Arizona Cancer Center, Tucson, AZ, United States

[*]these authors contributed equally

Corresponding Author:
David B Buller, PhD
Klein Buendel
1667 Cole Blvd
Ste 220
Golden, CO, 80401
United States
Phone: 1 303 565 4321
Email: dbuller@kleinbuendel.com

Abstract

Background: Many emerging adults (EAs) are prone to making unhealthy choices, which increase their risk of premature cancer morbidity and mortality. In the era of social media, rigorous research on interventions to promote health behaviors for cancer risk reduction among EAs delivered over social media is limited. Cancer prevention information and recommendations may reach EAs more effectively over social media than in settings such as health care, schools, and workplaces, particularly for EAs residing in rural areas.

Objective: This pragmatic randomized trial aims to evaluate a multirisk factor intervention using a social media campaign designed with community advisers aimed at decreasing cancer risk factors among EAs. The trial will target EAs from diverse backgrounds living in rural counties in the *Four Corners* states of Arizona, Colorado, New Mexico, and Utah.

Methods: We will recruit a sample of EAs (n=1000) aged 18 to 26 years residing in rural counties (Rural-Urban Continuum Codes 4 to 9) in the Four Corners states from the Qualtrics' research panel and enroll them in a randomized stepped-wedge, quasi-experimental design. The inclusion criteria include English proficiency and regular social media engagement. A social

media intervention will promote guideline-related goals for increased physical activity, healthy eating, and human papillomavirus vaccination and reduced nicotine product use, alcohol intake, and solar UV radiation exposure. Campaign posts will cover digital and media literacy skills, responses to misinformation, communication with family and friends, and referral to community resources. The intervention will be delivered over 12 months in Facebook private groups and will be guided by advisory groups of community stakeholders and EAs and focus groups with EAs. The EAs will complete assessments at baseline and at 12, 26, 39, 52, and 104 weeks after randomization. Assessments will measure 6 cancer risk behaviors, theoretical mediators, and participants' engagement with the social media campaign.

Results: The trial is in its start-up phase. It is being led by a steering committee. Team members are working in 3 subcommittees to optimize community engagement, the social media intervention, and the measures to be used. The Stakeholder Organization Advisory Board and Emerging Adult Advisory Board were formed and provided initial input on the priority of cancer risk factors to target, social media use by EAs, and community resources available. A framework for the social media campaign with topics, format, and theoretical mediators has been created, along with protocols for campaign management.

Conclusions: Social media can be used as a platform to counter misinformation and improve reliable health information to promote health behaviors that reduce cancer risks among EAs. Because of the popularity of web-based information sources among EAs, an innovative, multirisk factor intervention using a social media campaign has the potential to reduce their cancer risk behaviors.

Trial Registration: ClinicalTrials.gov NCT05618158; https://classic.clinicaltrials.gov/ct2/show/NCT05618158

International Registered Report Identifier (IRRID): PRR1-10.2196/50392

(JMIR Res Protoc 2024;13:e50392) doi:10.2196/50392

KEYWORDS

cancer prevention; young adults; rural; social media; physical activity; diet; alcohol; tobacco control; sunburn; human papillomavirus; HPV vaccination

Introduction

Background

Emerging adulthood is an important habit-forming period of life. The lives of emerging adults aged 18 to 26 years are in flux [1], as they experience lifestyle transitions and increased autonomy while taking on adult-related responsibilities (eg, financial, residential, and employment). It is an important time for health behaviors because with increased autonomy, numerous emerging adults are at risk of making unhealthy choices [2,3].

Health-compromising behaviors that increase cancer risk later in life are especially prevalent among emerging adults [4] and are linked to future cancer morbidity and mortality [5]. Many emerging adults have reduced physical activity and unhealthy eating patterns that do not meet the 2020 American Cancer Society guidelines [6] (are overweight, eat fast food [7,8], and have low self-efficacy for making healthy food choices) [9-13]. Emerging adults' use of nicotine products [9-12,14] and multiple combustible and noncombustible products [15,16] and their alcohol use and heavy drinking (bingeing) are high [17,18]. Emerging adults are also more prone to intentional UV exposure (solar and artificial tanning) [19]; sporadic sun safety practices [20-23]; and a lack of human papillomavirus (HPV) knowledge [24,25], resulting in incomplete vaccination rates [26,27]. These modifiable cancer risk behaviors are important targets of primary prevention for emerging adults by promoting moderate to vigorous physical activity (MVPA) and dietary and sun safety skills, supporting the use of brief interventions for tobacco or alcohol use, and encouraging emerging adults to make their own health care decisions such as HPV vaccination. However, there is a lack of rigorous research on interventions for emerging adults, and information on their cancer risk behaviors is limited [28].

In the United States, rural populations have substantially higher rates of cancer [29] related to unhealthy eating [30,31], high rates of smoking and alcohol use, exposure to UV radiation and radon (riskier for smokers) [32,33], and persistent HPV infection compared with urban populations. Rural cancer disparities are exacerbated by a lack of health insurance and preventive care [34,35], low socioeconomic status [36,37], poor health literacy [36,38], fatalistic beliefs and ambiguous health information [25], and pervasive barriers to preventive health care [37,39,40].

Social media may offer a superior intervention channel for reaching and influencing emerging adults compared with health care, schools, and workplaces, including in rural areas. Emerging adults (90%) are the most engaged age group on the internet [41], and the internet is a preferred channel for health information among rural and urban emerging adults [40,42]. Rural adults use the internet (85%), as do most Hispanic (86%) and African American (85%) individuals [42]. Social media platforms are very popular with emerging adults [41,43]. Social media provide flexible, responsive, accessible, and low-cost platforms for distributing cancer information to the public from trusted voices [44]. Social media can improve information dissemination, credibility, and relevance and are often used to detect and respond to emerging issues [45] and promote engagement with personalized and impactful user-generated content [46]. Although use varies across platforms, there is growing evidence that interventions delivered using social media can improve physical activity, diet, nicotine product use, skin cancer prevention, and HPV vaccination outcomes among young adults [47-57]. By contrast, it can be challenging to implement a cancer prevention intervention in health care organizations,

schools, and workplaces in low-resourced rural communities. Interventions in these channels also may not reach many emerging adults who have low preventive health care use, school enrollment, or employment. However, social media platforms also circulate inaccurate, misleading, and harmful information [58,59]. For instance, social media has spread misinformation on tobacco products [60], breast cancer prevention [61], the efficacy of cannabidiol for cancer care [62], cancer-related nutrition [63], and the mistrust of HPV vaccines [64,65], which can undermine cancer prevention efforts. Thus, interventions also need strategies to correct misinformation and provide digital and media literacy skills [66-70].

In summary, emerging adulthood is an important period for establishing cancer prevention. Many rural emerging adults experience several cancer risk factors, but successful interventions for them are lacking. With the popularity of web-based resources for emerging adults, an innovative multirisk factor intervention over social media has the potential to reach this underserved population and reduce emerging adults' cancer risks. The goal of this trial is to modify cancer risk factors among emerging adults aged 18 to 26 years living in rural counties in the Four Corners states of Arizona, Colorado, New Mexico, and Utah using a unique, theory-based social media campaign designed with community advisers that delivers relevant, credible, and timely content on reducing multiple cancer risks to emerging adults. A multirisk factor approach [71,72] is adopted because (1) emerging adults vary in cancer risk profiles, (2) several risks cooccur and are affected by similar mechanisms [73-76], and (3) coverage of a variety of topics in the campaign will be engaging. Furthermore, the Four Corners region has a relatively high burden of poverty [77,78], significant population diversity with large Hispanic and American Indian populations [79], and low population density where distance and transportation are health care access barriers [37,80], providing a rich environment to test the efficacy of a multibehavior health promotion intervention.

Objectives

Our proposed intervention will aim to aid rural emerging adults in making informed decisions to reduce cancer risks related to infrequent physical activity, unhealthy diet, alcohol intake (per 2020 American Cancer Society guidelines [6]), nicotine product use, UV exposure, and lack of HPV vaccination uptake. In addition, it will help them critically evaluate and resist misinformation and marketing that promote cancer and other health risk behaviors and support emerging adults to be media literate when using digital media. The trial will test the following hypotheses:

- Hypothesis 1: emerging adults will increase MVPA and healthy eating patterns, reduce nicotine product and alcohol use and sunburns, and increase HPV vaccine uptake from baseline to final assessment when receiving the social media intervention.
- Hypothesis 2: the positive impact of the social media campaign on cancer risk factors among emerging adults will be mediated by improved cancer risk knowledge and beliefs (ie, self-efficacy and response efficacy, norms, social support, and vaccine antecedents), digital and media literacy skills, misinformation identification, and family communication.

Analyses will also explore whether the impact of the campaign differs according to (1) the level of emerging adults' engagement with it, (2) cancer risk factors, and (3) the biological sex of the participants. The prospective randomized quasi-experimental design and its large sample will provide a rigorous evaluation of the social media campaign compared with many previous studies on social media that have used less rigorous nonrandomized controlled trial designs and small samples [81-86].

Methods

We will test a social media campaign to reduce cancer risk factors among emerging adults in rural counties in the Four Corners states using a randomized stepped-wedge trial design.

Target Population and Recruitment Procedures

Emerging adults (N=1000) aged 18 to 26 years residing in rural counties in the states of Arizona, Colorado, New Mexico, and Utah will be enrolled in the study (refer to Textbox 1 for the inclusion and exclusion criteria). Many emerging adults will report ≥1 cancer risk behavior and will be residing in a variety of living arrangements, from multigenerational families to roommates to spouses or partners to alone. In the Four Corners states, 99 counties are rural (ie, Rural-Urban Continuum Codes [RUCC] 4 to 9 [87]), with >2 million residents (176,737 residents aged 19 to 25 years; annual income) [88]. Pregnant individuals will be excluded because the intervention will not provide individualized counseling and could lead to behavioral changes in diet or exercise that might be contraindicated during pregnancy.

Textbox 1. Inclusion and exclusion criteria for the sample of emerging adults.

Inclusion criteria

- Member of the Qualtrics survey panel in year 2
- Aged 18 to 26 years
- Resides in a county coded as Rural-Urban Continuum Codes 4 to 9 in Arizona, Colorado, New Mexico, or Utah
- Able to speak and read English
- Has regular social media engagement
- Accepts screening call from the study staff
- Provides consent to participate

Exclusion criteria

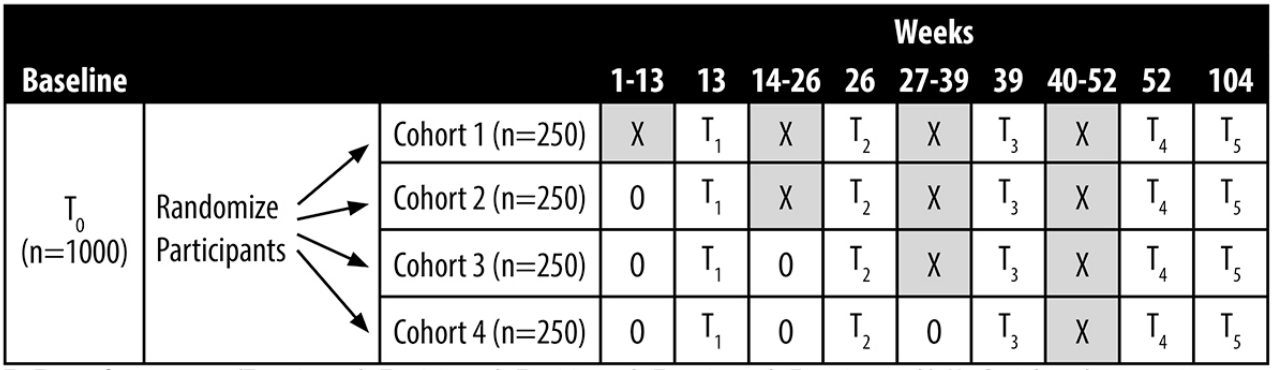
- Participated in community engagement activities
- Cannot speak and read English
- Has low or no social media engagement
- Does not accept a screening call from the study staff
- Does not provide consent to participate
- Does not give permission for engagement data to be extracted from the Facebook private groups
- If biologically female, currently pregnant

Emerging adults will be recruited from Qualtrics' research panel, built from multiple providers that use by-invitation or double opt-in methods. Qualtrics will select adults aged 18 to 26 years residing in counties designated as RUCC 4 to 9 in the 4 selected states [87], balanced on gender, and refer emerging adults to the project's registration website to complete a consent form. Fake, duplicate, and unqualified respondents will be screened out, and steps will be taken to ensure that they participate only once. The project staff will contact the consented emerging adults by telephone and confirm their eligibility. To avoid clustering, only 1 emerging adult per household will be enrolled. If recruitment lags, we will add Mountain West states with similar populations (ie, Idaho, Montana, Nevada, and Wyoming). We will use quotas so that the sample matches the education and the race and ethnicity of the counties. Although research panel members are required to have internet access, selection bias will be reduced as most US adults (90%), including emerging adults (100%) and rural adults (85%), have access to the internet [42]. We will confirm that the emerging adults have regular social media use (post ≥1 time per week) to allow them to engage with our campaign. We acknowledge that this criterion may impact generalizability, but social media influence those who view them regularly [89,90]. The escalating compensation schedule is designed to achieve retention for postintervention assessments.

Randomized Stepped-Wedge Trial Design

The cancer prevention social media campaign will be tested using a randomized stepped-wedge design (Figure 1).

Figure 1. Randomized stepped-wedge trial design.



Following baseline assessment (T_0), emerging adults will be stratified by state, ethnicity (racial and ethnic minority individuals vs non-Hispanic White individuals), and biological sex (male vs female) and randomly assigned to 1 of 4 cohorts differing in intervention duration by the project biostatistician. All cohorts will complete postintervention assessments at weeks

13 (T_1), 26 (T_2), 39 (T_3), 52 (T_4), and 104 (T_5). All data collection will be conducted using the secure web-based REDCap (Research Electronic Data Capture; Vanderbilt University) application. The primary outcomes measured at all assessment times will be MVPA, healthy eating patterns, nicotine product use, alcohol intake, sunburn, and HPV vaccination.

The social media campaign will be conducted over 12 months in 4 separate Facebook private groups. The intervention will start in each cohort at successive 13-week intervals, so cohorts will receive varying doses of campaign exposure (ie, 180 posts per 13-week interval) via stepped entry. Specifically, cohort 1 (250/1000, 25%) will start the social media campaign at week 1, receiving approximately 720 posts in 52 weeks. Cohort 2 (250/1000, 25%) will start the campaign at week 13 (approximately 540 posts), cohort 3 (250/1000, 25%) at week 26 (approximately 360 posts), and cohort 4 (250/1000, 25%) at week 39 (approximately 180 posts). Emerging adults will be told to read, react to, and comment on posts as often as they like. Exposure to cancer risk information and misinformation from other sources will be controlled by randomization.

The stepped-wedge quasi-experimental design was selected because it has several methodological advantages [91]. First, it allows for the random assignment of participants to 1 of the 4 cohorts, ensuring that potential confounding factors are evenly distributed across the groups. Each cohort is assigned to start the intervention at different times, creating a staggered, time-sequenced implementation schedule across the cohorts that creates the controlled nature of our trial. This design element allows for the within-study comparison of outcomes across different cohorts, with each cohort serving as a control for the others before they receive the intervention. Specifically, the control condition is represented by the periods when the cohorts have not yet started the intervention. For example, cohort 2 serves as a control group for cohort 1 before they commence their intervention in week 13. Second, the design also allows for comparisons between cohorts that have received the intervention for different durations. Third, by collecting data at multiple time points (T_1-T_5), the design facilitates the assessment of outcomes over an extended period that allows for the evaluation of trends and changes in outcomes over time within each cohort as well as comparisons between cohorts. The multiple baseline measures in cohorts 2, 3, and 4 will permit the examination of any trends or patterns before the intervention is introduced and will control threats to validity [92], as we can account for potential confounding factors, such as time-related effects or external factors, and compare cohorts at different stages of intervention exposure. This strengthens the internal validity of the study. Fourth, the design optimizes study resources by focusing on recruiting and retaining a longitudinal sample. This approach differs from securing a sample where half remain untreated, mitigating problems associated with control groups such as loss to follow-up, demoralization, disengagement, or noncomparability. It adheres to ethical standards by having all participants eventually receive the intervention but still preserves the controlled trial's integrity.

Cancer Prevention Social Media Campaign

The social media campaign will deliver 2 posts per day (n=approximately 720 posts) over 12 months, addressing cancer risk reduction, teaching digital and media literacy, encouraging family and friend communication, responding to misinformation, and highlighting community resources. The diverse content should be engaging and should avoid fatigue, but we will assess information overload and compare varying intervention durations (ie, 13, 26, 36, and 52 weeks).

Theoretical Approach to Social Media Intervention

We will adopt a multitheoretical approach to influencing rural emerging adults' health behaviors. Social cognitive theory (SCT) [93] and self-determination theory (SDT) [94] will provide a framework and guide message development and measures of theoretical mediators, including cancer risk perceptions, self-efficacy and response efficacy, norms, social support, relatedness, autonomy, and motivation. SCT constructs address the environment (eg, environmental risks [UV exposure] and settings [health care access]), situation (eg, social norms of risk behaviors), behavior (eg, risk-reduction knowledge and skills), expectations (eg, good health outcomes), observational learning (eg, behavioral modeling), and self-efficacy (eg, confidence to perform prevention) [95]. Three needs must be satisfied when using SDT to foster well-being [94]: (1) competence—ability to control outcomes and feel self-efficacy, (2) relatedness—innate desire to interact with others, and (3) autonomy—need to be in charge of one's life. Effective interventions implement techniques and strategies that support these 3 basic psychological needs. In need-supportive environments and contexts, extrinsic motivation can be transformed into higher-quality, intrinsic motivation, which is linked to positive health behavior change [96].

Posts will also include engagement strategies to encourage user-generated content and incorporate testimonials. The diffusion of innovations theory (DIT) and social network principles [97] explain that social media are uniquely influential because (1) user activity increases dissemination [98] and (2) information spread among social media communities, notably by knowledgeable peers, reduces uncertainty; makes sentiments dominant [65,99]; and motivates collective action [97,100] via social comparison [97,101] and collective identity that stabilizes actions [101]. Social media's influence is further clarified by transportation theory [102]. According to this theory, personal stories can be more influential than didactic messages and expert advice [103] partly because of the audience's identification with the characters [104]. Users often share stories on social media.

Digital and media literacy principles, including "active inquiry and critical thinking about mediated messages" [105], will be addressed in the campaign because many emerging adults are not critical media consumers [106]. Strategies to help emerging adults navigate the media landscape, combat echo chambers of misinformation, counterargue critical information, and develop trust in public health voices are imperative [107,108]. Fact-checking and corrections are important strategies for the campaign, but counternarratives, peer correction, factual elaboration, coherence and credibility appeals, media literacy [109-113], eHealth literacy [114], and advice on safe content

sharing are also essential for the posts [69,115]. Media literacy interventions have helped health-related decisions and provided skills to combat unhealthy messages across health topics [116-120], suggesting they will make emerging adults "better prepared and willing to take preventive actions recommended by health professionals" [121]. We will convey how to identify media sources, their intentions, and misinformation; conduct web searches; overcome discomfort of new behaviors; converse with others about cancer risks (skills acquisition); highlight benefits to self, family, and friends (positive outcome expectations); and reinforce that they can reduce risks (self-efficacy). We will measure digital and media literacy skills and the level of misinformation (ie, holding inaccurate beliefs) about cancer prevention as mediators.

Social Media Posts

Social media posts will contain text with images, infographics, videos, and links to websites or other social media platforms (eg, Instagram and YouTube) from government, health care, news media, and trusted sources. Preferred health content for emerging adults of any gender and various social groups (eg, race, ethnicity, income, education, and living circumstances) will be identified through community engagement methods. Messages will address SCT [93], SDT [94], DIT [97], and media literacy principles [122] described earlier. The posts will be positive, at the seventh-grade reading level, and in English. The posts will cover 5 content areas:

- Cancer prevention: posts will address 6 cancer risk factors and various methods to improve them including behavioral skills for risk reduction, benefits of engaging in such behaviors, social support for these efforts, and strategies to minimize the social and financial costs associated with cancer risk reduction. In addition, advice from health care providers will be shared to help individuals overcome barriers to adopting healthier behaviors. Risk-reducing behaviors will be targeted by the posts include increasing MVPA and healthy eating behavior (more vegetables, fruits, and whole grains and less red and processed meats, sugar-sweetened beverages, highly processed foods, and refined grains); decreasing nicotine product use, alcohol intake, and UV exposure (sunburn); and increasing HPV vaccination. Posts will seek to improve several theoretical mediators, including self-efficacy and response efficacy and perceived risk, and to link cancer prevention to personal goals, including compatibility with values, observable benefits, and simplicity. Posts will also address cost of cancer prevention, present descriptive norms related to healthy and unhealthy behaviors, and highlight social support from family, friends, and partners. They will also promote emerging adults autonomy for their own health and decisions to adopt healthy behaviors. Posts will highlight the cancer prevention benefits of these behaviors and other benefits that may motivate emerging adults to adopt risk-reduction behaviors, including appearance (eg, avoiding skin aging), social (eg, reducing alcohol-induced partner violence), financial (eg, cost savings from quitting nicotine products), and disease prevention (eg, cardiovascular health) benefits. We will use a rotation pattern that covers the 6 cancer risk factors in at least 1 post per week and highlights 1 cancer risk factor in a series of posts each week to provide an in-depth intervention.
- Digital and media literacy skills: media literacy posts will focus on critical thinking, skill acquisition, and misinformation correction. Posts will aim to improve emerging adults' digital and media literacy competencies related to (1) access, (2) analysis, (3) creation, (4) reflection, and (5) action [122]. Posts will focus on assessing message credibility and quality (eg, authorship [eg, bots], purpose [eg, marketing], construction, and algorithms) and validity (eg, original source identification, images, deep fake videos, and scientific evidence). Differences in storytelling and scientific evidence will be discussed. Marketing messages will be addressed because advertisers (eg, tobacco, alcohol, and tanning industries) reach emerging adults through social media promotions [41]. Even brief exposure to these marketing messages can instill positive attitudes toward the products [123].
- Responding to misinformation: we will use our best practices to respond to misinformation [124], that is, messages in conflict with scientific and medical information and advice. Misinformation will be identified by monitoring users' reactions and comments, auditing the media landscape, and responding immediately [125] to forestall it from going viral. We will respond both proactively in the feed and reactively in replies to the comments. Responses will show empathic engagement and acknowledge users' uncertainty, confusion, or motivations to prevent defensiveness and maintain trust [125]. Posts will then debunk misinformation by fact-checking, providing factual elaboration and coherence appeals with evidence-based sources [110,111], reframing information to fit existing beliefs, using resistance-to-persuasion tactics (2-sided appeals [126,127] and inoculation [128-130]), telling stories that offer personalized advice, presenting credible statistics and science [111,112,131,132], highlighting prevention actions by resistant groups [132], and depicting patient-provider interactions [132].
- Family and friend communication: emerging adults are expected to reside in several living arrangements, often with other adults, so posts will present prompts to talk with family (eg, parents, siblings, and partners) and friends about cancer prevention (and content from the campaign posts). Posts will focus on skills for active listening, self-disclosure, support, and conflict management.
- Referral to community resources: a website will be created that contains links to web-based tools and brief interventions to help emerging adults alter cancer risk behaviors, especially those that may be unknown to emerging adults. Examples include quit-smoking services, portals to state vaccination records, tools for managing the multidose HPV vaccination schedule, and fact sheets and guidelines from health authorities. Resources will be identified by the community advisers and maintained by the investigators. A link to this website and its relevant resources will be included regularly in posts.

Development of Cancer Prevention Posts

An agile, just-in-time process will be used to create and adapt posts to be responsive to emerging adults and to reflect current events [133]. Investigators will prepare a campaign framework for developing posts, identifying target behaviors for each cancer risk factor and key theoretical principles. Project staff will continuously audit cancer prevention information and misinformation in (1) published literature, government reports, and national surveys; (2) participant comments on posts; (3) quarterly web-based emerging adult focus groups; and (4) advisory board input. The investigators and media developers will revise posts, add emerging themes, and tailor posts to key subgroups. Initially, 3 months of campaign posts will be prepared, with additional posts developed during the campaign, creating a planned adaptive campaign. Social media posts will be written in English because rural emerging adults are the primary target group, with Hispanic and American Indian emerging adults comprising a minority of them. English continues to be the most common language on the internet, especially in the United States [134,135]. Nearly all young adults in the United States are proficient in English, even most foreign-born young adults [136].

To ensure campaign exposure, posts must regularly engage users because the Facebook algorithm presents posts from the private groups more frequently and prominently in participants' newsfeeds when they engage more with the group's posts. To achieve high visibility and engagement, we will post twice per day and (1) provide novel, high-interest, useful, and current-event content; (2) adjust for season; (3) link to content from other emerging adults to create descriptive norms; (4) address age differences and cultural barriers and facilitators; (5) use ethnically diverse emerging adult images that can improve health communication [137]; and (6) use formats such as stories, polls, questions and answers, videos, and visuals, and invite comments [58,98,138-141].

The campaign will be pilot-tested with rural emerging adults (N=25) meeting the inclusion and exclusion criteria displayed in Textbox 1 (13/25, 52% female individuals and ethnically diverse). It will contain a feed of 56 campaign posts (2 per day) over 4 weeks, and participants will provide feedback in focus group discussions.

Implementation of Social Media Campaign

The social media campaign will be implemented through Facebook private groups. A staff person will serve as the community manager and schedule posts twice a day on all 7 days of the week (1 message in the morning and 1 in the afternoon) to achieve reach [142,143]. In each cohort, emerging adults will receive welcome posts on purpose and ground rules (eg, respect for others) and then receive the ongoing feed delivered in their separate private group so that posts are identical across cohorts, timely, linked to current events and news stories, relevant for seasons, and engaging. We will not start each cohort at the beginning of the feed because it would require adjusting earlier posts to be current, making them dissimilar across cohorts. The community manager will monitor reactions and comments from emerging adults, answer questions, address uncertainty, and correct misinformation [58,124,133]. The community manager will promote peer influence by, for example, (1) recruiting high-frequency emerging adult users to be guest moderators for up to 3 days to schedule posts and reply to comments and (2) hosting Facebook Live events with emerging adult experts (eg, an emerging adult dietitian). If any bullying arises, the community manager will de-escalate it by (1) highlighting empathy and (2) sending direct messages to stop it. If participants leave a group, they will be contacted to see why. Project staff, except the community manager and the project coordinator, will be blinded to the cohort membership.

Facebook's private group function possesses unique features not found in other social media platforms. These distinctive qualities offer practical methodological advantages and enhance experimental rigor. Facebook remains one of the most popular social media platforms for emerging adults, used by 70% of the population nationally (among which 70% use it daily), with the majority reporting use in nearly all demographic groups, including by age, rurality, race, ethnicity, and income [43]. Thus, nearly all emerging adults will have existing accounts and be familiar with its interface. Other social media place limits on content delivery that would restrict cancer prevention messaging, including by restricting format (eg, YouTube and Instagram mainly use video and images), length (Snapchat and TikTok deliver short videos), and permanence (Snapchat posts last for 24 hours after posting), and they all restrict the ability to link to other web content more than Facebook. Facebook's private group function will also help ensure that posts appear in users' feed and will limit access to posts to group members (posts cannot be shared on other social media) to avoid contamination. Finally, Facebook has superior data analytics for tracking exposure to content compared with other platforms.

Community Engagement Methods

Community-based participatory research methods will inform the study and cancer prevention campaign. Partnership processes aligned with the model by Sandoval et al [144] will provide a framework for the study: (1) knowledge of *contexts* that inform catchment area needs; (2) culturally informed *partnership processes* guiding engagement; (3) *intervention and research* protocols responsive to rural, low-income, and underserved conditions; and (4) participatory *outcomes* disseminated to partners. The research team will draw on the community networks of the Four Corners Cancer Centers Collaborative through each cancer center's Community Outreach and Engagement program [145] to convene 2 community advisory boards for the project—an Emerging Adult Advisory Board (EAAB) and a Stakeholder Organization Advisory Board (SOAB). Up to 16 emerging adults from rural counties in the Four Corners states, diverse in gender and ethnicity, will be recruited to serve on the EAAB. The EAAB will meet quarterly with investigators in years 2 and 3 and biannually in years 1, 4, and 5. Members provide input on the social media campaign and implementation protocols (year 1) and review proposed posts (years 2 to 3), with attention to the relevance of posts for the circumstances experienced by rural emerging adults, especially the challenges experienced by low-income and marginalized emerging adults. Up to 4 stakeholder organizations that provide health promotion and cancer prevention services to rural emerging adults in each of the 4 states will be recruited

for the SOAB. The SOAB will meet twice annually to review messaging, identify local resources, and plan dissemination efforts. Both advisory boards will advise on trial findings and dissemination efforts in years 4 to 5.

A series of focus groups with up to 8 rural emerging adults per group, meeting the inclusion and exclusion criteria (Textbox 1), will be conducted during the project to help develop the social media campaign. Discussions will cover cancer risk behaviors, social media use, health information seeking, misinformation, the context of health behaviors, and current issues and trends. Emerging adults will review social media posts and suggest how to engage rural emerging adults and reflect local contexts and issues. The results will be summarized and used to adapt posts to be responsive, timely, and engaging for emerging adults and targeted to key subgroups.

Measures

Primary Outcomes: Cancer Risk Behavior Outcome Measures

We will use validated self-report measures of each cancer risk behavior in the T_0-T_5 surveys presented in Table 1.

Table 1. Primary and secondary cancer risk behavior outcome measures.

Cancer risk behavior	Measure	Metric
Physical activity	• Primary and secondary: Global Physical Activity Questionnaire [146]	• Minutes per week of MVPA[a] (primary) • Meet 150 minutes per week goal (secondary)
Diet	• Primary: Dietary Screener Questionnaire [147,148] • Secondary: other meal behaviors [149-152]	• Intake per day of fruits, vegetables, whole grains or fiber, added sugars (from sugar-sweetened beverages), and red or processed meats • Frequency of eating meals and snacks, fast food, and skipping meals
Nicotine product use	• Primary: 30-day prolonged tobacco or nicotine product abstinence [153] • Secondary: 7-day point prevalence of smoking [153] • Secondary: readiness to quit [154]	• Use in the past 30 days (every day, some days, and not at all) • Use in the past 7 days (every day, some days, and not at all) • 10-point rating (1=no thought of quitting and 10=taking action to quit)
Alcohol intake	• Primary: consumption of alcoholic drinks [155] • Secondary: binge drinking (male individuals: 5 drinks per sitting and female individuals: 3 drinks per sitting)	• Number of days in the past 30 days; number of drinks per occasion • Number of times in the past 30 days
UV exposure	• Primary: sunburn prevalence [156] • Secondary: sun protection behavior [157]	• Number of sunburns • Percentage of sun exposure days using sun protection
HPV[b] vaccination	• Primary: any dose of HPV vaccine [158] • Secondary: completion of vaccine series	• Received 1 or more doses • Received 2 or 3 doses as recommended for age

[a]MVPA: moderate to vigorous physical activity.

[b]HPV: human papillomavirus.

Self-report measures are most practical for this pragmatic trial, with the large sample of emerging adults in 4 geographically large states (approximately 1,100,700 sq km), web-based recruitment, and a multirisk factor approach that makes clinical and observational measures infeasible. The recall period for nicotine abstinence, alcohol use, and sunburn prevalence measures will be 30 days, which improves reliability [156]. Physical activity and other meal behaviors will be measured for the past 7 days, and HPV vaccination will be measured from baseline.

The primary outcome measures of physical activity, diet, and nicotine abstinence will be validated in subsamples of emerging adult participants at baseline and at the 52-week posttest stage. Physical activity and diet self-report measures will be verified with (1) accelerometry (ActiGraph GT9X) [159,160] and (2) 24-hour recalls (for 3 random days; 2 weekdays and 1 weekend day) [161] in a subsample of emerging adults (139/1000, 13.9%) at baseline and repeated at 52 weeks. Nicotine abstinence self-report measures will be verified via saliva cotinine assays (Salimetrics assay) on a subsample of 15% emerging adults reporting abstinence at 52 weeks [153]. Objective measurement of alcohol use, sunburn, and HPV vaccination is infeasible within the scope of the trial.

Mediators

Mediators will be assessed in all surveys. These include theoretical antecedents—cancer risk (SCT; severity and susceptibility: 6 items); self-efficacy and response efficacy (SCT) [162]; cost of cancer prevention [162]; descriptive norms (SCT; 2 items; prevalence among people you know and 5 people you know best) [163]; social support from family, friends, and partners (SCT); relatedness (SDT; 4 items) [164]; autonomy and motivation (SDT; 10-point contemplation ladder) [154,165]—family and friend communication about cancer prevention (SDT and DIT; if emerging adults shared information from feed with family and friends) [166]; and vaccine antecedents (ie, confidence, constraints, complacency,

calculation, and collective responsibility [167]). Digital and media literacy will be assessed with 3 competency measures—self-perceived media literacy (4 items) [168], perceived social media literacy (6 items) [169], and eHealth literacy (8 items) [170]—along with cancer prevention misinformation (8 accurate and 8 inaccurate Likert statements recoded for belief in misinformation).

Potential Covariates

The following variables, measured at baseline, will be assessed as covariates:

- Participant characteristics: race, Hispanic ethnicity, gender identity, biological sex, RUCC codes (4 to 9), age, education, employment, and emerging adults' height and weight for BMI (treated as a covariate because of stability at this age) [171]
- Household features: marital status, parenting status (children at home), household composition, food insufficiency [149], and use of government nutrition assistance programs [155]
- Health care use: insurance status [172] and prior visit to a physician for routine preventive care
- Cancer history: personal and family history of cancer
- Cancer messaging: exposure to cancer information (ie, topics and sources [health care provider, social media, website, news media, and conversations]) [64] and perceived credibility of various media [133]
- Social desirability: a socially desirable response set 5-item measure [173] to account for socially favorable response bias.

Social Media Campaign Engagement Measures

Behavioral and experiential measures of campaign engagement [174,175] will be collected, guided by the model of engagement by Perski et al [176]. Behavioral measures will be (1) staff records of posts; (2) counts of emerging adults' views, reactions (eg, like or sad), and comments extracted in identified format using our custom-written app and coded for content and pro, anti, or neutral sentiment by 2 trained research assistants [113]; and (3) use of resources on the project website recorded by the web server. Experiential measures will be collected in each postintervention test, including time spent and frequency of reading posts, flow experience (ie, social interaction, enjoyment, and concentration) [177], cancer information overload [178], and sharing post content with others.

Statistical Analysis Plan

Hypothesis Testing

We plan to use advanced statistical methods suitable for stepped-wedge designs to compare outcomes between different cohorts and time points, which will account for both time effects and intervention effects. This includes using mixed-effects models or generalized estimating equations that can adjust for time-related trends and cohort effects. In addition, by comparing cohorts that start the intervention at different times, we will isolate the effect of our campaign from other external factors and assess whether changes in the cancer risk behaviors are more pronounced or accelerated following the introduction of our intervention compared with the periods before the intervention. In addition, our analysis will adjust for potential confounding factors that might influence cancer risk behaviors, such as age, sex, ethnicity, and other relevant sociodemographic factors. This approach ensures that the control aspects of the design are rigorously analyzed.

Specifically, the 2 hypotheses and exploratory research questions will be tested using R (R Foundation for Statistical Computing) [179] and Mplus, V8.2 (Munthén & Munthén) [180], a structural equation modeling program that allows for growth models and latent constructs (to model measurement error appropriately), repeated measures, direct and indirect effects, and moderators using interaction terms and multiple group analysis [181]. Mplus will handle missing data via full information maximum likelihood. All tests will be intent to treat. To mitigate false discovery (type I error), an α of .008 will be used (ie, the traditional α=.05÷6 [number of cancer risk factors considered]) [182]. Once the full sample is recruited, baseline data will be described and plotted, measurement models will be assessed, and transformations for normality will be examined and applied.

The effect of the treatment on each of the primary outcomes will be examined using a linear mixed-effects model for a stepped-wedge design, as outlined by Hussey and Hughes [183] and Li et al [184]. Repeated measures (6 per individual—T_0, T_1, T_2, T_3, T_4, and T_5 in Figure 1) will be regressed on time since the start of the study ("calendar time") and time since the start of message exposure ("exposure time"), both of which are expressed as categorical variables via dummy codes. Any mediators found to be significantly impacted by the treatment will be subsequently examined as mediators of the treatment effect on the outcomes via formal mediation models. Multilevel mediation models will be fit as described by Preacher [185] using the structural equation modeling program. As moderation tests require a vastly larger sample than tests of main effects [186], we will examine them without conducting null hypothesis significance tests [187]. We will estimate each model, evaluate the effect magnitude as a function of the moderator, construct bootstrap CIs to illustrate uncertainty, and use false discovery rate controls [182,187]. Linear mixed-effects models for hypothesis 1 will be extended to consider effect modification because of cancer risk behaviors, campaign exposure variables, biological sex, and the time of year of data collection (to control for seasonal fluctuations in UV levels, food availability, and alcohol intake).

Finally, behavioral and experiential engagement will be tested for campaign dose response (ie, duration of the campaign) related to cancer risk behaviors. In addition, behavioral engagement with posts (ie, views, reactions, and comments) on certain topics (eg, risk behaviors, media literacy, or family communication) and formats (eg, text, video, or interactive features such as polls) will be examined to determine if they have an impact on campaign effectiveness.

Power Analysis

To determine the appropriate sample size for the stepped-wedge design, we used the Shiny Cluster Randomized Trial calculator [188], setting α at .008 and assuming, conservatively, that the within-person correlation of the repeated measures is 0.5. Power

analysis focused on the main effect on outcomes at the 104-week posttest score being significantly better than preintervention scores (ie, the time-averaged intervention effect). We considered a mean standardized difference between pre- and postexposure measure of 0.2 for a continuous outcome and a difference in pre- versus postexposure prevalence of 0.40 versus 0.48 for a binary outcome. These are conservative and relatively small effects based on our past assessment of a social media campaign [166,189] and the expectation that emerging adults are unlikely to see all posts. We will achieve a power of 0.80 with 115 people per cohort for a continuous outcome and 175 per cohort for a binary outcome. We have planned for a 30% (300/1000) dropout rate, so we will enroll 1000 emerging adult participants and expect to finish the trial with approximately 175 individuals in each cohort. We will use full information maximum likelihood methods for estimation; thus, even incomplete cases will be retained.

Ethical Considerations

The WCG Institutional Review Board reviewed and approved the protocols for the research (study #20223673). Participation will be voluntary, and participants will read and sign an informed consent form approved by the institutional review board. The consent form will present the purpose of the research, the procedures, known risks and benefits, and the use and security of the data. All data collected in the study will be confidential, and participant identity will not be disclosed publicly. Emerging adults that participate in a focus group discussion will be compensated US $40. In the stepped-wedge design, participants will be paid US $30 for baseline, US $15 for 13-week, US $15 for 26-week, US $15 for 39-week, US $30 for 52-week, and US $30 for 104-week postintervention tests (US $135 in total). Those who are selected for the verification of outcome measures via accelerometry, 24-hour dietary recalls, and saliva cotinine assays will receive US $25 compensation for each measure.

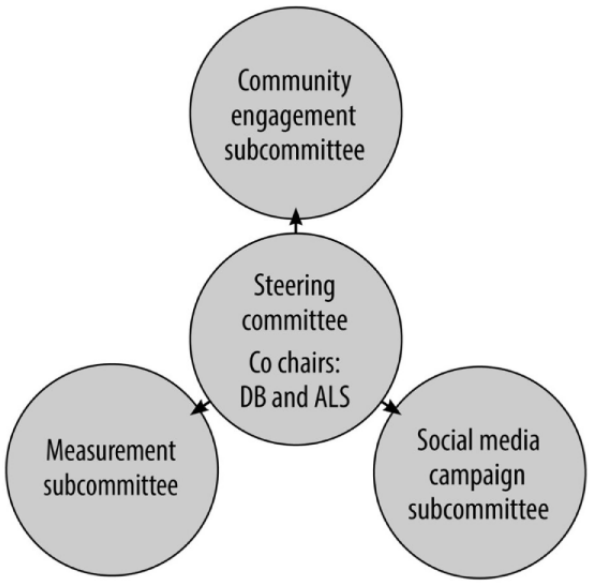
Results

Project Initiation and Administration

The study commenced in September 2022. It is supervised by a steering committee comprising the project principal investigators (D Buller and A Sussman) and coinvestigators from each site. The steering committee is meeting once a month to make design and administration decisions, plan activities, track progress, troubleshoot problems, maintain consistency in actions, implement quality controls, and communicate with the funding agency and institutional review board. In addition, the project staff at each site meet monthly with the coordinating center lead staff to ensure timely and regular communication and timeline adherence.

Project activities are being conducted by 3 subcommittees of investigators and project staff, meeting bimonthly (Figure 2). The Community Engagement Subcommittee is managing the partnerships with emerging adults and key stakeholder organizations in the rural counties of the Four Corners states. Advisory boards with members of these 2 groups have been convened and meet regularly with the research team. The Social Media Campaign Subcommittee is developing campaign content and implementation procedures. It has created a framework and procedures for creating social media posts and protocols for the community manager and responding to misinformation. The Measurement Subcommittee has identified assessment instruments, is piloting the measures with samples of emerging adults, and is developing data collection and retention procedures. A subcommittee guiding statistical analysis will be created in the future once the trial commences. The steering committee is functioning as a working group on trial recruitment issues and procedures.

Figure 2. Steering committee and subcommittees for project management.



Project Advisory Boards Meetings

The EAAB and SOAB have been formed with members recruited from each of the 4 states and met with the project investigators and staff in 2023. The EAAB members (3/8, 38% from Arizona, 2/8, 25% from Colorado, 1/8, 12% from New Mexico, and 2/8, 25% from Utah) are diverse in gender (6/8, 75% women and 2/8, 25% men), race and ethnicity (4/8, 50% White, 3/8, 38% American Indian, and 3/8, 38% Hispanic), and age (mean 22.4 years, SD 2.0; range 19-25 years). Nearly all (7/8, 88%) are students (only 1/8, 12% was employed for wages), but 62% (5/8) of the EAAB members have ≥4 years of college education. In addition, 12% (1/8) of the members live alone, 25% (2/8) of the members live with parents, 38% (3/8) of the members live with other people (not with family), and 25% (2/8) of the members live in a college dormitory. The SOAB members represent a diversity of organizations serving the health and education needs of rural counties, specifically emerging adults. Advisers self-identify as female and White (2/14, 20% were Hispanic) and have a mean age of 49.9, SD 9.1 (range 41-63) years, and all completed some college education, with most having a ≥4-year degree education. Advisory boards will meet twice a year (with the EAAB meeting quarterly during project years 2 and 3) and also communicate through Facebook groups to provide ongoing input.

The initial advisory board meeting agendas focused on introducing the project and discussing important health issues for emerging adults, social media use, misinformation on social media, and community resources for emerging adults (SOAB only). In the EAAB, participants identified nicotine product use, healthy eating, and alcohol intake as the most important health priority areas for emerging adults. The emerging adults described a passive approach to reviewing health information on social media, noting that they do not routinely initiate a search but instead encounter a high volume of posts. Furthermore, members of the EAAB were generally confident in their ability to discern the trustworthiness of the posted health information. The EAAB reviewed initially created posts on cancer risk factor reduction, providing input on text, visuals, and links to outside sources. The SOAB cited the importance of HPV vaccination, alcohol intake, and healthy eating as major health priorities for emerging adults among the 6 cancer risk factors. Most organizations represented on the SOAB use social media to reach emerging adults. The SOAB members expressed a higher degree of concern compared with emerging adults in determining the trustworthiness of posted health information. Finally, most SOAB members indicated that there are not enough community resources to address the complete list of risk factors included in our study. Subsequent EAAB and SOAB meetings will deepen the exploration of these issues.

Social Media Campaign Framework Development

A framework has been created to guide the development of social media posts. It contains information that will be used to track messages by topic, primary and secondary outcomes, theoretical mediators, communication mediators, media literacy mediators, message design features, and engagement techniques. The message text, corresponding link, and image or video used in the post will also be tracked. In addition, the date and time the post is published to the Facebook feed and the Facebook link for the message will be recorded. Investigators with content expertise in each of the 6 cancer risk behaviors have identified key precursor behaviors and effective past interventions, especially with young adults, to incorporate into the framework. In addition, specific protocols were developed for the community manager, who will administer the social media campaign, the process of responding to misinformation during the campaign, and the process for the research team to review messages before posting to the social media feed. A style guide for the post content is also in development.

Discussion

Principal Findings

Emerging adulthood is an important period for the promotion and sustainment of guideline-recommended cancer prevention behaviors. Many rural emerging adults experience several cancer risk factors, but successful interventions for them are lacking. Emerging adults in the rural areas of the Four Corners states may be at a particularly high risk of adopting unhealthy cancer-preventive behaviors. With the popularity of web-based resources for emerging adults, an innovative multirisk factor intervention over social media should be able to reach this underserved population and reduce emerging adults' cancer risk behaviors. Web-based health programs have been effective in past research [46,64,190-197]. In particular, social media has influenced cancer risk behaviors in some past studies [47-57], although studies evaluating social media with only emerging adults are uncommon, as are prospective randomized study designs [83,198-203].

Strengths and Limitations

The planned trial has several methodological strengths, including the unique multi-institutional team of investigators with expertise in each of the health behaviors of interest as well as cancer prevention and control; a diverse, rural population; an understudied age group; extensive community engagement; a multirisk factor approach; the use of social media; a rigorous study design; and high dissemination potential. The stepped-wedge design will provide experimental control, reduce error variance, avoid problems with control groups, model campaign dose, and efficiently use resources to recruit and retain the sample. We will recruit from an internet panel rather than from the community to obtain a large sample from the sparsely populated Mountain West. The social media campaign will be based on theories of health behavior change and social media influence. The stepped-wedge design and a multifaceted analysis of campaign engagement will be used to assess campaign dose effects.

Several design decisions were made to avoid or reduce potential weaknesses. Using a research panel to improve sample diversity is appropriate for a field experiment that does not aim to estimate population prevalence [204]. Research panel members may participate in multiple studies, but this does not appear to cause low-quality results [205]. Social media advertising was considered for delivering the intervention, but it is difficult to achieve advertising exposure [206] and control contamination, and any test would require a very large sample. Emerging adults

with a history of cancer will be included because (1) their numbers are small [207], (2) many engage in cancer risk behaviors [208] and can benefit, and (3) excluding them would reduce generalizability. Self-report measures can contain errors; however, given the large geography and virtual environment, they are practical. We have selected validated self-report measures and will verify physical activity, diet, and nicotine abstinence measures using a subgroup validation cohort that provides more rigorously measured health behavior data. The primary evaluation will test the impact of the overall social media campaign, not the individual message strategies. To obtain insights on which strategies impact outcomes, we will examine campaign engagement measures, theoretical mediators, and the association of message topic and format with changes in cancer risk behaviors and theoretical mediators. Although most emerging adults engage with a variety of social media platforms, we have chosen to use the Facebook platform for delivering our social media campaign. This decision is based on its practicality and widespread use among emerging adults as well as its features that enhance experimental rigor.

Conclusions

New strategies are needed to improve public health information dissemination, correct misinformation [66-68], and promote skills to help emerging adults judge the veracity of web-based content to promote cancer risk reduction. The study will provide this innovation in several ways. A unique, theory-based social media campaign will be created that delivers relevant, credible, and timely content on reducing multiple cancer risks among emerging adults and can be translated to emerging adults in other rural regions. It promotes the reduction of cancer risk behaviors in the diverse (based on ethnicity and education) emerging adult population in the Four Corners area, which has been largely overlooked in past research. This will be one of the first studies using participatory strategies to focus an intervention on behavioral and environmental cancer risk factors and health disparities in an emerging adult population. Emerging strategies will be used to correct misinformation about cancer risk behaviors on social media, along with promoting digital and media literacy skills to emerging adults. The study should have a major impact on emerging adults' cancer risk behavior decisions and the consumption of accurate cancer information. Finally, the findings should be applicable to other cancer communications and disease prevention efforts for rural emerging adults.

Acknowledgments

This study was supported by grants from the National Cancer Institute (R01CA268037, P30CA118100, P30CA046934, P30CA023074, and P30CA042014). The opinions are those of the authors. The funding agency had no input on the contents of this paper.

Data Availability

The data collected in this study will be made available in a publicly accessible data repository at the conclusion of the research.

Authors' Contributions

DBB, ALS, CAT, DK, DT, KLH, ELW, BJW, WGW, KN, CKB, DDG, EAB, JSG, JH, and DW conceptualized the study, designed methods, and secured extramural funding. DBB, ALS, CAT, DK, and DT are supervising project activities. AK, DDG, AKY, CFJ, KC, JB, JAT, EYBP, and AS are managing day-to-day study activities. All authors reviewed and approved the manuscript before submission.

Conflicts of Interest

DBB, BJW, WGW, KN, JB, AS, and AK receive a salary from Klein Buendel, Inc. DBB's spouse is an owner of Klein Buendel, Inc. DK is a consultant for Merck and has received 2 Merck Investigator Studies Program research awards. All other authors declare no other conflicts of interest.

References

1. Schwartz SJ. Turning point for a turning point: advancing emerging adulthood theory and research. Emerg Adulthood 2016 Jul 08;4(5):307-317. [doi: 10.1177/2167696815624640]
2. Nelson MC, Story M, Larson NI, Neumark-Sztainer D, Lytle LA. Emerging adulthood and college-aged youth: an overlooked age for weight-related behavior change. Obesity (Silver Spring) 2008 Oct;16(10):2205-2211 [FREE Full text] [doi: 10.1038/oby.2008.365] [Medline: 18719665]
3. White MC, Peipins LA, Watson M, Trivers KF, Holman DM, Rodriguez JL. Cancer prevention for the next generation. J Adolesc Health 2013 May;52(5 Suppl):S1-S7 [FREE Full text] [doi: 10.1016/j.jadohealth.2013.02.016] [Medline: 23601606]
4. Islami F, Goding Sauer A, Miller KD, Siegel RL, Fedewa SA, Jacobs EJ, et al. Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. CA Cancer J Clin 2018 Jan 21;68(1):31-54 [FREE Full text] [doi: 10.3322/caac.21440] [Medline: 29160902]

5. Colditz GA, Wolin KY, Gehlert S. Applying what we know to accelerate cancer prevention. Sci Transl Med 2012 Mar 28;4(127):127rv4. [doi: 10.1126/scitranslmed.3003218] [Medline: 22461645]
6. Rock CL, Thomson C, Gansler T, Gapstur SM, McCullough ML, Patel AV, et al. American Cancer Society guideline for diet and physical activity for cancer prevention. CA Cancer J Clin 2020 Jul 09;70(4):245-271 [FREE Full text] [doi: 10.3322/caac.21591] [Medline: 32515498]
7. Hertzler AA, Frary R. Dietary status and eating out practices of college students. J Am Diet Assoc 1992 Jul;92(7):867-869. [Medline: 1624659]
8. Bowman SA, Gortmaker SL, Ebbeling CB, Pereira MA, Ludwig DS. Effects of fast-food consumption on energy intake and diet quality among children in a national household survey. Pediatrics 2004 Jan;113(1 Pt 1):112-118. [doi: 10.1542/peds.113.1.112] [Medline: 14702458]
9. American College Health Association - National college health assessment II: reference group data report spring 2013. American College Health Association. 2013. URL: https://www.acha.org/documents/ncha/ACHA-NCHA-II_ReferenceGroup_DataReport_Spring2013.pdf [accessed 2024-01-22]
10. Gordon-Larsen P, Adair LS, Nelson MC, Popkin BM. Five-year obesity incidence in the transition period between adolescence and adulthood: the National Longitudinal Study of Adolescent Health. Am J Clin Nutr 2004 Sep;80(3):569-575 [FREE Full text] [doi: 10.1093/ajcn/80.3.569] [Medline: 15321794]
11. Mulye TP, Park MJ, Nelson CD, Adams SH, Irwin CEJ, Brindis CD. Trends in adolescent and young adult health in the United States. J Adolesc Health 2009 Jul;45(1):8-24. [doi: 10.1016/j.jadohealth.2009.03.013] [Medline: 19541245]
12. Merten MJ. Weight status continuity and change from adolescence to young adulthood: examining disease and health risk conditions. Obesity (Silver Spring) 2010 Jul;18(7):1423-1428 [FREE Full text] [doi: 10.1038/oby.2009.365] [Medline: 19851300]
13. Poobalan AS, Aucott LS, Precious E, Crombie IK, Smith WC. Weight loss interventions in young people (18 to 25 year olds): a systematic review. Obes Rev 2010 Aug;11(8):580-592. [doi: 10.1111/j.1467-789X.2009.00673.x] [Medline: 19874531]
14. Halperin AC, Smith SS, Heiligenstein E, Brown D, Fleming MF. Cigarette smoking and associated health risks among students at five universities. Nicotine Tob Res 2010 Feb;12(2):96-104 [FREE Full text] [doi: 10.1093/ntr/ntp182] [Medline: 20018947]
15. Richardson A, Williams V, Rath J, Villanti AC, Vallone D. The next generation of users: prevalence and longitudinal patterns of tobacco use among US young adults. Am J Public Health 2014 Aug;104(8):1429-1436. [doi: 10.2105/AJPH.2013.301802] [Medline: 24922152]
16. Levy DT, Warner KE, Cummings KM, Hammond D, Kuo C, Fong GT, et al. Examining the relationship of vaping to smoking initiation among US youth and young adults: a reality check. Tob Control 2019 Nov;28(6):629-635 [FREE Full text] [doi: 10.1136/tobaccocontrol-2018-054446] [Medline: 30459182]
17. McKnight-Eily LR, Henley SJ, Green PP, Odom EC, Hungerford DW. Alcohol screening and brief intervention: a potential role in cancer prevention for young adults. Am J Prev Med 2017 Sep;53(3S1):S55-S62 [FREE Full text] [doi: 10.1016/j.amepre.2017.04.021] [Medline: 28818247]
18. Smith DC, Dumas TM, Davis JP. Emerging adult development and substance use disorders. In: Smith DC, editor. Emerging Adults and Substance Use Disorder Treatment: Developmental Considerations and Innovative Approaches. New York, NY: Oxford University Press; 2018:16-37.
19. Guy GPJ, Berkowitz Z, Holman DM, Hartman AM. Recent changes in the prevalence of and factors associated with frequency of indoor tanning among US adults. JAMA Dermatol 2015 Nov;151(11):1256-1259 [FREE Full text] [doi: 10.1001/jamadermatol.2015.1568] [Medline: 26131768]
20. Buller DB, Cokkinides V, Hall HI, Hartman AM, Saraiya M, Miller E, et al. Prevalence of sunburn, sun protection, and indoor tanning behaviors among Americans: review from national surveys and case studies of 3 states. J Am Acad Dermatol 2011 Nov;65(5 Suppl 1):S114-S123. [doi: 10.1016/j.jaad.2011.05.033] [Medline: 22018060]
21. Heckman CJ, Auerbach MV, Darlow S, Handorf EA, Raivitch S, Manne SL. Association of skin cancer risk and protective behaviors with health literacy among young adults in the USA. Int J Behav Med 2019 Aug;26(4):372-379 [FREE Full text] [doi: 10.1007/s12529-019-09788-1] [Medline: 31147962]
22. Heckman CJ, Manne SL, Kloss JD, Bass SB, Collins B, Lessin SR. Beliefs and intentions for skin protection and UV exposure in young adults. Am J Health Behav 2011 Nov;35(6):699-711 [FREE Full text] [Medline: 22251761]
23. Bowers JM, Geller AC, Schofield E, Li Y, Hay JL. Indoor tanning trends among US adults, 2007-2018. Am J Public Health 2020 Jun;110(6):823-828. [doi: 10.2105/AJPH.2020.305605] [Medline: 32298165]
24. Gerend MA, Shepherd JE. Correlates of HPV knowledge in the era of HPV vaccination: a study of unvaccinated young adult women. Women Health 2011 Jan;51(1):25-40 [FREE Full text] [doi: 10.1080/03630242.2011.540744] [Medline: 21391159]
25. Mills LA, Head KJ, Vanderpool RC. HPV vaccination among young adult women: a perspective from Appalachian Kentucky. Prev Chronic Dis 2013;10:E17 [FREE Full text] [doi: 10.5888/pcd10.120183] [Medline: 23391293]
26. Boersma P, Black LI. Human papillomavirus vaccination among adults aged 18-26, 2013-2018. NCHS Data Brief 2020 Jan(354):1-8 [FREE Full text] [Medline: 32487295]

27. Henry KA, Stroup AM, Warner EL, Kepka D. Geographic factors and human papillomavirus (HPV) vaccination initiation among adolescent girls in the United States. Cancer Epidemiol Biomarkers Prev 2016 Feb;25(2):309-317 [FREE Full text] [doi: 10.1158/1055-9965.EPI-15-0658] [Medline: 26768989]
28. Xu L, Odum M. Cancer awareness and behavioral determinants associated with cancer prevention-a quantitative study among young adults in rural settings. J Cancer Educ 2019 Jun;34(3):562-570. [doi: 10.1007/s13187-018-1342-8] [Medline: 29508230]
29. Blake KD, Moss JL, Gaysynsky A, Srinivasan S, Croyle RT. Making the case for investment in rural cancer control: an analysis of rural cancer incidence, mortality, and funding trends. Cancer Epidemiol Biomarkers Prev 2017 Jul;26(7):992-997 [FREE Full text] [doi: 10.1158/1055-9965.EPI-17-0092] [Medline: 28600296]
30. Weaver KE, Geiger AM, Lu L, Case LD. Rural-urban disparities in health status among US cancer survivors. Cancer 2013 Mar 01;119(5):1050-1057 [FREE Full text] [doi: 10.1002/cncr.27840] [Medline: 23096263]
31. Singh GK, Williams SD, Siahpush M, Mulhollen A. Socioeconomic, rural-urban, and racial inequalities in US cancer mortality: part I-all cancers and lung cancer and. J Cancer Epidemiol 2011;2011:107497 [FREE Full text] [doi: 10.1155/2011/107497] [Medline: 22496688]
32. Agency for Toxic Substances and Disease Registry.. Toxicological profile for radon. Centers for Disease Control and Prevention website: Centers for Disease Control and Prevention, U.S. Department of Health and Human Services; 2014 Mar 26. URL: https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=407&tid=71 [accessed 2024-01-25]
33. Fioletov VE, Kimlin MG, Krotkov N, McArthur LJ, Kerr JB, Wardle DI, et al. UV index climatology over the United States and Canada from ground‐based and satellite estimates. J Geophys Res Atmos 2004 Nov 25;109(D22):308 [FREE Full text] [doi: 10.1029/2004jd004820]
34. Colorado health access survey. Colorado Health Institute. URL: https://www.coloradohealthinstitute.org/programs/colorado-health-access-survey [accessed 2023-12-20]
35. State health facts. Kaiser Family Foundation. URL: https://www.kff.org/statedata/?state=co [accessed 2023-12-20]
36. Blumling AA, Thomas TL, Stephens DP. Researching and respecting the intricacies of isolated communities. Online J Rural Nurs Health Care 2013;13(2) [FREE Full text] [Medline: 24817833]
37. Shell R, Tudiver F. Barriers to cancer screening by rural Appalachian primary care providers. J Rural Health 2004;20(4):368-373. [doi: 10.1111/j.1748-0361.2004.tb00051.x] [Medline: 15551854]
38. Head KJ, Vanderpool RC, Mills LA. Health care providers' perspectives on low HPV vaccine uptake and adherence in Appalachian Kentucky. Public Health Nurs 2013 Jul;30(4):351-360 [FREE Full text] [doi: 10.1111/phn.12044] [Medline: 23808860]
39. Vanderpool RC, Dressler EV, Stradtman LR, Crosby RA. Fatalistic beliefs and completion of the HPV vaccination series among a sample of young Appalachian Kentucky women. J Rural Health 2015;31(2):199-205 [FREE Full text] [doi: 10.1111/jrh.12102] [Medline: 25640763]
40. Befort CA, Nazir N, Engelman K, Choi W. Fatalistic cancer beliefs and information sources among rural and urban adults in the USA. J Cancer Educ 2013 Sep;28(3):521-526 [FREE Full text] [doi: 10.1007/s13187-013-0496-7] [Medline: 23813489]
41. McCloud RF, Kohler RE, Viswanath K. Cancer risk-promoting information: the communication environment of young adults. Am J Prev Med 2017 Sep;53(3S1):S63-S72 [FREE Full text] [doi: 10.1016/j.amepre.2017.03.025] [Medline: 28818248]
42. Internet/broadband fact sheet. Pew Research Center. 2021 Apr 7. URL: https://www.pewresearch.org/internet/fact-sheet/internet-broadband/ [accessed 2023-12-20]
43. Social media fact sheet. Pew Research Center. 2021 Apr 7. URL: https://www.pewresearch.org/internet/fact-sheet/social-media/ [accessed 2023-12-20]
44. Sarkar U, Le GM, Lyles CR, Ramo D, Linos E, Bibbins-Domingo K. Using social media to target cancer prevention in young adults: viewpoint. J Med Internet Res 2018 Jun 05;20(6):e203 [FREE Full text] [doi: 10.2196/jmir.8882] [Medline: 29871850]
45. Breland JY, Quintiliani LM, Schneider KL, May CN, Pagoto S. Social media as a tool to increase the impact of public health research. Am J Public Health 2017 Dec;107(12):1890-1891. [doi: 10.2105/AJPH.2017.304098] [Medline: 29116846]
46. Walther JB, Pingree S, Hawkins RP, Buller DB. Attributes of interactive online health information systems. J Med Internet Res 2005 Jul 01;7(3):e33 [FREE Full text] [doi: 10.2196/jmir.7.3.e33] [Medline: 15998624]
47. Goodyear VA, Wood G, Skinner B, Thompson JL. The effect of social media interventions on physical activity and dietary behaviours in young people and adults: a systematic review. Int J Behav Nutr Phys Act 2021 Jun 05;18(1):72 [FREE Full text] [doi: 10.1186/s12966-021-01138-3] [Medline: 34090469]
48. Chau MM, Burgermaster M, Mamykina L. The use of social media in nutrition interventions for adolescents and young adults-a systematic review. Int J Med Inform 2018 Dec;120:77-91 [FREE Full text] [doi: 10.1016/j.ijmedinf.2018.10.001] [Medline: 30409348]
49. Luo T, Li MS, Williams D, Phillippi S, Yu Q, Kantrow S, et al. Using social media for smoking cessation interventions: a systematic review. Perspect Public Health 2021 Jan 20;141(1):50-63. [doi: 10.1177/1757913920906845] [Medline: 32077368]

50. Li D, Fu L, Yang Y, An R. Social media-assisted interventions on human papillomavirus and vaccination-related knowledge, intention and behavior: a scoping review. Health Educ Res 2022 Mar 24;37(2):104-132. [doi: 10.1093/her/cyac007] [Medline: 35305019]
51. Niu Z, Bhurosy T, Heckman CJ. Digital interventions for promoting sun protection and skin self-examination behaviors: a systematic review. Prev Med Rep 2022 Apr;26:101709 [FREE Full text] [doi: 10.1016/j.pmedr.2022.101709] [Medline: 35529530]
52. Mingoia J, Hutchinson AD, Gleaves DH, Wilson C. The impact of a social media literacy intervention on positive attitudes to tanning: a pilot study. Comput Hum Behav 2019 Jan;90:188-195 [FREE Full text] [doi: 10.1016/j.chb.2018.09.004]
53. Pagoto SL, Waring ME, Groshon LC, Rosen AO, Schroeder MW, Goetz JM. Proof-of-concept feasibility trial of a dissonance-based sun safety intervention for young adult tanners. Ann Behav Med 2022 Aug 02;56(8):830-841 [FREE Full text] [doi: 10.1093/abm/kaab116] [Medline: 35179176]
54. Piedimonte S, Leung A, Zakhari A, Giordano C, Tellier PP, Lau S. Impact of an HPV education and vaccination campaign among Canadian university students. J Obstet Gynaecol Can 2018 Apr;40(4):440-446. [doi: 10.1016/j.jogc.2017.07.028] [Medline: 29102218]
55. Sundstrom B, Brandt HM, Gray L, Young Pierce J. It's my time: applying the health belief model to prevent cervical cancer among college-age women. J Commun Manag 2018 May 08;22(2):161-178. [doi: 10.1108/jcom-06-2016-0044]
56. Kim M, Lee H, Kiang P, Aronowitz T, Sheldon LK, Shi L, et al. A storytelling intervention in a mobile, web-based platform: a pilot randomized controlled trial to evaluate the preliminary effectiveness to promote human papillomavirus vaccination in Korean American College Women. Health Educ Behav 2020 Apr 20;47(2):258-263 [FREE Full text] [doi: 10.1177/1090198119894589] [Medline: 31958991]
57. Gerend MA, Murdock C, Grove K. An intervention for increasing HPV vaccination on a university campus. Vaccine 2020 Jan 22;38(4):725-729. [doi: 10.1016/j.vaccine.2019.11.028] [Medline: 31767468]
58. Steffens MS, Dunn AG, Leask J, Wiley KE. Using social media for vaccination promotion: practices and challenges. Digit Health 2020 Nov 03;6:2055207620970785 [FREE Full text] [doi: 10.1177/2055207620970785] [Medline: 35173976]
59. Broniatowski DA, Jamison AM, Qi S, AlKulaib L, Chen T, Benton A, et al. Weaponized health communication: Twitter bots and Russian trolls amplify the vaccine debate. Am J Public Health 2018 Oct;108(10):1378-1384. [doi: 10.2105/AJPH.2018.304567] [Medline: 30138075]
60. Tan AS, Bigman CA. Misinformation about commercial tobacco products on social media—implications and research opportunities for reducing tobacco-related health disparities. Am J Public Health 2020 Oct;110(S3):S281-S283. [doi: 10.2105/ajph.2020.305910]
61. Wilner T, Holton A. Breast cancer prevention and treatment: misinformation on Pinterest, 2018. Am J Public Health 2020 Oct;110(S3):S300-S304. [doi: 10.2105/ajph.2020.305812]
62. Zenone M, Snyder J, Caulfield T. Crowdfunding cannabidiol (CBD) for cancer: hype and misinformation on GoFundMe. Am J Public Health 2020 Oct;110(S3):S294-S299. [doi: 10.2105/AJPH.2020.305768] [Medline: 33001729]
63. Warner EL, Basen-Engquist KM, Badger TA, Crane TE, Raber-Ramsey M. The online cancer nutrition misinformation: a framework of behavior change based on exposure to cancer nutrition misinformation. Cancer 2022 Jul 01;128(13):2540-2548 [FREE Full text] [doi: 10.1002/cncr.34218] [Medline: 35383913]
64. Margolis MA, Brewer NT, Shah PD, Calo WA, Gilkey MB. Stories about HPV vaccine in social media, traditional media, and conversations. Prev Med 2019 Jan;118:251-256. [doi: 10.1016/j.ypmed.2018.11.005] [Medline: 30414396]
65. Hoffman BL, Felter EM, Chu KH, Shensa A, Hermann C, Wolynn T, et al. It's not all about autism: the emerging landscape of anti-vaccination sentiment on Facebook. Vaccine 2019 Apr 10;37(16):2216-2223. [doi: 10.1016/j.vaccine.2019.03.003] [Medline: 30905530]
66. Vaccine safety communication in the digital age: 2018 meeting report, 4-5 June 2018, Les Pensieres center for global health, Veyrier-du-Lac, France. World Health Organization. 2019 Jan 15. URL: https://www.who.int/publications/i/item/WHO-MVP-EMP-SAV-2019.02 [accessed 2024-02-02]
67. Yang YT, Broniatowski DA, Reiss DR. Government role in regulating vaccine misinformation on social media platforms. JAMA Pediatr 2019 Nov 01;173(11):1011-1012. [doi: 10.1001/jamapediatrics.2019.2838] [Medline: 31479099]
68. Chou WYS, Gaysynsky A, Cappella JN. Where we go from here: health misinformation on social media. Am J Public Health 2020 Oct;110(S3):S273-S275. [doi: 10.2105/AJPH.2020.305905] [Medline: 33001722]
69. Chou WYS, Gaysynsky A, Vanderpool RC. The COVID-19 misinfodemic: moving beyond fact-checking. Health Educ Behav 2021 Feb;48(1):9-13 [FREE Full text] [doi: 10.1177/1090198120980675] [Medline: 33322939]
70. Immunizing the public against misinformation. World Health Organization. 2020 Aug 25. URL: https://www.who.int/news-room/feature-stories/detail/immunizing-the-public-against-misinformation [accessed 2023-12-20]
71. Spring B, King AC, Pagoto SL, Van Horn L, Fisher JD. Fostering multiple healthy lifestyle behaviors for primary prevention of cancer. Am Psychol 2015;70(2):75-90 [FREE Full text] [doi: 10.1037/a0038806] [Medline: 25730716]
72. Geller K, Lippke S, Nigg CR. Future directions of multiple behavior change research. J Behav Med 2017 Feb;40(1):194-202. [doi: 10.1007/s10865-016-9809-8] [Medline: 27785652]

73. Cox-Martin E, Cox MG, Basen-Engquist K, Bradley C, Blalock JA. Changing multiple health behaviors in cancer survivors: smoking and exercise. Psychol Health Med 2020 Mar;25(3):331-343 [FREE Full text] [doi: 10.1080/13548506.2019.1679849] [Medline: 31630537]
74. Green AC, Hayman LL, Cooley ME. Multiple health behavior change in adults with or at risk for cancer: a systematic review. Am J Health Behav 2015 May;39(3):380-394. [doi: 10.5993/AJHB.39.3.11] [Medline: 25741683]
75. Prochaska JO. Multiple health behavior research represents the future of preventive medicine. Prev Med 2008 Mar;46(3):281-285. [doi: 10.1016/j.ypmed.2008.01.015] [Medline: 18319100]
76. Noar SM, Mehrotra P. Toward a new methodological paradigm for testing theories of health behavior and health behavior change. Patient Educ Couns 2011 Mar;82(3):468-474. [doi: 10.1016/j.pec.2010.11.016] [Medline: 21185144]
77. 2018 median household income in the United States. United States Census Bureau. 2019 Sep 26. URL: https://www.census.gov/library/visualizations/interactive/2018-median-household-income.html [accessed 2023-12-20]
78. Dalaker J. The 10-20-30 provision: defining persistent poverty counties. Congressional Research Service. 2022 Apr 14. URL: https://sgp.fas.org/crs/misc/R45100.pdf [accessed 2024-02-02]
79. LoConte NK, Gershenwald JE, Thomson CA, Crane TE, Harmon GE, Rechis R. Lifestyle modifications and policy implications for primary and secondary cancer prevention: diet, exercise, sun safety, and alcohol reduction. Am Soc Clin Oncol Educ Book 2018 May 23;38:88-100 [FREE Full text] [doi: 10.1200/EDBK_200093] [Medline: 30231343]
80. Lai D, Ding Q, Bodson J, Warner EL, Kepka D. Factors associated with increased HPV vaccine use in rural-frontier U.S. States. Public Health Nurs 2016 Jul;33(4):283-294 [FREE Full text] [doi: 10.1111/phn.12223] [Medline: 26331614]
81. Vereen RN, Kurtzman R, Noar SM. Are social media interventions for health behavior change efficacious among populations with health disparities?: a meta-analytic review. Health Commun 2023 Jan 21;38(1):133-140 [FREE Full text] [doi: 10.1080/10410236.2021.1937830] [Medline: 34148445]
82. Key KV, Adegboyega A, Bush H, Aleshire ME, Contreras OA, Hatcher J. #CRCFREE: using social media to reduce colorectal cancer risk in rural adults. Am J Health Behav 2020 May 01;44(3):353-363 [FREE Full text] [doi: 10.5993/AJHB.44.3.8] [Medline: 32295683]
83. Pope ZC, Barr-Anderson DJ, Lewis BA, Pereira MA, Gao Z. Use of wearable technology and social media to improve physical activity and dietary behaviors among college students: a 12-week randomized pilot study. Int J Environ Res Public Health 2019 Sep 25;16(19):3579 [FREE Full text] [doi: 10.3390/ijerph16193579] [Medline: 31557812]
84. Sundstrom B, Cartmell KB, White AA, Russo N, Well H, Pierce JY, et al. HPV vaccination champions: evaluating a technology-mediated intervention for parents. Front Digit Health 2021;3:636161 [FREE Full text] [doi: 10.3389/fdgth.2021.636161] [Medline: 34713108]
85. Todorovic J, Terzic-Supic Z, Djikanovic B, Nesic D, Piperac P, Stamenkovic Z. Can social media intervention improve physical activity of medical students? Public Health 2019 Sep;174:69-73. [doi: 10.1016/j.puhe.2019.05.030] [Medline: 31323599]
86. Chung AE, Skinner AC, Hasty SE, Perrin EM. Tweeting to health: a novel mHealth intervention using Fitbits and Twitter to foster healthy lifestyles. Clin Pediatr (Phila) 2017 Jan;56(1):26-32. [doi: 10.1177/0009922816653385] [Medline: 27317609]
87. Rural-urban continuum codes. U.S. Department of Agriculture Economic Research Service. URL: https://www.ers.usda.gov/data-products/rural-urban-continuum-codes.aspx [accessed 2023-12-20]
88. 2015-2019 American Community Survey 5-year estimates. United States Census Bureau. URL: https://www.census.gov/programs-surveys/acs/technical-documentation/table-and-geography-changes/2019/5-year.html [accessed 2024-01-30]
89. Mabe AG, Forney KJ, Keel PK. Do you "like" my photo? Facebook use maintains eating disorder risk. Int J Eat Disord 2014 Jul;47(5):516-523. [doi: 10.1002/eat.22254] [Medline: 25035882]
90. Vogel EA, Ramo DE, Rubinstein ML, Delucchi KL, Darrow S, Costello C, et al. Effects of social media on adolescents' willingness and intention to use e-cigarettes: an experimental investigation. Nicotine Tob Res 2021 Mar 19;23(4):694-701 [FREE Full text] [doi: 10.1093/ntr/ntaa003] [Medline: 31912147]
91. Hughes JP, Granston TS, Heagerty PJ. Current issues in the design and analysis of stepped wedge trials. Contemp Clin Trials 2015 Nov;45(Pt A):55-60 [FREE Full text] [doi: 10.1016/j.cct.2015.07.006] [Medline: 26247569]
92. Shadish WR, Cook TD, Campbell DT. Experimental and Quasi-Experimental Designs for Generalized Causal Inference. Boston, MA: Houghton Mifflin Company; 2002.
93. Bandura A. Social Foundations of Thought and Action: A Social Cognitive Theory. Englewood Cliffs, NJ: Prentice Hall; 1986.
94. Deci EL, Ryan RM. Self-determination theory. In: Van Lange PA, Kruglanski AW, Higgins ET, editors. Handbook of Theories of Social Psychology. Thousand Oaks, CA: SAGE Publications Ltd; 2012:416-437.
95. Bandura A. Health promotion by social cognitive means. Health Educ Behav 2004 Apr;31(2):143-164. [doi: 10.1177/1090198104263660] [Medline: 15090118]
96. Silva MN, Marques MM, Teixeira PJ. Testing theory in practice: the example of self-determination theory-based interventions. Eur Health Psychol 2014;16(5):171-180. [doi: 10.4135/9781483346427.n483]
97. Rogers EM. Diffusion of Innovations, 5th Edition. New York, NY: Free Press; 2003.

98. Vos SC, Sutton J, Yu Y, Renshaw SL, Olson MK, Gibson CB, et al. Retweeting risk communication: the role of threat and efficacy. Risk Anal 2018 Dec;38(12):2580-2598. [doi: 10.1111/risa.13140] [Medline: 30080933]
99. Himelboim I, Xiao X, Lee DK, Wang MY, Borah P. A social networks approach to understanding vaccine conversations on Twitter: network clusters, sentiment, and certainty in HPV social networks. Health Commun 2020 May;35(5):607-615. [doi: 10.1080/10410236.2019.1573446] [Medline: 31199698]
100. Pescosolido BA. Beyond rational choice: the social dynamics of how people seek help. Am J Sociol 1992 Jan;97(4):1096-1138. [doi: 10.1086/229863]
101. Turner RH, Killian LM. Collective Behavior, 3rd Edition. Englewood Cliffs, NJ: Prentice-Hall; 1992.
102. Green MC, Brock TC. The role of transportation in the persuasiveness of public narratives. J Pers Soc Psychol 2000 Nov;79(5):701-721. [doi: 10.1037//0022-3514.79.5.701] [Medline: 11079236]
103. Green MC. Narratives and cancer communication. J Commun 2006;56(suppl_1):S163-S183. [doi: 10.1111/j.1460-2466.2006.00288.x]
104. Slater MD, Buller DB, Waters E, Archibeque M, LeBlanc M. A test of conversational and testimonial messages versus didactic presentations of nutrition information. J Nutr Educ Behav 2003;35(5):255-259. [doi: 10.1016/s1499-4046(06)60056-0] [Medline: 14521825]
105. Hobbs R, Jensen A. The past, present, and future of media literacy education. J Media Lit Educ 2009;1(1) [FREE Full text] [doi: 10.23860/jmle-1-1-1]
106. Rasi P, Vuojärvi H, Ruokamo H. Media literacy education for all ages. J Media Literacy Educ 2019 Sep 1;11(2):1-19. [doi: 10.23860/JMLE-2019-11-2-1]
107. Sutton J. Health communication trolls and bots versus public health agencies' trusted voices. Am J Public Health 2018 Oct;108(10):1281-1282. [doi: 10.2105/AJPH.2018.304661] [Medline: 30207762]
108. Hou Z, Du F, Zhou X, Jiang H, Martin S, Larson H, et al. Cross-country comparison of public awareness, rumors, and behavioral responses to the COVID-19 epidemic: infodemiology study. J Med Internet Res 2020 Aug 03;22(8):e21143 [FREE Full text] [doi: 10.2196/21143] [Medline: 32701460]
109. Vraga EK, Bode L. I do not believe you: how providing a source corrects health misperceptions across social media platforms. Inf Commun Soc 2017 Apr 19;21(10):1337-1353. [doi: 10.1080/1369118x.2017.1313883]
110. van der Meer TG, Jin Y. Seeking formula for misinformation treatment in public health crises: the effects of corrective information type and source. Health Commun 2020 May;35(5):560-575. [doi: 10.1080/10410236.2019.1573295] [Medline: 30761917]
111. Walter N, Murphy ST. How to unring the bell: a meta-analytic approach to correction of misinformation. Commun Monogr 2018 May 15;85(3):423-441. [doi: 10.1080/03637751.2018.1467564]
112. Jacobs L, Kattumana T, Konnova A, Obasa M, Smlatic E, Vandendriessche V, et al. How storytelling can combat vaccine hesitancy: a transdisciplinary approach. Transdiscipl Insights 2018 Dec 15;2(1):92-103. [doi: 10.11116/TDI2018.2.4]
113. Buller DB, Walkosz BJ, Berteletti J, Pagoto SL, Bibeau J, Baker K, et al. Insights on HPV vaccination in the United States from mothers' comments on Facebook posts in a randomized trial. Hum Vaccin Immunother 2019 Jul 11;15(7-8):1479-1487 [FREE Full text] [doi: 10.1080/21645515.2019.1581555] [Medline: 30785361]
114. Tangcharoensathien V, Calleja N, Nguyen T, Purnat T, D'Agostino M, Garcia-Saiso S, et al. Framework for managing the COVID-19 infodemic: methods and results of an online, crowdsourced WHO technical consultation. J Med Internet Res 2020 Jun 26;22(6):e19659 [FREE Full text] [doi: 10.2196/19659] [Medline: 32558655]
115. Li X, Liu Q. Social media use, eHealth literacy, disease knowledge, and preventive behaviors in the COVID-19 pandemic: cross-sectional study on Chinese netizens. J Med Internet Res 2020 Oct 09;22(10):e19684 [FREE Full text] [doi: 10.2196/19684] [Medline: 33006940]
116. Primack BA, Douglas EL, Land SR, Miller E, Fine MJ. Comparison of media literacy and usual education to prevent tobacco use: a cluster-randomized trial. J Sch Health 2014 Feb 14;84(2):106-115 [FREE Full text] [doi: 10.1111/josh.12130] [Medline: 25099425]
117. Jeong SH, Cho H, Hwang Y. Media literacy interventions: a meta-analytic review. J Commun 2012 Jun 01;62(3):454-472 [FREE Full text] [doi: 10.1111/j.1460-2466.2012.01643.x] [Medline: 22736807]
118. Austin EW, Austin BW, French BF, Cohen MA. The effects of a nutrition media literacy intervention on parents' and youths' communication about food. J Health Commun 2018;23(2):190-199. [doi: 10.1080/10810730.2018.1423649] [Medline: 29338585]
119. Wade TD, Wilksch SM, Paxton SJ, Byrne SM, Austin SB. Do universal media literacy programs have an effect on weight and shape concern by influencing media internalization? Int J Eat Disord 2017 Jul;50(7):731-738. [doi: 10.1002/eat.22689] [Medline: 28152232]
120. Chang FC, Miao NF, Lee CM, Chen PH, Chiu CH, Lee SC. The association of media exposure and media literacy with adolescent alcohol and tobacco use. J Health Psychol 2016 Apr;21(4):513-525. [doi: 10.1177/1359105314530451] [Medline: 24788103]
121. Austin EW, Austin BW, Willoughby JF, Amram O, Domgaard S. How media literacy and science media literacy predicted the adoption of protective behaviors amidst the COVID-19 pandemic. J Health Commun 2021 Apr 03;26(4):239-252. [doi: 10.1080/10810730.2021.1899345] [Medline: 33928871]

122. Hobbs R. Digital and media literacy: a plan of action. The Aspen Institute. 2010. URL: https://www.aspeninstitute.org/wp-content/uploads/files/content/docs/Digital_and_Media_Literacy.pdf [accessed 2024-02-02]
123. Buchanan L, Kelly B, Yeatman H. Exposure to digital marketing enhances young adults' interest in energy drinks: an exploratory investigation. PLoS One 2017 Feb 2;12(2):e0171226 [FREE Full text] [doi: 10.1371/journal.pone.0171226] [Medline: 28152016]
124. Buller DB, Pagoto S, Walkosz BJ, Woodall WG, Berteletti J, Kinsey A, et al. The process of responding to COVID-19 misinformation in a social media feed. J Public Health Manag Pract 2023;29(4):E124-E127 [FREE Full text] [doi: 10.1097/PHH.0000000000001679] [Medline: 36383086]
125. Scales D, Gorman J, Jamieson KH. The Covid-19 infodemic - applying the epidemiologic model to counter misinformation. N Engl J Med 2021 Aug 19;385(8):678-681. [doi: 10.1056/NEJMp2103798] [Medline: 33979506]
126. Allen M. Meta‐analysis comparing the persuasiveness of one‐sided and two‐sided messages. West J Speech Commun 1991 Dec 30;55(4):390-404. [doi: 10.1080/10570319109374395]
127. O'Keefe DJ. How to handle opposing arguments in persuasive messages: a meta-analytic review of the effects of one-sided and two-sided messages. Ann Int Commun Assoc 1999;22(1):209-249 ePublished on: May 18, 2016. [doi: 10.1080/23808985.1999.11678963]
128. Godbold LC, Pfau M. Conferring resistance to peer pressure among adolescents: using inoculation theory to discourage alcohol use. Commun Res 2016 Jun 30;27(4):411-437. [doi: 10.1177/009365000027004001]
129. Pfau M, Bockern SV, Kang JG. Use of inoculation to promote resistance to smoking initiation among adolescents. Commun Monogr 1992;59(3):213-230 ePublished on: June 2, 2009. [doi: 10.1080/03637759209376266]
130. Compton J, Pfau M. Spreading inoculation: inoculation, resistance to influence, and word-of-mouth communication. Commun Theory 2009 Feb;19(1):9-28. [doi: 10.1111/j.1468-2885.2008.01330.x]
131. Hopfer S. Effects of a narrative HPV vaccination intervention aimed at reaching college women: a randomized controlled trial. Prev Sci 2012 Apr;13(2):173-182. [doi: 10.1007/s11121-011-0254-1] [Medline: 21993613]
132. Shelby A, Ernst K. Story and science: how providers and parents can utilize storytelling to combat anti-vaccine misinformation. Hum Vaccin Immunother 2013 Aug;9(8):1795-1801 [FREE Full text] [doi: 10.4161/hv.24828] [Medline: 23811786]
133. Buller D, Walkosz B, Henry K, Woodall WG, Pagoto S, Berteletti J, et al. Promoting social distancing and COVID-19 vaccine intentions to mothers: randomized comparison of information sources in social media messages. JMIR Infodemiology 2022 Aug 23;2(2):e36210 [FREE Full text] [doi: 10.2196/36210] [Medline: 36039372]
134. Pimienta D, Prado D, Blanco A. Twelve years of measuring linguistic diversity in the Internet: balance and perspectives. United Nations Educational, Scientific and Cultural Organization. 2009. URL: https://unesdoc.unesco.org/ark:/48223/pf0000187016 [accessed 2024-01-22]
135. Petrosyan A. Common languages used for web content 2023, by share of websites. Statista. 2023 Feb 24. URL: https://www.statista.com/statistics/262946/most-common-languages-on-the-internet/ [accessed 2023-12-20]
136. Dietrich S, Hernandez E. Language use in the United States: 2019. United States Department of Commerce United States Census Bureau. 2022 Aug. URL: https://www.census.gov/content/dam/Census/library/publications/2022/acs/acs-50.pdf [accessed 2024-02-02]
137. Buller MK, Bettinghaus EP, Fluharty L, Andersen PA, Slater MD, Henry KL, et al. Improving health communication with photographic images that increase identification in three minority populations. Health Educ Res 2019 Apr 01;34(2):145-158 [FREE Full text] [doi: 10.1093/her/cyy054] [Medline: 30726902]
138. Sutton J, Gibson CB, Phillips NE, Spiro ES, League C, Johnson B, et al. A cross-hazard analysis of terse message retransmission on Twitter. Proc Natl Acad Sci U S A 2015 Dec 01;112(48):14793-14798 [FREE Full text] [doi: 10.1073/pnas.1508916112] [Medline: 26627233]
139. Edney S, Bogomolova S, Ryan J, Olds T, Sanders I, Maher C. Creating engaging health promotion campaigns on social media: observations and lessons from Fitbit and Garmin. J Med Internet Res 2018 Dec 10;20(12):e10911 [FREE Full text] [doi: 10.2196/10911] [Medline: 30530449]
140. Rus HM, Cameron LD. Health communication in social media: message features predicting user engagement on diabetes-related Facebook pages. Ann Behav Med 2016 Oct;50(5):678-689. [doi: 10.1007/s12160-016-9793-9] [Medline: 27059761]
141. Hales SB, Davidson C, Turner-McGrievy GM. Varying social media post types differentially impacts engagement in a behavioral weight loss intervention. Transl Behav Med 2014 Dec;4(4):355-362 [FREE Full text] [doi: 10.1007/s13142-014-0274-z] [Medline: 25584084]
142. Cox LK. How often should you post on Facebook? [New benchmark data]. HubSpot. 2015 Apr 20. URL: https://blog.hubspot.com/marketing/facebook-post-frequency-benchmarks [accessed 2024-02-02]
143. How often should you post on your social media pages? NOW Marketing Group. 2017 May 16. URL: https://blog.nowmarketinggroup.com/often-post-social-media-pages [accessed 2023-12-20]
144. Sandoval JA, Lucero J, Oetzel J, Avila M, Belone L, Mau M, et al. Process and outcome constructs for evaluating community-based participatory research projects: a matrix of existing measures. Health Educ Res 2012 Aug;27(4):680-690 [FREE Full text] [doi: 10.1093/her/cyr087] [Medline: 21940460]

145. Bradley CJ, Anderson-Mellies A, Borrayo EA, Doherty JA, Escontrías OA, Garcia DO, et al. Ethnicity, socioeconomic status, income inequality, and colorectal cancer outcomes: evidence from the 4C2 collaboration. Cancer Causes Control 2022 Apr;33(4):533-546. [doi: 10.1007/s10552-021-01547-6] [Medline: 34982317]
146. Armstrong T, Bull F. Development of the World Health Organization Global Physical Activity Questionnaire (GPAQ). J Public Health 2006 Mar 2;14:66-70. [doi: 10.1007/s10389-006-0024-x]
147. Thompson FE, Midthune D, Subar AF, Kahle LL, Schatzkin A, Kipnis V. Performance of a short tool to assess dietary intakes of fruits and vegetables, percentage energy from fat and fibre. Public Health Nutr 2004 Dec;7(8):1097-1105. [doi: 10.1079/PHN2004642] [Medline: 15548349]
148. Hewawitharana SC, Thompson FE, Loria CM, Strauss W, Nagaraja J, Ritchie L, et al. Comparison of the NHANES dietary screener questionnaire to the automated self-administered 24-hour recall for children in the healthy communities study. Nutr J 2018 Nov 27;17(1):111 [FREE Full text] [doi: 10.1186/s12937-018-0415-1] [Medline: 30482218]
149. Larson NI, Neumark-Sztainer D, Story M, Burgess-Champoux T. Whole-grain intake correlates among adolescents and young adults: findings from Project EAT. J Am Diet Assoc 2010 Feb;110(2):230-237. [doi: 10.1016/j.jada.2009.10.034] [Medline: 20102850]
150. Neumark-Sztainer D, Wall M, Guo J, Story M, Haines J, Eisenberg M. Obesity, disordered eating, and eating disorders in a longitudinal study of adolescents: how do dieters fare 5 years later? J Am Diet Assoc 2006 Apr;106(4):559-568. [doi: 10.1016/j.jada.2006.01.003] [Medline: 16567152]
151. Neumark-Sztainer DR, Wall MM, Haines JI, Story MT, Sherwood NE, van den Berg PA. Shared risk and protective factors for overweight and disordered eating in adolescents. Am J Prev Med 2007 Nov;33(5):359-369. [doi: 10.1016/j.amepre.2007.07.031] [Medline: 17950400]
152. Perrigue MM, Kantor ED, Hastert TA, Patterson R, Potter JD, Neuhouser ML, et al. Eating frequency and risk of colorectal cancer. Cancer Causes Control 2013 Dec;24(12):2107-2115 [FREE Full text] [doi: 10.1007/s10552-013-0288-8] [Medline: 24057417]
153. Piper ME, Bullen C, Krishnan-Sarin S, Rigotti NA, Steinberg ML, Streck JM, et al. Defining and measuring abstinence in clinical trials of smoking cessation interventions: an updated review. Nicotine Tob Res 2020 Jun 12;22(7):1098-1106 [FREE Full text] [doi: 10.1093/ntr/ntz110] [Medline: 31271211]
154. Biener L, Abrams DB. The contemplation ladder: validation of a measure of readiness to consider smoking cessation. Health Psychol 1991;10(5):360-365. [doi: 10.1037//0278-6133.10.5.360] [Medline: 1935872]
155. 2019 BRFSS questionnaire. Centers for Disease Control and Prevention. URL: https://www.cdc.gov/brfss/questionnaires/pdf-ques/2019-BRFSS-Questionnaire-508.pdf [accessed 2023-12-20]
156. Køster B, Søndergaard J, Nielsen JB, Olsen A, Bentzen J. Reliability and consistency of a validated sun exposure questionnaire in a population-based Danish sample. Prev Med Rep 2018 Feb 10;10:43-48 [FREE Full text] [doi: 10.1016/j.pmedr.2018.02.002] [Medline: 29552457]
157. Hillhouse J, Turrisi R, Jaccard J, Robinson J. Accuracy of self-reported sun exposure and sun protection behavior. Prev Sci 2012 Oct;13(5):519-531 [FREE Full text] [doi: 10.1007/s11121-012-0278-1] [Medline: 22855253]
158. Health information national trends survey. National Institutes of Health, National Cancer Institute, Health Information National Trends Survey. URL: https://hints.cancer.gov/ [accessed 2023-12-20]
159. Hwang J, Fernandez AM, Lu AS. Application and validation of activity monitors' Epoch lengths and placement sites for physical activity assessment in exergaming. J Clin Med 2018 Sep 11;7(9):268 [FREE Full text] [doi: 10.3390/jcm7090268] [Medline: 30208567]
160. Crane TE, Skiba MB, Miller A, Garcia DO, Thomson CA. Development and evaluation of an accelerometer-based protocol for measuring physical activity levels in cancer survivors: development and usability study. JMIR Mhealth Uhealth 2020 Sep 24;8(9):e18491 [FREE Full text] [doi: 10.2196/18491] [Medline: 32969828]
161. Harnack L, Stevens M, Van Heel N, Schakel S, Dwyer JT, Himes J. A computer-based approach for assessing dietary supplement use in conjunction with dietary recalls. J Food Compost Anal 2008 Feb;21(Suppliment 1):S78-S82 [FREE Full text] [doi: 10.1016/j.jfca.2007.05.004] [Medline: 19190705]
162. Sherer M, Maddux JE, Mercandante B, Prentice-Dunn S, Jacobs B, Rogers RW. The self-efficacy scale: construction and validation. Psychol Rep 1982;51(2):663-671. [doi: 10.2466/pr0.1982.51.2.663]
163. Sheeran P, Orbell S. Augmenting the theory of planned behavior: roles for anticipated regret and descriptive norms. J Appl Soc Psychol 1999 Oct;29(10):2107-2142. [doi: 10.1111/j.1559-1816.1999.tb02298.x]
164. Vlachopoulos SP, Michailidou S. Development and initial validation of a measure of autonomy, competence, and relatedness in exercise: the basic psychological needs in exercise scale. Meas Phys Educ Exerc Sci 2006;10(3):179-201. [doi: 10.1207/s15327841mpee1003_4]
165. McGee R, Williams S, Kypri K. College students' readiness to reduce binge drinking: criterion validity of a brief measure. Drug Alcohol Depend 2010 Jun 01;109(1-3):236-238. [doi: 10.1016/j.drugalcdep.2009.12.009] [Medline: 20106607]
166. Buller DB, Pagoto S, Baker K, Walkosz BJ, Hillhouse J, Henry KL, et al. Results of a social media campaign to prevent indoor tanning by teens: a randomized controlled trial. Prev Med Rep 2021 Apr 18;22:101382 [FREE Full text] [doi: 10.1016/j.pmedr.2021.101382] [Medline: 33996394]

167. Betsch C, Schmid P, Heinemeier D, Korn L, Holtmann C, Böhm R. Beyond confidence: development of a measure assessing the 5C psychological antecedents of vaccination. PLoS One 2018 Dec 07;13(12):e0208601 [FREE Full text] [doi: 10.1371/journal.pone.0208601] [Medline: 30532274]
168. Tully M, Vraga EK, Bode L. Designing and testing news literacy messages for social media. Mass Commun Soc 2020;23(1):22-46. [doi: 10.1080/15205436.2019.1604970]
169. Tandoc E, Yee AZ, Ong J, Lee JC, Duan X, Zheng H, et al. Developing a perceived social media literacy scale: evidence from Singapore. Int J Commun 2021 Jun;15:2484-2505.
170. Norman CD, Skinner HA. eHEALS: the eHealth literacy scale. J Med Internet Res 2006 Nov 14;8(4):e27 [FREE Full text] [doi: 10.2196/jmir.8.4.e27] [Medline: 17213046]
171. Ross KM, Eastman A, Wing RR. Accuracy of self-report versus objective smart-scale weights during a 12-week weight management intervention. Obesity (Silver Spring) 2019 Mar;27(3):385-390 [FREE Full text] [doi: 10.1002/oby.22400] [Medline: 30703282]
172. 2018 NSCH guide to topics and questions. Data Resource Center for Child & Adolescent Health. 2018. URL: https://www.childhealthdata.org/learn-about-the-nsch/topics_questions/2018-nsch-guide-to-topics-and-questions [accessed 2023-12-20]
173. Hays RD, Hayashi T, Stewart AL. A five-item measure of socially desirable response set. Educ Psychol Meas 1989;49(3):629-636. [doi: 10.1177/001316448904900315]
174. Michie S, Yardley L, West R, Patrick K, Greaves F. Developing and evaluating digital interventions to promote behavior change in health and health care: recommendations resulting from an international workshop. J Med Internet Res 2017 Jun 29;19(6):e232 [FREE Full text] [doi: 10.2196/jmir.7126] [Medline: 28663162]
175. Short CE, DeSmet A, Woods C, Williams SL, Maher C, Middelweerd A, et al. Measuring engagement in eHealth and mHealth behavior change interventions: viewpoint of methodologies. J Med Internet Res 2018 Nov 16;20(11):e292 [FREE Full text] [doi: 10.2196/jmir.9397] [Medline: 30446482]
176. Perski O, Blandford A, West R, Michie S. Conceptualising engagement with digital behaviour change interventions: a systematic review using principles from critical interpretive synthesis. Transl Behav Med 2017 Jun;7(2):254-267 [FREE Full text] [doi: 10.1007/s13142-016-0453-1] [Medline: 27966189]
177. Kaur P, Dhir A, Rajala R. Assessing flow experience in social networking site based brand communities. Comput Hum Behav 2016 Nov;64:217-225 [FREE Full text] [doi: 10.1016/j.chb.2016.06.045]
178. Jensen JD, Pokharel M, Carcioppolo N, Upshaw S, John KK, Katz RA. Cancer information overload: discriminant validity and relationship to sun safe behaviors. Patient Educ Couns 2020 Feb;103(2):309-314 [FREE Full text] [doi: 10.1016/j.pec.2019.08.039] [Medline: 31522897]
179. R Core Team. R: a language and environment for statistical computing. The Comprehensive R Archive Network. URL: https://www.gbif.org/tool/81287/r-a-language-and-environment-for-statistical-computing [accessed 2024-02-02]
180. Muthen LK, Muthen BO. Mplus User's Guide. Eighth Edition. Los Angeles, CA: Muthen & Muthen; 2017.
181. Ryu E, Cheong J. Comparing indirect effects in different groups in single-group and multi-group structural equation models. Front Psychol 2017 May 11;8:747 [FREE Full text] [doi: 10.3389/fpsyg.2017.00747] [Medline: 28553248]
182. Glickman ME, Rao SR, Schultz MR. False discovery rate control is a recommended alternative to Bonferroni-type adjustments in health studies. J Clin Epidemiol 2014 Aug;67(8):850-857. [doi: 10.1016/j.jclinepi.2014.03.012] [Medline: 24831050]
183. Hussey MA, Hughes JP. Design and analysis of stepped wedge cluster randomized trials. Contemp Clin Trials 2007 Feb;28(2):182-191. [doi: 10.1016/j.cct.2006.05.007] [Medline: 16829207]
184. Li F, Hughes JP, Hemming K, Taljaard M, Melnick ER, Heagerty PJ. Mixed-effects models for the design and analysis of stepped wedge cluster randomized trials: an overview. Stat Methods Med Res 2021 Feb;30(2):612-639 [FREE Full text] [doi: 10.1177/0962280220932962] [Medline: 32631142]
185. Preacher KJ, Zyphur MJ, Zhang Z. A general multilevel SEM framework for assessing multilevel mediation. Psychol Methods 2010 Sep;15(3):209-233. [doi: 10.1037/a0020141] [Medline: 20822249]
186. Gelman A, Hill J, Vehtari A. Regression and Other Stories. Cambridge, UK: Cambridge University Press; Jul 23, 2020.
187. Cumming G. The new statistics: why and how. Psychol Sci 2014 Jan;25(1):7-29. [doi: 10.1177/0956797613504966] [Medline: 24220629]
188. Hemming K, Kasza J, Hooper R, Forbes A, Jaljaard M. A tutorial on sample size calculation for multiple-period cluster randomized parallel, cross-over and stepped-wedge trials using the Shiny CRT Calculator. Int J Epidemiol 2020 Jun 01;49(3):979-995. [doi: 10.1093/ije/dyz237] [Medline: 32087011]
189. Buller DB, Pagoto S, Henry KL, Baker K, Walkosz BJ, Hillhouse J, et al. Persisting effects of a social media campaign to prevent indoor tanning: a randomized trial. Cancer Epidemiol Biomarkers Prev 2022 Apr 01;31(4):885-892 [FREE Full text] [doi: 10.1158/1055-9965.EPI-21-0059] [Medline: 35064063]
190. Villarruel AM, Loveland-Cherry CJ, Ronis DL. Testing the efficacy of a computer-based parent-adolescent sexual communication intervention for Latino parents. Fam Relat 2010 Dec 01;59(5):533-543 [FREE Full text] [doi: 10.1111/j.1741-3729.2010.00621.x] [Medline: 21116466]
191. Deitz DK, Cook RF, Billings DW, Hendrickson A. A web-based mental health program: reaching parents at work. J Pediatr Psychol 2009 Jun;34(5):488-494 [FREE Full text] [doi: 10.1093/jpepsy/jsn108] [Medline: 18845585]

192. Donovan E, Wood M, Frayjo K, Black RA, Surette DA. A randomized, controlled trial to test the efficacy of an online, parent-based intervention for reducing the risks associated with college-student alcohol use. Addict Behav 2012 Jan;37(1):25-35 [FREE Full text] [doi: 10.1016/j.addbeh.2011.09.007] [Medline: 21963316]
193. Williamson DA, Walden HM, White MA, York-Crowe E, Newton RL, Alfonso A, et al. Two-year internet-based randomized controlled trial for weight loss in African-American girls. Obesity (Silver Spring) 2006 Jul;14(7):1231-1243 [FREE Full text] [doi: 10.1038/oby.2006.140] [Medline: 16899804]
194. Cavallo DN, Tate DF, Ries AV, Brown JD, DeVellis RF, Ammerman AS. A social media-based physical activity intervention: a randomized controlled trial. Am J Prev Med 2012 Nov;43(5):527-532 [FREE Full text] [doi: 10.1016/j.amepre.2012.07.019] [Medline: 23079176]
195. Napolitano MA, Hayes S, Bennett GG, Ives AK, Foster GD. Using Facebook and text messaging to deliver a weight loss program to college students. Obesity (Silver Spring) 2013 Jan;21(1):25-31 [FREE Full text] [doi: 10.1002/oby.20232] [Medline: 23505165]
196. Valle CG, Tate DF, Mayer DK, Allicock M, Cai J. A randomized trial of a Facebook-based physical activity intervention for young adult cancer survivors. J Cancer Surviv 2013 Sep;7(3):355-368 [FREE Full text] [doi: 10.1007/s11764-013-0279-5] [Medline: 23532799]
197. Young SD, Cumberland WG, Lee SJ, Jaganath D, Szekeres G, Coates T. Social networking technologies as an emerging tool for HIV prevention: a cluster randomized trial. Ann Intern Med 2013 Sep 03;159(5):318-324 [FREE Full text] [doi: 10.7326/0003-4819-159-5-201309030-00005] [Medline: 24026317]
198. Morrison L, Chen C, Torres JS, Wehner M, Junn A, Linos E. Facebook advertising for cancer prevention: a pilot study. Br J Dermatol 2019 Oct;181(4):858-859 [FREE Full text] [doi: 10.1111/bjd.17993] [Medline: 30972743]
199. Brandt HM, Sundstrom B, Monroe CM, Turner-McGrievy G, Larsen C, Stansbury M, et al. Evaluating a technology-mediated HPV vaccination awareness intervention: a controlled, quasi-experimental, mixed methods study. Vaccines (Basel) 2020 Dec 10;8(4):749 [FREE Full text] [doi: 10.3390/vaccines8040749] [Medline: 33321975]
200. Sinicrope PS, Koller KR, Prochaska JJ, Hughes CA, Bock MJ, Decker PA, et al. Social media intervention to promote smoking treatment utilization and cessation among Alaska native people who smoke: protocol for the connecting Alaska native people to quit smoking (CAN quit) pilot study. JMIR Res Protoc 2019 Nov 22;8(11):e15155 [FREE Full text] [doi: 10.2196/15155] [Medline: 31755867]
201. Jane M, Hagger M, Foster J, Ho S, Kane R, Pal S. Effects of a weight management program delivered by social media on weight and metabolic syndrome risk factors in overweight and obese adults: a randomised controlled trial. PLoS One 2017 Jun 02;12(6):e0178326 [FREE Full text] [doi: 10.1371/journal.pone.0178326] [Medline: 28575048]
202. Meacham MC, Ramo DE, Prochaska JJ, Maier LJ, Delucchi KL, Kaur M, et al. A Facebook intervention to address cigarette smoking and heavy episodic drinking: a pilot randomized controlled trial. J Subst Abuse Treat 2021 Mar;122:108211 [FREE Full text] [doi: 10.1016/j.jsat.2020.108211] [Medline: 33509414]
203. Ramo DE, Kaur M, Corpuz ES, Satre DD, Delucchi K, Brown SA, et al. Using Facebook to address smoking and heavy drinking in young adults: protocol for a randomized, controlled trial. Contemp Clin Trials 2018 May;68:52-60 [FREE Full text] [doi: 10.1016/j.cct.2018.02.014] [Medline: 29510223]
204. Schonlau M, Couper MP. Options for conducting web surveys. Statist Sci 2017 May;32(2):279-292. [doi: 10.1214/16-sts597]
205. Matthijsse SM, de Leeuw ED, Hox JJ. Internet panels, professional respondents, and data quality. Methodology 2015 Oct;11(3):81-88. [doi: 10.1027/1614-2241/a000094]
206. Hornik R. Measuring campaign message exposure and public communication environment exposure: some implications of the distinction in the context of social media. Commun Methods Meas 2016 Apr 20;10(2-3):167-169 [FREE Full text] [doi: 10.1080/19312458.2016.1150976] [Medline: 27766123]
207. Cancer stat facts: cancer among adolescents and young adults (AYAs) (Ages 15-39). National Institutes of Health, National Cancer Institute, Surveillance, Epidemiology, and End Results Program. URL: https://seer.cancer.gov/statfacts/html/aya.html [accessed 2023-12-20]
208. Choi DK, Helenowski I, Hijiya N. Secondary malignancies in pediatric cancer survivors: perspectives and review of the literature. Int J Cancer 2014 Oct 15;135(8):1764-1773 [FREE Full text] [doi: 10.1002/ijc.28991] [Medline: 24945137]

Abbreviations

DIT: diffusion of innovations theory
EAAB: Emerging Adult Advisory Board
HPV: human papillomavirus
MVPA: moderate to vigorous physical activity
REDCap: Research Electronic Data Capture
RUCC: Rural-Urban Continuum Codes
SCT: social cognitive theory
SDT: self-determination theory
SOAB: Stakeholder Organization Advisory Board

Edited by A Mavragani; submitted 29.06.23; peer-reviewed by M Skiba, J Makin, J Gorman; comments to author 06.11.23; revised version received 28.12.23; accepted 02.01.24; published 22.02.24.

Please cite as:
Buller DB, Sussman AL, Thomson CA, Kepka D, Taren D, Henry KL, Warner EL, Walkosz BJ, Woodall WG, Nuss K, Blair CK, Guest DD, Borrayo EA, Gordon JS, Hatcher J, Wetter DW, Kinsey A, Jones CF, Yung AK, Christini K, Berteletti J, Torres JA, Barraza Perez EY, Small A
#4Corners4Health Social Media Cancer Prevention Campaign for Emerging Adults: Protocol for a Randomized Stepped-Wedge Trial
JMIR Res Protoc 2024;13:e50392
URL: https://www.researchprotocols.org/2024/1/e50392
doi:10.2196/50392
PMID:38386396

Protocol

Development of Continuous Assessment of Muscle Quality and Frailty in Older Patients Using Multiparametric Combinations of Ultrasound and Blood Biomarkers: Protocol for the ECOFRAIL Study

Naiara Virto[1*], MSc; Xabier Río[1*], PhD; Garazi Angulo-Garay[1], MSc; Rafael García Molina[2,3], PhD; Almudena Avendaño Céspedes[2,3,4], MSc; Elisa Belen Cortés Zamora[2,3], MSc; Elena Gómez Jiménez[2], MSc; Ruben Alcantud Córcoles[2,3], PhD; Leocadio Rodriguez Mañas[3,5], PhD; Alba Costa-Grille[5], MSc; Ander Matheu[3,6,7], PhD; Diego Marcos-Pérez[2], PhD; Uxue Lazcano[6], MSc; Itziar Vergara[6,7,8,9], PhD; Laura Arjona[10*], PhD; Morelva Saeteros[10], MSc; Diego Lopez-de-Ipiña[10], PhD; Aitor Coca[11*], PhD; Pedro Abizanda Soler[2,3,12*], PhD; Sergio J Sanabria[7,10,13*], PhD

[1]Department of Physical Activity and Sport Science, Faculty of Education and Sport, University of Deusto, Bilbao, Spain

[2]Department of Geriatrics, Complejo Hospitalario Universitario de Albacete, Albacete, Spain

[3]Center for Biomedical Research Network on Fragility and Healthy Aging (CIBERfes), Instituto de Salud Carlos III, Madrid, Spain

[4]Facultad de Enfermería de Albacete, Universidad de Castilla-La Mancha, Albacete, Spain

[5]Geriatrics Department, University Hospital of Getafe, Getafe, Spain

[6]Biodonostia, Health Research Institute, Donostia, Spain

[7]IKERBASQUE, Basque Foundation for Science, Bilbao, Spain

[8]Osakidetza, Health Care Department, Research Unit APOSIs, Gipuzkoa, Spain

[9]Research Network in Chronicity, Primary Care and Health Promotion (RICAPPS), Barakaldo, Spain

[10]Deusto Institute of Technology, University of Deusto, Bilbao, Spain

[11]Department of Physical Activity and Sports Sciences, Faculty of Health Sciences, Euneiz University, Vitoria-Gasteiz, Spain

[12]Facultad de Medicina de Albacete, Universidad de Castilla-La Mancha, Albacete, Spain

[13]Department of Radiology, Stanford University, Palo Alto, CA, United States

[*]these authors contributed equally

Corresponding Author:
Sergio J Sanabria, PhD
Department of Radiology
Stanford University
3155 Porter Drive
Palo Alto, CA, 94304
United States
Phone: 1 1 650 723 6855
Email: sergio.sanabria@deusto.es

Abstract

Background: Frailty resulting from the loss of muscle quality can potentially be delayed through early detection and physical exercise interventions. There is a demand for cost-effective tools for the objective evaluation of muscle quality, in both cross-sectional and longitudinal assessments. Literature suggests that quantitative analysis of ultrasound data captures morphometric, compositional, and microstructural muscle properties, while biological assays derived from blood samples are associated with functional information.

Objective: This study aims to assess multiparametric combinations of ultrasound and blood-based biomarkers to offer a cross-sectional evaluation of the patient frailty phenotype and to track changes in muscle quality associated with supervised exercise programs.

Methods: This prospective observational multicenter study will include patients aged 70 years and older who are capable of providing informed consent. We aim to recruit 100 patients from hospital environments and 100 from primary care facilities. Each patient will undergo at least two examinations (baseline and follow-up), totaling a minimum of 400 examinations. In hospital

environments, 50 patients will be measured before/after a 16-week individualized and supervised exercise program, while another 50 patients will be followed up after the same period without intervention. Primary care patients will undergo a 1-year follow-up evaluation. The primary objective is to compare cross-sectional evaluations of physical performance, functional capacity, body composition, and derived scales of sarcopenia and frailty with biomarker combinations obtained from muscle ultrasound and blood-based assays. We will analyze ultrasound raw data obtained with a point-of-care device, along with a set of biomarkers previously associated with frailty, using quantitative real-time polymerase chain reaction and enzyme-linked immunosorbent assay. Additionally, we will examine the sensitivity of these biomarkers to detect short-term muscle quality changes and functional improvement after a supervised exercise intervention compared with usual care.

Results: At the time of manuscript submission, the enrollment of volunteers is ongoing. Recruitment started on March 1, 2022, and ends on June 30, 2024.

Conclusions: The outlined study protocol will integrate portable technologies, using quantitative muscle ultrasound and blood biomarkers, to facilitate an objective cross-sectional assessment of muscle quality in both hospital and primary care settings. The primary objective is to generate data that can be used to explore associations between biomarker combinations and the cross-sectional clinical assessment of frailty and sarcopenia. Additionally, the study aims to investigate musculoskeletal changes following multicomponent physical exercise programs.

Trial Registration: ClinicalTrials.gov NCT05294757; https://clinicaltrials.gov/ct2/show/NCT05294757

International Registered Report Identifier (IRRID): DERR1-10.2196/50325

(JMIR Res Protoc 2024;13:e50325) doi:10.2196/50325

KEYWORDS

muscle; ultrasound; blood-based biomarkers; sarcopenia; frailty; older adults

Introduction

Aging is associated with a gradual decline in muscle mass and function, contributing to an increased incidence and prevalence of chronic diseases [1,2]. This, in turn, often leads to situations of multimorbidity [3] and adversely affects functional autonomy [4]. The most severe manifestation of this condition is frailty, described as “a progressive decline in physiological systems that leads to decreased reserves of intrinsic capacity. This confers extreme vulnerability to stressors and increases the risk of various adverse health outcomes” [5]. Frailty is linked to dependency, hospitalization, institutionalization, falls, poor quality of life, and mortality [6-10], along with elevated health care costs [11,12]. While standardized diagnostic criteria are not universally established, the 2 most widely accepted ones [13,14] are rooted in the phenotype construct [4]. According to this construct, frailty is diagnosed when 3 or more of the following criteria are met: unintentional weight loss, self-reported exhaustion, reduced grip strength, slow gait speed, and low levels of physical activity. Moreover, the Cumulative Deficit Model—Frailty Index encompasses cognitive, functional, emotional, and nutritional status [15,16].

The frailty phenotype, as outlined by Fried et al [4], centers around muscle dysfunction [17]. Considering that weakness, slowness, and impairment of the muscular system are characteristic features of frailty, sarcopenia is likely a crucial physiopathological contributor [13,18]. Sarcopenia is a progressive skeletal muscle disease, and its prevalence tends to increase with age. Estimates suggest that sarcopenia affects between 6% and 19% of the general population aged 60 years and older, with variations depending on the applied definition [19]. Currently, the most widely used definitions come from the European Working Group on Sarcopenia in Older People 2 (EWGSOP-2) [20], the Definition and Outcomes Consortium (DOCS) [21], and the National Institute of Health Foundation (NIHF) [22]. According to the EWGSOP-2, reduced muscle strength serves as the initial criterion for probable sarcopenia, and the diagnosis is confirmed by reduced muscle mass and quality. Furthermore, when low physical performance is identified, sarcopenia is categorized as severe [20]. The DOCS supports the inclusion of both weakness (defined by low grip strength) and slowness (defined by low usual gait speed) in the definition of sarcopenia [21]. The NIHF defines sarcopenia as a loss of strength diagnosed by low grip strength, accompanied by low muscle mass [22].

In clinical care, the assessment of muscle mass and quality involves a semiquantitative evaluation using 2D images through dual-energy X-ray absorptiometry (DXA) and a body composition estimate through bioelectrical impedance analysis (BIA) [20]. It is worth noting that these techniques can be influenced by other variables, such as skeletal mass and a high BMI [23]. Radiological imaging enables comprehensive 3D mapping of muscle composition and microstructure. The proposed methods are magnetic resonance imaging (MRI) and computed tomography (CT) sequences, allowing the assessment of adipose fraction and fibrous microstructure, among other parameters [24-26]. However, because of their high cost and the potential for patient complications, these imaging methods are presently limited to research applications or as supplementary examinations for different primary indications [27].

Sarcopenia and frailty, although connected and associated with aging, are distinct conditions. Sarcopenia primarily centers around the musculoskeletal system, while frailty is a more multifactorial condition [28,29]. Various studies indicate that the prevalence of sarcopenia among older adults with frailty is higher than the prevalence of frailty among those with sarcopenia [28,30-32]. Adverse outcomes linked to muscular

decline can be mitigated, delayed, or even reversed through early detection and interventions, including nutritional support and physical exercise programs [13,18,33]. Nonetheless, there exists a need for straightforward and dependable tools that facilitate the assessment of muscle quality and its implications for frailty [28,34].

Ultrasound, as a fast, noninvasive, and cost-effective imaging modality, is gaining rapid prominence for musculoskeletal examination [35,36]. Currently, clinical ultrasound images (B-mode) enable the assessment of muscle mass and morphology, encompassing measures such as muscle thickness, pennation angle, cross-sectional area, echo intensity, and fascicle length [37-39]. Despite ongoing efforts for standardization, these measurements remain highly reliant on the expertise and skills of the operator, and they do not provide definitive results for the early staging of muscle quality loss [37,40]. Ultrasound morphometric measurements of sarcopenia in older adults have demonstrated mild to moderate associations with frailty [41]. More recently, various quantitative ultrasound techniques have surfaced, involving the analysis of echogenicity, texture parameters, elastography, and acoustic wave properties. However, their translation to clinical practice is still limited [42-51]. Artificial intelligence is presenting new opportunities to objectify musculoskeletal ultrasound, with recent studies showcasing automatic muscle segmentation, fiber angle detection, and textural discrimination of muscle microstructures [52-55].

Biological biomarkers serve as valuable tools in diagnosing and stratifying patients, as well as in comprehending the underlying pathophysiology of diseases. Oxidative stress, a proinflammatory state, and immune aging play significant roles in the connection between nonspecific biomarkers and specific biological systems related to frailty and sarcopenia [56-59]. Recent studies have delved into the intricate interrelationships among various systems that underlie frailty through multi-omics approaches [60]. As an example, the FRAILOMIC initiative used blood samples to delineate a collection of biological biomarkers, encompassing both protective and risk factors. Notably, oxidative stress, vitamin D, and the cardiovascular system were found to be associated with frailty [61]. Despite these advancements, the currently available biomarkers exhibit weak individual associations with the clinical outcomes of sarcopenia and frailty. Furthermore, their ability to detect changes after physical intervention remains largely unknown.

A limited number of studies have explored the combination of ultrasound and blood-based biomarkers. In one study, changes in circulating biomarkers corresponding to a short-term resistance exercise intervention in older adults were identified. These changes were found to be significantly related to ultrasound leg cross-sectional area [62]. Associations were discovered between combined genetic and methylation scores and ultrasound-derived skeletal muscle morphometry in older women [63]. In another cross-sectional study, ultrasound characteristics of the quadriceps femoris in patients with sarcopenia were correlated with blood and urinary biomarkers [64].

In summary, there is a lack of simple and objective screening tools for diagnosing frailty and sarcopenia [28,34]. While clinical standardization of B-mode images is essential, there is also a requirement for advancements in ultrasound technology to develop quantitative indicators for assessing muscle quality [65,66]. This study is designed to assess objective methods for evaluating muscle quality using quantitative analysis techniques based on the analysis of ultrasound raw data combined with blood-based biomarkers. Additionally, the study aims to investigate the capability of these biomarkers to detect changes in muscle quality resulting from a physical exercise intervention program in older individuals with frailty.

The primary aim of this study is to assess the feasibility of combining point-of-care quantitative ultrasound parameters with blood-based assays for evaluating muscle quality and frailty in older adults. This evaluation will encompass both hospital settings and community care, with a focus on comparing the findings with traditional clinical evaluations.

Methods

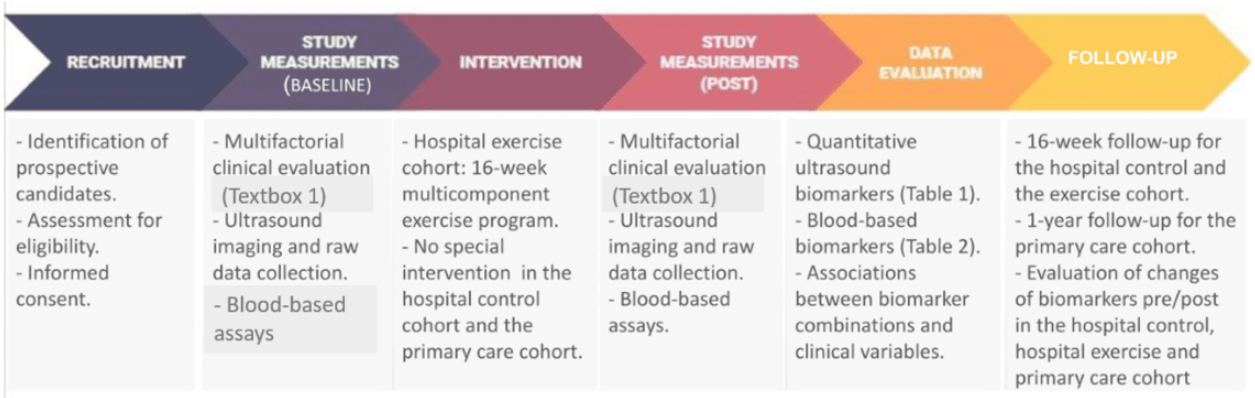
Study Setting

This study is designed as a prospective, experimental, multicenter, 3-cohort investigation. The research will be performed at Albacete University Hospital Complex, Spain (with the coordinating Clinical Research Ethics Committee; hospital 1); Getafe University Hospital, Spain (hospital 2); and primary care units of Donostialdea, Osakidetza, Spain (primary care units). The primary health care units involved in the study will be located in 2 districts/regions of Gipuzkoa: the region of Donostialdea and the region of Tolosaldea. The design of this study protocol, characterized as exploratory, adheres to the SPIRIT (Standard Protocol Items of the Recommendations for Interventional Trials; Multimedia Appendix 1) 2013 guidelines, as depicted in Figures 1 and 2.

Figure 1. SPIRIT (Standard Protocol Items of the Recommendations for Interventional Trials) figure.

	STUDY PERIOD						
	Enrolment	Allocation	Intervention Period			Close out	
TIMEPOINT	0 week	0 week	0 week	1-16 weeks	1 year	17 weeks (Hospital exercise and control cohort)	1 year (Primary care cohort)
Enrolment:							
Eligibility screen (Inclusion and exclusion criteria)	X						
Informed consent	X						
Allocation		X					
Interventions:							
Hospital exercise cohort (1)				1			
Hospital control cohort (2)				2			
Primary care cohort (3)					3		
Assessments:							
Body composition			1-2-3			1-2	3
GDS			1-2-3			1-2	3
Charlson Comorbidity index.			1-2-3			1-2	3
Barthel index			1-2-3			1-2	3
Lawton and Brody index			1-2-3			1-2	3
SPPB			1-2-3			1-2	3
SARC-F			1-2-3			1-2	3
FRAIL			1-2-3			1-2	3
Frailty phenotype of frailty			1-2-3			1-2	3
MNA-SF			1-2-3			1-2	3
IPAQ			1-2-3			1-2	3
EQ 5D-5L			1-2-3			1-2	3
Gait speed test			1-2-3			1-2	3
Grip strength			1-2-3			1-2	3
Ultrasound			1-2-3			1-2	3
Blood sample testing			1-2-3			1-2	3
Dropout reasons						1-2	3
Adverse events						1-2	3

Figure 2. Flow diagram of the study protocol.



Study Population Recruitment

Hospital Exercise Cohort

Participants will be consecutively recruited from the scheduled patient list of the falls unit and the outpatient clinics of hospital 1. Upon obtaining informed consent, patients will undergo a baseline clinical evaluation. Subsequently, ultrasound measurements and a DXA scan will be conducted, and blood samples will be collected, processed, and stored. These patients will then be enrolled in a 16-week multicomponent physical exercise program (discussed later). Following the completion of the exercise program, at the 16-week follow-up, a repetition of clinical evaluation, ultrasound, DXA, and blood-sample testing will be performed.

Hospital Control Cohort

Participants will be consecutively recruited from the scheduled patient list of the frailty unit, day hospital, and the outpatient clinic of the Geriatrics Department of hospital 2. Upon obtaining informed consent, baseline study variables will be collected. These patients will be followed up for 16 weeks under usual care. After the follow-up period, a repetition of the baseline evaluation will be conducted.

Primary Care Cohort

Participants will be consecutively recruited from the scheduled patient list of the primary care units. Upon obtaining informed consent, baseline study variables will be collected. These patients will be followed up for 1 year under usual care. After the 1-year follow-up, a repetition of the baseline evaluation will be conducted.

Recruitment is conducted by the study coordinator staff at each site, under the overall supervision of the clinical principal investigator at each site. Participants will sign the informed consent at the beginning of the first visit. The professional overseeing the assessment will provide an explanation of the project, and the participant will sign both the information sheet and the informed consent to participate. The principal investigator at each site will be responsible for collecting and monitoring the documentation related to informed consent. The inclusion and exclusion criteria are listed in Textbox 1.

Textbox 1. Inclusion, exclusion, and termination criteria.

1. Inclusion criteria

- Age of at least 70 years.
- Either gender.
- Ability to provide informed consent.
- Ability to perform all the functional tests.
- In the hospital exercise cohort, the ability to participate in the physical exercise program.

2. Exclusion criteria

- Expected survival of <1 year.
- Barthel Scale score <70.
- Moderate-to-severe cognitive impairment.
- Refusal to participate.
- Medical conditions that may compromise or impede follow-up assessments.
- Older adults already enrolled in regular physical exercise programs will be excluded from participating in the hospital exercise cohort.

3. Termination criteria

- Refusal to continue participation.
- Complications during or in between examinations and intervention.

Allocation

The allocation sequence in this multicentric study is institution-based. Patients recruited at the Department of Geriatrics of the Complejo Hospitalario Universitario de Albacete will be automatically allocated to the supervised exercise program by default. By contrast, patients recruited at the Geriatrics Department of the University Hospital of Getafe will not be assigned to any specific interventions. Similar sociodemographic characteristics are anticipated for both patient populations. At each institution, patients will be recruited from the falls unit, outpatient clinics, and day hospital. Within each acquisition site, patient selection will be conducted based on the clinical agenda until the recruitment goals are met.

The allocation sequence is sequential, aligned with the clinical agenda, and overseen by the clinical principal investigator at each site. Any deviations from the recruitment plan outlined in the clinical agenda must be thoroughly justified and meticulously documented.

Interventions

In the hospital exercise cohort, a 16-week supervised multicomponent physical exercise program will be implemented. The individualized exercise intervention, tailored to each

individual's functional capacity, comorbidities, and previous experience, will consist of 2 supervised sessions per week, each lasting 45 minutes. These sessions will be conducted in small groups, with 4-6 older adults per group. The sessions are divided into warm-up, main part (strength, power, and coordination exercises), and cool down (flexibility and stretching). The main part of the exercise program comprises 8 exercises targeting the major muscle groups. The progression starts with low-intensity and high-volume sessions, gradually advancing to higher intensities and lower volumes. Depending on the stage, participants will complete 2-4 sets, consisting of 4-15 repetitions, with a 30-second rest between sets and exercises. For each exercise, loads and intensities will be adjusted to achieve a total of 30 repetitions. All exercise sessions are to be conducted in the gym of the Geriatrics Department of the hospital. Participants will be encouraged to incorporate additional 90-minute walks per week into their routine. It is important to note that the exercise program is aligned with the guidelines of the VIVIFRAIL program [67], which specifically aims to prevent weakness and reduce the risk of falls.

In the hospital control and primary care cohorts, no specific intervention will be implemented.

Retention

In alignment with the VIVIFRAIL program guidelines, our intervention program is designed to prevent weakness and reduce the risk of falls. Patients will be informed about the program's benefits during recruitment and follow-up. Within the supervised exercise program, interventions and patient progress will be personalized and monitored, taking into account functional capacity, comorbidities, and the individual's previous experiences. The sessions will be closely monitored at the gym of the Geriatrics Department of the hospital. The individualized sessions will enable discussions on progress with the patient throughout the intervention, fostering motivation for retention and completing the follow-up. Participants will also be encouraged to adopt healthy habits, such as incorporating an additional 90-minute walk per week. In case participants require medical care that may interfere with the ongoing study procedures, they will be managed according to the clinical routine and subsequently excluded from the study. In these cases, the data collected during the baseline examination will be used for a cross-sectional clinical evaluation of frailty and sarcopenia. However, musculoskeletal changes following the multicomponent exercise program will not be assessed.

Safety Monitoring

Each principal investigator at every data acquisition center will oversee the monitoring and follow-up of participants included in their respective cohorts under usual care. They will make decisions regarding patient exclusion and assignment to interventions, and monitor termination criteria as deemed necessary. Additionally, participation in an exercise program is generally associated with a low risk (–1%) of adverse events [68], most of which are typically low-grade responses to exercise, such as muscle soreness [69]. However, in the event of adverse events or serious adverse events, they will be promptly reported to the Clinical Research Ethics Committees.

Randomization and Blinding

Data analysis will be conducted independently of cohort recruitment and follow-up. The evaluation of data will take place at the Deusto Institute of Technology (Ultrasound Data Evaluation Center) and Biodonostia (Blood-based Assays Evaluation Center). Initially, only anonymized data, including ultrasound images, raw data, and blood-based assays, will be transmitted to the data evaluation centers. In the case of combination models, a training set of clinical variables will also be transferred to the data evaluation centers. Reserved data sets will be kept at the clinical acquisition centers for independent testing. This includes data from various sites and information obtained during follow-up examinations.

Sample Size

A population of 200 participants will be recruited, with 100 participants in the primary care cohort, 50 participants in the hospital exercise cohort, and 50 participants in the hospital control cohort (2:1:1 ratio). Patient selection within each acquisition site will be conducted based on the clinical agenda until the recruitment goals are met. Each participant will undergo 2 examinations (baseline and follow-up), resulting in a minimum total of 400 examinations.

An estimated distribution of 85% of patients with frailty to 15% of healthy participants is anticipated in the hospital cohorts, while a distribution of 15% of patients with frailty to 85% of healthy participants is expected in the primary care cohort. Consequently, an accrual of 139 robust participants and 86 patients with frailty is projected. It is assumed that up to 10% of the participants may be excluded in data evaluation as a result of failed measurements or logistical challenges in collecting all variables. In cases where follow-up measurements are not feasible for patients, the baseline measurement will still be included in the evaluation of the primary outcomes. With 80% power, the planned population will enable the detection of a biomarker medium effect size of E/S=0.39, considering a 2-sided α level of .05. For the secondary goal, our sample size of 100 provides 80% power to detect a biomarker with a medium effect size (E/S=0.284) at a 2-sided α level of .05. The sample size was calculated using RiskCalc (Moody's Analytics) [70].

Outcomes

Primary Outcomes

Investigating the association between quantitative ultrasound biomarkers related to muscle mass and quality (thickness [mm], cross-sectional area [cm^2], perimeter [mm], pennation angle [degrees]) extracted from raw data and blood-based biomarkers, as well as their combinations with clinical variables. These clinical variables encompass frailty (FRAIL [short 5-question assessment of Fatigue, Resistance, Aerobic capacity, Illnesses, and Loss of weight] scale ranging from 0 to 5, with 0 indicating robustness and 5 indicating frailty, and Frailty phenotype by Fried et al [4], ranging from 0 [robust] to 5 [frail]), sarcopenia (SARC-F [Strength, Assistance with walking, Rising from a chair, Climbing stairs, and Falls] scale scores ranging from 0 [robust] to 10 [sarcopenic]), physical function (Short Physical Performance Battery [SPPB] Scale score ranging from 0 to 12, where 0 indicates the lowest physical performance and 12

indicates the highest performance), International Physical Activity Questionnaire scores ranging from 0 (lowest) to 3 (highest), Gait Speed Test in seconds, grip strength measured by Jamar dynamometer in kilogram, disability (Global Deterioration Scale, consisting of 7 stages), Barthel Index (ranging from 0 [total dependent] to 100 [independent]), Lawton and Brody Index (scores from 0 [dependent] to 8 [independent]), nutritional status (Mini Nutritional Assessment—Short Form), body composition (DXA), and quality of life (EQ-5D-5L) within 3 cohorts of older adults: hospital control cohort, hospital exercise cohort, and primary care cohort.

Secondary Outcomes

- In the hospital exercise cohort, we will assess changes in quantitative ultrasound and blood-based biomarkers, as well as clinical variables, following a 16-week multicomponent physical exercise program. Additionally, exploring associations between ultrasound and blood-based biomarkers and the remaining clinical variables both before and after the exercise program.
- In the hospital control cohort, we will examine changes in quantitative ultrasound and blood-based biomarkers, along with clinical variables, following a 16-week follow-up period without intervention. Furthermore, we will explore associations between quantitative ultrasound and blood-based biomarkers and the remaining clinical variables after the 16-week follow-up period.
- In the primary care cohort, we will assess changes in quantitative ultrasound and blood-based biomarkers, along with clinical variables, following a 1-year follow-up period without intervention. Additionally, we will explore associations between quantitative ultrasound and blood-based biomarkers and the remaining clinical variables after the 1-year follow-up.
- We will evaluate differences in the changes of all measurements among the 3 cohorts. A direct comparison will be made between the 2 hospital cohorts, while the primary care cohort will serve as a reference for understanding changes in nonhospital populations.

Outcome Measurements

The list of clinical variables collected at baseline and follow-up assessments is included in Textbox 2.

Textbox 2. Clinical variables in baseline and follow-up examination.

- Global Deterioration Scale of Reisberg for assessment of cognitive function.
- Charlson Comorbidity Index.
- Barthel Index of independence to perform basic activities of daily living.
- Lawton and Brody Index of independence to perform instrumental activities of daily living.
- Short Physical Performance Battery for Physical Function Assessment.
- SARC-F (Strength, Assistance with walking, Rising from a chair, Climbing stairs, and Falls) scale of sarcopenia screening.
- FRAIL (short 5-question assessment of Fatigue, Resistance, Aerobic capacity, Illnesses, and Loss of weight) scale of frailty evaluation.
- Frailty phenotype of frailty proposed and validated by Fried et al [4].
- Mini Nutritional Assessment—Short Form for nutritional screening.
- International Physical Activity Questionnaire for physical activity levels.
- EQ-5D-5L for health-related quality of life assessment.
- Gait Speed Test for Physical Function Assessment.
- Grip strength with Jamar dynamometer.
- Population characteristics: age, sex, and BMI.
- Body composition (dual-energy X-ray absorptiometry; total muscle mass, appendicular lean soft tissue mass [ALM], dual-energy X-ray absorptiometry [ALM/h^2 or ALM divided by height squared], total fat, and fat percentage)

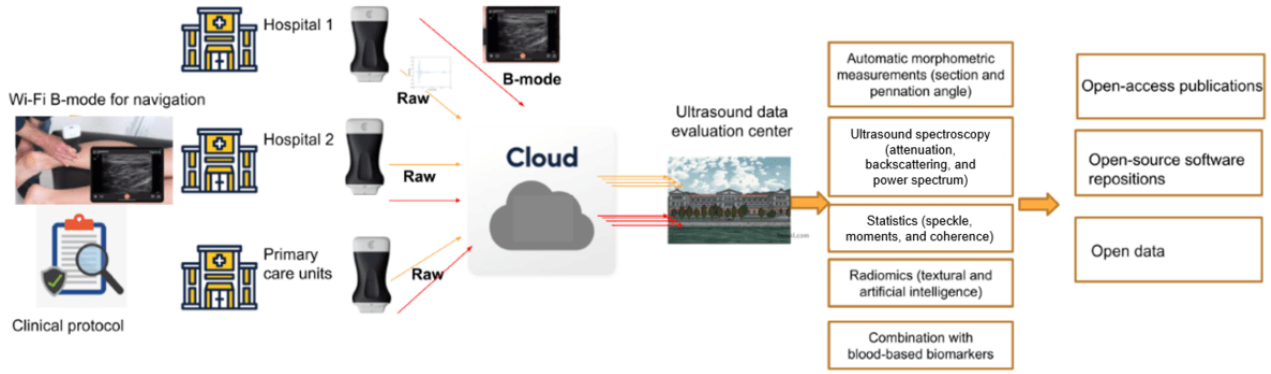
Ultrasound Imaging and Raw Data Acquisition

The ultrasound equipment used in this study is the L7 HD3 portable linear scanner (Clarius Mobile Health Corp.). Specifically designed for point-of-care ultrasound examinations, the probe of this device boasts a frequency range of 4-13 MHz with a center frequency of 7 MHz. To facilitate seamless data transfer, anonymized digital ultrasound data are transmitted from the scanner through a customized Wi-Fi network to a smart device, enabling real-time B-mode navigation and data storage. The important feature of the scanner is an integrated image processing package designed to optimize B-mode musculoskeletal image quality. This technology enhances the clarity and quality of musculoskeletal imaging during examinations. Additionally, the scanner is equipped with a research package designed to capture raw beamformed backscattering ultrasound data after the beamformer. These raw data are presented in an in-phase/quadrature complex baseband representation, commonly referred to as IQ data. The IQ data serve as the foundation for the implementation of tailored quantitative ultrasound algorithms [71].

All examinations will be conducted within a depth range of 0-60 mm, using 50% of the maximum acoustic output offered by the scanner. During measurements, efforts will be made to minimize skin-probe compression to maintain acceptable image

quality. Following each examination, the acquired data will be uploaded to a HIPAA (Health Insurance Portability and Accountability Act)-compliant cloud service, offered by the scanner's manufacturer, enabling the centralization of data (Figure 3).

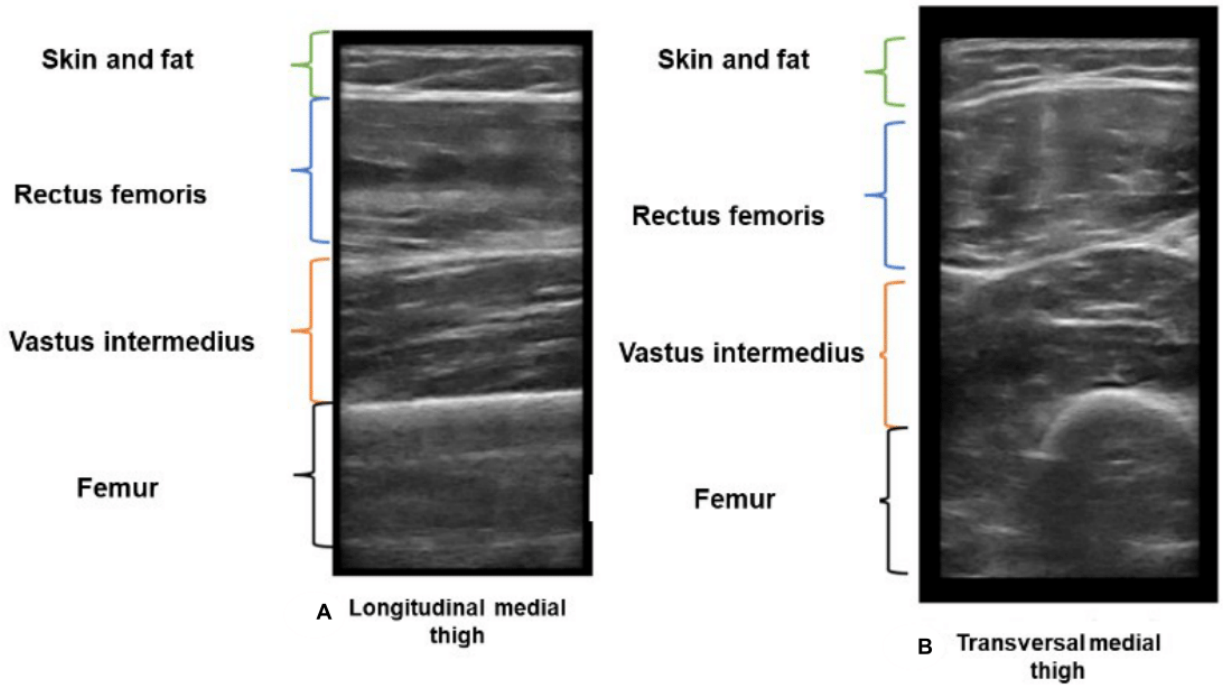
Figure 3. Ultrasound data flow and management from clinical acquisition centers to ultrasound data evaluation center.



Ultrasound Examination Protocol

The midpoint of the thigh will be determined and marked as the half-distance between the superior border of the patella and the anterior-superior iliac crest. Using the femur as a guide in the transverse view, the midpoint of each thigh will be located, and the various components of the quadriceps muscles (rectus femoris, vastus intermedius, vastus medialis, and vastus lateralis) will be identified (Figure 4).

Figure 4. Echographic B-mode appearance of mid-thigh in the (A) transverse and (B) longitudinal views.



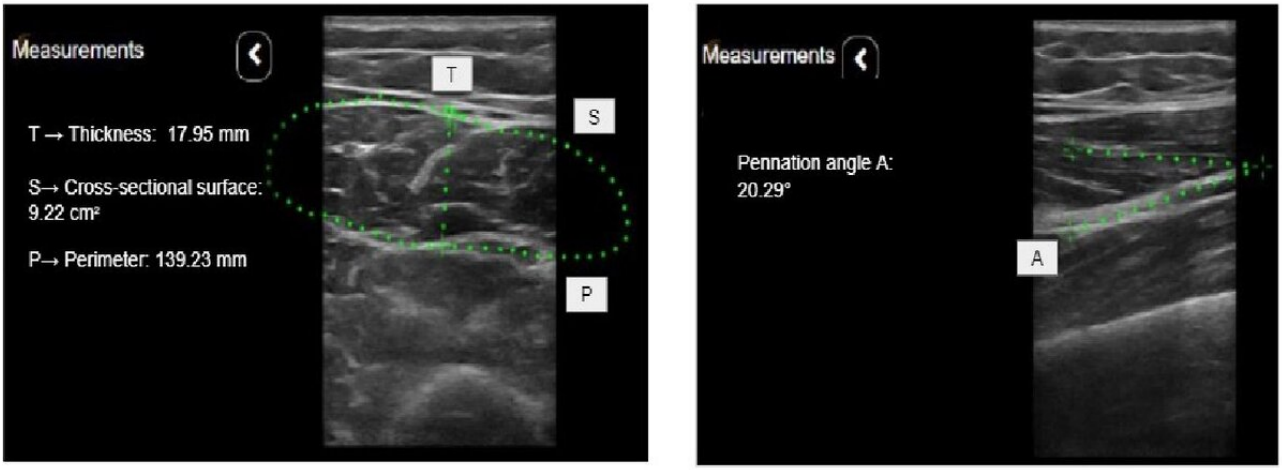
In each examination, a minimum of 12 coregistered B-scan and raw data frames will be obtained. This will include 3 transverse and 3 longitudinal views for both thighs. The longitudinal examination will be conducted in a plane where fasciculations are visible, ensuring comprehensive coverage and detailed assessment of the musculoskeletal structures.

Evaluation of Quantitative Ultrasound Biomarkers

Morphometric Ultrasound Measures

Throughout the examination, the sonographer will record morphometric ultrasound measurements using the online ultrasound scanner's interface (Figure 5). This includes capturing the thickness of the rectus femoris in the transverse view at the midsection point, measuring the perimeter and cross-sectional area of the rectus femoris in the transverse view, and determining the pennation angle in the longitudinal view.

Figure 5. Morphometric ultrasound measurements. (A) Rectus femoris thickness, cross-sectional surface, and perimeter (transverse view). (B) Pennation angle (longitudinal view).



Raw Data Evaluation

Quantitative ultrasound biomarkers will be assessed offline using the acquired raw IQ data. Regions of interest encompassing the rectus femoris will be delineated in the raw data domain by automatically generating B-mode images from the raw data. This process will use the coregistered clinical B-mode images and sonographer annotations as a reference for the definition of the accurate region of interest. Table 1 presents a list of state-of-the-art quantitative ultrasound biomarkers, the hyperparameters of which will be systematically adjusted through experimental adaptation for musculoskeletal examinations. These adjustments will be made and subsequently evaluated using the raw data obtained from the ultrasound probes during the study.

Table 1. Quantitative ultrasound biomarkers based on raw data.

Biomarker	Description	Literature references
Automatic morphometric measurements	Automatic muscle morphometric analysis based on neural network segmentation models trained with respect to sonographer annotations of rectus femoris cross section, and 2D Fourier analysis of pennation angle.	[72,73]
Attenuation coefficient	Measurement of loss of signal intensity with depth.	[47,48,50]
Backscattering coefficient	Measurement of tissue reflectivity after attenuation compensation.	[74,75]
Power spectrum (Lizzi-Feleppa parameters)	Spectroscopy measurement of backscattered signal variation with frequency, including parametrizations such as spectral slope, spectral intercept, and midband fit	[49]
Speckle statistics	Fitting of raw envelope signal to speckle statistical distribution models, including Rayleigh, Nakagami, and homodyned K-distribution. Estimation of scatterer concentration, spacing, and coherence from fitted model parameters.	[49,76,77]
Statistical moments	Nonparametric statistical moments capturing scatterer distribution and concentration, such as entropy, kurtosis, skewness, variance, anisotropy, and signal-to-noise ratio.	[78,79]
Coherence and speed of sound	Generalized spectrum analysis and estimation of coherence, mean scatterer spacing, and speed-of-sound in muscle.	[80,81]
Textural radiomics	First- and second-order texture features extracted from both B-mode (eg, based on gray-scale co-occurrence matrices) and raw data (eg, based on wavelet and Laplacian transformations) and combined with machine learning models trained with respect to clinical outcomes.	[51,53,54]
Artificial intelligence radiomics	Radiofrequency data and B-mode features extracted automatically with end-to-end neural network models trained with respect to clinical outcomes	[52,82-84]

Evaluation of Blood-Based Biomarkers

During both basal and follow-up acquisitions, venipuncture will be performed to collect one 10-mL serum blood tube and two 5-mL ethylenediaminetetraacetic acid (EDTA) blood tubes. The serum sample will undergo centrifugation and will be stored in 4 aliquots. One of the EDTA samples will be promptly frozen and stored at –80°C, while the other will be subjected to centrifugation for plasma and buffy coat extraction. These samples will be stored at –80°C at the clinical sites until transportation, which will be carried out with dry ice to the Blood-Assay Evaluation Center for subsequent processing and storage (Figure 6).

The expression of previously described biomarkers, including vitamin D, lutein zeaxanthin, troponin T, pro-brain natriuretic peptide, soluble receptor for advanced glycation end products

(sRAGE) [85], and microRNAs, along with those associated with relevant pathways related to frailty such as inflammation (interleukin 6) and senescence (p16INK4A and p21CIP [56]), will be assessed in cells obtained from a blood sample. This evaluation will be conducted in a subsample of patients in baseline conditions and after intervention at both the transcriptional and protein levels, as outlined in Table 2. Erythrocytes will be lysed using Buffer EL (Qiagen), and total RNA from leukocytes will be isolated using the miRNeasy Mini Kit (Qiagen). Initially, RNA samples will undergo purification with the RNeasy Kit (Qiagen). Subsequently, the RNA will be retro-transcribed, and gene expressions will be quantified through quantitative polymerase chain reaction (PCR) using specific primers or probes and the ABI Prism SDS 7300 Real-Time PCR System (Applied Biosystems). Expression levels will be normalized to the expression of the enzyme glyceraldehyde-3-phosphate dehydrogenase (GAPDH) [86]. Furthermore, protein levels will be assessed in serum samples using Quantikine enzyme-linked immunosorbent assays and Luminex, as previously outlined [87].

Figure 6. Biomarkers data flow and management from clinical centers to blood-essay evaluation center. ELISA: enzyme-linked immunosorbent assay; qRT-PCR: real-time quantitative reverse transcription polymerase chain reaction.

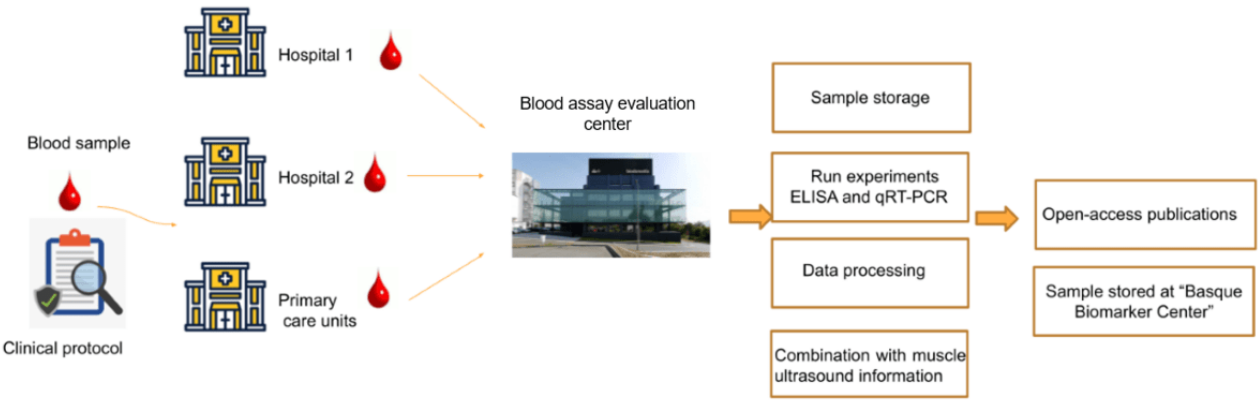


Table 2. Blood-based biomarkers.

Biomarker	Method of measurement
Vitamin D	ELISA[a]
Lutein zeaxanthin	ELISA
Troponin T	ELISA
Pro-brain natriuretic peptide	ELISA
Soluble receptor for advanced glycation end products	ELISA
MicroRNA 125	qRT-PCR[b]
MicroRNA 194	qRT-PCR
MicroRNA 454	qRT-PCR
Interleukin-6	ELISA and Luminex
$P16^{INK4A}$	qRT-PCR
$P21^{CIP}$	qRT-PCR
New unpublished	qRT-PCR and ELISA

[a]ELISA: enzyme-linked immunosorbent assay.

[b]qRT-PCR: real-time quantitative reverse transcription polymerase chain reaction.

Statistical Analysis

The study population will be characterized based on demographic and clinical attributes. Categorical data will be summarized with frequency and percentage representations. Continuous data will be described using mean, SD, median, and the 25th and 75th percentiles. Furthermore, the distribution of ultrasound parameters with respect to the primary endpoint will be depicted using graphical techniques. The correlation of quantitative biomarkers will be evaluated for each multifactorial clinical evaluation parameter using the Pearson correlation coefficient for continuous variables and the Spearman correlation coefficient for categorical variables [88]. Unpaired tests, such as the Student *t* test, will be used for comparing means of biomarkers among various acquired patient cohorts and for stratified patient subgroups based on the frailty scales outlined in Textbox 1. To manage the extensive array of ultrasound and blood biomarkers, a robust statistical analysis

plan will be implemented. This plan will incorporate correction methods to address the risk of type I errors associated with multiple comparisons. Specifically, for the primary outcome concerning biomarker-clinical associations, we will use Lasso regression. This technique automates the selection of relevant variables, reducing the necessity for extensive corrections and improving interpretability. Paired statistics will be applied in the statistical analysis for longitudinal monitoring, encompassing both interventions and clinical follow-up. The monitoring period in hospital and primary care environments will differ to accommodate the distinct follow-up workflows in each setting. The duration of primary care follow-up aligns with established norms [89,90]. To account for differences in follow-up duration among cohorts over time, our data analysis will incorporate appropriate statistical methods, potentially enabling adjustments for these variations. For the secondary objective, the impact of physical intervention in 50 patients will be compared with 50 patients with no intervention. With 80% power, the planned population size will enable the detection of a biomarker with a medium effect size of E/S=0.284 at a 2-sided α level of .05.

In the context of multiparametric data science models, unsupervised learning techniques will be assessed to cluster patient populations based on biomarker expression. Moreover, supervised multi-omics models will be trained using a training set of clinical variables. Stratified cross-validation will be used to derive model performance statistics, ensuring separate patient data in the training and validation folds and maintaining a balanced distribution of health participants and those with frailty in both training and validation sets. Consecutively, sample imputation will be used to address missing data in the training set, while missing reference variables will be excluded during validation and testing. Sensitivity analyses will be conducted to evaluate the impact of the imputation method on the robustness of our results. Reserve data sets, comprising data from various sites and follow-up examinations, will be used for model testing.

Biomarker reproducibility will be evaluated using the interclass correlation coefficient and the Bland-Altmann method, taking into account repeated measurements within an examination. Subgroup analyses will be conducted to explore variations across patient subpopulations, and regression models will be used to examine the influence of covariates, thereby enhancing methodological precision.

Ethical Considerations

This study protocol received approval from the Research Ethics Committee of Albacete (Spain) with reference CEIm-2021-51. The study will be conducted in adherence to the principles outlined in the Declaration of Helsinki [91]. Before participation, written informed consent will be obtained from all participants, and their data will be handled in accordance with HIPAA guidelines. Additionally, consent will be sought for the review of participants' medical records and for the collection of blood samples to assess biomarkers. In the event of necessary modifications to this protocol during the clinical research, the changes will undergo review by the hospital ethics committee and will be implemented only after obtaining approval. The trial results will be communicated to participants via email by the investigators. Participants involved in this study will not receive any form of compensation for their participation.

The study information will be stored in Microsoft Excel 365 within an electronic database. This database will comprehensively capture individual data, including baseline characteristics, pre- and postassessment data, and any potential adverse events. Notably, no personally identifiable patient information, apart from the unique trial identification number, will be included in the metadata associated with the recorded ultrasound and biomarker data. Ultrasound and biomarker data will be uploaded to a HIPAA-compliant cloud service provided by the ultrasound system manufacturer, enabling centralized evaluation by team members. As outlined in the reference manuscript, upon completion of the study, digitized data sets encompassing ultrasound data, biomarkers, digitized blood-based biomarkers, and anonymized multifactorial clinical evaluations will be published in open-access repositories, such as Zenodo (CERN). Biological samples will be securely stored in the Basque Biomarker Center (Biobanco). Additionally, software models derived from ultrasound raw data will be made accessible through open-source software repositories (eg, GitLab).

Results

The initial analysis results indicate a correlation between ultrasound morphometric parameters and clinical variables (Table 3). This table examines the correlations of ultrasound geometric parameters with clinical variables. The clinical data considered in this analysis are derived from a subset of the hospital cohort, comprising a total of 66 participants. Specifically, correlations between clinical variables and ultrasound parameters during the basal examination have been included in the table.

Table 3. Preliminary correlations at baseline visit for the hospital cohort (n=66).

Correlations	Thickness run average, *r* (*P* value)	Area run average, *r* (*P* value)	Angle run average, *r* (*P* value)
Age	–0.023 (.82)	0.002 (.98)	–0.072 (.47)
BMI	0.269 (.009)[a,b]	–0.016 (.88)	0.167 (.09)
Charlson	–0.180 (.09)	–0.213 (.04)[a,b]	–0.018 (.85)
Barthel Index	0.058 (.58)	0.176 (.09)	0.224 (.02)[a,b]
Lawton and Brody Index	–0.002 (.98)	–0.056 (.60)	0.220 (.02)[a,b]
Mini Nutritional Assessment—Short Form	0.183 (.08)	0.036 (.74)	0.210 (.03)[a,b]
SARC-F[c]	–0.098 (.35)	–0.236 (.02)[a,b]	–0.158 (.11)
Grip strength	0.240 (.02)[a,b]	0.372 (<.001)[a,b]	0.105 (.32)
Short Physical Performance Battery total	0.288 (.005)[a,b]	0.355 (.001)[a,b]	0.197 (.04)[a,b]
Gait speed	0.168 (.11)	0.327 (.002)[a,b]	0.241 (.01)[a,b]
Frailty phenotype (Fried et al [4])	–0.101 (.34)	–0.211 (.04)[a,b]	–0.044 (.68)
FRAIL[d]	–0.125 (.24)	–0.284 (.006)[a,b]	–0.034 (.73)
DXA[e] total muscle mass	0.473 (<.001)[b,f]	0.498 (<.001)[b,f]	0.143 (.28)
DXA ALM[g]	0.440 (<.001)[b,f]	0.539 (<.001)[b,f]	0.100 (.45)
DXA ALM/h^2	0.529 (<.001)[b,f]	0.493 (<.001)[b,f]	0.115 (.38)
DXA total fat	0.271 (.04)[a,b]	0.29 (.83)	0.130 (.32)
DXA fat percentage	0.132 (.31)	–0.239 (.07)	0.064 (.63)

[a]Significant weak correlations (r<0.4).

[b]Significant correlations (P<.05).

[c]SARC-F: Strength, Assistance with walking, Rising from a chair, Climbing stairs, and Falls.

[d]FRAIL: short 5-question assessment of Fatigue, Resistance, Aerobic capacity, Illnesses, and Loss of weight.

[e]DXA: dual-energy X-ray absorptiometry.

[f]Significant moderate and strong correlations (r>0.4).

[g]ALM: appendicular lean soft tissue mass.

The analysis revealed significant moderate correlations between muscle cross-section and thickness and DXA parameters (Table 3). Notably, the highest correlation (r=0.539, P<.001) was observed between DXA appendicular mass and muscle cross section. Additionally, significant weak correlations were identified between functional variables (such as gait speed, grip strength, and SPPB) and ultrasound morphometric parameters (including muscle section, thickness, and pennation angle; indicated in Table 3 in rows 7, 8, and 9, respectively). The frailty scale (FRAIL, Fried et al [4]) and the sarcopenia scale (SARC-F) exhibited weak but significant associations with muscle cross section as illustrated in row 2 of Table 3. Additionally, significant weak correlations were identified between pennation angle and measures of independence (Barthel and Lawton Index) as well as nutritional assessment (Mini Nutritional Assessment—Short Form) as detailed in Table 3. Notably, age did not demonstrate a significant association with ultrasound morphometric variables (r=–0.023, P=.82; r=0.002, P=.98; and r=–0.072, P=.47, respectively). However, a weak correlation was observed between BMI and muscle thickness.

Discussion

Principal Findings

The anticipated outcomes of this study are the identification of associations and the development of combination models between quantitative ultrasound and blood-based assays with multifactorial clinical assessments, specifically focusing on muscle quality and frailty. The use of noninvasive portable technologies facilitates the implementation of the clinical protocol in both hospital and primary care environments [92].

The primary findings concerning the correlations of ultrasound geometric variables with clinical and functional variables align with existing clinical literature [17,35,36,41]. These preliminary results are encouraging, demonstrating robust correlations between echo geometric parameters, measured in a standardized manner, and various clinical parameters. Notably, moderate correlations are observed between ultrasound geometrical parameters and muscle mass (DXA), while functional parameters and global scales of sarcopenia and frailty exhibit weak yet significant associations. These results serve as a

foundational baseline for the development of advanced models based on raw data (Table 1) and blood biomarkers. It is anticipated that these advanced models will exhibit superior correlations with basal characteristics and enhanced sensitivity to changes in muscle quality.

Comparison With Prior Work

Recent literature indicates that impaired mobility associated with aging is not solely attributed to changes in skeletal muscle mass; other factors contributing to muscle quality also play a crucial role. Notably, alterations in muscle tissue composition, characterized by elevated levels of intramuscular adipose tissue and intramyocellular lipids, have been identified as factors that negatively impact muscle functional capacity [17,65,93]. Our hypothesis suggests that quantitative ultrasound biomarkers derived from raw data may exhibit superior discriminative performance, greater reproducibility, and enhanced ease of use compared with the current state-of-the-art assessments based on B-mode images. B-mode morphological ultrasound parameters are primarily linked to muscle mass and demonstrate limited sensitivity in the diagnosis of sarcopenia. Quantitative ultrasound biomarkers derived from raw data have consistently demonstrated their ability to capture both tissue composition and microstructural properties. Furthermore, they have exhibited a greater capacity to encode richer information content compared with ultrasound B-mode images in artificial intelligence models, as highlighted in prior research [52,54,83,84]. Ultrasound spectroscopy parameters and tissue acoustic properties, such as speed of sound and attenuation, have been associated with tissue composition [47] and viscoelastic changes in muscle [49] among older individuals with sarcopenia. Specifically, speed of sound has demonstrated correlations with MRI adiposity estimates in the calf muscles [94], CT assessment of the psoas muscle [95], and short-term changes in muscle due to immobilization [96]. The ultrasound statistical analysis of the envelope signal in soft tissues has been correlated with the concentration, spacing, and directionality of microstructural scatterers [78]. Additionally, texture features derived from radiomics analysis capture musculoskeletal composition and microstructure. This approach has been successfully applied to differentiate various musculoskeletal conditions, including muscle spasticity, dynapenia, myositis, fibromyalgia, Duchenne muscular dystrophy, and exercise-induced muscle damage [55,97]. Being acquired at the early stages of ultrasound image formation, ultrasound raw data may play a crucial role in minimizing equipment- and operator-dependent bias. Additionally, they have the potential to provide data-based guidance for examiners with limited sonographic acquisition expertise.

Molecular biomarkers obtained from blood assays are linked to functional changes between healthy individuals and those with frailty. However, the absence of single established predictor biomarkers is primarily attributed to several factors. These include the heterogeneity and limitations of the scales or indices used to detect sarcopenia and frailty; variations in age, sex, and characteristics across different populations; small sample sizes; limited longitudinal clinical studies; a lack of characterization on interventions to assess their potential reversibility; and differences in techniques and cut-offs used for biomarker measurement. In this study, we incorporate a panel of biomarkers rather than assessing individual molecules. This approach is aimed at providing a more comprehensive reflection of the accumulation of damage associated with age-related syndromes [98]. Additionally, the potential of these biomarkers to assess reversibility, a critical characteristic of frailty, will be evaluated upon completion of an intervention based on an exercise program, followed by a 16-week follow-up.

Sarcopenia and frailty, although related, are distinct aging phenotypes. Notably, the prevalence of sarcopenia is higher among older individuals with frailty than the prevalence of frailty among those with sarcopenia [28-32]. As part of our exploratory outcomes, we will consider the coexistence of sarcopenia and frailty, redefining the frailty prognosis based on the presence or absence of sarcopenia.

To the best of our knowledge, this cohort study stands out as one of the few that integrates raw data ultrasound measurements with blood samples to extract noninvasive biomarkers of frailty and sarcopenia in older adults. Notably, this study represents the first of its kind to establish a connection between quantitative ultrasound and blood biomarkers with the cross-sectional evaluation of frailty and sarcopenia in both hospital and primary care environments. The utilization of point-of-care ultrasound devices presents an opportunity to introduce ultrasound quantitative technology across various clinical settings. Notably, this study marks the pioneering effort to combine quantitative ultrasound with blood-based biomarkers to evaluate musculoskeletal changes following multicomponent physical exercise programs.

Limitations

The study does have certain limitations, notably the absence of access to a gold standard for muscle quality assessment. Established radiological techniques such as CT and MRI serve as references for muscle composition and microstructure but come with patient complications and are not widely accessible in the clinical environments under investigation. Instead, we rely on a multifactorial clinical assessment, patient stratification, and carefully controlled interventions to evaluate changes in muscle quality. The exploration of ultrasound technology is limited to backscattering ultrasound data derived from beamformed raw data. Other ultrasound quantitative technologies, such as shear wave elastography [43] and blood flow measurements based on Doppler sequences [99], are excluded from the scope because of their lack of routine availability in point-of-care ultrasound devices and the added complexity they introduce to the protocol execution. The disparate monitoring periods in hospital (16 weeks) and primary care environments (1 year) are designed to accommodate the distinct follow-up workflows in both settings. We also acknowledge that the randomization of populations in the secondary goal is conducted on an institutional basis, which could introduce statistical bias if the populations in the 2 institutions differ. To address this potential bias, we will perform a *post hoc* analysis to examine the characteristics of the populations in the various recruitment centers. The dimensioning of the primary care follow-up aligns with periods established in previous studies for the general population [89,90].

Conclusions

In summary, the outlined study protocol aims to integrate portable technologies, leveraging quantitative muscle ultrasound and blood-based biomarkers, for an objective cross-sectional assessment of muscle quality in both hospital and primary care environments. The study endeavors to yield data that will facilitate the exploration of associations between biomarker combinations and the cross-sectional clinical evaluation of frailty and sarcopenia, alongside an examination of musculoskeletal changes following multicomponent physical exercise programs.

Acknowledgments

This project has received a public grant for its development in the call for RIS3 Basque Government Health Department (project number 2021333036). NV received a University of Deusto grant from the researcher education program (reference ID FPI UD_2022_10). DM-P received a Sara Borrell postdoctoral fellowship from the Institute of Health Carlos III (CD21/00117). The funders had no role in the design of this study and will not have any role during its execution, analyses, interpretation of data, or submission of outcomes. As part of grant specifications, yearly reports are submitted to the funding institution. As part of IRB specifications, auditing may be performed by the ethics committee during the study.

Availability of Data and Materials

The outcomes of this study will be disseminated through publication in an academic journal. Additionally, we plan to organize at least two interdisciplinary workshops involving geriatrics and imaging specialists. To promote transparency and encourage further research, digitalized data sets, comprising ultrasound data and biomarkers, digitized blood-based biomarkers, and multifactorial clinical evaluations, will be published in open-access repositories such as Zenodo. Biological samples will be securely stored at the Basque Biomarker Center (Biobanco). Furthermore, software models derived from ultrasound raw data will be made accessible through open-source software repositories such as GitLab.

Authors' Contributions

SJS and A Coca contributed to the study conceptualization. XR, NV, A Coca, and SJS contributed to the writing of the original draft. XR, NV, RGM, A Coca, RAC, A Costa-Grille, UL, MS, LA, DLI, and SJS contributed to the manuscript review and revisions. PAS, LRM, IV, DLI, A Coca, and SJS contributed to the project administration. XR, NV, GA, RGM, AAC, RAC, EBCZ, EGJ, PAS, LRM, A Coca, DM-P, AM, IV, A Costa-Grille, and SJS contributed to the methodology, investigation, and data acquisition. RG, AAC, EBCZ, and EGJ contributed to the data curation. PAS, LRM, A Coca, DLI, and SJS contributed to the study supervision. All authors have read, provided feedback, and agreed to the final version of the manuscript for publication. Authorship will be decided before publication depending on the researchers' contributions to the specific manuscripts.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items of the Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 315 KB - resprot_v13i1e50325_app1.pdf]

References

1. Roser M, Ortiz-Ospina E, Ritchie H. Life expectancy. Our World in Data. 2013. URL: https://ourworldindata.org/life-expectancy/ [accessed 2024-01-30]
2. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. Cell 2013 Jun 06;153(6):1194-1217 [FREE Full text] [doi: 10.1016/j.cell.2013.05.039] [Medline: 23746838]
3. Marengoni A, Angleman S, Melis R, Mangialasche F, Karp A, Garmen A, et al. Aging with multimorbidity: a systematic review of the literature. Ageing Res Rev 2011 Sep;10(4):430-439. [doi: 10.1016/j.arr.2011.03.003] [Medline: 21402176]
4. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001 Mar 01;56(3):M146-M156. [doi: 10.1093/gerona/56.3.m146] [Medline: 11253156]
5. Rodríguez-Laso A, Caballero Mora MA, García Sánchez I, Alonso Bouzón C, Rodríguez Mañas L, Bernabei R, et al. Updated state of the art report on the prevention and management of frailty. Advantageja. 2019. URL: https://www.advantageja.eu/images/SoAR-AdvantageJA_Fulltext.pdf [accessed 2024-01-30]
6. Hoogendijk EO, Romero L, Sánchez-Jurado PM, Flores Ruano T, Viña J, Rodríguez-Mañas L, et al. A new functional classification based on frailty and disability stratifies the risk for mortality among older adults: the FRADEA study. J Am Med Dir Assoc 2019 Sep;20(9):1105-1110. [doi: 10.1016/j.jamda.2019.01.129] [Medline: 30853426]

7. Kojima G. Frailty as a predictor of future falls among community-dwelling older people: a systematic review and meta-analysis. J Am Med Dir Assoc 2015 Dec;16(12):1027-1033. [doi: 10.1016/j.jamda.2015.06.018] [Medline: 26255098]
8. Kojima G, Iliffe S, Jivraj S, Walters K. Association between frailty and quality of life among community-dwelling older people: a systematic review and meta-analysis. J Epidemiol Community Health 2016 Jul 18;70(7):716-721. [doi: 10.1136/jech-2015-206717] [Medline: 26783304]
9. Kojima G. Frailty as a predictor of hospitalisation among community-dwelling older people: a systematic review and meta-analysis. J Epidemiol Community Health 2016 Jul 01;70(7):722-729. [doi: 10.1136/jech-2015-206978] [Medline: 26933121]
10. Kojima G. Frailty as a predictor of nursing home placement among community-dwelling older adults: a systematic review and meta-analysis. J Geriatr Phys Ther 2018;41(1):42-48. [doi: 10.1519/JPT.0000000000000097] [Medline: 27341327]
11. Kojima G. Increased healthcare costs associated with frailty among community-dwelling older people: a systematic review and meta-analysis. Arch Gerontol Geriatr 2019;84:103898. [doi: 10.1016/j.archger.2019.06.003] [Medline: 31228673]
12. García-Nogueras I, Aranda-Reneo I, Peña-Longobardo LM, Oliva-Moreno J, Abizanda P. Use of health resources and healthcare costs associated with frailty: the FRADEA study. J Nutr Health Aging 2017 Apr 22;21(2):207-214. [doi: 10.1007/s12603-016-0727-9] [Medline: 28112778]
13. Chen X, Mao G, Leng S. Frailty syndrome: an overview. CIA 2014 Mar:433. [doi: 10.2147/cia.s45300]
14. Faller JW, Pereira DDN, de Souza S, Nampo FK, Orlandi FDS, Matumoto S. Instruments for the detection of frailty syndrome in older adults: a systematic review. PLoS One 2019 Apr 29;14(4):e0216166 [FREE Full text] [doi: 10.1371/journal.pone.0216166] [Medline: 31034516]
15. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. ScientificWorldJournal 2001 Aug 08;1:323-336 [FREE Full text] [doi: 10.1100/tsw.2001.58] [Medline: 12806071]
16. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005 Aug 30;173(5):489-495 [FREE Full text] [doi: 10.1503/cmaj.050051] [Medline: 16129869]
17. Bartley JM, Studenski SA. Muscle ultrasound as a link to muscle quality and frailty in the clinic. J Am Geriatr Soc 2017 Dec 07;65(12):2562-2563. [doi: 10.1111/jgs.15075] [Medline: 28884786]
18. Landi F, Calvani R, Cesari M, Tosato M, Martone AM, Bernabei R, et al. Sarcopenia as the biological substrate of physical frailty. Clin Geriatr Med 2015 Aug;31(3):367-374. [doi: 10.1016/j.cger.2015.04.005] [Medline: 26195096]
19. Cruz-Jentoft AJ, Landi F, Schneider SM, Zúñiga C, Arai H, Boirie Y, et al. Prevalence of and interventions for sarcopenia in ageing adults: a systematic review. Report of the International Sarcopenia Initiative (EWGSOP and IWGS). Age Ageing 2014 Nov 21;43(6):748-759 [FREE Full text] [doi: 10.1093/ageing/afu115] [Medline: 25241753]
20. Cruz-Jentoft A, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, Writing Group for the European Working Group on Sarcopenia in Older People 2 (EWGSOP2),the Extended Group for EWGSOP2. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 2019 Jan 01;48(1):16-31 [FREE Full text] [doi: 10.1093/ageing/afy169] [Medline: 30312372]
21. Bhasin S, Travison TG, Manini TM, Patel S, Pencina KM, Fielding RA, et al. Sarcopenia definition: the position statements of the Sarcopenia Definition and Outcomes Consortium. J Am Geriatr Soc 2020 Jul 09;68(7):1410-1418. [doi: 10.1111/jgs.16372] [Medline: 32150289]
22. Studenski S, Peters K, Alley D, Cawthon P, McLean R, Harris T, et al. The FNIH sarcopenia project: rationale, study description, conference recommendations, and final estimates. J Gerontol A Biol Sci Med Sci 2014 May;69(5):547-558 [FREE Full text] [doi: 10.1093/gerona/glu010] [Medline: 24737557]
23. Gonzalez MC, Barbosa-Silva TG, Heymsfield SB. Bioelectrical impedance analysis in the assessment of sarcopenia. Curr Opin Clin Nutr Metab Care 2018 Sep;21(5):366-374. [doi: 10.1097/MCO.0000000000000496] [Medline: 29957677]
24. Huber FA, Del Grande F, Rizzo S, Guglielmi G, Guggenberger R. MRI in the assessment of adipose tissues and muscle composition: how to use it. Quant Imaging Med Surg 2020 Aug;10(8):1636-1649 [FREE Full text] [doi: 10.21037/qims.2020.02.06] [Medline: 32742957]
25. Giraudo C, Cavaliere A, Lupi A, Guglielmi G, Quaia E. Established paths and new avenues: a review of the main radiological techniques for investigating sarcopenia. Quant Imaging Med Surg 2020 Aug;10(8):1602-1613 [FREE Full text] [doi: 10.21037/qims.2019.12.15] [Medline: 32742955]
26. Grimm A, Nickel MD, Chaudry O, Uder M, Jakob F, Kemmler W, et al. Feasibility of Dixon magnetic resonance imaging to quantify effects of physical training on muscle composition-A pilot study in young and healthy men. Eur J Radiol 2019 May;114:160-166. [doi: 10.1016/j.ejrad.2019.03.019] [Medline: 31005168]
27. Sergi G, Trevisan C, Veronese N, Lucato P, Manzato E. Imaging of sarcopenia. Eur J Radiol 2016 Aug;85(8):1519-1524. [doi: 10.1016/j.ejrad.2016.04.009] [Medline: 27117135]
28. Davies B, García F, Ara I, Artalejo FR, Rodriguez-Mañas L, Walter S. Relationship between sarcopenia and frailty in the Toledo Study of Healthy Aging: a population based cross-sectional study. Journal of the American Medical Directors Association 2018 Apr;19(4):282-286. [doi: 10.1016/j.jamda.2017.09.014] [Medline: 29079029]

29. Reijnierse EM, Trappenburg MC, Blauw GJ, Verlaan S, de van der Schueren MA, Meskers CG, et al. Common ground? The concordance of sarcopenia and frailty definitions. J Am Med Dir Assoc 2016 Apr 01;17(4):371.e7-371.12. [doi: 10.1016/j.jamda.2016.01.013] [Medline: 26922807]
30. Mijnarends DM, Schols JM, Meijers JM, Tan FE, Verlaan S, Luiking YC, et al. Instruments to assess sarcopenia and physical frailty in older people living in a community (care) setting: similarities and discrepancies. J Am Med Dir Assoc 2015 Apr;16(4):301-308. [doi: 10.1016/j.jamda.2014.11.011] [Medline: 25530211]
31. Nishiguchi S, Yamada M, Fukutani N, Adachi D, Tashiro Y, Hotta T, et al. Differential association of frailty with cognitive decline and sarcopenia in community-dwelling older adults. J Am Med Dir Assoc 2015 Mar;16(2):120-124 [FREE Full text] [doi: 10.1016/j.jamda.2014.07.010] [Medline: 25244957]
32. Spira D, Buchmann N, Nikolov J, Demuth I, Steinhagen-Thiessen E, Eckardt R, et al. Association of low lean mass with frailty and physical performance: a comparison between two operational definitions of sarcopenia–data from the Berlin Aging Study II (BASE-II). J Gerontol A Biol Sci Med Sci 2015 Jun 31;70(6):779-784. [doi: 10.1093/gerona/glu246] [Medline: 25638537]
33. Casas-Herrero Á, Sáez de Asteasu ML, Antón-Rodrigo I, Sánchez-Sánchez JL, Montero-Odasso M, Marín-Epelde I, et al. Effects of Vivifrail multicomponent intervention on functional capacity: a multicentre, randomized controlled trial. J Cachexia Sarcopenia Muscle 2022 Apr 11;13(2):884-893 [FREE Full text] [doi: 10.1002/jcsm.12925] [Medline: 35150086]
34. Oviedo-Briones M, Laso ?, Carnicero JA, Cesari M, Grodzicki T, Gryglewska B, et al. A comparison of frailty assessment instruments in different clinical and social care settings: the Frailtools Project. J Am Med Dir Assoc 2021 Mar;22(3):607.e7-607.e12. [doi: 10.1016/j.jamda.2020.09.024] [Medline: 33162359]
35. Patil P, Dasgupta B. Role of diagnostic ultrasound in the assessment of musculoskeletal diseases. Therapeutic Advances in Musculoskeletal 2012 Apr 23;4(5):341-355. [doi: 10.1177/1759720x12442112]
36. Sconfienza LM, Albano D, Allen G, Bazzocchi A, Bignotti B, Chianca V, et al. Clinical indications for musculoskeletal ultrasound updated in 2017 by European Society of Musculoskeletal Radiology (ESSR) consensus. Eur Radiol 2018 Dec 06;28(12):5338-5351. [doi: 10.1007/s00330-018-5474-3] [Medline: 29876703]
37. Perkisas S, Baudry S, Bauer J, Beckwée D, De Cock A, Hobbelen H, et al. Application of ultrasound for muscle assessment in sarcopenia: towards standardized measurements. Eur Geriatr Med 2018 Dec 17;9(6):739-757. [doi: 10.1007/s41999-018-0104-9] [Medline: 34674473]
38. Ramírez-Fuentes C, Mínguez-Blasco P, Ostiz F, Sánchez-Rodríguez D, Messaggi-Sartor M, Macías R, et al. Ultrasound assessment of rectus femoris muscle in rehabilitation patients with chronic obstructive pulmonary disease screened for sarcopenia: correlation of muscle size with quadriceps strength and fat-free mass. Eur Geriatr Med 2019 Mar 14;10(1):89-97. [doi: 10.1007/s41999-018-0130-7] [Medline: 32720275]
39. López Jiménez E, Neira Álvarez M, Ramírez Martín R, Alonso Bouzón C, Amor Andrés MS, Bermejo Boixareu C, et al. "Sarcopenia Measured by Ultrasound in Hospitalized Older Adults" (ECOSARC): multi-centre, prospective observational study protocol. BMC Geriatr 2023 Mar 22;23(1):163 [FREE Full text] [doi: 10.1186/s12877-023-03891-5] [Medline: 36949412]
40. Ticinesi A, Meschi T, Narici MV, Lauretani F, Maggio M. Muscle ultrasound and sarcopenia in older individuals: a clinical perspective. J Am Med Dir Assoc 2017 Apr 01;18(4):290-300. [doi: 10.1016/j.jamda.2016.11.013] [Medline: 28202349]
41. Benton E, Liteplo AS, Shokoohi H, Loesche MA, Yacoub S, Thatphet P, et al. A pilot study examining the use of ultrasound to measure sarcopenia, frailty and fall in older patients. Am J Emerg Med 2021 Aug;46:310-316. [doi: 10.1016/j.ajem.2020.07.081] [Medline: 33041131]
42. Harris-Love MO, Monfaredi R, Ismail C, Blackman MR, Cleary K. Quantitative ultrasound: measurement considerations for the assessment of muscular dystrophy and sarcopenia. Front Aging Neurosci 2014 Jul 14;6:172 [FREE Full text] [doi: 10.3389/fnagi.2014.00172] [Medline: 25071570]
43. Özçakar L, Ata AM, Kaymak B, Kara M, Kumbhare D. Ultrasound imaging for sarcopenia, spasticity and painful muscle syndromes. Curr Opin Support Palliat Care 2018 Sep;12(3):373-381. [doi: 10.1097/SPC.0000000000000354] [Medline: 29912727]
44. Matsumoto H, Tanimura C, Tanishima S, Hagino H. Association between speed of sound of calcaneal bone assessed by quantitative ultrasound and sarcopenia in a general older adult population: a cross-sectional study. J Orthop Sci 2019 Sep;24(5):906-911. [doi: 10.1016/j.jos.2019.01.003] [Medline: 30733130]
45. Sanabria SJ, Martini K, Freystätter G, Ruby L, Goksel O, Frauenfelder T, et al. Speed of sound ultrasound: a pilot study on a novel technique to identify sarcopenia in seniors. Eur Radiol 2019 Jan 15;29(1):3-12. [doi: 10.1007/s00330-018-5742-2] [Medline: 30324383]
46. Ou L, Chang Y, Chang C, Chiu C, Chao T, Sun Z, et al. Epidemiological survey of the feasibility of broadband ultrasound attenuation measured using calcaneal quantitative ultrasound to predict the incidence of falls in the middle aged and elderly. BMJ Open 2017 Jan 09;7(1):e013420 [FREE Full text] [doi: 10.1136/bmjopen-2016-013420] [Medline: 28069623]
47. Berger G. Correlation between ultrasound attenuation in muscle and pathological fatty infiltration. Ultrasonic Imaging 1987 Jan;9(1):66. [doi: 10.1016/0161-7346(87)90054-x]
48. Shore D, Miles C. Experimental estimation of the viscous component of ultrasound attenuation in suspensions of bovine skeletal muscle myofibrils. Ultrasonics 1988 Jan;26(1):31-36. [doi: 10.1016/0041-624x(88)90046-7] [Medline: 3336920]

49. Thomson H, Yang S, Cochran S. Machine learning-enabled quantitative ultrasound techniques for tissue differentiation. J Med Ultrason (2001) 2022 Oct 15;49(4):517-528 [FREE Full text] [doi: 10.1007/s10396-022-01230-6] [Medline: 35840774]
50. Weng W, Lin C, Shen H, Chang C, Tsui P. Instantaneous frequency as a new approach for evaluating the clinical severity of Duchenne muscular dystrophy through ultrasound imaging. Ultrasonics 2019 Apr;94:235-241. [doi: 10.1016/j.ultras.2018.09.004] [Medline: 30287072]
51. Paris MT, Mourtzakis M. Muscle composition analysis of ultrasound images: a narrative review of texture analysis. Ultrasound Med Biol 2021 Apr;47(4):880-895. [doi: 10.1016/j.ultrasmedbio.2020.12.012] [Medline: 33451817]
52. Shin Y, Yang J, Lee YH, Kim S. Artificial intelligence in musculoskeletal ultrasound imaging. Ultrasonography 2021 Jan;40(1):30-44 [FREE Full text] [doi: 10.14366/usg.20080] [Medline: 33242932]
53. Zhang Y, Du G, Zhan Y, Guo K, Zheng Y, Tang L, et al. Muscle atrophy evaluation via radiomics analysis using ultrasound images: a cohort data study. IEEE Trans Biomed Eng 2022 Oct;69(10):3163-3174. [doi: 10.1109/tbme.2022.3162223]
54. Liu P, Wei T, Ching CT. Quantitative ultrasound texture analysis to assess the spastic muscles in stroke patients. Applied Sciences 2020 Dec 22;11(1):11. [doi: 10.3390/app11010011]
55. Yang K, Liao Y, Chang K, Huang K, Han D. The quantitative skeletal muscle ultrasonography in elderly with dynapenia but not sarcopenia using texture analysis. Diagnostics (Basel) 2020 Jun 12;10(6):400 [FREE Full text] [doi: 10.3390/diagnostics10060400] [Medline: 32545558]
56. Álvarez-Satta M, Berna-Erro A, Carrasco-Garcia E, Alberro A, Saenz-Antoñanzas A, Vergara I, et al. Relevance of oxidative stress and inflammation in frailty based on human studies and mouse models. Aging (Albany NY) 2020 May 27;12(10):9982-9999 [FREE Full text] [doi: 10.18632/aging.103295] [Medline: 32461379]
57. Cardoso AL, Fernandes A, Aguilar-Pimentel JA, de Angelis MH, Guedes JR, Brito MA, et al. Towards frailty biomarkers: candidates from genes and pathways regulated in aging and age-related diseases. Ageing Res Rev 2018 Nov;47:214-277 [FREE Full text] [doi: 10.1016/j.arr.2018.07.004] [Medline: 30071357]
58. Kwak JY, Hwang H, Kim S, Choi JY, Lee S, Bang H, et al. Prediction of sarcopenia using a combination of multiple serum biomarkers. Sci Rep 2018 Jun 05;8(1):8574 [FREE Full text] [doi: 10.1038/s41598-018-26617-9] [Medline: 29872072]
59. Picca A, Calvani R, Cesari M, Landi F, Bernabei R, Coelho-Júnior HJ, et al. Biomarkers of physical frailty and sarcopenia: coming up to the place? Int J Mol Sci 2020 Aug 06;21(16):5635 [FREE Full text] [doi: 10.3390/ijms21165635] [Medline: 32781619]
60. Duan X, Wang B, Zhu J, Shao W, Wang H, Shen J, et al. Assessment of patient-based real-time quality control algorithm performance on different types of analytical error. Clin Chim Acta 2020 Dec;511:329-335. [doi: 10.1016/j.cca.2020.10.006] [Medline: 33127347]
61. Gomez-Cabrero D, Walter S, Abugessaisa I, Miñambres-Herraiz R, Palomares LB, Butcher L, FRAILOMIC initiative. A robust machine learning framework to identify signatures for frailty: a nested case-control study in four aging European cohorts. Geroscience 2021 Jun 18;43(3):1317-1329 [FREE Full text] [doi: 10.1007/s11357-021-00334-0] [Medline: 33599920]
62. Fragala MS, Jajtner AR, Beyer KS, Townsend JR, Emerson NS, Scanlon TC, et al. Biomarkers of muscle quality: N-terminal propeptide of type III procollagen and C-terminal agrin fragment responses to resistance exercise training in older adults. J Cachexia Sarcopenia Muscle 2014 Jun 07;5(2):139-148 [FREE Full text] [doi: 10.1007/s13539-013-0120-z] [Medline: 24197815]
63. He L, Khanal P, Morse CI, Williams A, Thomis M. Associations of combined genetic and epigenetic scores with muscle size and muscle strength: a pilot study in older women. J Cachexia Sarcopenia Muscle 2020 Dec 15;11(6):1548-1561 [FREE Full text] [doi: 10.1002/jcsm.12585] [Medline: 33058541]
64. Fuentes-Abolafio IJ, Ricci M, Bernal-López MR, Gómez-Huelgas R, Cuesta-Vargas AI, Pérez-Belmonte LM. Biomarkers and the quadriceps femoris muscle architecture assessed by ultrasound in older adults with heart failure with preserved ejection fraction: a cross-sectional study. Aging Clin Exp Res 2022 Oct 08;34(10):2493-2504 [FREE Full text] [doi: 10.1007/s40520-022-02189-7] [Medline: 35939260]
65. Correa-de-Araujo R, Harris-Love MO, Miljkovic I, Fragala MS, Anthony BW, Manini TM. The need for standardized assessment of muscle quality in skeletal muscle function deficit and other aging-related muscle dysfunctions: a symposium report. Front Physiol 2017 Feb 15;8:87 [FREE Full text] [doi: 10.3389/fphys.2017.00087] [Medline: 28261109]
66. Wang J, Wu W, Chang K, Chen L, Chi S, Kara M, et al. Ultrasound imaging for the diagnosis and evaluation of sarcopenia: an umbrella review. Life (Basel) 2021 Dec 22;12(1):9 [FREE Full text] [doi: 10.3390/life12010009] [Medline: 35054402]
67. Izquierdo M. [Multicomponent physical exercise program: Vivifrail]. Nutr Hosp 2019 Jul 01;36(Spec No2):50-56. [doi: 10.20960/nh.02680] [Medline: 31189323]
68. Valenzuela PL, Morales JS, Castillo-García A, Mayordomo-Cava J, García-Hermoso A, Izquierdo M, et al. Effects of exercise interventions on the functional status of acutely hospitalised older adults: a systematic review and meta-analysis. Ageing Res Rev 2020 Aug;61:101076. [doi: 10.1016/j.arr.2020.101076] [Medline: 32330558]
69. Singh B, Hayes SC, Spence RR, Steele ML, Millet GY, Gergele L. Exercise and colorectal cancer: a systematic review and meta-analysis of exercise safety, feasibility and effectiveness. Int J Behav Nutr Phys Act 2020 Sep 24;17(1):122 [FREE Full text] [doi: 10.1186/s12966-020-01021-7] [Medline: 32972439]

70. Wang X, Ji X. Sample size estimation in clinical research: from randomized controlled trials to observational studies. Chest 2020 Jul;158(1S):S12-S20. [doi: 10.1016/j.chest.2020.03.010] [Medline: 32658647]
71. Mamou J, Oelze ML. Quantitative Ultrasound in Soft Tissues. Cham, Switzerland: Springer; 2013.
72. Jabbar SI, Day C, Chadwick E. Automated measurements of morphological parameters of muscles and tendons. Biomed Phys Eng Express 2021 Jan 06;7(2):025002. [doi: 10.1088/2057-1976/abd3de]
73. Liu S, Wang Y, Yang X, Lei B, Liu L, Li SX, et al. Deep learning in medical ultrasound analysis: a review. Engineering 2019 Apr;5(2):261-275. [doi: 10.1016/j.eng.2018.11.020]
74. Roy B, Darras BT, Zaidman CM, Wu JS, Kapur K, Rutkove SB. Exploring the relationship between electrical impedance myography and quantitative ultrasound parameters in Duchenne muscular dystrophy. Clin Neurophysiol 2019 Apr;130(4):515-520 [FREE Full text] [doi: 10.1016/j.clinph.2019.01.018] [Medline: 30772764]
75. Young H, Jenkins NT, Zhao Q, Mccully KK. Measurement of intramuscular fat by muscle echo intensity. Muscle Nerve 2015 Dec 07;52(6):963-971 [FREE Full text] [doi: 10.1002/mus.24656] [Medline: 25787260]
76. Nillesen MM, Lopata RG, Gerrits IH, Kapusta L, Thijssen JM, de Korte CL. Modeling envelope statistics of blood and myocardium for segmentation of echocardiographic images. Ultrasound Med Biol 2008 Apr;34(4):674-680. [doi: 10.1016/j.ultrasmedbio.2007.10.008] [Medline: 18096305]
77. Harris-Love MO, Gonzales TI, Wei Q, Ismail C, Zabal J, Woletz P, et al. Association Between Muscle Strength and Modeling Estimates of Muscle Tissue Heterogeneity in Young and Old Adults. J Ultrasound Med 2019 Jul 12;38(7):1757-1768 [FREE Full text] [doi: 10.1002/jum.14864] [Medline: 30548644]
78. Dubois GJ, Bachasson D, Lacourpaille L, Benveniste O, Hogrel J. Local texture anisotropy as an estimate of muscle quality in ultrasound imaging. Ultrasound Med Biol 2018 May;44(5):1133-1140 [FREE Full text] [doi: 10.1016/j.ultrasmedbio.2017.12.017] [Medline: 29428167]
79. Matta TTD, Pereira WCDA, Radaelli R, Pinto RS, Oliveira LFD. Texture analysis of ultrasound images is a sensitive method to follow-up muscle damage induced by eccentric exercise. Clin Physiol Funct Imaging 2018 May 07;38(3):477-482. [doi: 10.1111/cpf.12441] [Medline: 28589670]
80. Papadacci C, Tanter M, Pernot M, Fink M. Ultrasound backscatter tensor imaging (BTI): analysis of the spatial coherence of ultrasonic speckle in anisotropic soft tissues. IEEE Trans Ultrason Ferroelect Freq Contr 2014 Jun;61(6):986-996. [doi: 10.1109/tuffc.2014.2994]
81. Kari M, Feltovich H, Hall TJ. Correlation length ratio as a parameter for determination of fiber-like structures in soft tissues. Phys Med Biol 2021 Mar 24;66(5):055017 [FREE Full text] [doi: 10.1088/1361-6560/abe0fb] [Medline: 33508818]
82. Burlina P, Billings S, Joshi N, Albayda J. Automated diagnosis of myositis from muscle ultrasound: exploring the use of machine learning and deep learning methods. PLoS One 2017 Aug 30;12(8):e0184059 [FREE Full text] [doi: 10.1371/journal.pone.0184059] [Medline: 28854220]
83. Brausch L, Hewener H, Lukowicz P. Towards a wearable low-cost ultrasound device for classification of muscle activity and muscle fatigue. 2019 Sep Presented at: the 23rd International Symposium on Wearable Computers, ISWC ?19. ?22; 2019; London p. 20. [doi: 10.1145/3341163.3347749]
84. Sanabria SJ, Pirmoazen AM, Dahl J, Kamaya A, El Kaffas A. Comparative study of raw ultrasound data representations in deep learning to classify hepatic steatosis. Ultrasound Med Biol 2022 Oct;48(10):2060-2078. [doi: 10.1016/j.ultrasmedbio.2022.05.031] [Medline: 35914993]
85. Polidori MC, Mecocci P. Modeling the dynamics of energy imbalance: the free radical theory of aging and frailty revisited. Free Radic Biol Med 2022 Mar;181:235-240. [doi: 10.1016/j.freeradbiomed.2022.02.009] [Medline: 35151828]
86. Fernández-Torrón R, García-Puga M, Emparanza J, Maneiro M, Cobo A, Poza J, et al. Cancer risk in DM1 is sex-related and linked to miRNA-200/141 downregulation. Neurology 2016 Sep 20;87(12):1250-1257. [doi: 10.1212/wnl.0000000000003124]
87. Alberro A, Iribarren-Lopez A, Sáenz-Cuesta M, Matheu A, Vergara I, Otaegui D. Inflammaging markers characteristic of advanced age show similar levels with frailty and dependency. Sci Rep 2021 Mar 23;11(1):4358 [FREE Full text] [doi: 10.1038/s41598-021-83991-7] [Medline: 33623057]
88. Stewart A. Basic Statistics and Epidemiology: A Practical Guide. 4th ed. Boca Raton, FL: CRC Press (Taylor & Francis Group); 2016.
89. Checa-López M, Oviedo-Briones M, Pardo-Gómez A, Gonzales-Turín J, Guevara-Guevara T, Carnicero JA, FRAILTOOLS consortium. FRAILTOOLS study protocol: a comprehensive validation of frailty assessment tools to screen and diagnose frailty in different clinical and social settings and to provide instruments for integrated care in older adults. BMC Geriatr 2019 Mar 18;19(1):86 [FREE Full text] [doi: 10.1186/s12877-019-1042-1] [Medline: 30885132]
90. Chicoulaa B, Escourrou E, Durrieu F, Milon V, Savary L, Gelibert M, et al. Challenges in management of frailty by primary healthcare teams: from identification to follow-up. La Presse Médicale Open 2022;3:100032. [doi: 10.1016/j.lpmope.2022.100032]
91. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013 Nov 27;310(20):2191-2194 [FREE Full text] [doi: 10.1001/jama.2013.281053] [Medline: 24141714]

92. Ponti F, De Cinque A, Fazio N, Napoli A, Guglielmi G, Bazzocchi A. Ultrasound imaging, a stethoscope for body composition assessment. Quant Imaging Med Surg 2020 Aug;10(8):1699-1722 [FREE Full text] [doi: 10.21037/qims-19-1048] [Medline: 32742962]
93. Newman AB, Kupelian V, Visser M, Simonsick EM, Goodpaster BH, Kritchevsky SB, et al. Strength, but not muscle mass, is associated with mortality in the health, aging and body composition study cohort. J Gerontol A Biol Sci Med Sci 2006 Jan 01;61(1):72-77. [doi: 10.1093/gerona/61.1.72] [Medline: 16456196]
94. Ruby L, Kunut A, Nakhostin DN, Huber FA, Finkenstaedt T, Frauenfelder T, et al. Speed of sound ultrasound: comparison with proton density fat fraction assessed with Dixon MRI for fat content quantification of the lower extremity. Eur Radiol 2020 Oct 08;30(10):5272-5280. [doi: 10.1007/s00330-020-06885-8] [Medline: 32385650]
95. Ruby L, Sanabria SJ, Saltybaeva N, Frauenfelder T, Alkadhi H, Rominger MB. Comparison of ultrasound speed-of-sound of the lower extremity and lumbar muscle assessed with computed tomography for muscle loss assessment. Medicine 2021;100(21):25947. [doi: 10.1097/md.0000000000025947]
96. Ruby L, Sanabria SJ, Martini K, Frauenfelder T, Jukema GN, Goksel O. Quantification of immobilization-induced changes in human calf muscle using speed-of-sound ultrasound: an observational pilot study. Medicine 2021;100(11):2356. [doi: 10.1097/md.0000000000023576]
97. Wong V, Spitz RW, Bell ZW, Viana RB, Chatakondi RN, Abe T, et al. Exercise induced changes in echo intensity within the muscle: a brief review. J Ultrasound 2020 Dec 10;23(4):457-472 [FREE Full text] [doi: 10.1007/s40477-019-00424-y] [Medline: 31925731]
98. Mitnitski A, Collerton J, Martin-Ruiz C, Jagger C, von Zglinicki T, Rockwood K, et al. Age-related frailty and its association with biological markers of ageing. BMC Med 2015 Jul 13;13:161 [FREE Full text] [doi: 10.1186/s12916-015-0400-x] [Medline: 26166298]
99. Holloszy JO, McCully KK, Posner JD. The Application of Blood Flow Measurements to the Study of Aging Muscle. J Gerontol A Biol Sci Med Sci 1995 Nov 01;50 Spec No(Special):130-136. [doi: 10.1093/gerona/50a.special_issue.130] [Medline: 7493206]

Abbreviations

CT: computed tomography
DOCS: Definition and Outcomes Consortium
DXA: dual-energy X-ray absorptiometry
EDTA: ethylenediaminetetraacetic acid
EWGSOP-2: European Working Group on Sarcopenia in Older People 2
FRAIL: short 5-question assessment of Fatigue, Resistance, Aerobic capacity, Illnesses, and Loss of weight
GAPDH: glyceraldehyde-3-phosphate dehydrogenase
HIPAA: Health Insurance Portability and Accountability Act
MRI: magnetic resonance imaging
NIHF: National Institute of Health Foundation
PCR: polymerase chain reaction
SARC-F: Strength, Assistance with walking, Rising from a chair, Climbing stairs, and Falls
SPIRIT: Standard Protocol Items of the Recommendations for Interventional Trials
SPPB: Short Physical Performance Battery
sRAGE: soluble receptor for advanced glycation end products (sRAGE)

Edited by A Mavragani; submitted 12.09.23; peer-reviewed by F Lauretani, LK Chen; comments to author 04.12.23; revised version received 11.12.23; accepted 02.01.24; published 23.02.24.

Please cite as:
Virto N, Río X, Angulo-Garay G, García Molina R, Avendaño Céspedes A, Cortés Zamora EB, Gómez Jiménez E, Alcantud Córcoles R, Rodriguez Mañas L, Costa-Grille A, Matheu A, Marcos-Pérez D, Lazcano U, Vergara I, Arjona L, Saeteros M, Lopez-de-Ipiña D, Coca A, Abizanda Soler P, Sanabria SJ
Development of Continuous Assessment of Muscle Quality and Frailty in Older Patients Using Multiparametric Combinations of Ultrasound and Blood Biomarkers: Protocol for the ECOFRAIL Study
JMIR Res Protoc 2024;13:e50325
URL: https://www.researchprotocols.org/2024/1/e50325
doi:10.2196/50325
PMID:38393761

Protocol

Effectiveness of a Serious Video Game (MOON) for Attention Deficit Hyperactivity Disorder: Protocol for a Randomized Clinical Trial

Marina Martin-Moratinos[1,2], MSc; Marcos Bella-Fernández[1,3,4], MSc; Maria Rodrigo-Yanguas[2], PhD; Carlos González-Tardón[5], PhD; Aaron Sújar[6], PhD; Chao Li[1,2], MSc; Ping Wang[1,2], MSc; Ana Royuela[7], PhD; Pilar Lopez-Garcia[2,8], MD, PhD; Hilario Blasco-Fontecilla[1,2,8,9,10], MD, PhD

[1]Department of Psychiatry, Puerta de Hierro University Hospital, Health Research Institute Puerta de Hierro-Segovia de Arana, Majadahonda, Madrid, Spain, Spain

[2]Faculty of Medicine, Autonoma University of Madrid, Madrid, Spain

[3]Faculty of Psychology, Autonoma University of Madrid, Madrid, Spain

[4]Department of Psychology, Pontifical University of Comillas, Madrid, Spain

[5]Tecnocampus – Universitat Pompeu Fabra, Mataro, Spain

[6]Department of Computer Engineering, Universidad Rey Juan Carlos, Móstoles, Madrid, Spain

[7]Clinical Biostatistics Unit, Consortium for Biomedical Research Network in Epidemiology and Public Health, Madrid, Spain

[8]Spain Biomedical Research Networking Center for Mental Health Network, Madrid, Spain

[9]ITA Center Mental Health Specialists, Madrid, Spain

[10]Health Sciences School and Medical Center, Universidad Internacional de La Rioja, Madrid, Spain

Corresponding Author:
Hilario Blasco-Fontecilla, MD, PhD
Department of Psychiatry
Puerta de Hierro University Hospital
Health Research Institute Puerta de Hierro-Segovia de Arana
Avenida Manuel de Falla 1
Majadahonda, Madrid, Spain, 28222
Spain
Phone: 34 911916019
Email: hmblasco@yahoo.es

Abstract

Background: Attention deficit hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder in childhood and adolescence, with a prevalence of 5% and associated difficulties and worse prognosis if undetected. Multimodal treatment is the treatment of choice. However, sometimes treatment can be insufficient or have drawbacks.

Objective: This study protocol aims to demonstrate the effectiveness of cognitive training through the serious video game The Secret Trail of Moon (MOON) in improving emotional regulation in people with ADHD.

Methods: This is a prospective, unicenter, randomized, unblinded, pre- and postintervention study. The groups will be randomized (MOON vs control) via an electronic case report form. The MOON intervention will be performed 2 times per week for 10 weeks (30 minutes per session). The first 5 weeks (10 sessions) will be conducted face-to-face at the Puerta de Hierro University Hospital, and the remaining weeks will be conducted via the internet at the participants' homes. The total sample consists of 152 patients aged between 7 and 18 years. All participants have a clinical diagnosis of ADHD under pharmacological treatment. Data collection will be used to obtain demographic and clinical data. The data will be recorded using REDCap. Measures will be made through clinical scales for parents and objective tests of cognitive functioning in patients. Additional information on academic performance will be collected. The study has a power greater than 80% to detect differences. Student *t* test, 2-factor analysis of variance (ANOVA), and Mann-Whitney analyses will be performed according to each variable's characteristics.

Results: The study was approved by the Research Ethics Committee of the Puerta de Hierro University Hospital on December 14, 2022. As of September 26, 2023, we have enrolled 62 participants, and 31 participants have completed the study. This clinical trial was funded by the Comunidad de Madrid (IND2020/BMD-17544). The approximate completion date is March 2024.

Conclusions: Serious video games such as MOON can be motivational tools that complement multimodal treatment for ADHD.

Trial Registration: ClinicalTrials.gov; NCT06006871; https://clinicaltrials.gov/study/NCT06006871

International Registered Report Identifier (IRRID): DERR1-10.2196/53191

(JMIR Res Protoc 2024;13:e53191) doi:10.2196/53191

KEYWORDS

attention deficit hyperactivity disorder; ADHD; emotional dysregulation; serious video games; virtual reality; cognitive training; music; chess; attention deficit hyperactivity disorder; video game; video games; children; child; adolescents; adolescent; teen; teens; emotional regulation; neurodevelopmental disorder; multimodal treatment; intervention; motivational tools

Introduction

Attention deficit hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder diagnosed in childhood and adolescence, affecting about 5% of people worldwide [1]. In addition to the classical clinical triad of ADHD (inattention, hyperactivity, and impulsivity) [2], the existence of comorbidity, executive dysfunction, or emotional dysregulation can complicate the prognosis [3]. A greater severity of ADHD symptoms is correlated with greater emotional dysregulation in both children [4] and adults [5]. Emotion regulation involves intrinsic and extrinsic processes responsible for managing the appraisal and control of emotional reactions, emotion intensity, temporality, and goal orientation [6]. Emotional dysregulation has a severe impact on social skills, academic performance, and adaptive skills, leading to a higher rate of usage of treatment services [4]. This impact on emotional regulation manifests diversely across broad age ranges in ADHD from children to adults [7-9]. Emotional regulation issues, even in patients aged 5 years and younger, predict inattention later on [10]. Guidelines recommend that emotional dysregulation be treated before the age of 7 years [11]. ADHD is considered a chronic disorder with a high economic cost [12,13], high accident rate, and increased risk of mortality [14].

Multimodal treatment is the most effective treatment for ADHD, and it encompasses pharmacological treatment, psychological treatment, and psychoeducation for parents and teachers. Pharmacological treatment is the treatment of choice in children and adolescents with severe ADHD [15] and the most common treatment in high-income countries [16]. Approximately 70% of patients observe a positive change in symptoms in the short term due to stimulants [17]. However, some drawbacks such as the side effects of pharmacological treatment (insomnia, appetite suppression, and growth retardation) make some parents reluctant [18]. Moreover, medication is more effective for the core symptoms of ADHD than for the bottom-up mechanisms associated with emotional regulation [19]. Cognitive behavioral therapy can help with social skills and problem-solving [20]. However, motivational difficulties in ADHD [3] and low adherence to treatment [18] have led to the development of additional interventions complementing multimodal treatments. Some studies show promising results with cognitive training [21], metacognitive interventions [22], music [23], and video games [24]. However, the overall results show small effect sizes and difficulties in maintaining long-term benefits and transferability to daily life (generalizability and transferability) [25]. More evidence is needed with greater control of risk biases.

Video games provide immersive and engaging entertainment experiences. They have been extended as tools in the field of health (eg, promoting physical exercise through exergames) to others for cognitive training, as discussed in the reviews by Peñuelas-Calvo et al [24] and Rodrigo-Yanguas et al [26]. In particular, a recent systematic review [27] showed the potential use of video games in improving emotional regulation. Using video games for ADHD treatment may be beneficial for several reasons, including their attractiveness, customization to suit the player's tastes, and immediate reinforcement [28]. Children and adolescents with ADHD have difficulties associated with poor verbal working memory (poor internal language), which can make it difficult for them to perform tasks. In addition, they may be more dependent on external stimuli (ie, they may have low intrinsic motivation), causing them to become bored earlier [3]. Therapeutic interventions based on gamification and video games can be a good strategy to decrease treatment dropout rates by encouraging patients to perform tasks as games.

The Secret Trail of Moon (MOON) is a serious video game based on cognitive training for people with ADHD. It comprises a set of different mini-games focused on enhancing the most affected cognitive abilities in ADHD according to the Executive Functions and Behavioral Inhibition Model [3,29,30]. The games progressively increase in difficulty according to the patient's needs. MOON was designed by a multidisciplinary team following a user-centered model (usability study) and an iterative redesign process [28,31]. Prior to this clinical trial, we completed another clinical trial. In that prospective, single-center, randomized clinical trial with 3 arms, MOON was tested in clinically stable patients with ADHD (on medication) aged 12 to 22 years (NCT04355065) for 3 months. The 105 patients were randomly assigned to the 3 groups: (1) cognitive training (12 sessions) with face-to-face MOON (n=31; 30); (2) cognitive training with online therapeutic chess (n=24; 23); and (3) control group with telephone monitoring (n=34; 32%). Contrary to our expectations, we did not find any statistically significant improvement in executive functioning, which was the primary outcome. However, we found some improvements in secondary outcomes, such as emotional intelligence, emotional regulation, and performance in the school context in both self-reports and parent reports [32]. Following these encouraging results, we designed the present clinical trial (NCT06006871) with the limitations of the previous clinical trial in mind, namely: (1) increasing sample size; (2) increasing the number of cognitive "doses" (20 sessions) and the access to the platform using virtual reality (VR) and computer interfaces; (3) improving some aspects of the MOON video

game, particularly emotional regulation, such as the aesthetics of the virtual environment, the introduction of music [23], rhythm-based gameplay, and motivational elements such as the reward system; and (4) simplifying the design (2 arms, case versus control, instead of 3 arms). The main objective is to test the efficacy of MOON in improving emotional regulation in patients aged 7 to 18 years with a clinical diagnosis of ADHD.

Methods

Ethical Considerations

This study was approved by the Research Ethics Committee of the Puerta de Hierro University Hospital on December 14, 2022 (PI 106/22). Authorization from the Spanish Agency of Medicines and Health Products was granted on February 14, 2023 (1061/22/EC-R). Informed consent will be requested from legal guardians and minors protecting their personal data to the provisions of the Organic Law (3/2018) passed on December 5, 2018, regarding personal data protection and guarantee of digital rights.

The Spanish Agency of Medicines and Medical Devices (AEMPS) authorized the clinical research with medical devices lacking Conformité Européenne (CE) marking on February 14, 2023 (1061/22/EC-R). The version approved by both entities was version 4 in the protocol, data collection, and recruitment material. The investigator's brochure was approved in version 3. The ethics committee requested the elimination of the rhythm-based game because it has not been previously tested in patients with ADHD. Monitoring of the clinical trial was deemed necessary.

Study Design

This is a prospective, unicentric, randomized, unblinded, pre- and postintervention study with a concealed randomization sequence. The groups will be randomized (MOON vs control) via an electronic case report form (CRF). The interventional study model is a parallel assignment. The allocation ratio will be equal in both groups.

Procedure

All participants will be recruited from the child and adolescent psychiatry outpatient clinics of Hospital Universitario Puerta de Hierro Majadahonda. The number of visits varies in each group—the MOON group will have 12 face-to-face visits, while the control group will have only 2 presential visits. The total duration of the research will be 90 days in total (3 months for each participant: 12 weeks including both the pre- and postevaluation periods; Figure 1). Table 1 summarizes all the visits.

Figure 1. Duration of the research. MOON: The Secret Trail of Moon; SDQ: Strengths and Difficulties Questionnaire.

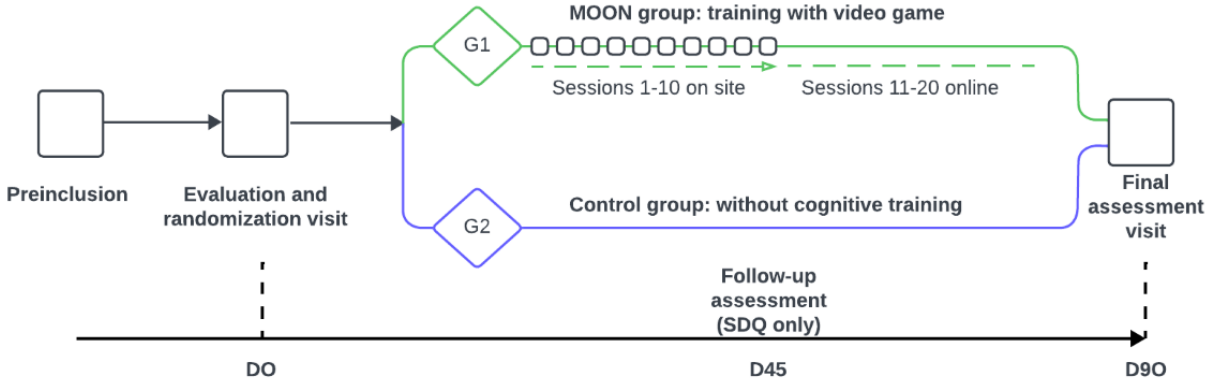


Table 1. Study flow.

Visit and day	Preinclusion (D1)	Inclusion (D0)	Training (D1-D90)	Final (D90)
Explanation protocol	✓			
CGI[a] (clinical)	✓			
Randomization		✓		
Informed consent		✓		
Data collection note		✓		
CGI (parents)		✓		✓
SDQ[b] (parents)		✓	✓	✓
CPRS-HI[c] (parents)		✓		✓
SNAP-IV[d] (parents)		✓		✓
SDSC[e] (parents)		✓		✓
BRIEF-2[f] (parents)		✓		✓
CPT-3[g] (patients)		✓		✓
Corsi cubes (patients)		✓		✓
CTMT-2[h] (patients)		✓		✓
GASA[i] (patients)		✓		✓
Academic mark		✓		✓
UKU[j] (patients)			✓	
Satisfaction questionnaire				✓

[a]CGI: Clinical Global Impression Scale.
[b]SDQ: Strengths and Difficulties Questionnaire.
[c]CPRS-HI: Conners Abbreviated Symptom Questionnaire.
[d]SNAP-IV: Swanson, Nolan, and Pelham Rating Scale.
[e]SDSC: Sleep Disturbance Scale for Children for Parents
[f]BRIEF-2: Behavior Rating Inventory Executive Function, Version 2.
[g]CPT-3: Conners Continuous Performance Test, Third Edition.
[h]CTMT-2: Comprehensive Trail-Making Test, Second Edition.
[i]GASA: Game Addiction Scale for Adolescents.
[j]UKU: Udvalg für Kliniske Undersolgester.

For the MOON group, the total number of sessions with the video game will be 20 (twice a week, adjusted according to the availability of the participants). Participants in the MOON group aged 12 years and over will perform the video game sessions in VR, while those under 12 years will perform the video game sessions on a computer. All participants in the MOON group will perform the cognitive training with MOON following the same order of the games reflected in Table 2. Each session will have a maximum duration of 30 minutes (approximately 20 minutes of MOON gameplay). The first 10 sessions will be held in person at the hospital. For participants over 12 years of age, the researchers will help to manually calibrate the eye distance of the VR headset to adjust the quality of vision. For those under 12 years of age, researchers will perform computer-based support to ensure proper use and understanding of the video game tasks. The researcher will explain the task, adapting the instructions to each participant's age. Once the researcher is assured of the understanding of the task, the difficulty level will be raised in a personalized way for each participant. Progress is signaled to the player by leveling up, parameters (eg, hits, errors, time taken), and stars earned (0 star=poor performance, must repeat the level; 1 star=acceptable performance; 2 stars=good performance; 3 stars=excellent) (Figures 2 and 3).

Table 2. Gameplay order by sessions.

Mode	Onsite at the hospital										At participants' homes									
Sessions	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Games																				
Smasher		1	2				1		2			1			2		1		2	
Kuburi		2		1		2			1	2				1		1		2		
Teka-Teki	1			2		1		2			1	2							1	2
Enigma	2				1		2			1			2		1	2				1
Chess			1		2			1			2		1	2			2	1		

Figure 2. The Secret Trail of Moon (MOON) progress.

Figure 3. The star system in The Secret Trail of Moon (MOON).

Parents in session 10 will receive a flash drive with the video game and training on how to use it at home. The last 10 sessions will take place at the participants' homes on their computers and will be monitored via the internet by the researchers. Data collected in the game (eg, completed levels, hits, errors, or reaction times) will be automatically sent to the PlayFab (Microsoft Corp) data server. The parents of MOON group participants will be asked in advance to provide their consent for the collection of these data.

For the control group, participants will be followed up with weekly calls to parents during this period. During this follow-up, psychoeducational support about ADHD will be provided to the parents.

Hypothesis

Our main hypothesis is that patients with ADHD using MOON will improve their emotional regulation more than the control group. The efficacy will be evaluated by measuring the change produced from the baseline evaluation (day 0) and the final evaluation visit (day 90), aiming for a decrease of 3 to 4 points in the global score of the Strengths and Difficulties Questionnaire (SDQ) filled by the patient's parents.

As secondary hypotheses, the difference with the control group in measures such as ADHD core symptomatology, cognitive abilities, and academic performance will be assessed. Our secondary hypotheses are listed in Textbox 1.

Textbox 1. Secondary hypotheses of the study.

- H2: Patients with Attention deficit hyperactivity disorder (ADHD) using The Secret Trail of Moon (MOON) video game will improve in core ADHD symptoms compared with the control group.
- H3: Patients with ADHD using MOON will improve their cognitive functioning compared to the control group.
- H4: Patients with ADHD using MOON will improve in academic performance with respect to the control group.
- H5: A change in platform (face-to-face, internet) will not entail differences in emotional regulation.
- H6: There will be no clinically meaningful side effects associated with the video game.

Participants

Sample

A total of 152 patients (76 cases versus 76 controls) with a clinical diagnosis of ADHD according to the DSM-V (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) will be enrolled. All participants will have a clinical diagnosis of ADHD, take ADHD medication, be clinically stable, and have a Clinical Global Impression (CGI) score between 3 and 6 before entering the trial. Medication will not change during the investigation unless changes are required for clinical reasons. A 15% loss rate is expected. The inclusion and exclusion criteria are summarized in Textbox 2.

Textbox 2. Participant inclusion and exclusion criteria.

Inclusion criteria:

- Age 7 to 17 years (may turn 18 during the study)
- Clinical diagnosis of attention deficit hyperactivity disorder (ADHD) in any presentation
- Taking pharmacological treatment for ADHD
- Ability to follow verbal instructions
- Ability to play a video game (not necessary to play regularly)
- Clinically stable, with ADHD symptomatology severity based on a clinician-assessed Clinical Global Impression (CGI) score between 3 and 6

Exclusion criteria:

- Patients with severe symptoms (> or equal to 5 CGI) or very mild symptoms (CGI < or equal to 1)
- Patient at risk of suicide (according to the clinical judgment of the professional in charge of the patient)
- Motor difficulties that prevent playing the video game
- Participation in other similar studies
- Intention to initiate any psychotherapeutic treatment (including cognitive-behavioral therapy) in the next 3 months of the course of participation in the clinical trial

Randomization and Masking

To warrant clinical trial randomization, a random block sequence of 76 “1” (experimental) and 76 “2” (control) in 4 blocks of 38 numbers (19 “1” and 19 “2”) will be generated using the R program (R Foundation for Statistical Computing) by author MBF [33]. The sequence will be unknown to the recruiters [34].

In the preinclusion phase, patients will be informed about the research by the principal investigator (author HBF) and their suitability will be assessed according to the inclusion and exclusion criteria (Textbox 2). Subsequently, another author (MMM) will explain the research procedure in detail and summon the prerecruited participants. Once the consent form is signed, they will be randomly assigned by blocks using the electronic CRF with a ratio of 1:1. Randomization of the groups (MOON vs control) will be performed by the electronic CRF REDCap.

Materials

Hardware

Materials to be used for this study include the video game (MOON) itself, VR goggles, PlayStation 4 (Sony Group Corp) controllers, test consoles, monitor screens, and headsets. The VR software runs on a PlayStation 4 test device (Figure 4). A computer with an internet connection will also be used in this study to ensure the proper transmission of game data to the PlayFab server.

Figure 4. User playing The Secret Trail of Moon (MOON).

Software: Video Game

MOON has been designed to be a therapeutic cognitive training video game for patients with ADHD. This serious video game can be used both on a computer and s PlayStation 4 VR console. The use of VR allows a more focused approach to the task and a greater impact on the participants' motivation. The use of a computer allows more accessibility. The game is set in a natural environment, potentially beneficial for people with ADHD with animals that accompany the player throughout the training session [25]. Various games or tasks are incorporated into the game design with the purpose of training the most affected cognitive functions in ADHD. MOON has 5 game mechanics. These are as follows: (1) SMASHER (sustained attention and inhibitory control) is a task based on the Continuous Performance Test, Third Version (CPT-3) [35], with a 2-item sequence similar to Sustained Attention Task in Childhood Test (CSAT) [36]; (2) in TEKATEKI (planning), the participant is asked to perform a minimum number of possible movements (based on the *Tower of Hanoi*); (3) in ENIGMA (working memory), the *span* of items to remember increases according to the difficulty curve [37]; (4) KUBURI (visuospatial ability) is a 3D cube rotation task; and (5) CHESS (reasoning) consists of tasks related to the rules of chess.

Psychometric Assessments

Preinclusion

CGI Scale for Clinicians

Symptom severity will be measured with the CGI scale [38] (approximately 1-minute duration). ADHD symptomatology severity based on clinician-assessed CGI score (between 3 and 6) for the inclusion criteria.

Clinical Anamnesis

The clinical anamnesis includes demographic, clinical, school, and medical history data.

SDQ For Parents

The SDQ has 25 items (approximately a 5-minute duration) [39]. It measures (1) emotional symptoms, (2) behavioral challenges, (3) hyperactivity, (4) conflicts/issues with peers, and (5) prosocial behavior. A decrease of 3 to 4 points in the postassessment visit (D70) concerning the preassessment visit (D0) will be considered an improvement in emotional regulation.

The Swanson, Nolan, and Pelham Rating Scale for Parents

The main ADHD symptomatology (inattention, hyperactivity, impulsivity) will be measured using subjective scales for parents. The Swanson, Nolan, and Pelham Rating Scale (SNAP-IV) is an 18-item questionnaire for assessing ADHD symptoms [40,41]. It has a Likert scale ranging from 0 to 4 (approximately 5 minutes long), among which 9 items assess attention deficit

and the other 9 items assess hyperactive impulsive component. The cut-off point for attention deficit is 1.78 for parents. For hyperactivity-impulsivity, the cut-off point is 1.44 for parents.

The Conners Abbreviated Symptom Questionnaire for Parents

The Conners Abbreviated Symptom Questionnaire (CPRS-HI) helps assess patients with ADHD [42,43]. It is a 10-item questionnaire with a Likert scale of 0 to 3 (approximately 2 minutes long). This revised and abbreviated version of the Conners scale is designed to be answered by parents of children aged 6 to 18 years. It contains Likert-type responses (0= not true at all/never; 1= just a little true/occasionally; 2= Pretty much true/often; 3=very much true/very often). The cut-off points are divided by sex. For boys, a score above 16 is suspected ADHD, while for girls, a suspected diagnosis of ADHD is above 12 points.

CGI for Parents

Symptom severity will be measured with the CGI adapted for parents (approximately 1-minute duration) consisting of a "thermometer" with a Likert scale ranging between 1 and 10 [44].

Behavior Rating Inventory Executive Function 2 Questionnaire for Parents

The Behavior Rating Inventory Executive Function, Version 2 (BRIEF-2) is a questionnaire designed to evaluate executive functions in children and adolescents [45]. It consists of 63 items with 3 answer options (never, sometimes, and frequently). Its correction provides 4 general indices: emotional regulation, cognitive regulation, behavioral regulation, and global index of executive function. It also provides 2 second-order factors and a general index.

CPT-3 for Patients with ADHD

The CPT-3 is a screening task for ADHD in addition to measuring sustained attention, impulse control, and processing speed [35]. It is a computerized, standardized, and validated application test for different age and gender groups. The task consists of pressing a button each time a letter (target) appears on the screen, except for the letter X (nontarget), which must not be pressed. The duration is 14 minutes, and the presentation interval between letters varies (1, 2, and 4 seconds). The test provides results on hits, errors of omission (undetected target) or commission (reacted nontarget), which are considered a measure of impulsivity. In addition, CPT3-3 provides information on hit mean reaction time and variability.

Sleep Disturbance Scale for Children for Parents

The Sleep Disturbance Scale for Children (SDSC) is a 26-item questionnaire with a Likert scale ranging between 1 and 5 (1: never; 5: always). It has an approximate duration of 5 minutes [46].

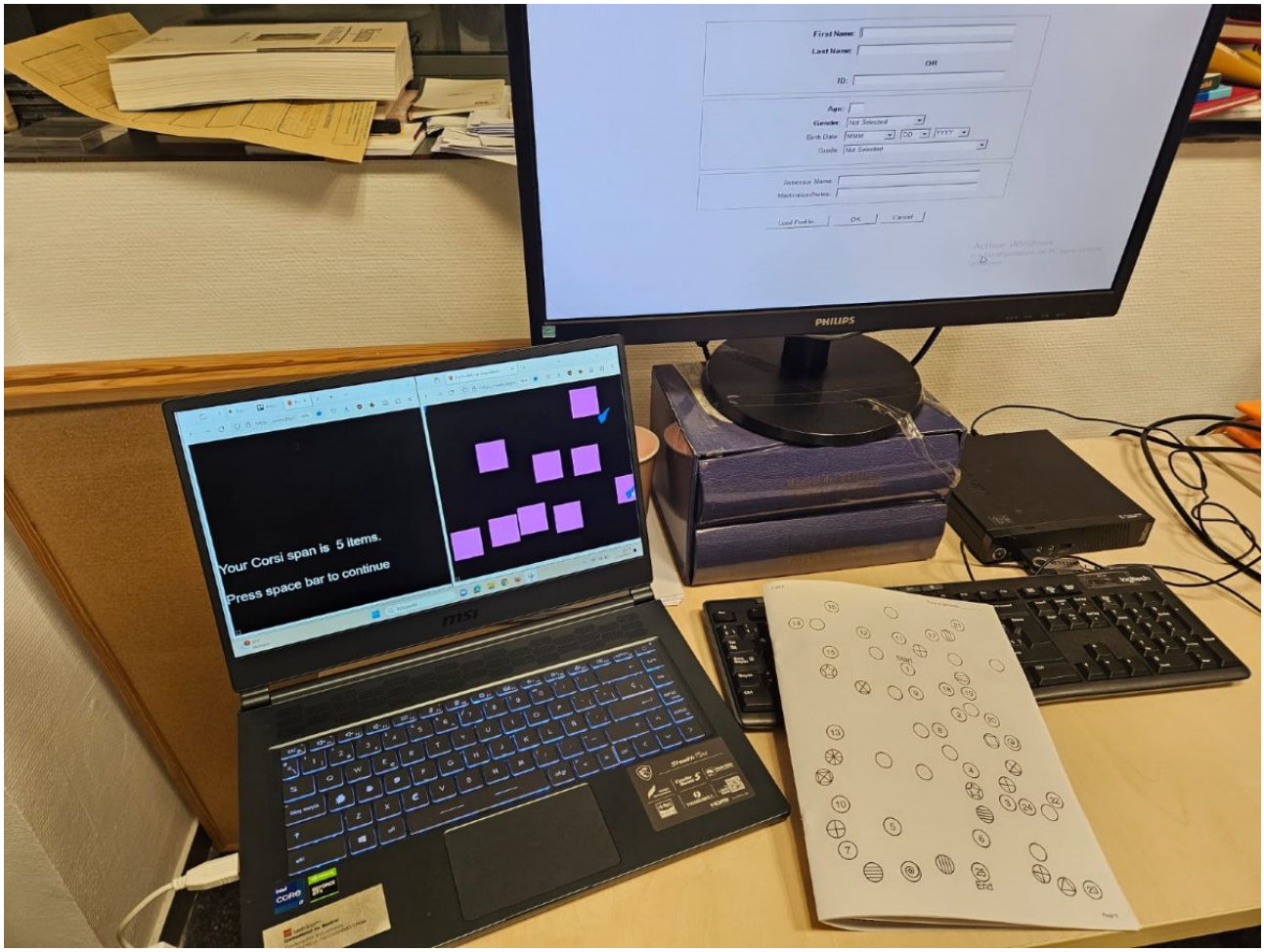
Corsi Cubes for Patients With ADHD

Corsi cubes are used to measure visuospatial working memory [37,47].

Comprehensive Trail-Making Test, Second Edition for Patients With ADHD

The Comprehensive Trail-Making Test, Second Edition (CTMT-2) is used to measure cognitive flexibility, with 3 indexes: inhibitory control, task switching, and total index (Figure 5) [48].

Figure 5. Psychometric assessments: Corsi Cubes, Continuous Performance Test, Third Version (CPT-3), and Comprehensive Trail-Making Test, Second Edition (CTMT-2).



Udvalg für Kliniske Undersogelser for Patients With ADHD

Udvalg für Kliniske Undersogelser (UKU) is a tool designed to evaluate possible secondary symptoms that happen during the week [49]. This scale is not included in the assessment phases. Only the participants playing VR will have to complete the scale after each cognitive training session.

Game Addiction Scale for Adolescents

The Game Addiction Scale for Adolescents (GASA) is a 7-item questionnaire to assess video game addiction [50,51].

Academic Performance

Information about academic performance will be obtained via the patients' grades.

Interventions

After the initial evaluation, 2 groups randomized by blocks will be formed. Group 1 (MOON) will receive personalized cognitive training with a video game in person and via the internet. Psychoeducational support on ADHD to parents will be provided during the research (n=76; 50%).

Group 2 (control) will receive the usual pharmacological treatment (without cognitive training intervention). Psychoeducational support on ADHD will be provided to the parents during the research (n=76; 50%).

Analyses

Sample Size Calculation

Based on similar investigations with hypotheses that are centered around the administration of the SDQ [52], our sample size calculation shows the need to perform the study on approximately 152 participants with a diagnosis of ADHD to cover most of the possibilities with a Cronbach α of 0.05 and a statistical power of 80%, taking into account a 15% dropout rate. We performed the sample size calculation to contrast a mean in the control group of 11 points on the SDQ global score versus a 2-point mean drop (symptomatologic improvement) in the experimental group with a pooled SD of 4. This estimate covers other less conservative situations, such as a difference of up to 4 points.

Study Population

The intention-to-treat (ITT) analysis population is defined as participants who are randomized and receive at least 10 sessions, and the per-protocol population is defined as participants who will complete 100% of the training. All analyses will be performed on the premise of the ITT analysis.

A 2-way analysis of variance (ANOVA) will be performed, with time (pre and post) and group (experimental vs control)

as factors and each measure as dependent variable. The difference between the study groups will be considered significant when P<.05.

Demographic and Baseline Characteristics

A data collection notebook will be used to obtain demographic and clinical data. The data will be recorded with electronic CRF (REDCap). Measures to answer the hypotheses will be made through clinical scales for parents and objective tests of cognitive abilities in patients. Additional information on academic performance will be collected.

Primary End Point Analysis

The main objective is to test the efficacy of the cognitive training treatment (MOON) in improving emotional regulation in patients aged 7 to 18 years who have a clinical diagnosis of ADHD. The effectiveness is evaluated by measuring the change produced between the baseline evaluation (day 0) and the final evaluation visit (day 90) in the decrease of 3 to 4 points in the global SDQ score evaluated by the parents. A decrease of 3 to 4 points on the postassessment visit (D70) concerning the preassessment visit (D0) will be considered an improvement in emotional regulation based on other similar studies [52].

Subsequently, 3 parent SDQ measures will be assessed: initial assessment (D0), midterm assessment (D45), and final assessment (D90) to evaluate hypothesis 5 (switching from face-to-face to web-based methods does not lead to differences in emotional regulation).

Secondary End Point Analysis

Two subjective scales will be used to assess hypothesis 2 (patients with ADHD using MOON will improve in ADHD symptomatology relative to the control group). The main ADHD symptomatology (inattention, hyperactivity, and impulsivity) will be measured with (1) SNAP, an 18-item questionnaire with a Likert scale ranging between 0 and 4 (approximately 5 minutes long) and (2) CPRS-HI, a 10-item questionnaire with a Likert scale ranging between 0 and 3 (approximately 2 minutes long). Symptom severity will be measured with the CGI adapted for parents (approximately 1-minute duration) consisting of a "thermometer" with a Likert scale ranging between 1 and 10.

Relative to hypothesis 3 (Patients with ADHD using MOON will improve their cognitive abilities more than the control group), executive dysfunction will be evaluated through subjective scales for parents and objective tests for patients. The subjective test for parents will be performed with the BRIEF-2 questionnaire. There will be three objective tests for the patients: (1) CPT-3, which is usually used to screen for ADHD in addition to measuring sustained attention, impulse control, and processing speed; (2) Corsi cubes, which are used to measure visuospatial working memory; and (3) CTMT-2, which is used to measure cognitive flexibility using 3 indexes, namely, inhibitory control, task switching, and total index.

Regarding hypothesis 4 (patients with ADHD using MOON will improve in academic performance relative to the control group), grades will be collected for each subject on the quarterly school report card immediately preceding (pre) and following (post) treatment.

Safety and Adherence Analysis

Additional measures have been taken concerning the previous clinical trial [32] to assess the occurrence of side effects. Hypothesis 6 (there will be no side effects associated with the video game) is related to this aspect. To mitigate the possibility of motion sickness due to VR use, the UKU test will be used. In the previous clinical trial, nonsignificant effects related to sleep were observed; therefore, in this clinical trial, the SDSC scale will be used to assess this symptomatology in depth. Since people with ADHD are more prone to addictive behaviors related to video games [53], two main precautions will be taken: (1) adapting the game design so as not to encourage addictive behaviors [28] and (2) collecting additional information with the GASA test.

Results

The clinical trial is funded by the Community of Madrid (2020 Industrial Doctorates IND2020/BMD-17544). The expected date of data collection was between May 2023 and January 2024. The approximate completion date is March 2024. As of September 26, 2023, we have enrolled 62 participants. A total of 31 (20%) participants completed the study. The analysis of the total results is expected to be published in May 2024.

Discussion

ADHD is a neurodevelopmental disorder with great variability. Some authors associate the symptoms of inattention with a disorder of "cool" executive function (dorsolateral prefrontal cortex pathway), while the symptoms of hyperactivity and impulsivity are associated with deficits of "hot" executive function (orbital and medial prefrontal cortex pathway) [54]. According to Gross [55,56], emotional regulation is a process whereby people modulate their emotions using strategies such as suppression, strategy modulation, or reappraisal. This process requires an interaction of executive functions with emotional regulation. In relation to these intrinsic-extrinsic processes, children with ADHD compared with typically developing children tend to overestimate their performance in different domains (social, school, and behavioral). Some authors call this term "positive illusory bias" (PIB), with consequent disparity between children's self-reports and parents' assessments [22,57].

The MOON video game was developed as a form of cognitive training to improve cognitive abilities, such as sustained attention, inhibitory control, working memory, visuospatial ability, reasoning, and planning [30,31]. However, after conducting the first clinical trial, our main hypothesis of improving executive functions measured with the BRIEF-2 test was not fulfilled [32]. Nevertheless, we did find improvements in emotional domains compared to the control group both in self-reports and parent reports (the most relevant being emotional intelligence, emotional regulation, and performance in the school context). Accordingly, in this second clinical trial, we wanted to replicate and extend our previous positive findings on different measures of emotion regulation. The global SDQ scale we used includes measurements of emotional symptoms, behavioral problems, hyperactivity, problems with peers, and prosocial behavior [39,52].

We believe that any improvement found in measures should be transferred or generalized to daily life. Thus, in this study, we will measure academic performance to assess whether the improvement in cognitive domains includes a transfer to other domains such as arithmetic or reading.

Additional measures have been adopted. Improvements have been added to make the video game more attractive (music, aesthetics, and rewards). To avoid the presence of PIB causing questionnaires to be completed by ”bad informants,” objective tasks, including CPT-3 [35], Corsi cubes [37], and CTMT-2 [48], were proposed for participants in this second clinical trial. To mitigate THE possible excessive use of video games or addiction, the video game design was controlled [28], and the GASA test will be incorporated [50,51].

However, this clinical trial has important limitations. First, a blinded study is not possible. Second, cognitive domains are difficult to measure in the absence of unified questionnaires; in fact, some laboratory measures related to executive function are moderately related to the main symptoms of ADHD and their impact on daily life. As for the video game, it was not possible to incorporate all the improvements designed. Despite the incorporation of children under 12 years of age into this clinical trial, it is possible that some difficulty levels are not well adjusted due to not having been able to perform a usability study prior to this new clinical trial. Moreover, typical of ADHD symptomatology, the decay of the video game sessions—especially those sessions conducted at home without researcher supervision—may occur. Participants could lose motivation for the treatment as the same game is played for a long time [58].

Video games can be a potential tool to improve different skills, such as emotional regulation [27]. In people with ADHD, it is especially important to incorporate motivational tools complementary to multimodal treatment that can facilitate treatment adherence.

Acknowledgments

The authors thank in advance all the staff involved in the research and the Gammera Nest company, especially Miguel Ruiz, the main programmer and composer of the game music, and the trainees who made the development of the video game possible. Special thanks are extended to all children, adolescents, and parents for their future participation in this study. This research is funded by the Comunidad de Madrid (Spain) through the Industrial Doctorate (IND2020/BMD-1755). This research was previously funded by the National Project (RTI2018-101857-B-I00 for author HBF, the Foundation for Health Innovation and Prospective in Spain (author HBF), the Center for Technological Development and Innovation (author MMM), and the Carlos III Health Institute (predoctoral contracts for training in health research for authors MRY and HBF). The Shibuya and Health Start awards also provided funding for this project.

Authors' Contributions

MMM, MBF, and HBF carried out the research. MMM and HBF will recruit the patients. MMM and MBF will perform the data collection. MMM will monitor the Calendly appointments and The Secret Trail of Moon (MOON) home training data collection via PlayFab. MMM designed the electronic case report form (REDCap) and MBF will enter the data into the program. MMM, MRY, CGT, and HBF designed the video game. AS made programming enhancements to this version of MOON. CL and PW provided research design ideas and statistical input. The sample size calculation was carried out by AR. MBF, HBF, MMM, and AR will perform the statistical analyses. PLG and HBF supervised the study.

Conflicts of Interest

Author HBF has received lecture fees from Takeda Pharmaceuticals, and the laboratories BIAL, Rubio, and Rovi. He has also been granted 3 prizes for developing the serious video to treat attention deficit hyperactivity disorder (ADHD): the Shibuya Prize by Takeda, the first prize from the College of Psychologists of Madrid, and a prize for the best innovative health initiative within the Health Start campaign. He is the principal investigator of predoctoral contracts for training in health research (IFI16/00039), the coprincipal investigator of a Ministry of Economy, Trade and Enterprise research grant (RTI2018-101857-B-I00), and the principal investigator of a Sincronia research, funded by the Start-up Bitsphi. Moreover, he is the recipient of (1) a Foundation for Innovation and Foresight in Health in Spain grant and (2) a Puerta de Hierro Segovia de Arana Institute of Health Research intensification grant and is involved in 2 clinical trials (Mensia Koala, Newrofeed study; ESKETSUI2002). He is also a cofounder of Haglaia Solutions and an employee and member of the advisory board of ITA Salud Mental (Korian).

References

1. Polanczyk GV, Salum GA, Sugaya LS, Caye A, Rohde LA. Annual research review: A meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. J Child Psychol Psychiatry 2015 Mar 03;56(3):345-365. [doi: 10.1111/jcpp.12381] [Medline: 25649325]
2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Health Disorders, 5th Edition. Washington, DC: American Psychiatric Association; 2013.
3. Barkley R. Attention-Deficit Hyperactivity Disorder: A Handbook for Diagnosis and Treatment, 4th Edition. New York, NY: Guilford Press; 2015.

4. Baykal S, Nalbantoglu A. An examination of emotion regulation and associated factors in attention deficit-hyperactivity disorder. Konuralp Medical Journal 2019;11(2):269-273. [doi: 10.18521/ktd.530900]
5. Rüfenacht E, Euler S, Prada P, Nicastro R, Dieben K, Hasler R, et al. Emotion dysregulation in adults suffering from attention deficit hyperactivity disorder (ADHD), a comparison with borderline personality disorder (BPD). Borderline Personal Disord Emot Dysregul 2019 Jul 18;6(1):11 [FREE Full text] [doi: 10.1186/s40479-019-0108-1] [Medline: 31360522]
6. Thompson RA. Emotion regulation: a theme in search of definition. Monogr Soc Res Child Dev 1994;59(2-3):25-52. [Medline: 7984164]
7. Graziano PA, Garcia A. Attention-deficit hyperactivity disorder and children's emotion dysregulation: A meta-analysis. Clin Psychol Rev 2016 Jun;46:106-123. [doi: 10.1016/j.cpr.2016.04.011] [Medline: 27180913]
8. Groves NB, Wells EL, Soto EF, Marsh CL, Jaisle EM, Harvey TK, et al. Executive functioning and emotion regulation in children with and without ADHD. Res Child Adolesc Psychopathol 2022 Jun 11;50(6):721-735 [FREE Full text] [doi: 10.1007/s10802-021-00883-0] [Medline: 34762251]
9. Christiansen H, Hirsch O, Albrecht B, Chavanon M. attention-deficit/hyperactivity disorder (ADHD) and emotion regulation over the life span. Curr Psychiatry Rep 2019 Mar 02;21(3):17. [doi: 10.1007/s11920-019-1003-6] [Medline: 30826879]
10. Brocki KC, Forslund T, Frick M, Bohlin G. Do individual differences in early affective and cognitive self-regulation predict developmental change in ADHD symptoms from preschool to adolescence? J Atten Disord 2019 Nov 01;23(13):1656-1666. [doi: 10.1177/1087054717693372] [Medline: 29254424]
11. Overgaard KR, Aase H, Torgersen S, Reichborn-Kjennerud T, Oerbeck B, Myhre A, et al. Continuity in features of anxiety and attention deficit/hyperactivity disorder in young preschool children. Eur Child Adolesc Psychiatry 2014 Sep 1;23(9):743-752 [FREE Full text] [doi: 10.1007/s00787-014-0538-7] [Medline: 24687273]
12. Doshi JA, Hodgkins P, Kahle J, Sikirica V, Cangelosi MJ, Setyawan J, et al. Economic impact of childhood and adult attention-deficit/hyperactivity disorder in the United States. J Am Acad Child Adolesc Psychiatry 2012 Oct;51(10):990-1002.e2. [doi: 10.1016/j.jaac.2012.07.008] [Medline: 23021476]
13. Holden SE, Jenkins-Jones S, Poole CD, Morgan CL, Coghill D, Currie CJ. The prevalence and incidence, resource use and financial costs of treating people with attention deficit/hyperactivity disorder (ADHD) in the United Kingdom (1998 to 2010). Child Adolesc Psychiatry Ment Health 2013 Oct 11;7(1):34 [FREE Full text] [doi: 10.1186/1753-2000-7-34] [Medline: 24119376]
14. Dalsgaard S, Østergaard SD, Leckman JF, Mortensen PB, Pedersen MG. Mortality in children, adolescents, and adults with attention deficit hyperactivity disorder: a nationwide cohort study. Lancet 2015 May;385(9983):2190-2196. [doi: 10.1016/s0140-6736(14)61684-6]
15. Faltinsen E, Zwi M, Castells X, Gluud C, Simonsen E, Storebø OJ. Updated 2018 NICE guideline on pharmacological treatments for people with ADHD: a critical look. BMJ Evid Based Med 2019 Jun;24(3):99-102. [doi: 10.1136/bmjebm-2018-111110] [Medline: 30530806]
16. Banaschewski T, Coghill D, Santosh P, Zuddas A, Asherson P, Buitelaar J, et al. [Long-acting medications for the treatment of hyperkinetic disorders - a systematic review and European treatment guidelines. Part 2: a quantitative evaluation of long-acting medications]. Z Kinder Jugendpsychiatr Psychother 2008 Mar;36(2):97-106; quiz 106 [FREE Full text] [doi: 10.1024/1422-4917.36.2.97] [Medline: 18622939]
17. Sandler AD. Practice parameter for the use of stimulant medications in the treatment of children, adolescents and adults. J Dev Behav Pediatr 2002;23(4):286-287. [doi: 10.1097/00004703-200208000-00024]
18. Toomey SL, Sox CM, Rusinak D, Finkelstein JA. Why do children with ADHD discontinue their medication? Clin Pediatr (Phila) 2012 Aug 14;51(8):763-769. [doi: 10.1177/0009922812446744] [Medline: 22584541]
19. Lenzi F, Cortese S, Harris J, Masi G. Pharmacotherapy of emotional dysregulation in adults with ADHD: A systematic review and meta-analysis. Neurosci Biobehav Rev 2018 Jan;84:359-367. [doi: 10.1016/j.neubiorev.2017.08.010] [Medline: 28837827]
20. Dalrymple RA, McKenna Maxwell L, Russell S, Duthie J. NICE guideline review: Attention deficit hyperactivity disorder: diagnosis and management (NG87). Arch Dis Child Educ Pract Ed 2020 Oct 27;105(5):289-293. [doi: 10.1136/archdischild-2019-316928] [Medline: 31776172]
21. Robledo-Castro C, Lerma-Castaño PR, Bonilla-Santos G. Effect of cognitive training programs based on computer systems on executive functions in children with ADHD: a systematic review. J Atten Disord 2023 Nov 21;27(13):1467-1487. [doi: 10.1177/10870547231187164] [Medline: 37477014]
22. Basile A, Toplak ME, Andrade BF. Using metacognitive methods to examine emotion recognition in children with ADHD. J Atten Disord 2021 Jan 16;25(2):245-257. [doi: 10.1177/1087054718808602] [Medline: 30442038]
23. Martin-Moratinos M, Bella-Fernández M, Blasco-Fontecilla H. Effects of music on attention-deficit/hyperactivity disorder (ADHD) and potential application in serious video games: systematic review. J Med Internet Res 2023 May 12;25:e37742 [FREE Full text] [doi: 10.2196/37742] [Medline: 37171837]
24. Peñuelas-Calvo I, Jiang-Lin LK, Girela-Serrano B, Delgado-Gomez D, Navarro-Jimenez R, Baca-Garcia E, et al. Video games for the assessment and treatment of attention-deficit/hyperactivity disorder: a systematic review. Eur Child Adolesc Psychiatry 2022 Jan 18;31(1):5-20. [doi: 10.1007/s00787-020-01557-w] [Medline: 32424511]

25. Rabipour S, Raz A. Training the brain: fact and fad in cognitive and behavioral remediation. Brain Cogn 2012 Jul;79(2):159-179. [doi: 10.1016/j.bandc.2012.02.006] [Medline: 22463872]
26. Rodrigo-Yanguas M, González-Tardón C, Bella-Fernández M, Blasco-Fontecilla H. Serious Video Games: Angels or Demons in Patients With Attention-Deficit Hyperactivity Disorder? A Quasi-Systematic Review. Front Psychiatry 2022 Apr 27;13:798480 [FREE Full text] [doi: 10.3389/fpsyt.2022.798480] [Medline: 35573357]
27. Villani D, Carissoli C, Triberti S, Marchetti A, Gilli G, Riva G. Videogames for emotion regulation: a systematic review. Games Health J 2018 Apr;7(2):85-99 [FREE Full text] [doi: 10.1089/g4h.2017.0108] [Medline: 29424555]
28. Sújar A, Martín-Moratinos M, Rodrigo-Yanguas M, Bella-Fernández M, González-Tardón C, Delgado-Gómez D, et al. Developing serious video games to treat attention deficit hyperactivity disorder: tutorial guide. JMIR Serious Games 2022 Aug 01;10(3):e33884 [FREE Full text] [doi: 10.2196/33884] [Medline: 35916694]
29. Brown TE. ADD/ADHD and impaired executive function in clinical practice. Curr Psychiatry Rep 2008 Oct 17;10(5):407-411. [doi: 10.1007/s11920-008-0065-7] [Medline: 18803914]
30. Rodrigo-Yanguas M, Martín-Moratinos M, Tardón C, Blasco-Fontecilla H. Virtual reality and chess. A video game for cognitive training in patients with ADHD. In: Proceedings of the VI Congreso de la Sociedad Española para las Ciencias del Videojuego. 2020 Presented at: VI Congreso de la Sociedad Española para las Ciencias del Videojuego; October 7-8; Online p. 205-215 URL: http://ceur-ws.org/Vol-2719/paper20.pdf [doi: 10.2196/preprints.39874]
31. Rodrigo-Yanguas M, Martin-Moratinos M, Menendez-Garcia A, Gonzalez-Tardon C, Royuela A, Blasco-Fontecilla H. A virtual reality game (The Secret Trail of Moon) for treating attention-deficit/hyperactivity disorder: development and usability study. JMIR Serious Games 2021 Sep 01;9(3):e26824 [FREE Full text] [doi: 10.2196/26824] [Medline: 34468332]
32. Rodrigo-Yanguas M, Martín-Moratinos M, González-Tardón C, Sanchez-Sanchez F, Royuela A, Bella-Fernández M, et al. Effectiveness of a personalized, chess-based training serious video game in the treatment of adolescents and young adults with attention-deficit/hyperactivity disorder: randomized controlled trial. JMIR Serious Games 2023 Apr 24;11:e39874 [FREE Full text] [doi: 10.2196/39874] [Medline: 37093628]
33. R: A language and environment for statistical computing. The R Project for Statistical Computing. Online; 2021. URL: https://www.R-project.org/ [accessed 2021-01-01]
34. Schulz KF, Grimes DA. Allocation concealment in randomised trials: defending against deciphering. Lancet 2002 Feb 16;359(9306):614-618. [doi: 10.1016/S0140-6736(02)07750-4] [Medline: 11867132]
35. Conners K. Conners Continuous Performance Test 3rd Edition (CPT 3). Toronto, ON: Multi-Health Systems; 2014.
36. Servera M, Llabrés J. CSAT Tarea de atención sostenida para niños. In: Hogrefe. Madrid, Spain: TEA Ediciones; 2004.
37. Corsi PM. Human Memory and the Medial Temporal Region of the Brain. Thesis. Ottawa, ON: McGill University; 1972.
38. Busner J, Targum SD. The clinical global impressions scale: applying a research tool in clinical practice. Psychiatry (Edgmont) 2007 Jul;4(7):28-37 [FREE Full text] [Medline: 20526405]
39. Goodman R. The Strengths and Difficulties Questionnaire: a research note. J Child Psychol Psychiatry 1997 Jul;38(5):581-586. [doi: 10.1111/j.1469-7610.1997.tb01545.x] [Medline: 9255702]
40. Swanson JM, Schuck S, Porter MM, Carlson C, Hartman CA, Sergeant JA, et al. Categorical and dimensional definitions and evaluations of symptoms of ADHD: history of the SNAP and the SWAN rating scales. Int J Educ Psychol Assess 2012 Apr;10(1):51-70 [FREE Full text] [Medline: 26504617]
41. Grañana N, Richaudeau A, Gorriti CR, O'Flaherty M, Scotti ME, Sixto L, et al. Assessment of attention deficit hyperactivity: SNAP-IV scale adapted to Argentina. Rev Panam Salud Publica 2011 May;29(5):344-349. [doi: 10.1590/s1020-49892011000500007] [Medline: 21709939]
42. Parker J, Sitarenios G, Conners C. Abbreviated Conners' Rating Scales revisited: A confirmatory factor analytic study. J Atten Disord 2016 Jul 26;1(1):55-62. [doi: 10.1177/108705479600100105]
43. Conners C, Sitarenios G, Parker J, Epstein J. The revised Conners' Parent Rating Scale (CPRS-R): factor structure, reliability, and criterion validity. J Abnorm Child Psychol 1998 Aug;26(4):257-268. [doi: 10.1023/a:1022602400621] [Medline: 9700518]
44. Busner J, Targum S. The clinical global impressions scale: applying a research tool in clinical practice. Psychiatry (Edgmont) 2007 Jul;4(7):28-37 [FREE Full text] [Medline: 20526405]
45. Gioia G, Isquith P, Guy S, Kenworthy L. Behavior Rating Inventory of Executive Function 2 | BRIEF2. In: Hogrefe. Online: PAR; 2017.
46. Bruni O, Ottaviano S, Guidetti V, Romoli M, Innocenzi M, Cortesi F, et al. The Sleep Disturbance Scale for Children (SDSC). Construction and validation of an instrument to evaluate sleep disturbances in childhood and adolescence. J Sleep Res 1996 Dec;5(4):251-261. [doi: 10.1111/j.1365-2869.1996.00251.x] [Medline: 9065877]
47. Kessels RPC, van Zandvoort MJE, Postma A, Kappelle LJ, de Haan EHF. The Corsi Block-Tapping task: standardization and normative data. Appl Neuropsychol 2000 Dec;7(4):252-258. [doi: 10.1207/s15324826an0704_8]
48. Reynolds. CTMT2 Comprehensive Trail Making Test, 2nd Edition. Austin, TX: PAR Inc; 2019.
49. Lingjaerde O, Ahlfors UG, Bech P, Dencker S, Elgen K. The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. Acta Psychiatr Scand Suppl 1987 Aug 23;334(s334):1-100. [doi: 10.1111/j.1600-0447.1987.tb10566.x] [Medline: 2887090]

50. Lemmens JS, Valkenburg PM, Peter J. Development and validation of a game addiction scale for adolescents. Media Psychol 2009 Mar 05;12(1):77-95. [doi: 10.1080/15213260802669458]
51. Lloret Irles D, Morell Gomis R, Marzo Campos JC, Tirado González S. Spanish validation of Game Addiction Scale for Adolescents (GASA). Aten Primaria 2018 Jun;50(6):350-358 [FREE Full text] [doi: 10.1016/j.aprim.2017.03.015] [Medline: 28939247]
52. Fenollar-Cortés J, Calvo-Fernández A, García-Sevilla J, Cantó-Díez TJ. La escala Strength and Difficulties Questionnaire (SDQ) como predictora del TDAH: comportamiento de los índices SDQ respecto a las dimensiones "hiperactividad/Impulsividad" e "inatención" en una muestra clínica. An Psicol 2016 Apr 03;32(2):313. [doi: 10.6018/analesps.32.2.203331]
53. Menéndez-García A, Jiménez-Arroyo A, Rodrigo-Yanguas M, Marin-Vila M, Sánchez-Sánchez F, Roman-Riechmann E, et al. Internet, video game and mobile phone addiction in children and adolescents diagnosed with ADHD: A case-control study. Adicciones 2022 Jul 01;34(3):208-217 [FREE Full text] [doi: 10.20882/adicciones.1469] [Medline: 33338245]
54. Castellanos FX, Sonuga-Barke EJ, Milham MP, Tannock R. Characterizing cognition in ADHD: beyond executive dysfunction. Trends Cogn Sci 2006 Mar;10(3):117-123. [doi: 10.1016/j.tics.2006.01.011] [Medline: 16460990]
55. Gross JJ. Emotion regulation: affective, cognitive, and social consequences. Psychophysiology 2002 May;39(3):281-291. [doi: 10.1017/s0048577201393198] [Medline: 12212647]
56. Gross JJ. Emotion regulation: current status and future prospects. Psychol Inq 2015 Mar 09;26(1):1-26. [doi: 10.1080/1047840X.2014.940781]
57. Hoza B, Pelham WE, Milich R, Pillow D, McBride K. The self-perceptions and attributions of attention deficit hyperactivity disordered and nonreferred boys. J Abnorm Child Psychol 1993 Jun;21(3):271-286. [doi: 10.1007/bf00917535]
58. Brilliant TD, Nouchi R, Kawashima R. Does video gaming have impacts on the brain: evidence from a systematic review. Brain Sci 2019 Sep 25;9(10):251 [FREE Full text] [doi: 10.3390/brainsci9100251] [Medline: 31557907]

Abbreviations

ADHD: attention deficit hyperactivity disorder
BRIEF-2: Behavior Rating Inventory Executive Function, Version 2
CGI: Clinical Global Impression
CPRS-HI: Conners Abbreviated Symptom Questionnaire
CPT-3: Continuous Performance Test, Third Edition
CRF: case report form
CSAT: Sustained Attention Task in Childhood Test
CTMT-2: Comprehensive Trail-Making Test, Second Edition
DSM-V: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ITT: intention to treat
MOON: The Secret Trail of Moon
PIB: positive illusory bias
SDQ: Strengths and Difficulties Questionnaire
SNAP-IV: Swanson, Nolan, and Pelham Rating Scale
VR: virtual reality

Edited by A Mavragani; submitted 28.09.23; peer-reviewed by L Winston, A Bustillo; comments to author 19.11.23; revised version received 20.12.23; accepted 11.01.24; published 23.02.24.

Please cite as:
Martin-Moratinos M, Bella-Fernández M, Rodrigo-Yanguas M, González-Tardón C, Sújar A, Li C, Wang P, Royuela A, Lopez-Garcia P, Blasco-Fontecilla H
Effectiveness of a Serious Video Game (MOON) for Attention Deficit Hyperactivity Disorder: Protocol for a Randomized Clinical Trial
JMIR Res Protoc 2024;13:e53191
URL: https://www.researchprotocols.org/2024/1/e53191
doi:10.2196/53191
PMID:38393773

Protocol

Efficacy of StepAdd, a Personalized mHealth Intervention Based on Social Cognitive Theory to Increase Physical Activity Among Patients With Type 2 Diabetes Mellitus: Protocol for a Randomized Controlled Trial

Kayo Waki[1,2,3], MD, MPH, PhD; Yuya Tsurutani[4], MD, PhD; Hironori Waki[5], MD, PhD; Syunpei Enomoto[3], MAS; Kosuke Kashiwabara[6], PhD; Akira Fujiwara[7], MD, PhD; Kazuki Orime[8], MD, PhD; Sho Kinguchi[9], MD, PhD; Toshimasa Yamauchi[2], MD, PhD; Nobuhito Hirawa[7], MD, PhD; Kouichi Tamura[9], MD, PhD; Yasuo Terauchi[10], MD, PhD; Masaomi Nangaku[11], MD, PhD; Kazuhiko Ohe[1,3], MD, PhD

[1]Department of Biomedical Informatics, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
[2]Department of Diabetes and Metabolic Diseases, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
[3]Department of Planning, Information and Management, The University of Tokyo Hospital, Tokyo, Japan
[4]Endocrinology and Diabetes Center, Yokohama Rosai Hospital, Yokohama, Japan
[5]Department of Metabolism and Endocrinology, Akita University Graduate School of Medicine, Akita, Japan
[6]Data Science Office, Clinical Research Promotion Center, The University of Tokyo Hospital, Tokyo, Japan
[7]Department of Nephrology and Hypertension, Yokohama City University Medical Center, Yokohama, Japan
[8]Department of Endocrinology and Diabetes, Yokohama City University Medical Center, Yokohama, Japan
[9]Department of Medical Science and Cardiorenal Medicine, Yokohama City University Graduate School of Medicine, Yokohama, Japan
[10]Department of Endocrinology and Metabolism, Yokohama City University Graduate School of Medicine, Yokohama, Japan
[11]Division of Nephrology and Endocrinology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Corresponding Author:
Kayo Waki, MD, MPH, PhD
Department of Biomedical Informatics
Graduate School of Medicine
The University of Tokyo
7-3-1 Hongo
Bunkyo-ku
Tokyo, 113-8655
Japan
Phone: 81 03 5800 9129
Email: kwaki-tky@m.u-tokyo.ac.jp

Abstract

Background: Increasing physical activity improves glycemic control in patients with type 2 diabetes (T2D). Mobile health (mHealth) interventions have been proven to increase exercise, but engagement often fades with time. As the use of health behavior theory in mHealth design can increase effectiveness, we developed StepAdd, an mHealth intervention based on the constructs of social cognitive theory (SCT). StepAdd improves exercise behavior self-efficacy and self-regulation through the use of goal-setting, barrier-identifying, and barrier-coping strategies, as well as automatic feedback functions. A single-arm pilot study of StepAdd among 33 patients with T2D showed a large increase in step count (mean change of 4714, SD 3638 daily steps or +86.7%), along with strong improvements in BMI (mean change of −0.3 kg/m^2) and hemoglobin A_{1c} level (mean change of −0.79 percentage points).

Objective: In this study, we aim to investigate the efficacy and safety of StepAdd, an mHealth exercise support system for patients with T2D, via a large, long, and controlled follow-up to the pilot study.

Methods: This is a randomized, open-label, multicenter study targeting 160 patients with T2D from 5 institutions in Japan with a 24-week intervention. The intervention group will record daily step counts, body weight, and blood pressure using the SCT-based mobile app, StepAdd, and receive feedback about these measurements. In addition, they will set weekly step count goals, identify

personal barriers to walking, and define strategies to overcome these barriers. The control group will record daily step counts, body weight, and blood pressure using a non–SCT-based placebo app. Both groups will receive monthly consultations with a physician who will advise patients regarding lifestyle modifications and use of the app. The 24-week intervention period will be followed by a 12-week observational period to investigate the sustainability of the intervention's effects. The primary outcome is between-group difference in the change in hemoglobin A_{1c} values at 24 weeks. The secondary outcomes include other health measures, measurements of steps, measurements of other behavior changes, and assessments of app use. The trial began in January 2023 and is intended to be completed in December 2025.

Results: As of September 5, 2023, we had recruited 44 patients. We expect the trial to be completed by October 8, 2025, with the follow-up observation period being completed by December 31, 2025.

Conclusions: This trial will provide important evidence about the efficacy of an SCT-based mHealth intervention in improving physical activities and glycemic control in patients with T2D. If this study proves the intervention to be effective and safe, it could be a key step toward the integration of mHealth as part of the standard treatment received by patients with T2D in Japan.

Trial Registration: Japan Registry of Clinical Trials (JRCT) jRCT2032220603; https://rctportal.niph.go.jp/en/detail?trial_id=jRCT2032220603

International Registered Report Identifier (IRRID): DERR1-10.2196/53514

(JMIR Res Protoc 2024;13:e53514) doi:10.2196/53514

KEYWORDS

digital therapeutics; behavior change; social cognitive theory; exercise; type 2 diabetes mellitus; mobile app; randomized controlled trial; mobile phone

Introduction

Background

Worldwide, approximately 537 million people aged between 20 and 79 years have type 2 diabetes (T2D) [1]. T2D is a serious public health concern with a considerable impact on health expenditures and human life, causing 4.2 million deaths per year [2,3]. T2D is a disease that is difficult to cure once it develops, and if left untreated, it causes complications such as cardiovascular disease and microvascular complications [4].

Exercise has been proven to improve glycemic control and other metabolic parameters, including low-density lipoprotein cholesterol, visceral adipose tissue, and blood pressure (BP) [5]. Patients with T2D are recommended to commit to a minimum of 150 minutes of moderate to vigorous physical activity per week. As walking has been rated as the most favored form of physical activity by sedentary groups, it is a suitable form of exercise for patients with T2D, who typically have low physical activity [6,7]. The recommended 150 minutes of activity translates into taking at least 7500 steps per day, of which 3000 steps should be at moderate to vigorous intensity [8]. Although physical exercise has been proven to be effective in improving blood glucose levels, reducing cardiovascular risk factors, and improving cardiorespiratory fitness in patients with T2D, lack of motivation has been reported to be a barrier [9]. It is difficult for patients to change their current exercise behavior by themselves [9]. It has also been reported that adherence to physical activities is lower than adherence to medication regimens [10].

Mobile health (mHealth) interventions such as mobile phone apps that support self-management have proven to be effective in increasing physical activity of patients [11,12] and improving glycemic control [13,14]. According to the American College of Sports Medicine, web-based fitness programs, exercise-related digital services, and use of mobile phones are becoming increasingly popular in the worldwide exercise community [15]. Recent meta-analyses found a moderate to large positive effect in daily step changes owing to the use of smartphone apps that focus on physical activities [16,17]. Although mHealth is effective, patients lose motivation to engage with the intervention after some time [18,19]. Personalization of intervention components has been shown to increase patient motivation and engagement in using the app [20]. Several studies have found that tailored interventions are more effective in changing health behavior than nontailored interventions [21,22].

Although several studies evaluating the effectiveness of personalized interventions have reported an increase in the physical activity levels of users [23,24], so far, studies generally do not use a theory-based framework with mHealth. In particular, social cognitive theory (SCT), with a human agency model in which individuals proactively self-reflect, self-regulate, and self-organize, offers a powerful framework that could support improved mHealth interventions [25,26]. SCT has been used to understand behaviors relating to physical activity owing to its emphasis on the dynamic interactions between the individual, environment, and behavior [27]. SCT-based interventions were found to be effective in changing physical activity behaviors among people with prediabetes [28].

To address this research gap, we developed a personalized smartphone-based mHealth intervention, StepAdd, to improve physical activity levels and T2D control among patients with T2D by using the SCT framework. In 2021, we conducted a pilot study of StepAdd among 33 patients with T2D attending Mitsui Memorial Hospital in Japan, using a pre-post evaluation design over 12 weeks. The results show very high retention (97%), very large increase in mean daily steps (from 5436 to 10,150 steps per day; 86.7% increase), and positive changes in BMI (mean change of −0.3 kg/m^2) and hemoglobin A_{1c} (HbA_{1c})

levels (mean change of −0.79 percentage points) [29]. Growth in step count continued throughout the intervention, as did growth in step count goals. The step goal achievement rate remained steady and high throughout the intervention period. With strong positive impacts and strong ongoing engagement in this pilot study, we concluded that StepAdd warranted a deep study.

This trial aims to investigate the efficacy of StepAdd, also known as diabetic kidney disease–exercise therapy, in a long (24 weeks), randomized controlled trial. The specific research objectives and hypotheses are as follows.

Objective 1

The first objective is to investigate the efficacy of StepAdd in improving physical activity levels, as measured using daily step count.

We hypothesize that, at the end of the intervention, the intervention group will achieve a statistically significant increase in daily step count relative to the counts of the control group.

Objective 2

The second objective is to investigate the efficacy of StepAdd in reducing HbA_{1c} levels.

We hypothesize that, at the end of the intervention, the intervention group will achieve a statistically significant reduction in the primary outcome, HbA_{1c} levels, relative to the HbA_{1c} levels in the control group.

Objective 3

The third objective is to assess the effect of StepAdd in improving 7 self-care behaviors (walking duration, adherence to T2D self-care, self-management behavior to enhance and maintain physical activity, self-regulation of physical activity, self-efficacy to achieve targeted daily steps, self-efficacy to deal with barriers to achieving the targeted daily steps, and self-efficacy for health-promoting behaviors) and 10 health indicators (fasting blood glucose, estimated glomerular filtration rate, BMI, BP, high-density lipoprotein, low-density lipoprotein, triglyceride, locomotive syndrome, T2D-related emotional distress, and T2D-dependent quality of life).

We hypothesize that, at the end of the intervention, the intervention group will achieve a statistically significant improvement in the 7 self-care behaviors and 10 health indicators.

Methods

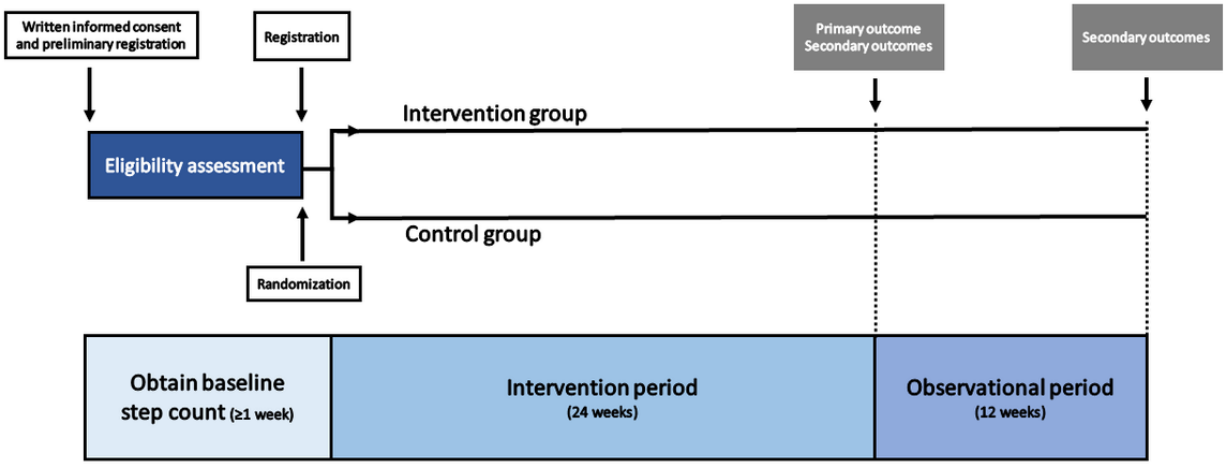
Study Design

This study is an open-label, multicenter (Textbox 1), confirmatory, 2-armed, randomized controlled trial to study the efficacy of an mHealth intervention, StepAdd, in promoting exercise behavior among patients with T2D. The conduct and reporting of the trial will follow the CONSORT (Consolidated Standards of Reporting Trials) guidelines. This study (Figure 1) begins with recruitment, a baseline measurement period (nominally 2 weeks, but at least 7 days), and randomized assignment to the intervention and control groups. The patients in the intervention group will use the SCT-based StepAdd smartphone app to measure body weight (BW), BP, and daily steps; receive personalized feedback; and develop updated step goals. The patients in the control group will use a placebo smartphone app that simply measures and reports BW, BP, and daily steps. Both groups will receive monthly consultations with their physician. The intervention will last for 24 weeks and will be followed by a 12-week observational period. This study will be conducted over 3 years, from January 1, 2023, to December 31, 2025.

Textbox 1. Participating institutions—5 medical centers within Japan.

- University of Tokyo Hospital
- Akita University Hospital
- Yokohama City University Hospital
- Yokohama City University Medical Center
- Yokohama Rosai Hospital

Figure 1. Overview of study timeline—at least 1 week of baselining, 24 weeks of intervention, and 12 weeks of observation.



Intervention Design

This mHealth intervention uses a pedometer; a body weighing scale; a BP monitor; and a smartphone with an mHealth app, StepAdd. The app is an iOS app on an iPhone that communicates with the StepAdd server. An administrative screen is used by a medical professional (either a physician or a clinical research coordinator who is overseen by a physician). Pedometer count, BP, and BW are measured at home. The pedometer count is synchronized with the app continuously during the day, and the BP and BW are synchronized with the app daily when patients open the app at the time of measurement. The app interacts with the patient to establish personalized goals, provide personalized feedback, and define and assess the efficacy of patient-specific coping skills (Figure 2 [29]). This app was developed in collaboration with foo.log Co Ltd, a software development company. The control group uses a placebo app supporting the same measurements but without personalized goals and feedback (Table 1).

Figure 2. StepAdd's process for implementing social cognitive theory (SCT)–based personalization on daily, weekly, and monthly timelines (adapted from Wei Thing Sze et al [29], Copyright 2023, used with permission from Elsevier).

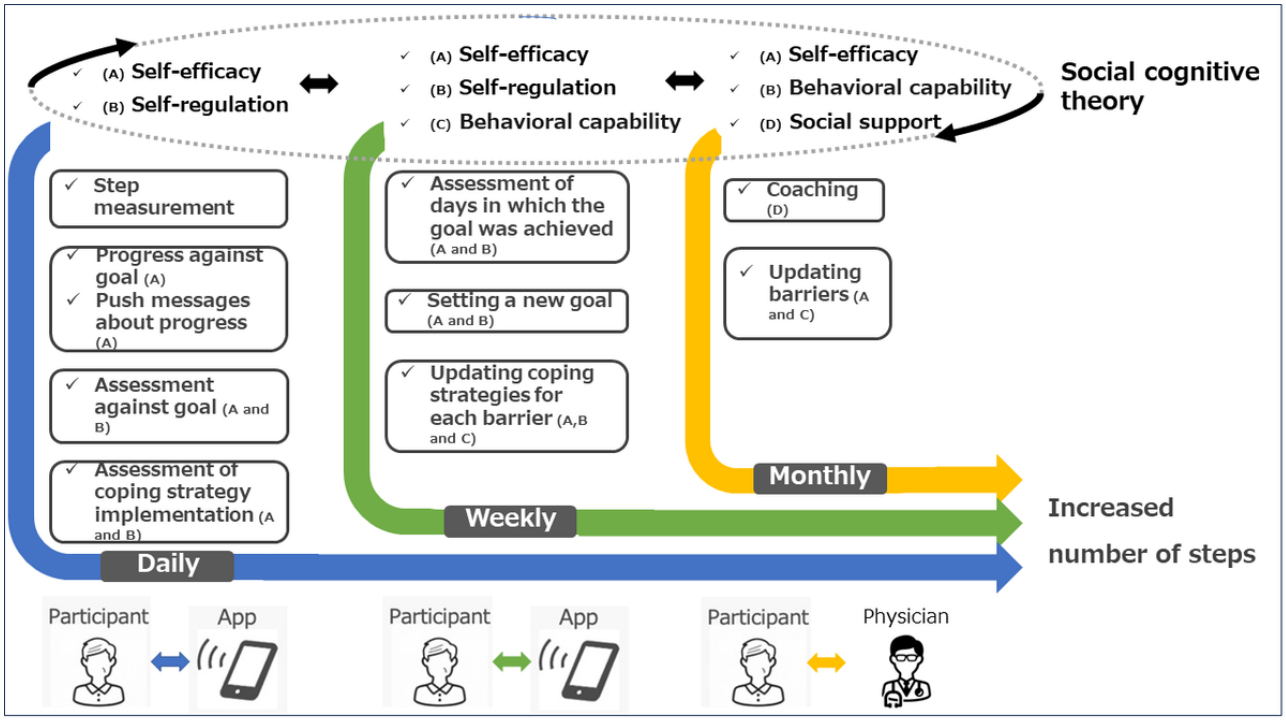


Table 1. Features of the trial's StepAdd and placebo apps and additional features provided to the intervention group.

Features	StepAdd app	Placebo app
Display, record, and upload step count, BW[a], and BP[b]	Yes	Yes
Reminders to measure BW and BP and to carry pedometer	Yes	Limited reminders to carry pedometer
Review of step count, BW, and BP	Yes	No
Exercise instructions	Yes	No
Goal setting	Yes	No
Coping strategies to overcome barriers to achieving step goals	Yes	No
Reminders about coping strategies	Yes	No
Display of recorded health data that were registered by physicians from the administrative screen	Yes	No
Daily reflection assistance	Yes	No
Weekly reflection assistance	Yes	No
Record about whether the tasks agreed with the health care professional are completed	Yes	No
Personalized feedback	Yes	No

[a]BW: body weight.

[b]BP: blood pressure.

The intervention uses the framework of SCT [25,26]. The intervention incorporates the SCT constructs that are most used in physical activity research: self-efficacy, self-regulation, behavioral capability, and social support [30]. Self-efficacy is an individual's belief in their ability to perform a particular behavior successfully. Individuals are less likely to engage in a behavior if they do not believe they are capable of producing the desired effects. Sources of self-efficacy include mastery experience (the successful accomplishment and mastering of a desired behavior) and verbal persuasion (receiving verbal encouragement from others for performing a behavior). Self-regulation, one of the constituent concepts of SCT that is closely linked with behavior change, is a dynamic feedback loop in which an individual sets a target goal and, by comparing this goal with their present state, is motivated to change their behavior to achieve the goal [31]. Motivation does not originate from the goals themselves but from the individual analyzing their own behavior with reference to their goal [32]. Self-regulation includes behaviors such as setting personal goals and planning courses of action to achieve them, and it is often motivated by expected positive outcomes. Behavioral capability is a person's actual ability to perform a behavior through essential knowledge and skills. Social support involves identifying others who will provide encouragement in the form of moral support, participation in the behavior, and accountability [33].

SCT constructs integrated in this app focused on a self-regulated walking habit using goal setting and perceived self-efficacy [34]. Users set small, progressive, and realistic goals for daily step counts (self-efficacy and goal setting), track and monitor daily step count performance (self-observation), and evaluate their own progress against the goals (self-judgment). The belief that one's progress is acceptable, along with the anticipated satisfaction of meeting a goal, enhances self-efficacy and motivation (self-reaction) [34]. The intervention provides social support through monthly meetings with a physician who examines the use of the app and provides advice, verbal encouragement, and support regarding the participants' exercise behavior (behavioral capability and social support).

The app proposes the target number of daily steps for the following week according to the achievement of the current week's step count against goals. Our algorithm [29] increases, maintains, or decreases the suggested goal based on the number of days in the previous week in which the user achieved their goal. Increases are either 300 or 500 steps, depending on past goal achievement levels. The patient may choose to decrease their goal by decrements of 200 steps if they are not confident in being able to complete the goal for ≥5 days. In this way, the app recommends goal adjustments according to the user's self-efficacy in goal achievement. Personalized goal setting also enhances self-regulation through forethought (setting a goal and deciding on goal strategies), performance control (using goal-directed actions and monitoring performance), and self-reflection (evaluating one's goal progress and adjusting the strategies to ensure success) [35].

The app provides automated feedback with individualized advice. Status against the daily goal is available continuously on the app. Self-regulation is enhanced as patients are able to self-monitor their behavior through the personalized feedback. The feedback also enhances self-efficacy as it acts as a means of verbal persuasion, which is a source of self-efficacy [25,26]. The app automatically communicates with the patients through push notifications 4 times a day (at 11 AM, 1 PM, 4 PM, and 6 PM) to communicate the achievement against the step goals. For example, if the target number of steps have not been reached at 11 AM, the message "The number of steps registered by 11 o'clock is [participants' registered number of steps]. The additional number of steps required is [target number of steps minus current number of steps] to achieve your goal" appears on the app. The day's achievement against the goal is shown at 6 PM. If the participant has reached the target step goal, the

message “Today’s steps have significantly exceeded your goal! Congratulations. You’re in good shape tomorrow. Don’t get tired” appears on the app. At the end of the week, the app provides feedback by displaying the number of days in the week that the step goals were achieved (Figure 3).

Individualized coping planning enhances self-regulation by allowing patients to evaluate the possible barriers to achieving their step goals. Each week, participants select or input 1 to 3 barriers that prevented them from achieving the targeted number of steps, and for each barrier, they suggest a coping strategy that could be useful to overcome the barrier (Figure 4). The coping strategies can be selected from a literature-based list of solutions to common barriers to walking [36-39] or can be freely described by the participants. At the end of each day, participants use the app to report about how many coping strategies they implemented that day. At the end of each week, the app provides feedback about the coping strategy use by displaying the average number implemented per day.

Figure 3. Example of end-of-week feedback (with English translation) showing daily and weekly performance against goals.

Figure 4. Example of personalized coping planning strategy on the app (with English translation) showing how patients select the strategy to use for the upcoming week.

Patient Recruitment

Patients will be recruited at 5 medical institutions in Japan: University of Tokyo Hospital, Akita University Hospital, Yokohama City University Hospital, Yokohama City University Medical Center, and Yokohama Rosai Hospital. Recruitment will be conducted by attending physicians during patients' regular consultations at outpatient clinics. Recruitment will be conducted over 2 years, starting from January 1, 2023, and ending on December 31, 2024.

To detect 0.35% difference in the primary outcome (change in HbA_{1c} level), assuming an SD of 0.74% as seen in a previous study [40], and to achieve a 2-sided significance level of .05 and a statistical power of 80%, the minimum sample size is 72 patients per group [41]. On the basis of an assumed dropout rate of 10%, we are targeting to recruit a total sample of 160 patients (n=80, 50% in the intervention group; n=80, 50% in the control group).

All participants will receive a thorough written and verbal explanation about participation. We will subsequently obtain written informed consent from all study participants before screening for eligibility to participate in the study. If findings regarding efficacy and safety that may affect patient consent are discovered at any points during the trial, we will swiftly disclose this information to participants and acquire their renewed consent.

To focus on patients who are likely to benefit and likely to be capable of participating, we will recruit patients who meet all the inclusion criteria (Textbox 2). To ensure that patients can safely and effectively participate in the intervention, we will recruit patients who do not meet any of the exclusion criteria (Textbox 3). We will use a transtheoretical model (TTM) questionnaire to categorize the participants who are currently at the contemplation stage (willing to change health behavior within the next 6 months), preparation stage (willing to change health behavior within the next month), or action stage (has made modifications to health behavior) [42]. In our previous study, patients who were in the contemplation and preparation stages of TTM were more likely to prefer to use smartphone-based self-management tools than those in the precontemplative stage [43]. Therefore, we targeted patients who are in the contemplation, preparation, or action stages of achieving the target goal of 10,000 steps a day.

We will provisionally register patients who meet the eligibility criteria. We will then provide them with a step-counting device and a smartphone with just the step-counting part of the placebo app. We will ask patients to record their daily step count for a baseline period (nominally 2 weeks, but at least 7 days), and then, we will measure their HbA_{1c} level at the end of the screening period. We will enroll patients who were able to measure their step count for ≥7 days during the baseline period (to ensure that we study patients who are able to adequately participate in the study) and who continue to have an HbA_{1c} level ≥7.5% (to ensure that patients continue to have high HbA_{1c} level after the screening period). We believe that the 2-week trial will have no significant effect on outcomes. We will then use the electronic data records to randomize eligible participants in 1:1 ratio to either the intervention group or the control group using the covariate-adaptive randomization by minimization method to ensure covariance balance for age (<65 years and ≥65 years), sex, HbA_{1c} level (<8.5% and ≥8.5%), and institution [44].

Textbox 2. Inclusion criteria of the study, focusing on patients who are likely to benefit from the intervention and are likely to be capable of participating.

Inclusion criteria

- Diagnosed with type 2 diabetes mellitus
- Being in the contemplation, preparation, or action stages of the transtheoretical model to achieve the target step count of 10,000 steps per day
- Hemoglobin A_{1c} level ≥7.5% and ≤10% at the time of consent acquisition
- No change in antidiabetic medication within 8 weeks before the time of consent acquisition
- Aged ≥18 years
- Systolic blood pressure <180 mm Hg and diastolic blood pressure <110 mm Hg at the time of consent acquisition
- eGFR ≥45 mL/min/1.73 m_2 recorded at least once in the 12 weeks before the time of initial registration (V0)
- Urine albumin-creatinine ratio is <300 mg/gCr on at least 1 occasion in the past year (52 weeks) before V0
- BMI ≥22 kg/m_2
- No incidences of severe hypoglycemic attacks where assistance by others was required in the 12 weeks before V0
- No symptoms of a possible hypoglycemic attack (including palpitations, tremors, dizziness, lightheadedness, anxiousness, loss of consciousness, sweating, pale face, tachycardia, headache, drowsiness, blurred vision, and convulsion) observed in the 12 weeks before V0
- Able to attend consultations at designated times during the trial
- Fully informed about participation in this study and has given free and voluntary written consent based on thorough understanding of the study

Textbox 3. Exclusion criteria, focusing on patients who may not be able to participate safely or whose participation may interfere with the effectiveness of the study.

Exclusion criteria

- Walked an average of ≥10,000 steps a day in the 4 weeks before V0 (must be verifiable by pedometer, etc)
- Wearing a pacemaker
- Using continuous glucose monitoring (but do not exclude if self-monitoring of blood glucose level or intermittently scanned continuous glucose monitoring was conducted ≥8 weeks before V0)
- Diagnosed with hyperthyroidism and have received treatment other than thyroid hormone replacement in the year before V0
- Diagnosed with a moderate to severe heart condition that requires exercise restriction as assessed by a physician
- Require exercise treatment restrictions as assessed by a physician at V0—decision made with reference to "Cases in which exercise therapy should be prohibited or restricted" in the Guidelines for Diabetes Treatment (Japan Diabetes Society; 2022-2023)
- Hemoglobin <10 g/dL in the 12 weeks before V0
- Serum albumin ≤3 g/dL in the 12 weeks before V0
- Diagnosed with preproliferative retinopathy or retinopathy of a later stage within the year before V0
- Cannot undergo exercise treatment
- Pregnancy, including any possibility or intention of pregnancy
- Participation in other trials at the time of initial registration (V0)
- Impaired cognitive function, as determined by the investigator or subinvestigator
- Any other reason that the patient is classified as unfit for participation by the investigator or subinvestigator (a record must be maintained about the reason the patient was determined to be ineligible)

Intervention Process

The study (Table 2) includes 10 events (V0-V9), a 24-week continuous measurement phase (M), and a 12-week follow-up observation phase. Initial measurements will be made at event V0. At V0, we will provide each participant with a near field communication–enabled pedometer (A&D; UW-204NFC) and an iPhone (iPhone 8 with iOS 16) prepared with the placebo app configured for step count only. We will direct the participants to wear the pedometer throughout the day except during sleep. We will use the step count gathered during V1 to confirm eligibility and to set a step count baseline.

The surveys that will be used in this study are listed in Textbox 4.

Table 2. Study events—1 measurement period and 10 visits spanning approximately 37 weeks.

Event	Focus	Time	Key activities
V0	Physical baseline assessments and initial registration	Enrollment—≥7 days before the beginning of the intervention	• Collect consent • Collect demographic information: date of birth, sex, smoking and drinking status, medical history, diet and exercise habit, household living condition, employment, use of smartphones, habit of step count measurement, and stage of behavior change according to the transtheoretical model of change regarding walking 10,000 steps a day • Collect physical data: blood tests to measure HbA_{1c}[a], FBG[b], LDL[c] cholesterol, HDL[d] cholesterol, TG[e], and eGFR[f]; urinalysis; and height, body weight, and BP[g] measurements • Collect medication and combination therapy status • Assess health literacy • Conduct surveys (Textbox 4) • Distribute pedometer and placebo-equipped phone
V1	Step count baseline	From V0 to the day before V2 (at least 7 days)	• Patients record daily steps and determine step count baseline
V2	Registration, allocation, and beginning of the intervention	Beginning of the intervention (end of week 0)	• Measure HbA_{1c} level • Finalize registration and allocation • Distribute BP monitor and scale • Activate all placebo and StepAdd features • Collect medication and combination therapy status • Check for adverse events
M	Ongoing measurement	From V2 to V8	• Daily measurements via app • Intervention only: daily feedback, weekly feedback, and weekly personalized goal setting via app • Check for defects
V3	Hospital visit 1	End of week 4	• Check app use and equipment • Check for adverse events • Intervention: coach goals and coping strategies • Collect medication and combination therapy status
V4	Hospital visit 2	End of week 8	• Check app use and equipment • Check for adverse events • Intervention: coach goals and coping strategies • Collect medication and combination therapy status
V5	Interim hospital visit	End of week 12	• Collect physical data: blood tests to measure HbA_{1c}, FBG, LDL cholesterol, HDL cholesterol, TG, and eGFR; urinalysis; and body weight and BP measurements • Check app use and equipment • Check for adverse events • Intervention: coach goals and coping strategies • Collect medication and combination therapy status • Conduct surveys (Textbox 4)
V6	Hospital visit 4	End of week 16	• Check app use and equipment • Check for adverse events • Intervention: coach goals and coping strategies • Collect medication and combination therapy status
V7	Hospital visit 5	End of week 20	• Check app use and equipment • Check for adverse events • Intervention: coach goals and coping strategies • Collect medication and combination therapy status

Event	Focus	Time	Key activities
V8	End of the intervention	End of week 24	• Collect physical data: blood tests to measure HbA_{1c}, FBG, LDL cholesterol, HDL cholesterol, TG, and eGFR; urinalysis; and body weight and BP measurements • Collect medication and combination therapy status • Check for adverse events • Conduct surveys (Textbox 4) • Assess usefulness and usability
V9	End of follow-up	End of week 36	• Collect physical data: blood tests to measure HbA_{1c}, FBG, LDL cholesterol, HDL cholesterol, TG, and eGFR; urinalysis; and body weight and BP measurements • Collect medication and combination therapy status • Check for adverse events • Conduct surveys (Textbox 4)

[a]HbA_{1c}: hemoglobin A_{1c}.

[b]FBG: fasting blood glucose.

[c]LDL: low-density lipoprotein.

[d]HDL: high-density lipoprotein.

[e]TG: triglyceride.

[f]eGFR: estimated glomerular filtration rate.

[g]BP: blood pressure.

Textbox 4. Surveys—9 surveys assessing type 2 diabetes–related behaviors and outcomes.

Problem Areas in Diabetes

- 20 items to assess type 2 diabetes–related emotional distress [45]

Locomo 25

- 25-question risk assessment to evaluate musculoskeletal disorders such as walking disability, difficulty in daily living, or pain in the body [46]

Evaluation Scale for Self-Management Behavior Related to Physical Activity of Type 2 Diabetic Patients

- Assessments of the following:
  - Self-management behavior to enhance daily physical activity
  - Self-management behavior to maintain the level of physical activity [47]

Steps achieved

- Self-Efficacy Scale relative to achieving the targeted daily steps [48]

Dealing with barriers to achieving the targeted daily steps

- Self-Efficacy Scale relative to dealing with barriers to achieving the targeted daily steps [49]

Physical Activity Self-Regulation Scale–12; Japanese version

- Addresses self-monitoring, goal setting, eliciting social support, reinforcement, time management, and relapse prevention
- Rated from 1 (never use strategy) to 5 (use strategy very often)
- Scores are the sum of the 2 individual item scores and summed self-regulation subscale scores for a measure of overall self-regulation [50]

The Summary of Diabetes Self-Care Activities Measure; Japanese version

- Assesses type 2 diabetes self-care activities [51]

Health behavior "active coping behavior with disease"

- Self-Efficacy Scale for health behavior "active coping behavior with disease" subscale [52]

Audit of Diabetes-Dependent Quality of Life; Japanese version

- Assesses type 2 diabetes–dependent quality of life [53]

Following randomization, we will begin the intervention. We will provide participants a Bluetooth-enabled sphygmomanometer (A&D; UA-651BLE Plus) and a Bluetooth-enabled weighing scale (A&D; UC-352BLE; in addition to the already provided pedometer and phone). For the control group, we will enable BP and BW measurement functions in the placebo app. For the intervention group, we will replace the placebo app with StepAdd and define the initial goals and barriers. Both the intervention and control groups will watch a video regarding lifestyle modification, self-management of T2D, and effect of exercise on glycemic control.

The main part of the intervention is the daily measurement by all patients throughout phase M. We will direct participants to measure their BW and BP daily upon awakening and wear the pedometer throughout the day except during sleep. All the participants will log the measurement data by syncing the recording devices (weighing scale, sphygmomanometer, and pedometer) to the app, rather than by manually inputting the data. These data are then uploaded to the server and made visible to health care professionals via the administrative screen. Intervention group participants receive personalized feedback about their step count performance 4 times a day. At the end of each week, intervention group participants review their weekly step count performance on the app, determine their personal barriers to achieving the step goals, and identify the possible coping strategies. StepAdd then provides a personalized step goal recommendation for the following week.

Every 4 weeks (events V3-V7), both groups will meet with a physician who will advise patients regarding lifestyle modifications and use of the app and, for the intervention group only, help with goals and coping strategies. Baseline measurements (other than collection of some background information) are repeated at the interim (V5), at the end of the intervention (V8), and at the end of the follow-up observation period (V9). We will collect the equipment at V8, before the follow-up observation period. The purpose of the observational period is to assess whether the intervention-induced effects are maintained after the end of the intervention.

During the study, we will not restrict the use of supplements and drinks that can affect blood glucose level and BP. In both the intervention and control groups, T2D treatment details, such as changes or additions of oral T2D medications, insulin, and glucagon-like peptide–1 receptor agonists and changes in medication dosage, can be changed at the discretion of the attending physician.

If patients discontinue the trial or stop using the app, we will define this as discontinuation, and we will collect the measurements within 7 days of this discontinuation. If participation in the study is discontinued during the intervention period, we will collect the V8 measurement items. If participation in the study is discontinued during the observation period, we will collect the V9 measurements items, except for urinalysis.

Monitoring, Quality Control, and Data Management

An auditor who is independent from the departments involved in the trial, including those responsible for monitoring, will inspect the medical institution and other facilities involved to ensure that the trial is conducted appropriately.

Ethical Considerations

This trial will be conducted in compliance with the Declaration of Helsinki, Pharmaceutical and Medical Device Act, Ministerial Ordinance on Good Clinical Practice for Medical Devices, and all other guidelines in relation to these regulations (jRCT2032220603). This study was approved by the institutional review board of the University of Tokyo School of Medicine (approval number 2022012-11DY). We will obtain written informed consent from all study participants. All patient data will be anonymized. Patients will be compensated JPY 7000 (approximately US $50) for each visit to the hospital.

Outcome Measures

Primary Outcome

The primary outcome of this study is the between-group differences in the change of HbA_{1c} value between baseline (V2) and either the end of the intervention period (week 24 [V8]) or, for patients who discontinue before V8, the point of discontinuation. Reduction of HbA_{1c} level by 0.35 percentage points is considered to be clinically significant [54,55].

Secondary Outcomes

Secondary outcomes (Table 3) include health measures, measurements of steps, measurements of other behavior changes, and assessments of app use. We will also assess safety outcomes such as hypertension requiring medical assistance (assessed from the system records), subjective hypoglycemia, pain in the lower back and lower extremities (tarsus, thighs, knees, calves, shins, ankles, and feet), and any other adverse events (all assessed through patient interviews).

Table 3. Secondary outcomes investigated in the study—22 areas spanning health outcomes, exercise outcomes, other behavior changes, and app assessments.

Categories and item numbers	Outcomes
Health outcomes	

1	• HbA_{1c}[a] level (%)
	  • Change in HbA_{1c} level[b]
	  • Proportion of patients with HbA_{1c} level <7%[c]

2[d]	• FBG[e] (mg/dL) >5 hours after a meal
3[d]	• eGFR[f] (L/min/1.73m2)
4[d]	• BMI (kg/m2)
5[g]	• Body weight measured at home (kg)

6	• Systolic and diastolic BP[h] (mm Hg)
	  • BP measured at hospital[d]
	  • BP measured at home[g]

7[d]	• HDL[i] (mg/dL), LDL[j] (mg/dL), and TG[k] (mg/dL)

8[l]	• Concomitant medication intake (type of medication and daily dosage or weekly dosage for weekly formulation)
	  • Change in type 2 diabetes medication intake (either increased, unchanged, or reduced)
	  • Introduction of new medications to treat type 2 diabetes, hypertension, or dyslipidemia

9[d]	• Type 2 diabetes–related emotional distress (assessed using Problem Areas in Diabetes) [45]
10[d]	• Type 2 diabetes–dependent quality of life (assessed using Audit of Diabetes-Dependent Quality of Life) [53]
Exercise outcomes	
11[g]	• Daily step count
12[d]	• Walking duration
Other behavior changes	
13[d]	• Locomotive syndrome (assessed using Locomo 25) [46]
14[d]	• Type 2 diabetes self-care, assessed using the Japanese version of the Summary of Diabetes Self-Care Activities Measure [51]
15[d]	• Self-management behaviors related to physical activity, assessed using Evaluation Scale for Self-Management Behavior Related to Physical Activity of Type 2 Diabetic Patients [47]
16[d]	• Self-regulation of physical activity, assessed using the Japanese version of Physical Activity Self-Regulation Scale–12 [50]

17[d]	• Changes in walking self-efficacy:
	  • Self-efficacy for achieving the targeted daily steps [48]
	  • Self-efficacy for dealing with barriers to achieving the targeted daily steps (assessed using Self-Efficacy Scale of Walking Behavior) [49]

18[d]	• Changes in self-efficacy in health-promoting behavior, assessed using Positive Coping Behavior Towards Illness subscale within Self-Efficacy Scale for Health Promoting Behaviors [52]
19[m]	• Health literacy, assessed using Health Literacy Scale 14 [56]
App assessments	

Categories and item numbers	Outcomes

20[n]	• App use is assessed through the following:
	  • Recording rate of body weight, step count, and BP and its change[o]
	  • Goal achievement rate[p]
	  • Goal increment rate[q]
	  • Goal reduction rate[r]
	  • Average number of coping planning strategies implemented per day[s]
	  • Number of barrier identifications[t]

21[u]	• System feasibility and usability (only for the intervention group)
22[v]	• Number of emails, SMSs, and calls to encourage registration

[a]HbA_{1c}: hemoglobin A_{1c}.

[b]Includes both differences between week 0 (registration at V2) and week 12 (V5; or point of discontinuation, if earlier) and between week 0 (registration at V2) and week 36 (V9; or point of discontinuation, if earlier), which are compared within group and between groups, and includes the difference between week 0 (registration at V2) and week 24 (V8; or point of discontinuation, if earlier), which are compared within group.

[c]Includes all 3 proportions that are compared between groups: latest HbA_{1c} level up to week 12 (V5; or point of discontinuation, if earlier) <7%, latest HbA_{1c} level up to week 24 (V8; or point of discontinuation, if earlier) <7%, and latest HbA_{1c} level up to week 36 (V9; or point of discontinuation, if earlier) <7%.

[d]Includes all 3 differences: between provisional registration (V0) and week 24 (V8; or point of discontinuation, if earlier), between provisional registration (V0) and week 12 (V5; or point of discontinuation, if earlier), and between provisional registration (V0) and week 36 (V9; or point of discontinuation, if earlier), which are compared between groups.

[e]FBG: fasting blood glucose.

[f]eGFR: estimated glomerular filtration rate.

[g]Includes differences between the beginning of the intervention (V2; or from baseline period [V1] for steps) and week 4 (V3) and differences between each visit and each subsequent visit, which are compared between groups. In addition, they include measurements at each period (between visits), which are to be compared between groups. Item 11 also includes difference between baseline (V1) and 2 weeks before week 12 (V5; or point of discontinuation, if earlier) and week 24 (V8; or point of discontinuation, if earlier), which are compared within group and between groups.

[h]BP: blood pressure.

[i]HDL: high-density lipoprotein.

[j]LDL: low-density lipoprotein.

[k]TG: triglyceride.

[l]Includes assessment at week 12 (V5), week 24 (V8), and week 36 (V9; or point of discontinuation, if earlier), respectively, and it will be compared between groups.

[m]Will be assessed at provisional registration (V0).

[n]Includes comparisons of the differences over the first period of the intervention (from week 0 [V2] to week 4 [V3]) and differences over each subsequent period (between subsequent visits), which are compared between groups (only the recording rate of body weight, step count, and BP and its change) and within group (all assessments).

[o]Formula: (number of days in which measurements for BW, step count, and BP are recorded/total number of days) × 100.

[p]Formula: (number of days in which step goal was achieved/total number of days) × 100; examined only for the intervention group.

[q]Formula: (number of days in which step goal was increased/total number of reset times) × 100; examined only for the intervention group.

[r]Formula: (number of days in which step goal was reduced/total number of reset times) × 100; examined only for the intervention group.

[s]Formula: total number of coping strategies implemented over the period/total number of days; examined only for the intervention group.

[t]Number of barriers identified every 4 weeks; examined only for the intervention group.

[u]Will be assessed for the intervention group only, at week 24 (V8; or point of discontinuation, if earlier).

[v]Will be assessed at week 24 (V8; or point of discontinuation, if earlier).

Statistical Analysis

In this study, we define 3 analysis populations: full analysis set (FAS), per protocol set (PPS), and safety analysis set (SAS). FAS is the set of all patients whose data were obtained at least once after randomization. We will follow the intention-to-treat principle and analyze data based on the assigned group in the FAS analysis. PPS is the FAS population with the exclusion of patients who were found to have violated the eligibility criteria after randomization or who did not use the app over a 3-week period. SAS is the set of all patients who used the StepAdd app or the placebo app at least once after randomization. In the safety analysis using SAS, we will analyze data based on the apps actually used by the patients, regardless of allocation. AS will be the primary analysis population, and PPS will provide supportive results. All safety analyses will be conducted in SAS.

Data about patients' characteristics will be presented as mean, SD, minimum, 25th percentile, median, 75th percentile, and

maximum for continuous variables and as frequency and proportion for categorical variables.

In the primary analysis, we will perform between-group comparison of the change in HbA_{1c} level from week 0 (V2) to week 24 (V8; or point of discontinuation, if earlier) using analysis of covariance, including baseline HbA_{1c} level (ie, HbA_{1c} level at week 0 [V2]) as a covariate in FAS. If participants discontinue the study, the latest measurement of HbA_{1c} level before V8 will be used.

We will also conduct 2 subgroup analyses with one classification by HbA_{1c} level at week 0 (V2; either <8.5% or ≥8.5%) and the other classification by BMI at the time of initial registration (V0; either <25 kg/m^2 or ≥25 kg/m^2). We will conduct subgroup analysis on the primary outcome in each analysis set to investigate whether the efficacy of StepAdd is consistent between these subgroups.

In the secondary analysis, the change in HbA_{1c} level at week 12 (V5) and week 36 (V9) will be analyzed as in the primary analysis. The proportion of patients with HbA_{1c} level <7% at week 12 (V5), week 24 (V8), and week 36 (V9; or point of discontinuation, if earlier) will be compared between the groups using Fisher exact test. The change from baseline in the step counts, various laboratory test values, and questionnaire scores at week 12 (V5), week 24 (V8), and week 36 (V9; or point of discontinuation, if earlier) will be analyzed as the primary end point. Changes in T2D medications, classified as weakened, unchanged, or strengthened, will be compared between groups using the Cochran-Mantel-Haenszel test. The proportion of new medications added will be compared between groups using Fisher exact test. Change in app data (step counts, BW, and BP) and their recording rates will be evaluated between each visit based on the week-0 (V2) to week-4 (V3) period and compared between groups using 2-tailed *t* tests. The McNemar test will be used for within-group comparison of the proportion of people who walked ≥10,000 steps in the 2 weeks before the intervention and the 2 weeks before week 24 (V8). A paired *t* test will be used for within-group comparison over the week-0 (V2) to week-4 (V3) period for goal achievement rate, goal increment rate, goal reduction rate, average number of coping planning strategies implemented per day, and number of barrier identifications.

As an exploratory analysis, we will use linear regression to investigate the relationship between the average number of coping strategies implemented per day and improvement in HbA_{1c} level in the intervention group. The analysis will use the average number of coping strategies implemented per day and baseline HbA_{1c} level as explanatory variables and the change in HbA_{1c} level as the response variable. The change from baseline to week 12 (V5), week 24 (V8), and week 36 (V9; or point of discontinuation, if earlier) will be evaluated.

We will conduct statistical analysis of safety outcomes. We will compare the proportion of incidences of hypoglycemia, joint pain, significantly elevated BP (≥145/95 mm Hg), and exacerbations of joint pain between groups using Fisher exact test. Other adverse events will be recorded using the Japanese version of the Medical Dictionary for Regulatory Activities categories for Preferred Term and System Organ Class, and their incidence proportions will be compared between groups using Fisher exact test. The severity of each incidence will be categorized into 3 grades (low, moderate, and high), and their between-group comparison will be conducted using the Cochran-Mantel-Haenszel test.

Results

Recruitment began on January 1, 2023. As of September 5, 2023, we have recruited 44 patients. We expect the trial to be completed by October 8, 2025, with the follow-up observation period being completed by December 31, 2025. We anticipate completing the analysis by March 30, 2026.

Discussion

Expected Outcomes

We have designed this study based on the foundational concept that this is a behavior change intervention, albeit one where we are measuring medical outcomes. We base the intervention on a specific theory of behavioral change, in this case SCT, to give a framework to the intervention, ensuring clarity about the targets of the intervention and keeping the focus on these targets to avoid scatter-shot ideas about how and where to intervene. We identified a specific and actionable target behavior, walking more, and designed a measurement and feedback system around this focused behavior. This focused approach brings clarity to the researchers and to the patients. The focus lets us determine if this specific intervention increases walking behavior while also assessing any resulting changes in physical parameters such as BMI and ultimately assessing changes in health. It is not sufficient to show that some behavior intervention leads to HbA_{1c} level improvement—we need to understand the steps in between, in particular, the behavior response, to fine-tune the intervention to expand on the aspects that work and eliminate the aspects that do not. We have designed this trial to provide evidence about the intermediate stages.

Our study uses objectively measured data for all primary and many secondary outcomes. The intervention uses wireless technology that allows step count, BW, and BP measurements to be synced automatically to the app. These simple, passive features make for easy-to-use objective measurements, especially for older patients. Daily monitoring of blood glucose level has been shown to have low measurement rates and to not be preferred by patients; therefore, we have not included it in this intervention [57].

We chose HbA_{1c} level as our primary outcome, as it is regarded as both a global standard for measuring glycemic control and an appropriate indicator of the effectiveness of T2D treatment [58]. According to The Japan Diabetes Society's treatment guideline, patients with T2D should aim to reduce their HbA_{1c} level to <7% to prevent the development of any complications [59]. Therefore, we decided to study the proportion of patients who achieved an HbA_{1c} level <7% in addition to studying the absolute change in HbA_{1c} levels.

In this study, we have elected to use a "formidable" control [60] using a fairly high-functioning placebo app. We have initial confirmation of proof of concept from the pilot, and now, we want to show whether our specific behavior change intervention methods are superior to simply giving patients access to their step count, BW, and BP. There is evidence suggesting that simply giving patients a pedometer increases their activity level [61]; thus, there is some risk that the study will induce a response in the control group, which may prevent statistical proof of any superiority of the StepAdd intervention. Most people who want a pedometer already have access to one in their smartphone, and we think this risk is modest. By giving the placebo group a functional app, albeit one lacking StepAdd's functionality, we have designed the study to give strong proof of the success of StepAdd, if in truth, it is effective.

Many behavior interventions show solid, short-term gains that fade later [62]. Our StepAdd pilot [29] showed results that continued to improve throughout the study, with no sign of fading. This study expands the trial time to 24 weeks with a 12-week observation period to examine whether the pilot results hold true over a long period. Behavior change maintenance is theorized as an outcome of active and ongoing self-regulation, and habit development follows a period of successful self-regulation of a new behavior [63]. Our objective is to change behavior in a sustainable way, such that the new pattern of behavior becomes a habit that can be sustained over the long haul.

A key to our approach is ensuring that the patients receive a strong introduction to the mechanics of the intervention and the StepAdd app. Patients have busy lives, and we work to make it clear and easy for them to meet the demands of the intervention. By providing training regarding the intervention and the app and by ensuring that all messaging in the intervention is simple and focused, we maximize the likelihood that the patients will use the tools of the intervention just as we intend them to.

Another key part of the approach is focusing first on the patients whom the intervention will serve. We designed the intervention for a specific target set, not all patients, and customized the intervention to meet their needs and accommodate their preferences. We have found that it is essential to design with cultural background and patient preference in mind, as we did in the StepAdd pilot [29]. Another key aspect of our approach is applying it only to patients who are already motivated to change their behavior. We filter based on TTM stages, and we have found this approach to be highly effective [29,43]. Our intervention is designed for high-motivation patients who are in need of some help in implementing their desired behavior—low-motivation patients are in need of an entirely different intervention focused on improving their motivation. We have found that large proportions of patients with T2D in Japan have high motivation, with a study showing that 92% are in the contemplation-through-action stages of TTM [64]. There is a very large pool of patients who would benefit from this targeted intervention. Exercise has been shown to improve health in patients with chronic kidney disease [65], and a recent meta-analysis confirms that exercise and diet programs improve the health of patients with T2D who are obese, including improving BMI and HbA_{1c} level [66]. This study is a multicenter randomized controlled trial, and this increases the generalizability of the findings to patients with T2D throughout Japan. Our techniques are general, and there is every reason to believe that these methods could be applied to increase exercise for patients with other diseases and in countries throughout the world.

Limitations

The study has limitations. The results of our trial may be specific to the population studied and may not be fully generalizable to other populations. Our participants will likely be older people of Japanese ethnicity. There are differences between Japanese and other populations in lifestyles and in the pathophysiology of T2D. The study is limited to patients who are able to use mobile phones; therefore, there may be biases owing to users' digital literacy. In contrast, results may differ with a young population [67], as it has been reported that young populations are able to complete tasks more successfully on mHealth apps [68] and have high satisfaction compared with their older counterparts [69]. Participants will not be blinded to randomization; therefore, social desirability bias may affect the results. We do not engage on or control for dietary changes, and changes in dietary behavior during the study may affect our results. Baseline step count is measured using pedometers provided to participants, and the resulting measurements may be higher than the true prestudy step count, as studies have found that providing a pedometer increases step count by >2000 steps [63], at least in the short term. This effect is mitigated by our 2-arm trial and the length of our trial, but it may lead us to underestimate the increases in step count and, therefore, overestimate the per-step impact on health outcomes.

This trial will provide important evidence about the efficacy of an SCT-based mHealth intervention in improving physical activities and glycemic control in patients with T2D. If this study proves the intervention to be effective and safe, it could be a key step toward the integration of mHealth as part of the standard treatment received by patients with T2D in Japan. Our findings will inform future studies of using theory-based behavior change techniques and may lead to practical use by exercise professionals in the real world [70].

Acknowledgments

The authors thank Nicholas Leung and Daniel Lane for their support in manuscript editing and scientific discussions.

Data Availability

Aggregate data analyzed in this study may be made available upon reasonable request by contacting the corresponding author via the email address provided.

Conflicts of Interest

The study was supported by Raxi Co Ltd. The patent that resulted from this study is issued to Raxi Co Ltd and The University of Tokyo. KW received support from Raxi Co., ltd. as a PI to conduct the study, and HW is their spouse.

References

1. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, et al. IDF diabetes atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract 2022 Jan;183:109119. [doi: 10.1016/j.diabres.2021.109119] [Medline: 34879977]
2. Williams R, Karuranga S, Malanda B, Saeedi P, Basit A, Besançon S, et al. Global and regional estimates and projections of diabetes-related health expenditure: results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract 2020 Apr;162:108072. [doi: 10.1016/j.diabres.2020.108072] [Medline: 32061820]
3. Saeedi P, Salpea P, Karuranga S, Petersohn I, Malanda B, Gregg EW, et al. Mortality attributable to diabetes in 20-79 years old adults, 2019 estimates: results from the International Diabetes Federation Diabetes Atlas, 9 edition. Diabetes Res Clin Pract 2020 Apr;162:108086. [doi: 10.1016/j.diabres.2020.108086] [Medline: 32068099]
4. Harding JL, Pavkov ME, Magliano DJ, Shaw JE, Gregg EW. Global trends in diabetes complications: a review of current evidence. Diabetologia 2019 Jan;62(1):3-16 [FREE Full text] [doi: 10.1007/s00125-018-4711-2] [Medline: 30171279]
5. Yanai H, Adachi H, Masui Y, Katsuyama H, Kawaguchi A, Hakoshima M, et al. Exercise therapy for patients with type 2 diabetes: a narrative review. J Clin Med Res 2018 May;10(5):365-369 [FREE Full text] [doi: 10.14740/jocmr3382w] [Medline: 29581797]
6. Murphy MH, Nevill AM, Murtagh EM, Holder RL. The effect of walking on fitness, fatness and resting blood pressure: a meta-analysis of randomised, controlled trials. Prev Med 2007 May;44(5):377-385. [doi: 10.1016/j.ypmed.2006.12.008] [Medline: 17275896]
7. Moghetti P, Balducci S, Guidetti L, Mazzuca P, Rossi E, Schena F, Italian Society of Diabetology (SID), Italian Association of Medical Diabetologists (AMD), Italian Society of MotorSports Sciences (SISMES). Walking for subjects with type 2 diabetes: a systematic review and joint AMD/SID/SISMES evidence-based practical guideline. Nutr Metab Cardiovasc Dis 2020 Oct 30;30(11):1882-1898 [FREE Full text] [doi: 10.1016/j.numecd.2020.08.021] [Medline: 32998820]
8. Tudor-Locke C, Craig CL, Brown WJ, Clemes SA, De Cocker K, Giles-Corti B, et al. How many steps/day are enough? For adults. Int J Behav Nutr Phys Act 2011 Jul 28;8:79 [FREE Full text] [doi: 10.1186/1479-5868-8-79] [Medline: 21798015]
9. Kemps H, Kränkel N, Dörr M, Moholdt T, Wilhelm M, Paneni F, et al. Exercise training for patients with type 2 diabetes and cardiovascular disease: what to pursue and how to do it. A position paper of the European Association of Preventive Cardiology (EAPC). Eur J Prev Cardiol 2019 May 14;26(7):709-727. [doi: 10.1177/2047487318820420] [Medline: 30642190]
10. García-Pérez LE, Alvarez M, Dilla T, Gil-Guillén V, Orozco-Beltrán D. Adherence to therapies in patients with type 2 diabetes. Diabetes Ther 2013 Dec 30;4(2):175-194 [FREE Full text] [doi: 10.1007/s13300-013-0034-y] [Medline: 23990497]
11. Khokhar B, Jones J, Ronksley PE, Armstrong MJ, Caird J, Rabi D. Effectiveness of mobile electronic devices in weight loss among overweight and obese populations: a systematic review and meta-analysis. BMC Obes 2014 Oct;1:22 [FREE Full text] [doi: 10.1186/s40608-014-0022-4] [Medline: 26217509]
12. Stephens J, Allen J. Mobile phone interventions to increase physical activity and reduce weight: a systematic review. J Cardiovasc Nurs 2013;28(4):320-329 [FREE Full text] [doi: 10.1097/JCN.0b013e318250a3e7] [Medline: 22635061]
13. Bonoto BC, de Araújo VE, Godói IP, de Lemos LL, Godman B, Bennie M, et al. Efficacy of mobile apps to support the care of patients with diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. JMIR Mhealth Uhealth 2017 Mar 01;5(3):e4 [FREE Full text] [doi: 10.2196/mhealth.6309] [Medline: 28249834]
14. Wu Y, Yao X, Vespasiani G, Nicolucci A, Dong Y, Kwong J, et al. Mobile app-based interventions to support diabetes self-management: a systematic review of randomized controlled trials to identify functions associated with Glycemic efficacy. JMIR Mhealth Uhealth 2017 Mar 14;5(3):e35 [FREE Full text] [doi: 10.2196/mhealth.6522] [Medline: 28292740]
15. Kercher VM, Kercher K, Levy P, Bennion T, Alexander C, Amaral PC, et al. 2023 Fitness Trends from Around the Globe. ACSMs Health Fit J 2023;27(1):19-30. [doi: 10.1249/fit.0000000000000836]
16. Romeo A, Edney S, Plotnikoff R, Curtis R, Ryan J, Sanders I, et al. Can smartphone apps increase physical activity? Systematic review and meta-analysis. J Med Internet Res 2019 Mar 19;21(3):e12053 [FREE Full text] [doi: 10.2196/12053] [Medline: 30888321]
17. Gal R, May AM, van Overmeeren EJ, Simons M, Monninkhof EM. The effect of physical activity interventions comprising wearables and smartphone applications on physical activity: a systematic review and meta-analysis. Sports Med Open 2018 Sep 03;4(1):42 [FREE Full text] [doi: 10.1186/s40798-018-0157-9] [Medline: 30178072]

18. Kondo M, Okitsu T, Waki K, Yamauchi T, Nangaku M, Ohe K. Effect of information and communication technology-based self-management system DialBeticsLite on treating abdominal obesity in the specific health guidance in Japan: randomized controlled trial. JMIR Form Res 2022 Mar 24;6(3):e33852 [FREE Full text] [doi: 10.2196/33852] [Medline: 35323122]
19. Yamaguchi S, Waki K, Nannya Y, Nangaku M, Kadowaki T, Ohe K. Usage patterns of GlucoNote, a self-management smartphone app, based on ResearchKit for patients with type 2 diabetes and prediabetes. JMIR Mhealth Uhealth 2019 Apr 24;7(4):e13204 [FREE Full text] [doi: 10.2196/13204] [Medline: 31017586]
20. Rabbi M, Pfammatter A, Zhang M, Spring B, Choudhury T. Automated personalized feedback for physical activity and dietary behavior change with mobile phones: a randomized controlled trial on adults. JMIR Mhealth Uhealth 2015 May 14;3(2):e42 [FREE Full text] [doi: 10.2196/mhealth.4160] [Medline: 25977197]
21. Thakkar J, Kurup R, Laba TL, Santo K, Thiagalingam A, Rodgers A, et al. Mobile telephone text messaging for medication adherence in chronic disease: a meta-analysis. JAMA Intern Med 2016 Mar;176(3):340-349. [doi: 10.1001/jamainternmed.2015.7667] [Medline: 26831740]
22. Chow CK, Redfern J, Hillis GS, Thakkar J, Santo K, Hackett ML, et al. Effect of lifestyle-focused text messaging on risk factor modification in patients with coronary heart disease: a randomized clinical trial. JAMA 2015;314(12):1255-1263. [doi: 10.1001/jama.2015.10945] [Medline: 26393848]
23. Orji R, Mandryk RL, Vassileva J. Improving the efficacy of games for change using personalization models. ACM Trans Comput Hum Interact 2017 Oct 06;24(5):1-22 [FREE Full text] [doi: 10.1145/3119929]
24. Zimmer P, Baumann FT, Oberste M, Schmitt J, Joisten N, Hartig P, et al. Influence of personalized exercise recommendations during rehabilitation on the sustainability of objectively measured physical activity levels, fatigue, and fatigue-related biomarkers in patients with breast cancer. Integr Cancer Ther 2018 Jun;17(2):306-311 [FREE Full text] [doi: 10.1177/1534735417713301] [Medline: 28617135]
25. Bandura A. Human agency in social cognitive theory. Am Psychol 1989 Sep;44(9):1175-1184. [doi: 10.1037/0003-066x.44.9.1175] [Medline: 2782727]
26. Bandura A. Self-regulation of motivation and action through goal systems. In: Hamilton V, Bower GH, Frijda NH, editors. Cognitive Perspectives on Emotion and Motivation. Dordrecht, the Netherlands: Springer; 1988:37-61.
27. Stacey FG, James EL, Chapman K, Courneya KS, Lubans DR. A systematic review and meta-analysis of social cognitive theory-based physical activity and/or nutrition behavior change interventions for cancer survivors. J Cancer Surviv 2015 Jun;9(2):305-338 [FREE Full text] [doi: 10.1007/s11764-014-0413-z] [Medline: 25432633]
28. Shamizadeh T, Jahangiry L, Sarbakhsh P, Ponnet K. Social cognitive theory-based intervention to promote physical activity among prediabetic rural people: a cluster randomized controlled trial. Trials 2019 Feb 04;20(1):98. [doi: 10.1186/s13063-019-3220-z] [Medline: 30717779]
29. Sze WT, Waki K, Enomoto S, Nagata Y, Nangaku M, Yamauchi T, et al. StepAdd: a personalized mHealth intervention based on social cognitive theory to increase physical activity among type 2 diabetes patients. J Biomed Inform 2023 Sep;145:104481 [FREE Full text] [doi: 10.1016/j.jbi.2023.104481] [Medline: 37648101]
30. Beauchamp MR, Crawford KL, Jackson B. Social cognitive theory and physical activity: mechanisms of behavior change, critique, and legacy. Psychol Sport Exerc 2019 May;42:110-117 [FREE Full text] [doi: 10.1016/j.psychsport.2018.11.009]
31. Fallon M, Schmidt K, Aydinguel O, Heinzl A. Feedback messages during goal pursuit: the dynamic impact on mHealth use. In: Proceedings of the 42nd International Conference on Information Systems. 2021 Presented at: ICIS '21; December 12-15, 2021; Austin, TX p. 1-17 URL: https://madoc.bib.uni-mannheim.de/60829/1/Fallon%20et%20al.%202021%20ICIS.pdf
32. Fallon M, Spohrer K, Heinzl A. Deep structure use of mHealth: a social cognitive theory perspective. In: Proceedings of the 27th European Conference on Information Systems. 2019 Presented at: ECIS '19; June 8-14, 2019; Stockholm, Sweden URL: https://aisel.aisnet.org/ecis2019_rip/24/#:~:text=We%20take%20a%20social%20cognitive,research%20in%20three%20key%20ways
33. Joseph RP, Ainsworth BE, Hollingshead K, Todd M, Keller C. Results of a culturally tailored smartphone-delivered physical activity intervention among midlife African American women: feasibility trial. JMIR Mhealth Uhealth 2021 Apr 22;9(4):e27383 [FREE Full text] [doi: 10.2196/27383] [Medline: 33885368]
34. Schunk DH. Goal setting and self-efficacy during self-regulated learning. Educ Psychol 2010 Jun 08;25(1):71-86 [FREE Full text] [doi: 10.1207/s15326985ep2501_6]
35. Zimmerman BJ. Academic studing and the development of personal skill: a self-regulatory perspective. Educ Psychol 1998;33(2-3):73-86 [FREE Full text] [doi: 10.1207/s15326985ep3302&3_3]
36. Thomas N, Alder E, Leese GP. Barriers to physical activity in patients with diabetes. Postgrad Med J 2004 May 01;80(943):287-291 [FREE Full text] [doi: 10.1136/pgmj.2003.010553] [Medline: 15138320]
37. Nishida Y, Suzuki H, Wang DH, Kira S. Psychological determinants of physical activity in Japanese female employees. J Occup Health 2003 Jan 21;45(1):15-22 [FREE Full text] [doi: 10.1539/joh.45.15] [Medline: 14605424]
38. Plotnikoff RC, Blanchard C, Hotz SB, Rhodes R. Validation of the decisional balance scales in the exercise domain from the transtheoretical model: a longitudinal test. Meas Phys Educ Exerc Sci 2001 Dec;5(4):191-206 [FREE Full text] [doi: 10.1207/S15327841MPEE0504_01]

39. Ishii K, Inoue S, Ohya Y, Odagiri Y, Takamiya T, Shimomitsu T. Development of a short version of the perceived benefits and barriers to exercise scale. Jpn J Phys Fitness Sports Med 2009;58(5):507-516 [FREE Full text] [doi: 10.7600/jspfsm.58.507]
40. Kawai Y, Sankoda A, Waki K, Miyake K, Hayashi A, Mieno M, et al. Efficacy of the self-management support system DialBetesPlus for diabetic kidney disease: protocol for a randomized controlled trial. JMIR Res Protoc 2021 Aug 17;10(8):e31061 [FREE Full text] [doi: 10.2196/31061] [Medline: 34402802]
41. Steel RG, Torrie JH, Dickey DA. Principles and Procedures of Statistics: A Biometrical Approach. New York, NY: McGraw-Hill College; 1980.
42. Prochaska JO, Velicer WF. The transtheoretical model of health behavior change. Am J Health Promot 1997 Sep;12(1):38-48. [doi: 10.4278/0890-1171-12.1.38] [Medline: 10170434]
43. Shibuta T, Waki K, Tomizawa N, Igarashi A, Yamamoto-Mitani N, Yamaguchi S, et al. Willingness of patients with diabetes to use an ICT-based self-management tool: a cross-sectional study. BMJ Open Diabetes Res Care 2017;5(1):e000322 [FREE Full text] [doi: 10.1136/bmjdrc-2016-000322] [Medline: 28243450]
44. Menon SM, Zink RC. Modern Approaches to Clinical Trials Using SAS: Classical, Adaptive, and Bayesian Methods. Cary, NC: SAS Institute; 2015.
45. Polonsky WH, Anderson BJ, Lohrer PA, Welch G, Jacobson AM, Aponte JE, et al. Assessment of diabetes-related distress. Diabetes Care 1995 Jun;18(6):754-760. [doi: 10.2337/diacare.18.6.754] [Medline: 7555499]
46. Hoshino Y, Seichi A. [Locomo 25--a screening tool for risk of locomotive syndrome]. Nihon Rinsho 2014 Oct;72(10):1839-1843. [Medline: 25509812]
47. Nakawatase Y, Taru C, Tsutou A, Shiotani H, Kido Y, Ohara T, et al. Development of an evaluation scale for self-management behavior related to physical activity of type 2 diabetic patients. Diabetes Care 2007 Nov;30(11):2843-2848. [doi: 10.2337/dc07-0685] [Medline: 17644618]
48. Oka K. [Stages of change for exercise behavior and self-efficacy for exercise among middle-aged adults]. Nihon Koshu Eisei Zasshi 2003 Mar;50(3):208-215. [Medline: 12704833]
49. Yamawaki K, Harada K, Lee E, Oka K, Nakamura Y. Stages of change in walking behavior and development of self-efficacy scale. J Jpn Soc Health Educ 2009;17(2):87-96 [FREE Full text] [doi: 10.11260/kenkokyoiku.17.87]
50. Watanabe K, Kawakami N, Adachi H, Inoue S, Meyer MR. Internal consistency, convergent validity, and structural validity of the Japanese version of the physical activity self-regulation scale (PASR-12) among Japanese workers: a validation study. J Occup Health 2017 Jan 24;59(1):24-32 [FREE Full text] [doi: 10.1539/joh.16-0143-OA] [Medline: 27885244]
51. Daitoku M, Honda I, Okumiya A, Kasayama M, Ikegami H, Miyagawa J, et al. Examination of the validity and reliability of the self-care behavior assessment scale SDSCA (the summary of diabetes self-care activities measure) in Japanese diabetic patients. Diabetes 2006;49(1):1-9 [FREE Full text] [doi: 10.11213/tonyobyo.49.1]
52. Woe S, Shimada H, Sakano Y. The relationship between self-efficacy on health behavior and stress responses in chronic disease patients. Jpn J Psychosom Med 1996;36(6):499-505 [FREE Full text]
53. Bradley C, Todd C, Gorton T, Symonds E, Martin A, Plowright R. The development of an individualized questionnaire measure of perceived impact of diabetes on quality of life: the ADDQoL. Qual Life Res 1999;8(1-2):79-91. [doi: 10.1023/a:1026485130100] [Medline: 10457741]
54. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) group. Lancet 1998 Sep 12;352(9131):837-853. [Medline: 9742976]
55. Diabetes Control and Complications Trial Research Group, Nathan DM, Genuth S, Lachin J, Cleary P, Crofford O, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993 Sep 30;329(14):977-986. [doi: 10.1056/NEJM199309303291401] [Medline: 8366922]
56. Suka M, Odajima T, Kasai M, Igarashi A, Ishikawa H, Kusama M, et al. The 14-item health literacy scale for Japanese adults (HLS-14). Environ Health Prev Med 2013 Sep 21;18(5):407-415 [FREE Full text] [doi: 10.1007/s12199-013-0340-z] [Medline: 23689952]
57. Karter AJ, Ferrara A, Darbinian JA, Ackerson LM, Selby JV. Self-monitoring of blood glucose: language and financial barriers in a managed care population with diabetes. Diabetes Care 2000 Apr;23(4):477-483. [doi: 10.2337/diacare.23.4.477] [Medline: 10857938]
58. Ghazanfari Z, Haghdoost AA, Alizadeh SM, Atapour J, Zolala F. A comparison of HbA1c and fasting blood sugar tests in general population. Int J Prev Med 2010;1(3):187-194 [FREE Full text] [Medline: 21566790]
59. Japan Diabetes Society. Treatment Guide for Diabetes 2022-2023. Tokyo, Japan: Bunkodo; 2022.
60. Freedland KE, King AC, Ambrosius WT, Mayo-Wilson E, Mohr DC, Czajkowski SM, National Institutes of Health Office of Behavioral and Social Sciences Research Expert Panel on Comparator Selection in BehavioralSocial Science Clinical Trials. The selection of comparators for randomized controlled trials of health-related behavioral interventions: recommendations of an NIH expert panel. J Clin Epidemiol 2019 Jun;110:74-81 [FREE Full text] [doi: 10.1016/j.jclinepi.2019.02.011] [Medline: 30826377]

61. Bravata DM, Smith-Spangler C, Sundaram V, Gienger AL, Lin N, Lewis R, et al. Using pedometers to increase physical activity and improve health: a systematic review. JAMA 2007 Nov 21;298(19):2296-2304. [doi: 10.1001/jama.298.19.2296] [Medline: 18029834]
62. Kwasnicka D, Dombrowski SU, White M, Sniehotta F. Theoretical explanations for maintenance of behaviour change: a systematic review of behaviour theories. Health Psychol Rev 2016 Sep;10(3):277-296 [FREE Full text] [doi: 10.1080/17437199.2016.1151372] [Medline: 26854092]
63. Gardner B, Rebar AL. Habit formation and behavior change. In: Braddick O, editor. Oxford Research Encyclopedias: Psychology. Oxford, UK: Oxford University Press; 2019.
64. Nakagawa Y, Moritani N, Ishikawa Y, Yoneshior T, Takezo M. Effects of disease duration and frequency of nutritional guidance on type 2 diabetes patients based on a transtheoretical model. J Jap Soc Health Med 2015;24(2):103-113 [FREE Full text]
65. Sovatzidis A, Chatzinikolaou A, Fatouros IG, Panagoutsos S, Draganidis D, Nikolaidou E, et al. Intradialytic cardiovascular exercise training alters redox status, reduces inflammation and improves physical performance in patients with chronic kidney disease. Antioxidants (Basel) 2020 Sep 15;9(9):868 [FREE Full text] [doi: 10.3390/antiox9090868] [Medline: 32942555]
66. Al-Mhanna SB, Rocha-Rodriguesc S, Mohamed M, Batrakoulis A, Aldhahi MI, Afolabi HA, et al. Effects of combined aerobic exercise and diet on cardiometabolic health in patients with obesity and type 2 diabetes: a systematic review and meta-analysis. BMC Sports Sci Med Rehabil 2023 Dec 04;15(1):165 [FREE Full text] [doi: 10.1186/s13102-023-00766-5] [Medline: 38049873]
67. Georgsson M, Staggers N. Quantifying usability: an evaluation of a diabetes mHealth system on effectiveness, efficiency, and satisfaction metrics with associated user characteristics. J Am Med Inform Assoc 2016 Jan;23(1):5-11. [doi: 10.1093/jamia/ocv099] [Medline: 26377990]
68. Fu HN, Adam TJ, Konstan JA, Wolfson JA, Clancy TR, Wyman JF. Influence of patient characteristics and psychological needs on diabetes mobile app usability in adults with type 1 or type 2 diabetes: crossover randomized trial. JMIR Diabetes 2019 Apr 30;4(2):e11462 [FREE Full text] [doi: 10.2196/11462] [Medline: 31038468]
69. Orrange S, Patel A, Mack WJ, Cassetta J. Patient satisfaction and trust in telemedicine during the COVID-19 pandemic: retrospective observational study. JMIR Hum Factors 2021 Apr 22;8(2):e28589 [FREE Full text] [doi: 10.2196/28589] [Medline: 33822736]
70. Batrakoulis A, Jamurtas AZ, Fatouros IG. Exercise and type II diabetes mellitus: a brief guide for exercise professionals. Strength Cond J 2022 Dec;44(6):64-72 [FREE Full text] [doi: 10.1519/ssc.0000000000000731]

Abbreviations

BP: blood pressure
BW: body weight
CONSORT: Consolidated Standards of Reporting Trials
FAS: full analysis set
HbA_{1c}: hemoglobin A_{1c}
mHealth: mobile health
PPS: per protocol set
SAS: safety analysis set
SCT: social cognitive theory
TTM: transtheoretical model
T2D: type 2 diabetes

Edited by A Mavragani; submitted 10.10.23; peer-reviewed by M Cozad, A Batrakoulis; comments to author 02.01.24; revised version received 03.01.24; accepted 04.01.24; published 23.02.24.

Please cite as:
Waki K, Tsurutani Y, Waki H, Enomoto S, Kashiwabara K, Fujiwara A, Orime K, Kinguchi S, Yamauchi T, Hirawa N, Tamura K, Terauchi Y, Nangaku M, Ohe K
Efficacy of StepAdd, a Personalized mHealth Intervention Based on Social Cognitive Theory to Increase Physical Activity Among Patients With Type 2 Diabetes Mellitus: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2024;13:e53514
URL: https://www.researchprotocols.org/2024/1/e53514
doi:10.2196/53514
PMID:38393770

Protocol

Decreasing Opioid Addiction and Diversion Using Behavioral Economics Applied Through a Digital Engagement Solution: Protocol for a Randomized Controlled Trial

Rubina Fatima Rizvi[1,2,3*], MD, PhD; Jamee Ann Schoephoerster[3*], MD; Sagar Satish Desphande[3,4], MPP, MD; Michael Usher[3,5], MD, PhD; Andy Elaine Oien[2], BS; Maya Marie Peters[2], BS, MPH; Matthew Scott Loth[2], PhD; Matthew William Bahr[5], BSN; Steffen Ventz[6], MPhil, MS, PhD; Joseph Stephen Koopmeiners[2,6], PhD; Genevieve B Melton[1,2,6,7], MD, PhD

[1]Division of Computational Health Sciences, Department of Surgery, University of Minnesota, Minneapolis, MN, United States

[2]Center for Learning Health System Sciences, University of Minnesota, Minneapolis, MN, United States

[3]University of Minnesota Medical School, Minneapolis, MN, United States

[4]Division of Plastic and Reconstructive Surgery, Department of Surgery, University of Minnesota, Minneapolis, MN, United States

[5]M Health Fairview Systems, Minneapolis, MN, United States

[6]Division of Biostatistics, School of Public Health, University of Minnesota, Minneapolis, MN, United States

[7]Division of Colon and Rectal Surgery, Department of Surgery, University of Minnesota, Minneapolis, MN, United States

[*]these authors contributed equally

Corresponding Author:
Genevieve B Melton, MD, PhD
Division of Computational Health Sciences
Department of Surgery
University of Minnesota
11-132 Phillips-Wangensteen Building
516 Delaware Street Southeast
Minneapolis, MN, 55455
United States
Phone: 1 612 626 1999
Email: gmelton@umn.edu

Abstract

Background: Despite strong and growing interest in ending the ongoing opioid health crisis, there has been limited success in reducing the prevalence of opioid addiction and the number of deaths associated with opioid overdoses. Further, 1 explanation for this is that existing interventions target those who are opiate-dependent but do not prevent opioid-naïve patients from becoming addicted.

Objective: Leveraging behavioral economics at the patient level could help patients successfully use, discontinue, and dispose of their opioid medications in an acute pain setting. The primary goal of this project is to evaluate the effect of the 3 versions of the Opioid Management for You (OPY) tool on measures of opioid use relative to the standard of care by leveraging a pragmatic randomized controlled trial (RCT).

Methods: A team of researchers from the Center for Learning Health System Sciences (CLHSS) at the University of Minnesota partnered with M Health Fairview to design, build, and test the 3 versions of the OPY tool: social influence, precommitment, and testimonial version. The tool is being built using the Epic Care Companion (Epic Inc) platform and interacts with the patient through their existing MyChart (Epic Systems Corporation) personal health record account, and Epic patient portal, accessed through a phone app or the MyChart website. We have demonstrated feasibility with pilot data of the social influence version of the OPY app by targeting our pilot to a specific cohort of patients undergoing upper-extremity procedures. This study will use a group sequential RCT design to test the impact of this important health system initiative. Patients who meet OPY inclusion criteria will be stratified into low, intermediate, and high risk of opiate use based on their type of surgery.

Results: This study is being funded and supported by the CLHSS Rapid Prospective Evaluation and Digital Technology Innovation Programs, and M Health Fairview. Support and coordination provided by CLHSS include the structure of engagement,

survey development, data collection, statistical analysis, and dissemination. The project was initially started in August 2022. The pilot was launched in February 2023 and is still running, with the data last counted in August 2023. The actual RCT is planned to start by early 2024.

Conclusions: Through this RCT, we will test our hypothesis that patient opioid use and diverted prescription opioid availability can both be improved by information delivery applied through a behavioral economics lens via sending nudges directly to the opioid users through their personal health record.

Trial Registration: ClinicalTrials.gov NCT06124079; https://clinicaltrials.gov/study/NCT06124079

International Registered Report Identifier (IRRID): PRR1-10.2196/52882

(JMIR Res Protoc 2024;13:e52882) doi:10.2196/52882

KEYWORDS

opioid abuse; opioid naïve patients; opioid addiction; behavioral economics; nudges; MyChart; personal health record; post-operative care; opioid; opioid use; randomized controlled trial; RCT; behavioral economics; digital engagement; health crisis; overdose; acute pain; pain; tool; tools; phone app; website; application

Introduction

Opioid-related overdose and death rates continue to soar in all age groups [1-3]. Today, it is the leading cause of unintentional, injury-related death in the United States [4]. As of 2020, prescription opioid-related deaths totaled more than 16,000 [5]. Even in 2021, despite opiate prescribing reaching a low point, opiate deaths continue to rise [6]. Further, 1 hypothesis to explain this is that existing interventions target those who are opiate-dependent but do not prevent opioid-naïve patients from becoming addicted [7-9]. Once a patient acquires and fills a prescription, they are free to use it however they choose. The continued skyrocketing trajectory of opioid deaths as well as the persistent conundrum of opioid use demonstrates the insufficiency of exclusively relying on prescriber-directed strategies. This highlights the critical need to directly empower individual patients to responsibly manage their use, weaning, discontinuation, and disposal of opioid medications.

Continuous perioperative interventions centered on opioid management and coming from many different angles could contribute to a solution. Evidence has shown that less than 10% of unused opioids are properly disposed of after surgery, suggesting that excess opioids remaining in the home after surgery is a widespread but targetable problem [10]. Diversion of opioids, which is defined as illegal distribution or abuse of opioids for purposes not intended by the prescriber, could be intentional (for example, sharing or selling of medications) or unintentional (for example, theft or ingestion by a child).

Behavioral economics is a field of study within human decision-making where the goal is to predictably influence human behavior and encourage people to do something without forcing, coercing, or penalizing them [11,12]. Several behavioral economics interventions have been leveraged to influence human behaviors but do not guarantee an improvement in the target population's target behavior. Nudging is a way to manipulate people's choices to lead them to make specific decisions. Nudging has previously been used to influence smoking, alcohol consumption, diet, and physical activity to improve population health and reduce health inequalities [13]. More recently, nudging has been used to improve medication compliance among patients with various medical conditions, for example, cardiac [14], kidney transplant recipients [15], patients with diabetes [16], HIV [17], and mental illness [18]. Behavioral economics also offers an opportunity to help individuals make choices consistent with responsibly using and disposing of their opioid medications [19].

The primary goal of this project is to evaluate the effect of the 3 versions of the Opioid Management for You (OPY) tool described in the methods section on measures of opioid use relative to the standard of care (SOC) leveraging a pragmatic randomized controlled trial (RCT). We hypothesize that appropriate patient opioid use and diverted prescription opioid availability can both be improved by information delivery applied through a behavioral economics lens via sending nudges directly to the opioid users, that is, patients. We anticipate not only better management of opioid use and its safe disposal but also expect to obtain a better understanding of the unresolved questions regarding how pain medication is used in acute perioperative settings. In the future, we could further optimize the OPY tool, integrating artificial intelligence and other machine learning models for a more enhanced patient experience.

Methods

OPY Tool

Overview

A team of researchers from the Center for Learning Health System Sciences (CLHSS) at the University of Minnesota partnered with M Health Fairview (MHFV) to design, build, and test the 3 versions of the OPY tool. Based on a literature review of current popular nudging theories implemented in various delivery modes, we incorporated 3 nudging tactics into the workflow of Care Companion to improve patient self-management, medication adherence, and overall health. Tactics were based on the following behavioral economic principles: social influence, precommitment, and testimonial version. Other forms of interventions, including reminders, feedback, and loss-framing, will also be partially incorporated as a component of the design but will not be considered as major guidelines.

The tool is being built using the Epic Care Companion platform and interacts with the patient through their existing MyChart personal health record account and Epic patient portal, accessed through their phone app or the MyChart website. As patients communicate their pill usage, pain scores, or other concerns, the intervention will communicate timely and relevant information regarding opioid use and addiction while also offering encouraging feedback to help patients successfully wean and safely dispose of their opioids. OPY saves the data that a patient enters and based on their responses, the care team is alerted to important issues through an in-basket message system. The alerts or flags are selected and color-coded based on the urgency of action required after discussion with the patient education specialist team.

Each of the 3 OPY versions will deliver the same instructions and information about pain management recommendations and collect the same information about patient pain experience and side effects; however, the behavioral economics techniques used to influence weaning and disposal are different across the 3 versions. The 3 versions will correspond to different treatment arms of the RCT.

Version 1, Social Influence and Commitment

Social influence refers to how individuals change their ideas and behaviors to meet the needs in a social environment [20]. Studies have found that social influence has proved effective for physical activity promotion when applied to mobile apps and is also promising in helping manage chronic diseases, including diabetes.

Patients are provided with text that communicates a social norm or expresses an expectation to the patient meant to decrease the average time it takes for patients to begin weaning. Textbox 1 provides an example of social influence text shown to patients.

Textbox 1. Example of social influence text shown to patients.

Opioid overdoses are at an all-time high. You can help us end this opioid epidemic! When you're ready, we'll help you wean as quickly as possible – and then get rid of your leftover medicine safely.

Version 2, Precommitment

Precommitment refers to a commitment we make in advance to ensure our future actions align with our current preferences and eventually reach the goal we set for ourselves [21]. Studies have shown that precommitment effectively ameliorates self-control problems by encouraging healthy diets, less smoking, and reducing temporary drinking. Being cost-effective in many cases [22], precommitment could have positive implications for chronic disease control and prevention [23].

Patients are given the same suggestions as in other versions but are asked to check a box next to the suggestions they are planning to try. Textbox 2 provides an example of precommitment options provided to patients.

Textbox 2. Example of precommitment options given to patients.

Let's try to reduce your opioid pain medicine. Set a goal to use one of the options below — and be sure to tell a friend or family member about your goal.

- Try taking a dose every X+2 hours (instead of X hours).
- For every other dose, take just half the dose.
- Try skipping a dose.

Version 3, Testimonial

Emerging evidence suggests that storytelling, or narrative communication, influences listeners by actively engaging them in a story, causing them to identify themselves with the storyteller and picture themselves taking part in the action. This approach of leveraging testimonials offers a unique opportunity to promote evidence-based choices in a culturally appropriate context. Stories and storytelling have been previously used as mechanisms to improve patient medication compliance for both hypertension [24] and diabetes [25], as well as improve other health education and literacy programs.

In this approach, instead of text-based nudges or setting goals, the patient receives short videos communicating risks and benefits through narrative storytelling. The videos use voice actors to depict patients who have experienced complications related to opioid use after surgery. A video clip of a person is presented to represent the patient sharing their personal story. Textbox 3 provides an example of testimonial audio presented to patients.

To ensure that videos and their content meet the current in-place requirements of the organization, we worked closely with the patient education team and followed their requirements. We also made sure that the videos were relatable to patients from diverse demographic backgrounds (ie, race, ethnicity, gender, and age) after judicious selection of individual stock video clips from University of Minnesota stock image resources [26] and collecting voice-over audio recordings from our team members who volunteered to read and record the scripts. We will collaborate with the IT team at our implementation sites to create reports on when each patient watched the video and if they watched the full video or left without finishing it. If patients do not complete the video, the task will be flagged to ensure the patient can see and come back later to finish watching the given video.

Textbox 3. Example of testimonial audio presented to patients.

> After having my appendix removed, I took opioids to help with the pain. But, even on the Vicodin my doctor prescribed, I didn't feel great. When my doctor suggested that I start reducing how much I was taking, I didn't want to do that. I wasn't feeling totally better yet. When day 5 came and I hadn't reduced the number of pain pills, I had another problem: constipation. Turns out the pain of going to the bathroom was much worse than the actual pain resulting from surgery. After taking stool softeners along with gradually reducing the dose, I started feeling better in a week. I wish I had started weaning sooner.

OPY Functional Description

OPY appears as a task within MyChart. The first OPY tasks present welcome text for first-time users that describes what OPY is and how to use it. OPY asks users if they want to use OPY or if they want to opt out. OPY tasks and questions will not appear again for people who opt out. OPY then asks patients about their comfort with filling out medical forms and their safety taking ibuprofen or acetaminophen. The medical form information is used to stratify results in our analysis, and the medication question is used to customize pain management suggestions on subsequent days. OPY users must complete these questions before receiving other content from OPY. OPY presents customized messages and questions based on the duration of time since surgery and the responses of the patient. On day 0 (the day of surgery), only the questions described will be asked. OPY patients will not know which version of OPY they are using, or that other versions exist. After day 0, a patient who has opted in will receive several questions every day offered in this order: OPY asks about side effects with prespecified suggestions for what to do for each side effect that they check, pain levels, and the number and frequency of pills they took in the last 24 hours (Figure 1).

Responses are then customized based on the number of days since surgery, patient pain level, and patient pill intake. Depending on their responses, patients receive some combination of pain management advice, including recommendations to take ibuprofen or acetaminophen if able and other standard nonmedication strategies, weaning advice on when and how to start, and disposal advice, including instructions on how and where to dispose of opioids.

At the end of the pathway, all patients will receive a patient satisfaction survey which is standard and exists as an important element of all Epic Care Companion protocols.

Once OPY patients indicate they are taking 0 opioids per day, they will be asked at most 5 times to dispose of the opioids over a span of at most 25 days. OPY will become inactive after 15 consecutive days of no response counted either from day 0 or the last response submitted. Figure 2 summarizes the flow of events that a patient encounters once they are enrolled in the OPY journey.

As per randomization strategy, patients would be assigned one of the following paths: null pathway, pathway 1, pathway 2, or pathway 3. The details are explained in Figure 3.

Figure 1. Epic Systems Corporation 2024 screenshots of OPY screen displaying questions and their responses for (A) social influence and (B) precommitment. OPY: Opioid Management for You.

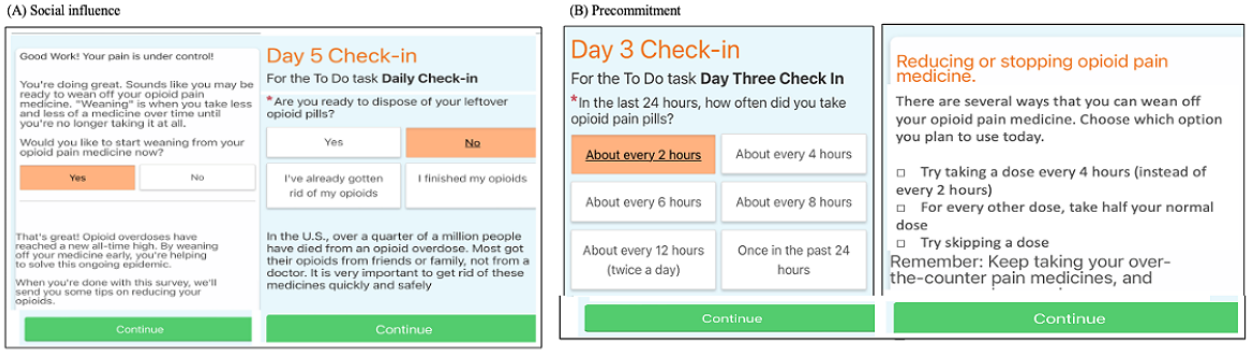


Figure 2. Flow of events once patients are enrolled in OPY. AVS is given to patients after medical appointments to summarize their health and guide future care. OPY: Opioid Management for You.

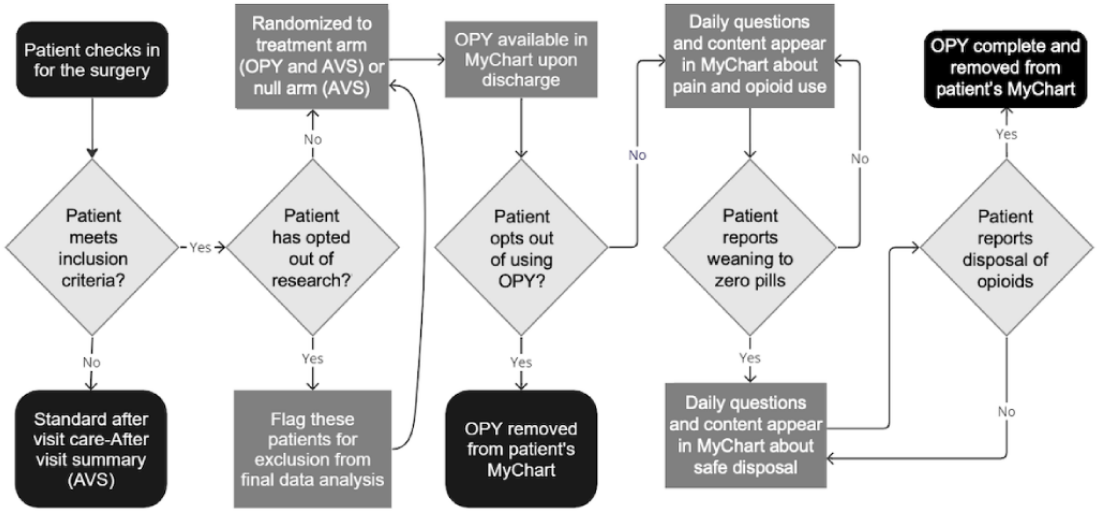
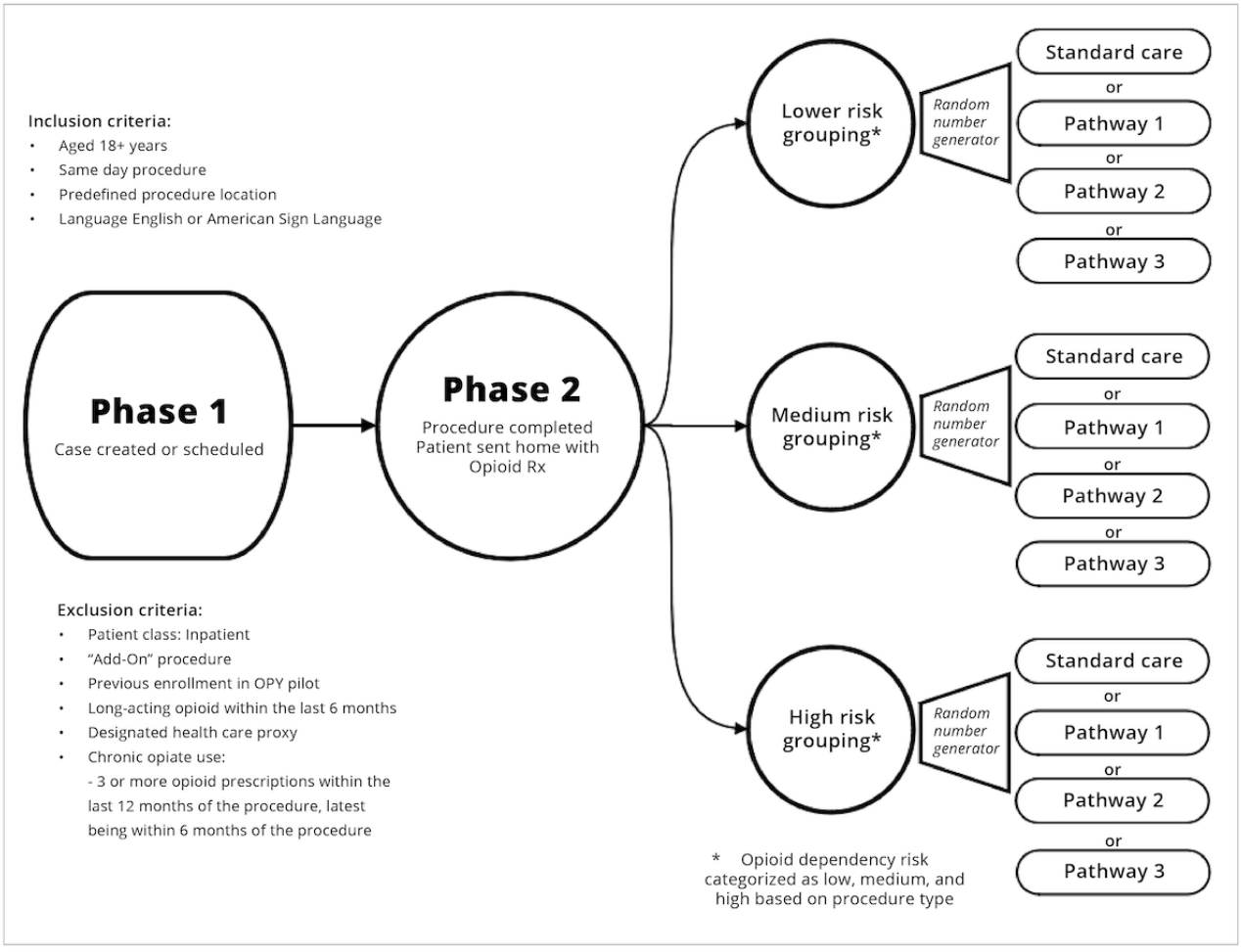


Figure 3. Randomization strategy. Standard care: null pathway; pathway 1: social influence; pathway 2: precommitment; and pathway 3: testimonial. First question patients receive: welcome to the Opioid Program for You! (OPY), Your care team has enrolled you in a digital opioid management program, "OPY," … Do you want to take part in OPY? Click Yes to continue. Click No to stop getting these messages (yes or no). The number of available OPY versions will change over time, which will change the randomization ratio (eg, 1 version available=1:1, standard care versus standard care + pathway 1; 2 versions available=1:1:1, standard care versus standard care + pathway 1 versus standard care + pathway 2). We will leverage an existing random number generator that is embedded within the NAÏVE tool platform which will in turn assign a designated OPY pathway based on the ratio prescription from the statistical team. Rx: doctor's prescription.



Preliminary Data From the Pilot

We have demonstrated feasibility with pilot data of the OPY app (Pathway 1) by targeting our pilot to a specific cohort of patients undergoing upper-extremity procedures. About 13% of opioid-naïve patients continue to fill opioid prescriptions 90 days after hand surgery, signaling that this patient population could benefit from tools to help manage opioid use [27]. Another population that we included in the pilot is breast surgery patients, specifically opioid-naïve patients undergoing lumpectomy, mastectomy, mastopexy, and reduction mammaplasty. In total, 10% of opioid-naïve women continued to fill their prescriptions 3 months after breast reconstruction surgery [28]. Over the initial 15 weeks from August of the pilot, 100 patients were eligible to use OPY. In total, 47 (44%) of eligible patients did not interact with OPY to either opt-in or opt-out. Further, 26 (26%) patients opted out of participating in OPY and 27 (27%) opted into using OPY. There is also evidence of persistent engagement with the OPY app, with 24 (65%) of opted-in patients using the tool at least once in the first 4 days after surgery, and 16 (33%) of opted-in patients using the tool at least twice in the first 4 days after surgery as of August 10, 2023.

The preliminary data from the pilot indicates low patient engagement in continuous use. To identify the exact reason why patients were not using the OPY tool as we expected them to, we reached out to patients, their families, and even perioperative nurses. We found a few reasons, the most prominent one being introducing patients and their families to a new tool such as OPY on the day of surgery which was not considered as an effective approach. Patients are already stressed, under the influence of anesthesia, and are overwhelmed with new information. To ensure that we address those concerns, we came up with certain strategies to improve patient compliance, for example, introducing OPY during preop clinic visits, sending epic care companion messages 3 days before surgery sharing what OPY is all about, and also considering options where a nurse (who normally call on postop day 1 to ask about patient progress or pain) to remind them about OPY tool and its benefits.

Study Design

This study will use a group-sequential RCT design to test the impact of this important health system initiative. Patients who meet OPY inclusion criteria will be stratified into low, intermediate, and high risk of opiate use based on their type of surgery. We used preliminary data to categorize surgery types according to their risk of opiate use. We ranked surgery types according to their opiate use rates at 14 days and categorized surgery types with use rates belonging to the lower 60 percentile, 60-75 percentile, and upper 25 percentile into low, intermediate, and high-risk opioid use groups (surgical risk groups in Multimedia Appendix 1). We estimate the prevalence of these subgroups to be approximately 49%, 34%, and 17%. Randomization will be stratified by baseline risk group, and, within a group, participants will be randomized equally to the SOC (the control group or nonintervention arm) or SOC plus one of the available OPY versions.

Participant Characteristics, Sample Size, and Recruitment Strategies

Inclusion Criteria

We will enroll opioid-naïve patients, aged 18 years or older, including pregnant women, prisoners, and underserved populations who can read and understand English and are undergoing surgery at the MHFV Clinics and Surgery Center—Maple Grove (Maple Grove) or MHFV Clinics and Surgery Center—Minneapolis. Currently, only outpatient surgeries are performed at MHFV Clinics and Surgery Center—Minneapolis and MHFV Clinics and Surgery Center—Maple Grove. Any patient on active opioid prescription (prescribed between 30 days before surgery and until the day of surgery) who was not previously randomized or exposed to OPY would be included. All patients with cancer would be included.

Exclusion Criteria

We will exclude patients aged younger than 18 years; those with chronic opioid use, defined as 3 or more opioid dispensing events in the last 12 months with at least 1 of these events in the last 6 months; patients with any long-acting opioid prescription in the last 6 months; patients with a health proxy (legal guardian) designated in Epic; patients who have opted out of clinical research; and patients with an active palliative care referral.

Children are excluded due to complexities in postoperative care and communication.

Sample Size

The study will enroll up to 3500 participants (approximately 1715, 1190, and 595 enrollments to the low, intermediate, and high-risk groups, respectively) in each OPY version.

Recruitment

We will recruit patients who are undergoing surgery with participating providers at the 2 predetermined locations, that is, MHFV Clinics and Surgery Center in Minneapolis and the Maple Grove locations. Patients who opt out of clinical research or for whom opt-out status is missing will be excluded. The patient is given a choice to consent or opt out of the OPY journey during their first postoperative interaction with the OPY questionnaire distributed through Epic Care Companion. The final decision to participate or not in the OPY journey would be collected from the patient on the day of the surgery (end of the day) through the OPY questionnaire distributed through Epic Care Companion leveraging MyChart.

Study Duration and Data Management

We anticipate that the pragmatic trial will be implemented over 24 months. Our trial will continue enrollments until we reach our 3500 patients enrollment goal. We rely entirely on collaboration with MHFV for data collection within the CLHSS and Fairview data specialist teams. This is because these efforts require the creation of new data fields that leverage a learning health system platform. Unless specified, we will use naturally collected NAÏVE data (including OPY usage) to assess process fidelity, patient safety, and impact on outcomes.

This project will use the existing CLHSS or Center for Quality Outcomes, Discovery, and Evaluation database covered by the institutional review board (IRB) under 597 Protocol (STUDY00014481). The research database lives within Fairview IT. At Fairview, IT access is facilitated by Fairview Research. Please see the data governance processes described in IRB 597 Protocol (STUDY00014481) for further details. This study will rely on the surgical data mart for data acquisition outside of (1) the data primarily generated through the patients' clinical participation in the OPY tool and (2) follow-up surveys.

Data will not be shared publicly. Access is regulated by the CLHSS and Fairview Data stewards. Additional sharing beyond the focus of this study would require additional IRB approval.

Data Collection

Patients meeting OPY inclusion criteria will receive a MyChart message notifying them of access to a specific OPY app. Each patient, regardless of assignment to an OPY version, will receive SOC information via the after-visit summary regarding the appropriate use and disposal of opiates and how to contact their care team if pain persists or worsens. Implementation of each app is primarily driven by the health system. The research team will assist with the allocation approach and subsequent analysis. OPY will collect and send data via the Epic care companion platform leveraging MyChart. Data generated through patient interactions with the OPY tool will live in the Epic environment while the patient is interacting with the tool. This includes data such as daily pain scores, daily opiate usage, daily deferrals of weaning, use of nonopiate medications, "red flag" triggers, and disposal of excess medication. Data generated through interaction with the tool will subsequently be transferred to an Academic Health Center Information Exchange–compliant server as described above. Data on various stakeholder (patients and clinicians) perspectives about their experience with the OPY tool or program would be collected periodically using surveys and or interviews.

Primary and Secondary Study Outcomes

Our primary outcome is the persistent use of opiates as measured by continued use at 14 days. Secondary end points we will seek to evaluate include the number of days between initiation of opioid therapy and opioid-free pain control; the interval time between opioid doses; daily pain scores; number and cause of patient-initiated outreach events (from the care companion app); the number of MyChart messages within the first 30 days postoperative; the number of phone notes in the first 30 days postoperative; 90-day hospitalization rates and hospital length of stay; repeat surgery rates; outpatient encounter rates; referral and completion of referral of pain management rates; 90- and 120-day opiate use rates; OPY usage at 1, 3, 7, 14, and 30 days, 90 days all-cause mortality; metrics around patients' reported disposal of remaining pills, for example, time to disposal and preferred disposal route.

Outcome data will be extracted from natural electronic health record data, common to pragmatic trials. Specific measures including tool usage, opioid prescribing rates, and the existence of comorbidities, are all validated as a part of quality reporting (opioid reduction optimal care map). Each measure is validated at the time of variable construction and immediately before statistical analysis.

Data Analysis

The analysis of the primary and secondary end points will be completed following the intention-to-treat principle. Participant data will be analyzed according to the randomly assigned treatment group. We will ensure that only records of patients who have agreed to have their information used for research are included in the analysis. We will include all patients who opted into the OPY experiment whether they ever used the OPY tool or not.

The baseline opioid use rate of patients varied substantially between the low, intermediate, and high-risk groups. Moreover, preliminary data suggested that our new tool's effectiveness may vary strongly across subgroups. Therefore, we opted out of pooled analyses including all 3 subgroups. Instead, we will conduct 3 prespecified subgroup analyses and each will use a 5% type I error level.

Efficacy Analysis

The study will enroll up to 3500 participants (approximately 1715, 1190, and 595 enrollments to the low, intermediate, and high-risk groups) in each OPY version. Interim and final analyses efficacy analyses will be conducted every 3 months, separately for each surgery risk group, using an O'Brien-Fleming type error-spending function approach to account for the multiple interim and final analyses. Risk-group-specific group-sequential hypothesis tests will use a 1-sided 5% type I error level, to control the overall type I error for each of the 3 interventions at a 15% type I error level.

Futility Interim Analyses

Futility interim analysis will be conducted every 3 months separately in each risk group. The study will stop testing an OPY version in a subgroup if, at the interim analysis, the predicted probability of a positive study outcome (predicted power) in this subgroup drops below 15%.

Power Analysis

Based on our initial estimates of the 14-day opioid use rates (0.03, 0.07, and 0.16) for the SOC in each of the 3 subgroups and an odds-ratio treatment effect of 2.0 (opioid use rates 0.015, 0.037, and 0.087), the group-sequential design has 64%, 82%, and 85% power to detect positive treatment effects in the low, intermediate, and high-risk subgroups.

Study Risks

In this minimal-risk study, there is a very low risk to participants. This risk extends to providers involved in the study or family members of participants. Breach of confidentiality is unlikely but remains a possibility. Data will be maintained in a secure, HIPAA (Health Insurance Portability and Accountability Act)-compliant environment.

Ethical Considerations

This study protocol is submitted to the University of Minnesota IRB and given the initial determination of "Not human subjects research." All patients will be e-consented to the study before

data collection. This will be verified by study staff before data collection and analysis. No data from patients outside the study group will be transmitted into the study database. The study obtained IRB approval on 31 August, 2023 (STUDY00019820). The trial was registered in ClinicalTrials.gov (NCT06124079).

Results

This study was originally started in August 2022 and is being supported by the Rapid Prospective Evaluation and Digital Technology Innovation programs at CLHSS. The implementation of this intervention has been fully resourced by MHFV. The structure of engagement, survey development, data collection, statistical analysis, and dissemination will be coordinated by the Rapid Prospective Evaluation Program and funded entirely. The pilot was launched in February 2023 and is still running. Preliminary data from the pilot collected in August 2023 is reported in the section Methods: Preliminary Data From the Pilot. The RCT is planned to start by the end of August 2023.

Discussion

Principal Results

In this paper, we present the protocol for the OPY study, a group-sequential pragmatic RCT design of patient-facing digital tools deployed using their existing chart personal health record platform. The purpose of this innovative tool is to effectively manage opioid use, weaning, and disposal among postoperative patients by directly interacting at patient levels leveraging behavioral economics principles. To our knowledge, this is one of the first-ever pragmatic clinical trials to study the impact of introducing behavioral economics techniques into a patient-facing, innovative digital technology on opioid management, leveraging the learning health system. The trial is set up as a hybrid implementation-effectiveness trial with strategies informed by behavioral economics theory.

The efficacy of artificial intelligence chatbots in promoting healthy lifestyles, smoking cessation, treatment or medication adherence, and reduction in substance misuse has been tested earlier; however, there were mixed results regarding feasibility, acceptability, and usability [17]. OPY is a novel solution to aid with weaning and disposal of opioids in opioid-naïve people and acts uniquely in a preventative manner. By using an OPY tool, equivalent to an archetype of a chatbot, we could integrate a natural language interface, delivering the pertinent information to the postoperative patients around opioid use at the relevant times and reporting graded alerts or flags to clinical staff to initiate a patient or provider communication if necessary. Earlier evidence has shown that patient characteristics (such as age and gender) play a pivotal role in determining the probability of filling an opioid prescription [3,18,19]. With the implementation of this patient-facing OPY tool, we could help postoperative, naïve patients who are at risk of addiction to more effectively manage these medicines.

By combining the OPY tool, a preliminary version of a chatbot, with behavioral economics, we can use social influence (social norms), precommitment, and testimonial-based “nudges” to encourage patients toward more responsible opioid usage. Future nudges may include social norms, loss aversion, salience effect, and IKEA effect to encourage patients [20]. In the future, we could include infographics showing harm from inappropriate opioid storage and disposal and create charts for patients on opioid use to reinforce patient decisions.

There is some evidence that the effect of behavioral economics nudges on human behavior is not guaranteed to have the desired effects. Introducing behavioral nudges in some instances, has induced the opposite behavior than desired [29-31]. For example, precommitment can unintentionally telegraph to the patient that the behavior has low urgency, decreasing their motivation to accomplish the task. Another well-established mechanism for influencing target behaviors is communicating social norms that support the intended behavior. Social norm nudges are generally accepted to operate by creating some amount of discomfort within the patient, by demonstrating that they are not doing what is typically done by others, to encourage the intended behavior [32]. Our study will help clarify if the behavioral economics techniques we have incorporated can inspire early weaning and disposal or not.

Limitations

A limitation of this study is that the app is currently only available in English, and we will only include patients who can read and write basic English. We are also excluding patients lacking the capacity to consent, as well as children, due to their inability to functionally and meaningfully interact with the app. We will only limit the enrollment to patients undergoing same-day surgery across 2 locations and not system-wide at this time. This limits the operational lift to execute this project and the number of staff needing new training on the OPY technology and care pathway. We do plan to expand to outpatient surgery at the hospital and then to inpatients. Further, in the testimonial version of OPY, the images or voices over the image are generic and the current technology does not have the capability of matching with the patient’s actual demographics.

Conclusions

In summary, by implementing OPY in opioid-naïve patients, we will be able to help prescribers remotely manage new opioid prescriptions. Given the significant limitation in physical proximity with the care team, we must empower patients with a practical tool to assist in weaning off and disposing of opioid medications that are available to them 24/7. Implementation of 3 versions of OPY, all designed to promote weaning from opioids and legal disposal in opioid-naïve patients, will produce generalizable evidence about the impact of behavioral economics on patient prescription behavior. If successful, OPY will advance the understanding and effectiveness of electronic health record–based strategies with patient interaction to improve the delivery of evidence-based care to patients at high risk for opioid addiction.

Acknowledgments

This research was supported by the Agency for Healthcare Research and Quality (AHRQ) and the Patient-Centered Outcomes Research Institute (PCORI; P30HS029744; RFR and GBM). Additional support for the Minnesota Learning Health System Mentored Career Development Program (MN-LHS) is offered by the University of Minnesota Office of Academic Clinical Affairs, Clinical Translational Science Institute, and the Center for Learning Health System Sciences (CLHSS). The content is solely the responsibility of the authors and does not necessarily represent the official views of AHRQ, PCORI, or MN-LHS. We wish to acknowledge MHFV IT and data sciences staff linked to the development of the Opioid Management for You (OPY) tool, especially Deneen Anderson and Iva Ninkovic for leading and managing the efforts. We are grateful to the MHFV Clinics and Surgery staff and clinicians at the Minneapolis location who facilitated us with running the pilot.

Authors' Contributions

The authors confirm contributions to this paper as follows: study conception and design were by SSD, RFR, MU, JSK, and GBM; data collection and analysis plan was done by SV, JSK, RFR, MSL, MWB, and MMP; draft paper preparation was performed by RFR, JAS, MSL, SSD, MMP, MWB, and AEO. All authors reviewed the results and approved the final version of this paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Ranking of surgery types according to their opiate use rates at 14 days. Surgeries are listed from lowest to highest rates of opiate use. Surgery types are additionally categorized by use rates into lower 60 percentile (low-risk opioid use group), 60-75 percentile (medium-risk opioid use group), and upper 24 percentile (high-risk opioid use group).

[XLSX File (Microsoft Excel File), 64 KB - resprot_v13i1e52882_app1.xlsx]

References

1. Gaither JR, Leventhal JM, Ryan SA, Camenga DR. National trends in hospitalizations for opioid poisonings among children and adolescents, 1997 to 2012. JAMA Pediatr 2016;170(12):1195-1201 [FREE Full text] [doi: 10.1001/jamapediatrics.2016.2154] [Medline: 27802492]
2. Allen JD, Casavant MJ, Spiller HA, Chounthirath T, Hodges NL, Smith GA. Prescription opioid exposures among children and aAdolescents in the United States: 2000-2015. Pediatrics 2017;139(4):e20163382. [doi: 10.1542/peds.2016-3382] [Medline: 28320869]
3. McCabe SE, West BT, Veliz P, McCabe VV, Stoddard SA, Boyd CJ. Trends in medical and nonmedical use of prescription opioids among US adolescents: 1976-2015. Pediatrics 2017;139(4):e20162387 [FREE Full text] [doi: 10.1542/peds.2016-2387] [Medline: 28320868]
4. Elzey MJ, Barden SM, Edwards ES. Patient characteristics and outcomes in unintentional, non-fatal prescription opioid overdoses: a systematic review. Pain Physician 2016;19(4):215-228 [FREE Full text] [Medline: 27228510]
5. Wide-Ranging Online Data for Epidemiologic Research (WONDER). Centers for Disease Control and Prevention. 2023. URL: http://wonder.cdc.gov [accessed 2023-11-01]
6. Robert M, Jouanjus E, Khouri C, Fouilhé Sam-Laï N, Revol B. The opioid epidemic: A worldwide exploratory study using the WHO pharmacovigilance database. Addiction 2023;118(4):771-775. [doi: 10.1111/add.16081] [Medline: 36331523]
7. Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC clinical practice guideline for prescribing opioids for pain - United States, 2022. MMWR Recomm Rep 2022;71(3):1-95 [FREE Full text] [doi: 10.15585/mmwr.rr7103a1] [Medline: 36327391]
8. Delgado MK, Huang Y, Meisel Z, Hennessy S, Yokell M, Polsky D, et al. National variation in opioid prescribing and risk of prolonged use for opioid-naive patients treated in the emergency department for ankle sprains. Ann Emerg Med 2018;72(4):389-400.e1 [FREE Full text] [doi: 10.1016/j.annemergmed.2018.06.003] [Medline: 30054152]
9. Larach DB, Sahara MJ, As-Sanie S, Moser SE, Urquhart AG, Lin J, et al. Patient factors associated with opioid consumption in the month following major surgery. Ann Surg 2021;273(3):507-515 [FREE Full text] [doi: 10.1097/SLA.0000000000003509] [Medline: 31389832]
10. Bicket MC, Long JJ, Pronovost PJ, Alexander GC, Wu CL. Prescription opioid analgesics commonly unused after surgery: a systematic review. JAMA Surg 2017;152(11):1066-1071 [FREE Full text] [doi: 10.1001/jamasurg.2017.0831] [Medline: 28768328]
11. Mullainathan S, Thaler RH. Behavioral economics. National Bureau of Economic Research Working Paper Series. 2000. URL: https://www.nber.org/system/files/working_papers/w7948/w7948.pdf [accessed 2024-02-02]
12. Matjasko JL, Cawley JH, Baker-Goering MM, Yokum DV. Applying behavioral economics to public health policy: illustrative examples and promising directions. Am J Prev Med 2016;50(5 Suppl 1):S13-S19 [FREE Full text] [doi: 10.1016/j.amepre.2016.02.007] [Medline: 27102853]

13. Vlaev I, King D, Dolan P, Darzi A. The theory and practice of “Nudging”: changing health behaviors. Public Administration Review 2016;76(4):550-561 [FREE Full text] [doi: 10.1111/puar.12564]
14. Horne BD, Muhlestein JB, Lappé DL, May HT, Le VT, Bair TL, et al. Behavioral nudges as patient decision support for medication adherence: the ENCOURAGE randomized controlled trial. Am Heart J 2022 Feb;244:125-134 [FREE Full text] [doi: 10.1016/j.ahj.2021.11.001] [Medline: 34798073]
15. Oberlin SR, Parente ST, Pruett TL. Improving medication adherence among kidney transplant recipients: findings from other industries, patient engagement, and behavioral economics-a scoping review. SAGE Open Med 2016;4:2050312115625026 [FREE Full text] [doi: 10.1177/2050312115625026] [Medline: 26835016]
16. Kwan YH, Cheng TY, Yoon S, Ho LYC, Huang CW, Chew EH, et al. A systematic review of nudge theories and strategies used to influence adult health behaviour and outcome in diabetes management. Diabetes Metab 2020 Nov;46(6):450-460 [FREE Full text] [doi: 10.1016/j.diabet.2020.04.002] [Medline: 32387700]
17. Linnemayr S, Stecher C, Saya U, MacCarthy S, Wagner Z, Jennings L, et al. Behavioral economics incentives to support HIV treatment adherence (BEST): protocol for a randomized controlled trial in Uganda. Trials 2020;21(1):9 [FREE Full text] [doi: 10.1186/s13063-019-3795-4] [Medline: 31900193]
18. Woodend A, Schölmerich V, Denktaş S. "Nudges" to prevent behavioral risk factors associated with major depressive disorder. Am J Public Health 2015;105(11):2318-2321 [FREE Full text] [doi: 10.2105/AJPH.2015.302820] [Medline: 26378823]
19. Martin A, Kunzler N, Nakagawa J, Lee B, Wakeman S, Weiner S, et al. Get waivered: a resident-driven campaign to address the opioid overdose crisis. Ann Emerg Med 2019;74(5):691-696 [FREE Full text] [doi: 10.1016/j.annemergmed.2019.04.035] [Medline: 31272821]
20. Aggarwal A, Tam CC, Wu D, Li X, Qiao S. Artificial intelligence-based chatbots for promoting health behavioral changes: systematic review. J Med Internet Res 2023;25:e40789 [FREE Full text] [doi: 10.2196/40789] [Medline: 36826990]
21. Precommitment. The Decision Lab. URL: https://thedecisionlab.com/reference-guide/psychology/precommitment [accessed 2023-11-01]
22. Fukuma S, Ikenoue T, Sasaki S, Saigusa Y, Misumi T, Saito Y, et al. Nudging patients with chronic kidney disease at screening to visit physicians: a protocol of a pragmatic randomized controlled trial. Contemp Clin Trials Commun 2019;16:100429 [FREE Full text] [doi: 10.1016/j.conctc.2019.100429] [Medline: 31497673]
23. Kullgren JT, Hafez D, Fedewa A, Heisler M. A scoping review of behavioral economic interventions for prevention and treatment of type 2 diabetes mellitus. Curr Diab Rep 2017;17(9):73 [FREE Full text] [doi: 10.1007/s11892-017-0894-z] [Medline: 28755061]
24. Houston TK, Allison JJ, Sussman M, Horn W, Holt CL, Trobaugh J, et al. Culturally appropriate storytelling to improve blood pressure: a randomized trial. Ann Intern Med 2011;154(2):77-84 [FREE Full text] [doi: 10.7326/0003-4819-154-2-201101180-00004] [Medline: 21242364]
25. Andreae SJ, Andreae LJ, Cherrington AL, Richman JS, Johnson E, Clark D, et al. Peer coach delivered storytelling program improved diabetes medication adherence: a cluster randomized trial. Contemp Clin Trials 2021;104:106358 [FREE Full text] [doi: 10.1016/j.cct.2021.106358] [Medline: 33737200]
26. Technology help: stock content. University of Minnesota. URL: https://it.umn.edu/services-technologies/stock-content-0/ [accessed 2023-08-01]
27. Johnson SP, Chung KC, Zhong L, Shauver MJ, Engelsbe MJ, Brummett C, et al. Risk of prolonged opioid use among opioid-naïve patients following common hand surgery procedures. J Hand Surg Am 2016;41(10):947-957.e3 [FREE Full text] [doi: 10.1016/j.jhsa.2016.07.113] [Medline: 27692801]
28. Kendall MC, Alves LJC. Prescription opioid use among opioid-naive women undergoing immediate breast reconstruction. Plast Reconstr Surg 2018;142(4):609e [FREE Full text] [doi: 10.1097/PRS.0000000000004756] [Medline: 30252831]
29. Beshears J, Dai H, Milkman KL, Benartzi S. Framing the future: the risks of pre-commitment nudges and potential of fresh start messaging. National Bureau of Economic Research Working Paper. 2016. URL: https://static1.squarespace.com/static/5353b838e4b0e68461b517cf/t/583ca5acd2b8571174b28e40/1480369581625/48-Beshears_et_al_2016.pdf [accessed 2019-09-04]
30. Thunström L, Gilbert B, Ritten CJ. Nudges that hurt those already hurting – distributional and unintended effects of salience nudges*. J Econ Behav Organ 2018;153:267-282 [FREE Full text] [doi: 10.1016/j.jebo.2018.07.005]
31. Bicchieri C, Dimant E. Nudging with care: the risks and benefits of social information. Public Choice 2022;191(3-4):443-464 [FREE Full text] [doi: 10.1007/s11127-019-00684-6]
32. Voigt K. Nudging, shaming and stigmatising to improve population health: comment on "nudging by shaming, shaming by nudging". Int J Health Policy Manag 2014;3(6):351-353 [FREE Full text] [doi: 10.15171/ijhpm.2014.114] [Medline: 25396213]

Abbreviations

CLHSS: Center for Learning Health System Sciences
HIPAA: Health Insurance Portability and Accountability Act

IRB: institutional review board
MHFV: M Health Fairview
OPY: Opioid Management for You
RCT: randomized controlled trial
SOC: standard of care

Edited by A Mavragani; submitted 20.11.23; peer-reviewed by H Sun, M Song; comments to author 02.01.24; revised version received 22.01.24; accepted 24.01.24; published 08.03.24.

Please cite as:
Rizvi RF, Schoephoerster JA, Desphande SS, Usher M, Oien AE, Peters MM, Loth MS, Bahr MW, Ventz S, Koopmeiners JS, Melton GB
Decreasing Opioid Addiction and Diversion Using Behavioral Economics Applied Through a Digital Engagement Solution: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2024;13:e52882
URL: https://www.researchprotocols.org/2024/1/e52882
doi:10.2196/52882
PMID:38457203

Protocol

Development of a Multiplatform Tool for the Prevention of Prevalent Mental Health Pathologies in Adults: Protocol for a Randomized Control Trial

Nadia Ramos[1,2], PhD; Felipe Besoain[3], PhD; Natalia Cancino[2,4], MSc; Ismael Gallardo[1], PhD; Paula Albornoz[2], MSc; Andres Fresno[1], PhD; Rosario Spencer[1], PhD; Soledad Schott[5], MSc; Daniel Núñez[1], PhD; Carolina Salgado[2,6], MD; Susana Campos[2], MSc

[1]Faculty of Psychology, University of Talca, Talca, Chile
[2]Center of Applied Psychology, Faculty of Psychology, University of Talca, Talca, Chile
[3]Faculty of Engineering, University of Talca, Talca, Chile
[4]Doctorate in Psychology, Faculty of Psychology, University of Talca, Talca, Chile
[5]Instituto Nacional de Capacitación, Talca, Chile
[6]Medical School, Universidad Catolica del Maule, Talca, Chile

Corresponding Author:
Susana Campos, MSc
Center of Applied Psychology
Faculty of Psychology
University of Talca
1 Poniente 1141
Talca, 3460000
Chile
Phone: 56 71 2 201783
Email: susana.campos@utalca.cl

Abstract

Background: The prevalence of depression and anxiety has increased in recent years, with many individuals having trouble accessing mental health support. Smartphones have become an integral part of modern life, with apps offering new ways to deliver evidence-based self-help strategies to cope with common mental health symptoms. However, most of them do not have empirical evidence of their overall effectiveness or the effectiveness of their components, which could pose a risk for users.

Objective: The aim of this study is to evaluate the effectiveness of the modules of evaluation, psychoeducation, and emotional regulation strategies in a multiplatform self-help mental health mobile app in the Maule region of Chile.

Methods: A sample of 196 adults will be selected, who will be randomly assigned to different components of the app for a fixed period to assess its ability to reduce symptomatology.

Results: The trial is not yet recruiting and is expected to end in October 2024. The first results are expected in April 2024.

Conclusions: This is the first study in Chile to develop and test the effectiveness of a mobile app to manage anxiety and depression symptoms in adults. The intervention proposed is based on evidence suggesting that the internet or remote intervention tools and self-management of prevalent symptomatology could be the future of mental health care systems in the digital era. If the effects of the intervention are positive, wide implementation in Chile and other Spanish-speaking countries could be possible in the future.

International Registered Report Identifier (IRRID): PRR1-10.2196/52324

(JMIR Res Protoc 2024;13:e52324) doi:10.2196/52324

KEYWORDS

adults; anxiety; depression; eHealth; mental health; mobile app; RCT

Introduction

Background and Rationale

Mental health disorders are common in the general population. In Chile, depression and anxiety are the most frequently observed psychopathologies, with a prevalence of 5% for depression and 6.5% for any form of anxiety [1]. However, the population affected by depression or anxiety symptoms may be greater, with 49.2% of Chileans reporting some level of depression symptoms [2]. These prevalences have become a significant issue in public health settings, where waitlists in public mental health services in Chile are mostly stagnant [3], and in the past 2 years have become extensive due to the COVID-19 pandemic. Thus, it becomes necessary to find alternatives that allow providers to respond to this need for mental health access [4].

In this context, the use of remote self-guided psychological interventions, such as those found in mental health mobile apps, has gained popularity [5]. It has been reported that this remote modality improves access, reduces waiting times for appointments, saves time, and reduces the effect of attitudinal barriers in patients seeking psychological support [6]. Studies indicate a high effectiveness rate of web-based care, with smartphone-based psychological interventions reducing user anxiety [7] and depression [8,9]. Accordingly, there has been an increased number of mental health mobile apps available to users. However, many of them do not have sufficient theoretical support for their effectiveness. In 2015, a total of 447 apps related to cognitive behavioral therapy (CBT) were found available in any App Store [10]. Conversely, 9 studies regarding the use of smartphones in cognitive-behavioral interventions were found, of which only 2 had readily available apps in the market [10]. Moreover, 10% of those who say they use cognitive behavioral interventions as a theoretical basis were not evidence-based [11]. It has been suggested that, without empirical support, these apps can be potentially harmful to users [12].

Among the small portion of mobile apps that have empirical support for their tools, 3 specific components or modules have the highest rates of applicability and effectiveness for reducing depression and anxiety: assessment, education, and self-regulation digital tools [13]. The assessment component allows for the recognition of the current symptomatic state of the user, while the constant evaluation helps the monitoring and the development of awareness of the process of change in the symptomatology [14]. The psychoeducation process allows users to be informed about what they are experiencing. Although psychoeducation alone is an effective strategy for the improvement of some anxiety and depression symptoms [15,16], its effectiveness increases when it is accompanied by other strategies [17]. The final component, the use of self-regulation tools, demonstrates a series of brief, easy-to-use self-guided activities that attempt to regulate, express, or otherwise manage psychological distress, low mood, and symptoms of anxiety.

The presentation of these modules normally follows the theoretical framework of CBT. This treatment model can be easily adapted to non–face-to-face environments and has been repeatedly tested in web-based modalities [18,19]. Moreover, other approaches theoretically derived from CBT, such as behavioral activation therapy or mindfulness-based behavioral therapy, also exhibit evidence of their effectiveness in non–face-to-face settings [20]. The behavioral activation treatment for depression attempts to regulate depression symptoms through the programming of pleasurable activities [21], while mindfulness-based CBT focuses primarily on breathing techniques, relaxation, self-compassion, and mindfulness abilities [22], aimed at regulating anxiety states.

According to the literature, there are no mobile apps with scientific support to address depression and anxiety symptoms in the adult population in Chile. The regular and widespread use of such apps could help provide self-care tools to individuals who are reticent about therapy.

Aims

The main aim of this study is to develop a multiplatform self-help mental health mobile app for adults and to test the effectiveness of its assessment, psychoeducation, and emotional regulation strategy modules post intervention and at 1-month follow-up. We hypothesize that the combination of psychoeducation and any self-regulatory strategies will prove more effective than the evaluation and psychoeducation components alone in decreasing symptomatology.

Trial Design

This is a protocol for a double-blind, 4-armed randomized controlled trial (ClinicalTrials.gov NCT05997849) evaluating changes in primary and secondary outcomes (symptomatology and well-being variables) post intervention and at follow-up. The 4 arms will be group 1 (control): the participants will have access only to the monitoring and psychoeducation module for 30 days; group 2: participants will have access to the monitoring module, psychoeducation, and mindfulness strategies for 30 days; group 3: participants will have access to the monitoring module, psychoeducation, and behavioral activation strategies for 30 days; and group 4: participants will have access to the monitoring, psychoeducation, and cognitive strategies module for 30 days. Additionally, 1 focus group per condition will be carried out to qualitatively assess the user experience with the app and its overall usability.

Methods

Study Setting

Participants will be adults (18 years of age and older) in the Maule Region of Chile and mixed-sex. We expect to recruit 49 participants per arm, configuring 196 participants in total.

Eligibility Criteria

Adult Chilean citizens, 18 years of age or older, with access to a computer, tablet, or smartphone (Android or iOS) with internet, and no untreated mental health diagnosis, will be included in the study. The mental health diagnosis and current treatment will be assessed solely by the participant's self-report.

Individuals who self-report substance abuse problems or any current serious mental health disorder and participants reporting

scores greater than 1 on question 9 (suicidal ideation) on the Patient Health Questionnaire–9 (PHQ-9) will be excluded from the study.

Ethical Considerations

This study and all associated documents were approved by the Scientific Ethics Committee of the University of Talca (14/2022). Informed consent will be obtained from all participants through web-based forms before the allocation process begins. The collected data are completely deidentified and stored in secure servers (see Data Management section). Participants will not receive any type of compensation for their participation in the study.

Recruitment and Informed Consent

For recruitment, invitations will be made through the social networks of the Center for Applied Psychology and the Faculty of Psychology of the University of Talca. In addition, the educational and health services of 4 districts in the region will be contacted to disseminate the multiplatform application Cuidandome to adults. The call for participation will include an explanatory video and an informed consent form, which will be available on and collected through the project website (under development). Participants will be recruited through convenience sampling and will be randomly assigned to 1 of the 4 groups by means of simple randomization (through the PHP: Hypertext Preprocessor rand() function).

Interventions

Description of Interventions

Cuidandome is a multiplatform self-help mental health app that does not constitute a psychological treatment. The mobile app will be available for iOS and Android operating systems, and it is composed of 3 modules: monitoring, psychoeducation, and strategies for people to learn to manage their emotional states and their depression or anxiety symptoms.

The modules of the app are given below.

Monitoring (M) Module

The aim of this assessment module is to acquire information on the symptoms and well-being of the participants in the process of using the app and their satisfaction with the strategies. This transversal component is composed of a weekly assessment and a brief daily mood assessment so that the person can monitor their own mood.

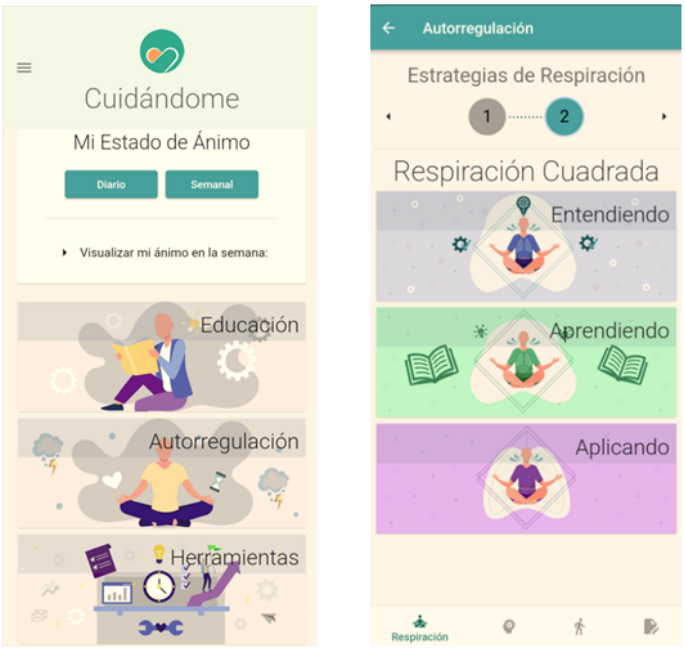
Psychoeducation (P) Module

The aim of this module is to provide information to the user about different aspects of mental health care, understanding depression and anxiety symptoms, and the fundamentals of the app and how to get the most out of it. Several studies have shown the relevance of psychoeducation in mental health care.

Regulation Strategies (RS) Module

This module is based on cognitive behavioral change techniques and strategies originating from the basic principles of CBT for the treatment of depression and generalized anxiety, behavioral activation therapy for depression, and mindfulness strategies for managing anxiety and depression. The module is organized into 3 types of strategies: cognitive (strategies to help modify cognitions that cause discomfort), behavioral activation (strategies focused on modifying behavior that causes discomfort), and mindfulness (strategies to help stay in the present moment and decrease activation of the sympathetic nervous system). Each of the strategies will be developed sequentially through 3 tasks: understanding, learning, and practicing; providing activities to understand why the strategy works and how it should be done; and finally, putting the strategy into practice. Figure 1 shows the overview of the dashboards.

Figure 1. Main dashboard (left) and regulation strategies: square breathing dashboard (right).



Criteria for Discontinuing or Modifying Allocated Interventions

Participants in any group can leave the study at any time if they wish without any consequences; this means that their information and collected data will not be analyzed.

Strategies to Improve Adherence to Interventions

No group will be monitored regarding adherence, as the app is essentially self-guided. However, the app sends daily messages to participants to remind them to access the app and complete at least 1 activity.

Outcomes

Primary Outcomes

Anxiety symptom is 1 of the 2 primary outcomes, and it will be measured by the Generalized Anxiety Disorder–7 Scale (GAD-7). It consists of 7 items that the person assesses on a scale of 0-3 according to the frequency with which each symptom has disturbed them during the past 2 weeks [23]. It shows high reliability in Chilean samples (Cronbach α=0.86 [24]).

Depression symptoms will be measured by the PHQ-9 depression scale, which consists of 9 items that evaluate the presence of depression symptoms present in the past 2 weeks, with a response scale of 0=never, 1=some days, 2=more than half the days, and 3=almost every day. With a Cronbach α of 0.83, its reliability is high in Chilean samples [25]. Additionally, depression and anxiety symptoms in the past week will be assessed through the Patient Health Questionnaire–4 (PHQ-4) [26].

Primary and secondary outcomes will be assessed at 3 time points: preintervention (baseline), immediately post intervention (30 days post intervention), and 1-month follow-up in all groups.

Secondary Outcomes

Well-Being

Perceived psychological and overall well-being is measured by the Pemberton Happiness Index scale (PHI), a 21-item instrument evaluated in 2 subscales: psychological well-being (experienced 5 positive and 5 negative experiences) and subjective well-being (remembered). The scale is Likert-type, with scores per item from 0 to 10 [27].

Resilience

Perceived resilience is measured by the Brief Resilience Scale (BRS), a 6-item instrument on a Likert scale from 1 to 5. It has 3 inverted items, and the rating results from the average of the scores obtained [28].

Ruminative Thoughts

Rumination and ruminative thoughts are assessed by the Ruminative Response Scale (RRS, short version), consisting of 10 items that measure ruminant thoughts in 2 dimensions: reflection and restlessness. It has a high level of internal consistency (Cronbach α=0.85). Each item is scored on a 4-point Likert scale from 1 (almost never) to 4 (almost always) [29].

Emotional Regulation

Emotional regulation is assessed by the Emotional Regulation Questionnaire (ERQ), a 10-item questionnaire designed to measure respondents' tendency to regulate their emotions in 2 ways: (1) cognitive reappraisal (1, 3, 5, 7, 8, and 10) and (2) expressive suppression (2, 4, 6, and 9) [30].

Mindfulness Skills

Mindfulness skills are assessed with the Mindfulness Attention Awareness Scale (MAAS), an instrument composed of 14 items on a Likert scale from 1 to 6. The scores obtained are added, and the higher the score, the greater the ability to pay attention fully and consciously. The average scores of the nonclinical participants are 65 points out of a total of 84 [31].

Participant Timeline

See Table 1 for the participant timeline.

Table 1. Participant timeline.

Time point	2023					2024								
	Enrollment			Allocation		Post allocation						Close-up		
	September	October	November	December	January	February	March	April	May	June	July	August	September	October
Enrollment														
Contact with health centers and prospects	✓	✓												
Eligibility screen		✓	✓	✓										
Allocation				✓	✓									
Informed consent					✓	✓								
Interventions														
Intervention all arms							✓							
Assessment														
Baseline variables						✓								
Outcome variables							✓	✓	✓					
Dissemination														
Analyses										✓	✓	✓		
Results presentation and publication													✓	✓

Sample Size

To achieve the aims of the study, we have considered 4 arms. To obtain a statistical power of 0.80, a minimum sample size of 36 participants is required for each of the 4 arms. Controlling for a dropout rate of 26%, as shown by the literature on behavioral experiments linked to mobile apps for symptoms related to mood and anxiety [32,33], a final sample size of 49 participants per group is required. The sample size approximation was made based on the literature on statistical power and sample sizes in clinical and social science research [34], while the estimate to reduce the effects of the percentage of abandonment in the experimental conditions was calculated based on Wang and Ji [33]. Thus, an estimate of 196 participants sufficiently obeys such parameters. In addition to the quantitative data collection, a qualitative collection of information will be carried out through focus groups. Regarding the number of focus groups, a total of 4 have been established, 1 for each study group. The size of the focus groups, following the recommendations in the literature [35], is estimated at a total of 32 participants (reaching an estimate of the saturation point), that is, 8 participants per focus group.

Recruitment

The strategies for achieving adequate participant enrollment to reach the target sample size will include contacting and presenting the study to municipality authorities, who are expected to help establish contact with public health authorities. Interested individuals can sign up to participate through the QR code available in pamphlets delivered to primary health clinics in the Maule area. Health staff in the selected public clinics will also encourage patients to participate in the study.

Assignment of Interventions: Allocation

Sequence Generation

Participants will be randomly assigned to any group with a 1:1 allocation through a website. The web system will generate randomization based on the rand() function of the PHP language. Through this function, a random number between 0 and 3 is generated and subsequently assigned to the participants upon recruitment.

Concealment Mechanism

After the randomization and allocation, participants will not receive information regarding the group they belong to. Instead, they will be instructed to access the app and complete the emotional regulation activities, regardless of the type. The participants will only have access to a version of the app that includes the strategies that correspond with their assigned group. Additionally, this information will not be disclosed to the assessment research team (outcome evaluators) to keep the participant allocation blind.

Allocation Implementation

Participants will be randomly assigned to any group with a 1:1 allocation through a website. The web system will generate randomization based on the rand() function of the PHP language. Through this function, a random number between 0 and 3 is generated and subsequently assigned to the participants upon recruitment. Depending on the random number assigned, a QR code will be sent to the participants, which will allow them to download a version of the app that contains the strategies pertinent to their study group.

Assignment of Interventions: Blinding

Who Will Be Blinded?

This is a double-blinded trial, blinded to the participants and the research team. A data analyst will work with the final data set, where the group condition will be masked.

Procedure of Unblinding If Needed

Unblinding will not occur in this study.

Data Collection and Management

Plans for Assessment and Collection of Outcomes

Self-report questionnaires assessing primary and secondary outcomes will be administered at baseline (immediately before intervention), post intervention, and follow-up. Primary outcomes will be assessed through the website and the app, and secondary outcomes will be measured only on the website.

Plans to Promote Participant Retention and Complete Follow-Up

Participants will receive extensive information about the study setup and requirements during the recruitment. This information will include and stress the importance of completion of the follow-up.

Data Management

After the participants have completed the web-based questionnaires both on the website and on the app, we will enter the confidential data into a secure platform without identifying information, as each participant will be assigned an encrypted ID number. Only the lead investigator, the research assistants in charge of partial data entry, and the statistician will have access to the complete database. All people with access to the data set will need to sign a confidential agreement to assure the commitment to not reveal identifying information.

Statistical Methods

Statistical Methods for Primary and Secondary Outcomes

We will use descriptive statistics to assess balance across groups at baseline. The primary between-group analysis will be carried out on an intention-to-treat basis for GAD-7 and PHQ-9 scores. We will use a linear mixed model for repeated measures (MMRM) analyses to compare all the intervention and control groups regarding the change in all outcome measures from baseline to post intervention and at follow-up. All the models will be adjusted for sex, age, educational level, and concurrent psychological or psychiatric treatment. Analysis will be carried out with SPSS 26 (IBM Corp) and Stata 15.01 (StataCorp).

Statistical Methods for Additional Analyses

Secondary analyses will mainly explore the complex associations between all outcomes. To this end, correlation analyses will be carried out between symptomatic and other psychological variables. Multiple regression analyses and logistic regression analyses among all variables, particularly between mindfulness skills and anxiety symptoms, rumination and depression symptoms, and gender and symptomatology variables will be carried out. Lastly, group comparisons by gender and hours of app use will also be performed. The analysis will be carried out with SPSS 26.

Interim Analyses

There will not be interim analyses because the data will be analyzed at the end of the trial.

Methods in Analysis to Handle Protocol Nonadherence and Any Statistical Methods to Handle Missing Data

Primary outcomes will be assessed using an intention-to-treat analysis. Missing data will be reduced to a minimum by (1) rendering it impossible to advance on the app if a questionnaire is not completed in full, and (2) using the appropriate measures to encourage participants to fill out the follow-up questionnaires. Multiple imputations will be used to handle any missing data in the analyses.

Plans to Give Access to the Full Protocol, Participant-Level Data, and Statistical Code

The data set produced during the study will be available upon reasonable request from the lead researcher NR.

Oversight and Monitoring

Composition of the Coordinating Center and Trial Steering Committee

Daily support for the trial will be provided by the lead investigator, who supervises the trial. Additionally, the study coordinator helps with trial registration and will coordinate and oversee the study visits and reports while organizing data collection and assuring data quality. The data analyst will handle the database and carry out all primary and secondary analyses once all data are collected. Lastly, the app developer will design and implement all content of the app, ensuring the proper functioning of fundamental features such as the randomization of participants, completeness of data collected, automatic creation of the database, etc. The main study team will meet weekly during the duration of the study and monthly with a secondary group of expert collaborators. There is no trial steering committee, stakeholder, or public involvement group. The Ethical Scientific Committee of the Universidad de Talca will check the completeness of the investigation.

Composition of the Data Monitoring Committee, Its Role, and Reporting Structure

A monitor from the Ethical Scientific Committee of the Universidad de Talca will check once a year the presence and completeness of the investigation. This committee is independent of the sponsor and has no competing interests. For further details, please contact cec@utalca.cl.

Adverse Event Reporting and Harms

The intervention does not cause any harm to the participants. However, if participants experience emotional distress upon using the app, they can contact the lead investigator at any time, who can provide them with options for referral to other public mental health services available. This procedure is explained in detail in the informed consent and initial training videos.

Frequency and Plans for Auditing Trial Conduct

A monitor from the Ethical Scientific Committee will check annually the presence and completeness of the investigation files, such as informed consent, inclusion and exclusion criteria, and data collection and storage.

Plans for Communicating Important Protocol Amendments to Relevant Parties (eg, Trial Participants and Ethical Committees)

All substantial amendments will be notified to the Ethics Committee of the Universidad de Talca. In case amendments concern or affect participants in any way, they will be informed about the changes. If needed, additional consent will be requested and registered. Additionally, web-based trial registries will be updated accordingly.

Dissemination Plans

All results of this research will be disclosed completely in international peer-reviewed journals. Executive summaries of the results will be given to government authorities and public entities acting as stakeholders. Lastly, preliminary relevant results will be presented at an international internet-based mental health seminar organized by the research team, to take place in mid-2024. The full protocol will be made publicly available on the original registry's website when the study is completed. Publications resulting from this protocol will consider the principal investigators and any participating analyst as authors.

Results

The trial is not yet recruiting and is expected to end in October 2024. The first results are expected in late April 2024.

Discussion

Overview

This study aims to develop a multiplatform self-help mental health mobile app for adults and test the effectiveness of its modules post intervention and at 1-month follow-up. This is the first study in Chile to develop and test the effectiveness of a mobile app to manage anxiety and depression symptoms in adults. The intervention proposed is based on evidence suggesting that the internet or remote intervention tools and self-management of prevalent symptomatology could be the future of mental health care systems in the digital era. If the effects of the intervention are positive, wide implementation in Chile and other Spanish-speaking countries could be possible in the future.

However, this project faces some challenges regarding feasibility and adoption of the intervention, where dropout rates could potentially hinder the results of the experimental procedure, even when accounted for [36]. Additionally, probable limitations are the exclusion of part of the clinical population from the study sample (ie, individuals not currently in treatment or at suicide risk) and the difficulty of controlling the effects of therapy on the primary outcomes in individuals simultaneously undergoing psychotherapy.

Conclusion

Implementing this research protocol, we expect to provide evidence for the effectiveness of a mental health mobile app in reducing depression and anxiety symptoms in Chilean adults. Moreover, we expect to provide evidence on the associations of these symptom variables and other risk or protective factors for mental health in adults in the context of digital platforms and interventions for health. The potential clinical and research implications derived from this study could help the mental health and well-being of the Chilean population significantly.

Acknowledgments

Funding for this study was granted by Gobierno Regional del Maule, through Fondo de Innovación para la Competitividad initiative number 40027682. NC received sponsorship from Agencia Nacional de Investigación y Desarrollo–Subdirección de Capital Humano/Doctorado Nacional/2022/21221538.

Data Availability

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

Authors' Contributions

NR conceived, designed, and applied for funding for the study. FB designed the mobile technology. NC contributed to the methodological design and reviewed the app content. IG contributed to the methodological design. PA created the media and content for the app and coordinated the project. AF, RS, SS, DN, and CS acted as theoretical and methodological advisors and reviewed app content. SC created content for the mobile app and wrote the protocol. Funder and committees did not have a role in study design, data management, or other areas.

Conflicts of Interest

None declared.

References

1. The burden of mental disorders in the region of the Americas. Pan American Health Organization. 2018. URL: https://iris.paho.org/handle/10665.2/49578?show=full [accessed 2023-08-25]
2. Hojman D, Krauze M, Llaupi M, Rojas G, Vergés Á. Resultados Primera Ola Estudio Longitudinal Social de Chile (ELSOC). Módulo 6: salud y bienestar. Salud mental en el Chile de hoy. Notas COES de política pública no.15. Centro de Estudios de Conflicto y Cohesión Social—COES. Santiago, Chile: COES; 2018. URL: https://coes.cl/publicaciones/no15-elsoc-salud-mental-en-el-chile-de-hoy/ [accessed 2024-02-07]
3. Gómez L, Núñez A. Vigilancia del Acceso a la salud en chile: Un sistema de indicadores Para Monitoreo multidimensional. [A system aimed at monitoring healthcare access in Chile]. Rev Med Chil 2021;149(1):62-75 [FREE Full text] [doi: 10.4067/S0034-98872021000100062] [Medline: 34106137]
4. Dos Santos Costa AC, Menon V, Phadke R, Dapke K, Miranda AV, Ahmad S, et al. Mental health in the post COVID-19 era: future perspectives. Einstein (Sao Paulo) 2022;20:eCE6760 [FREE Full text] [doi: 10.31744/einstein_journal/2022CE6760] [Medline: 35584448]
5. Torous J, Myrick KJ, Rauseo-Ricupero N, Firth J. Digital mental health and COVID-19: using technology today to accelerate the curve on access and quality tomorrow. JMIR Ment Health 2020;7(3):e18848 [FREE Full text] [doi: 10.2196/18848] [Medline: 32213476]
6. Miralles I, Granell C, Díaz-Sanahuja L, Van Woensel W, Bretón-López J, Mira A, et al. Smartphone apps for the treatment of mental disorders: systematic review. JMIR Mhealth Uhealth 2020;8(4):e14897 [FREE Full text] [doi: 10.2196/14897] [Medline: 32238332]
7. Firth J, Torous J, Nicholas J, Carney R, Rosenbaum S, Sarris J. Can smartphone mental health interventions reduce symptoms of anxiety? A meta-analysis of randomized controlled trials. J Affect Disord 2017;218:15-22 [FREE Full text] [doi: 10.1016/j.jad.2017.04.046] [Medline: 28456072]
8. Bert F, Giacometti M, Gualano MR, Siliquini R. Smartphones and health promotion: a review of the evidence. J Med Syst 2014;38(1):9995 [FREE Full text] [doi: 10.1007/s10916-013-9995-7] [Medline: 24346929]
9. Watts S, Mackenzie A, Thomas C, Griskaitis A, Mewton L, Williams A, et al. CBT for depression: a pilot RCT comparing mobile phone vs. computer. BMC Psychiatry 2013;13:49 [FREE Full text] [doi: 10.1186/1471-244X-13-49] [Medline: 23391304]
10. Torous J, Levin ME, Ahern DK, Oser ML. Cognitive behavioral mobile applications: clinical studies, marketplace overview, and research agenda. Cogn Behav Pract 2017;24(2):215-225. [doi: 10.1016/j.cbpra.2016.05.007]
11. Stawarz K, Preist C, Tallon D, Wiles N, Coyle D. User experience of cognitive behavioral therapy apps for depression: an analysis of app functionality and user reviews. J Med Internet Res 2018;20(6):e10120 [FREE Full text] [doi: 10.2196/10120] [Medline: 29875087]
12. Baumel A, Torous J, Edan S, Kane JM. There is a non-evidence-based app for that: a systematic review and mixed methods analysis of depression- and anxiety-related apps that incorporate unrecognized techniques. J Affect Disord 2020;273:410-421. [doi: 10.1016/j.jad.2020.05.011] [Medline: 32560936]
13. Lagan S, D'Mello R, Vaidyam A, Bilden R, Torous J. Assessing mental health apps marketplaces with objective metrics from 29,190 data points from 278 apps. Acta Psychiatr Scand 2021;144(2):201-210. [doi: 10.1111/acps.13306] [Medline: 33835483]
14. Ritterband LM, Thorndike FP, Cox DJ, Kovatchev BP, Gonder-Frederick LA. A behavior change model for internet interventions. Ann Behav Med 2009;38(1):18-27 [FREE Full text] [doi: 10.1007/s12160-009-9133-4] [Medline: 19802647]
15. Carlbring P, Hägglund M, Luthström A, Dahlin M, Kadowaki Å, Vernmark K, et al. Internet-based behavioral activation and acceptance-based treatment for depression: a randomized controlled trial. J Affect Disord 2013;148(2-3):331-337. [doi: 10.1016/j.jad.2012.12.020] [Medline: 23357657]
16. Qu C, Sas C, Roquet CD, Doherty G. Functionality of top-rated mobile apps for depression: systematic search and evaluation. JMIR Ment Health 2020;7(1):e15321 [FREE Full text] [doi: 10.2196/15321] [Medline: 32012079]
17. Shen N, Levitan MJ, Johnson A, Bender JL, Hamilton-Page M, Jadad AAR, et al. Finding a depression app: a review and content analysis of the depression app marketplace. JMIR Mhealth Uhealth 2015;3(1):e16 [FREE Full text] [doi: 10.2196/mhealth.3713] [Medline: 25689790]
18. Andersson G, Hesser H, Veilord A, Svedling L, Andersson F, Sleman O, et al. Randomised controlled non-inferiority trial with 3-year follow-up of internet-delivered versus face-to-face group cognitive behavioural therapy for depression. J Affect Disord 2013;151(3):986-994. [doi: 10.1016/j.jad.2013.08.022] [Medline: 24035673]
19. Andrews G, Basu A, Cuijpers P, Craske MG, McEvoy P, English CL, et al. Computer therapy for the anxiety and depression disorders is effective, acceptable and practical health care: an updated meta-analysis. J Anxiety Disord 2018;55:70-78 [FREE Full text] [doi: 10.1016/j.janxdis.2018.01.001] [Medline: 29422409]
20. Mancinelli E, Dell'Arciprete G, Pattarozzi D, Gabrielli S, Salcuni S. Digital behavioral activation interventions during the perinatal period: scoping review. JMIR Pediatr Parent 2023;6:e40937 [FREE Full text] [doi: 10.2196/40937] [Medline: 36853756]
21. Bianchi J, Henao Á. Activación conductual y depresión: conceptualización, evidencia y aplicaciones en Iberoamérica. [Behavioral activation and depression: conceptualization, evidence and applications in Latin America]. Ter Psicol 2015;33(2):69-80 [FREE Full text] [doi: 10.4067/s0718-48082015000200002]

22. Schanche E, Vøllestad J, Visted E, Svendsen JL, Osnes B, Binder PE, et al. The effects of mindfulness-based cognitive therapy on risk and protective factors of depressive relapse—a randomized wait-list controlled trial. BMC Psychol 2020;8(1):57 [FREE Full text] [doi: 10.1186/s40359-020-00417-1] [Medline: 32503649]
23. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006;166(10):1092-1097 [FREE Full text] [doi: 10.1001/archinte.166.10.1092] [Medline: 16717171]
24. Crockett MA, Martínez V, Ordóñez-Carrasco JL. Propiedades psicométricas de la escala Generalized Anxiety Disorder 7-Item (GAD-7) en una muestra comunitaria de adolescentes en Chile. Rev Med Chil 2022;150(4):458-464 [FREE Full text] [doi: 10.4067/S0034-98872022000400458] [Medline: 36155755]
25. Baader TM, Molina JLF, Venezian SB, Rojas CC, Farías RS, Fierro-Freixenet C, et al. Validación y utilidad de la encuesta PHQ-9 (Patient Health Questionnaire) en el diagnóstico de depresión en pacientes usuarios de atención primaria en Chile. Rev Chil Neuro Psiquiatr 2012;50(1):10-22 [FREE Full text] [doi: 10.4067/s0717-92272012000100002]
26. Kroenke K, Spitzer RL, Williams JBW, Löwe B. An ultra-brief screening scale for anxiety and depression: the PHQ-4. Psychosomatics 2009;50(6):613-621. [doi: 10.1176/appi.psy.50.6.613] [Medline: 19996233]
27. Paiva BSR, de Camargos MG, Demarzo MMP, Hervás G, Vázquez C, Paiva CE. The Pemberton Happiness Index: validation of the universal Portuguese version in a large Brazilian sample. Medicine (Baltimore) 2016;95(38):e4915 [FREE Full text] [doi: 10.1097/MD.0000000000004915] [Medline: 27661039]
28. Smith BW, Dalen J, Wiggins K, Tooley E, Christopher P, Bernard J. The brief resilience scale: assessing the ability to bounce back. Int J Behav Med 2008;15(3):194-200. [doi: 10.1080/10705500802222972] [Medline: 18696313]
29. Treynor W, Gonzalez R, Nolen-Hoeksema S. Rumination reconsidered: a psychometric analysis. Cognit Ther Res 2003;27:247-259. [doi: 10.1023/A:1023910315561]
30. Gross JJ, John OP. Individual differences in two emotion regulation processes: implications for affect, relationships, and well-being. J Pers Soc Psychol 2003;85(2):348-362. [doi: 10.1037/0022-3514.85.2.348] [Medline: 12916575]
31. Brown KW, Ryan RM. The benefits of being present: mindfulness and its role in psychological well-being. J Pers Soc Psychol 2003;84(4):822-848. [doi: 10.1037/0022-3514.84.4.822] [Medline: 12703651]
32. Torous J, Andersson G, Bertagnoli A, Christensen H, Cuijpers P, Firth J, et al. Towards a consensus around standards for smartphone apps and digital mental health. World Psychiatry 2019;18(1):97-98 [FREE Full text] [doi: 10.1002/wps.20592] [Medline: 30600619]
33. Wang X, Ji X. Sample size estimation in clinical research: from randomized controlled trials to observational studies. Chest 2020;158(1S):S12-S20 [FREE Full text] [doi: 10.1016/j.chest.2020.03.010] [Medline: 32658647]
34. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 2007;39(2):175-191 [FREE Full text] [doi: 10.3758/bf03193146] [Medline: 17695343]
35. Carlsen B, Glenton C. What about N? A methodological study of sample-size reporting in focus group studies. BMC Med Res Methodol 2011;11:26 [FREE Full text] [doi: 10.1186/1471-2288-11-26] [Medline: 21396104]
36. Hernández-Rodríguez JC, García-Muñoz C, Ortiz-Álvarez J, Saigí-Rubió F, Conejo-Mir J, Pereyra-Rodriguez JJ. Dropout rate in digital health interventions for the prevention of skin cancer: systematic review, meta-analysis, and metaregression. J Med Internet Res 2022;24(12):e42397 [FREE Full text] [doi: 10.2196/42397] [Medline: 36485027]

Abbreviations

BRS: Brief Resilience Scale
CBT: cognitive behavioral therapy
ERQ: Emotional Regulation Questionnaire
GAD-7: Generalized Anxiety Disorder-7 scale
MAAS: Mindfulness attention awareness scale
MMRM: mixed model for repeated measures
PHI: Pemberton Happiness Index scale
PHQ-4: Patient Health Questionnaire-4
PHQ-9: Patient Health Questionnaire-9
RRS: Ruminative Response Scale

Edited by A Mavragani; submitted 31.08.23; peer-reviewed by T Benham, M Musker; comments to author 03.01.24; revised version received 18.01.24; accepted 01.02.24; published 11.03.24.

Please cite as:
Ramos N, Besoain F, Cancino N, Gallardo I, Albornoz P, Fresno A, Spencer R, Schott S, Núñez D, Salgado C, Campos S
Development of a Multiplatform Tool for the Prevention of Prevalent Mental Health Pathologies in Adults: Protocol for a Randomized Control Trial
JMIR Res Protoc 2024;13:e52324
URL: https://www.researchprotocols.org/2024/1/e52324
doi:10.2196/52324
PMID:38466982

Protocol

Promoting Return to Work After Vocational Rehabilitation Using a Work-Related Fitness App: Protocol for a Cluster-Randomized Controlled Trial

David Bühne[1], Dr; Jan Mathis Elling[1], PhD; Christian Hetzel[1], Dr; Torsten Alles[1], PhD

Institute for Quality Assurance in Prevention and Rehabilitation (IQPR), German Sport University Cologne, Köln, Germany

Corresponding Author:
David Bühne, Dr
Institute for Quality Assurance in Prevention and Rehabilitation (IQPR)
German Sport University Cologne
Eupener Str 70
Köln, 50933
Germany
Phone: 49 221 27759920
Email: buehne@iqpr.de

Abstract

Background: Retraining programs in vocational rehabilitation are often characterized by a low level of physical activity, even when targeting jobs with primarily physical demands. They might therefore be accompanied by a decline in functional capacity if the lack of physical activity is not compensated by increased activity during leisure time. The implementation of a work-related exercise app might be a promising approach to promoting a return to work in vocational rehabilitation. We developed the "WORKout-app" which provides exercise plans based on a comparison of the physical demands of the retraining profession and the current functional capacity.

Objective: The aim of this study is to examine the effects of app-based exercise during vocational rehabilitation on perceived work ability (primary outcome), occupational self-efficacy, days of sick leave, and return to work (secondary outcomes).

Methods: We conducted a cluster-randomized controlled trial with 2 arms (intervention: WORKout-app vs control: treatment as usual) in 4 cohorts of 5 vocational rehabilitation centers in Germany. Participants are nested within retraining classes per vocational rehabilitation center and per cohort assigned to either the intervention condition or the control condition. The target sample size at the participant level is 598. Measurement time points include baseline, the end of rehabilitation, 3 months after the end of rehabilitation, and 6 months after the end of rehabilitation. Linear and generalized linear mixed-effects models are performed to test for treatment differences in outcomes.

Results: This study is funded by the German Federal Pension Insurance. The trial is registered with the German Clinical Trials Register (DRKS00030775) and approved by the Ethics Committee of the German Sport University Cologne (145/2022).

Conclusions: The findings of the study will inform researchers and practitioners about the effectiveness of an exercise app developed to counteract the effects of physical inactivity during vocational rehabilitation.

International Registered Report Identifier (IRRID): DERR1-10.2196/50200

(JMIR Res Protoc 2024;13:e50200) doi:10.2196/50200

KEYWORDS

digital health; eHealth; physical activity; profile comparison; vocational rehabilitation

Introduction

In 2020, more than 125,000 services for participation in working life were provided by the German Pension Insurance. Of these, 27% among women and 17% among men were educational services. A total of 6 months after finishing, nearly 1 in 2 individuals was either on long-term sick leave (12%), unemployed (22%), receiving further services to promote the participation of disabled people in working life (5%), or receiving a disability pension (4%) [1]. The demands of retraining programs, usually carried out over a period of 12-24 months, are often largely mental in nature, even when targeting jobs with primarily physical work demands. Overall, they are

therefore characterized by a low level of physical activity. A lack of physical activity in turn is associated with increased morbidity [2], mortality [3], and low physical capacity [4,5]. Among college students, an association was found between inactivity and self-reported depression, self-harm, and suicidal attempts [6]. A negative perception of the health condition increases the likelihood of failure to return to work [7,8]. These negative effects are not limited to individuals in professions with high physical demands. Even among white-collar workers, higher physical activity is associated with better work ability [9].

Unfortunately, there is no evidence in vocational rehabilitation that a lack of physical activity is commonly compensated by increased activity during leisure time, for example, by using the exercise and sports programs that are offered within the facilities. In contrast, rehabilitants frequently report low levels of physical activity [10]. An increased risk can be assumed for the period of exam preparation in particular. Among college students, physical activity is found to decline significantly in the graduation year [11]. Furthermore, the overall negative impact of the COVID-19 pandemic on physical activity likely amplified this issue [12].

The implementation of work-related functional capacity training, as successfully established in work-related medical rehabilitation, might be a promising approach to promoting a successful return to work. Being a key component of these measures, the demonstrated positive effects of work-related medical rehabilitation on return to work, self-rated work ability [13], and days of sick leave [14] are in large part attributable to the work-related functional capacity training. However, an implementation within vocational rehabilitation would fail as personnel and spatial preconditions are not given. Exercise apps can be considered the opposite in this context. The low personnel and spatial requirements, as well as the possibility of access at any time, constitute their utility and attractiveness. A positive effect on physical activity levels has already been demonstrated meta-analytically for app-based fitness programs [15]. However, there are currently no exercise apps available that are focused on the critical physical demands of work.

The aim of this study is to examine whether providing an app-based exercise intervention focused on the critical physical demands of work can improve the conditions for successful reintegration among individuals in vocational rehabilitation. A cluster-randomized controlled trial is conducted to avoid contamination effects. We hypothesize that participants receiving the job-related exercise app (“WORKout-app”) will report better work ability at the end of rehabilitation as well as 3 and 6 months thereafter compared to participants in the control condition. A further beneficial effect is expected for secondary outcomes, which include occupational self-efficacy, days of sick leave within the follow-up period, and return to work. We hypothesize that these effects are primarily manifested among participants who use the app regularly during the period between the start of the intervention and the end of rehabilitation. Regular use is defined as 12 or more workouts completed in the app.

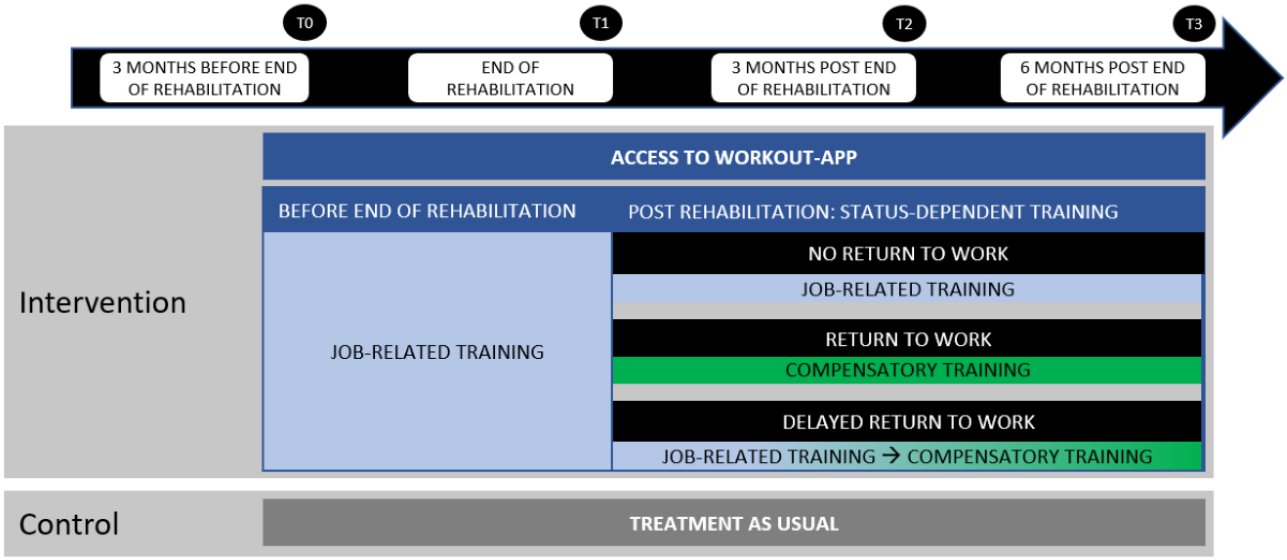
Methods

Study Design

A 9-month cluster-randomized controlled trial with 2 arms (intervention condition vs control condition) is conducted in 5 vocational rehabilitation centers in Germany. In those centers, referral diagnoses are dominated by diseases of the musculoskeletal system and connective tissue, as well as mental and behavioral disorders. The majority of participants are aged between 30 and 49 years and are mostly male candidates [7].

A flowchart of the study design is presented in Figure 1. Participants in the intervention condition receive an exercise app (“WORKout-app”). Access to the app is provided between 6 and 3 months before the regular end of rehabilitation and ends 6 months after the termination of rehabilitation. Participants in the control condition receive treatment as usual. Participants in both conditions are asked to answer a total of 4 questionnaires. The first questionnaire is distributed at baseline (T0), that is, approximately 3-6 months before the end of rehabilitation. Follow-up questionnaires are distributed at the end of rehabilitation (T1), 3 months post end of rehabilitation (T2), and 6 months post end of rehabilitation. The participating vocational rehabilitation centers (“Berufsförderungswerke”) are located in Berlin/Brandenburg, Cologne, Dortmund, Munich, and Oberhausen.

Figure 1. Study design overview.



Study Sample and Recruitment

We intend to include about 598 participants in total, which provides 80% power (α=.05) to detect a small effect (d=0.25) assuming a design effect of 1.18 (intracluster correlation coefficient=0.02) and a medium cluster size of 10. The sample size was calculated with G*Power (Erdfelder, Faul, and Buchner) [16]. An exclusion criterion at the participant level is a limited ability to exercise safely due to health problems.

Randomization

Randomization is conducted at the cluster level. Vocational rehabilitation centers in Germany are divided into classes based on the retraining occupations pursued by the rehabilitants. These classes serve as clusters in this study. Whole classes at each vocational rehabilitation center are allocated in a 1:1 ratio to either the intervention or control condition.

Block randomization is carried out within 5 groups of professions that have a similar level of physical work demands. This means that within each group, the classes are randomly assigned to either the intervention or control condition. This procedure is repeated in 4 cohorts per center.

Measures

Primary Outcome

An overview of all constructs and their measurement points is provided in Multimedia Appendix 1. The primary outcome of this study is the perceived work ability, as assessed by the Work Ability Score [17]. This is an 11-point scale used to estimate the current work ability compared to the lifetime best (“Assume that your work ability at its best has a value of 10 points. How many points would you give your current work ability?”).

Secondary Outcomes

Secondary outcomes include occupational self-efficacy, days of sick leave within the last 3 months, and return to work (ie, the current employment status). Occupational self-efficacy is assessed using a 6-item scale (eg, “I face difficulties in my job calmly, because I can trust my abilities”), rated on a 5-point response scale ranging from 1 (strongly disagree) to 5 (strongly agree) [18].

Characteristics and Covariates

Sociodemographic characteristics include age, gender, migration background, highest school degree, highest vocational qualification, relationship status, and income in the last regularly performed job. Moreover, the county of residence is assessed to determine the regional unemployment rate [19].

The employment biography is assessed by years of employment throughout the entire working life, periods of unemployment as well as periods of sick leave in the 2 years before the start of retraining, and the type of work demand (psychologically demanding, physically demanding, and physically and psychologically demanding) in the last regularly performed job. The retraining profession is divided into 4 categories (commercial and administrative professions, professions in technology and industry, social professions, and electrical and IT professions).

Rehabilitation-related characteristics include the retraining profession, the housing situation (resident of the boarding school vs commuter), and the sponsor of the retraining (German Pension Insurance, Federal Employment Agency, and others). Health-related characteristics include BMI, work ability in relation to physical and mental job demands [17], the type of condition underlying the retraining approval (predominantly physical factors, predominantly psychological factors, physical and psychological factors, and others), general health perception (1=poor to 5=excellent), 5 items of the “Functionality in everyday life” scale of the Indicators of the Rehabilitation Status-24 Questionnaire [20], and the 4-item Patient Health Questionnaire [21]. Furthermore, with regard to the last 3 months, participants are asked whether new health impairments have arisen that have limited their sporting activities.

Physical activity-related characteristics include sports preference (eg, sports disinterested and recreational athletes), sports activity per week, locomotion by bike or on foot in everyday life, as well as the adoption of new exercise or sport habits within the

past 3 months. Furthermore, participants' motives for physical activity are assessed by a selection of items of the Attitude Toward Physical Activity Scales [22,23]. The following motives are assessed: social experience ("…want to be with others"), ascetic experience ("…want to overcome myself"), pursuit of vertigo ("…need excitement and thrill"), health and fitness ("…want to keep myself healthy and fit"), aesthetic experience ("…enjoy aesthetic movements"), and catharsis ("…want to relax"). The items are rated on a 5-point response scale ranging from 1 (strongly disagree) to 5 (strongly agree).

Variables concerning physical activity apps include app experience (eg, "How many physical activity apps have you downloaded so far?"), motives for app use (eg, "I expect a physical activity app to help me reduce or maintain my weight"), the perceived usefulness of physical activity apps ("I consider the use of a physical activity app helpful in achieving my health goals"), the perceived ease-of-use of physical activity apps ("I find it easy to learn how to use a physical activity app"), the social influence regarding the use of physical activity apps ("People whose opinions matter to me would approve of me using a physical activity app"), the behavioral intention to use a physical activity app ("I intend to use a physical activity app in the future"), and technology competence beliefs ("I find dealing with new technology difficult—I just cannot do it most of the time"; eg, [24] and [25]). The items are rated on a 5-point response scale ranging from 1 (strongly disagree) to 5 (strongly agree). The usability of the WORKout-app is assessed by the System Usability Scale [26]. Furthermore, an overall grade for the WORKout-app is measured on a scale ranging from 1 (very bad) to 10 (very good).

Usage behavior is evaluated based on the number of workouts, exercise plans, and self-tests completed. Cut-off values are used to sort out activities in which participants did not actually perform the behavior in question but only clicked through the app (eg, a workout must last at least 10 minutes; otherwise, it does not count). Furthermore, at the completion of each workout, the perceived exertion ("How strenuous did you find this workout?") is surveyed on a 5-point scale ranging from 1 (too easy) to 5 (too difficult).

With the exception of app usage behavior, all measures are self-reported by respondents.

Data Analysis

Statistical analyses are performed using R (R Core Team). Descriptive statistics are used to describe the study sample in terms of sociodemographic, vocational, and health characteristics. The primary outcome (ie, work ability) is assessed by linear mixed-effects models. The effect is estimated as the coefficient of the study condition adjusted for the baseline measure, with the follow-up measure as the dependent variable. Random intercepts for the cluster are included. Age, general health perception, retraining profession, and termination of rehabilitation with graduation are included as additional covariates [8]. Participants are nested within retraining classes per vocational rehabilitation center and per cohort assigned to either the intervention condition or the control condition.

Secondary outcomes are assessed in a similar manner, using linear or generalized linear mixed-effects models as appropriate. In the analyses of return to work and days of sick leave, the baseline measures are not included as covariates because there are no baseline measures for these variables. Covariates in the analyses of return to work and days of sick leave include age, general health perception, retraining profession, termination of rehabilitation with graduation [8], regional unemployment rate [19], and periods of unemployment or periods of sick leave in the 2 years before the start of retraining. Covariates in the analysis of occupational self-efficacy include the baseline measure, age, general health perception, retraining profession, termination of rehabilitation with graduation, and the type of condition underlying the retraining approval.

Discontinuation of app use among intervention participants is analyzed by 2 generalized linear mixed-effects models. The first model includes sociodemographic predictors, and the second model additionally includes motives for app use, the system usability scale, and the overall grade.

Introductory Session and Telephone Support

A joint introductory session (approximately 1-2 hours) led by sports scientists or health psychologists is held as the official start of the intervention in each cluster of the intervention condition. The introductory session begins with an educational part that includes information about the dose-response relationship between physical activity and mortality, the beneficial effects of physical activity on physical and mental health, as well as the recommendations of the World Health Organization regarding physical activity. This educational part aims to raise participants' awareness and initiate reflection on their own physical activity and the health benefits that can be achieved through increased physical activity. The second and main part of the session is to become familiar with the app and learn how to use its various features in order to enhance participants' attitudes toward the app and increase their self-efficacy in using it. The session ends with an action planning section, which consists of setting a specific, measurable, attractive, realistic, and time-bound (SMART) goal for training with the app and forming implementation intentions for barriers to training with the app.

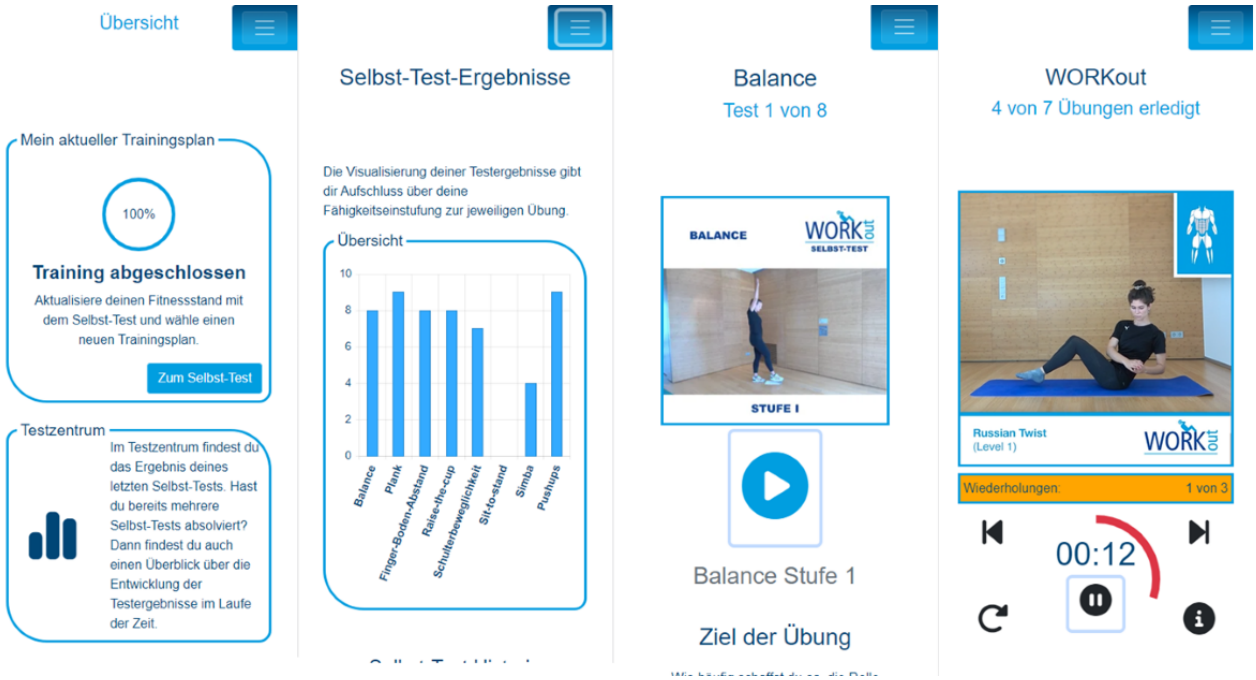
During the intervention period, participants are offered weekly opportunities to contact sports scientists within a 2-hour time slot to discuss difficulties and uncertainties in using and training with the app. Participants will be able to get in touch during these time slots by telephone as well as videotelephony on Microsoft Teams (Microsoft Corporation).

WORKout-App

The WORKout-app is a web app that was created with Blazor (ie, a Microsoft web application framework). Screenshots of the web app are presented in Figure 2. The app contains various exercises that are grouped into workouts, which are in turn integrated into training plans. The primary characteristic of the WORKout-app is that the training is specifically focused on those physical demands of work that could potentially limit return to work in the individual case. The underlying concept is a profile comparison, a comparison of physical abilities and

the individual physical demands of the retraining profession. A total of seven characteristics are thereby distinguished: (1) sitting, (2) standing, (3) trunk movements and compulsory trunk postures, (4) demands regarding upper extremities, (5) demands regarding lower extremities including locomotion and endurance, (6) load handling, and (7) balance.

Figure 2. Screens of the WORKout-app used for the intervention.



Classification of Physical Demands of Work

Before the development of the app, the physical demands of work were estimated for all retraining professions according to the 7 characteristics mentioned above. A 6-point scale based on the "Integration von Menschen mit Behinderung in die Arbeitswelt" method [27] was used for this purpose (1=very low demands and 6=demands that require at least above-average abilities).

The individual retraining profession must be specified when setting up the app, which allows for assigning an individual level of physical capacity that should be reached in order to be able to cope with the physical demands of work. Tax clerks, for example, only require a roughly average capacity for sitting, while the other 6 characteristics are weakly pronounced. In the case of in-house technicians, on the other hand, low demands are only given in terms of sitting.

Physical Capacity Examination

The app contains a self-test with 5 motor tests designed to estimate the ability to cope with the aforementioned physical demands of work. The motor tests include static strength endurance of the trunk (reference for work demands 1 to 3), static strength endurance of the upper extremities (4), physical endurance (5), weight handling (6), and balance (7). The convergent validity of the motor tests was evaluated in advance. The tests for weight handling and balance were strongly correlated with the results of a Functional Capacity Evaluation test [28]. In contrast, only moderate correlations were observed for the remaining motor tests. Given the limited convergent validity, self-ratings are therefore additionally included. A 6-point scale is used for the 5 self-ratings, which are weighted equally with the motor test results.

Work-Related Training

With regard to all exercises, workouts, and training plans, a distinction is made regarding the expected effect on coping with the physical demands of the work mentioned above. Furthermore, 3 levels of intensity (low, medium, and high) are distinguished. After the completion of the self-test, an automated profile comparison is performed. Depending on the result of this profile comparison, training plans are provided that address those abilities that are below the level required in the profession and that also correspond to the individual's physical capacity. This profile comparison is the key characteristic of the app, characterized by a demand-related orientation toward the individual physical requirements of work. For example, if the profile comparison indicates excessive demands in the characteristic “trunk movements and compulsory trunk postures” and the subject performed roughly average in the self-test, the training plan includes exercises such as back extensions in a lying position and good mornings. If an additional overload were to be expected with regard to the characteristic weight handling, exercises such as curl to press and rowing from a high plank position would also be included. In addition, the training is aimed at those abilities that are poorly manifested (a score of less than 3).

With the transition into work—directly after finishing vocational rehabilitation or in a further course—the workouts turn into compensatory training (Figure 1). The focus shifts to avoiding potential muscle imbalances resulting from the demands of the job. In podiatrists, for example, who are confronted with prolonged sitting as well as stress on the lower back muscles,

compensatory training is focused on dynamic exercises of the lower extremities as well as the abdominal muscles.

The information on perceived exertion following completed workouts is used to identify inappropriate training intensities. If participants report twice in a row that a workout was too hard or too easy, they are advised to end the training plan prematurely, after which the training intensity is automatically adjusted.

Behavior Change Techniques Integrated in the App

The behavior change techniques (BCTs) are described according to the taxonomy of Michie et al [29]. Only the BCTs integrated in the app are described here; the introductory session is described in detail above. The app includes extensive instructions for all exercises in the workouts as well as for all tests of the self-test (BCTs: provide instruction on how to perform the behavior and model or demonstrate the behavior). The instructions are presented in the form of videos in which people perform the exercises or tests (Figure 2), and the execution is explained in detail through voice-over. In the videos of the tests, on-screen text is used sparingly to highlight important issues. In the videos of the exercises, the trained muscle groups are marked in a pictogram of the body. After each completed self-test, the performance in the individual tests is displayed in a graph (Figure 2; BCT: provide feedback on performance). The progress over time can be viewed in separate graphs per test that show the results of the last 5 self-tests. Moreover, a fun feature is implemented in which participants can earn virtual badges for completing workouts and self-tests, as well as for exercising for several weeks in a row (BCT: provide rewards contingent on successful behavior). The app also includes a knowledge section with 12 health- and physical activity-related videos, as well as daily tips and trivia with motivational or scientific content (BCT: provide information on the consequences of behavior in general).

Ethical Considerations

The trial is registered with the German Clinical Trials Register (DRKS00030775) and approved by the ethics committee of the German Sport University Cologne (145/2022). All participants need to provide written, informed consent to participate.

Results

This study is funded by the German Federal Pension Insurance. Patient recruitment takes place between March 2023 and July 2024. Considering the follow-up period of 6 months post end of rehabilitation, results are expected to be published in the first quarter of 2026.

Discussion

The study aims to evaluate the effectiveness of a work-related physical activity intervention through a web app to promote self-reported work ability in vocational rehabilitation. The rationale for the development of the intervention lies in the primarily mental demands of retraining, which favor a decrease in physical performance and thus in the chance of a successful return to work, unless the low demands of retraining are compensated by increased physical activity in leisure time.

User motivation is crucial in digital physical activity interventions [15]. In this study, the timing of receiving the intervention may be a barrier to continued participation. Access to the app is given between 3 and 6 months before the regular end of retraining. This is the period of exam preparation, which has been associated with a decline in physical activity among college students [11]. The focus on the physical demands of work does not necessarily have a positive effect on individual motivation, despite the physiological meaningfulness, if, for example, rehabilitants seek a distance from occupational issues in their leisure time due to a high stress load.

This study underlines the opportunity of adopting holistic approaches in rehabilitation, where physical activity is integrated with innovative digital interventions. Such an approach aligns with the evolving landscape of digitalization. The insights derived from this research are particularly relevant for practitioners and policy makers in the field of vocational rehabilitation. Moreover, the findings may be relevant for digital health interventions in related fields, such as regular vocational training, higher education, or use in aftercare.

Acknowledgments

This study is funded by Deutsche Rentenversicherung Bund (German Federal Pension Insurance) as part of the research focus “Further development of vocational rehabilitation.”

Data Availability

Data sharing is not applicable to this research protocol as no data sets were generated or analyzed.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Overview of constructs and corresponding measurement points.
[DOCX File , 25 KB - resprot_v13i1e50200_app1.docx]

References

1. Deutsche Rentenversicherung. Reha-Bericht 2021: Die medizinische und berufliche Rehabilitation der Rentenversicherung im Licht der Statistik. Deutsche Rentenversicherung. 2021. URL: https://www.deutsche-rentenversicherung.de/SharedDocs/Downloads/DE/Statistiken-und-Berichte/Berichte/rehabericht_2021.html
2. Kyu HH, Bachman VF, Alexander LT, Mumford JE, Afshin A, Estep K, et al. Physical activity and risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events: systematic review and dose-response meta-analysis for the Global Burden of Disease Study 2013. BMJ 2016;354:i3857 [FREE Full text] [doi: 10.1136/bmj.i3857] [Medline: 27510511]
3. Arem H, Moore SC, Patel A, Hartge P, de Gonzalez AB, Visvanathan K, et al. Leisure time physical activity and mortality: a detailed pooled analysis of the dose-response relationship. JAMA Intern Med 2015;175(6):959-967 [FREE Full text] [doi: 10.1001/jamainternmed.2015.0533] [Medline: 25844730]
4. Vaara JP, Vasankari T, Wyss T, Pihlainen K, Ojanen T, Raitanen J, et al. Device-based measures of sedentary time and physical activity are associated with physical fitness and body fat content. Front Sports Act Living 2020;2:587789 [FREE Full text] [doi: 10.3389/fspor.2020.587789] [Medline: 33367277]
5. Silva FM, Duarte-Mendes P, Rusenhack MC, Furmann M, Nobre PR, Fachada M, et al. Objectively measured sedentary behavior and physical fitness in adults: a systematic review and meta-analysis. Int J Environ Res Public Health 2020;17(22):8660 [FREE Full text] [doi: 10.3390/ijerph17228660] [Medline: 33233451]
6. Grasdalsmoen M, Eriksen HR, Lønning KJ, Sivertsen B. Physical exercise, mental health problems, and suicide attempts in university students. BMC Psychiatry 2020;20(1):175 [FREE Full text] [doi: 10.1186/s12888-020-02583-3] [Medline: 32299418]
7. Meschnig A, von Kardorff E, Klaus S. Return to work from vocational retraining a long-term analysis of individual trajectories: biografical and structural conditions of success and failure. Rehabilitation (Stuttg) 2019;58(3):153-162 [FREE Full text] [doi: 10.1055/s-0044-101814] [Medline: 29590692]
8. Streibelt M, Egner U. A systematic review of the predictors of return to work following vocational retraining. Rehabilitation (Stuttg) 2013;52(2):111-118 [FREE Full text] [doi: 10.1055/s-0032-1323670] [Medline: 23233341]
9. Nawrocka A, Garbaciak W, Cholewa J, Mynarski W. The relationship between meeting of recommendations on physical activity for health and perceived work ability among white-collar workers. Eur J Sport Sci 2018;18(3):415-422 [FREE Full text] [doi: 10.1080/17461391.2018.1424257] [Medline: 29355091]
10. Baumann R. Bewegungsmangel als Faktor für somatische Beschwerden in der beruflichen Rehabilitation. Tagungsband zum 27. Reha-Kolloquium. Berlin: Deutsche Rentenversicherung Bund; 2018. URL: https://www.deutsche-rentenversicherung.de/SharedDocs/Downloads/DE/Experten/reha_forschung/reha_kolloquium/TB-27Reha-Koll.pdf [accessed 2024-01-23]
11. Romero-Blanco C, Rodríguez-Almagro J, Onieva-Zafra MD, Parra-Fernández ML, Prado-Laguna MDC, Hernández-Martínez A. Physical activity and sedentary lifestyle in university students: changes during confinement due to the COVID-19 pandemic. Int J Environ Res Public Health 2020;17(18):6567 [FREE Full text] [doi: 10.3390/ijerph17186567] [Medline: 32916972]
12. Wunsch K, Kienberger K, Niessner C. Changes in physical activity patterns due to the Covid-19 pandemic: a systematic review and meta-analysis. Int J Environ Res Public Health 2022;19(4):2250 [FREE Full text] [doi: 10.3390/ijerph19042250] [Medline: 35206434]
13. Bethge M, Markus M, Streibelt M, Gerlich C, Schuler M. Effects of nationwide implementation of work-related medical rehabilitation in Germany: propensity score matched analysis. Occup Environ Med 2019;76(12):913-919 [FREE Full text] [doi: 10.1136/oemed-2019-106065] [Medline: 31594839]
14. Bethge M. Work-related medical rehabilitation. Rehabilitation (Stuttg) 2017;56(1):14-21 [FREE Full text] [doi: 10.1055/s-0042-118579] [Medline: 28219096]
15. Laranjo L, Ding D, Heleno B, Kocaballi B, Quiroz JC, Tong HL, et al. Do smartphone applications and activity trackers increase physical activity in adults? Systematic review, meta-analysis and metaregression. Br J Sports Med 2021;55(8):422-432 [FREE Full text] [doi: 10.1136/bjsports-2020-102892] [Medline: 33355160]
16. Erdfelder E, Faul F, Buchner A. GPOWER: a general power analysis program. Beh Res Meth Instr Comp 1996;28(1):1-11 [FREE Full text] [doi: 10.3758/bf03203630]
17. Ilmarinen J. The Work Ability Index (WAI). Occup Med 2006;57(2):160 [FREE Full text] [doi: 10.1093/occmed/kqm008]
18. Abele AE, Stief M, Andrä MS. Zur ökonomischen Rrfassung beruflicher Selbstwirksamkeitserwartungen - Neukonstruktion einer BSW-Skala. Z fur Arb Organ A&O 2000;44(3):145-151 [FREE Full text] [doi: 10.1026//0932-4089.44.3.145]
19. Hetzel C, Streibelt M. Does return to work after vocational retraining depend on labour market? Rehabilitation (Stuttg) 2016;55(5):290-298 [FREE Full text] [doi: 10.1055/s-0042-113932] [Medline: 27728935]
20. Wirtz M, Farin E, Bengel J, Jäckel WH, Hämmerer D, Gerdes N. IRES-24 Patientenfragebogen. Diagnostica 2005;51(2):75-87 [FREE Full text] [doi: 10.1026/0012-1924.51.2.75]
21. Kroenke K, Spitzer RL, Williams JBW, Löwe B. An ultra-brief screening scale for anxiety and depression: the PHQ-4. Psychosomatics 2009;50(6):613-621. [doi: 10.1176/appi.psy.50.6.613] [Medline: 19996233]

22. Singer R. Die ATPA-D-Skalen - Eine deutsche Version der Skalen von Kenyon zur Erfassung der Einstellung gegenüber sportlicher Aktivität. In: Forschungsmethoden in der Sportwissenschaft, Bd. 4. Bad Homburg: Limpert; 1980.
23. Kenyon GS. Six scales for assessing attitude toward physical activity. Res Q 1968;39(3):566-574. [Medline: 5246960]
24. Vinnikova A, Lu L, Wei J, Fang G, Yan J. The use of smartphone fitness applications: the role of self-efficacy and self-regulation. Int J Environ Res Public Health 2020;17(20):7639 [FREE Full text] [doi: 10.3390/ijerph17207639] [Medline: 33092090]
25. Neyer FJ, Felber J, Gebhardt C. Entwicklung und Validierung einer Kurzskala zur Erfassung von Technikbereitschaft. Diagnostica 2012;58(2):87-99 [FREE Full text] [doi: 10.1026/0012-1924/a000067]
26. Brooke J. A quick and dirty usability scale. In: Thomas B, Weerdmeester B, McClelland IL, Jordan PW, editors. Usability Evaluation In Industry. London, Bristol, PA: CRC Press; 1996:189.
27. Hennaert S, Decuman S, Désiron H, Alles T, Bühne D, Braeckman L, et al. Linking of the 'Integration von Menschen mit Behinderungen in die Arbeitswelt' (IMBA) to the 'International Classification of Functioning, disability and health' (ICF). Work 2022;72(4):1359-1380 [FREE Full text] [doi: 10.3233/WOR-210257] [Medline: 35723143]
28. Bühne D, Hetzel C, Alles T. Die konvergente Validität eines Selbst-Tests für ein arbeitsbezogenes motorisches App-Training. 32. Rehabilitationswissenschaftliches Kolloquium. Berlin: Deutsche Rentenversicherung Bund; 2023. URL: https://www.deutsche-rentenversicherung.de/SharedDocs/Downloads/DE/Experten/reha_forschung/reha_kolloquium/TB-32Reha-Koll.pdf [accessed 2024-01-23]
29. Michie S, Ashford S, Sniehotta FF, Dombrowski SU, Bishop A, French DP. A refined taxonomy of behaviour change techniques to help people change their physical activity and healthy eating behaviours: the CALO-RE taxonomy. Psychol Health 2011;26(11):1479-1498 [FREE Full text] [doi: 10.1080/08870446.2010.540664] [Medline: 21678185]

Abbreviations

BCT: behavior change technique
SMART: specific, measurable, attractive, realistic, and time-bound

Edited by A Mavragani; submitted 22.06.23; peer-reviewed by P Postigo-Martin; comments to author 29.12.23; revised version received 03.01.24; accepted 04.01.24; published 18.03.24.

Please cite as:
Bühne D, Elling JM, Hetzel C, Alles T
Promoting Return to Work After Vocational Rehabilitation Using a Work-Related Fitness App: Protocol for a Cluster-Randomized Controlled Trial
JMIR Res Protoc 2024;13:e50200
URL: https://www.researchprotocols.org/2024/1/e50200
doi:10.2196/50200
PMID:38498051

Protocol

Telemedicine-Based Risk Program to Prevent Falls Among Older Adults: Protocol for a Randomized Quality Improvement Trial

David B Rein[1], PhD; Madeleine E Hackney[2,3,4,5], PhD; Yara K Haddad[6], PharmD, MPH; Farah A Sublett[1], MPH; Briana Moreland[6], MPH; Laurie Imhof[7], MPP; Cora Peterson[6], PhD; Jaswinder K Legha[6], MD, MPH; Janice Mark[8], DNP, FNP-BC, RN; Camille P Vaughan[2,3,4], MD, MS; Theodore M Johnson II[4,9,10], MD, MPH; Gwen Bergen[6], PhD, MS; Emory STEADI Implementation team[11]

[1]Department of Public Health, NORC at the University of Chicago, Atlanta, GA, United States
[2]Department of Medicine, Division of Geriatrics and Gerontology, Emory University School of Medicine, Atlanta, GA, United States
[3]Atlanta Veterans Affairs Center for Visual & Neurocognitive Rehabilitation, Atlanta, GA, United States
[4]Birmingham/Atlanta VA Geriatric Research Education Clinical Center, Atlanta, GA, United States
[5]Department of Rehabilitation Medicine, Emory University School of Medicine, Atlanta, GA, United States
[6]National Center for Injury Prevention and Control, Centers for Disease Control and Prevention, Atlanta, GA, United States
[7]Department of Health Sciences, NORC at the University of Chicago, Chicago, IL, United States
[8]School of Nursing and Health Professions, University of San Francisco, San Francisco, CA, United States
[9]Department of Family and Preventive Medicine, Emory University School of Medicine, Atlanta, GA, United States
[10]Department of Medicine, Division of General Internal Medicine, Emory University School of Medicine, Atlanta, GA, United States
[11]See Acknowledgments

Corresponding Author:
David B Rein, PhD
Department of Public Health
NORC at the University of Chicago
1447 Peachtree St NE #700
Atlanta, GA, 30309
United States
Phone: 1 4048230318
Email: rein-david@norc.org

Abstract

Background: The Center for Disease Control and Prevention's Stopping Elderly Accidents, Deaths, and Injuries (STEADI) initiative offers health care providers tools and resources to assist with fall risk screening and multifactorial fall risk assessment and interventions. Its effectiveness has never been evaluated in a randomized trial.

Objective: This study aims to describe the protocol for the STEADI Options Randomized Quality Improvement Trial (RQIT), which was designed to evaluate the impact on falls and all-cause health expenditures of a telemedicine-based form of STEADI implemented among older adults aged 65 years and older, within a primary care setting.

Methods: STEADI Options was a pragmatic RQIT implemented within a health system comparing a telemedicine version of the STEADI fall risk assessment to the standard of care (SOC). Before screening, we randomized all eligible patients in participating clinics into the STEADI arm or SOC arm based on their scheduled provider. All received the Stay Independent screener (SIS) to determine fall risk. Patients were considered at risk for falls if they scored 4 or more on the SIS or answered affirmatively to any 1 of the 3 key questions within the SIS. Patients screened at risk for falls and randomized to the STEADI arm were offered a registered nurse (RN)–led STEADI assessment through telemedicine; the RN provided assessment results and recommendations to the providers, who were advised to discuss fall-prevention strategies with their patients. Patients screened at risk for falls and randomized to the SOC arm were asked to participate in study data collection only. Data on recruitment, STEADI assessments, use of recommended prevention services, medications, and fall occurrences were collected using electronic health records and patient surveys. Using staff time diaries and administrative records, the study prospectively collected data on STEADI implementation costs and all-cause outpatient and inpatient charges incurred over the year following enrollment.

Results: The study enrolled 720 patients (n=307, 42.6% STEADI arm; n=353, 49% SOC arm; and n=60, 8.3% discontinued arm) from September 2020 to December 2021. Follow-up data collection was completed in January 2023. As of February 2024, data analysis is complete, and results are expected to be published by the end of 2025.

Conclusions: The STEADI RQIT evaluates the impact of a telemedicine-based, STEADI-based fall risk assessment on falls and all-cause health expenditures and can provide information on the intervention's effectiveness and cost-effectiveness.

Trial Registration: ClinicalTrials.gov NCT05390736, http://clinicaltrials.gov/ct2/show/NCT05390736

International Registered Report Identifier (IRRID): RR1-10.2196/54395

(JMIR Res Protoc 2024;13:e54395) doi:10.2196/54395

KEYWORDS

aging; cost-effectiveness; elderly; fall risk screening; fall risk; falls; medication management; older adults; physical therapy; prevention; public health; telemedicine

Introduction

Falls were the leading cause of nonfatal injuries and the leading cause of unintentional injury-related deaths among older adults (aged ≥65 years) in the United States in 2020, resulting in approximately 37,000 deaths, 3 million emergency department visits, and 1 million hospitalizations [1]. Falls among older adults are expensive, resulting in US medical costs of US $50 billion in 2015 [2]. With the aging population, the burden of falls on health care systems will continue to rise if fall prevention efforts are not expanded in clinical settings [3]. In a systematic review, Gillespie et al [4] found that multifactorial interventions significantly reduced the rate of falling among community-dwelling older adults. In more recent years, digital and telehealth programs for older adults have been implemented to evaluate their effectiveness in improving overall health and fall prevention [5-7].

The Stopping Elderly Accidents, Deaths, and Injuries (STEADI) initiative, developed by the US Centers for Disease Control and Prevention (CDC), offers health care providers tools and resources to assist with fall risk screening and multifactorial fall risk assessment and interventions [8]. The core components of STEADI are to screen, assess, and intervene: (1) screen older adults for fall risk using the 3 key questions (Have you fallen in the past year? Do you feel unsteady when walking or standing? and Do you have a fear of falling?) or the CDC's Stay Independent screener (SIS) to identify patients at risk of falls [9]; (2) assess those who screened at risk for modifiable risk factors including gait and balance disturbances, medication risk, home hazards, orthostatic blood pressure, vision changes, concerns about feet and footwear, need for vitamin D supplementation, and comorbidities that increase fall risk [10]; and (3) intervene with evidence-based clinical and community strategies to reduce fall risk by addressing modifiable risk factors identified during the assessment [11,12]. STEADI has been implemented in full in primary care settings and in abbreviated versions in pharmacy and inpatient settings [9,13,14].

Evaluations of STEADI's impact on outcomes has been limited. In a previous implementation of abbreviated STEADI in community pharmacies, Blalock et al [13] conducted a randomized controlled trial that compared the fall reduction impact of a pharmacist-led abbreviated medication management assessment implemented in 65 community pharmacies in North Carolina and usual care. The intervention successfully identified medication risks but found no statistically significant differences between the intervention and usual care groups in subsequent prescribing or fall outcomes during the observation period.

A recent multicenter clinical fall prevention study, the Strategies to Reduce Injuries and Develop Confidence in Elders (STRIDE), implemented a cluster-randomized trial of a nurse-administered multifactorial intervention in 86 primary care practices. The study compared the effects of a multifactorial intervention targeting modifiable risk factors to enhanced usual care [15]. They found that the intervention resulted in a significantly lower rate of a first self-reported fall injury compared to enhanced usual care, but no significant differences in rates of a first adjudicated serious fall injury, hospitalization, or death were found between the 2 groups [15]. Additional efforts are needed to evaluate the impact of clinical fall prevention on various health outcomes in clinical settings, including through telemedicine.

This paper describes the implementation protocol of the STEADI Options Randomized Quality Improvement Trial (RQIT) as implemented through telemedicine in primary care clinics to reduce falls among community-dwelling older adults. We designed the STEADI Options RQIT to estimate the effectiveness and cost-effectiveness of the STEADI assessment when pragmatically implemented through telemedicine.

Methods

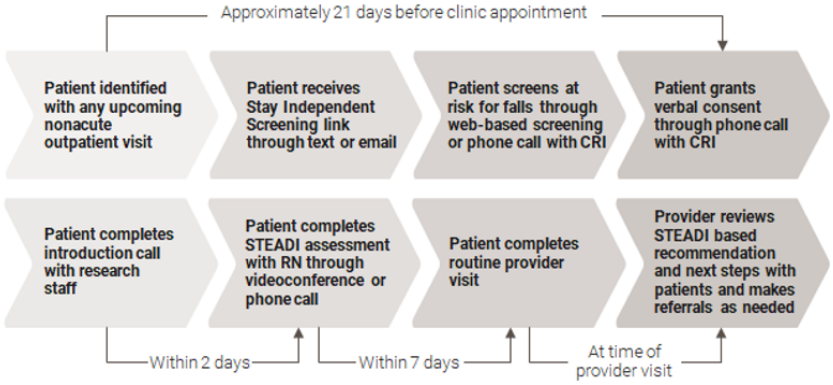
Study Design

The STEADI Options RQIT was implemented in 5 primary care clinics between September 1, 2020, and December 31, 2021. The RQIT used a randomized design to compare patients at risk for falls who were assigned to receive a one-time telemedicine fall prevention assessment to a control group of patients at risk for falls who received the standard of care (SOC) of general disease state management. Due to the COVID-19 pandemic, screening was conducted through SMS text messaging–initiated surveys and phone calls, and we adapted the STEADI fall assessment to be implemented through phone- or video-supported telemedicine encounters conducted by a designated RN. Primary care providers were sent assessment information that they could access during the patient's scheduled visit. We collected patient-level data on recruitment,

assessments, health service use, prescriptions, fall events, implementation costs, and all-cause outpatient and inpatient costs incurred over one year using administrative and electronic health records (EHRs) and patient surveys. The following sections describe the study's implementation and procedures (Figure 1).

The STEADI Options RQIT was a quality improvement initiative supported by health system leadership. Team members obtained verbal consent from study participants to share contact information with an evaluation partner outside the institution for the purpose of surveying (National Opinion Research Center [NORC] at the University of Chicago). Willingness to participate in the evaluation phase did not impact whether the patient received the STEADI evaluation as part of the quality improvement program.

Figure 1. Clinical workflow of the Stopping Elderly Accidents, Deaths, and Injuries (STEADI) Options Trial: recruitment, screening, STEADI assessment, and intervention recommendation (Emory Health Services, 2020-2021). Those who screened at risk for falls but were assigned to the standard of care arm did not complete steps 5, 6, and 8. CRI: clinical research interviewers; RN: research nurses.



Ethical Considerations

The study protocol was reviewed and approved by the US Office of Management and Budget to assure its compliance with the Paperwork Reduction Act (Office of Management and Budget control number, 0920-1281). Evaluation aspects of the RQIT deemed to be human subjects research (patient surveys) were reviewed by the Emory Institutional Review Board to assure the safety and ethical treatment of human subjects (00111996), and the RQIT was registered (ClinicalTrials.gov NCT05390736).

Study Setting and Staffing

We selected 5 primary care clinics based on the willingness of clinic leadership to participate, clinic patient population diversity, and the number of older adults served. The research team included representatives from CDC's Division of Injury Prevention, NORC at the University of Chicago, and the Emory School of Medicine and Emory Healthcare primary care clinicians and staff. The Division of Injury Prevention was responsible for project oversight and fall prevention expertise, NORC designed the study protocol and data collection instruments and managed the project, and Emory was responsible for clinical implementation. Emory hired clinical research interviewers (CRIs), a clinical research coordinator, and RNs to conduct recruitment, coordination, and assessments. CRIs were responsible for screening patients for fall risk, recruiting and enrolling those at risk, scheduling STEADI assessments, and conducting preassessment coordination calls. The clinical research coordinator managed the workloads of the CRIs. The RN was responsible for conducting assessments, providing patient education, creating recommendations based on assessment information, and disseminating those recommendations to the patient's provider. Providers were responsible for determining whether to act on recommendations through the creation of clinical referrals to services or by managing medications. Emory implementation staff participated in monthly calls with the research team to discuss recruitment and implementation. Emory additionally convened monthly meetings between Emory implementation staff and primary care clinic staff to communicate the study design, intent, and responsibilities.

Information Technology Infrastructure

Before the implementation, Emory integrated the SIS into Tonic (Tonic Solutions), an electronic platform used to administer previsit screening. Through Tonic, patients were able to take the SIS on a web-based device before their appointment using a phone, tablet, or computer, with the results automatically populating the patients' EHR. The research team used REDCap (Research Electronic Data Capture; Vanderbilt University), a secure, internally hosted web-based application, to capture STEADI assessment results. The RN sent conclusions and recommendations to the provider using the EHR messaging center.

Study Eligibility

Patients aged 65 years or older with a nonacute outpatient visit scheduled at participating primary care clinics were eligible for screening. Patients completed the SIS, and those with an SIS score of 4 or higher or those who answered "Yes" to any of the statements used as proxy to the 3 key questions within the SIS were eligible for enrollment (Textbox 1) [9]. Patients needed to be cognitively able to participate in the assessment, be able to converse in English, and have access to an able-bodied person to help with or respond to an emergency during the STEADI gait and balance assessments conducted by telemedicine (Textbox 1). Patients without valid phone numbers and those who opted out of receiving health system text messaging were excluded.

Textbox 1. Stopping Elderly Accidents, Deaths, and Injuries (STEADI) Options trial patient eligibility criteria, Emory Health Services, 2020-2021.

Patients aged 65 years or older with a qualifying (ie, nonacute) visit scheduled at 1 of the 5 designated Emory clinic implementation sites and:

- Identified as high risk for falls through the Stay Independent screener by scoring 4 or more or answering affirmatively to any of the following statements in the Stay Independent screener as proxy to the 3 key questions:
  - Sometimes I feel unsteady when I am walking.
  - I am worried about falling.
  - I have fallen in the past year.
- Able to participate in the STEADI assessments:
  - Cognitively able to answer screening questions and participate in assessment.
  - English-speaking.
  - Have a computer, tablet, phone with internet and a webcam, or telephone.
  - Have an able-bodied helper who can be available to help or called for help during the STEADI gait and balance assessment (in case of unsteadiness or a fall).

Randomization

Providers were randomized each week 1:1 to either the STEADI or SOC arms based on a dice roll, and their scheduled patients were assigned to study arms based on the provider's assignment. Providers were rerandomized each week; however, patient assignment remained the same even if they rescheduled an appointment to another week. During 3 weeks in the summer of 2021 when the RN was unavailable, all providers and their patients were assigned to the SOC arm. Over the subsequent 6 weeks, providers and their patients were assigned to the STEADI arm on a 2:1 basis to restore assignment balance, after which the study returned to 1:1 assignment. A total of 2 additional study arms with modified STEADI assessments were discontinued early in the study due to low overall enrollment.

Screening, Recruitment, and Enrollment

Before their scheduled primary care visit, all eligible patients received a web-based or text link to a web-based SIS to complete. CRIs attempted to contact patients who had not completed the SIS on the web up to 3 times and completed the screener with them by phone if they were reached. Patients who screened at risk through the web-based SIS or through CRI contact and were randomized to the STEADI arm depending on the provider they were seeing were asked if they had (1) a computer, tablet, or phone with a camera and internet—if not, if they could participate by phone; (2) a clear hallway and corner in their home with space to assess gait or balance; and (3) someone nearby they could call upon for help if needed during the assessment. Those patients who answered yes to all 3 questions were then asked to provide informed consent to participate in the study. Patients who consented were asked if they had a blood pressure cuff at home (if not, the CRI ordered a cuff to be sent to their address), scheduled for a preassessment technology and home set-up call, and scheduled for a STEADI assessment before the primary care visit. Patients received an email with study information and instructions outlining the assessment process. Patients who were reached but did not consent to study inclusion were offered and provided STEADI assessments, although their data were not transmitted to the analytic team and were not included in analyses. Patients who were not reached were not included in analyses.

Preassessment Technology and Home Set-Up Call

A total of 2 days before the STEADI assessment, CRIs called each patient and provided setup instructions based on a script. CRIs confirmed the patient had a stable internet connection and was able to start the videoconferencing software (Zoom; Zoom Video Communications). They asked the patient to use tape to mark 5 feet of space from their video call device for the visual acuity test and to mark a 10-foot path for the Timed Up and Go (TUG) physical therapy assessment. CRIs also had patients choose a safe corner of their homes for the modified 4-Stage Balance physical therapy assessment and ensured that the patient had an appropriate chair and wall space to set the chair against for the 30-Second Chair Stand physical therapy assessment. CRIs presented demonstration videos of STEADI's 3 physical therapy assessments and helped patients adjust camera angles. Those patients scheduled for phone assessments were reminded of the scheduled assessment visit and given information regarding what to expect.

STEADI Assessments

Overview

During the subsequent assessment call, the RN conducted 6 standardized assessments to identify the patient's risk factors for falls. The protocol prioritized video calls but allowed for phone assessments for those unable or unwilling to participate in video assessments. Summaries of each assessment component, possible component findings, intended recommendations and interventions, and adaptations for phone assessments are described below and in table form (Multimedia Appendix 1).

Comorbidity Review

Before the assessment, the RN reviewed the patient's EHR problem list for diagnoses of 6 comorbidities (Multimedia Appendix 2) associated with fall risk: cognition problems, Parkinson disease, cardiac arrhythmia, depression, or urinary incontinence [16,17]. Comorbidities were shared with providers in the RN's recommendation statement.

Medication Review

Before the assessment, the RN reviewed the patient's EHR medication list for any prescriptions from 10 classes of medications known to increase fall risk based on the Beers criteria (Multimedia Appendix 3) [18]. The RN additionally checked for polypharmacy, most commonly defined as prescriptions for 5 or more medications [19]. During the assessment, the RN confirmed with the patient the accuracy of the prescriptions listed in the EHR. The RN reported medication-related fall risk in her or his report for the provider and provided medication management educational materials to the patient (Multimedia Appendix 4). The RN also shared a recommendation to assess and adjust medications considered to increase risk of falls with providers.

Falls History

The RN asked how many times the patient had fallen in the past 12 months. If the patient reported a fall within the past 12 months, the RN asked if the patient sought medical attention for any fall or experienced loss of consciousness or broken or fractured bone or bones resulting from a fall. Fall history information was added to the provider report to increase the salience of fall prevention information.

Assessment of Feet or Footwear and Diabetes Assessment

The RN observed (through video) or asked about the patient's current footwear, asked about foot pain or loss of sensation, and when applicable noted a diabetes diagnosis. Patient reports of foot pain, loss of sensation, or diabetes resulted in a RN note to the provider to examine the patient's feet and the potential need for a referral to podiatry. The RN also reviewed a safe footwear handout (Multimedia Appendix 4) with all patients and emailed it to patients following the call.

Assessment of Visual Acuity

The RN projected the Banner eye chart on Zoom for the patient to read with their contact lenses or eyeglasses from five feet away (the distance was marked during the technology set up call) for both eyes together and each eye individually [20]. Phone patients were asked to self-report any vision problems. If the video screening or self-report indicated vision problems, the RN noted the result and recommended an eye health referral.

Gait and Balance

For video patients, the RN conducted the 30-Second Chair Stand test, the TUG, and the first three stages of CDC's 4-Stage Balance Test [21-23]. During the 30-Second Chair Stand test, the RN counted the number of times in 30 seconds the patient rose to a full standing position from sitting in a chair without using their hands. For the TUG test, the RN timed how long it took a patient to stand up from their chair, walk 10 feet, turn around, walk back to their chair, and sit down. During the balance test, the RN observed the patient in 3 progressively difficult standing positions: (1) feet side-by-side, (2) one foot touching the big toe of the other foot, and (3) one foot in front of the other, heel touching toe. Patients assessed by phone without video were asked 10 questions (Multimedia Appendix 1) that corresponded with the physical domains tested by the 30 Second Chair Test, TUG, and the first three stages of 4-Stage Balance Test.

If a patient failed any of the mobility tests, exhibited signs of unstable gait, or reported difficulties, the RN discontinued gait and balance assessments and recommended physical therapy referral through the provider messaging center. With the increased popularity of fitness programs for older adults [24], the RN recommended a web-based tai chi for arthritis program (Multimedia Appendix 4) for patients that passed all 3 tests, as all patients were still considered to be at risk for falls based on the SIS [25].

Orthostatic Hypotension

The RNs evaluated observed changes in systolic blood pressure by measuring sit-to-standing blood pressure. Sit-to-standing was chosen over a supine-to-standing test to increase feasibility for in-home assessment [26]. The patient measured their blood pressure using their own cuff or one provided by the study and sat for at least 2 minutes before standing. Patients experiencing a systolic blood pressure drop of more than 15 mm Hg when standing from their chair were given STEADI-based educational materials on managing orthostatic hypotension (Multimedia Appendix 4), and the RN reported the finding to the provider for management [27]. The RN also asked the patient about dizziness and relayed any reports of dizziness to the provider.

Home Safety Risks

The RN reviewed the CDC brochure *Check for Safety: A Home Fall Prevention Checklist for Older Adults* (Multimedia Appendix 4) with each patient [28]. *Check for Safety* asks 17 questions about the home's floors, stairs and steps, kitchen, bathrooms, and bedrooms and suggests ideas for removing or reducing fall hazards. The RN communicated home safety risks and a recommendation for occupational therapy to the provider for indicated patients.

Vitamin D Deficiency

Vitamin D deficiency is common and often underdiagnosed among older adults, although recommendations on supplementation are mixed [29]. The RN asked the patient if they usually take a vitamin D supplement with their other medications. If the patient did not take a vitamin D supplement, the RN recommended the provider check vitamin D levels and consider supplementation if vitamin D levels were less than 20 ng/ml.

RN Recommendations and Provider Action

The RN reviewed health education materials with the patient and sent these materials in an email follow up. RNs compiled assessment results, the educational materials presented to the patient, and their recommendations for referrals and care management and entered them into the patient's EHR and sent assessment results and recommendations to the provider using the EHR messaging center. Providers in each participating clinic were informed about the study protocol, communication methods, and actions they could take to act on information contained in the RN report. Provider actions included ordering patient referrals to physical therapy, optometry, podiatry, the neurovestibular clinic (ie, dizzy clinic), and occupational

therapy; reviewing and changing patient medications when indicated; and testing patients for vitamin D levels. Providers acted on RN recommendations at their clinical discretion (Multimedia Appendix 5). For example, at the patient's upcoming primary care visit, providers would evaluate whether the medications identified by the RN should be adjusted or if a referral to Emory's Dizziness and Balance Center and providing the Epley maneuver home exercise handout was warranted [30].

Data Collection

To evaluate the intervention, we collected screening and assessment records, self-reported patient survey data, EHR health records, administrative medical cost information, implementation cost information through cost diaries, and qualitative interview data. Screening and assessment information was collected using a REDCap template. This included tracking compliance for the STEADI arm by recording whether each patient's planned STEADI assessment occurred. Self-reported surveys were administered in 4 waves through web and phone follow up. We administered a baseline survey within 1 month of enrollment, and 3 follow-up surveys were administered at 4, 8, and 12 months after enrollment. The baseline survey collected patient information on fall perceptions, fall history, health status, and self-reported service and prescription use. Follow-up surveys collected information on fall events and on patient adherence to recommended treatments and STEADI-related service use (eg, physical therapy and occupational therapy). Survey respondents initially received a token of appreciation of US $3 in US postage stamps after completing each wave of the survey. After 13 months of implementation, we added a US $2 cash pre-incentive and a study-branded glasses cleaning cloth to increase response rates.

We extracted EHR and cost information from Emory records for each enrolled patient for the period of the participant's enrollment date through 365 days of follow up. We also collected retrospective EHR and cost data for the 365 days before enrollment. We used time diaries completed by the CRI and RN to estimate implementation costs. We collected qualitative data from 45-minute phone interviews with the project RN and CRI and a sample of providers drawn from the Emory clinics implementing the study. All interviews were recorded and transcribed before being uploaded and coded in NVivo (Lumivero). A written summary of findings to contextualize quantitative data was developed.

Evaluation

We will analyze process outcomes, short- and long-term outcomes, costs, and cost-effectiveness of the implementation (Multimedia Appendix 6). Process analyses will evaluate the extent to which assessments were conducted through phone or Zoom calls, evaluated intended risk factors, and identified risks among participants who were assessed. Qualitative interviews with providers will be thematically analyzed to provide details on whether the intervention was implemented as intended and provide additional information on intervention feasibility, communication between implementation staff, perceived efficacy, and patient engagement.

Using an intent-to-treat approach, we will evaluate sample balance and assess short- and long-term outcomes comparing the STEADI and SOC arms. We will use survey and EHR data to evaluate differences between the arms in the short-term outcomes of (1) STEADI-indicated service use (eg, physical therapy and occupational therapy) and (2) prescriptions for medications that increase fall risks. For the long-term outcomes of (1) medically treated and self-reported falls and (2) all-cause health care costs from the Emory Healthcare system, we will use EHR data and administrative cost data. We will use the *International Classification Definition, 10th Revision, Clinical Modification* (ICD-10-CM) codes (Multimedia Appendix 2) and chart text notes to identify medically treated falls at Emory. Preliminary analyses indicate that ICD-10-CM codes without text note review are insufficient to differentiate individual fall episodes or determine fall severity. Therefore, we will also use self-report of falling with treatment at Emory to guide additional text note reviews for fall events that may not have been coded in the EHR. Falls will be coded as EHR-confirmed, self-reported medically treated falls outside the Emory system (EHR not confirmed), and self-reported and not medically treated to support analyses. We will additionally evaluate the impact of STEADI using a per protocol approach using a 2-stage residual inclusion approach.

For cost and cost-effectiveness, using time diaries and programmatic records, we will estimate the total implementation cost of the intervention per person. Cost will be assessed both based on an intent-to-treat perspective per person and based on the per-protocol cost of implementation per person associated with full compliance with the study protocol. Using estimates of the implementation costs per person assessed and the intervention effect (if any) on falls and all-cause health expenditures, we will estimate the incremental cost-effectiveness of STEADI from the health care perspective. This will be compared to the SOC over one year using an incremental net benefit framework anchored to the willingness to pay to prevent 1 fall.

Sample Size Estimation

We estimated a sample size based on the sample size required to detect a difference in the relative risk (RR) of falling at least once during the year between the STEADI arm and SOC arm. We assumed an absolute risk of any fall in the control group of 0.5 and a design effect of 1.05. We assumed a 50% risk of falling based on the expected performance of a screening tool to detect fall risk [31] and assumed a relatively small design effect under the assumption that individuals assessed were largely independent of each other in behavior given the telemedicine implementation. The results indicated that a sample of 500 in each arm would have 80% power of detecting an RR of 0.82, a sample of 350 would have 80% power of detecting an RR of 0.78, and a sample of 250 would have 80% power of detecting an RR of 0.75. Based on this, we sought to recruit at least 250 people in each arm with a recruitment goal of 500 per arm.

Statistical Procedures

We will impute missing values in the survey data using multiple imputations by chained equations. Imputation will be conducted

using logistic models for categorical variables and predictive mean matching for continuous and count variables. Analyses using imputed data will use methods that appropriately estimate standard errors for multiply imputed data. Quantitative analyses will include bivariate and multivariable logistic, Poisson, and linear regression models estimating the intent-to-treat effect of the STEADI initiative on fall outcomes. We will use prespecified multivariable statistical models to control for unbalanced covariates and reduce residual variance. Per-protocol estimates of the effect of STEADI on outcomes will be estimated using treatment assignment as an instrument for the STEADI risk screening and assessment. Finally, 2-part models [32] will be used to estimate health expenditures.

Results

From September 1, 2020, to December 31, 2021, the study enrolled 720 patients, of whom 307 (42.6%) were assigned to the STEADI arm, 353 (49%) were assigned to the SOC arm, and 60 (8.3%) were assigned to arms that were discontinued. Process and implementation cost data were collected. Follow-up data collection was completed in January 2023. As of February 2024, data analysis is complete, and results are expected to be published in the end of 2025.

Discussion

Overview

The primary purpose of the CDC's STEADI Options RQIT was to evaluate the impact of a telemedicine-based form of the STEADI fall risk screening and assessment on falls and all-cause health expenditures among older adults when implemented within a primary care setting. We hypothesize that intervention patients will experience fewer fall-related outcomes compared to the control group; however, this relationship may be challenging to detect. For example, the STRIDE study found that a multifactorial intervention was associated with an 8% reduction in the rate of a first adjudicated serious fall compared to an enhanced usual care, but this result was not statistically significant [33]. The STRIDE study considered fall injuries but not falls without injuries in their outcomes and required one source of independent adjudication to determine the primary outcome.

This study includes patient self-reports of falls that did not require medical attention and falls that resulted in medical attention obtained outside the Emory health care system. Sustaining a serious injury from a fall requiring medical care or serious injury requiring hospitalization or prolonged care is likely dependent on individual health and functional characteristics. Therefore, detecting differences in all falls, including those that did not require medical intervention, is important in understanding the potential impact of a fall prevention intervention. Further, our survey captures falls that required medical attention but were treated outside the Emory Healthcare System because patients may turn to alternative settings such as urgent care centers to treat injuries.

This study collects detailed data on the STEADI risk screening and assessment process, allowing us to measure implementation fidelity. We are also collecting data on short-term outcomes of service use and prescriptions for medications that increase fall risk. Having this level of detail will allow us to evaluate whether the intervention translated into patient use of preventive health services with the potential to prevent falls, even if no difference in falls is detected. Additionally, we collected time diary data on STEADI implementation to estimate the costs of replicating the intervention and the cost-effectiveness of the intervention.

Limitations

Several factors limit this study. First, the COVID-19 pandemic required us to adapt STEADI from primary care, in-person risk screening, and assessment to telemedicine. As initially conceptualized, it was intended that all participants assigned to the intervention group would receive in-home video assessments through the Zoom platform. However, not all patients were able or willing to conduct assessments over video, so we adjusted the protocol to allow for some participants to be assessed by phone. We hypothesize that phone evaluations are less effective than video assessments because they replaced visual assessments of gait and balance, footwear, and vision problems with patient self-reported values likely underestimating risk. Ideally, the study design would have assigned patients to phone or Zoom assessments to compare outcomes by assessment type. However, the randomization of participants to phone or video calls was infeasible.

Second, conditions of the COVID-19 pandemic may have impacted the intervention's effectiveness if patients avoided encounters with the health care system for social distancing reasons. Avoiding health care encounters would reduce use of fall preventive services and might result in a lower number of medically treated falls if patients deferred medical care for falls they would have sought care for in the absence of COVID-19. This limitation is likely to bias our results toward the null hypothesis of no intervention effect.

Third, the instance of the Emory EHR deployed at the time of the study did not track referrals. Therefore, if patients did not access services indicated by the assessment, we are unable to determine if this was due to a lack of provider referrals or low patient adherence. Further, a change in Emory's EHR vendor resulted in a loss of approximately 6 weeks of follow-up data from 80 enrolled patients, a limitation we are adjusting for in statistical models. Fourth, not all patients completed each wave of the patient survey due to survey nonresponse. We will attempt to mitigate this limitation by using poststratification weights or imputation methods. Fifth, preliminary analyses have indicated that fall-related diagnosis codes in the EHR by themselves are limited in their ability to detect medically treated falls and differentiate unique fall events. We will attempt to mitigate this limitation using chart reviews but will likely miss some medically treated falls, biasing results toward the null. Sixth, because providers were randomized into STEADI and SOC arms by week, possible contamination in favor of fall-related interventions may have been introduced during the weeks providers were assigned to SOC, a limitation which would also bias results toward the null.

Conclusion

Many older adult falls are preventable. The CDC's STEADI initiative [10] offers tools and resources for health care providers to conduct clinical fall prevention efforts with their older patients. We designed this study to capture detailed information on the implementation, short-term outcomes, and long-term outcomes of STEADI fall risk assessment and screening when implemented through telemedicine through a pragmatic design in collaboration with a primary care setting. The main advantage of this study is the collection of self-reported fall outcomes and health service use information from the entire sample of participants. This study can provide evidence to support future implementations and adaptations of multifactorial fall prevention interventions such as STEADI.

Acknowledgments

This project was supported by funding from the Centers for Disease Control and Prevention via Contract 200-2017-F-96101: Evaluating the cost-effectiveness of Stopping Elderly Accidents, Deaths, and Injuries older adult fall prevention in primary care settings. TMJ and CPV receive support from Health Resources and Services Administration award U1QHP33070.

The members of the Emory STEADI Implementation team are Dipak Vashi, MD, Emory Healthcare, Atlanta, GA; Kimberly Shumate, MD, Emory School of Medicine, Atlanta, GA; Sarah K John, NP-BC, Emory Specialty Associates Internal Medicine, Smyrna,GA; Tina-Ann K Thompson, MD, MBA, Emory at Rockbridge Primary Care, Atlanta, GA; Paul T Baird, MD, Emory School of Medicine, The Emory Clinic, Atlanta, GA; Sanjay Khant, MD, Emory School of Medicine, Atlanta, GA; Karina Khouri Belinfante, MD, Emory Healthcare (ESA Belmont), Smyrna,GA.

Conflicts of Interest

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention. The authors declare no conflicts of interest in this work.

Multimedia Appendix 1
Protocol for assessment of Stopping Elderly Accidents, Deaths, and Injuries (STEADI) Options Trial, Emory Health Services, 2020-2021.
[DOCX File , 21 KB - resprot_v13i1e54395_app1.docx]

Multimedia Appendix 2
International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis codes indicating potential fall occurrences and comorbidities.
[DOCX File , 14 KB - resprot_v13i1e54395_app2.docx]

Multimedia Appendix 3
Stopping Elderly Accidents, Deaths, and Injuries (STEADI) Options Trial electronic record medication flag list for medication management assessment component.
[DOCX File , 17 KB - resprot_v13i1e54395_app3.docx]

Multimedia Appendix 4
Stopping Elderly Accidents, Deaths, and Injuries (STEADI) Options Trial educational materials distributed and reviewed to patients during assessment.
[DOCX File , 16 KB - resprot_v13i1e54395_app4.docx]

Multimedia Appendix 5
Collaboration between clinical research nurse (RN) and provider in the Stopping Elderly Accidents, Deaths, and Injuries (STEADI) Options Trial, Emory Health Services, 2020-2021.
[DOCX File , 21 KB - resprot_v13i1e54395_app5.docx]

Multimedia Appendix 6
Stopping Elderly Accidents, Deaths, and Injuries (STEADI) Options Trial evaluation design, Emory Health Services, 2020-2021.
[DOCX File , 16 KB - resprot_v13i1e54395_app6.docx]

References

1. WISQARS™—Web-based Injury Statistics Query and Reporting System. CDC Division of Injury Prevention and Control. URL: https://www.cdc.gov/injury/wisqars/index.html [accessed 2023-05-01]

2. Florence CS, Bergen G, Atherly A, Burns E, Stevens J, Drake C. Medical costs of fatal and nonfatal falls in older adults. J Am Geriatr Soc 2018;66(4):693-698 [FREE Full text] [doi: 10.1111/jgs.15304] [Medline: 29512120]
3. Houry D, Florence C, Baldwin G, Stevens J, McClure R. The CDC Injury Center's response to the growing public health problem of falls among older adults. Am J Lifestyle Med 2016;10(1):74-77 [FREE Full text] [doi: 10.1177/1559827615600137] [Medline: 26688674]
4. Gillespie LD, Robertson MC, Gillespie WJ, Sherrington C, Gates S, Clemson LM, et al. Interventions for preventing falls in older people living in the community. Cochrane Database Syst Rev 2012;2012(9):CD007146 [FREE Full text] [doi: 10.1002/14651858.CD007146.pub3] [Medline: 22972103]
5. Jacobson CL, Foster LC, Arul H, Rees A, Stafford RS. A digital health fall prevention program for older adults: feasibility study. JMIR Form Res 2021;5(12):e30558 [FREE Full text] [doi: 10.2196/30558] [Medline: 34837492]
6. Thomsen MJ, Liston M, Christensen MG, Vestergaard P, Hirata R. A combination of web-based and in-person training reduced fall accidents in older adults during the COVID-19 pandemic. Iproceedings 2022;8(1):e41105 [FREE Full text] [doi: 10.2196/41105]
7. Hawley-Hague H, Tacconi C, Mellone S, Martinez E, Chiari L, Helbostad J, et al. One-to-one and group-based teleconferencing for falls rehabilitation: usability, acceptability, and feasibility study. JMIR Rehabil Assist Technol 2021;8(1):e19690 [FREE Full text] [doi: 10.2196/19690] [Medline: 33433398]
8. Lee R. The CDC's STEADI initiative: promoting older adult health and independence through fall prevention. Am Fam Physician 2017;96(4):220-221 [FREE Full text] [Medline: 28925662]
9. Eckstrom E, Parker EM, Lambert GH, Winkler G, Dowler D, Casey CM. Implementing STEADI in academic primary care to address older adult fall risk. Innov Aging 2017;1(2):igx028 [FREE Full text] [doi: 10.1093/geroni/igx028] [Medline: 29955671]
10. STEADI—older adult fall prevention. Centers for Disease Control and Prevention. URL: https://www.cdc.gov/STEADI/ [accessed 2023-05-02]
11. Clinical resources. CDC Division of Injury Prevention and Control. URL: https://www.cdc.gov/steadi/materials.html [accessed 2024-05-01]
12. Phelan EA, Mahoney JE, Voit JC, Stevens JA. Assessment and management of fall risk in primary care settings. Med Clin North Am 2015;99(2):281-293 [FREE Full text] [doi: 10.1016/j.mcna.2014.11.004] [Medline: 25700584]
13. Blalock SJ, Ferreri SP, Renfro CP, Robinson JM, Farley JF, Ray N, et al. Impact of STEADI-Rx: a community pharmacy-based fall prevention intervention. J Am Geriatr Soc 2020;68(8):1778-1786. [doi: 10.1111/jgs.16459] [Medline: 32315461]
14. Stevens JA, Smith ML, Parker EM, Jiang L, Floyd FD. Implementing a clinically based fall prevention program. Am J Lifestyle Med 2020;14(1):71-77 [FREE Full text] [doi: 10.1177/1559827617716085] [Medline: 31903086]
15. Ganz DA, Yuan AH, Greene EJ, Latham NK, Araujo K, Siu AL, et al. Effect of the STRIDE fall injury prevention intervention on falls, fall injuries, and health-related quality of life. J Am Geriatr Soc 2022;70(11):3221-3229 [FREE Full text] [doi: 10.1111/jgs.17964] [Medline: 35932279]
16. Dionyssiotis Y. Analyzing the problem of falls among older people. Int J Gen Med 2012;5:805-813 [FREE Full text] [doi: 10.2147/IJGM.S32651] [Medline: 23055770]
17. Kwon KY, Park S, Lee EJ, Lee M, Ju H. Association of fall risk factors and non-motor symptoms in patients with early Parkinson's disease. Sci Rep 2021;11(1):5171 [FREE Full text] [doi: 10.1038/s41598-021-84720-w] [Medline: 33664423]
18. By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. J Am Geriatr Soc 2019;67(4):674-694. [doi: 10.1111/jgs.15767] [Medline: 30693946]
19. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? a systematic review of definitions. BMC Geriatr 2017;17(1):230 [FREE Full text] [doi: 10.1186/s12877-017-0621-2] [Medline: 29017448]
20. Guide to in-home vision testing. University of Arizona Opthalmology and Vision Science. URL: https://www.cdc.gov/steadi/pdf/4-Stage_Balance_Test-print.pdf [accessed 2021-11-15]
21. 30-Second Chair Stand. Centers for Disease Control and Prevention. URL: https://www.cdc.gov/steadi/pdf/STEADI-Assessment-30Sec-508.pdf [accessed 2021-11-15]
22. Timed Up and Go (TUG). Centers for Disease Control and Prevention. URL: https://www.cdc.gov/steadi/pdf/TUG_test-print.pdf [accessed 2021-11-15]
23. The 4-Stage Balance Test. Centers for Disease Control and Prevention. URL: https://www.cdc.gov/steadi/pdf/4-Stage_Balance_Test-print.pdf [accessed 2021-11-15]
24. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, et al. American College of Sports Medicine position stand. quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc 2011;43(7):1334-1359 [FREE Full text] [doi: 10.1249/MSS.0b013e318213fefb] [Medline: 21694556]
25. Lomas-Vega R, Obrero-Gaitán E, Molina-Ortega FJ, Del-Pino-Casado R. Tai chi for risk of falls. a meta-analysis. J Am Geriatr Soc 2017;65(9):2037-2043. [doi: 10.1111/jgs.15008] [Medline: 28736853]

26. Shaw BH, Garland EM, Black BK, Paranjape SY, Shibao CA, Okamoto LE, et al. Optimal diagnostic thresholds for diagnosis of orthostatic hypotension with a 'sit-to-stand test'. J Hypertens 2017;35(5):1019-1025 [FREE Full text] [doi: 10.1097/HJH.0000000000001265] [Medline: 28129252]
27. Postural Hypotension: what it is and how to manage it. Centers for Disease Control and Prevention. URL: https://www.cdc.gov/steadi/pdf/STEADI-Brochure-Postural-Hypotension-508.pdf [accessed 2021-11-15]
28. Check for safety: a home fall prevention checklist for older adults. Centers for Disease Control and Prevention. URL: https://www.cdc.gov/steadi/pdf/check_for_safety_brochure-a.pdf [accessed 2021-11-15]
29. Vitamin D deficiency in adults: screening. U.S. Preventive Services Task Force. URL: https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/vitamin-d-deficiency-screening [accessed 2021-11-15]
30. Home epley maneuver. John Hopkins Medicine. URL: https://www.hopkinsmedicine.org/health/treatment-tests-and-therapies/home-epley-maneuver [accessed 2021-11-15]
31. Ye C, Li J, Hao S, Liu M, Jin H, Zheng L, et al. Identification of elders at higher risk for fall with statewide electronic health records and a machine learning algorithm. Int J Med Inform 2020;137:104105 [FREE Full text] [doi: 10.1016/j.ijmedinf.2020.104105] [Medline: 32193089]
32. Belotti F, Deb P, Manning WG, Norton EC. Twopm: two-part models. Stata J 2015;15(1):3-20 [FREE Full text] [doi: 10.1177/1536867x1501500102]
33. Bhasin S, Gill TM, Reuben DB, Latham NK, Ganz DA, Greene EJ, et al. A randomized trial of a multifactorial strategy to prevent serious fall injuries. N Engl J Med 2020;383(2):129-140 [FREE Full text] [doi: 10.1056/NEJMoa2002183] [Medline: 32640131]

Abbreviations

CDC: Centers for Disease Control and Prevention
CRI: clinical research interviewer
EHR: electronic health record
ICD-10-CM: International Classification Definition, 10th Revision, Clinical Modification
NORC: National Opinion Research Center
REDCap: Research Electronic Data Capture
RN: registered nurse
RQIT: Randomized Quality Improvement Trial
RR: relative risk
SIS: Stay Independent screener
SOC: standard of care
STEADI: Stopping Elderly Accidents, Deaths, and Injuries
STRIDE: Strategies to Reduce Injuries and Develop Confidence in Elders
TUG: Timed Up and Go

Edited by A Mavragani; submitted 09.11.23; peer-reviewed by D Dinh, A Batrakoulis; comments to author 20.01.24; revised version received 08.02.24; accepted 09.02.24; published 26.03.24.

Please cite as:
Rein DB, Hackney ME, Haddad YK, Sublett FA, Moreland B, Imhof L, Peterson C, Legha JK, Mark J, Vaughan CP, Johnson II TM, Bergen G, Emory STEADI Implementation team
Telemedicine-Based Risk Program to Prevent Falls Among Older Adults: Protocol for a Randomized Quality Improvement Trial
JMIR Res Protoc 2024;13:e54395
URL: https://www.researchprotocols.org/2024/1/e54395
doi:10.2196/54395
PMID:38346180

Protocol

A Digital Platform (Telepalliation) for Patients in Palliative Care and Their Relatives: Protocol for a Multimethod Randomized Controlled Trial

Jarl Voss Andersen Sigaard[1,2*], MD; Nanna Celina Henneberg[2*], MSc; Cathrine Skov Schacksen[2*], MSc; Sissel Højsted Kronborg[2*], MSc; Laura Petrini[3*], MSc, PhD; Kristian Kidholm[4*], MSc, PhD; Una Rósa Birgisdóttir[2*], BMed; Helle Spindler[5*], MSc, PhD; Birthe Dinesen[2*], MSc, PhD

[1]Hospital of Southwest Jutland, University Hospital of Southern Denmark, Esbjerg, Denmark

[2]Laboratory for Welfare Technology—Digital Health & Rehabilitation, ExerciseTech, Department of Health Science and Technology, Aalborg University, Aalborg, Denmark

[3]Center for Neuroplasticity and Pain, Department of Health Science and Technology, Aalborg University, Aalborg, Denmark

[4]Centre for Innovative Medical Technology, Odense University Hospital, University of Southern Denmark, Odense, Denmark

[5]Department of Psychology and Behavioural Scienses, Aarhus University, Aarhus, Denmark

[*]all authors contributed equally

Corresponding Author:
Jarl Voss Andersen Sigaard, MD
Hospital of Southwest Jutland
University Hospital of Southern Denmark
Finsensgade 35
Esbjerg, 6700
Denmark
Phone: 45 23832739
Email: jarl.sigaard@rsyd.dk

Abstract

Background: The World Health Organization defines end-of-life palliative care as “prevention and relief of suffering, by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.” Over 20 million people worldwide are in need of palliative care. In Denmark, palliative care is given at a general and a specialist level. The general level comprises health care professionals (HCPs) who do not perform palliative care full-time. The specialist level comprises specialized palliative care (SPC), where HCPs perform palliative care full-time. In total, 20%-30% of patients who need palliative care are referred to SPC. Challenges with SPC include a short time span from referral to end of life, patients who are very ill and may therefore find it hard to travel to an outpatient clinic, and the SPC unit having a relatively small staff. The need for SPC is expected to rise, as the number of patients dying from terminal diseases is increasing. Telehealth has been successfully implemented in different home care settings, including palliative care.

Objective: The aim of the study is to present the research design of the clinical testing of a telepalliation program by the use of a digital platform for patients in palliative care and their relatives.

Methods: The telepalliation program will be conducted as a multimethod randomized controlled trial. The intervention group will follow the telepalliation program, while the control group will follow the traditional standard of care program for palliative care. The primary outcome of the study is increased quality of life. Secondary outcomes include enhanced sense of security; reduced experience of pain; satisfactory experiences of patients and relatives with the TelePal platform and degree of satisfaction in being a part of the program; experiences with the use of the TelePal platform on the part of HCPs and the professionals’ experiences of being a part of the program; the use of a cross-sector communication platform and the telepalliation program by patients, relatives, and HCPs; and the projected lower cost of health care services. These outcomes will be assessed using questionnaires, data generated by digital technologies, and semistructured interviews.

Results: The collection of data began in May 2021 and will be completed in August 2024. The results of the study will be published in peer-reviewed journals and presented at international conferences. Results from the telepalliation program are expected to be published by fall 2024.

Conclusions: The expected outcomes of the study are increased quality of life and increased sense of security. We also expect that the study will have a clinical impact on future telepalliation for those patients who are referred to a palliative team.

Trial Registration: ClinicalTrials.gov NCT04995848; https://clinicaltrials.gov/study/NCT04995848

International Registered Report Identifier (IRRID): DERR1-10.2196/49946

(JMIR Res Protoc 2024;13:e49946) doi:10.2196/49946

KEYWORDS

palliative care; digital health; quality of life; telehealth; interdisciplinary research; randomized controlled trial

Introduction

The World Health Organization defines end-of-life palliative care as "prevention and relief of suffering, by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual" [1]. The aim of palliative care is to provide relief from pain and other distressing symptoms offered by health care professionals (HCPs) at a general or specialist level, with a focus on addressing the needs of patients and their families [1,2]. More than 20 million people worldwide are estimated to be in need of end-of-life palliative care, equivalent to 377 adults in a population of 100,000, the majority of these being adults aged 60 years and older [2].

In Denmark, as in most other Western European countries, palliative care is provided at 2 different levels, a general and a specialist. The general level comprises HCPs, such as general practitioners (GPs) and primary care nurses, who do not perform palliative care on a full-time basis. The specialist level comprises specialized palliative care (SPC), where HCPs perform palliative care on a full-time basis at a specialist level [3]. It is expected that the basic level palliative care can address around 70%-80% of the patients in need of palliative care. The remaining 20%-30% of patients, having more complex problems, need SPC. SPC consists of specialized palliative care teams (SPCTs) placed at large hospitals serving a wider geographical area with home visits and cross-sector communication with patients, relatives, and other HCPs capable of caring for the patients.

Among patients receiving SPC, more than 90% are diagnosed with cancer [4], with the remaining cases divided among patients diagnosed with terminal cardiac insufficiency, terminal chronic obstructive pulmonary disease, and terminal neurological disorders [2,4].

There are several challenges associated with SPC, such as the very short time span from referral to the end of the patient's life [4] and the fact that patients are very ill and may therefore find it hard to travel to an outpatient clinic and that SPC unit often has a relatively small staff [2,5-7]. The need for SPC is expected to rise in the future, as the number of patients dying from life-threatening diseases, including cancer, is increasing [5,8]. As an increasing number of these patients prefer to be cared for at home, the demand for SPC is expected to increase [5,8].

The use of telehealth has been introduced in different settings and at different levels of home care and has also been used with success in palliative care [8,9]. Demand for telehealth solutions in palliative care has also increased due to the COVID-19 pandemic [10,11]. The use of information and communication technologies within palliative care can be defined as "telepalliation."

The overall purpose of the telepalliation study is to test, implement, analyze, and evaluate a telepalliation program for patients receiving palliative care. To accomplish this goal, we combine clinical, psychosocial, interorganizational, and health economic approaches. The telepalliation study will be implemented and evaluated in a randomized controlled trial (RCT). The aim of this paper is to describe the research design of the telepalliation study, the data collection methods used, and the outcome measures.

Methods

Research Design

The telepalliation program will be conducted as a multimethod RCT using qualitative and quantitative data collection techniques [12,13]. The intervention group will take part in the telepalliation program, while the control group will follow a traditional palliation program at Southwest Jutland Hospital, Esbjerg, Denmark. Enrollment of patients began in May 2021, and the RCT will end in August 2024. The study will be reported following the SQUIRE (Standards for Quality Improvement Reporting Excellence) guidelines [14].

The purpose of the telepalliation study is to test, implement, and evaluate a telepalliation program for patients receiving SPC at the Hospital of Southwest Jutland, Esbjerg, Denmark. To accomplish this goal, we combine clinical, psychosocial, interorganizational, and health economic approaches. This will be done by collecting data on symptom scores over time, patients scoring their feeling of security over time, and interviews with patients, their families, HCPs of the specialist team, and primary HCPs. Interviews will focus on the use of the TelePal platform but also on the interorganizational perspective of the communication between primary and secondary health systems. Evaluation of overall economic implications will be done separately at the end of the study. The telepalliation study will be implemented and evaluated in an RCT.

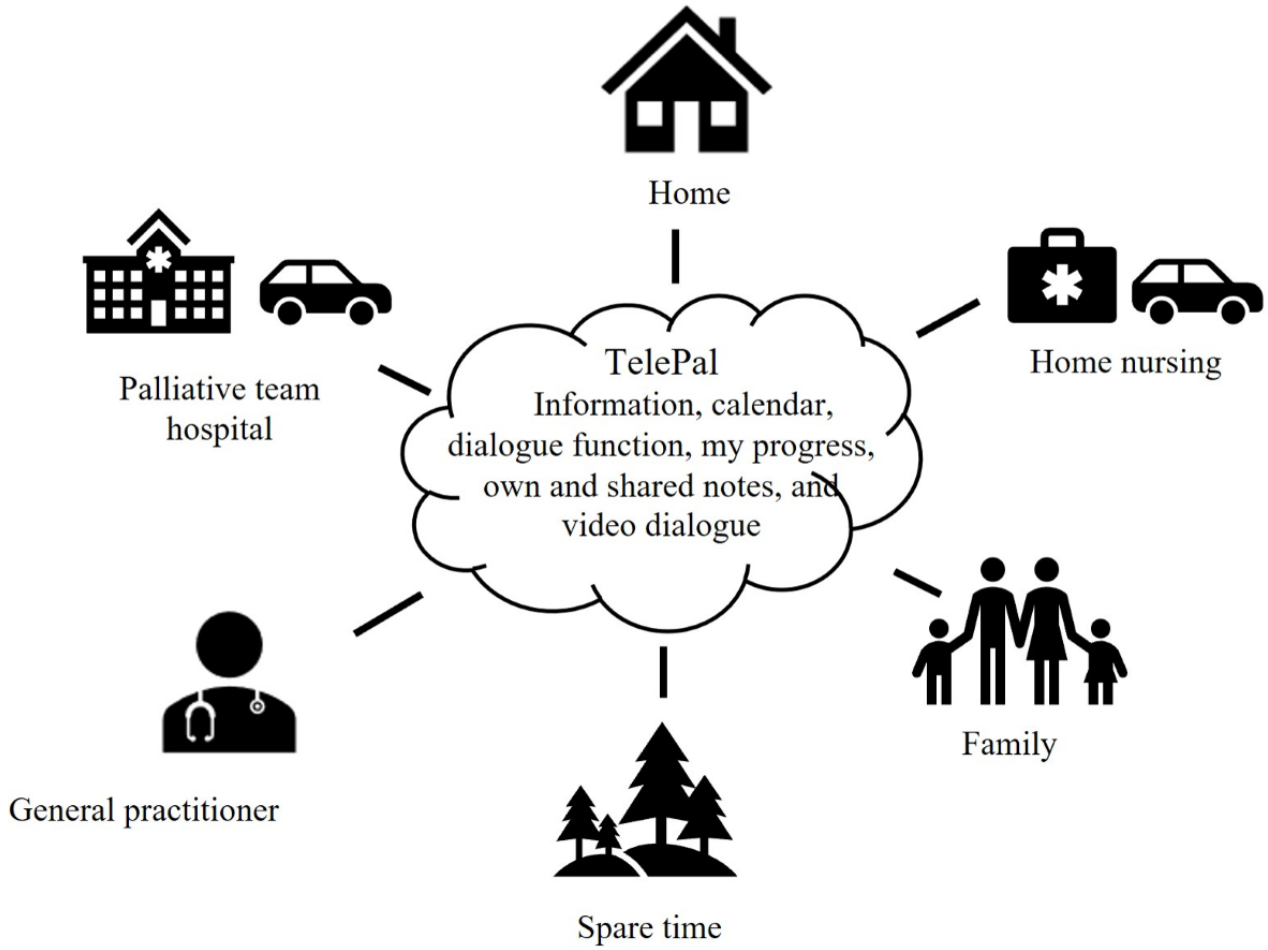
The TelePal Platform

The telepalliation program and platform have been developed through a participatory design process [15], involving patients who have received SPC and their relatives, HCPs working in palliative care, district nurses, GPs, and an interdisciplinary research team.

The study uses a TelePal platform, a communication platform that is shared among the patient, his or her relatives, and related HCPs. The platform can be used to communicate between patients, their families, and HCPs in primary and secondary health care. The patients must give their written consent as to whom they want to share their data. All information will be available and presented in the same way to all participating parties. The HCPs and researchers have extra tools with which to administer care, gain an overview of the patient's condition, and monitor multiple patients at the same time. The digital platform is not an electronic patient record but a platform for coordination and communication across sectors between patients, relatives, and HCPs.

All the measured values are stored on a secure database at Aalborg University (AAU). The TelePal web portal (Figure 1) is a web-based platform that encompasses multiple features that have been selected and developed through user-driven innovation [16]. Facilities and entered data (symptom scores, etc) of the specific patient are available to the persons, to whom the patient allows access to the platform. The features are described in Textbox 1.

Figure 1. Overview of the TelePal platform.



Textbox 1. Features of the TelePal web portal.

My page/front page (*Min side* in Danish); used to give the patient an overall overview of the different features)

- New messages
- Video consultations (the patient can have video conversations with the palliative team, district nurses, and GPs via TelePal. However, only the HCPs can book meetings with patients and their relatives)
- Questionnaires for patients to fill out

My treatment (*Mit forløb* in Danish)

- Dialogue function (here, the patients can send and reply to messages to the palliative team and the district nurses; if the patient so desires, an SMS function can be used to inform the patient about new messages on TelePal)
- Calendar (gives the patient the opportunity to register coming appointments with the palliative team or any other activity for an overview)
- Joint notes (notes related to the patient's treatment are written here by either the palliative team, the home nurse, or GPs)
- Own notes (these are the patient's own notes, thoughts, questions, and reflections, if they want to use this function)

My status (this site provides the patient with an overview of the results from all the questionnaires they have filled out)

- The data from the questionnaires are visible to the patient's relatives and HCPs, if the patient has allowed them to see and follow their data on TelePal.
- Patients may decide themselves whether they want to allow up to 2 relatives to have access to their TelePal platform. It is also the patient who defines what relatives should have access.

Data and Network Security

The TelePal platform is web-based. It is possible to access the platform from any internet-enabled device, for example, a PC or Mac computer or a tablet, via any modern browser. The most optimal experience and resolution will appear when using an iPad or tablet. All communication and data are secured based with SSL and a 2-factor log-in. The portal will be kept at AAU on servers provided by AAU IT services.

Eligibility Criteria

All participants will be recruited by 2 project nurses at the palliative team at Southwest Jutland Hospital, Esbjerg, Denmark. Recruitment will take place by personal contact and by a recruitment letter. Enrollment will proceed if the participant fits the inclusion and exclusion criteria. Inclusion criteria for participants are that they must be patients under SPC at the Hospital of Southwest Jutland; be aged 18 years or older; live in Esbjerg, Varde, Billund, Fanø, or Vejen municipalities; have cancer, heart failure, chronic obstructive pulmonary disease, or motor neuron disease; and have basic computer skills or have a relative who is able to help them. The exclusion criteria are delirium at enrollment based on the Confusion Assessment Method score; an active psychiatric history other than depression or anxiety related to the main diagnosis, which refers to the reason for palliative care; and a lack of cooperation. Enrollment will take place at the patient's home, where a doctor and a nurse from the palliative team will take the inclusion and exclusion criteria into consideration. Patients who are moribund are not assessed for participation in the study. The patient will be given complete information about the project, and the palliative team will obtain informed consent. The project nurse will then proceed to explain to the patient how to use the equipment and the TelePal portal. If the patient meets the inclusion criteria and agrees to be included, randomization to either the intervention group or standard care will be made.

Details on the RCT

The randomization is performed randomly by a digital tool. The randomization was designed as a block with equal numbers for the intervention and control groups. Only 1 person was blinded. The intervention group participated in the telepalliation program, and the control group received standard SPC [1,3] that was individualized for each patient.

Sample Size

The sample size of the telepalliation study was determined to be 91 patients in both the intervention and the control groups when calculating values based on Ramsenthaler et al [17]. This was done using a 95% CI, an 80% power, an SD of 20.5, a mean quality-of-life score of 59.5 determined by the European Organisation for Research and Treatment of Cancer, and a mean quality-of-life score of 68.43 determined by the European Organisation for Research and Treatment of Cancer when operating with a 15% change in quality of life (QoL).

Theoretical Framework

The theoretical framework is applied as lenses in qualitative analysis.

Psychosocial

In recent years, increasing attention has been paid to the importance of psychosocial factors in palliative care and how these factors can play a crucial role for good end-of-life care in terms of alleviating pain and other distressing symptoms [18]. The World Health Organization [1,19] stated that control of pain, psychological disorders like anxiety and depression, and social and spiritual problems is paramount in palliative care.

Research shows that an intervention focused on the assessment of pain and psychosocial symptoms, establishment of goals of care, assistance with decision-making regarding treatment, and individualized coordination of care can all significantly improve

patient QoL. Patients reported less depression and physical symptom burden and lived an average of 2.7 months longer than the usual care group, despite receiving less aggressive care [20].

Interorganizational Theory

Collaboration across sectors in the telepalliation program will be studied through the lenses of interorganizational theory by Alter and Hage [21]. The network approach facilitates an exploration of the interplay, communication, collaboration, and dynamics between the HCPs, for example, palliative team, district nurses, and GPs across borders and sectors when developing and implementing the telepalliation program. Alter and Hage [21] define a network as follows: "Networks constitute the basic social form that permits inter-organizational interactions of exchange, converted action, and joint production. Networks are unbounded or bounded clusters of organizations that, by definition, are non-hierarchical collectives of legally separate units."

Ethical Considerations

This study was approved by the ethical committee in Northern Jutland (N-202000094) and registered at ClinicalTrials.gov (NCT04995848). This study will be conducted according to the Declaration of Helsinki. Patients in palliative care and their relatives are a vulnerable group and will be informed thoroughly about the purpose of the study. Accordingly, it is specified that the patient can withdraw their consent at any given time in the study without having any consequences for their treatment. Individuals will be considered as participants in the trial, whereas their relatives will not be considered as participants. However, they are invited to voluntarily participate in the use of the digital platform TelePal. To clarify and ensure that all relatives are fully informed about the study and feel safe about their participation, a written letter of information was sent to all relatives. Patients are enrolled in the study for a maximum of 6 months or until (1) they stop being followed by the palliative team due to lack of symptoms or (2) they are diagnosed with delirium based upon the Confusion Assessment Method score [22,23]. Patients who develop cognitive impairment will be dismissed from the study, and patients who develop delirium will also be dismissed, and data collection will end immediately.

Baseline Data

Baseline data on demographics and diagnosis will be collected for both the intervention and the control groups. Questionnaires regarding QoL, sense of security, pain assessment, and quality-adjusted life years (QALYs) will be combined in questionnaire packages matching the time of measurement illustrated in Table 1. The intervention and the control group will be asked to fill in identical questionnaire packages at the same point in time. All years will be answered by both the intervention and the control group, thereby meaning that both groups obtain identical questions and the same number of questionnaires. All questionnaires will be filled out on TelePal. However, the control group can choose to complete the questionnaires on paper if they desire.

Table 1. Primary and secondary outcome measures.

Outcomes	Time of measurement	Group	
		Intervention	Control
Primary			
Quality of life	Once weekly	✓	✓
Secondary			
Changes in medicine	Weekly for 6 months	✓	✓
Pain assessment	Weekly	✓	✓
Feeling of security	Twice a week	✓	✓
Patients' experiences	Interviews will be conducted after 4 weeks	✓	
Relatives' experiences	Interviews will be conducted after 4 weeks and after 3 months	✓	
Health care professionals' experiences	Interviews will be conducted at 6 and 12 months		
Use of the TelePal platform and telepalliation program	Analysis at the end of the project	✓	✓
Cost of health care services	Week 1 and week 4, and analysis at the end of the project	✓	✓
Quality of life associated with cost of health care services	Week 1 and week 4, and analysis at the end of the project	✓	✓

Outcome Measures

Overview

Primary and secondary outcome measures will be collected as shown in Table 1. The data collection process is described in the following sections.

Quality of Life

The EORTC QLQ-C15-PAL (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 15 Palliative Care) [24] questionnaire will be used to measure QoL as the primary outcome. The EORTC QLQ-C15-PAL was developed by the European Organization for Research and Treatment of Cancer to measure the QoL for

patients in palliative care. It is a briefer version of the EORTC QLQ-C30-PAL I, as this patient group is often not able to complete extensive self-report measures. It consists of 15 items, of which, all but one (global QoL) is self-rated on a 4-point Likert scale (1=not at all to 4=very much), whereas global QoL is rated on a 7-point Likert scale (1=very poor to 7=excellent). In this study, we did not use the global QoL item. Items are used to calculate scores on 2 multi-item functional scales (emotional and physical), 2 multi-item symptom scales (fatigue and pain), and finally, they contribute to 5 single-item symptom scales (nausea or vomiting, lack of appetite, shortness of breath, constipation, and sleeping difficulties). The EORTC QLQ-C15-PAL is considered to have good content validity [24], and a recent study comparing measures of QoL in palliative care found acceptable internal consistency and test-retest reliability as well as sensitivity of the EORTC QLQ-C15-PAL, while overall results indicated that no other QoL measure is superior to use in this patient group [25].

In addition, the EQ-5D health questionnaire was used to determine QALY to support our analysis on the cost of health care services, as no other QoL measure is validated for this purpose. Hence, we incorporated EQ-5D, the EQ Visual Analog Scale from the EQ-5D, which records the patient's self-rated health on a vertical visual analog scale using the end points, the best health you can imagine and the worst health you can imagine. This scale can be used as a quantitative measure of health outcomes that reflect the patient's own judgment [26]. Studies have shown good construct validity and responsiveness in palliative care [27], and a recent systematic review finds that the EQ-5D has excellent psychometric properties across a broad range of populations [28].

Changes in Medicine

Information on medicine for both groups will be collected at enrollment and every week from the electronic patient record during a 6-month period. Changes in medicine over time will be analyzed.

Pain Assessment

In line with the recommendations for supplementing the EORTC QLQ-C15-PAL with focused measures, if more information on a specific content area is warranted [29], and in accordance with the Expert Working Group of the European Association for Palliative Care [30], we incorporated the Brief Pain Inventory Short Form, a pain measurement tool [31]. The Brief Pain Inventory rapidly assesses the severity of pain and its impact on the patient's functioning. In this study, we incorporated the 11-point numeric rating scale (0-10) for pain intensity as well as 7 items focusing on the impact of pain on functioning in relation to activity, mood, ability to walk, work, relation to other people, sleep, and general joy of life rated on an 11-point numeric rating scale (0=no impact to 10=full impact). The internal consistency of the Brief Pain Inventory (Cronbach α) ranges from .77 to .91, and more specifically, for the pain intensity scale, Cronbach α ranges from .78 to .96 [32].

Sense of Security

To evaluate the patient's sense of security using the TelePal platform, we developed a single item ("Overall, how would you rate your sense of security over the past 24 hours?"), rated on a 5-point scale (1=very unsafe to 5=very safe), to be used in this study.

Use of TelePal Platform and Experiences Using the TelePal Platform

Qualitative exploration of the patients', their relatives', and the HCPs' experiences using the TelePal platform will be collected during semistructured interviews inspired by Brinkmann and Kvale [33]. Patients will be selected randomly to participate in interviews. Interviews with patients and relatives will be conducted after 4, 8, and 12 weeks. Interviews with HCPs will be conducted after 6 and 12 months. All interviews with patients, relatives, and HCPs will be conducted until data saturation has been reached. To analyze which parts of the TelePal platform are being used and for how long, time log files for log-in and log-out of patients, relatives, and HCPs will be analyzed at the end of the project. Consent for the extraction of log files from the database will be received from patients, relatives, and HCPs.

Evaluation of Cost of Health Care Services

The data used to determine QALYs will come from the EQ Visual Analog Scale of the EQ-5D questionnaire [26] (see description in the Quality of Life section). Patients will be asked to answer the EQ-5D health questionnaire twice, first in week 1 of the study and then in week 4, in order to determine QALYs [26]. The questionnaire will be completed by the intervention group on TelePal, and the control group will complete the questionnaire on TelePal or on paper. Furthermore, a cost-effectiveness analysis will be conducted by calculating the differences in clinical efficacy and differences in average cost per patient [34,35]. The cost parameters are numbers of phone or video calls from the palliative team, equipment used, driving distance, personal use in palliative care, visits from GPs, outpatient clinic visits, numbers of hospitalizations, readmissions, length of stay, and visits from the palliative team.

Adverse Events and Dropouts

All adverse events, deaths, dropouts, or withdrawals from the study will be recorded and documented. If the patients no longer want to participate in the study, they can withdraw their consent at any time without having to give a reason. After withdrawing they will be given standard care treatment. The patient's reason for withdrawal, if any is given, will be documented. In this case, the project team will collect the equipment upon request. Patients who do not participate actively in the intervention will still be included in the study and analyzed according to the intention-to-treat approach. These patients will be allowed to use the project equipment as long as they want. Technical problems with the equipment will be recorded and documented.

Statistical Analysis

The applied statistical methods will be used to investigate differences between patients in the intervention group and the control group. Statistical analyses will be used to explore the normal distribution of the sample, the SD, the hypothesis tests, and the *P* values. Nevertheless, a 2-tailed *t* test between the intervention and control groups will be performed in order to compare baseline data between the 2 groups, and a 2-way ANOVA with repeated measures will also be performed to

compare the 2 groups in relation to their outcomes. All the statistical analyses will be performed using SPSS Statistics (version 25; IBM Corp). Data will be analyzed for gender differences in both primary and secondary outcomes. If there is any missing data, it will be analyzed based on the data received from the questionnaires. If there is too much data missing, a sensitivity test will be performed based on the demographic data.

Qualitative Analysis

All interviews will be transcribed into Word (Microsoft Corp) files. The data will be coded in NVivo (version 12.0; QSR International) inspired by methods developed by Brinkmann and Kvale [33]. Two researchers (JVAS and BD) will conduct the interviews and analysis of the data. The data will be presented in themes, findings, and with citations.

Results

Results from the RCT will be analyzed in spring 2024, published in peer-reviewed journals in the fields of palliative care and telepalliation, and presented at relevant international conferences by fall 2024.

Discussion

Principal Findings

The aim of the telepalliation study is to test, implement, and evaluate the telepalliation program for patients receiving palliative care. The study is carried out using combined clinical, psychosocial, interorganizational, and health economic approaches.

A scoping review by Steindal et al [36] has shown that the use of telehealth in palliative homecare improves access to HCPs at home and enhances patients' sense of security and safety. The review indicated that there are contradicting results as to whether the use of telehealth will improve burdensome symptoms and QoL [36]. A study by Caraceni et al [11] has shown that telemedicine facilitates patient-clinician interaction, but the investigation of clinical impact should be better documented.

The TelePal platform and program have been developed in a participatory design process, and an important part of the study is to explore how patients in palliative care and their relatives experience the TelePal program and use the digital platform. Important questions to explore are whether the patients have the resources to use the technology, and if so, what functions are they and their relatives using and what value do they attribute to these functions. Another important question revolves around the ethical issues of using a digital platform in the collaboration between patients in palliative care and HCPs. Steindal et al [36] stated that there is a need for increased knowledge about these issues. We hope that the platform can help increase the feeling of security for the patients and relatives and ease communication, collaboration, and coordination among the HCPs across sectors.

In palliative settings, video has been used for conferences between patient's homes and between rural health professionals and specialist centers to support patients and their relatives at home [8]. The use of video can increase the collaboration between SPCTs and GPs [6] and fit the practice of home-based palliative care, thus resulting in a more empathetic patient-professional relationship [37]. In the TelePal study, we will explore how the platform will affect the patient care process and interorganizational collaboration among the HCPs across sectors. We have not identified other studies using a telepalliation platform and a program.

What are the health economy costs of running a telepalliation program? Caraceni et al [11] highlighted the lack of cost-effectiveness studies within telepalliation. In the TelePal study, we will conduct a cost-effectiveness evaluation to show that it will be cost-effective, reduce the cost for transportation, and reduce patients' travel to the hospitals.

Limitations

A limitation of this study is that it is a 1-center study and therefore reflects the findings of only a single SPCT. The fact that it has been conducted only in Denmark means that it reflects findings within a Danish context. These findings may not necessarily be applicable to other settings and in different contexts.

Conclusions

The expected outcomes are increased QoL and increased sense of security for patients in the intervention group. We expect that the study will have a clinical impact on future telepalliation for patients who are referred to a palliative team.

Acknowledgments

The authors wish to thank the Danish Cancer Society for funding the study and the Hospital of Southwest Jutland in Esbjerg for supporting with technology. All partners have also supported the project with hours in kind. The authors also wish to thank the patients and relatives for participating in this important study. The authors thank the project nurses Hanne Christensen and Sanne Skov for their valuable comments to the design of the protocol.

Conflicts of Interest

None declared.

References

1. WHO definition of palliative care. World Health Organization. 2020. URL: https://www.who.int/news-room/fact-sheets/detail/palliative-care [accessed 2023-09-29]
2. Connor SR, Bermedo M. Global atlas of palliative care at the end of life. Worldwide Palliative Care Alliance, World Health Organization. 2014. URL: https://www.iccp-portal.org/system/files/resources/Global_Atlas_of_Palliative_Care.pdf [accessed 2024-03-12]
3. Anbefalinger for den palliative indsats. Danish Health Authorities. 2011. URL: https://www.sst.dk/-/media/Udgivelser/2011/Publ2011/SYB/Palliation/Anbefalinger-for-den-palliative-indsats-2011.ashx [accessed 2024-03-08]
4. Hansen MB, Adsersen M, Grønvold M. Dansk multidisciplinaer cancer gruppe for palliativ indsats. Dansk Multidisciplinær Cancer Gruppe for Palliativ Indsats. URL: http://www.dmcgpal.dk/ [accessed 2024-03-08]
5. Worster B, Swartz K. Telemedicine and palliative care: an increasing role in supportive oncology. Curr Oncol Rep 2017 Jun;19(6):37. [doi: 10.1007/s11912-017-0600-y] [Medline: 28417310]
6. van Gurp J, van Selm M, van Leeuwen E, Vissers K, Hasselaar J. Teleconsultation for integrated palliative care at home: a qualitative study. Palliat Med 2016 Mar;30(3):257-269. [doi: 10.1177/0269216315598068] [Medline: 26269323]
7. Bates BM. Innovation comes to palliative care. IEEE Pulse 2016:25-29. [doi: 10.1109/MPUL.2016.2606467]
8. Hoek PD, Schers HJ, Bronkhorst EM, Vissers KCP, Hasselaar JGJ. The effect of weekly specialist palliative care teleconsultations in patients with advanced cancer—a randomized clinical trial. BMC Med 2017 Jun 19;15(1):119 [FREE Full text] [doi: 10.1186/s12916-017-0866-9] [Medline: 28625164]
9. Funderskov KF, Raunkiær M, Danbjørg DB, Zwisler AD, Munk L, Jess M, et al. Experiences with video consultations in specialized palliative home-care: qualitative study of patient and relative perspectives. J Med Internet Res 2019 Mar 21;21(3):e10208 [FREE Full text] [doi: 10.2196/10208] [Medline: 30896436]
10. Steindal SA, Nes AAG, Godskesen TE, Holmen H, Winger A, Österlind J, et al. Advantages and challenges of using telehealth for home-based palliative care: systematic mixed studies review. J Med Internet Res 2023 Mar 13;25:e43684 [FREE Full text] [doi: 10.2196/43684] [Medline: 36912876]
11. Caraceni A, Pellegrini C, Shkodra M, Zecca E, Bracchi P, Lo Dico S, et al. Telemedicine for outpatient palliative care during COVID-19 pandemics: a longitudinal study. BMJ Support Palliat Care 2022 Jun 16:1-7 [FREE Full text] [doi: 10.1136/bmjspcare-2022-003585] [Medline: 35710705]
12. Greene JC. Mixed Methods in Social Inquiry. San Francisco, CA: Jossey-Bass; 2007.
13. Creswell JW, Plano CVL. Designing and Conducting Mixed Methods Research. 3rd Edition. Thousand Oaks, CA: SAGE Publications; 2017:520.
14. Ogrinc G, Davies L, Goodman D, Batalden P, Davidoff F, Stevens D. SQUIRE 2.0 (Standards for QUality Improvement Reporting Excellence): revised publication guidelines from a detailed consensus process. BMJ Qual Saf 2016;25(12):986-992 [FREE Full text] [doi: 10.1136/bmjqs-2015-004411] [Medline: 26369893]
15. Clemensen J, Rothmann MJ, Smith AC, Caffery LJ, Danbjorg DB. Participatory design methods in telemedicine research. J Telemed Telecare 2017;23(9):780-785 [FREE Full text] [doi: 10.1177/1357633X16686747] [Medline: 28027678]
16. von Hippel E. Democratizing Innovation. London, UK: MIT Press; 2005:216.
17. Ramsenthaler C, Osborne TR, Gao W, Siegert RJ, Edmonds PM, Schey SA, et al. The impact of disease-related symptoms and palliative care concerns on health-related quality of life in multiple myeloma: a multi-centre study. BMC Cancer 2016;16:427 [FREE Full text] [doi: 10.1186/s12885-016-2410-2] [Medline: 27387201]
18. Dworkin R, Breitbart W. Psychosocial Aspects of Pain: A Handbook for Health Care Providers. Vol. 27, Progress in Pain Research and Management. Portland, OR: IASP Press; 2004:87.
19. Connor SR. Global atlas of palliative care. 2nd edition. Worldwide Hospice Palliative Care Alliance, World Health Organization. 2020. URL: https://cdn.who.int/media/docs/default-source/integrated-health-services-(ihs)/csy/palliative-care/whpca_global_atlas_p5_digital_final.pdf?sfvrsn=1b54423a_3 [accessed 2023-09-29]
20. Rosenstein DL. Depression and end-of-life care for patients with cancer. Dialogues Clin Neurosci 2011;13(1):101-108 [FREE Full text] [Medline: 21485750]
21. Alter C, Hage J. In: Hage J, editor. Organizations Working Together. Newbury Park, CA: Sage Publications; 1993.
22. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med 1990 Dec 15;113(12):941-948. [doi: 10.7326/0003-4819-113-12-941] [Medline: 2240918]
23. Ryan K, Leonard M, Guerin S, Donnelly S, Conroy M, Meagher D. Validation of the confusion assessment method in the palliative care setting. Palliat Med 2009 Jan;23(1):40-45. [doi: 10.1177/0269216308099210] [Medline: 19010967]
24. Groenvold M, Petersen MA, Aaronson NK, Arraras JI, Blazeby JM, Bottomley A, EORTC Quality of Life Group. The development of the EORTC QLQ-C15-PAL: a shortened questionnaire for cancer patients in palliative care. Eur J Cancer 2006 Jan;42(1):55-64. [doi: 10.1016/j.ejca.2005.06.022] [Medline: 16162404]
25. King MT, Agar M, Currow DC, Hardy J, Fazekas B, McCaffrey N. Assessing quality of life in palliative care settings: head-to-head comparison of four patient-reported outcome measures (EORTC QLQ-C15-PAL, FACT-Pal, FACT-Pal-14, FACT-G7). Support Care Cancer 2020 Jan;28(1):141-153 [FREE Full text] [doi: 10.1007/s00520-019-04754-9] [Medline: 30993452]

26. Devlin N, Parkin DW, Janssen MFB. Methods for analysing and reporting EQ-5D data. EuroQol Research Foundation. 2020. URL: https://www.ncbi.nlm.nih.gov/books/NBK565678/ [accessed 2024-03-16]
27. Obradovic M, Lal A, Liedgens H. Validity and responsiveness of EuroQol-5 dimension (EQ-5D) versus Short Form-6 dimension (SF-6D) questionnaire in chronic pain. Health Qual Life Outcomes 2013 Jul 01;11:110 [FREE Full text] [doi: 10.1186/1477-7525-11-110] [Medline: 23815777]
28. Feng YS, Kohlmann T, Janssen MF, Buchholz I. Psychometric properties of the EQ-5D-5L: a systematic review of the literature. Qual Life Res 2021 Mar;30(3):647-673 [FREE Full text] [doi: 10.1007/s11136-020-02688-y] [Medline: 33284428]
29. Bausewein C, Daveson BA, Currow DC, Downing J, Deliens L, Radbruch L, et al. EAPC White Paper on outcome measurement in palliative care: improving practice, attaining outcomes and delivering quality services—recommendations from the European Association for Palliative Care (EAPC) Task Force on Outcome Measurement. Palliat Med 2016 Jan;30(1):6-22. [doi: 10.1177/0269216315589898] [Medline: 26068193]
30. Caraceni A, Cherny N, Fainsinger R, Kaasa S, Poulain P, Radbruch L, et al. Pain measurement tools and methods in clinical research in palliative care: recommendations of an Expert Working Group of the European Association of Palliative Care. J Pain Symptom Manage 2002 Mar;23(3):239-255 [FREE Full text] [doi: 10.1016/s0885-3924(01)00409-2] [Medline: 11888722]
31. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singap 1994 Mar;23(2):129-138. [Medline: 8080219]
32. Atkinson TM, Mendoza TR, Sit L, Passik S, Scher HI, Cleeland C, et al. The Brief Pain Inventory and its "pain at its worst in the last 24 hours" item: clinical trial endpoint considerations. Pain Med 2010 Mar;11(3):337-346 [FREE Full text] [doi: 10.1111/j.1526-4637.2009.00774.x] [Medline: 20030743]
33. Brinkmann S, Kvale S. InterViews: Learning the Craft of Qualitative Research Interviewing. 3rd Edition. Los Angeles, CA: Sage Publications; 2015.
34. Drummond MF, Torrance G, O'Brien B, Stoddart G. In: Drummond MF, editor. Methods for the Economic Evaluation of Health Care Programmes. 3rd Edition. Oxford, UK: Oxford University Press; 2005.
35. Kidholm K, Kristensen MBD. A scoping review of economic evaluations alongside randomised controlled trials of home monitoring in chronic disease management. Appl Health Econ Health Policy 2018 Apr;16(2):167-176. [doi: 10.1007/s40258-017-0351-9] [Medline: 28871514]
36. Steindal SA, Nes AAG, Godskesen TE, Dihle A, Lind S, Winger A, et al. Patients' experiences of telehealth in palliative home care: scoping review. J Med Internet Res 2020 May 05;22(5):e16218. [doi: 10.2196/16218] [Medline: 32369037]
37. van Gurp J, van Selm M, Vissers K, van Leeuwen E, Hasselaar J. How outpatient palliative care teleconsultation facilitates empathic patient-professional relationships: a qualitative study. PLoS One 2015;10(4):e0124387 [FREE Full text] [doi: 10.1371/journal.pone.0124387] [Medline: 25902263]

Abbreviations

AAU: Aalborg University
EORTC QLQ-C15-PAL: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 15 Palliative Care
GP: general practitioner
HCP: health care professional
QALY: quality-adjusted life year
QoL: quality of life
RCT: randomized controlled trial
SPC: specialized palliative care
SPCT: specialized palliative care team
SQUIRE: Standards for Quality Improvement Reporting Excellence

Edited by A Mavragani; submitted 14.06.23; peer-reviewed by A Klarare, SA Steindal; comments to author 31.08.23; revised version received 29.10.23; accepted 25.01.24; published 02.04.24.

Please cite as:
Sigaard JVA, Henneberg NC, Schacksen CS, Kronborg SH, Petrini L, Kidholm K, Birgisdóttir UR, Spindler H, Dinesen B
A Digital Platform (Telepalliation) for Patients in Palliative Care and Their Relatives: Protocol for a Multimethod Randomized Controlled Trial
JMIR Res Protoc 2024;13:e49946
URL: https://www.researchprotocols.org/2024/1/e49946
doi:10.2196/49946
PMID:38564264

Protocol

Understanding Physician's Perspectives on AI in Health Care: Protocol for a Sequential Multiple Assignment Randomized Vignette Study

Jane Paik Kim[1], PhD; Hyun-Joon Yang[1], BS; Bohye Kim[1], BA, MA; Katie Ryan[1], BA, MA; Laura Weiss Roberts[1], MD, MA

Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, United States

Corresponding Author:
Jane Paik Kim, PhD
Department of Psychiatry and Behavioral Sciences
Stanford University School of Medicine
1070 Arastradero Rd
Stanford, CA, 94304
United States
Phone: 1 650 736 8996
Email: janepkim@stanford.edu

Abstract

Background: As the availability and performance of artificial intelligence (AI)–based clinical decision support (CDS) systems improve, physicians and other care providers poised to be on the front lines will be increasingly tasked with using these tools in patient care and incorporating their outputs into clinical decision-making processes. Vignette studies provide a means to explore emerging hypotheses regarding how context-specific factors, such as clinical risk, the amount of information provided about the AI, and the AI result, may impact physician acceptance and use of AI-based CDS tools. To best anticipate how such factors influence the decision-making of frontline physicians in clinical scenarios involving AI decision-support tools, hypothesis-driven research is needed that enables scenario testing before the implementation and deployment of these tools.

Objective: This study's objectives are to (1) design an original, web-based vignette-based survey that features hypothetical scenarios based on emerging or real-world applications of AI-based CDS systems that will vary systematically by features related to clinical risk, the amount of information provided about the AI, and the AI result; and (2) test and determine causal effects of specific factors on the judgments and perceptions salient to physicians' clinical decision-making.

Methods: US-based physicians with specialties in family or internal medicine will be recruited through email and mail (target n=420). Through a web-based survey, participants will be randomized to a 3-part "sequential multiple assignment randomization trial (SMART) vignette" detailing a hypothetical clinical scenario involving an AI decision support tool. The SMART vignette design is similar to the SMART design but adapted to a survey design. Each respondent will be randomly assigned to 1 of the possible vignette variations of the factors we are testing at each stage, which include the level of clinical risk, the amount of information provided about the AI, and the certainty of the AI output. Respondents will be given questions regarding their hypothetical decision-making in response to the hypothetical scenarios.

Results: The study is currently in progress and data collection is anticipated to be completed in 2024.

Conclusions: The web-based vignette study will provide information on how contextual factors such as clinical risk, the amount of information provided about an AI tool, and the AI result influence physicians' reactions to hypothetical scenarios that are based on emerging applications of AI in frontline health care settings. Our newly proposed "SMART vignette" design offers several benefits not afforded by the extensively used traditional vignette design, due to the 2 aforementioned features. These advantages are (1) increased validity of analyses targeted at understanding the impact of a factor on the decision outcome, given previous outcomes and other contextual factors; and (2) balanced sample sizes across groups. This study will generate a better understanding of physician decision-making within this context.

International Registered Report Identifier (IRRID): DERR1-10.2196/54787

(JMIR Res Protoc 2024;13:e54787) doi:10.2196/54787

KEYWORDS

AI-based clinical decision support; decision-making; hypothetical vignettes; physician perspective; web-based survey; hypothesis-driven research; ethics; stakeholder attitudes

Introduction

The implementation of artificial intelligence (AI) in health care is recognized as a promising means to advance medicine by providing timelier diagnoses, reducing administrative burden, and predicting outcomes with higher accuracy. As the availability and performance of AI-based clinical decision support (CDS) systems improve, physicians and other care providers poised to be on the front lines will be increasingly tasked with using these tools in patient care and incorporating their outputs into clinical decision-making processes. Due to the few instances of CDS systems in current use by frontline physicians, there is limited empirical research studying how these tools and the specific characteristics of these tools influence physicians' engagement with AI and their clinical decision-making.

Previous research has identified factors that may influence physicians' use and decision-making in the context of AI-based CDS systems, including clinical risk, explainability, as well as trust and transparency [1,2]. While the role of trust and transparency in clinician acceptance has been emphasized in the literature in recent years, findings supporting the claim that transparency about AI can actually support clinical decision-making are mixed [3-5]. Jussupow et al [6] used vignette-based experiments with physicians to understand how AI influences their decision-making, finding that the timing of the presentation of the AI result, whether or not the AI result aligns with the physician's opinion, and the experience level of the physician may all be factors that influence the decision-making of a physician who is tasked with incorporating an AI-based CDS system in their diagnostic care. Such knowledge is critical to ensuring successful implementation of AI in health care, but due to the many differences in the types of applications of AI, subspecialties, and health care systems, there is a high degree of heterogeneity in physician attitudes regarding acceptance, and factors influential to their decision-making are likely to be context specific.

Experimental vignette studies such as Jussupow et al [6] provide an effective means to explore emerging hypotheses regarding how context-specific factors may impact physician acceptance and use of AI-based CDS tools or to generate new hypotheses regarding how individuals may react to specific scenarios involving new applications where much is unknown. Vignettes are narrative representations of real-world scenarios, providing context-specific stimuli and characteristics with which respondents may practice decision-making without actual exposure to such scenarios [7-9]. Experimental vignette studies have been used to understand reactions toward algorithmic errors [10], physician liability while using AI [11], and physician diagnostic accuracy in the context of AI [12].

In this study, we use a novel vignette survey design—"sequential multiple assignment randomization trial (SMART) vignettes," proposed by JP Kim and HJ Yang (unpublished data)—which uses the SMART design developed by Murphy [13] in a web-based vignette survey. The novelty of this survey design is that it features 2 design elements previously not seen in conventional designs: sequential randomization and adaptive allocation. In experimental vignette studies, hypothetical characteristics (factors) are varied according to levels. Each respondent is randomly assigned to 1 vignette characterized by a specific realization of each factor in order to test how the factors influence responses. In conventional vignette studies, this randomization typically occurs once before the study is administered at baseline, followed by a complete set of questions. Sequential randomization, on the other hand, involves randomly assigning respondents to vignettes multiple times throughout the survey, with each randomization point followed by a subset of questions pertaining to the factor being tested. This latter approach allows inferences about the final response based on previous factors and responses. In contrast, baseline randomization in traditional designs is limited to inferences on how likely each combination of responses is based on given factors. Adaptive allocation is a way to adjust randomization probabilities to encourage more balanced groups for such inference. While these 2 concepts are not novel in and of themselves—the former appears in the field of SMARTs [13,14] and the latter is from Efron [15]—the application of such concepts in the context of vignette survey methodology is novel, to the best of our knowledge.

To best anticipate the decision-making of frontline physicians in scenarios involving AI CDS tools, a hypothesis-driven approach that enables scenario testing in advance of clinical implementation of these tools is urgently needed. As such, we propose to undertake an empirical study engaging frontline physicians in order to better understand the causal effects of specific contextual and algorithmic features on their clinical judgments and perspectives. For our approach, we will conduct a "SMART vignette" web-based survey that features hypothetical scenarios based on emerging or real-world applications of AI-based CDS systems. These scenarios will vary systematically by features related to clinical risk, the amount of information provided about the AI, and the AI result in order to test and determine the causal effects of specific factors on the judgments and perceptions salient to physicians' clinical decision-making.

Methods

Overview

The purpose of this study is to better understand the impact of algorithm-related features on physician acceptance and attitudes related to clinical decision-making in the context of AI CDS tools. US-based physicians with specialties in the family or internal medicine (ie, those most poised to be on the "front lines" of nonemergency patient care) who are listed in the most recent version of the American Medical Association (AMA) Physician Masterfile (PMF) will be recruited through email and

mail (target n=420). Through a web-based survey, participants will respond to baseline questionnaires regarding their demographics, professional experience, and attitudes toward and experience with AI or machine learning (ML) in medicine. They will then be randomly assigned to a 3-part "SMART vignette" detailing a hypothetical clinical scenario involving an AI decision support tool. Each respondent will progress through the multistage vignette survey, and at each stage, they will be randomly assigned to one of the possible vignette variations. The 3 randomization points will vary in regard to the level of clinical risk (higher risk vs lower risk), the amount of information provided about the AI (more information vs less information), and the certainty of the AI output (higher certainty vs lower certainty). After each randomization point, participants will be asked to respond to questions regarding their hypothetical decision-making as it relates to these factors.

This study is part of a broader project studying stakeholder views regarding the development and use of AI and ML in medicine (National Center for Advancing Translational Sciences R01-TR-003505). It is built upon findings from the first phase of the broader project, in which AI and ML researchers and physicians were interviewed regarding ethical considerations they have encountered or anticipated in the development, refinement, and application of AI and ML in medicine [16,17]. Insights from this phase of research were used to create hypothetical but realistic scenarios for this study and to inform the development of questions assessing physician decision-making in these scenarios.

Recruitment

US-based physicians who are listed in the most recent version of the AMA PMF as specializing in family medicine or internal medicine will be eligible to participate in this study. The PMF is a comprehensive database of US physicians used for verifying professional credentials. Through the AMA-approved third-party vendor Medical Marketing Services, Inc, we will obtain the email and mailing addresses of a sampling frame of 10,000 physicians who meet our inclusion criteria. Physicians who are identified in this sampling frame will be contacted with invitations to participate in our web-based survey.

Through the third-party vendor Medical Marketing Services, Inc, we will send up to 4 email invitations to each physician in the sampling frame. Each email will provide a short description of our study and a web link to the web-based survey. Based on previous studies of this method of recruitment, we anticipate a 1.5% response rate [18]. If the target recruitment goal of 420 is not reached after 4 email invitations are sent, we will send a follow-up invitation by mail to any physicians in the original sampling frame who have not yet responded to the survey. Each mailed invitation will briefly describe our study and will contain a web address for the web-based survey.

Ethical Considerations

This project has received human participant research ethics approval from the Stanford University Institutional Review Board (65168). Upon navigating to the web-based survey, potential participants will be presented with a web-based informed consent form that details the content of the survey and the anticipated risks and benefits of participation. Participants will only proceed to the web-based vignette survey if they provide consent. Participation will be voluntary, and all responses will be anonymous. All participants will be compensated for their time and effort with a US $10 Amazon gift code at the completion of the survey.

Hypotheses and Outcome Variables

Our hypotheses are the following:

1. Hypothesis 1: higher degrees of clinical risk associated with the algorithm will influence lower levels of physician agreement with the effectiveness of and confidence in using the algorithm to help guide treatment decisions.
2. Hypothesis 2: disclosure of details of the algorithm will impact physicians' attitudes of confidence and efficacy, depending on their previous exposure to AI (ie, education, training, and clinical experience). We hypothesize that greater disclosure will influence positive attitudes among physicians with greater exposure but will have a negative or no impact on physicians with less exposure.

The primary outcome variables will be physicians' ratings, on a Likert scale, of perceived confidence in the AI algorithm in helping the physician make the best treatment recommendation for their patient (eg, "The AI result improved the confidence I have in my final decision"; from 1="strongly disagree" to 5="strongly agree"), as well as the perceived effectiveness of the use of the AI algorithm (eg, "Overall, the AI improved the care that I was able to provide to the patient"; rated on a 5-point scale from 1="strongly disagree" to 5="strongly agree").

Survey Design

Survey Instruments

Demographic characteristics (age, gender, educational level, race, and ethnicity) and professional characteristics (specialty type and years of experience) will be assessed through a baseline demographics questionnaire (13 questions). Experience with and attitudes toward AI and ML applications in medicine will be assessed using adapted measures (7-10 questions assessing experience and 11 questions assessing attitudes) [19,20]. A 3-part sequentially randomized vignette detailing a clinical scenario involving a CDS system will be presented to each participant; follow-up questions will assess participant attitudes and decision-making in the context of the vignette scenario (21 questions).

Vignette Development and Design

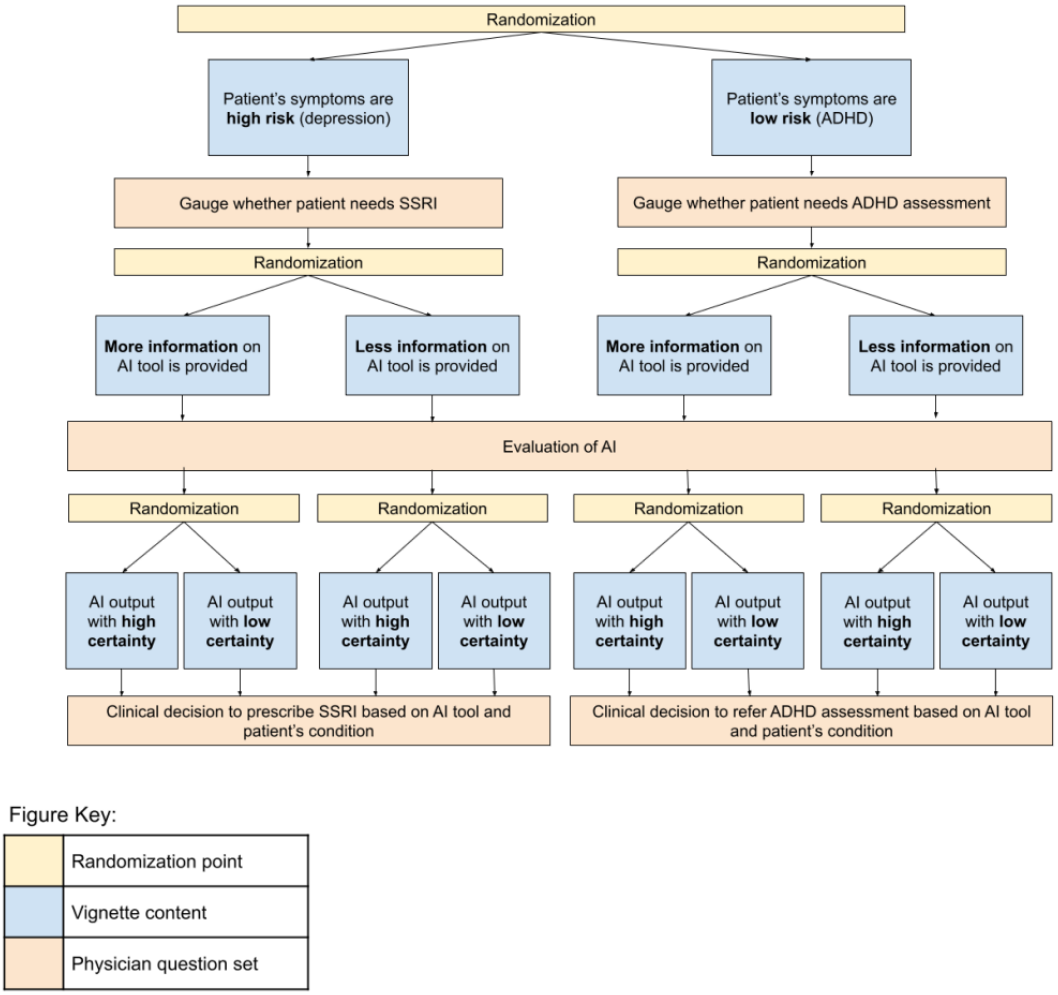
The vignettes used in this study were developed based on scenarios encountered by researchers and clinicians, as told in interviews in the first phase of this project [16]. Based on these findings, the dimensions in which the vignettes are systematically varied include the context of the decision-making scenario (higher risk vs lower risk), the amount of information provided regarding the algorithm (more information vs less information), and the certainty of the AI output (higher certainty vs lower certainty). The full content of the vignettes is available in Multimedia Appendix 1.

SMART Design

We have harnessed a design element that originates from clinical trial design: SMART [13,21,22]. JP Kim and HJ Yang (unpublished data) report the design. First, we use randomization probabilities to assign the subsequent vignette, which allows for tailoring the sequence of assigned vignettes to the individual instead of predetermined assignments of combinations of vignettes. The web-based survey format is particularly amenable to the design in which the subsequent questions are randomized. To the best of our knowledge, the SMART design has not yet been applied in the area of survey designs. SMART designs have been used in the evaluation of treatment algorithms for several psychiatric disorders (eg, depression in the Sequenced Treatment Alternatives to Relieve Depression and Clinical Antipsychotic Trials of Intervention Effectiveness studies) and for the treatment of advanced prostate cancer [23,24].

As shown by Figure 1 (adapted from JP Kim and HJ Yang—unpublished data), we configured our SMART vignette to have 3 dimensions, each with 2 levels: patient risk (higher risk vs lower risk), information on AI (more information vs less information), and certainty of AI output (higher certainty vs lower certainty), respectively. Corresponding vignette scenarios and question sets were input for each combination of randomization sequences. One question from every question set was flagged to serve as a primary question, the response for which was used to adaptively allocate the participants [16,17]. For 5-point Likert scale primary questions, participants who respond from "1" to "3" are assigned to response group 0, while those who respond with "4" to "5" are assigned to response group 1. For yes or no questions, "yes" corresponds to response group 1 and "no" to response group 0. The probability of Efron's [15] biased coin was prespecified to be 0.667.

Figure 1. Study design for the web-based vignette survey featuring sequential randomization. Yellow boxes indicate a randomization point, blue boxes indicate vignette content, and orange boxes indicate responses. Respondents will be physicians in family medicine or internal medicine across the United States. ADHD: attention-deficit/hyperactivity disorder; AI: artificial intelligence; SSRI: selective serotonin reuptake inhibitors.



Power Analysis

We performed a sample size estimation for determining the best embedded dynamic treatment regime using the approach outlined in Artman et al [25] for power analysis in a SMART design. Using the R package *smartsizer* (R Foundation for Statistical Computing) that implements Monte Carlo simulations in Artman et al [25], we calculated that the number of individuals needed to enroll in the vignette experiment is 420 to guarantee at least 80% power to detect an effect size of 0.15.

Survey Implementation

The SMART vignette survey will be administered on the internet using a web application created by our research team and hosted by Stanford University [26]. The application was developed using Python Flask and deployed using Amazon Beanstalk and Elastic File System, with survey responses stored on a secure SQLite database. This platform allows sequential randomization and adaptive allocation, which are features not yet offered by other survey software such as Qualtrics or Research Electronic Data Capture (REDCap; Vanderbilt University).

The study survey went through a round of internal testing before its launch. Dummy responses were created to ensure data were being properly parsed and stored. The research team tested the application on various devices to identify errors and provide feedback on the user experience and user interface. After a few rounds of internal testing, all study responses and parameters were reset for launch.

Unique user IDs were generated for each potential participant. As part of the recruitment emails and letters, participants will be asked to log into the SMART vignette survey using their assigned user ID and a provided study ID. Respondents have the option to exit and return to the survey at any time. Once a respondent has submitted a complete response, a US $10 Amazon gift card code will be claimed and displayed. The study will remain open to responses until the target number of responses is reached.

Statistical Analysis

Regression models will be used to determine the causal effects of contextual dimensions on clinician judgments, where confidence is an outcome and the assignment indicator, age, gender, and race are variables. We will estimate "conditional vignette effects" on physicians' judgments (ie, the effect of the vignette context within subgroups defined by strata of the baseline variables).

Results

This study was funded in September 2020 by the National Center for Advancing Translational Sciences. After the completion of internal testing, the survey was officially launched on May 16, 2023. Email recruitment occurred between May 16 and August 18 and resulted in 35 complete responses. Mail recruitment began on October 1, 2023, and will continue until the target number of 420 participants is reached. It is anticipated that we will reach this number by 2024. The survey will be closed, and data analysis will begin immediately after the target number of responses is reached.

Discussion

As AI technologies in medicine continue to advance, AI-based CDS tools are expected to be increasingly integrated into frontline care, and physicians will be faced with incorporating these tools to inform the evaluation and management of large numbers of patients with diverse needs. This web-based SMART vignette study will generate a better understanding of frontline physician decision-making in the context of AI-based CDS systems and will provide information on how specific factors, such as the level of clinical risk, the amount of information provided to the physician about the AI, and the certainty of the AI output, may influence physician decision-making and related attitudes.

The clinical and algorithmic factors tested in this project will expand on insights from previous research. In at least 1 previous study, risk perception was indicated to influence physicians' willingness to adopt AI-based tools in clinical practice [27]. By testing this factor in controlled scenarios involving moderately varied levels of clinical risk, our study will offer the opportunity to fine-tune our understanding regarding the effect of risk on physician decision-making involving AI. Additionally, while previous studies have demonstrated physician's preferences for greater explainability, this has not had a demonstrated effect on their overall clinical decision-making [1]. As a possible alternative to explainable AI, our study will examine whether simply providing more information about an AI affects frontline physicians' attitudes and their related decision-making. Finally, the analysis of physician decision-making in the context of varied AI output certainties will expand on Jussupow et al [6] by allowing us to identify the individual and context-specific factors that may contribute to a physician's overall acceptance of an AI output.

To empirically test these factors, this study uses a novel vignette study method, "SMART vignettes," an adaptation of the SMART design developed by Murphy [13], applied to web-based survey designs. Further details on the methodology can be found in JP Kim and HJ Yang (unpublished data). This novel method leverages 2 new design characteristics, namely sequential randomization and adaptive allocation. Our newly proposed "SMART vignette" design offers several benefits not afforded by the extensively used traditional vignette design, due to the 2 aforementioned features. These advantages are (1) increased validity of analyses targeted at understanding the impact of a factor on the decision outcome, given previous outcomes and other contextual factors; and (2) balanced sample sizes across groups.

Strengths of the proposed survey include the use of the sequential randomization design feature, which will allow the presentation of vignettes to be tailored to the individual. Our design offers an advantage above a "rule-based, branching logic approach," the predominant approach used in web-based surveys, in which a particular response determines the subsequent question to be the same across all respondents [28,29], as well as a single-time baseline randomization in conventional vignette studies. The use of sequential randomization in this web-based survey will enable assessments of the causal effects of contextual information in the algorithms on the judgments of physicians entrusted with applying and implementing the use of the algorithms. In addition, the adaptive quality of the survey may allow for a greater sense of interactivity from the perspective of the survey respondent. Potential limitations of this study include a low response rate, as previously documented in the literature regarding physicians, as well as possible response fatigue, as is commonly experienced in survey studies. Another limitation is that the novel design features we presented are not yet widely available on existing

survey platforms (eg, REDCap and Qualtrics) and thus may limit the reproducibility of this particular method. This represents an area of future research.

AI-augmented tools have the potential to improve physicians' decision-making and productivity by automating referrals and triage, augmenting in-person and between-visit treatment, and assisting with minimally invasive procedures. Given this potential, there is a need to better anticipate decision-making in AI-augmented settings as well as identify potential vulnerabilities that may compromise decision-making [30]. Our proposed study comes from the approach of "stakeholder research," the work of seeking perspectives from individuals impacted by the situation at hand, and fills a missing gap in the literature. As Rahwan et al [31] noted in their study, "machine behavior...cannot be fully understood without the integrated study of algorithms and the social environments in which algorithms operate." Such work is needed to understand the range of physician decisions and the causal impact of attributes of AI-embedded care, particularly in high-stakes settings, and vignettes are well suited to address this need.

Acknowledgments

The authors would like to acknowledge Gabriel Termuehlen for his editorial input on this manuscript. This work is supported by the National Institutes of Health (NIH R01TR003505).

Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Vignettes.
[DOCX File , 15 KB - resprot_v13i1e54787_app1.docx]

References

1. Diprose WK, Buist N, Hua N, Thurier Q, Shand G, Robinson R. Physician understanding, explainability, and trust in a hypothetical machine learning risk calculator. J Am Med Inform Assoc 2020;27(4):592-600 [FREE Full text] [doi: 10.1093/jamia/ocz229] [Medline: 32106285]
2. Lambert SI, Madi M, Sopka S, Lenes A, Stange H, Buszello CP, et al. An integrative review on the acceptance of artificial intelligence among healthcare professionals in hospitals. NPJ Digit Med 2023;6(1):111 [FREE Full text] [doi: 10.1038/s41746-023-00852-5] [Medline: 37301946]
3. Asan O, Bayrak AE, Choudhury A. Artificial intelligence and human trust in healthcare: focus on clinicians. J Med Internet Res 2020;22(6):e15154 [FREE Full text] [doi: 10.2196/15154] [Medline: 32558657]
4. Clement J, Ren Y, Curley S. Increasing system transparency about medical AI recommendations may not improve clinical experts' decision quality. SSRN Journal Preprint posted online on November 18 2021 [FREE Full text] [doi: 10.2139/ssrn.3961156]
5. Tucci V, Saary J, Doyle TE. Factors influencing trust in medical artificial intelligence for healthcare professionals: a narrative review. J Med Artif Intell 2022;5:4-4 [FREE Full text] [doi: 10.21037/jmai-21-25]
6. Jussupow E, Spohrer K, Heinzl A, Gawlitza J. Augmenting medical diagnosis decisions? an investigation into physicians' decision-making process with artificial intelligence. Inf Syst Res 2021;32(3):713-735. [doi: 10.1287/isre.2020.0980]
7. Atzmüller C, Steiner PM. Experimental vignette studies in survey research. Methodology 2010;6(3):128-138. [doi: 10.1027/1614-2241/a000014]
8. Hughes R, Huby M. The application of vignettes in social and nursing research. J Adv Nurs 2002;37(4):382-386. [doi: 10.1046/j.1365-2648.2002.02100.x] [Medline: 11872108]
9. Steiner PM, Atzmüller C, Su D. Designing valid and reliable vignette experiments for survey research: a case study on the fair gender income gap. J Methods Meas Soc Sci 2016;7(2):52-94 [FREE Full text] [doi: 10.2458/v7i2.20321]
10. Renier LA, Mast MS, Bekbergenova A. To err is human, not algorithmic—robust reactions to erring algorithms. Comput Hum Behav 2021;124:106879 [FREE Full text] [doi: 10.1016/j.chb.2021.106879]
11. Tobia K, Nielsen A, Stremitzer A. When does physician use of AI increase liability? J Nucl Med 2021;62(1):17-21 [FREE Full text] [doi: 10.2967/jnumed.120.256032] [Medline: 32978285]
12. Jabbour S, Fouhey D, Shepard S, Valley TS, Kazerooni EA, Banovic N, et al. Measuring the impact of AI in the diagnosis of hospitalized patients: a randomized clinical vignette survey study. JAMA 2023;330(23):2275-2284. [doi: 10.1001/jama.2023.22295] [Medline: 38112814]

13. Murphy SA. An experimental design for the development of adaptive treatment strategies. Stat Med 2005;24(10):1455-1481 [FREE Full text] [doi: 10.1002/sim.2022] [Medline: 15586395]
14. Kidwell KM, Almirall D. Sequential, multiple assignment, randomized trial designs. JAMA 2023;329(4):336-337 [FREE Full text] [doi: 10.1001/jama.2022.24324] [Medline: 36692577]
15. Efron B. Forcing a sequential experiment to be balanced. Biometrika 1971;58(3):403-417. [doi: 10.1093/biomet/58.3.403]
16. Kim JP, Ryan K, Kasun M, Hogg J, Dunn LB, Roberts LW. Physicians' and machine learning researchers' perspectives on ethical issues in the early development of clinical machine learning tools: qualitative interview study. JMIR AI 2023;2:e47449 [FREE Full text] [doi: 10.2196/47449]
17. Kasun M, Ryan K, Paik J, Lane-McKinley K, Dunn LB, Roberts LW, et al. Academic machine learning researchers' ethical perspectives on algorithm development for health care: a qualitative study. J Am Med Inform Assoc 2024;31(3):563-573. [doi: 10.1093/jamia/ocad238] [Medline: 38069455]
18. Murphy CC, Lee SJC, Geiger AM, Cox JV, Ahn C, Nair R, et al. A randomized trial of mail and email recruitment strategies for a physician survey on clinical trial accrual. BMC Med Res Methodol 2020;20(1):123 [FREE Full text] [doi: 10.1186/s12874-020-01014-x] [Medline: 32429848]
19. Oh S, Kim JH, Choi SW, Lee HJ, Hong J, Kwon SH. Physician confidence in artificial intelligence: an online mobile survey. J Med Internet Res 2019;21(3):e12422 [FREE Full text] [doi: 10.2196/12422] [Medline: 30907742]
20. Staartjes VE, Stumpo V, Kernbach JM, Klukowska AM, Gadjradj PS, Schröder ML, et al. Machine learning in neurosurgery: a global survey. Acta Neurochir (Wien) 2020;162(12):3081-3091 [FREE Full text] [doi: 10.1007/s00701-020-04532-1] [Medline: 32812067]
21. Dawson R, Lavori PW. Placebo-free designs for evaluating new mental health treatments: the use of adaptive treatment strategies. Stat Med 2004;23(21):3249-3262. [doi: 10.1002/sim.1920] [Medline: 15490427]
22. Lavori PW, Dawson R. Introduction to dynamic treatment strategies and sequential multiple assignment randomization. Clin Trials 2014;11(4):393-399 [FREE Full text] [doi: 10.1177/1740774514527651] [Medline: 24784487]
23. Rush AJ, Fava M, Wisniewski SR, Lavori PW, Trivedi MH, Sackeim HA, et al. Sequenced Treatment Alternatives to Relieve Depression (STAR*D): rationale and design. Control Clin Trials 2004;25(1):119-142. [doi: 10.1016/s0197-2456(03)00112-0] [Medline: 15061154]
24. Swartz MS, Perkins DO, Stroup TS, McEvoy JP, Nieri JM, Haak DC. Assessing clinical and functional outcomes in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial. Schizophr Bull 2003;29(1):33-43 [FREE Full text] [doi: 10.1093/oxfordjournals.schbul.a006989] [Medline: 12908659]
25. Artman WJ, Nahum-Shani I, Wu T, Mckay JR, Ertefaie A. Power analysis in a SMART design: sample size estimation for determining the best embedded dynamic treatment regime. Biostatistics 2020;21(3):432-448 [FREE Full text] [doi: 10.1093/biostatistics/kxy064] [Medline: 30380020]
26. SMART vignettes. Stanford Universiry. URL: https://smartvignettes.stanford.edu/ [accessed 2024-03-03]
27. Shamszare H, Choudhury A. Clinicians' perceptions of artificial intelligence: focus on workload, risk, trust, clinical decision making, and clinical integration. Healthcare (Basel) 2023;11(16):2308 [FREE Full text] [doi: 10.3390/healthcare11162308] [Medline: 37628506]
28. Bouamrane MM, Rector A, Hurrell M. Using ontologies for an intelligent patient modelling, adaptation and management system. In: Meersman R, Tari Z, editors. On the Move to Meaningful Internet Systems: OTM 2008. Lecture Notes in Computer Science, Volume 5332. Berlin, Heidelberg: Springer; 2008:1458-1470.
29. Pitkow JE, Recker MM. Using the web as a survey tool: results from the second WWW user survey. Comput Netw ISDN Syst 1995;27(6):809-822. [doi: 10.1016/0169-7552(95)00018-3]
30. Grunhut J, Wyatt AT, Marques O. Educating future physicians in artificial intelligence (AI): an integrative review and proposed changes. J Med Educ Curric Dev 2021;8:23821205211036836 [FREE Full text] [doi: 10.1177/23821205211036836] [Medline: 34778562]
31. Rahwan I, Cebrian M, Obradovich N, Bongard J, Bonnefon JF, Breazeal C, et al. Machine behaviour. Nature 2019;568(7753):477-486 [FREE Full text] [doi: 10.1038/s41586-019-1138-y] [Medline: 31019318]

Abbreviations

AI: artificial intelligence
AMA: American Medical Association
CDS: clinical decision support
ML: machine learning
PMF: Physician Masterfile
REDCap: Research Electronic Data Capture
SMART: sequential multiple assignment randomization trial

Edited by A Mavragani; submitted 21.11.23; peer-reviewed by B Jackson, M Frasch; comments to author 21.12.23; revised version received 11.01.24; accepted 06.02.24; published 04.04.24.

Please cite as:
Kim JP, Yang HJ, Kim B, Ryan K, Roberts LW
Understanding Physician's Perspectives on AI in Health Care: Protocol for a Sequential Multiple Assignment Randomized Vignette Study
JMIR Res Protoc 2024;13:e54787
URL: https://www.researchprotocols.org/2024/1/e54787
doi:10.2196/54787
PMID:38573756

Protocol

Implementation of an Electronic Clinical Decision Support System for the Early Recognition and Management of Dysglycemia in an Inpatient Mental Health Setting Using CogStack: Protocol for a Pilot Hybrid Type 3 Effectiveness-Implementation Randomized Controlled Cluster Trial

Dipen Patel[1,2,3], MBBS, MRCPsych; Yamiko Joseph Msosa[2,4], PhD; Tao Wang[2,4], PhD; Julie Williams[5], PhD; Omar G Mustafa[6,7], MBChB, MRCP; Siobhan Gee[3], PhD; Barbara Arroyo[3], MRCPsych, MSc; Damian Larkin[3], BSc; Trevor Tiedt[3], BEng; Angus Roberts[2,4], PhD; Richard J B Dobson[2,4,8,9], PhD; Fiona Gaughran[1,2,3], MD, MRCPsych

[1]Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom

[2]National Institute for Health Research, Maudsley Biomedical Research Centre, South London and Maudsley National Health Service Foundation Trust, London, United Kingdom

[3]South London and Maudsley National Health Service Foundation Trust, London, United Kingdom

[4]Department of Biostatistics and Health Informatics, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom

[5]Centre for Implementation Science, Health Service and Population Research Department, King's College London, London, United Kingdom

[6]Department of Diabetes, King's College Hospital National Health Service Foundation Trust, London, United Kingdom

[7]Centre for Education, Faculty of Life Sciences and Medicine, King's College London, London, United Kingdom

[8]Institute for Health Informatics, University College London, London, United Kingdom

[9]Health Data Research UK, University College London, London, United Kingdom

Corresponding Author:
Dipen Patel, MBBS, MRCPsych
Department of Psychosis Studies
Institute of Psychiatry, Psychology and Neuroscience
King's College London
De Crespigny Park
London, SE5 8AB
United Kingdom
Phone: 44 0203 228 7200
Email: dipen.1.patel@kcl.ac.uk

Abstract

Background: Severe mental illnesses (SMIs), including schizophrenia, bipolar affective disorder, and major depressive disorder, are associated with an increased risk of physical health comorbidities and premature mortality from conditions including cardiovascular disease and diabetes. Digital technologies such as electronic clinical decision support systems (eCDSSs) could play a crucial role in improving the clinician-led management of conditions such as dysglycemia (deranged blood sugar levels) and associated conditions such as diabetes in people with a diagnosis of SMI in mental health settings.

Objective: We have developed a real-time eCDSS using CogStack, an information retrieval and extraction platform, to automatically alert clinicians with National Health Service Trust–approved, guideline-based recommendations for dysglycemia monitoring and management in secondary mental health care. This novel system aims to improve the management of dysglycemia and associated conditions, such as diabetes, in SMI. This protocol describes a pilot study to explore the acceptability, feasibility, and evaluation of its implementation in a mental health inpatient setting.

Methods: This will be a pilot hybrid type 3 effectiveness-implementation randomized controlled cluster trial in inpatient mental health wards. A ward will be the unit of recruitment, where it will be randomly allocated to receive either access to the eCDSS plus usual care or usual care alone over a 4-month period. We will measure implementation outcomes, including the feasibility and acceptability of the eCDSS to clinicians, as primary outcomes, alongside secondary outcomes relating to the process of care

measures such as dysglycemia screening rates. An evaluation of other implementation outcomes relating to the eCDSS will be conducted, identifying facilitators and barriers based on established implementation science frameworks.

Results: Enrollment of wards began in April 2022, after which clinical staff were recruited to take part in surveys and interviews. The intervention period of the trial began in February 2023, and subsequent data collection was completed in August 2023. Data are currently being analyzed, and results are expected to be available in June 2024.

Conclusions: An eCDSS can have the potential to improve clinician-led management of dysglycemia in inpatient mental health settings. If found to be feasible and acceptable, then, in combination with the results of the implementation evaluation, the system can be refined and improved to support future successful implementation. A larger and more definitive effectiveness trial should then be conducted to assess its impact on clinical outcomes and to inform scalability and application to other conditions in wider mental health care settings.

Trial Registration: ClinicalTrials.gov NCT04792268; https://clinicaltrials.gov/study/NCT04792268

International Registered Report Identifier (IRRID): DERR1-10.2196/49548

(JMIR Res Protoc 2024;13:e49548) doi:10.2196/49548

KEYWORDS

blood sugar; CDSS; clinical decision support system; decision support; diabetes; diabetic; dysglycemia; electronic clinical decision support; hyperglycemia; hypoglycemia; implementation; medical informatics; mental health; mental healthcare; mental illness; metabolic health; randomized controlled trial; RCT

Introduction

Overview

People with severe mental illnesses (SMIs) such as schizophrenia, bipolar affective disorder, and schizoaffective disorders have a significantly reduced life expectancy in comparison with the general population. These groups have higher rates of cardiovascular disease (CVD) risk factors such as central obesity, high blood pressure, raised cholesterol levels, and raised blood sugar levels compared with the general population [1,2].

Improvements to the primary prevention of diabetes in the general population have not been replicated to the same degree in people with SMI [3]. Diabetes refers to a group of metabolic disorders characterized by a high blood sugar level (dysglycemia) over an extended period of time [4]. If unrecognized, untreated, or poorly managed, diabetes can lead to long-term health complications, including CVD, stroke, chronic kidney disease, foot ulcers, retinopathy, and peripheral neuropathy [4,5].

Diabetes accounts for approximately 10% of health care resources in the United Kingdom, and this is set to rise to 17%, with total costs of GBP 39.8 (US $50.7) billion estimated by 2035, when direct health care costs and indirect costs on productivity are taken into account [6]. Recorded rates of diabetes among ethnically diverse middle-aged people with a diagnosis of established psychosis in South London reach 20%, with a further 30% evidencing raised blood sugar levels (dysglycemia) [7]. Likewise, the prevalence of both diabetes and dysglycemia is higher in inpatient psychiatric settings than in the general community [8]. Furthermore, rates of dysglycemia double in the first year after a first psychotic episode, creating a unique window for prevention strategies to address these risks as early as possible [9].

Diabetes outcomes are poor in SMI groups, with people with schizophrenia and cooccurring diabetes having an increased risk of excess mortality, including postcomplication mortality [10]. A key inequality affecting people with SMI is the less than–adequate assessment and management of physical health conditions such as diabetes. In order to target the physical health care of people with SMI and close the life expectancy gap, a number of evidence-based clinical guidelines and policies have been published over the past decade [11-13].

Unfortunately, there remains significant variation in the implementation of these guidelines and recommendations in mental health care services, as outlined by the National Audit of Schizophrenia [14]. A retrospective audit of people diagnosed with schizophrenia or schizoaffective disorder revealed that among those with dysglycemia, only 53.5% were recorded as receiving an appropriate intervention, and among those with dyslipidemia, this was only 19.9% [15]. Another study found that people with SMI and diabetes were not receiving the expected standards of care in glucose monitoring or access to specialist diabetes services when admitted to a psychiatric unit [16].

Globally, studies evaluating the provision of care by clinicians reveal a suboptimal uptake of clinical guidelines into practice. The underlying reasons for this are complex and noted to occur at a combination of patient, clinician, and wider systemic levels [17]. There is therefore a need for more targeted and clinically informed interventions that improve the standard of physical health care screening and interventions offered to people with SMI across both primary and secondary care settings.

Digital health solutions have the potential to improve the delivery of care through tools such as clinical decision support systems [18]. An electronic clinical decision support system (eCDSS) consists of digital-enabled tools and interventions [19,20] that can be “based on a software algorithm designed to aid directly in clinical decision-making, in which characteristics of individual patients are used to generate patient-specific assessments or recommendations that are then presented to clinicians for consideration” [19]. An eCDSS has the potential to overcome problems associated with the use and

implementation of traditional paper-based guidelines. Interventions involving clinical decision support systems appear to achieve small to moderate improvements in targeted processes of care in acute physical health care settings [21]. However, the evidence base for eCDSSs in mental health care settings remains sparse.

Given the high disease burden of diabetes in SMI and the deficits in providing evidence-based care for diabetes prevention and treatment, there is a pressing need to identify novel systems-focused solutions. The adoption of digital technology to improve physical health in people with a diagnosis of SMI presents a unique opportunity but requires evidence of acceptability, feasibility, and effectiveness.

Digital systems that are not accepted by their users cannot be expected to contribute to improving the quality of care; hence, facilitators, barriers, and other unintended consequences need to be understood for the successful implementation of novel digital tools and could also serve as a basis for future system reengineering. Hence, there is a call for research to include evaluating its implementation to improve the chances of successful future scalability [22].

Given that patients with SMI have a high risk of CVD factors, including dysglycemia and diabetes, and that there is typically a suboptimal uptake of clinical guidelines, there is a need for more targeted and clinically informed interventions that improve the standard of physical health care screening and interventions offered to people with SMI. Assessing the physical health of patients with SMI when they are admitted under mental health services offers an opportunity to identify risk factors for developing conditions such as CVD or diabetes and provide advice and support to their care teams on services that can be accessed in hospitals and in the community.

We have previously reported on the design and development of a novel eCDSS built using the information retrieval and extraction platform CogStack, deployed at the South London and Maudsley National Health Service (NHS) Foundation Trust, UK (CogStack@Maudsley), comprising a real-time computerized alerting and clinical decision support system for dysglycemia management that has been previously validated for use in secondary mental health care [23].

Objectives

The primary objective of this study is to establish the acceptability, feasibility, and other implementation challenges of the eCDSS (CogStack@Maudsley), comprising a real-time computerized alerting and clinical decision support system, in supporting dysglycemia management in an inpatient secondary mental health care setting.

Our secondary objective is to assess the change in rates of guideline-indicated tests or interventions for dysglycemia on the test wards before and after the introduction of the eCDSS, compared to comparator wards without access to the eCDSS.

This will be measured using pseudonymized group observational data gathered from the South London and Maudsley NHS Foundation Trust Biomedical Research Centre's Clinical Records Interactive Search (CRIS) system. Since 2006, the South London and Maudsley NHS Trust has operated fully electronic health records. The CRIS system, established in 2008, is an ethically approved electronic health records interface system that allows researchers to access deidentified electronic health records from this trust for research purposes [24-26].

Data gathered from this study will allow us to refine the system, address potential challenges with future successful implementation, and inform a larger and more definitive effectiveness trial that will examine for hypothesized improvements in (1) rates of clinician-delivered, evidence-based interventions for patients with dysglycemia and (2) clinical outcomes relating to diabetes care.

Methods

Study Design

We will conduct a pilot hybrid type 3 effectiveness-implementation randomized controlled cluster trial in inpatient mental health ward settings [27]. This specific study design was chosen as the primary aim is focused on implementation outcomes, while the secondary aims relate to effectiveness outcomes. Wards will be the unit of recruitment and will be assigned to deliver care with either the eCDSS platform alongside usual care processes (treatment as usual [TAU]) or to follow TAU alone. The trial will last for a period of 4 months. Qualitative implementation outcome data will be obtained from participating clinicians on all recruited wards using implementation pre- and poststudy surveys and individual semistructured interviews. Quantitative indicative effectiveness data to inform future work will be gathered using pseudonymized group data, including rates of adherence to dysglycemia guidelines and process of care measures.

Setting

The study will be conducted with clinicians in 5 general adult psychiatry inpatient wards at South London and Maudsley NHS Foundation Trust in the United Kingdom.

Recruitment and Eligibility

Screening for dysglycemia is indicated in all people admitted to general adult inpatient wards at the host NHS Trust hospital. All general adult inpatient wards in the hospital will be eligible for inclusion in the study, with the study publicized at consultant continuing professional development meetings and to senior management of all wards at the trust. Managers of wards who show an initial interest will be approached and their wards invited to participate until a total of 5 participating wards is reached. All clinicians on participating wards who are routinely involved in dysglycemia management, including consultant psychiatrists, medical doctors, ward pharmacists, and the ward nursing team, will be eligible and invited to consent to participate in the preintervention surveys and interviews and postintervention surveys and interviews if they were on an intervention ward at the end of the study.

Processes of care in each participating ward will be obtained using the available pseudonymized observational data of all people receiving inpatient care in participating wards during the trial period. Individual patient outcomes will not be recorded.

Randomization

Wards will be the unit of recruitment and will be assigned randomly to either the intervention or TAU group to receive either the eCDSS platform alongside usual care or to follow usual care processes only for a period of 4 months. We will recruit and randomly allocate 2 wards to the intervention arm and 3 wards to the comparator arm using fixed block randomization. Random allocation of the wards will be done by an independent trial manager who is outside of the research team to ensure there is no bias in allocations.

Sample Size

The primary end points of this study are implementation outcomes rather than direct measures of intervention effects on clinical outcomes. Hence, power analyses for intervention outcomes have not been undertaken in advance. A total of 5 wards will be recruited in total, which will be a large enough sample of wards to recruit enough staff to take part in preintervention qualitative work, and to inform the practicalities of implementing the system and collecting sufficient outcome data.

Intervention

We previously developed an eCDSS for dysglycemia hosted within CogStack@Maudsley [23]. The eCDSS is designed to alert clinicians automatically when patients are admitted under their care regarding the need for screening for, or management of, dysglycemia. Prompts are triggered by the presence of new, old, or absent HbA_{1c} pathology reports in the electronic health record.

Digital-enabled clinical decision support is provided as a combination of visual prompts on a dashboard embedded within an existing electronic platform used at the NHS Trust and email supplements sent to NHS Trust email accounts of participating wards. The eCDSS was designed to integrate as easily as possible within existing workflows by building it into the existing NHS Trust electronic systems that clinicians use in inpatient wards.

The alerts in this study will include NHS Trust "Quality Centre"–approved, guideline-based recommendations for clinician-led monitoring and management of dysglycemia and known diabetes, tailored to the individual patient's reported HbA_{1c} values. The eCDSS algorithm is based on gold-standard clinical management guidelines, which were developed and agreed upon by the NHS Trust [23].

Clinicians on intervention wards will be able to view priority-tagged prompts in the EHR system, corresponding to guideline-based recommended actions they can access for further patient-specific guidance with regard to their care. Clinicians are already familiar with the platform for other uses, but a demonstration of the system will be given to users before the intervention period, so they are aware of how the system is accessed and used. Access to the system will be restricted to the intervention wards only, but access to it can be expanded in the future to more wards and teams.

The research team will be available to provide support to clinicians participating in the study to ensure that any technical queries relating to the eCDSS are dealt with appropriately. The research team will also work closely with the host trust IT department so that any potential technical issues are responded to quickly.

Study Procedure

Ward managers of the selected wards will notify ward staff of the study and the opportunity to participate in interviews and surveys as part of this study. All clinical staff working on recruited wards who express an initial interest to their ward manager will be approached by members of the research team and given a participant information leaflet and an opportunity to ask and discuss any further questions regarding the study. They will be invited to take part in an initial survey and an individual interview with a member of the research team at the start of the study, and then again at the end of the trial, should their ward be randomized to the intervention arm.

Consented participants will be invited to complete an initial survey and to take part in an individual interview lasting approximately 30 minutes. The interview will follow a semistructured interview topic guide with key prompts to direct the discussion, but researchers will be able to direct further questions if additional themes or content arise during the course of the interview. The survey and interview aim to scope the experiences of clinicians in managing diabetes and related physical health conditions in secondary mental health care settings and to explore their attitudes toward the use of novel digital technology as a means of improving physical health care provision in secondary mental health care settings.

Participants in the intervention arm of the study will be invited, a minimum of 4 months from the start of the study, to complete a follow-up survey and individual interview lasting approximately 30 minutes, which will aim to scope their experiences and attitudes toward using the eCDSS and their perceptions of its impact upon diabetes and dysglycemia care. The interview will again follow a semistructured interview topic guide with key prompts to direct the discussion, but researchers will be able to direct further questions if additional themes or content arise during the course of the interview.

Service-level process of care outcome data will be collected at the level of participating wards using pseudonymized observational group-level data from the CRIS system [25]. Approvals for the acquisition of relevant deidentified data through the CRIS system will be applied for through the CRIS oversight committee.

Ethical Considerations

This study was reviewed and approved by the NHS Health Research Authority and Health and Care Research Wales (reference 285509). The eCDSS has received NHS digital clinical safety sign-off by the host trust, and any immediate patient safety issues will be reported in line with the digital safety policy at the host NHS Trust. The eCDSS is built within existing IT systems at the trust; therefore, data do not leave the firewall of the existing systems.

Each participant will be given an identification number. All information collected will be kept confidential; all identifiable

data will be securely stored; and forms with identifiable data, such as consent forms, will be kept separate from the outcome data in a locked cupboard. All data generated will be stored securely, such that participants can only be identified by their unique study identifier, and all stored electronic data will be password-protected.

Outcomes and Data Collection

As this is a feasibility study, the primary outcome relates to acceptability, feasibility, and other implementation outcomes relating to the intervention (Table 1). Secondary outcomes relate to the process of care measures (ie, screening rates for dysglycemia, documentation of interventions relating to dysglycemia and diabetes care, and documentation of communication to other relevant care professionals regarding follow-up). The study is not powered to detect impacts on clinical outcomes. As this is a pilot study, the primary outcomes will be used to inform further work to refine the system before progressing to a full trial.

Table 1. Outcome measures.

Outcomes	Definition	Data collection
Primary outcomes (implementation outcomes)		
Acceptability	• Extent to which eCDSS[a] is perceived by clinical users to be acceptable in prompting evidence-based dysglycemia management, and an effective system for improving dysglycemia and, where applicable, diabetes care. 1. Experience of the system 2. Effect on workload 3. Barriers and facilitators to its use 4. Impact on clinicians' time compared to usual care 5. Perceived effectiveness of the system 6. Intention to continue to use the system	• Qualitative: pre- and postsurvey and semistructured individual interviews
Feasibility	• Ability to recruit wards and clinicians to the study. • Retention and participation of clinicians on recruited wards through to the end of the study. • Usefulness and limitations of CRIS to collect process of care outcome measures	• Quantitative and qualitative: survey and semistructured individual interviews
Adoption	• Individual clinicians and the wider system's intention to adopt and use the system for dysglycemia management.	• Qualitative: survey and semistructured individual interview
Reach	• Number of clinicians who make use of the system as a proportion of the total number of clinicians expected to use the system	• Qualitative: survey and semistructured individual interview • Quantitative: audit trail on eCDSS platform
Appropriateness	• Extent to which the novel system is perceived to be fit and relevant for dysglycemia management by users	• Qualitative: survey and semistructured individual interview
Fidelity of Delivery	• Extent to which the eCDSS system alerts are delivered as intended.	• Qualitative: survey and semistructured individual interview • Quantitative: eCDSS platform
Sustainability	• Facilitators and barriers to sustained use of the system. • Clinician attitudes toward the system.	• Qualitative: survey and semistructured individual interview
Contextual Factors	• Facilitators and barriers to the implementation of the system	• Qualitative: survey and semistructured individual interview
Maintenance	• Satisfaction of, and intention to use eCDSS, by clinicians	• Qualitative: survey and semistructured individual interview
Secondary outcomes (processes of care)		
HbA_{1c}[b] testing	• Rates of HbA_{1c} testing on inpatients	• Quantitative
Documentation of dysglycemia or diabetes in clinical notes	• Documentation of diabetes or prediabetes diagnosis in case notes during inpatient stay (where indicated)	• Quantitative
Documentation of discussion with patient regarding exercise, diet, and smoking cessation	• Documentation of advice by clinician given to the patient regarding lifestyle changes—exercise, diet, and smoking cessation in patients with dysglycemia	• Quantitative
Documentation of diabetes-related screening interventions	• Documentation of completed foot check for patients with diabetes	• Quantitative
Delivery of evidence-based pharmacological interventions for diabetes or prediabetes where clinically indicated	• Documentation of discussion regarding diabetes-related medication changes post alerting where clinically indicated: • Initiation of diabetes-related medication • Intensification of medication (dose change or introduction of new agent in accordance with guidance)	• Quantitative

Outcomes	Definition	Data collection
Communication with general practitioner or community mental health team regarding diabetes or dysglycemia follow-up	• Documentation to relevant community teams and GP[c] regarding follow-up plans for dysglycemia management post discharge where indicated	• Quantitative

[a]eCDSS: electronic clinical decision support system.

[b]HbA_{1c}: glycated hemoglobin.

[c]GP: general practitioner.

A process evaluation of the implementation of the intervention will be conducted to identify factors that inhibit or facilitate implementation. A mixed methods approach will be adopted to establish feasibility, acceptability, and other implementation outcomes.

Details of the study were first shared among ward managers and consultants in January 2022, and formal enrollment of eligible wards began in April 2022. Clinical staff on recruited wards were then individually recruited to take part in surveys and interviews starting in June 2022. The intervention period of the trial began in February 2023, and qualitative data collection was completed in August 2023. All interviews were recorded and subsequently transcribed verbatim.

Baseline Measurements

We will collect the following sociodemographic data on participating clinicians from recruited wards: age, gender, years of clinical experience, specialty or profession, and grade.

No identifiable data will be collected on patients on the recruited wards. However, a separate application will be made to the CRIS oversight committee to gather the following pseudonymized information at a ward or group level: age, gender, ethnicity, HbA_{1c} levels, recorded history of diabetes, International Classification of Diseases-10th revision (ICD-10) mental disorder diagnosis, and history of referral to diabetes specialist teams.

Analysis

Mixed methods will be used to analyze the outcome data generated.

Qualitative analysis of data generated through semistructured interviews and surveys of clinician users will be used to evaluate the primary outcome measures relating to implementation. A thematic analysis of interview transcripts will be conducted. We will then use a qualitative process evaluation, grounded within established implementation science frameworks, to analyze and report on the implementation outcomes generated [28-30].

We will compare changes in the process of care measures between intervention and control groups to evaluate the eCDSS impact on the process of care measures by analyzing group-level pseudonymized observational data through the CRIS platform. Descriptive statistics will be used to report on these results.

Key stakeholders will be informed of the outcomes of the study through internal report and the presentation of the study results at local meetings. It is planned that the methods and findings of the study will be incorporated into an original research paper that can be widely shared, following peer review in a journal.

Results

As this paper is a study protocol, no results are currently available. Enrollment of wards began in April 2022, after which clinical staff were recruited to take part in preintervention surveys and interviews. The intervention period of the trial began in February 2023, and subsequent data collection for postintervention interviews and surveys was completed in August 2023. Data are currently being analyzed, and results are expected to be available in June 2024.

Discussion

Overview

To our knowledge, this will be the first-ever trial of an eCDSS comprising an automated electronic physical health monitoring and alerting platform developed for use in a secondary care mental health setting, which aims to improve the clinician-led management of dysglycemia and diabetes care to patients with SMI. eCDSS has the potential to radically improve the standards of physical health care offered to patients with SMI and may be a crucial step in reducing the morbidity and mortality associated with chronic physical health conditions in SMI.

Implementation of eCDSS for use in clinical settings has previously been shown to be time-consuming, and its complexity can result in slow adoption into practice [20]. To bridge this gap, we have adopted a stepwise approach, starting with technical development and in silico evaluation [23], and progressing to this pilot, with the aim of informing further refinement, development, and engineering of the eCDSS, to enable its longer-term successful adoption in clinical practice.

Integration of eCDSS into existing clinical workflows is not simple, and digital health systems that are not wholly accepted by their users cannot be expected to contribute to improving care, hence the need for research into facilitators and barriers to adoption. These need to be well understood to support the successful implementation of novel digital tools, with calls for research to include evaluating eCDSS implementation for successful future scalability [22].

Gaining a good understanding of the factors that affect the adoption and integration of digital health tools into routine practice could also serve as a basis for creating frameworks for delivering future impactful digital tools. For this reason, we have included implementation outcomes alongside other

measures of effectiveness, to inform further work that aims to facilitate smoother implementation of digital technologies into clinical settings. This knowledge can then be used to apply and scale the eCDSS for other physical health conditions in SMI, such as atrial fibrillation, hypertension, and hypercholesterolemia.

This study does have some limitations. Recruitment is limited to 1 NHS Trust, with 2 wards allocated to the intervention arm from 1 site, thus limiting the extent to which broader conclusions can be made as the findings are not generalizable. There could be a self-selection bias in regard to staff who agree to participate in interviews and surveys, as it is possible that they are more likely to be interested in or accustomed to novel digital technologies. All staff will be encouraged to ask the research team about any concerns they may have so that they can be addressed with a view to reducing the risk of this. It is possible that different data might be generated if it were conducted in settings across multiple sites. Given the study design, there is also the possibility of the Hawthorne effect, which is well documented in research, when participants may knowingly or unknowingly alter their behaviors as a result of being observed as part of the study [28]. Nonetheless, this pilot study still serves as a useful basis for preliminary research in a setting that has not been explored in depth previously.

We have previously demonstrated that it is technically feasible to design and deploy a functional monitoring and alerting eCDSS for dysglycemia in a secondary care setting for mental health [23]. This pilot feasibility trial seeks to further improve our understanding of the implementation challenges of implementing a new digital system that aims to improve physical health care provision to patients in mental health settings and inform a further, more comprehensive evaluation of the eCDSS. Key implementation outcomes, including acceptability and feasibility, will be evaluated alongside outcomes relating to impacts on care processes and based on established implementation science methods [29-31].

Conclusion

An eCDSS can have the potential to improve clinician-led management of dysglycemia in inpatient mental health settings. If found to be feasible and acceptable in this study, then, in combination with the results of the implementation evaluation, the system can be refined and improved to support future successful implementation. A larger and more definitive effectiveness trial should then be conducted to assess its impact on clinical outcomes over a longer period of time and to guide its scalability and application to other conditions in wider mental health care settings.

Acknowledgments

This work was supported by (1) the Maudsley Charity; (2) the National Institute for Health Research's (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London; (3) the Maudsley Charity; and (4) the National Institute for Health Research (NIHR) Applied Research Collaboration South London (NIHR ARC South London) at King's College Hospital NHS Foundation Trust. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Conflicts of Interest

RJBD is the Co-founder and director of CogStack Ltd. FG has received honoraria for talks from Boehringer Ingelheim, Lundbeck, Otsuka and Sunovion. FG is in part supported by the National Institute for Health Research's (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London and the NIHR Applied Research Collaboration South London (NIHR ARC South London) at King's College Hospital NHS Foundation Trust. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

References

1. Chang CK, Hayes RD, Perera G, Broadbent MTM, Fernandes AC, Lee WE, et al. Life expectancy at birth for people with serious mental illness and other major disorders from a secondary mental health care case register in London. PLoS One 2011;6(5):e19590 [FREE Full text] [doi: 10.1371/journal.pone.0019590] [Medline: 21611123]
2. Vancampfort D, Stubbs B, Mitchell AJ, De Hert M, Wampers M, Ward PB, et al. Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: a systematic review and meta-analysis. World Psychiatry 2015;14(3):339-347 [FREE Full text] [doi: 10.1002/wps.20252] [Medline: 26407790]
3. Hayes JF, Marston L, Walters K, King MB, Osborn DPJ. Mortality gap for people with bipolar disorder and schizophrenia: UK-based cohort study 2000-2014. Br J Psychiatry 2017;211(3):175-181 [FREE Full text] [doi: 10.1192/bjp.bp.117.202606] [Medline: 28684403]
4. Alam U, Asghar O, Azmi S, Malik RA. General aspects of diabetes mellitus. Handb Clin Neurol 2014;126:211-222. [doi: 10.1016/B978-0-444-53480-4.00015-1] [Medline: 25410224]

5. Nathan DM. Long-term complications of diabetes mellitus. N Engl J Med 1993;328(23):1676-1685. [doi: 10.1056/NEJM199306103282306] [Medline: 8487827]
6. Hex N, Bartlett C, Wright D, Taylor M, Varley D. Estimating the current and future costs of type 1 and type 2 diabetes in the UK, including direct health costs and indirect societal and productivity costs. Diabet Med 2012;29(7):855-862. [doi: 10.1111/j.1464-5491.2012.03698.x] [Medline: 22537247]
7. Gardner-Sood P, Lally J, Smith S, Atakan Z, Ismail K, Greenwood KE, et al. Cardiovascular risk factors and metabolic syndrome in people with established psychotic illnesses: baseline data from the IMPaCT randomized controlled trial. Psychol Med 2015;45(12):2619-2629 [FREE Full text] [doi: 10.1017/S0033291715000562] [Medline: 25961431]
8. Roberts E, Jones L, Blackman A, Dewhurst T, Matcham F, Kan C, et al. The prevalence of diabetes mellitus and abnormal glucose metabolism in the inpatient psychiatric setting: a systematic review and meta-analysis. Gen Hosp Psychiatry 2017;45:76-84 [FREE Full text] [doi: 10.1016/j.genhosppsych.2017.01.003] [Medline: 28274344]
9. Gaughran F, Stahl D, Stringer D, Hopkins D, Atakan Z, Greenwood K, et al. Effect of lifestyle, medication and ethnicity on cardiometabolic risk in the year following the first episode of psychosis: prospective cohort study. Br J Psychiatry 2019;215(6):712-719 [FREE Full text] [doi: 10.1192/bjp.2019.159] [Medline: 31347480]
10. Chan JKN, Wong CSM, Or PCF, Chen EYH, Chang WC. Risk of mortality and complications in patients with schizophrenia and diabetes mellitus: population-based cohort study. Br J Psychiatry 2021;219(1):375-382 [FREE Full text] [doi: 10.1192/bjp.2020.248] [Medline: 33407970]
11. Bipolar disorder: assessment and management clinical guideline [CG185]. National Institute for Health and Care Excellence. 2014. URL: https://www.nice.org.uk/guidance/cg185 [accessed 2024-03-07]
12. Taylor M, Perera U. NICE CG178 psychosis and schizophrenia in adults: treatment and management—an evidence-based guideline? Br J Psychiatry 2015;206(5):357-359 [FREE Full text] [doi: 10.1192/bjp.bp.114.155945] [Medline: 25934299]
13. Price HC, Ismail K, Joint British Diabetes Societies (JBDS) for Inpatient Care. Royal College of Psychiatrists Liaison Faculty and Joint British Diabetes Societies (JBDS): guidelines for the management of diabetes in adults and children with psychiatric disorders in inpatient settings. Diabet Med 2018;35(8):997-1004. [doi: 10.1111/dme.13673] [Medline: 30152583]
14. Royal College of Psychiatrists. Report of the second round of the National Audit of Schizophrenia (NAS) 2014. Healthcare Quality Improvement Partnership. 2014. URL: https://www.rcpsych.ac.uk/docs/default-source/improving-care/ccqi/national-clinical-audits/ncap-library/national-audit-of-schizophrenia-document-library/nas_round-2-report.pdf?sfvrsn=6356a4b0_4 [accessed 2024-03-12]
15. Crawford MJ, Jayakumar S, Lemmey SJ, Zalewska K, Patel MX, Cooper SJ, et al. Assessment and treatment of physical health problems among people with schizophrenia: national cross-sectional study. Br J Psychiatry 2014;205(6):473-477 [FREE Full text] [doi: 10.1192/bjp.bp.113.142521] [Medline: 25323141]
16. Kan C, Kaar SJ, Eisa M, Jones L, Beckett J, Mustafa O, et al. Diabetes management in psychiatric inpatients: time to change? Diabet Med 2016;33(3):407-408 [FREE Full text] [doi: 10.1111/dme.12838] [Medline: 26104060]
17. Grol R, Grimshaw J. From best evidence to best practice: effective implementation of change in patients' care. Lancet 2003;362(9391):1225-1230 [FREE Full text] [doi: 10.1016/S0140-6736(03)14546-1] [Medline: 14568747]
18. Iyawa GE, Herselman M, Botha A. Digital health innovation ecosystems: from systematic literature review to conceptual framework. Procedia Comput Sci 2016;100:244-252 [FREE Full text] [doi: 10.1016/j.procs.2016.09.149]
19. Kawamoto K, Houlihan CA, Balas EA, Lobach DF. Improving clinical practice using clinical decision support systems: a systematic review of trials to identify features critical to success. BMJ 2005;330(7494):765 [FREE Full text] [doi: 10.1136/bmj.38398.500764.8F] [Medline: 15767266]
20. Wasylewicz ATM, Scheepers-Hoeks AMJW. Clinical decision support systems. In: Dekker A, Dumontier M, Kubben P, editors. Fundamentals of Clinical Data Science. Cham: Springer International Publishing; 2019:153-169.
21. Kwan JL, Lo L, Ferguson J, Goldberg H, Diaz-Martinez JP, Tomlinson G, et al. Computerised clinical decision support systems and absolute improvements in care: meta-analysis of controlled clinical trials. BMJ 2020;370:m3216 [FREE Full text] [doi: 10.1136/bmj.m3216] [Medline: 32943437]
22. Kilsdonk E, Peute LW, Jaspers MWM. Factors influencing implementation success of guideline-based clinical decision support systems: a systematic review and gaps analysis. Int J Med Inform 2017;98:56-64 [FREE Full text] [doi: 10.1016/j.ijmedinf.2016.12.001] [Medline: 28034413]
23. Patel D, Msosa YJ, Wang T, Mustafa OG, Gee S, Williams J, et al. An implementation framework and a feasibility evaluation of a clinical decision support system for diabetes management in secondary mental healthcare using CogStack. BMC Med Inform Decis Mak 2022;22(1):100 [FREE Full text] [doi: 10.1186/s12911-022-01842-5] [Medline: 35421974]
24. Fernandes AC, Cloete D, Broadbent MTM, Hayes RD, Chang CK, Jackson RG, et al. Development and evaluation of a de-identification procedure for a case register sourced from mental health electronic records. BMC Med Inform Decis Mak 2013;13:71 [FREE Full text] [doi: 10.1186/1472-6947-13-71] [Medline: 23842533]
25. Perera G, Broadbent M, Callard F, Chang CK, Downs J, Dutta R, et al. Cohort profile of the South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLaM BRC) case register: current status and recent enhancement of an electronic mental health record-derived data resource. BMJ Open 2016;6(3):e008721 [FREE Full text] [doi: 10.1136/bmjopen-2015-008721] [Medline: 26932138]

26. Stewart R, Soremekun M, Perera G, Broadbent M, Callard F, Denis M, et al. The South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLAM BRC) case register: development and descriptive data. BMC Psychiatry 2009;9:51 [FREE Full text] [doi: 10.1186/1471-244X-9-51] [Medline: 19674459]
27. Curran GM, Bauer M, Mittman B, Pyne JM, Stetler C. Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact. Med Care 2012;50(3):217-226 [FREE Full text] [doi: 10.1097/MLR.0b013e3182408812] [Medline: 22310560]
28. Roethlisberger FJ, Dickson WJ. Management and the Worker. Cambridge, Massachusetts: Harvard University Press; 1961.
29. Damschroder LJ, Aron DC, Keith RE, Kirsh SR, Alexander JA, Lowery JC. Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. Implement Sci 2009;4(1):50 [FREE Full text] [doi: 10.1186/1748-5908-4-50] [Medline: 19664226]
30. Greenhalgh T, Wherton J, Papoutsi C, Lynch J, Hughes G, A'Court C, et al. Beyond adoption: a new framework for theorizing and evaluating nonadoption, abandonment, and challenges to the scale-up, spread, and sustainability of health and care technologies. J Med Internet Res 2017;19(11):e367 [FREE Full text] [doi: 10.2196/jmir.8775] [Medline: 29092808]
31. Van de Velde S, Kunnamo I, Roshanov P, Kortteisto T, Aertgeerts B, Vandvik PO, et al. The GUIDES checklist: development of a tool to improve the successful use of guideline-based computerised clinical decision support. Implement Sci 2018;13(1):86 [FREE Full text] [doi: 10.1186/s13012-018-0772-3] [Medline: 29941007]

Abbreviations

CRIS: Clinical Records Interactive Search
CVD: cardiovascular disease
eCDSS: electronic clinical decision support system
ICD-10: International Classification of Disease-10th revision
NHS: National Health Service
SMI: severe mental illness
TAU: treatment as usual

Edited by A Mavragani; submitted 02.06.23; peer-reviewed by Y Chu, G Lim; comments to author 19.08.23; revised version received 03.11.23; accepted 17.12.23; published 05.04.24.

Please cite as:
Patel D, Msosa YJ, Wang T, Williams J, Mustafa OG, Gee S, Arroyo B, Larkin D, Tiedt T, Roberts A, Dobson RJB, Gaughran F Implementation of an Electronic Clinical Decision Support System for the Early Recognition and Management of Dysglycemia in an Inpatient Mental Health Setting Using CogStack: Protocol for a Pilot Hybrid Type 3 Effectiveness-Implementation Randomized Controlled Cluster Trial
JMIR Res Protoc 2024;13:e49548
URL: https://www.researchprotocols.org/2024/1/e49548
doi:10.2196/49548
PMID:38578666

Protocol

Telepractice Parent Training of Enhanced Milieu Teaching With Phonological Emphasis (EMT+PE) For Persian-Speaking Toddlers With Nonsyndromic Cleft Palate: Protocol for a Randomized Controlled Trial

Neda Tahmasebi[1]; Talieh Zarifian[1], PhD; Atieh Ashtari[1], PhD; Akbar Biglarian[2], PhD

[1]Department of Speech Therapy, Pediatric Neurorehabilitation Research Center, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran

[2]Department of Biostatistics and Epidemiology, Social Determinants of Health Research Center, Social Health Research Institute, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran

Corresponding Author:
Talieh Zarifian, PhD
Department of Speech Therapy
Pediatric Neurorehabilitation Research Center
University of Social Welfare and Rehabilitation Sciences
Koudakyar Ave
Daneshjou Blv
Tehran, 1985713871
Iran
Phone: 98 2122180139
Email: ta.zarifian@uswr.ac.ir

Abstract

Background: Children born with a cleft palate with or without a cleft lip (CP/L) are at increased risk for delayed language development and speech sound disorders. Enhanced Milieu Teaching with Phonological Emphasis (EMT+PE) is a recommended naturalistic intervention for toddlers with CP/L. The parents' role in providing naturalistic interventions is critical and they need training based on learning principles to implement these interventions. Telepractice is an appropriate method for training parents and children with various speech-related disorders.

Objective: This study aims to determine and compare the effectiveness of telepractice and the parent-implemented EMT+PE intervention on language and speech measures in toddlers with CP/L with usual interventions and determine the effectiveness maintenance of the intervention.

Methods: A randomized controlled trial (RCT) will assess the efficacy of telepractice and the parent-implemented EMT+PE intervention in enhancing speech and language measures in toddlers with CP/L. Eligible participants will be randomly assigned to one of 2 groups: the conventional intervention group and the EMT+PE intervention group. Participants' speech and language measures will be evaluated remotely by trained raters before and after the intervention and 2 months after the intervention. Parents of participants in the intervention group will receive 3 months of training in speech and language supportive strategies from trained therapists using telehealth fidelity scales. Parents of participants in the control group will receive the conventional speech and language intervention by cleft team therapists. Study outcomes will include language variables (mean length of utterance) and speech production variables (percent correct consonants).

Results: The protocol was approved by the Research Ethics Committee of the University of Social Welfare and Rehabilitation Sciences in February 2022. The selection process of participants, as well as training therapists and raters, commenced in January 2022, the therapy and follow-up period ended in June 2023, and pre- and postintervention assessments have been conducted. Data analysis is ongoing, and we expect to publish our results by the summer of 2024. Funding is yet to be received.

Conclusions: The results of this study may help us develop a speech and language intervention with a different delivery model for toddlers with CP/L, and the cleft team care can use these results in service delivery. Consistent with our hypothesis, speech and language measures are expected to improve.

International Registered Report Identifier (IRRID): DERR1-10.2196/54426

(JMIR Res Protoc 2024;13:e54426) doi:10.2196/54426

KEYWORDS

telepractice; cleft palate; language intervention; parent training; Phonological Emphasis; Enhanced Milieu Teaching; Persian-speaking toddlers; toddler; toddlers; children; child; cleft lip; language development; speech sound disorders; speech sound disorder; effectiveness; parent-based; intervention; speech; therapy

Introduction

Background

Cleft palate with or without cleft lip (CP/L) frequently leads to difficulties with speech and language [1-5]. Previous studies have reported that children with CP/L have limited consonant inventory, which leads to decreased expressive vocabularies [6-8]. Thus, trained and experienced speech-language pathologists (SLPs) in cleft and craniofacial teams often provide speech-language therapy services for these children. Team-based cleft care for this population follows particular intervention protocols. However, due to limited cleft teams in some countries or regions, especially in low-income and transitional countries, and the long distance between the cleft teams and families' residences, many of these children are unable to receive appropriate speech-language therapy services. Parent training and telepractice therapy sessions could help fill this gap [9-12].

Training and coaching for parent-implemented interventions have been known as practical methods to prevent or improve speech-language disorders in children [9-14]. Parents are considered the first teachers of their children's speech and language development since they spend considerable time with their children in a natural environment, which provides them many opportunities to teach their children through daily routines. Intervention approaches in speech-language pathology have highlighted the crucial role of parents in these approaches. Parents are trained to use supportive language and speech strategies while interacting with their children [14]. Training strategies parents use in a child's environment also facilitate the transfer of therapy from clinical settings to the child's natural environment [15-17]. A systematic review of 18 studies [18] analyzing parent-implemented interventions revealed that parents who received training increased their responsiveness, usage of language models, and rate of communication with their children—in addition to the use of language-supportive strategies—had positive impacts on expressive language in preschool children with or without language impairments.

Language and motor intervention approaches have been used for children with CP/L. A systematic review [19] comparing the benefits of linguistic and phonological versus motor phonetics approaches revealed that although all the studies reported significant findings, they did not report a more effective intervention approach. Other studies [8] showed that both approaches improved consonant inventory; however, the linguistic and phonological approach was more effective in improving speech outcomes. Most of these studies have been conducted with children older than 4 years. It seems that the naturalistic-based approach is more effective in and applicable to younger children [20]. Enhanced Milieu Teaching (EMT) is one of the approaches of the naturalistic approach. It is a conversation-based naturalistic model for early language intervention that uses children's interests and initiations as opportunities to model and encourage language use in daily routines [15]. EMT with Phonological Emphasis (EMT+PE) extends the prompting strategies of EMT to include Phonological Emphasis (PE). PE or speech recasts are a subset of recasts that target correct phonological production in response to the child's incorrect productions [5,11,12,21]. Studies have reported positive effects of EMT+PE on language and speech outcomes including the percentage of correct consonants (PCC), consonant inventory, word production speed, compensatory errors, expressive vocabulary, and receptive language [5,21,22]. EMT+PE delivery methods are flexible for children with CP/L. Two pilot studies have demonstrated the effectiveness of the EMT+PE intervention via telepractice [11,12].

Telepractice refers to services delivered over long distances using videoconferencing or other technologies. Also, it is a service delivery model for different purposes in specific populations with communication disorders [13,23]. Telepractice is used to train parents in parent-implemented approaches [11,12,24]. Parent training via telepractice is implemented through different media such as videoconferences, YouTube videos, and web-based modules. The type of media for service delivery depends on the media facilities [24,25]. Previous research has indicated that treatment outcomes are comparable for both in-person and telepractice service delivery, and these methods are used as alternatives or as a hybrid approach [26].

The prevalence of cleft lip and palate (CLP) in Iran has been reported as 1.24 per 1000 births, with an incidence rate of 1 in 1000 births [27,28] There are 6 active cleft teams in Iran, all located in the center of major provinces. Iran, with a population of over 80 million individuals, of which 26% live in rural areas and 74% in cities, most families with a child with CLP are likely to face significant challenges in accessing team services or may not have the opportunity to use them due to their living conditions. According to various studies [26,29], telepractice service delivery can largely address the problems of health care services and provide timely access to services for children and families; therefore, our objective is to develop a protocol to evaluate the effect of a parent-based telepractice EMT+PE intervention on speech and language outcomes in Persian-speaking toddlers with nonsyndromic cleft palate, and compare this intervention to conventional, usual-care interventions.

Aims

Primary Objectives

Our primary objective is to determine the effectiveness of a parent-based telepractice EMT+PE intervention on language and speech outcomes in toddlers with CP/L.

Secondary Objectives

Our secondary objectives are to compare the effectiveness of this parent-based telepractice EMT+PE intervention with usual-care interventions and determine the effectiveness of the intervention in the follow-up period.

Methods

Study Design

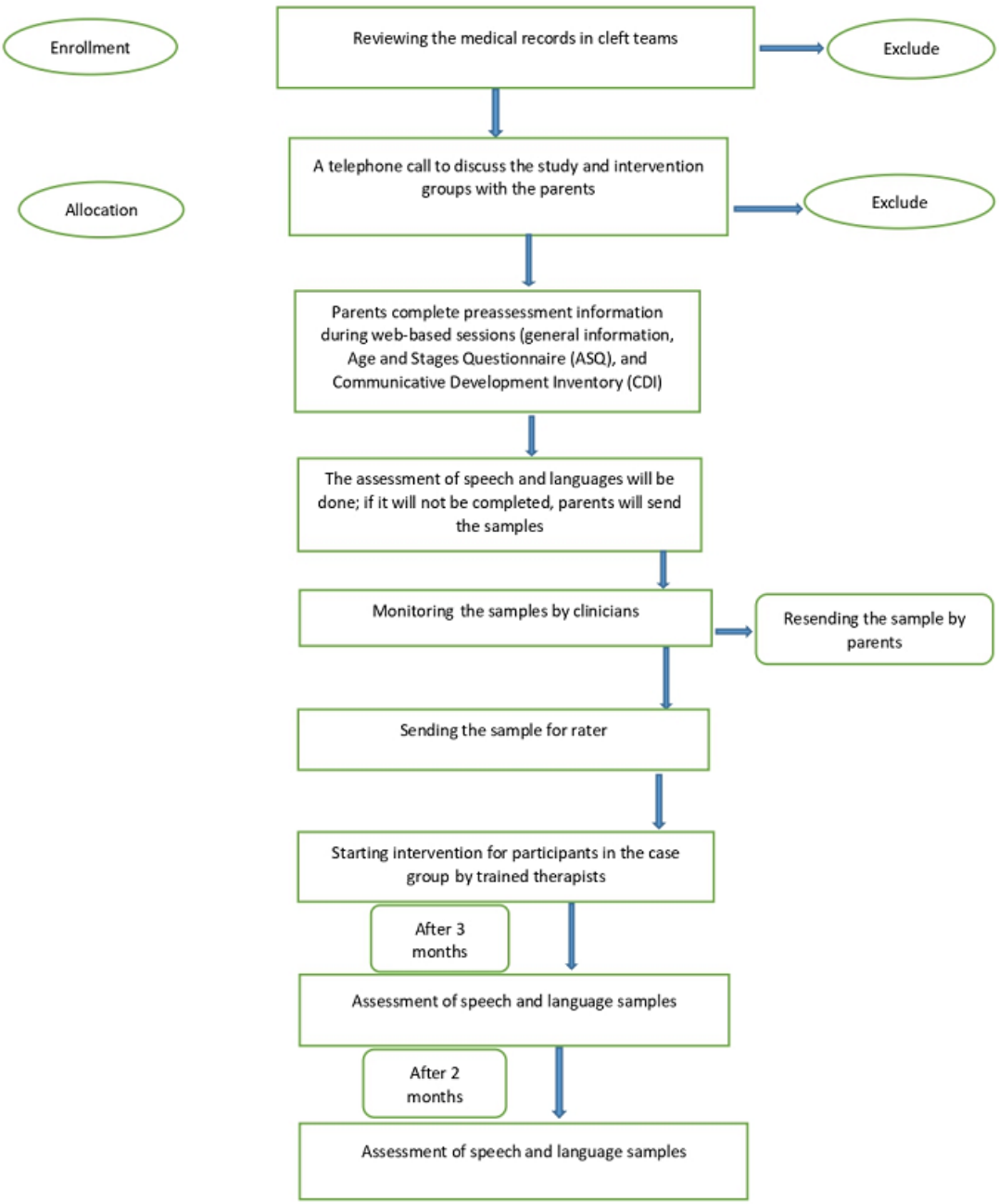
This is a single-blind, 2-arm, parallel randomized controlled trial (RCT).

Study Population and Setting

The study will enroll 32 children with different types of oral cleft including unilateral cleft lip and palate, bilateral cleft lip and palate, and isolated cleft palate (Figure 1).

Participants will be recruited through local cleft palate teams in 3 major provinces (Esfahan, Tehran, and Shiraz), social media support groups, and local speech and language centers. All child-parent dyads will be required to meet the inclusion criteria.

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flowchart showing the flow of participants in both groups.



Inclusion and Exclusion Criteria

Eligible participants including children, their parents, and SLPs will be recruited through a rigorous review of the literature in this field [4,11,12,21].

Inclusion Criteria

Children

The inclusion criteria for children are as follows: (1) Persian-speaking children with CP/L aged between 18 and 36

months before the intervention, (2) lack of a diagnosis of a syndrome by a geneticist and by referring medical records to cleft care teams, (3) undergoing primary palate repair by the age of 15 months, (4) absence of sensorineural hearing loss or a sound field hearing threshold greater than 30 dB HL (decibels in hearing level), (5) preintervention assessment of typically developing children wherein scores on the Age and Stages Questionnaire in all domains (communication, fine motor, gross motor, personal and social, and problem-solving skills) are within the normal range (±1 SD from the cutoff points in each domain), (6) the child's sufficient joint attention with the parent during the collection of play-based language samples, (7) at least 1 type of compensatory error throughout the speech sample, and (8) the child can produce at least 5 different words as measured using the Macarthur-Bates Communicative Development Inventory (MCDI).

Parents

The inclusion criteria for parents are as follows: (1) having literacy skills at least at the level of elementary school education, (2) being interested in participating in the assessment and telepractice training sessions, and (3) being able to use a cell phone containing apps that will be used in the intervention.

SLPs

The inclusion criteria for SLPs are as follows: (1) having at least 5 years of experience in providing treatment approaches for children with speech-language disorders, (2) not currently delivering EMT+PE and not previously trained in the interventional approach, and (3) having experience in treating children with various speech-language disorders via telepractice.

Exclusion Criteria

Children

Children will be excluded from the study if they (1) are bilingual or do not speak Persian, (2) have other dysmorphic features that affect speech (fistula in the palate), (3) have been receiving either therapy in the last 6 months or speech therapy in private clinics, or (4) are participating in another research study involving an intervention or multiple assessments.

Parents

Parents will be excluded from the study if they are (1) unable to properly implement speech- and language-supportive strategies or (2) unwilling to continue with the intervention process.

SLPs

SLPs will be excluded from the study if they are unable to provide weekly family therapy sessions.

Randomization and Blinding

Overview

After preassessments, participants will be allocated to either of 2 intervention groups to eliminate selection bias and control for any extraneous variables: EMT+PE or the usual-care intervention. Block randomized trials will be conducted for each age group using the blockrand package in R software (version 4.1.3; The R Foundation). Randomization will be based on age (3 age groups) and the 2 interventions. The flow of participants through the study is illustrated using the CONSORT (Consolidated Standards of Reporting Trials) flowchart in Figure 1.

Blinding of Raters and Reliability of the Data

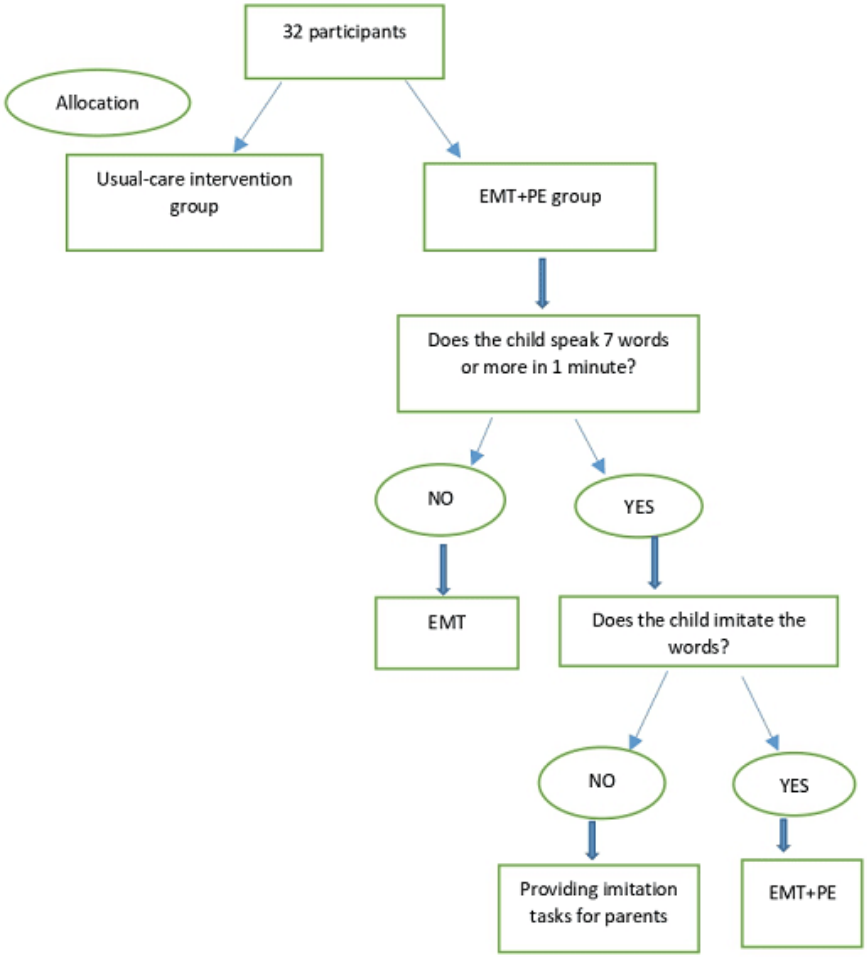
Trained and experienced raters who are blinded to the grouping of participants will transcribe audio and video samples of speech and language. The samples will be collected from the parents at home as they are interacting with their children using toys and pictures, using the Profiles of Early Expressive Phonological Skills (PEEPS) assessment.

Intervention

EMT+PE Intervention

The EMT+PE intervention consists of implementing supportive speech and language strategies by parents in their interaction with their children. All parents will be trained in accordance with the Teach-Model-Coach-Review (TMCR) instructional model that has been adapted for the telepractice environment [9,30]. The Teach component of the instructional approach involves introducing targeted supportive strategies. The Model component includes the implementation of strategies by a clinician when interacting with a child—we will implement this component by showing recorded video examples of strategies. The Coaching aspect entails parents using strategies during their interaction with their children. The Review component includes monitoring and evaluating the entire session and planning for the next session at the end of every session. EMT+PE treatment principles for the intervention group are illustrated in Figure 2.

Figure 2. Principles of the EMT+PE (Enhanced Milieu Teaching with Phonological Emphasis) intervention. EMT: Enhanced Milieu Teaching.



Speech Target Selection

Speech targets for each child are determined by analyzing the errors produced in their speech sounds during the PEEPS assessment. A list of sample words will be created from the speech sound errors observed in the children's PEEPS assessment. To select the target speech sounds, developmental norms and the frequency of speech sound errors related to cleft palate, including high-pressure and fricative consonants in words with the syllabic consonant-vowel-consonant-vowel structure, are taken into account. For each child, place, and manner of articulation, pre- and postvocalic voicing are considered. Once a participant can produce 7-10 words per minute, a speech recast strategy is integrated into the intervention process.

Usual-Care Intervention

Children assigned to the usual-care intervention (control) group will be assessed twice before and after the 3-month intervention. If they are not, they will be enrolled in cleft teams. They will receive speech and language therapy there in accordance with a specific protocol. Regular evaluations administrated every 3-6 months, are part of the usual speech and language intervention for children aged up to 3 years undergoing team care. Based on each child's evaluation, early counseling is provided to parents in person or remotely. Parents are expected to apply the recommendations provided until the next visit. The EMT+PE will not be administered to participants in the control group throughout the experimental intervention period.

Procedure

Therapist Training

We will recruit 3 eligible SLPs based on the study inclusion criteria. The process of implementing the protocol will be explained to them by the first author; if they are responsible for implementing it, they will participate in training sessions. They will receive training regarding the study methodology, participants, EMT+PE intervention, strategies, and fidelity of implementation for therapists and parents. SLPs will receive at least 3 in-person training sessions in accordance with the TMCR instructional model. For the Teach component, the research team will introduce speech and language strategies and their rationale. For the Model component, video examples related to the implementation of strategies by professional therapists in interacting with a child with a language disorder will be shown [12]. In the Coach component, therapists will implement strategies through role-playing. Thereafter, for the Review component, all training sessions will be monitored by researchers and therapists, and questions related to session content will be discussed and answered. For the competency-based assessment according to telehealth fidelity scales, each therapist will train a parent of a child with CP/L on the telegram platform so that the groups will consist of a therapist, a parent, and the main researcher. Then, the therapist

will train the parent in at least 1 language strategy during offline and web-based sessions, and the parent will send a video of using the trained strategy when interacting with her child. Two independent experts will observe the skills-based assessment sessions and rate the therapists' performance using telehealth fidelity scales.

Parent Training

Parents will receive training on specific strategies and apply them while interacting with their children at home. The competency-based assessment of parents will be defined using fidelity scales that are based on the trained strategies. The therapist will connect with parents twice a week for 3 months during the intervention course. The training sessions will be held in both offline and web-based modes. The therapist will share the material with the parents during offline sessions to teach them the strategies. For the model component, the therapist will send video examples of the strategies to the parents. Parents will be provided sufficient time to study the documents and view the video examples of the strategies. At the next stage of the administration process, the therapist will schedule a video call with the parents and they will discuss the content of the documents and video examples that would be sent, and talk about how to apply the strategies when interacting with their child. After the discussion, the parents will submit a video that shows them implementing the taught strategy. The therapist will review the videos sent. Next, the weaknesses and strengths of the video will be described on the basis of a fidelity checklist through a video call. Trainees will learn 7 supportive speech and language strategies that are arranged hierarchically from easy to difficult, including environment arrangement, match turns, modeling, prompting, time delay, expansion, and recasting [12,22]. The environment arrangement strategy aims to enhance the child's engagement with the physical setup by selecting, arranging, and managing materials. In the matched turns strategy, parents are encouraged to match their turns of conversation with those of their child and carry out language mapping, in which parents are encouraged to mirror their child's actions during play and incorporate language into the shared actions. Modeling involves a verbal model by the parent in which the child is encouraged to imitate. In the prompting strategy, the parent encourages the child to use an utterance at the target level in a conversational interaction. In the time delay strategy, parents encourage their child to promote initiation by providing nonverbal cues rather than relying on verbal models and commands; this includes assistance, pause in routine action (when the parent is interacting with their child), visual selection, and inadequate portion (ie, parents must ensure that the toys or equipment that they provide to their children are complete and ready to use; for example, if a doll is in a box, the child may require assistance in unboxing it and starting to play with it). In the expansion strategy, the parents repeat their child's utterance and add a word or phrase to complete its utterance. Speech recasting involves repeating a child's phrases with modified grammar or speech production (or both).

Rater Training

The child's speech and language samples are transcribed by 4 experienced and trained raters who are blinded to the child's group allocation (intervention or control). Before transcribing the samples, they will be provided instructions on how to rate the samples. To assess the reliability of the data, 25% of each rater's samples will be scored by an independent expert. In case of inadequate agreement (ie, <85%) differences will be identified, and the samples will be reevaluated.

Fidelity Assessment

Fidelity of Implementation for Therapists

Therapist fidelity will be assessed using an observational checklist with Likert scales. This checklist is designed in accordance with the components of the TMCR instructional model and the telepractice environment (Kaiser Telehealth Fidelity Scale). The checklist includes 5 sections: teach, model, coach, review, and overall interaction. Each section has several statements to measure implementation quality by the therapist. After training sessions with the therapists and before starting the intervention, they will be assessed using the fidelity checklist while delivering the intervention to a parent. The reliability of each therapist will be assessed (Multimedia Appendix 1).

Fidelity of Implementation for Parents

Parents' ability to implement the trained EMT+PE strategies with procedural fidelity will be determined through formative visual analysis based on established learning criteria. To ensure fidelity, therapists and an independent expert will assess parents' use of each strategy during 8 monthly sessions, using a checklist. The criteria for the strategies are as follows: environment arrangement (80%), language mapping (75%), match turns (75%), expansions (50%), modeling (40%), child's target level (50%), prompt (80%), delay (80%), and speech recast (40%). The reliability of parents' fidelity will be measured during the intervention [12,13] (Multimedia Appendix 2).

Data Collection

In total, 32 children with CP/L in different provinces of Iran (Isfahan, Tehran, and Shiraz) who meet the primary inclusion criteria will be recruited. Next, the first author will call the parents and explain the process and the study's terms of acceptance. Then, she will schedule a web-based session to complete the assessment. Parents will complete demographic information forms followed by the Age and Stages Questionnaire for their children's developmental screening. Parents will collect speech and language samples before and after the intervention for their child in the naturalistic environment (Multimedia Appendix 3).

Primary Outcomes

Speech Outcome Measures

The early phonological development of Persian-speaking monolingual children with CP/L is assessed using the Persian adaptation of the PEEPS assessment, which focuses on early acquired vocabulary [31]. The PEEPS assessment consists of 60 words that are expected to be expressed by Persian-speaking monolingual children aged 18-36 months. When administering the PEEPS assessment, an assessor first presents a picture or toy to the child as a target word; at this stage, the child is expected to respond independently. If the child does not respond,

the assessor asks a question that requires the child to cue a specific word (eg, “What is this?”). If the child fails to respond again, the assessor utters a sentence that the child must complete with the target word (eg, “The baby has...”). Finally, if the child cannot produce the target word despite these cues, the assessor provides a direct command (eg, “Say...”). If the child still cannot produce the target word in response to the final command, it is marked as having provided no response.

In this study, the PEEPS assessment will be administered to assess consonant inventory based on the word-initial and word-final consonants. Also, the accuracy of speech production will be assessed by determining the total PCC, PCC stops, whole structure match, and whole-word accuracy match by an expert during a web-based session [32,33]. The evaluation session will be recorded. If the child does not participate actively in the web-based PEEPS assessment session, the parent will follow the assessor’s instructions to record their child’s responses to the speech sample and send them to the assessor.

The second version of MCDI provides parents with a categorized vocabulary list and asks them to indicate whether their children can express each word or phrase. The scale has 2 sections and assesses 680 expressive vocabulary items in 22 semantic categories among young children aged 16-30 months [34].

Language Outcome Measures

During the assessment, parents will engage in play sessions with their children using various toys. A 15-minute language sample will be collected remotely to determine the child’s number of different words, number of total words, and language complexity measured by mean length utterances. The assessment session will be video recorded. If the child does not engage during the web-based assessment session to collect language samples, the parent will follow the assessor’s instructions for recording the child’s responses and send the video recording to the assessor.

Secondary Outcomes

Speech intelligibility will be measured using the Intelligibility in Context Scale, which is a parent-reported social validity tool [35]. The intelligibility rating is determined by the average response on a 5-point rating scale over 7 questions [36].

>Parents will be required to complete a postintervention satisfaction survey. The questionnaire aims to measure parent satisfaction with the telepractice EMT+PE intervention and parent training sessions (Multimedia Appendix 3).

Statistical Analysis

Analysis

The analysis will be carried out using descriptive and analytical statistics. Descriptive statistics appropriate for summarizing demographic information and assessment data will be used. Preintervention differences between groups will also be estimated. The data analysis will be carried out using the SPSS (version 19; IBM Corp). The study’s outcomes will be presented as an estimation of the difference between groups, with a 95% CI and its associated *P* value. The statistical significance level will be set at α=.05. We will use analysis of covariance, an efficient statistical test that provides impartial estimations of an intervention’s effects, assuming random treatment assignment; this test is more powerful than other alternative statistical strategies. We will also carry out a paired samples *t* test, which compares the means of 2 variables within a single group; it estimates the differences between the values of 2 variables for each case and tests whether their average is significantly different from 0. Additionally, data from all randomized participants will be included in the intention-to-treat analysis.

Intended Sample Size

Based on comparable studies with a 95% confidence level, 80% power of the test, variance of 0.0036 units, and an accuracy (improvement) of 0.06 units in the PCC, each group requires a maximum sample size of 16 participants.

Ethical Considerations

Participants’ safety risk will not be increased by participating in this trial. Each participant’s information will be stored under a unique number, and the coded information will be appropriately stored. When the research is completed, the results will be presented at scientific conferences or published in scientific journals, and the identities of study participants will remain confidential. The parents will be required to complete the informed consent form before participating in the study, and both the researcher and the participant must sign the document, with a copy provided to the participant. This study has been approved by the Research Ethics Committee of the University of Social Welfare and Rehabilitation Sciences, Iran (IR.USWR.REC.1400.310).

Results

The protocol was approved by the Research Ethics Committee of the University of Social Welfare and Rehabilitation Sciences in February 2022. The selection process of participants, training therapists, and raters, commenced in January 2022, the therapy and follow-up periods ended in June 2023, and pre- and postintervention assessments have been conducted. Data analysis is ongoing, and we expect to publish our results by the summer of 2024. Funding is yet to be obtained.

Discussion

This study is the first RCT with follow-up, which aims to develop a protocol to evaluate the effect of parent-based EMT+PE through telepractice in Persian-speaking toddlers with nonsyndromic cleft palate.

In this study, the impact of the interventions will be evaluated by language and speech outcomes as primary outcome measures. Language outcomes include a vocabulary inventory, collected using the MCDI, mean length utterances, number of total words, and number of different words, collected through language samples and during the parent-child interaction. Speech outcomes including PCC, consonant inventory, whole-word accuracy match, and whole structure match will be collected during the PEEPS assessment. The effect of interventions will be examined for 12 weeks, with an additional 8-week follow-up

period for the EMT+PE group to exclude any temporary effects that may have limited clinical value. Our results will provide information about the efficacy of the parent-implemented EMT+PE telepractice intervention in enhancing speech skills while also promoting speech production and language measures and its stability over a prolonged period. In addition, we will obtain parents' satisfaction and score on the Intelligibility in Context Scale before and after delivering interventions as secondary outcome measures. Improvement of speech intelligibility is a long-term target of most speech therapy interventions.

The study's limitations include its small sample size for each age group. To address the effects of such interventions, a larger-scale clinical trial is necessary. Additionally, the intervention and follow-up periods are limited in demonstrating effects. It is important to note that toddlers are in different age ranges and may require more time to develop their language and speech skills.

In summary, we anticipate demonstrable effects of the parent-implemented EMT+PE telepractice intervention on language and speech outcomes in toddlers with CP/L; these should specifically include not only an extended vocabulary inventory but also an improved consonant inventory and speech intelligibility. This study's results may help develop a specific intervention with a different delivery model for toddlers. Parent training through telepractice has multiple benefits for families, including providing therapy for children with speech-language disorders, reduced costs, unrestricted access to therapy services for people living in rural areas, and saving time and expenses [24-26]; therefore, cleft care teams can harness our results in service delivery.

Acknowledgments

We wish to express our gratitude to the participants who cooperated with us in this randomized controlled trial. We also thank Prof Nancy Scherer, Ann P Kaiser, Jennifer Nietfeld, and Dr Akram Ahmadi for their valuable contributions and sincere assistance. All authors declared that they had insufficient or no funding to support open access publication of this manuscript, including from affiliated organizations or institutions, funding agencies, or other organizations. JMIR Publications provided article processing fee (APF) support for the publication of this article.

Data Availability

The research team will retain all the data obtained from the study. In compliance with applicable legal and statutory obligations, the coordinating principal investigator will archive all study-related documents for 5 years upon completion of the study.

Authors' Contributions

All authors contributed to the protocol's design, construction, and writing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Telehealth Fidelity Scales.
[PDF File (Adobe PDF File), 314 KB - resprot_v13i1e54426_app1.pdf]

Multimedia Appendix 2
EMT+PE Fidelity Rating Form. EMT+PE: Enhanced Milieu Teaching with Phonological Emphasis.
[PDF File (Adobe PDF File), 157 KB - resprot_v13i1e54426_app2.pdf]

Multimedia Appendix 3
Study timeline.
[DOCX File , 24 KB - resprot_v13i1e54426_app3.docx]

References

1. Hardin-Jones M, Chapman K. The impact of early intervention on speech and lexical development for toddlers with cleft palate: a retrospective look at outcome. Lang Speech Hear Serv Sch 2008 Jan;39(1):89-96 [FREE Full text] [doi: 10.1044/0161-1461(2008/009)] [Medline: 18162651]
2. Jones C, Chapman K, Hardin-Jones M. Speech development of children with cleft palate before and after palatal surgery. Cleft Palate Craniofac J 2003 Jan;40(1):19-31 [FREE Full text] [doi: 10.1597/1545-1569_2003_040_0019_sdocwc_2.0.co_2] [Medline: 12498602]

3. Scherer N, Baker S, Kaiser A, Frey J. Longitudinal comparison of the speech and language performance of United States-born and internationally adopted toddlers with cleft lip and palate: a pilot study. Cleft Palate Craniofac J 2018 Aug;55(7):941-953 [FREE Full text] [doi: 10.1597/15-237] [Medline: 27723377]
4. Scherer N, D'Antonio L, McGahey H. Early intervention for speech impairment in children with cleft palate. Cleft Palate Craniofac J 2008 Jan;45(1):18-31 [FREE Full text] [doi: 10.1597/06-085.1] [Medline: 18215094]
5. Kaiser A, Scherer N, Frey J, Roberts M. The effects of enhanced milieu teaching with phonological emphasis on the speech and language skills of young children with cleft palate: a pilot study. Am J Speech Lang Pathol 2017 Aug 15;26(3):806-818 [FREE Full text] [doi: 10.1044/2016_ajslp-16-0008]
6. Meinusch M, Romonath R. Early language intervention for children with cleft lip and/or palate: a systematic review. Evid-Based Commun Assess Interv 2011 Dec;5(4):197-215 [FREE Full text] [doi: 10.1080/17489539.2012.678093]
7. Lane H, Harding S, Wren Y. A systematic review of early speech interventions for children with cleft palate. Int J Lang Commun Disord 2022 Jan;57(1):226-245 [FREE Full text] [doi: 10.1111/1460-6984.12683] [Medline: 34767284]
8. Bessell A, Sell D, Whiting P, Roulstone S, Albery L, Persson M, et al. Speech and language therapy interventions for children with cleft palate: a systematic review. Cleft Palate Craniofac J 2013 Jan;50(1):e1-e17 [FREE Full text] [doi: 10.1597/11-202] [Medline: 22433039]
9. Roberts M, Kaiser A, Wolfe C, Bryant J, Spidalieri A. Effects of the teach-model-coach-review instructional approach on caregiver use of language support strategies and children's expressive language skills. J Speech Lang Hear Res 2014 Oct;57(5):1851-1869 [FREE Full text] [doi: 10.1044/2014_jslhr-l-13-0113]
10. Ha S. Effectiveness of a parent-implemented intervention program for young children with cleft palate. Int J Pediatr Otorhinolaryngol 2015 May;79(5):707-715 [FREE Full text] [doi: 10.1016/j.ijporl.2015.02.023] [Medline: 25796294]
11. Ellis P, Scherer N, Lien K. Enhanced milieu teaching with phonological emphasis: a pilot, telepractice study for parent training in early intervention. Int J Speech Lang Pathol 2023 Jun 02:1-15 [FREE Full text] [doi: 10.1080/17549507.2023.2199176] [Medline: 37265060]
12. Philp J, Ellis P, Scherer N, Lien K. Enhanced milieu teaching with phonological emphasis: a pilot telepractice parent training study for toddlers with clefts. Children (Basel) 2021 Aug 26;8(9):A [FREE Full text] [doi: 10.3390/children8090736] [Medline: 34572168]
13. Snodgrass M, Chung M, Biller M, Appel K, Meadan H, Halle J. Telepractice in speech–language therapy: the use of online technologies for parent training and coaching. Commun Disord Q 2016 Nov 24;38(4):242-254 [FREE Full text] [doi: 10.1177/1525740116680424]
14. Kaiser AP, Hancock TB. Teaching parents new skills to support their young children s development. Infants Young Child 2003;16(1):9-21. [doi: 10.1097/00001163-200301000-00003]
15. Kaiser A, Roberts M. Parent-implemented enhanced milieu teaching with preschool children who have intellectual disabilities. J Speech Lang Hear Res 2013 Feb;56(1):295-309 [FREE Full text] [doi: 10.1044/1092-4388(2012/11-0231)] [Medline: 22744141]
16. Hemmeter M, Kaiser A. Enhanced milieu teaching. J Early Interv 2016 Sep 14;18(3):269-289 [FREE Full text] [doi: 10.1177/105381519401800303]
17. Trembath D, Mahler N, Hudry K. Evidence from systematic review indicates that parents can learn to implement naturalistic interventions leading to improved language skills in their children with disabilities. Evid-Based Commun Assess Interv 2016 Oct 17;10(2):101-107 [FREE Full text] [doi: 10.1080/17489539.2016.1231387]
18. Roberts M, Kaiser A. The effectiveness of parent-implemented language interventions: a meta-analysis. Am J Speech Lang Pathol 2011 Aug;20(3):180-199 [FREE Full text] [doi: 10.1044/1058-0360(2011/10-0055)] [Medline: 21478280]
19. Alighieri C, Bettens K, Bruneel L, Sseremba D, Musasizi D, Ojok I, et al. Comparison of motor-phonetic versus phonetic-phonological speech therapy approaches in patients with a cleft (lip and) palate: a study in Uganda. Int J Pediatr Otorhinolaryngol 2020 Apr;131:109849 [FREE Full text] [doi: 10.1016/j.ijporl.2019.109849] [Medline: 31918243]
20. Lancaster H, Lien K, Chow J, Frey J, Scherer N, Kaiser A. Early speech and language development in children with nonsyndromic cleft lip and/or palate: a meta-analysis. J Speech Lang Hear Res 2020 Jan 22;63(1):14-31 [FREE Full text] [doi: 10.1044/2019_jslhr-19-00162]
21. Scherer N, Kaiser A, Frey J, Lancaster H, Lien K, Roberts M. Effects of a naturalistic intervention on the speech outcomes of young children with cleft palate. Int J Speech Lang Pathol 2020 Oct;22(5):549-558 [FREE Full text] [doi: 10.1080/17549507.2019.1702719] [Medline: 32164442]
22. Scherer N, Yamashita R, de Oliveira DN, DiLallo J, Trindade I, Fukushiro A, et al. Early speech and language intervention in Brazilian-Portuguese toddlers with cleft lip and/or palate. Clin Linguist Phon 2022 Jan 02;36(1):34-53 [FREE Full text] [doi: 10.1080/02699206.2021.1912187] [Medline: 33899624]
23. Whitehead E, Dorfman V, Tremper G, Kramer A, Sigler A, Gosman A. Telemedicine as a means of effective speech evaluation for patients with cleft palate. Ann Plast Surg 2012 Apr;68(4):415-417 [FREE Full text] [doi: 10.1097/SAP.0b013e31823b6897] [Medline: 22421491]
24. Quinn E, Kaiser A, Ledford J. Hybrid telepractice delivery of enhanced milieu teaching: effects on caregiver implementation and child communication. J Speech Lang Hear Res 2021 Aug 09;64(8):3074-3099 [FREE Full text] [doi: 10.1044/2021_jslhr-20-00430]

25. Bellon-Harn M, Morris L, Manchaiah V, Harn W. Use of videos and digital media in parent-implemented interventions for parents of children with primary speech sound and/or language disorders: a scoping review. J Child Fam Stud 2020;29(12):3596-3608 [FREE Full text] [doi: 10.1007/s10826-020-01842-x] [Medline: 33024404]
26. Akemoglu Y, Muharib R, Meadan H. A systematic and quality review of parent-implemented language and communication interventions conducted via telepractice. J Behav Educ 2019 Nov 11;29(2):282-316 [FREE Full text] [doi: 10.1007/s10864-019-09356-3]
27. Khazaei S, Shirani AM, Khazaei M, Najafi F. Incidence of cleft lip and palate in Iran. A meta-analysis. Saudi Med J 2011 Apr;32(4):390-393. [Medline: 21483999]
28. Haseli A, Hajimirzaie S, Bagheri L, Sadeghian A, Ahmadnia E. Prevalence of cleft lip and cleft palate in Iran: a systematic review and meta-analysis. J Mazandaran Univ Med Sci 2019;28(168):A.
29. Palomares-Aguilera M, Inostroza-Allende F, Solar L. Speech pathology telepractice intervention during the COVID-19 pandemic for Spanish-speaking children with cleft palate: a systematic review. Int J Pediatr Otorhinolaryngol 2021 May;144:110700 [FREE Full text] [doi: 10.1016/j.ijporl.2021.110700] [Medline: 33862334]
30. Kaiser A, Roberts M. Parents as communication partners: an evidence-based strategy for improving parent support for language and communication in everyday settings. Perspect Lang Learn Educ 2013 Aug;20(3):96-111 [FREE Full text] [doi: 10.1044/lle20.3.96]
31. Sakhai F, Golmohammadi G, Tohidast SA, Baghejari Z, Nouhi K, Jafari N. Development of a vocabulary list for the Persian version of the profile of early expressive phonological skills: a pilot study. Speech Lang Hear 2024 Mar 04:1-10. [doi: 10.1080/2050571x.2024.2321733]
32. Stoel-gammon C. Relationships between lexical and phonological development in young children. J Child Lang 2010 Oct 18;38(1):1-34 [FREE Full text] [doi: 10.1017/s0305000910000425]
33. Stoel-Gammon C, Williams A. Early phonological development: creating an assessment test. Clin Linguist Phon 2013 Apr;27(4):278-286 [FREE Full text] [doi: 10.3109/02699206.2013.766764] [Medline: 23489340]
34. Mahmoudi BB, Soraya M, Badiee Z, Kazemi Y, Soleimani B. The size of expressive lexicon in 18-to-36-month-old children raised in Farsi-speaking families: a comparative study. J Res Rehabil Sci 2012;7(5):a [FREE Full text] [doi: 10.22122/JRRS.V7I5.190]
35. McLeod S. Intelligibility in Context Scale: cross-linguistic use, validity, and reliability. Speech Lang Hear 2020 Feb 10;23(1):9-16 [FREE Full text] [doi: 10.1080/2050571x.2020.1718837]
36. Aghaz A, Kazemi Y, Hemmati E, Zarifian T. Psychometric properties of Persian version of Intelligibility Context Scale in Persian-Speaking Children. Sci J Rehabil Med 2022;10(6):1270-1283 [FREE Full text] [doi: 10.32598/SJRM.10.6.22]

Abbreviations

CLP: cleft lip and palate
CONSORT: Consolidated Standards of Reporting Trials
CP/L: cleft palate with or without cleft lip
dB HL: decibels in hearing level
EMT: Enhanced Milieu Teaching
EMT+PE: Enhanced Milieu Teaching with Phonological Emphasis
MCDI: Macarthur-Bates Communicative Development Inventory
PCC: percentage of correct consonants
PE: Phonological Emphasis
PEEPS: Profiles Of Early Expressive Phonological Skills
RCT: randomized controlled trial
SLP: speech-language pathologist
TMCR: Teach-Model-Coach-Review

Edited by A Mavragani; submitted 09.11.23; peer-reviewed by N Tahmasebifard, M Fotuhi; comments to author 06.02.24; revised version received 14.02.24; accepted 22.02.24; published 19.04.24.

Please cite as:
Tahmasebi N, Zarifian T, Ashtari A, Biglarian A
Telepractice Parent Training of Enhanced Milieu Teaching With Phonological Emphasis (EMT+PE) For Persian-Speaking Toddlers With Nonsyndromic Cleft Palate: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2024;13:e54426
URL: https://www.researchprotocols.org/2024/1/e54426
doi:10.2196/54426
PMID:38640014

Protocol

Testing the Effectiveness of an Intervention to Improve Romanian Teachers' LGBT+-Related Attitudes, Cognitions, Behaviors, and Affect: Protocol for a Randomized Controlled Trial

Ioana Latu[1,2], PhD; Nastasia Sălăgean[3], PhD; Torill M B Larsen[4], PhD; Andreea Bogdana Isbasoiu[5], PhD; Florin Alin Sava[1], PhD

[1]Department of Psychology, Faculty of Sociology and Psychology, West University of Timisoara, Timisoara, Romania

[2]School of Psychology, Queen's University Beflast, Beflast, United Kingdom

[3]Department of Scientific Research in Economy, Law and Human-Environment Interaction, Institute for Advanced Environmental Research, West University of Timi oara, Timisoara, Romania

[4]Department of Health Promotion and Development, Faculty of Psychology at University of Bergen, Bergen, Norway

[5]Department of Psychology and Education Sciences, Transilvania University of Brasov, Brasov, Romania

Corresponding Author:
Ioana Latu, PhD
Department of Psychology
Faculty of Sociology and Psychology
West University of Timisoara
Bulevardul Vasile Pârvan 4
Timisoara, 300223
Romania
Phone: 40 7901037222
Email: i.latu@qub.ac.uk

Abstract

Background: Repeated stigmatization due to group membership constitutes a recurrent stressor with negative impact on physical and mental health (minority stress model). Among European countries, Romania ranks low on LGBT+ (lesbian, gay, bisexual, and transgender people. The "+" represents individuals whose identities do not fit typical binary notions of male and female [nonbinary]) inclusion, with 45% of Romanian LGBT+ respondents reporting discrimination in at least 1 area of life in the year preceding the survey. Importantly, while all LGBT+ people might experience minority stress, younger sexual minority individuals are more prone to the detrimental impacts of stigma on their mental and physical health. As such, interventions are necessary to improve the inclusion climate within schools, where young people spend most of their time. Until now, most interventions addressing this topic have been conducted on undergraduate students in Western countries, with no studies conducted in countries that have widespread anti-LGBT+ attitudes.

Objective: This paper describes the research protocol for a randomized controlled trial investigating whether LGBT+ stigma and bias among Romanian school teachers can be reduced using an internet-based intervention focusing on education and contact as primary training elements.

Methods: A sample of 175 school teachers will be randomly assigned to either the control or experimental group. The experimental group participants will receive the intervention first and then complete the outcome measures, whereas the control group will complete the outcome measures first and then receive the intervention. The 1-hour multimedia intervention is developed for internet-based delivery under controlled conditions. It includes 2 interactive exercises, 2 recorded presentations, animations, and testimonies from LGBT+ individuals. Data for attitudinal, behavioral, cognitive, and affective measures will be collected during the same session (before or after the intervention, depending on the condition). We also plan to conduct a brief mixed methods follow-up study at 6 to 8 months post participation to investigate potential long-term effects of training. However, due to attrition and lack of experimental control (all participants will have completed the intervention, regardless of the condition), these data will be analyzed and reported separately using a mixed methods approach.

Results: This paper details the protocol for the teacher intervention study. Data collection began in December 2022 and was completed by February 2023. Data analysis will be performed upon protocol acceptance. Follow-up measures will be completed in 2024. Results are expected to be submitted for publication following analysis in the spring of 2024.

Conclusions: The findings of this study will establish the effectiveness of an internet-based intervention intended to lessen anti-LGBT stigma and sentiment in a nation where these views have long been prevalent. If successful, the intervention could end up serving as a resource for Romanian teachers and guidance counselors in high schools.

Trial Registration: ISRCTN 84290049; https://doi.org/10.1186/ISRCTN84290049

International Registered Report Identifier (IRRID): DERR1-10.2196/54254

(JMIR Res Protoc 2024;13:e54254) doi:10.2196/54254

KEYWORDS

discrimination; intervention; school; lesbian, gay, bisexual, and transgender; attitude; behavior; cognition; stigma; stigmatization; negative impact; physical health; mental health; minority stress model; European; Europe; Romania; stress; young; student; students; undergraduate; bias; data analysis; online intervention; lesbian, gay, bisexual, and transgender stigma; sentiment

Introduction

Overview

The experience of stigmatization based on group membership can lead to negative effects on physical and mental health via repeated experiences of stress which, in the long term, accumulate to impact health negatively (minority stress model) [1]. Stigmatization can occur based on membership in any group that is discriminated against. In this research, we focus on LGBT+ (lesbian, gay, bisexual, and transgender people. The "+" symbol represents individuals whose identities do not fit typical binary notions of male and female [nonbinary]) stigmatization and its reduction in Romania.

Among European countries, Romania tends to fare poorly when it comes to LGBT+ inclusion. A recent survey [2] showed that 45% of Romanian LGBT+ respondents felt discriminated against in at least 1 area of life during the year before the survey. Similarly, 43% of respondents experienced harassment due to being LGBT+, a rate that ranks second among all European countries. Much of this discrimination and harassment happens in schools for young people, with 44% of LGBT+ students (15-17 years of age) in Romania saying they are hiding being LGBT+ at school, a rate that is 3 to 4 times higher than in countries such as Luxembourg (11%), the Netherlands (16%), or Malta (17%). Indeed, schools seem to be a fertile ground for LGBT+ harassment, with 51% of incidents involving perpetrators from schools [2], a finding reinforced by a UNESCO (The United Nations Educational, Scientific and Cultural Organization) report on school violence [3].

Such high rates of LGBT+ discrimination among Romanian students are concerning, because stigma impacts young LGBT+ people's mental and physical health. A meta-analysis [4] including 35 studies of over 2 million heterosexual young people and over 100,000 LGBT+ young individuals (age range 12-20 years) showed that suicide risk was higher for LGBT+ young people compared to those who were not LGBT+. For every heterosexual young person, the chance of suicide was 3.71 higher for gay and lesbian young people, 4.87 higher for bisexual youth, and 5.87 higher for young transgender people. This risk is paired with a higher likelihood for sexual minority youth to experience mental health issues such as anxiety and depression but also impaired academic performance [5]. The findings for sexual minority youth are consistent with sexual minority individuals in general—a systematic review showed that the majority of studies revealed a higher risk for mental health issues, substance abuse, and suicide risk for sexual minorities [6]. LGBT+ people are also more likely to endure physical health issues due to minority stress, including an increased risk for cancer, cardiovascular disease, and chronic conditions such as asthma and diabetes [7].

Importantly, although minority stress can affect all LGBT+ people, younger sexual minority individuals seem to be most vulnerable to the negative effects of stigma on their mental and physical health. A meta-analysis indicated age as a significant moderator, such that youth younger than 17 years of age experienced higher negative outcomes due to LGBT-related victimization compared to those older than 17 years of age [8].

Together, these findings indicate a strong need to implement effective interventions to reduce LGBT+ stigma and bias in Romanian schools, to improve the mental and physical health of LGBT+ students in Romania. These interventions may be most efficient particularly among teachers, as they can impact their students' experiences either directly or indirectly, via establishing inclusivity norms in the classroom.

To be effective, interventions should not only focus on reducing teachers' biases toward LGBT+ students, but also on learning, implementing, and modeling behaviors that would equip them to intervene when students experience LGBT+-related victimization. A meta-analysis [9] showed that interventions can be moderately successful in reducing sexual prejudice, resulting in changes ranging from one-third to one-half of an SD in size. Moreover, the meta-analysis specified the most effective strategies in reducing different outcomes—educational interventions, contact with LGBT+ individuals, and interventions combining education with contact. A more careful analysis reveals that most intervention studies have been conducted on undergraduate students in Western countries and none in Eastern Europe or other countries with strong antigay attitudes. Although more recent research has started to test interventions in other countries such as Jamaica [10] or Brazil [11], no such adaptation exists in Romania (or Eastern Europe), particularly for teachers. Adapting interventions to the cultural and institutional context seems vital, given that a recent qualitative analysis suggests that participants tend to criticize many interventions for their mismatch with the context in which they are conducted, possibly as a rationale for resisting change [12].

The primary goal of this research line is to design and test an intervention that is geared toward Romanian teachers. Importantly, we plan to achieve this goal by deliberately taking into account specific cultural and institutional characteristics, rather than indiscriminately applying previous intervention strategies. More specifically, although we plan to use education and contact as primary training elements, consistent with meta-analytic findings [9], we plan to design the educational components to respond to the needs of our particular target group. For example, we drew from recent research conducted in Russia [13], a country with a similar culture and history regarding LGBT+ attitudes. Building on these findings, we propose that the educational component should include information regarding the biological (vs social) causes of homosexuality, given that attributions of causality are related to perceived threat, and subsequently lead to biased outcomes. In addition, given the importance of threat in predicting antigay bias, and consistent with intergroup threat theory [14], education should explicitly address potential feelings or perceptions of threat (for example, the perception that exposure to LGBT+ people will "make" children gay).

A second novel aspect is that the intervention will aim not only to improve attitudes and knowledge as an outcome but also target behavioral change by imparting tools that teachers can use to address LGBT+-related victimization in schools. This strategy has been used successfully in the past in a web-based intervention program for Brazilian health practitioners [11]. As a result, we are likely to increase the impact of the intervention of LGBT+ students, not only by improving the inclusion climate within the schools but also by improving teachers' actual behavioral intentions and skills that may improve LGBT+ students' outcomes.

Aims and Hypotheses

In this research, we design and report the protocol of a randomized controlled trial (RCT) intervention and evaluation. The intervention is based on existing evidence about the efficacy of strategies identified in Bartoş et al's [9] meta-analysis. According to their results, the most effective strategies in reducing LGBT+ stigma combine educational elements with contact with LGBT+ people. We also add elements that were found to be useful in other bias-reducing interventions such as perspective taking [15] and self-efficacy [16,17], and which we deem culturally appropriate. A summary of intervention components, subcomponents, and contents is presented in Table 1. For each element, we include the supporting reference, as an evidence base for their efficiency in reducing bias.

Using an RCT in which teachers are randomly assigned to complete the intervention before assessing outcomes (experimental) or after assessing outcomes (control), we predict that the intervention will have a positive effect on attitudinal, cognitive, behavioral, and affective measures of LGBT+ bias among teachers. Specifically, we predict that teachers randomly assigned to the experimental condition, compared to those randomly assigned to the control condition will experience (1) more positive attitudes toward LGBT+ individuals, (2) more factual knowledge about LGBT+ issues, (3) stronger behavioral intentions and self-efficacy about addressing LGBT+ issues in the classroom, and (4) more positive affect toward LGBT+ individuals.

Table 1. Training elements for the randomized controlled trial intervention designed to improve Romanian teachers' LGBT+[a] related attitudes, cognitions, behaviors, and affect[b].

Intervention component and subcomponent	Duration and timestamps	Content and supporting references
Introduction	• Duration: 02 minutes 50 seconds • Timestamps: 00.00-02.50	Introduction from academic research team, highlighting the goals and the evidence-based nature of the intervention
Education [9]		
Definition of terms	• Duration: 05 minutes 40 seconds • Timestamps: 02.50-08.30	• Definition of LGBT+ terms • Definition of sexual orientation • Differentiation between sex versus gender • Definition of intersex • Description of gender identity and transgender
Threat reduction	• Duration: 03 minutes 40 seconds • Timestamps: 08.30-12.10	• LGBT+ children and their families: meta-analysis on children raised by LGBT+ families • Sexuality and sexual orientation in humans and animals. • Normalizing varied sexual orientations across species • The function of same-sex sexual behavior in ensuring survival
Effects of stigma to understand minority stress [1]	• Duration: 05 minutes 35 seconds • Timestamps: 12.10-17.45	• Suicide rates of LGBT+ youth • The role of stress from exposure to prejudice, ridicule, physical, and verbal aggression in understanding mental health outcomes • The role of social support and family or school acceptance in improving mental health and the danger of conversion therapy • Bullying as a special case of discrimination, types of bullying, the role of sexual orientation
Behavioral tools [11]	• Duration: 04 minutes 00 second • Timestamps: 24.45-28.45	• Presentation of tools that can be used by teachers, including the following: • Romania's new antibullying law and bullying protocol in schools • Lesson plans to discuss and combat bullying in the classroom • UNICEF[c] intervention model for bullying • Procedure to report bullying and harassment with the Romanian National Council for Combating Discrimination • Support groups for LGBT+ students in Romania • For all resources links were shared in the presentation and then sent in PDF format to all participants
Perspective taking [15]		
Writing exercise, 7 minutes	• Duration: 07 minutes 00 second • Timestamps: 17.45-24.45	• Writing prompt: "Imagine a day in the life of a gay student—write a few paragraphs about what this student is living and feeling on a school day. What are his/her thoughts and feelings that day? Please write down your answers."
Contact [9,10]		

Intervention component and subcomponent	Duration and timestamps	Content and supporting references
Indirect contact via recorded testimonials	• Duration: 15 minutes 00 second • Timestamps: 28.45-43:45	• Video testimonials of 3 university students (1 gay man, 1 bisexual woman, and a lesbian woman) and 1 teacher (lesbian woman). • Testimonial prompts for students included the following: • Tell us about yourself • When did you come out? What were your barriers during this process • How was your experience in school? Were there teachers who supported you? • What would you have needed when you were a high school student? • What would you say to teachers to help them support their LGBT+ students? • Testimonial prompts for the teacher included the following: • Tell us about yourself • How do you see LGBT+ students' experiences in schools currently? • What is missing from our educational system in supporting LGBT+ students? • What would you say to teachers to help them support their LGBT+ students?
Self-efficacy		
Writing exercise, 5 minutes	• Duration: 5 minutes 00 second • Timestamps: 43.45-48:45	• Writing prompt: "Imagine now that, as a teacher, you are interacting with the student you previously imagined. For example, the student asks for your help in a discussion after class. Knowing what you know now about the LGBT+ community and how we can help LGBT+ students, please imagine this interaction in which you offer suggestions and support. What would you say to this student? Please write down your answers."
Conclusion	• Duration: 1 minutes 10 seconds • Timestamps: 48.45-49:55	• Acknowledging the advisory board representatives from the LGBT+ community for their input and feedback

[a]LGBT+: lesbian, gay, bisexual, and transgender people. The "+" symbol represents individuals whose identities do not fit typical binary notions of male and female (nonbinary).

[b]All intervention elements are drawn from empirical evidence. We present timestamps and specific content which is included in the multimedia intervention resource.

[c]UNICEF: United Nations Children's Fund.

Methods

Participants and Recruitment

We plan to collect data exclusively from teachers or counselors working in Romanian public schools. All participants will be required to speak Romanian because of the language used in the intervention and measures. Participants who complete the intervention will be sent a participation certificate which could be used for continuing education credits and are given the option to enter a raffle where they can win a 500 RON (equivalent to US $110) gift certificate.

Our recruitment strategy is to ask the local Center for Educational Resources and Assistance to distribute a message nationally, to all their members who are teachers or counselors employed in Romanian schools. If interested, they have the opportunity to sign up for 1 of the several sessions depending on their availability. The sessions are capped at 30, with an average of 25 participants signing up for each (range 24-27). We will advertise a total of 17 sessions across 3 months at different times during the day.

Study Design

This intervention's experimental design is an RCT. We use a 2-group random assignment design, such that participants are randomly assigned to either the experimental condition in which they receive the intervention first and then complete the outcome measures, or to a control condition in which they complete the outcome measures first and then receive the intervention. From an ethical perspective, we chose this design so that all participants will receive the intervention and associated resources by the end of their participation. From a validity perspective, the outcome measures of those in the control condition are not affected by the intervention, thus serving as an appropriate control comparison to participants in the experimental condition.

Participants will join sessions in groups of up to 30 participants, depending on their availability. Cluster randomization will be

done at the session level, such that each session will be randomly assigned to either experimental or control conditions. Individual randomization within the session is not possible given that the intervention will be presented to all participants at the same time. Sessions will be scheduled across different times and days outside typical working hours, so we do not anticipate any systematic biases arising from participants' session choices. To ensure experimental control, each session will be led by 2 researchers who deliver scripted instructions, answer questions, and ensure all participants complete the study at a similar pace and with minimal distraction.

Intervention

The intervention is designed for internet-based delivery and is multimedia, containing a recorded presentation, animations, testimonials of LGBT+ people, as well as 2 exercises. Whereas the intervention is rooted in empirical evidence, we also ensured cultural sensitivity by collaborating with local LGBT+ educational and advocacy nongovernmental organizations who offered feedback on intervention components. A detailed summary of the evidence-based components, as well as timestamps and duration for each subcomponent, are included in Table 1.

Ethical Considerations

Ethics approval was obtained from the West University of Timisoara, Romania, ethical panel (74505/10.11.2022), based on an application containing the procedure, measures, and materials used. Upon being presented with detailed information regarding the study, informed consent will be obtained from all participants before starting their participation. All data will be anonymously collected, with no personal or identifiable information being recorded. All fully anonymous data will be stored on password-protected computers and servers. Compensation consists of a participation certificate which could be used for continuing education credits and the option to enter a raffle where they can win a 500 RON (equivalent to US $110) gift certificate. There is no identification of individual participants in any images within the paper.

Outcomes

Overview

With 1 exception (the factual knowledge variable), we will use validated scales to measure intervention outcomes. Where possible, we will use previously translated and validated scales in Romanian, selected from ResearchCentral repository, a free internet-based platform dedicated to the development of Romanian psychology by providing researchers with free, validated assessment tools. Where translations did not previously exist, 2 Romanian researchers, who are fluent in English, translated and then back-translated the scales to ensure accuracy. For all scales, before computing a final score, we will ensure sufficient reliability by computing Cronbach α, with a cutoff minimal score of 0.70.

Attitudinal

Overview

Given the wide divergence in the definition of antigay bias or homophobia, several scales have been developed across time [18] and will be used in this research.

Attitudes Toward Lesbians and Gay Men Scale

This 10-item scale measures beliefs and attitudes toward gay men and lesbians ("Sex between two men is just plain wrong" and "Female homosexuality is a perversion") [19]. Items are rated on a Likert scale from 1 (strongly disagree) to 5 (strongly agree). After reverse coding 4 items, scores will be averaged into a final score with higher values denoting more negative attitudes.

Homophobia Scale

This 25-item scale measures attitudes but also social avoidance and aggression toward gay people ("If I discovered a friend was gay I would end the friendship" and "I tease and make jokes about gay people") [20]. Items are rated from 1 (strongly disagree) to 5 (strongly agree) on a Likert scale. After reverse coding 9 items, scores will be averaged into a final score with higher values denoting more negative attitudes.

Attitudes Toward Homosexuals Scale

This 12-item scale measures attitudes toward gay people ("Homosexuality is disgusting in the eyes of God" and "If I can, I prefer to not be in the company of homosexuals") [21]. Items are rated from 1 (strongly disagree) to 5 (strongly agree) Likert scale. After reverse coding 5 items, scores will be averaged into a final score with higher values denoting more negative attitudes.

Behavioral

Behavioral Intentions

This 16-item scale measures intentions for supportive professional behaviors that teachers would perform in the classroom ("I would talk with a student about questions regarding sexual orientation" and "I would have books about gay and lesbian issues in my classroom") [22,23]. Items are rated on a Likert scale from 1 (strongly disagree) to 5 (strongly agree). Scores will be averaged into a final score with higher values denoting more willingness to engage in LGBT+ supportive behaviors in the classroom.

Self-Efficacy

This 10-item scale adapted the original scale to working with LGBT+ students in the school context ("If I try hard, I can solve difficult issues related to LGBT+ students" and "I can deal with unexpected situations that arise with LGBT+ students") [24]. Items were rated from 1 (Not at all true for me) to 4 (Perfectly true for me). Scores will be averaged into a final score with higher values denoting more self-efficacy in dealing with LGBT+-related behaviors in the classroom.

Cognitive: Factual Knowledge About LGBT+ Issues

We constructed 7 items based on training content to assess participants' knowledge about LGBT+ issues ("Gender is a biological construct, unrelated to cultural associations" and "Heterosexual youth are 1.5 to 3 times more likely to attempt

suicide compared to LGBT+ youth"). Items are rated as true or false, and a final score will be computed by adding up the number of correct responses, with higher scores denoting more knowledge about LGBT+ issues.

Affective

Feeling Thermometer (1 Item Each for Gay, Lesbian, and Bisexual)

We will use a feeling thermometer [25] to assess participants' feelings toward gay, lesbian, and bisexual people by asking them to rate how they feel about each group using a slider thermometer scale from 0 (very negative feeling) to 100 (very positive feeling).

Perspective Taking

This 5-item measure assesses the extent to which participants take the perspective of LGBT+ people ("Can you imagine how an LGBT+ person feels?" and "Do you have an understanding of issues that are important for LGBT+ people") on a scale from 1 (Never) to 5 (All the time) [26]. Scores will be computed by averaging the 5 items, with higher final scores denoting more perspective-taking.

Intergroup Disgust Sensitivity

We adapted this 7-item scale to measure repulsion toward LGBT+ groups ("I feel disgusted when people with a different sexual orientation invade my personal space" and "After shaking hands with someone who has a different sexual orientation, even if their hands were clean, I would want to wash my hands.") [27]. Items are rated from 1 (strongly disagree) to 5 (strongly agree) on a Likert scale. After reverse scoring 1 item, scores will be averaged into a final score with higher values denoting more disgust toward LGBT+ outgroups.

Intergroup Anxiety

This 10-item scale measures anxiety-related emotions when interacting with people of another sexual orientation by asking them to rate their likelihood of feeling several emotions (embarrassed, unsure, irritated, suspicious, etc) on a scale from 1 (not at all) to 10 (extremely) [28]. A total of 2 scores will be computed, 1 for positive emotions and another for negative emotions.

Toronto Empathy Questionnaire

This 16-item scale measures the general tendency to empathize with other people ("It upsets me to see someone being treated disrespectfully" and "I find that I am 'in tune' with other people's moods") [29,30]. Items are rated on a Likert scale from 1 (strongly disagree) to 5 (strongly agree). After reverse scoring 7 items, scores will be averaged into a final score with higher values denoting more empathy.

Demographic and Control Variables

Demographics

It consists of age, gender, and sexual orientation.

Contact With LGBT+ People

We will ask participants how often they have contact (eg, talk) with a gay man, a lesbian woman, a bisexual woman or man, or a transgender person on a scale from 1 (almost daily) to 6 (never).

Religiosity

Religiosity (Duke University Religion Index) [31] is a 5-item scale measure of religious involvement, measuring organizational religious activity, nonorganizational religious activity, and intrinsic religiosity (or subjective religiosity). Responses are averaged in 1 single score with higher scores denoting more religiosity.

Ideology

Ideology was measured by asking people to indicate their political orientation on a 100-point sliding scale from 0 (very conservative) to 50 (center) to 100 (very liberal or progressive).

Statistical Analysis

Power

To determine our sample size, we conducted a power analysis using an average effect size of d=0.66 computed from Bartoş et al's [9] meta-analysis to ensure a statistical power of 0.80. The analysis indicated a sample of 122, but we aim to overrecruit, if possible, up to 200 participants given multiple outcomes. We do not have a stopping rule—we will recruit until all interested participants are given the chance to participate within 1 of the 17 sessions posted.

Data Exclusion

We will use data from all participants who completed their participation in the study, without any exclusions. Before computing final scores for each outcome variable, we will ensure sufficient reliability using Cronbach α, using a threshold of 0.70. To test our hypotheses, we will perform a series of 1-way between-subjects ANOVAs to compare attitudinal, cognitive, behavioral, and affective outcomes between the participants in the experimental and control conditions. For the effective measures we will perform the analyses (1) while controlling for contact with LBGT+ individuals and (2) separately by LGBT+ status (given the nature of the measures). We will report F test and P values, as well as all descriptive statistics (n, mean, and SD). We will also compute Cohen d for estimating the effect size, using means and SDs. Violin plots in R ggplot2 will also be included to visually represent means, CIs, as well as score distributions for each outcome.

Results

This paper details the protocol for the teacher intervention study. Data collection began in December 2022 and was completed by February 2023. Data analysis will be performed upon protocol acceptance. Follow-up measures will be completed in 2024. Results are expected to be submitted for publication following analysis in the spring of 2024.

Discussion

This paper describes the research protocol design and planned evaluation of an RCT aimed at improving attitudinal, cognitive, behavioral, and affective outcomes in Romanian teachers regarding LGBT+ inclusion. Strengths of the intervention

include its evidence-based nature—all components included were derived from research showing positive outcomes on LGBT+ or other bias reduction. All elements were, however, adapted to be appropriate and sensitive to the Romanian cultural system and educational context. The intervention was also engaging and multimedia, thus increasing engagement. Importantly, it offers evidence-based tools to further address LGBT+ biases and bullying in schools, thus, potentially leading to stronger behavioral effects.

Limitations include the fact that outcomes will be assessed immediately after the intervention, so we are unsure about the long-term effects, as well as whether potential positive effects further impact LGBT+ students' lives. Further studies should investigate the effects on a larger sample of teachers, with a wider range of initial attitudes toward LGBT+ inclusion.

If successful, however, the intervention has the potential of becoming a valuable, nationally available resource for teachers and high school counselors across Romania. The materials developed, especially those around education, perspective-taking, and self-efficacy can be further used to educate students about LGBT+ issues and increase their willingness and capacity to support LGBT+ peers. The findings resulting from this protocol are important, as they are the first to test the effectiveness of an evidence-based intervention in improving LGBT+ stigma in Romanian schools.

Acknowledgments

The research leading to these results has received funding from the Norway grants 2014-2021 (17⁄2020). The authors thank Sebastian Bartos, Lavinia Chirica, and Andre Rădulescu for their advice and assistance in developing the intervention.

Data Availability

The data sets generated and analyzed during this study will be published in anonymous form on Open Science Framework and the European Commission Funded Research (OpenAire) community platform. This will be done after the successful publication of the results.

Conflicts of Interest

None declared.

References

1. Meyer IH. Prejudice, social stress, and mental health in lesbian, gay, and bisexual populations: conceptual issues and research evidence. Psychol Bull 2003;129(5):674-697 [FREE Full text] [doi: 10.1037/0033-2909.129.5.674] [Medline: 12956539]
2. EU-LGBTI II: a long way to go for LGBTI equality. European Union Agency for Fundamental Rights. 2020. URL: https://fra.europa.eu/sites/default/files/fra_uploads/fra-2020-lgbti-equality-1_en.pdf [accessed 2024-03-15]
3. Behind the Numbers: Ending School Violence and Bullying. Paris: United Nations Educational, Scientific and Cultural Organization; 2020.
4. di Giacomo E, Krausz M, Colmegna F, Aspesi F, Clerici M. Estimating the risk of attempted suicide among sexual minority youths: a systematic review and meta-analysis. JAMA Pediatr 2018;172(12):1145-1152 [FREE Full text] [doi: 10.1001/jamapediatrics.2018.2731] [Medline: 30304350]
5. Oswalt SB, Wyatt TJ. Sexual orientation and differences in mental health, stress, and academic performance in a national sample of U.S. college students. J Homosex 2011;58(9):1255-1280. [doi: 10.1080/00918369.2011.605738] [Medline: 21957858]
6. Plöderl M, Tremblay P. Mental health of sexual minorities. A systematic review. Int Rev Psychiatry 2015;27(5):367-385. [doi: 10.3109/09540261.2015.1083949] [Medline: 26552495]
7. Lick DJ, Durso LE, Johnson KL. Minority stress and physical health among sexual minorities. Perspect Psychol Sci 2013;8(5):521-548. [doi: 10.1177/1745691613497965] [Medline: 26173210]
8. Fedewa AL, Ahn S. The effects of bullying and peer victimization on sexual-minority and heterosexual youths: a quantitative meta-analysis of the literature. J GLBT Fam Stud 2011;7(4):398-418. [doi: 10.1080/1550428x.2011.592968]
9. Bartoş SE, Berger I, Hegarty P. Interventions to reduce sexual prejudice: a study-space analysis and meta-analytic review. J Sex Res 2014;51(4):363-382. [doi: 10.1080/00224499.2013.871625] [Medline: 24754358]
10. West K. Understanding and reducing sexual prejudice in Jamaica: theoretical and practical insights from a severely anti-gay society. J Sex Res 2018;55(4-5):472-485. [doi: 10.1080/00224499.2017.1416055] [Medline: 29411998]
11. Costa AB, Pase PF, de Camargo ES, Guaranha C, Caetano AH, Kveller D, et al. Effectiveness of a multidimensional web-based intervention program to change Brazilian health practitioners' attitudes toward the lesbian, gay, bisexual and transgender population. J Health Psychol 2016;21(3):356-368. [doi: 10.1177/1359105316628748] [Medline: 26987830]
12. Barto SE, Hegarty P. Negotiating theory when doing practice: a systematic review of qualitative research on interventions to reduce homophobia. J Homosex 2019;66(9):1262-1286. [doi: 10.1080/00918369.2018.1500780] [Medline: 30095380]

13. Gulevich OA, Osin EN, Isaenko NA, Brainis LM. Scrutinizing homophobia: a model of perception of homosexuals in Russia. J Homosex 2018;65(13):1838-1866. [doi: 10.1080/00918369.2017.1391017] [Medline: 29016250]
14. Stephan WG, Renfro CL, Davis MD. The role of threat in intergroup relations. In: Wagner U, Tropp LR, Finchilescu G, Tredoux C, editors. Improving Intergroup Relations: Building on the Legacy of Thomas F. Pettigrew. Oxford: Blackwell Publishing; 2008:55-72.
15. Tompkins TL, Shields CN, Hillman KM, White K. Reducing stigma toward the transgender community: an evaluation of a humanizing and perspective-taking intervention. Psychol Sex Orientat Gend Divers 2015;2(1):34-42. [doi: 10.1037/sgd0000088]
16. van Zomeren M, Postmes T, Spears R. Toward an integrative social identity model of collective action: a quantitative research synthesis of three socio-psychological perspectives. Psychol Bull 2008;134(4):504-535 [FREE Full text] [doi: 10.1037/0033-2909.134.4.504] [Medline: 18605818]
17. Stewart TL, Latu IM, Branscombe NR, Denney HT. Yes we can!: prejudice reduction through seeing (inequality) and believing (in social change). Psychol Sci 2010;21(11):1557-1562. [doi: 10.1177/0956797610385354] [Medline: 20889931]
18. Costa AB, Bandeira DR, Nardi HC. Systematic review of instruments measuring homophobia and related constructs. J Applied Social Pyschol 2013;43(6):1324-1332. [doi: 10.1111/jasp.12140]
19. Herek GM, MCLemore KA. Attitudes toward lesbiansgay men scale. In: Fisher TD, Davis CM, Yarber WL, Davis SL, editors. Handbook of Sexuality-Related Measures, 2nd Edition. New York: Sage Publications; 1998:392-394.
20. Wright LW, Adams HE, Bernat J. Development and validation of the homophobia scale. J Psychopathol Behav Assess 1999;21:337-347. [doi: 10.1023/A:1022172816258]
21. Altemeyer B. Enemies of Freedom: Understanding Right-Wing Authoritarianism. San Francisco: Jossey-Bass; 1988.
22. Riggs AD, Rosenthal AR, Smith-Bonahue T. The impact of a combined cognitive–affective intervention on pre-service teachers' attitudes, knowledge, and anticipated professional behaviors regarding homosexuality and gay and lesbian issues. Teach Teach Educ 2011;27(1):201-209. [doi: 10.1016/j.tate.2010.08.002]
23. Bailey NJ. Attitudes/feelings, knowledge, and anticipated professional behaviors of middle level teachers regarding homosexuality and gay and lesbian issues as they relate to middle level students. University of Northern Colorado. 1996. URL: https://www.unco.edu/ [accessed 2024-03-15]
24. Jerusalem M, Schwarzer R. Self-efficacy as a resource factor in stress appraisal processes. In: Schwarzer R, editor. Self-Efficacy: Thought Control of Action. Washington, DC: Hemisphere; 1992:195-213.
25. Nelson SC. Feeling thermometer. In: Lavrakas PJ, editor. Encyclopedia of Survey Research Methods. Thousand Oaks, California: Sage Publications; 2008:275-277.
26. Dessel AB. Measuring the effects of intergroup dialogue on teachers' attitudes, feelings and behaviors regarding lesbian, gay and bisexual students and parents. University of Tennessee. 2008. URL: https://trace.tennessee.edu/utk_graddiss/426/ [accessed 2024-03-15]
27. Hodson G, Choma BL, Boisvert J, Hafer CL, MacInnis CC, Costello K. The role of intergroup disgust in predicting negative outgroup evaluations. J Exp Soc Psychol 2013;49(2):195-205. [doi: 10.1016/j.jesp.2012.11.002]
28. Stephan WG, Stephan CW. Intergroup anxiety. J Soc Issues 1985;41(3):157-175. [doi: 10.1111/j.1540-4560.1985.tb01134.x]
29. Spreng RN, McKinnon MC, Mar RA, Levine B. The Toronto empathy questionnaire: scale development and initial validation of a factor-analytic solution to multiple empathy measures. J Pers Assess 2009;91(1):62-71 [FREE Full text] [doi: 10.1080/00223890802484381] [Medline: 19085285]
30. Ursoniu S, Serban CL, Giurgi-Oncu C, Rivis IA, Bucur A, Bredicean AC, et al. Validation of the Romanian version of the Toronto Empathy Questionnaire (TEQ) among undergraduate medical students. Int J Environ Res Public Health 2021;18(24):12871 [FREE Full text] [doi: 10.3390/ijerph182412871] [Medline: 34948481]
31. Koenig HG, Büssing A. The Duke University Religion Index (DUREL): a five-item measure for use in epidemological studies. Religions 2010;1(1):78-85 [FREE Full text] [doi: 10.3390/rel1010078]

Abbreviations

LGBT+: lesbian, gay, bisexual, and transgender people. The "+" symbol represents individuals whose identities do not fit typical binary notions of male and female (nonbinary)
RCT: randomized controlled trial
UNESCO: The United Nations Educational, Scientific and Cultural Organization

Edited by A Mavragani; submitted 02.11.23; peer-reviewed by J Rendina, J Xu; comments to author 05.02.24; revised version received 07.02.24; accepted 04.03.24; published 23.04.24.

Please cite as:
Latu I, Sălăgean N, Larsen TMB, Isbasoiu AB, Sava FA
Testing the Effectiveness of an Intervention to Improve Romanian Teachers' LGBT+-Related Attitudes, Cognitions, Behaviors, and Affect: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2024;13:e54254
URL: https://www.researchprotocols.org/2024/1/e54254
doi:10.2196/54254
PMID:38652533

Protocol

An Integrated mHealth App for Smoking Cessation in Black Smokers With HIV: Protocol for a Randomized Controlled Trial

Andre Bizier[1], BS; Arielle Jones[1], BS; Michael Businelle[2,3], PhD; Krista Kezbers[2], PhD; Bettina B Hoeppner[4,5], PhD; Thomas P Giordano[6], MD, MPH; Jessica M Thai[1], BSc; Jacqueline Charles[1], MA; Audrey Montgomery[2], MEd; Matthew W Gallagher[1,7,8], PhD; Marshall K Cheney[9], PhD; Michael Zvolensky[1,7,10], PhD; Lorra Garey[1,7], PhD

[1]University of Houston, Houston, TX, United States

[2]TSET Health Promotion Research Center, Stephenson Cancer Center, Oklahoma City, OK, United States

[3]Department of Family and Preventive Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK, United States

[4]Massachusetts General Hospital, Boston, MA, United States

[5]Harvard Medical School, Boston, MA, United States

[6]Baylor College of Medicine, Houston, TX, United States

[7]HEALTH Institute, Houston, TX, United States

[8]Texas Institute for Measurement, Evaluation, and Statistics, Houston, TX, United States

[9]Department of Health and Exercise Science, University of Oklahoma, Norman, OK, United States

[10]The University of Texas MD Anderson Cancer Center, Houston, TX, United States

Corresponding Author:
Lorra Garey, PhD
University of Houston
3695 Cullen Blvd, Fred J. Heyne Building, Suite 126
Houston, TX
United States
Phone: 1 7137438056
Email: llgarey@uh.edu

Abstract

Background: Black adults who smoke and have HIV experience immense stressors (eg, racial discrimination and HIV stigma) that impede smoking cessation success and perpetuate smoking-related health disparities. These stressors also place Black adults who smoke and have HIV at an increased risk of elevated interoceptive stress (eg, anxiety and uncomfortable bodily sensations) and smoking to manage symptoms. In turn, this population is more likely to smoke to manage interoceptive stress, which contributes to worse HIV-related outcomes in this group. However, no specialized treatment exists to address smoking cessation, interoceptive stress, and HIV management for Black smokers with HIV.

Objective: This study aims to test a culturally adapted and novel mobile intervention that targets combustible cigarette smoking, HIV treatment engagement and adherence, and anxiety sensitivity (a proxy for difficulty and responsivity to interoceptive stress) among Black smokers with HIV (ie, Mobile Anxiety Sensitivity Program for Smoking and HIV [MASP+]). Various culturally tailored components of the app are being evaluated for their ability to help users quit smoking, manage physiological stress, and improve health care management.

Methods: This study is a pilot randomized controlled trial in which Black combustible cigarette smokers with HIV (N=72) are being recruited and randomly assigned to use either (1) the National Cancer Institute's QuitGuide app or (2) MASP+. Study procedures include a web-based prescreener; active intervention period for 6 weeks; smartphone-based assessments, including daily app-based ecological momentary assessments for 6 weeks (4 ecological momentary assessments each day); a video-based qualitative interview using Zoom Video Communications software at week 6 for participants in all study conditions; and smartphone-based follow-up assessments at 0, 1, 2 (quit date), 3, 4, 5, 6, and 28 weeks postbaseline (26 weeks postquitting date).

Results: Primary outcomes include biochemically verified 7-day point prevalence of abstinence, HIV-related quality of life, use of antiretroviral therapy, and HIV care appointment adherence at 26 weeks postquitting date. Qualitative data are also being collected and assessed to obtain feedback that will guide further tailoring of app content and evaluation of efficacy.

Conclusions: The results of this study will determine whether the MASP+ app serves as a successful aid for combustible cigarette smoking cessation, HIV treatment engagement, and physiological stress outcomes among Black people with HIV

infection. If successful, this study will provide evidence for the efficacy of a new means of addressing major mental and physical health difficulties for this high-risk population. If the results are promising, the data from this study will be used to update and tailor the MASP+ app for testing in a fully powered randomized controlled trial that will evaluate its efficacy in real-world behavioral health and social service settings.

Trial Registration: ClinicalTrials.gov NCT05709002; https://clinicaltrials.gov/study/NCT05709002

International Registered Report Identifier (IRRID): PRR1-10.2196/52090

(JMIR Res Protoc 2024;13:e52090) doi:10.2196/52090

KEYWORDS

smoking cessation; Black; HIV; anxiety sensitivity; mobile health; mHealth; just-in-time adaptive intervention; mobile phone

Introduction

Background

People with HIV/AIDS smoke at a rate 3 times higher (33.6% vs 12.5%) than that of the general population [1,2]. This group is also less likely to quit smoking and is more susceptible to the harmful effects of smoking (eg, increased risk for cancer and lung disease) [1,3,4], likely due to the combined impact of several social determinants of health, including behavioral risk factors, limited resources, and diminished access to health care, as well as immune system dysfunction and chronic inflammation caused by HIV [5-10]. Indeed, cigarette smoking is a leading risk factor for HIV-related and non–HIV-related morbidity and mortality among people with HIV/AIDS [11,12], even among those taking antiretroviral medications [13], and contributes to more life-years lost than HIV-related complications among those effectively treated with antiretroviral therapy (ART) [13-15]. Furthermore, people with HIV/AIDS who smoke are less adherent to ART than nonsmokers and experience poorer viral and immunologic responses to ART [16,17], a greater risk of virologic rebound, and more frequent immunologic failure [18].

Among people with HIV/AIDS who smoke, those who identify as members of a racial minority group are at an elevated risk for negative health consequences of smoking and poorer HIV-related outcomes. Evidence suggests that Black adults with HIV, in particular, experience high rates of discrimination and stigma that lead to the onset and maintenance of maladaptive coping, including smoking [19,20]. Consistent with these data, Black adults with HIV are more likely to smoke [4], less likely to quit [4,21-24], and experience greater quit difficulty when attempting to quit than White smokers or smokers without HIV [21]. Black adults with HIV also have lower rates of compliance with routine HIV care (ie, ART adherence), retention in long-term care, and are less likely to be virally suppressed relative to other groups [25-28]. This is a public health problem because Black adults account for the highest proportion (42%) of new HIV diagnoses and experience higher mortality than White adults with HIV [25,27,28]. From an intersectional stigma and discrimination perspective and socioecological models of social determinants of health [29,30], Black adults who smoke and have HIV may be at elevated risk for worse HIV disease management and smoking outcomes and ultimately experience increased health disparities [6].

Emotional models of coping suggest that Black adults with HIV may smoke and continue to smoke despite health problems to manage interoceptive stress and uncomfortable physiological arousal associated with minority status stressors such as racial discrimination and HIV-related stigma. Anxiety sensitivity (AS) is one of the most noteworthy constructs related to physiological distress and manifestations of elevated internal distress, including psychopathologies. AS refers to the fear of anxiety or anxiety-related symptoms [31]. AS amplifies negative mood states via enhanced threat perception (eg anxiety) [32,33], contributing to the development of anxiety and depressive problems [34]. Notably, anxiety and depression contribute to an increased likelihood of poor ART adherence [35]. Among people with HIV/AIDS, AS is related to more severe social anxiety symptoms, anxious arousal symptoms, HIV-related stigma, and HIV symptom distress [36,37]. AS has also been implicated as a contributing factor in smoking initiation, maintenance, and relapse [38,39]. Emerging data indicate that AS is elevated in both Black adults who smoke and people with HIV/AIDS who smoke [40], placing this group at greater odds of early lapse and relapse [41,42]. Without appropriate interventions to address susceptibility to the negative impact of interoceptive stress, Black adults with HIV who smoke and have elevated AS may be inclined to return to smoking to alleviate abstinence-induced increases in anxiety and to manage uncomfortable HIV-related bodily symptoms that may increase with smoking cessation.

Although smoking cessation treatments that target AS exist, they are limited in their reach, adaptability, and potential for adoption and do not consider critical barriers to smoking cessation or HIV treatment engagement and adherence. For example, current combined AS and smoking treatments focus primarily on multisession, intensive treatments, particularly those that rely on in-person, clinician-administered psychosocial protocols [43-46]. Participation in these treatments often requires notable time commitments, practical limitations, and expense [47]. Such burdens are barriers to treatment and may contribute to the low treatment participation rates [47]. An additional limitation of current treatments is that no readily available smoking cessation treatments that target AS integrate information to improve HIV treatment engagement and adherence. Given the robust evidence that targeting AS and promoting smoking cessation may lead to improved HIV outcomes, this is a major limitation. Finally, the required human resources, specialized training, and financial support that are needed to administer currently available combined AS and

smoking treatments discourage the adoption of these treatments in communities most in need, such as those that serve Black adults with HIV who smoke. Therefore, it is essential to develop a digital AS intervention that can be culturally adapted for this population.

Objectives

On the basis of our prior work [48], we modified our previously developed and tested novel, integrated, smartphone-delivered intervention for AS reduction and smoking (ie, Mobile Anxiety Sensitivity Program [MASP]) [49] for Black people with HIV/AIDS who smoke, integrating HIV information and care support that is culturally tailored to create the new smartphone-based app: Mobile Anxiety Sensitivity Program for Smoking and HIV (MASP+). MASP+ contains features and content designed to aid Black adults with combustible smoking cessation, HIV care adherence, and AS reduction. The initial efficacy of MASP+ relative to an established control intervention, the National Cancer Institute's (NCI) QuitGuide app, on combustible cigarette smoking cessation, HIV-related outcomes, and AS reduction is currently being tested in a pilot randomized controlled trial (RCT). We expect that MASP+ participants will report greater biochemically confirmed smoking abstinence at 26 weeks postquitting date relative to the QuitGuide group. In addition, we hypothesize that MASP+ participants will report greater HIV-specific quality of life, ART adherence, and HIV treatment engagement at 26 weeks postquitting date relative to the QuitGuide group. Finally, we expect that improvement in AS will mediate the relationship between treatment and (1) smoking abstinence and (2) HIV-related outcomes and that daily experiences of discrimination (race and HIV) will moderate these relationships. We will also examine qualitative and quantitative data to guide the refinement and further adaptation of MASP+ and support the development of a high-quality, culturally relevant, and scalable intervention.

Methods

Ethical Consideration

The Institutional Review Board at the University of Houston (UH) approved the protocol presented in this study under STUDY00003811, whereas the University of Oklahoma Health Sciences Center and Baylor College of Medicine relied on the UH Institutional Review Board. This trial has been registered at ClinicalTrials.gov (NCT05709002; protocol ID: QKWEF8XLMTT3).

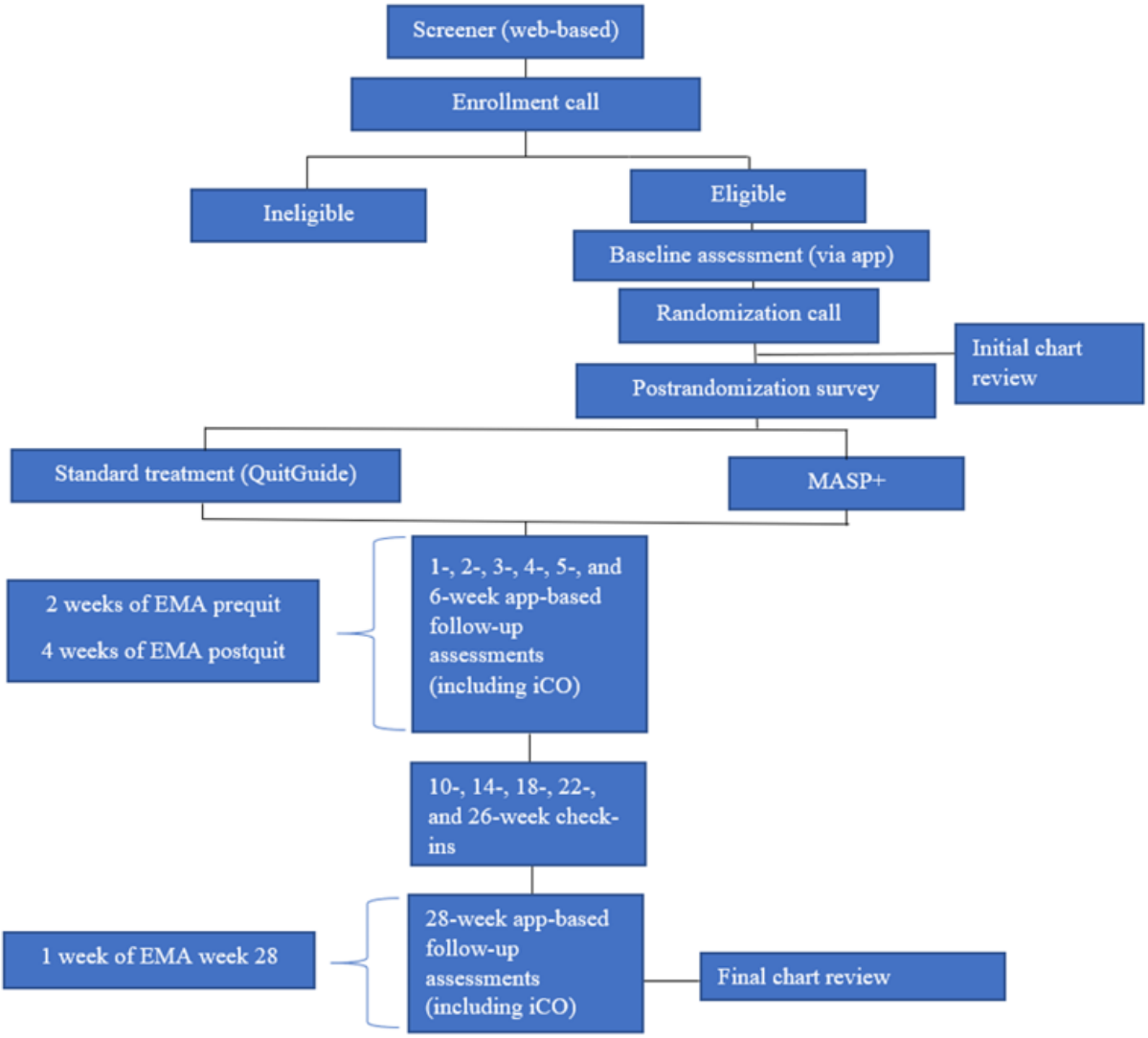
Study Eligibility

The study eligibility criteria included being aged ≥18 years, having HIV, self-identification as Black or African American, providing a current picture of their cigarette package to verify smoking status [48], possessing at least a grade 6 reading level (≥4 on the Rapid Estimate of Adult Literacy in Medicine [REALM]) [50], experiencing elevated AS (ie, Short Scale Anxiety Sensitivity Index [SSASI] score of ≥5) [51], reporting daily smoking with a minimum of 10 cigarettes per day for at least 2 years, being motivated to quit smoking (>5 on a 10-point scale) [52], willingness to complete all study surveys or assessments, agreeing to use nicotine replacement medications (nicotine replacement therapy [NRT]; nicotine patch and lozenges), and agreeing to attempt to quit smoking 2 weeks after the date of randomization. Exclusion criteria included not being fluent in English; high blood pressure that is not under control (eg, medicated); experiencing a heart attack (myocardial infarction) within the past 2 weeks; use of any pharmacotherapy targeting smoking cessation beyond what is provided by this study; legal status that would interfere with participation (eg, incarceration with restricted access to mobile devices); cognitive impairment (assessed via the 6-item Cognitive Impairment Test) [53]; and being non-Black, pregnant, or younger than 18 years.

Recruitment and Procedures

Participants are recruited via web-based advertisement materials, as well as physical materials placed throughout the city of Houston. Study materials provide contact information for UH if a potential participant has questions about the study. Study advertisements also include a QR code linked to a REDCap (Research Electronic Data Capture; Vanderbilt University) prescreener survey. Those who complete the prescreening are deemed either ineligible or pre-eligible. For those recruited from Thomas Street at Quentin Mease Health Center, a clinic in Houston that provides routine medical care to ≥5000 people with HIV/AIDS study team members at Thomas Street perform a chart review to confirm HIV status. Pre-eligible participants are then contacted to complete an enrollment call wherein they provide informed consent and complete the final eligibility screening for the study (refer to Figure 1 for the participant enrollment flowchart).

Figure 1. Mobile Anxiety Sensitivity Program for Smoking and HIV (MASP+) participant enrollment flowchart. Note: after initial eligibility screening, participants will complete an enrollment call, baseline survey, randomization call, postrandomization survey, 6-week ecological momentary assessment (EMA) period, monthly check-ins for 5 months, and a final survey and week of EMAs at week 28. iCO: iCarbon Monoxide.



Persons deemed eligible at the enrollment call download the Insight app onto their personal smartphone or study phone. The Insight app houses the MASP+ content and is used to administer smartphone-based surveys and ecological momentary assessments (EMAs) to all participants. The study smartphones are provided to those without a smartphone and those with a smartphone that is incompatible with the Insight platform. Insight is supported on most Android smartphones (Android versions 6.0-14.0). Participants with a personal phone that is incompatible with Insight are sent a study phone. For those using their personal smartphone, the study staff instruct participants on how to download the app onto their personal phone. Insight adjusts according to the font size selected by participants on their phones. Participants who experience issues reading text in the app due to font size are instructed to increase font size in the phone settings. Once Insight is downloaded, participants are given a unique single-use code that enables them to use the app to complete the baseline assessment, which must be completed within 6 days after inputting the code. If participants do not complete the baseline survey within 6 days, they are no longer eligible to participate in the study. All participants are mailed a baseline package that includes a Bedfont iCO (iCarbon Monoxide) quit smokerlyzer, a Greenphire Mastercard, and NRT. The Bedfont iCO is used to biochemically verify self-reported abstinence at follow-ups.

Upon completion of the baseline survey and receipt of the baseline package, the participants complete a randomization call with the study staff. During the randomization call, the participants are randomized to receive the MASP+ or QuitGuide interventions based on the randomization chart developed by the study statistician (MWG). Block randomization was used and stratified according to binary sex (assigned at birth). Variable-sized permuted block randomization (block sizes vary from 4 to 12) is used. Before data analyses, the balance of randomization will be checked and controlled for imbalanced factors by including any factors that differ between groups as covariates. The participants are provided with a unique code to access the app to which they are randomized. MASP+ participants have access to all MASP+ features (ie, Treatment Videos, Coping Toolkit, Quit Tips, and Stress Management Trainings) through the Insight platform. Participants randomized

to the control intervention (ie, QuitGuide) have access to limited features (ie, App Instructions, Payment Tracking, Call Staff, and Record Stress) through the Insight platform and receive intervention content (ie, Track My Craving, Manage My Mood, and Learn To Quit) through the QuitGuide app. Participants assigned to the control intervention receive assistance with downloading the QuitGuide app through the Google Play Store. Both intervention groups use the Insight app to complete the study assessments, which include the baseline survey, weekly follow-ups, the 28-week follow-up, and EMAs. Once the code is entered, the research staff orients the participant to the app features and the iCO carbon monoxide (CO) breath testing device. Participants have access to MASP+ or QuitGuide content through the final follow-up (ie, the 28-week follow-up). At the end of the randomization call, participants are directed to take a brief postrandomization survey, which must be completed within 6 days after the randomization call. Failure to complete the postrandomization survey within 6 days does not affect participants' status in the study.

Following randomization, the participants complete 4 daily EMAs for 6 weeks. Participants also complete app-based follow-up surveys each week of the treatment period (ie, weeks 1-6) and at 26 weeks postquitting date (28 weeks postbaseline). Between weeks 6 and 28, all participants are prompted to complete a brief check-in survey each month, which reminds them about available app features and assesses their current smoking status. The participants complete a final series of EMAs (4 per day) for 7 days before the 28-week follow-up assessment. The Insight app prompts daily EMAs and follow-up assessments for both treatment groups. In addition, participants complete a Zoom-based qualitative interview to assess their experience with the app and capture recommendations for improving app features and content at 6 weeks postrandomization. Participants who received loaned study smartphones are required to return them after their final follow-up assessment at week 28.

Compensation

Each participant who enrolls receives a Greenphire Mastercard gift card that is loaded with compensation for survey completion. Participants receive all compensation in USD. Participants receive US $30 for completing the baseline assessment and US $10 for completing the postrandomization survey. Participants receive US $10 for completing each weekly follow-up assessment at weeks 1, 2 (quit date), 3, 4, and 5 as well as 6 weeks postbaseline (including the app-based survey, iCO breath test, and Zoom-based qualitative interview at week 6 only). Participants receive US $50 for completing the 28-week follow-up assessment (via Insight) and iCO breath test. Participants are compensated at the end of week 6 for EMA completion during weeks 1 to 6 and at the end of week 28 for EMAs completed during week 28. Specifically, participants receive a total of US $60 for completing 50% to 74% of the brief EMAs (4 per day×7 days=28 weekly EMAs) prompted during weeks 1 to 6, US $90 for completing 75% to 89% of EMAs, or US $120 for completing ≥90% of EMAs. For week 28, participants will receive US $10 for completing 50% to 74% of the brief EMAs, US $15 for completing 75% to 89% of EMAs, or US $20 for completing ≥90% of EMAs. Participants can use the "Payment" and "Weekly Survey Payment" buttons on the app's home screen whenever desired to view an up-to-the-moment summary of EMAs presented and their current completion rate. Payments for completed EMAs are loaded onto participants' Greenphire cards following week 6 and week 28.

Study Conditions

Both Conditions

Given that clinical guidelines recommend that all smokers attempting to quit should receive and use pharmacotherapy [54], both MASP+ and QuitGuide participants are sent NRT with their baseline package. Transdermal nicotine patches and nicotine lozenges are provided for use during the first 4 weeks postquitting date, and each participant is given the option order up to 4 weeks of additional NRT. For those in the MASP+ condition, an additional NRT can be ordered by clicking a button on the app home screen, which sends an encrypted email to the study team informing them of NRT requests. For those in the QuitGuide condition, NRT orders are placed by calling the number provided to participants and speaking with a member of the study team (Figure 2). In a prior study, 66% of enrolled participants used a similar app button or feature to place NRT orders [55]. Patches and lozenges were chosen for use in this study because of their safety and effectiveness (especially in combination with NRT), ease of use, and relatively benign side effects compared to other forms of NRT [56,57].

Figure 2. Mobile Anxiety Sensitivity Program for Smoking and HIV (MASP+) app home screen. Note: app features include App Instructions, Treatment Videos, Coping Toolkit, Quit Tips, Stress Management Trainings, Order Patches/Lozenges, Record Stress, Record Cigarette About to Smoke, Record Cigarette I Already Smoked, Payment, and Weekly Survey Payment.

NCI QuitGuide Condition

The NCI's QuitGuide app (available for free by request from the NCI Smokefree [58] server, on Google Play, or from the Google Play Store) is a free smartphone app that complies with many of the clinical practice guidelines for quitting smoking [54]. QuitGuide aims to orient smokers to their own smoking patterns and support users in developing the skills needed to quit smoking. Participants with a compatible smartphone who are randomly assigned to use QuitGuide are directed to download the app to their personal devices. Those who do not own a compatible device receive a study smartphone and are directed to download the QuitGuide app during the randomization call. Information explaining how to use the QuitGuide app is shared and reviewed during the randomization phone call. QuitGuide participants also download and use a modified version of the Insight EMA app with all MASP+ intervention features removed, which allows participants to receive EMAs and baseline or follow-up assessments. Refer to Table 1 for a list of QuitGuide features.

Table 1. Comparison of treatment conditions[a].

App components	MASP+[b]	QuitGuide
EMA[c]	✓	✓ (add on for this study)
Set a quit date	Quit date is set to 2 weeks after randomization	Quit date is set to 2 weeks after randomization
Share quit information on social media		✓
Smoking cessation psychoeducation	✓	✓
Content specific to Black smokers with HIV	✓	
NRT[d] tips and use advice	✓	
AS[e] psychoeducation	✓	
On-demand tips and exercises		
Coping with cravings	✓	✓
Coping with mood	✓	✓
Coping with stress	✓	
Coping with HIV stigma	✓	
HIV care management	✓	
Inspirational messages	✓	✓
Scheduled tips		✓
Treatment messages tailored to currently present smoking lapse triggers	✓	
Coping toolkit	✓	
Guided relaxation and mindfulness exercises	✓	
Challenging automatic thoughts	✓	
Tips for coping with stress	✓	
Interoceptive exposure	✓	
Resources to help distract participants if they experience elevated distress	✓	
Individualized quit plan		✓
Document smoking triggers		✓
List reasons for quitting		✓
Savings from smoking fewer cigarettes		✓
Create journal entries		✓

[a]Some treatment components will be available to all participants regardless of group or app assignment during randomization (eg, smoking cessation psychoeducation and inspirational messages). Other components will be exclusive to either the MASP + condition (eg, content specific to Black smokers with HIV and guidance for challenging automatic thoughts) or the QuitGuide condition (eg, scheduled tips and individualized quit plan).

[b]MASP+: Mobile Anxiety Sensitivity Program for Smoking and HIV.

[c]EMA: ecological momentary assessment.

[d]NRT: nicotine replacement therapy.

[e]AS: anxiety sensitivity.

MASP+ Condition

The MASP+ app was adapted from MASP materials and focuses on smoking cessation, HIV treatment engagement or adherence, and AS reduction among Black smokers with HIV [59,60]. Specifically, treatment video scripts were updated from MASP to reflect language and life experiences particular to those with HIV (eg, “Smoking can cause infections, slow down healing, and make it harder for HIV medications to keep your immune system strong.”). EMA messages underwent similar tailoring (eg, “Thinking about the stress of HIV treatment can sometimes feel overwhelming. Relieve your stress by doing one of the relaxation exercises in the app’s Coping Toolkit.”), and 2 new features were added to the app: “How to Improve my Treatment Outcomes” and “Tips on Living with a Chronic Disease.”

Within a culturally adapted framework, MASP+ integrates both standard cognitive behavioral therapy practices for smoking cessation (in accordance with clinical practice guidelines) and

transdiagnostic treatment for AS reduction [54]. MASP+ provides participants with (1) scheduled treatment content, (2) participant-initiated and scheduled stress exposure sessions, (3) personalized messages following each completed EMA (both pre- and postquit), and (4) numerous "on-demand" features (eg, Quit Tips and Coping Toolkit; both pre- and postquit). Culturally tailored components (eg, educational content related to menthol tobacco products in the Black community, the history of tobacco marketing directly to Black people, HIV treatment management and HIV disparities, and the impact of discrimination and racism on smoking and stress) are featured throughout MASP+. To support cultural tailoring, subject matter experts, including coinvestigators specializing in health disparities and HIV research and members of a Community Research Advisory Board, provided feedback on the cultural tailoring of the study materials for Black participants with HIV.

MASP+ App Features

Treatment on a Schedule

MASP+ includes 17 videos that are 4 to 6 minutes long. These videos provide psychoeducation on topics such as nicotine withdrawal, unhelpful thinking, coping with others smoking nearby, managing uncomfortable sensations, chronic stress and HIV, myths about smoking, strategies for cessation and relapse prevention, smoking as a temporary coping mechanism to avoid experiencing negative emotions, thinking flexibly, stress management, stress and smoking, interoceptive exposure techniques, and the importance of using NRT. All videos were based on those deployed in the MASP study; however, scripts and content were updated to reflect the life experiences of Black adults with HIV (eg, smoking can cause infections, slow down healing, and make it harder for HIV medications to keep your immune system strong). In addition, 1 video was split into 2 videos to reduce the length of individual videos and thereby reduce participant burden. Two new videos become available each day for the first 8 days of the intervention. Participants are able to watch videos as they become available or later by clicking on the on-demand "Treatment Videos" button (Figure 2). There is no limit on how frequently each video can be viewed. The app records date-, time-, and location-stamped information each time a video is watched. This process occurs at both initiation and completion.

Exposure Sessions

Empirical studies demonstrate that internet-based stress exposure is well tolerated, acceptable, and effective [61,62]. The MASP+ treatment videos introduce graduated exposure to anxiety- and distress-provoking situations and response prevention to target AS. Originally, these exposure exercises were created for the MASP pilot study (that is, straw breathing, running in place, head rush, overbreathing, and chair spinning) [49]. Participants are instructed to press the "Stress Management Trainings" button to initiate a stress exposure session (Figure 2). The MASP+ app randomly selects 1 of the 5 exercises each time a participant presses the Stress Management Trainings button. The participants are then guided through stress exposures: the app explains to the participant the purpose of the assigned activity and how to perform it, normalizes the physiological symptoms experienced during the exercise, and relates this experience to their quit attempt. As in the MASP pilot [49], when the participant is ready to begin, the app assesses their level of distress (0-100 scale), displays a countdown timer while the exercise is being completed, and then assesses their level of distress again (0-100 scale) following the expiration of the countdown. The app suggests repeating the exercise up to 3 additional times if the participant's current reported distress is >50 on a 1 to 100 scale. The aim of this strategy is to increase habituation to feared physiological sensations. Participants in the MASP pilot study accessed the Stress Management Training exercises on 6 out of 13 days before their quit date [63]. A recent review of phone-delivered interventions for anxiety and depression showed that treatments involving interoceptive exposure were safe and effective for participants [61,62,64].

EMAs With Tailored Real-Time Treatment Messages

During the prequit date period (ie, a participant's first 2 weeks in the study), the MASP+ app delivers a message at the end of each EMA (4 per day) intended to increase motivation and provide information about quitting (eg, "Everyone experiences negative emotions, such as stress. These emotions do not last forever, but they can lead to relapse. Make a specific plan to cope with such feelings."). During the postquitting date period (weeks 3-6 postbaseline), participants receive tailored messages following each EMA. These messages are based upon their responses to the EMA items they answered, which assess constructs such as ART adherence (eg, "Did you miss a dose of your HIV medication yesterday?") and reported the likelihood of smoking today (ie, 0%-100%). HIV-related EMA messages were specifically developed for the MASP+ study. When participants report that they missed a dose of medication, they are prompted to select the reason that they missed their medication (eg, "Simply forgot" or "Away from home"). On the basis of the response or responses they provide, a tailored message is shared with the participant. For example, selecting that a dose was missed due to forgetting leads the app to display 1 of several possible messages to encourage participants to take their medication as prescribed (eg, "Taking your medications every day is a step toward improving your health!"). The type of message (eg, motivational, coping with urges or stress, and tips for HIV care management) that is delivered following each EMA is recorded and uploaded to our server for future analyses that examine the effects of messages on targeted smoking lapse triggers, HIV outcomes, and anxiety or depression in future EMAs. In addition, participants are instructed to review and practice stress management exercises (ie, interoceptive exposure exercises) to normalize and learn to manage symptoms of anxiety and withdrawal. These exposure exercises have been deployed without incident in the MASP study [49].

On-Demand Features

On-demand features including Quit Tips (Figure 3) and Coping Toolkit (Figure 4) are available to participants via buttons found on the MASP+ home screen. Each of the available icons provides a specific message related to the content area or an activity to support participants in that moment. The research team has developed hundreds of unique messages that address various triggers for smoking relapse [55,65]; the large message bank is intended to reduce repetition. Two new on-demand

features were developed for this study: How to Improve My Treatment Outcomes and Tips on Living with a Chronic Disease. When selected, these features provide on-demand tips and messages of support regarding managing HIV care (eg, "Set reminders on your phone to help you remember appointments and when to take your medication.") and coping with health stress (eg, "Going on a daily walk, even if just for a few minutes, can help you relax and sort through your thoughts!"), respectively. LG and MB led the development of these messages and activities.

Figure 3. Mobile Anxiety Sensitivity Program for Smoking and HIV (MASP+) quit tips feature. Note: the Quit Tips button will bring participants to a screen where they can select to receive advice on the following topics: Nicotine Medication Tips; General Help for Quitting; Benefits of Quitting; Ways to Cope with Urges; Managing Stress/Mood; Motivate Me to Stay Quit; I've Slipped, Now What?; Harms of Smoking; and Coping with Others Smoking.

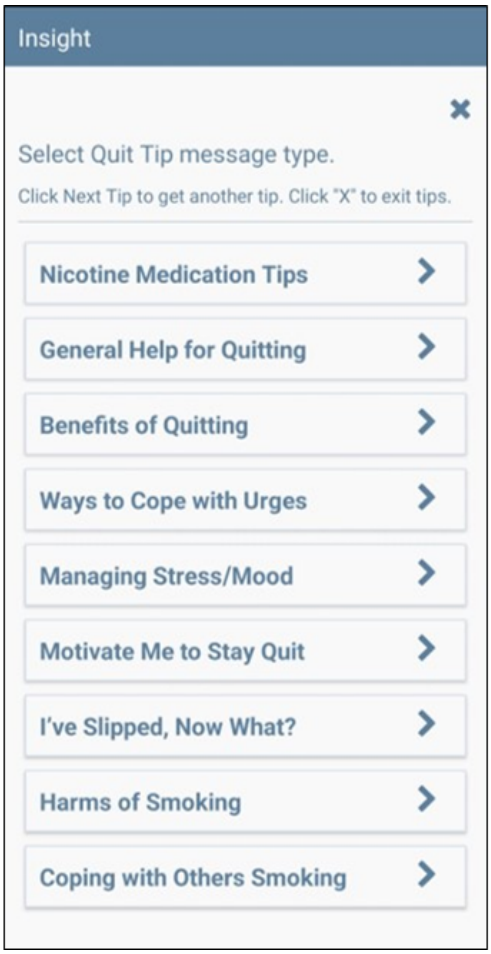
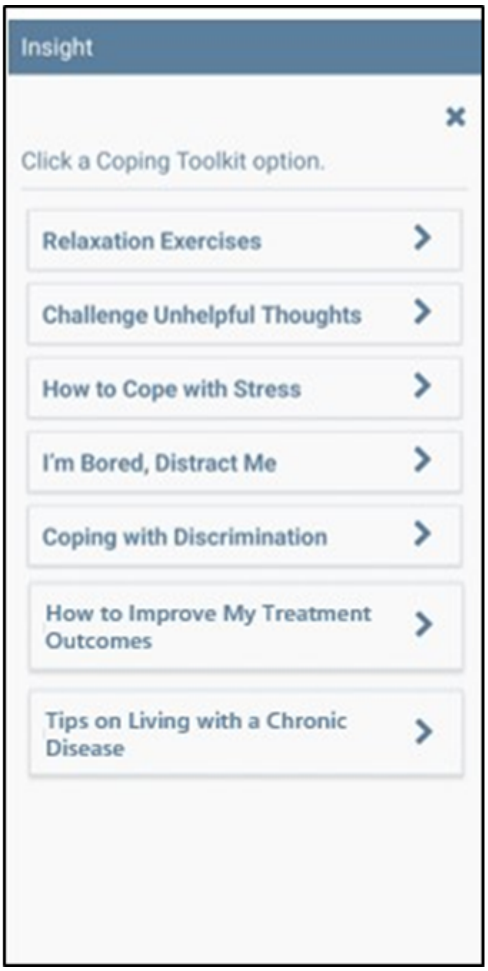


Figure 4. Mobile Anxiety Sensitivity Program for Smoking and HIV (MASP+) coping toolkit feature. Note: the Coping Toolkit button will bring participants to a screen where they can select to receive help with the following topics: Relaxation Exercises; Challenge Unhelpful Thoughts; How to Cope With Stress; I'm Bored, Distract Me; Coping With Discrimination; How to Improve My Treatment Outcomes; and Tips on Living With a Chronic Disease.



Measures

Overview

To reduce the potential for data entry errors and the need to retain paper copies of raw data, baseline and follow-up data are collected via smartphone using the Insight mHealth platform app software [66]. Questions appear on the phone screen, and answers are provided via touch screen. Tables 2-4 provides the schedule for when each measure is administered. The baseline survey takes approximately 30 minutes to complete; the postrandomization survey takes approximately 10 minutes to complete, the EMAs take approximately 2 to 4 minutes to complete, and the follow-up assessments take up to 15 minutes to complete.

Table 2. Table of measures[a].

Survey measures	Total number of items, n	Screener, n	Baseline, n	Postrandomization, n	Week 1 to week 6, n	Week 28, n
Screener Survey	41	41	—[b]	—	—	—
6-Item Cognitive Impairment Test (cognitive screener; eligibility)	7	7	—	—	—	—
Rapid Estimate of Adult Literacy in Medicine-Short Form [50] (eligibility)	9	9	—	—	—	—
Demographics or background information	19	—	19	—	—	—
MacArthur Scale of Subjective Social Status	2	—	2	—	2	2
Everyday Discrimination Scale	10	—	10	—	—	—
HIV adherence and treatment	17	—	—	17	—	17
Qualitative interview	24 (MASP+[c]); 20 (QG[d])	—	—	—	24 (MASP+ week 6); 20 (QG)	—
ART[e] adherence	6	—	6	—	6 (week 6)	6
AIDS Clinical Trials Group Adherence Questionnaire	24	—	24	—	19 (week 6)	19
Index of Engagement in HIV Care	10	—	10	—	10 (week 6)	10
WHO[f] Quality of Life-HIV	36	—	36	—	8 (week 6)	8
Carbon Monoxide Analysis (Phone Bedfont iCO[g])	1	—	1	—	1	1
SSASI[h] (eligibility)	5	5	5	—	5	5
System Usability Scale	10	—	—	—	10 (week 6)	—

[a]Various measures will be deployed during the eligibility screener, baseline and randomization surveys, weekly surveys, and daily EMAs. Daily EMAs will include items assessing sleep quality, HIV medication adherence, and discrimination, whereas random and event EMAs will include items assessing social interactions and smoking availability.

[b]Not available.

[c]MASP+: Mobile Anxiety Sensitivity Program for Smoking and HIV.

[d]QG: QuitGuide.

[e]ART: antiretroviral therapy.

[f]WHO: World Health Organization.

[g]iCO: iCarbon Monoxide.

[h]SSASI: Short Scale Anxiety Sensitivity Index.

Table 3. Daily diary ecological momentary assessment.

Survey measures	Items	Prequit morning	Prequit evening	Postquit morning	Postquit evening
Smoking behavior	3	1	1	3	2
Sleep quality	2	2	__[a]	2	—
Distress levels	2	2	—	2	—
HIV adherence	2	2	—	2	—
Other substance or medication use	4	2	2	2	2
General health or quality of life	2	—	2	—	2
Discrimination	2	—	2	—	2
Motivation levels	2	—	1	1	2
NRT[b] use and side effects	8	—	—	8	—
Watch a brief video	1	1	1	—	—
Confidence levels	4	—	—	3	4
Single-item anxiety assessment	1	—	—	1	1
Single-item depression assessment	1	—	—	1	1
Location	1	—	—	1	1
Take lozenge now	1	—	—	1	1

[a]Not available.

[b]NRT: nicotine replacement therapy.

Table 4. Random and event sampling ecological momentary assessment.

Survey measures	Items	Prequit	Postquit
Smoking behavior and availability	3	3	3
Stress and coping	2	2	2
Social interactions	1	1	1
Motivation levels	1	1	1
Other substance or medication use	1	1	1
Confidence levels	3	3	3
Single-item anxiety assessment	1	1	1
Single-item depression assessment	1	1	1
Location	1	1	1
Coping toolkit	1	1	1
Take lozenge now	1	__[a]	1

[a]Not available.

Screening

The prescreener includes a demographic questionnaire that assesses demographics (eg, sex, age, race, and ethnicity), smoking history, motivation to quit, and smartphone and data plan details. The REALM-Short Form was used to assess literacy (>grade 6 English literacy level is required to complete EMAs) [50]. Participants read the REALM words from their phone screen back to the research assistant during the enrollment call. If a participant has trouble reading the words due to vision issues, they have the option to use their phone settings to enlarge the font. The 6-item Cognitive Impairment Test is used to assess impairment in cognitive function (participants with scores <8 will be excluded) [53]. After participants recruited from Thomas Street Clinic complete the prescreener, a team member at Thomas Street Clinic performs a chart review to verify HIV status and record relevant details of health history, including history of respiratory illnesses related to smoking (eg, chronic obstructive pulmonary disease; COPD), height or weight, and number of missed appointments in preceding months. All other participants progress without a chart review.

Smoking Outcomes

During each weekly follow-up survey, smoking status is biochemically confirmed using the Insight platform and the Bedfont Scientific iCO smokerlyzer device. Biochemically

confirmed 7-day point prevalence abstinence (PPA) at 26 weeks postquitting date is the primary study outcome. This is consistent with best practices as well as most published smoking cessation RCTs (refer to the clinical practice guidelines) [54,67]. In their baseline package, participants receive the Bedfont iCO smokerlyzer, which they use to verify smoking status at each weekly follow-up assessment (weeks 1-6 and week 26 postquitting date). At the end of each assessment, the participants are directed by the Insight app to connect the iCO device to the smartphone (simply by pressing the power button on the device) and complete the iCO test. The date and time of completion are collected and saved to our server along with the test results. Our CO criteria are informed by numerous studies that have used CO cutoffs of <7 ppm [68-74]. The CO level is a validated indicator of smoking status and outcomes and is strongly correlated with cotinine and other biochemical measures that have longer detection windows [75-77].

HIV Outcomes

HIV outcomes are assessed using several measures. HIV-specific quality of life is assessed using the World Health Organization Quality of Life-HIV [78], a questionnaire comprising 36 items related to the quality of life in individuals with HIV. The items assess psychological well-being, functional limitations resulting from HIV status, pain, and the impact of HIV status on interpersonal relationships. ART adherence is assessed using 2 measures: the ART Adherence Scale [79], which consists of 7 items that assess adherence to ART medication regimens and attendance of HIV-specific medical appointments, and the AIDS Clinical Trial Group Adherence Baseline Questionnaire [80], which assesses ART adherence and reasons for missed medication, and nonadherence across 20 items. HIV treatment engagement is assessed using the Index of Engagement in HIV Care [81], a 10-item scale that asks participants about their experience of HIV care.

Discrimination

Race-based and HIV status–based discrimination is assessed using the Everyday Discrimination Scale [82]. This 5-item measure allows participants to report how often they face various forms of discrimination. Consistent with past work [83], the 5 items were adapted to assess both race-based and HIV status–based discrimination for a total of 10 items.

Anxiety Sensitivity

We assess AS using the SSASI [51]. The SSASI is derived from the ASI-3 and consists of 5 items that measure AS using a 5-point Likert-type scale (0=very little to 4=very much) [31].

MASP+ Feedback

We assess the perceived utility of MASP+ using the standardized System Usability Scale (a participant-completed, reliable, and valid metric for measuring usability and acceptability of technologies), which is administered during a 6-week follow-up survey [84-86]. Using a 5-point Likert-type scale (1=strongly agree to 5=strongly disagree), participants indicate their level of agreement with statements about the app's usefulness (eg, "I thought the smoking cessation app was easy to use").

MASP+ Feedback: Qualitative Interviews

Participant experience is assessed via a Zoom-based qualitative interview conducted at the end of treatment (week 6). The semistructured qualitative interview is conducted by trained members of the research team and audio recorded. These interviews focus on the ease of interacting with the app, the usefulness of app features, how the app can be improved, how sociocultural factors that affect Black smokers with HIV could be further woven into the intervention, and their willingness to refer the app to a friend. As participants in both study arms use the Insight app to complete EMAs and receive intervention content via the Insight app or QuitGuide app, the qualitative interview questions primarily concern participants' experiences with Insight (MASP+ and EMA, or EMA only) and QuitGuide (intervention content). During the qualitative interviews, participants provide details about the features of the different apps that they did and did not like (eg, "What did you like about the app?"), how app features impacted relevant study outcomes (eg, "Which, if any, app features helped you manage your HIV better?"), and how the app or apps they used could be improved (eg, "How can we make the app fit better with your life experiences?"). Combined with the primary outcomes and other quantitative data, qualitative interview data will be used to refine MASP+, which will then be tested in a large-scale RCT.

Ecological Momentary Assessments

Overview

At present, EMAs are the most accurate way to measure phenomena in real-time, natural settings [87,88]. EMA items are less biased than traditional in-person assessments and identify fluctuations in key variables related to the study outcomes. EMA data are used to tailor the MASP+ treatment content and identify both treatment mechanisms and moments of high risk for smoking lapse.

The EMA methodology used in this study mimics that used in our previous studies and by other researchers [49,55,65,87,89-95]. The EMA items assess multiple constructs hypothesized to be related to HIV care and smoking lapse. Three types of EMAs are used in this study: daily diary, random sampling, and event sampling. Random and daily diary EMAs are prompted and initiated by the app. The phone audibly and visually notifies the participants of these EMAs for 30 seconds. If participants do not respond after 5 prompts, the assessment is recorded as "missed. All assessments are date and time stamped for future analyses.

Daily Diary

Each morning during weeks 1 to 6 and week 28, participants complete a daily diary EMA, for which they receive a notification 30 minutes after waking. Likewise, participants receive a notification to complete their evening daily diary 75 minutes before their reported bedtime. Questions from the morning daily diary ask about thoughts, experiences, feelings, and behaviors from both the previous day and the present (eg, "Did you miss a dose of your HIV medication yesterday?" and "Today, how long ago did you last smoke a cigarette?"). The participants are also asked about smoking cessation medication use, ART adherence, and sleep quality from the previous day.

During evening daily diaries, participants are asked about thoughts, experiences, feelings, and behaviors from the same day (eg, "How is your health in general today?" and "How would you rate your quality of life today?").

Random Sampling

Twice each day during weeks 1 to 6 and week 28, participants are prompted to complete EMAs that are scheduled to occur randomly during each participant's normal waking hours. Participants rate their affect by indicating their level of agreement with several statements on a 5-point scale from "strongly disagree" to "strongly agree" (eg, "I feel stressed"). In addition, participants are asked about smoking triggers (eg, "I have an urge to smoke"), current depression level ("Rate your current level of depression [feeling sad]"), and anxiety level ("Rate your current level of anxiety [feeling nervous]"). Participants are also asked to describe their current environment (eg, home and work) and social setting.

Event Sampling

Throughout the treatment period, participants are asked to initiate Smoking Assessments (prequit date), Lapse Assessments (postquitting date), and Stress Assessments (pre- and postquitting date).

Before their quit date, participants are instructed to click a Record Cigarette button every time they feel they are about to smoke or have already smoked a cigarette. In addition, 10% of the time, this triggers a brief survey asking participants about their affect, stress, and experiences while smoking (eg, "Smoking improved my mood" and "Smoking was pleasurable"). These smoking assessments are date, time, and location stamped for future analyses.

Participants are instructed to press the Record Cigarette I Am About to Slip or the I Already Slipped button and complete a lapse assessment each time they smoke after their quitting date. Items on these assessments are similar to those presented in the random and smoking assessments and worded to separately assess the participants' responses immediately before and after the lapse.

Participants are instructed to press the Report Stress button and complete the resulting assessment each time they "experience a significant increase in stress."

Importantly, each MASP+ pre- and postquitting date EMA is followed by a treatment message that is tailored to the participant's responses and current situation. Those assigned to the QuitGuide group complete EMAs identical to the MASP+ group, although they do not receive tailored intervention messages after completion.

EMA Alert Settings

During the enrollment call, the participants' sleep-wake times for each day of the week are recorded and stored (Note: these sleep-wake times can be changed by calling the study team). This practice is intended to prevent or reduce the chance of the phone ringing while participants are asleep. When an EMA is prompted, participants can delay ("snooze") EMAs by up to 30 minutes by clicking the Snooze Assessment option on the smartphone screen.

Data Loss Prevention

To avoid potential data loss as a result of participants losing their phones, each device is programmed to synchronize and upload encrypted data with our secure server multiple times each day (Note: in most studies, <1% of phones have been lost) [48]. These procedures prevent the collected EMA data from being lost, allow the researchers to remotely monitor participants' EMA completion rates, and identify when participants need to be contacted for low survey completion. Notably, EMA data are encrypted and password protected on each study phone. Therefore, the study data are only accessible to the research team. The lost phones are wiped remotely. Participants who lose their phones are provided up to 1 replacement.

The Insight Platform

Overview

The Insight mHealth platform was developed by the mHealth Shared Resource at the University of Oklahoma Health Sciences Center and the Stephenson Cancer Center. This platform offers resources to help researchers build, test, and launch technology-based assessment and intervention tools [66]. The mHealth resource uses a sizeable team that includes 1 program manager, 4 project coordinators, and 4.5 computer scientists or engineers. Together, they develop and maintain web and mobile apps and relational databases. These apps are developed using cutting-edge, cross-platform design tools.

Smartphone Training

Our team has developed and implemented a brief user-friendly training protocol to aid those with limited smartphone experience. During the randomization call, all participants, depending on condition assignment, receive training on how to use either the MASP+ app or the EMA-only Insight app and the QuitGuide app. Both versions of the Insight app (MASP+ and EMA only) contain an "App Instructions" button to remind participants of how each app feature functions (Figure 2). In previous studies, similar protocols have resulted in high EMA compliance rates (eg, 82%-87% of all EMAs completed) in samples of socioeconomically disadvantaged and nondisadvantaged adults [55,65,95,96]. All smartphones used in this study automatically collect data on intervention delivery (eg, number of times features are used and number of minutes treatment videos are watched).

Data Analyses

Overview

To test the hypothesis that MASP+ produces higher rates of smoking abstinence compared to the NCI QuitGuide app, a biochemically verified measure of 7-day PPA that is collected during weekly assessments via Bedfont iCO will be used. PPA is defined as no smoking, not even a puff, in the 7 days before follow-up assessments and biochemical verification of smoking abstinence (ie, CO levels <7 ppm according to an iCO test). We will calculate odds ratio effect sizes (with 95% CI) to estimate between-group differences for PPA at each follow-up assessment. The effect size for the comparison between conditions at the 26-week postquitting date assessment will

serve as the primary analysis of the impact of treatment condition on smoking cessation.

We will then conduct a series of conditional latent growth curve models (LGM) to examine the impact of treatment condition on abstinence trajectories. First, an LGM will be specified using CO breath tests at 2 (quit date), 3, 4, 5, 6, and 28 weeks. The intercept of these models will be centered on the baseline assessment and will be specified to model linear change across the major assessments. A dummy code representing the treatment condition will be specified as a predictor of the intercept and slope factors to quantify the effect of MASP+ on the longitudinal course of abstinence.

The impact of treatment conditions on HIV quality of life, ART adherence, and HIV treatment engagement (hypothesis 2) will be examined using the same sequence of analyses: between-condition effect sizes followed by conditional LGM. We will then conduct univariate LGM to explore changes in AS a function of treatment (hypothesis 3), followed by a series of parallel process LGM to examine how changes in AS relate to changes in smoking and HIV outcomes. The indirect effects of treatment via AS will be evaluated by calculating bootstrapped CIs of the indirect effect using the MODEL INDIRECT command in MPlus.

Mixed Methodology

Triangulation mixed methods quantitative and qualitative data analysis will be used to evaluate quantitative and qualitative data [97]. Using an explanatory sequential mixed methods design, qualitative data collection and analysis will increase the investigators' understanding of participant experiences of the tailored material for both cultural relevance and relevance to living with HIV.

Quantitative Data

Quantitative data analysis will focus on (1) behavioral markers of engagement with the app (ie, completion of >75% of all assigned videos and completion of >75% of all assigned exercises); (2) self-report evaluations of the app including ease of interacting with the app (ie, >75% of all participants agreeing that MASP+ is easy to use based on a rating of ≥3 on the scale), that the MASP+ features (eg, automated treatment messages that follow EMA and treatment videos) are useful and helpful on a similar scale, and that at least 75% of participants would be likely to recommend the app to a friend; and (3) data from the System Usability Scale [98-100]. Low engagement and evaluation of MASP+ will be discussed with each participant during the qualitative interview.

Qualitative Data

Qualitative data analysis will focus on participants' experiences with the app and incorporating their feedback to improve the app interface and features. Individual interviews will be transcribed following completion of participant treatment and then reviewed by the research team to monitor data quality. The transcribed interviews will be coded using NVivo (version 12; Lumivero). Following a first reading of the transcripts, the interviews will be coded using 2 coding passes [101]. The first coding pass will be use focused [102], with initial codes developed from the question path questions and additional codes based on responses to the System Usability Scale. The qualitative researcher (MKC) will code the interviews, and the coding will be reviewed by a second member of the research team trained in qualitative methods. The coding disagreements will then be discussed and resolved. Memos and notes will be reviewed and discussed. A second coding pass will then be conducted based on additional codes identified during the discussion, which may be process based or theoretically based, depending on what emerges from the first round of coding. Following the review of both coding passes, the research team will conduct a thematic analysis in several steps, beginning with the MASP+ participants, where themes will be identified both within and between codes. The team will then create data displays and review the patterns of responses between related sets of codes [103]. Points of integration between the MASP+ qualitative and quantitative data will be identified, a joint analysis will be conducted, and joint displays will be created [104]. Following the joint analysis, the transcripts will be read again for additional confirming and disconfirming evidence of themes [103], and representative quotes will then be selected. The QuitGuide responses will then be analyzed and compared to the MASP+ responses.

Sample Size Determination

As this is the first empirical evaluation of the MASP+ intervention in this population, our focus is on determining the feasibility of the new intervention and obtaining preliminary estimates of effect sizes on smoking and HIV outcomes and the hypothesized mechanism of change, rather than conducting a full-scale and statistically powered examination of comparative efficacy. We expect that MASP+ will be superior to the NCI QuitGuide on all outcomes examined, but that the effects of MASP+ may vary and be larger for smoking outcomes than for HIV outcomes. On the basis of power calculations conducted using Repeated Measures and Sample Size and simulation studies identifying the sample sizes necessary to detect indirect effects [105,106], a target sample size of 72 would provide sufficient statistical power to detect a medium to large effect (Cohen $d \geq 0.6$) and an indirect effect for H3 if the treatment effect on AS is large (Cohen $d=0.8$) and the effect of AS on outcomes is medium to large (Cohen $d=0.5$). Our conclusions will primarily be based on effect sizes and associated CIs, and the effect size estimates (and associated CIs) from this trial will be used to guide future larger trials of comparative efficacy.

Qualitative interviews are conducted with all MASP+ and QuitGuide participants. The recommended minimum size for any subgroup is 20 interviews [107]. However, based on our prior work [48], interviews vary substantially in the content provided, so interviews will be conducted with all enrolled study participants in MASP+ and QuitGuide to meet the saturation of key study questions. Interviewing all MASP+ participants should be sufficient for the saturation of key study questions. The QuitGuide interviews will be used as a comparative group following the analysis of the MASP+ content, based on our prior work.

Results

This study received IRB approval on November 29, 2022, under STUDY00003811 and began data collection on October 16, 2023. As of manuscript submission, a total of 9 participants have been fully enrolled in this trial. Data enrollment is scheduled to be completed by June 2024, and data collection is scheduled to be completed by December 2024. Data analysis will begin February 2025 and results will be published March 2024.

Discussion

Expected Findings

Data collection is currently underway. Results are expected to indicate that MASP+, relative to QuitGuide, will lead to improved biochemically verified 7-day PPA, increased adherence to ART, and improved attendance at HIV-related health appointments at 26 weeks postquitting date. Qualitative interviews will be integrated with quantitative data to further refine and adapt MASP+ and support the development of an iterative intervention that is high quality, culturally relevant, scalable, and ready for rigorous testing as part of an R01-level grant.

Study Implications

This study is the first to culturally tailor a smoking cessation smartphone-delivered intervention that is integrated with AS reduction skills for Black people with HIV/AIDS who smoke and elevated AS. Smartphone interventions such as MASP+ have the potential to provide low-cost, scalable treatments to diverse populations who may not be as likely to have access to in-person treatment or may not have health insurance to cover costs. A 2021 survey found that 85% of US adults reported owning a smartphone [108], and other studies have found that smartphone ownership is high among minoritized populations (83% among Black adults) as well as individuals with low socioeconomic status (76% among those earning <US $30,000/y) [108]. Given the widespread ownership of smartphones, MASP+ has the potential to overcome traditional barriers to care and enhance the accessibility and reach of culturally appropriate, clinical-grade care for hard-to-reach populations.

Clinically, the cultural tailoring and integration of AS reduction skills within MASP+ represents a groundbreaking approach. Experiences of AS and related mental health factors (eg, anxiety, depression, and drug withdrawal or craving) can vary over time and among individuals [109]. By assessing these factors throughout the day and providing support as these symptoms arise, MASP+ constitutes a just-in-time tailored intervention for smoking cessation, AS, and HIV management. Such an approach may serve as a potential solution to address the documented health disparities experienced by Black people with HIV/AIDS who smoke [6,110]. MASP+ is also distinguished by the specificity with which it can respond to the unique stressors, needs, and challenges experienced by Black smokers with HIV and AS. This underscores the potential for MASP+ to serve as a stand-alone or adjunctive treatment for smoking cessation. Indeed, MASP+ offers personalized care to address factors that impede successful behavioral change in a culturally appropriate and person-centered manner, which may have strong implications for mitigating health disparities for Black smokers with HIV.

Understanding the role of AS in the process of quitting cigarettes and better managing HIV among Black adults with HIV has several theoretical implications. First, this work bridges together disparate yet complementary work on AS, smoking, and HIV [111,112]. Thus, findings from this trial may provide a holistic understanding of how these constructs relate to and influence one another. This greatly advances the current models for the role of interoceptive distress as a risk factor for worse smoking cessation and HIV-related outcomes [113-116]. Second, several models related to minority stress indicate the need for culturally tailored interventions, particularly those targeting smoking cessation [117-119]. Expanding these efforts to produce tailored interventions for Black smokers with HIV that focus on a mechanism implicated in worse health outcomes among this group (ie, AS) allows providers and researchers to address documented health disparities among this population in a culturally specific manner [120]. Further studies of the mechanisms underlying quit success among Black smokers with HIV and AS will guide future efforts to tailor smoking cessation interventions for this population. This study will provide insights about which risk factors to target during smoking cessation treatment among this group, the ideal timing of intervention efforts, and the preferred content of intervention messages.

Anticipated Limitations

This study has several limitations. Daily EMAs can be disruptive as they are prompted throughout the day rather than clustered in a single study appointment. This could potentially discourage participation in the daily EMA component of this study. In addition, some study measures rely on self-reporting, and participants may not respond in real time. In addition, recruiting a population as specific as Black people with HIV/AIDS who smoke only combustible cigarettes may prove challenging for the study team. Finally, although participants will be responding to items while navigating daily life, thereby increasing ecological validity, this comes at the expense of depriving experimenters of a high degree of control over participants' environmental conditions.

Conclusions

This study may provide insights into precision medicine treatment that is not otherwise available by providing a smoking cessation and HIV management intervention with tailored treatment content based on the psychological and environmental context in real time. Pending tests of its efficacy, an intervention that is automated, scalable, and culturally informed could be easily incorporated into other real-world settings and aid in the reduction of health disparities. This novel mobile intervention has the potential to address the mental and physical barriers to smoking cessation and treatment engagement that are unique to Black people with HIV/AIDS. Despite any potential difficulties in recruiting such a specific group or capturing EMA data, the benefits of this study far outweigh any drawbacks.

Additional work is essential for the successful translation and cultural adaption of effective in-person smoking cessation interventions into mobile, remotely delivered treatments such as MASP+. Compared to current treatment options, mobile interventions have the potential to produce even greater cessation outcomes and provide wider access for historically oppressed and underserved populations such as Black smokers with HIV and high AS. In light of prior studies that demonstrate the feasibility of mobile smoking cessation technology [49,55,121], mobile treatments that integrate AS constitute a vital "next step" for addressing tobacco-related health disparities among Black smokers with HIV. This study will extend our work in this area as well as in the wider field of smoking–emotional disorder comorbidity by adapting and testing a fully automated, culturally tailored, mobile AS smoking cessation intervention for Black smokers with HIV. Future work will focus on testing the MASP+ app in a larger, fully powered efficacy trial; national dissemination of intervention materials; and implementation across diverse health care settings.

Acknowledgments

This study was supported by funding from the National Institute on Minority Health and Health Disparities to the University of Houston (U54MD015946; principal investigator: Ezemenari Obasi). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. LG and MB are the Multiple Principal Investigators in the Supplement Project titled MASP+ described in this paper. This work was also partially supported by the Oklahoma Tobacco Settlement Endowment Trust (R21-02 to MSB) and the National Cancer Institute (P30CA225520) awarded to the Stephenson Cancer Center, and the work used the Stephenson Cancer Center's mHealth Shared Resource. TPG is supported by the MD Anderson Foundation Chair at Baylor College of Medicine and the Texas Developmental Center for AIDS Research (P01AI161943; principal investigator: TPG). The manuscript and its revisions were supported by the National Institute on Drug Abuse of the National Institutes of Health (R25DA054015; Multiple Principal Investigators: Obasi and Reitzel).

Data Availability

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

Conflicts of Interest

MB is an inventor of the Insight mobile health platform and receives royalties related to the use of this platform by investigators external to the University of Oklahoma Health Sciences Center. As MB is one of multiple principal investigators in this study, he did not receive royalties for the use of the platform to create the Mobile Anxiety Sensitivity Program for Smoking and HIV (MASP+) app.

References

1. Frazier EL, Sutton MY, Brooks JT, Shouse RL, Weiser J. Trends in cigarette smoking among adults with HIV compared with the general adult population, United States - 2009-2014. Prev Med 2018 Jun;111:231-234. [doi: 10.1016/j.ypmed.2018.03.007] [Medline: 29550303]
2. Cornelius ME, Loretan CG, Wang TW, Jamal A, Homa DM. Tobacco product use among adults - United States, 2020. MMWR Morb Mortal Wkly Rep 2022 Mar 18;71(11):397-405 [FREE Full text] [doi: 10.15585/mmwr.mm7111a1] [Medline: 35298455]
3. Rahmanian S, Wewers ME, Koletar S, Reynolds N, Ferketich A, Diaz P. Cigarette smoking in the HIV-infected population. Proc Am Thorac Soc 2011 Jun;8(3):313-319 [FREE Full text] [doi: 10.1513/pats.201009-058WR] [Medline: 21653534]
4. Mdodo R, Frazier EL, Dube SR, Mattson CL, Sutton MY, Brooks JT, et al. Cigarette smoking prevalence among adults with HIV compared with the general adult population in the United States: cross-sectional surveys. Ann Intern Med 2015 Mar 03;162(5):335-344. [doi: 10.7326/M14-0954] [Medline: 25732274]
5. Burkhalter JE, Springer CM, Chhabra R, Ostroff JS, Rapkin BD. Tobacco use and readiness to quit smoking in low-income HIV-infected persons. Nicotine Tob Res 2005 Aug 1;7(4):511-522. [doi: 10.1080/14622200500186064] [Medline: 16085522]
6. Gritz ER, Vidrine DJ, Lazev AB, Amick BC, Arduino RC. Smoking behavior in a low-income multiethnic HIV/AIDS population. Nicotine Tob Res 2004 Feb 1;6(1):71-77. [doi: 10.1080/14622200310001656885] [Medline: 14982690]
7. Sigel K, Makinson A, Thaler J. Lung cancer in persons with HIV. Curr Opin HIV AIDS 2017 Jan;12(1):31-38 [FREE Full text] [doi: 10.1097/COH.0000000000000326] [Medline: 27607596]
8. Presti RM, Flores SC, Palmer BE, Atkinson JJ, Lesko CR, Lau B, et al. Mechanisms underlying HIV-associated noninfectious lung disease. Chest 2017 Nov;152(5):1053-1060 [FREE Full text] [doi: 10.1016/j.chest.2017.04.154] [Medline: 28427967]
9. Ntsekhe M, Baker JV. Cardiovascular disease among persons living with HIV: new insights into pathogenesis and clinical manifestations in a global context. Circulation 2023 Jan 03;147(1):83-100. [doi: 10.1161/circulationaha.122.057443]
10. Feinstein MJ, Hsue PY, Benjamin LA, Bloomfield GS, Currier JS, Freiberg MS, et al. Characteristics, prevention, and management of cardiovascular disease in people living with HIV: a scientific statement from the American Heart Association. Circulation 2019 Jul 09;140(2):e98-124 [FREE Full text] [doi: 10.1161/CIR.0000000000000695] [Medline: 31154814]

11. Hemkens LG, Bucher HC. HIV infection and cardiovascular disease. Eur Heart J 2014 Jun 01;35(21):1373-1381. [doi: 10.1093/eurheartj/eht528] [Medline: 24408888]
12. Islam F, Wu J, Jansson J, Wilson D. Relative risk of cardiovascular disease among people living with HIV: a systematic review and meta-analysis. HIV Med 2012 Sep 14;13(8):453-468 [FREE Full text] [doi: 10.1111/j.1468-1293.2012.00996.x] [Medline: 22413967]
13. Helleberg M, May MT, Ingle SM, Dabis F, Reiss P, Fätkenheuer G, et al. Smoking and life expectancy among HIV-infected individuals on antiretroviral therapy in Europe and North America. AIDS 2015 Jan 14;29(2):221-229 [FREE Full text] [doi: 10.1097/QAD.0000000000000540] [Medline: 25426809]
14. Helleberg M, Gerstoft J, Afzal S, Kronborg G, Larsen CS, Pedersen C, et al. Risk of cancer among HIV-infected individuals compared to the background population: impact of smoking and HIV. AIDS 2014 Jun 19;28(10):1499-1508. [doi: 10.1097/QAD.0000000000000283] [Medline: 24785952]
15. Reddy KP, Parker RA, Losina E, Baggett TP, Paltiel AD, Rigotti NA, et al. Impact of cigarette smoking and smoking cessation on life expectancy among people with HIV: a US-based modeling study. J Infect Dis 2016 Dec 01;214(11):1672-1681 [FREE Full text] [doi: 10.1093/infdis/jiw430] [Medline: 27815384]
16. Ditre JW, Brandon TH, Zale EL, Meagher MM. Pain, nicotine, and smoking: research findings and mechanistic considerations. Psychol Bull 2011 Nov;137(6):1065-1093 [FREE Full text] [doi: 10.1037/a0025544] [Medline: 21967450]
17. Pomerleau OF, Turk DC, Fertig JB. The effects of cigarette smoking on pain and anxiety. Addict Behav 1984 Jan;9(3):265-271. [doi: 10.1016/0306-4603(84)90018-2] [Medline: 6496202]
18. Labbe AK, Wilner JG, Kosiba JD, Gonzalez A, Smits JA, Zvolensky MJ, et al. Demonstration of an integrated treatment for smoking cessation and anxiety symptoms in people with HIV: a clinical case study. Cogn Behav Pract 2017 May;24(2):200-214. [doi: 10.1016/j.cbpra.2016.03.009]
19. Crockett KB, Rice WS, Turan B. Associations between multiple forms of discrimination and tobacco use among people living with HIV: the mediating role of avoidance coping. J Acquir Immune Defic Syndr 2018 May 01;78(1):9-15 [FREE Full text] [doi: 10.1097/QAI.0000000000001636] [Medline: 29373394]
20. Martinez DA, Goggin K, Catley D, Gerkovich MM, Williams K, Wright J, MOTIV8. Do coping styles mediate the relationship between substance use and educational attainment and antiretroviral adherence? AIDS Behav 2012 Nov 7;16(8):2319-2329 [FREE Full text] [doi: 10.1007/s10461-012-0222-1] [Medline: 22673969]
21. Lloyd-Richardson EE, Stanton CA, Papandonatos GD, Shadel WG, Stein M, Tashima K, et al. Motivation and patch treatment for HIV+ smokers: a randomized controlled trial. Addiction 2009 Nov 09;104(11):1891-1900 [FREE Full text] [doi: 10.1111/j.1360-0443.2009.02623.x] [Medline: 19719796]
22. Simoni JM, Huh D, Wilson IB, Shen J, Goggin K, Reynolds NR, et al. Racial/Ethnic disparities in ART adherence in the United States: findings from the MACH14 study. J Acquir Immune Defic Syndr 2012 Aug 15;60(5):466-472 [FREE Full text] [doi: 10.1097/QAI.0b013e31825db0bd] [Medline: 22595873]
23. Silverberg MJ, Leyden W, Quesenberry CP, Horberg MA. Race/ethnicity and risk of AIDS and death among HIV-infected patients with access to care. J Gen Intern Med 2009 Sep 16;24(9):1065-1072 [FREE Full text] [doi: 10.1007/s11606-009-1049-y] [Medline: 19609624]
24. Mugavero MJ, Lin HY, Allison JJ, Giordano TP, Willig JH, Raper JL, et al. Racial disparities in HIV virologic failure: do missed visits matter? J Acquir Immune Defic Syndr 2009 Jan 01;50(1):100-108 [FREE Full text] [doi: 10.1097/QAI.0b013e31818d5c37] [Medline: 19295340]
25. Beer L, McCree DH, Jeffries WL, Lemons A, Sionean C. Recent US Centers for Disease Control and Prevention activities to reduce HIV stigma. J Int Assoc Provid AIDS Care 2019 Jan 24;18:2325958218823541 [FREE Full text] [doi: 10.1177/2325958218823541] [Medline: 30798667]
26. Lyons SJ, Johnson AS, Hu X, Yu C, Jin C, Yu C, et al. Monitoring selected national HIV prevention and care objectives by using HIV surveillance data: United States and 6 dependent areas. Centers for Disease Control and Prevention. 2018. URL: https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-supplemental-report-vol-25-2.pdf [accessed 2024-03-05]
27. HIV surveillance reports. Centers for Disease Control and Prevention. 2019. URL: https://www.cdc.gov/hiv/library/reports/hiv-surveillance.html [accessed 2024-03-05]
28. Randolph SD, Golin C, Welgus H, Lightfoot AF, Harding CJ, Riggins LF. How perceived structural racism and discrimination and medical mistrust in the health system influences participation in HIV health services for black women living in the United States South: a qualitative, descriptive study. J Assoc Nurses AIDS Care 2020;31(5):598-605. [doi: 10.1097/JNC.0000000000000189] [Medline: 32868634]
29. Kilanowski JF. Breadth of the socio-ecological model. J Agromedicine 2017;22(4):295-297. [doi: 10.1080/1059924X.2017.1358971] [Medline: 28742433]
30. Crenshaw K. Demarginalizing the intersection of race and sex: a black feminist critique of antidiscrimination doctrine, feminist theory, and antiracist politics. In: Bartlett K, editor. Feminist Legal Theory. New York, NY: Routledge; 2013:23-51.
31. Taylor S, Zvolensky MJ, Cox BJ, Deacon B, Heimberg RG, Ledley DR, et al. Robust dimensions of anxiety sensitivity: development and initial validation of the Anxiety Sensitivity Index-3. Psychol Assess 2007 Jun;19(2):176-188. [doi: 10.1037/1040-3590.19.2.176] [Medline: 17563199]

32. Reiss S. Expectancy model of fear, anxiety, and panic. Clin Psychol Rev 1991 Jan;11(2):141-153 [FREE Full text] [doi: 10.1016/0272-7358(91)90092-9]
33. Zinbarg RE, Barlow DH, Brown TA. Hierarchical structure and general factor saturation of the Anxiety Sensitivity Index: evidence and implications. Psychol Assess 1997;9(3):277-284. [doi: 10.1037//1040-3590.9.3.277]
34. Taylor S. Anxiety Sensitivity: Theory, Research, and Treatment of the Fear of Anxiety. Oxfordshire, UK: Routledge; 1999.
35. Wykowski J, Kemp CG, Velloza J, Rao D, Drain PK. Associations between anxiety and adherence to antiretroviral medications in low- and middle-income countries: a systematic review and meta-analysis. AIDS Behav 2019 Aug 18;23(8):2059-2071 [FREE Full text] [doi: 10.1007/s10461-018-02390-8] [Medline: 30659424]
36. Leyro TM, Vujanovic AA, Bonn-Miller MO. Examining associations between cognitive-affective vulnerability and HIV symptom severity, perceived barriers to treatment adherence, and viral load among HIV-positive adults. Int J Behav Med 2015 Feb 19;22(1):139-148. [doi: 10.1007/s12529-014-9404-8] [Medline: 24643444]
37. Brandt CP, Paulus DJ, Jardin C, Heggeness L, Lemaire C, Zvolensky MJ. Examining anxiety sensitivity as an explanatory construct underlying HIV-related stigma: relations to anxious arousal, social anxiety, and HIV symptoms among persons living with HIV. J Anxiety Disord 2017 May;48:95-101 [FREE Full text] [doi: 10.1016/j.janxdis.2016.08.001] [Medline: 27527687]
38. Leventhal AM, Zvolensky MJ. Anxiety, depression, and cigarette smoking: a transdiagnostic vulnerability framework to understanding emotion-smoking comorbidity. Psychol Bull 2015 Jan;141(1):176-212 [FREE Full text] [doi: 10.1037/bul0000003] [Medline: 25365764]
39. Gregor KL, Zvolensky MJ, McLeish AC, Bernstein A, Morissette S. Anxiety sensitivity and perceived control over anxiety-related events: associations with smoking outcome expectancies and perceived cessation barriers among daily smokers. Nicotine Tob Res 2008 Apr;10(4):627-635. [doi: 10.1080/14622200801978706] [Medline: 18418785]
40. Alcántara C, Giorgio Cosenzo LA, Fan W, Doyle DM, Shaffer JA. Anxiety sensitivity and racial differences in sleep duration: results from a national survey of adults with cardiovascular disease. J Anxiety Disord 2017 May;48:102-108 [FREE Full text] [doi: 10.1016/j.janxdis.2016.10.002] [Medline: 27760717]
41. Assayag Y, Bernstein A, Zvolensky MJ, Steeves D, Stewart SS. Nature and role of change in anxiety sensitivity during NRT-aided cognitive-behavioral smoking cessation treatment. Cogn Behav Ther 2012 Mar;41(1):51-62. [doi: 10.1080/16506073.2011.632437] [Medline: 22375732]
42. Brown RA, Kahler CW, Zvolensky MJ, Lejuez C, Ramsey SE. Anxiety sensitivity: relationship to negative affect smoking and smoking cessation in smokers with past major depressive disorder. Addict Behav 2001 Nov;26(6):887-899. [doi: 10.1016/s0306-4603(01)00241-6] [Medline: 11768550]
43. Smits JA, Zvolensky MJ, Davis ML, Rosenfield D, Marcus BH, Church TS, et al. The efficacy of vigorous-intensity exercise as an aid to smoking cessation in adults with high anxiety sensitivity: a randomized controlled trial. Psychosom Med 2016 Apr;78(3):354-364 [FREE Full text] [doi: 10.1097/PSY.0000000000000264] [Medline: 26513517]
44. Zvolensky MJ, Bogiaizian D, Salazar PL, Farris SG, Bakhshaie J. An anxiety sensitivity reduction smoking-cessation program for Spanish-speaking smokers (Argentina). Cognitive and Behavioral Practice 2014 Aug;21(3):350-363. [doi: 10.1016/j.cbpra.2013.10.005]
45. Zvolensky MJ, Lejuez C, Kahler CW, Brown RA. Integrating an interoceptive exposure-based smoking cessation program into the cognitive-behavioral treatment of panic disorder: theoretical relevance and case demonstration. Cogn Behav Pract 2003 Sep;10(4):347-357. [doi: 10.1016/s1077-7229(03)80052-4]
46. Schmidt NB, Raines AM, Allan NP, Zvolensky MJ. Anxiety sensitivity risk reduction in smokers: a randomized control trial examining effects on panic. Behav Res Ther 2016 Feb;77:138-146 [FREE Full text] [doi: 10.1016/j.brat.2015.12.011] [Medline: 26752327]
47. Shiffman S, Brockwell SE, Pillitteri JL, Gitchell JG. Use of smoking-cessation treatments in the United States. Am J Prev Med 2008 Feb;34(2):102-111. [doi: 10.1016/j.amepre.2007.09.033] [Medline: 18201639]
48. Businelle MS, Garey L, Gallagher MW, Hébert ET, Vujanovic A, Alexander A, et al. An integrated mHealth app for smoking cessation in black smokers with anxiety: protocol for a randomized controlled trial. JMIR Res Protoc 2022 May 30;11(5):e38905 [FREE Full text] [doi: 10.2196/38905] [Medline: 35635746]
49. Garey L, Hébert ET, Mayorga NA, Chavez J, Shepherd JM, Businelle MS, et al. Evaluating the feasibility and acceptability of a mobile-based health technology for smoking cessation: mobile anxiety sensitivity program. Br J Clin Psychol 2022 Jan 03;61 Suppl 1(Suppl 1):111-129 [FREE Full text] [doi: 10.1111/bjc.12294] [Medline: 33939190]
50. Arozullah AM, Yarnold PR, Bennett CL, Soltysik RC, Wolf MS, Ferreira RM, et al. Development and validation of a short-form, rapid estimate of adult literacy in medicine. Med Care 2007 Nov;45(11):1026-1033. [doi: 10.1097/MLR.0b013e3180616c1b] [Medline: 18049342]
51. Zvolensky MJ, Garey L, Fergus TA, Gallagher MW, Viana AG, Shepherd JM, et al. Refinement of anxiety sensitivity measurement: the Short Scale Anxiety Sensitivity Index (SSASI). Psychiatry Res 2018 Nov;269:549-557 [FREE Full text] [doi: 10.1016/j.psychres.2018.08.115] [Medline: 30199696]
52. Boardman T, Catley D, Mayo MS, Ahluwalia JS. Self-efficacy and motivation to quit during participation in a smoking cessation program. Int J Behav Med 2005 Dec;12(4):266-272. [doi: 10.1207/s15327558ijbm1204_7] [Medline: 16262545]

53. Brooke P, Bullock R. Validation of a 6 item cognitive impairment test with a view to primary care usage. Int J Geriatr Psychiatry 1999 Nov;14(11):936-940. [Medline: 10556864]
54. 2008 PHS Guideline Update Panel, Liaisons,Staff. Treating tobacco use and dependence: 2008 update U.S. public health service clinical practice guideline executive summary. Respir Care 2008 Sep;53(9):1217-1222 [FREE Full text] [Medline: 18807274]
55. Hébert ET, Ra CK, Alexander AC, Helt A, Moisiuc R, Kendzor DE, et al. A mobile just-in-time adaptive intervention for smoking cessation: pilot randomized controlled trial. J Med Internet Res 2020 Mar 09;22(3):e16907 [FREE Full text] [doi: 10.2196/16907] [Medline: 32149716]
56. Treating tobacco use and dependence: 2008 update. US Department of Health and Human Services. 2008. URL: https://www.ncbi.nlm.nih.gov/books/NBK63952/ [accessed 2024-03-05]
57. Sweeney CT, Fant RV, Fagerstrom KO, McGovern JF, Henningfield JE. Combination nicotine replacement therapy for smoking cessation: rationale, efficacy and tolerability. CNS Drugs 2001;15(6):453-467. [doi: 10.2165/00023210-200115060-00004] [Medline: 11524024]
58. Home page. U.S. Department of Health and Human Services. URL: https://smokefree.gov/ [accessed 2024-04-03]
59. Forney DJ, Sheehan DM, Dale SK, Li T, De La Rosa M, Spencer EC, et al. The impact of HIV-related stigma on racial/ethnic disparities in retention in HIV care among adults living with HIV in Florida. J Racial Ethn Health Disparities (Forthcoming) 2023 Jul 26. [doi: 10.1007/s40615-023-01715-1] [Medline: 37495905]
60. Williams DR, Mohammed SA. Discrimination and racial disparities in health: evidence and needed research. J Behav Med 2009 Feb 22;32(1):20-47 [FREE Full text] [doi: 10.1007/s10865-008-9185-0] [Medline: 19030981]
61. van Ballegooijen W, Klein B, Lindefors N. ICBT for panic disorder and agoraphobia: from the computer at home to real-life 'In Vivo' exposure. In: Lindefors N, Andersson G, editors. Guided Internet-Based Treatments in Psychiatry. Cham, Switzerland: Springer; 2016:33-52.
62. Ebenfeld L, Kleine Stegemann S, Lehr D, Ebert DD, Jazaieri H, van Ballegooijen W, et al. Efficacy of a hybrid online training for panic symptoms and agoraphobia: study protocol for a randomized controlled trial. Trials 2014 Nov 04;15(1):427 [FREE Full text] [doi: 10.1186/1745-6215-15-427] [Medline: 25370504]
63. Neal AM, Turner SM. Anxiety disorders research with African Americans: current status. Psychol Bull 1991;109(3):400-410. [doi: 10.1037//0033-2909.109.3.400]
64. Coughtrey AE, Pistrang N. The effectiveness of telephone-delivered psychological therapies for depression and anxiety: a systematic review. J Telemed Telecare 2018 Feb;24(2):65-74. [doi: 10.1177/1357633X16686547] [Medline: 28038505]
65. Businelle MS, Ma P, Kendzor DE, Frank SG, Vidrine DJ, Wetter DW. An ecological momentary intervention for smoking cessation: evaluation of feasibility and effectiveness. J Med Internet Res 2016 Dec 12;18(12):e321 [FREE Full text] [doi: 10.2196/jmir.6058] [Medline: 27956375]
66. Insight mHealth platform on the app store. Apple Store. URL: https://apps.apple.com/us/app/insight-mhealth-platform/id1582652446 [accessed 2024-03-05]
67. Benowitz NL, Bernert JT, Foulds J, Hecht SS, Jacob III P, Jarvis MJ, et al. Biochemical verification of tobacco use and abstinence: 2019 update. Nicotine Tob Res 2020 Jun 12;22(7):1086-1097 [FREE Full text] [doi: 10.1093/ntr/ntz132] [Medline: 31570931]
68. Perkins KA, Karelitz JL, Jao NC. Optimal carbon monoxide criteria to confirm 24-hr smoking abstinence. Nicotine Tob Res 2013 May 18;15(5):978-982 [FREE Full text] [doi: 10.1093/ntr/nts205] [Medline: 22990219]
69. Tevyaw TO, Colby SM, Tidey JW, Kahler CW, Rohsenow DJ, Barnett NP, et al. Contingency management and motivational enhancement: a randomized clinical trial for college student smokers. Nicotine Tob Res 2009 Jun;11(6):739-749 [FREE Full text] [doi: 10.1093/ntr/ntp058] [Medline: 19443788]
70. Heil SH, Higgins ST, Bernstein IM, Solomon LJ, Rogers RE, Thomas CS, et al. Effects of voucher-based incentives on abstinence from cigarette smoking and fetal growth among pregnant women. Addiction 2008 Jun 28;103(6):1009-1018 [FREE Full text] [doi: 10.1111/j.1360-0443.2008.02237.x] [Medline: 18482424]
71. Higgins ST, Bernstein IM, Washio Y, Heil SH, Badger GJ, Skelly JM, et al. Effects of smoking cessation with voucher-based contingency management on birth outcomes. Addiction 2010 Nov 15;105(11):2023-2030 [FREE Full text] [doi: 10.1111/j.1360-0443.2010.03073.x] [Medline: 20840188]
72. Stoops WW, Dallery J, Fields NM, Nuzzo PA, Schoenberg NE, Martin CA, et al. An internet-based abstinence reinforcement smoking cessation intervention in rural smokers. Drug Alcohol Depend 2009 Nov 01;105(1-2):56-62 [FREE Full text] [doi: 10.1016/j.drugalcdep.2009.06.010] [Medline: 19615830]
73. Dunn KE, Sigmon SC, Thomas CS, Heil SH, Higgins ST. Voucher-based contingent reinforcement of smoking abstinence among methadone-maintained patients: a pilot study. J Appl Behav Anal 2008 Feb 27;41(4):527-538 [FREE Full text] [doi: 10.1901/jaba.2008.41-527] [Medline: 19192857]
74. Etter JF. Financial incentives for smoking cessation in low-income smokers: study protocol for a randomized controlled trial. Trials 2012 Jun 21;13(1):88 [FREE Full text] [doi: 10.1186/1745-6215-13-88] [Medline: 22721577]
75. Berlin I, Radzius A, Henningfield JE, Moolchan ET. Correlates of expired air carbon monoxide: effect of ethnicity and relationship with saliva cotinine and nicotine. Nicotine Tob Res 2001 Nov 1;3(4):325-331. [doi: 10.1080/14622200110050400] [Medline: 11694199]

76. Jarvis MJ, Tunstall-Pedoe H, Feyerabend C, Vesey C, Saloojee Y. Comparison of tests used to distinguish smokers from nonsmokers. Am J Public Health 1987 Nov;77(11):1435-1438. [doi: 10.2105/ajph.77.11.1435] [Medline: 3661797]
77. Fritz M, Wallner R, Grohs U, Kemmler G, Saria A, Zernig G. Comparable sensitivities of urine cotinine and breath carbon monoxide at follow-up time points of three months or more in a smoking cessation trial. Pharmacology 2010 Mar 17;85(4):234-240. [doi: 10.1159/000280435] [Medline: 20299823]
78. WHOQOL-HIV BREF, 2012 revision. World Health Organization. URL: https://www.who.int/publications/i/item/WHO-MSD-MER-Rev-2012-02 [accessed 2024-03-05]
79. Lu M, Safren SA, Skolnik PR, Rogers WH, Coady W, Hardy H, et al. Optimal recall period and response task for self-reported HIV medication adherence. AIDS Behav 2008 Jan 19;12(1):86-94. [doi: 10.1007/s10461-007-9261-4] [Medline: 17577653]
80. Chesney MA, Ickovics JR, Chambers DB, Gifford AL, Neidig J, Zwickl B, et al. AIDS Care 2000 Jun 27;12(3):255-266. [doi: 10.1080/09540120050042891] [Medline: 10928201]
81. Johnson MO, Neilands TB, Koester KA, Wood T, Sauceda JA, Dilworth SE, et al. Detecting disengagement from HIV care before it is too late: development and preliminary validation of a novel index of engagement in HIV care. J Acquir Immune Defic Syndr 2019 Jun 01;81(2):145-152 [FREE Full text] [doi: 10.1097/QAI.0000000000002000] [Medline: 30865180]
82. Sternthal MJ, Slopen N, Williams DR. Racial disparities in health: how much does stress really matter? Du Bois Rev 2011;8(1):95-113 [FREE Full text] [doi: 10.1017/S1742058X11000087] [Medline: 29887911]
83. Peek ME, Nunez-Smith M, Drum M, Lewis TT. Adapting the everyday discrimination scale to medical settings: reliability and validity testing in a sample of African American patients. Ethn Dis 2011;21(4):502-509 [FREE Full text] [Medline: 22428358]
84. Bevan N, Kirakowski J, Maissel J. What is usability? In: Bullinger HJ, editor. Human Aspects in Computing: Design and Use of Interactive Systems and Work With Terminals. Cambridge, MA: Elsevier Academic Press; 1991.
85. Kirakowski J, Corbett M. Measuring user satisfaction. In: Proceedings of the 4th Conference of the British Computer Society on People and computers IV. 1988 Presented at: BSC HCI '88; August 5-9, 1988; Manchester, UK p. 329-338 URL: https://dl.acm.org/doi/proceedings/10.5555/54675
86. Lewis JR. The system usability scale: past, present, and future. Int J Hum Comput Interact 2018 Mar 30;34(7):577-590. [doi: 10.1080/10447318.2018.1455307]
87. Shiffman S, Hufford M, Hickcox M, Paty JA, Gnys M, Kassel JD. Remember that? A comparison of real-time versus retrospective recall of smoking lapses. J Consult Clin Psychol 1997 Apr;65(2):292-300. [doi: 10.1037/0022-006x.65.2.292.a] [Medline: 9086693]
88. Stone AA, Shiffman S, Schwartz JE, Broderick JE, Hufford MR. Patient non-compliance with paper diaries. BMJ 2002 May 18;324(7347):1193-1194 [FREE Full text] [doi: 10.1136/bmj.324.7347.1193] [Medline: 12016186]
89. Wetter DW, McClure JB, Cofta-Woerpel L, Costello TJ, Reitzel LR, Businelle MS, et al. A randomized clinical trial of a palmtop computer-delivered treatment for smoking relapse prevention among women. Psychol Addict Behav 2011 Jun;25(2):365-371 [FREE Full text] [doi: 10.1037/a0022797] [Medline: 21500879]
90. Stone AA, Schwartz JE, Neale JM, Shiffman S, Marco CA, Hickcox M, et al. A comparison of coping assessed by ecological momentary assessment and retrospective recall. J Pers Soc Psychol 1998 Jun;74(6):1670-1680. [doi: 10.1037//0022-3514.74.6.1670] [Medline: 9654765]
91. Shiffman S, Paty JA, Gnys M, Kassel JA, Hickcox M. First lapses to smoking: within-subjects analysis of real-time reports. J Consult Clin Psychol 1996 Apr;64(2):366-379. [doi: 10.1037//0022-006x.64.2.366] [Medline: 8871421]
92. Piasecki TM, Cooper ML, Wood PK, Sher KJ, Shiffman S, Heath AC. Dispositional drinking motives: associations with appraised alcohol effects and alcohol consumption in an ecological momentary assessment investigation. Psychol Assess 2014 Jun;26(2):363-369 [FREE Full text] [doi: 10.1037/a0035153] [Medline: 24274049]
93. Simons JS, Dvorak RD, Batien BD, Wray TB. Event-level associations between affect, alcohol intoxication, and acute dependence symptoms: effects of urgency, self-control, and drinking experience. Addict Behav 2010 Dec;35(12):1045-1053 [FREE Full text] [doi: 10.1016/j.addbeh.2010.07.001] [Medline: 20685044]
94. Swendsen JD, Tennen H, Carney MA, Affleck G, Willard A, Hromi A. Mood and alcohol consumption: an experience sampling test of the self-medication hypothesis. J Abnorm Psychol 2000;109(2):198-204. [doi: 10.1037//0021-843x.109.2.198]
95. Kendzor DE, Shuval K, Gabriel KP, Businelle MS, Ma P, High RR, et al. Impact of a mobile phone intervention to reduce sedentary behavior in a community sample of adults: a quasi-experimental evaluation. J Med Internet Res 2016 Jan 25;18(1):e19 [FREE Full text] [doi: 10.2196/jmir.5137] [Medline: 26810027]
96. Businelle MS, Kendzor DE, Kesh A, Cuate EL, Poonawalla IB, Reitzel LR, et al. Small financial incentives increase smoking cessation in homeless smokers: a pilot study. Addict Behav 2014 Mar;39(3):717-720. [doi: 10.1016/j.addbeh.2013.11.017] [Medline: 24321696]
97. Wilson V. Research methods: triangulation. Evid Based Libr Inf Pract 2014 Mar 05;9(1):74-75 [FREE Full text] [doi: 10.18438/b8ww3x]
98. Rooke SE, Gates PJ, Norberg MM, Copeland J. Applying technology to the treatment of cannabis use disorder: comparing telephone versus Internet delivery using data from two completed trials. J Subst Abuse Treat 2014 Jan;46(1):78-84. [doi: 10.1016/j.jsat.2013.08.007] [Medline: 24051076]

99. Hindson J, Hanstock T, Dunlop A, Kay-Lambkin F. Internet-delivered tobacco treatment for people using cannabis: a randomized trial in two Australian cannabis clinics. JMIR Form Res 2020 Dec 07;4(12):e14344 [FREE Full text] [doi: 10.2196/14344] [Medline: 33284121]
100. Macatee RJ, Albanese BJ, Okey SA, Afshar K, Carr M, Rosenthal MZ, et al. Impact of a computerized intervention for high distress intolerance on cannabis use outcomes: a randomized controlled trial. J Subst Abuse Treat 2021 Feb;121:108194 [FREE Full text] [doi: 10.1016/j.jsat.2020.108194] [Medline: 33357604]
101. Saldaña J. The Coding Manual for Qualitative Researchers. Thousand Oaks, CA: Sage Publications; Oct 18, 2016.
102. Patton MQ, Campbell-Patton CE. Utilization-Focused Evaluation. Thousand Oaks, CA: Sage Publications; 2008.
103. Miles MB, Huberman AM, Saldaña J. Qualitative Data Analysis: A Methods Sourcebook. Thousand Oaks, CA: Sage Publications; 2019.
104. Creswell JW, Clark VL. Designing and Conducting Mixed Methods Research. Thousand Oaks, CA: Sage Publications; 2017.
105. Hedeker D, Gibbons RD, Waternaux C. Sample size estimation for longitudinal designs with attrition: comparing time-related contrasts between two groups. J Educ Behav Stat 1999;24(1):70. [doi: 10.2307/1165262]
106. Fritz MS, Mackinnon DP. Required sample size to detect the mediated effect. Psychol Sci 2007 Mar 04;18(3):233-239 [FREE Full text] [doi: 10.1111/j.1467-9280.2007.01882.x] [Medline: 17444920]
107. Morse JM. Strategies for sampling. In: Morse JM, editor. Qualitative Nursing Research: A Contemporary Dialogue. Thousand Oaks, CA: Sage Publications; 1991:127-145.
108. Mobile fact sheet. Pew Research Center. 2021. URL: https://www.pewresearch.org/internet/fact-sheet/mobile/ [accessed 2024-03-05]
109. Hovenkamp-Hermelink JH, van der Veen DC, Oude Voshaar RC, Batelaan NM, Penninx BW, Jeronimus BF, et al. Anxiety sensitivity, its stability and longitudinal association with severity of anxiety symptoms. Sci Rep 2019 Mar 13;9(1):4314 [FREE Full text] [doi: 10.1038/s41598-019-39931-7] [Medline: 30867472]
110. Aral SO, Adimora AA, Fenton KA. Understanding and responding to disparities in HIV and other sexually transmitted infections in African Americans. Lancet 2008 Jul;372(9635):337-340. [doi: 10.1016/s0140-6736(08)61118-6]
111. Brandt CP, Bakhshaie J, Jardin C, Lemaire C, Kauffman BY, Sharp C, et al. The moderating effect of smoking status on the relation between anxiety sensitivity, sexual compulsivity, and suicidality among people with HIV/AIDS. Int J Behav Med 2017 Feb 11;24(1):92-100 [FREE Full text] [doi: 10.1007/s12529-016-9568-5] [Medline: 27169410]
112. Paulus DJ, Jardin C, Bakhshaie J, Sharp C, Woods SP, Lemaire C, et al. Anxiety sensitivity and hazardous drinking among persons living with HIV/AIDS: an examination of the role of emotion dysregulation. Addict Behav 2016 Dec;63:141-148 [FREE Full text] [doi: 10.1016/j.addbeh.2016.07.013] [Medline: 27497249]
113. Millon EM, Shors TJ. How mental health relates to everyday stress, rumination, trauma and interoception in women living with HIV: a factor analytic study. Learn Motiv 2021 Feb;73:101680. [doi: 10.1016/j.lmot.2020.101680]
114. Farris SG, Langdon KJ, DiBello AM, Zvolensky MJ. Why do anxiety sensitive smokers perceive quitting as difficult? The role of expecting “interoceptive threat” during acute abstinence. Cogn Ther Res 2014 Sep 26;39(2):236-244. [doi: 10.1007/s10608-014-9644-6]
115. Hina F, Aspell JE. Altered interoceptive processing in smokers: evidence from the heartbeat tracking task. Int J Psychophysiol 2019 Aug;142:10-16. [doi: 10.1016/j.ijpsycho.2019.05.012] [Medline: 31152763]
116. Kim M, Park YJ, Kim K, Lee JH. Effect of heightened interoceptive awareness among smokers on misinterpretation of emotional arousal. Soc Behav Pers 2020 Feb 05;48(2):1-8. [doi: 10.2224/sbp.8681]
117. Matthews AK, McConnell EA, Li CC, Vargas MC, King A. Design of a comparative effectiveness evaluation of a culturally tailored versus standard community-based smoking cessation treatment program for LGBT smokers. BMC Psychol 2014 May 30;2(1):12 [FREE Full text] [doi: 10.1186/2050-7283-2-12] [Medline: 25566383]
118. Kong G, Singh N, Krishnan-Sarin S. A review of culturally targeted/tailored tobacco prevention and cessation interventions for minority adolescents. Nicotine Tob Res 2012 Dec 21;14(12):1394-1406 [FREE Full text] [doi: 10.1093/ntr/nts118] [Medline: 22614548]
119. Tan AS, Chen JT, Keen R, Scout N, Gordon B, Applegate J, et al. Culturally tailored anti-smoking messages: a randomized trial with U.S. sexual minority young women. Am J Prev Med (Forthcoming) 2023 Dec 07 [FREE Full text] [doi: 10.1016/j.amepre.2023.12.001] [Medline: 38065403]
120. Hai AH, Batey DS, Lee CS, Li S, Schnall R. Examining the intersection of ethnoracial disparities and HIV status in substance use risks among U.S. adults. AIDS Behav (Forthcoming) 2024 Jan 31. [doi: 10.1007/s10461-024-04277-3] [Medline: 38294646]
121. Bricker JB, Watson NL, Mull KE, Sullivan BM, Heffner JL. Efficacy of smartphone applications for smoking cessation: a randomized clinical trial. JAMA Intern Med 2020 Nov 01;180(11):1472-1480 [FREE Full text] [doi: 10.1001/jamainternmed.2020.4055] [Medline: 32955554]

Abbreviations

ART: antiretroviral therapy

AS: anxiety sensitivity
CO: carbon monoxide
EMA: ecological momentary assessment
MASP: Mobile Anxiety Sensitivity Program
MASP+: Mobile Anxiety Sensitivity Program for Smoking and HIV
NCI: National Cancer Institute
NRT: nicotine replacement therapy
PPA: point prevalence abstinence
RCT: randomized controlled trial
REALM: Rapid Estimate of Adult Literacy in Medicine
REDCap: Research Electronic Data Capture
SSASI: short scale anxiety sensitivity index
UH: University of Houston

Edited by A Mavragani; submitted 22.08.23; peer-reviewed by R Rosen, C Baxter; comments to author 17.12.23; revised version received 09.02.24; accepted 14.02.24; published 24.04.24.

Please cite as:
Bizier A, Jones A, Businelle M, Kezbers K, Hoeppner BB, Giordano TP, Thai JM, Charles J, Montgomery A, Gallagher MW, Cheney MK, Zvolensky M, Garey L
An Integrated mHealth App for Smoking Cessation in Black Smokers With HIV: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2024;13:e52090
URL: https://www.researchprotocols.org/2024/1/e52090
doi:10.2196/52090
PMID:38657227

Protocol

A Hybrid Digital Parenting Program Delivered Within the Malaysian Preschool System: Protocol for a Feasibility Study of a Small-Scale Factorial Cluster Randomized Trial

Hal Cooper[1], MA, MSc; Farah Zeehan Mohd Nadzri[2], BSc; Seema Vyas[1], PhD; Rumaya Juhari[2], Prof Dr; Nellie Ismail[2], PhD; Zarinah Arshat[2], Prof Dr; Durgesh Rajandiran[3], MEd; Laurie Markle[3], MA; Francisco Calderon[1], MSc; Inge Vallance[1], PhD; G J Melendez-Torres[4], DPhil; Chiara Facciolà[5], PhD; Vanisa Senesathith[1], BA; Frances Gardner[1], DPhil; Jamie M Lachman[1,3,6], DPhil

[1]Department of Social Policy and Intervention, University of Oxford, Oxford, United Kingdom

[2]Faculty of Human Ecology, Universiti Putra Malaysia, Selangor, Malaysia

[3]Parenting for Lifelong Health, Oxford, United Kingdom

[4]The Medical School, University of Exeter, Exeter, United Kingdom

[5]Innovations in Development, Education and the Mathematical Sciences International, Reading, United Kingdom

[6]Centre for Social Science Research, University of Cape Town, Cape Town, South Africa

Corresponding Author:
Hal Cooper, MA, MSc
Department of Social Policy and Intervention
University of Oxford
Barnett House, 32-37 Wellington Square
Oxford, OX1 2ER
United Kingdom
Phone: 44 01865 270325
Email: hallam.cooper@spi.ox.ac.uk

Abstract

Background: The United Nations' Sustainable Development Goal 4, and particularly target 4.2, which seeks to ensure that, by 2030, all children have access to quality early childhood development, care, and preprimary education so that they are ready for primary education, is far from being achieved. The COVID-19 pandemic compromised progress by disrupting education, reducing access to well-being resources, and increasing family violence. Evidence from low- and middle-income countries suggests that in-person parenting interventions are effective at improving child learning and preventing family violence. However, scaling up these programs is challenging because of resource constraints. Integrating digital and human-delivered intervention components is a potential solution to these challenges. There is a need to understand the feasibility and effectiveness of such interventions in low-resource settings.

Objective: This study aims to determine the feasibility and effectiveness of a digital parenting program (called Naungan Kasih in Bahasa Melayu [Protection through Love]) delivered in Malaysia, with varying combinations of 2 components included to encourage engagement. The study is framed around the following objectives: (1) to determine the recruitment, retention, and engagement rates in each intervention condition; (2) to document implementation fidelity; (3) to explore program acceptability among key stakeholders; (4) to estimate intervention costs; and (5) to provide indications of the effectiveness of the 2 components.

Methods: This 10-week factorial cluster randomized trial compares *ParentText*, a chatbot that delivers parenting and family violence prevention content to caregivers of preschool-aged children in combination with 2 engagement components: (1) a WhatsApp support group and (2) either 1 or 2 in-person sessions. The trial aims to recruit 160 primary and 160 secondary caregivers of children aged 4-6 years from 8 schools split equally across 2 locations: Kuala Lumpur and Negeri Sembilan. The primary outcomes concern the feasibility and acceptability of the intervention and its components, including recruitment, retention, and engagement. The effectiveness outcomes include caregiver parenting practices, mental health and relationship quality, and child development. The evaluation involves mixed methods: quantitative caregiver surveys, digitally tracked engagement data of caregivers' use of the digital intervention components, direct assessments of children, and focus group discussions with caregivers and key stakeholders.

Results: Overall, 208 parents were recruited at baseline December 2023: 151 (72.6%) primary caregivers and 57 (27.4%) secondary caregivers. In January 2024, of these 208 parents, 168 (80.8%) enrolled in the program, which was completed in February. Postintervention data collection was completed in March 2024. Findings will be reported in the second half of 2024.

Conclusions: This is the first factorial cluster randomized trial to assess the feasibility of a hybrid human-digital playful parenting program in Southeast Asia. The results will inform a large-scale optimization trial to establish the most effective, cost-effective, and scalable version of the intervention.

Trial Registration: OSF Registries; https://osf.io/f32ky

International Registered Report Identifier (IRRID): DERR1-10.2196/55491

(JMIR Res Protoc 2024;13:e55491) doi:10.2196/55491

KEYWORDS

parenting intervention; chatbot-led public health intervention; engagement; implementation science; feasibility; evidence-based program

Introduction

Background

Globally, while gains have been made in promoting access to education, the United Nations' Sustainable Development Goal 4 and, in particular target 4.2, to ensure that, by 2030, all girls and boys have access to quality early childhood development, care, and preprimary education so that they are ready for primary education, is far from being achieved [1]. Before the COVID-19 pandemic, 43% of children in low- and middle-income countries (LMICs) were at risk of not achieving their developmental potential [2]. The COVID-19 pandemic has exacerbated this risk; between March 2020 and February 2021, an estimated 167 million preprimary-aged children had no access to early childhood education and care [3] at an age that represents a sensitive period in children's educational development. Early childhood experiences and skills predict future academic achievement [4], with the strongest predictors being school entry–level mathematics, reading, and attention skills [5]. Furthermore, children who enter school with a knowledge of letters and numbers are likely to have achieved this because of parental instruction [6]. Thus, the *home learning environment*—the availability of educational resources (eg, books) and the quality of parenting activities (eg, reading to children and playing number games) [7]—is important for the development of foundational skills, including literacy and numeracy [8].

A World Bank review in 2023 of preschool education in Malaysia reported that preschools in the country aim to develop children's "school readiness" for entry into compulsory primary school at age 7 years [9]. Malaysia endured one of the region's longest periods of school closure because of the COVID-19 pandemic. Consequently, many children were poorly prepared to start primary school because of learning loss that had particularly impacted early literacy [9]. Other dimensions of children's development, such as socioemotional and psychomotor development, were also adversely affected. Households with low incomes were disproportionately affected because state-funded preschools, that is, those in the Jabatan Kemajuan Masyarakat (Department of Community Development in Bahasa Melayu [KEMAS]), which is part of the Ministry of Rural and Regional Development) system, were closed longer than private preschools, and children from households with low incomes were less likely to have engaged in web-based schooling activities.

In addition to improving access to, and the quality of, public preschool education in Malaysia, the World Bank report recommends supporting parents' improved involvement in preschool-aged children's education and learning at home [9]. A national health survey in 2016 found that just 25% of children in Malaysia receive early learning stimulation at home [10]. Research has shown parenting interventions to be effective in supporting children's learning. A meta-analysis of 14 studies in high-income countries found that parenting interventions (such as training parents to share books with their children) improved the reading development of children aged 4 to 8 years [11]. These findings have also been obtained in LMICs; for example, a randomized controlled trial of children aged 3 to 5 years in the Philippines found that, compared to the control group, children whose parents had received 1 of 3 types of training—dialogic reading coaching, early literacy skills development coaching, and numeracy skills development coaching—improved significantly in several dimensions of their development, including preliteracy skills (eg, phonological awareness and letter name knowledge) and numeracy skills [12]. This evidence reinforces the World Bank's recommendation that parents should be supported in promoting their preschool children's learning and development.

Preschools in Malaysia are an essential component of the country's education system. Formal education in Malaysia typically commences at age 4 years; however, it is not compulsory. Nevertheless, most children aged <6 years are enrolled in preschool to prepare them for formal schooling and to lay the foundation for their future academic and personal development. Several agencies are involved in providing preschool education in Malaysia, including the Ministry of Education, public entities (eg, Tabika Perpaduan [Unity Kindergarten] and Taman Bimbingan Kanak-Kanak (Children's Guidance Park [TABIKA]) KEMAS), state government–supervised institutions (eg, Majlis Agama Islam Wilayah Persekutuan [Islamic Religious Council of the Federal Territory] Islamic kindergartens and Jabatan Agama Islam Selangor [Selangor Islamic Religious Department] preschools), and private kindergartens. The early childhood education

program TABIKA, organized by KEMAS, provides early education opportunities for children aged 4 to 6 years. TABIKA KEMAS preschools use a *learning through play* pedagogical approach, which aligns with children's natural drive to play, be curious, and experiment [13].

Learning through play is essential for child development and refers to the process by which children acquire knowledge, develop skills, and explore their world through play activities. Play is a natural and instinctive behavior for children, and it serves as a powerful tool for their cognitive, social, emotional, and physical development. Positive parenting emphasizes building a strong, supportive, and nurturing relationship between parents and children. Parents can facilitate learning through play with positive parenting by providing safe and stimulating environments and play materials, allowing children to take the lead during playtime [14], and encouraging opportunities for social interactions for playing to facilitate learning [15].

Despite compelling evidence of the benefits of playful and nurturing parenting for improved learning and educational outcomes, there are significant challenges to the uptake of in-person interventions aimed at promoting such parenting [16]. In addition, local governments and service providers face multiple challenges implementing face-to-face or in-person parenting programs [17-20]. Parenting programs are often too expensive to deliver effectively at scale in low-resource settings due to their complexity, intensity, and length [21]. In Malaysia, barriers to the scale-up of in-person parenting programs include limited financing and resource allocation for such programs, and those that are implemented are usually one-off workshops with a limited or no evidence base [22].

In response to the COVID-19 pandemic and the need to create cost-effective and scalable interventions, remote-delivered parenting programs have been tested by several researchers [23]. A recent systematic review suggests positive impacts on parenting skills and childhood outcomes, although the effect may not be as great when compared to in-person–delivered programs [24]. The main barrier to implementation is difficulty in contacting parents by telephone. However, a study that used a combination of methods (SMS text messaging and group meetings) to address the restrictions associated with remote-only delivery showed an improvement in the effectiveness of the program [25].

In Malaysia, a feasibility pilot study of an in-person program highlighted the demand from parents for flexible delivery modalities [26]. Thus, a collaboration among Universiti Putra Malaysia (UPM), the University of Oxford, United Nations Children's Fund (UNICEF) Malaysia, Malaysian government ministries, and civil society organizations has identified the need for digital and hybrid solutions to address such challenges in the scale-up of parenting programs. Web-based and hybrid delivery of such interventions has the advantage of lower costs compared to in-person–only programs, which is central to ensuring scale-up, and can potentially improve accessibility for parents who would otherwise not participate, or who have difficulty participating, in in-person programs, such as male caregivers, migrant families, and people living with disabilities.

In addition to improved learning and educational outcomes, evidence has shown parenting interventions to be effective in reducing violence against children and promoting child well-being more generally in LMICs [21,27-31]. These interventions aim to improve caregiver-child relationships through positive parenting and support parents in controlling their children's behavioral issues with age-appropriate and effective nonviolent discipline methods. These dimensions of children's development and welfare are particularly important in Malaysia and must also be considered. A review of the prevalence of child abuse and neglect in Malaysia reports evidence of 53% of children experiencing physical parental maltreatment, 20% experiencing emotional abuse, and 21.3% experiencing sexual abuse [32]. The impact of multitype childhood abuse is associated with negative effects on children's psychological status (depression, anxiety, and stress) when they grow into adults [33].

In Malaysia, the Naungan Kasih (Protection through Love) Positive Parenting Program was developed in collaboration with the Malaysian government's National Population and Family Development Board, UPM, UNICEF Malaysia, the Malaysian Association of Social Workers, Maestral International, and Parenting for Lifelong Health. National Population and Family Development Board staff members were trained to deliver the program in person to parents. Despite challenges to uptake, the intervention was effective in providing support to caregivers, improving parent-child relationships, and significantly reducing child maltreatment [26].

This study, conducted within the TABIKA KEMAS program, will assess the feasibility, acceptability, and effectiveness of ParentText delivered (1) with a WhatsApp support group and (2) with 1 or 2 in-person sessions. The results will inform a full optimization trial to determine the most effective and cost-effective version of the program, which is planned to take place across Malaysia with 800 families in the second half of 2024.

Aims and Objectives

The primary aims of this pilot factorial cluster randomized trial are two-fold: (1) to determine the feasibility of the intervention and (2) to examine preliminary indications of the relative effectiveness of a multicomponent human-digital hybrid playful parenting intervention (ParentText combined with a WhatsApp support group and either 1 or 2 in-person sessions) at government-run preschools in Malaysia.

The objectives are as follows:

1. To determine the recruitment, retention, and engagement rates in all 4 intervention conditions and explore reasons for these rates
2. To document the extent to which the intervention was implemented in line with the program model (fidelity) in rural and periurban school settings
3. To explore the acceptability of the parenting program among caregivers, facilitators, supervisors, and members of the KEMAS leadership team
4. To estimate the costs of delivering the different intervention components

5. To provide preliminary indications of the relative effectiveness and cost-effectiveness of the different intervention components on the intended intervention outcomes, including proximal outcomes (ie, positive parenting, child physical and emotional abuse, and parent mental health and stress) and distal outcomes (ie, child learning [namely literacy, numeracy, and socioemotional development], child behavior, intimate partner relationships, financial stress, and parent quality of life).

Methods

Study Setting

The study will take place within the preschool system in 2 locations in Malaysia: the federal territory of Kuala Lumpur and Negeri Sembilan. Kuala Lumpur is a periurban location, while Negeri Sembilan is more rural. This contrast will provide comprehensive information pertaining to the feasibility and acceptability of the program across different contexts.

Trial Design

This feasibility pilot is a 2×2 factorial cluster randomized trial that compares ParentText (chatbot-led parenting program) delivered to all participants, with different combinations of two engagement components: (1) a WhatsApp support group (yes or no) and (2) either 1 or 2 in-person sessions (Table 1). This study will adopt a parallel design using a 1:1:1:1 allocation ratio (each cluster at each study site exposed to 1 experimental condition).

Table 1. Experimental conditions from 2×2 factorial design (n=8 clusters; n=160 families).

Condition	Clusters (schools; n=8), n (%)	Caregivers (primary, n=160; primary and secondary, n=320), n (%)	Children (n=160), n (%)	Facilitators (n=8), n (%)	ParentText	WhatsApp support group (yes or no)	In-person sessions, n
1	2 (25)	40 (25); 80 (25)	40 (25)	2 (25)	On	No	1
2	2 (25)	40 (25); 80 (25)	40 (25)	2 (25)	On	Yes	1
3	2 (25)	40 (25); 80 (25)	40 (25)	2 (25)	On	No	2
4	2 (25)	40 (25); 80 (25)	40 (25)	2 (25)	On	Yes	2

Eligibility Criteria

Study participants include caregivers, children, program facilitators, KEMAS supervisors, and members of the KEMAS leadership team. Participants must provide informed consent (parents, caregivers, program facilitators, program supervisors, and KEMAS leadership team members) or verbal assent (children) to participate in the study and before any study procedures take place.

Inclusion Criteria

Caregivers eligible for the trial must be aged ≥18 years, be responsible for a child aged between 4 and 6 years who is registered with a KEMAS preschool, live in the same household with the child for at least 4 nights a month, and have access to a mobile phone compatible with WhatsApp.

Children eligible for the trial must be aged between 4 and 6 years, be enrolled in a KEMAS preschool, and have parental consent to participate in the study.

Teachers and facilitators of the program must be aged ≥18 years, be registered employees of a KEMAS preschool, have a diploma or certificate in early childhood education or equivalent, have participated in a facilitator training workshop, and be available to deliver the intervention package.

KEMAS supervisors must be aged ≥18 years, be registered supervisors with KEMAS, have a diploma or certificate in early childhood education or equivalent, have participated in 2 intervention program trainings (facilitator training workshop [for new facilitators to deliver the program] and training of trainers workshop [supervisors who completed the facilitator training workshop were trained to deliver training to new facilitators]).

KEMAS leadership team members must be aged ≥18 years and be federal or state administrative staff members of the Division of Early Childhood Education within KEMAS.

Schools

Preschools from the 2 study sites were eligible for inclusion if they had sufficiently sized classes (20-25 children aged 4-6 years/class). Eight preschools were selected from a list of eligible preschools (provided by KEMAS; Multimedia Appendix 1) in Kuala Lumpur and Negeri Sembilan (4 schools per study site). Within each selected preschool, 1 class will be selected (randomly if >1 class) from which 20 families will be invited to participate in the study. Teachers of the selected classes will act as facilitators and contact the families of the children and invite 2 caregivers to participate in the study. Four children in each cluster (ie, 32 in total) will be randomly selected to participate in direct assessments.

Intervention

The intervention is a hybrid human-digital playful parenting program Naungan Kasih, which consists of a chatbot-led parenting program (ParentText 2.0) delivered to all participants and two intervention engagement components: (1) a WhatsApp support group (yes or no) and (2) either 1 or 2 in-person sessions.

ParentText

ParentText is a chatbot-led parenting intervention that delivers personalized, gamified, scheduled, and on-demand messages through WhatsApp, audio, and visual messages to caregivers of children at different developmental stages, that is, from ages 0 to 23 months, 2 to 9 years, and 10 to 17 years. It was developed by the UK-based charities Parenting for Lifelong

Health and IDEMS International. The version targeting caregivers of children aged 2 to 9 years is used in this trial, with additional content specifically relevant for caregivers of children aged 4 to 6 years.

The ParentText version used for this intervention was adapted in response to key findings from previous research in Malaysia by project partners; for example, a pre-post evaluation of the in-person version of Naungan Kasih delivered in 2 communities with low-income status between November 2018 and April 2019 found promising intervention effects on some caregiver self-reports (n=74), including reductions in overall child maltreatment, physical abuse, emotional abuse, attitudes supporting corporal punishment, and child behavior problems, as well as improvements in early childhood involvement [26]. However, no effects were found on positive parenting, harsh parenting, parental mental health, and marital satisfaction; nor were there any significant intervention effects on child (aged 10 to 17 years) reports (n=26). Qualitative findings highlighted tangible benefits for female program recipients, such as reduced use of harsh physical and verbal punishment toward their child and lower stress associated with parenting, as well as improved communications with partners [26]. However, program facilitators reported that the traveling required to facilitate in-person sessions on top of their daily work left them feeling overburdened and highlighted the potential of digital modalities.

ParentChat, a digital parenting program delivered through WhatsApp, was piloted in 2021 in Malaysia. The study found a 23% reduction in parenting stress, a 24% reduction in parental report of child behavior problems, a 15% increase in parental self-efficacy to prevent sexual abuse, and a 39% increase in intimate partner respect [34]. Caregiver attendance during the 8-week program was high; on average, parents attended 81% of the 16 sessions. In addition, a pilot of ParentText with 82 caregivers in Malaysia showed a 68% enrollment rate, with average engagement of 13 days in the chatbot. Topics most frequently accessed were *Keeping Calm*, *One-on-One Time*, and *Helping Your Children Learn*. When parents interacted with a WhatsApp message, they requested additional content provided within the chatbot 78.8% of the time. Exploratory analyses of program effects found significant improvements in positive parenting behavior. Pilot tests across Malaysia, Jamaica, the Philippines, and South Africa between 2021 and 2022 highlighted five principal areas for attention in improving ParentText [34]: (1) structural issues leading to participant dropout, (2) multimedia being insufficiently engaging, (3) the need for more and improved personalization features, (4) the need for mechanisms to promote re-engagement, and (5) issues with ease of use.

As such, the ParentText program designed for this study has been streamlined, and the goals have broadened to include those more relevant to the Malaysian preschool context; for example, content has been developed to specifically target improving learning through play and child educational outcomes. ParentText is structured around 6 goals, each with several modules (28 modules in total; Textbox 1) that take approximately 5 minutes to complete.

At program onset, caregivers choose which goal they want to start with, and each day, receive a prompt asking them whether they can complete a module related to this goal. On completion of this goal, they choose which one they would like to start next. Caregivers will have 33 days between starting and finishing the program, a time frame that allows 1 day for each module (28 days) plus 5 days to catch up on the days on which they were unable to complete a module.

Although the self-guided nature of ParentText is advantageous in terms of scalability, engagement boosters (such as social networking tools) are commonly used in parenting programs and in digital interventions more broadly to support participation [35-38]. There is evidence for the effectiveness of such engagement boosters; for example, parents taking part in a web-based version of the Triple P parenting intervention who received telephone-delivered support from practitioners engaged more with the program and reported greater program satisfaction than parents who did not receive phone support [39]. However, such improvements in engagement are not always found, as other parenting studies have documented [40]. Another option is to supplement digital interventions with in-person sessions where participants interact with program facilitators (eg, clinicians or counselors), which has been found to improve program adherence [41,42]. However, in-person sessions accrue costs associated with facilitator training [43]. This study seeks to establish whether the use of WhatsApp support groups and in-person sessions promotes engagement, satisfaction, and the effectiveness of the ParentText intervention.

Textbox 1. Overview of ParentText content and number of modules.

Goal and number of modules

- Improve My Relationship with My Child: 5
- Support My Child's Development: 3
- Prepare My Child for Success in School: 6
- Give My Child Structure: 5
- Support Positive Child Behavior: 4
- Keep My Child Safe and Healthy: 5

Component 1: WhatsApp Support Group (Yes or No)

WhatsApp support groups will be facilitated by the preschool teachers (facilitators). Each week, the teacher (facilitator) will share preformulated content on the WhatsApp group using a share button on a facilitator app. Caregivers can use the group to interact with each other and share tips, thoughts, and feelings. Facilitators will not moderate WhatsApp groups; they will only intervene if the content discussed goes against positive parenting practices.

Component 2: In-Person Sessions (1 or 2)

This study aims to investigate rates of engagement and acceptability for the program when participants attend 1 or 2 in-person sessions that are facilitated by preschool teachers. All participants receive the first session, which will comprise an introduction to the program and an onboarding to ParentText. Half of the participants will attend an additional second session at the end of the program, in which they will review content, role-play examples of practices they have learned, and receive a certificate of completion. It is hypothesized that this session will improve the acceptability of the program to caregivers, improve outcomes related to the content of the program thanks to the review and practice, and improve engagement by motivating parents to complete the program and receive a certificate.

Outcomes

Overview

Recruitment, retention, and engagement rates (objective 1) will be measured by the indicators presented in Textbox 2.

Program fidelity (objective 2) is defined as the completion of at least 80% of facilitator-delivered components of the program. This is measured via a checklist that facilitators will complete using a dedicated app in which they will report whether they carried out planned in-person activities and whether they sent weekly WhatsApp support group messages (for those delivering this component of the intervention).

Program acceptability (objective 3) will be assessed using qualitative focus group and interview data, which will gather information from caregivers and facilitators on their views and experiences of the intervention, including what they perceive to be barriers and enablers to using it (among caregivers) and to implementing it (among facilitators). Program acceptability will also be assessed via 2 parent self-report quantitative measures (Textbox 3).

Figure 1 shows the hypothesized association among intervention components, process outcomes, and the intended primary intervention outcomes. Findings relevant to the aforementioned objectives will inform an understanding of the relationship between the intervention components and the process outcomes. Furthermore, these findings will facilitate an understanding of the relationship between process outcomes and the proximal outcome of positive parenting.

The cost of implementation (objective 4) will be measured from the provider perspective and will consider all resource inputs required for intervention. Cost indicators estimated will include the total cost of the intervention (set-up and operation), cost for each intervention component, and the average cost per participant enrolled (unit cost). Costs will be estimated from data gathered on actual expenditures (financial costs) and the market value of all donated and subsidized resource inputs (economic costs).

Preliminary intervention effects (objective 5) will be assessed for the main outcomes of interest, which are described in the following subsections.

Textbox 2. Outcomes and indicators to measure recruitment, retention, and engagement rates (objective 1).

Outcomes and indicators

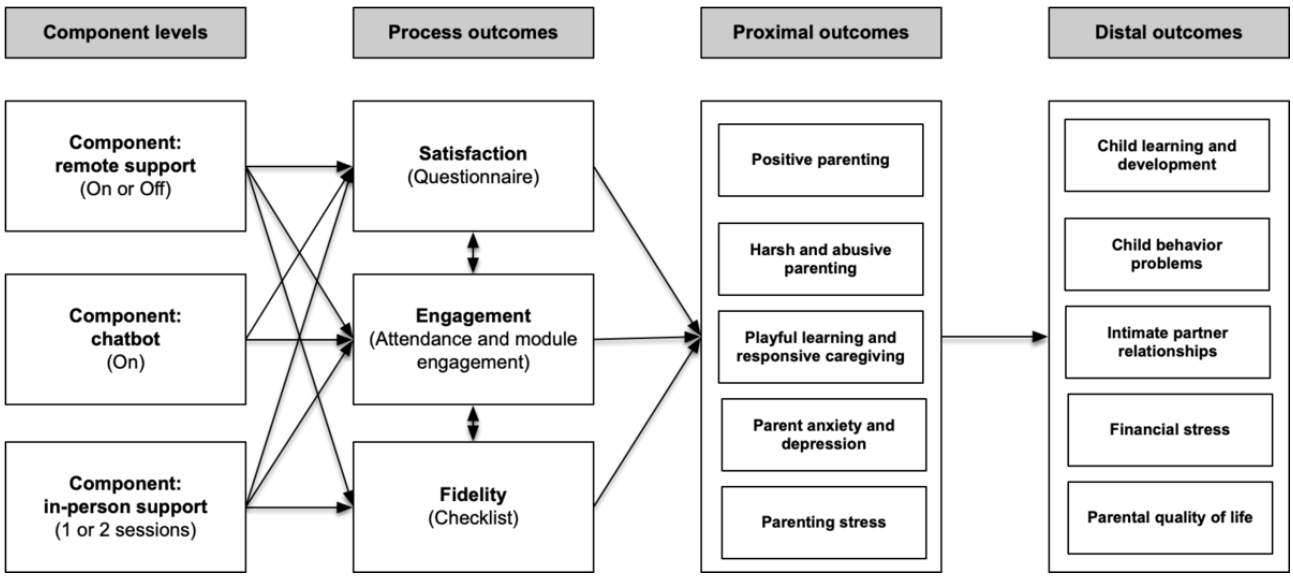
- Recruitment
  - Number of eligible primary caregivers invited to participate and consented
  - Number of eligible secondary caregivers invited to participate and consented
  - Number of baseline assessments completed with primary caregivers
  - Number of baseline assessments completed with secondary caregivers
  - Number of child direct assessments completed at baseline
- Retention
  - Number of posttest assessments completed with primary caregivers
  - Number of posttest assessments completed with secondary caregivers
  - Number of child direct posttest assessments completed
- Engagement
  - Number of ParentText modules completed by primary caregivers
  - Number of ParentText modules completed by secondary caregivers
  - Number of primary caregivers who attended in-person sessions
  - Number of secondary caregivers who attended in-person sessions
  - Number of primary caregivers who participated in WhatsApp support groups
  - Number of secondary caregivers who participated in WhatsApp support groups

Textbox 3. Caregiver outcomes and measures related to program acceptability (objective 3).

Outcomes and measures

- Partner participation in program (postintervention assessment only)
- 8 items adapted from previous studies of Parenting for Lifelong Health interventions
- Program satisfaction (postintervention assessment only)
- 4 items adapted from previous studies of Parenting for Lifelong Health interventions

Figure 1. The hypothesized association among intervention components, process outcomes, and the intended primary intervention outcomes based on the theory of change conceptual model.



Proximal Outcomes

Harsh and Abusive Parenting

Two indicators of harsh and abusive parenting (physical and emotional abuse) will be measured using items from the International Society for the Prevention of Child Abuse and Neglect Child Abuse Screening Tool–Parent version [44]. Each item measures responses on 9-point count scales, asking the number of times a behavior occurred in the previous 2 weeks (ranging from 0=0 times to 8=8 or more times).

Child physical abuse will be measured using 4 items from the physical abuse subscale that ask questions regarding the frequency of the parents disciplining their children physically (eg, "In the last 2 weeks, how often did you discipline your child by slapping, spanking, or hitting with your hand?").

Child emotional abuse will be measured using 5 items from the emotional abuse subscale that ask questions regarding the frequency of the parents disciplining their children emotionally (eg, "In the last 2 weeks, how often did you shout, yell, or scream at your child in an aggressive manner?").

Parent-child playful learning or responsive caregiving

This will be measured using the UNICEF Multiple Indicator Cluster Surveys child development module and family care indicators [45]. The module consists of 4 items that ask parents to state the frequency of a series of learning activities on a scale ranging from 0 to 8 (eg, "How many times in the past 2 weeks (14 days) did you play with your child?").

Positive Parenting

This will be measured using 2 subscales from the Parenting Young Children Scale [46], with 7 items in each scale. Parents will be asked about the frequency of these parenting practices on a scale ranging from 0=not at all to 6=most of the time during the last 2 weeks (last 14 days). The first subscale is *supporting positive behavior* (eg, "Were you able to spend time with your child in ways that were fun for both of you?"). The second subscale is *setting limits* (eg, "Were you able to stick to your rules and not change your mind?").

Parent Anxiety and Depression

This will be measured using the Patient Health Questionnaire-4 [47]. This comprises 4 items relating to anxiety and depression, such as "Over the last 2 weeks, how often have you been bothered by the following problems? Feeling nervous, anxious, or on edge?" Parents are asked to respond on a 4-point Likert scale (ranging from 0=not at all to 3=nearly every day) that addresses parents' perception of the frequency of the problems.

Parenting Stress

This will be measured using the Parenting Stress Scale [48], which comprises 6 items, such as "The major source of stress in my life is my child(ren)," and responses are on a 5-point Likert scale (ranging from 0=strongly disagree to 4=strongly agree) that will address the extent of agreement with the items.

Distal Outcomes

Child Learning and Development

Parent Report

Child learning or *child development* will be measured using the Measure of Development and Early Learning, a module from the Measuring Early Learning Quality and Outcomes (MELQO) framework [49]. The survey consists of 38 items asking caregivers about their child's development across four dimensions: (1) literacy (5 items), (2) mathematics (10 items), (3) socioemotional development (21 items), and (4) executive function (2 items). Examples of items include (1) "Can [name] write his/her own name?" (literacy development), (2) "Can [name] add 3 and 2 together?" (mathematics), (3) "Does [name] share with his/her peers?" (socioemotional development), and (4) "When asked to do several things, how often does [name] remember all the instructions?" (executive function).

Direct Child Assessment

A subset of items from the International Development and Early Learning Assessment (IDELA) [50] will be used to measure 3 dimensions of children's learning and development: emergent literacy (3 items), emergent numeracy (3 items), and socioemotional awareness (2 items); for example, for emergent literacy, the assessor will ask the child to identify letters in a chart; for emergent numeracy, the child will be asked to perform simple addition and subtraction tasks; and for socioemotional awareness, the child will be asked to identify the emotion being experienced by a cartoon girl who is crying.

The items chosen make up 6 of the items from the IDELA *short form*, with 2 questions related to motor skills removed, and 1 question each related to emergent literacy and emergent numeracy added. This was decided because of the ParentText intervention's greater prioritization of these dimensions of children's early learning with respect to motor skills.

Child Behavior

Externalizing problems of the child will be measured using the Child and Adolescent Behavior Inventory [51]. The scale consists of 12 items asking parents about their child's behavior, such as physical aggression, defiance, theft, and vandalism, in the past 2 weeks. Examples of items are "He/she is quick-tempered and has fits of anger" and "He/she destroys things." Responses are based on a 3-point Likert scale (ranging from 0=not true to 2=very true).

Intimate Partner Relationships

Gender-Equitable Behaviors

Four items will assess the frequency of a selection of gender-equitable behaviors; for example, "In the past 2 weeks, how often did you and your partner share housework and caregiving tasks equally?" Responses are based on a 5-point Likert scale (ranging from 1=never to 5=most of the time).

Marital Health Quality

The Marital Health Scale [52] will be used to assess the marital health of the parents. The 5-item scale will ask parents about the extent of agreement in regard to 5 questions about their marriage. Each item will include a similar theme (in parentheses)

for the parents to consider when providing answers regarding their marriage (eg, "My marriage is satisfactory" [content, fulfilled, gratified]). Responses will be based on a 5-point Likert scale (ranging from 1=strongly disagree to 5=strongly agree).

Financial Stress

This will be measured using the Financial Self-Efficacy Scale [53], which consists of 6 items that ask about financial behavior (eg, "It is hard to stick to my spending plan when unexpected expenses arise" and "I lack confidence in my ability to manage my finances"). Responses are based on a 4-point Likert scale.

Parents' Health-Related Quality of Life

The Assessment of Quality of Life-4D instrument [54] will be used to evaluate the parents' health-related quality of life, which will be measured to facilitate an economic evaluation of the program's impact on quality-adjusted life years. There are 12 items that ask questions related to dimensions such as sleep, relationships, and pain, and responses are chosen on a 4-point Likert scale (eg, "Because of your health, your relationships [for example: with your friends, partner or parents] generally: [responses range from] Are very close and warm [to] I have no close and warm relationships").

Partner Participation in Program

This will be measured at postintervention assessment only. Primary caregivers will be asked 8 questions about their partner's participation or nonparticipation in the program (eg, "If your partner or spouse participated in the program, did s/he share with you what they had learnt in the training?"). Items will be measured on a 3-point Likert scale.

Program Satisfaction

This will be measured after the intervention only. Caregivers will be asked 4 questions related to their satisfaction with the program on a 5-point Likert scale (eg, "Would you recommend the program to a friend or relative?" Responses range from 1=strongly not recommend to 5=strongly recommend).

Textbox 4 presents a summary of the intervention effectiveness outcomes, along with measures and number of items.

Textbox 4. Summary of intervention effectiveness outcomes.

Outcomes and measures

- Proximal outcomes
- Child physical abuse: International Society for the Prevention of Child Abuse and Neglect (ISPCAN) Child Abuse Screening Tool–Trial, physical abuse subscale (4 items)
    - Child emotional abuse: ISPCAN Child Abuse Screening Tool–Parent version, emotional abuse subscale (5 items)
    - Playful learning: United Nations Children's Fund Multiple Indicator Cluster Surveys child development module and family care indicators (4 items)
    - Parenting: Parenting Young Children Scale (supporting positive behavior, and setting limits; 14 items)
    - Parent mental health: Patient Health Questionnaire-4 (4 items)
    - Parenting stress: Parenting Stress Scale (6 items)
- Distal outcomes
- Child learning and development: MELQO framework's Measure of Development and Early Learning module teacher or caregiver report item (38 items); IDELA (8 overarching items, total 21 subitems)
- Child behavior—externalizing problems: Child and Adolescent Behavior Inventory, externalizing subscale (12 items)
- Gender-equitable behaviors: adapted from questionnaires used in previous violence prevention studies (4 items)
- Marital health or quality: Marital Health Scale (5 items)
- Financial stress: Financial Self-Efficacy Scale (5 items)
- Quality of life: Assessment of Quality of Life-4D (12 items)

Demographic Information

Caregiver and child demographic information will be collected at baseline and include caregiver age, marital status, employment, educational attainment, literacy, and household socioeconomic status; child age; family health (eg, parent and child disability) and family vulnerabilities (eg, substance abuse by household member); child's relationship to caregiver; presence of child's biological parents and other child in the house; and presence of another person who shares the responsibility of child rearing and their relationship with the caregiver.

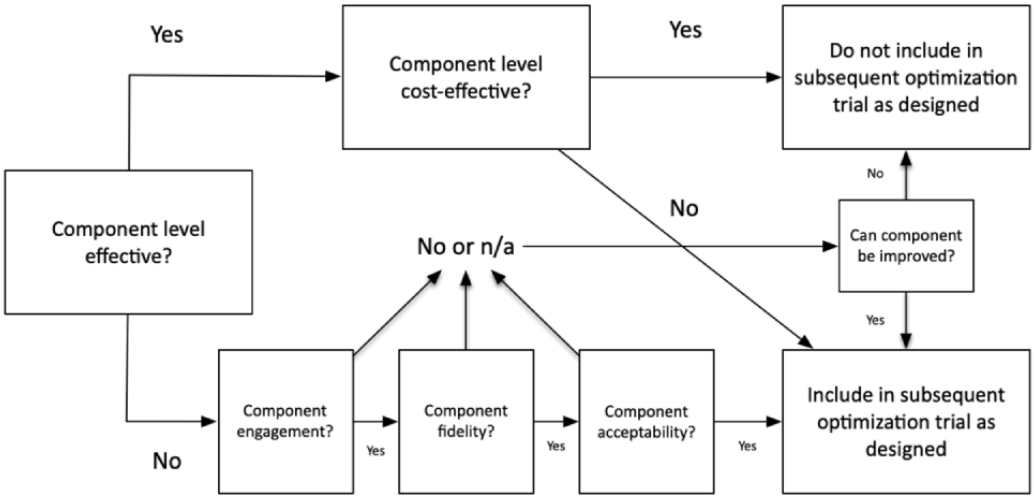
Intervention Effectiveness

Findings related to intervention effectiveness will inform the extent to which intervention components and their related process outcomes are associated with the primary proximal outcome of positive parenting, the primary distal outcome of child development, and other outcomes, namely child maltreatment, child behavior problems, and parent mental health.

Overall, findings related to the 5 study objectives will inform decision-making regarding whether to include intervention components or which level of intervention component to include in future evaluations of the optimized version of the Naungan Kasih program. This is illustrated in Figure 2. Thus, if a

component level is both effective and cost-effective, it will not be included in a subsequent optimization trial. If it is effective but not cost-effective, it will be evaluated in a subsequent optimization trial. If it is not effective but is feasible (ie, there is engagement, it is acceptable, and it is implemented with fidelity), it will be included in a subsequent optimization trial. If it is not effective and not feasible but can be improved, the improved version will be evaluated in a subsequent optimization trial. If it is not effective, not feasible, and cannot be improved, then it will not be included in a subsequent optimization trial.

Figure 2. Decision-making model to determine the inclusion of intervention components in a full trial. N/A: not applicable.



Participant Timeline

The participant timeline is summarized in Table 2. Parents invited to participate by facilitators will be asked to attend an in-person session that will include (1) eligibility screening, (2) informed consent, and (3) baseline assessment. The baseline sessions took place in schools from December 6 to 16, 2023. Schools were then randomly allocated to the 4 treatment conditions. The intervention began with onboarding sessions that took place in schools from January 4 to 6, 2024. The intervention ran until February 7, 2024. Qualitative assessments with facilitators, supervisors, and KEMAS leadership team members were conducted between February 5 and 16, 2024. Posttest data collection was carried out with parents and children between February 24 and March 12, 2024.

Table 2. The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) schedule for participant enrollment, intervention, and assessments. FGD: focus group discussion; KEMAS: Jabatan Kemajuan Masyarakat (Department of Community Development).

	Study period			
	Enrollment and baseline (time point 1)	Allocation	After allocation (intervention)	After the intervention (time point 1)
Enrollment				
Eligibility screen	✓			
Informed consent	✓			
Allocation		✓		
Interventions				
Condition 1			✓	
Condition 2			✓	
Condition 3			✓	
Condition 4			✓	
Assessments				
Recruitment	✓			✓
Retention				
Adherence			✓	
Engagement			✓	
Parent survey				
Recruitment	✓			✓
Demographics	✓			
Child physical abuse	✓			✓
Child emotional abuse	✓			✓
Playful learning	✓			✓
Child learning and development (parent report)	✓			✓
Child behavior—externalizing problems	✓			✓
Parenting	✓			✓
Parent mental health	✓			✓
Parenting stress	✓			✓
Gender-equitable behaviors	✓			✓
Marital health	✓			✓
Financial stress	✓			✓
Quality of life	✓			✓
Partner participation in program	✓			✓
Program satisfaction	✓			✓
Child development and learning (child direct assessment)	✓			✓
Costs			✓	
Qualitative assessments				
Parent FGDs[a]				✓

	Study period			
	Enrollment and baseline (time point 1)	Allocation	After allocation (intervention)	After the intervention (time point 1)
Facilitator interviews				✓
Supervisor FGD				✓
KEMAS[b] leadership FGD				✓

[a]FGD: focus group discussion.

[b]KEMAS: Jabatan Kemajuan Masyarakat (Department of Community Development).

Sample Size

A formal sample size calculation was not used for this feasibility pilot study. It is anticipated that the sample size of 160 families (160 primary caregivers and up to 160 secondary caregivers, as well as 160 children from the same households) split equally across 8 preschools (4 at each study site) will provide sufficient information on the study objectives to inform a future main trial. In 20% (32/160) of the families at each preschool, direct assessments will be conducted with the child. The 8 project facilitators will be invited to participate in interviews. Five supervisors will be invited to participate in a focus group discussion (FGD). Finally, 5 KEMAS leadership team members will be invited to participate in an FGD.

Recruitment

Recruitment of KEMAS leadership team members, supervisors, and facilitators took place between July 4 and September 15, 2023. Supervisors and facilitators took part in the Naungan Kasih training during the second week of November 2023.

KEMAS Leadership Team Members

UPM used existing contacts with KEMAS to invite members to participate in the study. KEMAS leadership team members were sent an information sheet and consent form via email.

KEMAS Supervisors

Members of the KEMAS leadership team identified and invited school supervisors in the KEMAS system to confirm their willingness to participate in a training of trainers session.

Facilitators

Members from the KEMAS leadership team identified and invited teachers at the selected preschools to confirm their willingness to participate as program facilitators.

Caregivers

Facilitators (class teachers) informed parents at the selected preschools about the study in mid-November 2023, after the training program. Two parents from each household have been invited to attend the registration and baseline data collection session. During the in-person data collection session, research assistants will screen the attendees to confirm their eligibility and establish which parent is the primary caregiver and which one the secondary caregiver. The research assistants will then ask parents to provide full written consent and complete the baseline assessment. Caregivers who do not attend the in-person data collection session but who indicated their interest in participating will be contacted by UPM researchers in the 2 weeks after the in-person session. The researcher will screen each caregiver to confirm their eligibility and establish which parent is the primary caregiver and which one the secondary caregiver. The researcher will then ask them to provide full verbal consent and carry out the baseline survey with them verbally over the telephone. Parents who provide consent and who complete the baseline assessment will be invited to participate in the first in-person session of the intervention, the onboarding session.

Children

A random subsample of 4 children from each cluster will be selected to participate in direct assessments. Primary caregivers attending the in-person baseline data collection session will be asked to provide written consent to their child's participation. The parent will then select a bead from a bag to determine the random selection of the child. For the children selected, the assessment will take place at the school during the 2 weeks after the parents' in-person informed consent and baseline data collection session. The children selected will be asked to provide verbal assent.

Assignment of the Intervention

Allocation

Sequence Generation

Within each study site, schools will be randomly allocated in a 1:1:1:1 ratio to 1 of the 4 treatment conditions (described in the Trial Design subsection) using a computerized random number function in Microsoft Excel. The list of schools will be sorted in Excel by study site (strata) and then by random number, and within each stratum, schools will be manually assigned to the 4 experimental conditions: the school with the lowest random number will be assigned to experimental condition 1, the school with the second lowest random number to experimental condition 2, and so on.

Allocation-Concealment Mechanism

Randomization will be conducted after the final baseline data collection session. Data collectors, facilitators, and participants will be concealed to allocation until the start of the intervention. The onboarding session will take place between the final data collection session and the start of the intervention, at which point the facilitators and the intervention recipients will be informed about condition allocation. Condition allocation will remain concealed throughout the study for data collectors. Those involved in analysis will remain blinded until main analyses

have been conducted; however, they may become aware of condition allocation when analyzing FGD data because of particular questions and answers related to components of the study relevant to the intervention conditions.

Implementation

Before randomization, a list of recruited schools will be sent to the University of Oxford by UPM researchers. The data manager, based at the University of Oxford, will then randomly assign schools to the experimental conditions. The randomization sequence will be in a password-protected file and accessed on a need-to-know basis. After randomization, the allocation of each school will be forwarded to UPM researchers, who will share this with the implementing facilitators at the relevant schools.

Blinding

During baseline assessment, UPM researchers and intervention participants will be blinded to condition allocation and will not be informed about the range of conditions and the allocation status of other schools to reduce the risk of contamination. During the intervention onboarding process, participants will be exposed to information pertaining to the condition to which they are assigned. Blinding will not be possible for the facilitators because of their involvement in program implementation. UPM research assistants will be blinded to the allocation of schools during the postintervention assessments. FGDs will take place after the collection of postintervention data. It is expected that research assistants will learn about the allocation of clusters, as will the teacher-facilitators, during the FGDs. Statisticians will be blinded to cluster and participant allocation when carrying out quantitative analyses.

Data Collection, Management, and Analysis

Data Collection

This feasibility pilot study will use a mixed methods approach using both quantitative and qualitative data.

Quantitative Data

These data will include digitally tracked engagement data, facilitator administrative data and self-reports on program implementation, caregiver baseline and posttest surveys, and direct assessments of children.

Digitally tracked data on parent engagement with the chatbot will be collected automatically through parent interactions with ParentText. These data will be linked to the individual participant ID. Facilitator administrative data will include a register of caregivers invited to participate in the intervention and whether they consented to participate. Facilitators will record caregiver participation in the WhatsApp support groups via the facilitator app. Information recorded will include whether caregivers sent a message (participated or did not participate) in the WhatsApp group over the week during which facilitation content messages were sent. Finally, facilitators will also complete checklists on the activities they carried out in in-person sessions and whether they shared program content on the WhatsApp support groups.

Caregiver self-completion assessments will be administered at 2 time points: baseline and after the intervention. A longer survey will be administered to primary caregivers, and a shorter version will be administered to secondary caregivers. Baseline data were collected between December 6 and 16, 2023. Postintervention data will be collected from all participants 3 weeks after the second in-person session (for participants receiving 2 in-person sessions); all other participants (those receiving only 1 in-person session) will be invited to the school to complete the assessment. All assessment data will be collected using Open Data Kit (ODK; Get ODK Inc). UPM researchers will provide assistance to caregivers with low digital literacy. Caregivers consenting to participate in ParentText but who are unable to attend the in-person session will be contacted by UPM researchers who will administer the survey over the telephone after informed consent and enter responses using ODK on tablet computers.

Direct assessments of a subsample of children (32/160, 20%) will be undertaken at baseline and after the intervention by 2 UPM researchers from the field of child development who will enter scores on the observational measure into ODK on tablet computers.

Qualitative Data

These data will include FGDs with caregivers, KEMAS supervisors, and KEMAS leadership team members as well as individual interviews with facilitators. All FGDs and interviews will be conducted by qualitative researchers from UPM. Participants will be asked for their consent to the discussions and interviews being audio recorded. If any participants decline, notes will be taken instead.

FGDs among caregivers will be conducted at 4 randomly selected schools, and each school will represent 1 condition. Caregivers from the selected schools will be invited to participate with other caregivers from the same school. Two FGDs for each class (1 FGD with male participants and 1 FGD with female participants) will be conducted, resulting in 8 FGDs.

In-depth interviews with 8 facilitators will be held in the 2 weeks after caregivers' completion of the intervention. Interviews will be conducted via web-based videoconferencing.

KEMAS supervisors will participate in an FGD that will be held via web-based video conferencing. KEMAS leadership team members will also participate in an FGD that will be held via web-based videoconferencing. These 2 FGDs will be held during the week after the interviews with the teacher-facilitators.

Data Management

Survey data collection will be carried out through computer-assisted self-interviews using tablet computers, which will be stored in a locked cabinet at the UPM research office and accessed only by authorized personnel on data collection dates. All data collected on tablet computers and exported to ODK will be encrypted as soon as the survey is completed by the interviewer and will be accessible only to senior research personnel on a need-to-know basis. Each tablet computer will have a GPS tracking application that will permit remote deletion of stored information in the event of theft.

Paper-based surveys will be used in cases where tablet computers malfunction. These surveys will also be stored in a locked cabinet at the UPM research office. They will be destroyed once data have been transferred to ODK via tablet computers and verified for accuracy by the research team.

Quantitative data from the baseline and postintervention assessments will be anonymized and stored in a password-protected University of Oxford secure server. Data on this server will be managed by the University of Oxford central IT team and the Global Parenting Initiative (GPI) data management team, with support from the Department of Social Policy and Intervention IT office. Access, which will be managed by the GPI data management team, will be restricted to study team members or partner organizations involved in the research. Engagement data from ParentText will be stored using end-to-end encryption on the UNICEF server. Participants will be assigned a unique ID number during data collection that will enable linkage of the data across data sets.

Audio recorders will be used for in-person FGDs. Web-based FGDs and interviews will be recorded using the Google Meet audio recording function. Audio recordings from the FGDs and interviews will be transcribed verbatim and stored on password-protected devices, then securely uploaded and backed up on the University of Oxford server. Subsequently, all audio files will be deleted from the recording devices. Transcripts will be anonymized and verified, after which audio recordings will be permanently deleted from the databases.

All electronic documents will be named following a standard format, including the date as version control. Access to anonymized transcripts will be granted only by the GPI data manager via OneDrive for Business (Microsoft Corp) at the University of Oxford. Anonymized data sets will be stored securely for perpetuity and use per UK Data Archive guidance [55]. Raw data will be owned by the University of Oxford and UPM and stored by the University of Oxford. External access to the data will require approval from both principal investigators.

Data cleaning will be conducted during data collection to monitor data quality. Individual raw data sets from the baseline and postintervention evaluations will be stored separately from the final merged data set so that data reference points are available in the data validation process. All electronic documents and data, including quantitative data and transcripts of qualitative data, will be stored on at least 2 servers with access granted individually on a need-to-know basis. Thus, data will be protected from both server failure and confidentiality breaches.

Statistical Methods

All statistical analyses will be performed using Stata (StataCorp LLC) or R statistical software (R Foundation for Statistical Computing). Summary statistics will be used to describe all variables of interest. Descriptive analysis will be conducted to analyze recruitment, retention, adherence, and engagement data (objective 1), and all statistical tests will be 2-tailed with α=.05.

Intervention effects on primary and secondary outcomes (objective 5) will be represented by point estimates and their SEs. The main effect for each intervention component on primary and secondary outcomes will be estimated using multilevel models (including mixed models where outcomes are continuous, Poisson models where outcomes are counts or count distributed, and logistic models where outcomes are binary). Each model will specify 3 levels to account for the longitudinal and clustered nature of the data: repeated measures are nested within individuals, which are, in turn, nested within schools. Level 1 will include a term for categorical time (before and after the intervention) and for the interaction between time and intervention status; level 2 will include terms for individual sociodemographics such as age (parent and child) and gender (parent) and other individual-level covariates, centered at the sample mean; and level 3 will include terms for the intervention components and the stratifying factor. Robust SEs will be estimated to adjust for clustering. This study will report the direction and magnitude of standardized betas, incidence risk ratios, and odds ratios at a significance level of P<.10 with 90% CIs. Two-tailed tests will be conducted across all analyses.

Intervention costs (objective 4) will be estimated from the provider perspective. Resource inputs valued to estimate costs will include facilitator costs, such as those associated with their training to deliver ParentText (captured as their time spent attending training sessions) and with preparing and delivering specific intervention components; physical space used to deliver in-person sessions, which will be audited and valued; and travel and supplies (such as internet data and mobile phones). Local researchers and coordinators will collect resource use data in real time (ie, alongside the full study trial) via the completion of weekly ODK-based surveys. Costs related to the development of ParentText and content adaptation and translation will be included as a capital start-up cost. As the cost analyses will be conducted from the provider perspective, costs incurred by participants (travel expenditure and opportunity costs) will be excluded. While the implementing organization's program monitoring and evaluation costs will be included in the cost estimates, broader research activity costs will be excluded. Program implementation costs and outcomes data will be recorded and analyzed in Excel. The total cost for each intervention condition will then be compared against the number of participants who completed all ParentText modules and for the positive parenting outcome.

Regarding qualitative data, the audio recordings from the interviews and FGDs will be transcribed by UPM researchers. Qualitative data will be analyzed in Bahasa Melayu using NVivo (Lumivero) and Microsoft Word using framework analysis. The analysis will include five stages: (1) familiarization, (2) the identification of themes, (3) indexing, (4) charting and summarization, and (5) interpretation and mapping. Researchers will begin by familiarizing themselves with the transcripts and identifying emerging themes. A code will then be assigned to each theme and subtheme at the indexing stage. After themes are indexed, they will be charted and summarized. Finally, interpretation and mapping will be used to develop a deeper understanding of the findings.

Data Monitoring

UPM and University of Oxford research teams will oversee the study procedures, including implementation, participant safety, and study conduct. The research teams will also monitor data management throughout its duration, including baseline and postintervention data collection, cleaning, and storage and analysis, and ensure the quality and rigor of the study conduct. A survey monitoring checklist will be created to keep track of errors in data quality checks, such as incorrectly entered names in the participant ID list and duplicates in the data.

Harms

This pilot study will carry out safeguarding strategies developed from universal principles of ethics, respect, beneficence, and justice. The local UPM research team will be trained on the safety protocol for this study. UPM also has its own guidelines on protection from sexual exploitation and abuse (PSEA) under the policy of zero tolerance toward sexual harassment. The guidelines define UPM's commitment to PSEA with regard to adults and children considered vulnerable. The PSEA guidelines fulfill the requirements of the United Nations in ensuring adequate safeguards and action related to PSEA.

Caregivers will be informed of any risks related to their participation in the study. They will have the right to decline any assessment and participation at any time. Caregivers can opt out of ParentText at any time by typing "STOP MESSAGES" in the ParentText WhatsApp chat. Any withdrawal from the study will not affect participants' rights to other services or result in any penalty.

Ethical Considerations

Ethics approval for this study was granted by the University of Oxford Research Ethics Committee (R88954/RE001) on September 18, 2023, and by the UPM Ethics Committee for Research Involving Human Subjects (JKEUPM-2023-1226) on October 15, 2023.

Consent or Assent

Caregivers and Children

Trained program facilitators will collect informed consent from adults and informed assent from children before baseline assessment at local schools in the communities where the study is taking place. Informed consent and assent forms will include clear descriptions of the intervention; study objectives; the use of, and protection measures for, participant data; and participants' rights to refuse to respond to survey questions or withdraw at any point from the study. Children's participation will be conditional on their parents providing consent and their providing verbal assent. Adults who agree to participate in the intervention will be invited to sign a paper-based informed consent form to indicate their consent.

KEMAS Leadership Team Members

UPM researchers will contact potential participants by telephone and read out the information sheet and consent form. If they agree to participate, they will be asked to sign the consent form and email it to the UPM research coordinator, who will print and securely store the form and delete the email.

KEMAS Supervisors

UPM researchers will obtain informed consent from supervisors after they attend an in-person training of trainers session. UPM researchers will read out the study information and respond to any questions or concerns that participants raise. Supervisors who agree to participate will be asked to sign a paper-based informed consent form. Those who sign will be invited to participate in an FGD after the completion of the program.

Facilitators

UPM researchers will obtain informed consent from teachers after they attend the Naungan Kasih training session. UPM researchers will read out the study information and respond to any questions or concerns that participants raise. Teachers who agree to participate will be asked to sign a paper-based informed consent form. Those who sign will be invited to participate in a qualitative interview after the completion of the program.

Privacy and Confidentiality

Anonymized baseline and postintervention data sets will be stored in a password-protected server at the University of Oxford. Access will be controlled and only granted to members of the study team or partner institutions that aided in the research project. Audio recordings of the interviews and FGDs will be transcribed verbatim and stored in password-protected devices and will then be securely uploaded and backed up at the University of Oxford server. Once uploaded to the server, the audio files will be deleted from the recording devices. After the transcripts have been anonymized and verified, the audio recordings will be permanently deleted from data repositories. All Excel and Word files will be named following a standardized protocol, including the download date, to ease version control. Deidentified interview transcripts and data sets will only be shared by the GPI data manager by granting access to specific files through OneDrive for Business at the University of Oxford. Deidentified data sets will be stored securely for perpetuity and use per UK Data Archive guidance. Raw baseline and postintervention data collected will be owned by UPM and the University of Oxford.

Data captured from ParentText is stored in an encrypted anonymous database managed by UNICEF Malaysia. Personally identifiable information, such as the user's telephone number, is never stored. Data captured from the facilitator app are also anonymous and stored in an encrypted server hosted by IDEMS International. Both the application and chatbot are General Data Protection Regulation compliant.

Compensation

Parents will receive compensation for their participation at 3 stages of the research: survey completion at baseline data collection, survey completion at postintervention data collection, and participation in FGDs at postintervention data collection. They will receive MYR 50 (US $10.5) for their participation at each stage. They can therefore receive up to MYR 150 (US $31.5) for participation in the study.

Access to Data

Only the University of Oxford and UPM will have access to the raw research data. Access to clean and pseudoanonymized

data sets and interview transcripts will be managed by the GPI data manager and evaluated on a need-to-know basis. UNICEF and the Malaysian Association of Social Workers, the implementing partners, will also have access to these data sets to assist with data quality checks.

Ancillary and Posttrial Care

Safeguarding procedures will be used to mitigate risks to participants. The informed consent form for study participants indicates that if the participant feels anxious or worried during their involvement in the trial, they will be offered support such as counseling.

Results

Recruitment began on December 6, 2023, and as of December 29, 2023, a total of 208 caregivers had been recruited into the trial. The intervention was completed on February 7, 2024. Follow-up data collection was completed on March 12, 2024. Data management is still in progress; therefore, data analysis has yet to be performed. Results are expected to be published in the second half of 2024.

Discussion

Summary

This factorial cluster randomized trial is the first to evaluate the feasibility of a hybrid human-digital playful parenting program in Southeast Asia. It explores this in 2 contrasting contexts in Malaysia—an urban setting in Kuala Lumpur and a rural setting in Negeri Sembilan—which aims to maximize the generalizability of its results. The findings from this study will contribute to understanding the viability for such a hybrid program to be scaled up in similar contexts to Malaysia. By examining the feasibility, acceptability, and effectiveness of ParentText, which is delivered along with a WhatsApp support group and 1 or 2 in-person sessions, the study will provide important insights into the optimal combination of intervention components. The findings may identify versions of the intervention that are considerably more or less feasible than others, which could inform their inclusion or exclusion in future evaluations of the program.

In addition to this trial, other trials of different versions of ParentText are currently underway that will further contribute to the evidence base on the feasibility and effectiveness of hybrid parenting programs. In South Africa and Tanzania, cluster randomized controlled trials are being conducted among caregivers of adolescent girls (in South Africa) [56] and caregivers of adolescents (in Tanzania) [36,57].

Limitations

This study has 2 main limitations. First, because the aim of the study is primarily to evaluate feasibility and not effectiveness, the sample size is likely too small to have the statistical power to detect significant differences in outcomes among the different program versions. Second, the study will not provide information on the reasons for nonparticipation of those who did not enroll. Given that this study aims to investigate the acceptability of the program, understanding barriers to participation would inform potential adaptations to its content and delivery in preparation for future testing to maximize recruitment and engagement.

Acknowledgments

This study is part of the Global Parenting Initiative, which is funded by the LEGO Foundation, the Oak Foundation, the World Childhood Foundation, The Human Safety Net, and the UK Research and Innovation Global Challenges Research Fund (ES/S008101/1). The study sponsors and funders had no role or influence in the conceptualization and design of this trial. They will not have any role in implementation, analysis, the interpretation of data, or the dissemination of results.

Data Availability

The data sets generated during and analyzed during this study will be available in the OSF repository [58].

Authors' Contributions

UPM and University of Oxford team members led the conceptualization and writing of this protocol. All authors contributed to the conceptualization, development, and writing of this manuscript. RJ and JML are the principal investigators on the study. HC, IV, NI, FZMD, ZA, FC, FG, and SV provided critical input in the selection of the quantitative measures in this study. HC and RJ led the development of qualitative measurements. SV, GJMT, and JML contributed to the proposed research design and statistical analysis. LM, CF, HC, and DR developed the content for the chatbot. All authors provided critical feedback and revised sections of the manuscript and approved the final manuscript.

Conflicts of Interest

ParentText was developed by members of the research team. JML is the chief executive officer of Parenting for Lifelong Health (PLH), which holds the intellectual property rights of the intervention content. HC, FG, IV, SV, FC, LM, DR, VS, and RJ work for or with PLH, and the University of Oxford receives research grants to support this work. All other authors declare no other conflicts of interest. The investigators will not benefit financially from the implementation and dissemination of the intervention.

Multimedia Appendix 1
List of Jabatan Kemajuan Masyarakat (Department of Community Development; KEMAS) preschools for the feasibility pilot study.
[DOCX File , 25 KB - resprot_v13i1e55491_app1.docx]

References

1. Transforming our world: the 2030 Agenda for Sustainable Development. Department of Economic and Social Affairs United Nations. 2015. URL: https://sdgs.un.org/2030agenda [accessed 2023-12-04]
2. Black MM, Walker SP, Fernald LC, Andersen CT, DiGirolamo AM, Lu C, et al. Early childhood development coming of age: science through the life course. Lancet 2017 Jan 07;389(10064):77-90 [FREE Full text] [doi: 10.1016/S0140-6736(16)31389-7] [Medline: 27717614]
3. McCoy A, Lachman JM, Ward CL, Tapanya S, Poomchaichote T, Kelly J, et al. Feasibility pilot of an adapted parenting program embedded within the Thai public health system. BMC Public Health 2021 May 29;21(1):1009 [FREE Full text] [doi: 10.1186/s12889-021-11081-4] [Medline: 34051772]
4. Sylva K, Roberts F, Mathers S. Quality in early childhood education. In: Pugh G, Duffy B, editors. Contemporary Issues in the Early Years. Thousand Oaks, CA: SAGE Publications; 2013:55-71.
5. Duncan GJ, Dowsett CJ, Claessens A, Magnuson K, Huston AC, Klebanov P, et al. School readiness and later achievement. Dev Psychol 2007 Nov;43(6):1428-1446. [doi: 10.1037/0012-1649.43.6.1428] [Medline: 18020822]
6. Manolitsis G, Georgiou GK, Tziraki N. Examining the effects of home literacy and numeracy environment on early reading and math acquisition. Early Child Res Q 2013 Oct;28(4):692-703. [doi: 10.1016/j.ecresq.2013.05.004]
7. Anders Y, Rossbach HG, Weinert S, Ebert S, Kuger S, Lehrl S, et al. Home and preschool learning environments and their relations to the development of early numeracy skills. Early Child Res Q 2012 Apr;27(2):231-244. [doi: 10.1016/j.ecresq.2011.08.003]
8. Melhuish EC, Phan MB, Sylva K, Sammons P, Siraj‐Blatchford I, Taggart B. Effects of the home learning environment and preschool center experience upon literacy and numeracy development in early primary school. J Soc Issues 2008 Feb 07;64(1):95-114. [doi: 10.1111/j.1540-4560.2008.00550.x]
9. Shaping first steps: a comprehensive review of preschool education in Malaysia. The World Bank. 2023 Jun 1. URL: https://openknowledge.worldbank.org/handle/10986/39851 [accessed 2023-12-04]
10. National health and morbidity survey 2016 : maternal and child health (MCH). Institute for Public Health, Ministry of Health, Malaysia. 2016. URL: https://iku.moh.gov.my/images/IKU/Document/REPORT/2016/NHMS2016ReportVolumeII-MaternalChildHealthFindingsv2.pdf [accessed 2023-12-04]
11. Sénéchal M, Young L. The effect of family literacy interventions on children's acquisition of reading from kindergarten to grade 3: a meta-analytic review. Rev Educ Res 2008 Dec 01;78(4):880-907 [FREE Full text] [doi: 10.3102/0034654308320319]
12. Dulay KM, Cheung SK, Reyes P, McBride C. Effects of parent coaching on Filipino children's numeracy, language, and literacy skills. J Educ Psychol 2019 May;111(4):641-662. [doi: 10.1037/edu0000315]
13. Fauzan N, Zani NM. Creative thinking among preschool children. Int J Tech Res Appl 2015 Jul(22):86-93.
14. Hirsh-Pasek K, Golinkoff RM. "Languagizing" their world why talking, reading, and singing are so important. ZERO TO THREE. 2018 Jan. URL: https://www.zerotothree.org/wp-content/uploads/2018/06/Journal-Article_-Languagizing-Their-World_-Why-Talking-Reading-and-Singing-Are-So-Important.pdf [accessed 2024-04-10]
15. Brown B, Larson J. 3 Peer relationships in adolescence. In: Brown BB, Larson J, editors. Handbook of Adolescent Psychology. Hoboken, NJ: John Wiley & Sons; Oct 30, 2009.
16. Weisenmuller C, Hilton D. Barriers to access, implementation, and utilization of parenting interventions: considerations for research and clinical applications. Am Psychol 2021 Jan;76(1):104-115. [doi: 10.1037/amp0000613] [Medline: 32134281]
17. Cooper J, Dermentzis J, Loftus H, Sahle BW, Reavley N, Jorm A. Barriers and facilitators to the implementation of parenting programs in real-world settings: a qualitative systematic review. Mental Health Prevent 2022 Jun;26:200236. [doi: 10.1016/j.mhp.2022.200236]
18. Hilton DC, Weisenmuller CM, Fields SA, Luzier JL, Emrick BB. Are brief behavioral parenting group interventions effective in rural communities? A feasibility study in Central Appalachia. J Rural Mental Health 2022 Jan;46(1):67-73. [doi: 10.1037/rmh0000193]
19. Norman Å, Swahnström S, Karlström NU, Enebrink P. Multi-level barriers and facilitators to implementing a parenting intervention in prison, perceptions from deliverers and responsible managers: a mixed-methods study. BMC Psychol 2022 Mar 24;10(1):79 [FREE Full text] [doi: 10.1186/s40359-022-00782-z] [Medline: 35331337]
20. Ramos A, Matos F, Soares H. Parenting programme structure, potential barriers, and facilitators: a scoping review. Int J Environ Res Public Health 2022 Oct 21;19(20):13655 [FREE Full text] [doi: 10.3390/ijerph192013655] [Medline: 36294249]
21. Knerr W, Gardner F, Cluver L. Improving positive parenting skills and reducing harsh and abusive parenting in low- and middle-income countries: a systematic review. Prev Sci 2013 Aug;14(4):352-363. [doi: 10.1007/s11121-012-0314-1] [Medline: 23315023]

22. Review and analysis of lessons learned from existing positive parenting programmes in East Asia and the Pacific. Global Initiative to Support Parents. URL: https://support-parents.org/resources/review-and-analysis-of-lessons-learned-from-existing-positive-parenting-programmes-in-east-asia-and-the-pacific/ [accessed 2024-04-10]
23. Smith JA, Chang SM, Brentani A, Fink G, Lopez-Boo F, Torino BM, et al. A remote parenting program and parent and staff perspectives: a randomized trial. Pediatrics 2023 May 01;151(Suppl 2):e2023060221F. [doi: 10.1542/peds.2023-060221F] [Medline: 37125881]
24. Solís-Cordero K, Duarte LS, Fujimori E. Effectiveness of remotely delivered parenting programs on caregiver-child interaction and child development: a systematic review. J Child Fam Stud 2022;31(11):3026-3036 [FREE Full text] [doi: 10.1007/s10826-022-02328-8] [Medline: 35615461]
25. Kumar V, Mohanty P, Sharma M. Promotion of early childhood development using mHealth: learnings from an implementation experience in haryana. Indian Pediatr 2021 Nov 15;58 Suppl 1:S37-S41 [FREE Full text] [Medline: 34687187]
26. Lachman JM, Juhari R, Stuer F, Zinser P, Han Q, Gardner F, et al. "Before I was like a Tarzan. But now, I take a pause": mixed methods feasibility study of the Naungan Kasih parenting program to prevent violence against children in Malaysia. BMC Public Health 2023 Mar 04;23(1):241 [FREE Full text] [doi: 10.1186/s12889-023-15065-4] [Medline: 36737719]
27. Mejia A, Calam R, Sanders MR. A review of parenting programs in developing countries: opportunities and challenges for preventing emotional and behavioral difficulties in children. Clin Child Fam Psychol Rev 2012 Jun;15(2):163-175. [doi: 10.1007/s10567-012-0116-9] [Medline: 22427004]
28. Pedersen GA, Smallegange E, Coetzee A, Hartog K, Turner J, Jordans MJ, et al. A systematic review of the evidence for family and parenting interventions in low- and middle-income countries: child and youth mental health outcomes. J Child Fam Stud 2019 Apr 29;28(8):2036-2055. [doi: 10.1007/s10826-019-01399-4]
29. Jeong J, Pitchik HO, Fink G. Short-term, medium-term and long-term effects of early parenting interventions in low- and middle-income countries: a systematic review. BMJ Glob Health 2021 Mar;6(3):e004067 [FREE Full text] [doi: 10.1136/bmjgh-2020-004067] [Medline: 33674266]
30. Barlow J, Johnston I, Kendrick D, Polnay L, Stewart-Brown S. Individual and group-based parenting programmes for the treatment of physical child abuse and neglect. Cochrane Database Syst Rev 2006 Jul 19(3):CD005463. [doi: 10.1002/14651858.CD005463.pub2] [Medline: 16856097]
31. Chen M, Chan KL. Effects of parenting programs on child maltreatment prevention: a meta-analysis. Trauma Violence Abuse 2016 Jan;17(1):88-104. [doi: 10.1177/1524838014566718] [Medline: 25573846]
32. Cheah IG, Choo WY. A review of research on child abuse in Malaysia. Med J Malaysia 2016 Jun;71(Suppl 1):87-99 [FREE Full text] [Medline: 27801391]
33. Azaf NS, Vizabaskaran K, Karisnan K, Juwaneeta AN. Impact of multi-type childhood abuse on psychological development and coping strategies among Perdana University students. Malays J Med Health Sci 2022 Jan;18(1):187-194 [FREE Full text]
34. Klapow M, Zinser P, Lachman J, Facciola C, Han Q, Ambrosia M, et al. Promoting family well-being at scale: optimising and re-designing a digital parenting programme for reducing violence against children in lmics using the 6squid framework. Popul Med 2023 Apr 26;5(Supplement):A1276. [doi: 10.18332/popmed/164209]
35. Axford N, Lehtonen M, Kaoukji D, Tobin K, Berry V. Engaging parents in parenting programs: lessons from research and practice. Child Youth Serv Rev 2012 Oct;34(10):2061-2071 [FREE Full text] [doi: 10.1016/j.childyouth.2012.06.011]
36. Janowski R, Green O, Shenderovich Y, Stern D, Clements L, Wamoyi J, et al. Optimising engagement in a digital parenting intervention to prevent violence against adolescents in Tanzania: protocol for a cluster randomised factorial trial. BMC Public Health 2023 Jun 23;23(1):1224 [FREE Full text] [doi: 10.1186/s12889-023-15989-x] [Medline: 37353844]
37. Koerting J, Smith E, Knowles MM, Latter S, Elsey H, McCann DC, et al. Barriers to, and facilitators of, parenting programmes for childhood behaviour problems: a qualitative synthesis of studies of parents' and professionals' perceptions. Eur Child Adolesc Psychiatry 2013 Nov;22(11):653-670 [FREE Full text] [doi: 10.1007/s00787-013-0401-2] [Medline: 23564207]
38. Rogers J, Gladstone T, Van Voorhees B, Bunge EL. The role of human support on engagement in an online depression prevention program for youth. Soc Sci 2021 Jul 27;10(8):285. [doi: 10.3390/socsci10080285]
39. Day JJ, Sanders MR. Do parents benefit from help when completing a self-guided parenting program online? A randomized controlled trial comparing triple p online with and without telephone support. Behav Ther 2018 Nov;49(6):1020-1038. [doi: 10.1016/j.beth.2018.03.002] [Medline: 30316482]
40. Epstein M, Oesterle S, Haggerty KP. Effectiveness of Facebook groups to boost participation in a parenting intervention. Prev Sci 2019 Aug 23;20(6):894-903 [FREE Full text] [doi: 10.1007/s11121-019-01018-0] [Medline: 31124023]
41. Kelders SM, Kok RN, Ossebaard HC, Van Gemert-Pijnen JE. Persuasive system design does matter: a systematic review of adherence to web-based interventions. J Med Internet Res 2012 Nov 14;14(6):e152 [FREE Full text] [doi: 10.2196/jmir.2104] [Medline: 23151820]
42. Schubart JR, Stuckey HL, Ganeshamoorthy A, Sciamanna CN. Chronic health conditions and internet behavioral interventions: a review of factors to enhance user engagement. Comput Inform Nurs 2011 Mar;29(2 Suppl):TC9-T20. [doi: 10.1097/NCN.0b013e3182155274] [Medline: 21372645]

43. Lachman JM, Kelly J, Cluver L, Ward CL, Hutchings J, Gardner F. Process evaluation of a parenting program for low-income families in South Africa. Res Soc Work Pract 2016 Apr 28;28(2):188-202. [doi: 10.1177/1049731516645665]
44. Runyan DK, Dunne MP, Zolotor AJ, Madrid B, Jain D, Gerbaka B, et al. ISPCAN Child Abuse Screening Tool—Parent Version (ICAST-P). APA PsycTests. 2009. URL: https://psycnet.apa.org/doiLanding?doi=10.1037%2Ft27248-000 [accessed 2024-04-15]
45. Kariger P, Frongillo EA, Engle P, Britto PM, Sywulka SM, Menon P. Indicators of family care for development for use in multicountry surveys. J Health Popul Nutr 2012 Dec;30(4):472-486 [FREE Full text] [doi: 10.3329/jhpn.v30i4.13417] [Medline: 23304914]
46. McEachern AD, Dishion TJ, Weaver CM, Shaw DS, Wilson MN, Gardner F. Parenting Young Children (PARYC): validation of a self-report parenting measure. J Child Fam Stud 2012 Jun 5;21(3):498-511 [FREE Full text] [doi: 10.1007/s10826-011-9503-y] [Medline: 22876108]
47. Kroenke K, Spitzer RL, Williams JB, Löwe B. An ultra-brief screening scale for anxiety and depression: the PHQ-4. Psychosomatics 2009;50(6):613-621. [doi: 10.1176/appi.psy.50.6.613] [Medline: 19996233]
48. Berry JO, Jones WH. The parental stress scale: initial psychometric evidence. J Soc Pers Relationsh 2016 Jun 30;12(3):463-472. [doi: 10.1177/0265407595123009]
49. UNESCO, UNICEF, World Bank, Brookings Institution (USA). Center for Universal Education. Overview: MELQO: Measuring Early Learning Quality and Outcomes. Paris, France: UNESCO Publishing; 2017.
50. Pisani L, Borisova I, Dowd AJ. Developing and validating the International Development and Early Learning Assessment (IDELA). Int J Educ Res 2018;91:1-15. [doi: 10.1016/j.ijer.2018.06.007]
51. Cianchetti C, Pittau A, Carta V, Campus G, Littarru R, Ledda MG, et al. Child and adolescent behavior inventory (CABI): a new instrument for epidemiological studies and pre-clinical evaluation. Clin Pract Epidemiol Ment Health 2013;9:51-61 [FREE Full text] [doi: 10.2174/1745017901309010051] [Medline: 23539369]
52. Development of marital health check-up model and receptivity towards intervention modality. MOHE FRGS. URL: https://www2.utar.edu.my/cv_V2/researchProject.jsp?cv=tansa&reqPageId=researchProj [accessed 2024-04-10]
53. Lown JM. Development and validation of a financial self-efficacy scale. J Financial Counsel Plan 2012 Feb 18;22(2):54 [FREE Full text] [doi: 10.1037/t69132-000]
54. Hawthorne G, Richardson J, Osborne R. The Assessment of Quality of Life (AQoL) instrument: a psychometric measure of health-related quality of life. Qual Life Res 1999 May;8(3):209-224. [doi: 10.1023/a:1008815005736] [Medline: 10472152]
55. Research data management. UK Data Service. URL: https://ukdataservice.ac.uk/learning-hub/research-data-management/ [accessed 2024-02-22]
56. Ambrosio MD, Lachman JM, Zinzer P, Gwebu H, Vyas S, Vallance I, et al. A factorial randomised controlled trial to optimise user engagement in a chatbot-led parenting intervention in South Africa: study protocol for the ParentText Optimisation Trial. JMIR Preprints. Preprint posted online August 24, 2023 2024. [doi: 10.2196/52145]
57. Baerecke L, Ornellas A, Wamoyi J, Wambura M, Klapwijk J, Chetty AN, et al. A hybrid digital parenting programme to prevent abuse of adolescents in Tanzania: study protocol for a pragmatic cluster-randomised controlled trial. Trials 2024 Mar 13;25(1):119 [FREE Full text] [doi: 10.1186/s13063-023-07893-x] [Medline: 38351094]
58. A pilot cluster randomised trial of a hybrid human-digital playful parenting programme to improve positive parenting, learning through play, and child educational outcomes among preschool children in Malaysia. OSF Registries. URL: https://osf.io/f32ky [accessed 2024-04-15]

Abbreviations

FGD: focus group discussion
GPI: Global Parenting Initiative
KEMAS: Jabatan Kemajuan Masyarakat (Department of Community Development)
LMIC: low- and middle-income country
ODK: Open Data Kit
PSEA: protection from sexual exploitation and abuse
TABIKA: Taman Bimbingan Kanak-Kanak (Children's Guidance Park)
UNICEF: United Nations Children's Fund
UPM: Universiti Putra Malaysia

Edited by A Mavragani; submitted 14.12.23; peer-reviewed by GK Gupta, D Chrimes; comments to author 21.02.24; revised version received 07.03.24; accepted 13.03.24; published 26.04.24.

Please cite as:
Cooper H, Nadzri FZM, Vyas S, Juhari R, Ismail N, Arshat Z, Rajandiran D, Markle L, Calderon F, Vallance I, Melendez-Torres GJ, Facciolà C, Senesathith V, Gardner F, Lachman JM
A Hybrid Digital Parenting Program Delivered Within the Malaysian Preschool System: Protocol for a Feasibility Study of a Small-Scale Factorial Cluster Randomized Trial
JMIR Res Protoc 2024;13:e55491
URL: https://www.researchprotocols.org/2024/1/e55491
doi:10.2196/55491
PMID:38669679

Protocol

Digital Intervention (Keep-On-Keep-Up Nutrition) to Improve Nutrition in Older Adults: Protocol for a Feasibility Randomized Controlled Trial

Chloe French[1], MA (Hons), MSc; Sorrel Burden[1], PhD; Emma Stanmore[1], PhD

School of Health Sciences, University of Manchester, Manchester, United Kingdom

Corresponding Author:
Emma Stanmore, PhD
School of Health Sciences
University of Manchester
176 Oxford Road
Manchester, M13 9PL
United Kingdom
Phone: 44 01613067856
Email: emma.stanmore@manchester.ac.uk

Abstract

Background: Digital health tools can support behavior change and allow interventions to be scalable at a minimal cost. Keep-on-Keep-up Nutrition (KOKU-Nut) is a free, tablet-based app that focuses on increasing physical activity and improving the dietary intake of older adults based on UK guidelines. The intervention targets an important research area identified as a research priority reported by the James Lind Alliance priority setting partnership for malnutrition.

Objective: This study aims to assess the feasibility of using the digital health tool KOKU-Nut among community-dwelling older adults to inform a future randomized controlled trial. The secondary aims are to determine the acceptability, usability, preliminary effect sizes, and safety of the study and the intervention (KOKU-Nut).

Methods: This is a feasibility randomized controlled trial. We plan to recruit a total of 36 community-dwelling older adults using purposive sampling. Participants will be randomized 1:1 to either the intervention or the control group. The intervention group will be asked to engage with KOKU-Nut 3 times a week for 12 weeks. Participants in the control group will receive a leaflet promoting a healthy lifestyle. All study participants will complete questionnaires at baseline and the end of the 12 weeks. A sample of participants will be asked to participate in an optional interview. The study will collect a range of data including anthropometry (height and weight), dietary intake (3-day food diary), physical function (grip strength and 5-times sit-to-stand), perceived quality of life (EQ-5D), usability (System Usability Scale), and safety (adverse events).

Results: Data collection commenced in March 2024, and the results will be ready for publication by January 2025. Feasibility will be determined on the basis of participants' self-reported engagement with the intervention, and recruitment and retention rates and will be summarized descriptively. We will also consider the amount of missing data and assess how outcomes are related to group assignment. Acceptability will be measured using the modified treatment evaluation inventory and one-to-one semistructured interviews. Transcripts from the interviews will be analyzed using NVivo (version 12; QSR International) software using framework analysis to understand any barriers to the recruitment process, the suitability of the assessment measures, and the acceptability of the intervention and study design.

Conclusions: The study aligns with guidelines developed by the Medical Research Council for developing a complex intervention by using qualitative and quantitative research to examine the barriers of the intervention and identify potential challenges around recruitment and retention. We anticipate that these results will inform the development of a future powered randomized controlled design trial to test the true effectiveness of KOKU-Nut.

Trial Registration: ClinicalTrials.gov NCT05943366; https://classic.clinicaltrials.gov/ct2/show/NCT05943366

International Registered Report Identifier (IRRID): PRR1-10.2196/50922

(JMIR Res Protoc 2024;13:e50922) doi:10.2196/50922

KEYWORDS

feasibility; usability; digital health; diet; gerontology; geriatric; geriatrics; older adult; older adults; elder; elderly; older person; older people; ageing; aging; dietary; nutrition; hydration; community dwelling; RCT; randomized; controlled trial; controlled trials

Introduction

It is well established that progressive resistance training combined with strength and balance exercises are safe and effective for improving muscle mass, hip and lumbar spine bone mineral density, and muscle strength and function [1] and for reducing the risk of falls [2], hospitalizations, fractures [3], and mortality. Furthermore, diet has a fundamental role in the health of older adults [4], and meta-analyses have found that nutritional interventions in addition to physical activity lead to greater improvements in physical function, body composition, and strength in frail and pre-frail older adults [5-7].

Advancements in technology have provided the opportunity for digital platforms to remotely deliver, monitor, and complement patient care. Digital platforms can complement traditional face-to-face programs or provide an alternative option based on the individual's preference and financial situation [8]. Furthermore, digital interventions can be scalable so they can maximize outreach at a minimum cost. Mobile apps are increasingly being used to support dietary change [9] and increase physical activity [10]; however, most are not designed for the older adult population. A recent systematic review identified that apps can be effective at increasing physical activity levels in community-dwelling older adults [8]; however, there has been little research investigating the effectiveness of apps to prevent malnutrition in this population [11].

Keep-on-Keep-up (KOKU) is a free, tablet-based gamified strength and balance exercise app that was soft launched in 2020 [12]. KOKU is approved by the National Health Service and Organization for the Review of Care and Health Apps as a lifestyle app and has been viewed positively by older adults after 6 weeks of independent use [13]. Anonymized Google analytics data show that there are more than 1000 users in the United Kingdom and users averaged 2.2 sessions per week, with an average weekly engagement of 1 hour 51 minutes. KOKU has a collection of health literacy games, and studies internationally found that engagement with the app led to increased exercise frequency and qualitative feedback found that the gamification was engaging and motivating [13]. Keep-on-Keep-up-Nutrition (KOKU-Nut) is a development of this gamification platform and includes an educational and interactive game based on the UK dietary guidelines to nudge older adults to improve their diet [14,15]. The game requires the user to choose a pair of cards to reveal food items, with the aim of finding matching food items. The user is presented with information about the different food items, and upon finding all the matching pairs, the user is provided with important tips to improve their diet and reduce their risk of malnutrition.

The intervention is based on qualitative work with 33 older adults to understand their determinants of dietary intake and barriers to healthy eating. Initial prototypes were tested on a diverse group of end users and health care professionals to facilitate co-design and ensure that the needs of the user were taken into consideration.

This study aims to assess the feasibility of conducting a randomized controlled trial (RCT) using KOKU-Nut to improve the dietary intake of community-dwelling older adults. The secondary aims are to determine the acceptability, usability, preliminary effect sizes, and safety of the study and the intervention (KOKU-Nut). These aims are in line with the Medical Research Council Framework that advocates conducting a feasibility study as part of the development and evaluation of complex interventions to assess the study design and the intervention itself [16].

Methods

Study Setting

This is a feasibility parallel group RCT study design using 1:1 randomization using both quantitative and qualitative methods to explore the feasibility and acceptability of KOKU-Nut (a digital service that aims to improve nutritional and fluid intake in community-dwelling older adults). Data will be collected from community-dwelling older adults living in Greater Manchester in the United Kingdom. The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement and CONSORT (Consolidated Standards of Reporting Trials) statement extended to randomized pilot and feasibility trials and associated checklist were used in the design and reporting of this study [17,18] (Multimedia Appendix 1). Version 3 of the protocol was last updated on February 5, 2024.

Eligibility Criteria

Participants will be included in the study if they are aged 65 years or older, living independently in the community, have access to the internet, and are willing to use an iPad or tablet (their own or one provided) for the duration of the study. Participants will be excluded if they are unable to communicate in English or have a known cognitive impairment.

Interventions

Participants in the intervention group will be helped to download KOKU-Nut onto their iPad or tablet during the baseline visit. The researcher (CF) will demonstrate the features and assist with any technical queries. In cases where participants do not have the necessary devices or data to join the intervention, a tablet with KOKU-Nut installed will be provided for the duration of the intervention. Participants will be asked to engage with KOKU-Nut at least 3 times a week throughout the 12-week period. This will involve carrying out strength and balance exercises and engaging with the gamification features relating to bone health and healthy eating. A crib sheet and contact details for the research team will be available if participants require additional support to help with technical issues.

Participants assigned to the control group will continue with usual care and receive a leaflet developed by Age UK about the importance of a healthy lifestyle including information on the importance of staying active and nutrition [19]. This will allow the comparison of a more traditional way to provide lifestyle advice compared to the digital health tool.

Outcomes

Primary outcomes will be related to feasibility and will assess engagement with the intervention, recruitment and retention rates, and acceptability of the intervention and study design. These findings are important to inform the development of a large-scale RCT in community-dwelling older adults to compare the effectiveness of KOKU-Nut to an information booklet about healthy living. Recruitment rates will be assessed as cumulative recruitment against the target rate each month. Retention rates will be calculated as the number of participants who completed the study divided by the number of participants randomized. Engagement with the intervention will be based on self-reported use of KOKU-Nut at the end of the 12 weeks (every day, 3-4 times a week, 1-2 times a week, and once or twice a month). A questionnaire previously developed and used by the research team for the KOKU app will assess the acceptability of KOKU-Nut [13]. Intervention acceptability will also be assessed using the 11-item, 7-point, modified Treatment Evaluation Inventory [20]. Higher scores indicate higher acceptability, with a score of 44 indicating moderate acceptability. Interviews will explore the acceptability of the intervention and the perceived impact of taking part in the study. Interviews will also consider the participant's experience of the recruitment process, the assessment tools used, and their experience and motivation for participating in the study (positive and negative).

Secondary outcomes will consider the usability and safety of the intervention and the practicality of collecting and assessing the effectiveness of KOKU-Nut compared to an information booklet about healthy living. The perceived usability of KOKU-Nut will be assessed using the validated 10-item system usability scale. Responses are measured on a 5-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree). A score >68 is considered above-average usability and >80 is considered high usability such that participants are likely to recommend the product to peers. The safety of the intervention will be based on the number of adverse events that occurred as a result of participation in the study. We will consider the practicality of collecting effectiveness data by documenting the amount and rationale for any missing data. Changes in means and SDs will be compared to consider the preliminary effectiveness of the intervention and to calculate sample sizes for a future trial. The study will be assessed against progression criteria based on Shanyinde et al [21] to determine progression to a powered RCT. Figure 1 shows the schedule of the intervention and assessment according to the SPIRIT statement.

Figure 1. Schedule of enrollment, interventions, and assessments.

Sample Size

As this is a feasibility study that is not designed to detect statistically significant differences in measures, no formal power calculation has been conducted to determine the sample size. Lancaster et al [22] recommend a sample size of 36 participants for feasibility and pilot studies, so after accounting for potential dropout (at 20%), we aim to recruit 18 participants in each arm.

Recruitment

Men and women aged 65 years and older living independently in the community will be recruited through purposive sampling via local age UK groups, assisted living facilities, and university networks. We plan to recruit a mixture of participants with and without access to a tablet computer to explore differences in the outcomes and the experiences between those with and without prior experience with tablets or iPads.

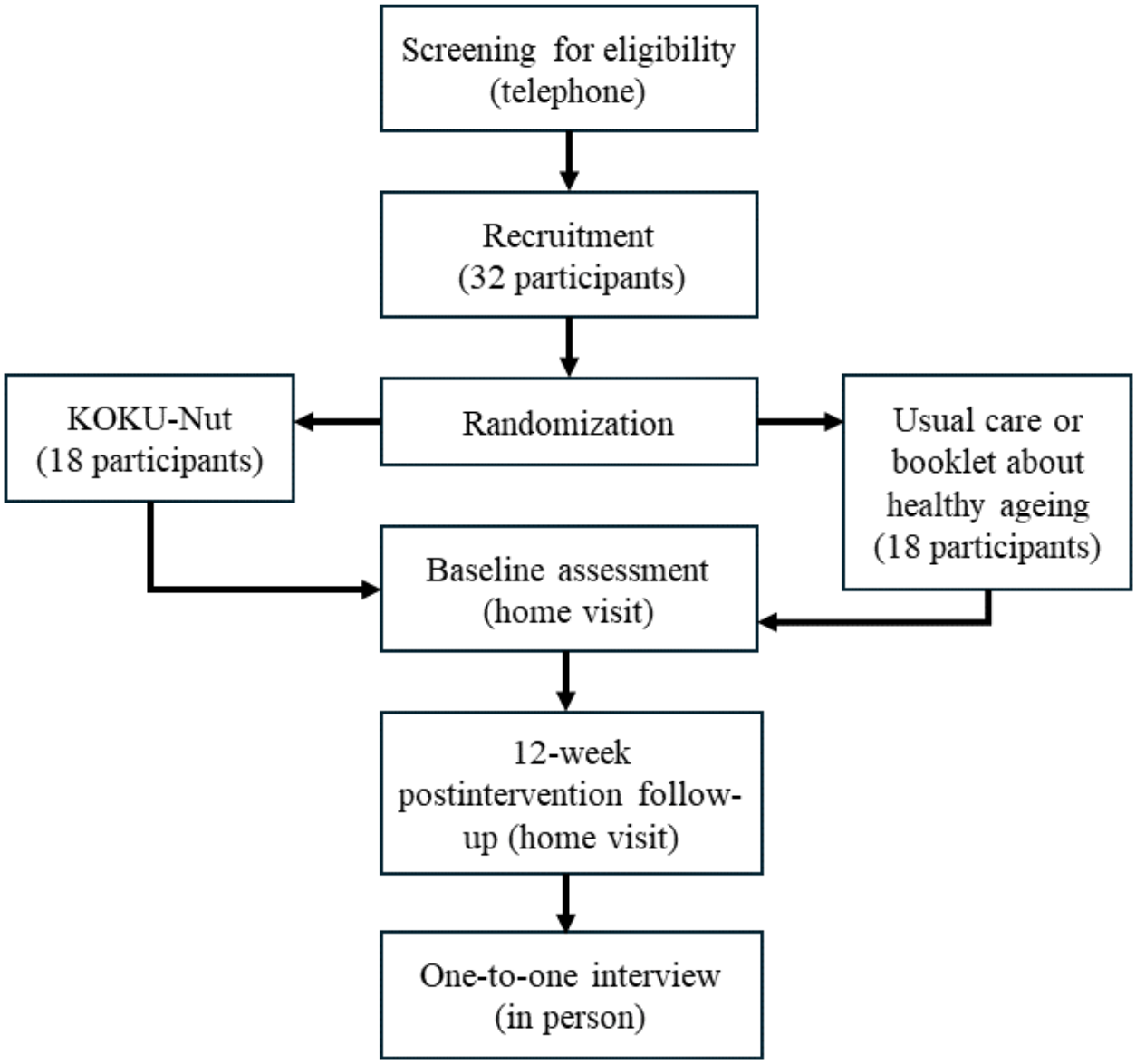
The study will be advertised using social media, posters, and through current collaborations with sheltered housing facilities,

local charities, and community-based organizations across Greater Manchester. Staff at assisted living facilities, charities, and community organizations will act as gatekeepers and will offer potential participants flyers about the study and participant information sheets. Older adults who are interested in participating can agree to have their details passed over to the research team (CF) and will complete the consent to contact form. The research team will follow up with participants who are interested in joining the study and screen potential participants. Alternatively, potential participants may contact the research team directly following the study advertisement in posters and on social media to find out more information and check their eligibility. An existing research database will also be used where older adults have previously consented to be contacted about future research. Participants on the research database will be contacted directly by the research team with the participant information sheet and summary of the research according to their preferred choice (via email, telephone, or letter). The research team will then arrange to conduct an initial telephone screening over the phone to determine eligibility, provide further information about the study, and answer any questions.

Recruitment for the qualitative interviews will be done purposefully, to recruit a demographically representative group of participants. To do this, the sample frame will be divided into a number of smaller groups, namely the treatment group, age, gender, and prior ownership of a tablet or iPad. Individuals will then be drawn at random from each of these groups. We also plan to contact any dropouts to understand their rationale for dropping out to optimize the retention of participants if continuing to a full RCT. Researchers will use the concept of information power [23] to determine the number of interviews, but we anticipate sufficient data will be obtained from interviewing 20% of participants recruited for the study. Figure 2 represents the overall flowchart of participants through the study.

Participants who meet the screening criteria and are interested in taking part will provide informed written consent (Multimedia Appendix 1) before being formally enrolled in the study. During the screening phone call, the researcher (CF) will arrange a date and time suitable for the participant to conduct the initial baseline assessment. Prior to completing baseline measures, participants will be randomized in a 1:1 ratio to receive the intervention (KOKU-Nut) or to the control group and receive usual care.

Figure 2. Flowchart of participants from screening to follow-up.



Allocation

Randomization will be undertaken by a separate member of the research team using the Sealed Envelope randomization service [24], and participants will be stratified by age group (65-75 years and 76 years and older), gender, and prior experience of using a tablet or iPad. Given the nature of the intervention, participants and researchers will be unblinded.

Data Collection Methods

Overview

All participants will receive in the post a baseline case report file to be completed before the baseline assessment to collect sociodemographic information including age, gender, ethnicity, marital status, occupation, use of digital technology, shopping, and cooking habits. Participants will also be asked to complete a 3-day food diary using Intake24 prior to the baseline visit [25]. This web-based dietary assessment tool is compliant with the general data protection regulations (2018), and participants will be sent a unique number that will enable the researcher to identify the digital dietary records. Data collected will be used to assess the consumption of different food groups to identify adherence to the Eatwell guide [14]. During the home visit, the researcher (CF) will collect baseline measurements to assess anthropometry, dietary intake, physical function, quality of life, mood, and frailty. All measurements are responsive to change, appropriate for use in this population, and easily assessed in a community setting.

At the end of the 12-week intervention period, all baseline measures will be repeated, and participants will complete a follow-up case report file to collect feasibility outcome data. The researcher will conduct one-to-one semistructured interviews with a selected group of participants from both the intervention and the control group. Interviews will be conducted in person or over the phone depending on the preference of the participant. Interviews will last approximately 60 minutes, will be audio-recorded, and then transcribed verbatim by the research

team. Additional consent will be collected prior to conducting the interview. A topic guide developed for the study will be used flexibly to guide the interviews.

Anthropometry

A member of the research team will measure height to the nearest centimeter using a stadiometer (Harpenden pocket stadiometer Practical Metrology) and body weight to the nearest 0.1 kg (TANITA, Arlington Heights). BMI will be calculated and categorized according to standard cutoffs [26].

Dietary Assessment

A researcher (CF) who is also a registered nutritionist will use the malnutrition universal screening tool as recommended by the European Society for Clinical Nutrition and Metabolism to assess the risk of malnutrition [27].

Physical Function

Participants will be asked to complete the 5-times sit-to-stand physical function test. The 5-times sit-to-stand requires participants to rise from a chair 5 times as quickly as possible with arms folded across their chest and the researcher will record the time taken to complete the task. The researcher will then calculate lower limb muscle power using the validated equation developed by Kirk et al [28] and Alcazar et al [29]. Grip strength will be assessed on a Takei 5001 analog hand grip dynamometer (Takei Scientific Instruments Co, Ltd) 3 times on each hand with the best score used for analysis.

Quality of Life

The participants' perceived state of health and quality of life will be assessed using the validated EQ-5D questionnaire in combination with the EQ-5D-5L [30]. The EQ-5D questionnaire comprises 5 questions assessing mobility, self-care, usual activities, pain or discomfort, and anxiety or depression to produce an overall score representing the participant's health profile. The score will range from 1 (full health) to 0 (state of health equitable to death), with the option to have negative values representing a state of health considered to be worse than death [31]. The EQ-5D-5L is a visual scale ranging from 0 (worst health imaginable) to 100 (best health imaginable), where participants indicate how they perceive their current health status both on a number line and numerically [31].

Mood

Participants will complete the 4-item Geriatric depression scale as part of the baseline questionnaire, given that mood can affect motivation and may affect the use of KOKU-Nut.

Frailty

The researcher will assess frailty status based on the descriptions and pictographs included in the clinical frailty scale, which has been well validated and is frequently used in adults aged 65 years and older [32,33].

Data Monitoring and Management

All digital and physical data will be stored securely at the University of Manchester and securely destroyed at the end of the data retention period as stated in the data management plan. Digital data will be stored on a backup drive on the university's central server accessible by the research team. On enrollment to the study, all participants will be assigned a unique identification number with all subsequent data stored against this pseudonymized number. Identifiable information (such as name and contact details) will be stored separately and will only be linked to study-collected data through a recruitment log which will be password protected and file access will be limited to researchers working on the study. All printed documentation including consent forms and participants' case files will be stored in a locked storage cabinet in a designated location at the University of Manchester. Interviews will be recorded on an encrypted Dictaphone. Audio recordings will be securely destroyed (digitally shredded) from the Dictaphone after being transcribed and validated by a member of the research team.

Statistical Analysis

All quantitative data will be analyzed in STATA (version 15; StataCorp). The primary outcome will be calculated with regard to the indicators of feasibility to investigate engagement with the intervention, recruitment and retention rates, and acceptability of the intervention and study design. These will be summarized appropriately using descriptive statistics including percentages, mean with SDs, and ranges. Pre-post intervention changes in health measures will be analyzed in an exploratory fashion to gain preliminary insights into the number of valid versus missing data and to assess how outcomes are associated with group assignment and intervention engagement. Effect sizes will be determined using Cohen *d* to calculate sample sizes for a powered RCT.

Qualitative interview transcripts will be managed using NVivo software (version 12; QSR International Pty Ltd) and analyzed using an inductive approach with the 5 stages of framework analysis [34,35] to understand any barriers to the recruitment process, the suitability of the assessment measures, and the practicality of using the KOKU-Nut intervention. The first stage of framework analysis involves familiarization of the data from the transcripts and audio-recordings. The second stage involves classifying the data into codes and identifying a thematic framework from the key themes identified. The third stage involves systematically indexing the data using the framework identified. The fourth stage involves charting and synthesizing the data to categorize and capture key concepts and themes. The final stage involves the mapping and interpretation of the data [34]. All stages of the analysis process will be discussed and reviewed with at least 2 researchers (ES and SB) to ensure rigor [36].

Ethical Considerations

Ethics approval was obtained from The University of Manchester Research Ethics Committee on August 18, 2023 (2023-17372-30569) to ensure that adequate safeguards are in place to protect the privacy of participants and to maintain the confidentiality of data. This study will be conducted in accordance with the UK Policy Framework for Health and Social Care Research and the Declaration of Helsinki guidelines. Prior to data collection, all the participants who agreed to participate in the study will sign a consent form, which includes a description of the study, its objectives, and participants' involvement and rights (Multimedia Appendix 1). Participation

in the study is entirely voluntary and participants can withdraw at any time. Participants will not receive financial compensation for their contribution to the study. Any deviations from the protocol will be put through the appropriate ethical amendment process. It is not anticipated that the study will be stopped prior to its intended end date. However, the study will be halted if safety issues arise regarding the intervention or resources to conduct the study are no longer available. Outcomes will be disseminated through conference presentations and publications in peer-reviewed journals in deidentified form. The findings will also be shared through presentations with digital inclusion teams and community stakeholders.

Results

We anticipate recruitment will commence in March 2024 and will continue until enrollment is complete (N=36). The analysis is expected to be completed by November 2024, and the results will be published by January 2025.

Discussion

Principal Findings

The intervention (KOKU-Nut) involves educating users about how and why to make lifestyle changes, encouraging participation in regular and progressive strength and balance activities, and nudging older adults to improve their dietary intake. These features are underpinned by behavior change theories and have been co-designed with end users.

In comparison to many physical activity digital health tools such as Nymbl and Standing Tall, KOKU-Nut incorporates a nutritional component with a focus on dietary protein and fluid intake, given their low intakes among older adults [37,38] and their role in health [39,40]. The impact of diet is well established and can help older adults maintain health status and physical function [41]. Furthermore, it is estimated that one-quarter of Europeans older than the age of 65 years are at a high risk of malnutrition [42], and this can increase the risk of frailty, musculoskeletal conditions, and mortality [43-45]. In addition to the high prevalence of malnutrition, a recent James Lind Alliance priority setting partnership identified early intervention in vulnerable groups as a top priority [46].

There has been a rapid development in the number and quality of mobile health apps, and there is a growing acceptance among older adults. These tools have many benefits including that they can increase motivation through notifications and tracking of progress and provide personalized feedback to the user and increase engagement through gamification. However, there are still many challenges around introducing new digital health apps to this population. The usability of digital technology is important to ensure sustained use and to allow users to engage with the product for its intended purpose. Acceptability refers to the extent to which users consider the digital technology appropriate. Mobile apps are more likely to be usable and acceptable to older adults if they are codeveloped with them using principles of human-centered design [47,48]. KOKU-Nut was co-designed with end users and health care professionals, and we hope this will maximize the usability and usefulness of the interface and content.

This study will provide information on the feasibility and usability of the mobile health app KOKU-Nut. To our knowledge, this is the first digital health app in the United Kingdom designed to empower community-dwelling older adults to increase their activity levels and improve their diet and fluid intake so that they can stay active and healthy for longer.

Study Limitations

This study has a number of limitations. We plan to recruit participants using purposive sampling from across Greater Manchester and thus this limits the generalizability of the results to the rest of the United Kingdom and internationally. However, this is a feasibility study that aims to inform a powered RCT that would then enable conclusions to be drawn. Furthermore, many of the study outcomes including dietary assessment and assessments of feasibility are self-reported and so prone to recall bias. Questionnaires will be checked for completeness and Intake24 appears to report similar data to intakes reported in interviewer-led dietary recall [49] and the gold standard assessment of energy intake using doubly labeled water [50].

Conclusions

To our knowledge, this will be the first RCT to evaluate a digital health tool that nudges community-dwelling older adults living in the United Kingdom to improve their dietary intake and reduce the risk of malnutrition. The study aligns with guidelines developed by the Medical Research Council for developing a complex intervention by using qualitative and quantitative research to examine the barriers to intervention from the perspective of users and identify potential challenges around recruitment and retention [51].

Acknowledgments

CF receives financial support from the Medical Research Council (CASE Entry: /R015767/1). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Data Availability

We plan to write up the findings for publication, which will include an overview of the anonymized data. The data sets generated and analyzed during this study are not publicly available in accordance with the data management plan but are available from the corresponding author on reasonable request.

Authors' Contributions

CF was involved in the study design and writing the manuscript. ES and SB were involved in the study design and editing of the manuscript.

Conflicts of Interest

ES is the Director of Keep-On-Keep-Up Health Community Interest Company. CF and SB declare no potential conflicts of interest with respect to the research, authorship, and publication of this article.

Multimedia Appendix 1
Supplementary material to demonstrate SPIRIT checklist (S1), CONSORT checklist (S2) and Consent form (S3).
[DOCX File , 40 KB - resprot_v13i1e50922_app1.docx]

References

1. Daly R, Gianoudis J, Kersh ME, Bailey CA, Ebeling PR, Krug R, et al. Effects of a 12-month supervised, community-based, multimodal exercise program followed by a 6-month research-to-practice transition on bone mineral density, trabecular microarchitecture, and physical function in older adults: a randomized controlled trial. J Bone Miner Res 2020;35(3):419-429 [FREE Full text] [doi: 10.1002/jbmr.3865] [Medline: 31498937]
2. Sherrington C, Fairhall N, Wallbank G, Tiedemann A, Michaleff ZA, Howard K, et al. Exercise for preventing falls in older people living in the community: an abridged Cochrane systematic review. Br J Sports Med 2020 Aug;54(15):885-891. [doi: 10.1136/bjsports-2019-101512] [Medline: 31792067]
3. Gianoudis J, Bailey CA, Ebeling PR, Nowson CA, Sanders KM, Hill K, et al. Effects of a targeted multimodal exercise program incorporating high-speed power training on falls and fracture risk factors in older adults: a community-based randomized controlled trial. J Bone Miner Res 2014 Jan;29(1):182-191 [FREE Full text] [doi: 10.1002/jbmr.2014] [Medline: 23775701]
4. Dominguez LJ, Veronese N, Baiamonte E, Guarrera M, Parisi A, Ruffolo C, et al. Healthy aging and dietary patterns. Nutrients 2022;14(4):889 [FREE Full text] [doi: 10.3390/nu14040889] [Medline: 35215539]
5. Gielen E, Beckwée D, Delaere A, De Breucker S, Vandewoude M, Bautmans I, Sarcopenia Guidelines Development Group of the Belgian Society of GerontologyGeriatrics (BSGG). Nutritional interventions to improve muscle mass, muscle strength, and physical performance in older people: an umbrella review of systematic reviews and meta-analyses. Nutr Rev 2021 Jan 09;79(2):121-147 [FREE Full text] [doi: 10.1093/nutrit/nuaa011] [Medline: 32483625]
6. Hsu KJ, Liao CD, Tsai MW, Chen CN. Effects of exercise and nutritional intervention on body composition, metabolic health, and physical performance in adults with sarcopenic obesity: a meta-analysis. Nutrients 2019;11(9):2163 [FREE Full text] [doi: 10.3390/nu11092163] [Medline: 31505890]
7. van den Helder J, Mehra S, van Dronkelaar C, Ter Riet G, Tieland M, Visser B, et al. Blended home-based exercise and dietary protein in community-dwelling older adults: a cluster randomized controlled trial. J Cachexia Sarcopenia Muscle 2020 Dec;11(6):1590-1602 [FREE Full text] [doi: 10.1002/jcsm.12634] [Medline: 33103379]
8. McGarrigle L, Boulton E, Todd C. Map the apps: a rapid review of digital approaches to support the engagement of older adults in strength and balance exercises. BMC Geriatr 2020 Nov 18;20(1):483 [FREE Full text] [doi: 10.1186/s12877-020-01880-6] [Medline: 33208117]
9. Chew HSJ, Koh WL, Ng JSHY, Tan KK. Sustainability of weight loss through smartphone apps: systematic review and meta-analysis on anthropometric, metabolic, and dietary outcomes. J Med Internet Res 2022 Sep 21;24(9):e40141 [FREE Full text] [doi: 10.2196/40141] [Medline: 36129739]
10. Yerrakalva D, Yerrakalva D, Hajna S, Griffin S. Effects of mobile health app interventions on sedentary time, physical activity, and fitness in older adults: systematic review and meta-analysis. J Med Internet Res 2019 Nov 28;21(11):e14343 [FREE Full text] [doi: 10.2196/14343] [Medline: 31778121]
11. Wegener EK, Kayser L. Smart health technologies used to support physical activity and nutritional intake in fall prevention among older adults: a scoping review. Exp Gerontol 2023 Oct 01;181:112282 [FREE Full text] [doi: 10.1016/j.exger.2023.112282] [Medline: 37660762]
12. Personalised strength and balance exercises for ageing well. KOKU. URL: https://kokuhealth.com/ [accessed 2024-04-05]
13. Choi NG, Stanmore E, Caamano J, Vences K, Gell NM. A feasibility study of multi-component fall prevention for homebound older adults facilitated by lay coaches and using a tablet-based, gamified exercise application. J Appl Gerontol 2021 Nov;40(11):1483-1491 [FREE Full text] [doi: 10.1177/0733464821991024] [Medline: 33541199]
14. The Eatwell guide: helping you eat a healthy, balanced diet. Public Health England. 2018. URL: https://assets.publishing.service.gov.uk/media/5ba8a50540f0b605084c9501/Eatwell_Guide_booklet_2018v4.pdf [accessed 2024-04-05]
15. SACN statement on nutrition and older adults living in the community. Scientific Advisory Committee on Nutrition (SACN). 2021. URL: https://www.gov.uk/government/publications/sacn-statement-on-nutrition-and-older-adults [accessed 2024-04-05]

16. Skivington K, Matthews L, Simpson SA, Craig P, Baird J, Blazeby JM, et al. A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance. BMJ 2021 Sep 30;374:n2061 [FREE Full text] [doi: 10.1136/bmj.n2061] [Medline: 34593508]
17. Eldridge SM, Lancaster GA, Campbell MJ, Thabane L, Hopewell S, Coleman CL, et al. Defining feasibility and pilot studies in preparation for randomised controlled trials: development of a conceptual framework. PLoS One 2016;11(3):e0150205 [FREE Full text] [doi: 10.1371/journal.pone.0150205] [Medline: 26978655]
18. Chan AW, Tetzlaff JM, Altman DG, Dickersin K, Moher D. SPIRIT 2013: new guidance for content of clinical trial protocols. Lancet 2013 Jan 12;381(9861):91-92. [doi: 10.1016/S0140-6736(12)62160-6] [Medline: 23305999]
19. Healthy living: looking after yourself physically and mentally. ageUK. 2022. URL: https://www.ageuk.org.uk/globalassets/age-uk/documents/information-guides/ageukig24_healthy_living_inf.pdf [accessed 2024-04-05]
20. Landreville P, Guérette A. Psychometric properties of a modified version of the treatment evaluation inventory for assessing the acceptability of treatments for geriatric depression. Can J Aging 2010 Nov 29;17(4):414-424. [doi: 10.1017/s071498080001268x]
21. Shanyinde M, Pickering RM, Weatherall M. Questions asked and answered in pilot and feasibility randomized controlled trials. BMC Med Res Methodol 2011 Aug 16;11:117 [FREE Full text] [doi: 10.1186/1471-2288-11-117] [Medline: 21846349]
22. Lancaster GA, Dodd S, Williamson PR. Design and analysis of pilot studies: recommendations for good practice. J Eval Clin Pract 2004 May;10(2):307-312. [doi: 10.1111/j..2002.384.doc.x] [Medline: 15189396]
23. Malterud K, Siersma VD, Guassora AD. Sample size in qualitative interview studies: guided by information power. Qual Health Res 2016 Nov;26(13):1753-1760. [doi: 10.1177/1049732315617444] [Medline: 26613970]
24. Simple randomisation service. Sealed Envelope Ltd. 2022. URL: https://www.sealedenvelope.com/simple-randomiser/v1/ [accessed 2024-04-05]
25. MyFood24. Dietary Assessment Ltd. URL: https://www.myfood24.org/about/the-company/ [accessed 2024-04-05]
26. Obesity: how should I confirm if a person is overweight or obese? National Institute for Health and Care Excellence. 2023. URL: https://cks.nice.org.uk/topics/obesity/diagnosis/identification-classification/ [accessed 2024-04-05]
27. Kondrup J, Allison SP, Elia M, Vellas B, Plauth M, EducationalClinical Practice Committee, European Society of ParenteralEnteral Nutrition (ESPEN). ESPEN guidelines for nutrition screening 2002. Clin Nutr 2003 Aug;22(4):415-421. [doi: 10.1016/s0261-5614(03)00098-0] [Medline: 12880610]
28. Kirk B, French C, Gebauer M, Vogrin S, Zanker J, Sales M, et al. Diagnostic power of relative sit-to-stand muscle power, grip strength, and gait speed for identifying a history of recurrent falls and fractures in older adults. Eur Geriatr Med 2023 Jun;14(3):421-428. [doi: 10.1007/s41999-023-00778-x] [Medline: 37058233]
29. Alcazar J, Losa-Reyna J, Rodriguez-Lopez C, Alfaro-Acha A, Rodriguez-Mañas L, Ara I, et al. The sit-to-stand muscle power test: an easy, inexpensive and portable procedure to assess muscle power in older people. Exp Gerontol 2018 Oct 02;112:38-43. [doi: 10.1016/j.exger.2018.08.006] [Medline: 30179662]
30. EQ-5D user guides. EUROQOL. 2020. URL: https://euroqol.org/publications/user-guides/ [accessed 2024-04-05]
31. Janssen B, Szende A. Population norms for the EQ-5D. In: Szende A, Janssen B, Cabases J, editors. Self-Reported Population Health: An International Perspective based on EQ-5D. Dordrecht, NL: Springer; 2014.
32. Church S, Rogers E, Rockwood K, Theou O. A scoping review of the clinical frailty scale. BMC Geriatr 2020;20(1):393 [FREE Full text] [doi: 10.1186/s12877-020-01801-7] [Medline: 33028215]
33. Mendiratta P, Schoo C, Latif R. Clinical frailty scale. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2023.
34. Ritchie J, Lewis J. Qualitative Research Practice: A Guide for Social Science Students and Researchers. London: Sage Publications; 2003.
35. Hackett A, Strickland K. Using the framework approach to analyse qualitative data: a worked example. Nurse Res 2019;26(2):8-13. [doi: 10.7748/nr.2018.e1580] [Medline: 30215482]
36. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol 2006 Jan;3(2):77-101. [doi: 10.1191/1478088706qp063oa]
37. Morris S, Cater JD, Green MA, Johnstone AM, Brunstrom JM, Stevenson EJ, et al. Inadequacy of protein intake in older UK adults. Geriatrics (Basel) 2020;5(1):6 [FREE Full text] [doi: 10.3390/geriatrics5010006] [Medline: 32059533]
38. Parkinson E, Hooper L, Fynn J, Wilsher SH, Oladosu T, Poland F, et al. Low-intake dehydration prevalence in non-hospitalised older adults: systematic review and meta-analysis. Clin Nutr 2023;42(8):1510-1520 [FREE Full text] [doi: 10.1016/j.clnu.2023.06.010] [Medline: 37330324]
39. Phillips SM, Martinson W. Nutrient-rich, high-quality, protein-containing dairy foods in combination with exercise in aging persons to mitigate sarcopenia. Nutr Rev 2019;77(4):216-229 [FREE Full text] [doi: 10.1093/nutrit/nuy062] [Medline: 30561677]
40. Beck AM, Seemer J, Knudsen AW, Munk T. Narrative review of low-intake dehydration in older adults. Nutrients 2021;13(9):3142 [FREE Full text] [doi: 10.3390/nu13093142] [Medline: 34579019]
41. Yeung SSY, Kwan M, Woo J. Healthy diet for healthy aging. Nutrients 2021;13(12):4310 [FREE Full text] [doi: 10.3390/nu13124310] [Medline: 34959862]
42. Leij-Halfwerk S, Verwijs MH, van Houdt S, Borkent JW, Guaitoli PR, Pelgrim T, et al. Prevalence of protein-energy malnutrition risk in European older adults in community, residential and hospital settings, according to 22 malnutrition

screening tools validated for use in adults ≥65 years: a systematic review and meta-analysis. Maturitas 2019;126:80-89. [doi: 10.1016/j.maturitas.2019.05.006] [Medline: 31239123]
43. Lengelé L, Bruyère O, Beaudart C, Reginster J, Locquet M. Impact of malnutrition status on muscle parameter changes over a 5-year follow-up of community-dwelling older adults from the SarcoPhAge cohort. Nutrients 2021;13(2):407 [FREE Full text] [doi: 10.3390/nu13020407] [Medline: 33525324]
44. Jeejeebhoy KN. Malnutrition, fatigue, frailty, vulnerability, sarcopenia and cachexia: overlap of clinical features. Curr Opin Clin Nutr Metab Care 2012;15(3):213-219. [doi: 10.1097/MCO.0b013e328352694f] [Medline: 22450775]
45. O'Keeffe M, Kelly M, O'Herlihy E, O'Toole PW, Kearney PM, Timmons S, et al. Potentially modifiable determinants of malnutrition in older adults: a systematic review. Clin Nutr 2019;38(6):2477-2498 [FREE Full text] [doi: 10.1016/j.clnu.2018.12.007] [Medline: 30685297]
46. Jones DJ, Baldwin C, Lal S, Stanmore E, Farrer K, Connolly E, et al. Priority setting for adult malnutrition and nutritional screening in healthcare: a James Lind Alliance. J Hum Nutr Diet 2020;33(2):274-283. [doi: 10.1111/jhn.12722] [Medline: 31858685]
47. Farao J, Malila B, Conrad N, Mutsvangwa T, Rangaka MX, Douglas TS. A user-centred design framework for mHealth. PLoS One 2020;15(8):e0237910 [FREE Full text] [doi: 10.1371/journal.pone.0237910] [Medline: 32813711]
48. Jessup RL, Osborne RH, Buchbinder R, Beauchamp A. Using co-design to develop interventions to address health literacy needs in a hospitalised population. BMC Health Serv Res 2018;18(1):989 [FREE Full text] [doi: 10.1186/s12913-018-3801-7] [Medline: 30572887]
49. Bradley J, Simpson E, Poliakov I, Matthews JNS, Olivier P, Adamson AJ, et al. Comparison of INTAKE24 (an online 24-h dietary recall tool) with interviewer-led 24-h recall in 11-24 year-old. Nutrients 2016;8(6):358 [FREE Full text] [doi: 10.3390/nu8060358] [Medline: 27294952]
50. Foster E, Lee C, Imamura F, Hollidge SE, Westgate KL, Venables MC, et al. Validity and reliability of an online self-report 24-h dietary recall method (Intake24): a doubly labelled water study and repeated-measures analysis. J Nutr Sci 2019;8:e29 [FREE Full text] [doi: 10.1017/jns.2019.20] [Medline: 31501691]
51. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M, Medical Research Council Guidance. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ 2008;337:a1655 [FREE Full text] [doi: 10.1136/bmj.a1655] [Medline: 18824488]

Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
KOKU: Keep-on-Keep-up
KOKU-Nut: Keep-on-Keep-up Nutrition
RCT: randomized controlled trial
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

Edited by A Mavragani; submitted 17.07.23; peer-reviewed by F Sheen, K Bochtler, D Chrimes; comments to author 25.01.24; revised version received 07.02.24; accepted 09.02.24; published 30.04.24.

Please cite as:
French C, Burden S, Stanmore E
Digital Intervention (Keep-On-Keep-Up Nutrition) to Improve Nutrition in Older Adults: Protocol for a Feasibility Randomized Controlled Trial
JMIR Res Protoc 2024;13:e50922
URL: https://www.researchprotocols.org/2024/1/e50922
doi:10.2196/50922
PMID:38687981

Protocol

An mHealth Intervention for Gay and Bisexual Men's Mental, Behavioral, and Sexual Health in a High-Stigma, Low-Resource Context (Project Comunic): Protocol for a Randomized Controlled Trial

Corina Lelu iu-Weinberger[1*], PhD, MPhil; Mircea L Filimon[1*], MA, MPA; Donald Hoover[2*], PhD; Mihai Lixandru[3], BA; Lucian Hanu[3], BA; Bogdan Dogaru[4], BA; Tudor Kovacs[4], MA; Cristina Fierbin eanu[3], MA; Florentina Ionescu[5], MA; Monica Manu[5], MA; Alexandra Mari [6], MA; Elena Pană[7], MA; Cristian Dorobăn escu[8], MA; Adrian Streinu-Cercel[9], MD, PhD; John E Pachankis[10*], PhD

[1]School of Nursing, Columbia University, New York, NY, United States

[2]Department of Statistics, Rutgers, the State University of New Jersey, Piscataway, NJ, United States

[3]The Romanian Association Against AIDS, Bucharest, Romania

[4]MozaiQ, Bucharest, Romania

[5]Insight, Bucharest, Romania

[6]Mari Alexandra - Cabinet Individual de Psihologie, Bucharest, Romania

[7]Obregia Hospital, Bucharest, Romania

[8]Data Center Solutions, Bucharest, Romania

[9]The National Institute of Infectious Diseases "Professor Dr. Matei Bal ", Bucharest, Romania

[10]Department of Social and Behavioral Sciences, Yale School of Public Health, New Haven, CT, United States

[*]these authors contributed equally

Corresponding Author:
Corina Lelu iu-Weinberger, PhD, MPhil
School of Nursing
Columbia University
560 West 168th Street
New York, NY, 10032
United States
Phone: 1 646 217 9205
Email: cl4265@cumc.columbia.edu

Abstract

Background: The World Health Organization reported that 80% of new HIV diagnoses in Europe in 2014 occurred in Central and Eastern Europe. Romania has a particularly high HIV incidence, AIDS prevalence, and number of related deaths. HIV incidence in Romania is largely attributed to sexual contact among gay and bisexual men. However, homophobic stigma in Romania serves as a risk factor for HIV infection for gay and bisexual men. The Comunică intervention aims to provide a much-needed HIV risk reduction strategy, and it entails the delivery of motivational interviewing and cognitive behavioral therapy skills across 8 live text-based counseling sessions on a mobile platform to gay and bisexual men at risk of HIV. The intervention is based on the information-motivation-behavior and minority stress models. There is preliminary evidence suggesting that Comunică holds promise for reducing gay and bisexual men's co-occurring sexual (eg, HIV transmission risk behavior), behavioral (eg, heavy alcohol use), and mental (eg, depression) health risks in Romania.

Objective: This paper describes the protocol for a randomized controlled trial designed to test the efficacy of Comunică in a national trial.

Methods: To test Comunică's efficacy, 305 gay and bisexual men were randomized to receive Comunică or a content-matched education attention control condition. The control condition consisted of 8 time-matched educational modules that present information regarding gay and bisexual men's identity development, information about HIV transmission and prevention, the importance of HIV and sexually transmitted infection testing and treatment, heavy alcohol use and its associations with HIV

transmission risk behavior, sexual health communication, finding social support, and creating sexual health goals. Participants undergo rapid HIV and syphilis testing and 3-site chlamydia and gonorrhea testing at baseline and the 12-month follow-up. Outcomes are measured before the intervention (baseline) and at the 4-, 8-, and 12-month follow-ups.

Results: The study was funded in September 2018, and data collection began in May 2019. The last participant follow-up was in January 2024. Currently, the data analyst is cleaning data sets in preparation for data analyses, which are scheduled to begin in April 2024. Data analysis meetings are scheduled regularly to establish timelines and examine the results as analyses are gradually being conducted. Upon completion, a list of manuscripts will be reviewed and prioritized, and the team will begin preparing them for publication.

Conclusions: This study is the first to test the efficacy of an intervention with the potential to simultaneously support the sexual, behavioral, and mental health of gay and bisexual men in Central and Eastern Europe using motivational interviewing support and sensitivity to the high-stigma context of the region. If efficacious, Comunică presents a scalable platform to provide support to gay and bisexual men living in Romania and similar high-stigma, low-resource countries.

Trial Registration: ClinicalTrials.gov NCT03912753; https://clinicaltrials.gov/study/NCT03912753

International Registered Report Identifier (IRRID): DERR1-10.2196/52853

(JMIR Res Protoc 2024;13:e52853) doi:10.2196/52853

KEYWORDS

gay and bisexual men; HIV prevention; heavy alcohol use; stigma; mental health; behavioral intervention; mobile phone

Introduction

Background

The World Health Organization reported that 80% of new HIV diagnoses in Europe in 2014 occurred in Central and Eastern Europe (CEE) [1]. Of the 15 surveyed European countries, Romania had the second-highest HIV incidence and AIDS prevalence and the highest number of AIDS-related deaths between 2005 and 2014 [1]. After the first wave of the HIV epidemic in Romania, which occurred in children via nosocomial infection in the 1980s [2-6], a new wave, largely attributed to male-to-male sexual contact, has emerged and is increasing [1,7,8]. The increased exposure of gay and bisexual men to HIV and other sexually transmitted infections (STIs) in the past 2 decades has purportedly resulted from more frequent travel to and from areas of high HIV prevalence outside Romania, including many European Union (EU) states in Western Europe [9]; lack of sexual education in Romania in general [10-12] and specifically sexual education that responds to gay and bisexual men's distinct sexual health needs [13]; and pervasive stigma against gay and bisexual men [14].

Despite these co-occurring threats resulting in increased HIV transmission risk, gay and bisexual men remain underprioritized in Romanian public health [2]. Furthermore, reporting of epidemiologic data might be unreliable in Romania due to ineffective surveillance systems and gay and bisexual men's anticipated stigma and normative identity concealment [15]. As a result, HIV transmission among gay and bisexual men is frequently underreported or misclassified as heterosexual [1,16,17]. For instance, an independent European survey found that the number of HIV diagnoses self-reported by Romanian gay and bisexual men respondents was 2.7 times the official national notification rate [17], suggesting that a significant proportion of HIV infections occurring among the gay and bisexual men community might be attributed to heterosexual transmission, thus yielding inaccurate guidance for national HIV-related priorities.

The best available evidence suggests that HIV prevalence among Romanian gay and bisexual men increased from <10% in 2009 to approximately 20% in 2014 [18-20]. An international biobehavioral survey of gay and bisexual men found that Romania had the highest rate of unrecognized HIV infections across all included European countries [19-22]. Untreated STIs represent a primary risk factor for HIV transmission [23], yet gay and bisexual men–sensitive screening for STIs is rare in Romania. For example, of 629 gay and bisexual men who sought an STI test over 1 year in the capital city of Bucharest, only 6.4% received both an anal swab and penile examination (compared to 72.4% in Amsterdam)—the lowest rate in all 40 cities participating in a European survey of gay and bisexual men (N=174,209). Furthermore, fewer than one-third of Romanian gay and bisexual men had been screened for STIs in the previous year, and fewer than half knew where they could access STI testing [20,24].

Insufficient sexual health knowledge specific to gay and bisexual men in Romania has direct implications for HIV transmission. A 2017 survey of 50 European and contiguous countries found that, of 2002 Romanian gay and bisexual men respondents, only 0.4% had ever used pre-exposure prophylaxis (PrEP) and 1.1% had ever used postexposure prophylaxis, whereas 62% were unaware of PrEP and only 56% were knowledgeable regarding *undetectable=untransmissible*. A total of 13% of respondents reported having at least 2 steady sex partners in the previous year with whom they did not use condoms (the third highest rate among the 50 surveyed countries); 32% reported having condomless sex due to lack of access to condoms (the seventh highest rate among the 50 surveyed countries) [25]. Of those who had never been tested for HIV (approximately 50% in the Romanian sample), half (51%) did not know where to get tested (the fifth highest rate among the 50 countries) [25].

In terms of mental and behavioral health needs that can co-occur with HIV transmission risk among gay and bisexual men [26,27], European surveys indicate that 12% of Romanian gay and bisexual men reported severe anxiety and depression during

the previous 2 weeks, 21% had thoughts of self-harm [25], and 14% met criteria for alcohol dependency. Homophobic stigma is also a risk factor for HIV transmission and co-occurring mental and behavioral health risks as it keeps most Romanian gay and bisexual men hidden and out of reach of official HIV and STI surveillance and the few available prevention services. Depression, anxiety, heavy alcohol use, and homophobic stigma combine to create a syndemic affecting gay and bisexual men [28-30].

Despite gains in some rights for lesbian, gay, bisexual, transgender, and queer (LGBTQ) individuals (eg, decriminalization of homosexuality) over the past 2 decades, Romania remains one of the most structurally homophobic countries in Europe [31,32], with structural homophobia being associated with low life satisfaction, poor mental health, social isolation, internalized homonegativity, and high degrees of identity concealment among gay and bisexual men [15,31,33]. Identifying as an ethnic minority group (eg, Roma) may further amplify the odds of encountering hate speech and harassment [34], and there might be intersectional challenges for ethnic minority gay and bisexual men in Romania [35]. A recent report by the EU Agency for Fundamental Rights found significant physical or sexual attacks against LGBTQ people in Romania (15%) [34]. Of 28 EU member states, Romania was among the top 3 countries in terms of the prevalence of hate-motivated physical or sexual attacks against LGBTQ people [34]. Perhaps as a further manifestation of structural stigma toward gay and bisexual men, no governmental funds are currently allocated for HIV and STI prevention among gay and bisexual men in Romania despite the clear and increasing need for such prevention, as outlined previously [2,18,22,36].

Evidence-based HIV prevention interventions for gay and bisexual men are not widely available in Romania and are rare in the CEE region, where most HIV-related interventions have been developed for people who inject drugs [37]. A systematic review in 2015 identified only 24 HIV prevention interventions for gay and bisexual men in Europe [38], none of which appeared to have been implemented in Romania. To address this gap and respond to the interlocking challenges facing gay and bisexual men in Romania that contribute to their increasing HIV transmission risk behavior, our team sought to adapt a promising intervention created for gay and bisexual men in the United States [39], which was recently pilot-tested in Romania, under the name of Comunică, to support this population's unmet needs of [40].

Comunică Intervention Background and Pilot

Comunică is based on the information–motivation–behavioral skills (IMB) model of health behavior change [41], which postulates that individuals must possess the requisite information for enacting sexual health; motivation to address their HIV transmission risk behavior, alcohol use, and mental health; and behavioral skills necessary for reducing risk behaviors. The Comunică intervention is guided by motivational interviewing (MI) principles and techniques [42] to provide accurate information about HIV transmission, heavy alcohol use, and local gay and bisexual men–affirmative health resources (eg, HIV-testing sites) and build motivation to improve behavioral skills via cognitive behavioral skill training (CBST) [43]. MI is an evidence-based form of person-centered therapeutic communication that privileges client values and preferences for change to help individuals resolve ambivalence and move toward their valued goals [41,44]. For individuals who attain a high degree of motivation for change [45], CBST is used to promote awareness of contextual triggers and unhealthy behavioral patterns and teach coping skills to reduce personal risk [46]. Given the stigmatizing context of Romania, the CBST skills in Comunică are presented in a manner that acknowledges the barriers posed by social stigma to gay and bisexual men's health while empowering them to circumvent these barriers by building self-efficacy, learning effective communication, and implementing planful problem-solving [47-49]. In this way, Comunică also draws on minority stress theory recognizing that stigmatizing societal contexts represent the ultimate source of health disparities affecting gay and bisexual men [50]. Minority stress content informs the context in which the aforementioned psychoeducational information is presented, such as through a focus on identity development in the context of stigma and the ways in which minority stress affects mental, behavioral, and sexual health.

The Comunică intervention is delivered across 8 sessions by a trained counselor via synchronous (ie, live) text-based chat on a mobile-optimized website that also contains features for weekly tracking of HIV transmission risk behavior, heavy drinking, and mood. The study platform allows gay and bisexual men randomized to the Comunică intervention to track their weekly number of condomless sex acts, number of partners, number of heavy alcohol use days, and positive and negative moods [51]. A review of this information with counselors during sessions is intended to support motivation and create contextually informed behavior change goals. Previous research has shown that mobile tools are the primary means for Romanian gay and bisexual men to form and navigate social and sexual networks, especially given normative identity concealment [31], offering an ideal intervention platform [40]. While session content is driven by participant-selected priorities, they are discussed within the general theoretical and counseling frameworks of the Comunică intervention.

The feasibility, acceptability, and preliminary efficacy of Comunică was established between 2014-2016 in an open-trial pilot study with 43 young gay and bisexual men in Romania (mean age 23.2, SD 3.6; range 17-29 years) who reported condomless anal sex (CAS) acts with a male partner and at least 5 days of heavy drinking (≥5 drinks on one occasion) in the previous 3 months [40]. Specifically, gay and bisexual men who received Comunică reported, from baseline to a 3-month follow-up, significantly reduced depression, anxiety, and heavy alcohol use (P=.005) and increased condom use self-efficacy (P=.01), HIV-related knowledge (P=.001), and HIV testing (P=.05) [40]. While reductions in CAS trended in the expected direction from baseline to postintervention follow-up (mean 14.7 vs mean 10.8), the analyses were not sufficiently powered to detect significant differences. The Comunică intervention was created through in-depth consultation with 22 Romanian gay and bisexual men and 6 community stakeholders (eg, gay and bisexual men advocates and service providers) and was

based on a chat-based MI intervention established in the United States [39].

Study Objectives

This study aims to test the efficacy of Comunică in reducing HIV transmission risk behavior (ie, number of CAS acts with HIV-positive or unknown-status partners outside the context of one's own or one's primary partner's adherent PrEP use or undetectable viral load in the past 30 days) in a randomized controlled trial of 305 Romanian gay and bisexual men. The secondary outcomes include depression, heavy alcohol use, and HIV and STI testing. The control condition consists of 8 time-matched educational modules that present information regarding gay and bisexual men identity development, HIV and STI prevention, heavy alcohol use and its associations with HIV transmission risk behavior, sexual health communication, and the importance of social support created in consultation with Romanian gay and bisexual men community members and advocates. The educational modules for the control condition are hosted on the same study website as the Comunică intervention but without access to counseling or behavioral and mood-tracking features.

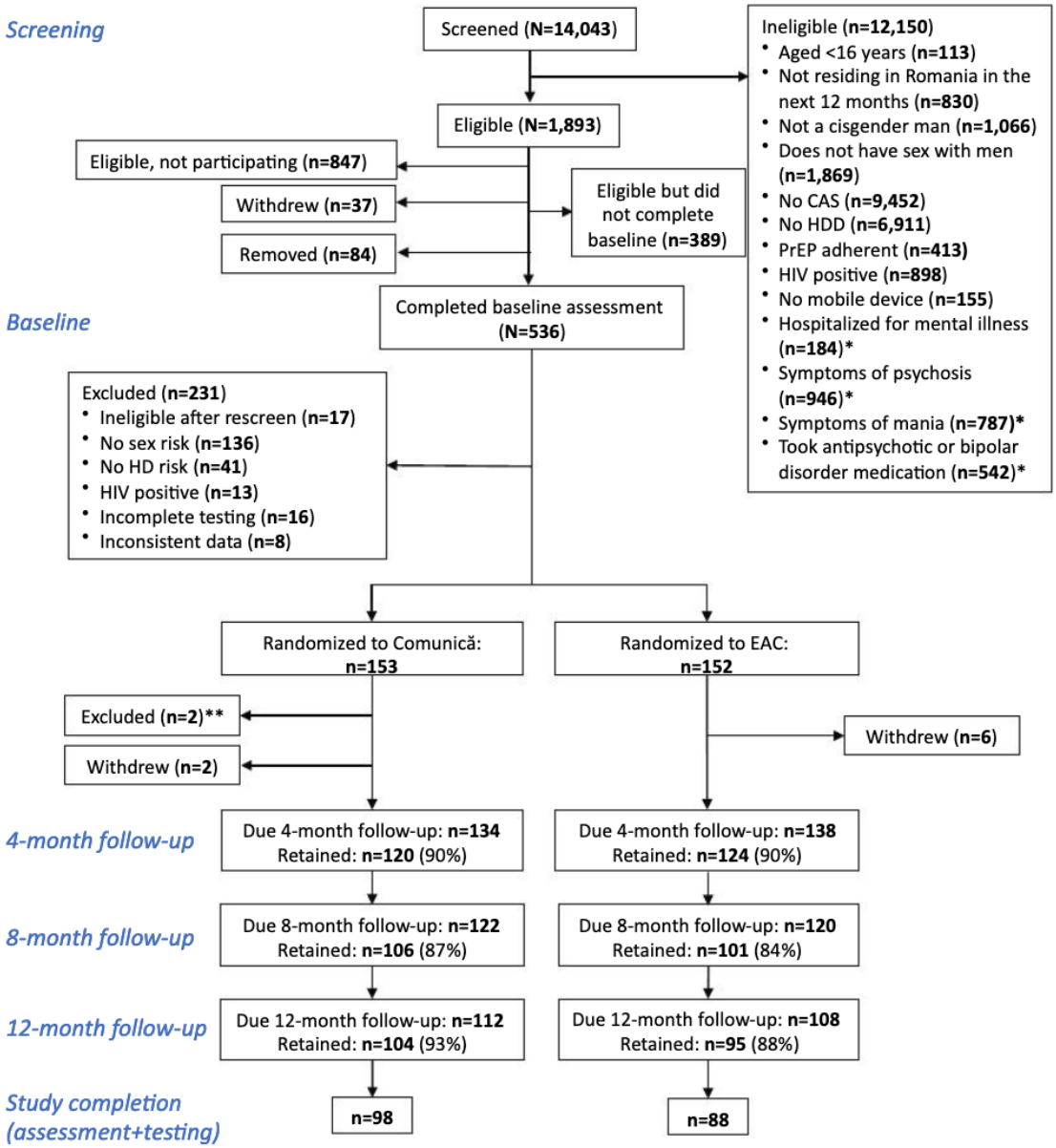
This study also tests two sets of mechanisms of intervention efficacy: (1) motivational mechanisms derived from the IMB model [41,44,52] (eg, knowledge of sexual health and alcohol use effects, motivation to reduce HIV risk and heavy alcohol use, and self-efficacy for safer sex and reductions in alcohol use) and (2) minority stress mechanisms derived from minority stress theory (eg, rejection sensitivity, stigma consciousness, and identity concealment) [53]. If shown to be efficacious in this trial, Comunică will constitute a unique mental, behavioral, and sexual health intervention that can be implemented in Romania and other high-stigma, low-resource national contexts in the future.

Methods

Design

In this randomized controlled trial, Comunică is compared to a content-matched education attention control (EAC) condition in changing (1) the primary outcome (frequency of CAS acts with HIV-positive or unknown-status partners outside the context of one's own or one's primary partner's adherent PrEP use or viral suppression) and (2) secondary outcomes (depression, anxiety, suicidal thoughts, heavy alcohol use, and HIV and STI testing). Both the intervention and control groups received 8 one-hour intervention sessions or educational modules, respectively, to be completed over the course of 4 months. Outcomes are measured before the intervention (baseline) and at the 4-, 8-, and 12-month follow-ups. All participants self-administer at-home rapid testing for HIV and syphilis, and self-collect sampling (urethral, pharyngeal, and rectal) for chlamydia and gonorrhea sent to a laboratory at baseline and the 12-month follow-up. The CONSORT (Consolidated Standards of Reporting Trials) diagram in Figure 1 outlines the flow of participants throughout the study as of September 12, 2023.

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram. *As of September 16, 2020, mental health screening questions are no longer part of eligibility criteria. **These participants admitted to providing false condomless anal sex (CAS) or heavy drinking days (HDD) data at baseline assessment. EAC: education attention control; HD: heavy drinking; PrEP: pre-exposure prophylaxis.



Recruitment

Recruitment and enrollment for the study ended in January 2023, with follow-up completion in January 2024. Gay and bisexual men living in or within 40 miles of 10 cities (ie, Bucure ti, Bra ov, Timi oara, Cluj-Napoca, Ia i, Constan a, Suceava, Craiova, Gala i, and Satu Mare) were recruited and screened. By selecting these cities, this study covers all regions of the country [54]. Collaborating LGBTQ advocacy organizations posted study advertisements on their websites, subscriber lists, and key virtual venues (eg, Grindr, Facebook, and Instagram). Study recruitment also relied on word of mouth; for instance, recruiters approached men in gay and bisexual men–prevalent venues (bars, events, and public cruising areas). Finally, enrolled participants were encouraged to share study information with their peers. Nevertheless, 44.9% (137/305) of participants were recruited on Grindr, and 41% (125/305) were recruited on Facebook.

Eligibility

Inclusion Criteria

Gay and bisexual men were eligible if they reported (1) male sex at birth and current male identity, (2) age of ≥16 years, (3) ≥1 act of CAS with an HIV-positive or status-unknown male partner in the previous 30 days, (4) ≥1 heavy drinking day in the previous 30 days (ie, ≥5 standard alcoholic drinks on 1 occasion per month [55,56]), (5) owning a mobile device (smartphone, tablet, or laptop), (6) residence in Romania for the duration of study participation (12 months), and (7) nonadherence to PrEP and (8) were confirmed to be HIV negative upon testing at baseline.

Exclusion Criteria

Participants were excluded if they demonstrated active suicidality, psychosis, or mania.

Screening

Potential participants completed an eligibility screener on Qualtrics (Qualtrics International Inc), a research-designated secure Health Insurance Portability and Accountability Act–compliant web-based software [57]. Eligible gay and bisexual men had the option to provide contact information at the end of the screener in a separate survey for research staff to later contact them to review the study in more detail and assess consent.

Consent

A research staff member contacted eligible participants via phone to review the consent form and verify their age. Points of confusion were clarified, and individuals still interested in participating submitted an electronic consent form via Qualtrics [57]. The research staff outlined the steps to take place immediately following consent, namely, that participants would receive a link to the baseline assessment and a numerical study identification number to be used for the duration of the study for confidentiality purposes, undergo HIV and STI testing, and be randomized to one of the study conditions. Participants were able to use any mobile device (smartphone, tablet, or laptop) to complete the sessions.

Randomization

After baseline, participants were randomized to the Comunică or EAC condition based on a list of random numbers generated by the study biostatistician. A blocked stratified randomization scheme was used, with 150 participants each being randomized 1:1 to each arm within the following four strata based on past 3-month self-reported baseline number of HIV transmission risk behavior sex acts and heavy alcohol use days as follows: (1) lower CAS acts (≤2 acts) and lower alcohol use (≤5 drinks); (2) lower CAS acts (≤2 acts) and higher alcohol use (>5 drinks); (3) higher CAS acts (>2 acts) and lower alcohol use (≤5 drinks); and (4) higher CAS acts (>2 acts) and higher alcohol use (>5 drinks). The 150 persons within each stratum were randomized using 15 blocks of size 4 and 15 blocks of size 6, with the order of the 30 total blocks being randomly permuted.

Counselors contacted participants assigned to the Comunică condition to schedule the first session, at which point they both logged onto the study platform. Group assignment was not masked from study staff given that all assessments were self-administered.

EAC Condition

The EAC condition consisted of 8 educational modules based on the team's experience with HIV prevention education with gay and bisexual men in the United States and Romania [15,39,40,48,58,59] and included the following topics: (1) gay and bisexual men identity, (2) "HIV 101" (eg, transmission risks, prevention, and treatment), (3) the importance of HIV and STI testing and treatment, (4) alcohol and the body, (5) the role of alcohol in HIV transmission risk behavior, (6) HIV status disclosure and sexual health communication, (7) finding social supports and safety, and (8) creating and reaching sexual health goals. The content was finalized in collaboration with staff of Romanian LGBTQ-supportive organizations. To maximize participant engagement and learning, each module contained a 5-item quiz (with correct answers subsequently provided) and exercises and vignettes prompting participants to provide answers based on their understanding of the topics and their own experience.

To minimize contamination, counselors who administered Comunică did not interact with EAC participants, and Comunică and EAC materials were only accessible through unique log-in credentials known only to participants.

Counselor Training and Fidelity Monitoring

In 2019, before trial commencement, 5 psychologists living in Romania completed a 2-day training on the intervention. Of these psychologists, 2 delivered the Comunică intervention in the pilot study [40], and 3 were recruited from a pool of 54 mental health professionals whom the principal investigators (PIs) had previously engaged in a separate study [60]. The training included didactic and experiential components; a review of MI, CBST, the IMB model, and minority stress theory; unique facets of delivering the intervention via text; and reviewing vignettes from the pilot study. The counselors practiced delivering each session on the intervention platform, taking turns being a mock participant and counselor, and receiving biweekly remote video supervision from a clinical supervisor. At the start of the trial, the team reviewed all session transcripts. Once intervention fidelity was attained, the team randomly selected slightly over half of the subsequent sessions to verify fidelity to the intervention content and adherence to MI principles and techniques. As in the pilot study, the counselors translated each session transcript into English for the clinical team's review.

Study Assessments

Participants provided assessment data at baseline and at 4-, 8-, and 12-month follow-up appointments, self-administered via Qualtrics [57] and a web-based platform designed specifically for this study to capture past–30-day sexual and alcohol use behaviors in a self-administered calendar review. Participants also completed biological testing for HIV, syphilis, gonorrhea, and chlamydia at the baseline and 12-month follow-up appointments. Finally, all retained participants completed an exit survey after their 12-month follow-up that assessed the acceptability of the intervention. Based on each completed portion of the study, participants were compensated in Romanian RON equivalent to US $20, US $25, US $30, and US $40 for the baseline, 4-, 8-, and 12-month assessments, respectively, and US $10 per session based on each completed portion of the study. The measures are described in the following sections.

Demographics

At baseline, as shown in Table 1, participants indicated their age, sexual orientation, sex assigned at birth, current gender identification, income, residence (rural vs urban), ethnicity, and educational level. Participants also indicated the age at which they attained sexual orientation developmental milestones (eg, age of awareness of attraction to men) [61].

Table 1. Baseline characteristics of the enrolled participants (N=305).

Characteristic	Participants, n (%)
Age (y)	
16-29	232 (76.1)
30-39	56 (18.4)
40-49	16 (5.2)
≥50	1 (0.3)
Sexual identity	
Gay	205 (67.2)
Bisexual	92 (30.2)
Queer	2 (0.7)
Pansexual	2 (0.7)
Uncertain	4 (1.3)
Educational level	
High school or lower	78 (25.6)
Vocational studies	9 (3)
Some college	108 (35.4)
College degree	57 (18.7)
Graduate degree	53 (17.4)
Relationship status	
Single and not dating	97 (31.8)
Dating	98 (32.1)
In a serious relationship	110 (36.1)
Ethnicity	
Romanian	279 (91.5)
Hungarian	22 (7.2)
Roma	3 (1)
Other	1 (0.3)
Employment	
Full time	149 (48.9)
Part time	18 (5.9)
Unemployed	15 (4.9)
Student	121 (39.7)
On disability	2 (0.7)
High school location	
Small town	161 (52.8)
Medium to large town or city	144 (47.2)
Age of awareness of attraction to men (y)	
4-14	230 (75.4)
15-25	72 (23.6)
26-34	3 (1)

Primary Outcome

This study's primary outcome, HIV transmission risk behavior, is the frequency of CAS acts with HIV-positive or unknown-status partners outside the context of one's own or one's primary partner's adherent PrEP use or undetectable viral load in the past 30 days. The partner's adherence to PrEP use was verified by the participant having witnessed their partner taking their medication daily. The partner's viral suppression in the past 30 days was verified by the participant having seen current test results or witnessing that partner taking antiretroviral therapy. To report past–30-day sexual behavior, participants completed a self-administered web-based Timeline Followback (TLFB) interview [62,63]. For each sexual act on each day, participants reported partner type (eg, primary or casual), partner gender, partner HIV status and known viral suppression (if applicable), type of sexual behavior (eg, insertive anal sex), condom use, PrEP use by themselves or their partner, and whether they were under the influence of alcohol during reported sex. TLFB collects retrospective day-level data and has been validated for electronic self-administration [62]. TLFB has good test-retest reliability, convergent validity, and agreement with collateral reports for sexual behavior [64,65] and alcohol use [66]. In this study, we developed a mobile-optimized web-based platform for the TLFB and iteratively improved it during a usability testing phase with local gay and bisexual men community members.

Secondary Outcomes

Heavy Alcohol Use

TLFB also asks participants to report their past–30-day heavy alcohol use, including whether it took place before or during sex. Participants also complete the 3-item Alcohol Use Disorders Identification Test–Consumption scale (AUDIT-C) [67], a standardized measure of alcohol-related problems.

Mental Health

Participants complete the Center for Epidemiologic Studies Depression Scale (CES-D) as a measure of depression symptoms [68], the Beck Anxiety Inventory (BAI) as a measure of anxiety symptoms [69], and the Suicidal Ideation Attributes Scale (SIDAS) [70] as a measure of suicidal ideation.

Potential Intervention Mediators

IMB Model

As informed by the IMB model, knowledge acquisition and motivation to reduce HIV transmission risk behavior and heavy alcohol use will be assessed as potential mechanisms of intervention efficacy. Information is measured using the Sexual Health Knowledge Questionnaire [71] and the Alcohol Attitudes Questionnaire [72]; motivation to reduce CAS and alcohol use is measured using the University of Rhode Island Change Assessment Scale [73] and the Stages of Change Readiness and Treatment Eagerness Scale [74], respectively; and behavioral self-efficacy to reduce HIV transmission risk behavior and heavy alcohol use is measured using the Safer Sex Efficacy Questionnaire [75] and Confidence in Reducing Alcohol Use Questionnaire [76], respectively.

Minority Stress Pathways

We measured potential mechanisms suggested by minority stress theory [77], including sexual orientation concealment using the concealment motivation subscale of the Lesbian, Gay, and Bisexual Identity Scale (LGBIS) [78]; rejection sensitivity using the acceptance concerns subscale of the LGBIS [78]; internalized stigma using the internalized homonegativity subscale of the LGBIS [78]; assertiveness using the Rathus Assertiveness Schedule [79]; and social support using the Multidimensional Scale of Perceived Social Support [80].

The protocol was also approved by the Bioethics Committee of the National Institute for Infectious Diseases the European Men-Who-Have-Sex-With-Men Internet Survey [21], participants indicate the frequency of their HIV or STI testing. Participants are asked whether they provided a blood sample to test for any STIs; whether their penis and anus were examined and swabbed as part of any STI testing in the previous 4 months; and whether and, if so, when (eg, past 7 days or 4 weeks) they were diagnosed with chlamydia, gonorrhea, genital warts, herpes, syphilis, hepatitis B or C, or urethritis.

HIV and STI Testing, Counseling, and Linkage to Services

Participants complete HIV and STI testing after providing consent and completing the baseline and 12-month follow-up assessments. Specifically, a testing counselor affiliated with the study and based at a Romanian nongovernmental organization specialized in HIV and STI prevention and treatment for gay and bisexual men and other marginalized populations contacts the participant to provide two options: (1) mail an HIV and STI test kit to their home or (2) have the participant pick up the test at their offices. Participants receive a self-testing kit containing a rapid HIV and syphilis test and swabs and a urine collection container for pharyngeal, rectal, and urethral testing of chlamydia and gonorrhea. The testing counselor guides participants through the testing steps [81,82]. The HIV and syphilis test results are available within 20 minutes of testing. Participants are required to take a photograph of the results (marked with their study ID) and upload it to a study platform. The chlamydia and gonorrhea self-collected samples are mailed back to the organization, which mails them for analysis to a laboratory. Upon receiving results for chlamydia and gonorrhea testing (usually within 1 week of laboratory receipt), the testing counselor communicates the results to the participant. For positive or inconclusive test results, the testing counselor provides participants with the name and contact information of the study-affiliated infectious disease care provider in their area for confirmatory testing and treatment, as appropriate, and offers to assist with this linkage. Finally, participants are asked to complete a satisfaction survey at the 12-month follow-up [83].

Ethical Considerations

Ethics Approval and Consent to Participate

This research was conducted in accordance with the Declaration of Helsinki, and all methods were carried out in accordance with relevant guidelines and regulations within the United States and Romania. This study was approved by the Columbia University Institutional Review Board (FWA0000263; protocol

AAAU2518), Yale University Institutional Review Board (FWA00002571; protocol 2000024286), and Rutgers University Institutional Review Board (FWA00003913; protocol Pro2018000725). The protocol was also approved by the Bioethics Committee of the National Institute for Infectious Diseases "Prof. Dr. Matei Bal " in Bucharest, Romania (FWA00013199). All enrolled participants provided informed consent to take part in this study.

Overall Assessment of Risk

Participants are at minimal risk of harm associated with study participation. Although unlikely, the risks of this study are potential emotional discomfort from completing the assessments or the intervention sessions and breaches of confidentiality. In addition, participants may experience discomfort during HIV and STI testing or emotional distress when receiving positive test results. All possible steps are taken to minimize such risks through our carefully designed protocols, staff training, and fidelity monitoring. All study staff are trained in and follow study clinical protocols to protect against risks. Risks are being monitored and addressed (as outlined in the following sections) during assessments (via direct real-time triggers signaling emotional distress) and counseling sessions and in between assessment points (via communication from participants in both arms with study staff).

Risk of Emotional Discomfort

Participants may experience emotional distress associated with the study content. The consent document indicates that participants do not have to respond to any questions they do not wish to answer and may discontinue their participation at any time while being compensated for the portions of the study they completed.

At each assessment point, participants complete the SIDAS, with a score of ≥21 triggering an email to the project staff, who immediately alert the study counselors, who contact the participant to assess their well-being and potential need for immediate intervention in case of severe distress. All counseling resources are available to participants regardless of their ability to pay.

Should participants experience discomfort during assessments or sessions, they are contacted as described previously to assess their mental state, need for referral or immediate intervention, and capacity to continue in the study. On the basis of the counselors' determination, the participant may continue with the study (if there is no concern about imminent harm or lack of capacity to consent) or be referred to local in-person or telehealth LGBTQ-affirmative counseling services. For any person judged to be a danger to themselves or others or in imminent need of medical or mental health services, the project staff contacts local emergency services to intervene.

Risk of Physical Discomfort

Biological testing for HIV, syphilis, chlamydia, and gonorrhea may be associated with physical discomfort from the finger prick or incorrect swabbing, of which participants are informed during the consent process. Information on appropriate testing procedures and risk reduction counseling is provided to all participants at the time of testing at baseline and the 12-month follow-up. Staff are available via phone and email to answer questions that participants may have about performing biological testing. These tests are routinely conducted, and therefore, potential risks are no greater than those encountered during routine medical examinations. At the start of the study, we trained 10 infectious disease physicians from the 10 study cities of Bucure ti, Bra ov, Timi oara, Cluj-Napoca, Ia i, Constan a, Suceava, Craiova, Gala i, and Satu Mare. These physicians agreed to provide confirmatory testing and treatment to participants who test positive for HIV or other STIs during the study.

Risk of Breach of Confidentiality

Before any assessments, all participants are assigned a study ID number. The name-ID link is kept under electronic password and firewall protection in one of the PIs' offices at the Columbia University research space. Electronically signed consent forms are kept in a database separate from the data under password protection. Records are kept confidential, and information provided by study participants is not released to outside sources unless written consent is provided by the study participant or it is required by law (eg, suspicion of child or elder abuse and threat of imminent action on suicidal or homicidal ideation) or to protect participant well-being (eg, in the event that immediate local intervention is required following a safety assessment). The web-based intervention platform is only accessible to study staff and participants, whose log-in information is not linked to any identifying information. All participants are required, as part of the consent process, to upload to REDCap (Research Electronic Data Capture; Vanderbilt University) a photograph of their HIV and syphilis test paddle showing the results and label marked with their unique study ID. Finally, all procedures are being monitored by the Human Subjects Protection Programs at Columbia University and the study's Data and Safety Monitoring Board (DSMB).

Risk Versus Benefit

Given the public health significance addressed by this first study of its kind in CEE, the social, psychological, and physical risks reviewed previously are likely to be outweighed by the new knowledge gained regarding the efficacy of this highly scalable and portable approach to reducing gay and bisexual men's HIV transmission risk behavior and increasing their well-being. Preventing the further spread of HIV presents clear public health implications, especially in high-stigma, low-resource contexts such as Romania and other CEE countries. By participating in this study, participants may gain insight into their sexual, behavioral, and mental health that could lead to sustained behavior change. In addition, study participants may reduce their risk of acquiring HIV and STIs through involvement in our counseling or education sessions and behavioral risk tracking. Of note, participants are the first to be involved in at-home STI testing in Romania, a procedure they may adopt routinely in their lives beyond the study, both reducing their personal health risk and potentially promoting these protective practices within their networks.

Data Safety Monitoring Plan

Any unexpected or serious adverse events (eg, hospitalization) that occur during the course of the study will be reported by the contact PI and to the Committee on Human Research (Institutional Review Board) at Columbia University in accordance with current guidelines for reporting adverse events. The PIs meet biweekly with the team to discuss study progress and address participant safety immediately as issues arise (eg, reported suicidal ideation).

DSMB Function

A 5-member monitoring committee has been convened to determine safe and effective conduct and recommend the conclusion of the study if significant risks develop or if the trial is unlikely to be concluded successfully. On May 6, 2019, the team held the first DSMB meeting and has been convening annually since. The 5 members have reviewed and approved the study design and procedures and a plan for monitoring study data and interim outcomes. Starting in year 2 and annually thereafter, the study statistician has prepared and presented to the DSMB both open (pooled) and closed (stratified and with treatment arm unidentified) reports on the following data by arm: suicidality, HIV and STI test results, depression, heavy alcohol use, and HIV transmission risk behavior. Upon review of study progress, the DSMB provides a determination about study continuation to the PIs, who share it with the Institutional Review Board and National Institute of Mental Health in their annual progress report.

Data Analyses

Primary and Secondary Outcomes

It is hypothesized that participants randomized to the Comunică intervention, compared to those randomized to the EAC condition, will report significantly greater decreases in the primary (HIV transmission risk behavior defined as CAS acts with HIV-positive or unknown-status partners outside the context of one's own or one's primary partner's adherent PrEP use or undetectable viral load in the past 30 days) and secondary (depressive and anxiety symptoms, suicidality, heavy alcohol use, and HIV and STI testing outside of study testing) outcomes at the 4-, 8-, and 12-month follow-up visits.

Sample Size Justification

As we approached the end of study recruitment, three factors were considered for estimation of power: (1) while 305 participants were finally enrolled, we had estimated that we would likely only be able to recruit 288 participants by December 31, 2022 (our date of termination of recruitment), and therefore, we re-estimated power based on this number; (2) the overall participation rate for all 3 postintervention visits was 85.9% (262/305), with a high proportion of the remaining sample completing 2 postintervention assessments; (3) we had normative distributions of the study outcomes that could be used in establishing a study design and metrics for powering the primary outcome. To that end, we re-estimated the study power as described in the following paragraphs. This new estimate was approved by the DSMB and our program officer at the National Institute of Mental Health.

In the original proposal, repeated-measures mixed linear model (or generalized estimating equations [GEE]) using all 4 study visits (baseline and 4-, 8-, and 12-month follow-ups) was planned. However, the distribution of our primary outcomes (HIV transmission risk behavior) based on collected data was problematic for fitting this type of model, which is based on a central limit theorem assumption that may not manifest. Namely, there were two issues to consider: (1) at each follow-up visit, >50% of participants manifested no HIV transmission risk behavior, creating a large point mass at the lower limit of 0.2; and (2) on the other hand, the distribution of HIV transmission risk behavior acts was very skewed, with numbers of acts of >50 leading to a skewness of >3, which again contradicts normality-based methods.

Although generally accepted approaches for power estimates for this situation do not readily exist, we found one approach that will satisfy assumptions for standard normal methods and that is also amenable to conducting a power estimation. This approach is to take the average behavior over all 3 follow-up time points (4-, 8-, and 12-month assessments) as a single within-person outcome rather than evaluating the repeated measures at the 4-, 8-, and 12-month follow-ups as separate within-person outcomes. For example, if a person reported 0, 1, and 2 high-risk acts at the 4-, 8-, and 12-month follow-up visits, respectively, these would be summed together (0 + 1 + 2 = 3) and averaged over the 3 visits (3/3=1) as a single outcome of 1 high-risk sex act over the previous 30 days per follow-up period. The details of what transpired when we examined this outcome in our (still unblinded to intervention condition) data follow in the next paragraphs.

When we took the average of HIV transmission risk behavior acts of all 3 follow-up time points (ie, during the previous 4 months), only 23.9% (73/305) of participants had no HIV transmission risk behavior acts over the entire 12-month period (ie, the point mass at 0), which, given our projected sample size of 288 (or 246 evaluable participants assuming 246/288, 85.4% or a 15% loss of data as we have been observing), is low enough to treat this average as a continuous variable in a normal approximation. However, due to a few individuals reporting very high numbers of risk acts (ie, >50), this variable was still skewed (>3), so we capped (ie, Winsorized) the maximum number of average per-assessment HIV transmission risk behavior acts at 15, the upper 97th percentile of HIV transmission risk behavior. When this was done, the HIV transmission risk behavior outcome was close enough to normal (ie, skewness=1.5) for the central limit theorem to apply to the linear model presented in the following paragraph.

The power estimation approach assumes that a linear model will fit $Y = a + bX + cT + \varepsilon$, where Y is the averaged (during the previous 4 months) previous–30-day high-risk sex behavior over the 12-month behavior; a is the intercept; X is the number of baseline previous–30-day HIV transmission risk behavior acts; T is 0 for control and 1 for the intervention; ε is the random error with a mean of 0 and constant variance; and a, b, and c are unknown parameters that are estimated in the model fit. The null hypothesis c=0 will be tested with an overall 2-sided type-1 error of 0.05.

Importantly for power estimation, the correlation between the baseline and the average 12-month HIV transmission risk behavior acts was 0.37, which means that, after adjustment for the preintervention behavior, the SD of the postintervention behavior would be the square root of $1 - 0.37^2 = 0.93$ of the unadjusted outcome. On the basis of this, and with 288 participants, 86.1% (248/288) of whom participated in all 3 visits, as we have been observing will happen (or, conservatively, 123/288, 42.7% in each treatment arm), there is 80% power to detect an effect size of 0.33, slightly greater than our originally estimated effect size of 0.25 to 0.27 and at the upper end of the range of effect sizes found for behavioral interventions addressing multiple health outcomes among sexual minority men [84]. We believe that 0.33 represents a plausible effect size to detect in this trial given the strong distinction between the 2 intervention conditions, with one involving an active therapist-guided intervention and the other consisting of self-guided psychoeducation only. The SD of the (Winsorized) averaged outcome over 12 months of per-assessment HIV transmission risk behavior acts was 3.46 acts. Multiplying this SD by the effect size of 0.33 gives 1.14 HIV transmission risk behavior acts. This means that the study will have 80% power to detect an overall mean reduction of 1.14 HIV transmission risk behavior acts in the previous 30 days per assessment period in the intervention compared to the control condition.

It should be noted that our final analysis will most likely incorporate the partial information from men with only 1 or 2 postintervention follow-up visits through imputations, or more exactly, adjustment of the partial information for the number of follow-up periods reported; if so, this would increase power, albeit by a very modest amount.

Data Preparation

Skewed variables will be recoded for analytic symmetry using appropriate log, square root, or other nonlinear transformations. Should we fail to be able to find a transformation that achieves sufficient linearized normality, then robust GEE (ie, with logit or log link function) will be fitted to dichotomized or count outcomes. We will also examine variable distributions, which may suggest dichotomous and multinomial recoding relevant to our primary research questions and would increase the statistical power of our models. Dependent and independent variable values will be cross-plotted as a function of time in study and summarized using parametric and nonparametric modeling methods such as loess curves. In addition to detecting trends and temporal patterns, graphic representations of time-series data will provide knowledge of within- and between-individual variability of measurements. The results will be used to construct more complex cross-group or time analytic models.

Analytic Plan

The analysis of the primary and secondary outcomes will use intent to treat, with participants analyzed according to their original treatment assignment. The SAS (version 9.4; SAS Institute), SPSS (version 26.0; IBM Corp), Stata (StataCorp), and R (R Foundation for Statistical Computing) software will be used for all analyses.

Comparability of Treatment Groups

Differences in baseline demographic characteristics between the 2 treatment arms will be assessed using appropriate graphical and statistical methods, including summary statistics and *P* values from exact, rank, chi-square, and 2-tailed *t* tests, and ANOVAs. Of note, as the analyses progress, we will control for variables related to the study outcome in the analyses. We will also investigate whether the randomization scheme was compromised.

For the HIV transmission risk behavior primary outcome (number of CAS acts in the past 30 days with HIV-positive or unknown-status partners outside the context of one's own or one's primary partner's adherent PrEP use or undetectable viral load) analyses, the statistical significance threshold for an intervention (vs control) arm effect will be a 2-sided *P* value of ≤.05. The primary outcome will be evaluated between the 2 arms at the 4-, 8-, and 12-month follow-ups combined in a repeated-measures analysis that adjusts for baseline behavior. This will be analyzed using negative binomial regression with the baseline and the 4-, 8-, and 12-month time points clustered within the same person. The main effect terms for 4, 8, and 12 months after the baseline (each time point vs baseline) will be included in the model. A single interaction term between the 4-, 8-, and 12-month measures and the intervention arm will be included in the model to test for pooled postbaseline treatment arm differences. The relative number of HIV transmission risk behavior acts with a 95% CI will quantify intervention effect. GEE with person as the cluster will be used to account for within-person repeated-measure collinearity. As a sensitivity analysis, this will be repeated including all baseline covariates that are statistically associated ($P<.05$ to enter and $P\geq.10$ to leave in a stepwise selection) with HIV transmission risk behavior in negative binomial GEE models with person as the cluster and adjusting for time of visit (eg, 4, 8, and 12 months each vs baseline). If there are excess zeros at each postbaseline visit, we will consider using a zero-inflated negative binomial model instead. However, this approach will split the intervention effect parameter into 2 models and, thus, may dampen the power to detect statistical significance for an intervention that affects both parts. Thus, in this setting, we will more likely use the sensitivity analysis approach described in the following paragraph.

As a further sensitivity analysis, averaged HIV transmission risk behavior over all 3 follow-up visits (or 2 postbaseline visits if 1 visit is missing) will be used as the outcome in an analysis of covariance linear regression model that adjusts for baseline HIV transmission risk behavior as a predictor and includes treatment arm assignment as a covariate. For those who are missing 1 follow-up visit, indicator variables as to which visit is missing will be included. The mean difference in HIV transmission risk behavior acts with a 95% CI will quantify intervention effect. This will be repeated including all baseline covariates that are statistically associated ($P<.05$) with HIV transmission risk behavior in stepwise selection ($P<.05$ to enter and $P\geq.10$ to leave) in the aforementioned model. Should the negative binomial model described previously fail to converge, this will become the primary analysis. The statistical significance

threshold for the new (vs control) intervention arm effect will again be a 2-sided *P* value of ≤.05.

The secondary outcomes of interest (all of these assessed at baseline and at the 4-, 8-, and 12-month follow-up visits) are depression and anxiety symptoms, suicidality, and heavy alcohol use. Depression, as measured using the CES-D, will be examined as a continuous and a binary variable using a cutoff of ≥16 (indicating clinical depression). Anxiety, as measured using the BAI, will be examined as a continuous variable and using a cutoff of ≥16 (indicating potentially concerning levels of anxiety). Suicidality, as measured using the SIDAS, will be examined as a continuous variable and as a binary outcome using a cutoff of ≥21 (indicating high risk of suicidality) as well as any score >0. Heavy alcohol use, as measured using the AUDIT-C, will be examined as a continuous variable and as a binary outcome using a cutoff of ≥4. The percentage of heavy drinking days in the previous 30 days before the visit, as measured using TLFB, will be examined as a continuous variable. Due to multiple comparison issues, these will each be tested individually using a 2-sided type-1 error of 0.01 and quantified using 99% CIs. The levels of these measures at the 4-, 8-, and 12-month follow-ups will be compared (adjusting for the level at the baseline visit) between the Comunică intervention and the EAC condition in repeated-measures analyses, as described in the following paragraph.

For continuous outcomes that are heavily skewed to the right and without an excessive point mass at 0 for the 4-, 8-, and 12-month follow-ups (eg, the BAI or number of heavy drinking days), a similar approach to that described for the primary outcome analyses will be used. For continuous outcomes that are not heavily skewed to the right at the 4-, 8-, and 12-month follow-ups (eg, CES-D or AUDIT-C), repeated-measure linear regression mixed models will be fitted for outcomes at baseline and the 4-, 8-, and 12-month follow-ups with participant intercept as a fixed effect; main effects for the 4-, 8-, and 12-month follow-ups; and the single interaction term between treatment arm assignment and the time point being follow-up. In sensitivity analyses, this will be repeated including all baseline covariates that are statistically associated ($P<.05$) with the outcome in models using stepwise selection ($P<.05$ to enter and $P\geq.10$ to leave). The mean postintervention difference in the outcome between the treatment arms with 99% CIs will quantify intervention effect. Binary outcomes (eg, >0 HIV transmission risk behaviors, CES-D score of ≥16, SIDAS score of ≥21, SIDAS score of ≥0, and AUDIT-C score of ≥4) will be analyzed in repeated-measures models using the baseline visit and follow-up visits at 4, 8, and 12 months. Repeated-measures GEE will be fit about individual as a cluster using a logit link function. The visit number (ie, 4, 8, and 12 months vs baseline) and treatment arm assignment will be included as main effects, as will the baseline level of the outcome being modeled. In sensitivity analyses, this will be repeated including all baseline covariates that are statistically associated ($P<.05$) with the outcome in models using stepwise selection ($P<.05$ to enter and $P\geq.10$ to leave). The intervention effect will be quantified using odds ratios with 99% CIs. Finally, we will also use exact tests to compare treatment arms for having ever been diagnosed with HIV, syphilis, chlamydia, and gonorrhea during a single time point (the 12-month study follow-up).

Mediation Analyses

In our mediation analyses, we will examine whether changes in the proposed mediators (eg, self-efficacy for condom use or heavy alcohol use prevention, identity concealment, and internalized homophobia) precede and statistically mediate intervention effects consistent with our IMB and minority stress models. We will use path analysis or structural equation modeling to model and assess the size of the indirect effect of intervention condition on 12-month outcomes through mediators assessed at 4 and 8 months controlling for the baseline effects of these mediators.

Results

The study was funded in September 2018, and data collection began in May 2019. The last participant follow-up was in January 2024. Currently, the data analyst is cleaning data sets for each assessment point, verifying the accuracy of scale calculations, and examining patterns of missing data in preparation for data analyses for the primary and secondary outcomes as a first step. Data analyses are scheduled to begin in April 2024. Data analysis meetings are scheduled regularly to establish timelines and examine the results as analyses are gradually being conducted. Upon completion, a list of manuscripts will be reviewed and prioritized, and the team will begin preparing them for publication.

Discussion

This study is the first to test the efficacy of an intervention with the potential to simultaneously support the sexual (eg, HIV transmission risk behavior), behavioral (eg, heavy alcohol use), and mental (eg, depression) health of gay and bisexual men in CEE using MI support and sensitivity to the high-stigma context of the region [39,40]. This study has some potential limitations. This study is only focused on cisgender men, whereas additional groups (eg, transgender and gender-expansive individuals) may present high HIV risk and could benefit from tailored interventions. Should this intervention be efficacious, future research should consider adaptations to apply this intervention to other groups at risk of HIV and associated comorbidities, such as heavy alcohol use. In addition, this study takes place in only 1 country, potentially limiting generalizability, including to other settings where this intervention might also be beneficial. Finally, this study includes only 1 comparison condition and takes place in the context of a controlled trial rather than a real-world context suitable to test the intervention's effectiveness. As such, pending this intervention's efficacy confirmation in this trial, future research ought to consider expansion to other target groups and countries and implementation in real-world settings in an effectiveness trial. The resulting intervention holds promise for building a bridge from initial web-based counseling support to on-the-ground service use. If efficacious and cost-effective, the Comunică intervention presents a scalable platform to address HIV and STI risk and provide behavioral and mental health support to gay and bisexual men in other high-stigma, low-resource areas

in the region (eg, Ukraine and Poland) and the United States (eg, rural areas). This study will also generate intervention content and protocols that can be replicated by international service providers who do not operate in a research capacity.

Acknowledgments

This study was funded by the National Institute of Mental Health (R01MH116829). The content herein does not necessarily represent the viewpoint of the National Institutes of Health. The authors would like to acknowledge Roberta Scheinmann for her support in preparing this manuscript.

Data Availability

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

Authors' Contributions

CL-W and JEP led the development of this protocol. CL-W prepared the initial manuscript draft, JEP provided substantive feedback on the manuscript, and DH drafted the data analytic sections and provided substantive feedback on the manuscript. MLF provided substantive feedback on the manuscript. All authors were involved in developing or implementing the study protocol. All authors have read and approved the final manuscript.

Conflicts of Interest

None declared.

References

1. Gökengin D, Oprea C, Uysal S, Begovac J. The growing HIV epidemic in Central Europe: a neglected issue? J Virus Erad 2016 Jul 01;2(3):156-161 [FREE Full text] [Medline: 27482455]
2. Maniu CL, Achimas Cadariu A. Epidemiological characteristics of HIV/AIDS pandemic in Romania. Appl Med Inform 2010;27(4):31-38 [FREE Full text]
3. Ferris M, Burau K, Schweitzer AM, Mihale S, Murray N, Preda A, et al. The influence of disclosure of HIV diagnosis on time to disease progression in a cohort of Romanian children and teens. AIDS Care 2007 Oct 06;19(9):1088-1094. [doi: 10.1080/09540120701367124] [Medline: 18058392]
4. Kline MW, Rugina S, Ilie M, Matusa RF, Schweitzer AM, Calles NR, et al. Long-term follow-up of 414 HIV-infected Romanian children and adolescents receiving lopinavir/ritonavir-containing highly active antiretroviral therapy. Pediatrics 2007 May;119(5):e1116-e1120. [doi: 10.1542/peds.2006-2802] [Medline: 17420261]
5. Vaz P, Pedro A, Le Bozec S, Macassa E, Salvador S, Biberfeld G, et al. Nonvertical, nonsexual transmission of human immunodeficiency virus in children. Pediatr Infect Dis J 2010 Mar;29(3):271-274. [doi: 10.1097/INF.0b013e3181c17a58] [Medline: 20016396]
6. Rutã S, Cernescu C. Influence of social changes on the evolution of HIV infection in Romania. Int J Environ Stud 2008 Aug;65(4):501-513 [FREE Full text] [doi: 10.1080/00207230802291629] [Medline: 19360137]
7. Likatavicius G, van de Laar MJ. HIV infection and AIDS in the European Union and European Economic Area, 2010. Euro Surveill 2011 Dec 01;16(48):20030 [FREE Full text] [Medline: 22172299]
8. Likatavicius G, Klavs I, Devaux I, Alix J, Nardone A. An increase in newly diagnosed HIV cases reported among men who have sex with men in Europe, 2000-6: implications for a European public health strategy. Sex Transm Infect 2008 Nov 01;84(6):499-505. [doi: 10.1136/sti.2008.031419] [Medline: 19028955]
9. Štulhofer A, Sandfort T. Sexuality and Gender in Postcommunist Eastern Europe and Russia. Philadelphia, PA: Haworth Press; 2005.
10. Mocanu L. Sex education is considered a taboo subject in schools from Romania. In: Proceedings of the European Integration Realities and Perspectives. 2018 Presented at: EIRP 2018; May 18-19, 2018; Galati, Romania URL: http://proceedings.univ-danubius.ro/index.php/eirp/article/view/1894
11. Rada C. Sexual behaviour and sexual and reproductive health education: a cross-sectional study in Romania. Reprod Health 2014 Jun 23;11(1):48 [FREE Full text] [doi: 10.1186/1742-4755-11-48] [Medline: 24957900]
12. Smith M. Understanding the barriers to implementing a national sexual health education strategy in Romania. University of Delaware. 2017. URL: https://udspace.udel.edu/items/63a1ed13-6bc7-4de7-acd2-feb7054800a5 [accessed 2024-04-03]
13. Thoreson T. Romania - Latest EU hotspot in backlash against LGBT rights. EU Observer. 2022 Jun 13. URL: https://www.hrw.org/news/2022/06/13/romania-latest-eu-hotspot-backlash-against-lgbt-rights [accessed 2023-05-10]
14. Leluţiu-Weinberger C, Rendina HJ, Mirandola M, Gios L, Folch C, Rafila A, et al. The role of gay-related stigma in HIV-risk behavior among sexual minority men in Europe. AIDS Behav 2019 Mar 9;23(3):684-694 [FREE Full text] [doi: 10.1007/s10461-018-2306-z] [Medline: 30302655]

15. Pachankis JE, Hatzenbuehler ML, Hickson F, Weatherburn P, Berg RC, Marcus U, et al. Hidden from health: structural stigma, sexual orientation concealment, and HIV across 38 countries in the European MSM Internet Survey. AIDS 2015 Jun 19;29(10):1239-1246 [FREE Full text] [doi: 10.1097/QAD.0000000000000724] [Medline: 26035323]
16. Novotny T, Haazen D, Adeyi O. HIV/AIDS in Southeastern Europe: case studies from Bulgaria, Croatia, and Romania. The World Bank. 2003 May 31. URL: https://tinyurl.com/4fr3szx8 [accessed 2024-04-03]
17. Marcus U, Hickson F, Weatherburn P, Schmidt AJ, EMIS Network. Estimating the size of the MSM populations for 38 European countries by calculating the survey-surveillance discrepancies (SSD) between self-reported new HIV diagnoses from the European MSM internet survey (EMIS) and surveillance-reported HIV diagnoses among MSM in 2009. BMC Public Health 2013 Oct 03;13:919 [FREE Full text] [doi: 10.1186/1471-2458-13-919] [Medline: 24088198]
18. Country progress report on AIDS reporting period January 2010 – December 2011. Joint United Nations Programme on HIV/AIDS. 2012. URL: https://www.unaids.org/sites/default/files/country/documents/ce_RO_Narrative_Report.pdf [accessed 2023-05-10]
19. City Profiles: recommendations on HIV prevention gaps and opportunities for health promotion among men who have sex with men. Sialon II Project. URL: https://fast-trackcities.org/sites/default/files/Sialon%20II%20City%20Profiles%20MSM%20Recommendations.pdf [accessed 2023-05-10]
20. Ferrer L, Furegato M, Foschia JP, Folch C, González V, Ramarli D, et al. Undiagnosed HIV infection in a population of MSM from six European cities: results from the Sialon project. Eur J Public Health 2015 Jun 26;25(3):494-500. [doi: 10.1093/eurpub/cku139] [Medline: 25161202]
21. EMIS 2010: the European men-who-have-sex-with-men internet survey: findings from 38 countries. European Center for Disease Prevention and Control. 2013. URL: http://ecdc.europa.eu/en/publications/Publications/EMIS-2010-european-men-who-have-sex-with-men-survey.pdf [accessed 2023-05-10]
22. AIDS in Romania: when ignorance is lethal. The Economist. 2012 Apr 7. URL: https://www.economist.com/blogs/easternapproaches/2012/04/aids-romania [accessed 2023-05-10]
23. Beyrer C, Baral SD, van Griensven F, Goodreau SM, Chariyalertsak S, Wirtz AL, et al. Global epidemiology of HIV infection in men who have sex with men. Lancet 2012 Jul 28;380(9839):367-377 [FREE Full text] [doi: 10.1016/S0140-6736(12)60821-6] [Medline: 22819660]
24. Schmidt AJ, Hickson F, Weatherburn P, Marcus U, EMIS Network. Comparison of the performance of STI screening services for gay and bisexual men across 40 European cities: results from the European MSM Internet Survey. Sex Transm Infect 2013 Nov 06;89(7):575-582 [FREE Full text] [doi: 10.1136/sextrans-2012-050973] [Medline: 23744961]
25. EMIS-2017: the European men-who-have-sex-with-men internet survey: key findings from 50 countries. European Centre for Disease Prevention and Control. 2019. URL: https://www.ecdc.europa.eu/sites/default/files/documents/European-MSM-internet-survey-2017-findings.pdf [accessed 2023-09-08]
26. Lelutiu-Weinberger C, Pachankis JE, Golub SA, Garrett-Walker JJ, Bamonte AJ, Parsons JT. Age cohort differences in the effects of gay-related stigma, anxiety and identification with the gay community on sexual risk and substance use. AIDS Behav 2013 Jan 30;17(1):340-349. [doi: 10.1007/s10461-011-0070-4] [Medline: 22038078]
27. Mustanski B, Garofalo R, Herrick A, Donenberg G. Psychosocial health problems increase risk for HIV among urban young men who have sex with men: preliminary evidence of a syndemic in need of attention. Ann Behav Med 2007 Aug;34(1):37-45 [FREE Full text] [doi: 10.1007/BF02879919] [Medline: 17688395]
28. Safren SA, Reisner SL, Herrick A, Mimiaga MJ, Stall RD. Mental health and HIV risk in men who have sex with men. J Acquir Immune Defic Syndr 2010 Dec;55 Suppl 2(Suppl 2):S74-S77 [FREE Full text] [doi: 10.1097/QAI.0b013e3181fbc939] [Medline: 21406991]
29. Walkup J, Blank MB, Gonzalez JS, Safren S, Schwartz R, Brown L, et al. The impact of mental health and substance abuse factors on HIV prevention and treatment. J Acquir Immune Defic Syndr 2008 Mar 01;47 Suppl 1(Suppl 1):S15-S19. [doi: 10.1097/QAI.0b013e3181605b26] [Medline: 18301129]
30. Stojanovski K, King EJ, Amico KR, Eisenberg MC, Geronimus AT, Baros S, et al. Stigmatizing policies interact with mental health and sexual behaviours to structurally induce HIV diagnoses among European men who have sex with men. AIDS Behav 2022 Oct 17;26(10):3400-3410 [FREE Full text] [doi: 10.1007/s10461-022-03683-9] [Medline: 35434774]
31. Pachankis JE, Bränström R. Hidden from happiness: structural stigma, sexual orientation concealment, and life satisfaction across 28 countries. J Consult Clin Psychol 2018 May;86(5):403-415. [doi: 10.1037/ccp0000299] [Medline: 29683698]
32. Berg RC, Ross MW, Weatherburn P, Schmidt AJ. Structural and environmental factors are associated with internalised homonegativity in men who have sex with men: findings from the European MSM Internet Survey (EMIS) in 38 countries. Soc Sci Med 2013 Feb;78:61-69 [FREE Full text] [doi: 10.1016/j.socscimed.2012.11.033] [Medline: 23261257]
33. Pachankis JE, Hatzenbuehler ML, Bränström R, Schmidt AJ, Berg RC, Jonas K, et al. Structural stigma and sexual minority men's depression and suicidality: a multilevel examination of mechanisms and mobility across 48 countries. J Abnorm Psychol 2021 Oct;130(7):713-726. [doi: 10.1037/abn0000693] [Medline: 34780228]
34. A long way to go for LGBTI equality. European Union Agency for Fundamental Rights. 2020 May 14. URL: https://fra.europa.eu/en/publication/2020/eu-lgbti-survey-results [accessed 2023-09-08]
35. Pachankis JE, Hatzenbuehler ML, Berg RC, Fernández-Dávila P, Mirandola M, Marcus U, et al. Anti-LGBT and anti-immigrant structural stigma: an intersectional analysis of sexual minority men's HIV risk when migrating to or within

Europe. J Acquir Immune Defic Syndr 2017 Dec 01;76(4):356-366 [FREE Full text] [doi: 10.1097/QAI.0000000000001519] [Medline: 28787329]
36. Country progress report on AIDS: reporting period January 2016 – December 2016. Joint United Nations Programme on HIV/AIDS. 2017 Apr. URL: https://www.unaids.org/sites/default/files/country/documents/ROU_2017_countryreport.pdf [accessed 2024-04-03]
37. Balayan T, Oprea C, Yurin O, Jevtovic D, Begovac J, Lakatos B, et al. People who inject drugs remain hard-to-reach population across all HIV continuum stages in Central, Eastern and South Eastern Europe - data from Euro-guidelines in Central and Eastern Europe Network. Infect Dis (Lond) 2019 Apr 21;51(4):277-286. [doi: 10.1080/23744235.2019.1565415] [Medline: 30786803]
38. Stromdahl S, Hickson F, Pharris A, Sabido M, Baral S, Thorson A. A systematic review of evidence to inform HIV prevention interventions among men who have sex with men in Europe. Euro Surveill 2015 Apr 16;20(15):21096 [FREE Full text] [doi: 10.2807/1560-7917.es2015.20.15.21096] [Medline: 25953133]
39. Lelutiu-Weinberger C, Pachankis JE, Gamarel KE, Surace A, Golub SA, Parsons JT. Feasibility, acceptability, and preliminary efficacy of a live-chat social media intervention to reduce HIV risk among young men who have sex with men. AIDS Behav 2015 Jul;19(7):1214-1227 [FREE Full text] [doi: 10.1007/s10461-014-0911-z] [Medline: 25256808]
40. Lelu iu-Weinberger C, Manu M, Ionescu F, Dogaru B, Kovacs T, Dorobăn escu C, et al. An mHealth intervention to improve young gay and bisexual men's sexual, behavioral, and mental health in a structurally stigmatizing national context. JMIR Mhealth Uhealth 2018 Nov 14;6(11):e183 [FREE Full text] [doi: 10.2196/mhealth.9283] [Medline: 30429117]
41. Fisher WA, Fisher JD, Harman J. The information-motivation-behavioral skills model: a general social psychological approach to understanding and promoting health behavior. In: Suls J, Wallston KA, editors. Social Psychological Foundations of Health and Illness. Victoria, Australia: Blackwell Publishing; 2003.
42. Miller WR, Rollnick S. Motivational Interviewing: Helping People Change and Grow. New York, NY: Guilford Press; 2023.
43. Beck AT. The current state of cognitive therapy: a 40-year retrospective. Arch Gen Psychiatry 2005 Sep 01;62(9):953-959. [doi: 10.1001/archpsyc.62.9.953] [Medline: 16143727]
44. Fisher WA, Fisher JD. A general social psychological model for changing AIDS risk behavior. In: Pryor JB, Reeder GD, editors. The Social Psychology of HIV Infection. Mahwah, NJ: Lawrence Erlbaum Associates, Inc; 1993.
45. Arkowitz H, Westra H, Miller WR. Motivational Interviewing in the Treatment of Psychological Problems. New York, NY: The Guilford Press; 2015.
46. Beck JS. Cognitive Behavior Therapy: Basics and Beyond. New York, NY: Guilford Press; 2011.
47. Pachankis JE. A transdiagnostic minority stress treatment approach for gay and bisexual men's syndemic health conditions. Arch Sex Behav 2015 Oct 30;44(7):1843-1860 [FREE Full text] [doi: 10.1007/s10508-015-0480-x] [Medline: 26123065]
48. Pachankis JE. Uncovering clinical principles and techniques to address minority stress, mental health, and related health risks among gay and bisexual men. Clin Psychol (New York) 2014 Dec;21(4):313-330 [FREE Full text] [doi: 10.1111/cpsp.12078] [Medline: 25554721]
49. Hatzenbuehler ML. How does sexual minority stigma "get under the skin"? A psychological mediation framework. Psychol Bull 2009 Sep;135(5):707-730 [FREE Full text] [doi: 10.1037/a0016441] [Medline: 19702379]
50. Lick DJ, Durso LE, Johnson KL. Minority stress and physical health among sexual minorities. Perspect Psychol Sci 2013 Sep;8(5):521-548. [doi: 10.1177/1745691613497965] [Medline: 26173210]
51. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. J Pers Soc Psychol 1988;54(6):1063-1070. [doi: 10.1037/0022-3514.54.6.1063]
52. Fisher JD, Fisher WA, Amico KR, Harman JJ. An information-motivation-behavioral skills model of adherence to antiretroviral therapy. Health Psychol 2006 Jul;25(4):462-473. [doi: 10.1037/0278-6133.25.4.462] [Medline: 16846321]
53. Meyer IH. Prejudice, social stress, and mental health in lesbian, gay, and bisexual populations: conceptual issues and research evidence. Psychol Bull 2003 Sep;129(5):674-697 [FREE Full text] [doi: 10.1037/0033-2909.129.5.674] [Medline: 12956539]
54. The evolution of HIV/AIDS infection in Romania. National Institute for Infectious Diseases “Prof. Dr. Matei Bals”. 2017. URL: https://www.cnlas.ro/images/doc/31122017_eng.pdf [accessed 2023-09-08]
55. Wechsler H, Dowdall GW, Davenport A, Rimm EB. A gender-specific measure of binge drinking among college students. Am J Public Health 1995 Jul;85(7):982-985. [doi: 10.2105/ajph.85.7.982] [Medline: 7604925]
56. Alcohol's effects on health: research-based information on drinking and its impact. National Institutes of Health National Institute on Alcohol Abuse and Alcoholism. URL: https://www.niaaa.nih.gov/alcohols-effects-health [accessed 2023-09-08]
57. Smith SM, Smith R, Smith J, Orgill S. Qualtrics software. Qualtrics Co., Ltd. 2002. URL: https://tinyurl.com/mr2sasnu [accessed 2024-04-03]
58. Pachankis JE, Hatzenbuehler ML, Rendina HJ, Safren SA, Parsons JT. LGB-affirmative cognitive-behavioral therapy for young adult gay and bisexual men: a randomized controlled trial of a transdiagnostic minority stress approach. J Consult Clin Psychol 2015 Oct;83(5):875-889 [FREE Full text] [doi: 10.1037/ccp0000037] [Medline: 26147563]
59. Pachankis JE, Goldfried MR. Clinical issues in working with lesbian, gay, and bisexual clients. Psychother Theor Res Pract Train 2004;41(3):227-246 [FREE Full text] [doi: 10.1037/0033-3204.41.3.227]

60. Lelutiu-Weinberger C, Pachankis JE. Acceptability and preliminary efficacy of a lesbian, gay, bisexual, and transgender-affirmative mental health practice training in a highly stigmatizing national context. LGBT Health 2017 Oct;4(5):360-370 [FREE Full text] [doi: 10.1089/lgbt.2016.0194] [Medline: 28891750]
61. D'augelli AR, Grossman AH, Starks MT. Gender atypicality and sexual orientation development among lesbian, gay, and bisexual youth. J Gay Lesbian Ment Health 2008 Oct 11;12(1-2):121-143 [FREE Full text] [doi: 10.1300/j529v12n01_08]
62. Sobell LC, Brown J, Leo GI, Sobell MB. The reliability of the Alcohol Timeline Followback when administered by telephone and by computer. Drug Alcohol Depend 1996 Sep;42(1):49-54 [FREE Full text] [doi: 10.1016/0376-8716(96)01263-x] [Medline: 8889403]
63. Sobell LC, Sobell MB. Alcohol consumption measures. In: Allen JP, Wilson VB, editors. Assessing Alcohol Problems: A Guide for Clinicians and Researchers. Bethesda, MD: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institute on Alcohol Abuse and Alcoholism; 2003.
64. Weinhardt LS, Carey MP, Maisto SA, Carey KB, Cohen MM, Wickramasinghe SM. Reliability of the Timeline Follow-Back sexual behavior interview. Ann Behav Med 1998 Mar;20(1):25-30. [doi: 10.1007/bf02893805]
65. Carey MP, Carey KB, Maisto SA, Gordon CM, Weinhardt LS. Assessing sexual risk behaviour with the Timeline Followback (TLFB) approach: continued development and psychometric evaluation with psychiatric outpatients. Int J STD AIDS 2001 Jun 25;12(6):365-375 [FREE Full text] [doi: 10.1258/0956462011923309] [Medline: 11368817]
66. Fals-Stewart W, O'Farrell TJ, Freitas TT, McFarlin SK, Rutigliano P. The Timeline Followback reports of psychoactive substance use by drug-abusing patients: psychometric properties. J Consult Clin Psychol 2000 Feb;68(1):134-144. [doi: 10.1037/0022-006x.68.1.134]
67. Bush K, Kivlahan DR, McDonell MB, Fihn SD, Bradley KA. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test. Arch Intern Med 1998 Sep 14;158(16):1789-1795. [doi: 10.1001/archinte.158.16.1789] [Medline: 9738608]
68. Radloff L. The CES-D scale: a self-report depression scale for research in the general population. Appl Psychol Meas 2016 Jul 26;1(3):385-401 [FREE Full text] [doi: 10.1177/014662167700100306]
69. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol 1988;56(6):893-897. [doi: 10.1037/0022-006x.56.6.893]
70. van Spijker BA, Batterham PJ, Calear AL, Farrer L, Christensen H, Reynolds J, et al. The suicidal ideation attributes scale (SIDAS): community-based validation study of a new scale for the measurement of suicidal ideation. Suicide Life Threat Behav 2014 Aug 24;44(4):408-419. [doi: 10.1111/sltb.12084] [Medline: 24612048]
71. Carey MP, Schroder KE. Development and psychometric evaluation of the brief HIV Knowledge Questionnaire. AIDS Educ Prev 2002 Apr 02;14(2):172-182 [FREE Full text] [doi: 10.1521/aeap.14.2.172.23902] [Medline: 12000234]
72. Engs RC, Hanson DJ. Student alcohol questionnaire and the alcohol attitude questionnaire (1981, 1993). IUScholarWorks. URL: https://scholarworks.iu.edu/dspace/items/9ae9c209-e2de-458e-8bbc-c890d68a7be2 [accessed 2024-04-03]
73. Prochaska JO, DiClemente CC. Stages of change in the modification of problem behaviors. Prog Behav Modif 1992;28:183-218. [Medline: 1620663]
74. Miller WR, Tonigan JS. Assessing drinkers' motivation for change: the stages of change readiness and treatment eagerness scale (SOCRATES). Psychol Addict Behav 1996 Jun;10(2):81-89 [FREE Full text] [doi: 10.1037/0893-164x.10.2.81]
75. Parsons JT, Halkitis PN, Bimbi D, Borkowski T. Perceptions of the benefits and costs associated with condom use and unprotected sex among late adolescent college students. J Adolesc 2000 Aug;23(4):377-391. [doi: 10.1006/jado.2000.0326] [Medline: 10936012]
76. Sklar SM, Annis HM, Turner NE. Development and validation of the drug-taking confidence questionnaire: a measure of coping self-efficacy. Addict Behav 1997 Sep;22(5):655-670. [doi: 10.1016/s0306-4603(97)00006-3] [Medline: 9347068]
77. Meyer IH. Prejudice as stress: conceptual and measurement problems. Am J Public Health 2003 Feb;93(2):262-265. [doi: 10.2105/ajph.93.2.262] [Medline: 12554580]
78. Mohr J, Fassinger R. Measuring dimensions of lesbian and gay male experience. Meas Eval Couns Dev 2019 Aug 29;33(2):66-90 [FREE Full text] [doi: 10.1080/07481756.2000.12068999]
79. Rathus SA. A 30-item schedule for assessing assertive behavior. Behav Ther 1973 May;4(3):398-406 [FREE Full text] [doi: 10.1016/s0005-7894(73)80120-0]
80. Zimet GD, Dahlem NW, Zimet SG, Farley GK. The multidimensional scale of perceived social support. J Pers Assess 1988;52:30-41 [FREE Full text] [doi: 10.1037/t02380-000]
81. Guidelines on HIV self-testing and partner notification: supplement to consolidated guidelines on HIV testing services. World Health Organization. 2016. URL: https://iris.who.int/handle/10665/251655 [accessed 2023-05-10]
82. Metcalf CA, Douglas JMJ, Malotte CK, Cross H, Dillon BA, Paul SM, et al. Relative efficacy of prevention counseling with rapid and standard HIV testing: a randomized, controlled trial (RESPECT-2). Sex Transm Dis 2005 Feb;32(2):130-138. [doi: 10.1097/01.olq.0000151421.97004.c0] [Medline: 15668621]
83. Attkisson CC, Zwick R. The client satisfaction questionnaire. Psychometric properties and correlations with service utilization and psychotherapy outcome. Eval Program Plann 1982;5(3):233-237. [doi: 10.1016/0149-7189(82)90074-x] [Medline: 10259963]

84. Pantalone DW, Nelson KM, Batchelder AW, Chiu C, Gunn HA, Horvath KJ. A systematic review and meta-analysis of combination behavioral interventions co-targeting psychosocial syndemics and HIV-related health behaviors for sexual minority men. J Sex Res 2020 Jul 20;57(6):681-708 [FREE Full text] [doi: 10.1080/00224499.2020.1728514] [Medline: 32077326]

Abbreviations

AUDIT-C: Alcohol Use Disorders Identification Test–Consumption scale
BAI: Beck Anxiety Inventory
CAS: condomless anal sex
CBST: cognitive behavioral skill training
CEE: Central and Eastern Europe
CES-D: Center for Epidemiologic Studies Depression Scale
CONSORT: Consolidated Standards of Reporting Trials
DSMB: Data and Safety Monitoring Board
EAC: education attention control
EU: European Union
GEE: generalized estimating equations
IMB: information–motivation–behavioral skills
LGBIS: Lesbian, Gay, and Bisexual Identity Scale
LGBTQ: lesbian, gay, bisexual, transgender, and queer
MI: motivational interviewing
PI: principal investigator
PrEP: pre-exposure prophylaxis
SIDAS: Suicidal Ideation Attributes Scale
STI: sexually transmitted infection
TLFB: Timeline Followback

Edited by A Mavragani; submitted 19.09.23; peer-reviewed by C Portugal, A AL-Asadi; comments to author 19.02.24; revised version received 07.03.24; accepted 14.03.24; published 06.05.24.

Please cite as:
Lelu iu-Weinberger C, Filimon ML, Hoover D, Lixandru M, Hanu L, Dogaru B, Kovacs T, Fierbin eanu C, Ionescu F, Manu M, Mari A, Pană E, Dorobăn escu C, Streinu-Cercel A, Pachankis JE
An mHealth Intervention for Gay and Bisexual Men's Mental, Behavioral, and Sexual Health in a High-Stigma, Low-Resource Context (Project Comunică): Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2024;13:e52853
URL: https://www.researchprotocols.org/2024/1/e52853
doi:10.2196/52853
PMID:38709550

Protocol

Self-Selected Versus Assigned Target to Reduce Smartphone Use and Improve Mental Health: Protocol for a Randomized Controlled Trial

Kamal Kant Sharma[1], MS; Jeeva Somasundaram[2], PhD; Ashish Sachdeva[1], PhD

[1]Max Institute of Healthcare Management, Indian School of Business, Sahibzada Ajit Singh Nagar, Punjab, India

[2]IE Business School, Madrid, Spain

Corresponding Author:
Ashish Sachdeva, PhD
Max Institute of Healthcare Management
Indian School of Business
Knowledge City, Sector 81
Sahibzada Ajit Singh Nagar, Punjab, 140306
India
Phone: 91 01724591831
Email: ashish_sachdeva@isb.edu

Abstract

Background: Smartphones have become integral to people's lives, with a noticeable increase in the average screen time, both on a global scale and, notably, in India. Existing research links mobile consumption to sleep problems, poor physical and mental health, and lower subjective well-being. The comparative effectiveness of monetary incentives given for self-selected versus assigned targets on reducing screen time and thereby improving mental health remains unanswered.

Objective: This study aims to assess the impact of monetary incentives and target selection on mobile screen time reduction and mental health.

Methods: We designed a 3-armed randomized controlled trial conducted with employees and students at an educational institution in India. The study is conducted digitally over 12 weeks, including baseline (2 weeks), randomization (1 week), intervention (5 weeks), and postintervention (4 week) periods. We emailed the employees and students to inquire about their interest in participation. Those who expressed interest received detailed study information and consent forms. After securing consent, participants were asked to complete the initial survey and provide their mobile screen time during the baseline period. At the beginning of the intervention period, the participants were randomly allocated into 1 of 3 study groups in a 2:2:1 ratio (self-selected vs assigned vs control). Participants in the self-selected group were presented with 3 target options: 10%, 20%, and 30%, and they were asked to self-select a target to reduce their mobile screen time from their baseline average mobile screen time. Participants in the assigned group were given a target to reduce their mobile screen time from their baseline average mobile screen time. The assigned target was set as the average of the targets selected by participants in the self-selected group. During the intervention period, participants in the self-selected and assigned group were eligible to receive a monetary incentive of INR (Indian Rupee) 50 (US $0.61) per day for successfully attaining their target. Participants in the control group neither received nor selected a target for reducing their mobile screen time and did not receive any monetary incentives during the intervention period. All participants received information regarding the advantages of reducing mobile screen time. As an incentive, all participants would receive INR 500 (US $6.06) upon completion of the study and a chance to win 1 of 2 lotteries valued at INR 5000 (US $60.55) for consistently sharing their mobile screen time data.

Results: Currently, the study intervention is being rolled out. Enrollment occurred between August 21, 2023, and September 2, 2023; data collection concluded in November 2023. We expect that results will be available by early 2024.

Conclusions: The monetary incentives and self-selected versus assigned targets might be effective interventions in reducing mobile screen time among working professionals and students.

Trial Registration: AsPredicted 142497; https://aspredicted.org/hr3nn.pdf

International Registered Report Identifier (IRRID): DERR1-10.2196/53756

(JMIR Res Protoc 2024;13:e53756) doi:10.2196/53756

KEYWORDS

screen time; monetary incentives; target selection; mental health; mobile phone

Introduction

Smartphones have become ubiquitous in people's lives. The global average for daily screen time is 6 hours and 37 minutes [1]. In 2021, India had a mobile subscriber count of 1.2 billion, and around 750 million of them were using smartphones [2]. The average screen time for Indians has increased to 7.3 hours [3]. As of 2019, the leading mental disorders are depression and anxiety, which affect 280 million and 301 million people worldwide, respectively [4]. Estimates suggest that over 197 million Indians, approximately 15% of our population, experience mental disorders. Of these, approximately 85 million experience depression- and anxiety-related disorders [5]. Existing research links excessive screen time to lower subjective well-being, depression, anxiety, sleep disorders, and poor physical health [6-13].

Numerous correlational studies have explored the relationship between digital media use and well-being, with many of them indicating that screen time and mobile consumption are negatively linked to subjective well-being [6-10,14]. For instance, Przybylski and Weinstein [15] explored the effect of digital media use on the well-being of adolescents, providing support for the Goldilocks hypothesis—individuals with moderate use have higher well-being than those with lower and higher use.

On the other hand, Twenge and Campbell [14] showed that although light users of digital media had higher well-being than people who abstain, moderate and heavy users had lower well-being than light users. Twenge and Martin [7] demonstrated that the associations between greater digital media use and psychological well-being are greater for female than male individuals. In their correlational study, Twenge and Campbell [14] found that individuals with moderate and heavy digital media use (smartphones, social media, and others) had lower well-being than those with lighter media use, especially individuals with greater than 5 hours of digital media use per day. Orben and Przybylski [16] used specification curve analysis to understand if there is any correlational relationship between digital media use and well-being among adolescents. They found a negative but small association, explaining at most 0.4% of the variation in well-being [16].

In addition, existing research has also shown that temporary monetary incentives and targets can be used to inculcate behavioral change in domains such as gym attendance [17], smoking, work behavior [18], alcohol abuse [19], and weight loss [20]. Research studies suggest that temporary monetary incentives and specific targets can effectively reduce social media use and allow people to limit their screen time [21].

However, the current body of research does not provide evidence regarding whether self-selected targets or externally imposed targets are more effective in promoting and maintaining behavioral change, especially in the context of smartphone use, thereby improving mental health. Reducing smartphone screen time is essential for maintaining a healthy and productive lifestyle.

In this study, we aim to nudge people to reduce their screen time by providing temporary monetary incentives and targets. Target is defined as the minimum percentage reduction in daily mobile screen time from the daily average mobile screen time during the baseline period.

The objectives of the study are as follows:

1. To estimate the impact of monetary incentives and targets on reducing mobile screen time during the treatment and posttreatment period.
2. To evaluate the efficacy of self-selected versus assigned targets in reducing mobile screen time.
3. To estimate the impact of screen time reduction on mental health. Mental health will be assessed using measures such as Generalized Anxiety Disorder–7 (GAD-7) for anxiety, Patient Health Questionnaire–9 (PHQ-9) for depression, daily mood survey for mood, and well-being scores for general well-being.

Methods

Study Design and Setting

To achieve the study objectives, we are conducting a pragmatic, 3-arm, parallel-group, randomized controlled trial involving students and employees of the Indian School of Business (ISB). The ISB operates across 2 campuses located in the states of Punjab and Telangana, India. The randomized controlled trial spans a 12-week duration, comprising 2 weeks of baseline, 1 week for randomization, 5 weeks of intervention, and 4 weeks of the postintervention period.

Participants and Eligibility Criteria

Current employees and students at both ISB campuses who had Android-operated mobile phones and were available throughout the 12-week study period were eligible to participate in the study. The study excluded employees affiliated with the implementing department, Max Institute of Healthcare Management, ISB, as they previously participated in the study's pilot.

Recruitment

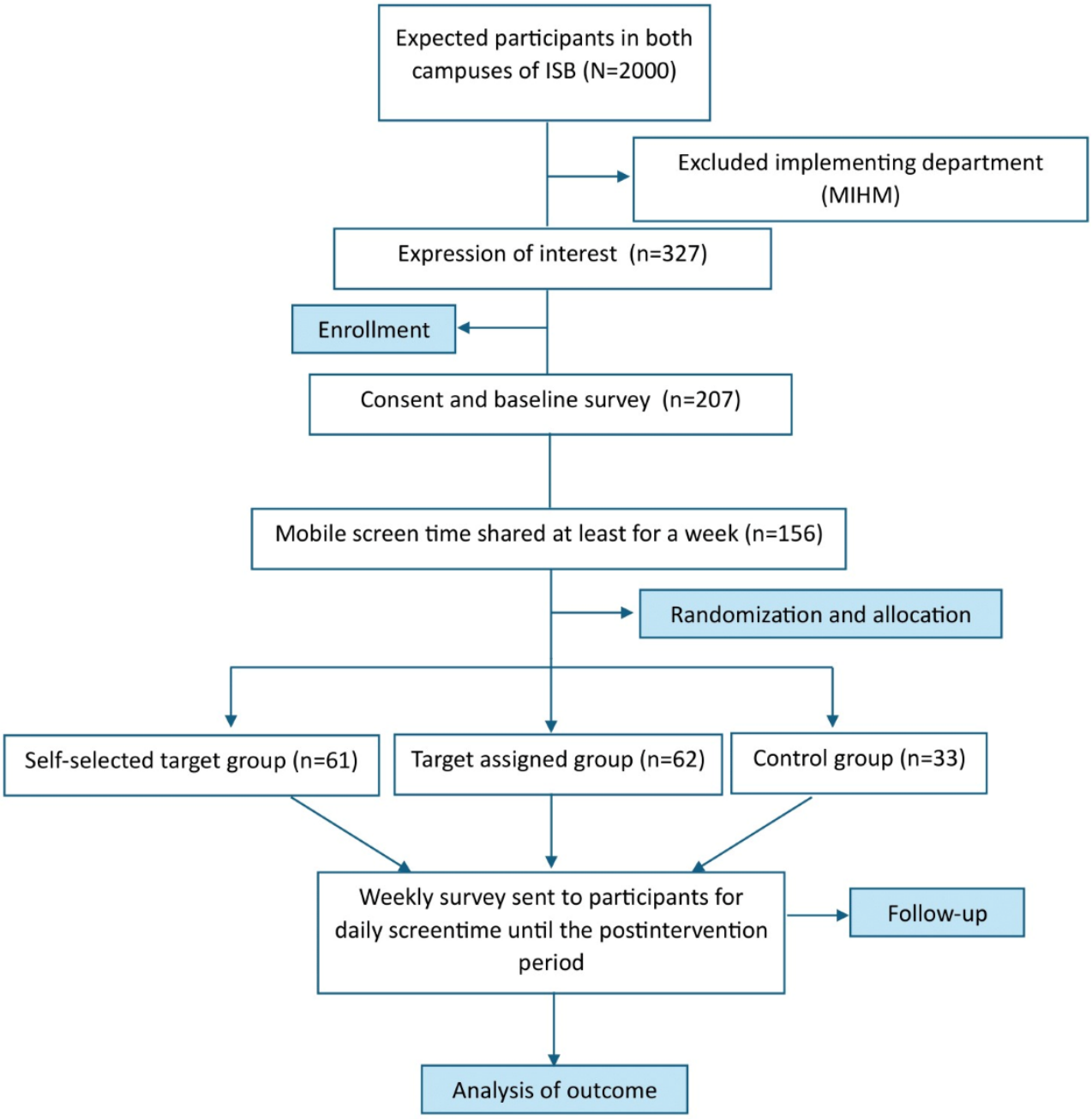
The study was conducted entirely through digital communication, avoiding the need for in-person interaction between the researchers and the participants. We initiated the study by sending an email through the Head of Student Affairs and Human Resources to both employees and students of ISB to their official email addresses. The email included a link to a form that allowed participants to express their interest in the study. This email was sent 3 times. Recruitment took place for 2 weeks, the preregistration period, to gather expressions of interest. Potential participants who expressed interest were

subsequently provided with study details and consent forms. Three email reminders were sent to the potential participants to provide consent. The participants who provided consent were asked to complete the baseline survey and provide their mobile screen time data during the baseline period.

Randomization and Blinding

After obtaining the baseline mobile screen time data, participants were randomly assigned to 1 of 3 groups in a 1:2:2 (control vs self-selected vs assigned) ratio. This assignment was carried out using a stratified randomized permuted block design with a block size of 5 using the *ralloc* command on Stata 17 software (StataCrop LLC). The allocation was stratified based on 2 variables: status in the institute (employee or student) and the quartile of baseline average mobile screen time. Following randomization, the research team became aware of the allocation groups. Blinding at the participant level was not possible due to the nature of the intervention. Participants were informed about their group before the start of the intervention period. They were not told about other groups or the groups of other participants. The CONSORT (Consolidated Standards of Reporting Trials) flow diagram for the study is provided in Figure 1.

Figure 1. The CONSORT (Consolidated Standards of Reporting Trials) flow diagram for the study.



Sample Size

The target sample was 300 participants, assuming a conservative effect size (*d*) of 0.12 for the difference between self-selected and assigned conditions and 0.15 for the difference between the intervention group and control conditions, with 80% power and an α of .05. The effect size was estimated based on past studies in this domain [22,23].

Interventions

At the end of the baseline period, the participants were randomized into 3 groups: the control group and 2 intervention groups.

Intervention-1 (Self-Selected Group)

In this group, participants were asked to select a target to reduce their mobile screen time from their baseline average mobile screen time. They were presented with 3 target options (10%, 20%, and 30%) and were asked to select one of the targets. The target options were chosen such that none of the targets is unreasonably high, ensuring that there are at least some participants who chose the target. Additionally, we want to ensure that the targets are sufficiently different so that participants are not indifferent between them. During the intervention period, participants in this group were eligible to receive a monetary incentive of INR (Indian Rupee) 50 (US $0.61) per day for successfully achieving the target they selected.

Intervention-2 (Assigned Group)

In this group, participants were assigned a target to reduce their mobile screen time from their baseline average. This target was determined after the participants in the self-selected group chose their respective targets. The assigned target was determined as the average of the targets selected by participants in the self-selected group. This was done such that both groups have the same average screen time reduction target, and thereby we can compare the average screen time reduction between the groups. This makes the intervention arms on average only differ in whether they chose or were assigned a screen time reduction target. During the intervention period, participants in this group were eligible to receive a monetary incentive of INR 50 (US $0.61) per day for successfully achieving the assigned target.

Control Group

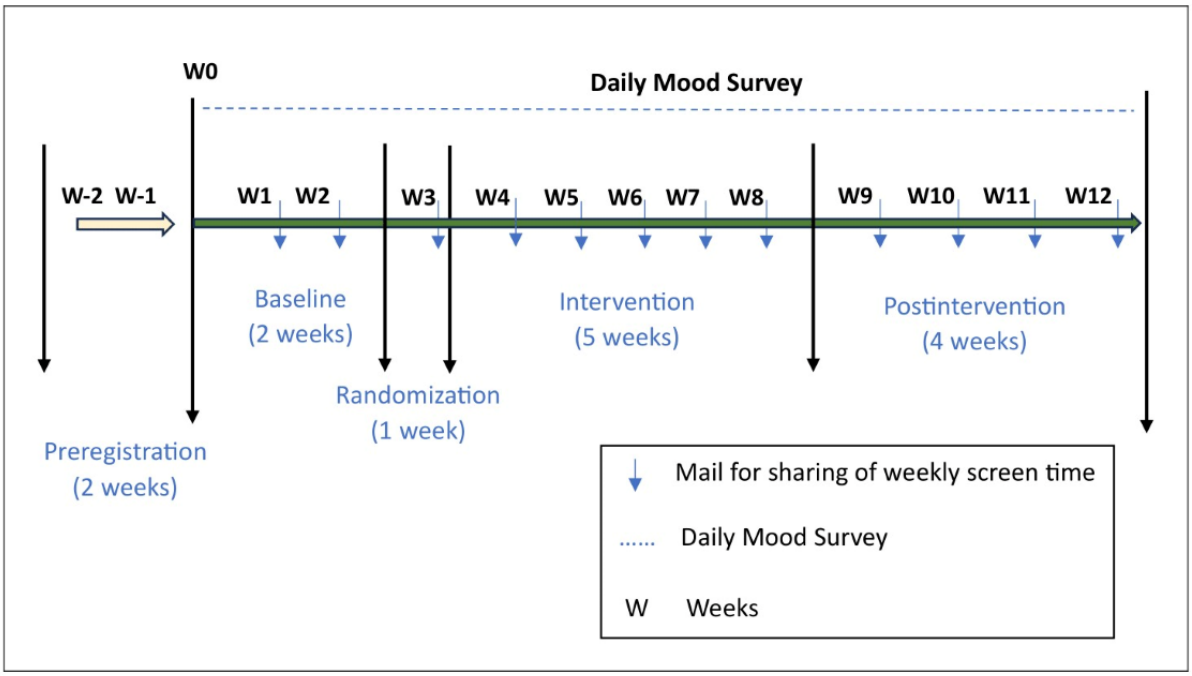
Control group participants were neither assigned nor asked to select a target for reducing their mobile screen. They were provided with standard information regarding the advantages of reducing their mobile screen time and received reminders to do so. They will not receive any monetary incentives for reducing their mobile screen time.

All participants, including the control group, received identical information regarding the advantages of reducing mobile screen time. All participants were informed that they would receive a fixed amount of INR 500 (US $6.06) upon completing the study. Additionally, participants in the study who report their mobile screen time every week will have the opportunity to win 1 of 2 lotteries, worth INR 5000 (US $60.55) each.

Study Procedures and Stages

The study has 5 stages: preregistration, baseline, group allocation, intervention, and postintervention, as presented in Figure 2.

Figure 2. An overview of the study.



Preregistration

Over 2 weeks, we conducted preregistration to gather expressions of interest. A total of 327 individuals expressed interest in the study. The individuals who displayed interest in the study were requested to complete the baseline survey, which included information regarding demographics, daily mobile phone time, past attempts to reduce screen time, willingness to reduce screen time, and GAD-7 and PHQ-9 for assessing anxiety and depression (a list of collected data is summarized in Table 1). Participants were also asked to report their daily mobile screen time and upload screenshots of the digital well-being app for the week before preregistration.

The digital well-being tools offer a daily overview of a person's phone use: the number of times the user checks their phone and the screen time. The screen time measures the total and app-wise time of the phone use. Participants share their mobile screen time through a weekly survey asking them to fill in the total time in hours and minutes of screen time for each day as displayed in the digital well-being app. As proof, the participants were asked to upload a screenshot of the digital well-being app for that week. A screenshot of the digital well-being app is shown in Figure 3. The study team checks whether the screen time in the survey matched with the screenshot. The study team provided step-by-step visual instructions for the process of uploading the screenshot from the digital well-being app. Of the 327 individuals interested in the study, 207 provided consent and completed the baseline survey.

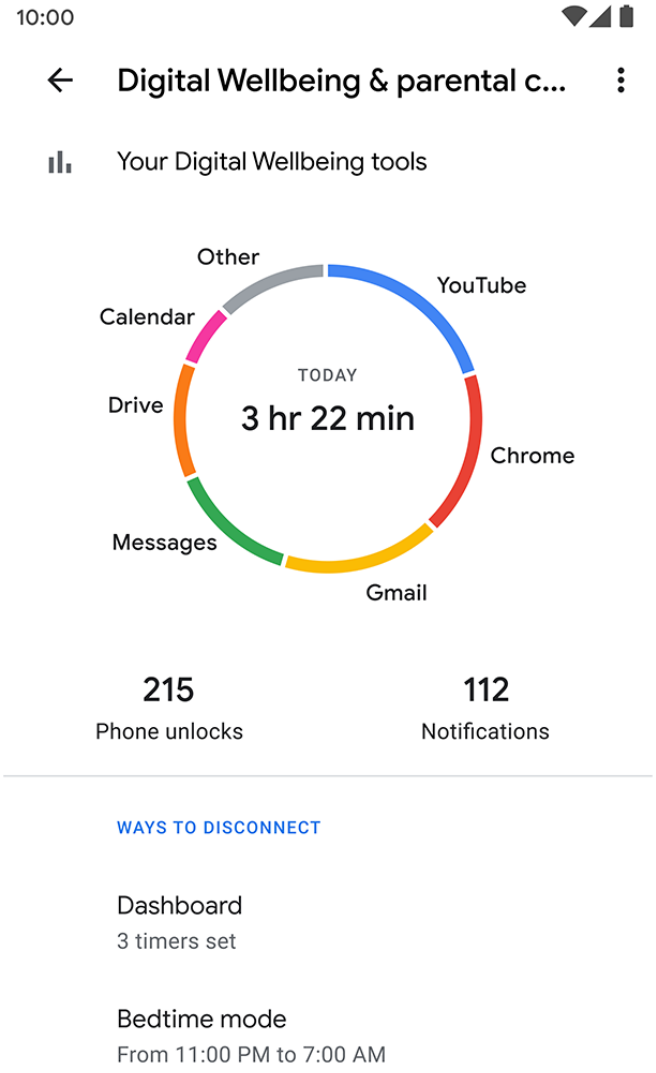
Table 1. Data collection at various stages of the study.

Data category	Expression of interest	Baseline[a,b]	End of intervention[a,b]	End of postintervention[a,b]
Basic information and contact details	✓	✓	✓	✓
Demographic		✓		
Information on willingness, difficulty, and magnitude in reducing mobile screentime		✓		
Information about mobile use		✓		✓
Phone addiction scale	✓	✓		✓
Generalized Anxiety Disorder–7		✓	✓	✓
Patient Health Questionnaire–9		✓	✓	✓

[a]Daily mobile screen time use: participants share their daily screen time and upload screenshots of their screen time by using the digital well-being feature on their Android mobile phones through self-administered weekly surveys.

[b]Daily mood survey: mood data are collected daily through WhatsApp messages, using a 1-10 scale that is sent at varied times of the day.

Figure 3. A screenshot of the digital well-being app.



Baseline (Mobile Screen Time)

The 2-week period following the preregistration was the baseline period. Every Sunday during this period, we emailed participants who had completed the baseline survey. They were instructed to provide their daily mobile screen time for the preceding week and upload a screenshot of the digital well-being app on their phones. Two reminder emails were sent to those who did not respond. Additionally, participants received a daily mood survey via WhatsApp (Meta) every day. Throughout the 2-week baseline period, 156 participants shared their mobile screen time for at least 1 week, while those who did not respond were excluded from the study.

Group Allocation

The 1-week period after the baseline was the group allocation period. During this period, the 156 participants who shared their mobile screen data were randomly assigned to 1 of 3 study groups. Initially, participants in the self-selected group were given information regarding their baseline average daily mobile screen time and asked to choose a target for reducing their mobile screen time based on this average. After the participants in the self-selected group had made their specific target choices, an email was sent to participants in the assigned group informing them about their given target.

All participants, including the control groups, received an email about the benefits of reducing mobile screen time and their baseline average daily mobile screen time.

Intervention Period

The period of 5 weeks following the group allocation is the intervention period. During this, the participants will receive an email every Sunday asking them to report their mobile screen time for the preceding week and provide a screenshot. Two reminder emails will be sent to those who do not respond. Additionally, participants will continue to receive a daily mood survey through WhatsApp. Every Wednesday, we will send out reminders to all groups via WhatsApp with information about the benefits of reducing mobile screen time and details about 2 lotteries. Participants in both intervention groups will also receive email reminders for their chosen and assigned targets. Participants in the intervention groups will receive a daily incentive of INR 50 (US $0.61) for successfully meeting their daily target. These incentives will be transferred to the participants via the Unified Payments Interface after the intervention period. At the end of the intervention, an

end-of-intervention survey will be administered to all participants.

Postintervention Period

The 4-week period following the intervention period is the postintervention period. During this, the participants will continue to receive an email requesting them to report their mobile screen time for the previous week and provide a screenshot. Two reminder emails will be sent to the participants who do not respond. Participants will also continue to receive a daily mood survey through WhatsApp. The participants will not receive monetary incentives for achieving their targets during this phase. After the postintervention period, an end-of-postintervention survey will be conducted.

Data Collection and Management

The following data are collected during various stages of the study (Table 1). Detailed survey instruments are presented in Multimedia Appendix 1.

We collect data through a web-based survey link shared over an email. All survey instruments are created using Qualtrics (Qualtrics International Inc), a secure web-based survey and database administration application. Data privacy is maintained with password protection for access to the Qualtrics platform. Only members of the research team have access to the database. We use the user-friendly WhatsApp platform for the daily mood survey to gather mood ratings on a scale. Upon concluding the study, the mood survey data will be extracted from WhatsApp and integrated with other data for subsequent analysis.

A pilot study was conducted with the implementing department (Max Institute of Healthcare Management) employees to evaluate and refine the study procedures and the survey tools.

Statistical Analysis

We will estimate the effects of mobile screen time, target achievement rate, GAD-7, PHQ-9, and daily mood scores by comparing variables of interest between the intervention and baseline and between the postintervention and baseline periods. To perform this analysis, we will use Stata 17 and R (version 4.2.2; Free Open-Source Software). The unadjusted effects will be calculated as differences in the means and conducting a 2-tailed Student *t* test for significance. For adjusted effects, we will use simple ordinary least square regression adjusting for participant-level covariates: age, gender, and employee or student. We assume errors to be correlated within each participant but uncorrelated across participants. A separate equation will be used for each dependent variable. The regression equations are provided in Multimedia Appendix 1. For mobile screen time, we will estimate a difference-in-difference ordinary least square regression. To account for the impact of the intervention and the postintervention period, we will incorporate dummy variables for the period. Specifically, assessing the effect on mobile screen time and target achievement rate postintervention will provide valuable insights into habit formation. Multilevel or hierarchical linear modeling will also be used to allow differential relationships between mood and screen time at the individual level.

Ethical Considerations

Ethical approval for this study was granted by the institutional review board of the ISB, Hyderabad, India (reference ISB-IRB2023-18; dated July 26, 2023).

Results

We started the recruitment process on August 21, 2023. We randomized 156 participants, and at the original submission of the protocol, we completed 3 weeks of the intervention period. The results are expected to be published in early 2024. The study results will be published in academic journals. These published findings have the potential to guide policy makers in establishing guidelines for monitoring and limiting excessive mobile screen exposure among both working professionals and students.

Discussion

Principal Findings

The study focuses on the impact of monetary incentives and self-selected versus assigned targets on reducing mobile screen time and thereby improving mental health and well-being during the intervention and postintervention periods.

Previous studies mainly focused on providing correlational evidence. For example, Mosquera et al [24] found that deactivating Facebook for 1 week made people less depressed and led them to engage in healthier activities. Allcott et al [25] found that deactivating Facebook for 4 weeks before the 2018 US election caused small but significant improvements in well-being, self-reported happiness, life satisfaction, depression, and anxiety. However, they did not find an effect on other well-being measures. In a follow-up paper, Allcott et al [21] monetarily incentivized people to reduce social media (Facebook, Instagram, Twitter, Snapchat, web browsers, and YouTube). The group that was monetarily incentivized over a period reduced their screen time by 56 minutes during the treatment period of 3 weeks. However, they found statistically insignificant changes in measures of happiness, life satisfaction, anxiety, and depression [21].

Compared with existing studies that have incentivized reduction over a period, this study offers everyday incentives and targets for people to reduce their overall smartphone use. While there is only 1 study that has used daily incentives, the focus of the study is on rational addiction and does not test the effects on anxiety and depression [22]. In addition, none of the studies have examined self-chosen targets versus given targets on the reduction, target achievement, and impact on well-being. Moreover. the existing studies do not study the effect of reduction on PHQ-9, GAD-7, and daily moods. Although Alcott et al [25] measured daily happiness, they did not have daily use data to understand the impact of daily use on happiness [25].

In this study, we expect the screentime reduction target to vary at the individual level. There might be cases when the average target is higher than the individual reduction that some individuals will prefer to achieve, while for some others there might be cases when the target is less than the individual

reduction they will aim to achieve. In the former case, the participants may not be able to achieve the average target, while in the latter case, they will achieve it. Other psychological factors, such as cognitive dissonance, support the idea that the self-selected condition is likely to outperform the assigned target condition. This is because participants are motivated to follow through on their personally chosen targets. So overall the reduction in exogenous (assigned group) condition could be lower due to this reason as well.

Through rigorous research design and a comprehensive examination of various factors, the results from the study make a substantial contribution to enhancing the comprehension of how self-selected versus assigned targets may potentially reduce mobile screen use and thereby improve mental health.

Strengths

The primary strength of the study is its intervention, which involves the use of monetary incentives and self-selected versus assigned to reduce mobile screen time and assess improvements in mental health through measures such as the GAD-7, PHQ-9, daily mood scores, and well-being scores. We will have daily mobile screen use data and therefore assess the impact of daily targets and incentives on daily screen use. Another strength advantage is that the study is conducted using digital communication, which removes the requirement for physical contact with participants.

Limitations

One of the potential limitations of the study is that the analyses in the study may lack sufficient power to detect the anticipated effects due to low enrollment. Another limitation is requesting the weekly submission of screen time through a mobile app, which might increase overall mobile screen time. However, this task only demands 4-5 minutes of weekly effort and will not impact the results, as the same procedure was also used at the baseline. The daily mood score was collected through a messaging app, WhatsApp, which is another limitation of the study.

Conclusions

The results of the study might add a significant layer of depth to the existing knowledge, guiding both researchers and policy practitioners toward more about monetary incentives, as well as self-selected versus assigned targets that might be effective interventions in changing health behavior including mobile screen use and thereby improving mental health for working professional and students.

Acknowledgments

The authors extend thanks for the active involvement of Indian School of Business (ISB) employees and students. The authors also value the contributions made by Akash Raj and Barsha Saha in tool development and study procedures, as well as the support from the administrative teams at the Max Institute of Healthcare Management and ISB. The study is funded by the Max Institute of Healthcare Management, ISB.

Data Availability

The data sets generated or analyzed during this study are available from the corresponding author on reasonable request. The data collected for this study will be stored in the central repository of the Indian Schools of Business.

Authors' Contributions

AS and JS had the original idea for the study and designed the study together. KKS is implementing the study and wrote the first draft of the manuscript. AS and JS reviewed the manuscript, and all authors approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Surveys, weekly reminders and emails, and statistical analysis.
[DOCX File , 69 KB - resprot_v13i1e53756_app1.docx]

References

1. Kemp S. Digital 2023: global overview report. DataReportal. 2023. URL: https://datareportal.com/reports/digital-2023-global-overview-report [accessed 2024-04-10]
2. Tandon A. India to have 1 billion smartphone users by 2026: Deloitte report. Business Today. New Delhi; 2022. URL: https://www.businesstoday.in/latest/economy/story/india-to-have-1-bn-smartphone-users-by-2026-deloitte-report-323534-2022-02-22 [accessed 2024-04-10]
3. Indians spend 7.3 hours on phone every day, more than Americans and Chinese: report. MoneyControl. 2022. URL: https://www.moneycontrol.com/news/technology/indians-spend-7-3-hours-on-phone-every-day-more-than-americans-and-chinese-report-9705211.html,? [accessed 2024-04-10]

4. Mental disorders. World Health Organization. 2022. URL: https://www.who.int/news-room/fact-sheets/detail/mental-disorders [accessed 2024-04-10]
5. India State-Level Disease Burden Initiative Mental Disorders Collaborators. The burden of mental disorders across the states of India: the Global Burden of Disease Study 1990-2017. Lancet Psychiatry 2020;7(2):148-161 [FREE Full text] [doi: 10.1016/S2215-0366(19)30475-4] [Medline: 31879245]
6. Liu M, Wu L, Yao S. Dose-response association of screen time-based sedentary behaviour in children and adolescents and depression: a meta-analysis of observational studies. Br J Sports Med 2016;50(20):1252-1258 [FREE Full text] [doi: 10.1136/bjsports-2015-095084] [Medline: 26552416]
7. Twenge JM, Martin GN. Gender differences in associations between digital media use and psychological well-being: evidence from three large datasets. J Adolesc 2020;79:91-102. [doi: 10.1016/j.adolescence.2019.12.018] [Medline: 31926450]
8. Twenge JM, Farley E. Not all screen time is created equal: associations with mental health vary by activity and gender. Soc Psychiatry Psychiatr Epidemiol 2021;56(2):207-217. [doi: 10.1007/s00127-020-01906-9] [Medline: 32743778]
9. Lee YK, Chang CT, Lin Y, Cheng ZH. The dark side of smartphone usage: psychological traits, compulsive behavior and technostress. Comput Hum Behav 2014;31:373-383. [doi: 10.1016/j.chb.2013.10.047]
10. Volkmer SA, Lermer E. Unhappy and addicted to your phone?—higher mobile phone use is associated with lower well-being. Comput Hum Behav 2019;93:210-218. [doi: 10.1016/j.chb.2018.12.015]
11. Thomée S, Härenstam A, Hagberg M. Mobile phone use and stress, sleep disturbances, and symptoms of depression among young adults--a prospective cohort study. BMC Public Health 2011;11:66 [FREE Full text] [doi: 10.1186/1471-2458-11-66] [Medline: 21281471]
12. Hisler G, Twenge JM, Krizan Z. Associations between screen time and short sleep duration among adolescents varies by media type: evidence from a cohort study. Sleep Med 2020;66:92-102. [doi: 10.1016/j.sleep.2019.08.007] [Medline: 31838456]
13. Levenson JC, Shensa A, Sidani JE, Colditz JB, Primack BA. Social media use before bed and sleep disturbance among young adults in the United States: a nationally representative study. Sleep 2017;40(9):zsx113 [FREE Full text] [doi: 10.1093/sleep/zsx113] [Medline: 28934521]
14. Twenge JM, Campbell WK. Media use is linked to lower psychological well-being: evidence from three datasets. Psychiatr Q 2019;90(2):311-331. [doi: 10.1007/s11126-019-09630-7] [Medline: 30859387]
15. Przybylski AK, Weinstein N. A large-scale test of the goldilocks hypothesis: quantifying the relations between digital-screen use and the mental well-being of adolescents. Psychol Sci 2017;28(2):204-215 [FREE Full text] [doi: 10.1177/0956797616678438] [Medline: 28085574]
16. Orben A, Przybylski AK. The association between adolescent well-being and digital technology use. Nat Hum Behav 2019;3(2):173-182. [doi: 10.1038/s41562-018-0506-1] [Medline: 30944443]
17. Charness G, Gneezy U. Incentives to exercise. Econometrica 2009;77(3):909-931 [FREE Full text] [doi: 10.3982/ecta7416]
18. Goerg SJ, Kube S. Goals (Th)at work—goals, monetary incentives, and workers‘ performance. MPI Collective Goods Preprint Preprint posted online on October 11, 2012 [FREE Full text] [doi: 10.2139/ssrn.2159663]
19. Sobell MB, Sobell LC, Bogardis J, Leo GI, Skinner W. Problem drinkers' perceptions of whether treatment goals should be self-selected or therapist-selected. Behavior Therapy 1992;23(1):43-52 [FREE Full text] [doi: 10.1016/s0005-7894(05)80307-7]
20. Perry C, Chhatralia K, Damesick D, Hobden S, Volpe L. Behavioural Insights in Health Care: Nudging to Reduce Inefficiency and Waste. London: The Health Foundation; 2015.
21. Allcott H, Gentzkow M, Song L. Digital addiction. Am Econ Rev 2022;112(7):2424-2463 [FREE Full text] [doi: 10.1257/aer.20210867]
22. Somasundaram J, Zimmermann L, Duc PQ. Rational addiction in mobile consumption. SSRN Journal Preprint posted online on October 29, 2020 [FREE Full text] [doi: 10.2139/ssrn.3719413]
23. Haidt J, Rausch Z, Twenge J. Social media and mental health: a collaborative review. New York University. URL: https://docs.google.com/document/d/1w-HOfseF2wF9YIpXwUUtP65-olnkPyWcgF5BiAtBEy0/edit [accessed 2024-04-10]
24. Mosquera R, Odunowo M, McNamara T, Guo X, Petrie R. The economic effects of Facebook. Exp Econ 2019;23(2):575-602 [FREE Full text] [doi: 10.1007/s10683-019-09625-y]
25. Allcott H, Braghieri L, Eichmeyer S, Gentzkow M. The welfare effects of social media. Am Econ Rev 2020;110(3):629-676 [FREE Full text] [doi: 10.1257/aer.20190658]

Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
GAD-7: Generalized Anxiety Disorder–7
ISB: Indian School of Business
INR: Indian Rupee
PHQ-9: Patient Health Questionnaire–9

Edited by A Mavragani; submitted 23.10.23; peer-reviewed by U Leong, TAR Sure; comments to author 28.12.23; revised version received 13.02.24; accepted 23.03.24; published 06.05.24.

Please cite as:
Sharma KK, Somasundaram J, Sachdeva A
Self-Selected Versus Assigned Target to Reduce Smartphone Use and Improve Mental Health: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2024;13:e53756
URL: https://www.researchprotocols.org/2024/1/e53756
doi:10.2196/53756
PMID:38709546

Protocol

Novel Strategy to Assess the Neurotoxicity of Organic Solvents Such as Glycol Ethers: Protocol for Combining In Vitro and In Silico Methods With Human-Controlled Exposure Experiments

Nancy B Hopf[1,2], PhD; Laura Suter-Dick[2,3], PhD; Jörg Huwyler[2,4], PhD; Myriam Borgatta[1,2], PhD; Lucie Hegg[1,2], MSc; David Pamies[2,5], PhD; Hélène Paschoud[1,2], MSc; Ramya Deepthi Puligilla[2,4], MSc; Elena Reale[1,2], PhD; Sophie Werner[2,3,4], MSc; Marie-Gabrielle Zurich[2,5], PhD

[1]Center for Primary Care and Public Health (Unisanté), University of Lausanne, Lausanne, Switzerland

[2]Swiss Centre for Applied Human Toxicology (SCAHT), Basel, Switzerland

[3]School of Life Sciences, University of Applied Sciences and Arts Northwestern Switzerland, Muttenz, Switzerland

[4]Division of Pharmaceutical Technology, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland

[5]Department of Biomedical Sciences, University of Lausanne, Lausanne, Switzerland

Corresponding Author:
Marie-Gabrielle Zurich, PhD
Department of Biomedical Sciences
University of Lausanne
Bugnon 7
Lausanne, 1005
Switzerland
Phone: 41 21 692 5542
Email: mzurich@unil.ch

Abstract

Background: Chemicals are not required to be tested systematically for their neurotoxic potency, although they may contribute to the development of several neurological diseases. The absence of systematic testing may be partially explained by the current Organisation for Economic Co-operation and Development (OECD) Test Guidelines, which rely on animal experiments that are expensive, laborious, and ethically debatable. Therefore, it is important to understand the risks to exposed workers and the general population exposed to domestic products. In this study, we propose a strategy to test the neurotoxicity of solvents using the commonly used glycol ethers as a case study.

Objective: This study aims to provide a strategy that can be used by regulatory agencies and industries to rank solvents according to their neurotoxicity and demonstrate the use of toxicokinetic modeling to predict air concentrations of solvents that are below the no observed adverse effect concentrations (NOAECs) for human neurotoxicity determined in in vitro assays.

Methods: The proposed strategy focuses on a complex 3D in vitro brain model (BrainSpheres) derived from human-induced pluripotent stem cells (hiPSCs). This model is accompanied by in vivo, in vitro, and in silico models for the blood-brain barrier (BBB) and in vitro models for liver metabolism. The data are integrated into a toxicokinetic model. Internal concentrations predicted using this toxicokinetic model are compared with the results from in vivo human-controlled exposure experiments for model validation. The toxicokinetic model is then used in reverse dosimetry to predict air concentrations, leading to brain concentrations lower than the NOAECs determined in the hiPSC-derived 3D brain model. These predictions will contribute to the protection of exposed workers and the general population with domestic exposures.

Results: The Swiss Centre for Applied Human Toxicology funded the project, commencing in January 2021. The Human Ethics Committee approval was obtained on November 16, 2022. Zebrafish experiments and in vitro methods started in February 2021, whereas recruitment of human volunteers started in 2022 after the COVID-19 pandemic–related restrictions were lifted. We anticipate that we will be able to provide a neurotoxicity testing strategy by 2026 and predicted air concentrations for 6 commonly used propylene glycol ethers based on toxicokinetic models incorporating liver metabolism, BBB leakage parameters, and brain toxicity.

Conclusions: This study will be of great interest to regulatory agencies and chemical industries needing and seeking novel solutions to develop human chemical risk assessments. It will contribute to protecting human health from the deleterious effects of environmental chemicals.

International Registered Report Identifier (IRRID): DERR1-10.2196/50300

(JMIR Res Protoc 2024;13:e50300) doi:10.2196/50300

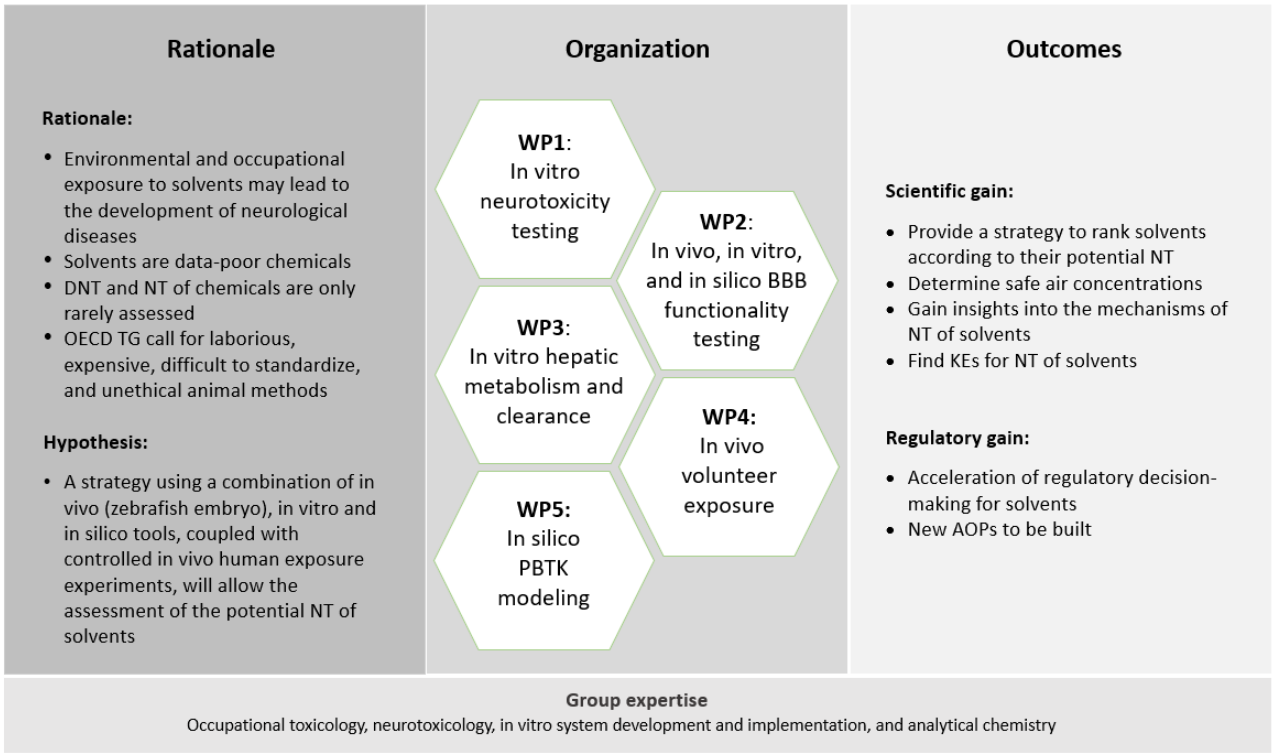
KEYWORDS

organic solvent exposure; workers; general population; neurotoxicity; blood-brain barrier; liver toxicity; human cell cultures

Introduction

Environmental and occupational exposure to chemicals may contribute to the development of several neurological diseases [1,2]. In particular, organic solvents used in industries such as car repair, painting, furniture manufacturing, printing, and cleaning have been associated with several central nervous system (CNS) conditions. These include mild to severe toxic encephalopathy [3]; deficits in cognitive function [4-7]; and, in some cases, neurodegenerative diseases [8,9]. The diffuse neuropathological effects of acute solvent intoxication reflect neurophysiological abnormalities involving multiple brain regions. With increasingly intense or prolonged exposure, the severity of acute impairment may progress along the spectrum of delirium. Chronic high-level exposure may lead to global cognitive impairment including deficits in memory, attention, energy, and personality, which are well-described forms of dementia [10-13]. Much of the initial work on organic solvent toxicity originated in Scandinavia, where a neurobehavioral syndrome in painters leading to their early retirement was first described [14]. However, although the neurotoxicity of solvents such as toluene, trichloroethylene, and n-hexane has been recognized, the neurotoxicity of common solvents currently on the market has not been evaluated. Notably, neurotoxicity testing is only required if the chemical is deemed a pesticide; otherwise, all other chemicals are evaluated on a case-by-case basis. The only exception is if the compound structure is suspected to have nervous system targets and no data are available for read-across or when effects on the nervous system are found in single-dose (Organisation for Economic Co-operation and Development [OECD] Test Guidelines [TGs] 402, 403, 420, 423, or 425) or repeated-dose toxicity studies (TG 407 or 408). Because the nervous system effect endpoints considered as triggers (ie, modifications of wet brain weight or basic histopathology, or both) are quite insensitive, high amounts of potentially neurotoxic compounds are available on the market. The European Union Classification, Labelling, and Packaging Regulation does not include a classification for neurotoxicity. Exposure to organic solvents, especially among workers with higher exposure than the general population, can produce neurotoxic effects, depending on the internal dose. Therefore, to efficiently protect the population from possible solvent toxicity, it is important to determine the air concentrations at which neurotoxicity does not occur. To this end, we propose a strategy using a combination of in vivo (zebrafish embryo), in vitro, and in silico tools coupled with controlled in vivo human exposure experiments to assess the neurotoxicity of solvents (Figure 1).

Figure 1. Overview of project rationale, organization, and outcomes. The project will develop a strategy based on various models to assess the neurotoxicity of solvents. Scientific and regulatory outcomes are foreseen. AOP: adverse outcome pathway; BBB: blood-brain barrier; DNT: developmental neurotoxicity; KE: key event; NT: neurotoxicity; OECD: Organisation for Economic Co-operation and Development; PBTK: physiologically based toxicokinetic; TG: Test Guideline; WP: work package.



The recognized method for the evaluation of the neurotoxic potential of chemicals, the OECD TG 424 (neurotoxicity in rodents), uses complex in vivo tests in rodents, which are laborious, expensive, difficult to apply in a standardized manner, and ethically debatable. Regulators from different agencies worldwide as well as the scientific community are becoming increasingly aware of the limitations of the current toxicity testing paradigm. Animal-based high-dose testing in typically 1 stand-alone guideline test is not always relevant for human exposure scenarios [15]. One of the most challenging aspects of this animal-centric approach is the impossibility of coping with the thousands of chemicals for which data are still lacking. Conducting animal tests is time consuming and expensive. Therefore, they cannot be carried out routinely because of the sheer number of chemicals that are currently on the market and those anticipated to enter it in the coming years [16]. In addition, there are shortcomings regarding interspecies concordance between different mammalian or rodent species as well as with respect to extrapolation from experimental animals to humans. These ambiguities in results or poor reproducibility performance call into question the relevance of such test methods for human risk assessment [16-21]. All this prompts a move away from animal testing toward a combination of in vitro and in silico approaches that address functional mechanistic endpoints [15,16,22].

Numerous in vitro models have been proposed for the evaluation of neurotoxicity in the last decades. Monolayer cultures of a single brain cell type are far from representing the human brain in terms of architecture and functionality. Given the sophistication of brain cell-to-cell interactions, some complexity is required to recapitulate human-relevant cellular processes and functions in vitro. However, a good balance must be found between this complexity and the simplicity needed to have robust and reproducible systems that can be applied for chemical screening in a high-throughput manner [23]. The 3D hiPSC–derived brain test system (BrainSpheres) we previously developed [24] will be used in this study, as it fulfills these requirements.

The blood-brain barrier (BBB) protects the brain parenchymal cells from the deleterious effects of xenobiotics. However, some chemicals are able to cross or impair the BBB [25]. The transient or permanent opening of the BBB provides xenobiotics, plasma proteins, and immunoregulatory mediators access to the CNS, where they can induce toxic effects. Therefore, we will implement a predictive model to assess the impact of solvents on BBB based on in vivo (zebrafish embryo), in vitro (human brain microvascular endothelial cells [hCMEC/D3]), and in silico models [26] to assist in the interpretation of the results obtained in in vitro neurotoxicity testing.

Glycol ethers will be used as a case study to evaluate the feasibility of our protocol. Glycol ethers form a wide family of a few dozen solvents with different physicochemical properties making them versatile and usable in a variety of industrial applications ranging from pharmaceuticals and microelectronics to domestic cleaning, personal care, and printing. The 2 main groups of glycol ethers are the E series (ie, ethylene glycol ethers [EGEs]) and the P series (ie, propylene glycol ethers [PGEs]). EGEs and PGEs show differences in their toxicological properties regarding teratogenicity, hemolysis, and testicular atrophy [23], apparently resulting from their distinct production

of metabolites [24,25]. EGEs have a primary alcohol group and are oxidized by alcohol dehydrogenase and aldehyde dehydrogenase to form the toxic alkoxyacetic acid. Therefore, PGEs are progressively introduced as a less toxic replacement of EGEs. PGEs are sold as a mixture of 2 isomers, with the bulk having a secondary alcohol (a) group and generally <5% of primary alcohol (b) groups [22]. The b-isomer is oxidized by alcohol dehydrogenase and aldehyde dehydrogenase to form the toxic alkoxypropionic acid in the body. However, the actual toxicity of PGEs is poorly characterized. Therefore, it is essential for our strategy to study not only the parent compound but also the metabolites. Metabolically competent liver cell models will be used to screen for liver toxicity of solvents and for the production of potential metabolites.

Exposure to solvents in human volunteers is fundamental when quantifying possible risks from chemicals because toxicological effects are related to internal exposure, that is, the concentration of a chemical inside the body and its biotransformation. Therefore, in vivo human volunteer studies are necessary to quantify absorption, distribution, metabolism, and excretion (ADME) kinetics in humans under controlled exposure conditions, which are necessary to understand the relationship between solvent concentrations in the air and biological samples, such as blood, urine, or exhaled air. These experiments provide important data on the total absorbed dose after inhaled solvent concentration, absorption rate (ie, from the site of absorption into the bloodstream), biotransformation rate (ie, metabolization of the parent chemical with production of metabolites), and elimination rate (ie, excretion of the parent chemical and metabolites from the body) [27]. These toxicokinetic parameters are representative of the target organ or of the tissue concentrations that may trigger an effect and are, therefore, relevant for understanding chemical risks in humans.

Toxicokinetic models quantitatively describe the body's ADME of a chemical or substance (different terms for this concept are preferred in different fields, including "toxicokinetics," "pharmacokinetics," and "biokinetics") [28]. Furthermore, using a toxicokinetic model in reverse dosimetry, we can predict the solvent air concentrations leading to brain concentrations below the levels found to produce neurotoxic effects in vitro in the BrainSpheres. The toxicokinetic model will incorporate metabolism parameters derived from the in vitro liver system and passage through or toxicity to BBB. Once calibrated, the toxicokinetic model can be used to simulate chronic exposure scenarios to predict cumulative brain concentrations and used in reverse dosimetry to predict air concentrations that will not likely result in brain concentrations associated with toxicity.

Methods

Ethical Considerations

Ethics committee approval was obtained from Swiss ethics (Commission cantonale d'éthique de la recherche sur l'être humain) in 2022 for this nonclinical human study (2022-01567). Healthy women and men were recruited as participants in our study. Each participant signed a written informed consent form before inclusion in the study. The participants will be reimbursed for their time and inconvenience according to the Swiss guidelines.

Global Strategy

The choice of solvents to be included in the study will be based on the amount annually placed on the European market and the number of products registered containing known glycol ethers. The selected organic solvents will be applied to various in vitro models to determine their neurotoxicity. They must be amphiphilic to be solubilized in the cell culture media. We established the following solvent selection criteria: (1) used or produced >1 metric ton per year, (2) incorporated in numerous industrial and commercial products, and (3) water solubility. This selection process involves consulting government databases and contacting different industry sectors. We will start the project concomitantly by testing 2 solvents of the P series, propylene glycol methyl ether (PGME), for which we have already developed a toxicokinetic model, and propylene glycol butyl ether. We will test 1 additional solvent from the E series with the in vitro test system, namely, ethylene glycol methyl ether (EGME), which has been banned for use in cosmetic products in Europe [29].

The study is organized into 5 work packages (WPs). The information workflow between the WPs is shown in Figure 2. All results collected from the abovementioned systems will contribute to refining the toxicokinetic model we previously developed for PGME [30]. The toxicokinetic parameters of the solvent and the metabolites will then be characterized in human volunteers after exposure to PGE vapors under controlled conditions. These results will be used to calibrate and expand our toxicokinetic model [30]. The toxicokinetic model will be constructed to predict brain concentrations of selected solvents and, consequently, will include a brain compartment to predict the target organ solvent and metabolite concentrations. BBB parameters such as barrier transport, transport of the solvent once in the brain, and solvent-brain binding will be incorporated. Solvent neurotoxicity may depend on the metabolic modifications of the substances; therefore, we will incorporate the parameters for the parent compound and the metabolites found in the in vitro liver system. The data necessary to build the model will be retrieved from peer-reviewed scientific literature for tissue:blood partition coefficients (PCs) [31] following the fit-for-purpose dose-response analysis approach. The toxicokinetic model should be able to predict human brain concentration for each of the tested solvents after inhalation exposure, given the air concentration of vapors and duration of exposure. The simulated human brain concentrations will then be compared with the no observed adverse effect concentrations (NOAECs) obtained from the neurotoxicity in vitro system (BrainSpheres). In addition, the toxicokinetic model will be used to predict solvent air concentrations that are unlikely to lead to brain concentration equal to or superior to the brain NOAECs using reverse dosimetry. The specific aims of each WP are summarized in Table 1.

Figure 2. Information workflow between the work package (WP). BBB: blood-brain barrier; IVIVE: in vitro-in vivo extrapolation; NOAEC: no observed adverse effect concentration; PBTK: physiologically based toxicokinetic.

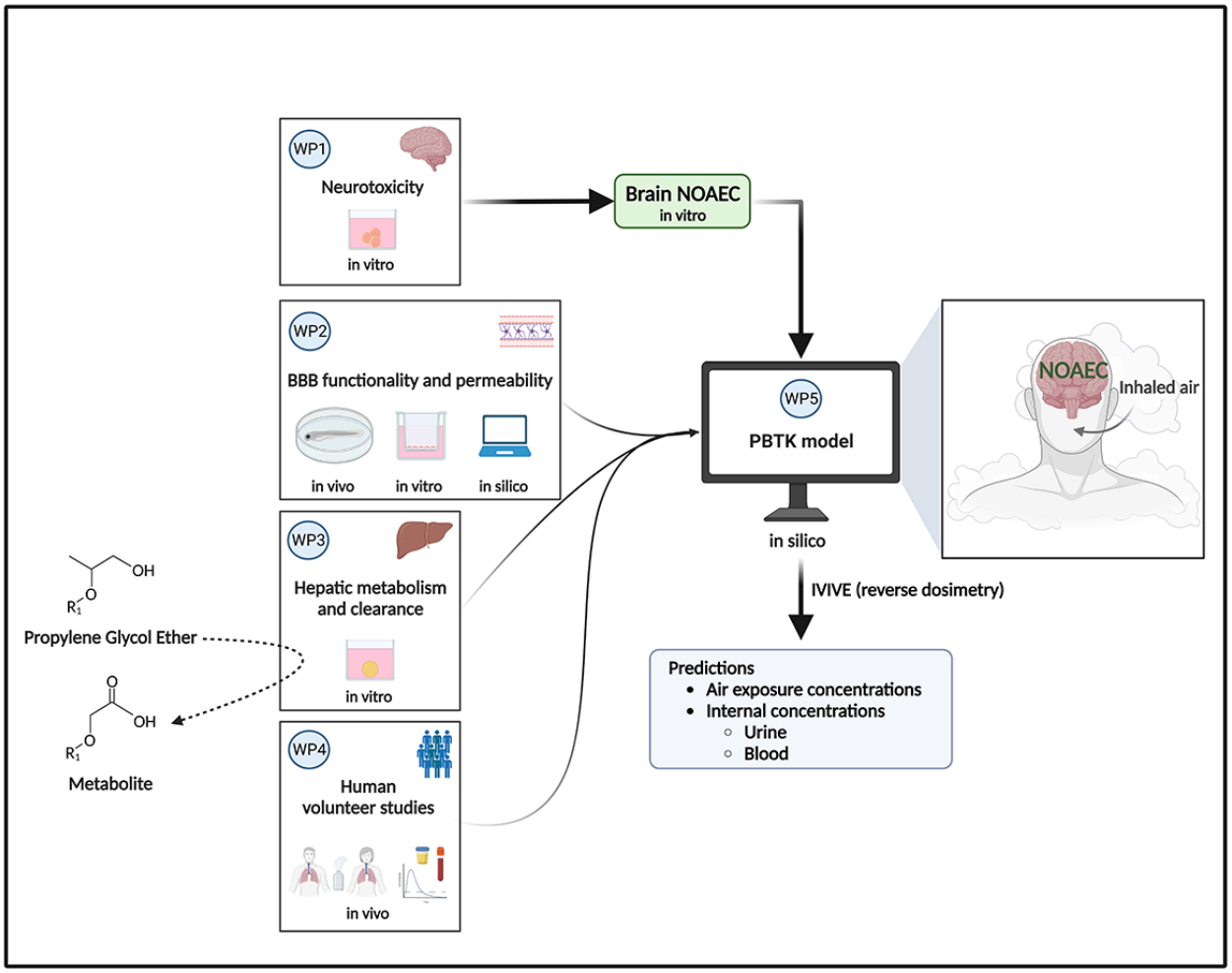


Table 1. Specific aims of the work packages (WPs).

WP	Name	Specific aims
WP1	In vitro neurotoxicity testing	1. Determine NOAEC[a] for neurotoxicity of each solvent 2. Determine the in vitro distribution kinetics of solvents 3. Identify toxicity pathways and KEs[b] for solvent neurotoxicity
WP2	In vivo or in vitro or in silico BBB[c] functionality testing	1. Evaluate the suitability of the zebrafish embryo model to study BBB integrity and functionality 2. Determine the impact of solvents on BBB integrity and transport in zebrafish and hCMEC/D3[d] 3. Determine the solvents permeability coefficient (Pe) 4. Provide quantitative data on BBB permeability and tissue distribution of solvents based on computational modeling
WP3	In vitro hepatic metabolism and clearance	1. Elucidate hepatic metabolism 2. Calculate substrate-enzymatic parameters (Vmax[e] and Km[f]) 3. Detect and identify possible metabolites produced by the liver
WP4	In vivo volunteer exposure	1. Characterize human blood absorption and urinary elimination kinetics for parent glycol ether as well as the metabolites identified in WP3 2. Find neurotoxic and vascular injury effect biomarkers for solvent exposure
WP5	In silico PBTK[g] modeling	1. Establish and calibrate the PBTK model for various organic solvents 2. Use reverse dosimetry to determine air concentrations below human brain toxicity concentrations

[a]NOAEC: no observed adverse effect concentration.

[b]KE: key event.

[c]BBB: blood-brain barrier.

[d]hCMEC/D3: human brain microvascular endothelial cells.

[e]V_{max}: maximum velocity.

[f]Km: Michaelis constant.

[g]PBTK: physiologically based toxicokinetic.

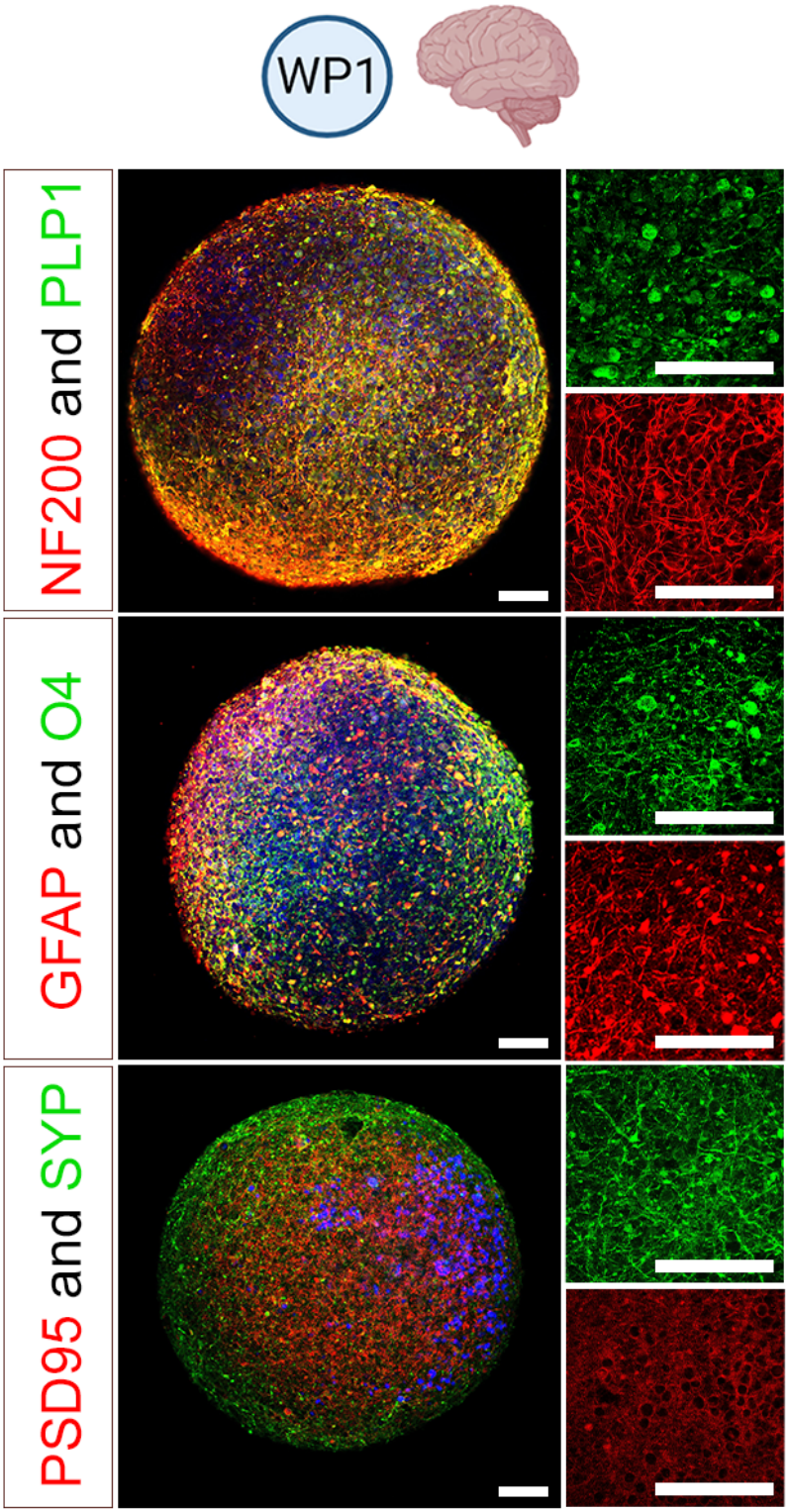
WP1: In Vitro Neurotoxicity Testing

Testing strategies are needed to evaluate the neurotoxicity of chemicals in a more cost-effective, efficient, and ethical manner. Participating in an international effort, we developed a 3D human-induced pluripotent stem cells (hiPSC)–derived brain model containing several subtypes of neurons, astrocytes, and oligodendrocytes [24]. This system allows the cells to reach a high level of differentiation and cellular maturation, exemplified by the presence of functional synapses and compact myelin. The presence of myelin is important for this project because solvents more easily target lipid-rich structures [32]. This 3D human brain model has already proven its usefulness for neurotoxicity testing [33-36]. We hypothesized that glycol ethers are neurotoxic. Therefore, we propose to take advantage of our hiPSC-derived BrainSpheres model to study the neurotoxicity induced by uncharacterized glycol ethers present on the market, which will be compared with the neurotoxicity of well-characterized solvents known to induce human encephalopathy.

Solvents are data-poor substances. It was originally hypothesized that they exert their toxic effects largely through nonspecific physicochemical effects that modulate membrane fluidity and perturb the hydrophobic force regulating macromolecular interactions [37]. However, recent evidence supports the view that solvents interact with lipophilic areas on protein receptors [38,39]. They have also been shown to induce lipid peroxidation, leading to mitochondrial dysfunction, failure of electron transport, and energy production [40,41]. In this study, omics (eg, proteomics, metabolomics, and lipidomics) technology will be used to decipher the mechanisms of glycol ether neurotoxicity and to identify potential biomarkers of toxic effects.

Primary 3D hiPSC-derived brain cell cultures will be prepared and maintained as previously described [24]. This model contains neurons that form synapses, astrocytes, and oligodendrocytes myelinating the axons (Figure 3). Cytotoxicity will be determined by a resazurin assay after repeated exposure (7 d) to the selected glycol ethers (parent compounds and metabolites). Gene expression for cell type–specific genes, markers of synapses and myelin, and markers of cell stress will be quantified by quantitative reverse transcription polymerase chain reaction at concentrations of solvents under half-maximal effective concentration (EC50) for cytotoxicity. Immunostaining will be performed to assess the effects of solvents on synapses, myelin, and astrocyte reaction, and immunofluorescence will be quantified. NOAECs (Figure 2) will be determined for all tested endpoints, as previously shown for gene expression [42]. Brain cell cultures will also be exposed to the metabolites of PGME, propylene glycol butyl ether, and EGME and to the metabolites of the newly selected uncharacterized solvents, potentially produced by liver metabolism (WP3).

Figure 3. Brain model used in work package (WP) 1. Immunostainings of human induced pluripotent stem cell–derived 3D BrainSpheres after 8 weeks of differentiation, showing the presence of proteins specific for neurons (neurofilament heavy polypeptide [NF200]), synapses (postsynaptic density-95 protein [PSD95] and synaptophysin [SYP]), astrocytes (glial fibrillary acidic protein [GFAP]) and oligodendrocyte (proteolipid protein 1 [PLP1]). Scale bars: 40 µm.

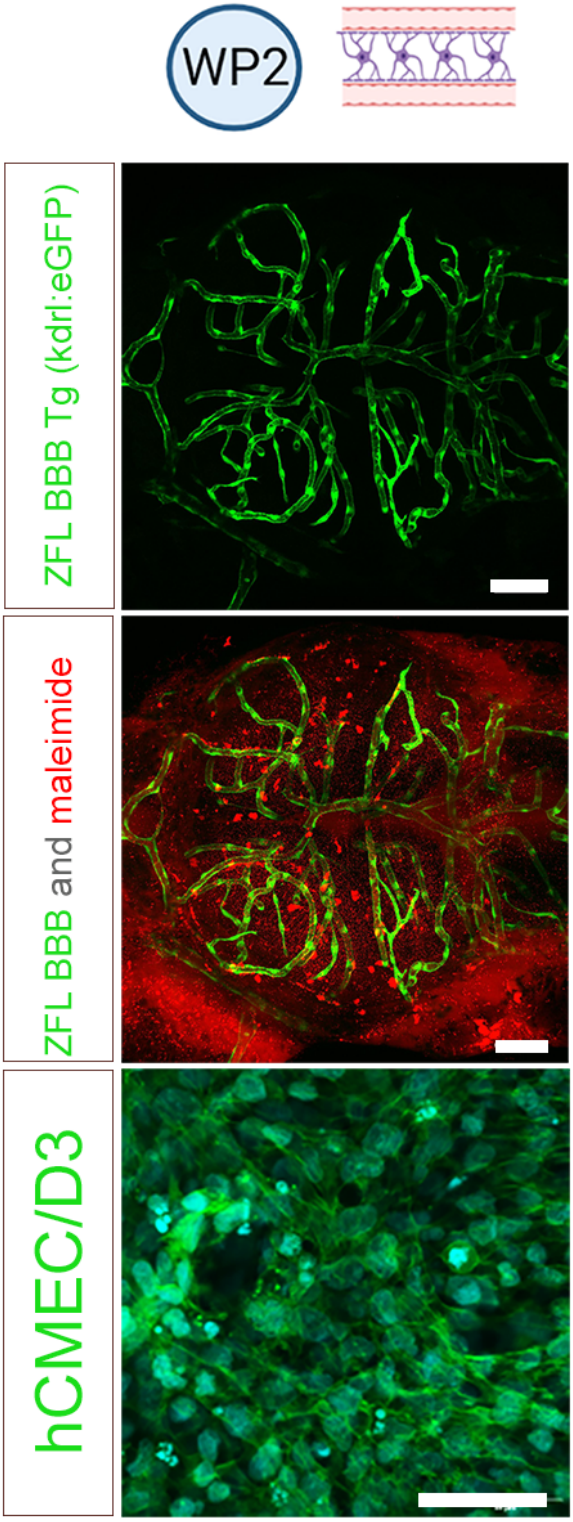


To establish the in vitro distribution kinetics of selected solvents necessary for toxicokinetic modeling, 3D brain cell cultures and medium will be collected 3, 6, 24, and 48 hours after the first exposure and after the last exposure of the repeated treatment. The solvent and its main metabolites (if relevant) will be quantified to establish a time course of disappearance from the medium and appearance in the cells as well as to assess the potential accumulation for the entire period of exposure. The fraction bound to culture plates' plastic will be quantified after desorption. In silico modeling of glycol ethers in vitro distribution kinetics will then be developed. This model will be able to predict the change in cell-associated concentrations of solvents in BrainSpheres with time, as previously shown for amiodarone [43].

WP2: In Vivo, In Vitro, and In Silico BBB Functionality Testing

We previously established the zebrafish as a predictive vertebrate screening model to study the systemic circulation and tissue distribution of particulate drug carriers [44,45]. At 72 hours postfertilization, zebrafish embryos have a functional CNS and, presumably, a fully functional BBB. Anatomical structures such as the vascular endothelium can be visualized using transgenic fish lines expressing fluorescent proteins (Figure 4). Defined exposure of the zebrafish can be achieved by the simple addition of solvents to the fish incubation medium within a closed container. Other advantages of the model include the possibility of studying BBB functionality under physiological conditions in vivo and the high throughput. A well-known in vitro model for the human brain endothelium, hCMEC/D3 cell line (Figure 4) showing the formation of tight junctions and the expression of most transporters and receptors of the in vivo BBB [46], cultured in a transwell system, will also be used. Furthermore, extrapolation of in silico, in vitro, and zebrafish data to higher vertebrates seems feasible [47].

Figure 4. Blood-brain barrier (BBB) models used in work package (WP) 2: zebrafish larvae (ZFL) and human brain microvasculatur endothelial cells (hCMEC/D3). ZFL (2 top panels): tracer permeability across BBB. Dorsal view of the midbrain region of the zebrafish lines Tg (kdrl:enhanced green fluorescent protein [eGFP]), which expresses eGFP (green signal) in the endothelial cell membranes. ZFL were injected with the tracer 1 kDa maleimide (red signal). Scale bars: 50 µm. hCMEC/D3 cells (lowest panel): actin filament stained with fluorescein isothiocyanate phalloidin. Scale bars: 100 µm.



Zebrafish larvae are frequently used in developmental biology or toxicological studies. However, in this study, we will use zebrafish larvae exclusively to study BBB integrity and functionality [48]. Fluorescently labeled reference compounds (Figure 4) will be intravenously injected into the Duct of Cuvier, as markers of paracellular permeability (eg, fluorescein isothiocyanate dextran 70 or fluorescently labeled liposomes), substrates of drug export transporters (eg, rhodamine-123 as P-glycoprotein substrate), or nutrient transporters (eg, fluorescently labeled transferrin as a marker for receptor-mediated transcytosis). PGME will be the first reference compound to be tested because of its high water miscibility. To precisely assess exposure, analytical methods (gas chromatography-tandem mass spectrometry [GC-MS/MS])

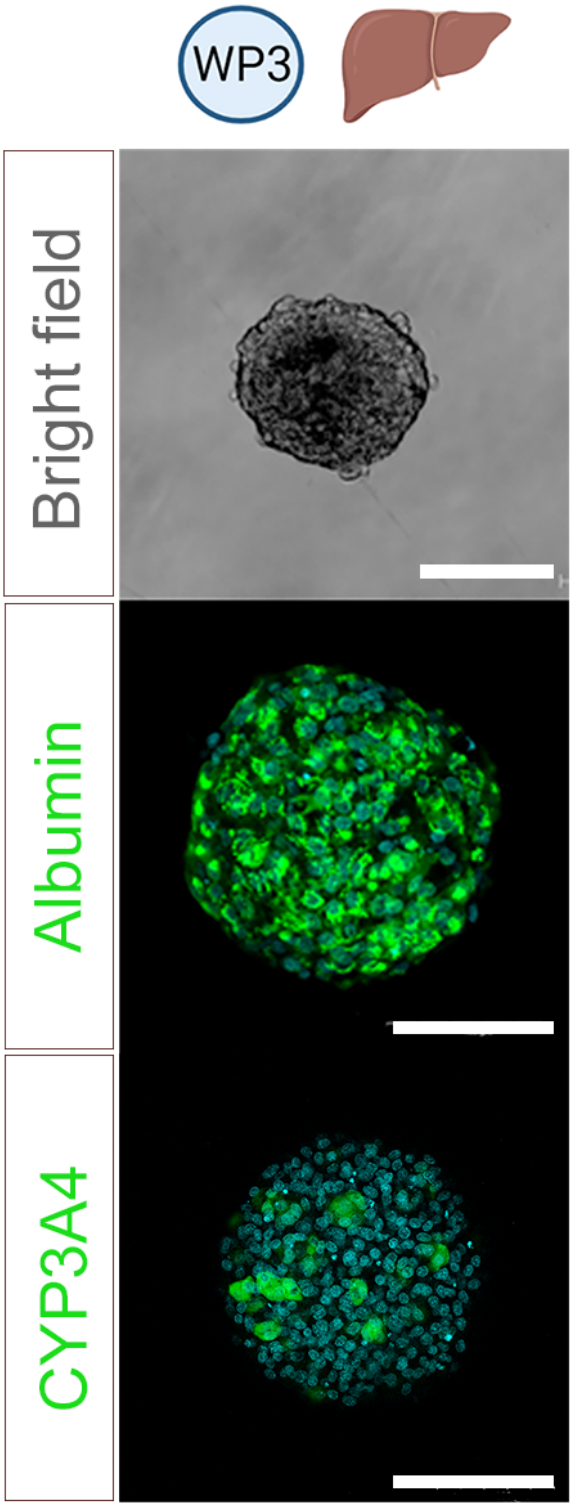
will be used to determine the concentrations of solvents and their metabolites in zebrafish medium, in the headspace of closed incubation vessels and tissue samples (ie, zebrafish homogenates). Circulation, tissue distribution, and brain uptake of the reference compounds will be monitored by confocal laser scanning microscopy (live imaging of anesthetized fish embryos for up to 24 hours). The concentration-dependent toxicity of solvents or their metabolites will be monitored based on the viability and malformations of embryos. The integrity of vasculature will be visualized in transgenic zebrafish kdrl: enhanced green fluorescent protein embryos. The metabolic capacity of the zebrafish will be determined by quantifying potential metabolites (determined in WP3; Figure 2) in zebrafish tissue homogenates. The concentration-dependent toxicity to BBB and the coefficient of permeation of solvents will additionally be evaluated in the hCMEC/D3 cell line cultured in a transwell system.

Finally, quantitative estimates of passive cellular uptake and BBB permeability of solvents and their metabolites will be provided based on computational modeling using physicochemical molecular descriptors according to the methods we previously established [26,49]. These methods provide very high throughput, allowing the screening of web-based chemical libraries.

WP3: In Vitro Hepatic Metabolism and Clearance

Because the liver is the main organ responsible for metabolism and a large contributor to compound clearance, we will implement a system suitable for predicting the hepatic metabolism of solvents. In recent years, 3D liver cell models have been proposed as an alternative to less physiological 2D cell monolayers, and their applications have progressed substantially [50]. They are widely used for the assessment of hepatotoxicity [51-55]. An advantage of spheroids is that they overcome the limitation of rapid decline of drug-metabolizing enzyme activities in primary human hepatocyte suspension culture and cell lysates [56], such as microsomes and liver S9 fractions. In this study, we will use 3D liver cultures of the well-characterized human HepaRG cell line (Figure 5), which represent a promising model to evaluate hepatotoxicity and hepatic metabolism [57].

Figure 5. Liver model used in work package (WP) 3. Bright field and immunostainings of liver 3D HepaRG cultures showing the presence of albumin and cytochrome P450 3A4 (CYP3A4). Bars: 100 µm.



Determining the appropriate experimental test system (eg, cell plate, incubation time, and exposure concentration) will be an essential part of the development of the 3D model. Moreover, analytical methods (GC-MS/MS and liquid chromatography-tandem mass spectrometry) to detect and quantify the solvents and the metabolites formed must be developed to calculate hepatic metabolism and clearance. Then, proof of metabolic competence and maintenance of the 3D HepaRG cells will be carried out by assessing the metabolism of known P450 substrates. The presence and secretion of albumin as a specific hepatocyte marker will be assessed using immunostaining and enzyme-linked immunosorbent assay. Solvent- and metabolite-induced cytotoxicity will be assessed after 48 hours and 7 days (repeated) of exposure to determine the nontoxic concentration range for subsequent experiments. The metabolic abilities of the 3D HepaRG model and 3D

primary human hepatocytes will be compared. Furthermore, the clearance data obtained from the 3D HepaRG model will be compared with the short-term clearance measured in the human liver cell lysate (S9 fractions). In addition, Michaelis-Menten-Kinetic parameters (V_{max} and Km) for the formation of the metabolites will be derived using the S9 fractions. These data will be used to build a physiologically based toxicokinetic (PBTK) model (Figure 2).

WP4: In Vivo Volunteer Exposure

Human biomonitoring refers to monitoring exposure-related health risks by analyzing biological samples, usually blood and urine samples [58]. The biomonitoring limit values (BMLVs) are set to protect human populations against the potential toxic effects of chemical substances. These limit values account for all routes through which a chemical can enter the body. These are most often the inhalation and skin routes in occupational and environmental settings. Kinetic studies that provide absorption, biotransformation, and elimination rates as well as the absorption and elimination half-lives of the parent compound and its metabolites are necessary to set BMLVs. The apparent urinary elimination half-lives of the parent compound and its metabolites will later be used to develop a biomonitoring method. Sample collection time is crucial and is determined by the apparent elimination half-life of the chemical. Blood concentrations will be used to calibrate the air:blood PC for the toxicokinetic models.

We will recruit 4 participants for 2 of the selected solvents. All participants must meet the following criteria: they should be healthy individuals who do not smoke or use contraceptive hormones, do not consume alcohol, be aged between 18 and 65 years, have normal red blood cells and hemoglobin concentrations, maintain a BMI between 18 and 25, and should not be working with glycol ethers. Pregnant and breastfeeding women will be excluded from this study. Participants will be recruited using flyers and announcements distributed at the teaching hospital, university websites, and bulletin boards. All participants will sign a written informed consent form before being included in the study.

The participants will be exposed to a single glycol ether for 4 hours under controlled conditions in an exposure chamber (12 m^3). PGE concentrations will be set at or below the Swiss occupational exposure level (OEL) if one exists. In the absence of an OEL, we will rely on existing OELs for other propylene glycols. The parent compound (free and conjugated) and the oxidative metabolites (free and conjugated) of the selected glycol ethers will be monitored in blood, urine, and exhaled air samples. These are noninvasive methods used for human participants, and the results will be used in WP5 to estimate brain concentrations. All compounds will be quantified using capillary gas (parent compound in blood, urine, and exhaled air) or liquid (metabolites in blood and urine) chromatograms with tandem mass spectroscopy detection.

WP5: In Silico PBTK Modeling

PBTK models can be used to estimate human brain concentrations. The risk of neurotoxic effects can be estimated by comparing the predicted solvent-brain concentrations with the NOAEC obtained from the in vitro models. Mathematical models such as PBTK models can be used to predict the ADME of a chemical and its metabolites. In these PBTK models, the body is represented by 1 or more compartments. Each compartment represents 1 or more tissues that are kinetically homogeneous, that is, that have similar perfusion rates and an assumed similar substance solubility. PBTK models are described by a set of parameters that define the compartments and a set of mass balance differential equations for each compartment.

A previously developed toxicokinetic model for PGME with metabolism that is assumed to follow Michaelis-Menten kinetics calibrated for different age groups serves as the basis for our development [30,31,59]. We aim to modify this previously developed toxicokinetic model to include a separate compartment for the brain using BBB flux rates obtained from in vivo, in vitro, and in silico models (WP2). In addition, we will implement PC obtained from empirical human experiments (WP4) and metabolic parameters assessed in a hepatocyte assay (WP3). The toxicokinetic models will be able to simulate not only acute but also chronic exposures; therefore, both short-term and long-term exposures can be explored in silico. We will develop the toxicokinetic model into a physiologically based pharmacokinetic model based on the existing inhalation-only toxicokinetic model originally developed for PGME [40] and build it in the Berkeley Madonna software or equivalent. We will model the brain as a single compartment with direct contact with the blood flow and where organic solvent uptake will be assumed to be diffusion limited, which is in line with other physiologically based pharmacokinetic models [60]. Values for physiological parameters (volume of vascular brain, as fraction of brain volume [FVvb], volume of extravascular brain, as fraction of brain volume [FVevb], volume fraction of brain tissue [FVB; as percent of body weight], BBB surface [Sh] in cm^2, fraction of cardiac output in brain at rest [BFbrainrest]/cardiac output in brain at light work [BFbrain]) required to build the TK model are from the scientific literature. Depending on the substance, values of chemical-specific parameters such as the pulmonary retention (Rpulm), central:air PC (Pca), blood:air PC (Pba), and brain tissue:vascular brain PC (Pevb_vb) are either taken from the literature or estimated in silico. Since the partitioning of organic compounds between human tissue homogenate and blood is a function of water and lipid content of tissues and the n-octanol:water PC (Kow), PCs are estimated in silico based on LogKow. Kinetic coefficients needed for each organic solvent included in this study will be found in WP3 for liver metabolism (Michaelis-Menten parameters [V_{max} and Km]), WP2 for BBB uptake (BBB permeability-surface area product [PS]). The fraction unbound in blood (Fu_blood) will be estimated based on the fraction unbound in plasma (Fu_plasma) and the blood-to-plasma ratio (Rb), and the fraction unbound in brain (Fu_brain) will be considered when modeling each solvent as only the free fraction is able to distribute to different tissues and is biologically active. The model will be calibrated by comparing the predicted and actual urinary organic solvent concentrations obtained from the controlled human experiments (WP4). Both the free and total

organic solvent concentrations (free+conjugated) will be obtained for calibration.

Results

With this project, we expect to provide a strategy to rank uncharacterized solvents and their potential liver-formed metabolites, according to their potential neurotoxicity, and in comparison with the banned EGME. More importantly, a series of PBTK simulations will be conducted to predict occupational exposure, assuming 8 hours of exposure per day, 5 days per week, physical activity for 12 hours per day, and rest for the remaining 12 hours. We will use the PBTK model in reverse dosimetry to estimate air concentrations that do not produce brain concentrations determined as neurotoxic in the hiPSC-derived 3D brain model. We will recommend that authorities setting occupational exposure and public health limits consult these values. Keeping the exposure below the brain effect level should ultimately increase the protection of exposed workers and the general population with domestic exposures.

We also anticipate gaining insights into the mechanisms of action of solvents of the glycol ether family. We will elucidate the possible toxic endpoints in the brain, liver, and zebrafish models. Furthermore, we will be able to establish how toxicity is related to the compounds' lipophilicity and metabolites.

Discussion

Overall, our strategy combining multiple, fit-for-purpose 3D advanced cell culture systems; zebrafish larvae; biomarker analysis; human ADME experiments; and in silico prediction is expected to contribute to the improvement of human risk assessment. Although we identified some risks we could encounter during the project, we are confident that our already determined mitigation measures will be able to overcome potential pitfalls.

Determination of the passage of solvent through the BBB may be challenging; hence, we are applying 3 different complementary methods: in vivo zebrafish larvae, in vitro human cells (hCMEC/D3), and in silico models. We are also considering and assessing the effects of the hepatic metabolites of the solvents on human BBB cells. With this experimental strategy, issues regarding the potential direct effect of solvents on cell membranes, the relatively low miscibility of solvents with water, and the physiological differences between zebrafish and humans (eg, metabolism and route of expected) should be overcome.

We have extensive experience in recruiting human volunteers for controlled human exposure sessions in the exposure chamber. Sometimes, recruitment takes longer than anticipated, and if that is the case, we will extend the timeline to not compromise the size of the study. New analytical chemical methods will need to be determined, which is time consuming. However, we will use a laboratory with extensive experience in analyzing PGME in urine and blood samples. This will also have to be accommodated with a delay in the timeline.

Future developments, not included in this study, are a strategy extended to include developmental neurotoxicity by determining other endpoints, such as proliferation and neurite outgrowth, after exposure of BrainSpheres to solvents at earlier developmental stages and by adding an in vitro test system to take into account the passage of solvents through the placental barrier [61]. We might also consider combining zebrafish embryo behavioral assays (eg, spontaneous tail coiling) with the BrainSpheres model as readouts for developmental neurotoxicity. Finally, the PBTK model could be adapted to determine solvent air concentrations that are unlikely to cause neurotoxic effects in fetuses or pregnant women.

Acknowledgments

This work was partially funded by the Swiss Centre for Human Applied Toxicology (SCAHT), Basel, Switzerland.

Data Availability

Data will be available from the corresponding author on reasonable request.

Authors' Contributions

NBH, LSD, JH, and MGZ conceptualized the paper. NBH, LSD, JH, and MGZ wrote the original draft. All authors reviewed and edited the paper. LH, DP, HP, RDP, and SW visualized the paper. NBH, LSD, JH, and MGZ administered the project. NBH, LSD, JH, and MGZ acquired the funding.

Conflicts of Interest

None declared.

References

1. Brown RC, Lockwood AH, Sonawane BR. Neurodegenerative diseases: an overview of environmental risk factors. Environ Health Perspect 2005 Sep;113(9):1250-1256 [FREE Full text] [doi: 10.1289/ehp.7567] [Medline: 16140637]
2. Pearce N, Kromhout H. Neurodegenerative disease: the next occupational disease epidemic? Occup Environ Med 2014 Sep;71(9):594-595. [doi: 10.1136/oemed-2013-101943] [Medline: 25035117]

3. van Valen E, Wekking E, van Hout M, van der Laan G, Hageman G, van Dijk F, et al. Chronic solvent-induced encephalopathy: course and prognostic factors of neuropsychological functioning. Int Arch Occup Environ Health 2018 Oct;91(7):843-858 [FREE Full text] [doi: 10.1007/s00420-018-1328-1] [Medline: 29943196]
4. Firestone JA, Gospe SMJ. Organic solvents. In: Dobbs MR, editor. Clinical Neurotoxicology: Syndromes, Substances, Environments. Amsterdam, The Netherlands: Elsevier Health Sciences; 2009.
5. Bates MN, Reed BR, Liu S, Eisen EA, Hammond SK. Solvent exposure and cognitive function in automotive technicians. Neurotoxicology 2016 Dec;57:22-30. [doi: 10.1016/j.neuro.2016.08.009] [Medline: 27545874]
6. Berr C, Vercambre MN, Bonenfant S, Manoux AS, Zins M, Goldberg M. Occupational exposure to solvents and cognitive performance in the GAZEL cohort: preliminary results. Dement Geriatr Cogn Disord 2010;30(1):12-19 [FREE Full text] [doi: 10.1159/000315498] [Medline: 20606440]
7. Meyer-Baron M, Blaszkewicz M, Henke H, Knapp G, Muttray A, Schäper M, et al. The impact of solvent mixtures on neurobehavioral performance: conclusions from epidemiological data. Neurotoxicology 2008 May;29(3):349-360. [doi: 10.1016/j.neuro.2008.02.005] [Medline: 18394708]
8. Hachim M, Elemam NM, Maghazachi AA. The beneficial and debilitating effects of environmental and microbial toxins, drugs, organic solvents and heavy metals on the onset and progression of multiple sclerosis. Toxins (Basel) 2019 Mar 05;11(3):147 [FREE Full text] [doi: 10.3390/toxins11030147] [Medline: 30841532]
9. Liu M, Shin EJ, Dang DK, Jin CH, Lee PH, Jeong JH, et al. Trichloroethylene and Parkinson's disease: risk assessment. Mol Neurobiol 2018 Jul;55(7):6201-6214. [doi: 10.1007/s12035-017-0830-x] [Medline: 29270919]
10. Sabbath EL, Gutierrez LA, Okechukwu CA, Singh-Manoux A, Amieva H, Goldberg M, et al. Time may not fully attenuate solvent-associated cognitive deficits in highly exposed workers. Neurology 2014 May 13;82(19):1716-1723 [FREE Full text] [doi: 10.1212/WNL.0000000000000413] [Medline: 24821933]
11. Golbabaei F, Dehghani F, Saatchi M, Zakerian SA. Evaluation of occupational exposure to different levels of mixed organic solvents and cognitive function in the painting unit of an automotive industry. Health Promot Perspect 2018 Oct 27;8(4):296-302 [FREE Full text] [doi: 10.15171/hpp.2018.42] [Medline: 30479984]
12. Filley CM, Heaton RK, Rosenberg NL. White matter dementia in chronic toluene abuse. Neurology 1990 Mar;40(3 Pt 1):532-534. [doi: 10.1212/wnl.40.3_part_1.532] [Medline: 2314597]
13. Filley CM, Halliday W, Kleinschmidt-DeMasters BK. The effects of toluene on the central nervous system. J Neuropathol Exp Neurol 2004 Jan;63(1):1-12. [doi: 10.1093/jnen/63.1.1] [Medline: 14748556]
14. Gregersen P, Mikkelsen S, Klausen H, Døssing M, Nielsen H, Thygesen P. [Chronic cerebral syndrome in painters. Dementia due to inhalation or is it of cryptogenic origin?]. Ugeskr Laeger 1978 Jul 03;140(27):1638-1644. [Medline: 684909]
15. Rovida C, Alépée N, Api AM, Basketter DA, Bois FY, Caloni F, et al. Integrated testing strategies (ITS) for safety assessment. ALTEX 2015;32(1):25-40 [FREE Full text] [doi: 10.14573/altex.1411011] [Medline: 25413849]
16. Schmeisser S, Miccoli A, von Bergen M, Berggren E, Braeuning A, Busch W, et al. New approach methodologies in human regulatory toxicology - not if, but how and when!. Environ Int 2023 Aug;178:108082 [FREE Full text] [doi: 10.1016/j.envint.2023.108082] [Medline: 37422975]
17. Karmaus AL, Mansouri K, To KT, Blake B, Fitzpatrick J, Strickland J, et al. Evaluation of variability across rat acute oral systemic toxicity studies. Toxicol Sci 2022 Jun 28;188(1):34-47 [FREE Full text] [doi: 10.1093/toxsci/kfac042] [Medline: 35426934]
18. Kleinstreuer NC, Ceger PC, Allen DG, Strickland J, Chang X, Hamm JT, et al. A curated database of rodent uterotrophic bioactivity. Environ Health Perspect 2016 May;124(5):556-562 [FREE Full text] [doi: 10.1289/ehp.1510183] [Medline: 26431337]
19. Luechtefeld T, Maertens A, Russo DP, Rovida C, Zhu H, Hartung T. Global analysis of publicly available safety data for 9,801 substances registered under REACH from 2008-2014. ALTEX 2016;33(2):95-109 [FREE Full text] [doi: 10.14573/altex.1510052] [Medline: 26863090]
20. Ly Pham L, Watford S, Pradeep P, Martin MT, Thomas R, Judson R, et al. Variability in studies: defining the upper limit of performance for predictions of systemic effect levels. Comput Toxicol 2020 Aug 01;15(August 2020):1-100126 [FREE Full text] [doi: 10.1016/j.comtox.2020.100126] [Medline: 33426408]
21. Wang B, Gray G. Concordance of noncarcinogenic endpoints in rodent chemical bioassays. Risk Anal 2015 Jun;35(6):1154-1166. [doi: 10.1111/risa.12314] [Medline: 25545328]
22. Hartung T. Opinion versus evidence for the need to move away from animal testing. ALTEX 2017;34(2):193-200 [FREE Full text] [doi: 10.14573/altex.1703291] [Medline: 28407174]
23. Hogberg HT, Smirnova L. The future of 3D brain cultures in developmental neurotoxicity testing. Front Toxicol 2022 Jan 27;4:808620 [FREE Full text] [doi: 10.3389/ftox.2022.808620] [Medline: 35295222]
24. Pamies D, Barreras P, Block K, Makri G, Kumar A, Wiersma D, et al. A human brain microphysiological system derived from induced pluripotent stem cells to study neurological diseases and toxicity. ALTEX 2017;34(3):362-376 [FREE Full text] [doi: 10.14573/altex.1609122] [Medline: 27883356]
25. Wardill HR, Mander KA, Van Sebille YZ, Gibson RJ, Logan RM, Bowen JM, et al. Cytokine-mediated blood brain barrier disruption as a conduit for cancer/chemotherapy-associated neurotoxicity and cognitive dysfunction. Int J Cancer 2016 Dec 15;139(12):2635-2645 [FREE Full text] [doi: 10.1002/ijc.30252] [Medline: 27367824]

26. Bendels S, Kansy M, Wagner B, Huwyler J. In silico prediction of brain and CSF permeation of small molecules using PLS regression models. Eur J Med Chem 2008 Aug;43(8):1581-1592. [doi: 10.1016/j.ejmech.2007.11.011] [Medline: 18206268]
27. Gupta PK. Principles and basic concepts of toxicokinetics. In: Fundamentals of Toxicology: Essential Concepts and Applications. Cambridge, MA: Academic Press; 2016.
28. Breen M, Ring CL, Kreutz A, Goldsmith MR, Wambaugh JF. High-throughput PBTK models for in vitro to in vivo extrapolation. Expert Opin Drug Metab Toxicol 2021 Aug;17(8):903-921 [FREE Full text] [doi: 10.1080/17425255.2021.1935867] [Medline: 34056988]
29. Substance regulatory obligations. European Chemicals Agency. URL: https://echa.europa.eu/legislation-obligation/-/obligations/100.003.377 [accessed 2023-12-19]
30. Hopf NB, Vernez D, Berthet A, Charriere N, Arnoux C, Tomicic C. Effect of age on toxicokinetics among human volunteers exposed to propylene glycol methyl ether (PGME). Toxicol Lett 2012 May 20;211(1):77-84 [FREE Full text] [doi: 10.1016/j.toxlet.2012.02.018] [Medline: 22421272]
31. Reale E, Sandstrom J, Culot M, Hechon J, Wellens S, Heymans M, et al. Predicting human neurotoxicity of propylene glycol methyl ether (PGME) by implementing in vitro neurotoxicity results into toxicokinetic modelling. Sci Total Environ 2023 Aug 15;886:163767 [FREE Full text] [doi: 10.1016/j.scitotenv.2023.163767] [Medline: 37156387]
32. Filley CM, Kleinschmidt-DeMasters BK. Toxic leukoencephalopathy. N Engl J Med 2001 Aug 09;345(6):425-432. [doi: 10.1056/NEJM200108093450606] [Medline: 11496854]
33. Pamies D, Block K, Lau P, Gribaldo L, Pardo CA, Barreras P, et al. Rotenone exerts developmental neurotoxicity in a human brain spheroid model. Toxicol Appl Pharmacol 2018 Sep 01;354:101-114 [FREE Full text] [doi: 10.1016/j.taap.2018.02.003] [Medline: 29428530]
34. Zhong X, Harris G, Smirnova L, Zufferey V, Sá RC, Baldino Russo F, et al. Antidepressant paroxetine exerts developmental neurotoxicity in an iPSC-derived 3D human brain model. Front Cell Neurosci 2020 Feb 21;14:25 [FREE Full text] [doi: 10.3389/fncel.2020.00025] [Medline: 32153365]
35. Nunes C, Singh P, Mazidi Z, Murphy C, Bourguignon A, Wellens S, et al. An in vitro strategy using multiple human induced pluripotent stem cell-derived models to assess the toxicity of chemicals: a case study on paraquat. Toxicol In Vitro 2022 Jun;81:105333 [FREE Full text] [doi: 10.1016/j.tiv.2022.105333] [Medline: 35182771]
36. Chesnut M, Paschoud H, Repond C, Smirnova L, Hartung T, Zurich MG, et al. Human IPSC-derived model to study myelin disruption. Int J Mol Sci 2021 Aug 31;22(17):9473 [FREE Full text] [doi: 10.3390/ijms22179473] [Medline: 34502381]
37. Goldstein DB. The effects of drugs on membrane fluidity. Annu Rev Pharmacol Toxicol 1984;24:43-64. [doi: 10.1146/annurev.pa.24.040184.000355] [Medline: 6329077]
38. Bowen SE, Batis JC, Paez-Martinez N, Cruz SL. The last decade of solvent research in animal models of abuse: mechanistic and behavioral studies. Neurotoxicol Teratol 2006;28(6):636-647. [doi: 10.1016/j.ntt.2006.09.005] [Medline: 17064879]
39. Balster RL. Neural basis of inhalant abuse. Drug Alcohol Depend 1998;51(1-2):207-214. [doi: 10.1016/s0376-8716(98)00078-7] [Medline: 9716942]
40. Fukumori R, Takarada T, Nakazato R, Fujikawa K, Kou M, Hinoi E, et al. Selective inhibition by ethanol of mitochondrial calcium influx mediated by uncoupling protein-2 in relation to N-methyl-D-aspartate cytotoxicity in cultured neurons. PLoS One 2013 Jul 16;8(7):e69718 [FREE Full text] [doi: 10.1371/journal.pone.0069718] [Medline: 23874988]
41. Revilla AS, Pestana CR, Pardo-Andreu GL, Santos AC, Uyemura SA, Gonzales ME, et al. Potential toxicity of toluene and xylene evoked by mitochondrial uncoupling. Toxicol In Vitro 2007 Aug;21(5):782-788. [doi: 10.1016/j.tiv.2007.01.012] [Medline: 17321102]
42. Zurich MG, Stanzel S, Kopp-Schneider A, Prieto P, Honegger P. Evaluation of aggregating brain cell cultures for the detection of acute organ-specific toxicity. Toxicol In Vitro 2013 Jun;27(4):1416-1424. [doi: 10.1016/j.tiv.2012.06.018] [Medline: 22954530]
43. Nunes C, Proença S, Ambrosini G, Pamies D, Thomas A, Kramer NI, et al. Integrating distribution kinetics and toxicodynamics to assess repeat dose neurotoxicity using human BrainSpheres: a case study on amiodarone. Front Pharmacol 2023 Sep 6;14:1248882 [FREE Full text] [doi: 10.3389/fphar.2023.1248882] [Medline: 37745076]
44. Sieber S, Grossen P, Bussmann J, Campbell F, Kros A, Witzigmann D, et al. Zebrafish as a preclinical in vivo screening model for nanomedicines. Adv Drug Deliv Rev 2019;151-152:152-168. [doi: 10.1016/j.addr.2019.01.001] [Medline: 30615917]
45. Rizzo LY, Golombek SK, Mertens ME, Pan Y, Laaf D, Broda J, et al. In vivo nanotoxicity testing using the zebrafish embryo assay. J Mater Chem B 2013 Jun 10;1:10.1039/C3TB20528B [FREE Full text] [doi: 10.1039/C3TB20528B] [Medline: 24179674]
46. Weksler B, Romero IA, Couraud PO. The hCMEC/D3 cell line as a model of the human blood brain barrier. Fluids Barriers CNS 2013 Mar 26;10(1):16 [FREE Full text] [doi: 10.1186/2045-8118-10-16] [Medline: 23531482]
47. Sieber S, Grossen P, Detampel P, Siegfried S, Witzigmann D, Huwyler J. Zebrafish as an early stage screening tool to study the systemic circulation of nanoparticulate drug delivery systems in vivo. J Control Release 2017 Oct 28;264:180-191. [doi: 10.1016/j.jconrel.2017.08.023] [Medline: 28851572]

48. Quiñonez-Silvero C, Hübner K, Herzog W. Development of the brain vasculature and the blood-brain barrier in zebrafish. Dev Biol 2020 Jan 15;457(2):181-190 [FREE Full text] [doi: 10.1016/j.ydbio.2019.03.005] [Medline: 30862465]
49. Suenderhauf C, Hammann F, Huwyler J. Computational prediction of blood-brain barrier permeability using decision tree induction. Molecules 2012 Aug 31;17(9):10429-10445 [FREE Full text] [doi: 10.3390/molecules170910429] [Medline: 22941223]
50. Duval K, Grover H, Han LH, Mou Y, Pegoraro AF, Fredberg J, et al. Modeling physiological events in 2D vs. 3D cell culture. Physiology (Bethesda) 2017 Jul;32(4):266-277 [FREE Full text] [doi: 10.1152/physiol.00036.2016] [Medline: 28615311]
51. Prestigiacomo V, Weston A, Messner S, Lampart F, Suter-Dick L. Pro-fibrotic compounds induce stellate cell activation, ECM-remodelling and Nrf2 activation in a human 3D-multicellular model of liver fibrosis. PLoS One 2017 Jun 30;12(6):e0179995 [FREE Full text] [doi: 10.1371/journal.pone.0179995] [Medline: 28665955]
52. Prestigiacomo V, Suter-Dick L. Nrf2 protects stellate cells from Smad-dependent cell activation. PLoS One 2018 Jul 20;13(7):e0201044 [FREE Full text] [doi: 10.1371/journal.pone.0201044] [Medline: 30028880]
53. Riede J, Wollmann BM, Molden E, Ingelman-Sundberg M. Primary human hepatocyte spheroids as an in vitro tool for investigating drug compounds with low clearance. Drug Metab Dispos 2021 Jun 01:DMD-AR-2020-000340 [FREE Full text] [doi: 10.1124/dmd.120.000340] [Medline: 34074732]
54. Ingelman-Sundberg M, Lauschke VM. 3D human liver spheroids for translational pharmacology and toxicology. Basic Clin Pharmacol Toxicol 2022 Jan;130 Suppl 1:5-15 [FREE Full text] [doi: 10.1111/bcpt.13587] [Medline: 33872466]
55. Proctor WR, Foster AJ, Vogt J, Summers C, Middleton B, Pilling MA, et al. Utility of spherical human liver microtissues for prediction of clinical drug-induced liver injury. Arch Toxicol 2017 Aug;91(8):2849-2863 [FREE Full text] [doi: 10.1007/s00204-017-2002-1] [Medline: 28612260]
56. Preiss LC, Lauschke VM, Georgi K, Petersson C. Multi-well array culture of primary human hepatocyte spheroids for clearance extrapolation of slowly metabolized compounds. AAPS J 2022 Mar 11;24(2):41. [doi: 10.1208/s12248-022-00689-y] [Medline: 35277751]
57. Ramaiahgari SC, Waidyanatha S, Dixon D, DeVito MJ, Paules RS, Ferguson SS. From the cover: three-dimensional (3D) HepaRG spheroid model with physiologically relevant xenobiotic metabolism competence and hepatocyte functionality for liver toxicity screening. Toxicol Sci 2017 Sep 01;159(1):124-136 [FREE Full text] [doi: 10.1093/toxsci/kfx122] [Medline: 28633424]
58. Costa C, Teixeira JP. Biomonitoring. In: Wexler P, editor. Encyclopedia of Toxicology (Third Edition). Cambridge, MA: Academic Press; 2014.
59. Tomicic C, Berode M, Oppliger A, Castella V, Leyvraz F, Praz-Christinaz SM, et al. Sex differences in urinary levels of several biological indicators of exposure: a human volunteer study. Toxicol Lett 2011 May 10;202(3):218-225 [FREE Full text] [doi: 10.1016/j.toxlet.2011.01.032] [Medline: 21352904]
60. Jongeneelen F, ten Berge W. Simulation of urinary excretion of 1-hydroxypyrene in various scenarios of exposure to polycyclic aromatic hydrocarbons with a generic, cross-chemical predictive PBTK-model. Int Arch Occup Environ Health 2012 Aug;85(6):689-702. [doi: 10.1007/s00420-011-0713-9] [Medline: 22038087]
61. Cherubini M, Erickson S, Haase K. Modelling the human placental interface in vitro-a review. Micromachines (Basel) 2021 Jul 27;12(8):884 [FREE Full text] [doi: 10.3390/mi12080884] [Medline: 34442506]

Abbreviations

ADME: absorption, distribution, metabolism, and excretion
BBB: blood-brain barrier
BFbrain: cardiac output in brain at light work
BFbrainrest: cardiac output in brain at rest
BMLV: biomonitoring limit value
CNS: central nervous system
EGE: ethylene glycol ether
EGME: ethylene glycol methyl ether
Fu_blood: fraction unbound in blood
Fu_brain: fraction unbound in brain
Fu_plasma: fraction unbound in plasma
FVB: volume fraction of brain tissue
FVevb: volume of extravascular brain, as fraction of brain volume
FVvb: volume of vascular brain, as fraction of brain volume
GC-MS/MS: gas chromatography-tandem mass spectrometry
hCMEC/D3: human brain microvascular endothelial cells
hiPSC: human induced pluripotent stem cell
NOAEC: no observed adverse effect concentration

OECD: Organisation for Economic Co-operation and Development
OEL: occupational exposure level
Pba: blood:air partition coefficient
PBTK: physiologically based toxicokinetic
PC: partition coefficient
Pca: central:air partition coefficient
Pevb_vb: brain tissue:vascular brain partition coefficient
PGE: propylene glycol ether
PGME: propylene glycol methyl ether
PS: blood-brain barrier permeability-surface area product
Rb: blood-to-plasma ratio
Rpulm: pulmonary retention
Sh: blood-brain barrier surface
TG: Test Guideline
Vmax: maximum velocity
WP: work package

Edited by A Mavragani; submitted 26.06.23; peer-reviewed by T Dong, J Parkin Kullmann; comments to author 18.09.23; revised version received 10.10.23; accepted 13.10.23; published 18.01.24.

Please cite as:
Hopf NB, Suter-Dick L, Huwyler J, Borgatta M, Hegg L, Pamies D, Paschoud H, Puligilla RD, Reale E, Werner S, Zurich MG
Novel Strategy to Assess the Neurotoxicity of Organic Solvents Such as Glycol Ethers: Protocol for Combining In Vitro and In Silico Methods With Human-Controlled Exposure Experiments
JMIR Res Protoc 2024;13:e50300
URL: https://www.researchprotocols.org/2024/1/e50300
doi:10.2196/50300
PMID:38236630

Protocol

Implementation of a Primary Prevention Program for Posttraumatic Stress Disorder in a Cohort of Professional Soldiers (PREPAR): Protocol for a Randomized Controlled Trial

Emmanuelle Le Barbenchon[1*], PhD; Marion Trousselard[2*], MD, PhD; Sonia Pellissier[3], PhD; Mathilde Moisseron-Baudé[4,5,6], PhD; Philippine Chachignon[1], MAST; Pierre Bouny[7], PhD; Emma Touré Cuq[7], PhD; Sandrine Jacob[2]; Cécile Vigier[2]; Maud Hidalgo[8], PhD; Damien Claverie[2*], MD, PhD; Anais M Duffaud[2*], PhD

[1]Laboratoire de Psychologie Sociale, Aix Marseille Université, Aix-en-Provence, France

[2]French Armed Forces Biomedical Research Institute, Brétigny-sur-Orge, France

[3]Univ Savoie Mont Blanc, Univ Grenoble Alpes, LIP/PC2S, Grenoble, France

[4]School of Practicing Psychologists, Paris, France

[5]VCR Team, School of Practicing Psychologists, Catholic Institute of Paris - Religion, Culture and Society Reception Team, Paris, France

[6]Center for Research on Work and Development, Conservatoire National des Arts et Métiers, EA4132, Paris, France

[7]URGOTECH, Paris, France

[8]Centre d'Epidémiologie et de Santé Publique des Armées, Marseille, France

[*]these authors contributed equally

Corresponding Author:
Anais M Duffaud, PhD
French Armed Forces Biomedical Research Institute
1, Place Général Valérie André
Brétigny-sur-Orge, 91223
France
Phone: 33 0618942117
Email: anaisduffaud1@gmail.com

Abstract

Background: Posttraumatic stress disorder (PTSD) is a psychiatric disorder that can manifest after a traumatic event where the individual perceives a threat to his or her life or that of others. Its estimated prevalence in the European population is 0.7% to 1.9%. According to the "dose-response" model, individuals who are most exposed to traumatic events are most at risk of developing PTSD. Hence, it is unsurprising that studies have observed a higher prevalence among the military population, ranging from 10% to 18%, or even up to 45%. This project's overall goal is to evaluate the primary prevention actions that can strengthen the resilience of at-risk professionals, notably military personnel, in the short term, with the medium- to long-term aim of preventing the occurrence of PTSD and improving the patient's prognosis.

Objective: This study's objectives are (1) to design a primary prevention program for PTSD, tailored to the studied military population and compatible with operational constraints; and (2) to implement and validate the Primary Prevention of Posttraumatic Stress Disorder in Military Professionals (PREPARE) program in the short term with operational personnel belonging to the French Mountain Infantry Brigade.

Methods: This is a single-center, prospective, randomized, parallel-group controlled cohort study. The cohort is divided into 2 groups: the nonintervention group receives no training, and the intervention group follows a dedicated prevention program (structured into 8 workshops and 2 debriefing and practice reinforcement workshops). Each participant is evaluated 4 times (at inclusion, +4 months, +6 months, and +12 months). During each visit, participants complete several psychosocial questionnaires (which take 15-80 minutes to complete). Samples (a 30-mL blood sample and three 5-mL saliva samples) are collected on 3 occasions: at inclusion, +4 months, and +12 months. Emotional reactivity (electrocardiogram and electrodermal activity) is measured before, during, and after the classic and the emotional Stroop task.

Results: The project is currently ongoing, and results are expected to be published by the end of 2024.

Conclusions: The study adopts an integrative approach to the processes that play a role in the risk of developing PTSD. Our biopsychosocial perspective makes it possible to target levers related to factors specific to the individual and socio-professional

factors. The following dimensions are addressed: (1) biophysiology (by studying markers of the neurobiological stress response, wear and tear, and vulnerability phenomena and reinforcing the flexibility of the autonomic nervous system), (2) psychology (by facilitating and measuring the development of flexible coping strategies to deal with stress and evaluating the moderating role of the individual's sense of duty in the development of PTSD), and (3) social (by facilitating community strategies aimed at reducing stigmatization and supporting the use of care by professionals in difficulty, in the institutional context).

Trial Registration: ClinicalTrials.gov NCT05094531; https://clinicaltrials.gov/study/NCT05094531

International Registered Report Identifier (IRRID): DERR1-10.2196/47175

(JMIR Res Protoc 2024;13:e47175) doi:10.2196/47175

KEYWORDS

posttraumatic stress disorder, military, primary prevention, biopsychosocial, resilience, coping, stigma, biophysiology; PTSD; implementation; soldier; veterans; prevention program

Introduction

Background and Rationale

Overview

Posttraumatic stress disorder (PTSD) is a psychiatric disorder that manifests following the experience of a traumatic event (TE) where the individual has perceived a threat to his or her life or that of others [1]. In France, it is considered to be the third most widespread psychiatric disorder, after major depression and specific phobias. Its prevalence in the European population is estimated to be between 0.7% and 1.9% [2,3]. According to the "dose-response" model, individuals who are most exposed to TEs are most at risk of developing PTSD [3-5]. At-risk occupations, such as the military, law enforcement, and first responders, carry an inherent risk of experiencing trauma. Hence, it is unsurprising to observe a high prevalence of PTSD in military populations, ranging from 10% to 18% or reaching up to 45% [5-9], depending on the study. Although cumulative exposure seems to be an important determinant in the general population [10], the literature does not establish a clear link among at-risk professionals. Nevertheless, it is reasonable to think that cumulative exposure is detrimental, and may even lead to fragilization, which would be consistent with the intensity of PTSD symptoms [11,12]. Repeated exposure triggers a reaction that builds on the consequences of previous exposures, increasing the complexity of the link between cumulative exposure and PTSD development, via multiple pathways.

PTSD Prevention

New medical research has influenced public policy, and the promotion of good health has become a key priority where policies seek to encourage certain behaviors that protect, improve, or restore the health of individuals, groups, or the entire population, while a prevention framework is used when the goal is to limit or prevent the development of a specific disease.

In the 1980s, evidence-based medicine emerged. The approach is founded on the principle of structuring prevention and public health decisions based on scientific evidence (eg, epidemiological studies and systematic clinical studies). A given health problem can be addressed by preventive interventions at primary, secondary, or tertiary levels. The objective of primary prevention is to intervene before the problem occurs; actions target the determinants of the problem by reducing risk factors or by promoting or reinforcing protective factors. In the context of PTSD, primary prevention can intervene at the level of preventing the trauma or at the level of PTSD prevention after the TEs. For at-risk professions in particular, PTSD prevention is the primary target, as the risk of exposure to trauma is integral to the profession. Secondary prevention seeks to define interventions once the problem is identified; it consists of early detection and referral for treatment (ie, after exposure to a TE). Finally, tertiary prevention seeks to manage the problem and prevent relapse. If necessary, the goal is to treat or limit any aggravation of the problem, notably any psychosocial consequences or comorbidities associated with PTSD. At all 3 levels, prevention must respect individual freedom [13].

Primary Prevention of PTSD

Effective primary prevention relies upon a sound theoretical understanding of the processes and determinants of the problem, knowledge of actions that have been scientifically validated in other populations, and clinical expertise in the field, which reflects the characteristics (eg, sociocultural) of the target population. This "selective prevention" approach seeks to target exposed participants.

In the domain of PTSD, primary interventions are rare, as such actions aim to prevent the impact of TEs before they occur. Nevertheless, this literature [14] gives us an insight into the potential effects of cumulative exposure to TEs during the career of military professionals. In this context, primary prevention interventions target several determinants that contribute to developing resilience following the TE. The approach underlines the need to characterize the factors that support individual and collective resilience processes, tailored to the characteristics of the population of at-risk professionals. This initial step is a prerequisite to the definition of relevant targets and the development of an appropriate prevention intervention for the population.

The proposed program (which we call Primary Prevention of Posttraumatic Stress Disorder in Military Professionals [PREPAR]) is part of a comprehensive prevention approach that synergistically links physiological, psychological, and social determinants. The approach stems from the etiological model proposed by Jones and Barlow [15]. This model is a comprehensive framework used in clinical psychology to understand the development and maintenance of psychological

disorders, particularly PTSD. It integrates various factors that contribute to the onset and perpetuation of these disorders. Several etiological factors, including biological, cognitive, and behavioral components, are implemented in this model. The model also takes into account predisposing factors and moderating variables. It emphasizes a holistic approach to understanding mental disorders, taking into account the complexity of the human experience.

The Physiological Dimension

PTSD is described as a failure of emotional extinction which develops following exposure to intense fear. Exposure to a stressful event leads to a neurobiological stress response, resulting in the activation of the sympatho-adrenergic neurovegetative system and the corticotropic neuroendocrine axis. Although this dual physiological response is effective in the short term, it comes with a biological cost; regulatory mechanisms aim to compensate for this loss by supporting poststress recovery. A repeated inability to recover and extinguish the stress response in the long term (repeated exposures over a short time period) creates a so-called "allostatic load" [16], which progressively limits the flexibility of the central and peripheral nervous system. The peripheral nervous system is of particular interest, due to its role as a mediator of the allostatic load. The parasympathetic branch plays a role in the emotional extinction and correction of the load, making it a key vulnerability factor for health when it is insufficiently effective [17]. Certain professions (frontline responders and military personnel) are at risk of developing a significant allostatic load, due to their repeated exposure to TEs (inherent in the nature of their work). On top of this, personnel must adapt, on a daily basis, to various environmental demands: physiological (sleep debt, altered sleeping patterns, etc), physical (hypoxia, etc), and cognitive and emotional (traumatic exposure, etc), among others. All of these factors test the flexibility of the individual's physiological systems, particularly the autonomic (ie, parasympathetic) nervous system, which, consequently, appears to be a key target for prevention measures.

The Psychological Dimension

Military personnel participate in multiple missions in conflict zones, and this is likely to alter the flexibility of their executive and emotional regulation functions. Although training programs aim to develop automated responses to well-known mission scenarios, they do not focus on developing the change in viewpoint that contributes to the resilience process. Moreover, preclinical data show that both acute and repeated stress are likely to reduce cognitive flexibility [18,19]. A slight reduction in cognitive flexibility likely reduces the flexibility of emotional regulation strategies following a TE, thus increasing the impact of exposure. This hypothesis draws upon the notion of "coping flexibility." The latter concept represents the individual's ability to evaluate the effectiveness of his or her strategies for coping with stress in a specific situation and then adopting alternative strategies, if necessary [20]. The evaluation of training in the diversification of emotional regulation strategies in military populations has found a reduced risk of PTSD after exposure to TEs. Furthermore, a relationship has been identified between cognitive flexibility and self-compassion [21]. The data also suggest that increasing self-compassion contributes to increasing cognitive flexibility [22].

Finally, a clear sense of duty has been found to counterbalance perceived constraints associated with the mission [23,24]. The literature reports that the meaning attributed to the work environment can, to a significant degree, compensate for the perception and impact of occupational stressors [25].

The Social Dimension

The social dimension targets normative pressure and stigmatization. These determinants are specific to the institutional context of military personnel and may represent risk factors. Thus, normative group pressure to follow codes that encourage the nonexpression of emotions [26] can be a risk factor, as military personnel can be reluctant to speak about their psychological and somatic symptoms, which delays treatment. A fear of stigmatization by the institution and peers is another potential barrier to care. Overall, these social factors are obstacles to both individual and collective positive health behaviors.

Research Hypotheses

Overview

The goal of this project is to evaluate a multidimensional biopsychosocial primary prevention intervention for PTSD aimed at strengthening the resilience of at-risk professionals, namely military personnel, in order to prevent the occurrence of PTSD or reduce its severity.

The objectives of the project are as follows: (1) to design a primary prevention program for PTSD specific to the studied military population and compatible with operational constraints; (2) to implement or validate the program with operational personnel belonging to the French Mountain Infantry Brigade (*Brigade d'Infanterie de Montagne*); and (3) to understand PTSD and its prevention from 3 perspectives: biophysiological (by studying key markers of the neurobiological stress response, strain and vulnerability and increasing the flexibility of the autonomic nervous system); psychological (by facilitating and measuring the development of flexible strategies to cope with stress and evaluating the moderating role of the meaning of the mission in the development of PTSD); and social (by facilitating community strategies aimed at reducing stigmatization and helping professionals in difficulty to access care in the institutional context).

Our biopsychosocial approach adopts an integrative understanding of the processes at play in the risk of developing PTSD. This perspective makes it possible to target levers related to factors specific to the individual (at physiological and psychological levels), and contextual and social factors (related to the working environment).

The Physiological Dimension

The change in parasympathetic vagal flexibility is an early and silent sign of physiological deterioration. It can be identified by noninvasive measurements (resting or tonic heart rate variability, and activation or phasic heart rate variability) and modulated by exercises that target vagal activity (cardiac

coherence techniques), which can be easily integrated into a busy professional agenda. A preliminary feasibility study among a group of firefighters (SDIS 73) demonstrated very good acceptance of this technique by the selected professionals and good adoption in daily life [24].

The Psychological Dimension

Two factors are targeted in the psychological dimension: coping flexibility and the sense of duty. These 2 determinants have rarely been targeted in studies of the prevention of occupational PTSD. The focus on coping flexibility and self-compassion seeks to improve emotional regulation, and the focus on the sense of duty seeks to target the silent determinants of occupational PTSD, with the overall aim of identifying an effective primary prevention intervention.

The Social Dimension

The targeted determinants are the beliefs and socio-normative processes that play a role in PTSD in a military population (self-stigmatization, stigmatization by others, normative pressure, and group cohesion). The intervention aims to establish a dedicated space to normalize the discourse, with the overall aim of discussing PTSD and making it visible, along with the signs of emerging psychological and somatic injuries. Specific group facilitation techniques are used, notably social modeling, which aims to reinforce feelings of self-efficacy that support the public expression of signs of injury and to support the search for appropriate care, when necessary [27].

Objectives of the Research

The main objective is to determine the effectiveness of a biopsychosocial program targeting the resilience (developing stable resources to adapt to occupational demands, in order to cope with TEs) of military personnel in the context of PTSD prevention.

The secondary objective is to better understand interindividual variability regarding the program's impact. We will study levels of vulnerability at inclusion and their impact on the program's effectiveness. We will also track postprogram changes in resilience (at 6 and 12 months). In addition, we will evaluate (1) the impact of the program on activation and psychobiological deterioration biomarkers and (2) the psychosocial determinants at 4 months (the end of the program) and 12 months (to evaluate persistence). In addition, we will measure adherence to the intervention at group and individual levels, through an evaluation at the end of the program. Finally, we will examine user satisfaction with the URGOfeel sensor and its application during workshops.

Methods

Ethical Considerations

Prior to their participation in the study, all participants will receive 2 separate notifications: one detailing the primary study and the other focusing on the genetic part. It is essential to emphasize that participation in the genetic segment is entirely optional, allowing individuals to engage solely in the main study if they prefer. Both of these notifications provide comprehensive information about the study's objectives, limitations, and legal requirements, especially in terms of privacy and confidentiality. Additionally, they clearly outline the potential benefits and risks associated with participation.

All collected data will undergo rigorous anonymization and processing in strict accordance with the MR001 reference methodology, in compliance with the regulations of the French Data Protection Authority (CNIL).

Our study maintains a steadfast commitment to ethical standards, in alignment with the principles set forth in the 1964 Helsinki declaration and its subsequent amendments. Furthermore, the ethics committee of Ile de France 8 formally approved the research protocol on January 12, 2021 (reference 20.12.10.58611). It is important to note that participants will not receive any form of compensation for their participation in this research.

Recruitment

The study will be conducted with members of the 27th Mountain Infantry Brigade, located in the Auvergne-Rhône-Alpes region of France. Participants will be recruited from companies proposed by the Brigade's line manager, depending on the ability to operationalize and implement measurement sessions, and the intervention.

Randomization

Individual randomization is not feasible for two reasons: (1) the logistics involved in deploying the training program and the availability of participants; and (2) the need to avoid a contagion effect between members of the Brigade who benefit from the program and those who do not.

Eligibility Criteria

After obtaining informed, written consent, the following inclusion criteria will be verified: affiliated to a social security scheme; a male adult; a member of a combat unit with external operations (OPEX) capability; a soldier with a current contract with the Brigade, lasting a minimum of 12 months; a soldier who is able to attend all measurement sessions and workshops, according to the schedule defined upstream; a soldier who is not a member of the *Groupements Commando Montagne* (to ensure homogeneity); and, finally, nonparticipation in one of the studies included in phase 1 of the PREPAR project. The latter social psychology study aimed to understand the day-to-day experience of frontline professionals and was approved by the ethics committee of the University of Aix-Marseille (2019-12-12-001). Noninclusion criteria are as follows: being female; receiving treatment for a chronic disorder (daily medication for at least 1 month); participation in an external operation planned within 12 months; and being an adult ward of court.

Participant Timeline

Figure 1 presents the timeline for participants, and Table 1 presents a synopsis of how the study will unfold.

Figure 1. Study timeline. *: 2 to 3 hours to take measurement; △: "debriefing and anchoring of the practice" workshop.

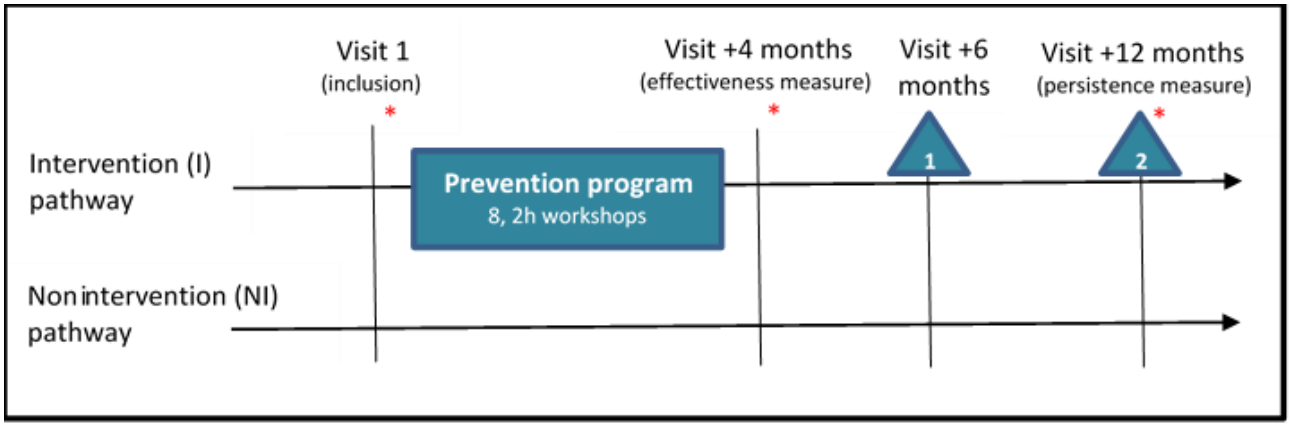


Table 1. Summary of the stages of the study.

	Visit 1 inclusion	+4 months	+6 months	+12 months
Information – consent	✓			
Sociodemographic data	✓			
Self-administered questionnaires	✓	✓	✓	✓
Blood and saliva collection (physio-biology and genetic)	✓	✓		✓
Emotional reactivity	✓	✓		✓
"Debriefing and anchoring of the practice" workshop			✓	✓

The first step is a briefing session with 2 of the Brigade's companies. Each individual will receive 2 information letters (1 regarding participation in this study, and 1 regarding participation in genetic studies), in order to allow time to reflect before the inclusion visit.

Visit 1: Inclusion

Inclusion will take place over a 3-week period. This time is needed to be able to disseminate information to the groups concerned and collect data. Once informed consent has been obtained, and eligibility criteria have been verified by one of the investigators, the following samples will be collected: (1) a 30-mL blood sample; (2) three 5-mL saliva samples (the participant will be asked to collect a sample on waking, getting up, and 30 minutes later [28]); (3) noninvasive measurements of cardiac variability and electrodermal conductance (using patches applied to the skin) during Stroop tasks, estimated to take 20 minutes; and (4) a psycho-cognitive evaluation (standardized and validated questionnaires). The latter will make it possible to evaluate the psychological and somatic symptoms (Patient Health Questionnaire [PHQ-15] [29]; psychosocial factors; Perceived Stress Scale [PSS] [30]; coping flexibility [20]; inner correspondence and peaceful harmony [ICPH] [31]; stigma and barriers to care [32]; Multidimensional Scale of Perceived Social Support [MSPSS] [33]; the Siebold vertical and horizontal cohesion questionnaire [34]; and the presence of any psychopathologies such as anxiety and depression: Hospital Anxiety and Depression Scale [HADS] [35,36], Posttraumatic Checklist-5 [PCL-5] [37], unsure, and Burnout Measure Short Version [BMS] [38,39]). The time required to fill out the questionnaires is estimated to be 45-60 minutes (184 items in total).

The Prevention Program: Workshops

Members of the intervention group will participate in 8 workshops. Each lasts 2 hours and is divided into three parts: (1) welcome participants with time allocated for inclusion (time approximately 20 minutes); (2) a presentation of the pedagogical objectives of the session, and its practical application; and (3) group wind-up (approximately 20 minutes). Please see Multimedia Appendix 1 for a description of the workshop program. At the end of the study, members of the nonintervention group, who wish to do so, will be able to benefit from the same prevention program during a later session, which will be scheduled as a function of operational constraints.

Visit +4 Months: Follow-up

A second round of data collection will take place at the end of the prevention program (approximately 4 months after inclusion). Each participant will be asked to allocate half a day to the collection of biopsychological measurements.

Visit +6 Months: Follow-up

Two months after the end of the program, during the first debriefing workshop, participants will be asked to complete a set of self-administered questionnaires (the same set as the one completed during the inclusion visit a part for the sociodemographic information).

Visit +12 Months: End of Study

Eight months after the end of the prevention program, each participant will take part in a final measurement session (lasting 2-3 hours). They will also be asked to allocate another half a day to the collection of biopsychological measurements.

Measurements recorded at +4 and +12 months are identical to those performed at inclusion, except for sociodemographic data, and the sample needed to assess vulnerability (genetic polymorphism).

Thus, all participants are required to attend 4 measurement sessions: visit 1, inclusion; +4 months; +6 months; and +12 months. During each of these visits, they will be asked to complete a self-administered (using a tablet) questionnaire to collect psychosocial data. In addition, at inclusion, +4 months, and +12 months, (1) biological samples will be collected for each participant (blood and saliva) and (2) activation of the autonomic nervous system (heart rate variability and electrodermal activity) will be measured at rest, during emotional activation (the classic, then the emotional Stroop task), and at recovery.

Outcomes

Primary End Point

There is no consensus in the literature regarding the definition of resilience, and there are references to several dimensions. Consequently, measuring the effect of the intervention on resilience requires the use of several indicators. A simple approach would be to measure PTSD symptomatology reported by participants, with the expectation that the intervention will result in a decrease in symptoms. Although this approach would be relevant for long-term measures [40], using this criterion in a short-term study, such as ours, would be restrictive and fail to support the processes that are assumed to be activated during the intervention [41]. The latter consists, in part, of removing barriers to seeking care when necessary, in order to support the building of resilience as a process, and not simply as a state. Our short-term approach is also justified by the difficulty of conducting studies in a military environment over the long term (personnel are transferred every 3 years) and attrition among professional soldiers.

The proposed composite criterion groups indicators of resilience that are described as protective factors for PTSD and are recognized to be sensitive to interventions. The first is the participant's emotional state. It is known to be highly impacted in PTSD, where there is an increase in negative emotions. At the same time, it is a marker of resilience in cases where emotions become positive following trauma. We will therefore use the Positive and Negative Affect Scale (PANAS) score [42], which measures the intensity of positive and negative emotional states. Our second indicator measures self-compassion, which refers to a general tendency to be kind to oneself, despite knowing one's failures and successes. Self-compassion is very directly linked to the process of self-acceptance and is a predictive criterion for both the development of PTSD (when it is deficient), and increased resilience (when stimulated by a psychotherapeutic intervention). Self-compassion also contributes to cognitive flexibility. Finally, the third indicator is the hardiness score. This measure is classically used in the literature to study, from a psychological point of view, an individual's ability to remain in good health under stressful conditions. It should be noted that this measure should not, by itself, be considered a sufficient criterion for resilience in our protocol, given that any modification is observed over the long term, based on a quasi-dispositional approach.

Consequently, the hardiness score will be combined with mood and self-compassion criteria. The composite criterion will be evaluated at 4 months (Figure 1). A change in resilience will be defined as favorable if at least two of the following three criteria are met: (1) a 20% improvement in the PANAS score; (2) given the military context, and the nonspecific nature of our intervention, a 20% improvement in scores on the Self-Compassion Scale; or (3) a 5% change in hardiness, measured using the Dispositional Resilience Scale (DRS-15) [43]. If these criteria are not met, any change will be considered to be unfavorable. The choice of thresholds for variables making up the composite criterion is based on data from research conducted by the project's teams.

Emotional State

The data based on the STEP study, carried out in the framework of Delphine Traber's thesis [24], show a 33.68% long-term increase in the PANAS score among members of the *Bataillon de Chasseurs Alpins* who had undergone training (pretraining score=12.32, posttraining score=15.21, and 6-month posttraining score=16.47). Thus, in the PREPAR study, we consider a 20% improvement as significant (for questionnaire details, see Multimedia Appendix 2 [42-44]).

Self-Compassion

According to Kotsou and Leys [44], the mean score is 2.88 in the French population. A score between 3.5 and 5.0 indicates a high level. Thus, in the context of this study, an increase of 20% (0.62) will be considered relevant (for questionnaire details see Multimedia Appendix 2).

Hardiness, the Ability to Stay Healthy Under Stressful Conditions

In the literature, global hardiness scores (measured by the DRS-15 scale) in military populations are around 29 (scores can range from 0 to 45). To the best of our knowledge, there are no studies that have evaluated the effect of a prevention program on this variable. Thus, as this is a dispositional measure, we consider a 5% increase as relevant (for questionnaire details see Multimedia Appendix 2).

Secondary End Points

The evaluation criteria used to meet the secondary objectives are provided in the following sections.

Objective 2.1: Vulnerability

We will assess the following regarding vulnerability:

1. Innate: based on a study of the polymorphism of genes involved in stress regulation mechanisms (see Multimedia Appendix 3). These analyses will not be used in a diagnosis.
2. Acquired: based on miRNAs that target regulatory phenomena established in earlier work (see Multimedia Appendix 4.
3. General psychological and somatic symptomatology (the PHQ-15, HADS, and PCL-5).

Objective 2.2: Change in Resilience

We will assess follow-up of the change in scores on composite end point questionnaires: PANAS, Self-Compassion Scale, and DRS-15 at 6 and 12 months after inclusion.

Objective 2.3: Change in Psychobiological Biomarkers of Activation and Deterioration

We will assess the following regarding change in physiobiological biomarkers of activation and deterioration:

1. Indirect markers of oxidative stress: lipoperoxidation markers thiobarbituric acid reactive substances and 8-iso-prostaglandin F2alpha [45,46].
2. Circulating markers of central nervous system activity: GABA, brain-derived neurotrophic factor, kynurenic acid, and dopamine [47-49].
3. Inflammation: proinflammatory cytokines (including C-reactive protein, TNF-alpha, IL23, and IL12), anti-inflammatories (IL10 and IL6), and chemokines [50,51].
4. Hypothalamic-pituitary-adrenal axis: cortisol (analysis of saliva on waking, getting up, and 30 minutes later), catecholamines, and neuropeptide Y [52].
5. Markers of physiological activation (autonomic nervous system): cardiac variability index (temporal, frequency, and nonlinear analysis of the electrocardiogram signal to measure indices of parasympathetic flexibility), and electrodermal conductance (level of tonic activity, and amplitude of phasic activity to assess activation of the sympathetic system and its persistence) [53,54].
6. Psychological: follow-up of perceived stress (Cohen questionnaire) and psychological symptomatology scores (the PCL-5, the HADS, and the BMS).

Objective 2.4: Change in Psychosocial Factors

We will assess the following regarding change in psychosocial factors:

1. Flexibility of coping strategies, Flex Cop [55].
2. Sense of duty, inner correspondence, and peaceful harmony (ICPH) questionnaire [31].
3. Emotional reactivity (scores on the emotional Stroop task are compared with the classic Stroop task before and after the intervention at 4 and 12 months) [56,57]. The aim of this task is to evaluate the flexibility of sympathetic and parasympathetic systems inherent in the emotional response to trauma. The classical Stroop task (baseline) will be followed by the emotional Stroop task (reactivity). No learning effect has been documented with using this experimental modality.
4. Self and public stigma scores of PTSD in the military.
5. Perceived social support (the multidimensional scale of perceived social support) [33], and institutional support (the Sieblod vertical and horizontal cohesion questionnaire).

Objective 2.5: Describe Changes in Adherence to the Intervention

Adherence will be assessed using quantitative criteria at 4, 6, and 12 months (the Treatment Motivation Questionnaire). This analysis will be based on (1) an analysis of the processes put in place to operationalize the intervention; (2) a focus group consisting of 8 participants, and 10 individual interviews carried out at 4 and 12 months after inclusion; and (3) a qualitative analysis of discussions that took place during workshops to anchor the practice held at 6 months and 1 year. The latter will also make it possible to identify both obstacles and drivers of adherence.

Objective 2.6: Describe User Satisfaction With the URGOfeel System

We will assess user satisfaction with the URGOfeel (Urgothech) application using visual analog scales, and short questionnaires that measure (1) the user experience and (2) its benefits.

Ancillary Study

We plan to run a qualitative analysis of the transferability of the intervention. The transferability assessment will be carried out at the very end of the research protocol (1 year after inclusion) and will use the transferability and support to the adaptation of health promotion interventions ASTAIRE tool. The aim is to facilitate the transfer of the intervention to other populations, both military and civilian. The intervention could then be tailored to other populations, based on this evaluation. The ancillary study will focus on qualitative details, notably the conditions, obstacles, and drivers facilitating the transferability of the intervention to other populations or other contexts. The criteria required by ASTAIRE will be supplemented by a qualitative evaluation based on interviews (n=20), and a focus group (n=8) at the end of the intervention. To limit bias, we will ensure that participants in the various segments of this ancillary study (ASTAIRE, focus groups, and interviews) are distinct from one another. A summary of the analysis of these criteria (qualitative, Astaire, and quantitative, in the long term) could be used as a guide for future deployments of the intervention.

Statistical Methods

Continuous variables will be presented as mean and SD, if the distribution is normal (the Shapiro-Wilk test will be used, if necessary). In case of a nonnormal distribution, data will be presented as median, quartiles, and extreme values. Scale variables will be treated as ordinal data and analyzed as above. Depending on the analysis, data may be classed as categorical variables. Categorical variables will be expressed as absolute values and percentages. To control for attrition, calculations will assume 20% of data are missing.

The primary analysis will examine the effectiveness of the prevention program. This will be evaluated by comparing the percentage of responses between intervention and nonintervention groups, using a χ^2 test. Secondary analyses will examine the abovementioned markers. Values for the intervention and the nonintervention group will be compared using a repeated measures ANOVA if the conditions for applying an ANOVA are met. Vulnerability will be initially identified using a cluster analysis of the measured biological variables (a *k*-means or Gaussian model mixture, depending on the distribution). The analysis will seek to identify the most biologically at-risk cluster (vulnerable compared with nonvulnerable). The effect of the intervention as a function of vulnerability status will be evaluated using repeated measures

ANOVA, by comparing vulnerable and nonvulnerable groups. Psychosocial variables will be compared between intervention and nonintervention groups using repeated measures ANOVA, if the conditions for its application are met. A regression analysis will aim to test the mediating role of psychosocial determinants in the improvement of the composite score.

Sample Size

The number of participants to be included is not based on an a priori calculation. This is due to the absence of data in the literature regarding the effectiveness of a primary prevention program in the military context, measured using a composite criterion that encompasses affect, self-compassion, and hardiness. In order to determine the sample size needed to observe a significant between-group difference, we used the following parameters: a 2-tailed statistical test; a 55% response rate in the intervention group; a 30% response rate in the nonintervention group (significance P=.50; power =0.80). If we take into account potential dropouts (estimated at 20%), each group should consist of 58 individuals, making a total of 116 participants.

Results

The project is currently ongoing, and results are expected to be published by the end of 2024.

Discussion

This project aims to evaluate an interventional research program for the primary prevention of occupational health problems. The program is as comprehensive as possible and synergistically links physiological, psychological, and social factors. We hope that the integration of biopsychosocial factors, which are suited to the characteristics of the occupational environment, will reinforce the effectiveness of current strategies. The project respects the three pillars of evidence-based prevention: (1) it investigates what is the best evidence and contributes to research-based knowledge; (2) it considers experiential knowledge; and (3) it takes into account the values, preferences, and characteristics of populations and individuals. This type of primary prevention intervention could provide a framework for other interventions that can be modified and adapted to different professional contexts. Data regarding transfer and feasibility collected during our study with operational military personnel could be used in further work to optimize the program for other army corps. Finally, it is imperative to stress that this study adopts an ecological approach, that is, it strives to reflect as closely as possible the real-life experiences of French army soldiers. This approach is essential to obtain information directly applicable to their daily routines and challenges. However, it is essential to recognize that there are potential limitations inherent in this approach, particularly with regard to adherence to the research protocol. Operational constraints within the military environment can sometimes override the ideal execution of the research program. These constraints may require adjustments to the protocol to ensure practicality and feasibility. For example, modifications in the number and frequency of workshops may be necessary to meet service needs and requirements, without compromising operationality. However, the encouraging exploratory results and the interest shown by the military personnel observed by Traber [24] mean that we can be confident that this study will provide a better understanding of the field of PTSD prevention in the military.

The research team is committed to maintaining the integrity of the study while adapting flexibly to these challenges, in order to obtain meaningful and relevant results that will contribute to the well-being and effectiveness of our soldiers in the French army.

Acknowledgments

The authors warmly thank officers and operational staff of the Mountain Infantry Brigade and, more specifically, the 4th company of the 3rd *Batallion de Chasseurs Alpins* and the 3rd company of the 7th *Bataillon de Chasseurs Alpins*. This work is supported by the French *Direction Générale de l'Armement*. The opinions or assertions expressed herein are the private views of the authors and are not to be considered as o cial, or as reflecting the views of the French Military Health Service.

Data Availability

The data sets generated during or analyzed during this study are not publicly available due to French Army data policy but are available from the French Military Health Service at dcssa-paris@sante.defense.gouv.fr upon request.

Authors' Contributions

SP, ELB, ETC, MH, MT, DC, and AMD were involved in the conception and design of the trial, and they were also responsible for obtaining ethics committee approval. SP, ELB, MMB, MH, MT, DC, and AMD wrote the paper. All the authors contributed to the refinement of the study protocol and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Workshop schedule.

[DOCX File , 18 KB - resprot_v13i1e47175_app1.docx]

Multimedia Appendix 2
Questionnaires used for the primary composite end point.
[DOCX File , 13 KB - resprot_v13i1e47175_app2.docx]

Multimedia Appendix 3
Genetic polymorphisms involved in stress regulation mechanisms studied in the project.
[DOCX File , 14 KB - resprot_v13i1e47175_app3.docx]

Multimedia Appendix 4
miRNAs targeting regulatory phenomena established by earlier work and studied in the project.
[DOCX File , 14 KB - resprot_v13i1e47175_app4.docx]

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorder. 5th Edition. Washington, DC: American Psychiatric Association; 2013.
2. Leray E, Camara A, Drapier D, Riou F, Bougeant N, Pelissolo A, et al. Prevalence, characteristics and comorbidities of anxiety disorders in France: results from the "Mental Health in General Population" survey (MHGP). Eur Psychiatry 2011;26(6):339-345. [doi: 10.1016/j.eurpsy.2009.12.001] [Medline: 20430592]
3. Ogle CM, Rubin DC, Siegler IC. Cumulative exposure to traumatic events in older adults. Aging Ment Health 2014;18(3):316-325 [FREE Full text] [doi: 10.1080/13607863.2013.832730] [Medline: 24011223]
4. Berger W, Coutinho ESF, Figueira I, Marques-Portella C, Luz MP, Neylan TC, et al. Rescuers at risk: a systematic review and meta-regression analysis of the worldwide current prevalence and correlates of PTSD in rescue workers. Soc Psychiatry Psychiatr Epidemiol 2012;47(6):1001-1011 [FREE Full text] [doi: 10.1007/s00127-011-0408-2] [Medline: 21681455]
5. Dunn AS, Julian T, Formolo LR, Green BN, Chicoine DR. Preliminary analysis of posttraumatic stress disorder screening within specialty clinic setting for OIF/OEF veterans seeking care for neck or back pain. J Rehabil Res Dev 2011;48(5):493-502 [FREE Full text] [doi: 10.1682/jrrd.2010.05.0104] [Medline: 21674400]
6. Kok BC, Herrell RK, Thomas JL, Hoge CW. Posttraumatic stress disorder associated with combat service in Iraq or Afghanistan: reconciling prevalence differences between studies. J Nerv Ment Dis 2012;200(5):444-450. [doi: 10.1097/NMD.0b013e3182532312] [Medline: 22551799]
7. Sundin J, Herrell RK, Hoge CW, Fear NT, Adler AB, Greenberg N, et al. Mental health outcomes in US and UK military personnel returning from Iraq. Br J Psychiatry 2014;204(3):200-207 [FREE Full text] [doi: 10.1192/bjp.bp.113.129569] [Medline: 24434071]
8. Judkins JL, Moore BA, Collette TL, Hale WJ, Peterson AL, Morissette SB. Incidence rates of posttraumatic stress disorder over a 17-year period in active duty military service members. J Trauma Stress 2020;33(6):994-1006. [doi: 10.1002/jts.22558] [Medline: 32598575]
9. Schulte-Herbrüggen O, Heinz A. Psychological trauma in soldiers-a challenge for the German Armed Forces (Bundeswehr). Dtsch Arztebl Int 2012;109(35-36):557-558 [FREE Full text] [doi: 10.3238/arztebl.2012.0557] [Medline: 23130088]
10. Kolassa IT, Ertl V, Eckart C, Kolassa S, Onyut LP, Elbert T. Spontaneous remission from PTSD depends on the number of traumatic event types experienced. Psychol Trauma Theory Res Pract 2010;2(3):169-174. [doi: 10.1037/a0019362]
11. Gurvits TV, Shenton ME, Hokama H, Ohta H, Lasko NB, Gilbertson MW, et al. Magnetic resonance imaging study of hippocampal volume in chronic, combat-related posttraumatic stress disorder. Biol Psychiatry 1996;40(11):1091-1099 [FREE Full text] [doi: 10.1016/S0006-3223(96)00229-6] [Medline: 8931911]
12. Bryant RA, Harvey AG. Posttraumatic stress in volunteer firefighters. predictors of distress. J Nerv Ment Dis 1995;183(4):267-271. [doi: 10.1097/00005053-199504000-00014] [Medline: 7714516]
13. Thurin JM. Limites de la médecine fondée sur des preuves et orientations actuelles : une nouvelle génération des recherches en psychothérapies. Article in French. Bulletin de Psychologie 2006;59(486):575-584 [FREE Full text] [doi: 10.3917/bupsy.486.0575]
14. Raza Z, Hussain SF, Ftouni S, Spitz G, Caplin N, Foster RG, et al. Dementia in military and veteran populations: a review of risk factors-traumatic brain injury, post-traumatic stress disorder, deployment, and sleep. Mil Med Res 2021;8(1):55 [FREE Full text] [doi: 10.1186/s40779-021-00346-z] [Medline: 34645526]
15. Jones JC, Barlow DH. The etiology of posttraumatic stress disorder. Clin Psychol Rev 1990;10(3):299-328 [FREE Full text] [doi: 10.1016/0272-7358(90)90064-h]
16. McEwen BS. Protection and damage from acute and chronic stress: allostasis and allostatic overload and relevance to the pathophysiology of psychiatric disorders. Ann N Y Acad Sci 2004;1032:1-7. [doi: 10.1196/annals.1314.001] [Medline: 15677391]

17. Rozanski A, Kubzansky LD. Psychologic functioning and physical health: a paradigm of flexibility. Psychosom Med 2005;67(Suppl 1):S47-S53. [doi: 10.1097/01.psy.0000164253.69550.49] [Medline: 15953801]
18. Brosschot JF, Gerin W, Thayer JF. The perseverative cognition hypothesis: a review of worry, prolonged stress-related physiological activation, and health. J Psychosom Res 2006;60(2):113-124. [doi: 10.1016/j.jpsychores.2005.06.074] [Medline: 16439263]
19. Brosschot JF, Verkuil B, Thayer JF. Conscious and unconscious perseverative cognition: is a large part of prolonged physiological activity due to unconscious stress? J Psychosom Res 2010;69(4):407-416. [doi: 10.1016/j.jpsychores.2010.02.002] [Medline: 20846542]
20. Kato T. Development of the coping flexibility scale: evidence for the coping flexibility hypothesis. J Couns Psychol 2012;59(2):262-273. [doi: 10.1037/a0027770] [Medline: 22506909]
21. Marshall EJ, Brockman RN. The relationships between psychological flexibility, self-compassion, and emotional well-being. J Cogn Psychother 2016;30(1):60-72. [doi: 10.1891/0889-8391.30.1.60] [Medline: 32755906]
22. Neff K. Self-compassion: an alternative conceptualization of a healthy attitude toward oneself. Self Identity 2003;2(2):85-101. [doi: 10.1080/15298860309032]
23. Friedman M, Higson-Smith C. Building psychological resilience: learning from the South African police service. In: Paton D, Violanti JM, Smith LM, editors. Promoting Capabilities to Manage Posttraumatic Stress: Perspectives on Resilience. Springfield, IL, US: Charles C Thomas Publisher; 2003:103-118.
24. Traber D. Comment prevenir le trouble de stress post traumatique? reflexion et application chez les professionnels à risques de la région auvergne rhône-alpes. 2019. URL: https://www.theses.fr/2019GREAS009 [accessed 2023-12-15]
25. Park CL, Folkman S. Meaning in the context of stress and coping. Rev Gen Psychol 1997;1(2):115-144. [doi: 10.1037/1089-2680.1.2.115]
26. St-Denis K. Entre reconnaissance sociale et cohérence personnelle. management des émotions chez les pompiers du Québec. Article in French. Reflets 2014;19(2):142-161. [doi: 10.7202/1021183ar]
27. Perceived Stigma and Barriers to Care for Psychological Treatment: Implications for Reactions to Stressors in Different Contexts. US: Guilford Publications; 2008.
28. Wilhelm I, Born J, Kudielka BM, Schlotz W, Wüst S. Is the cortisol awakening rise a response to awakening? Psychoneuroendocrinology 2007;32(4):358-366. [doi: 10.1016/j.psyneuen.2007.01.008] [Medline: 17408865]
29. Kroenke K, Spitzer RL, Williams JBW. The PHQ-15: validity of a new measure for evaluating the severity of somatic symptoms. Psychosom Med 2002;64(2):258-266. [doi: 10.1097/00006842-200203000-00008] [Medline: 11914441]
30. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav 1983;24(4):385-396. [Medline: 6668417]
31. Büssing A, Edelhäuser F, Weisskircher A, Fouladbakhsh JM, Heusser P. Inner correspondence and peacefulness with practices among participants in eurythmy therapy and yoga: a validation study. Evid Based Complement Alternat Med 2011;2011:329023 [FREE Full text] [doi: 10.1155/2011/329023] [Medline: 20953427]
32. Britt TW, Jennings KS, Cheung JH, Pury CLS, Zinzow HM. The role of different stigma perceptions in treatment seeking and dropout among active duty military personnel. Psychiatr Rehabil J 2015;38(2):142-149. [doi: 10.1037/prj0000120] [Medline: 25799296]
33. Zimet GD, Dahlem NW, Zimet SG, Farley GK. The Multidimensional Scale of Perceived Social Support. J Pers Assess 1988;52(1):30-41. [doi: 10.1207/s15327752jpa5201_2]
34. Siebold GL. The essence of military group cohesion. Armed Forces Soc 2016;33(2):286-295. [doi: 10.1177/0095327x06294173]
35. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 2007;67(6):361-370. [doi: 10.1111/j.1600-0447.1983.tb09716.x]
36. Bocéréan C, Dupret E. A validation study of the Hospital Anxiety and Depression Scale (HADS) in a large sample of French employees. BMC Psychiatry 2014;14:354 [FREE Full text] [doi: 10.1186/s12888-014-0354-0] [Medline: 25511175]
37. Ashbaugh AR, Houle-Johnson S, Herbert C, El-Hage W, Brunet A. Psychometric validation of the English and French versions of the posttraumatic stress disorder checklist for DSM-5 (PCL-5). PLoS One 2016;11(10):e0161645 [FREE Full text] [doi: 10.1371/journal.pone.0161645] [Medline: 27723815]
38. Lourel M, Gueguen N, Mouda F. L'évaluation du burnout de Pines: adaptation et validation en version Française de l'instrument Burnout Measure Short version (BMS-10). Article in French. Prat Psychol 2007;13(3):353-364 [FREE Full text] [doi: 10.1016/j.prps.2007.06.001]
39. Malach-Pines A. The Burnout Measure, Short Version. Int J Stress Management 2005;12(1):78-88. [doi: 10.1037/1072-5245.12.1.78]
40. Biggs QM, Ursano RJ, Wang J, Krantz DS, Carr RB, Wynn GH, et al. Daily variation in post traumatic stress symptoms in individuals with and without probable post traumatic stress disorder. BMC Psychiatry 2019;19(1):56 [FREE Full text] [doi: 10.1186/s12888-019-2041-7] [Medline: 30717731]
41. Palmer L, Norton S, Rona RJ, Fear NT, Stevelink SAM. The evolution of PTSD symptoms in serving and ex-serving personnel of the UK armed forces from 2004 to 16: a longitudinal examination. J Psychiatr Res 2023;157:18-25. [doi: 10.1016/j.jpsychires.2022.11.007] [Medline: 36436424]

42. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. J Pers Soc Psychol 1988;54(6):1063-1070. [doi: 10.1037//0022-3514.54.6.1063] [Medline: 3397865]
43. Bartone PT. Test-retest reliability of the Dispositional Resilience Scale-15, a brief hardiness scale. Psychol Rep 2007;101(3 Pt 1):943-944. [doi: 10.2466/pr0.101.3.943-944] [Medline: 18232452]
44. Kotsou I, Leys C. Self-Compassion Scale (SCS): psychometric properties of the French translation and its relations with psychological well-being, affect and depression. PLoS One 2016;11(4):e0152880 [FREE Full text] [doi: 10.1371/journal.pone.0152880] [Medline: 27078886]
45. Schuch FB, Vasconcelos-Moreno MP, Borowsky C, Zimmermann AB, Wollenhaupt-Aguiar B, Ferrari P, et al. The effects of exercise on oxidative stress (TBARS) and BDNF in severely depressed inpatients. Eur Arch Psychiatry Clin Neurosci 2014;264(7):605-613. [doi: 10.1007/s00406-014-0489-5] [Medline: 24487616]
46. Dimopoulos N, Piperi C, Psarra V, Lea RW, Kalofoutis A. Increased plasma levels of 8-iso-PGF2alpha and IL-6 in an elderly population with depression. Psychiatry Res 2008;161(1):59-66. [doi: 10.1016/j.psychres.2007.07.019] [Medline: 18783834]
47. Trousselard M, Claverie D, Fromage D, Becker C, Houël JG, Benoliel JJ, et al. The relationship between allostasis and mental health patterns in a pre-deployment French military cohort. Eur J Investig Health Psychol Educ 2021;11(4):1239-1253 [FREE Full text] [doi: 10.3390/ejihpe11040090] [Medline: 34698145]
48. Trousselard M, Lefebvre B, Caillet L, Andruetan Y, de Montleau F, Denis J, et al. Is plasma GABA level a biomarker of post-traumatic stress disorder (PTSD) severity? a preliminary study. Psychiatry Res 2016;241:273-279. [doi: 10.1016/j.psychres.2016.05.013] [Medline: 27208514]
49. Francis HM, Stevenson RJ, Tan LSY, Ehrenfeld L, Byeon S, Attuquayefio T, et al. Kynurenic acid as a biochemical factor underlying the association between Western-style diet and depression: a cross-sectional study. Front Nutr 2022;9:945538 [FREE Full text] [doi: 10.3389/fnut.2022.945538] [Medline: 36299996]
50. Scheller J, Chalaris A, Schmidt-Arras D, Rose-John S. The pro- and anti-inflammatory properties of the cytokine interleukin-6. Biochim Biophys Acta 2011;1813(5):878-888 [FREE Full text] [doi: 10.1016/j.bbamcr.2011.01.034] [Medline: 21296109]
51. Xing Z, Gauldie J, Cox G, Baumann H, Jordana M, Lei XF, et al. IL-6 is an antiinflammatory cytokine required for controlling local or systemic acute inflammatory responses. J Clin Invest 1998;101(2):311-320 [FREE Full text] [doi: 10.1172/JCI1368] [Medline: 9435302]
52. Morales-Medina JC, Dumont Y, Quirion R. A possible role of neuropeptide Y in depression and stress. Brain Res 2010;1314:194-205. [doi: 10.1016/j.brainres.2009.09.077] [Medline: 19782662]
53. Ghiasi S, Greco A, Barbieri R, Scilingo EP, Valenza G. Assessing autonomic function from electrodermal activity and heart rate variability during cold-pressor test and emotional challenge. Sci Rep 2020;10(1):5406 [FREE Full text] [doi: 10.1038/s41598-020-62225-2] [Medline: 32214158]
54. NA. Heart rate variability: standards of measurement, physiological interpretation and clinical use. task force of the European society of cardiology and the North American Society of Pacing and Electrophysiology. Circulation 1996;93(5):1043-1065. [Medline: 8598068]
55. Bonanno GA, Pat-Horenczyk R, Noll J. Coping flexibility and trauma: the Perceived Ability to Cope with Trauma (PACT) scale. Psychol Trauma 2011;3(2):117-129. [doi: 10.1037/a0020921]
56. Sagaspe P, Sanchez-Ortuno M, Charles A, Taillard J, Valtat C, Bioulac B, et al. Effects of sleep deprivation on color-word, emotional, and specific stroop interference and on self-reported anxiety. Brain Cogn 2006;60(1):76-87. [doi: 10.1016/j.bandc.2005.10.001] [Medline: 16314019]
57. Renaud P, Blondin JP. The stress of Stroop performance: physiological and emotional responses to color-word interference, task pacing, and pacing speed. Int J Psychophysiol 1997;27(2):87-97. [doi: 10.1016/s0167-8760(97)00049-4] [Medline: 9342640]

Abbreviations

BMS: Burnout Measure Short Version
DRS-15: Dispositional Resilience Scale
HADS: Hospital Anxiety and Depression Scale
ICPH: inner correspondence and peaceful harmony
MSPSS: Multidimensional Scale of Perceived Social Support
OPEX: external operation
PANAS: Positive and Negative Affect Scale
PCL-5: Posttraumatic Checklist-5
PHQ-15: Patient Health Questionnaire
PREPAR: Primary Prevention of Posttraumatic Stress Disorder in Military Professionals
PSS: Perceived Stress Scale
PTSD: posttraumatic stress disorder
TE: traumatic event

Edited by A Mavragani; submitted 10.03.23; peer-reviewed by C Gissel, S Markham, S Ekblad; comments to author 10.08.23; revised version received 26.09.23; accepted 27.09.23; published 26.01.24.

Please cite as:
Le Barbenchon E, Trousselard M, Pellissier S, Moisseron-Baudé M, Chachignon P, Bouny P, Touré Cuq E, Jacob S, Vigier C, Hidalgo M, Claverie D, Duffaud AM
Implementation of a Primary Prevention Program for Posttraumatic Stress Disorder in a Cohort of Professional Soldiers (PREPAR): Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2024;13:e47175
URL: https://www.researchprotocols.org/2024/1/e47175
doi:10.2196/47175
PMID:38277204

Protocol

Investigation of the Association Between e-Cigarette Smoking and Oral Mucosal Health Status Among Young People: Protocol for a Case-Control Trial

Siyuan Cheng[1], MD

Massachusetts College of Pharmacy and Health Sciences, Boston, MA, United States

Corresponding Author:
Siyuan Cheng, MD
Massachusetts College of Pharmacy and Health Sciences
179 Longwood Avenue
Boston, MA, 02115
United States
Phone: 1 617 732 2850
Email: m0496197@stu.mcphs.edu

Abstract

Background: Given the paucity of current safety studies related to e-cigarettes, there are no definitive studies on whether e-cigarettes cause oral mucosal lesions or even oral cancer. Although it is still undetermined whether e-cigarettes are harmless, an increasing number of teenagers choose to smoke e-cigarettes and believe that they are not harmful to the human body.

Objective: This aims to determine whether e-cigarettes cause damage to the oral mucosa. This study also aims to evaluate the association between e-cigarette smoking and oral mucous membrane lesions in young adults. The objectives are to (1) compare the oral mucosal conditions in participants with and without e-cigarette smoking habits, (2) assess the effect of the amount of e-cigarette smoking on oral mucosal conditions, and (3) assess the effect of the duration of e-cigarette smoking on oral mucosal conditions.

Methods: In this prospective study, 304 youths aged 15 to 24 years (n=152, 50% who smoke only e-cigarettes and n=152, 50% who do not smoke e-cigarettes or cigarettes) will be divided into 2 groups for a controlled study. Whether e-cigarettes cause oral mucosal lesions will be verified by comparing the odds of oral mucosal lesions in the 2 experimental groups. For this experiment, the predefined power is 80% (P=.04), and the predefined proportions of groups 1 and 2 are 11% and 2.5%, respectively.

Results: This experiment is at the conceptualization phase and has not yet been carried out. Experimenters have not been recruited and no data have been collected.

Conclusions: e-Cigarettes are still an unfamiliar topic to the public, and it is still unknown whether they can cause damage to the oral mucosa. This experiment aims to find out whether there is a link between the 2. There are still many limitations in this study, such as the lack of categorization of e-cigarettes and the lack of testing methods for oral mucosal status. These limitations are expected to be addressed in the future as the experiment is formally conducted and further optimized.

International Registered Report Identifier (IRRID): PRR1-10.2196/53644

(JMIR Res Protoc 2024;13:e53644) doi:10.2196/53644

KEYWORDS

oral mucosal lesions; e-cigarette; youth; oral; moth; lesion; lesions; cigarette; cigarettes; smoker; smoking; smokers; smoke; mucosa; mucosal; dental; dentist; dentistry

Introduction

Background

Oral cavity cancer is the most prevalent head and neck malignancy worldwide [1,2]. This malignant phenotype is often associated with habitual and lifestyle factors, such as tobacco smoking, excessive alcohol consumption, betel nut chewing, and low intake of fruits and vegetables [1]. Due to restrictive government policies and proven negative health effects in many parts of the world, the use of tobacco has declined in recent decades [3]. Electronic cigarettes (e-cigarettes) were invented by a Chinese pharmacist, Hon Lik, in 2003, who envisioned that they would replace conventional cigarettes due to their

deleterious effects [4]. e-Cigarette companies claim that handheld devices can provide smokers with the same experience as conventional cigarettes while reducing their negative effects. e-Cigarettes were introduced with the hope that the smoking population would gradually stop using conventional cigarettes and switch to e-cigarettes. With the waning consumption of regular cigarettes, the use of e-cigarettes has surged worldwide, indicating that smokers now consider e-cigarettes viable replacements. Moreover, recent data have indicated that e-cigarette smoking practices are more common among teenagers and young adults [5,6]. However, most people do not take this soaring statistic seriously and allow young people to use e-cigarettes freely. Most people believe that the health hazards of smoking only manifest with increasing age and, thus, concern is unnecessary regarding the use of e-cigarettes by young people.

It is no surprise that young adults are the primary habitual e-cigarette users. The portability of the devices, different flavors with less nicotine, and convenient use of e-cigarettes make them appealing to young people. Data from the 2011-2018 National Youth Tobacco Survey in the United States demonstrated that e-cigarette use among high school students increased from 1.5% in 2011 to 20.8% in 2018 [3]. In 2022, the Centers for Disease Control and Prevention indicated that 2.55 million US middle and high school students reported current (past 30 days) e-cigarette use; nearly 85% of these young people used flavored e-cigarettes, and more than half used disposable e-cigarettes [7]. This increase has also become noticeable in community settings. Unfortunately, adults do not pay enough attention to the use of e-cigarettes, especially in schools.

Current research on e-cigarettes has solely focused on their ingredients and compared satisfaction levels of e-cigarettes with those of regular cigarettes [8,9]. The safety of e-cigarettes, especially regarding the etiology of oral and maxillofacial diseases or other possible intraoral side effects, is still unclear. Moreover, few studies have reported on the adverse effects of e-cigarette smoking [10]. Recent experiments have only indicated that the use of e-cigarettes could impact the balance in the oral microbiome while allowing for the rapid growth of foreign microorganisms [4]. Nevertheless, many studies recommend that individuals replace cigarettes with e-cigarettes irrespective of concerns about their safety.

Smoking causes damage to the oral mucosa as well as lesions that can lead to the progressive development of oral cancer [11]. According to research, smoking can cause “oral mucosal leukoplakia” and a variety of other oral mucosal diseases. Additionally, it has been shown that leukoplakia is the oral mucosal lesion that is most likely to lead to oral cancer [12]. Most of the white spots on the lips occur on the lower lip, in the junction of the middle, and on the outer third of the lip, which is where people usually hold cigarettes; this can explain the relationship between holding cigarettes and white spots on the lip. White spots are precancerous lesions, and approximately 4% to 7% can develop into oral cancer. According to statistics, 93.1% of patients with oral white spots are smokers [13]. The development of oral mucosal lesions is based on the principle that tobacco irritates the oral mucosa (through cigarette smoke and the chemicals in cigarettes), causing it to react adversely to prolonged irritation. e-Cigarettes operate in a similar way to tobacco, which also irritates the oral mucosa through atomization and chemicals.

The only difference between e-cigarettes and cigarettes is simply that e-cigarettes do not contain tar; both contain many chemicals as well as nicotine. e-Cigarettes tend to have more types of chemicals than cigarettes because of the wide variety of flavors.

Given that it is still unknown whether e-cigarettes influence the development of oral mucosal lesions, the possibility that e-cigarettes can cause damage to the oral mucosa and increase the risk of oral cancer similar to tobacco needs to be studied.

To date, no definite investigation of the association between e-cigarettes and oral cavity cancer has been conducted. When available, this study will be the first to determine whether e-cigarettes are mechanistically linked to the development of oral cancer to further educate young users and students on the potential for malignancy due to e-cigarette use. It is assumed that e-cigarettes cause damage to the oral mucosa and oral cancer, which is similar to cigarettes. The following experimental studies and designs will be conducted to test this hypothesis. Therefore, this study aims to investigate the association between e-cigarette smoking and oral mucosal health status among young adults and determine whether e-cigarettes cause damage to the oral mucosa and increase the risk of oral cancer. Compared to that of other similar studies, the methodology of this study is simpler, and the results will be clearly comparable. If the results show that e-cigarettes can cause damage to the oral mucosa similar to that caused by cigarettes, this study could provide strong support for subsequent experiments to determine whether e-cigarettes cause oral cancer.

Hypothesis

This study hypothesizes that e-cigarettes, in the speculated absence of tobacco, may still induce carcinogenesis. Alternatively, it is suggested that this habit may trigger an imbalance in the oral microbiome that predisposes the mucosal epithelium to oral cavity cancer with other etiological factors. This presupposed risk is likely proportional to the frequency and duration of e-cigarette smoking. The oral mucosal health of participants will be determined by determining the presence of white spots in the mouth (the main feature of the oral mucosa that is damaged by smoking behavior).

Primary Outcome

The primary outcome is the effect of e-cigarette smoking on oral mucosal conditions.

Research Significance

The results of this study will provide preliminary evidence of the malignant potential of e-cigarettes in the deterioration of oral mucosal conditions or exclude them as a cause of oral carcinogenesis. If a direct association is observed, the results of this study would be vital to inform e-cigarette users of the harmful and even carcinogenic nature of e-cigarette smoking, despite e-cigarettes being considered tobacco free. In addition, this would help guide the implementation of legislative policies to bring awareness to the additional risks associated with the use of e-cigarettes and vaporizers. Moreover, these findings, if

positive, will pave the way for future research on chemical products that may be present in e-cigarettes that are directly involved in the malignant transformation of oral keratinocytes.

Methods

Trial Registration

Given that this study is at this stage of conceptualization and has received no support or sponsorship from any organization at this time, this experiment has not yet been applied for trial registration. The registration will be done in the future when support is received from the relevant organizations.

Ethical Considerations

This study has not yet been submitted to the ethical review board for assessment, mainly due to lack of financial support and lack of assistance from large organizations. We emphasize that this is an independent study and is still at the research protocol stage. As the project has not received sufficient financial support, we are unable to cover the costs of applying for evaluation by the ethics review committee at this time. At this stage, we are working to ensure that the study design meets ethical standards and will seek possible review and approval at a future stage. We understand and value participant rights and will take appropriate measures to ensure the ethical and legal nature of the study.

Study Design

The adoption of a case-control, prospective, observational study design is motivated by the relatively low incidence of oral mucosal lesions within the general population. This design allows for a focused exploration of the relationship between e-cigarette smoking and oral mucosal health.

Case-control design is particularly suitable for investigating rare outcomes such as oral mucosal lesions, as it efficiently compares individuals with the outcome of interest (cases) to those without (controls).

A prospective design involves following participants over time, allowing for the collection of data on exposures and outcomes as they occur. By prospectively tracking participants, the study can gather real-time information on e-cigarette smoking habits and observe the development of oral mucosal lesions, providing a temporal sequence crucial for establishing causation.

An observational design is chosen over an experimental one due to ethical considerations and the nature of the research question. Since randomly assigning participants to smoke e-cigarettes for an extended period is ethically challenging, an observational approach allows for the examination of naturally occurring exposure to e-cigarette smoking in real-world settings.

The low incidence of oral mucosal lesions in the general population necessitates a design that efficiently targets and investigates this specific outcome. By focusing on a population at risk (e-cigarette smokers) and carefully selecting controls, the study maximizes its ability to detect and understand the potential impact of e-cigarette smoking on oral mucosal health.

Study Population

According to the United Nation definition, people between the ages of 15 and 24 years are defined as young people [14]. This age group coincides with the rapidly growing population of e-cigarette smokers, which is not a concern to mainstream society. Therefore, the 15- to 24-year-old group has been selected as the study population. American participants between 15 and 24 years of age will be recruited irrespective of their sex, race, occupation type, and socioeconomic status and divided into “e-cigarette case” and “control” groups. The selection criteria for each group are as follows.

The exclusion criteria for the two groups (the following criteria will be applicable in both groups and do not need to be listed repeatedly) are (1) participants with histologically diagnosed recurrent oral cavity cancer whose primary tumors occurred outside the recruitment timeframe (2 years before the first diagnosis); (2) participants with synchronous solid or hematological malignancies in other regions at the time of oral cavity cancer diagnosis; (3) participants with a genetic predisposition to oral cavity cancer, including those with Fanconi anemia, systemic lupus erythematosus, and dyskeratosis congenita; (4) participants who meet the inclusion criteria but are unwilling to participate in the study after detailed information has been provided; and (5) participants with severely debilitating systemic conditions that preclude participation in the study.

Selection of the “e-Cigarette Case” Group

Inclusion Criteria

A prospective study among experimental participants who smoked e-cigarettes over the last 210 days or 7 months will be conducted. According to the article “Effects of Duration of Electronic Cigarette Use,” the average duration of use among e-cigarette smokers is 210 days or 6.8 months [15]. The same criteria will be used in this study to standardize the duration of use for both the conventional cigarette smoking population and the e-cigarette smoking population.

Exclusion Criterion

The exclusion criterion is participants who smoke tobacco.

Selection of Controls

Inclusion criteria are individuals without a history of smoking e-cigarettes, drinking alcohol, and smoking tobacco at the time of recruitment.

Exclusion criteria are participants who smoke e-cigarettes and tobacco.

Recruitment Strategy

Overview

The recruitment strategy, targeting customers at e-cigarette stores and pedestrians, is strategically aligned with the study’s focus on e-cigarette users. The inclusion of community selection for matching controls, if quotas are not met, demonstrates flexibility in the recruitment approach. The disclosure of convenience and nonprobability sampling methods ensures transparency, thereby acknowledging the limitations inherent

in these methods. A nuanced understanding of participant selection challenges is crucial for the accurate interpretation of study findings.

Community Selection Details

If quotas for controls are not met through the initial recruitment strategy, a community selection approach will be considered. This involves identifying and recruiting controls from community settings, ensuring a diverse representation.

Clinical Recruitment Procedures

e-Cigarette Store Recruitment

The e-cigarette store recruitment consists of 3 stages, which are as follows:

1. Approach: e-cigarette stores will be approached to seek their cooperation in the recruitment process.
2. Informed consent: store owners and managers will be provided with detailed information about the study objectives, procedures, and ethical considerations. Upon agreement, consent forms may be obtained from the store owners to allow recruitment on their premises.
3. Participant identification: e-cigarette users within the specified age range will be approached, and the study will be explained to them. Interested individuals will be given detailed information about the study and their consent will be sought.

Pedestrian Recruitment

The pedestrian recruitment consists of 2 stages, which are as follows:

1. Approach: pedestrians in high-traffic areas will be approached with an invitation to participate in the study.
2. Informed consent: similar to the e-cigarette store recruitment, detailed information will be provided to potential participants, and consent will be obtained before proceeding with any study-related activities.

Community Selection (if Necessary)

If quotas for controls are not met through the initial recruitment strategy, community selection may be considered.

1. Approach: community settings such as local community centers or public spaces will be identified. Consent from relevant authorities and community leaders will be sought.
2. Participant identification: controls meeting the study criteria will be approached in these settings, and recruitment will follow the same informed consent procedures.

Sampling Methods

Convenience and nonprobability sampling methods will be used for the recruitment of cases and controls. The detailed sample size determination is shown in Multimedia Appendix 1 [16]. Briefly, the predefined power is 80% (P=.04), and the predefined proportions of the case and controlled groups are 11% and 2.5%, respectively. In all, 304 youths aged 15 to 24 years (n=152, 50% who smoke only e-cigarettes and n=152, 50% who do not smoke e-cigarettes or cigarettes) will be recruited.

Data Collection: Questionnaire

Interviewer-administered questionnaires will be used to collect data on demographic, lifestyle, and socioeconomic variables for the cases and controls. The questionnaire tool will comprise 2 parts: exposure information (part A) and sociodemographic information (part B). A life grid sheet will be used during interviews to efficiently collect retrospective information on lifestyle habits and other risk factors. To reduce observer bias, interviewers will not initially be informed about the aim of the research. Once cases are identified and interviewed, matching controls will be recruited and interviewed. Answers provided by participants will be converted to objective scores after data collection by the investigator (SC). The details on the parts of the questionnaire are as follows.

Exposure information (part A) will include (1) oral mucosal health status (whether white spots are present), (2) smoking habits, (3) type of products used, (4) e-cigarette smoking status (yes or no and current or previous), (5) age of onset, (6) duration of smoking, (7) pattern of smoking duration (continuous or intermittent), (8) frequency of smoking (daily, weekly, and occasionally), (9) number of cartridges (frequency), and (10) Tobacco consumption. Sociodemographic information (part B) will include (1) age, (2) sex, (3) occupation type, (4) education level, (5) income, and (6) ethnicity.

Questionnaire Validity and Reliability

Before the deployment of the questionnaire for field use, face validity and qualitative content validity will be determined by a panel of experts in oral and maxillofacial surgery, dental public health, biostatistics, and laypersons. The internal consistency of the scales used to measure e-cigarette smoking exposure will be determined using Cronbach α, with a minimum α value of .70 indicating good and acceptable reliability.

Data Analysis

Descriptive statistics will be used for all binary, categorical, and continuous variables and expressed as tables, texts, and figures. Bivariate analysis will then be performed for relevant variables. The Shapiro-Wilks test will be performed for continuous variables to determine whether they follow the Gaussian distribution. Afterward, the independent 1-tailed t test and 1-way ANOVA will be used; otherwise, the Mann-Whitney U test and Kruskal-Wallis test will be performed. For cross-tabulation of 2 categorical variables, the chi-square test will be used. Variables that do not fulfill the assumption of this test will be analyzed using Fisher exact test. Comparisons with P=20 will be used to implement multivariable analysis using multiple logistic regression. Odds ratios and 95% CIs will be determined for e-cigarette smoking and other individual factors. For all analyses, P<.05 will be used to denote statistical significance. Statistical analyses will be performed using the SPSS (version 27; IBM Corp).

The control and e-cigarette groups will be subjected to a t test (assuming the data meet the normality criteria and do not meet the criteria for the rank sum test) to verify whether e-cigarettes cause harm.

Results

This experiment is at the conceptualization phase and has not yet been carried out. Experimenters have not been recruited and no data have been collected.

Discussion

In examining the potential negative impact of e-cigarettes on the oral mucosa, this study deliberately focused its investigation on this specific aspect, excluding other potential confounding factors that might influence the results. Notably, variables such as alcohol consumption, daily routines, and gender differences were not considered in the experimental design. While these factors were omitted from this study, they were duly documented in the questionnaire phase, laying the groundwork for future investigations to delve into these variables. This strategic choice aimed to isolate the primary relationship between e-cigarette use and oral mucosal health, with the intention to refine and expand the scope in subsequent research endeavors.

The findings of this study align with existing literature on e-cigarettes, which suggests a correlation between the chemicals present in e-cigarettes and cytotoxicity, leading to damage to the oral mucosa. This corroborates with prior research, providing further evidence of the potential harm associated with e-cigarette use [10,16,17]. The recognition of this association holds significant implications for public health, emphasizing the need for awareness campaigns and regulatory measures to mitigate the adverse effects on oral health. Moreover, the study acknowledges the diverse landscape of e-cigarettes in the United States, encompassing various brands and flavors, each containing distinct chemical compositions. Given this complexity, it is acknowledged that the study does not comprehensively analyze all individual chemicals present in different e-cigarettes. This limitation prompts a call for future experiments to undertake a more nuanced examination of the diverse chemical profiles within e-cigarettes to better understand their distinct impacts on oral mucosal tissues.

Despite the valuable insights provided by this study, certain limitations should be acknowledged. The decision to exclude factors such as alcohol consumption and daily routines may have implications for the generalizability of the findings. In addition, the complexity of e-cigarette compositions poses a challenge, as the study did not extensively investigate the myriad chemicals present in different e-cigarette products. Future research endeavors should consider a more comprehensive approach, encompassing a broader range of variables and a detailed analysis of the chemical constituents of various e-cigarettes.

In conclusion, this study contributes valuable evidence to the growing body of knowledge on the potential negative impact of e-cigarettes on oral mucosal health. By focusing on a specific aspect while recognizing its limitations, this research paves the way for future investigations to build upon these findings. The implications extend beyond the immediate scope of oral health, emphasizing the broader need for public health interventions and regulatory measures in response to the evolving landscape of e-cigarette use.

Data Availability

Data sharing is not applicable to this paper as no data sets were generated or analyzed during this study.

Authors' Contributions

SC was in charge of the study conceptualization, writing and reviewing the original draft, and editing the final draft.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Sample size determination.
[DOCX File , 15 KB - resprot_v13i1e53644_app1.docx]

References

1. Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral Oncol 2009;45(4-5):309-316. [doi: 10.1016/j.oraloncology.2008.06.002] [Medline: 18804401]
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71(3):209-249 [FREE Full text] [doi: 10.3322/caac.21660] [Medline: 33538338]
3. WHO launches new report on global tobacco use trends. World Health Organization. Geneva, Switzerland; 2019. URL: https://www.who.int/news/item/19-12-2019-who-launches-new-report-on-global-tobacco-use-trends [accessed 2024-01-05]
4. Guardian T. Hon Lik invented the e-cigarette to quit smoking—but now he's a dual user. The Guardian. 2015. URL: https://www.theguardian.com/society/2015/jun/09/hon-lik-e-cigarette-inventor-quit-smoking-dual-user [accessed 2024-01-05]
5. Jiang N, Cleland CM, Wang MP, Kwong A, Lai V, Lam TH. Perceptions and use of e-cigarettes among young adults in Hong Kong. BMC Public Health 2019;19(1):1123 [FREE Full text] [doi: 10.1186/s12889-019-7464-z] [Medline: 31420031]

6. Teens are 16 times more likely to use JUUL than older age groups. Truth Initiative. 2018. URL: https://truthinitiative.org/research-resources/emerging-tobacco-products/teens-are-16-times-more-likely-use-juul-older-age [accessed 2024-01-05]
7. More than 2.5 million youth reported e-cigarette use in 2022. Centers for Disease Control and Prevention. Atlanta, Georgia; 2022. URL: https://www.cdc.gov/media/releases/2022/p1007-e-cigarette-use.html [accessed 2024-01-05]
8. Huang J, Feng B, Weaver SR, Pechacek TF, Slovic P, Eriksen MP. Changing perceptions of harm of e-Cigarette vs cigarette use among adults in 2 US National Surveys from 2012 to 2017. JAMA Netw Open 2019;2(3):e191047 [FREE Full text] [doi: 10.1001/jamanetworkopen.2019.1047] [Medline: 30924893]
9. Pulvers K, Nollen NL, Rice M, Schmid CH, Qu K, Benowitz NL, et al. Effect of pod e-cigarettes vs cigarettes on carcinogen exposure among African American and Latinx smokers: a randomized clinical trial. JAMA Netw Open 2020;3(11):e2026324 [FREE Full text] [doi: 10.1001/jamanetworkopen.2020.26324] [Medline: 33206193]
10. Marques P, Piqueras L, Sanz M. An updated overview of e-cigarette impact on human health. Respir Res 2021;22(1):151 [FREE Full text] [doi: 10.1186/s12931-021-01737-5] [Medline: 34006276]
11. Jiang X, Wu J, Wang J, Huang R. Tobacco and oral squamous cell carcinoma: a review of carcinogenic pathways. Tob Induc Dis 2019;17:29 [FREE Full text] [doi: 10.18332/tid/105844] [Medline: 31582940]
12. Onda T, Hayashi K, Katakura A, Takano M. Oral leukoplakia and oral cancer. Cleve Clin J Med 2023;90(2):79-80 [FREE Full text] [doi: 10.3949/ccjm.90a.22044] [Medline: 36724918]
13. A Cigarette in Your Mouth is Damaged—Tobacco Control Column Qilu Hospital of Shandong University. 2012. URL: http://www.qiluhospital.com/show-52017165-1.html [accessed 2024-01-05]
14. Youth. United Nations. URL: https://www.un.org/en/global-issues/youth [accessed 2024-01-05]
15. Lechner WV, Tackett AP, Grant DM, Tahirkheli NN, Driskill LM, Wagener TL. Effects of duration of electronic cigarette use. Nicotine Tob Res 2015;17(2):180-185 [FREE Full text] [doi: 10.1093/ntr/ntu061] [Medline: 24827788]
16. Kumar S, Muniyandi M. Tobacco use and oral leukoplakia: cross-sectional study among the Gond tribe in Madhya Pradesh. Asian Pac J Cancer Prev 2015;16(4):1515-1518 [FREE Full text] [doi: 10.7314/apjcp.2015.16.4.1515] [Medline: 25743823]
17. Behar RZ, Wang Y, Talbot P. Comparing the cytotoxicity of electronic cigarette fluids, aerosols and solvents. Tob Control 2018;27(3):325-333 [FREE Full text] [doi: 10.1136/tobaccocontrol-2016-053472] [Medline: 28596276]

Edited by A Mavragani; submitted 13.10.23; peer-reviewed by S Gorthy; comments to author 10.11.23; revised version received 30.12.23; accepted 02.01.24; published 26.01.24.

Please cite as:
Cheng S
Investigation of the Association Between e-Cigarette Smoking and Oral Mucosal Health Status Among Young People: Protocol for a Case-Control Trial
JMIR Res Protoc 2024;13:e53644
URL: https://www.researchprotocols.org/2024/1/e53644
doi:10.2196/53644
PMID:38171545

Protocol

An Individual Music Intervention for Adults With Intellectual Disabilities and Challenging Behavior: Protocol for a Randomized Controlled Trial

Gerianne Smeets[1], MSc; Karin Volkers[1], PhD; Erik Scherder[2], Prof Dr; Xavier Moonen[3], Prof Dr

[1]Philadelphia Care Foundation, Amersfoort, Netherlands

[2]Department of Clinical Neuropsychology, VU University Amsterdam, Amsterdam, Netherlands

[3]Research Institute of Child Development and Education, University of Amsterdam, Amsterdam, Netherlands

Corresponding Author:
Gerianne Smeets, MSc
Philadelphia Care Foundation
PO Box 1255
Amersfoort, 3800 BG
Netherlands
Phone: 31 610886011
Email: g.smeets@philadelphia.nl

Abstract

Background: Individuals with intellectual disabilities (ID) are more likely to have problems with executive functioning (EF) and challenging behavior (CB), which are negatively linked to well-being. Among clinical populations, music interventions have been shown to improve various outcome measures, such as CB and EF. Until now, no randomized controlled trials (RCTs) have been conducted to examine the effectiveness of an individual music intervention for adults with ID and CB.

Objective: The study aims to identify the effect and feasibility of an individual music intervention compared with care-as-usual for people with ID and CB.

Methods: In this study, a 2-group RCT with a pretest, posttest, and follow-up assessment after 8 weeks is presented. Participants of the music intervention condition will receive 16 individual music sessions within 8 to 10 weeks. The music intervention will be guided by a manual for music workers, in which every session will have a different focus (introduction, emotions, different EF, and end performance). Participants receiving care as usual will function as a control group. After the research is finished, they will be offered a budget, which they can spend on musical activities or musical instruments as they wish. Assessments will include caregiver rating scales and self-report questionnaires and tests, which will assess outcome measures of CB, well-being, depression, anxiety, self-esteem, and 4 domains of EF. A process evaluation will be conducted after the completion of the study, which entails the analysis of data on multiple aspects of the intervention and the study overall.

Results: Enrollment commenced in July 2021, and data collection ended in May 2023. A total of 97 participants were recruited, with 44 participants allocated to the intervention group and 53 allocated to the control group. Data will be analyzed after this protocol has been accepted for publication.

Conclusions: Because there are currently no published RCTs of an individual music intervention for adults with ID and CB, this study will provide insight into the effectiveness and experiences of an individual music intervention for this target group.

Trial Registration: International Clinical Trials Registry Platform NL8482; http://tinyurl.com/4565s5pd

International Registered Report Identifier (IRRID): DERR1-10.2196/52497

(JMIR Res Protoc 2024;13:e52497) doi:10.2196/52497

KEYWORDS

music intervention; intellectual disability; challenging behavior; executive functioning; self-esteem; anxiety; depression; randomized controlled trial; RCT; study protocol; well-being

Introduction

Background

Intellectual disability (ID) is characterized by significant limitations in both intellectual functioning and adaptive abilities, such as conceptual, social, and practical skills. ID originates before the age of 18 years and can be categorized as mild, moderate, or profound [1]. Besides having a lower IQ and problems with adaptive functioning, people with ID are more likely to develop mental health problems, for example, affective and anxiety disorders and challenging behavior (CB) [2,3]. Mental health and CB are negatively linked to quality of life (QoL) [4].

People with ID not only have a higher chance of developing mental health problems and CB, but there is evidence that their executive functioning (EF) is also impacted [5]. EF refers to the set of abilities involved in planning, self-monitoring, and purposive action, which are "at the heart of all socially useful, personally enhancing, constructive, and creative activities" ([6], p. 281). There is broad consensus that there are 3 core EFs: inhibition, working memory, and cognitive flexibility [7,8]. Some studies in the ID field use a broader definition that includes attention [9,10], planning, and categorization [9]. A few studies suggest that regarding EF, people with ID perform at levels commensurate with their mental age [11,12]. Mental age can be calculated from raw scores on intelligence tests: mental age = (IQ score × chronological age) / 100 [13].

Poorer performance on EF tests is linked to more CB, especially externalizing behavior problems, among children, adolescents, and adults with ID. This holds for tests that measure inhibition [14], working memory [15], and cognitive flexibility [16]. Because CB has a major impact on the lives of people with ID and their caregivers, attempts to help diminish CB cover a wide range of different approaches, from environmental approaches [17] and support staff training [18-20], to pharmacological interventions [21]. In 2 meta-analyses, effects were found in reducing CB among people with ID for biological and nonpharmacological (such as psychotherapeutic and contextual) interventions [22,23]. Another example of such a nonpharmacological intervention is music therapy, which a recent review found to have a positive effect on CB, anxiety, self-esteem, management of emotions, cognitive measures, and QoL of people with ID [24]. However, this review concluded that most of these studies had several shortcomings, such as no control group, small sample sizes, lack of follow-up measurements, and no use of self-reports.

Several empirically valid studies have been carried out with participants who have other cognitive or communication disabilities, such as dementia, acquired brain injury, or autism spectrum disorder [25]. In these studies, beneficial effects of music interventions on various outcomes were found, such as self-esteem [26], anxiety [26-29], CB [27], mood [28,30,31], QoL [30,31], and EF (ie, working memory, attention, and EF in general) [30]. However, even in these well-researched fields, there seems to be a paucity of high-quality empirical studies [32,33], which emphasizes the need for more rigorous randomized controlled trials (RCTs) with sufficiently large sample sizes studying the different effects of music interventions.

Although music interventions seem effective on CB, anxiety, mood, self-esteem, management of emotions, cognitive measures, and QoL, it is worth noting that the type of music interventions used can vary widely, depending on the goal and the characteristics of the participant. Some interventions are group sessions, whereas others are individual music sessions that can be tailored more to a participant's individual needs and that show tangentially higher effects, for instance, on agitation in persons with dementia [34]. Some interventions include music therapy (which involves a trained professional using music to address specific therapeutic goals), music listening, or general music-based interventions [35]. It is not uncommon to follow a guideline, with specified principles and procedures of the music intervention, while still leaving enough flexibility to tailor the intervention to the characteristics and needs of the participant and the specific requirements of the situation [33]. Music interventions range from daily to weekly, lasting 10 to 60 minutes, and can have "passive" (listening) or "active" (making music or sounds together) components [33,36]. Active music interventions generally provide greater individual benefits than passive music engagement among older people [37,38], people with autism spectrum disorder [36], and in the general population [39].

Overall, evidence suggests that active music participation can enhance one's emotional, psychological, and social well-being and even increases EF (eg, working memory and attention) in specific clinical populations; however, to the best of our knowledge, no RCTs are available assessing the effectiveness of an individual music intervention for adults with ID, let alone for adults with ID and CB. In this protocol paper, the design and rationale of an RCT are described, in which a manual for an individual active music intervention for adults with ID and CB is presented, matched with persons with ID and CB who receive care as usual (CAU) functioning as a control group.

Objectives

Primary Objective

The primary objective of the proposed RCT is to evaluate the effect of receiving 16 individual active music sessions compared with CAU in adults with a mild or moderate ID with CB on various outcome measures such as CB, well-being, depression, anxiety, self-esteem, and 4 domains of EF.

Secondary Objective

A secondary goal of this study is to evaluate the implementation, impact, and context of the individual music intervention with input from participants, caregivers, and music workers.

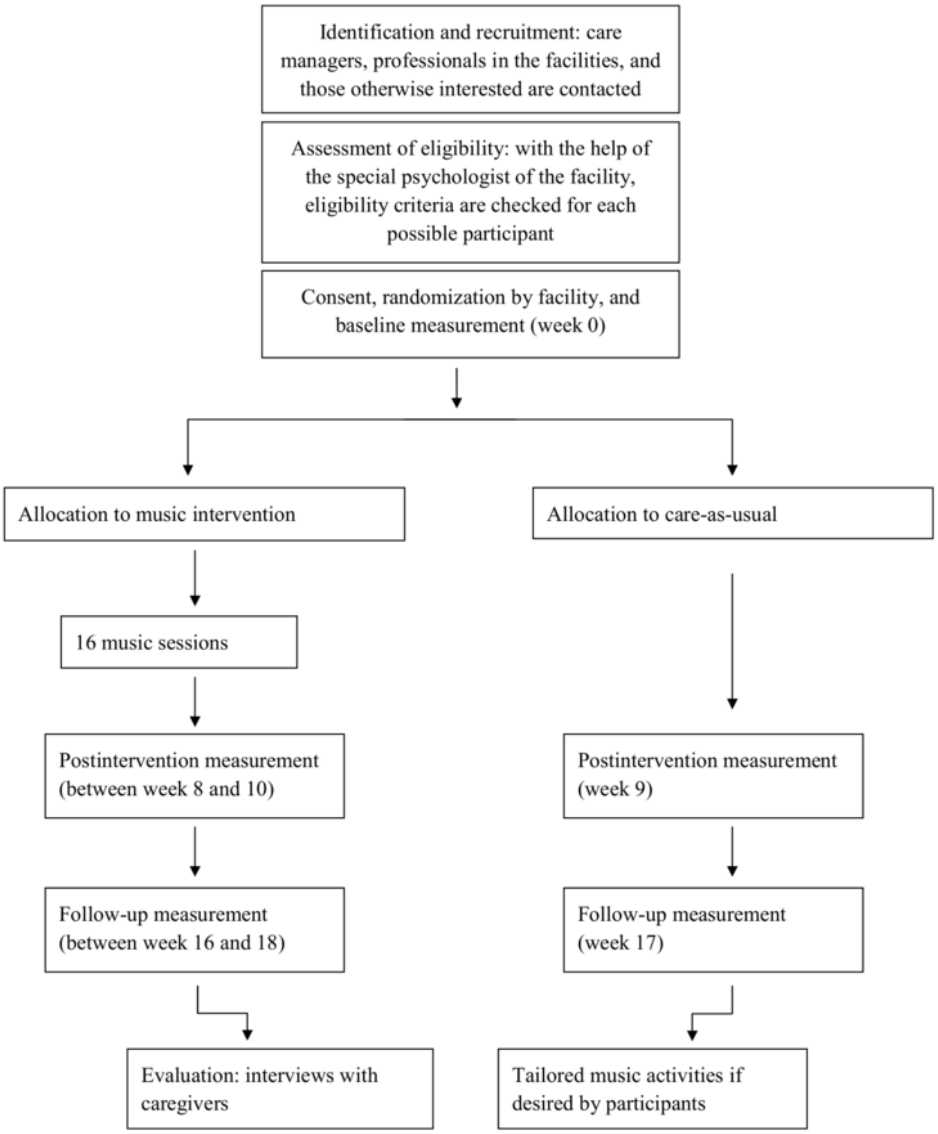
Methods

Study Design

This study is an RCT with a pretest (T1), posttest (T2, 9 weeks after T1, unless the last intervention session was not yet completed; posttest was postponed by 1 or 2 weeks until the week after the final session), and follow-up assessment (T3, 8 weeks after T2), including 2 groups of individual participants

(see Figure 1). Participants belonging to the music condition will receive 16 individual music sessions within 8 to 10 weeks, and participants belonging to the control condition will receive (individual) CAU. Randomization will be performed at a facility level for 3 reasons: first, to prevent possible interference between participants belonging to both groups in a facility; second, it is deemed unethical and difficult to explain to people with ID who are assessed to the control condition that they have to wait for the music sessions, whereas fellow residents already receive them; finally, it can also promote recruitment [17]. For randomization, a computerized random number generator will be used. There is no maximum number of participants per facility. Blinding is not possible because it is clear to the caregivers, participants, and research assistants which type of intervention a participant receives. The independent research assistants are also not blinded because the participants of the music intervention have to fill in an extra questionnaire at the second and third assessment.

Figure 1. Study flowchart.



Study Population

Participants will be included based on 4 criteria and 3 exclusion criteria. The inclusion criteria are as follows: (1) participants must have a mild or moderate ID, (2) they are 18 years or older, (3) they show either internalizing or externalizing CB, and (4) they are mentally competent to give consent to participate in this research. The exclusion criteria are as follows: (1) inability to participate in an intervention for at least 1 hour; (2) a hearing impairment that cannot be corrected with a hearing aid; and (3) a serious medical condition that limits participation, such as dementia. Already being involved in prior musical activities is not an exclusion criterion.

Procedure

Participants will be recruited from residential facilities for people with ID of the Philadelphia Care Foundation throughout the Netherlands. Because participating in this study requires time and effort of their staff, care managers of facilities serving adult residents with mild to moderate ID are contacted about their willingness to participate in the study. Managers with interest will receive an information letter explaining the research aims and responsibilities of all parties involved. Next, the special

psychologist of the facility will check which residents are eligible for inclusion, who then will receive an information letter and an informed consent form in a Dutch easy-to-read format [40]. Caregivers will be asked to read the letter together with potential participants and help them to fully understand the text, if needed. Legal representatives of the eligible residents will also receive an information letter and an informed consent form, whereas nonlegal representatives of the eligible residents will only receive an information letter. Residents will only become participants in the study if (both) informed consent forms are signed. Subsequently, the special psychologist of the facility will be asked for the participant characteristics, which are age, gender, level of ID, syndrome (when applicable), and comorbid psychiatric diagnoses.

After all assessments are completed, participants will receive a compliment postcard from the Philadelphia Care Foundation and a gift card of €15 (US $17.82 when enrollment commenced).

Intervention

In this RCT, 2 conditions are compared: a music intervention and CAU.

Music Intervention Group

The music intervention consists of 16 individual music sessions held twice a week within 8 to 10 weeks. Besides this individual music intervention, regular musical activities that participants already are involved in before the start of this study will continue, as music participation is a central theme of the Philadelphia Care Foundation. The 16 music sessions will be conducted by a music worker, who can be anyone who is able to play an instrument and is enthusiastic and capable to conduct musical sessions with a person with ID. Music workers are not music therapists because the focus is not on therapy but on a general active music intervention. Before the start of the music intervention, the facility in which it will take place will receive a box with an assortment of different kinds of musical instruments, including rhythm instruments (eg, cajon, djembe, and small percussion) and harmony and melody instruments (eg, keyboard and guitar). In general, during the sessions, the music worker adapts the genre or specific pieces of music to the wishes and preferences of the participant. The music intervention will be guided by a training manual for the music workers, in which the frequency, average time per (elements of the) session, and the content of every music session are outlined. The manual is designed based on the input of different advisory groups with professional music coaches, caregivers, and people with ID.

In the manual, intervention procedures are specified, such as the setting, general goals, contents of the music sessions, basic principles of the intervention, and exemplifications. An outline of the music session can be seen in Table 1. Every session will be centered around a different aspect (introduction, emotions, different EF, and end performance), and in the training manual, example exercises are described focusing on every aspect. These examples are provided by advisory groups of professional music coaches and stem from different other manuals [41-43]. Each session will start with a welcome song, after which a listening exercise will take place. Then, a warm-up of the voice and body is scheduled, and subsequently, participants actively engage in music activities by singing or playing an instrument, after which a cool-down and a farewell song are performed. The manual provides a fixed frame for the intervention, but it leaves enough flexibility to tailor the intervention to the characteristics and needs of every participant. Participants will receive a diploma at the final session.

To study for exploratory purposes the impact of the music sessions' frequency, some participants will receive extra music sessions, resulting in 24 to 27 sessions within the same time period, aiming at approximately 3 sessions a week.

Table 1. Outline music session.

Music intervention	Time (minutes)	Attendees
Preliminary meeting	30	Music worker, participant, and caregiver
Music session • 1: Welcoming or introduction • 2-6: Emotions • 7+10: EF[a] (Inhibition) • 8+11: EF (Cognitive flexibility) • 9+12: EF (Working memory) • 13-15: Working toward the end performance or song • 16: End performance or song	60	Music worker and participant
Final meeting	30	Music worker, participant, and caregiver

[a]EF: executive functioning.

CAU Group

Participants receiving CAU will function as a control group. CAU includes regular care such as assistance with acts of daily living and day care activities. CAU can include musical activities that participants already performed before the start of this study, as music is a central theme of the Philadelphia Care Foundation. However, new individual musical activities will be postponed for these participants until after the follow-up measurement. Participants receiving CAU will be offered a budget at the end of the study, which they can spend on musical activities or musical instruments to their own wishes, with the help of a musical specialist who works at the Philadelphia Care Foundation.

Measures

All assessments (T1, T2, and T3) will take place by applying caregiver rating scales and self-report questionnaires and tests and all will be conducted in the same week. Students from several Dutch universities will work as research assistants assisting with the data collection. Research assistants receive theoretical and practical training in assessment through a training program in the test administration protocol. They will administer all irregularities and deviations from this protocol in a study log report. The research assistants will not be involved in the intervention itself. An overview of the outcome measures and the process evaluation can be seen in Table 2.

Table 2. Overview outcome measures and process evaluation.

Assessment	Proxy or self-report			Measurement moment				
	Caregiver	Music worker	Person with ID[a]	Each music session	Baseline (T1)	Postintervention (T2)	Follow-up (T3)	After follow-up
Outcome measures								
Self-reports and tests			✓		✓	✓	✓	
Proxy questionnaires	✓				✓	✓	✓	
Evaluation[b]								
Evaluation questionnaire music sessions		✓	✓			✓		
Follow-up evaluation	✓		✓				✓	
Self-report with emoticons			✓	✓				
Log reports music sessions		✓		✓				
Semistructured interview	✓							✓

[a]ID: intellectual disabilities.

[b]Only in the music intervention.

Outcome Measures

Challenging Behavior

The Dutch version of the Aberrant Behavior Checklist (ABC) will be used to assess CB, and the form will be filled out by a caregiver [44]. The ABC consists of 58 items, which are rated on a 4-point Likert scale, ranging from 0 (“not at all a problem”) to 3 (“the problem is severe in degree”). The sum of the questions provides a total score (range 0-174), with higher scores indicating more CB. In this study, the cluster structure as suggested by Kaat et al [45] will be used. The first cluster (28 items; α=.96, β=.57) represents behavior that is directed outward (ie, externalizing CB). The second cluster (26 items; α=.93, β=.76) represents behavior that is directed inward (ie, internalizing CB). For externalizing CB, the score ranges from 0 to 84, and for internalizing CB, the score ranges from 0 to 78. The total score on cluster 1 (ie, externalizing CB) will be used to assess externalizing CB, the total score on cluster 2 (ie, internalizing CB) will be used to assess internalizing CB, and the total score on all items of the ABC will be used to assess overall CB.

Well-Being

Subjective well-being will be assessed using the Dutch version of the 7-item Personal Well-being Index—Intellectual Disability (PWI-ID) [46]. An example of an item is as follows: “How happy do you feel about the things you have? Like the money you have and the things you own?” Each item is scored on a 3-point Likert scale (0=sad, 1=neither happy nor sad, and 2=happy). Three pictures of colored smileys are used to represent the 3 answers. The pretesting protocol, which screens for acquiescent responding, will not be applied, to diminish the data collection burden for participants. PWI-ID scores range from 7 to 24, with higher scores indicating a better subjective well-being. The PWI-ID seems to be an appropriate measure for people with a mild or upper moderate level of ID [47].

Depression and Anxiety

Symptoms of depression and anxiety will be assessed using the Depressed Mood and General Anxiety subscales from the Dutch version of the Anxiety, Depression and Mood Scale [48]. This questionnaire will be completed by the caregiver. The Depressed Mood subscale consists of 13 items, for example, “somber mood,” which are scored on a 4-point Likert scale (0=behavior has not occurred or is not a problem, 1=behavior sometimes occurs or is a slight problem, 2=behavior often occurs or is a relatively large/moderate problem, and 3=behavior occurs a lot or is a severe problem). Depression scores can range from 0 to 39. The General Anxiety subscale of 7 items, for example, “nervous or anxious,” are also scored on this 4-point Likert scale. Anxiety scores range from 0 to 21. For both subscales, a higher score indicates more symptoms. Its reliability and validity are satisfactory to good [49].

Self-Esteem

Self-esteem will be assessed using the 5-item Global Self-Worth subscale of the Self-Perception Profile for Adolescents [50]. In this study, the Dutch adaptation of the Self-Perception Profile for Adolescents [51] will be used, with a Cronbach α of >.70 and 1 statement per item [52]. An example of an item is “I am quite happy with myself.” Each item is scored on a 4-point Likert scale (1=completely untrue for me, 2=a little untrue for

me, 3=a little true for me, and 4=completely true for me). The total score can range from 5 to 20, and a higher score indicates higher self-worth.

EF Tasks

Overview

EF will be assessed on a tablet using 3 computer-based games to assess cognitive flexibility, attention, inhibition, and working memory, which were custom-developed in earlier research and are adapted to the needs of individuals with ID, that is, fewer trials, shorter tasks, visual support during test instructions, and attractive stimuli [14,53]. After each game, the research assistant will complete 2 questions about how often the participant needed to be motivated and how often the participant was distracted during the games.

Cognitive Flexibility

The game to assess cognitive flexibility is based on the flanker task [54]. The principle of the flanker task is that participants have to respond to a target arrow, which is flanked by distracter arrows. In this study, this task will consist of 5 arrows per trial, with 32 random trials per condition, with 3 conditions. In the first condition, there are 5 green arrows pointing in different directions (left or right). Participants have to ignore the irrelevant stimuli and press the button in the same direction as the green arrow in the middle. In the second condition, the participants are presented with red arrows. Unlike the previous condition, participants have to press the button with the opposite direction as the arrow in the middle. In the third condition, participants are presented with alternating trials of red or green arrows and are requested to press the button with the opposite direction if the arrow in the middle is red and to press the button with the same direction if the arrow in the middle is green. All 3 conditions had a practice round before the official task. The score used to measure cognitive flexibility consists of the correct responses in the third condition (range 0-32). A higher score implies a higher degree of cognitive flexibility.

Attention

Attention will be assessed with the first condition of the already mentioned flanker task, where participants have to respond to the green arrow in the middle, regardless of the nature of the flanking distractor items, by pressing the right button for right-faced arrows and the left button for left-faced arrows. Both correct and incorrect (ie, missing or lack of on-time response) responses will be added, standardized as *z* scores, to create a composite total attention score. The incorrect responses will be reversed to create a variable in which a higher score represents better attention.

Inhibition

Inhibition will be assessed using two different tasks: (1) the second condition with red arrows of the already mentioned flanker task, which measures interference control [54] and (2) the go or no-go paradigm, which measures the inhibition of a prepotent motor response [55]. The *z* scores on both outcome variables will be added to create a composite total inhibition score for each participant. This new variable will be reversed, so a higher score represents better inhibition skills.

The outcome variable from the flanker task that will be used is the number of faults in the task with only red arrows, representing the inability to suppress an initial response. In this task, participants have to press the arrow corresponding with the opposite direction of the central arrow.

The go or no-go task consists of 2 parts. In the first part, the participant is requested to press the button as soon as a green apple, that is, a “go” stimulus, appears on the screen. In the second part, participants have to tap on the button when the green apple appears, but they have to inhibit their response when a red cross appears through the apple, that is, a “no-go” stimulus. An incorrect answer is given when the participant presses the button, and the green apple appears with a red cross. Both conditions had a practice round before the official task. The outcome measure for the go or no-go task is the total incorrect answers in part 2.

Working Memory

To assess the working memory construct, a visuospatial computerized task, based on the Klingberg principles for working memory, will be used [56,57]. In the Klingberg task, participants have to remember the order that a circle shifts over a 4-by-4 grid of open squares. The task consists of 2 conditions that both start with an instruction and a 4-trial practice session before the regular session. The regular session starts with a pattern of 2 circles on adjacent units and gradually increases in length and difficulty with each trial. Each trial consists of 2 patterns of the same length and difficulty. In the first condition, patterns with a green circle are presented to the participants who have to tap on the squares in the grid in the same order afterward (forward version). In the second condition, patterns of red dots are shown which participants have to tap in the reverse order afterward (backward version). When a participant taps a wrong pattern twice on a trial of the same length and difficulty, the task ends. In this study, the average number of total correct trials in the forward and backward task will be used as a measure of working memory [56,58]. A higher score represents better working memory. There is no absolute maximum score; in theory, the task can go on indefinitely.

Process Evaluation

Overview

Because conducting clinical trials in the field of adults with ID and CB seems to be challenging [25], it is also important to share the practical experiences when conducting trials using a process evaluation [59]. For conducting a process evaluation, different frameworks are developed, which all focus on several process evaluation components. For this study, the following frameworks are used: the Medical Research Council guidance [59], process evaluations for cluster-randomized trials of complex interventions as proposed by Grant et al [60], and the RE-AIM (Reach, Effectiveness, Adoption, Implementation, and Maintenance) framework [61,62]. The Medical Research Council guidance and the RE-AIM framework have recently been used in the ID-research field [19,63-65].

Evaluation per Music Session

The music worker will ask the participant before and after each music session how he or she feels at that moment: happy, sad, scared, angry, or tired. Sheets representing 5 emoticons with associated feelings are shown to help the participant. If possible, the participant also indicates whether this feeling is little, normal, or intense. When it is too difficult for a participant to choose a specific emotion, the participant is asked whether he or she feels pleasant or nonpleasant.

Music workers will also complete a log report after each music session. The log report contains questions about that specific session: whether the session was performed according to the manual and how much time was spent on active music making.

Evaluation of Music Intervention

Participants in the music intervention and music workers will be asked to complete an evaluation questionnaire after the last music session. These questionnaires are designed to gain the participants' personal views about the music intervention and their satisfaction with specific elements of it (eg, musical instruments and frequency of the sessions). The music workers will share their observations regarding behavioral, cognitive, and emotional changes within a participant during sessions.

After the last music session, caregivers will be asked to participate in a semistructured interview. This interview will focus on observed changes in the participants' behavior and the experiences of caregivers with this music intervention study. Topics that will be covered are related to acceptability or satisfaction, reach, and context. The interviews will be recorded with the permission of the respondents and transcribed.

Follow-Up Evaluation

The participants in the music intervention and caregivers from participants in the music intervention will answer a few questions about the long-term use of musical activities after the last music session. For participants, this questionnaire will be conducted at T3, and for caregivers, it will be conducted 6 months after the last session.

Sample Size Calculation

The sample size is calculated using G*Power software (version 3.1.9.7) [66]. The sample size calculation is based on a small effect size of 0.2, a statistical power of 0.95, and a type I error probability of α=.05, which results in an unadjusted sample size of 67 participants. Because cluster randomization negatively affects the power, the sample size needs to be adjusted. With the average cluster size of 2 participants per residential facility and allowing an intraclass correlation of 0.2, the adjusted sample size is 80. To allow for a dropout rate of 20% over the course of the study, we will aim at recruiting a total of at least 96 participants.

Data Analysis

Participant characteristics will be compared between the group receiving the individual music intervention and the group receiving CAU. Further analyses will be adjusted for any potential significant differences. The primary analyses will be undertaken on an intention-to-treat basis, and 2-sided tests will be applied at a 5% α level. In addition, per-protocol analyses will be conducted based on the sample of participants who adequately adhered to the intervention protocol by completing at least 12 of the 16 music sessions (ie, 75%), which is similar to 67% and 80% of 2 other intervention studies among adults with mild to moderate ID [67,68]. In addition, by setting the threshold at 12 sessions, we know for sure that all intervention participants followed at least 1 or 2 sessions with a focus on emotions and EF.

To minimize the number of analyses on outcome domains, the 4 different EF measures will be converted into *z* scores and, according to factor analysis, summed up into an EF domain if possible. Subsequently, to test differences in changes from baseline to follow-up between the 2 conditions, a linear mixed model analysis for each treatment variable will be used. Within each analysis, only time and the interaction between the treatment variable and time will be used [69], making it possible to adjust for the dependence of the repeated observations within the subjects. The effect of the intervention on the 2 follow-up measurements will be assessed. This analysis allows for participants with only a baseline measurement but with missing data at follow-up to be included. The normality of the residuals from the linear mixed model analysis will be visually inspected.

Secondary analyses will be performed as well. The effect of extra music interventions will be tested applying a Mann-Whitney *U* test for the between-group comparisons. The self-reported feelings before and after each music session will be compared using a Wilcoxon signed rank test.

Descriptive statistics will be used to summarize the quantitative data of the log reports, evaluation questionnaires, and the follow-up evaluation.

Qualitative data of log reports, evaluation questionnaires, follow-up evaluation, recruitment log, trial log, and semistructured interviews will be analyzed using thematic context analysis on multiple aspects of the intervention and the overall study process, including recruitment, retention, acceptability or satisfaction, maintenance, dose, fidelity, reach, adaptation, and context.

Ethical Considerations

Participation in the study will be voluntary. Participants and their legal representatives can withdraw consent at any time during the intervention and have the right to demand the removal of the original data. Random allocation of participants to 1 of the 2 conditions is considered reasonable as no adverse effects are expected in any of the conditions. Inconveniences caused by the necessity to attend 2 or 3 music sessions per week are considered tolerable in view of the anticipated benefit for the participant receiving music sessions. Participants assigned to CAU will receive a considerable budget after the study has ended, which they can spend on musical activities or musical instruments to their own wishes. Ethical approval for this study was granted by the review board of the Faculty of Behavioral and Movement Sciences of the VU University Amsterdam (protocol VCWE-2021-081). The Medical Ethical Committee of the VU University Medical Center stated that the research was not subject to the Dutch Medical Research Involving Human

Subjects Act. The trial has been registered in the International Clinical Trial Registry Platform (NL8482).

Data Management

To ensure the accuracy of the data, all entered data will be triple-checked by different research assistants. Every participant will be assigned an anonymous code after their informed consent form is received to store and identify their trial data. The coding key and person-related data will be saved in a password-protected file in a restricted folder, which will only be accessible by the study-related researchers. All paper files will be kept in locked cabinets in the researcher's office for the duration of the study, and digital files will be stored on a password-protected and secure system, which is also exclusively accessible by the study-related researchers.

Results

Enrollment commenced in July 2021, and data collection ended in May 2023. The aim to recruit at least 96 participants has been achieved with a total of 97 participants, of whom 44 were randomized in the intervention group. Data will be analyzed after this study protocol has been accepted for publication.

Discussion

In this paper, the design of an RCT is presented, which aims at exploring the effectiveness of and experiences with a music intervention for adults with ID and CB on various outcome measures, including CB, well-being, depression, anxiety, self-esteem, and EF. The first strength of this study is that it concerns a clustered RCT design with a sufficient sample size. The second strength is that the multisource data collection, including the use of self-report questionnaires and tests as well as proxy measures, improves the research quality. Third, because distal outcomes (measured over a longer period of time) and proximal outcomes (measured immediately after the intervention) will be used, immediate effects can be assessed too. Lastly, as qualitative data are collected alongside quantitative data, further insight into the process or mechanisms of change can be gained.

However, some limitations also have to be taken into consideration. First, blinding is not possible in the design because the nature of the intervention and the different questionnaires at the data collection points for both groups precludes blinding of the assignment for all parties involved. The absence of an active control condition might entail difficulties in ascribing possibly disclosed effects to power factors of the music intervention, such as level of attention [70]. Furthermore, there are several anticipated challenges, which are based on previous work conducting RCTs with adults with ID. These include challenges with recruiting adequate numbers, resistance to the use of control groups, assessing participants through gatekeepers (ie, the caregivers), and staff turnover that impacts the data collection [25]. The following steps to minimize attrition are considered in this study: (1) the research team follows a flexible participant-led approach to gathering all data—with contacts being at times suggested by participants and at the convenience of the facility of the participant; (2) the incentive to complete all questionnaires and tests is increased with the compliment card that participants receive after every data collection measurement; (3) caregivers will receive multiple reminders, either live, via mail, or telephone, to return the questionnaires on time; and (4) the combination of collecting data from both participants and caregivers reduces the burden for them and diminishes the impact of participant dropout or staff turnover.

In sum, more evidence-based interventions are needed to help improve the mental well-being of this population. It is important to not only fill this evidence-base gap with the outcomes of the ID RCTs but also share the practical experiences conducting trials through the reporting of process evaluations. Therefore, it is expected that this study will provide insight into the effectiveness and experiences of an individual music intervention for adults with ID and CB. If the intervention proves to be effective, broad-scale implementation in the care for people with ID can be considered and results can guide further music intervention guidelines and enrich the work environment of music workers engaging in supporting people with ID.

Conflicts of Interest

None declared.

References

1. Diagnostic and Statistical Manual of Mental Disorders: 5th Edition. Washington, DC: American Psychiatric Assocation; 2013.
2. Dosen A. Psychische Stoornissen, Gedragsproblemen en Verstandelijke Handicap: een Integratieve Benadering bij Kinderen en Volwassenen. 4th ed. Assen: Koninklijke Van Gorcum; 2010.
3. Richards M, Maughan B, Hardy R, Hall I, Strydom A, Wadsworth M. Long-term affective disorder in people with mild learning disability. Br J Psychiatry 2001;179(6):523-527 [FREE Full text] [doi: 10.1192/bjp.179.6.523] [Medline: 11731356]
4. Koch AD, Vogel A, Becker T, Salize HJ, Voss E, Werner A, et al. Proxy and self-reported quality of life in adults with intellectual disabilities: impact of psychiatric symptoms, problem behaviour, psychotropic medication and unmet needs. Res Dev Disabil 2015;45-46:136-146 [FREE Full text] [doi: 10.1016/j.ridd.2015.07.022] [Medline: 26233765]
5. Zagaria T, Antonucci G, Buono S, Recupero M, Zoccolotti P. Executive functions and attention processes in adolescents and young adults with intellectual disability. Brain Sci 2021;11(1):42 [FREE Full text] [doi: 10.3390/brainsci11010042] [Medline: 33401550]

6. Lezak MD. The problem of assessing executive functions. Int J Psychol 1982;17(1-4):281-297. [doi: 10.1080/00207598208247445]
7. Diamond A. Executive functions. Annu Rev Psychol 2013;64:135-168 [FREE Full text] [doi: 10.1146/annurev-psych-113011-143750] [Medline: 23020641]
8. Miyake A, Friedman NP, Emerson MJ, Witzki AH, Howerter A, Wager TD. The unity and diversity of executive functions and their contributions to complex "Frontal Lobe" tasks: a latent variable analysis. Cogn Psychol 2000;41(1):49-100. [doi: 10.1006/cogp.1999.0734] [Medline: 10945922]
9. Costanzo F, Varuzza C, Menghini D, Addona F, Gianesini T, Vicari S. Executive functions in intellectual disabilities: a comparison between Williams syndrome and down syndrome. Res Dev Disabil 2013;34(5):1770-1780 [FREE Full text] [doi: 10.1016/j.ridd.2013.01.024] [Medline: 23501586]
10. Spaniol M, Danielsson H. A meta-analysis of the executive function components inhibition, shifting, and attention in intellectual disabilities. J Intellect Disabil Res 2022;66(1-2):9-31 [FREE Full text] [doi: 10.1111/jir.12878] [Medline: 34498787]
11. Henry LA. How does the severity of a learning disability affect working memory performance? Memory 2001;9(4-6):233-247 [FREE Full text] [doi: 10.1080/09658210042000085] [Medline: 11594349]
12. Van der Molen MJ, Van Luit JEH, Jongmans MJ, Van der Molen MW. Verbal working memory in children with mild intellectual disabilities. J Intellect Disabil Res 2007;51(Pt 2):162-169 [FREE Full text] [doi: 10.1111/j.1365-2788.2006.00863.x] [Medline: 17217480]
13. Van der Molen MJ, Van Luit JEH, Jongmans MJ, Van der Molen MW. Memory profiles in children with mild intellectual disabilities: strengths and weaknesses. Res Dev Disabil 2009;30(6):1237-1247 [FREE Full text] [doi: 10.1016/j.ridd.2009.04.005] [Medline: 19477617]
14. Van Rest MM, Matthys W, Van Nieuwenhuijzen M, De Moor MHM, Vriens A, Schuengel C. Social information processing skills link executive functions to aggression in adolescents with mild to borderline intellectual disability. Child Neuropsychol 2019;25(5):573-598 [FREE Full text] [doi: 10.1080/09297049.2018.1495186] [Medline: 30010484]
15. Schuiringa H, van Nieuwenhuijzen M, de Castro BO, Matthys W. Executive functions and processing speed in children with mild to borderline intellectual disabilities and externalizing behavior problems. Child Neuropsychol 2017;23(4):442-462 [FREE Full text] [doi: 10.1080/09297049.2015.1135421] [Medline: 26796344]
16. Visser EM, Berger HJC, Van Schrojenstein Lantman-De Valk HMJ, Prins JB, Teunisse JP. Cognitive shifting and externalising problem behaviour in intellectual disability and autism spectrum disorder. J Intellect Disabil Res 2015;59(8):755-766. [doi: 10.1111/jir.12182] [Medline: 25559338]
17. Tyrer P, Tarabi SA, Bassett P, Liedtka N, Hall R, Nagar J, et al. Nidotherapy compared with enhanced care programme approach training for adults with aggressive challenging behaviour and intellectual disability (NIDABID): cluster-randomised controlled trial. J Intellect Disabil Res 2017;61(6):521-531 [FREE Full text] [doi: 10.1111/jir.12360] [Medline: 28124397]
18. Randell E, Hastings RP, McNamara R, Knight R, Gillespie D, Taylor Z. Effectiveness of the 'who's challenging who' support staff training intervention to improve attitudes and empathy towards adults with intellectual disability and challenging behaviours: study protocol for a cluster randomised controlled trial. Trials 2017;18(1):460 [FREE Full text] [doi: 10.1186/s13063-017-2175-1] [Medline: 28982380]
19. Bosco A, Paulauskaite L, Hall I, Crabtree J, Soni S, Biswas A, et al. Process evaluation of a randomised controlled trial of PBS-based staff training for challenging behaviour in adults with intellectual disability. PLoS One 2019;14(8):e0221507 [FREE Full text] [doi: 10.1371/journal.pone.0221507] [Medline: 31437228]
20. Hassiotis A, Poppe M, Strydom A, Vickerstaff V, Hall IS, Crabtree J, et al. Clinical outcomes of staff training in positive behaviour support to reduce challenging behaviour in adults with intellectual disability: cluster randomised controlled trial. Br J Psychiatry 2018;212(3):161-168 [FREE Full text] [doi: 10.1192/bjp.2017.34] [Medline: 29436314]
21. Ramerman L, de Kuijper G, Scheers T, Vink M, Vrijmoeth P, Hoekstra PJ. Is risperidone effective in reducing challenging behaviours in individuals with intellectual disabilities after 1 year or longer use? a placebo-controlled, randomised, double-blind discontinuation study. J Intellect Disabil Res 2019;63(5):418-428 [FREE Full text] [doi: 10.1111/jir.12584] [Medline: 30609152]
22. Heyvaert M, Maes B, Onghena P. A meta-analysis of intervention effects on challenging behaviour among persons with intellectual disabilities. J Intellect Disabil Res 2010;54(7):634-649 [FREE Full text] [doi: 10.1111/j.1365-2788.2010.01291.x] [Medline: 20492347]
23. Bruinsma E, van den Hoofdakker BJ, Groenman AP, Hoekstra PJ, de Kuijper GM, Klaver M, et al. Non-pharmacological interventions for challenging behaviours of adults with intellectual disabilities: a meta-analysis. J Intellect Disabil Res 2020;64(8):561-578 [FREE Full text] [doi: 10.1111/jir.12736] [Medline: 32558050]
24. Mino‐Roy J, St‐Jean J, Lemus‐Folgar O, Caron K, Constant‐Nolett O, Després JP, et al. Effects of music, dance and drama therapies for people with an intellectual disability: a scoping review. Brit J Learn Disabil 2021;50(3):385-401 [FREE Full text] [doi: 10.1111/bld.12402]
25. Mulhall P, Taggart L, Coates V, McAloon T, Hassiotis A. A systematic review of the methodological and practical challenges of undertaking randomised-controlled trials with cognitive disability populations. Soc Sci Med 2018;200:114-128 [FREE Full text] [doi: 10.1016/j.socscimed.2018.01.032] [Medline: 29421458]

26. Hillier A, Greher G, Poto N, Dougherty M. Positive outcomes following participation in a music intervention for adolescents and young adults on the autism spectrum. Psychology of Music 2011;40(2):201-215 [FREE Full text] [doi: 10.1177/0305735610386837]
27. Gómez-Romero M, Jiménez-Palomares M, Rodríguez-Mansilla J, Flores-Nieto A, Garrido-Ardila EM, López-Arza MVG. Benefits of music therapy on behaviour disorders in subjects diagnosed with dementia: a systematic review. Neurologia 2017;32(4):253-263 [FREE Full text] [doi: 10.1016/j.nrl.2014.11.001] [Medline: 25553932]
28. Guétin S, Portet F, Picot MC, Pommié C, Messaoudi M, Djabelkir L, et al. Effect of music therapy on anxiety and depression in patients with Alzheimer's type dementia: randomised, controlled study. Dement Geriatr Cogn Disord 2009;28(1):36-46 [FREE Full text] [doi: 10.1159/000229024] [Medline: 19628939]
29. Ing-Randolph AR, Phillips LR, Williams AB. Group music interventions for dementia-associated anxiety: a systematic review. Int J Nurs Stud 2015;52(11):1775-1784 [FREE Full text] [doi: 10.1016/j.ijnurstu.2015.06.014] [Medline: 26228591]
30. Särkämö T, Tervaniemi M, Laitinen S, Numminen A, Kurki M, Johnson JK, et al. Cognitive, emotional, and social benefits of regular musical activities in early dementia: randomized controlled study. Gerontologist 2014;54(4):634-650 [FREE Full text] [doi: 10.1093/geront/gnt100] [Medline: 24009169]
31. Gassner L, Geretsegger M, Mayer-Ferbas J. Effectiveness of music therapy for autism spectrum disorder, dementia, depression, insomnia and schizophrenia: update of systematic reviews. Eur J Public Health 2022;32(1):27-34 [FREE Full text] [doi: 10.1093/eurpub/ckab042] [Medline: 34595510]
32. Magee WL, Clark I, Tamplin J, Bradt J. Music interventions for acquired brain injury. Cochrane Database Syst Rev 2017;1(1):CD006787 [FREE Full text] [doi: 10.1002/14651858.CD006787.pub3] [Medline: 28103638]
33. Geretsegger M, Fusar-Poli L, Elefant C, Mössler KA, Vitale G, Gold C. Music therapy for autistic people. Cochrane Database Syst Rev 2022;5(5):CD004381 [FREE Full text] [doi: 10.1002/14651858.CD004381.pub4] [Medline: 35532041]
34. Matziorinis AM, Koelsch S. The promise of music therapy for Alzheimer's disease: a review. Ann N Y Acad Sci 2022;1516(1):11-17 [FREE Full text] [doi: 10.1111/nyas.14864] [Medline: 35851957]
35. Raglio A, Oasi O. Music and health: what interventions for what results? Front Psychol 2015;6:230 [FREE Full text] [doi: 10.3389/fpsyg.2015.00230] [Medline: 25784891]
36. Haering S. Are music-based interventions a way to improve executive function in autism? Int J Learn Teach 2018;10(1):27-37 [FREE Full text] [doi: 10.18844/ijlt.v10i1.3143]
37. Pedersen SKA, Andersen PN, Lugo RG, Andreassen M, Sütterlin S. Effects of music on agitation in dementia: a meta-analysis. Front Psychol 2017;8:742 [FREE Full text] [doi: 10.3389/fpsyg.2017.00742] [Medline: 28559865]
38. Sakamoto M, Ando H, Tsutou A. Comparing the effects of different individualized music interventions for elderly individuals with severe dementia. Int Psychogeriatr 2013;25(5):775-784 [FREE Full text] [doi: 10.1017/S1041610212002256] [Medline: 23298693]
39. Weinberg MK, Joseph D. If you're happy and you know it: music engagement and subjective wellbeing. Psychology of Music 2016;45(2):257-267 [FREE Full text] [doi: 10.1177/0305735616659552]
40. Moonen X. Easy language in the Netherlands. In: Lindholm C, Vanhatalo U, editors. Handbook of Easy Languages in Europe. Berlijn: Frank & Timme; 2021:345-370.
41. Het Koninklijk Concertgebouw. 5 Minuten Muziek. Helmond: Uitgeverij OMJS; 2016.
42. Houtman M, Losekoot M, van der Waals T, Waringa M. Wijzer in executieve functies – groep 5 t/m 8. Huizen: Uitgeverij PICA; 2017.
43. Storms G. Muzikaal Spelenboek: 101 Muziek- en Geluidsspelletjes voor Kinderen van 6-16 Jaar. Katwijk: Panta Rhei; 2005.
44. Aman MG, Singh NN, Stewart AW, Field CJ. The aberrant behavior checklist: a behavior rating scale for the assessment of treatment effects. Am J Ment Defic 1985;89(5):485-491. [Medline: 3993694]
45. Kaat AJ, Zelko F, Wilkening G, Berg AT. Evaluation of the aberrant behavior checklist for developmental and epileptic encephalopathies. Epilepsy Behav 2021;119:107958 [FREE Full text] [doi: 10.1016/j.yebeh.2021.107958] [Medline: 33892287]
46. Cummins RA, Lau ALD. Personal Wellbeing Index—Intellectual Disability (PWI-ID): Manual. Melbourne, Australia: School of Psychology Deakin University; 2005.
47. Cummins RA, Lau ALD, Davey G, McGillivray J. Measuring subjective wellbeing: the personal wellbeing index – intellectual disability. In: Kober R, editor. Enhancing the Quality of Life of People with Intellectual Disabilities: From Theory to Practice. Dordrecht: Springer; 2010:33-46.
48. Hermans H, Hamers H, Jelluma N, Evenhuis H. Handleiding Angst, Depressie en Stemming Schaal (ADESS) voor mensen met een verstandelijke beperking. In: Geneeskunde voor Verstandelijk Gehandicapten. Rotterdam: Erasmus MC Rotterdam & Consortium Gezond Ouder met een verstandelijke beperking; 2018.
49. Esbensen AJ, Rojahn J, Aman MG, Ruedrich S. Reliability and validity of an assessment instrument for anxiety, depression, and mood among individuals with mental retardation. J Autism Dev Disord 2003;33(6):617-629 [FREE Full text] [doi: 10.1023/b:jadd.0000005999.27178.55] [Medline: 14714931]
50. Harter S. Manual for the Self-perception Profile for Adolescents. Denver: University of Denver; 1988.

51. Treffers PDA, Goedhart AW, Veerman JW, Van den Bergh B, Ackaert L, de Rycke L. Competentiebelevingsschaal voor Adolescenten (CBSA): Handleiding. Amsterdam: Pearson Clinical Assessment; 2002.
52. Wichstrøm L. Harter's self-perception profile for adolescents: reliability, validity, and evaluation of the question format. J Pers Assess 1995;65(1):100-116 [FREE Full text] [doi: 10.1207/s15327752jpa6501_8] [Medline: 7643294]
53. Schalock RL, Borthwick-Duffy SA, Bradley VJ, Buntinx WHE, Coulter DL, Craig EM, et al. Intellectual Disability: Definition, Classification, and Systems of Supports. 11th ed. Washington, DC: American Association on Intellectual and Developmental Disabilities; 2010.
54. Eriksen BA, Eriksen CW. Effects of noise letters upon the identification of a target letter in a nonsearch task. Percept Psychophys 1974;16(1):143-149 [FREE Full text] [doi: 10.3758/bf03203267]
55. Trommer BL, Hoeppner JA, Lorber R, Armstrong K. The go-no-go paradigm in attention deficit disorder. Ann Neurol 1988;24(5):610-614. [doi: 10.1002/ana.410240504] [Medline: 3202613]
56. Klingberg T, Forssberg H, Westerberg H. Training of working memory in children with ADHD. J Clin Exp Neuropsychol 2002;24(6):781-791 [FREE Full text] [doi: 10.1076/jcen.24.6.781.8395] [Medline: 12424652]
57. Olesen PJ, Westerberg H, Klingberg T. Increased prefrontal and parietal activity after training of working memory. Nat Neurosci 2004;7(1):75-79 [FREE Full text] [doi: 10.1038/nn1165] [Medline: 14699419]
58. Thorell LB, Lindqvist S, Nutley SB, Bohlin G, Klingberg T. Training and transfer effects of executive functions in preschool children. Dev Sci 2009;12(1):106-113 [FREE Full text] [doi: 10.1111/j.1467-7687.2008.00745.x] [Medline: 19120418]
59. Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, et al. Process evaluation of complex interventions: medical research council guidance. BMJ 2015;350:h1258 [FREE Full text] [doi: 10.1136/bmj.h1258] [Medline: 25791983]
60. Grant A, Treweek S, Dreischulte T, Foy R, Guthrie B. Process evaluations for cluster-randomised trials of complex interventions: a proposed framework for design and reporting. Trials 2013;14(1):15 [FREE Full text] [doi: 10.1186/1745-6215-14-15] [Medline: 23311722]
61. Glasgow RE, Vogt TM, Boles SM. Evaluating the public health impact of health promotion interventions: the RE-AIM framework. Am J Public Health 1999;89(9):1322-1327. [doi: 10.2105/ajph.89.9.1322] [Medline: 10474547]
62. Glasgow RE, Harden SM, Gaglio B, Rabin B, Smith ML, Porter GC, et al. RE-AIM planning and evaluation framework: adapting to new science and practice with a 20-year review. Front Public Health 2019;7:64 [FREE Full text] [doi: 10.3389/fpubh.2019.00064] [Medline: 30984733]
63. Hanzen G, Waninge A, van Nispen RMA, Vlaskamp C, Post WJ, van der Putten AAJ. Intervention effects on professionals' attitudes towards the participation of adults with visual and severe or profound intellectual disabilities. J Appl Res Intellect Disabil 2021;34(1):129-139 [FREE Full text] [doi: 10.1111/jar.12792] [Medline: 32789929]
64. Lai J, Klag M, Shikako-Thomas K. Designing a program evaluation for a medical-dental service for adults with autism and intellectual disabilities using the RE-AIM framework. Learn Health Syst 2019;3(3):e10192 [FREE Full text] [doi: 10.1002/lrh2.10192] [Medline: 31317073]
65. Schaap FD, Dijkstra GJ, Finnema EJ, Reijneveld SA. The first use of dementia care mapping in the care for older people with intellectual disability: a process analysis according to the RE-AIM framework. Aging Ment Health 2018;22(7):912-919 [FREE Full text] [doi: 10.1080/13607863.2017.1401582] [Medline: 29171286]
66. Faul F, Erdfelder E, Buchner A, Lang AG. Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. Behav Res Methods 2009 Nov;41(4):1149-1160. [doi: 10.3758/BRM.41.4.1149] [Medline: 19897823]
67. Martínez-Aldao D, Martínez-Lemos I, Bouzas-Rico S, Ayán-Pérez C. Feasibility of a dance and exercise with music programme on adults with intellectual disability. J Intellect Disabil Res 2019;63(6):519-527 [FREE Full text] [doi: 10.1111/jir.12585] [Medline: 30609165]
68. Willner P, Rose J, Jahoda A, Kroese BS, Felce D, Cohen D, et al. Group-based cognitive-behavioural anger management for people with mild to moderate intellectual disabilities: cluster randomised controlled trial. Br J Psychiatry 2013;203(3):288-296 [FREE Full text] [doi: 10.1192/bjp.bp.112.124529] [Medline: 23520220]
69. Twisk J, Bosman L, Hoekstra T, Rijnhart J, Welten M, Heymans M. Different ways to estimate treatment effects in randomised controlled trials. Contemp Clin Trials Commun 2018;10:80-85 [FREE Full text] [doi: 10.1016/j.conctc.2018.03.008] [Medline: 29696162]
70. Vink AC, Zuidersma M, Boersma F, de Jonge P, Zuidema SU, Slaets JPJ. The effect of music therapy compared with general recreational activities in reducing agitation in people with dementia: a randomised controlled trial. Int J Geriatr Psychiatry 2013;28(10):1031-1038 [FREE Full text] [doi: 10.1002/gps.3924] [Medline: 23280604]

Abbreviations

ABC: Aberrant Behavior Checklist
CAU: care as usual
CB: challenging behavior
EF: executive functioning
ID: intellectual disabilities
PWI-ID: Personal Well-being Index—Intellectual Disability

RCT: randomized controlled trial
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance
QoL: quality of life

Edited by A Mavragani; submitted 05.09.23; peer-reviewed by E Kawamoto, M Pritchard; comments to author 02.12.23; revised version received 22.12.23; accepted 24.12.23; published 07.02.24.

Please cite as:
Smeets G, Volkers K, Scherder E, Moonen X
An Individual Music Intervention for Adults With Intellectual Disabilities and Challenging Behavior: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2024;13:e52497
URL: https://www.researchprotocols.org/2024/1/e52497
doi:10.2196/52497
PMID:38324357

Protocol

Survivorship Care for Women Living With Ovarian Cancer: Protocol for a Randomized Controlled Trial

Elizabeth Kvale[1], MD, MSPH; Farya Phillips[2], PhD; Samiran Ghosh[3], PhD; Jayanthi Lea[4], MD; Claire Hoppenot[5], MD; Anthony Costales[5], MD; Jan Sunde[5], MD; Hoda Badr[6], PhD; Eberechi Nwogu-Onyemkpa[1], MD, MHS; Nimrah Saleem[1], MPH; Rikki Ward[7], MPH; Bijal Balasubramanian[8], MBBS, PhD

[1]Section of Geriatrics and Palliative Medicine, Department of Medicine, Baylor College of Medicine, Houston, TX, United States

[2]Steve Hicks School of Social Work, The University of Texas at Austin, Austin, TX, United States

[3]Department of Biostatistics and Data Science, School of Public Health, University of Texas Health Science Center, Houston, TX, United States

[4]Department of Obstetrics and Gynecology, University of Texas Southwestern Medical Center, Dallas, TX, United States

[5]Department of Gynecologic Oncology, Dan L Duncan Cancer Center, Baylor College of Medicine, Houston, TX, United States

[6]Department of Epidemiology and Population Sciences, Baylor College of Medicine, Houston, TX, United States

[7]University of Texas Health Houston School of Public Health - Dallas Campus, Dallas, TX, United States

[8]Department of Epidemiology, Human Genetics, and Environmental Sciences, School of Public Health, University of Texas Health Science Center, Houston, TX, United States

Corresponding Author:
Elizabeth Kvale, MD, MSPH
Section of Geriatrics and Palliative Medicine
Department of Medicine
Baylor College of Medicine
1 Baylor Plaza
Houston, TX, 77030
United States
Phone: 1 713 798 2272
Email: Elizabeth.kvale@bcm.edu

Abstract

Background: Ovarian cancer ranks 12th in cancer incidence among women in the United States and 5th among causes of cancer-related death. The typical treatment of ovarian cancer focuses on disease management, with little attention given to the survivorship needs of the patient. Qualitative work alludes to a gap in survivorship care; yet, evidence is lacking to support the delivery of survivorship care for individuals living with ovarian cancer. We developed the POSTCare survivorship platform with input from survivors of ovarian cancer and care partners as a means of delivering patient-centered survivorship care. This process is framed by the chronic care model and relevant behavioral theory.

Objective: The overall goal of this study is to test processes of care that support quality of life (QOL) in survivorship. The specific aims are threefold: first, to test the efficacy of the POSTCare platform in supporting QOL, reducing depressive symptom burden, and reducing recurrence worry. In our second aim, we will examine factors that mediate the effect of the intervention. Our final aim focuses on understanding aspects of care platform design and delivery that may affect the potential for dissemination.

Methods: We will enroll 120 survivors of ovarian cancer in a randomized controlled trial and collect data at 12 and 24 weeks. Each participant will be randomized to either the POSTCare platform or the standard of care process for survivorship. Our population will be derived from 3 clinics in Texas; each participant will have received some combination of treatment modalities; continued maintenance therapy is not exclusionary.

Results: We will examine the impact of the POSTCare-O platform on QOL at 12 weeks after intervention as the primary end point. We will look at secondary outcomes, including depressive symptom burden, recurrence anxiety, and physical symptom burden. We will identify mediators important to the impact of the intervention to inform revisions of the intervention for subsequent studies. Data collection was initiated in November 2023 and will continue for approximately 2 years. We expect results from this study to be published in early 2026.

Conclusions: This study will contribute to the body of survivorship science by testing a flexible platform for survivorship care delivery adapted for the specific survivorship needs of patients with ovarian cancer. The completion of this project will contribute to the growing body of science to guide survivorship care for persons living with cancer.

Trial Registration: ClinicalTrials.gov NCT05752448; https://clinicaltrials.gov/study/NCT05752448

International Registered Report Identifier (IRRID): PRR1-10.2196/48069

(JMIR Res Protoc 2024;13:e48069) doi:10.2196/48069

KEYWORDS

chronic survivorship; metastatic survivor; metavivor; ovarian cancer; persons living with cancer; quality of life; survivor; survivorship care; survivorship transition

Introduction

Ovarian cancer ranks twelfth in cancer incidence among women in the United States but fifth among causes of cancer-related death [1,2]. Treatment of ovarian cancer has benefited from recent scientific advances; however, the impact of novel treatments, including maintenance therapies, on life expectancy remains unclear [3]. Women with ovarian cancer typically complete their initial round of treatment with no evidence of disease but have a high risk of recurrence, with a majority of patients experiencing recurrence 18-24 months after the completion of initial platinum-based chemotherapy [4,5]. The focus becomes disease management, with an emphasis on treatment of cancer, minimization of toxicities, and optimization of quality of life (QOL). Historically, little attention has been paid to the survivorship needs of persons living with controlled cancer, advanced disease, and cancers that have high recurrence rates [6]. Qualitative work describes the unmet need for survivorship in this space of uncertainty, but there is little evidence to guide the delivery of survivorship care for persons living with cancer as a chronic condition.

Cancer health services science incorporated cancer survivorship as a target for care improvement following the 2006 publication of the seminal work "*From Cancer Patient to Cancer Survivor: Lost in Transition*" [7]. This foundational work summarized the challenges associated with cancer survivorship care, including the absence of systematic strategies for care provision, coordination of care across settings, unmet symptom management and psychosocial needs, and an unclear locus of responsibility for care. Subsequent years have seen dramatic increases in cancer survivorship science publications and the development of interventions and programs to meet the needs of cancer survivors. Science, however, has disproportionately focused on breast cancer and other "curable" cancers, and gaps in science and care for persons living with serious or incurable cancer remain to be addressed.

Ovarian cancer is a model of those cancers not typically encompassed in survivorship science and care. Over 19,000 women in the United States will receive a new diagnosis of ovarian cancer this year. For most of them, the point of diagnosis is the beginning of several years of living with cancer, treatment, and uncertainty. Most of these women will be diagnosed with advanced disease; 4 out of 5 patients have regional or advanced disease at the time of diagnosis. This contributes to the unfortunate outcomes associated with ovarian cancer, and 5-year survival rates remain below 50% despite improvements over the past 10 years. Women with ovarian cancer typically undergo treatments including surgery, chemotherapy, sometimes radiation therapy, and increasingly maintenance therapy with targeted therapies [8]. Survivorship care needs for women with ovarian cancer are unique, and frequently, their gynecologic oncology treatment program will also serve as the site of much of their cancer-focused survivorship care [9,10]. Most patients experience residual physical and psychological symptoms posttreatment [11]. Recurrence anxiety, psychosocial needs, sexual functioning, depressive symptoms, and uncertainty related to the care plan moving forward are all reported as sources of impaired well-being among ovarian cancer survivors [12-16]. Women with ovarian cancer being treated in safety net systems are more likely to have poor QOL and less likely to comply with follow-up visits, etc, making it more imperative to develop systems and processes to facilitate their survivorship transition.

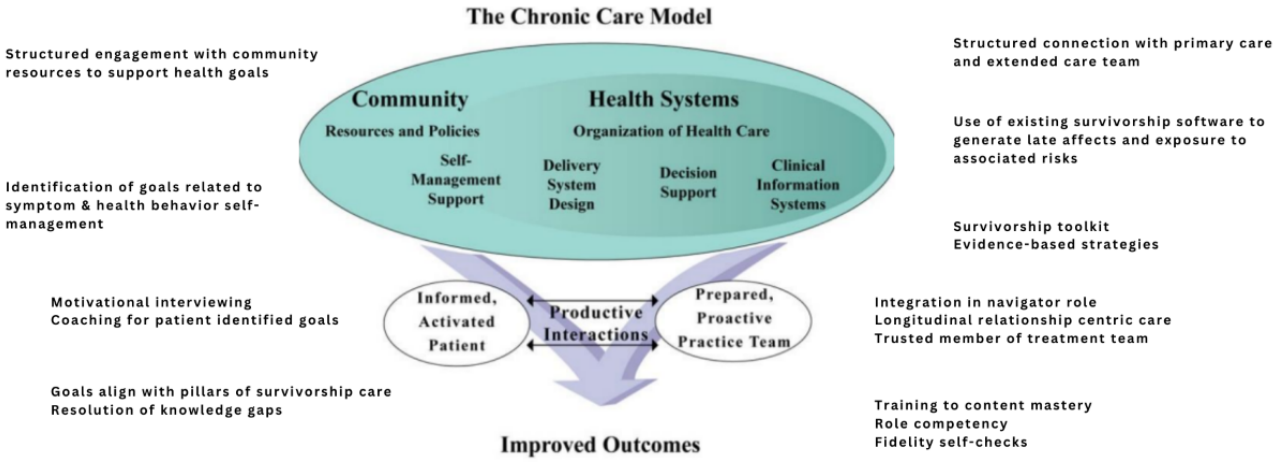
Few studies have examined the impact of survivorship care plans (SCPs) for survivors of ovarian cancer on their QOL. The Registration System Oncological Gynecology trial was a pragmatic cluster randomized trial in which 12 hospitals were randomized to deliver computer-generated SCPs or usual care. The SCP was based on a Dutch translation of the Institute of Medicine format [7]. A total of 174 patients with ovarian cancer enrolled in the trial, of whom 61 received care at an SCP hospital and 113 received care at a usual care hospital. The primary analysis outcomes included satisfaction with care, illness perception, and health care use. There were no overall effects of SCP delivery on any of the scales of satisfaction with care; at 12 months of intention to treat (ITT) analysis, patients in the SCP arm rated the interpersonal skills of nurses lower than patients in the usual care arm. Patients in the SCP arm experienced more symptoms, were more concerned about their illness, and were more emotionally affected than patients in the usual care arm [17]. Further analyses showed increases in health care use among women with anxiety symptoms and those who received radiotherapy [18,19]. Investigators found that patients with ovarian cancer who had lower trust that the treatment would cure their disease due to the SCP reported worse emotional functioning 6 months after treatment [20]. Taken in total, the Registration System Oncological Gynecology trial underscores that for women with ovarian cancer, a templated SCP that emphasizes the frightening long-term outcomes of this disease may impair outcomes. In response to this study and the concerns of our patients, we engaged patients with ovarian cancer and

providers to provide input on the development of POSTCare-O. Their input resulted in a goal related to living well with a serious illness and the inclusion of specific strategies to cope with recurrence anxiety.

We developed the POSTCare survivorship transition platform to deliver a patient-centered and Institute of Medicine (now National Academy of Medicine)–adherent SCP in breast cancer. Women with ovarian cancer experience a significant symptom burden resulting from depression and anxiety [12]. This burden is substantially higher compared with that observed in healthy populations of women and is a phenomenon that persists years into survivorship [15]. The impact of the POSTCare survivorship transition platform on reducing depressive symptom burden has been observed among survivors of breast cancer [21]. However, it remains unknown what effect the adapted intervention may have on patients with ovarian cancer. For this population, the intervention has been modified to target coaching toward the concept of "living well with a serious illness" and symptom self-management. Participants identifying a goal related to recurrence anxiety will receive a brief cognitive intervention based on acceptance and commitment therapy [22]. Strategies to address these issues in survivors of ovarian cancer are currently lacking, and this study may identify potential pathways for improved psychosocial well-being.

The POSTCare survivorship care platform is framed by the chronic care model [23,24] and is also informed by the wealth of literature on care setting transition support [25-27] and patient informants (Figure 1) [28]. Designed to be delivered through telehealth or in-person, POSTCare is best understood as a health services delivery platform that coaches the survivor to engage as an activated agent in her own survivorship care. Recommendations are anchored in existing evidence-based approaches that have historically not found avenues for effective dissemination. The POSTCare platform explicitly maps onto the chronic care model essential elements, including self-management coaching and support directed at both symptoms and wellbeing for survivors. The engagement of community resources occurs with services such as exercise or mental health care to support patients' goals. Delivery system design includes the platform's "plug and play" approach to evidence-based behavioral change support that allows the nature of survivorship support to adjust to patients' needs and goals. Decision support for providers delivering care is built into the platform in a "tool kit" of evidence-based behavioral interventions to support patients' goals [29]. We hypothesize that POSTCare will increase the effective use of evidence-based care and improve outcomes for patients.

Figure 1. Alignment of POSTCare elements with the chronic care model. Developed by The ACT Center, formerly known as the MacColl Center for Health Care Innovation, reprinted with permission from ACP-ASIM Journals and Book.



In POSTCare-O, the POSTCare platform is adapted to meet the needs of survivors of ovarian cancer. We worked with members of the CanSurvive GYN Cancer Support Group in Birmingham, Alabama, and gynecologic oncologists to identify survivorship priorities and needs. Patients with ovarian cancer and their caregivers were clear that they wanted to focus on living well during the survivorship transition, and clinicians felt that concerns that may be important for other cancer types, such as transition to primary care, might be of lesser priority in the context of ovarian cancer. They helped us understand that the essential "work" of cancer survivorship in ovarian cancer is the work of living well despite serious illness and the specter of mortality. Using the palliative dual framework, a technique used to assist patients in the task of living well despite serious illness [30,31], and a brief acceptance and commitment therapy intervention [22], we have incorporated a goal focused on living well with a serious illness that was not a component of the breast cancer POSTCare platform.

The overarching goal of this study is to test processes of care that support outcomes, including QOL, in survivorship. We will use QOL as a primary outcome, but we will also look at factors such as recurrence worry, depressive symptom burden, and survivorship efficacy that may also be influenced by improved care processes. The specific aims of this study are to conduct a randomized controlled trial (RCT) enrolling 120 women with advanced ovarian cancer. We will test the efficacy of the POSTCare platform in supporting QOL, reducing depressive symptom burden, and reducing recurrence worry. In our second aim, we will examine factors associated with the impact of the intervention. Our final aim focuses on understanding aspects of care platform design and delivery that are likely to affect the potential for dissemination. We will use both qualitative and

quantitative methods to assess patient experience, provider experience, and pragmatic aspects of clinical implementation, with the goal of redesigning the implementation for greater dissemination potential.

Methods

Study Design

We will conduct a 2-arm RCT to evaluate the impact of a telehealth-delivered survivorship transition care platform. Survivors of ovarian cancer (N=120) will be randomly allocated to receive survivorship care either using the POSTCare Platform or standard of care. Study design and reporting will be in accordance with the CONSORT (Consolidated Standards of Reporting Trials) checklist. We will use quantitative and qualitative methodologies in a concurrent triangulation mixed methods design using qualitative data to augment our interpretation of quantitative data. Outcomes will be collected at baseline, 12 weeks, and 24 weeks, with the primary outcome being a QOL assessment at 12 weeks after the survivorship transition (Figures 2 and 3).

Figure 2. POSTCare-O randomized clinical trial flow demonstrating enrollment, randomization, and data collection time points.

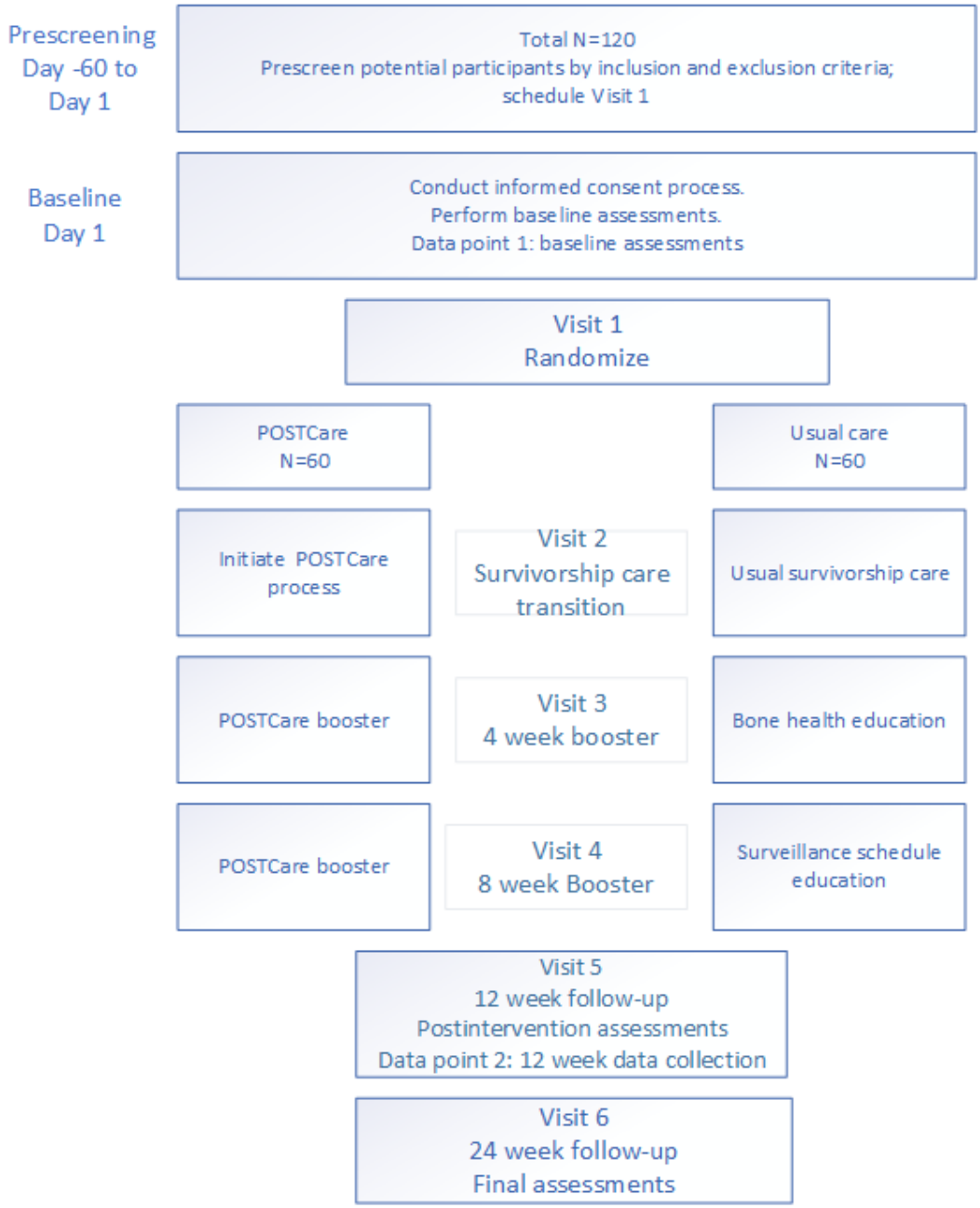
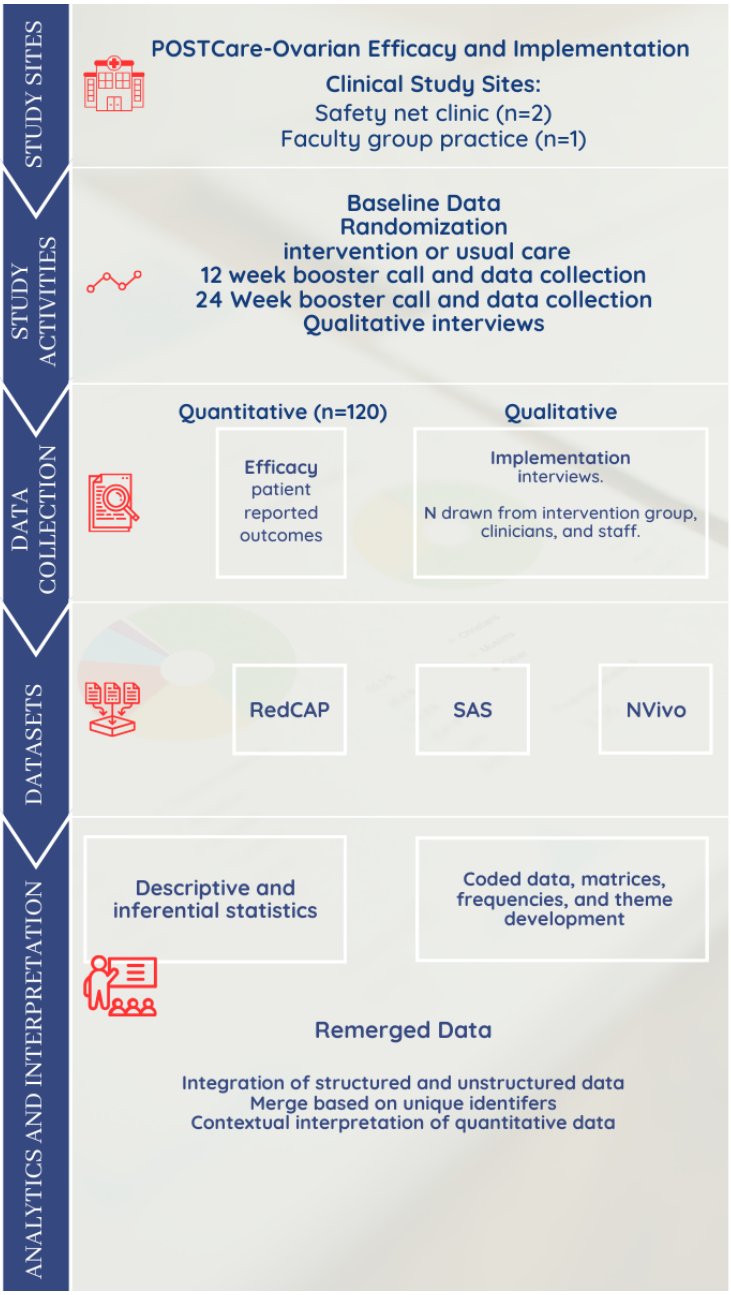


Figure 3. Mixed methods framework demonstrating data sources and integration schema.



Sample Size

We will enroll 120 women completing primary treatment for stage 2-4 ovarian cancer from 3 urban gynecologic oncology clinics located in the US state of Texas. Participants will have received some combination of surgery, chemotherapy, radiation therapy, and biologics. Continued maintenance therapy is not an exclusion factor. The disease-stage sample frame was developed with input from our gynecologic oncology collaborators based on treatment exposures and the similarity of survivorship challenges. Aim 1 proposes to implement a RCT devised to compare QOL measures among patients with ovarian cancer randomized to receive usual care versus the POSTCare survivorship care transition program. The Functional Assessment of Cancer Therapy-Ovarian (FACT-O) QOL survey will be collected at baseline as well as 12 and 24 weeks after the initial course of adjuvant chemotherapy. The primary end point will be the 12-week survey. The sample size of 120 patients provides at least 80% power to detect a 7% increase in the mean FACT-O score for women randomized to the POSTCare survivorship care intervention. This is sufficient to ascertain a minimally important difference of 8 points [32].

Recruitment and Setting

We will recruit participants from gynecologic oncology practices at 3 clinic settings in Texas: 1 safety net practice located in Dallas, 1 safety net practice located in Houston, and 1 faculty group practice located in Houston. Cumulatively, the sites serve approximately 140 eligible patients per year and ensure a diverse population of 120 participants can be recruited during the 24-month recruitment period. A total of 60 participants will be randomly assigned to the intervention group and receive care using the POSTCare process, and another 60 will be randomly assigned to the control group. To be included, patients must (1)

be diagnosed with ovarian cancer at the age of 18 years or older; (2) be within 3 months of completing initial treatment for stage 2-4 ovarian cancer. Treatment may include surgery, chemotherapy, radiation therapy, immunotherapy, or other biologics. Participants may be on maintenance therapy; and (3) be able to provide consent in English or Spanish. Patients who are enrolled in hospice care directly following the treatment conclusion will not be eligible for the study. It is anticipated that this study sample will reflect the ethnic and racial diversity of our clinical settings.

Recruitment Procedures

Study research coordinators will have access to the electronic medical record at each site. They will collaborate with clinical personnel to identify patients who will be completing initial therapy. Coordinators will work to identify patients in treatment at least 8 weeks before the completion of therapy. They will identify an upcoming clinical appointment, either in clinic or infusion, where the team will approach patients to provide information about the study, answer questions they may have, and obtain informed consent. Enrolled participants will be asked to complete a web-based, self-administered survey using a smart device to collect baseline measurements before randomization.

Randomization

After the baseline survey is administered, the biostatistician will use SAS (SAS Institute) to perform a permuted stratified blocked randomization [33]. The stratification variable used maintenance therapy versus no maintenance therapy. The rationale for this stratification is that those patients with ovarian cancer who receive maintenance therapy with a poly (ADP-ribose) polymerase (PARP) inhibitor may experience a different symptom burden or illness trajectory that impacts outcomes [3]. Survivors will be randomly allocated to either the control group or the POSTCare intervention group with a 1:1 ratio (N=120). Stratification will be based on disease stage and maintenance therapy (a PARP inhibitor vs Bevicizumab vs no maintenance). Each of these factors is associated with overall QOL and symptom burden. Participants, clinicians, data collectors, biostatisticians, and investigators will be blinded to allocation. The research nurse interventionist (described below) will not be blinded but will not conduct study activities related to measuring, collecting, or interpreting outcomes. Although this is a low-risk intervention, unblinding decisions will be made by the investigators in the context of serious adverse events attributable to the study. If a decision is made to unblind a participant, the study data coordinating center will undertake the unblinding and protect the confidentiality of treatment assignments for other participants. The treatment assignment will be communicated to the participant and the participant's treating physician. The unblinding event will be reported to the Baylor College of Medicine institutional review board, documented in trial records, and the analysis of study outcomes may be adjusted to account for the unblinded participant to ensure that the integrity of the overall trial results is maintained. Criteria for study dropout include withdrawal of consent, failure to adhere to protocol, loss to follow-up, health changes making further participation burdensome, and personal reasons or changes in life circumstances.

Control Group

The control group will receive standard survivorship care delivered through telehealth. All sites have a standard survivorship visit that includes the use of a software package to generate the delivery of a paper SCP based on American Society of Clinical Oncology guidelines. This comprises a treatment summary, an upcoming surveillance visit schedule, and guidance on late effects. This visit includes the delivery of information and specifically does not include goal setting, use of the dual framework technique (described in the "Intervention" section), acceptance and commitment intervention (described in the "Intervention" section), self-management coaching, or the use of motivational interviewing techniques. To ensure fidelity to control group standards, all visits will be audio-recorded and reviewed to evaluate for evidence of contamination of the control condition. Telephone-based booster contacts will serve as attention control with structured delivery of educational material on surveillance visits and bone health.

Intervention

POSTCare is a structured cancer survivorship navigation platform that seeks to improve cancer outcomes for survivors. Key elements of the platform include personalized self-management support and tailored SCP delivery. The platform is delivered through telehealth (a video platform) and comprises an initial survivorship care transition visit that includes the development and delivery of a personalized care plan. Within the platform framework, a trained nurse uses motivational interviewing and communication skills to engage patients in the development of a POSTCare plan that incorporates health goals and strategies related to surveillance, symptom management, and health behavior [34,35]. Survivor engagement with the POSTCare plan is supported by monthly navigator phone booster follow-up for 2 months, also delivered by the nurse survivorship navigator. Participants will be offered an additional nonstructured phone check-in before their first follow-up visit at 3 months.

Patient-Centered Design

The POSTCare session begins with the coach engaging the survivor in sharing her cancer treatment narrative, anchoring the activity to the patient's experience and needs. The identification of health goals is the central activity of POSTCare and distinguishes this approach to survivorship care from those that simply deliver information. The survivor is asked to think about identifying 1 or more goals in the following survivorship domains: social support, healthy habits, symptom management, and coping with uncertainty. Resource and activity support materials related to goals are maintained in the POSTCare-O web-based survivorship toolkit and used by coaches. As an adaptation for the needs of survivors of ovarian cancer, the dual framework [31] is introduced by coaches in goal-setting as a strategy for living with uncertainty. The dual framework is a strategy used in palliative encounters to help patients focus on what living well means to them while holding the possibility of advancing illness or death in the same cognitive frame. It provides a structure to anchor the focus on living well across the longitudinal trajectory of survivorship navigation. We will introduce a brief cognitive exercise derived from acceptance

and commitment therapy to address recurrence worry if participants articulate this as a survivorship concern and goal [22,36-38]. Our informants indicated that using a focus on what it means to live well despite serious illness is an acceptable palliative intervention even at the initiation of the survivorship period when they wish to be focused on the positive aspects of treatment completion.

The coach and survivor strategize about potential barriers to goal accomplishment and explore ways to address barriers, with the coach using motivational interviewing techniques to explore survivor ambiguity about health goals and nurture self-efficacy in working toward goals. The components of the platform, drawn from an evidence-based approach to care setting transition [24,25,27,39-41], include an emphasis on survivor engagement and activation. The average length of the coaching session is 75 minutes, which includes the creation of the SCP [21].

Booster survivorship navigation telephone contacts occur at 4 weeks and 8 weeks after baseline. The survivorship coaches will review health goals, including living well, adjust goals as needed, discuss progress, identify barriers, and brainstorm about strategies to overcome barriers. The survivorship coaching intervention is delivered through telehealth by the nurse survivorship navigation coach. For participants who do not have a smart device, the intervention can be delivered through a smart device provided by the study in a clinic setting.

Qualitative Methods

Qualitative methods will be used to inform the adaptation and refinement of the intervention. Interviews will be undertaken with 3 groups of informants: women living with ovarian cancer; nurses who have been trained in the POSTCare model; and gynecologic oncologists, clinic staff, and administrators. Semistructured exit interviews will be conducted by specially trained research team members within 30 days of completing the intervention. Although the exit interview questions will be stated as broad questions, the researcher will be trained to probe for details, including asking for specifics and operational examples.

We will partner with women enrolled in this study to conduct semistructured interviews on the POSTCare survivorship care experience. Interview topics will include (1) timing of survivorship care—both initiation of survivorship transition and longitudinal care; (2) critique of proposed intervention content and existing materials; (3) understanding the meaning of this intervention for participants; (4) exploring individual differences between experiences and outcomes; and (5) evaluation of intervention length, intensity, frequency, and mode of delivery. Interviews will be conducted with gynecologic oncology nurses who have completed the POSTCare-O web-based training and used components of the POSTCare model to provide the intervention. Finally, we will explore the same interview topics with clinic staff at each study site to learn what elements of the POSTCare model work well in their clinical setting, which elements they are able to use routinely, which components seem to most meet the needs of their patients, and which elements of survivorship care they find most satisfying.

Outcome Measures

We will use the FACT-O instrument as the primary end point for the clinical trial. The FACT-O is a 38-item assessment that comprises a core QOL instrument (the FACT-General) and a 12-item ovarian module. The internal consistency for the complete instrument is Cronbach α=.92, and the test-retest reliability is r=0.81 [42]. The subscales demonstrate similar acceptable psychometrics. This instrument is widely used in trials and will allow us to meaningfully compare the results of this trial to those of other studies that examine QOL. The minimally important difference is the “smallest difference” in FACT-O scores that patients perceive as clinically important and is 3-8 points [43]. We have powered the study to identify this level of change.

The Patient Health Questionnaire-9 (PHQ-9) is a widely used screening tool for depression, consisting of 9 items [44]. It takes approximately 5 minutes to complete and has been found to be a valid and reliable measure of depressive symptoms in various populations, including patients with cancer. The total score on the PHQ-9 can range from 9 to 27, with higher scores indicating a higher level of depressive symptom burden. A study by Thekkumpurath et al [45] found that the PHQ-9 was a valid and reliable measure of depression in patients with cancer and recommended its use in clinical practice. Additionally, the PHQ-9 has been used as an outcome measure in various interventions for depression, including those targeting patients with cancer [46]. The PHQ-9 has demonstrated good internal consistency and test-retest reliability, with a coefficient α=.89 and an intraclass correlation coefficient of 0.84, respectively [44].

The Fear of Cancer Recurrence-7 (FCR-7) is a 7-item questionnaire designed to offer a psychometrically sound assessment of fear of cancer recurrence with a limited response burden. The instrument comprises 7 questions: 5 that use a 5-point Likert scale ranging from 1 (not at all) to 5 (all the time), and a single question that uses an 11-point Likert scale ranging from 0 (not at all) to 10 (a great deal). Total scores on the measure range from 6 to 45 [47]. A cutoff score of 17 or above reflects moderate fear of cancer recurrence, and a score of 27 or above indicates severe fear of cancer recurrence. The measure demonstrates good internal consistency (Cronbach α=.92) and validity as compared to measures of anxiety and depression [48].

Other measures used as secondary outcomes and potential predictors were selected with a priority on acceptable psychometric performance in similar populations and acceptable performance in one of our previous studies.

“Aim 1” proposes to implement a RCT devised to compare QOL measures among patients with ovarian cancer randomized to receive usual care versus the POSTCare survivorship care transition program. Outcome measures, including the FACT-O QOL survey, the FCR-7 survey, and the PHQ-9, will be collected at baseline as well as 12 and 24 weeks after the initial course of adjuvant chemotherapy. The primary end point will consist of the 12-week FACT-O survey. The sample size of 120 patients provides at least 80% power to detect a 7% increase in the mean FACT-O score for women randomized to the

POSTCare survivorship care intervention. This is sufficient to ascertain a minimally important difference of 8 points. Secondary outcomes (Table 1) will also be assessed at 12 and 24 weeks. Baseline descriptive statistics will be presented by site. Longitudinal analysis of the FACT-O QOL scores will use a mixed effects linear model with a restricted maximum likelihood estimation method, and an unstructured covariance matrix will be used to estimate trends. An interaction between intervention and time will be estimated to explore the effectiveness of POSTCare for time-varying trends [49]. Though the mixed effect model can accommodate some degree of missing data under the ignorability assumption, we also plan to use multiple imputations using the random forest method [50,51] to accommodate missing data (if greater than 10% of survey items), which will be assumed to be missing at random. In the event of a sign of a violation of that assumption, a pattern mixture model will be used to mitigate the effect of informative missingness. Secondary analyses will evaluate relationships between baseline and 12-week FACT-O scores and clinical end points progression-free survival (PFS) and overall survival (OS). Cox proportional hazard models will be used to estimate the relative risk of PFS and death per increase in FACT-O [52]. Ties in failure times will be handled with the approximate likelihood of Efron. PFS and OS will be measured from the date of randomization. PFS is defined as the minimum amount of time until clinical progression, death, or the date of last contact. OS is the duration from randomization to death or to the date of last contact (right-censoring). As is customary, secondary analyses are not powered but may help generate additional evidence that needs to be tested in the future by a properly powered study.

Table 1. Summary of variables and outcomes.

Variables for outcome analysis	Measures	Reliability, *r*	Source
Primary outcomes			
Quality of Life	• Functional Assessment of Cancer Therapy-Ovarian [42]	• .92	Patient self-report
Depression	• Patient Health Questionnaire-9 [45]	• .94	Patient self-report
Recurrence anxiety	• Fear of Cancer Recurrence-7 [47]	• .93	Patient self-report
Secondary outcomes			
Patient self-efficacy	• Stanford Chronic Illness Self-Efficacy Scale [53] • Patient Activation Measure [54]	• .91 • .87-.91	Patient self-report
Satisfaction with communication	• Stanford communication with physicians [55]	• .89	Patient self-report
Health care use	• Stanford Health Care Utilization [53]	• .76-.97	Patient self-report
Satisfaction with care coordination	• Stanford Self Efficacy [55]	• .91	Patient self-report
Perception of Informational Support	• Patient-Reported Outcomes Measurement Information System: informational support measure [56]	• __[a]	Patient self-report
Symptom Burden	• MD Anderson Symptom Inventory for ovarian cancer • Stanford Social/Role Activities Limitations	• .89-.90 • .91	Patient self-report
Predictor variables			
Demographic or medical information	• Demographic questionnaire: will include gender, race, and treatment history	• N/A[b]	Electronic medical record
Cancer coping style	• Brief version of the Coping Orientation to Problems Experienced [57]	• .75	Patient self-report
Social support	• Social Provisions Scale [58]	• .92	Patient self-report
Education level	• Stanford Education [59]	• N/A	Patient self-report

[a]Not available.

[b]N/A: not applicable.

"Aim 2" applies mediation analysis to the data acquired from the RCT proposed in Aim 1. Aim 2 explores the potential for heterogeneity in the effectiveness of the POSTCare survivorship program. The primary end point for aim 2 is QOL at 6 months, as measured by the FACT-O. Combining both study arms, subgroup analysis will assess the distributions of potential prognostic factors for QOL at 6 months. Analyses will adjust for statistically significant prognostic factors. Mediation

modeling will be applied to decompose the relationships among the care plans, intermediate surrogate markers of QOL acquired during the course of follow-up, and QOL at 6 months. Surrogate markers include patient activation, goal setting, self-efficacy, and care satisfaction, to be collected at 12 weeks and 24 weeks from surveys identified in Table 1. For each surrogate marker, an intermediate response will be defined. The direct and indirect impact of POSTCare will be estimated for each surrogate response using mediation analysis [60-62] to elucidate the causal mechanisms of QOL and assist with planning for larger confirmatory studies and studies in other disease types.

Qualitative data for intervention adaptation will be analyzed using a thematic analysis framework. At the outset of the process of analysis and interpretation, the qualitative team will read each transcript from interviews in its entirety to achieve a global sense of substance and context. Working independently of one another, we will engage in a line-by-line search for recurring ideas, coding each transcript for themes. After identifying dominant themes, we will evaluate the degree of consensus among participants. An initial codebook will be developed from the interview guide and adaptation framework. A master code book will be entered into NVivo (version 11; QSR International). The data will be merged with the quantitative data to inform interpretation and draw stronger inferences. As described by Farquhar et al [63], mixed methods are particularly beneficial where the interventions are complex and the platform for evaluation and identification of suitable outcomes is challenging. Insights gained from quantitative and qualitative approaches complement each other to provide a more in-depth understanding. This deeper understanding can inform the process of refining interventions and hypothesis generation and facilitate replication of the intervention through greater knowledge of the active components and potential barriers to implementation. Moreover, qualitative research can be used to examine and address key uncertainties before dissemination efforts [64]. Interviews will be conducted by experienced qualitative interviewers on our established research team. We anticipate conducting up to 30 interviews at the outset of the process of analysis and interpretation. We will use all data sources to inform the revision of the POSTCare-O platform before active dissemination [65-68].

Ethical Considerations

Ethical approval for this trial has been obtained through the Baylor College of Medicine Institutional Review Board (H52939). All participants in the trial will provide informed consent before the initiation of study activities. The primary risk in this study is a risk to confidentiality. All study data will be uploaded directly to the data coordinating center, REDCap (Research Electronic Data Capture; Vanderbilt University), which is implemented to be compliant with HIPAA (Health Insurance Portability and Accountability Act) standards. Participants will receive compensation for their participation in the trial in a longitudinal manner, with US $10 at baseline and 12 week data collection timepoints and US $30 at the 24 week time point. Total participant compensation is US $50.

Results

This study will be conducted over a period of 3 years. Data collection was initiated in November 2023 and will continue for approximately 2 years. Approval for the study protocol has been obtained from the institutional review board of Baylor College of Medicine, and a reliance agreement has been approved by the University of Texas Southwestern Medical Center and Parkland Health. We will report on the outcomes identified above as a primary study activity. We also plan to collaborate with patients and clinicians to identify adaptations to the POSTCare-O platform to optimize dissemination potential. Results from this study will inform preparation to study survivorship care for patients living with advanced cancer and other disease types. We expect results from this study to be published in early 2026.

Discussion

Overview

The overarching goal of this research program is to improve QOL and well-being for women living with ovarian cancer. This paper details the protocol for a randomized, controlled, dual-blinded study testing a survivorship care platform for women completing initial treatment for ovarian cancer. The gaps in science related to the care of patients with advanced or incurable cancer are thoughtfully articulated in a recent National Cancer Institute meeting report [6].

This study will address several of the gaps in science that exist relative to women living with ovarian cancer. Much of the science focused on the needs of survivors of cancer has been conducted in breast cancer populations; however, a solid body of work exists that characterizes the impact of ovarian cancer and treatment on QOL, sexual well-being, care preferences, and health care use. This study, with a collection of measures related to symptom burden and psychosocial well-being, will characterize unmet needs at baseline among survivors of ovarian cancer, and we will be able to place our work in the context of the existing science for interpretation. Further, our qualitative stream will provide additional context for interpretation of our quantitative data as we work to better understand the patients' experience.

Although overt efforts have been made to minimize limitations by design, this study will have several limitations. While we expect to meet our sample size target of recruiting 120 women with ovarian cancer, practical aspects of participant recruitment and budgetary constraints will constrain our ability to stratify the population and evaluate potential mediators. Furthermore, the highly structured nature of care delivery for this study, including consistent intervention delivery by a single research nurse, may not reflect the conditions encountered in a "real-world" implementation of this health services intervention that is intended to be optimized for dissemination. While we have put in place measures to address concerns related to intervention fidelity, including review of recordings of intervention sessions with fidelity checklists and ongoing education to ensure consistent delivery, inconsistent delivery remains a potential source of bias for this study. This study will

take place at 2 US "safety net" clinics that serve economically disadvantaged patients primarily, as well as a university practice that serves individuals with private or federal insurance. While this design should give us a representative sample within our geographic region, the results may not be generalizable to other regions of the United States or health care systems outside the United States. Despite these limitations, this study will make a significant contribution to survivorship science in ovarian cancer by examining aspects of supportive care that may improve QOL for patients.

Acknowledgments

The authors would like to gratefully acknowledge all the participants and their families, especially the CanSurvive GYN Cancer Support Group in Birmingham, Alabama, United States.

Data Availability

The data sets generated during and/or analyzed during this study are available in the Palliative Care Research Collaborative De-Identified Data Repository [69].

Conflicts of Interest

None declared.

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin 2022;72(1):7-33 [FREE Full text] [doi: 10.3322/caac.21708] [Medline: 35020204]
2. American Cancer Society. URL: https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2022.html [accessed 2023-01-23]
3. Tattersall A, Ryan N, Wiggans AJ, Rogozińska E, Morrison J. Poly(ADP-ribose) polymerase (PARP) inhibitors for the treatment of ovarian cancer. Cochrane Database Syst Rev 2022;2(2):CD007929 [FREE Full text] [doi: 10.1002/14651858.CD007929.pub4] [Medline: 35170751]
4. Friedrich M, Friedrich D, Kraft C, Rogmans C. Multimodal treatment of primary advanced ovarian cancer. Anticancer Res 2021;41(7):3253-3260 [FREE Full text] [doi: 10.21873/anticanres.15111] [Medline: 34230119]
5. Gadducci A, Guarneri V, Peccatori FA, Ronzino G, Scandurra G, Zamagni C, et al. Current strategies for the targeted treatment of high-grade serous epithelial ovarian cancer and relevance of BRCA mutational status. J Ovarian Res 2019;12(1):9 [FREE Full text] [doi: 10.1186/s13048-019-0484-6] [Medline: 30691488]
6. Mollica MA, Smith AW, Tonorezos E, Castro K, Filipski KK, Guida J, et al. Survivorship for individuals living with advanced and metastatic cancers: national cancer institute meeting report. J Natl Cancer Inst 2022;114(4):489-495 [FREE Full text] [doi: 10.1093/jnci/djab223] [Medline: 34878107]
7. National Research Council, Institute of Medicine, National Cancer Policy Board, Committee on Cancer Survivorship, Improving Care and Quality of Life. In: Hewitt M, Greenfield S, Stovall E, editors. From Cancer Patient to Cancer Survivor: Lost in Transition. Washington, DC: The National Academies Press; 2006.
8. National Academies of Sciences, Engineering, and Medicine, Institute of Medicine, Board on Health Care Services, Committee on the State of the Science in Ovarian Cancer Research. Ovarian Cancers: Evolving Paradigms in Research and Care. Washington, D.C: National Academies Press (US); 2016.
9. Hay CM, Lefkowits C, Crowley-Matoka M, Bakitas MA, Clark LH, Duska LR, et al. Strategies for introducing outpatient specialty palliative care in gynecologic oncology. J Oncol Pract 2017;13(9):e712-e720 [FREE Full text] [doi: 10.1200/JOP.2017.020818] [Medline: 28763259]
10. Hay CM, Lefkowits C, Crowley-Matoka M, Bakitas MA, Clark LH, Duska LR, et al. Gynecologic oncologist views influencing referral to outpatient specialty palliative care. Int J Gynecol Cancer 2017;27(3):588-596 [FREE Full text] [doi: 10.1097/IGC.0000000000000893] [Medline: 28060140]
11. Stavraka C, Ford A, Ghaem-Maghami S, Crook T, Agarwal R, Gabra H, et al. A study of symptoms described by ovarian cancer survivors. Gynecol Oncol 2012;125(1):59-64. [doi: 10.1016/j.ygyno.2011.12.421] [Medline: 22155797]
12. Watts S, Prescott P, Mason J, McLeod N, Lewith G. Depression and anxiety in ovarian cancer: a systematic review and meta-analysis of prevalence rates. BMJ Open 2015;5(11):e007618 [FREE Full text] [doi: 10.1136/bmjopen-2015-007618] [Medline: 26621509]
13. Hopkins TG, Stavraka C, Gabra H, Fallowfield L, Hood C, Blagden S. Sexual activity and functioning in ovarian cancer survivors: an internet-based evaluation. Climacteric 2015;18(1):94-98. [doi: 10.3109/13697137.2014.929104] [Medline: 25029389]
14. Lockwood-Rayermann S. Survivorship issues in ovarian cancer: a review. Oncol Nurs Forum 2006;33(3):553-562. [doi: 10.1188/06.ONF.553-562] [Medline: 16676012]

15. Horsboel TA, Kjaer SK, Johansen C, Suppli NP, Ammitzbøll G, Frøding LP, et al. Increased risk for depression persists for years among women treated for gynecological cancers—a register-based cohort study with up to 19 years of follow-up. Gynecol Oncol 2019;153(3):625-632. [doi: 10.1016/j.ygyno.2019.03.259] [Medline: 30975472]
16. Carey MS, Bacon M, Tu D, Butler L, Bezjak A, Stuart GC. The prognostic effects of performance status and quality of life scores on progression-free survival and overall survival in advanced ovarian cancer. Gynecol Oncol 2008;108(1):100-105. [doi: 10.1016/j.ygyno.2007.08.088] [Medline: 17920108]
17. Nicolaije KAH, Ezendam NPM, Vos MC, Pijnenborg JMA, Boll D, Boss EA, et al. Impact of an automatically generated cancer survivorship care plan on patient-reported outcomes in routine clinical practice: longitudinal outcomes of a pragmatic, cluster randomized trial. J Clin Oncol 2015;33(31):3550-3559 [FREE Full text] [doi: 10.1200/JCO.2014.60.3399] [Medline: 26304900]
18. Jeppesen MM, Ezendam NPM, Pijnenborg JMA, Vos MC, Boll D, Kruitwagen RFPM, et al. The impact of the survivorship care plan on health care use: 2-year follow-up results of the ROGY care trial. J Cancer Surviv 2018;12(1):18-27. [doi: 10.1007/s11764-017-0639-7] [Medline: 28875470]
19. de Rooij BH, Ikiz H, Boll D, Pijnenborg JMA, Pijlman BM, Kruitwagen RFPM, et al. Recurrent cancer is associated with dissatisfaction with care-a longitudinal analysis among ovarian and endometrial cancer patients. Int J Gynecol Cancer 2018;28(3):614-622. [doi: 10.1097/IGC.0000000000001204] [Medline: 29466257]
20. de Rooij BH, Ezendam NPM, Nicolaije KAH, Lodder P, Vos MC, Pijnenborg JMA, et al. Survivorship care plans have a negative impact on long-term quality of life and anxiety through more threatening illness perceptions in gynecological cancer patients: the ROGY care trial. Qual Life Res 2018;27(6):1533-1544 [FREE Full text] [doi: 10.1007/s11136-018-1825-4] [Medline: 29511906]
21. Kvale EA, Huang CHS, Meneses KM, Demark-Wahnefried W, Bae S, Azuero CB, et al. Patient-centered support in the survivorship care transition: outcomes from the patient-owned survivorship care plan intervention. Cancer 2016;122(20):3232-3242 [FREE Full text] [doi: 10.1002/cncr.30136] [Medline: 27387096]
22. Serfaty M, Armstrong M, Vickerstaff V, Davis S, Gola A, McNamee P, et al. Acceptance and Commitment Therapy for Adults with Advanced Cancer (CanACT): a feasibility randomised controlled trial. Psychooncology 2019;28(3):488-496. [doi: 10.1002/pon.4960] [Medline: 30511788]
23. McCorkle R, Ercolano E, Lazenby M, Schulman-Green D, Schilling LS, Lorig K, et al. Self-management: enabling and empowering patients living with cancer as a chronic illness. CA Cancer J Clin 2011;61(1):50-62 [FREE Full text] [doi: 10.3322/caac.20093] [Medline: 21205833]
24. Coleman K, Austin BT, Brach C, Wagner EH. Evidence on the chronic care model in the new millennium. Health Aff (Millwood) 2009;28(1):75-85 [FREE Full text] [doi: 10.1377/hlthaff.28.1.75] [Medline: 19124857]
25. Coleman EA, Smith JD, Frank JC, Min SJ, Parry C, Kramer AM. Preparing patients and caregivers to participate in care delivered across settings: the care transitions intervention. J Am Geriatr Soc 2004;52(11):1817-1825. [doi: 10.1111/j.1532-5415.2004.52504.x] [Medline: 15507057]
26. Coleman EA. Falling through the cracks: challenges and opportunities for improving transitional care for persons with continuous complex care needs. J Am Geriatr Soc 2003;51(4):549-555. [doi: 10.1046/j.1532-5415.2003.51185.x] [Medline: 12657078]
27. Coleman EA, Parry C, Chalmers S, Min SJ. The care transitions intervention: results of a randomized controlled trial. Arch Intern Med 2006;166(17):1822-1828 [FREE Full text] [doi: 10.1001/archinte.166.17.1822] [Medline: 17000937]
28. Kvale EA, Meneses K, Demark-Wahnefried W, Bakitas M, Ritchie C. Formative research in the development of a care transition intervention in breast cancer survivors. Eur J Oncol Nurs 2015;19(4):329-335. [doi: 10.1016/j.ejon.2015.01.010] [Medline: 25726359]
29. Kazdin AE, Blase SL. Rebooting psychotherapy research and practice to reduce the burden of mental illness. Perspect Psychol Sci 2011;6(1):21-37 [FREE Full text] [doi: 10.1177/1745691610393527] [Medline: 26162113]
30. Jacobsen J, Kvale E, Rabow M, Rinaldi S, Cohen S, Weissman D, et al. Helping patients with serious illness live well through the promotion of adaptive coping: a report from the Improving Outpatient Palliative Care (IPAL-OP) initiative. J Palliat Med 2014;17(4):463-468. [doi: 10.1089/jpm.2013.0254] [Medline: 24579823]
31. Jacobsen J, Brenner K, Greer JA, Jacobo M, Rosenberg L, Nipp RD, et al. When a patient is reluctant to talk about it: a dual framework to focus on living well and tolerate the possibility of dying. J Palliat Med 2018;21(3):322-327. [doi: 10.1089/jpm.2017.0109] [Medline: 28972862]
32. Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd Edition. Hillsdale, NJ: Erlbaum; 1988.
33. Kernan WN, Viscoli CM, Makuch RW, Brass LM, Horwitz RI. Stratified randomization for clinical trials. J Clin Epidemiol 1999;52(1):19-26 [FREE Full text] [doi: 10.1016/s0895-4356(98)00138-3] [Medline: 9973070]
34. National Research Council, Institute of Medicine, National Cancer Policy Board, Committee on Cancer Survivorship, Improving Care and Quality of Life. In: Hewitt M, Greenfield S, Stovall E, editors. From Cancer Patient to Cancer Survivor: Lost in Transition. Washington, DC: National Academies Press; 2006.
35. The LiveSTRONG essential elements of survivorship care: definitions and recommendations. Livestrong. 2011. URL: https://www.livestrong.org/what-we-do/reports/survivorship/the-essential-elements-of-survivorship-care-definitions-and-recommendations [accessed 2024-01-06]

36. Low J, Serfaty M, Davis S, Vickerstaff V, Gola A, Omar RZ, et al. Acceptance and commitment therapy for adults with advanced cancer (CanACT): study protocol for a feasibility randomised controlled trial. Trials 2016;17(1):77 [FREE Full text] [doi: 10.1186/s13063-016-1169-8] [Medline: 26865162]
37. Li H, Wong CL, Jin X, Chen J, Chong YY, Bai Y. Effects of acceptance and commitment therapy on health-related outcomes for patients with advanced cancer: a systematic review. Int J Nurs Stud 2021;115:103876. [doi: 10.1016/j.ijnurstu.2021.103876] [Medline: 33517079]
38. Hulbert-Williams NJ, Hulbert-Williams L, Patterson P, Suleman S, Howells L. Acceptance and Commitment Therapy (ACT)-enhanced communication skills: development and evaluation of a novel training programme. BMJ Support Palliat Care 2021. [doi: 10.1136/bmjspcare-2020-002786] [Medline: 33762268]
39. Coleman EA, Berenson RA. Lost in transition: challenges and opportunities for improving the quality of transitional care. Ann Intern Med 2004;141(7):533-536. [doi: 10.7326/0003-4819-141-7-200410050-00009] [Medline: 15466770]
40. Coleman EA, Rosenbek SA, Roman SP. Disseminating evidence-based care into practice. Popul Health Manag 2013;16(4):227-234. [doi: 10.1089/pop.2012.0069] [Medline: 23537156]
41. Coleman EA, Min SJ. Patients' and family caregivers' goals for care during transitions out of the hospital. Home Health Care Serv Q 2015;34(3-4):173-184. [doi: 10.1080/01621424.2015.1095149] [Medline: 26496503]
42. Basen-Engquist K, Bodurka-Bevers D, Fitzgerald MA, Webster K, Cella D, Hu S, et al. Reliability and validity of the functional assessment of cancer therapy-ovarian. J Clin Oncol 2001;19(6):1809-1817. [doi: 10.1200/JCO.2001.19.6.1809] [Medline: 11251013]
43. von Gruenigen VE, Huang HQ, Gil KM, Gibbons HE, Monk BJ, Rose PG, et al. A comparison of quality-of-life domains and clinical factors in ovarian cancer patients: a Gynecologic Oncology Group study. J Pain Symptom Manage 2010;39(5):839-846 [FREE Full text] [doi: 10.1016/j.jpainsymman.2009.09.022] [Medline: 20471545]
44. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001;16(9):606-613 [FREE Full text] [doi: 10.1046/j.1525-1497.2001.016009606.x] [Medline: 11556941]
45. Thekkumpurath P, Walker J, Butcher I, Hodges L, Kleiboer A, O'Connor M, et al. Screening for major depression in cancer outpatients: the diagnostic accuracy of the 9-item patient health questionnaire. Cancer 2011;117(1):218-227 [FREE Full text] [doi: 10.1002/cncr.25514] [Medline: 20737537]
46. Osborn RL, Demoncada AC, Feuerstein M. Psychosocial interventions for depression, anxiety, and quality of life in cancer survivors: meta-analyses. Int J Psychiatry Med 2006;36(1):13-34. [doi: 10.2190/EUFN-RV1K-Y3TR-FK0L] [Medline: 16927576]
47. Humphris GM, Watson E, Sharpe M, Ozakinci G. Unidimensional scales for fears of cancer recurrence and their psychometric properties: the FCR4 and FCR7. Health Qual Life Outcomes 2018;16(1):30 [FREE Full text] [doi: 10.1186/s12955-018-0850-x] [Medline: 29471823]
48. Bergerot CD, Ferreira LN, Molina LNM, Pagung LB, Pedersen BDS, de Andrade TG, et al. Fear of cancer recurrence among Brazilian patients with cancer: translation and cultural adaptation of FCR4/7 and FCRI-SF measures. J Psychosom Res 2023;165:111125. [doi: 10.1016/j.jpsychores.2022.111125] [Medline: 36610336]
49. Laird NM. Missing data in longitudinal studies. Stat Med 1988;7(1-2):305-315. [doi: 10.1002/sim.4780070131] [Medline: 3353609]
50. Meyer M. Fast imputation of missing values. missRanger. 2023. URL: https://cran.r-project.org/web/packages/missRanger/missRanger.pdf [accessed 2024-01-06]
51. Hong S, Lynn HS. Accuracy of random-forest-based imputation of missing data in the presence of non-normality, non-linearity, and interaction. BMC Med Res Methodol 2020;20(1):199 [FREE Full text] [doi: 10.1186/s12874-020-01080-1] [Medline: 32711455]
52. Kleinbaum DG, Klein M. The cox proportional hazards model and its characteristics. Survival Analysis 2012:97-159 [FREE Full text] [doi: 10.1007/978-1-4757-2555-1_3]
53. Lorig KR, Sobel DS, Ritter PL, Laurent D, Hobbs M. Effect of a self-management program on patients with chronic disease. Eff Clin Pract 2001;4(6):256-262. [Medline: 11769298]
54. Hibbard JH, Stockard J, Mahoney ER, Tusler M. Development of the Patient Activation Measure (PAM): conceptualizing and measuring activation in patients and consumers. Health Serv Res 2004;39(4 Pt 1):1005-1026 [FREE Full text] [doi: 10.1111/j.1475-6773.2004.00269.x] [Medline: 15230939]
55. Lorig K, Stewart A, Ritter P, Gonzalez V, Laurent D, Lynch J. Outcome Measures for Health Education and Other Health Care Interventions. Thousand Oaks, CA: Sage Publications; 1996.
56. Garcia SF, Cella D, Clauser SB, Flynn KE, Lad T, Lai JS, et al. Standardizing patient-reported outcomes assessment in cancer clinical trials: a patient-reported outcomes measurement information system initiative. J Clin Oncol 2007;25(32):5106-5112. [doi: 10.1200/JCO.2007.12.2341] [Medline: 17991929]
57. Hagan TL, Fishbein JN, Nipp RD, Jacobs JM, Traeger L, Irwin KE, et al. Coping in patients with incurable lung and gastrointestinal cancers: a validation study of the brief COPE. J Pain Symptom Manage 2017;53(1):131-138 [FREE Full text] [doi: 10.1016/j.jpainsymman.2016.06.005] [Medline: 27725249]
58. Cutrona C, Russelll D. The provisions of social relationships and adaptation to stress. In: Advances in Personal Relationships. Chicago, IL: JAI Press; 1987:37-67.

59. Lorig KR, Sobel DS, Stewart AL, Brown BW, Bandura A, Ritter P, et al. Evidence suggesting that a chronic disease self-management program can improve health status while reducing hospitalization: a randomized trial. Med Care 1999;37(1):5-14. [doi: 10.1097/00005650-199901000-00003] [Medline: 10413387]
60. Yuan Y, MacKinnon DP. Bayesian mediation analysis. Psychol Methods 2009;14(4):301-322 [FREE Full text] [doi: 10.1037/a0016972] [Medline: 19968395]
61. Kraemer HC, Wilson GT, Fairburn CG, Agras WS. Mediators and moderators of treatment effects in randomized clinical trials. Arch Gen Psychiatry 2002;59(10):877-883. [doi: 10.1001/archpsyc.59.10.877] [Medline: 12365874]
62. Kraemer HC, Mintz J, Noda A, Tinklenberg J, Yesavage JA. Caution regarding the use of pilot studies to guide power calculations for study proposals. Arch Gen Psychiatry 2006;63(5):484-489. [doi: 10.1001/archpsyc.63.5.484] [Medline: 16651505]
63. Farquhar MC, Ewing G, Booth S. Using mixed methods to develop and evaluate complex interventions in palliative care research. Palliat Med 2011;25(8):748-757 [FREE Full text] [doi: 10.1177/0269216311417919] [Medline: 21807749]
64. O'Cathain A, Croot L, Sworn K, Duncan E, Rousseau N, Turner K, et al. Taxonomy of approaches to developing interventions to improve health: a systematic methods overview. Pilot Feasibility Stud 2019;5:41 [FREE Full text] [doi: 10.1186/s40814-019-0425-6] [Medline: 30923626]
65. Mayer DK, Birken SA, Chen RC. Avoiding implementation errors in cancer survivorship care plan effectiveness studies. J Clin Oncol 2015;33(31):3528-3530 [FREE Full text] [doi: 10.1200/JCO.2015.62.6937] [Medline: 26304906]
66. Palmer SC, Jacobs LA, DeMichele A, Risendal B, Jones AF, Stricker CT. Metrics to evaluate treatment summaries and survivorship care plans: a scorecard. Support Care Cancer 2014;22(6):1475-1483 [FREE Full text] [doi: 10.1007/s00520-013-2107-x] [Medline: 24414997]
67. Dulko D, Pace CM, Dittus KL, Sprague BL, Pollack LA, Hawkins NA, et al. Barriers and facilitators to implementing cancer survivorship care plans. Oncol Nurs Forum 2013;40(6):575-580 [FREE Full text] [doi: 10.1188/13.ONF.575-580] [Medline: 24161636]
68. Birken SA, Ellis SD, Walker JS, DiMartino LD, Check DK, Gerstel AA, et al. Guidelines for the use of survivorship care plans: a systematic quality appraisal using the AGREE II instrument. Implement Sci 2015;10(1):63 [FREE Full text] [doi: 10.1186/s13012-015-0254-9] [Medline: 25935752]
69. PCRC De-identified Data Repository (DiDR). URL: https://palliativecareresearch.org/corescenters/data-informatics-statistics-core-disc/pcrc-de-identified-data-repository-didr [accessed 2024-02-02]

Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
FACT-O: Functional Assessment of Cancer Therapy-Ovarian
FCR-7: Fear of Cancer Recurrence-7
HIPAA: Health Insurance Portability and Accountability Act
ITT: intention to treat
OS: overall survival
PARP: poly (ADP-ribose) polymerase
PFS: progression-free survival
PHQ-9: Patient Health Questionnaire-9
QOL: quality of life
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SCP: survivorship care plan

Edited by A Mavragani; submitted 26.05.23; peer-reviewed by H Shin, S Chaudhry; comments to author 06.11.23; revised version received 01.12.23; accepted 13.12.23; published 09.02.24.

Please cite as:
Kvale E, Phillips F, Ghosh S, Lea J, Hoppenot C, Costales A, Sunde J, Badr H, Nwogu-Onyemkpa E, Saleem N, Ward R, Balasubramanian B
Survivorship Care for Women Living With Ovarian Cancer: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2024;13:e48069
URL: https://www.researchprotocols.org/2024/1/e48069
doi:10.2196/48069
PMID:38335019

Protocol

Cerebral Mechanism of Tuina on the Descending Pain Inhibitory System in Knee Osteoarthritis: Protocol for a Randomized Controlled Trial

Hui Xu[1,2*], PhD; Zheng Wang[1,2*], PhD; Zhen Wang[1,2*], PhD; Hang Zhou[1,2], MM; Juan Guo[1,2], MM; Wanyu Li[1,2], MM; Yunfeng Zhou[1,2], MM

[1]School of Acupuncture-moxibustion and Tuina, Henan University of Chinese Medicine, Zhengzhou, China

[2]Tuina Department, The Third Affiliated Hospital of Henan University of Chinese Medicine, Zhengzhou, China

[*]these authors contributed equally

Corresponding Author:
Yunfeng Zhou, MM
School of Acupuncture-moxibustion and Tuina
Henan University of Chinese Medicine
63 Dongming Road, Jinshu District, China
Zhengzhou, 450046
China
Phone: 86 15036065036
Email: zyf5680198@126.com

Abstract

Background: Knee osteoarthritis (KOA) is reputedly the most common musculoskeletal disease of the lower limbs and the main cause of pain and disability among older individuals. Pain is the most significant and widespread symptom of KOA. The descending pain inhibitory system has a cardinal role in normal pain consciousness, and its malfunction may be one of the pathophysiological mechanisms in KOA. Crucially, the rostral ventromedial medulla (RVM) and periaqueductal gray (PAG), as important components of the descending pain inhibitory system, directly modulate the activity of the spinal neurons involved in pain transmission. Tuina, a manual therapy, is effective and safe for reducing clinical symptoms of KOA; however, the mechanism that influences pain through the descending pain inhibitory system in KOA is unclear.

Objective: This study aims to investigate the modulatory implications of Tuina on the RVM and PAG, which have critical roles in the descending pain inhibitory system in patients with KOA.

Methods: This randomized controlled parallel trial will be conducted at the Tuina Clinic of the Third Affiliated Hospital of Henan University of Chinese Medicine (Zhengzhou, China). Patients with KOA will be randomly assigned (1:1) to 6 weeks of health education or Tuina. All patients in both groups will accept a resting-state functional magnetic resonance scan at the beginning and end of the experiment, and the resting-state functional connectivity and the voxel-based morphometry analysis will be performed to detect the RVM and PAG function and structure changes. The clinical outcome assessments will be (1) the pressure pain thresholds, (2) the Numerical Rating Scale, (3) the Hamilton Depression Scale (HAMD), and (4) the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Considering that this trial is a study of resting-state functional magnetic resonance imaging technology, resting-state functional connectivity and voxel-based morphometry are the primary outcomes, and clinical outcome assessments are secondary outcomes. Adverse events will be documented and assessed throughout. All main analyses will be carried out on the basis of the intention-to-treat principle. The outcome evaluators and data statisticians will be masked to the treatment group assignment to reduce the risk of bias.

Results: This trial was approved by the ethics committee of the Third Affiliated Hospital of Henan University of Chinese Medicine. Enrollment began in December 2023, and the results of this trial are expected to be submitted for publication in May 2025.

Conclusions: This trial will identify a possible relationship between function and structure changes of RVM and PAG and the improvement of clinical variables, elucidating the effect of Tuina on the descending pain inhibitory system of patients with KOA. This trial will provide much-needed knowledge for Tuina for patients with KOA.

Trial Registration: Chinese Clinical Trial Registry ChiCTR2300070289; https://www.chictr.org.cn/showproj.html?proj=182570

International Registered Report Identifier (IRRID): PRR1-10.2196/52820

(JMIR Res Protoc 2024;13:e52820) doi:10.2196/52820

KEYWORDS

brain; knee osteoarthritis; magnetic resonance imaging; pain; Tuina

Introduction

Knee osteoarthritis (KOA) is reputedly the most common musculoskeletal disease of the lower limbs and the main cause of pain and disability among older individuals. Approximately 80% of individuals aged 65 years or older show radiological symptoms of KOA [1]. Pain is the most significant and widespread symptom of KOA. International recommendations for KOA treatment consist of pain alleviation and physical interventions via a combination of pharmacological and nonpharmacological therapies, such as massages [2,3]. Tuina, a massage remedy built on Chinese Medicine meridian theories and Zang-Fu organs, consolidates contemporary scientific knowledge, including anatomy, biomechanical role, and physiology. Previous randomized controlled trials (RCTs) have supported the effectiveness of Tuina for the treatment of different health conditions, such as acute bronchitis [4] and musculoskeletal disorders [5,6]. In relation to KOA, 2 systematic reviews have identified positive clinical effects of Tuina in improving the outcomes of patients with KOA [7,8]. Furthermore, our recent RCT demonstrated the safety and effectiveness of Tuina for improving pain, increasing joint flexibility, and improving KOA-related disability [9].

The pathogenesis of KOA is complex and involves heterogeneous factors in the central and peripheral nervous systems. However, peripheral candidate mechanisms are insufficient to explain widespread pain and the range of concomitant symptoms; thus, centrally driven mechanisms are deemed pivotal in the etiology of KOA. Our recent research demonstrated that the brain also participates in the pathophysiological changes in KOA and that central nervous system remodeling and function modifications may be among the central mechanisms associated with KOA [10]. Patients who reported higher levels of arthritic pain had greater opioid receptor availability in the periaqueductal gray (PAG), a key region of the descending pain inhibitory system, suggesting the alteration of this system in KOA [11]. Additionally, a functional magnetic resonance imaging (fMRI) trial demonstrated that the degree of PAG activation provides a sensitive and objective assessment of patellofemoral pain pressure in patients with KOA [12]. The descending pain inhibitory system originates in the PAG of the midbrain conduction duct and exerts its analgesic function through the relay of the rostral ventromedial medulla (RVM), inferior projection neuron of the cephalic medulla, and spinal-thalamic projection neurons in the superficial dorsal horn of the spinal cord [13]. Moreover, the subcortical structures and multiple cortices of the brain, comprising the anterior cingulate cortex, amygdala, insula, and hypothalamus, are also involved in pain modulation via the descending pain inhibitory system. The function of the descending pain inhibitory system in pain modulation and the management of the same have been substantially referenced [14,15].

We have, therefore, designed a single-center, parallel RCT to investigate the implications of Tuina and health education on KOA pain, resting-state functional connectivity (rsFC) of the cardinal regions of the descending pain inhibitory system (RVM and PAG), modifications of the voxel-based morphometry (VBM) of RVM and PAG, and behavioral alterations and their connections. We hypothesized that all treatments would relieve knee pain and share common pathways and that pain relief would be associated with the descending pain inhibitory system.

Methods

Trial Design

Patients will be recruited through advertisement in the Tuina clinic of the Third Affiliated Hospital of Henan University of Chinese Medicine, Zhengzhou, China. We will follow the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 statement [16] to guide the reporting and development of our protocol. All eligible participants will be required to sign an informed consent form and will be notified that the trial will not contain any collection of human biological specimens.

Eligibility Criteria

The inclusion criteria are as follows: (1) met the classification and reporting of KOA, per the 1986 American College of Rheumatology criteria [17]; (2) age between 40 and 70 years; (3) experienced knee pain for ≥3 months; (4) knee pain score is ≥3 on the Numerical Rating Scale (NRS) [18]; and (5) radiologically confirmed KOA (Kellgren and Lawrence [K-L] score of 2 or 3) [19].

Exclusion Criteria

The exclusion criteria are as follows: (1) knee pain associated with other diseases, (2) the individual has undergone intra-articular injections within the last 6 months, (3) a history of knee surgery, (4) psychiatric disorders or chronic severe or acute organic diseases, (5) bleeding disorders, and (6) magnetic resonance imaging (MRI) contraindications, such as phobias or pacemakers.

Exit Criteria and Management

Exit criteria are as follows: (1) request by the participant and (2) intratreatment side effects.

Sample Size

The sample size of 64 patients was planned, based on our previous clinical research [9]. The formula is determined:

wherein *N* refers to the sample size in each group, σ represents the SD, α represents type I error, β represents type II error, 1–β represents the test power, and δ represents the difference between mean groups.

The pressure pain threshold (PPT) values of the treatment and control groups were 9.53 (1.26) and 9.02 (2.62), respectively. We took α=0.05, β=0.10, 1–β=0.90, set the 2-sided test level α=0.05, and found out from the *t*-distribution boundary value table: u_{α}=1.96, u_{β}=1.282. In this study, δ=0.51, σ with the larger SD of 1.36, and an approximate *N* of 29 after substituting the formula. With an estimated drop-off rate of 10%, a total of 64 patients with KOA were needed.

Recruitment Strategies and Enrollment

The participants will be recruited between December 2023 and December 2024. Participants will also be recruited through a multi-modal strategy, including dissemination through WeChat and posters at community service centers. Figure 1 presents a flow diagram consisting of recruitment, screening, and randomization. Table 1 presents a schematic overview of our trial designs, conduct, review, and analysis.

Figure 1. Flowchart of the trial. fMRI: functional magnetic resonance imaging; HAMD: Hamilton Depression Scale; NRS: Numerical Rating Scale; PPT: pressure pain threshold; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

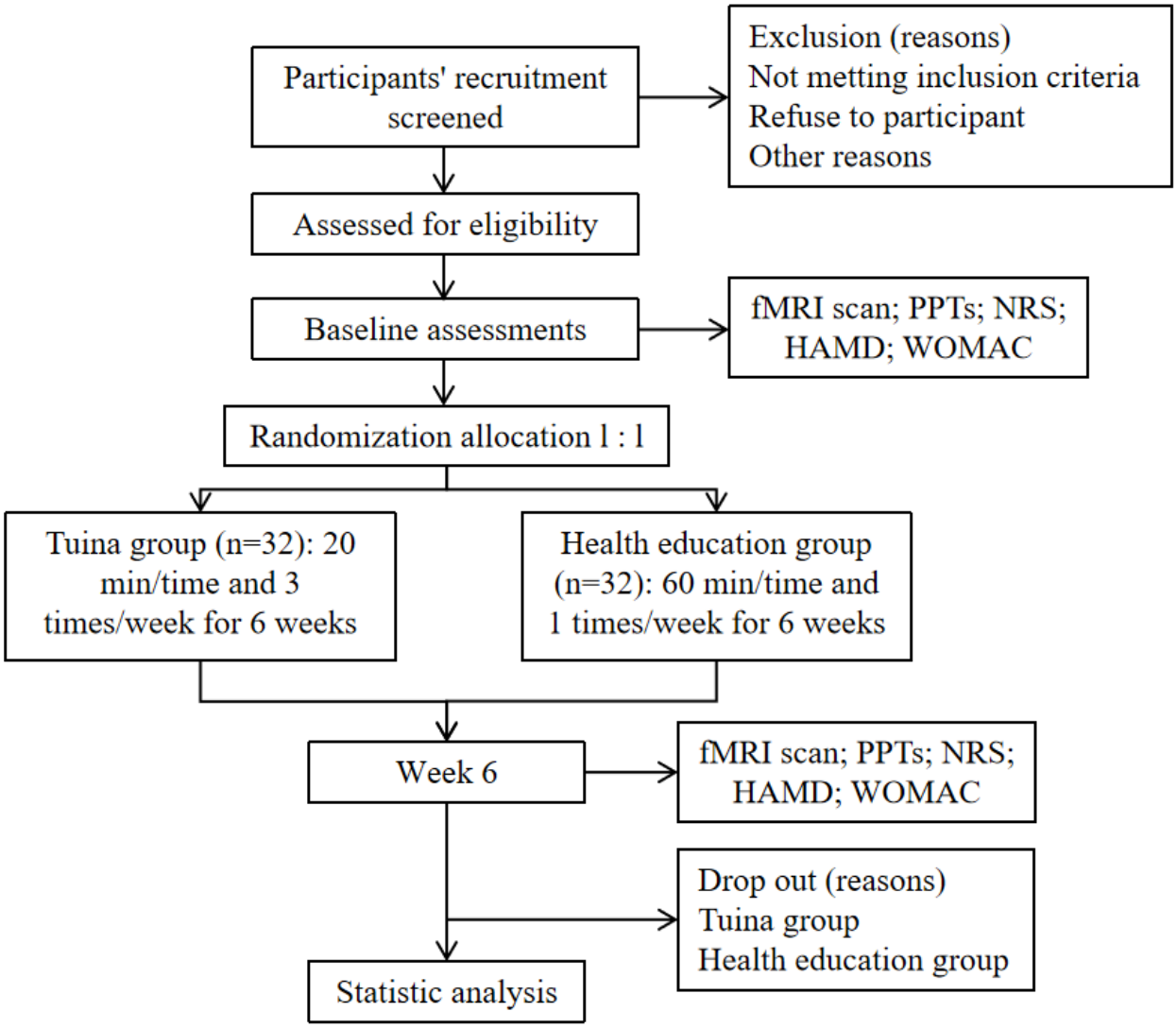


Table 1. Chart of the trial's time points.

Research process	Enrollment	Allocation	Beginning	End of the experiment
Eligibility screen	✓			
Demographic variables	✓			
Medical variables	✓			
Allocation		✓		
Consent			✓	
fMRI[a] scan			✓	✓
PPTs[b]			✓	✓
NRS[c]			✓	✓
HAMD[d]			✓	✓
WOMAC[e]			✓	✓
Adverse events			✓	✓
Working practice record			✓	✓

[a]fMRI: functional magnetic resonance imaging.

[b]PPT: pressure pain threshold.

[c]NRS: Numerical Rating Scale.

[d]HAMD: Hamilton Depression Scale.

[e]WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

Randomization

Independent research staff will use SPSS 25.0 (IBM Corp) to generate a randomly numbered sequence for complete randomization. Participants will be randomly assigned into 1 of 2 groups (ie, health education or Tuina group) and applied in a 1:1 allocation ratio. The random sequence will be sealed by a self-governing research assistant via an opaque envelope that contains information regarding the participant's allocation.

Blinding

The outcome evaluators and data statisticians will all be masked to the group assignment to prevent bias.

Interventions

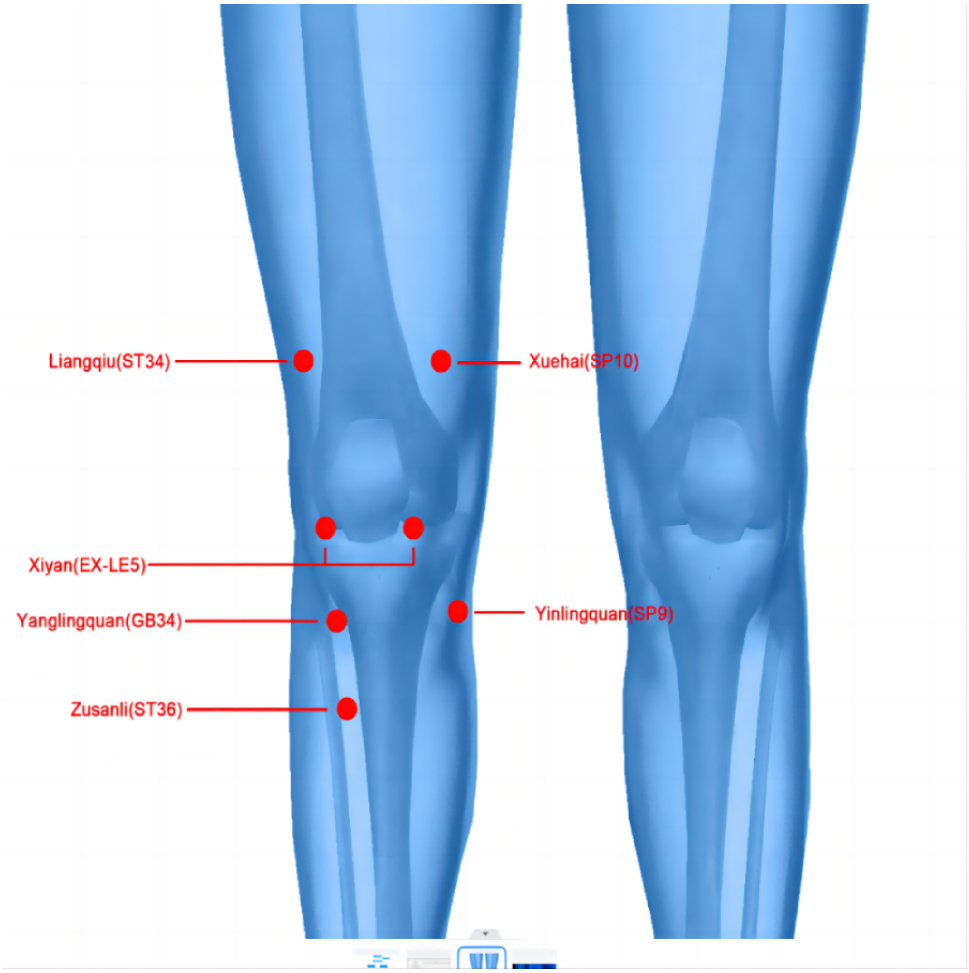
A panel of 2 clinical medical professionals with an academic background in Tuina and clinical medicine agreed to develop a standard protocol for Tuina and health education. The protocol's feasibility will be examined to determine whether it is practicable and acceptable and to identify any realistic issues caused by the procedures. Given the nature of the treatment, participants will be informed that the trial will be without harm, compensation, and posttrial care.

Clinical medical professionals with ≥3 years of experience with Tuina will conduct the health education for the participants. Before the trial, clinicians will be trained to ensure standard procedures and compliance with treatment protocol. All participants in the Tuina group will receive three 20-minute sessions a week over a 6-week treatment course. The participants in the health education group will participate in health education sessions lasting 1 hour each (administered once weekly for 6 weeks). The participants are to maintain their dietary habits and regular physical activity throughout the study period. Throughout the trial, they will be informed that they are not permitted to entertain other remedies. To guarantee compliance, all participants are required to register for therapy in a written log.

Tuina Group

The standard Tuina procedure will be performed based on Tuina Therapy, a textbook of the 13th Five-year Plan [20]. The specific administration procedure will first start with the hand disinfection of the Tuina clinical medical professional. Second, the specific application of Tuina will be performed according to the following methods [9]: (1) the participant will be placed supine on the treatment bed, and the Tuina therapist will press at the points Xuehai (SP10), Yinlingquan (SP9), Yanglingquan (GB34), Liangqiu (ST34), Xiyan (EX-LE5), and Zusanli (ST36; based on the standard of the World Health Organization [21]; Figure 2); (2) the participant will be asked to sit in a chair, the knee will be flexed to 90 degrees, and the Tuina therapist will revolve the foot of the participant to a neutral position and lightly press the patella's lower edge; the therapist's other fingers will then be wrapped around the knee's rear without force. The participant will be instructed to stand, and the therapist will push the patella. The participant will then be required to sit down. This process will be repeated 3 times.

Figure 2. Location of the acupoints.



Health Education

We will introduce the basic concepts of KOA and the methods used to manage the associated risks to help participants protect their knees.

MRI Data Acquisition

MRI will be performed at the MRI Center of The Third Affiliated Hospital of Henan University of Chinese Medicine. Resting-state fMRI will be performed at the beginning and end of the experiment. MRI data will be acquired using a 3.0-T magnetic resonance scanner (General Electric) with a 32-channel phase-array head coil. During the full scanning period, the participants will be asked to remain awake and motionless with their eyes closed.

Blood oxygen level independent resting-state functional images will be acquired using the following parameters: TR=2000 ms, TE=30 ms, flip angle=90°, 33 axial slices, and field of view (FOV) = 220 mm × 220 mm. T1-weighted images will be collected using the following parameters: 160 axial slices, TE=2.93 ms, flip angle=9°, TR=1900 ms, TE=30 ms, and FOV = 256 mm × 256 mm. T2-weighted images will be collected with the following parameters: 25 axial slices, TE=2.93 ms, flip angle=150°, TR=6300 ms, TE=86.0 ms, and FOV = 240 mm × 240 mm.

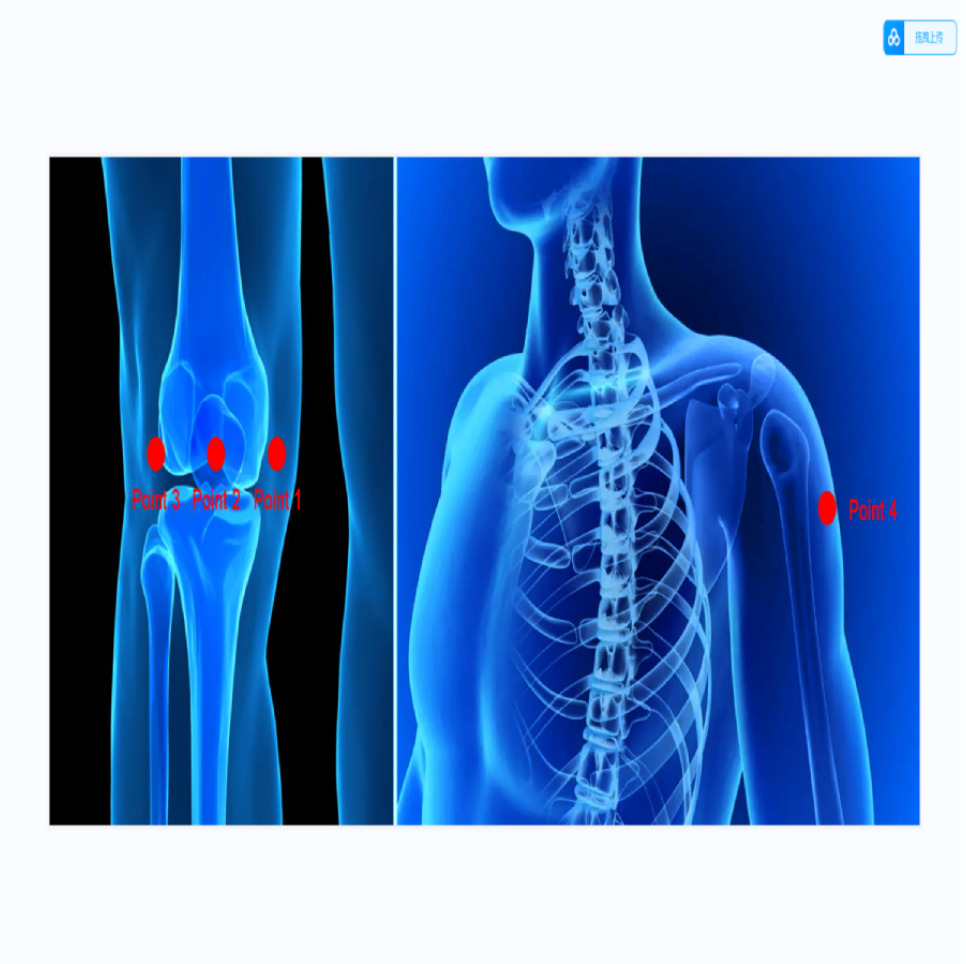
Clinical Outcome Assessments

Validated pain detectors and questionnaires will be used to assess knee pain, psychological characteristics, and function at the beginning and end of the experiment. The clinical outcome assessments will be (1) the PPTs, (2) the NRS, (3) the Hamilton Depression Scale (HAMD), and (4) the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Additional outcome indices included the adverse events of treatment.

Pressure Pain Thresholds

The PPT is a form of quantitative sensory testing that enhances the understanding of pain sensitivity and musculoskeletal pain [22-24]. Moreover, it has strong interrater reliability across multiple raters [25]. The PPT effectively depicts pain intensity and is widely applied in patients with KOA. PPTs will be measured using a portable machine (FDX50, Digital Force Gauge, Wagner Instruments) [26,27]. The patient will be placed in a supine position. The variable collector will select four points for measurement: (1) 3 cm medial to the midpoint of the medial patellar border, (2) the center of the patella, (3) 3 cm lateral to the midpoint of the lateral patellar border, and (4) the belly of the deltoid muscle of the affected upper limb (Figure 3) [28]. The pain test needle will be moved slowly at 0.1 kg/s until the participant feels pain. The measurement will be repeated 3 times at each site with an interval of 25 s, and the average will be calculated [29].

Figure 3. Points used to measure the PPTs. PPT: pressure pain threshold.



Numerical Rating Scale

The NRS is an elementary well-managed scale to assess pain intensity. Patients express the intensity of rest and movement pain using the numbers 0-10.

Hamilton Depression Scale

The HAMD comprises 24 items, most of which are evaluated on a 5-point scale (0-4 points): 0="none," 1="mild," 2="moderate," 3="serious," and 4="very serious." A few items are assessed on a 3-point scale (0-2 points): 0="none," 1="mild to moderate," and 2="serious."

Western Ontario and McMaster Universities Osteoarthritis Index

The WOMAC (0-10 cm) comprises 3 dimensions (ie, pain, stiffness, and joint function). The score ranges from 0 to 96, with higher scores indicating worse symptoms.

Adverse Events of Treatment

All adverse events that may occur throughout the trial will be documented, including the time of occurrence, symptoms of discomfort, particular indications, severity, remedy supplied, time course of the action of amelioration, time of determination, and date of remedy termination.

Demographic or Medical Variables

The following demographic and medical variables will be collected for analysis: sex, age, marital status, occupation, ethnicity, education level, blood pressure, temperature, respiration, pulse, height, weight, body mass index, combination of disease and medication, K-L score, course of KOA, and history of major surgeries.

Data Management

Clinical data will be carefully saved using printed and electronic case report forms (CRFs). Only outcome assessors will access the CRFs for data entry to guarantee data quality. CRFs will be verified for double entry and accuracy. During the trial, the Third Affiliated Hospital of the Henan University of Chinese Medicine will conduct regular visits (once a week) to review the conduct of the trial.

Data Monitoring

The ethics committee will monitor for trial breaches and guarantee no conflicts of interest exist. Statisticians can obtain the last trial data set, which will exclusively accommodate coded data. The safety, advancement, and research integrity will be supervised throughout the research team conferences.

fMRI Preprocessing

rsFC Preprocessing

rsFC will be conducted by applying a seed-based approach using the CONN toolbox (Version 17.f) [30]. CONN is Matlab/statistical parametric mapping (SPM)–based software for the analysis of functional connectivity data. This analysis will use predefined regions of interest (ROIs) based on masks of the a priori specified brainstem nuclei (PAG and RVM) [31], as previously described [32].

Preprocessing of fMRI data will be performed using a pipeline in the CONN toolbox, including translation by centering to (0, 0, 0) coordinates, slice-timing correction, realignment, coregistration to participants' respective structural images, normalization, artifact detection, smoothing with an 8 mm Gaussian kernel, and segmentation into gray matter volume (GMV), white matter (WM), and cerebrospinal fluid volume (CSF). Linear detrending will be performed with a frequency window of 0.008-0.09 Hz. Linear detrending will be executed, and a frequency window of 0.008-0.09 Hz will be applied. Artifact detection will be run using the ART toolbox to eliminate correlations caused by head motion and artifacts. During the denoising processes, WM, CSF, and outliers will be detected using the ART toolbox and entered into the linear regression analysis as confounding effects.

Subsequently, a correlation map will be produced for each participant by extracting the blood oxygen level independent time course from the left/right PAG and left/right RVM seeds separately and computing the Pearson correlation coefficients between the time course in the PAG or RVM and every voxel of the whole brain. Correlation coefficients will be converted by applying Fisher transformation into *z* scores to raise their normality.

VBM Preprocessing

We will use the Diffeomorphic Anatomical Registration With Exponentiated Lie Algebra (DARTEL) SPM 12's segmentation algorithm for whole brain VBM analysis. All T1-weighted images will be analyzed using SPM 8 (Wellcome Institute) software, as implemented in Matlab (Matlab 2013a, Math Works). First, the new segmentation algorithm from SPM 8 will be applied to every T1-weighted image will be segmented into GMV, WM, and CSF. Second, all segmented tissue maps will be used to create a vervet population template using the DARTEL template-creation tool. We will use a set of standard Montreal Neurological Institute tissue maps and a multivariate tissue-affinity-registration and segmentation algorithm carried by SPM's VBM DARTEL for that process. Finally, each patient's GMV map will be warped using its corresponding smooth (Gaussian kernel of 8 mm full-width at half maximum), reversible martensitic parameters to transform it to the customized template space and then to the Montreal Neurological Institute template space.

Statistical Analysis

Prior to the analysis, a statistical program will be undertaken by a statistician. The program will embrace the processing approaches and the demanded data. Variables will be analyzed with IBM SPSS Statistics for Windows (version 25; IBM Corp).

rsFC Analysis

For the ROI analysis, the ROI-to-ROI connectivity connections will be placed to a threshold by the intensity at the false discovery rate-corrected $P<.05$ (2-sided).

For the analysis of rsFC, we will use ROIs derived from the rsFC results. For the ROIs, we will use a threshold of voxel-wise $P<.005$ uncorrected and $P<.05$ corrected using Monte Carlo simulations with the 3dFWHMx and 3dClustSim applied [33].

VBM Analysis

After completing these image analyses, we will obtain the GMV values of the key regions derived from rsFC for subsequent statistical analysis. The statistical significance between-group differences will be set at $P<.05$ with family-wise error correction.

Data Analysis of Clinical Outcomes

Measurement Data

The Shapiro-Wilk test will foremost be conducted to confirm the normality of the uninterrupted data distribution. Independent sample *t* tests will be conducted for normally distributed data to evaluate the baseline characteristics. The Mann-Whitney U test will evaluate between-group differences for nonnormally distributed data.

Ranked Data and Count Data

The body mass index categorization, K-L score, NRS score, and WOMAC score are the rank data. Therefore, the Mann-Whitney U test will be applied for the between-group comparisons, and the Wilcoxon symbolic test will be applied for the intragroup comparisons. Count data will involve the ratio of the sex variable and knee constituent ratio, compared between the 2 groups via χ^2 test of 4-fold table or Fisher test. Statistical significance will be set at $P<.05$ (2-sided).

Ethical Considerations

This trial was registered in the Chinese Clinical Trials Registry in 2023 (ChiCTR2300070289). The ethics committee of the Third Affiliated Hospital of Henan University of Chinese Medicine has approved this study protocol (ethics approval number 2022HL-031).

This RCT will adhere to the ethical principles governing biomedical research on human participants and respect fundamental human rights in accordance with international recommendations included in the Declaration of Helsinki and its subsequent revisions.

Participants will be given both written and oral information about why the trial will be conducted, its objectives, the potential risks associated, and the guidelines set out during the monitoring period. If a patient fulfills the inclusion criteria and agrees to enroll in the trial, they will provide written informed consent. Patients are free to withdraw consent and discontinue the trial at any time and for any reason.

Results

This trial was approved by the ethics committee of the Third Affiliated Hospital of Henan University of Chinese Medicine. Enrollment began in December 2023, and the results of this trial are expected to be submitted for publication in May 2025.

Discussion

Overview

To the best of our knowledge, our trial will be the first to assess the modulatory effect of Tuina on the descending pain inhibitory system in patients with KOA. The results will improve the apprehension regarding Tuina's mechanisms in patients with KOA.

KOA can cause joint dysfunction, reduce physical fitness and capability to tackle activities of daily living, and cause depression and anxiety [3,34,35]. Previous researchers have indicated that peripheral factors such as synovial inflammation and articular cartilage devastation may have a cardinal role [36-38]. However, many studies found that the severity of radiographic KOA and the inflammatory response of the synovial membrane do not positively correlate with KOA [39-41]. Consequently, peripheral mechanisms cannot completely explain KOA. Patients with KOA have simultaneously raised pain sensitivity in affected and nonaffected areas. Therefore, some investigators suggest that an "abnormal central processing" of afferent pain messages may be a cardinal factor in KOA [26].

Based on the theory of traditional Chinese Tuina, all the acupoints can treat the disease of the adjacent area and local area. In our study, 6 local acupoints are selected in the Tuina group, including Xuehai (SP10), Yinlingquan (SP9), Yanglingquan (GB34), Liangqiu (ST34), Xiyan (EX-LE5), and Zusanli (ST36). Yanglingquan (GB34) and Yinlingquan (SP9) are also known as the converging point of the tendon footprint and are usually recommended to relieve knee pain. Xuehai (SP10) and Liangqiu (ST34) are the most commonly used acupoints for the treatment of dysfunction caused by KOA. Xiyan (EX-LE5) is supplemented to adjust the tension of soft tissue. Zusanli (ST36) is commonly used for the treatment of inflammation and pain. Our previous results showed that the above 6 acupoints used together can effectively improve the pain of patients with KOA [7].

Moreover, Tuina is safe and effective for pain, physical function, stiffness, and other clinical symptoms associated with KOA [42]. It likewise has been demonstrated to activate and modulate functional connectivity in the hippocampus to facilitate cognitive function in patients with poststroke depression [43]. The brain has a powerful control over nociceptive input in the spinal cord at the brain stem level. This top-down control occurs through the "descending modulation" of the pain transmission pathway mechanism [44-46]. The descending pain inhibitory system has a cardinal role in normal pain consciousness, and its malfunction may be one of the pathophysiological mechanisms in KOA. This factor possibly clarifies how other centrally mediated processes, such as sleep, mood, the placebo effect, and cognition, influence the pain experience [47]. Crucially, the PAG and RVM, as important components of the descending pain inhibitory system, directly modulate the activity of the spinal neurons involved in pain transmission [48]. Furthermore, animal experiments have demonstrated that the PAG is involved in opioid-mediated analgesia since the microinjection of morphine into this nucleus produces a reduction in sensory pain behaviors [49]. Similarly, the analgesic effects of stimulating the PAG directly have also been evidenced in humans [50]. Moreover, direct PAG stimulation is used to diminish chronic pain intensity in individuals [51]. The RVM is the pontomedullary area where opioid microinjection generates analgesia [48]. Making allowances for this, the PAG-RVM axis, as a significant component of the descending pain inhibitory system, can possess an inhibitory implication on harmful transmission. However, the mechanism of the descending pain inhibitory system in the analgesic effect of Tuina in the treatment of KOA is unclear, especially the relationships among PAG and RVM and clinical behavioral indicators, which limits its promotion and application. Therefore, fully exploring the central analgesic mechanism is necessary to alleviate the pain of KOA. As a main type of fMRI, resting-state fMRI has the advantage of providing more comprehensive information on the functional architecture of the brain. Resting-state fMRI is widely used to study the analgesic mechanism of Tuina in the treatment of KOA [52].

In summary, this clinical trial will aim to investigate the influence of Tuina on the descending pain inhibitory system in order to explain the potential central mechanism of Tuina treatment. We will use a combination of resting-state MRI and clinical behavior indicators such as rsFC and VBM to perform research and analysis of Tuina analgesia.

Limitations and Strengths

Although this study's potential strengths, it anticipates limitations. First, there is potential for methodological bias, as blinding is particularly difficult when delivering a physical intervention or health education. Second, the long-term implications of Tuina will not be investigated; thus, further research is warranted. Despite these several different limitations, this study's strengths lie in its focused investigation of the potential central mechanism of Tuina treatment, which contributes valuable insights into the modulatory effect of Tuina on the descending pain inhibitory system in patients with KOA.

Conclusions

This trial is designed to investigate the central mechanism of Tuina in the treatment of KOA, with the involvement of health education as a control intervention. We expect that Tuina would relieve pain symptoms in patients with KOA and that pain relief would be associated with the descending pain inhibitory system.

Acknowledgments

This work was supported by The 2022 Central Plains Talent Plan (Talent Cultivation Series) - Central Plains Youth Top Talent Project (Yu Talent Office, 2022, number 5); Henan Province Science and Technology Research Project (222102310214); 2022 Henan Province Traditional Chinese Medicine Science Research Special Project (2022ZY1108); 2023 Henan Province Traditional Chinese Medicine “Double First Class” Creation Scientific Research Project (HSRP-DFCTCM-2023-7-09); 2024 Henan Province Traditional Chinese Medicine Science Research Special Project (2024ZY3060); and 2023 Henan Province Traditional Chinese Medicine “Double First Class” Creation Scientific Research Project (HSRP-DFCTCM-2023-8-11). The funding sources have no role in the design or conduct of the trial.

Data Availability

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

Authors' Contributions

YZ will be the sponsor. HX will take responsibility for designing the trial. Zheng Wang will take responsibility for supervising the trial. Zhen Wang drafted and revised the manuscript. HX takes responsibility for ethics approval and clinical trial registration. HZ planned the statistical analysis protocol. WL will be the evaluator. JG will be responsible for all data collection. All bylined authors will follow the trials’ authorship guidelines and have consented to publication.

Conflicts of Interest

None declared.

References

1. Ye J, Cai S, Zhong W, Cai S, Zheng Q. Effects of tai chi for patients with knee osteoarthritis: a systematic review. J Phys Ther Sci 2014;26(7):1133-1137 [FREE Full text] [doi: 10.1589/jpts.26.1133] [Medline: 25140112]
2. Bruyère O, Cooper C, Pelletier JP, Branco J, Brandi ML, Guillemin F, et al. An algorithm recommendation for the management of knee osteoarthritis in Europe and internationally: a report from a task force of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). Semin Arthritis Rheum 2014;44(3):253-263 [FREE Full text] [doi: 10.1016/j.semarthrit.2014.05.014] [Medline: 24953861]
3. McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, Berenbaum F, Bierma-Zeinstra SM, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis Cartilage 2014 Mar;22(3):363-388 [FREE Full text] [doi: 10.1016/j.joca.2014.01.003] [Medline: 24462672]
4. Feng H, Rong J, Pei K, Jing F, Zhuang Q, Lu T, et al. A systematic review protocol of Tuina for children with acute bronchitis: a protocol for systematic review. Medicine (Baltimore) 2020 Jan;99(4):e18899 [FREE Full text] [doi: 10.1097/MD.0000000000018899] [Medline: 31977901]
5. Plastaras CT, Schran S, Kim N, Sorosky S, Darr D, Chen MS, et al. Complementary and alternative treatment for neck pain: chiropractic, acupuncture, tens, massage, yoga, tai chi, and feldenkrais. Phys Med Rehabil Clin N Am 2011;22(3):521-537, ix. [doi: 10.1016/j.pmr.2011.02.011] [Medline: 21824591]
6. Yuan QL, Guo TM, Liu L, Sun F, Zhang YG. Traditional Chinese medicine for neck pain and low back pain: a systematic review and meta-analysis. PLoS One 2015;10(2):e0117146 [FREE Full text] [doi: 10.1371/journal.pone.0117146] [Medline: 25710765]
7. Field T. Knee osteoarthritis pain in the elderly can be reduced by massage therapy, yoga and tai chi: a review. Complement Ther Clin Pract 2016;22:87-92. [doi: 10.1016/j.ctcp.2016.01.001] [Medline: 26850812]
8. Lee NW, Kim GH, Heo I, Kim KW, Ha IH, Lee JH, et al. Chuna (or Tuina) manual therapy for musculoskeletal disorders: a systematic review and meta-analysis of randomized controlled trials. Evid Based Complement Alternat Med 2017;2017:8218139 [FREE Full text] [doi: 10.1155/2017/8218139] [Medline: 29441114]
9. Xu H, Zhao C, Guo G, Li Y, Qiu G, Wang Y, et al. The effectiveness of tuina in relieving pain, negative emotions, and disability in knee osteoarthritis: a randomized controlled trial. Pain Med 2023;24(3):244-257. [doi: 10.1093/pm/pnac127] [Medline: 35997590]
10. Kang BX, Ma J, Shen J, Xu H, Wang HQ, Zhao C, et al. Altered brain activity in end-stage knee osteoarthritis revealed by resting-state functional magnetic resonance imaging. Brain Behav 2022 Jan;12(1):e2479 [FREE Full text] [doi: 10.1002/brb3.2479] [Medline: 34967156]
11. Brown CA, Matthews J, Fairclough M, McMahon A, Barnett E, Al-Kaysi A, et al. Striatal opioid receptor availability is related to acute and chronic pain perception in arthritis: does opioid adaptation increase resilience to chronic pain? Pain 2015;156(11):2267-2275 [FREE Full text] [doi: 10.1097/j.pain.0000000000000299] [Medline: 26176892]
12. Monfort J, Pujol J, Contreras-Rodríguez O, Llorente-Onaindia J, López-Solà M, Blanco-Hinojo L, et al. Effects of chondroitin sulfate on brain response to painful stimulation in knee osteoarthritis patients. a randomized, double-blind, placebo-controlled

functional magnetic resonance imaging study. Med Clin (Barc) 2017;148(12):539-547. [doi: 10.1016/j.medcli.2016.12.036] [Medline: 28237612]
13. Hammond DL. Control systems for nociceptive afferent processing: the descending inhibitory pathways. In: Yaksh TL, editor. Spinal Afferent Processing. Boston, MA: Springer; 1986:363-390.
14. Nguyen E, Smith KM, Cramer N, Holland RA, Bleimeister IH, Flores-Felix K, et al. Medullary kappa-opioid receptor neurons inhibit pain and itch through a descending circuit. Brain 2022 Jul 29;145(7):2586-2601 [FREE Full text] [doi: 10.1093/brain/awac189] [Medline: 35598161]
15. Ellingson LD, Stegner AJ, Schwabacher IJ, Koltyn KF, Cook DB. Exercise strengthens central nervous system modulation of pain in fibromyalgia. Brain Sci 2016 Feb 26;6(1):8 [FREE Full text] [doi: 10.3390/brainsci6010008] [Medline: 26927193]
16. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med 2013 Feb 05;158(3):200-207 [FREE Full text] [doi: 10.7326/0003-4819-158-3-201302050-00583] [Medline: 23295957]
17. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al. Development of criteria for the classification and reporting of osteoarthritis. classification of osteoarthritis of the knee. diagnostic and therapeutic criteria committee of the American Rheumatism Association. Arthritis Rheum 1986;29(8):1039-1049. [doi: 10.1002/art.1780290816] [Medline: 3741515]
18. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). Arthritis Care Res (Hoboken) 2011;63(Suppl 11):S240-S252 [FREE Full text] [doi: 10.1002/acr.20543] [Medline: 22588748]
19. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957;16(4):494-502 [FREE Full text] [doi: 10.1136/ard.16.4.494] [Medline: 13498604]
20. Bing-Hua F. Tuina therapy-13th five-year plan textbook. In: Tuina Therapy-13th Five-Year Plan Textbook. Beijing: China Chinese Medicine Publishing House; Aug 01, 2016:40-42.
21. World Health Organization, Regional Office for the Western Pacific. WHO Standard Acupuncture Point Locations in the Western Pacific Region. Manila: World Health Organization, Western Pacific Region; Jul 01, 2008.
22. Gierthmühlen J, Schneider U, Seemann M, Freitag-Wolf S, Maihöfner C, Enax-Krumova EK, et al. Can self-reported pain characteristics and bedside test be used for the assessment of pain mechanisms? an analysis of results of neuropathic pain questionnaires and quantitative sensory testing. Pain 2019;160(9):2093-2104. [doi: 10.1097/j.pain.0000000000001601] [Medline: 31162335]
23. Moss P, Sluka K, Wright A. The initial effects of knee joint mobilization on osteoarthritic hyperalgesia. Man Ther 2007;12(2):109-118. [doi: 10.1016/j.math.2006.02.009] [Medline: 16777467]
24. Mutlu EK, Ozdincler AR. Reliability and responsiveness of algometry for measuring pressure pain threshold in patients with knee osteoarthritis. J Phys Ther Sci 2015;27(6):1961-1965 [FREE Full text] [doi: 10.1589/jpts.27.1961] [Medline: 26180358]
25. Hastie BA, Riley JL, Robinson ME, Glover T, Campbell CM, Staud R, et al. Cluster analysis of multiple experimental pain modalities. Pain 2005;116(3):227-237. [doi: 10.1016/j.pain.2005.04.016] [Medline: 15964682]
26. Arendt-Nielsen L, Graven-Nielsen T. Central sensitization in fibromyalgia and other musculoskeletal disorders. Curr Pain Headache Rep 2003;7(5):355-361. [doi: 10.1007/s11916-003-0034-0] [Medline: 12946288]
27. Cudejko T, van der Esch M, van den Noort JC, Rijnhart JJM, van der Leeden M, Roorda LD, et al. Decreased pain and improved dynamic knee instability mediate the beneficial effect of wearing a soft knee brace on activity limitations in patients with knee osteoarthritis. Arthritis Care Res (Hoboken) 2019;71(8):1036-1043 [FREE Full text] [doi: 10.1002/acr.23722] [Medline: 30099859]
28. Jaber K, O'Leary S, Pedler A, Sterling M, McAuliffe M. Evidence of generalised mechanical hyperalgesia in patients with advanced knee osteoarthritis undergoing total knee arthroplasty. Knee 2018 Jun;25(3):459-465. [doi: 10.1016/j.knee.2018.03.002] [Medline: 29685500]
29. Arendt-Nielsen L, Simonsen O, Laursen MB, Roos EM, Rathleff MS, Rasmussen S, et al. Pain and sensitization after total knee replacement or nonsurgical treatment in patients with knee osteoarthritis: identifying potential predictors of outcome at 12 months. Eur J Pain 2018;22(6):1088-1102. [doi: 10.1002/ejp.1193] [Medline: 29369450]
30. Whitfield-Gabrieli S, Nieto-Castanon A. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. Brain Connect 2012;2(3):125-141. [doi: 10.1089/brain.2012.0073] [Medline: 22642651]
31. Brooks JCW, Davies WE, Pickering AE. Resolving the brainstem contributions to attentional analgesia. J Neurosci 2017 Mar 01;37(9):2279-2291 [FREE Full text] [doi: 10.1523/JNEUROSCI.2193-16.2016] [Medline: 28096471]
32. Oliva V, Gregory R, Brooks JCW, Pickering AE. Central pain modulatory mechanisms of attentional analgesia are preserved in fibromyalgia. Pain 2022 Jan 01;163(1):125-136 [FREE Full text] [doi: 10.1097/j.pain.0000000000002319] [Medline: 33941755]

33. Gollub RL, Kirsch I, Maleki N, Wasan AD, Edwards RR, Tu Y, et al. A functional neuroimaging study of expectancy effects on pain response in patients with knee osteoarthritis. J Pain 2018 May;19(5):515-527 [FREE Full text] [doi: 10.1016/j.jpain.2017.12.260] [Medline: 29325883]
34. Axford J, Heron C, Ross F, Victor CR. Management of knee osteoarthritis in primary care: pain and depression are the major obstacles. J Psychosom Res 2008 May;64(5):461-467. [doi: 10.1016/j.jpsychores.2007.11.009] [Medline: 18440398]
35. Roos EM, Arden NK. Strategies for the prevention of knee osteoarthritis. Nat Rev Rheumatol 2016;12(2):92-101 [FREE Full text] [doi: 10.1038/nrrheum.2015.135] [Medline: 26439406]
36. English A, Jones EA, Corscadden D, Henshaw K, Chapman T, Emery P, et al. A comparative assessment of cartilage and joint fat pad as a potential source of cells for autologous therapy development in knee osteoarthritis. Rheumatology (Oxford) 2007;46(11):1676-1683 [FREE Full text] [doi: 10.1093/rheumatology/kem217] [Medline: 17901063]
37. Nanus DE, Badoume A, Wijesinghe SN, Halsey AM, Hurley P, Ahmed Z, et al. Synovial tissue from sites of joint pain in knee osteoarthritis patients exhibits a differential phenotype with distinct fibroblast subsets. EBioMedicine 2021 Oct;72:103618 [FREE Full text] [doi: 10.1016/j.ebiom.2021.103618] [Medline: 34628351]
38. Neybecker P, Henrionnet C, Pape E, Mainard D, Galois L, Loeuille D, et al. In vitro and in vivo potentialities for cartilage repair from human advanced knee osteoarthritis synovial fluid-derived mesenchymal stem cells. Stem Cell Res Ther 2018;9(1):329 [FREE Full text] [doi: 10.1186/s13287-018-1071-2] [Medline: 30486903]
39. Bedson J, Croft PR. The discordance between clinical and radiographic knee osteoarthritis: a systematic search and summary of the literature. BMC Musculoskelet Disord 2008;9:116 [FREE Full text] [doi: 10.1186/1471-2474-9-116] [Medline: 18764949]
40. Felson DT. The sources of pain in knee osteoarthritis. Curr Opin Rheumatol 2005;17(5):624-628. [doi: 10.1097/01.bor.0000172800.49120.97] [Medline: 16093843]
41. Hannan MT, Felson DT, Pincus T. Analysis of the discordance between radiographic changes and knee pain in osteoarthritis of the knee. J Rheumatol 2000;27(6):1513-1517. [Medline: 10852280]
42. Xu Q, Chen B, Wang Y, Wang X, Han D, Ding D, et al. The effectiveness of manual therapy for relieving pain, stiffness, and dysfunction in knee osteoarthritis: a systematic review and meta-analysis. Pain Physician 2017;20(4):229-243 [FREE Full text] [Medline: 28535547]
43. Tao J, Zhang S, Kong L, Zhu Q, Yao C, Guo Q, et al. Effectiveness and functional magnetic resonance imaging outcomes of Tuina therapy in patients with post-stroke depression: a randomized controlled trial. Front Psychiatry 2022;13:923721 [FREE Full text] [doi: 10.3389/fpsyt.2022.923721] [Medline: 35845459]
44. Basbaum AI, Fields HL. Endogenous pain control systems: brainstem spinal pathways and endorphin circuitry. Annu Rev Neurosci 1984;7:309-338. [doi: 10.1146/annurev.ne.07.030184.001521] [Medline: 6143527]
45. Liang H, Watson C, Paxinos G. Terminations of reticulospinal fibers originating from the gigantocellular reticular formation in the mouse spinal cord. Brain Struct Funct 2016;221(3):1623-1633. [doi: 10.1007/s00429-015-0993-z] [Medline: 25633472]
46. Millan MJ. Descending control of pain. Prog Neurobiol 2002;66(6):355-474. [doi: 10.1016/s0301-0082(02)00009-6] [Medline: 12034378]
47. Tracey I, Dickenson A. SnapShot: pain perception. Cell 2012;148(6):1308-1308.e2 [FREE Full text] [doi: 10.1016/j.cell.2012.03.004] [Medline: 22424237]
48. Heinricher MM, Tavares I, Leith JL, Lumb BM. Descending control of nociception: specificity, recruitment and plasticity. Brain Res Rev 2009;60(1):214-225 [FREE Full text] [doi: 10.1016/j.brainresrev.2008.12.009] [Medline: 19146877]
49. Lewis VA, Gebhart GF. Evaluation of the Periaqueductal Central Gray (PAG) as a morphine-specific locus of action and examination of morphine-induced and stimulation-produced analgesia at coincident PAG loci. Brain Res 1977;124(2):283-303. [doi: 10.1016/0006-8993(77)90886-1] [Medline: 191150]
50. Adams JE. Naloxone reversal of analgesia produced by brain stimulation in the human. Pain 1976;2(2):161-166. [Medline: 800249]
51. Levy RM, Lamb S, Adams JE. Treatment of chronic pain by deep brain stimulation: long term follow-up and review of the literature. Neurosurgery 1987;21(6):885-893. [doi: 10.1227/00006123-198712000-00017] [Medline: 3325851]
52. Guo G, Kong Y, Zhu Q, Wu Z, Zhang S, Sun W, et al. Cerebral mechanism of tuina analgesia in management of knee osteoarthritis using multimodal MRI: study protocol for a randomised controlled trial. Trials 2022;23(1):694 [FREE Full text] [doi: 10.1186/s13063-022-06633-x] [Medline: 35986403]

Abbreviations

CRF: case report form
CSF: cerebrospinal fluid volume
DARTEL: Diffeomorphic Anatomical Registration With Exponentiated Lie Algebra
fMRI: functional magnetic resonance imaging
FOV: field of view
GMV: gray matter volume
HAMD: Hamilton Depression Scale

K-L: Kellgren and Lawrence
KOA: knee osteoarthritis
MRI: magnetic resonance imaging
NRS: Numerical Rating Scale
PAG: periaqueductal gray
PPT: pressure pain threshold
RCT: randomized controlled trial
ROI: regions of interest
rsFC: resting-state functional connectivity
RVM: rostral ventromedial medulla
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
SPM: statistical parametric mapping
VBM: voxel-based morphometry
WM: white matter
WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

Edited by A Mavragani; submitted 16.09.23; peer-reviewed by F Yao, F Xie; comments to author 01.12.23; revised version received 17.12.23; accepted 17.01.24; published 12.02.24.

Please cite as:
Xu H, Wang Z, Wang Z, Zhou H, Guo J, Li W, Zhou Y
Cerebral Mechanism of Tuina on the Descending Pain Inhibitory System in Knee Osteoarthritis: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2024;13:e52820
URL: https://www.researchprotocols.org/2024/1/e52820
doi:10.2196/52820
PMID:38238645

Protocol

Comparing Repeated (Annual) Couples HIV Testing and Counseling to Individual HIV Testing and Counseling Among Male Couples at High Risk of HIV Infection: Protocol for a Randomized Control Trial

Tyrel J Starks[1,2], PhD; Kory Kyre[1], BS; Juan Castiblanco[1]; Jayelin N Parker[3], MPH; Erin Kahle[4,5], MPH, PhD; Rob Stephenson[5], PhD; Demetria Cain[1], MPH, PhD

[1]Department of Psychology, Hunter College, City University of New York, New York, NY, United States

[2]Doctoral Program in Health Psychology and Clinical Science, Graduate Center of CUNY, New York, NY, United States

[3]Department of Obstetrics and Gynecology, University of Michigan Medical School, Ann Arbor, MI, United States

[4]Department of Health Behavior and Biological Sciences, School of Nursing, University of Michigan, Ann Arbor, MI, United States

[5]The Center for Sexuality and Health Disparities, School of Nursing, University of Michigan, Ann Arbor, MI, United States

Corresponding Author:
Tyrel J Starks, PhD
Department of Psychology
Hunter College
City University of New York
611 Hunter North
695 Park Ave
New York, NY, 10065
United States
Phone: 1 2122067919
Email: tstarks@hunter.cuny.edu

Abstract

Background: Couples HIV testing and counseling (CHTC) is now a standard of care prevention strategy recommended by the Centers for Disease Control and Prevention for sexual minority men (SMM) in relationships. Despite standard recommendations that couples complete CHTC every 6-12 months, no study has empirically evaluated the effects associated with CHTC retesting.

Objective: This study aims to understand the benefits associated with continued dyadic engagement in the HIV prevention continuum through routine CHTC retesting, which is of particular importance for emerging-adult SMM in relationships who use drugs.

Methods: Eligible couples for this CHTC retesting trial must already be enrolled in the 4Us trial, where they completed a CHTC session after their baseline survey. The purpose of the original 4Us trial was to test the efficacy of 2 intervention components for CHTC: a communication skills training video and a substance use module. Couples were eligible for the original 4Us trial if they identified as cisgender male, were in a relationship for 3 months or longer, were aged 17 years or older, and communicated in English. At least 1 partner had to be aged 17-29 years, report HIV negative or unknown serostatus, report use of at least 1 drug (cannabis, cocaine or crack, crystal methamphetamine, ketamine, gamma-hydroxybuterate [GHB], psychedelics, ecstasy, prescription medication misuse, opiates, and nitrates) use, and engage in condomless anal sex (CAS) acts with a casual partner or have a main partner who is nonmonogamous or serodiscordant. Those who complete the 4Us 12-month follow-up and remain in a relationship with the partner they participated in 4Us with are offered the opportunity to participate in this CHTC retesting trial. Those consenting are randomized to either CHTC retesting or individual HIV testing. Follow-up assessments are conducted 3 and 6 months after randomization to evaluate the effects of repeat CHTC on 2 primary outcomes: (1) CAS with a casual partner in the absence of preexposure prophylaxis (PrEP), and (2) CAS with a serodiscordant main partner who is not virally suppressed or concurrent CAS between main and casual partners in the absence of PrEP.

Results: The CHTC retesting trial launched in January 2023, and enrollment is ongoing. As of February 2024, the study had enrolled 106 eligible participants (n=53 couples).

Conclusions: Findings from this CHTC retesting study will contribute to knowledge about the benefits associated with regular (repeated) CHTC testing versus routine individual HIV testing for SMM in relationships. The results of this trial will inform CHTC retesting guidance.

Trial Registration: ClinicalTrials.gov NCT05833074; https://www.clinicaltrials.gov/study/NCT05833074

International Registered Report Identifier (IRRID): DERR1-10.2196/53023

(JMIR Res Protoc 2024;13:e53023) doi:10.2196/53023

KEYWORDS

club drugs; counseling; dyadic interventions; emerging adults; gay and bisexual men; HIV; male couples; men who have sex with men; randomized controlled trial; RCT; relationships

Introduction

Background

Sexual minority men (SMM), a group that encompasses gay, bisexual, and other men who have sex with men, account for 69% of new HIV infections in the United States [1]. Despite the emergence of novel biomedical prevention options (eg, preexposure prophylaxis [PrEP], postexposure prophylaxis [PEP], and HIV undetectable=untransmittable, or treatment as prevention), this overall rate has changed little over the past decade [2]. The majority (68%) of these new infections occur among SMM under the age of 35 years [2]—a proportion that was largely unchanged in the decade between 2009 and 2019 [2].

Nearly 2 decades of research have indicated that HIV prevention interventions that address the needs of SMM in relationships are an essential component of any comprehensive US national HIV prevention plan. Findings first emerged in the early 2000s, indicating that primary partnerships were often a risk for HIV infection [3-5]. Subsequently, epidemiological modeling estimated that between 35% and 68% of HIV infections among SMM are among main partners [6-8]. Rates of primary partner transmission were particularly high (accounting for between 79% and 84% of new infections) among emerging adult SMM (aged 18-29 years) [6]. More recently, Starks et al [9] found that SMM in nonmonogamous relationships (where sex with outside partners is permitted in some way) engage in condomless anal sex (CAS) with casual partners at rates comparable to those who are single. Although men in monogamous relationships were less likely to engage in CAS with casual partners, those who do have CAS with casual partners report doing so more frequently than nonmonogamous men [9].

As evidence of the risk for HIV acquisition in couples has increased, couples HIV testing and counseling (CHTC) has emerged as a standard of care prevention strategy recommended by the World Health Organization and is now considered a proven and effective public health strategy by the US Centers for Disease Control and Prevention [10]. Protocols have been adapted for SMM in the United States [11] and demonstrated safety (with no evidence of increasing intimate partner violence [IPV] among those participating in CHTC) [12]. During CHTC, couples receive all elements of the counseling, testing, and results delivery together. In addition, the HIV tester facilitates a future-oriented dialogue between the partners about their HIV prevention practices, sexual agreement, and communication related to HIV risk. The goal is for the couple to leave with a shared vision—a set of agreed-upon actions—about HIV prevention and relevant sexual practices [13,14]. CHTC has shown marginally significant reductions in HIV-related sexual risk-taking in men who test HIV negative [15] as well as men who were newly diagnosed with HIV [12,15]. A recent trial showed that participation in CHTC also increased rates of viral suppression among serodiscordant male couples [16].

There are 3 rationales that indicate the potential importance of CHTC retesting. First, sexual health outcomes for relationship partners are interdependent. A coordinated effort maximizes prevention outcomes for both partners. Second, the potential for fluidity and change in behavior means that ongoing communication about sexual behavior and dyadic participation in HIV prevention is essential for partners to maintain effective coordination. Third, CHTC works by activating prevention communication among partners, conferring benefits for SMM in relationships that routine individual HIV testing cannot.

The Interdependence of Sexual Health Outcomes

Much of the research on couples HIV prevention has been organized by interdependence theory [17] and dyadic coping [18]. Within this framework, HIV prevention can be understood as a shared or joint goal, one that requires effort from both partners to be accomplished. The shared nature of this goal is evident in data on main partner HIV transmission risk behavior (TRB). If 1 partner in the relationship engages in sexual risk behavior leading to HIV infection, or if 1 partner in the relationship is not aware that he is living with HIV for whatever reason, the likelihood of transmission between main partners is high. In short, prevention outcomes for both partners in a relationship are maximized when they coordinate or contribute joint effort to accomplish HIV prevention goals.

Interdependence theory [19] suggests coordination is easier for couples with better relationship functioning and communication. Interdependence theory suggests that in relationships characterized by a high degree of satisfaction, commitment, and emotional investment, partners are more likely to consider the impact of their behavior on one another and their relationship overall. This transformation of motivation, away from a focus on personal priorities and toward a consideration of one's partner, enhances partners' motivation to reach consensus around shared sexual agreements and related HIV prevention plans. It also provides the impetus for partners to then support one another in adhering to these agreements or accomplishing the goals implied within them.

The Importance of Ongoing Communication—Why One-Time Agreement on a Goal Is Not Enough

Research on the prevalence of sexual agreements in male couples suggests a substantial number disagree about the nature of their sexual agreement. For example, 1 partner believes that sex with outside partners is in some way permitted; meanwhile, the other believes they are monogamous. While estimates vary widely, Stephenson and colleagues [20] found that, even in a sample of couples where 84.7% of men reported having an agreement, partners had discrepant perceptions of what that agreement was in 58.7% of couples. Perhaps not surprisingly, couples with discrepant perceptions of their sexual agreement score lower on measures of adaptive communication compared to those whose perceptions are aligned. The completion of CHTC resolves discrepant perceptions by catalyzing direct, explicit communication about the couple's rules and understandings related to sex with outside partners.

Once formed, sexual agreements and HIV prevention plans are neither fixed nor static. They have the potential to change over time as the needs and priorities of the individual partners in the couple evolve. Stephenson and colleagues [21] recently found that just 6 months after completing CHTC, partners in 22.6% of couples had discrepant perceptions of their sexual agreements, and 12.7% had broken (or failed to fully adhere to) their agreement. Cross-sectional studies consistently indicate that couples who have been together longer are more likely to develop sexual agreements that permit sex with outside partners [9,22-24]. This trend has been observed even in samples of couples that are age-restricted to emerging adulthood [25]. Some findings also show that partners reporting discrepant perceptions of their sexual agreement and breaking their agreement increase with relationship length [24].

This potential for change over time necessitates ongoing communication about sexual agreements and HIV prevention practices to maintain partners' alignment and coordination and underscores the need for repeat CHTC. Unfortunately, several factors complicate HIV prevention communication for relationship partners. In general, partnered SMM perceive themselves to be at lower risk of HIV infection and test for HIV less often compared to single SMM [26,27]. For at least some couples, forfeiting HIV prevention, engaging in CAS together, or stopping PrEP is interpreted as an indicator of commitment or emotional closeness [28-31]. As a result, the introduction of condom use, PrEP, or PEP to prevent HIV infection is complicated by the potential that it might convey a lack of commitment to or trust in their partner [32-37] for these couples.

For SMM in Relationships, CHTC Retesting May Confer Specific Benefits Above and Beyond Those Associated With Routine Individual HIV Retesting

During CHTC, partners obtain updated information on their own and one another's HIV status. As part of routine CHTC retesting, the CHTC provider can reinforce the couple's relationship functioning. The CHTC provider also initiates a conversation among partners with the goal of updating their HIV prevention plan and clarifying any changes in behavior or perception that would impact the couple's sexual agreement. These provider-initiated interactions may be of critical importance in couples where 1 partner desires to discuss such changes but is concerned that raising the topic might harm the relationship or is uncertain about how to initiate conversation.

Understanding the benefits associated with continued dyadic engagement in the HIV prevention continuum through routine CHTC retesting is of particular importance for emerging adult SMM in relationships who use drugs. Rates of illicit drug use are generally higher among SMM (11.1% to 27.1%) compared to heterosexual men (5.7% to 16.2%) [38,39]. Rates of cannabis use are also higher among SMM (36%) compared to heterosexual men (20.4% to 24.7%).

High rates of drug use and associated sexual risk-taking extend to partnered SMM, particularly those in nonmonogamous agreements. SMM in nonmonogamous relationships consistently report rates of illicit drug use that are comparable to single SMM; meanwhile, men in monogamous relationships are significantly less likely to use illicit drugs [9,22,23,40]. Extensive research has shown that SMM who use cannabis and illicit drugs are more likely to have CAS [41-44] with casual partners. Associations between drug use and sexual risk-taking are comparable for partnered and single SMM. Our research suggests the association between illicit drug use (excluding cannabis) and the odds of CAS with casual partners is comparable for single SMM and those in nonmonogamous agreements [9]. Meanwhile, the association between cannabis use and the odds of CAS with casual partners is comparable for single SMM and those in monogamous agreements—for whom the behavior breaks their agreement. This converges with other evidence suggesting that drug use during sex is associated with breaking a sexual agreement [45] and decreased condom use among partnered SMM [40,46].

Objective

The purpose of this study is to evaluate the efficacy of annual CHTC retesting to reduce indicators of sexual risk relative to routine individual HIV testing and counseling among male couples.

Methods

Trial Design

This study uses a randomized controlled trial design integrated with the ongoing 4Us trial [47]. The purpose of the original 4Us trial is to test the efficacy of 2 intervention components for CHTC: a communication skills training video and a substance use module. Couples are eligible for the original 4Us trial if at least 1 partner reports HIV negative or unknown serostatus, reports at least 1 drug, and engages in HIV TRB. Participants in this ongoing trial (4Us) complete an individual baseline assessment, after which couples complete a CHTC session following the standard CHTC protocol. In a full-factorial design, half of the couples are randomly assigned to complete an adjunct module addressing drug use, and half are assigned to view an assertive communication training (ACT) video (later referred to respectively as the substance use calendar and ACT video). This results in 4 study conditions (CHTC as usual, CHTC plus the substance use calendar, CHTC plus the ACT video, and CHTC plus both adjunct components). Follow-up assessments

occur 3, 6, 9, and 12 months post intervention using procedures analogous to the baseline. Participants who complete the 12-month follow-up of the 4Us trial and meet eligibility criteria for the CHTC retesting trial are consented individually to participate in this protocol. If both couples consent into this protocol during their 12-month assessment, they are randomly assigned to either couples retesting or individual HIV testing. Those randomized to couples retesting complete the same 4Us condition they were assigned at baseline. Follow-ups are then completed 3 and 6 months later (15 and 18 months post completion of the baseline in the original 4Us trial).

Rationale for Comparison Condition (Individual HIV Testing and Counseling)

Current Centers for Disease Control and Prevention (CDC) recommendations advise that all individuals between the ages of 13 and 64 years should be tested for HIV at least once. Individuals with additional risk factors, including men who have sex with men, are advised to test at least annually [48]. Recommendations for retesting every 3-6 months apply to the highest-risk groups. CDC has summarized the benefits of routine individual HIV testing [48]. Routine testing reduces the onward transmission of HIV infection. It is estimated that 40% of new HIV infections are transmitted by individuals who do not know they are HIV positive. HIV diagnosis is a prerequisite to the initiation of antiretroviral treatment (ART) for those who are living with HIV, and achieving viral suppression through ART nearly eliminates the likelihood of sexual HIV transmission. For those who learn they are HIV-negative, routine HIV testing presents an opportunity to discuss HIV prevention options and risk reduction practices.

Study Setting

All research staff are based at a university research center at Hunter College of the City, University of New York. All study assessments and intervention sessions are conducted remotely through Zoom (Zoom Video Communications, Inc), a Health Insurance Portability and Accountability Act (HIPAA)–compliant videoconferencing software.

Eligibility Criteria

All participants must be enrolled in the original 4Us trial [47] and complete their assigned intervention condition after baseline. Eligibility criteria for the original 4Us trial necessitate that partners in a couple identify one another as “main partners.” In addition, both partners in each couple must identify as cisgender male, be 17 years of age or older, and have a US residence. In addition, at least 1 participant in each couple must (1) be aged 17-29 years; (2) self-report HIV-negative or unknown serostatus; (3) report use of at least 1 illicit drug (cocaine or crack, opiates, misuse of prescription medication, stimulants, psychedelics, ecstasy, ketamine, and GHB) in the past 30 days; (4) have engaged in CAS with a casual partner or a main partner who is nonmonogamous or serodiscordant in the past 90 days; and (5) be able to speak and read in English. If a serodiscordant couple enrolls in the study, the partner living with HIV is not asked to submit viral load test results.

To be eligible for participation in this CHTC retesting study, participants must complete the 12-month follow-up assessment associated with the 4Us trial [47]. In addition, they must remain in a relationship with the same partner with whom they completed their intervention session after baseline in that trial, and that partner must also agree to enroll in this study.

Participants will be excluded from the study if they indicate that they are single or if they are in a relationship with a new main partner (different from the person with whom they completed their initial 4Us intervention session with the following baseline). Participants will also be excluded if they exhibit signs of serious mental illness or cognitive deficit that impair their functioning during routine research interactions; report IPV with their main partner accompanied by ongoing safety concerns in the current relationship; or indicate being coerced to participate.

Recruitment and Enrollment

Following completion of their 12-month follow-up in the 4Us trial, [47] eligible participants will be offered the opportunity to enroll in this study. Those who are interested will be given a separate consent form detailing the purpose and activities involved. Assessments are conducted separately with each partner in a couple. The first partner in a couple to complete their 12-month follow-up and consent to continue in this study will be told that the couple’s intervention session will be scheduled after their partner also completes the follow-up and pending their partner’s individual consent to participate.

Interventions

All participants will be randomly assigned to either CHTC retesting or individual rapid HIV testing session. Intervention sessions for both conditions are conducted remotely over Zoom. All sessions are audio-recorded for data collection, fidelity monitoring, and supervision.

CHTC Retesting

CHTC retesting involves the completion of the CDC standard CHTC protocol [49]. This includes (1) introducing the CHTC process and receiving testing consent from the couple, (2) explaining the HIV test and potential results and collecting the sample, (3) building rapport by exploring the couple’s relationship, (4) discussing HIV risk concerns and reasons for testing, (5) discussing the couple’s sexual agreement and how they handle sex outside of the relationship, (6) providing the results to each partner in the couple, (7) developing a care, treatment, and prevention plan based on results, and (8) providing referrals as needed. Each participant provides a saliva sample for an Oraquick Home testing kit. The test develops during the CHTC session while the counselor discusses steps 3 through 5.

Participants assigned in the original 4Us trial to a condition that includes viewing ACT videos before completing CHTC. The ACT video portrays 4 couples in scenes discussing HIV testing, drug use, sexual agreements, and drug use during sex. Each scene is depicted twice. The initial viewing shows the couple making one or more communication errors. The second viewing shows the couple using more effective communication skills, resolving the situations more adaptively.

Participants assigned to a condition that includes the substance use calendar module complete this module just before the delivery of HIV testing results. The substance use calendar occurs in the CHTC session before the HIV test results are given. The couple is asked to collectively complete a 30-day calendar of daily drug and alcohol use. The counselor provides the calendar on a shared computer screen as a Microsoft Excel (Microsoft Corporation) document. After the completion of the calendar, the counselor engages the couple in a discussion about their use, establishes the couple's goals and limits for drug use, and makes plans to achieve these goals. Additional details about the content of these intervention components are available elsewhere [47]. The intervention session in the CHTC retesting study follows the same procedures as the original 4Us trial. The same counselor may or may not conduct the resting intervention, which mirrors how testing may occur in a community setting.

Individual Rapid HIV Testing Session

Individual rapid HIV testing session, also known as the individual HIV counseling, testing, and referral (CTR), is the current standard of care for individual testing and first involves preparing to conduct an HIV test (explaining the HIV test and possible results the participant could receive). After answering any participant questions and gaining consent to conduct the test, the HIV counselor walks the participant through the rapid, oral HIV test. While the HIV test is processing for 20 minutes, the counselor and participant discuss a prevention plan, avoiding the topic of their partner and steering the conversation to address only the individual. HIV-negative individuals are given a standard referral list for future HIV testing, sexually transmitted infection (STI) testing, and PrEP options. Those testing HIV positive are counseled about their test result and referred to confirmatory testing. When serodiscordant couples are randomized to individual rapid HIV testing control condition, individuals who are living with HIV do not receive HIV testing. Instead, they receive information about ART adherence, undetectable=untransmittable, and STI testing.

Intervention Training

As part of the ongoing 4Us trial [47], all interventionists complete Sullivan et al [11] CHTC training curriculum (adapted by the CDC) as well as training in motivational interviewing. Each counselor role played motivational interviewing–spirited CHTC at least 3 times with fellow project staff and at least once with principal investigators TJS and RS. All role-play practice sessions were audio-recorded for training purposes. Booster training was offered at least once per year for counselors by TJS. In addition to CHTC and motivational interviewing training, counselors were refreshed on individual HIV CTR during 2 half-day training sessions. During these trainings, counselors practiced through a plethora of role-play scenarios, and a standard protocol was developed. These trainings were followed by at least 3 audio-recorded, role-play practice sessions with fellow project staff. TJS conducted individual and group feedback and skills coaching sessions for the CTR counselors. Following training, the counselors maintained weekly supervision with TJS.

Fidelity Monitoring and Supervision

TJS provides weekly supervision to study counselors. These sessions involve a review of participant CHTC session audio recordings, discussion, and additional skills training as needed. In addition, 20% of CHTC session recordings are assessed using the CDC's CHTC fidelity checklist [11]. Separately, fidelity to motivational interviewing during delivery of the substance use calendar is assessed using the Motivational Interviewing Treatment Integrity system [50] with supplemental codes developed by Starks et al [51].

Primary Outcomes

Primary analyses focus on 2 (individual-level) behavioral indicators of HIV transmission risk: (1) the number of CAS acts with a casual partner in the absence of the respondent taking PrEP and (2) CAS with a serodiscordant main partner who is not virally suppressed or concurrent CAS between main and casual partners in the absence of the respondent taking PrEP. The availability of day-level data generated by the timeline followback (TLFB) assessment allows for an examination of event-driven PrEP dosing as well as overall day-level adherence. Self-reported sexual behavior will be corroborated with results from bacterial STI (gonorrhea and chlamydia) testing. In instances where these indicators of HIV TRB suggest CAS with a casual (or main) partner occurred but was not reported, we will use data from the objective indicator.

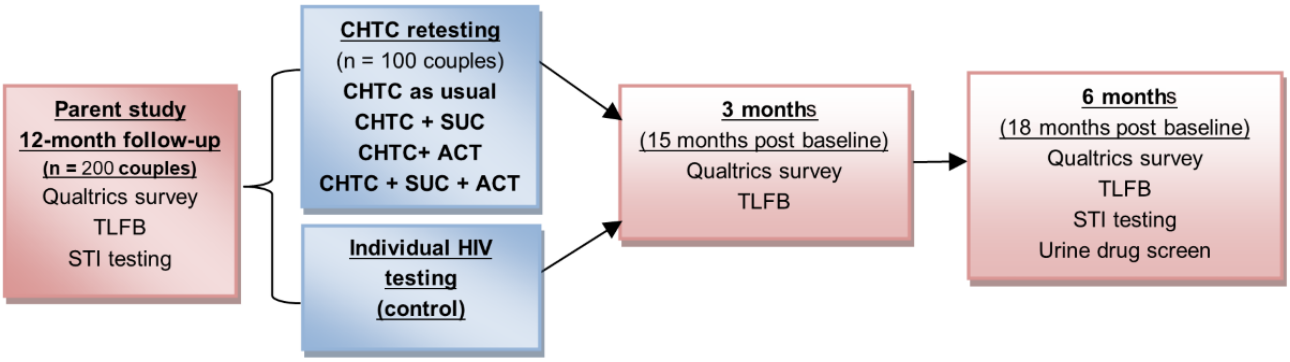
Secondary Outcomes

Secondary analyses focus on indicators of drug use and severity (primary outcomes in the parent study). Drug use is operationalized in 2 ways. First, using TLFB interview data, the quantity of drug use will be operationalized using the total number of instances reported during the assessment period. We will examine cannabis and other illicit drug use frequency separately. Urine assay will corroborate the self-report. In instances where urine results signal the use of drugs not reported, we will use data from the objective indicator. Second, drug use severity will be assessed using the Drug Abuse Screening Test [52] total score.

Participant Timeline

See Figure 1 for a timeline of participant flow through the study.

Figure 1. Timeline of participation. ACT: assertive communication training; CHTC: couples HIV testing and counseling; STI: sexually transmitted infection; SUC: substance use calendar; TLFB: timeline followback.



Sample Size

Power to detect significant between-group differences in primary outcomes was calculated using the PASS program (version 2022; NCSS, LLC). Analyses focused on power to detect a significant between-group difference at any 1 follow-up time point. Results from the tests for difference between 2 Poisson rates in a cluster randomized design module indicated the study had power of >0.80 to detect a 20% or greater reduction in the rate of CAS with casual partners. This estimate assumed a sample of 200 couples with equal allocation to condition, and models were tested with based rates of 2-4 instances of CAS with a casual partner among the control (individual HIV testing and counseling) condition. Results from the tests for 2 proportions in a cluster-randomized design suggested proposed study has power of >0.80 to detect a 22% reduction in the proportion of reporting main partner TRB, assuming a sample of 200 couples and a 70% base rate in the control condition.

Assignment of Interventions

Randomization

Couples will be randomly assigned to 1 of 2 conditions, CHTC retesting or individual rapid HIV testing. Randomization will be stratified for previous randomization in the 4Us trial (CHTC as usual, CHTC plus the substance use calendar, CHTC plus the ACT video, and CHTC plus both adjunct components). The random assignment will be performed by the project manager, who will enter the stratification criteria in Qualtrics to obtain the condition before intervention delivery.

Blinding

Intervention staff cannot be blinded to the condition they are delivering. Likewise, participants cannot be blinded to the condition. The 12-month follow-up in the 4Us trial (which serves as the preintervention data point for this study) is completed before participants are consented to this study. Assessment staff are blinded to condition at follow-up. Where blinding is possible, unblinding is not anticipated.

Data Collection, Management, and Analyses

Data Collection for Primary Outcomes

Self-Reported Sexual Behavior

Procedures are the same as those used in the ongoing 4Us protocol [47]. Research assistants gather self-reported sexual behavior data for the past 30 days using a structured TLFB interview (Sobell and Sobell [53]). A Microsoft Access (Microsoft Corporation) database is used to facilitate the capture of data, including “anchor dates” or significant events; missed PrEP doses (for those on PrEP); heavy drinking and drug use; and sexual events. Sexual event data further comprise partner type (main or casual), the sex act performed (eg, anal insertive and anal receptive), and whether a condom was used.

Biological Testing

The Molecular Testing Laboratory (MTL) coordinates at-home STI testing. Materials necessary for collection and return shipping are delivered before the scheduled assessment meeting with the research assistant. Specimen collection is completed at a time designated in the assessment. The research assistant is available to review collection procedures, confirm the accuracy of shipping information, and observe the packaging of specimens for shipment.

The presence of urethral STIs will be tested in urine specimens; meanwhile, the presence of rectal STIs will be tested in (self-administered) rectal swab. The Abbott RealTime CT/NG assay is used to evaluate the presence of *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. This is a Food and Drug Administration (FDA)–cleared real-time polymerase chain reaction assay for direct, qualitative detection of a region of the cryptic plasmid DNA of *C trachomatis* and the Opa gene of *N gonorrhoeae*.

HIV Testing

HIV testing, during CHTC and individual HIV testing sessions, will be performed using the Oraquick 4th generation testing kit. These kits are approved for at-home self-testing, and FDA-approved instructions are included. At follow-up (6 months), HIV testing will be conducted individually using self-administered dried bloodspot, giving participants the option of an Oraquick HIV to complete their HIV test if they prefer.

Retention Plan

Retention procedures continue those used in the ongoing 4Us trial [47], from which participants for this study are recruited. Assessments are conducted individually to retain participants who break up and whose relationship may have ended during the course of their participation in the study and to reduce the burden associated with coordinating a single assessment session with both partners. Study staff have at least quarterly contact with participants through email, SMS text messaging, and

telephone (based on participant preference), which serves to maintain engagement and the accuracy of contact information over the study period.

Data Management

TLFB data are gathered by a trained interviewer using a data-entry system programmed in Microsoft Access. The institutional review board of Hunter College has reviewed all study procedures. In addition, procedures are reviewed by the Data Safety Monitoring Board (DSMB), which consists of experts in sexual health and substance use intervention research with SMM.

Data Analysis Plan

Data Screening Procedures and Analyses of Attrition

We will follow standard procedures for cleaning data and assess whether variables conform to the distributional assumptions of our analyses. The 12-month follow-up assessment in the parent study serves as prerandomization (ie, baseline) data for the purposes of these analyses. We will begin with a sensitivity analysis to examine whether couples enrolled into the randomized controlled trial proposed in this revision differ from those participants in the parent study (DA050508) who are not enrolled either due to relationship termination or lack of interest. This analysis will serve to identify behavioral factors (eg, drug use or sexual risk-taking) and relationship factors (eg, satisfaction, commitment, or communication skills) that are associated with relationship termination and uptake of CHTC retesting (among those couples who remain together). Subsequently, we will conduct an analysis of randomization success and attrition to determine if either is associated with (1) demographic variables or (2) drug use or TRB outcomes assessed at the 12-month 4Us follow-up. Factors that are observed to covary significantly with randomization or attrition will be incorporated in outcome analyses.

Primary Analyses of Intervention Effects

The primary hypothesis is that CHTC retesting will be associated with significant reductions in sexual HIV TRB (primary) outcomes compared to individual HIV testing. Using procedures similar to our previously published studies [54], outcome analyses will be conducted in a multilevel modeling framework. Analyses will use full-information maximum likelihood estimation and specify a negative binomial distribution consistent with the count nature of primary outcomes. The appropriateness of a Poisson distribution will be determined by inspection of the significance of the dispersion parameter in negative binomial models. This accounts for the nesting of individuals within couple. Because randomization occurs at the couple level, condition is a level 2 variable. The effect of the intervention will be evaluated by examining the regression coefficient (and associated *P* value). Separate models will be calculated to predict outcomes at 3- and 6-month follow-ups (with Bonferroni correction for repeated nonorthogonal tests). Mplus (Muthén and Muthén) accommodates count and dichotomous outcomes within the multilevel modeling context. Analysis of secondary outcomes will follow analogous analytic procedures.

Moderation or Mediation Analyses

Where possible, we will evaluate whether retesting using the adjunct (substance use calendar and ACT video) components is associated with specific reductions in primary (HIV TRB) outcomes. While the primary goal of this analysis is to test whether CHTC retesting, in general, is associated with benefits above and beyond individual HIV testing, the study design permits a preliminary examination of whether retesting that involves these adjunct components developed by our team is associated with additional benefits above and beyond retesting using the standard CHTC protocol. We will conduct a preliminary examination of this possibility using analytic procedures analogous to those used to evaluate effects on secondary drug use outcomes.

Data Monitoring

The DSMB, comprising 3 independent experts in the fields of HIV prevention, substance use intervention, and biostatistics, was convened in accordance with NIH policy to oversee the original 4Us trial (NCT05000866). The DSMB convenes at least annually in response to the occurrence of any serious adverse events.

Study staff will monitor the occurrence of 2 anticipated adverse events, including HIV incidence and IPV. Participants provide data on these at each follow-up, and responses are reported to the DSMB annually by the primary investigator. The primary investigator will report unanticipated events and those reported spontaneously by participants to the DSMB on an ongoing basis. These are also summarized in their annual meeting report.

Trial Modification and Discontinuation

There are no plans to conduct interim analyses, and no a priori stopping rule has been established for this trial. Randomization may be discontinued, and the trial stopped under the guidance of the DSMB in response to adverse event review. Sponsor and DSMB approval are required for substantive changes to trial design. Changes also require institutional review board approval before implementation, and the clinicaltrials.gov record would be updated to reflect modifications.

Confidentiality

Unique study ID numbers, assigned in the 4Us trial, are used to link participant data. Only essential study staff have access to the password-protected file that links contact information to study ID. All materials will be stored in databases that are HIPAA-compliant. Laboratory test results are ordered and received through a HIPAA-compliant platform maintained by the MTL. Participants consent to having the MTL conduct state-level, name-based reporting for positive HIV or STI results.

All study-affiliated staff complete mandatory training in good clinical practice and the responsible conduct of research. Standard operating procedures are created to minimize breaches in confidentiality. Participants indicate their preferred mode of communicating with staff (eg, telephone call, SMS text messaging, email) and may request that study staff use discretion when leaving messages. As a standard measure, NIH grants a federal certificate of confidentiality.

Posttrial Care

The study team has compiled an index of national resources that are made available to participants. These include search engines that identify HIV prevention and care providers in the United States. Positive HIV or STI results are delivered by study staff, and linkage to care is discussed. The MTL also complies with state-level, name-based reporting procedures, and local or state department of health staff may follow up in some instances. Participants who exhibit signs of serious mental illness or clinically significant distress in interactions with study staff will be evaluated by a study team member with training in mental health counseling and crisis risk assessment.

Dissemination

The authorship team is committed to the dissemination of study results. This will be accomplished through several mechanisms. First, we convey information on study activities and progress to participants through a newsletter to participants. Second, the investigative team regularly attends local, national, and international conferences to share findings with other researchers, service providers, and policymakers. Finally, the investigative team will prepare manuscripts for publication in peer-reviewed journal articles. Authorship in publications will be based upon intellectual contribution and guided by American Psychological Association guidelines for authorship. There are no plans to make participant-level data available to the public. Data will be available to other researchers upon request from the study principal investigator.

Ethical Considerations

This study protocol was approved by the City University of New York's Human Research Protection Program (2022-0630) and is registered with ClinicalTrials.gov (NCT NCT05833074). All participants who complete their original 4Us 12-month appointment, meet study eligibility, and agree to be enrolled in this CHTC retesting trial provide consent individually over Zoom. After reading the consent form, the research assistant obtains verbal consent to participate. Given the remote nature of study activities and the geographic diversity of the sample, a waiver of documentation of consent was obtained. All data are deidentified to protect participants' privacy by assigning each participant a unique identifier. Data systems are established to only keep participants' name and their unique identifier in a secured database. Participants are compensated US $20 for attending the intervention session, US $40 for completing the 3-month assessment (US $30 for survey and TLFB and US $10 for urine drug testing), and US $60 for completing the 6-month assessment (US $30 for survey and TLFB and US $30 for urine drug testing, STI, HIV testing, and PrEP adherence, if applicable). Compensation for this trial's baseline is paid as the 12-month assessment for the original 4Us trial.

Results

This study began recruitment in January 2023, and all participant components are projected to end in May 2025. As of December 2023, 102 individuals (51 couples) have enrolled in the CHTC retesting trial.

Discussion

The results of this trial have the potential to inform a previously unstudied aspect of CHTC—the utility of repeated, annual completion. This trial will be the first experimental evaluation of CHTC retesting. Results therefore have the potential to substantively inform CHTC guidance.

At the same time, several limitations arise as a function of study design. Both partners in a couple must consent to participate in resting. We are therefore unable to compare CHTC to a condition in which 1 (but not both) partner receives an individual HIV test. In addition, this trial is subject to the limitations of the 4Us study from which participants are recruited. Briefly, the demands of dyadic participation may present barriers to study enrollment or engagement, particularly for couples with relatively lower relationship quality [55]. The sample will not include partnered SMM in relationships where one partner is unable or unwilling to participate. The 4Us sample is recruited through advertisements on social networking and dating applications. It, therefore, underrepresents SMM who do not engage in these digital spaces. Furthermore, all participants in the 4Us study are aged 17 years or older, and at least 1 partner must be aged 17-29 years. This limits the generalizability of findings to adolescents and older adults.

Despite these limitations, this study has the potential to enhance knowledge about the effects of CHTC on the sexual health of SMM couples. This may inform future efforts to disseminate the intervention in the United States and internationally, as well as to gender-diverse couples.

Conflicts of Interest

None declared.

References

1. Estimated HIV incidence and prevalence in the United States, 2015-2019. Centers for Disease Control and Prevention. 2021. URL: https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-supplemental-report-vol-26-1.pdf [accessed 2022-02-01]
2. Pitasi MA, Beer L, Cha S, Lyons SJ, Hernandez AL, Prejean J, et al. Vital signs: HIV infection, diagnosis, treatment, and prevention among gay, bisexual, and other men who have sex with men--United States, 2010-2019. MMWR Morb Mortal Wkly Rep 2021;70(48):1669-1675 [FREE Full text] [doi: 10.15585/mmwr.mm7048e1] [Medline: 34855721]

3. Davidovich U, de Wit JB, Stroebe W. Assessing sexual risk behaviour of young gay men in primary relationships: the incorporation of negotiated safety and negotiated safety compliance. AIDS 2000;14(6):701-706 [FREE Full text] [doi: 10.1097/00002030-200004140-00009] [Medline: 10807193]
4. Davidovich U, de Wit J, Albrecht N, Geskus R, Stroebe W, Coutinho R. Increase in the share of steady partners as a source of HIV infection: a 17-year study of seroconversion among gay men. AIDS 2001;15(10):1303-1308 [FREE Full text] [doi: 10.1097/00002030-200107060-00013] [Medline: 11426076]
5. Davidovich U, de Wit JBF, Stroebe W. Behavioral and cognitive barriers to safer sex between men in steady relationships: implications for prevention strategies. AIDS Educ Prev 2004;16(4):304-314. [doi: 10.1521/aeap.16.4.304.40398] [Medline: 15342333]
6. Sullivan PS, Salazar L, Buchbinder S, Sanchez TH. Estimating the proportion of HIV transmissions from main sex partners among men who have sex with men in five US cities. AIDS 2009;23(9):1153-1162 [FREE Full text] [doi: 10.1097/QAD.0b013e32832baa34] [Medline: 19417579]
7. Goodreau SM, Carnegie NB, Vittinghoff E, Lama JR, Sanchez J, Grinsztejn B, et al. Correction: what drives the US and peruvian HIV epidemics in men who have sex with men (MSM)? PLoS ONE 2013;8(7) [FREE Full text] [doi: 10.1371/annotation/9a6a0c8e-2d01-4f36-9ab8-f9fdfce6497b]
8. Goodreau SM, Carnegie NB, Vittinghoff E, Lama JR, Sanchez J, Grinsztejn B, et al. What drives the US and Peruvian HIV epidemics in men who have sex with men (MSM)? PLoS One 2012;7(11):e50522 [FREE Full text] [doi: 10.1371/journal.pone.0050522] [Medline: 23209768]
9. Starks TJ, Jones SS, Kyre K, Robles G, Cain D, Jimenez R, et al. Testing the drug use and condomless anal sex link among sexual minority men: the predictive utility of marijuana and interactions with relationship status. Drug Alcohol Depend 2020;216:108318 [FREE Full text] [doi: 10.1016/j.drugalcdep.2020.108318] [Medline: 33022531]
10. Volpe R, Lewko JH, Batra A. A compendium of effective, evidence-based best practices in the prevention of neurotrauma. In: Index. Toronto: University of Toronto Press; 2002:365-371.
11. Sullivan PS, Stephenson R, Grazter B, Wingood G, Diclemente R, Allen S, et al. Adaptation of the African couples HIV testing and counseling model for men who have sex with men in the United States: an application of the ADAPT-ITT framework. Springerplus 2014;3(1):249 [FREE Full text] [doi: 10.1186/2193-1801-3-249] [Medline: 24877036]
12. Sullivan PS, White D, Rosenberg ES, Barnes J, Jones J, Dasgupta S, et al. Safety and acceptability of couples HIV testing and counseling for US men who have sex with men: a randomized prevention study. J Int Assoc Provid AIDS Care 2014;13(2):135-144 [FREE Full text] [doi: 10.1177/2325957413500534] [Medline: 23995295]
13. Darbes LA, McGrath NM, Hosegood V, Johnson MO, Fritz K, Ngubane T, et al. Results of a couples-based randomized controlled trial aimed to increase testing for HIV. J Acquir Immune Defic Syndr 2019;80(4):404-413 [FREE Full text] [doi: 10.1097/QAI.0000000000001948] [Medline: 30730356]
14. Coates TJ. Efficacy of voluntary HIV-1 counselling and testing in individuals and couples in Kenya, Tanzania, and Trinidad: a randomised trial. The voluntary HIV-1 counseling and testing efficacy study group. Lancet 2000;356(9224):103-112. [Medline: 10963246]
15. Stephenson R, Vwalika B, Greenberg L, Ahmed Y, Vwalika C, Chomba E, et al. A randomized controlled trial to promote long-term contraceptive use among HIV-serodiscordant and concordant positive couples in Zambia. J Womens Health (Larchmt) 2011;20(4):567-574 [FREE Full text] [doi: 10.1089/jwh.2010.2113] [Medline: 21410332]
16. Stephenson R, Garofalo R, Sullivan PS, Hidalgo MA, Bazzi AR, Hoehnle S, et al. Stronger together: results from a randomized controlled efficacy trial of a dyadic intervention to improve engagement in HIV care among serodiscordant male couples in three US cities. AIDS Behav 2021;25(8):2369-2381 [FREE Full text] [doi: 10.1007/s10461-021-03199-8] [Medline: 33630199]
17. Rusbult CE, Van Lange PAM. Why we need interdependence theory. Soc Personal Psychol Compass 2008;2(5):2049-2070 [FREE Full text] [doi: 10.1111/j.1751-9004.2008.00147.x]
18. Lewis MA, McBride CM, Pollak KI, Puleo E, Butterfield RM, Emmons KM. Understanding health behavior change among couples: an interdependence and communal coping approach. Soc Sci Med 2006;62(6):1369-1380 [FREE Full text] [doi: 10.1016/j.socscimed.2005.08.006] [Medline: 16146666]
19. Rusbult CE, Van Lange PAM. Interdependence, interaction, and relationships. Annu Rev Psychol 2003;54(1):351-375 [FREE Full text] [doi: 10.1146/annurev.psych.54.101601.145059] [Medline: 12415073]
20. Stephenson R, Sullivan S, Sharma A, Kahle E. Discordant reporting of partner labels, HIV testing and sexual behavior among a sample of partnered men who have sex with men in the US. AIDS Behav 2020;24(2):540-550 [FREE Full text] [doi: 10.1007/s10461-019-02725-z] [Medline: 31691044]
21. Stephenson R, Sullivan SP, Mitchell JW, Johnson BA, Sullvian PS. Efficacy of a telehealth delivered couples' HIV counseling and testing (CHTC) intervention to improve formation and adherence to safer sexual agreements among male couples in the US: results from a randomized control trial. AIDS Behav 2022;26(8):2813-2824 [FREE Full text] [doi: 10.1007/s10461-022-03619-3] [Medline: 35194698]
22. Parsons JT, Starks TJ, DuBois S, Grov C, Golub SA. Alternatives to monogamy among gay male couples in a community survey: implications for mental health and sexual risk. Arch Sex Behav 2013;42(2):303-312 [FREE Full text] [doi: 10.1007/s10508-011-9885-3] [Medline: 22187028]

23. Starks TJ, Robles G, Bosco SC, Dellucci TV, Grov C, Parsons JT. The prevalence and correlates of sexual arrangements in a national cohort of HIV-Negative gay and bisexual men in the United States. Arch Sex Behav 2019;48(1):369-382 [FREE Full text] [doi: 10.1007/s10508-018-1282-8] [Medline: 30465312]
24. Mitchell JW. Aspects of gay male couples' sexual agreements vary by their relationship length. AIDS Care 2014;26(9):1164-1170 [FREE Full text] [doi: 10.1080/09540121.2014.882491] [Medline: 24512593]
25. Starks TJ, Robles G, Bosco SC, Doyle KM, Dellucci TV. Relationship functioning and substance use in same-sex male couples. Drug Alcohol Depend 2019;201:101-108 [FREE Full text] [doi: 10.1016/j.drugalcdep.2019.04.009] [Medline: 31203148]
26. Mitchell JW, Petroll AE. HIV testing rates and factors associated with recent HIV testing among male couples. Sex Transm Dis 2012;39(5):379-381 [FREE Full text] [doi: 10.1097/OLQ.0b013e3182479108] [Medline: 22504604]
27. Stephenson R, White D, Darbes L, Hoff C, Sullivan P. HIV testing behaviors and perceptions of risk of HIV infection among MSM with main partners. AIDS Behav 2015;19(3):553-560 [FREE Full text] [doi: 10.1007/s10461-014-0862-4] [Medline: 25081599]
28. Mustanski B, Newcomb ME, Clerkin EM. Relationship characteristics and sexual risk-taking in young men who have sex with men. Health Psychol 2011;30(5):597-605 [FREE Full text] [doi: 10.1037/a0023858] [Medline: 21604883]
29. Golub SA, Starks TJ, Payton G, Parsons JT. The critical role of intimacy in the sexual risk behaviors of gay and bisexual men. AIDS Behav 2012;16(3):626-632 [FREE Full text] [doi: 10.1007/s10461-011-9972-4] [Medline: 21630012]
30. Starks TJ, Payton G, Golub SA, Weinberger CL, Parsons JT. Contextualizing condom use: intimacy interference, stigma, and unprotected sex. J Health Psychol 2014;19(6):711-720 [FREE Full text] [doi: 10.1177/1359105313478643] [Medline: 23520349]
31. Campbell CK, Gómez AM, Dworkin S, Wilson PA, Grisham KK, McReynolds J, et al. Health, trust, or "just understood": explicit and implicit condom decision-making processes among black, white, and interracial same-sex male couples. Arch Sex Behav 2014;43(4):697-706 [FREE Full text] [doi: 10.1007/s10508-013-0146-5] [Medline: 23912774]
32. Bosco SC, Pawson M, Parsons JT, Starks TJ. Biomedical HIV prevention among gay male couples: a qualitative study of motivations and concerns. J Homosex 2021;68(8):1353-1370 [FREE Full text] [doi: 10.1080/00918369.2019.1696105] [Medline: 31809246]
33. Starks TJ, John SA, Doyle K, Shalhav O, Parsons JT. Identifying motivations forbarriers to PrEP uptake among gay couples. 2017 Presented at: Adherence 2017, 12th International Conference on HIV Treatment and Prevention Adherence; June 4-6, 2017; Miami, FL.
34. Starks TJ, Pawson M, Stephenson R, Sullivan P, Parsons JT. Dyadic qualitative analysis of condom use scripts among emerging adult gay male couples. J Sex Marital Ther 2018;44(3):269-280 [FREE Full text] [doi: 10.1080/0092623X.2017.1359713] [Medline: 28745559]
35. Goldenberg T, Finneran C, Andes KL, Stephenson R. 'Sometimes people let love conquer them': how love, intimacy, and trust in relationships between men who have sex with men influence perceptions of sexual risk and sexual decision-making. Cult Health Sex 2015;17(5):607-622 [FREE Full text] [doi: 10.1080/13691058.2014.979884] [Medline: 25465292]
36. Mimiaga MJ, Suarez N, Garofalo R, Frank J, Ogunbajo A, Brown E, et al. Relationship dynamics in the context of binge drinking and polydrug use among same-sex male couples in Atlanta, Boston, and Chicago. Arch Sex Behav 2019;48(4):1171-1184 [FREE Full text] [doi: 10.1007/s10508-018-1324-2] [Medline: 30806868]
37. Cain D, Sauermilch D, Starks TJ. Client responses to video-based communication skills training involving PrEP for HIV: tailoring an individual sexual health intervention for sexual minority men in relationships. AIDS Behav 2023;27(8):2463-2477 [FREE Full text] [doi: 10.1007/s10461-023-03985-6] [Medline: 36658446]
38. Medley G, Lipari RN, Bose J, Cribb DS, Kroutil LA, McHenry G, RTI International. Sexual orientation and estimates of adult substance use and mental health: results from the 2015 National Survey on drug use and health. National Survey on Drug Use and Health Data Review. 2016. URL: https://www.samhsa.gov/data/sites/default/files/NSDUH-SexualOrientation-2015/NSDUH-SexualOrientation-2015/NSDUH-SexualOrientation-2015.htm [accessed 2024-01-06]
39. McCabe SE, Engstrom CW, Kcomt L, Evans-Polce R, West BT. Trends in binge drinking, marijuana use, illicit drug use, and polysubstance use by sexual identity in the United States (2006-2017). Subst Abus 2022;43(1):194-203 [FREE Full text] [doi: 10.1080/08897077.2021.1913696] [Medline: 34344281]
40. Parsons JT, Starks TJ. Drug use and sexual arrangements among gay couples: frequency, interdependence, and associations with sexual risk. Arch Sex Behav 2014;43(1):89-98 [FREE Full text] [doi: 10.1007/s10508-013-0237-3] [Medline: 24322670]
41. Vosburgh HW, Mansergh G, Sullivan PS, Purcell DW. A review of the literature on event-level substance use and sexual risk behavior among men who have sex with men. AIDS Behav 2012;16(6):1394-1410 [FREE Full text] [doi: 10.1007/s10461-011-0131-8] [Medline: 22323004]
42. John SA, Parsons JT, Rendina HJ, Grov C. Club drug users had higher odds of reporting a bacterial STI compared with non-club drug users: results from a cross-sectional analysis of gay and bisexual men on HIV pre-exposure prophylaxis. Sex Transm Infect 2019;95(8):626-628 [FREE Full text] [doi: 10.1136/sextrans-2018-053591] [Medline: 30126949]
43. Patel P, Borkowf CB, Brooks JT, Lasry A, Lansky A, Mermin J. Estimating per-act HIV transmission risk: a systematic review. AIDS 2014;28(10):1509-1519 [FREE Full text] [doi: 10.1097/QAD.0000000000000298] [Medline: 24809629]

44. Rendina HJ, Moody RL, Ventuneac A, Grov C, Parsons JT. Aggregate and event-level associations between substance use and sexual behavior among gay and bisexual men: comparing retrospective and prospective data. Drug Alcohol Depend 2015;154:199-207 [FREE Full text] [doi: 10.1016/j.drugalcdep.2015.06.045] [Medline: 26190557]
45. Mitchell JW, Boyd C, McCabe S, Stephenson R. A cause for concern: male couples' sexual agreements and their use of substances with sex. AIDS Behav 2014;18(7):1401-1411 [FREE Full text] [doi: 10.1007/s10461-014-0736-9] [Medline: 24584415]
46. Mitchell JW, Pan Y, Feaster D. Actor-partner effects of male couples substance use with sex and engagement in condomless anal sex. AIDS Behav 2016;20(12):2904-2913 [FREE Full text] [doi: 10.1007/s10461-016-1355-4] [Medline: 26979417]
47. Starks TJ, Kyre KD, Cowles CB, Castiblanco J, Washington C, Parker JN, et al. A full-factorial randomized controlled trial of adjunct couples HIV testing and counseling components addressing drug use and communication skills among sexual minority male couples. BMC Public Health 2021;21(1):2158 [FREE Full text] [doi: 10.1186/s12889-021-12208-3] [Medline: 34819058]
48. HIV testing: getting tested. division of HIV prevention, National Center for HIV, Viral Hepatitis, STD, and TB Prevention. Centers for Disease Control and Prevention. 2022. URL: https://www.cdc.gov/nchhstp/default.htm [accessed 2024-01-06]
49. Implementing HIV testing in nonclinical settings: a guide for HIV testing providers. Centers for Disease Control and Prevention. 2016. URL: https://www.cdc.gov/hiv/pdf/testing/cdc_hiv_implementing_hiv_testing_in_nonclinical_settings.pdf [accessed 2024-01-06]
50. Moyers TB, Manuel JK, Ernst D. Motivational interviewing treatment integrity coding manual 4.0. Unpublished Manual. 2014. URL: https://www.academiemg.nl/library/downloads/1536662018.1447.pdf [accessed 2024-01-06]
51. Starks TJ, Robles G, Doyle KM, Pawson M, Bertone P, Millar BM, et al. Motivational interviewing with male couples to reduce substance use and HIV risk: manifestations of partner discord and strategies for facilitating dyadic functioning. Psychotherapy (Chic) 2020;57(1):58-67 [FREE Full text] [doi: 10.1037/pst0000278] [Medline: 31999189]
52. Skinner HA. The drug abuse screening test. Addict Behav 1982;7(4):363-371 [FREE Full text] [doi: 10.1016/0306-4603(82)90005-3] [Medline: 7183189]
53. Sobell LC, Sobell MB. Timeline Followback User's Guide. Baltimore: Alcohol Research Foundation; 1996.
54. Starks TJ, Adebayo T, Kyre KD, Millar BM, Stratton MJ, Gandhi M, et al. Pilot randomized controlled trial of motivational interviewing with sexual minority male couples to reduce drug use and sexual risk: the couples health project. AIDS Behav 2022;26(2):310-327 [FREE Full text] [doi: 10.1007/s10461-021-03384-9] [Medline: 34297275]
55. Starks TJ, Millar BM, Parsons JT. Correlates of individual versus joint participation in online survey research with same-sex male couples. AIDS Behav 2015;19(6):963-969 [FREE Full text] [doi: 10.1007/s10461-014-0962-1] [Medline: 25432879]

Abbreviations

ACT: assertive communication training
CAS: condomless anal sex
CDC: Centers for Disease Control and Prevention
CHTC: couples HIV testing and counseling
CTR: counseling, testing, and referral
DSMB: Data Safety and Monitoring Board
FDA: Food and Drug Administration
GHB: gamma-hydroxybuterate
HIPAA: Health Insurance Portability and Accountability Act
IPV: intimate partner violence
MTL: Molecular Testing Laboratory
NIH: National Institutes of Health
OR: odds ratio
PEP: postexposure prophylaxis
PrEP: preexposure prophylaxis
SMM: sexual minority men
STI: sexually transmitted infection
TLFB: timeline followback
TRB: transmission risk behavior

Edited by A Mavragani; submitted 22.09.23; peer-reviewed by A Conroy, G Rebchook; comments to author 14.12.23; revised version received 20.12.23; accepted 21.12.23; published 13.02.24.

Please cite as:
Starks TJ, Kyre K, Castiblanco J, Parker JN, Kahle E, Stephenson R, Cain D
Comparing Repeated (Annual) Couples HIV Testing and Counseling to Individual HIV Testing and Counseling Among Male Couples at High Risk of HIV Infection: Protocol for a Randomized Control Trial
JMIR Res Protoc 2024;13:e53023
URL: https://www.researchprotocols.org/2024/1/e53023
doi:10.2196/53023
PMID:38349737

Protocol

Pan-Indian Clinical Registry of Invasive Fungal Infections Among Patients in the Intensive Care Unit: Protocol for a Multicentric Prospective Study

Anup Kumar Ojha[1], PhD; Venencia Albert[1], PhD; Saurabh Sharma[2], MD; Vinaykumar Hallur[3], MD; Gagandeep Singh[4], MD; Umabala Pamidimukkala[5], MD; Kh Jitenkumar Singh[2], PhD; Harleen Kaur[2], MSc; Tadepalli Karuna[6], MD; Jayanthi Savio[7], MD; Reema Nath[8], MD; Immaculata Xess[4], MD; Prashant Gupta[9], MD; Anjali Shetty[10], MBBS; Madhuchhanda Das[1], MBBS, PhD

[1]Indian Council of Medical Research, New Delhi, India

[2]Indian Council of Medical Research-National Institute of Medical Statistics, New Delhi, India

[3]All India Institute of Medical Sciences, Bhubaneswar (AIIMS, Bhubaneswar), Bhubaneswar, Odisha, India

[4]All India Institute of Medical Sciences, New Delhi (AIIMS-New Delhi), New Delhi, India

[5]Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India

[6]All India Institute of Medical Sciences, Bhopal (AIIMS-Bhopal), Bhopal, Madhya Pradesh, India

[7]St John's Medical College and Hospital, Bangalore, Karnataka, India

[8]Assam Medical College and Hospital, Dibrugarh, Assam, India

[9]King George's Medical University, Lucknow, Uttar Pradesh, India

[10]Parmanand Deepchand Hinduja Hospital (PD Hinduja Hospital), Mumbai, Maharashtra, India

Corresponding Author:
Madhuchhanda Das, MBBS, PhD
Indian Council of Medical Research
Ansari Nagar
New Delhi, 110029
India
Phone: 91 2658 8895 ext 11
Email: dasm.hq@icmr.gov.in

Abstract

Background: Fungal infections are now a great public health threat, especially in those with underlying risk factors such as neutropenia, diabetes, high-dose steroid treatment, cancer chemotherapy, prolonged intensive care unit stay, and so on, which can lead to mycoses with higher mortality rates. The rates of these infections have been steadily increasing over the past 2 decades due to the increasing population of patients who are immunocompromised. However, the data regarding the exact burden of such infection are still not available from India. Therefore, this registry was initiated to collate systematic data on invasive fungal infections (IFIs) across the country.

Objective: The primary aim of this study is to create a multicenter digital clinical registry and monitor trends of IFIs and emerging fungal diseases, as well as early signals of any potential fungal outbreak in any region. The registry will also capture information on the antifungal resistance patterns and the contribution of fungal infections on overall morbidity and inpatient mortality across various conditions.

Methods: This multicenter, prospective, noninterventional observational study will be conducted by the Indian Council of Medical Research through a web-based data collection method from 8 Advanced Mycology Diagnostic and Research Centers across the country. Data on age, gender, clinical signs and symptoms, date of admission, date of discharge or death, diagnostic tests performed, identified pathogen details, antifungal susceptibility testing, outcome, and so on will be obtained from hospital records. Descriptive and multivariate statistical methods will be applied to investigate clinical manifestations, risk variables, and treatment outcomes.

Results: These Advanced Mycology Diagnostic and Research Centers are expected to find the hidden cases of fungal infections in the intensive care unit setting. The study will facilitate the enhancement of the precision of fungal infection diagnosis and

prompt treatment modalities in response to antifungal drug sensitivity tests. This registry will improve our understanding of IFIs, support evidence-based clinical decision-making ability, and encourage public health policies and actions.

Conclusions: Fungal diseases are a neglected public health problem. Fewer diagnostic facilities, scanty published data, and increased vulnerable patient groups make the situation worse. This is the first systematic clinical registry of IFIs in India. Data generated from this registry will increase our understanding related to the diagnosis, treatment, and prevention of fungal diseases in India by addressing pertinent gaps in mycology. This initiative will ensure a visible impact on public health in the country.

International Registered Report Identifier (IRRID): DERR1-10.2196/54672

(JMIR Res Protoc 2024;13:e54672) doi:10.2196/54672

KEYWORDS

mycology; invasive fungal infections; diagnosis; clinical registry; public health; fungal infections; fungal infection; ICU patients; ICU patient; in-patient; in-patients; long-term stay; mortality; mycoses; India; knowledge gaps; epidemiological; epidemiological factor; antifungal resistance; antifungal; descriptive method

Introduction

Background

Public health is seriously threatened by fungal infections, especially in people with immunosuppression and underlying illnesses such as uncontrolled diabetes, influenza, and COVID-19, where they can result in fatal mycoses and elevated death rates [1,2]. Fungal infections manifest in various clinical forms, each with a different severity range, including superficial, cutaneous, subcutaneous, mucosal, and systemic infections. Some fungi that are a part of the microbiota, such as *Candida* spp, can transform into opportunistic pathogens affecting people who are immunocompromised, including those with HIV, patients with cancer receiving chemotherapy, and people on immunosuppressive medications [2-6]. In 2022, the World Health Organization (WHO) aimed to draw attention to the significance of combating fungal infections. There were 3 categories on this list: critical, high, and medium priority. The WHO described it as “the first global effort to systematically prioritize fungal pathogens, considering their unmet research and development needs and perceived public health importance” [7]. Nevertheless, despite the enormous prevalence of fungal propagules in the environment, which makes exposure inevitable, fungal infections are very uncommon in healthy people and animals with strong immune systems compared to bacterial and viral illnesses [8,9]. However, over the past few decades, there has been an increasing trend of persistent and recurrent fungal infections affecting both humans and animals worldwide, which are driven by both true and opportunistic pathogens [8,10-14]. A small but gradually growing number of ubiquitous fungus species that usually pose little harm to humans have emerged as carriers of deadly illnesses, especially in those with compromised immune systems [12]. The natural warmth of a mammalian body has historically constrained fungi’s ability to cause disease [15]. However, many once harmless fungal species have evolved into infectious agents due to climatic changes brought out by human activity [16,17]. Additionally, the recognized geographic ranges of known fungal infections have grown due to the continually rising global temperatures and increased moisture in some areas [18].

To overcome these lacunae and strengthen the diagnosis and research on fungal diseases in India with a focus on high throughput nonculture antigen, antibody, and molecular testing, the Indian Council of Medical Research (ICMR) has established 8 state-of-the-art Advanced Mycology Diagnostic and Research Centers (AMDRCs) in the country under ICMR-MycoNet Task Force Program. This national network of laboratories aims to improve human resources training and enhance fungal diagnostics, clinical care, research, and public health policies. The primary focus of all these centers is to create awareness of different fungal infections among the general population, develop research, cater diagnostic facilities to its catchment areas, and assess the impact of mycology laboratories on patient care and fungal mapping in the country. As an additional component of this Task Force project, it is proposed to develop a Web-based Mycology Inpatient Clinical Registry to perform prospective surveillance of all fungal infections among patients hospitalized at the ICMR AMDRCs in India. It aims to improve the knowledge gaps related to different fungal infections and understand current approaches to the diagnosis and treatment of invasive fungal infections (IFIs).

Aim and Objectives

The primary aim of the proposed study is to establish a national clinical registry in mycology to overcome the lack of knowledge on epidemiology, clinical course, and pathological characteristics of IFIs for evidence-based decision-making in clinical practice, public health programs and policy in the Indian context. The objectives of this study are to (1) develop advanced diagnostic facilities (culture, serology, molecular, therapeutic drug monitoring [TDM], and antifungal drug sensitivity test [AFST]) for fungal infections and a comprehensive digital clinical registry of IFIs; (2) describe the overall trends of fungal diseases, emerging fungal infections, and antifungal resistance; (3) map the distribution of fungi in the country through regional surveillance; (4) investigate the clinical features, diagnostics, treatment and patient outcomes among intensive care unit (ICU) patients with IFIs; (5) study the contribution of IFIs in the morbidity and mortality caused by different diseases in ICUs; and (6) investigate the clinical features, diagnostics, treatment, and outcomes among patients with chronic subcutaneous infections, such as mycetoma and chromoblastomycosis (neglected tropical diseases) [19].

Methods

Case Definition of IFIs

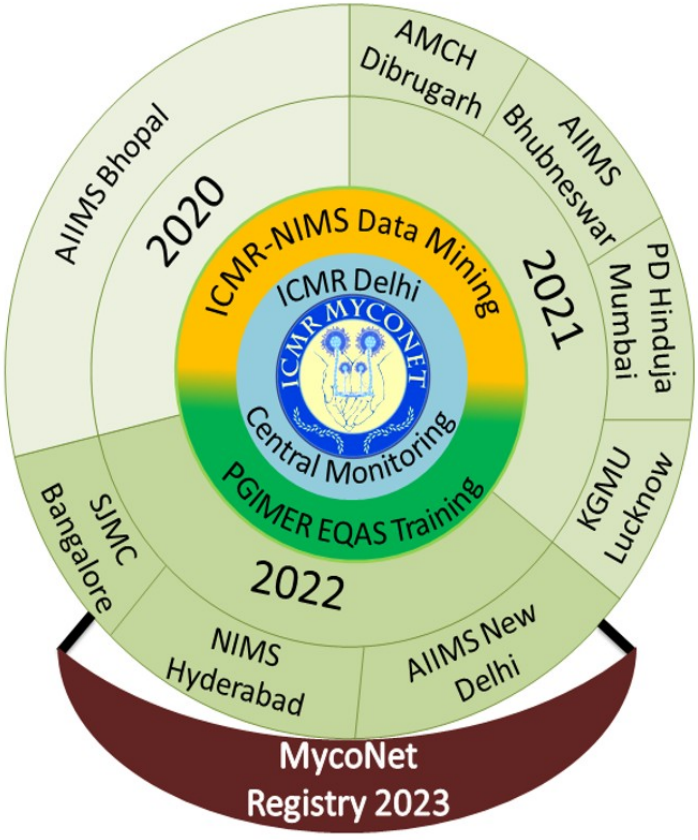
The proposed study will include proven and probable cases of IFIs as per the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium (EORTC/MSG; proven cases) or Blot criteria and Modified EORTC/MSG (probable cases) [20-22] (Multimedia Appendix 1).

Study Design

A hospital-based multicenter, prospective, noninterventional, observational clinical registry with prospective data collection through ICMR AMDRCs was established under the ongoing MycoNet Task Force project. The project duration is 5 years, with staggered entry of clinical sites following a standardized training and onboarding process.

This multicentric, Pan-India study was initiated with 5 AMDRCs in 2019. With a scope of increasing the number of reference centers in the next sequential phases of the Task Force project by the expert committee, 3 more centers were introduced and initiated in the financial year 2022-2023. Currently, the network has 8 AMDRCs dispersed across various regions of India. These AMDRCs include (1) All India Institute of Medical Sciences (AIIMS), Bhopal; (2) Assam Medical College and Hospital, Dibrugarh; (3) AIIMS, Bhubaneswar; (4) King George's Medical University, Lucknow; (5) P.D. Hinduja Hospital, Mumbai; (6) AIIMS, New Delhi; (7) Nizam's Institute of Medical Sciences, Hyderabad; and (8) St. John's Medical College, Bengaluru. A timeline for the respective centers with a structural makeup is depicted in Figure 1. To develop a comprehensive network, apart from 8 data collection centers, Postgraduate Institute of Medical Education and Research, Chandigarh, for External Quality Assurance Scheme and laboratory training and ICMR-National Institute of Medical Statistics for data management have been included. ICMR is the overall coordinator of the project. The structural organization of ICMR-MycoNet is depicted in Figure 1. The network offers cutting-edge diagnostic tools for fungi, performs laboratory training to develop trained labor, investigates outbreaks, and conducts research on the epidemiology of fungi and antifungal resistance. The inclusion and exclusion criteria are given in Textbox 1.

Figure 1. Structural organization of Indian Council of Medical Research (ICMR) Advanced Mycology Diagnostic and Research Centers: 4-tier structure of MycoNet clinical registry. In 2020, 1 site was initiated (All India Institute of Medical Sciences [AIIMS], Bhopal). In 2021, 4 sites were initiated (Assam Medical College and Hospital [AMCH], Dibrugarh; AIIMS, Bhubneswar; P.D. Hinduja, Mumbai; and King George's Medical University [KGMU], Lucknow). In 2022, 3 centers were initiated (St. John's Medical College and Hospital [SJMC], Bangalore; Nizam's Institute of Medical Sciences [NIMS], Hyderabad; and AIIMS, New Delhi). ICMR-NIMS is the data monitoring center; Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, is the External Quality Assurance Scheme (EQAS) and Laboratory Training Center; and the ICMR headquarters is the overall coordinator.



Textbox 1. Inclusion and exclusion criteria for MycoNet clinical registry.

Inclusion criteria

- Intensive care unit or hospitalized patients with proven or probable invasive fungal infections confirmed by culture, histopathology, microscopy, or DNA evidence of any age and gender as per European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium guidelines.
- For individual cases where invasiveness remains unclear, data will be documented, but analysis will be limited to patients with proven and probable invasive fungal infections.
- All patients with a diagnosis of chromoblastomycosis or mycetoma.

Exclusion criteria

- Outpatient department or referral patients, patients who may be possible cases of invasive fungal infections, and patients without evidence of invasive disease or those with colonization only will not be included in the registry.
- Additionally, patients with superficial infections, infections limited to the skin, and allergic fungal diseases like allergic bronchopulmonary aspergillosis will be excluded.

Each team consists of a principal investigator from the mycology department and coprincipal investigators from different clinical divisions; including critical care; dermatology; ear, nose, and throat; hematology; infectious disease; internal medicine; and oncology to obtain patient samples. The AMDRCs also work closely with all ICUs, including hemato-oncology, trauma, respiratory, cardiac, and newborn care.

Data Collection and Management

A case report form (CRF) and standard operating procedures or data entry guidelines were developed. CRF field testing was done to identify the gaps in generated CRF through real-time data recording. Based on the finalized CRF, the electronic CRF was developed using the programming language by ICMR–National Institute of Medical Statistics. Data entry was facilitated through an interactive macrodesigned within the software that can be accessed from any web browser. A digital database will automatically store all the recorded data. The CRF is designed with a drop-down menu to minimize data entry errors. For additional security, a double data entry method will be followed.

The MycoNet Registry app will be maintained on a secure web server at ICMR New Delhi. The hospitals participating in the study will be able to register digitally to initiate the work.

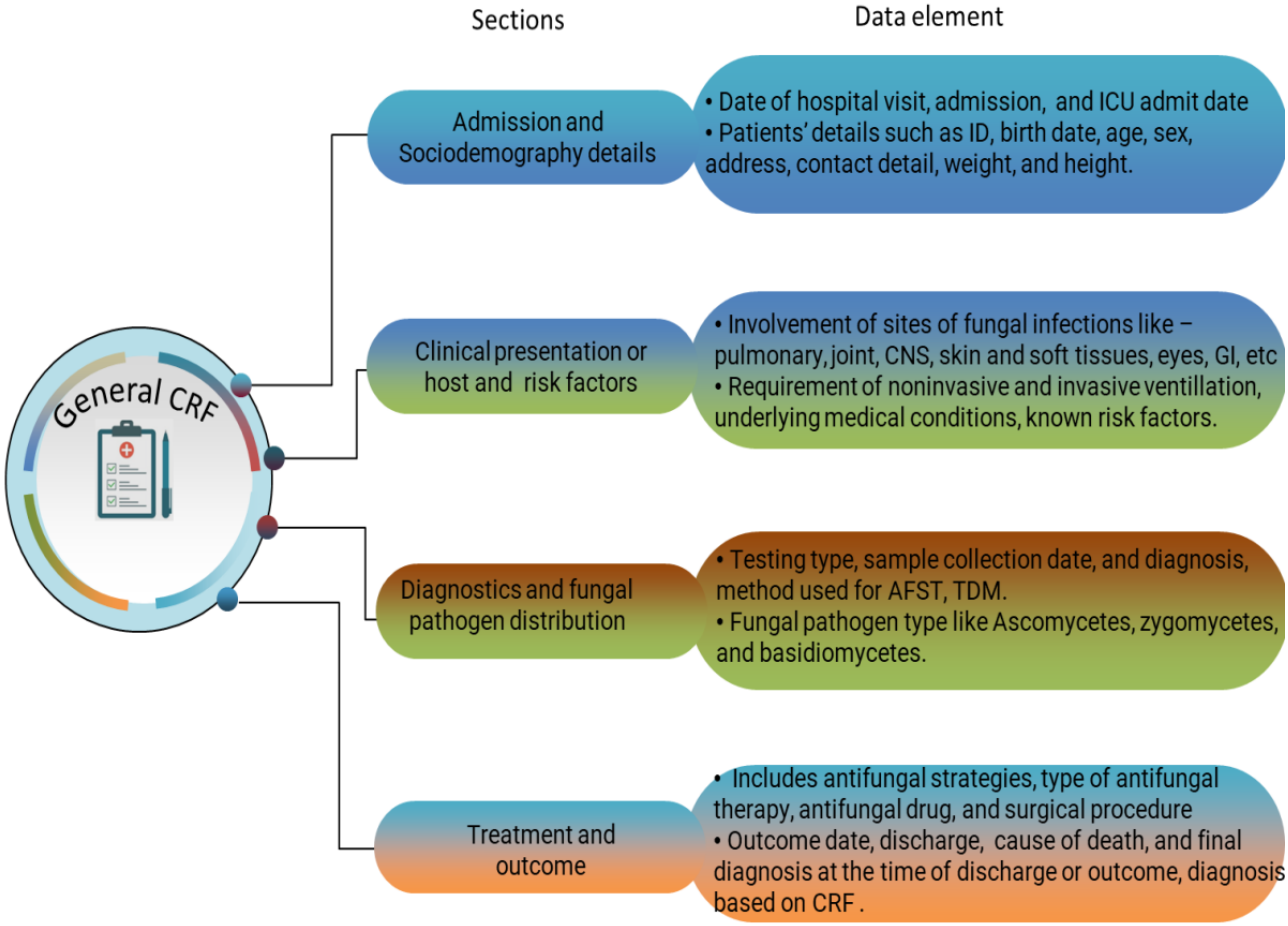
Each AMDRC would receive log-in credentials with access control for data entry, data monitoring, and data download. Data validation will be done by the principal investigator. A dashboard for a snapshot of the data collected from all the AMDRCs (day wise, weekly, or time period) will also be developed for real-time monitoring.

The data on age, sex, signs, symptoms, date of admission, date of discharge or death, diagnostic tests, identified pathogen, treatment history, AFST report, TDM, any other disease or immunosuppression condition, medical history, outcome, and so on will be obtained from the hospital CRF record. A national fungal strain repository for clinically important and rare fungal strains (yeast and molds) will be developed for future research (Figure 2).

Descriptive analysis of the data will be performed by generating means and proportions. Univariate and multivariate analyses will be undertaken. Further, data analysis will be performed based on the expert committee's suggestions.

A descriptive analysis of the pattern of clinical presentations by age, sex, and association with risk factors and comorbid conditions across urban and rural regions and states in India will be accomplished. Predictive factors for hospital clinical courses and outcomes will be derived for different treatment settings. The burden of IFIs and associated manifestations will be assessed using standard case definitions and reporting frameworks. Additionally, developing treatment guidelines will be aided by the pattern of comorbidities or risk factors affecting clinical recovery among with patients IFIs.

Figure 2. Overview of data variables in the general CRF. AFST: antifungal drug sensitivity test; CNS: central nervous system; CRF: case report form; GI: gastrointestinal; ICU: intensive care unit; TDM: therapeutic drug monitoring.



Ethical Considerations

There is no interventional aspect to this study. Therefore, there are neither associated risks nor benefits for the patient when participating in the study. The data will be extracted from medical records with no interaction with patients to undertake the secondary data analysis. The study was granted the "waiver of consent," and ethical approval of the study (CECHR 009/2022) was obtained from the ICMR–Central Ethics Committee on Human Research (reference NCDIR/BEU/ICMR-CECHR/75/2020) as well as the following ethical committees: AIIMS, Bhopal (IHEC-LOP/2021/EF0160); Assam Medical College & Hospital (AMCH), Dibrugarh (2022/AMC/EC/1937); AIIMS, Bhubneswar (T/EMF/Micro/22/38); PD Hinduja Hospital, Mumbai (IRB/1552/AL/22/41); King George's Medical University (KGMU), Lucknow (1515/Ethics/2022); AIIMS, New Delhi (IEC-695/02.09.2022); Nizam's Institute of Medical Sciences (NIMS), Hyderabad (EC/NIMS/3038/2022); St John's Medical College (SJMC), Bangalore (IEC/1/1061/2022) and ICMR–National Institute of Medical Statistics (ICRM-NIMS), New Delhi (11/2022). Memorandums of agreement were signed between the ICMR and all established AMDRCs for shared principles, objectives, and responsibilities. Data security and patient privacy were given the utmost importance throughout the entire process. All information and data extracted from the medical records of the patients for this registry will be considered confidential. The digital documentation of the clinical data will take place in an anonymized fashion. No identifiable data, for example, name or date of birth, will be entered into the database. There will also be no pseudonyms, which would make a retrospective reidentification of the patient possible. Clinical data collected refer to common conditions and treatment modalities in medical care, such that no reidentification of the individual case based on these data will be possible. Any data manipulation by users and administrators will be logged into an audit trail allowing complete data reconstruction. All data and results will be stored for at least 10 years after the publication of the results.

Administration of the electronic CRF will be limited to selected and named administrators at AMDRCs, who will receive comprehensive training in the system before access. Secure passwords are also enforced for administrators, and they must regularly change their passwords.

Results

This study has been funded by the ICMR. Data collection began in January 2023 in all 8 AMDRCs study sites, after approval from the central and local ethics committee in June 2022. The registry has also been registered with the Clinical Trial Registry–India (registration CTRI/2022/09/045489). To date, 531 cases of IFI, 29 cases of mycetoma, and 1 case of chromoblastomycosis were enrolled in the registry. First-year

data analysis has been initiated to be published by the second quarter of 2024. Data from the study are expected to improve the knowledge gaps related to different fungal infections and understand current approaches to diagnosing and treating IFIs. The trends of IFIs, AFST patterns, and the contribution of IFIs to total ICU mortality will be the most valuable outcome of this project. Data on rare fungal diseases such as mycetoma and chromoblastomycosis will be obtained.

Discussion

Principal Findings

ICMR has set up a network of laboratories established to address the long need for modern facilities for fungal diagnostics, antifungal resistance mapping, and advanced fungal research in the different geographical regions of the country. Through the ICMR-MycoNet, the generation and systematic collection of robust comprehensive data on IFIs in ICU patients have the potential to fill in important knowledge gaps and guide evidence-based decision-making in clinical practice, public health efforts, and policy reforms in India.

The proposed study has great potential for filling critical knowledge gaps regarding invasive fungal diseases and their effects on public health. A national clinical registry in mycology is being established to lay a solid platform for evidence-based decision-making in clinical practice, public health efforts, and policy creation. The main goals include creating a multicenter digital clinical registry, a thorough examination of epidemiological variables, research into clinical issues, and monitoring of emerging fungal disease trends, which are essential steps toward gaining a thorough understanding of this significant health care issue. Additionally, achieving the secondary goals, which include analyzing the role of fungal infections in morbidity and inpatient mortality across a range of diseases and identifying emerging antifungal resistance patterns, will undoubtedly improve our capacity to control and treat these infections successfully. We can learn a lot more about IFIs from this work, which could greatly impact health care plans and policy.

Impact of AMDRCs

AMDRC is a new initiative of ICMR headquarters in Delhi to support the establishment of AMDRCs in different geographical regions of the country. Mycology has been one of the neglected areas of research in India. Therefore, advanced diagnostic services and research are required in addition to the cutting-edge research and training of health care professionals to combat IFIs. AMDRCs have considerably increased the diagnostic capacity for fungi illnesses, with a notable improvement in accuracy that has reached up to 95%. The increased diagnosis accuracy ensures that patients get the right care when needed. The AMDRCs have attained a remarkable 95% to 100% detection rate of fungal infections. This lowers the risk of poor management because the majority of cases that were previously undetected are now effectively diagnosed. One of the outstanding advantages of AMDRCs is the free diagnostic services they offer. As a result, patients no longer need to rely on expensive private laboratories for fungal testing, thereby improving access to and affordability of treatment. With AMDRCs' better diagnostic capabilities, referring patients for identification to higher tier medical centers is no longer necessary. This eliminates the workload on tertiary health care facilities, speeds up the diagnostic process, and decreases treatment delays. AMDRCs have significantly reduced the time it takes to diagnose fungal diseases. It now just takes a few weeks to complete what used to take many months. Clinicians can start prompt and accurate therapy because of the quick reporting, which eventually leads to better patient outcomes. Programs for antifungal stewardship have been made easier by the development of AMDRCs. Clinicians are now better equipped to make decisions about antifungal treatment, and ensuring judicious use of these drugs is a vital step in preventing antifungal resistance. The ability of AMDRCs to provide real-time diagnostic reports has reduced the need for empiric antifungal treatment. By adjusting therapies based on precise fungal identifications, clinicians can lower the likelihood of overmedicating. Drug toxicity is decreased, and therapeutic efficacy is increased due to AMDRCs' integration of TDM. With this personalized approach, patients are assured of receiving the best antifungal care with minimal side effects. Apart from helping diagnose fungal diseases, adding *Aspergillus* antigen or antibody testing to AMDRC services benefits the overall health care system. These tests demonstrate the adaptability and significance of AMDRCs beyond the control of fungal illness by supporting tuberculosis elimination programs. Thus, this study will be able to address a long-neglected public health issue. However, to get access to diagnostics and antifungal treatment, the study may face regional limitations due to the exclusion of some territories or countries with a hostile environment, poor communication, and fewer populations [23,24].

Future Plan

WHO on Global Antimicrobial Resistance Surveillance System Fungi Program (Global Collaborative Effort to Compile Available Data on IFIs)

The goal of this program is to compile a complete database of information on these diseases, including data concerning the various types of fungi causing the infections, the geographical areas where they tend to be more prevalent, the patterns of antifungal resistance, and other pertinent aspects. By gathering this information, the WHO and its collaborators expect to comprehend better and address the problems caused by IFIs and antifungal resistance.

Extended Multicenter Registry Development to Obtain More Validated Data

The purpose of expanding the registries is to include more centers to produce a more robust and extensive database. This is in the context of gathering information on invasive fungal diseases from a wider geographical area and multiple health care facilities for the study. Data gathered from multiple centers will enhance the validity and authenticity of the information.

Collaborative Approach

In collaboration with other data sharing registries, researchers can find patterns, trends, and potential treatments for fungal infections by pooling their data more efficiently. Similar to

other registries, it encourages teamwork in problem-solving and may result in more efficient diagnosis, treatment, and prevention approaches [25,26]. For surveillance of neglected tropical diseases, a database of mycetoma and chromoblastomycosis will help to identify different nodal areas for future surveillance through active case searches.

One Health Approach

Fungi are ubiquitous. Their interaction with agriculture and animals is certain. As part of the "One Health" concept, keeping in view the data of drug-resistant fungi reported through the registry, we can further collaborate with the Indian Council of Agricultural Research and Indian Veterinary Research Institute (both under the Ministry of Agriculture and Farmer Welfare) to study the effect of use of different fungicides in agriculture and animals and study the transmission dynamics within these.

Conclusions

IFIs are hidden ICU killers. Unfortunately, in a tropical country such as India with a high potential population for fungal infections, mycology is still a neglected area. The present recommendations mostly rely on a compilation of case reports, studies from specific medical facilities, and professional judgments. Analyses must be performed on a large cohort of patients to make treatment recommendations based on sound evidence. It is imperative to explore the contribution of opportunistic fungal infections in the morbidity and mortality of immunocompromised patients and determine the frequency of occurrence of this condition in the country by establishing a registry. Therefore, the development of a Mycology Clinical Registry through the established ICMR-MycoNet centers is proposed to improve the lack of knowledge on epidemiology, clinical course-biology, pathology mechanisms of IFIs and their trends, and AFST and to aid in facilitating an evidence-based diagnostic therapeutic integrated approach to IFI. Antifungal stewardship through this unique initiative will help to reduce empirical antifungal therapy. Any emerging threats, such as the spread of resistant strains or outbreak signals, can be picked up quickly through this real-time database for quick action and policy decisions. These state-of-the-art facilities will be the game changers and able to find cryptic fungal cases successfully, which will visibly change the public health profile of the country.

Acknowledgments

The authors acknowledge the Indian Council of Medical Research, Delhi, for providing financial assistance for the study.

Data Availability

The data sets used or analyzed during the study will be made available from the corresponding author on reasonable request.

Authors' Contributions

AKO contributed to writing and revising the paper. VA, SS, VH, GS, UP, KJS, HK, and JS critically reviewed and revised the manuscript. TK, RN, IX, PG, and AS reviewed the manuscript. MD developed and conceptualized the study and contributed to review and revise the manuscript. All authors have read and approved the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Guidelines for invasive fungal infection (IFI) diagnosis for respective case definitions.
[DOCX File , 25 KB - resprot_v13i1e54672_app1.docx]

References

1. Ray A, Aayilliath KA, Banerjee S, Chakrabarti A, Denning DW. Burden of serious fungal infections in India. Open Forum Infect Dis 2022;9(12):ofac603 [FREE Full text] [doi: 10.1093/ofid/ofac603] [Medline: 36589484]
2. Reddy GKK, Padmavathi AR, Nancharaiah YV. Fungal infections: pathogenesis, antifungals and alternate treatment approaches. Curr Res Microb Sci 2022;3:100137 [FREE Full text] [doi: 10.1016/j.crmicr.2022.100137] [Medline: 35909631]
3. Riley MMS. Invasive fungal infections among immunocompromised patients in critical care settings: infection prevention risk mitigation. Crit Care Nurs Clin North Am 2021;33(4):395-405. [doi: 10.1016/j.cnc.2021.07.002] [Medline: 34742496]
4. Clark C, Drummond RA. The hidden cost of modern medical interventions: how medical advances have shaped the prevalence of human fungal disease. Pathogens 2019;8(2):45 [FREE Full text] [doi: 10.3390/pathogens8020045] [Medline: 30987351]
5. Rajasingham R, Smith RM, Park BJ, Jarvis JN, Govender NP, Chiller TM, et al. Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. Lancet Infect Dis 2017;17(8):873-881 [FREE Full text] [doi: 10.1016/S1473-3099(17)30243-8] [Medline: 28483415]
6. Badiee P, Hashemizadeh Z. Opportunistic invasive fungal infections: diagnosis and clinical management. Indian J Med Res 2014;139(2):195-204 [FREE Full text] [Medline: 24718393]

7. WHO fungal priority pathogens list to guide research, development and public health action. World Health Organization. Geneva, Switzerland; 2018. URL: https://www.who.int/publications/i/item/9789240060241 [accessed 2024-01-23]
8. Gnat S, Łagowski D, Nowakiewicz A, Dyląg M. A global view on fungal infections in humans and animals: opportunistic infections and microsporidioses. J Appl Microbiol 2021;131(5):2095-2113. [doi: 10.1111/jam.15032] [Medline: 33556223]
9. Pathakumari B, Liang G, Liu W. Immune defence to invasive fungal infections: a comprehensive review. Biomed Pharmacother 2020;130:110550 [FREE Full text] [doi: 10.1016/j.biopha.2020.110550] [Medline: 32739740]
10. Bishnoi A, Vinay K, Dogra S. Emergence of recalcitrant dermatophytosis in India. Lancet Infect Dis 2018;18(3):250-251 [FREE Full text] [doi: 10.1016/S1473-3099(18)30079-3] [Medline: 29485088]
11. Gnat S, Łagowski D, Nowakiewicz A, Osińska M, Kopiński L. Population differentiation, antifungal susceptibility, and host range of trichophyton mentagrophytes isolates causing recalcitrant infections in humans and animals. Eur J Clin Microbiol Infect Dis 2020;39(11):2099-2113 [FREE Full text] [doi: 10.1007/s10096-020-03952-2] [Medline: 32607909]
12. Köhler JR, Casadevall A, Perfect J. The spectrum of fungi that infects humans. Cold Spring Harb Perspect Med 2014;5(1):a019273 [FREE Full text] [doi: 10.1101/cshperspect.a019273] [Medline: 25367975]
13. Köhler JR, Hube B, Puccia R, Casadevall A, Perfect JR. Fungi that infect humans. Microbiol Spectr 2017;5(3):1-29 [FREE Full text] [doi: 10.1128/microbiolspec.FUNK-0014-2016] [Medline: 28597822]
14. Shenoy MM, Jayaraman J. Epidemic of difficult-to-treat tinea in India: current scenario, culprits, and curbing strategies. Arch Med Health Sci 2019;7(1):112 [FREE Full text] [doi: 10.4103/amhs.amhs_72_19]
15. Casadevall A. Climate change brings the specter of new infectious diseases. J Clin Invest 2020;130(2):553-555 [FREE Full text] [doi: 10.1172/JCI135003] [Medline: 31904588]
16. de Crecy E, Jaronski S, Lyons B, Lyons TJ, Keyhani NO. Directed evolution of a filamentous fungus for thermotolerance. BMC Biotechnol 2009;9:74 [FREE Full text] [doi: 10.1186/1472-6750-9-74] [Medline: 19709419]
17. Casadevall A, Kontoyiannis DP, Robert V. On the emergence of candida auris: climate change, azoles, swamps, and birds. mBio 2019;10(4):e01397-19 [FREE Full text] [doi: 10.1128/mBio.01397-19] [Medline: 31337723]
18. Friedman DZP, Schwartz IS. Emerging fungal infections: new patients, new patterns, and new pathogens. J Fungi (Basel) 2019;5(3):67 [FREE Full text] [doi: 10.3390/jof5030067] [Medline: 31330862]
19. Control of neglected tropical diseases. World Health Organization. 2017. URL: https://www.who.int/neglected_diseases/diseases/en/ [accessed 2019-09-03]
20. De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) consensus group. Clin Infect Dis 2008;46(12):1813-1821 [FREE Full text] [doi: 10.1086/588660] [Medline: 18462102]
21. Blot SI, Taccone FS, Van den Abeele AM, Bulpa P, Meersseman W, Brusselaers N, et al. A clinical algorithm to diagnose invasive pulmonary aspergillosis in critically ill patients. Am J Respir Crit Care Med 2012;186(1):56-64 [FREE Full text] [doi: 10.1164/rccm.201111-1978OC] [Medline: 22517788]
22. Donnelly JP, Chen SC, Kauffman CA, Steinbach WJ, Baddley JW, Verweij PE, et al. Revision and update of the consensus definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research consortium. Clin Infect Dis 2020;71(6):1367-1376 [FREE Full text] [doi: 10.1093/cid/ciz1008] [Medline: 31802125]
23. Salmanton-García J, Au WY, Hoenigl M, Chai LYA, Badali H, Basher A, et al. The current state of laboratory mycology in Asia/Pacific: a survey from the European Confederation of Medical Mycology (ECMM) and International Society for Human and Animal Mycology (ISHAM). Int J Antimicrob Agents 2023;61(3):106718 [FREE Full text] [doi: 10.1016/j.ijantimicag.2023.106718] [Medline: 36640851]
24. Tan BH, Chakrabarti A, Patel A, Chua MMM, Sun PL, Liu Z, et al. Clinicians' challenges in managing patients with invasive fungal diseases in seven Asian countries: an Asia Fungal Working Group (AFWG) survey. Int J Infect Dis 2020;95:471-480 [FREE Full text] [doi: 10.1016/j.ijid.2020.01.007] [Medline: 31945491]
25. Salmanton-García J, Busca A, Cornely OA, Corradini P, Hoenigl M, Klimko N, et al. EPICOVIDEHA: a ready to use platform for epidemiological studies in hematological patients with COVID-19. Hemasphere 2021;5(7):e612 [FREE Full text] [doi: 10.1097/HS9.0000000000000612] [Medline: 34235404]
26. Koehler P, Arendrup MC, Arikan-Akdagli S, Bassetti M, Bretagne S, Klingspor L, et al. ECMM CandiReg-a ready to use platform for outbreaks and epidemiological studies. Mycoses 2019;62(10):920-927 [FREE Full text] [doi: 10.1111/myc.12963] [Medline: 31271702]

Abbreviations

AFST: antifungal drug sensitivity test
AIIMS: All India Institute of Medical Sciences
AMDRC: Advanced Mycology Diagnostic and Research Center
CRF: case report form

EORTC/MSG: European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium
ICMR: Indian Council of Medical Research
ICU: intensive care unit
IFI: invasive fungal infection
TDM: therapeutic drug monitoring
WHO: World Health Organization

Edited by A Mavragani; submitted 18.11.23; peer-reviewed by A Kindo, J Salmanton-García; comments to author 13.12.23; revised version received 20.12.23; accepted 21.12.23; published 16.02.24.

Please cite as:
Ojha AK, Albert V, Sharma S, Hallur V, Singh G, Pamidimukkala U, Singh KJ, Kaur H, Karuna T, Savio J, Nath R, Xess I, Gupta P, Shetty A, Das M
Pan-Indian Clinical Registry of Invasive Fungal Infections Among Patients in the Intensive Care Unit: Protocol for a Multicentric Prospective Study
JMIR Res Protoc 2024;13:e54672
URL: https://www.researchprotocols.org/2024/1/e54672
doi:10.2196/54672
PMID:38363632

Protocol

The Efficacy of Bepotastine Besilate Compared With Hydroxyzine Pamoate for Preventing Infusion Reactions to the First Dose of Rituximab in Patients With Non-Hodgkin Lymphoma: Protocol for a Phase II, Double-Blind, Multicenter Randomized Trial

Yumi Kitahiro[1], PhD; Kazuhiro Yamamoto[1], PhD; Kimikazu Yakushijin[2], MD, PhD; Takeshi Ioroi[1], PhD; Masaaki Tanda[1], PhD; Kotaro Itohara[1], PhD; Tomohiro Omura[1], PhD; Hironobu Minami[2], MD, PhD; Ikuko Yano[1], PhD

[1]Department of Pharmacy, Kobe University Hospital, Kobe, Japan

[2]Division of Medical Oncology/Hematology, Department of Medicine, Kobe University Hospital and Graduate School of Medicine, Kobe, Japan

Corresponding Author:
Ikuko Yano, PhD
Department of Pharmacy
Kobe University Hospital
7-5-2, Kusunoki-cho
Chuo-ku
Kobe, 650-0017
Japan
Phone: 81 78 382 6640
Email: iyano@med.kobe-u.ac.jp

Abstract

Background: Rituximab, an anti-CD20 monoclonal antibody, can cause infusion reactions (IRs), especially during the initial rituximab infusion therapy. Generally, patients are administered a histamine H_1-receptor antagonist before the rituximab infusion, along with an antipyretic analgesic, to prevent or reduce IRs. Multiple retrospective case-control studies indicate that the second generation of histamine H_1-receptor antagonists might be more effective than the first generation in suppressing IRs caused by the rituximab infusion.

Objective: This study aimed to assess the efficacy of first- and second-generation histamine H_1-receptor antagonists for preventing IRs resulting from the initial infusion of rituximab in patients diagnosed with non-Hodgkin lymphoma.

Methods: This is a phase II, double-blind, active-controlled randomized trial. It will be a multicenter study conducted across 3 facilities that aims to enroll a total of 40 patients diagnosed with non-Hodgkin lymphoma who will receive their initial rituximab infusion. Participating patients will be administered hydroxyzine pamoate or bepotastine besilate, representing first- or second-generation histamine H_1-receptor antagonists, respectively. This will be combined with 400-mg acetaminophen tablets taken approximately 30 minutes before the first infusion of rituximab. The primary end point of this trial is to assess severe IRs, equivalent to grade 2 or higher as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0, that occur within a 4-hour period after the initiation of rituximab infusion. The secondary end points include assessing the severity of the initial IR, the maximum severity of the IR, and the duration between rituximab infusion initiation and the onset of the first IR within a 4-hour period. Additionally, the trial will evaluate histamine H_1-receptor antagonist–induced drowsiness using the visual analogue scale, with each patient providing their individual response.

Results: This study began with patient recruitment in April 2023, with 17 participants enrolled as of November 12, 2023. The anticipated study completion is set for February 2026.

Conclusions: This study is the first randomized controlled trial comparing the effects of oral first- and second-generation histamine H_1-receptor antagonists in preventing IRs induced by the initial administration of rituximab. The findings from this study hold the potential to establish the rationale for a phase III study aimed at determining the standard premedication protocol for rituximab infusion.

Trial Registration: Japan Registry of Clinical Trials jRCTs051220169; https://jrct.niph.go.jp/latest-detail/jRCTs051220169

International Registered Report Identifier (IRRID): DERR1-10.2196/54882

(JMIR Res Protoc 2024;13:e54882) doi:10.2196/54882

KEYWORDS

non-Hodgkin lymphoma; rituximab; infusion reactions; bepotastine besilate; histamine H1-receptor antagonist; hydroxyzine pamoate; drowsiness

Introduction

Background

Rituximab, an anti-CD20 monoclonal antibody, is one of the most common chemotherapy agents used for non-Hodgkin lymphoma (NHL) [1-3]. Specifically, treatment protocols involving rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), as well as polatuzumab combined with rituximab, cyclophosphamide, doxorubicin, and prednisolone (Pola-R-CHP), have emerged as the established therapeutic standards for various NHL types, including diffuse large B-cell lymphoma [4,5]. In addition, a rituximab plus bendamustine (BR) regimen is a chemotherapy option for follicular lymphoma categorized as the NHL type [6].

Infusion reactions (IRs) commonly occur within the initial 24 hours of rituximab infusion and are a troublesome side effect associated with this treatment. Typically, the first rituximab infusion begins at a rate of 50 mg/h, increasing by 50 mg/h every 30 minutes, reaching a maximum of 400 mg/h [7]. Severe IRs tend to manifest 30 to 120 minutes after the initiation of rituximab infusion, especially during the escalation of the rituximab infusion rate [7]. The key symptoms include fever, pruritus, rash, and anaphylaxis-like symptoms, with reported instances of fatalities in severe cases [8,9]. While the precise mechanisms behind IRs remain unclear, the presence of tumor necrosis factor–α, interleukin-6, and other cytokines in the bloodstream at the time of administration might be responsible [10]. Moreover, immunoglobulin E–mediated type I reactions associated with histamine release have been identified as a potential mechanism for IR development in patients who previously experienced allergic reactions to rituximab [7,11]. Therefore, patients usually take an antipyretic analgesic and a histamine H_1-receptor antagonist 30 minutes before rituximab infusion to mitigate or prevent an IR. However, as there is no standard premedication, the combination of an antipyretic analgesic and a histamine H_1-receptor antagonist varies among medical facilities. Despite the frequent use of first-generation histamine H_1-receptor antagonists [12,13], patients frequently experience IRs, particularly during the first rituximab infusion, even with these premedications [8]. In addition, first-generation histamine H_1-receptor antagonists have potent central nervous system effects [14], causing drowsiness in patients both during and after rituximab infusion.

Nowadays, various retrospective case-control studies have indicated the potential superiority of the second generation of histamine H_1-receptor antagonists over the first generation in suppressing the occurrence of IRs due to rituximab infusion [15,16]. However, these retrospective studies had a significant limitation, as they subjectively evaluated IRs based on individual physicians' assessments. While a prospective study investigating the supplementary effects of second-generation drugs has been conducted, it specifically examined montelukast, a leukotriene receptor; rupatadine, a second-generation H_1-receptor antagonist; or their combination alongside a standard premedication consisting of the first-generation H_1-receptor antagonist diphenhydramine hydrochloride and acetaminophen [17]. Since the previous prospective study did not directly compare first-generation histamine H_1-receptor antagonists with second-generation ones, its immediate applicability in clinical settings might be limited. Consequently, there is a need to establish an effective and safe premedication regimen that significantly suppresses IRs while causing minimal drowsiness.

Hence, we designed a prospective study to compare the impact of 2 antihistamines during the initial rituximab dose for NHL patients: hydroxyzine pamoate, a first-generation H_1-receptor antagonist frequently used in clinical settings, and bepotastine besilate, a second-generation antihistamine identified in a retrospective case-control study as potentially superior in suppressing IRs triggered by rituximab infusion [15]. Hydroxyzine pamoate is superior to other first-generation H_1-receptor antagonists such as chlorpheniramine and diphenhydramine, since it has no contraindications for angle-closure glaucoma or prostatic hyperplasia patients. It will be combined with acetaminophen to assess its effect on IR occurrence. This is an exploratory study, laying the groundwork by providing basic evidence for subsequent confirmatory studies.

Study Objectives

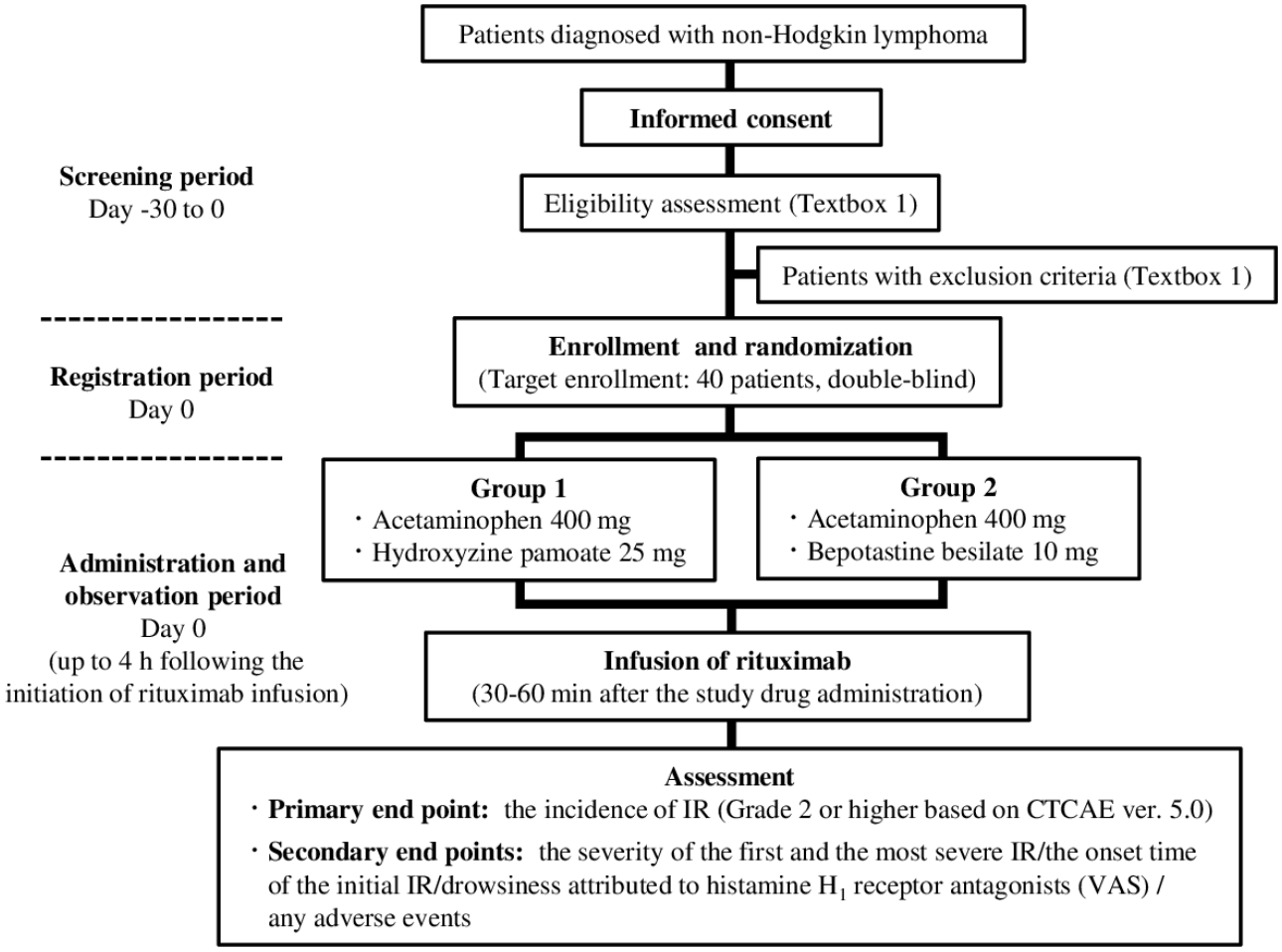
The primary objective of this study is to estimate the incidence rate of IRs (grade 2 or higher) based on the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 [18], in each of the 2 study drug groups within the 4-hour period following the initiation of rituximab infusion. The secondary objectives include (1) estimating the severity of the first and the most severe IR within the same 4-hour time frame after rituximab infusion; (2) estimating the time of onset for the initial IR during this 4-hour period; and (3) estimating the rate of adverse events, including drowsiness attributed to histamine H_1-receptor antagonists, using the visual analog scale (VAS).

Methods

Study Design and Study Location

This study is an ongoing phase II, double-blind, active-controlled randomized trial (Figure 1). It is a multicenter study conducted across 3 facilities, including Kobe University Hospital.

Figure 1. Flowchart illustrating the study design. CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; IR: infusion reaction; VAS: visual analogue scale.



Ethical Considerations

This study was approved by the Kobe University Clinical Research Ethical Committee (C220009) on December 22, 2022. All participants will sign an informed consent form after receiving detailed explanations from the researchers. This study will adhere to the protocols and principles outlined in the Declaration of Helsinki. Any proposed changes to the protocol will require prior approval from the ethics committee before implementation.

Inclusion and Exclusion Criteria

Textbox 1 outlines the criteria for inclusion and exclusion in this study. In addition, Table 1 shows the periods of restricted use of concomitant medication, which are listed in the exclusion criteria (Textbox 1; exclusion criteria 1-3). The specific time frames are determined by the half-life of each medication.

Textbox 1. Study inclusion and exclusion criteria.

Inclusion criteria

1. Aged 18 years or older at the time of consent
2. Written informed consent and voluntary participation in this clinical study
3. Diagnosed with non-Hodgkin lymphoma
4. Receiving a first rituximab infusion, irrespective of regimen
5. Receiving rituximab as a standalone treatment before other anticancer agents in one of the following regimens: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP); polatuzumab combined with rituximab, cyclophosphamide, doxorubicin, and prednisolone (Pola-R-CHP); and rituximab plus bendamustine (BR)

Exclusion criteria

1. Administered or scheduled to receive the following medications orally or intravenously within 2 days of the study drug administration: a short half-life antipyretic analgesic (listed in Table 1) or corticosteroid
2. Administered or scheduled to receive histamine H_1-receptor antagonists orally or intravenously within 5 days of the study drug administration
3. Administered or scheduled to receive a long half-life antipyretic analgesic (listed in Table 1) orally or intravenously within 10 days of the study drug administration
4. Received obinutuzumab before the rituximab treatment
5. Presence of renal dysfunction, indicated by a creatinine clearance <50 mL/min
6. Presence of liver dysfunction, indicated by a Child-Pugh score of C
7. Severe interstitial pneumonia
8. Porphyria
9. Pregnancy or possible pregnancy
10. Known allergies or sensitivities to the drugs used in this clinical study
11. Determined to be unsuitable for inclusion by the investigator

Table 1. Prohibited period of concomitant use of medications as part of the exclusion criteria.

Prohibited period before study drug administration	Category and nonproprietary name
10 days	Antipyretic analgesics with a long half-life (oxaprozin, piroxicam, meloxicam, nabumetone, sulindac, and naproxen)
5 days	All histamine H_1-receptor antagonists
2 days	Antipyretic analgesics with a short half-life (acetaminophen, etodolac, celecoxib, flurbiprofen axetil, pranoprofen, flurbiprofen, lornoxicam, ibuprofen, tiaprofenic acid, ketoprofen, indometacin, loxoprofen sodium hydrate, diclofenac sodium, and acetylsalicylic acid), all corticosteroids

Study Drugs

The study drugs are prepared at the Department of Pharmacy, Kobe University Hospital. To maintain the blind nature of the study, the drug preparation involves placing either a 25-mg hydroxyzine pamoate capsule or a 10-mg bepotastine besilate tablet inside an opaque capsule (size 2).

Intervention

Patients are randomly allocated to receive either hydroxyzine pamoate or bepotastine besilate based on the presence or absence of bone marrow infiltration [19]. Approximately 30 minutes before the rituximab infusion, patients will take a combination of the assigned H_1-receptor antagonist with acetaminophen tablets (400 mg). To maintain the blind nature of the study, the block size used for randomization will remain undisclosed and concealed until the completion of all analyses. Throughout the study's duration, the randomization information will be kept confidential by the data management and statistical analysis team. The allocation manager, independent of the study, will retain the randomization details. The study schedule is outlined in Table 2. Rituximab administration follows the regimen specific to each facility and is delivered intravenously. In general, the first infusion starts at an initial rate of 50 mg/h, escalating every 30 minutes by increments of 50 mg/h to a maximum of 400 mg/h [17]. All rituximab products (original or biosimilar) are allowed in each facility and the information on the rituximab administration schedule will be recorded.

Table 2. Summary of the study schedule.

	Screening period (day –30 to 0)	Registration period (day 0)	Administration and observation period (day 0)
Informed consent	✓		
Eligibility screening	✓		
Registration		✓	
Randomization		✓	
Patients' backgrounds[a]	✓	✓	
Ann Arbor classification	✓		
Eastern Cooperative Oncology Group Performance Status Scale	✓		
Child-Pugh score	✓		
Stratification factors (the presence or absence of bone marrow involvement)	✓		
Hematology[b] and biochemistry[c] tests	✓		
B symptoms (the presence or absence of fever, night sweat, or weight loss)	✓		
Administration of study drug			✓
Evaluation of infusion reaction			✓
Observation of adverse events			✓
Evaluation of drowsiness (visual analogue scale; performed 90, SD 15 minutes after study drug administration)			✓

[a]Including age, sex, weight, height, diagnosis, medical history, complications, and concomitant medications.

[b]Hematology tests encompass red blood cell counts, hemoglobin, hematocrit, differential leukocyte counts, and platelet counts.

[c]Biochemistry tests include aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transpeptidase, total bilirubin, albumin, creatinine, blood urea nitrogen, lactate dehydrogenase, IL-2 receptor, and prothrombin activity.

Data Collection and Management

Upon receiving consent from prospective patients, the investigators assess their eligibility. Subsequently, either the research secretariat or the branch have access to the REDCap (Research Electronic Data Capture; an electronic data system for clinical research) system to confirm eligibility before inputting essential information for case registration and assigning a case number. The registration process concludes upon the display of a confirmation of the case registration.

Study Outcomes

Primary End Point

The primary end point of this study is the incidence of IR (grade 2 or higher) according to CTCAE within the time frame of up to 4 hours following the initiation of rituximab infusion.

Secondary End Points

The secondary end points of this study include assessing the severity of the initial IR, the maximum severity of the IR, the duration between rituximab infusion initiation and the onset of the first IR within a 4-hour period, evaluating drowsiness due to histamine H_1-receptor antagonists, and determining the incidence rate of any adverse events resulting from participation in clinical research.

Assessments

Evaluation of IR

Investigators assess the severity of the IR using the CTCAE (Table 3) as a reference. Furthermore, they evaluate IR severity based on the specific criteria outlined in this study, aligned with routine medical care. Grade 1 is a temporary interruption of rituximab infusion followed by a restart at the same rate. Grade 2 or higher necessitates a temporary halt in infusion along with interventions such as additional symptom treatment or resumption of infusion at a reduced rate. Grade 2 or higher also includes situations where the rituximab infusion rate remains unchanged due to concerns about the patient's condition. In the event of an IR, standard rescue care protocols specified by the medical facility are implemented. Procedures for rituximab dosing rates and rate adjustments are also implemented.

Table 3. The Common Terminology Criteria for Adverse Events, version 5.0, defines infusion-related reaction. The items in the Criteria column are extracted directly from the source [18].

Grade	Criteria
1	Mild transient reaction; infusion interruption not indicated; intervention not indicated
2	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, intravenous injection fluids); prophylactic medications indicated for < = 24 h
3	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae
4	Life-threatening consequences; urgent intervention indicated
5	Death

Evaluation of Drowsiness Caused by Histamine H_1-Receptor Antagonists

Patients report the severity of drowsiness using a VAS ranging from 0 mm (awake) to 100 mm (falling asleep) approximately 90 (SD 15) minutes after taking the study medication.

Statistical Procedure

All analyses will be carried out using R (R Foundation for Statistical Computing). There will be no interim analyses conducted.

Sample Size Calculation

The target sample size for this study is 40 participants, evenly divided into groups receiving hydroxyzine pamoate and bepotastine besilate, with 20 patients in each group. The main objective is to compare the incidence of IR (grade 2 or higher) according to the CTCAE within 4 hours after initiating rituximab infusion in the 2 study drug groups. In our retrospective exploratory study at Kobe University Hospital, grade 2 or higher IR incidence was 8/30 (27%) in NHL patients who received hydroxyzine pamoate before their first rituximab dose. In contrast, a previous report indicated that the incidence was 3/33 (9%) in patients treated with bepotastine besilate [15]. Therefore, we conservatively estimated that the grade 2 or higher IR incidence would be 25% for hydroxyzine pamoate and 10% for bepotastine besilate. This assumption implies a 15% difference in the IR incidence rate between the 2 groups. Assuming 20 patients in each group, the calculated 90% and 95% CIs of the incidence difference between the 2 groups are –0.044 to 0.344 (width 38.8%) and –0.081 to 0.381(width 46.2%), respectively. If both widths for the 90% and 95% CIs of the incidence difference of observed data are narrower than the presumed interval widths, respectively, we consider the accuracy of the estimates suitable for planning a phase III trial.

Primary Analysis

In this study, a full analysis set (FAS) comprises patients randomly assigned to the study who completed the evaluation of IR within 4 hours after rituximab infusion initiation. We will analyze the difference in IR incidence between the 2 study drug groups within the FAS and determine their respective 90% and 95% CIs. The calculation of Clopper-Pearson CIs will be used for this analysis.

Secondary Analysis

A supplementary assessment will be conducted using the per-protocol set (PPS) for the primary outcome. In this study, the PPS consists of patients excluded from the FAS due to significant violations, such as incompatibility in meeting the selection or exclusion criteria and severe noncompliance with the research protocol. For each analysis, the null hypothesis will be that the IR incidence rate is equal between the 2 groups. Following this, we will calculate the *P* value using the Pearson chi-square test. The analysis of secondary outcomes aims to provide additional insights into the primary outcome. The severity of the initial and the maximum severity of IR will be indicated by the number and percentage within each grade. The null hypothesis for each analysis population will be that the IR incidence rate is equal to each grade within the 2 groups. The *P* value will be calculated using the Fisher exact test. The time to the onset of the initial IR and the VAS value indicate drowsiness caused by histamine H_1-receptor antagonists. These will be presented as the mean (SD) for each group, along with the 95% CI for the mean difference.

Data Monitoring and Pharmacovigilance

The study will undergo regular monitoring to safeguard human rights and welfare. The research will be conducted in strict adherence to the protocol and all relevant regulatory requirements, ensuring safety. The principal investigator has designated responsible individuals to oversee the outlined procedures for study monitoring. To ensure quality control, the monitor will assess adherence to the protocol and outlined procedures during the study.

In this research, an adverse event encompasses any illness, disability, infection, or death occurring during the study specifically related to the study drugs but excluding those related to rituximab and acetaminophen. Investigators will document these adverse events in the electronic case report form (eCRF). Affected patients will receive appropriate treatment and continued monitoring until symptoms resolve, as managed by the investigators. If there are cases in which the investigators identify unpredictable adverse events or deaths potentially linked to the study drug, these occurrences will be promptly reported to the review board. To address potential claims resulting from health issues related to the study's conduct, the principal investigator has secured clinical research insurance covering compensation for death, serious disability, medical expenses, and medical benefits.

Privacy and Confidentiality

The eCRF will be protected by using a password. Additionally, privacy measures will involve using deidentified data instead of personal identifiers across all eCRF entries to further enhance security.

Results

This study is ongoing, and recruitment of participants began in April 2023, with 17 patients enrolled as of November 12, 2023. Anticipated study completion is scheduled for February 2026. The study protocol and statistical analysis plan will be made available on the Japan Registry of Clinical Trials. The study findings will be presented at medical conferences and published in scientific papers. Subsequent to publication, the corresponding author will make the collected data accessible in a non–personally identifiable form on reasonable request from other researchers within a prescribed period.

Discussion

Principal Findings

This phase II study is designed as a double-blind, prospective investigation, building upon insights from our retrospective exploratory study at Kobe University Hospital and a previous retrospective study [15]. While various reports have discussed IR prophylaxis during rituximab infusion, most have primarily assessed the efficacy of first-generation histamine H_1-receptor antagonists. Recent retrospective case-control studies have suggested the potential superiority of second-generation histamine H_1-receptor antagonists in suppressing IRs triggered by rituximab infusion. However, these studies often carried significant limitations, as IR assessments were subjective and varied among physicians [15,16]. This prospective study aims to address the research bias commonly found in retrospective studies and aims to provide more reliable results.

Severe IRs typically tend to manifest between 30 to 120 minutes after the commencement of rituximab infusion, as well as when the rituximab infusion rate is escalated [7]. Given that our study involves both inpatients and outpatients, assessing IRs over an entire day becomes challenging as outpatients leave the outpatient chemotherapy room after the rituximab infusion. To streamline the evaluation process without having the assessments focus only on inpatients, we considered a practical time frame for evaluation. Our retrospective exploratory study showed that the total rituximab infusion time was approximately 4 hours. Therefore, we have set the evaluation period for IR up to 4 hours following the initiation of rituximab infusion to align with actual practice.

It has been reported that the time to maximum concentration (T_{max}) of histamine H_1-receptor antagonists when used as premedication can impact prophylaxis against an IR [15]. In our retrospective exploratory study at Kobe University Hospital, we observed that the incidence time of IR was a median 90 (IQR 60-135) minutes after the onset of rituximab infusion in NHL patients who had received hydroxyzine pamoate before their initial rituximab dose. The reported mean T_{max} values for hydroxyzine pamoate and bepotastine besilate are 2.1 (SD 0.4) hours [20] and 1.2 (SD 0.2) hours [21], respectively. Notably, when patients take the H_1-receptor antagonist approximately 30 minutes before rituximab infusion, bepotastine besilate reaches T_{max} before the median IR incidence time. To maintain blinding in this study, the study drug is encapsulated in an opaque gelatin capsule. Considering that the mean disintegration time for these capsules in the fed state was reported to be 12 (SD 4) minutes [22], we do not anticipate that the use of capsules will influence the study results. However, it is unclear whether the T_{max} of histamine H_1-receptor antagonists only impacts prophylaxis against IRs. Among first-generation H_1-receptor antagonists used for rituximab premedication in a clinical setting, the T_{max} of hydroxyzine pamoate is closest to bepotastine. We assume that class effects other than T_{max} contribute to the prevention of IRs. Furthermore, it is essential to consider that drowsiness resulting from histamine H_1-receptor antagonists is influenced not only by their half-lives but also by their interaction with H_1 receptors in the central nervous system [23,24]. These factors will be taken into consideration during the final assessment.

Several studies have investigated the correlation between the development of an IR and various risk factors. Factors such as soluble interleukin-2 receptor, hemoglobin, bone marrow infiltration, and lactate dehydrogenase levels have been identified as potential risk factors for IRs [19,25,26]. In this study, bone marrow infiltration is being treated as a stratification factor. We will also explore the potential associations between IR occurrence and multiple factors in an exploratory manner. However, due to the inclusion of a small and limited number of patients, our study serves as a preliminary investigation to determine whether further confirmation studies are warranted.

If this study demonstrates increased effectiveness of bepotastine besilate, a second-generation histamine H_1-receptor antagonist, a confirmatory study will be designed to gather robust evidence supporting its effective use in routine practice.

Conclusions

This study is the first randomized controlled trial comparing the effects of oral first- and second-generation histamine H_1-receptor antagonists in preventing IRs induced by the initial administration of rituximab. The findings from this study have the potential to establish a rationale for a phase III study aimed at determining a standard premedication protocol for rituximab infusion.

Acknowledgments

We would like to thank Enago for conducting the English-language review. There was no use of generative artificial intelligence technology in the generation of the text, figures, or other informational content of this manuscript.

Data Availability

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

Authors' Contributions

YK conceptualized the study, formulated the study protocol, and drafted the manuscript. K Yamamoto, TI, and MT provided support in drafting the study protocol. HM and K Yakushijin reviewed the study protocol. IY supervised the study protocol and reviewed the final manuscript. All authors have reviewed and approved the final manuscript. The authors attest that there was no use of generative artificial intelligence technology in the generation of text, figures, or other informational content of this manuscript.

Conflicts of Interest

K Yakushijin declares receiving an honorarium from Pfizer. HM declares receiving honoraria from Pfizer and Nipro.

References

1. Omachi K. JSH practical guidelines for hematological malignancies, 2018: II. Lymphoma-overview. Int J Hematol 2019 Jul;110(1):3-10. [doi: 10.1007/s12185-019-02676-0] [Medline: 31152416]
2. Ohmachi K. JSH practical guidelines for hematological malignancies, 2018: II. Lymphoma-5-diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS). Int J Hematol 2019 Aug;110(2):131-146. [doi: 10.1007/s12185-019-02681-3] [Medline: 31177376]
3. Matasar MJ, Zelenetz AD. Overview of lymphoma diagnosis and management. Radiol Clin North Am 2008 Mar;46(2):175-98, vii. [doi: 10.1016/j.rcl.2008.03.005] [Medline: 18619375]
4. Major A, Smith SM. DA-R-EPOCH vs R-CHOP in DLBCL: How do we choose? Clin Adv Hematol Oncol 2021 Nov;19(11):698-709 [FREE Full text] [Medline: 34807015]
5. Tilly H, Morschhauser F, Bartlett NL, Mehta A, Salles G, Haioun C, et al. Polatuzumab vedotin in combination with immunochemotherapy in patients with previously untreated diffuse large B-cell lymphoma: an open-label, non-randomised, phase 1b-2 study. Lancet Oncol 2019 Jul;20(7):998-1010. [doi: 10.1016/S1470-2045(19)30091-9] [Medline: 31101489]
6. Izutsu K. JSH practical guidelines for hematological malignancies, 2018: II. Lymphoma-1. Follicular lymphoma (FL). Int J Hematol 2019 Jul;110(1):11-19. [doi: 10.1007/s12185-019-02655-5] [Medline: 31172373]
7. Vultaggio A, Matucci A, Nencini F, Pratesi S, Petroni G, Cammelli D, et al. Drug-specific Th2 cells and IgE antibodies in a patient with anaphylaxis to rituximab. Int Arch Allergy Immunol 2012;159(3):321-326. [doi: 10.1159/000336839] [Medline: 22846615]
8. Schwartzberg LS, Stepanski EJ, Fortner BV, Houts AC. Retrospective chart review of severe infusion reactions with rituximab, cetuximab, and bevacizumab in community oncology practices: assessment of clinical consequences. Support Care Cancer 2008 Apr;16(4):393-398. [doi: 10.1007/s00520-007-0329-5] [Medline: 17909865]
9. Salles G, Barrett M, Foà R, Maurer J, O'Brien S, Valente N, et al. Rituximab in B-cell hematologic malignancies: a review of 20 years of clinical experience. Adv Ther 2017 Oct;34(10):2232-2273 [FREE Full text] [doi: 10.1007/s12325-017-0612-x] [Medline: 28983798]
10. Winkler U, Jensen M, Manzke O, Schulz H, Diehl V, Engert A. Cytokine-release syndrome in patients with B-cell chronic lymphocytic leukemia and high lymphocyte counts after treatment with an anti-CD20 monoclonal antibody (rituximab, IDEC-C2B8). Blood 1999 Oct 01;94(7):2217-2224 [FREE Full text] [Medline: 10498591]
11. Polito V, Barbacki A, Isabwe G. Type I allergic reaction to rituximab upon first lifetime exposure: a case report. Allergy Asthma Clin Immunol 2020;16:56 [FREE Full text] [doi: 10.1186/s13223-020-00448-8] [Medline: 32607108]
12. Tobinai K, Kobayashi Y, Narabayashi M, Ogura M, Kagami Y, Morishima Y, et al. Feasibility and pharmacokinetic study of a chimeric anti-CD20 monoclonal antibody (IDEC-C2B8, rituximab) in relapsed B-cell lymphoma. The IDEC-C2B8 Study Group. Ann Oncol 1998 May;9(5):527-534 [FREE Full text] [doi: 10.1023/a:1008265313133] [Medline: 9653494]
13. Igarashi T, Kobayashi Y, Ogura M, Kinoshita T, Ohtsu T, Sasaki Y, et al. Factors affecting toxicity, response and progression-free survival in relapsed patients with indolent B-cell lymphoma and mantle cell lymphoma treated with rituximab: a Japanese phase II study. Ann Oncol 2002 Jun;13(6):928-943 [FREE Full text] [doi: 10.1093/annonc/mdf155] [Medline: 12123339]
14. Simons FER. Advances in H1-antihistamines. N Engl J Med 2004 Nov 18;351(21):2203-2217. [doi: 10.1056/NEJMra033121] [Medline: 15548781]
15. Matsui N, Ishihara N, Mochizuki Y, Tamaki H, Nishimura N, Naora K. Inhibitory effect on rituximab-induced infusion reaction by premedication with fexofenadine or bepotastine. Iryo Yakugaku (Jpn J Pharm Health Care Sci) 2019;45(7):396-403. [doi: 10.5649/jjphcs.45.396]
16. Durham CG, Thotakura D, Sager L, Foster J, Herrington JD. Cetirizine versus diphenhydramine in the prevention of chemotherapy-related hypersensitivity reactions. J Oncol Pharm Pract 2019 Sep;25(6):1396-1401. [doi: 10.1177/1078155218811505] [Medline: 30419768]

17. Kotchetkov R, McLean J, Nay D, Gerard L, Hopkins S, Didiodato G. Premedication with montelukast and rupatadine decreased rituximab infusion time, rate, severity of reactions and use of rescue medications. Int J Cancer 2020 Oct 01;147(7):1979-1986 [FREE Full text] [doi: 10.1002/ijc.32985] [Medline: 32189328]
18. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. US Department of Health and Human Services. URL: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf [accessed 2024-02-13]
19. Ohata S, Takenaka K, Sugiyama D, Sugimoto T. Bone marrow infiltration is a distinctive risk factor for rituximab infusion-related reactions in CD20-positive B-cell non-Hodgkin lymphoma. Adv Hematol 2022;2022:3688727 [FREE Full text] [doi: 10.1155/2022/3688727] [Medline: 35189630]
20. Simons FE, Simons KJ, Frith EM. The pharmacokinetics and antihistaminic of the H1 receptor antagonist hydroxyzine. J Allergy Clin Immunol 1984 Jan;73(1 Pt 1):69-75. [doi: 10.1016/0091-6749(84)90486-x] [Medline: 6141198]
21. Yokota H, Mizuuchi H, Maki T, Banno K, Sato T. Phase I study of TAU-284: single oral administration in healthy male volunteers. J Clin Therap Med Apr 1997;13(5):1137-1153 [FREE Full text]
22. Jones BE, Basit AW, Tuleu C. The disintegration behaviour of capsules in fed subjects: a comparison of hypromellose (carrageenan) capsules and standard gelatin capsules. Int J Pharm 2012 Mar 15;424(1-2):40-43. [doi: 10.1016/j.ijpharm.2011.12.034] [Medline: 22214655]
23. Kanamitsu K, Nozaki Y, Nagaya Y, Sugiyama Y, Kusuhara H. Quantitative prediction of histamine H1 receptor occupancy by the sedative and non-sedative antagonists in the human central nervous system based on systemic exposure and preclinical data. Drug Metab Pharmacokinet 2017 Apr;32(2):135-144. [doi: 10.1016/j.dmpk.2016.11.007] [Medline: 28190755]
24. Yanai K, Yoshikawa T, Yanai A, Nakamura T, Iida T, Leurs R, et al. The clinical pharmacology of non-sedating antihistamines. Pharmacol Ther 2017 Oct;178:148-156. [doi: 10.1016/j.pharmthera.2017.04.004] [Medline: 28457804]
25. Kuromatsu M, Kajita T, Taruno M, Nishikawa Y, Akasaka T, Okuno T. Search for risk factors influencing the occurrence of infusion reaction after initial treatment with obinutuzumab. Iryo Yakugaku (Jpn J Pharm Health Care Sci) 2021;47(11):631-638. [doi: 10.5649/JJPHCS.47.631]
26. Tachi T, Yasuda M, Usui K, Umeda M, Nagaya K, Osawa T, et al. Risk factors for developing infusion reaction after rituximab administration in patients with B-cell non-Hodgkin's lymphoma. Pharmazie 2015 Oct;70(10):674-677. [Medline: 26601425]

Abbreviations

BR: bendamustine hydrochloride plus rituximab
CTCAE: Common Terminology Criteria for Adverse Events
eCRF: electronic case report form
FAS: full analysis set
IR: infusion reaction
NHL: non-Hodgkin lymphoma
Pola-R-CHP: polatuzumab plus rituximab, cyclophosphamide hydrate, doxorubicin hydrochloride, and prednisolone
PPS: per-protocol set
R-CHOP: rituximab plus cyclophosphamide hydrate, doxorubicin hydrochloride, vincristine sulfate, and prednisolone
REDCap: Research Electronic Data Capture
Tmax: time to maximum concentration
VAS: visual analogue scale

Edited by A Mavragani; submitted 27.11.23; peer-reviewed by K Naora, T Terada; comments to author 24.01.24; revised version received 31.01.24; accepted 31.01.24; published 22.02.24.

Please cite as:
Kitahiro Y, Yamamoto K, Yakushijin K, Ioroi T, Tanda M, Itohara K, Omura T, Minami H, Yano I
The Efficacy of Bepotastine Besilate Compared With Hydroxyzine Pamoate for Preventing Infusion Reactions to the First Dose of Rituximab in Patients With Non-Hodgkin Lymphoma: Protocol for a Phase II, Double-Blind, Multicenter Randomized Trial
JMIR Res Protoc 2024;13:e54882
URL: https://www.researchprotocols.org/2024/1/e54882
doi:10.2196/54882
PMID:38386393

Protocol

Changes in Oral Health and Dental Esthetic in Smokers Switching to Combustion-Free Nicotine Alternatives: Protocol for a Multicenter and Prospective Randomized Controlled Trial

Gianluca Conte[1], MSD; Sebastiano Antonio Pacino[1,2], MSD; Salvatore Urso[2,3], MSc; Doris Greiling[4], PhD; Pasquale Caponnetto[5,6], PhD; Eugenio Pedullà[5,7], DDS, PhD; Luigi Generali[8], DDS; Ugo Consolo[8], MD, DDS; Vittorio Checchi[8], DDS, PhD; Stefan Gospodaru[9], MSD; Gheorghe Bordeniuc[9], PhD; Valeriu Fala[9], SCD, PhD; Jan Kowalski[10], DDS, PhD; Maciej Nowak[10], DDS, PhD; Renata Górska[10], DDS, PhD; Amaliya Amaliya[11], MSc, DDS; Iain Chapple[12], BDS, CCST, PhD; Michael Milward[12], BDS, PhD; Robert Maclure[13], BDS, BSc; Gianna Maria Nardi[14], DH; Riccardo Polosa[15], MD, PhD

[1]Addendo srl, Dental Clinic, Catania, Italy

[2]ECLAT Srl, Spin-off of the University of Catania, Catania, Italy

[3]Department of Biological, Geological and Environmental Sciences, University of Catania, Catania, Italy

[4]Forschungsdock CRO GmbH, Schenefeld, Germany

[5]Center of Excellence for the Acceleration of HArm Reduction, University of Catania, Catania, Italy

[6]Department of Educational Sciences, Section of Psychology, University of Catania, Catania, Italy

[7]Department of General Surgery and Medical-Surgical Specialties, University of Catania, Catania, Italy

[8]Department of Surgery, Medicine, Dentistry and Morphological Sciences with Transplant Surgery, Oncology and Regenerative Medicine Relevance, University of Modena and Reggio Emilia, Modena, Italy

[9]Faladental, Chi inău, Republic of Moldova

[10]Department of Periodontology, Medical University of Warsaw, Warsaw, Poland

[11]Department of Periodontology, Faculty of Dentistry, Universitas Padjadjaran, West Java, Indonesia

[12]Periodontal Research Group, The University of Birmingham & Birmingham Community Healthcare Trust, Birmingham, United Kingdom

[13]R Maclure Clinical Research Ltd, Irby, Wirral, United Kingdom

[14]Department of Dental and Maxillofacial Sciences, Sapienza University, Rome, Italy

[15]Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy

Corresponding Author:
Riccardo Polosa, MD, PhD
Department of Clinical and Experimental Medicine
University of Catania
via S. Sofia, 78 - Ed. 4, p. 2
Catania, 95123
Italy
Phone: 39 0953781566
Email: polosa@unict.it

Abstract

Background: Although the detrimental effects of conventional combustible cigarettes on oral health and dental esthetics are well known, there is limited information about the long-term impact of combustion-free nicotine alternatives (C-F NA) such as e-cigarettes or heated tobacco products.

Objective: This multicenter, prospective, 3-parallel-arm randomized controlled trial will investigate whether switching from combustible cigarettes to C-F NA will lead to measurable improvements in oral health parameters and dental esthetics over 18 months in adult smokers with limited gum disease.

Methods: Regular smokers not intending to quit and without clinical signs of periodontitis will be randomly assigned (1:4 ratio) to either standard of care with brief cessation advice (control group; arm A) or C-F NA use (intervention group; arm B). The study will also include a reference group of never smokers (reference group; arm C). The primary end point is the change in the

Modified Gingival Index (MGI) score from baseline between the control arm (arm A) and the intervention arm (arm B) at the 18-month follow-up. In addition, the study will analyze the within- and between-group (arms A, B, and C) changes in MGI assessment, plaque imaging, dental shade quantitation, tooth stain scores, and oral health–related quality of life questionnaires measured at each study time point. All participants will attend a total of 7 clinic visits: screening, enrollment, and randomization (visit 0); baseline visit—day 14 (visit 1); day 90 (visit 2); day 180 (visit 3); day 360 (visit 4); and day 540 (visit 5). This multicenter study will be conducted in 4 dental clinics in 4 countries. The statistical analysis will involve descriptive statistics for continuous and categorical data. Primary end points will undergo tests for normality and, based on distribution, either a 2-sided *t* test or Mann-Whitney *U* test. Linear mixed model with random factors center and study arms by center will also be applied. Secondary end points, including MGI assessment and quality of life, will be subjected to similar tests and comparisons. Only if one value of the parameter MGI is missing after day 1, the last available observation will be carried forward. The analysis will be performed on the substituted data. Secondary parameters will not have missing value replacement.

Results: Participant recruitment began in October 2021, and enrollment was completed in June 2023. Results will be reported in 2025.

Conclusions: This will be the first study to provide key insights into oral health benefits or risks associated with using C-F NA in smokers who are seeking alternatives to cigarette smoking.

Trial Registration: ClinicalTrials.gov NCT04649645; https://clinicaltrials.gov/ct2/show/NCT04649645

International Registered Report Identifier (IRRID): DERR1-10.2196/53222

(JMIR Res Protoc 2024;13:e53222) doi:10.2196/53222

KEYWORDS

electronic cigarettes; heated tobacco products; tobacco harm reduction; smoking; oral health; gingivitis; periodontitis; Modified Gingival Index; MGI; dental plaque imaging; dental shade; smartphone; mobile phone

Introduction

Background

Periodontal diseases, commonly including gingivitis and periodontitis, arise in response to the accumulation of oral bacteria in the gingival sulcus and are characterized by tissue changes in the periodontium that occur as part of the inflammatory process [1]. Gingivitis is characterized by inflammation such as redness, swelling, or bleeding on gentle provocation of the gingival sulcus, whereas periodontitis exhibits increased probing depth, clinical attachment loss, and radiographic alveolar bone loss, reflecting the destructive aspects of the disease process [2,3].

Periodontal disease is a well-known independent risk factor for cardiovascular disease [4,5], and reducing gingivitis and periodontitis is likely to have an overall positive impact on human health in general.

There are multiple risk factors for periodontal disease, and cigarette smoking is considered among the key independent risk factors for the development and progression of periodontal disease [6-9]. Depending on the disease definition and extent of exposure to cigarette smoke, the risk of developing destructive periodontal disease is 5- to 20-fold higher in smokers than in nonsmokers [10]. Cigarette smokers appear to be prone to more severe periodontal manifestations even after adjusting for age, education level, history of diabetes, BMI, alcohol consumption, perceived mental stress, and oral hygiene levels [11]. In addition to periodontal diseases, cigarette smoking can cause visible dental manifestations, including dental discoloration and tobacco stains, the intensity of which mainly depends on smoking duration and frequency [12]. In a large cross-sectional study in the United Kingdom [13], smokers were more likely to report dental discoloration and being dissatisfied with their own tooth color compared with nonsmokers. Dissatisfaction with teeth appearance (because of enamel discoloration and tobacco stains) is often perceived as a significant social problem for smokers [14,15].

The importance of dental care and oral health for healthy longevity is emphasized in the 2022 declaration of the World Health Organization (WHO) for which greater advocacy is needed to increase the prominence of oral health on the global health agenda. Moreover, reducing oral health issues calls for stronger policies addressing the determinants of oral diseases and no communicable diseases and to tackle inequalities through inclusive universal health care access [16]. More recently, the WHO has provided policy recommendations for integrating brief tobacco interventions into oral health programs in primary care in accordance with the WHO Oral Health Program and as part of the WHO Global action plan on the prevention and control of noncommunicable diseases, particularly pertaining to the needs of low- and middle-income countries [17].

Although it is clear that abstaining from smoking will have beneficial effects on oral health and overall dental esthetic, most smokers are reluctant to seek formal treatment to stop smoking, with the vast majority making attempts to quit without assistance [18,19]. Consequently, novel and efficient approaches are required.

Although not authorized as medications for smoking cessation, combustion-free technologies for nicotine delivery, such as e-cigarettes (ECs) and heated tobacco products (HTPs), have become de facto harm reduction tools from cigarette smoke [20,21] and aid in quitting smoking [22,23].

Combustion-free technologies for nicotine delivery such as ECs and HTPs offer substantial reduction in exposure and harm to harmful constituents compared with tobacco cigarettes [24-27],

but there is limited information about the long-term impact on oral health and dental esthetics in people who use combustion-free nicotine alternatives (C-F NA).

Objectives

This multicenter, prospective, randomized, controlled, 3–parallel arm trial will be the first to determine whether adult smokers who switch to C-F NA will experience measurable improvements in oral health parameters and dental esthetics. A group of never smokers will also be recruited for comparative measures of the study parameters.

Data from this study will provide valuable insights into the overall potential of C-F NA in reducing the risk of periodontal diseases and consequential cardiovascular risk. In addition, the findings may have important implications for reducing the smoking burden globally, especially for smokers for whom bad breath or poor dental esthetic is a significant concern. For these individuals, an oral-centric narrative (such as achieving a healthier and brighter smile) may serve as a more compelling reason to quit smoking than the fear of future lung cancer or cardiopulmonary diseases.

Methods

This is a multicenter, 3-parallel-arm, randomized controlled trial of 18 months duration designed to assess whether cigarette smokers switching to C-F NA will undergo measurable improvements in oral health parameters and dental esthetics as a consequence of avoiding exposure to cigarette smoke. This study aims to assess differences in study end points of oral health parameters and dental esthetics at multiple study time points between smokers switching to C-F NA and smokers who continue to smoke.

Study Population

Eligible participants will be healthy adult regular cigarette smokers (self-reported daily smoking of >10 cigarettes per day for at least 5 consecutive years) and never smokers without clinical signs of periodontitis.

Smokers will be offered access to free smoking cessation programs. Only those who refuse to participate in the smoking cessation program and express willingness to switch to C-F NA will be eligible for randomization.

Never smokers (those who have smoked <100 tobacco cigarettes in their lifetime) will also be included as a reference group.

Participants will be required to satisfy all the inclusion criteria as presented in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria for smokers (study arms A and B)

- Adults (aged 18-50 years)
- Cigarette smokers of ≥10 cigarettes per day
- Smoked for at least 5 consecutive years before screening
- Verified smoking status by exhaled breath carbon monoxide (CO) ≥7 ppm at screening
- Willingness to switch to a combustion-free nicotine alternatives, if required by the randomization
- Refusal to participate in smoking cessation programs
- Presence of at least 10 natural anterior teeth in total (cuspid to cuspid and lower and upper jaw)
- Healthy participants, not taking regular medications for chronic medical conditions
- Accepting to comply with the requirements of the study, including installing an app on their smartphone

Inclusion criteria for never smokers (study arm C)

- Adults (aged 18-50 years)
- Have not smoked >100 tobacco cigarettes in their lifetime
- Verified nonsmoking status by exhaled breath CO <7 ppm at screening
- Presence of at least 10 natural anterior teeth in total (cuspid to cuspid and lower and upper jaw)
- Healthy participants, not taking regular medications for chronic medical conditions
- Accepting to comply with the requirements of the study, including installing an app on their smartphone

Exclusion criteria for smokers (study arms A and B) and never smokers (study arm C)

- Significant oral soft tissue pathology or any type of gingival overgrowth other than plaque-induced gingivitis
- Periodontitis based on the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions [28], which requires the following:
  - Detectable interdental clinical attachment loss ≥3 mm at ≥2 nonadjacent teeth
  - Buccal or oral clinical attachment loss ≥3 mm with pocketing ≥3 mm detectable at ≥2 teeth
  - Only participants with mild to moderate gingivitis will be recruited
- Fixed and removable orthodontic appliances or removable dentures
- Any other medical condition that, in the opinion of the principal investigator, would jeopardize the participant's safety or diminish the validity of the study results
- A course of treatment with any medications that
  - interfere with the cyclooxygenase pathway (eg, anti-inflammatory drugs including aspirin and ibuprofen) within 3 days before each visit
  - are known to have antibacterial activity (eg, antibiotics) within 7 days before each visit
- Significant history of alcohol or drug abuse within 24 months before screening, as determined by the investigator
- For smokers, planning to quit smoking within the next 6 months
- For smokers, regular use of nicotine (eg, e-cigarettes, nicotine replacement therapy, nicotine pouches) or tobacco products (eg, heated tobacco products, oral smokeless) other than their cigarettes within 14 days of screening
- Pregnant or breastfeeding or intention to become pregnant during the study
- Active participation in another clinical trial

Study Design

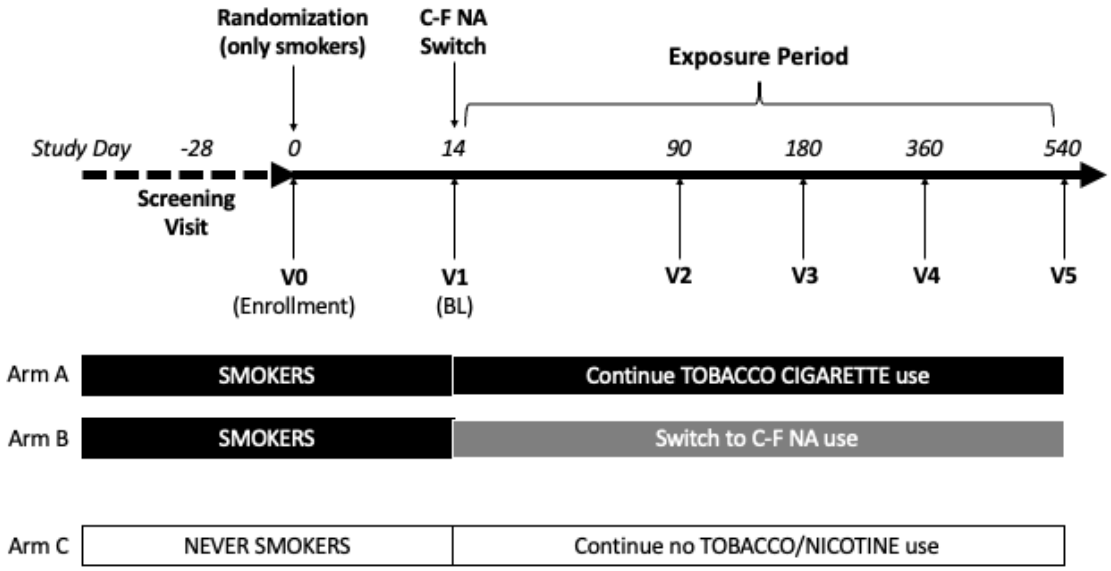
This is an 18-month, prospective, multicenter, open-label study with 3 parallel arms, using randomization and control to assess a range of oral health and dental esthetic metrics (Figure 1). The primary objective is to compare these metrics between cigarette smokers transitioning to C-F NA and those who continue smoking.

Eligible smokers will be allocated randomly to either the control group (arm A), which will receive standard care inclusive of cessation counseling (ie, very brief advice [VBA]) or the intervention group (arm B), which will be given a C-F NA of their choice and will also receive VBA. Individuals who have

never smoked will form a reference group (arm C). Throughout the study, participants from all 3 groups will undergo regular assessments of their oral health and dental esthetic. The study will be conducted in 4 dental clinics across 4 different countries (Italy, Poland, Moldova, and Indonesia).

The study protocol adheres to the guidelines stipulated by the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.

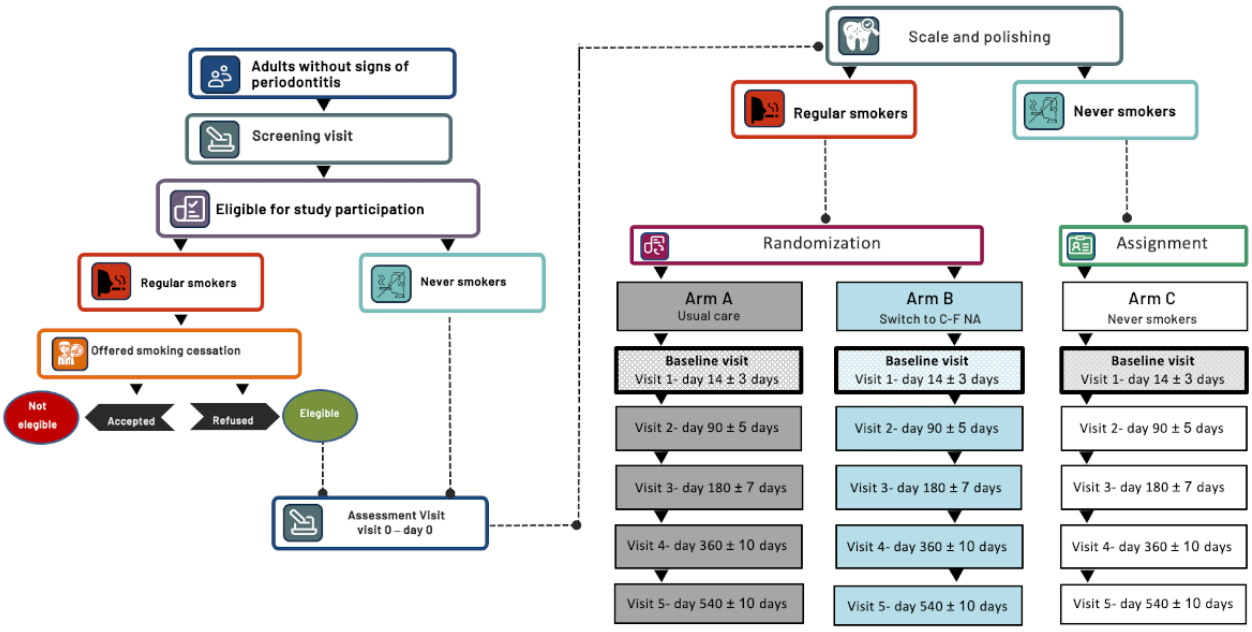
Figure 1. Study design. Smokers not intending to quit and without clinical signs of periodontitis were randomized to either standard care (arm A) or combustion-free nicotine alternatives (C-F NA; arm B). A reference group of never smokers will also be included but not randomized (arm C). Participants were prospectively reviewed at 4 dental clinics for cigarette consumption and C-F NA use, oral health and dental esthetic measurements, vital signs, and adverse events for up to 18 months.



The study flow is illustrated in Figure 2.

All participants will attend a total of 7 clinic visits: day −28 to day −1—screening; day 0—enrollment and randomization (visit 0); day 14—baseline visit (visit 1); day 90—week 12 (visit 2); day 180—week 24 (visit 3); day 360—week 52 (visit 4); day 540—week 76 (visit 5).

Figure 2. Study flow diagram of study participants. C-F NA: combustion-free nicotine alternatives.



Screening visits will be performed within 28 days before enrollment to verify the eligibility criteria (visit 0; Figure 2). During the screening visit, sociodemographic data, medical and oral health history, detailed information about nicotine and tobacco consumption, and interest in trying C-F NA will be recorded. Screening for periodontal disease will be performed to exclude periodontitis, as per the definition of the guidelines of the 2017 Classification of Periodontal and Peri-implant Diseases and Conditions [28]. Smokers will be offered a smoking cessation program as per local guidelines. Any smokers who express the intention of booking for the cessation program or to quit smoking in the next 6 months will be urged to do so and will not be recruited in the study. Participants taking part in the study will be informed that they are free to quit smoking and withdraw from the study at any time. Moreover, smokers will be encouraged to quit smoking at every contact throughout the study.

Within 28 days of the screening visit, eligible participants will be invited to attend an enrollment visit (visit 0). Inclusion and exclusion criteria will be verified again. Smokers will be reminded of the risks associated with smoking before enrollment in the study and that they are free to voluntarily quit smoking and nicotine or withdraw from the study at any time. All participants will undergo a series of measurements (Tables 1-3) followed by dental scaling and polishing procedures to remove calculus, plaque, and stain.

Smokers not intending to quit will then be randomly assigned to either the control (arm A) or the intervention (arm B) group. The randomization sequence will be generated by a computer, with an allocation ratio of 1:4 (arm A: arm B) to accommodate for the estimated 25% proportion of participants achieving a sustained reduction in cigarette consumption of at least 90% in arm B (as detailed in the Statistical Considerations section). Smokers in the control group (arm A) will receive standard care, inclusive of cessation counseling (ie, VBA) at each study visit. Smokers in the intervention group (arm B) will have the option to try and choose a preferred C-F NA (ECs and HTPs) from a given pool of popular options present in the respective markets and will also receive VBA.

Individuals who have never smoked will be allocated to the reference group (arm C). Never smokers in the reference group will serve as comparators for assessing any background changes in the primary study end point (ie, Modified Gingival Index [MGI]) that may occur over time. Although never smokers will not undergo randomization, efforts will be made to achieve a comparable distribution of sex and age across all study arms.

The trial is designed as an unblinded trial because of the nature of the intervention, where participants and trial staff cannot be blinded to the specific intervention being provided. However, data analyses will be conducted blind to study arms allocation. All other trial staff who have access to outcome data will remain blinded until prespecified data analyses will be completed.

Baseline measurements will be performed at visit 1 (baseline visit) and 14 days after scaling and polishing procedures at enrollment (visit 0). Study measurements will include MGI assessment, plaque imaging, dental shade quantitation, tooth stain scores, and oral health–related quality of life questionnaires (Tables 1-3).

Smokers in arm B will be provided with a C-F NA of their choice. They will receive training and counseling on how to use the chosen C-F NA and will be provided with a full 2-week supply of the required consumables (cartridges or pods or e-liquid refill bottles for ECs and tobacco sticks for HTPs). Participants wishing to use an HTP will receive one kit and a supply of tobacco sticks of their choice. They will receive the number of tobacco sticks per day corresponding to the number of cigarettes smoked per day at baseline. Participants wishing to use a vaping product will receive one vaping kit and a supply of e-liquids of their choice. Products will be supplied at each subsequent visit throughout the study according to the study product supply schedule in Table 4.

After the baseline visit, participants will be invited to attend 4 more clinical visits (visits 2-5) to repeat study measurements (Tables 1-3).

Throughout the study, monitoring of cigarette consumption, daily C-F NA use, and oral hygiene routine will be carried out regularly using the tracker app and personal diaries. Monitoring of cigarette consumption and daily C-F NA use will also be achieved by asking participants in arm B to return all empty, partly used, and unused consumables (tobacco sticks, EC cartridges, and e-liquid refill bottles) at each study visit. The tracker app will also identify any protocol violations, collect adverse events (AEs), and send reminders (eg, next scheduled appointment, study restrictions, and instructions) throughout the study duration. The use of a dedicated tracker app adds an innovative element to continuously collect data and enhances adherence to the study protocol.

Before each study visit (visits 1-5), all participants will be required to refrain from scaling and polishing procedures, avoid modifying their habitual oral hygiene (eg, mouthwash, mouth rinse, and interdental floss), refrain from flossing for at least 72 hours before each study visit, refrain from mouth rinsing for at least 24 hours before each study visit, refrain from tooth brushing for at least 2 hours before each study visit, refrain from eating and drinking (except water) for at least 2 hours before each visit, and abstain from smoking for 2 hours before each visit. This is to minimize any potential interference with study outcomes and to maintain consistency in data collection. Throughout the study, any modifications in the oral hygiene routine of participants will be recorded using the tracker app.

A detailed description of the measurements that will be specifically performed at each trial visit is provided in Multimedia Appendix 1.

Table 1. Study schedule of procedures (control group—arm A).

Procedure	Screening	Enrollment (V0); day 0	Baseline (V1); day 14±3	Week 12 (V2); day 90±5	Week 24 (V3), day 180±7	Week 52 (V4); day 360±7	Week 76 (V5); day 540±7
Eligibility criteria check	✓	✓					
Medical and oral health Hx[a]	✓						
Smoking Hx	✓						
Intention to quit smoking	✓						
Smoking cessation advice	✓	✓	✓	✓	✓	✓	✓
Cigarette consumption	✓	✓	✓	✓	✓	✓	✓
Exhaled CO[b]	✓	✓	✓	✓	✓	✓	✓
Interest to switch to C-F NA[c]	✓						
Informed consent		✓					
FTND[d]		✓					
Oral hygiene check	✓	✓	✓	✓	✓	✓	✓
Periodontal examination	✓						
Scaling and polishing		✓					✓
Randomization		✓					
Tracker app installation		✓					
BP[e], HR[f], weight, height, and BMI		✓	✓	✓	✓	✓	✓
MGI[g] assessment		✓	✓	✓	✓	✓	✓
Plaque score imaging		✓	✓	✓	✓	✓	✓
Dental shade quantitation		✓	✓	✓	✓	✓	✓
Tooth stain assessment		✓	✓	✓	✓	✓	✓
QoL[h] questionnaires (OHQoL[i] and EQ VAS[j])		✓	✓	✓	✓	✓	✓
Safety reporting		✓	✓	✓	✓	✓	✓

[a]Hx: history.

[b]CO: carbon monoxide.

[c]C-F NA: combustion-free nicotine alternatives.

[d]FTND: Fagerström Test for Nicotine Dependence.

[e]BP: blood pressure.

[f]HR: heart rate.

[g]MGI: Modified Gingival Index.

[h]QoL: Quality of Life.

[i]OHQoL: Oral Health Quality of Life.

[j]EQ VAS: EuroQoL Visual Analog Scale.

Table 2. Study schedule of procedures (intervention group—arm B).

Procedure	Screening	Enrollment (V0); day 0	Baseline (V1); day 14±3	Week 12 (V2); day 90±5	Week 24 (V3); day 180±7	Week 52 (V4); day 360±7	Week 76 (V5); day 540±7
Eligibility criteria check	✓	✓					
Medical and oral health Hx[a]	✓						
Smoking Hx	✓						
Intention to quit smoking	✓						
Smoking cessation advice	✓	✓	✓	✓	✓	✓	✓
Cigarette consumption	✓	✓	✓	✓	✓	✓	✓
Exhaled CO[b]	✓	✓	✓	✓	✓	✓	✓
Interest to switch to C-F NA[c]	✓						
Informed consent		✓					
FTND[d]		✓					
Oral hygiene check	✓	✓	✓	✓	✓	✓	✓
Periodontal examination	✓						
Scaling and polishing		✓					✓
Randomization		✓					
Familiarization with C-F NA			✓				
C-F NA use				✓	✓	✓	✓
Tracker app installation		✓					
BP[e], HR[f], weight, height, and BMI		✓	✓	✓	✓	✓	✓
MGI[g] assessment		✓	✓	✓	✓	✓	✓
Plaque score imaging		✓	✓	✓	✓	✓	✓
Dental shade quantitation		✓	✓	✓	✓	✓	✓
Tooth stain assessment		✓	✓	✓	✓	✓	✓
QoL[h] questionnaires (OHQoL[i] and EQ VAS[j])		✓	✓	✓	✓	✓	✓
Safety reporting		✓	✓	✓	✓	✓	✓

[a]Hx: history.
[b]CO: carbon monoxide.
[c]C-F NA: combustion-free nicotine alternatives.
[d]FTND: Fagerström Test for Nicotine Dependence.
[e]BP: blood pressure.
[f]HR: heart rate.
[g]MGI: Modified Gingival Index.
[h]QoL: Quality of Life.
[i]OHQoL: Oral Health Quality of Life.
[j]EQ VAS: EuroQoL Visual Analog Scale.

Table 3. Study schedule of procedures (reference group—arm C).

Procedure	Screening	Enrollment (V0); day 0	Baseline (V1); day 14±3	Week 12 (V2); day 90±5	Week 24 (V3); day 180±7	Week 52 (V4); day 360±7	Week 76 (V5); day 540±7
Eligibility criteria check	✓	✓					
Medical and oral health Hx[a]	✓						
Smoking Hx	✓						
Cigarette consumption	✓	✓	✓	✓	✓	✓	✓
Exhaled CO[b]	✓						
Informed consent		✓					
Oral hygiene check	✓	✓	✓	✓	✓	✓	✓
Periodontal examination	✓						
Scaling and polishing		✓					✓
Assignment to arm C		✓					
Tracker app installation		✓					
BP[c], HR[d], weight, height, and BMI		✓	✓	✓	✓	✓	✓
MGI[e] assessment		✓	✓	✓	✓	✓	✓
Plaque score imaging		✓	✓	✓	✓	✓	✓
Dental shade quantitation		✓	✓	✓	✓	✓	✓
Tooth stain assessment		✓	✓	✓	✓	✓	✓
QoL[f] questionnaires (OHQoL[g] and EQ VAS[h])		✓	✓	✓	✓	✓	✓
Safety reporting		✓	✓	✓	✓	✓	✓

[a]Hx: history.
[b]CO: carbon monoxide.
[c]BP: blood pressure.
[d]HR: heart rate.
[e]MGI: Modified Gingival Index.
[f]QoL: Quality of Life.
[g]OHQoL: Oral Health Quality of Life.
[h]EQ VAS: EuroQoL Visual Analog Scale.

Table 4. Study schedule of combustion-free nicotine alternatives (C-F NA) supply and use checks (only for arm B).

Procedure	Screening	Enrollment (V0)	Baseline (V1)	Week											
				4	8	12 (V2)	20	24 (V3)	32	40	48	52 (V4)	60	68	76 (V5)
C-F NA use			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Provide C-F NA device			✓												
Hand out 2 weeks supply of consumables[b]			✓												
Hand out 4 weeks supply of consumables[a]				✓	✓		✓				✓				
Hand out 2×4 weeks supply of consumables[b]						✓		✓	✓	✓		✓	✓	✓	✓
Product use checks (collect used and unused consumables[b])				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

[a]Participants wishing to use a heated tobacco product will receive one kit and supply of tobacco sticks of their choice; they will receive the number of tobacco sticks per day corresponding to the number of cigarettes smoked per day at baseline. Participants wishing to use a vaping product will receive one vaping kit and supply of e-liquids of their choice.

Study End Points

Primary End Points

The primary objective of the study is to compare changes in MGI by Lobene et al [29] between baseline and end of the study (ie, 18 months' time point) among participants who continue to smoke tobacco cigarettes (arm A) and participants who switch to C-F NA (arm B).

Secondary End Points

In addition, the study will analyze the number of secondary objectives, including within- and between-group variations at each study time point from baseline for MGI assessment, plaque imaging, dental shade quantitation, tooth stain scores, and oral health–related quality of life questionnaires.

Study Measurements and Calibration

A detailed description of the study measurements that will be specifically carried out at the dental clinic is provided in Multimedia Appendix 2.

All assessors will be trained on MGI scoring, tooth stain assessment, and the correct use of technologies and software used to quantify dental plaque, tooth discoloration, exhaled carbon monoxide monitoring, and electronic case report form (eCRF) use. Assessors will be periodically calibrated on MGI scoring and tooth stain assessment. To ensure consistency in the measurements, the same assessor will collect all study end points in the same participant over the entire study period.

Data Monitoring and Study Safety

A trial monitoring plan will be developed based on the trial risk assessment and includes on-site monitoring. The clinical research organization will arrange an independent monitor, separate from the investigators and the sponsor, to ensure compliance with trial protocols and policies, participant protection, and accurate data collection.

AEs and serious AEs (SAEs; eg, those related to oral conditions, tobacco cigarette smoking, C-F NA use, nicotine withdrawal symptoms, or nicotine overdosing) will be recorded on the AE page of the eCRF throughout the study. Participants will be interviewed at each visit to investigate signs or symptoms. Signs or symptoms will be elicited at each visit by open questioning, such as "How have you been feeling since your last visit?" "How have you been feeling regarding your oral cavity?" Participants will also be encouraged to spontaneously report AEs occurring at any other time during the study via the dedicated mobile app or the communication channels provided for the study. The investigator must gather sufficient information to determine the outcome and causality of AEs and SAEs and promptly notify the competent authority, if necessary.

Study Withdrawal

Participants may be withdrawn from the study prematurely for the following reasons: (1) experience an SAE, (2) develop a

concurrent disease which at the discretion of the investigator no longer justifies the participant's participation in this study, (3) sustain any uncorrectable protocol deviations during the study, (4) decide to stop their participation, (5) become pregnant, and (6) exhibit uncooperative behavior or nonattendance. After consultation with the clinical research organization, the investigator will notify participants' discontinuation from the study.

Data Collection and Protection

For data collection, each participant will be allocated an eCRF. Anonymized data from each study visit will be entered directly into the eCRF, which will then serve as a source document for the trial. This data entry process ensures that data are collected accurately and consistently at all study sites.

Each participant will be assigned a unique study identification number (participant ID). Participant's personal data will not be linked to the research results, and only a limited number of members of the research team will have access to the decoding list that links participant IDs to their personal information. All information obtained during the study procedures, including participant data and personal details, will be treated as private and confidential in accordance with ethical and privacy regulations.

The trial will reach its formal conclusion on the date of the final visit of the last participant in the last country involved in the study.

Ethical Considerations

The study will be conducted in accordance with the Principles of Good Clinical Practice and the Declaration of Helsinki. All 4 local ethics review boards reviewed and approved the study and, where appropriate, translated the relevant documentation (eg, informed consent form, participant's information sheet). The trial is registered with ClinicalTrials.gov (NCT04649645). The study was approved by the ethics review board of the coordinating center, the Azienda Ospedaliera di Rilievo Nazionale e di Alta Specializzazione "Garibaldi" (697/CE; dated November 11, 2020). Informed consent was obtained from all the participants.

The intention is to disseminate the study results through articles in peer-reviewed journals and conference presentations. A summary of the results will be available on the study website for public access. The anonymized data will be available to researchers upon reasonable request.

Statistical Considerations

Sample Size Calculation

For a valid sample size calculation, literature research was performed for the primary end point of the study (ie, MGI). Unfortunately, no data were available for such a study. However, data from studies with mouth rinse were available, and based on these studies [30,31], a mean MGI change of 0.08 with an SD of 0.18 of the MGI seemed relevant.

However, in these studies, higher mean MGI changes were observed because active treatment was administered, which was not the case in this study. Thus, several scenarios with different mean MGI changes and SDs will be applied.

The following hypotheses will be tested with a 1-sided independent *t* test:

H0: $\mu A \leq \mu B$ versus H1: $\mu A > \mu B$

where μA denotes the mean change MGI from baseline to after 18 months of regular smoking and μB denotes the mean MGI from baseline to after 18 months of C-F NA use.

For sample size calculation, SAS software (version 9.4; SAS Institute) was used and several scenarios were applied, assuming that the data are normally distributed. The results are summarized in Table 5, which presents the calculated sample sizes for the comparison of μA versus μB by a 1-sided independent *t* test, a significance level of 5%, and a power of 90%, depending on the expected MGI change and SD.

As no active treatment is given in this study, a lower effect than the observed values needs to be assumed. Therefore, a mean MGI change of 0.1 with an SD of 0.21 was chosen. Hence, a sample size of 77 patients per treatment group is required. Considering a dropout rate of 20% over 2 years' observation phase [32,33], a sample size of at least 92 per treatment group is required. In addition, it is estimated that approximately 25% of those switching to C-F NA use will abstain or substantially (≥90%) reduce smoking [34], and only these participants deliver valid results. Therefore, 4 times more participants should be recruited in the C-F NA group (4 × 92 = 368). This results in a total sample size of 460 (92 in arm A+368 in arm B).

In arm C, we have determined a sample size of 40, empirically with no formal statistical analysis, as this cohort's primary study end point (ie, MGI) is expected to be stable throughout the study.

Table 5. Summary table including the sample size for each arm of the study depending on the mean Modified Gingival Index (MGI) change and SD.

Nominal power	Mean MGI change	SD[a]				
		0.20	0.21	0.22	0.23	0.24
0.9	0.10	70	77	84	92	100
0.9	0.15	32	35	38	41	45
0.9	0.20	18	20	22	24	26

[a]Expected sample size is the same per each group and it is indicated by the rows (ie, 70-100, 32-45, and 18-26) according to the SD and MGI combinations.

Statistical Analyses

Statistical methods used in the analysis of this study will include descriptive statistics with the descriptive presentation of the total sample value, mean, SD, median, minimum, maximum, and 95% CIs for (pseudo) continuous data and categorical data. Further evaluations will be summarized in tables by counts and percentage of scores.

Statistical methods for primary study end points will include the following: the Shapiro-Wilk test of normality on calculated values (in case of normal distribution, a 2-sided independent *t* test and in case of nonnormal distribution: a 2-sided Mann-Whitney *U* test) and a linear mixed model with the random factors "center" and "study arms by center."

Designated as study arm C, the never-smoker group will establish a baseline reference for the oral health parameters. This group is anticipated to provide insights into the underlying changes in the primary study end point (MGI) that may emerge over time in individuals who have never smoked.

Statistical methods for secondary study end points will include the following: for comparisons of each study arm for parameters such as MGI assessment, plaque imaging, dental shade quantitation, tooth stains scores, and oral health–related quality of life questionnaires, the Shapiro-Wilk test of normality on calculated values (in case of normal distribution, a 2-sided independent *t* test and in case of nonnormal distribution: a 2-sided Mann-Whitney *U* test); for comparisons of each assessment time for parameters such as MGI assessment, plaque imaging, dental shade quantitation, tooth stains scores, and oral health–related quality of life questionnaires, the Shapiro-Wilk test of normality on calculated values (in case of normal distribution, a 2-sided independent *t* test and in case of nonnormal distribution: a 2-sided Mann-Whitney *U* test); accounting for missing, unused, and spurious data.

If only one value of the parameter MGI is missing after day 1, the last available observation will be carried forward. The analysis will be performed on the substituted data. For secondary parameters, no replacement of missing values will be applied.

A generalized linear regression model will be used to adjust for all identified confounders. To identify possible predictors of primary and secondary study end points, a regression model will be estimated in which each study end point will be entered as the dependent variable. Possible predictors will be entered into the model as independent variables (including study group; age; gender; cigarette consumption; combustion-free nicotine delivery systems use; and frequency of personal oral hygiene, eg, tooth brushing, mouth washing, and dental flossing frequency) to assess the interactions. Following the results obtained from each regression model, comparisons between and within study groups will be performed using analysis of covariance adjusted for age, gender, and frequency of personal oral hygiene followed by the Tukey post hoc comparison test.

The goal of our study is to help smokers abstain from cigarette smoking to assess changes in oral health regardless of the product used. This study is not designed to compare the efficacy between HTPs and ECs in terms of smoking cessation. Nonetheless, we will consider a secondary analysis that takes into account the potential different impact of HTPs versus ECs in terms of oral health outcomes.

Results

Participant recruitment began in October 2021, and enrollment has been completed in June 2023. Results will be reported in 2025.

Discussion

Overview

Although the negative effects of cigarette smoking on oral health and tooth discoloration are well known [35,36], there are only limited data about the impact of C-F NA such as ECs and HTPs. In particular, there are no long-term studies assessing the impact on oral health and teeth appearance when substituting conventional cigarettes for these combustion-free alternatives. This study was specifically designed to address these research questions. In particular, this study tests the hypothesis that avoiding exposure to cigarette smoke toxicants may translate into measurable amelioration in gingival response, dental plaque build-up, enamel discoloration, and tooth staining in participants with mild to moderate gingivitis by comparing participants who smoke tobacco cigarette with those who switch to using C-F NA or participants who never smoked.

In addition to its obvious relevance to health and esthetic concerns, this study seeks to expand on regulatory science. Regulatory authorities (eg, the US Food and Drug Administration) recommend investigating the oral health effects of novel tobacco and nicotine products to better understand their impact at individual and population levels as well as exploring additional study end points for the assessment of their short- and long-term effects in oral health studies [37]. Our study is designed to provide improved design knowledge for oral health switching studies and, most importantly, to streamline new innovative cutting-edge technologies that can be used for future studies on existing and emerging tobacco and nicotine products (including oral smokeless products).

The study design incorporates several significant and groundbreaking characteristics. First, we aim to enhance adherence to C-F NA and optimize overall compliance with the study's instructions through the provision of a diverse range of products, encompassing the most popular options available in the market. This approach allows participants to tailor their own gratifying "nicotine experience" by selecting the C-F NA that aligns with their preferences. By doing so, we anticipate not only fostering a transition to the latest technology but also facilitating the reduction of cigarette smoking and bolstering long-term prevention of relapse [38-42]. It is worth highlighting that this aspect of personal choice is notably absent in studies of harm reduction. Furthermore, it is important to emphasize that the outcomes of this research will not be product specific, thereby minimizing constraints on generalizability.

Second, the study is being run in many different locations across the globe and so the challenge was to find a primary end point that could be measured by different operators in different sites, using a standardized measurement system that has been used

previously and so has provenance. The index to be used had to be simple, reproducible, and relatively easy to compare between different sites and different operators. Ideally, the assessors should be able to calibrate the index to be used and compare the calibration results. The MGI is a widely used industry-standard index to determine changes in the gingival health of volunteers in clinical studies [29,43,44]. This index is simple, noninvasive, and reproducible, and it is hoped that it will be possible to train different examiners in different locations to align their assessments, thus making the results comparable. As the MGI is noninvasive, there is no gingival probing, and it is thought to be easier to calibrate examiners and compare kappa scores. Although subjective in nature, the lack of probing removes one of the variables present in using pressure to probe the gingivae. It is also thought to afford greater sensitivity in determining therapeutic efficacy [45]. This study will be the first to investigate the long-term impact of smoking or C-F NA intervention on MGI.

Third, the selection of secondary study end points is strategic because it considers what drives smokers to turn to cleaner nicotine and tobacco products. This is particularly persuasive for young adults, for whom a cardiovascular-cancer-respiratory risk–based narrative is either ineffective or even counterproductive, and for whom concern about bad breath and poor dental esthetic (because of enamel discoloration and “tar” stains) may be a much more significant reason to refrain from smoking. Although experimental work comparing the effects of C-F NA on tooth staining and discoloration has been published [46-48], this study is the first to consider this powerful narrative of oral health in a clinical trial; therefore, we have included innovative 21st century technologies for objective and consistent quantitation of dental shade discoloration (by calibrated spectrophotometry) and dental plaque changes (by digital imaging technology; quantitative light-induced fluorescence) among the study end points to investigate whether switching completely from cigarettes to C-F NA can improve gum health, reduce bad breath, and restore teeth appearance. Small-scale clinical trials have been recently conducted at the Center of Excellence for the Acceleration of Harm Reduction of the Catania University to confirm the validity and reproducibility of dental shade assessment by digital spectrophotometry and dental plaque quantitation by light-induced fluorescence technology in current, former, and never smokers [49,50].

Fourth, maximizing the magnitude of observable changes at the study end points is critically important. Given that several factors (including duration of smoking exposure, variations in oral hygiene practices, type of diet, and level of alcohol consumption) can significantly affect assessments of gum health and dental esthetics, we reduced baseline variability by using data obtained after the visit during which scaling and polishing was carried out. By removing dental plaque, calculus, and stains, we provide all study participants with the best possible oral health status (gum health and teeth appearance) at the beginning of the study. Considering that a 14-day interval is generally required to allow gingival restoration from tissue trauma caused by scaling and polishing [51], measurements that will be considered for this normalized baseline will be obtained 14 days after scaling and polishing. Any progressive change in gum health or tooth appearance will be compared with the reference data of this baseline. In addition to the inclusion of a full scale and polish at the beginning of the study in an attempt to maximize the magnitude of observable changes of study end points, it is also important to consider that the length of the study is adequate and that the study population will have to be one that allows the possibility of measuring such a change. Although the long-term impact of smoking and smoking cessation on gingival health and tooth appearance has never been investigated in a prospective trial, the planned 18 months duration of the study is deemed to be adequate for the detection of significant changes in study end points. Chronic periodontal disease is common in smokers and is an irreversible condition that may stabilize with active treatment [52]; however, it is unlikely to improve with the simple measure of smoking cessation alone. Therefore, participants with periodontitis will be excluded and only participants with mild to moderate gingivitis will be recruited, as they are more likely to show measurable changes in study end points with continuing to smoke, smoking cessation, or the use of C-F NA.

Fifth, personal oral hygiene and dietary patterns can significantly influence both primary and secondary study end points. To mitigate this impact, a standardized approach to oral hygiene will be implemented within the study parameters. Participants will be explicitly advised against altering their established oral hygiene practices for the duration of the study. Furthermore, adherence to specific restriction criteria before each scheduled study visit will be emphasized, aiming to prevent any confounding of the collected data. Recognizing the variable effects stemming from individual oral hygiene and dietary habits, we incorporated a cohort of never smokers as a reference group. This inclusion serves to establish a benchmark for comparison and analysis. To address the inherent challenge of ensuring consistent measurement of study end points, especially in cases involving diverse operators across multiple sites, we will provide comprehensive training and implement meticulous calibration procedures.

Finally, compliance with the research protocol is important because it would decrease or nullify the anticipated improvements in study end points if cigarettes were not fully or largely replaced with C-F NA. Participants will be reminded of the importance of adhering to their randomized product allocation and of abstaining from or substantially reducing the daily consumption of cigarettes (by at least 90% of their regular cigarette smoking at baseline) at every study visit. A significant feature of switching studies is close reporting of cigarette consumption and (or) C-F NA use; participants will record the consumption of cigarettes and use of C-F NA on each visit in their study diary. In addition, participants will be asked to return all empty, partly used, and unused consumables. Throughout the study, smoking and C-F NA use will be monitored via an app. The SMILE Tracker app is an integral component of the Smile study designed to monitor participants’ behaviors and lifestyle choices. Through daily prompts, the app assists in tracking cigarette consumption, use of combustion-free nicotine delivery systems, and regular oral hygiene practices such as brushing, flossing, and mouthwash use. In addition, it functions

as a personal diary for participants to log any changes in their oral care routine. Moreover, the SMILE Tracker app features a system to monitor protocol adherence, identify deviations, and gather data on potential AEs and SAEs. It sends automated reminders to participants for their upcoming appointments and study restrictions and provides instructions to ensure adherence and accurate data collection during the study. Furthermore, it includes a step counter to encourage physical activity among users. Of note, noncompliance with the study items is an interesting outcome in itself (particularly in consideration of the wide selection of different products offered in the study). Although compliance with this study is not expected to be significantly different compared with other comparable studies, our power calculations are overestimated to account for a 75% noncompliance rate. The C-F NA population would therefore be overrepresented by recruiting4 times the number of participants in the C-F NA category (ie, for every participant randomized in the control population, 4 will be randomized in the C-F NA population).

The acknowledgment of the impact of COVID-19 pandemic restrictions on recruitment is duly noted. However, it is deemed unlikely that these restrictions will exert a significant impact. This assertion is based on the fact that recruitment proceedings were initiated in October 2021, a period during which well-defined guidelines had already been established at the dental clinic across all 4 participating sites.

Conclusions

This study represents a pioneering effort in assessing the long-term effects of smoking and smoking abstinence on oral health. Through a prospective approach, it aims to provide novel insights into the relationship between smoking habits and oral well-being. The data derived from this study will significantly enhance our existing understanding of the impact of smoking on oral health. Moreover, the study outcomes hold the potential to shed light on the role of C-F NA as a potentially cleaner nicotine alternative to tobacco smoking. This is particularly relevant for individuals who prioritize concerns such as bad breath and dental esthetics. This study's emphasis on oral health aligns with a broader objective of alleviating the burden of smoking. Several parameters measured in this study (including MGI and dental plaque build-up) are linked to the development of periodontal disease. It is noteworthy that the progression from chronic gingivitis to periodontitis raises the risk of cardiovascular disease [4,5], thereby underscoring the broader health implications of the study's results.

Acknowledgments

Funding for this study was provided by ECLAT Srl, a spinoff of the University of Catania, through a grant from the Foundation for a Smoke-Free World. The Foundation for a Smoke-Free World is a US-based nonprofit 501(c)(3) private foundation dedicated to ending smoking in the current generation. The authors are solely responsible for the content, selection, and presentation of facts as well as any opinions expressed in this study. These views should not be interpreted as reflecting the positions of the Foundation for a Smoke-Free World, Inc. ECLAT, a spinoff company of the University of Catania, focuses on delivering solutions to global health issues with a particular emphasis on harm reduction and technological innovation.

Data Availability

The data sets used during or analyzed during this study will be available from the corresponding author upon reasonable request.

Authors' Contributions

GC, DG, PC, RM, and RP conceived and designed the study. GC, DG, and RM formalized the statistical analysis plan. GC, DG, SU, and RP drafted the manuscript. SU designed the figures and tables. All authors have provided critical revisions to the working draft and have read and approved the submitted manuscript.

Conflicts of Interest

RP is a full-time professor of internal medicine at the University of Catania (Italy) and medical director of the Institute for Internal Medicine and Clinical Immunology at the same university. He has received grants from U-BIOPRED (Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes) and AIRPROM (Airway Disease Predicting Outcomes through Patient Specific Computational Modelling); Integral Rheumatology & Immunology Specialists Network; Foundation for a Smoke-Free World; Pfizer; GlaxoSmithKline; CV Therapeutics; NeuroSearch A/S; Sandoz; Merk Sharp & Dohme; Boehringer Ingelheim; Novartis; Arbi Group Srl; Duska Therapeutics; Forest Laboratories; Ministero dell Universita' e della Ricerca (MUR) Bando PNRR 3277/2021 (CUP E63C22000900006) and 341/2022 (CUP E63C22002080006), funded by NextGenerationEU of the European Union; and the ministerial grant PON REACT-EU 2021 GREEN-Bando 3411/2021 by MUR—PNRR EU Community. He is the founder of the Center for Tobacco Prevention and Treatment at the University of Catania and of the Center of Excellence for the Acceleration of Harm Reduction at the same university. He receives consultancy fees from Pfizer, Boehringer Ingelheim, Duska Therapeutics, Forest Laboratories, CV Therapeutics, Sermo Inc, GRG Health, Clarivate Analytics, Guidepoint Expert Network, and the GLG Group. He receives textbook royalties from Elsevier and is also involved in a patent application for ECLAT Srl. He is a pro bono scientific advisor for Lega Italiana Anti Fumo and the International Network of Nicotine Consumer Organizations), and he is chair of the European Technical Committee for Standardization on "Requirements and test methods for emissions of

electronic cigarettes" (CEN/TC 437; WG4). SAP is a professional dentist and the chairman of the Board of Directors of ECLAT Srl, the spinoff of the University of Catania that sponsors this study through a grant from the Foundation for a Smoke-Free World Inc, a US nonprofit 501(c)(3) private foundation. PC has been affiliated with the Center of Excellence for the Acceleration of Harm Reduction since December 2019 in a pro bono role. He is the coauthor of a protocol paper supported by the Investigator-Initiated Study award program established by Philip Morris International in 2017.

Multimedia Appendix 1
Study activities—detailed description of the measurements that will be specifically performed at each trial visit.
[DOCX File , 45 KB - resprot_v13i1e53222_app1.docx]

Multimedia Appendix 2
Study procedures—detailed description of the study measurements that will be specifically carried out at the dental clinic.
[DOCX File , 87 KB - resprot_v13i1e53222_app2.docx]

Multimedia Appendix 3
CONSORT checklist.
[PDF File (Adobe PDF File), 54 KB - resprot_v13i1e53222_app3.pdf]

References

1. Offenbacher S. Periodontal diseases: pathogenesis. Ann Periodontol 1996;1(1):821-878. [doi: 10.1902/annals.1996.1.1.821] [Medline: 9118282]
2. Research, Science and Therapy Committee. Position paper: diagnosis of periodontal diseases. J Periodontol 2003 Aug;74(8):1237-1247. [doi: 10.1902/jop.2003.74.8.1237] [Medline: 29539063]
3. Armitage GC. Clinical evaluation of periodontal diseases. Periodontol 2000 1995 Feb 23;7(1):39-53. [doi: 10.1111/j.1600-0757.1995.tb00035.x] [Medline: 9567929]
4. Czesnikiewicz-Guzik M, D'Aiuto F, Deanfield JE. Understanding residual inflammatory risk sheds new light on the clinical importance of periodontitis in cardiovascular disease. Eur Heart J 2020 Feb 14;41(7):818-819. [doi: 10.1093/eurheartj/ehaa107] [Medline: 32058578]
5. Armitage GC. Periodontal infections and cardiovascular disease--how strong is the association? Oral Dis 2000 Nov 28;6(6):335-350. [doi: 10.1111/j.1601-0825.2000.tb00126.x] [Medline: 11355266]
6. Bergström J. Cigarette smoking as risk factor in chronic periodontal disease. Community Dent Oral Epidemiol 1989 Oct 29;17(5):245-247. [doi: 10.1111/j.1600-0528.1989.tb00626.x] [Medline: 2791514]
7. Bergström J, Preber H. Tobacco use as a risk factor. J Periodontol 1994 May;65 Suppl 5S(5S):545-550. [doi: 10.1902/jop.1994.65.5s.545] [Medline: 29539765]
8. Haber J. Smoking is a major risk factor for periodontitis. Curr Opin Periodontol 1994:12-18. [Medline: 8032453]
9. Haber J. Cigarette smoking: a major risk factor for periodontitis. Compendium 1994 Aug;15(8):1002, 1004-8 passim; quiz 1014. [Medline: 7987894]
10. Bergström J. Tobacco smoking and chronic destructive periodontal disease. Odontology 2004 Sep;92(1):1-8. [doi: 10.1007/s10266-004-0043-4] [Medline: 15490298]
11. Ueno M, Ohara S, Sawada N, Inoue M, Tsugane S, Kawaguchi Y. The association of active and secondhand smoking with oral health in adults: Japan public health center-based study. Tob Induc Dis 2015 Jul 29;13(1):19 [FREE Full text] [doi: 10.1186/s12971-015-0047-6] [Medline: 26225132]
12. Eriksen HM, Nordbø H. Extrinsic discoloration of teeth. J Clin Periodontol 1978 Nov;5(4):229-236. [doi: 10.1111/j.1600-051x.1978.tb01916.x] [Medline: 363748]
13. Alkhatib MN, Holt RD, Bedi R. Smoking and tooth discolouration: findings from a national cross-sectional study. BMC Public Health 2005 Mar 24;5(1):27 [FREE Full text] [doi: 10.1186/1471-2458-5-27] [Medline: 15790389]
14. Christen AG. The impact of tobacco use and cessation on oral and dental diseases and conditions. Am J Med 1992 Jul 15;93(1A):25S-31S. [doi: 10.1016/0002-9343(92)90624-k] [Medline: 1497000]
15. Hattab FN, Qudeimat MA, al-Rimawi HS. Dental discoloration: an overview. J Esthet Dent 1999;11(6):291-310 [FREE Full text] [doi: 10.1111/j.1708-8240.1999.tb00413.x] [Medline: 10825865]
16. Follow-up to the political declaration of the third high-level meeting of the General Assembly on the prevention and control of non-communicable disease. World Health Organization. 2022. URL: https://apps.who.int/gb/ebwha/pdf_files/WHA75/A75_10Add1-en.pdf [accessed 2024-01-18]
17. WHO monograph on tobacco cessation and oral health integration. World Health Organization. 2017 Jun 14. URL: https://www.who.int/publications/i/item/who-monograph-on-tobacco-cessation-and-oral-health-integration [accessed 2024-01-25]
18. Zhu S, Melcer T, Sun J, Rosbrook B, Pierce JP. Smoking cessation with and without assistance: a population-based analysis. Am J Prev Med 2000 May;18(4):305-311. [doi: 10.1016/s0749-3797(00)00124-0] [Medline: 10788733]

19. West R, Zhou X. Is nicotine replacement therapy for smoking cessation effective in the "real world"? Findings from a prospective multinational cohort study. Thorax 2007 Nov;62(11):998-1002 [FREE Full text] [doi: 10.1136/thx.2007.078758] [Medline: 17573444]
20. Polosa R, Emma R, Cibella F, Caruso M, Conte G, Benfatto F, et al. Impact of exclusive e-cigarettes and heated tobacco products use on muco-ciliary clearance. Ther Adv Chronic Dis 2021 Aug 12;12:20406223211035267 [FREE Full text] [doi: 10.1177/20406223211035267] [Medline: 34422253]
21. O'Leary R, Polosa R. Tobacco harm reduction in the 21st century. Drugs Alcohol Today 2020 Jul 13;20(3):219-234 [FREE Full text] [doi: 10.1108/dat-02-2020-0007]
22. Hartmann-Boyce J, Lindson N, Butler AR, McRobbie H, Bullen C, Begh R, et al. Electronic cigarettes for smoking cessation. Cochrane Database Syst Rev 2022 Nov 17;11(11):CD010216 [FREE Full text] [doi: 10.1002/14651858.CD010216.pub7] [Medline: 36384212]
23. Caponnetto P, Campagna D, Maglia M, Benfatto F, Emma R, Caruso M, et al. Comparing the effectiveness, tolerability, and acceptability of heated tobacco products and refillable electronic cigarettes for cigarette substitution (CEASEFIRE): randomized controlled trial. JMIR Public Health Surveill 2023 Apr 04;9:e42628 [FREE Full text] [doi: 10.2196/42628] [Medline: 37014673]
24. Daynard R. Public health consequences of e-cigarettes: a consensus study report of the National Academies of Sciences, Engineering, and Medicine. J Public Health Pol 2018 Jul 5;39(3):379-381. [doi: 10.1057/s41271-018-0132-1]
25. Haziza C, de La Bourdonnaye G, Merlet S, Benzimra M, Ancerewicz J, Donelli A, et al. Assessment of the reduction in levels of exposure to harmful and potentially harmful constituents in Japanese subjects using a novel tobacco heating system compared with conventional cigarettes and smoking abstinence: a randomized controlled study in confinement. Regul Toxicol Pharmacol 2016 Nov;81:489-499 [FREE Full text] [doi: 10.1016/j.yrtph.2016.09.014] [Medline: 27693654]
26. Gale N, McEwan M, Camacho OM, Hardie G, Murphy J, Proctor CJ. Changes in biomarkers of exposure on switching from a conventional cigarette to the glo tobacco heating product: a randomized, controlled ambulatory study. Nicotine Tob Res 2021 Feb 16;23(3):584-591 [FREE Full text] [doi: 10.1093/ntr/ntaa135] [Medline: 32776101]
27. Caruso M, Emma R, Distefano A, Rust S, Poulas K, Giordano A, et al. Comparative assessment of electronic nicotine delivery systems aerosol and cigarette smoke on endothelial cell migration: the Replica Project. Drug Test Anal 2023 Oct 29;15(10):1164-1174. [doi: 10.1002/dta.3349] [Medline: 35877466]
28. Papapanou PN, Sanz M, Buduneli N, Dietrich T, Feres M, Fine DH, et al. Periodontitis: consensus report of workgroup 2 of the 2017 world workshop on the classification of periodontal and peri-implant diseases and conditions. J Periodontol 2018 Jun;89 Suppl 1:S173-S182. [doi: 10.1002/JPER.17-0721] [Medline: 29926951]
29. Lobene RR, Weatherford T, Ross NM, Lamm RA, Menaker L. A modified gingival index for use in clinical trials. Clin Prev Dent 1986;8(1):3-6. [Medline: 3485495]
30. Cortelli SC, Cortelli JR, Shang H, Costa R, Charles CA. Gingival health benefits of essential-oil and cetylpyridinium chloride mouthrinses: a 6-month randomized clinical study. Am J Dent 2014 Jun;27(3):119-126. [Medline: 25208357]
31. Lynch MC, Cortelli SC, McGuire JA, Zhang J, Ricci-Nittel D, Mordas CJ, et al. The effects of essential oil mouthrinses with or without alcohol on plaque and gingivitis: a randomized controlled clinical study. BMC Oral Health 2018 Jan 10;18(1):6 [FREE Full text] [doi: 10.1186/s12903-017-0454-6] [Medline: 29321067]
32. Preshaw PM, Novak MJ, Mellonig J, Magnusson I, Polson A, Giannobile WV, et al. Modified-release subantimicrobial dose doxycycline enhances scaling and root planing in subjects with periodontal disease. J Periodontol 2008 Mar;79(3):440-452 [FREE Full text] [doi: 10.1902/jop.2008.070375] [Medline: 18315426]
33. Van Leeuwen M, Rosema N, Versteeg PA, Slot DE, Hennequin-Hoenderdos NL, Van der Weijden GA. Effectiveness of various interventions on maintenance of gingival health during 1 year - a randomized clinical trial. Int J Dent Hyg 2017 Nov 08;15(4):e16-e27. [doi: 10.1111/idh.12213] [Medline: 26953228]
34. Hajek P, Phillips-Waller A, Przulj D, Pesola F, Myers Smith K, Bisal N, et al. A randomized trial of e-cigarettes versus nicotine-replacement therapy. N Engl J Med 2019 Feb 14;380(7):629-637. [doi: 10.1056/nejmoa1808779]
35. Warnakulasuriya S, Dietrich T, Bornstein MM, Casals Peidró E, Preshaw PM, Walter C, et al. Oral health risks of tobacco use and effects of cessation. Int Dent J 2010 Feb;60(1):7-30. [Medline: 20361572]
36. Johnson N, Bain C. Tobacco and oral disease. Br Dent J 2000 Aug 26;189(4):200-206 [FREE Full text] [doi: 10.1038/sj.bdj.4800721a]
37. Premarket tobacco product applications for electronic nicotine delivery systems (ENDS). U.S. Food & Drug Administration. 2023 Mar. URL: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/premarket-tobacco-product-applications-electronic-nicotine-delivery-systems-ends [accessed 2024-01-25]
38. Russell C, McKeganey N, Dickson T, Nides M. Changing patterns of first e-cigarette flavor used and current flavors used by 20,836 adult frequent e-cigarette users in the USA. Harm Reduct J 2018 Jun 28;15(1):33 [FREE Full text] [doi: 10.1186/s12954-018-0238-6] [Medline: 29954412]
39. Zare S, Nemati M, Zheng Y. A systematic review of consumer preference for e-cigarette attributes: flavor, nicotine strength, and type. PLoS One 2018;13(3):e0194145 [FREE Full text] [doi: 10.1371/journal.pone.0194145] [Medline: 29543907]

40. Evans AT, Henderson KC, Geier A, Weaver SR, Spears CA, Ashley DL, et al. What motivates smokers to switch to ends? A qualitative study of perceptions and use. Int J Environ Res Public Health 2020 Nov 28;17(23):8865 [FREE Full text] [doi: 10.3390/ijerph17238865] [Medline: 33260570]
41. Caponnetto P, Maglia M, Polosa R. Commentary on Dawkins et al. (2015): electronic cigarettes - from smoking cessation to smoking sensation and back. Addiction 2015 Apr 15;110(4):678-679. [doi: 10.1111/add.12854] [Medline: 25771692]
42. DiPiazza J, Caponnetto P, Askin G, Christos P, Maglia ML, Gautam R, et al. Sensory experiences and cues among E-cigarette users. Harm Reduct J 2020 Oct 15;17(1):75 [FREE Full text] [doi: 10.1186/s12954-020-00420-0] [Medline: 33059666]
43. Mielczarek A, Klukowska M, Kaiser E, Stoerkel U, Mandl C, Walters P, et al. A novel power toothbrush with multi-directional, triple zone cleaning technology. Am J Dent 2012 Sep;25 Spec No A(A):3A-9A. [Medline: 23248892]
44. Araujo MW, Charles CA, Weinstein RB, McGuire JA, Parikh-Das AM, Du Q, et al. Meta-analysis of the effect of an essential oil-containing mouthrinse on gingivitis and plaque. J Am Dent Assoc 2015 Aug;146(8):610-622 [FREE Full text] [doi: 10.1016/j.adaj.2015.02.011] [Medline: 26227646]
45. Lobene RR, Mankodi SM, Ciancio SG, Lamm RA, Charles CH, Ross NM. Correlations among gingival indices: a methodology study. J Periodontol 1989 Mar;60(3):159-162. [doi: 10.1902/jop.1989.60.3.159] [Medline: 2746448]
46. Dalrymple A, Badrock TC, Terry A, Barber M, Hall PJ, Thorne D, et al. Assessment of enamel discoloration in vitro following exposure to cigarette smoke and emissions from novel vapor and tobacco heating products. Am J Dent 2018 Oct;31(5):227-233. [Medline: 30346667]
47. Zanetti F, Zhao X, Pan J, Peitsch MC, Hoeng J, Ren Y. Effects of cigarette smoke and tobacco heating aerosol on color stability of dental enamel, dentin, and composite resin restorations. Quintessence Int 2019 Jan 25;50(2):156-166. [doi: 10.3290/j.qi.a41601] [Medline: 30564805]
48. Haiduc A, Zanetti F, Zhao X, Schlage WK, Scherer M, Pluym N, et al. Analysis of chemical deposits on tooth enamel exposed to total particulate matter from cigarette smoke and tobacco heating system 2.2 aerosol by novel GC-MS deconvolution procedures. J Chromatogr B Analyt Technol Biomed Life Sci 2020 Sep 01;1152:122228 [FREE Full text] [doi: 10.1016/j.jchromb.2020.122228] [Medline: 32585495]
49. Conte G, Pacino SA, Urso S, Emma R, Pedullà E, Cibella F, et al. Repeatability of dental shade by digital spectrophotometry in current, former, and never smokers. Odontology 2022 Jul 10;110(3):605-618 [FREE Full text] [doi: 10.1007/s10266-022-00692-x] [Medline: 35266059]
50. Conte G, Amaliya A, Gupta S, Emma R, Gospodaru S, Bordeniuc G, et al. Repeatability of dental plaque quantitation by light induced fluorescence technology in current, former, and never smokers. BMC Oral Health 2023 Jul 13;23(1):480 [FREE Full text] [doi: 10.1186/s12903-023-03154-0] [Medline: 37443061]
51. Waerhaug J. Healing of the dento-epithelial junction following subgingival plaque control. I. As observed in human biopsy material. J Periodontol 1978 Jan;49(1):1-8. [doi: 10.1902/jop.1978.49.1.1] [Medline: 340634]
52. Tonetti MS, Greenwell H, Kornman KS. Staging and grading of periodontitis: framework and proposal of a new classification and case definition. J Periodontol 2018 Jun;89 Suppl 1:S159-S172. [doi: 10.1002/JPER.18-0006] [Medline: 29926952]

Abbreviations

AE: adverse event
C-F NA: combustion-free nicotine alternatives
eCRF: electronic case report form
EC: e-cigarette
HTP: heated tobacco product
MGI: Modified Gingival Index
SAE: serious adverse event
VBA: very brief advice
WHO: World Health Organization

Edited by A Mavragani; submitted 29.09.23; peer-reviewed by Y Ren, Anonymous; comments to author 11.12.23; revised version received 27.12.23; accepted 28.12.23; published 23.02.24.

Please cite as:
Conte G, Pacino SA, Urso S, Greiling D, Caponnetto P, Pedullà E, Generali L, Consolo U, Checchi V, Gospodaru S, Bordeniuc G, Fala V, Kowalski J, Nowak M, Górska R, Amaliya A, Chapple I, Milward M, Maclure R, Nardi GM, Polosa R
Changes in Oral Health and Dental Esthetic in Smokers Switching to Combustion-Free Nicotine Alternatives: Protocol for a Multicenter and Prospective Randomized Controlled Trial
JMIR Res Protoc 2024;13:e53222
URL: https://www.researchprotocols.org/2024/1/e53222
doi:10.2196/53222
PMID:38393754

Protocol

Matrix Metalloproteinase-9 Testing of Golden Rice Cookies With Piper Crocatum Active Extract for Preventing Foot Ulcers in Patients With Diabetes: Protocol for a Randomized Controlled Trial

Andina Setyawati[1*], Dr; Ariyanti Saleh[2*], Prof Dr; Takdir Tahir[1*], Dr; Saldy Yusuf[1*], Dr; Syahrul Syahrul[1*], MN; Aminuddin Aminuddin[3*], Dr; Muhammad Raihan[4*], MSc; Nuurhidayat Jafar[5*], MN; Hasyrul Hamzah[6], Dr; Nur Arfian[7*], Dr

[1]Medical Surgical Nursing Department, Faculty of Nursing, Hasanuddin University, Makassar, Indonesia
[2]Department of Psychiatric Nursing, Faculty of Nursing, Hasanuddin University, Makassar, Indonesia
[3]Department of Nutrition, Medicine Faculty, Hasanuddin University, Makassar, Indonesia
[4]Faculty of Pharmacy, Hasanuddin University, Makassar, Indonesia
[5]Community Health Nursing Department, Nursing Faculty, Hasanuddin University, Makassar, Indonesia
[6]Faculty of Pharmacy, Universitas Muhammadiyah Kalimantan Timur, Kalimantan Timur, Indonesia
[7]Department of Anatomy, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia
[*]these authors contributed equally

Corresponding Author:
Andina Setyawati, Dr
Medical Surgical Nursing Department
Faculty of Nursing
Hasanuddin University
Jl Perintis Kemerdekaan km 10
Tamalanrea
Makassar, 92111
Indonesia
Phone: 62 8121521639
Email: andina@unhas.ac.id

Abstract

Background: Diabetic foot ulcers (DFUs) present a formidable challenge to both patients and health care systems. DFUs significantly reduce the quality of life for patients, prolong hospital stays, and are the cause of approximately 70,000 lower limb amputations across the globe annually. Prevention of DFUs primarily involves the optimization of blood sugar levels and the effective management of complications, particularly peripheral neuropathy. Golden Rice has been proven to lower blood sugar levels due to its beta-carotene content, and Piper crocatum (*P. crocatum*) has been found to be effective in reducing the risk factors of DFUs through biomolecular regulation because of its polyphenol content.

Objective: The principal objective of this study is to identify the efficacy of *P. crocatum*–enriched cookies, with Golden Rice as their primary ingredient, in preventing DFUs. The evaluation will center on their impact on the expression of matrix metalloproteinase-9 (MMP-9), a pivotal factor in the development of DFUs.

Methods: This study is an experimental clinical research that follows the randomized controlled trial method and uses a single-blind design. The participants in the study are outpatients from primary health centers in Makassar, Indonesia, who have been diagnosed with diabetes mellitus. The sample for the study will be randomly selected and subsequently categorized into 2 groups: the intervention group and the control group. The intervention group consumes *P. crocatum*–enriched Golden Rice cookies, while the control group receives cookies without these additives. The participants from both groups will consume their respective cookies (packaged identically) twice a day for 14 days. The cookies will be prepared according to a modified recipe with an emphasis on low glucose content, resulting in 51 calories per cookie, comprising 1% carbohydrates, 6% fat, 4% cholesterol, and 4% fiber, excluding gluten, sugar, and salt. They will be baked at 158°C for 20 minutes. The process involves the addition of 20% Golden Rice and 10% *P. crocatum* ethanol extract, both prepared via maceration with 96% ethanol. The dependent

variable in this study is the expression of gelatinases matrix metalloproteinase, to be assessed at 2 distinct time points—preintervention (pretest) and postintervention (posttest)—with the evaluation conducted through the western blotting method.

Results: The recruitment and testing phase started in January 2024. The study is scheduled to be completed by the end of March 2024. Data analysis will commence in April 2024, and the publication of the results is anticipated in the same year (2024). The study will report on the changes in primary data, encompassing gelatinases matrix metalloproteinase, as well as secondary data, including the ankle-brachial index, neuropathy score, and random blood glucose level.

Conclusions: The findings of this trial are expected to significantly impact the selection of strategies by health care practitioners to enhance diabetes self-management, particularly in the domain of therapeutic snacking, for patients diagnosed with diabetes mellitus.

Trial Registration: Thai Clinical Trials Registry TCTR20230502001; https://www.thaiclinicaltrials.org/show/TCTR20230502001

International Registered Report Identifier (IRRID): PRR1-10.2196/49940

(JMIR Res Protoc 2024;13:e49940) doi:10.2196/49940

KEYWORDS

diabetic foot ulcer; prevention; diabetic neuropathy; cookies; food supplement; study protocol

Introduction

Diabetic foot ulcer (DFU) is a major problem in patients with diabetes, affecting 15% of the diabetic population. DFUs significantly reduce the quality of life for patients, prolong hospital stays, and are the cause of approximately 70,000 lower limb amputations across the globe each year [1]. Diabetic foot disease is among the top 10 medical conditions in terms of burden, and it is estimated that up to 34% of individuals with diabetes will experience DFU at some point in their lives [2]. Preventing DFUs and amputations is of utmost importance to alleviate this significant burden on patients, health care systems, and society as a whole [3].

Peripheral neuropathy, the most prevalent type of diabetic neuropathy, primarily affects the nerves in the extremities, especially the feet. It accounts for 6.4% of all complications related to diabetes [4]. This condition predominantly disrupts sensory function, leading to gradual numbness, which increases the susceptibility to developing ulcers due to external injuries. It is crucial to identify these risk factors to enhance the effectiveness of preventive measures for DFUs [5]. Treating diabetic neuropathy presents a significant clinical hurdle. According to some studies, the gelatinase matrix metalloproteinase 9 (MMP-9) has been found to play a vital role in the demyelination of axons and the development of diabetic neuropathy in rodents [6,7]. As gelatinase MMP-9 plays a pivotal role in the initial onset of neuropathy, it is considered crucial in the progression of diabetic neuropathy and could potentially be targeted for treatment purposes [6,7].

Elevated levels of blood sugar and insulin resistance in patients with type 2 diabetes further contribute to the generation of reactive oxygen species (ROS), which intensifies the complications associated with this disease [8]. The activity of vascular MMP-9 is heightened in individuals with diabetes mellitus, partly due to increased production by vascular endothelial cells. Additionally, the activity of ROS plays a significant role in this process [9]. The high levels of ROS and MMP-9 have been found to be associated with glycemic index and diabetes complications [10].

Different types of diabetic-friendly cookies and breads are already in circulation, such as cassava bread, flax meal powder, and grape seed oil bread. However, their purpose is solely to limit glucose intake rather than directly affecting insulin levels. In contrast, noncookie products made with Golden Rice as the main ingredient contain beta-carotene, which can stimulate insulin production in the body by boosting the beta pancreas and decreasing the glycemic index [11]. However, the reduction in glycemic index needs to be supported by the biomolecular environment as an effort to prevent DFUs. The suitable herbal ingredient for combination in these cookies is *Piper crocatum (P. crocatum*). The oral consumption of *P. crocatum*, belonging to the Piperaceae family, has been proven safe among the population in Indonesia [12].

The use of *P. crocatum* has been documented to exhibit numerous therapeutic activities, such as anti-inflammatory effects. It has shown to reduce the expression of tumor necrosis factor alpha, nitric oxide, and interleukin-1β in a liver injury model using rats [13]. In addition, *P. crocatum* also exhibits wound healing activities by increasing the expression of superoxide dismutase 1, alpha-smooth muscle actin, and E-cadherin, and reducing p53 in hyperglycemic fibroblasts [14]. It has antibacterial properties when used topically [15]. *P. crocatum* acts as an antioxidant by reducing the expression of ROS and increasing glutathione peroxidase and cytochrome P450 2E1 [16]. It also demonstrates antihyperglycemic effects when administered orally [17].

Based on relevant studies on *P. crocatum* and its various mechanisms, *P. crocatum* can be used as a base ingredient for cookie-based therapies for the prevention of DFU. If the reduction of MMP-9 is recognized as a beneficial therapeutic target for DFU treatment [18], MMP-9 would also be a favorable target for DFU prevention. This is because the activity and expression of vascular MMP-9 in patients with diabetes mellitus are inherently elevated [19]. Furthermore, the gelatinase MMP-9 plays a crucial role in the pathogenesis of diabetic neuropathy through axonal demyelination, which is one of the risk factors for DFU [6]. Therefore, this study aims to identify the effectiveness of *P. crocatum* cookies with Golden Rice as the

main ingredient for preventing DFUs through the regulation mechanism of MMP-9.

Methods

Study Design

This randomized controlled trial will be conducted at a public health center in Makassar, Indonesia, following a 2-arm, parallel-group, randomized, double-blind, placebo-controlled design. The study protocol was developed in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 checklist (Multimedia Appendix 1). Figure 1 shows the flowchart detailing participant enrollment, allocation, intervention, and assessment, and Table 1 presents the participant timeline.

Figure 1. The CONSORT (Consolidated Standards of Reporting Trials) flowchart for participant recruitment and progress through a randomized controlled trial investigating the efficacy of Golden Rice cookies with Piper crocatum (*P. crocatum*) active extract in preventing foot ulcers among patients with diabetes at a public health center in Makassar, Indonesia, from November to December 2023.

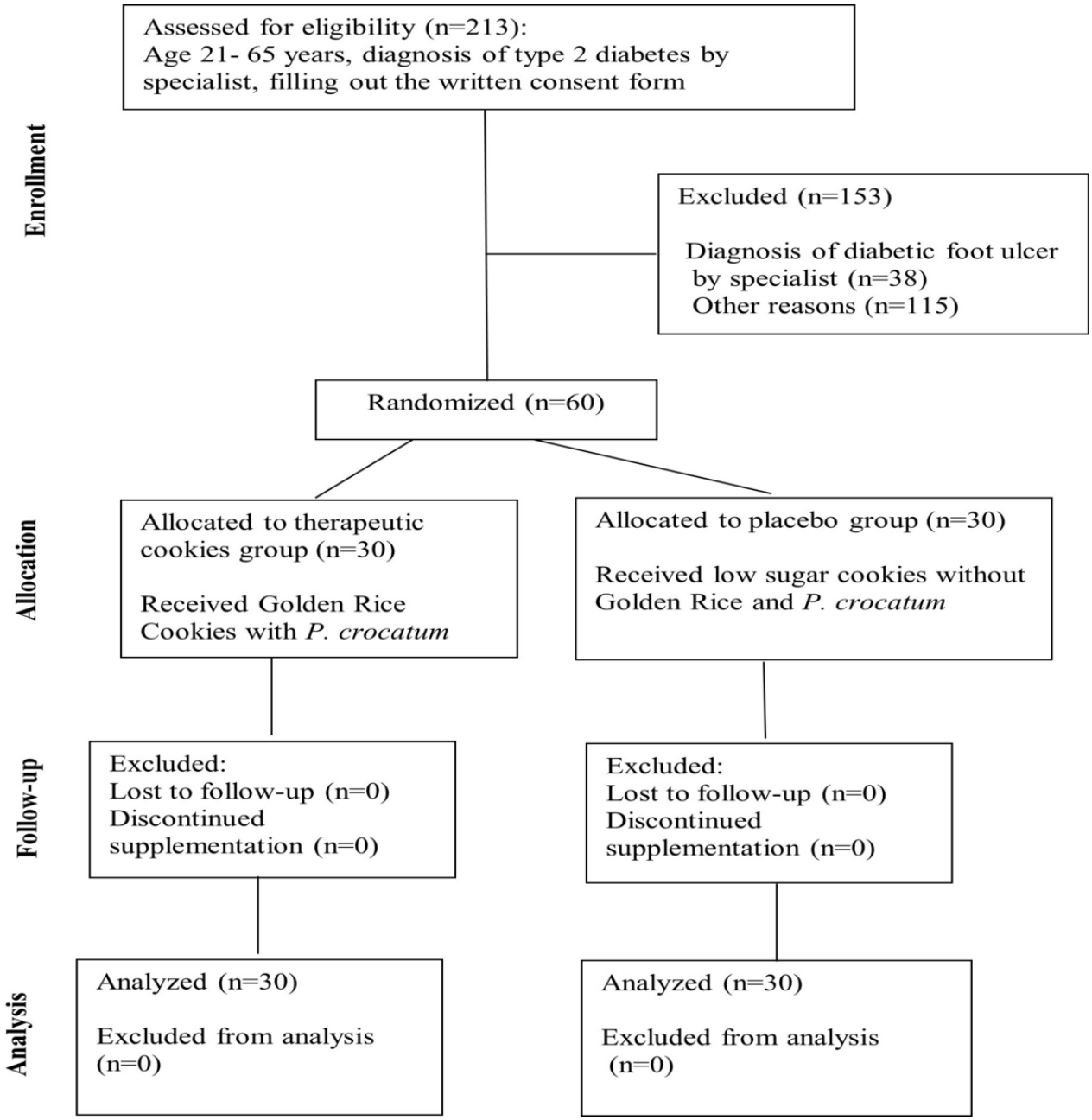


Table 1. Participant timeline in a randomized controlled trial investigating the efficacy of Golden Rice cookies with Piper crocatum active extract in preventing foot ulcers among patients with diabetes at a public health center in Makassar, Indonesia, from November to December 2023.

Activities	Enrollment	Allocation	Postallocation		Close-out
	Week 1	Week 2	Week 3	Week 4	Week 5
Enrollment					
Eligibility screening	✓				
Informed consent	✓				
Randomization		✓			
Allocation		✓			
Patients training		✓			
Intervention					
Supplementation			✓	✓	
Compliance			✓	✓	
Adverse events			✓	✓	
Assessment					
Demographics		✓			✓
Clinical information		✓			✓
Neuropathy score		✓			✓
Ankle-brachial index		✓			✓
Random blood glucose		✓			✓
Supplement checklist					✓

Outcomes

The main focus of this study, or the primary outcome, is determining the level of MMP-9. The secondary outcomes include examining neuropathy scores and ankle-brachial index (ABI) as well as assessing random blood glucose.

Randomization and Blinding

After obtaining informed consent and discussing the research objectives, a total of 60 eligible participants will be divided into 2 equal groups. Block randomization with a 1:1 allocation ratio will be used. An assistant will conduct the block randomization, ensuring that both the investigators and participants remain blinded to the intervention allocation. The sequence of the blocks will be generated using a random numbers table. All participants will be randomly assigned to either the intervention group or the placebo group. The manufacturer responsible for preparing the supplements will be requested to label the cans containing either therapeutic cookies or placebos with a unique code.

Sample Size Calculation

With a significance level (type 1 error) of 5% and a statistical power of 90%, the sample size for each study group will be calculated to be 25, using a 2-sided *t* test, taking into account the changes in MMP-9 values as one of the primary outcomes [20]. We will clarify that the block lengths in our randomization process will be constant. To account for an estimated attrition rate of approximately 20% during the study, the final sample size will be increased to 30 participants in each group. The estimation of the sample size is calculated using the following formula:

In this formula, α=5%, 1-β=90%, SD1=2.7, SD2=2.7, *d*=2.5.

Cookies Production

Cookies will be created by following the formula provided by Olawoye et al [21], with some modifications. They will be made with a low glucose ingredient composition, resulting in each cookie containing 51 calories, with a composition of 1% carbohydrates, 6% fat, 4% cholesterol, and 4% fiber, free from gluten, sugar, and salt. Following the optimal conditions for producing gluten-free cookies for patients with diabetes, the cookies are baked at a temperature of 158°C for 20 minutes. The procedure is modified by incorporating 20% Golden Rice extract and 10% *P. crocatum* ethanol extract. Each extract will be prepared using the maceration method with 96% ethanol, and its yield will be calculated. The specific details of the *P. crocatum* extraction procedure are mentioned in a previous study [14].

Intervention

A total of 60 eligible participants diagnosed with type 2 diabetes will be assigned randomly to either the therapeutic cookies group (n=30) or the placebo group (n=30). Over 14 weeks, participants in the intervention group will take therapeutic cookies (20 g) twice daily, while participants in the control group will take identical placebo cookies. The therapeutic cookies will be provided by Evelyn Food Supplement company,

chosen for their reputation for providing high-quality, standardized ingredients, which is essential for the integrity of the study. Both therapeutic and placebo cookies will be indistinguishable in terms of weight, size, shape, taste, color, and odor. The placebo cookies are also produced by Evelyn Food Supplement company. The choice of company was made to maintain the highest research standards and to ensure that there are no conflicts of interest, financial support, or other compensation for the researchers.

The trial will consist of 3 study visits: before the intervention, 1 week after the intervention, and at the end of the intervention period. Study participants will receive instructions on how to use their supplements and will be followed up with phone calls every 3 days throughout the study. Compliance will be assessed by evaluating the number of unused supplements returned by each individual, with the remaining cookies counted to determine total supplement intake. Additionally, participants will be asked to maintain a reporting diary to document any adverse events experienced following the consumption of therapeutic cookies. If any adverse events are attributed to the consumption of therapeutic cookies, participants will be instructed to discontinue taking the supplements and will be promptly referred to a specialist for appropriate treatment. The study participants will not receive any specific dietary recommendations or dietary regimens.

Blood Sample Collection

Blood samples for the identification of MMP-9 will be collected from each participant at a specific time point in the morning, following an overnight fast. The samples will be drawn at approximately 8 AM to ensure consistency and minimize potential variations in MMP-9 levels due to diurnal rhythms. This fasting state collection will aim to provide a baseline measurement of MMP-9 levels. Additionally, blood samples will be collected both before and after the intervention involving the administration of cookies to assess potential changes in MMP-9 levels in response to the intervention.

Measures and Measurements

Demographic Questions

Participants will be requested to provide information about their gender, age, marital status, the medication and herbs currently being consumed, profession, educational level, distance from the place of residence to the nearest health care service, residence in a city or rural area, duration of having diabetes, and any other diseases or illnesses experienced.

Primary Outcome

A blood sample of 5 mL will be collected, and the samples will be centrifuged at 3000 rpm for 5 minutes to separate the serum samples before and after the intervention. The levels of MMP-9 will be determined using western blotting in triplicate. Proteins will be extracted using M-PER Mammalian Protein Extraction Reagent (Thermo; catalog number 87785) according to the manufacturer's instructions. Protein quantification will be performed using Pierce 660 nm protein assay reagent (Thermo; catalog number 22660). The proteins will be separated on a 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis and transferred to a polyvinylidene fluoride membrane (Immun-Blot, Bio-Rad). Then, the membrane will be incubated with specific primary antibodies, including anti–MMP-9 (catalog number EP1254; anti-rabbit; 1:500 dilution) and anti–β-actin (catalog number ab8227; anti-rabbit; 1:1000 dilution). Blocking will be performed using 5% skim milk in Tris-Buffered Saline with Tween 20, followed by incubation with the appropriate secondary antibody. The protein bands will be visualized using enhanced chemiluminescence Prime Western Blotting Detection Reagents (GE Health Care; catalog number RPN2232), and the blots will be captured using a Gel Doc machine (Geldoc Syngene Gbox Seri Chemi xrq) [22].

Secondary Outcomes

The secondary outcomes include examining neuropathy score, ABI, and random blood glucose. The neuropathy score will be assessed following a previous study [23], using a 10-g Semmes-Weinstein Monofilament. During the monofilament testing, the participants will be instructed to lie flat on the examination table. To ensure that they could not see their feet, a standard monofilament (5.07/10-gram Semmes-Weinstein nylon monofilament) will be used to lightly apply pressure to three specific areas of the participants' feet: (1) the underside of the first metatarsal head, (2) the underside of the fifth metatarsal head, and (3) the top surface between the first and second metatarsals. The monofilament will be positioned on the foot's surface, forming a perpendicular angle with the skin. The pressure will be gradually intensified until the filament is bent, indicating the application of a predetermined level of pressure. The sites will be examined in a random order, rather than following a specific sequence. If the examinee provided the correct response at any site during the test, further testing at that site was not necessary. However, if the examinee could not correctly identify the interval in which the stimulus was applied, the test would be repeated at that site up to 2 times, aiming to obtain 2 similar correct responses. A site will be considered sensate if either the first response is correct or 2 out of 3 tests yield a correct response. On the other hand, a site will be classified as insensate if there are 2 incorrect responses and 2 "unable to determine" responses or 1 incorrect response and 1 "unable to determine" response. The presence of an insensate area at any of the 3 sites indicates a positive result for peripheral neuropathy in the monofilament test [24,25].

The ABI will be determined by measuring the systolic blood pressure in the arm and leg after a 10-minute rest in a supine position, with both arms and legs straight and relaxed [26]. Manual cuffs will be used for all blood pressure measurements, and the appropriate cuff size will be selected based on the arm circumference determined during screening. The same cuff size will be used for the lower leg, and a straight wrapping technique will be employed. The arm blood pressure will be measured using a sphygmomanometer along with an 8 MHz Doppler device to detect pulses. A single measurement will be taken at each of the 6 sites in the following sequence: left arm, left ankle (dorsalis pedis and posterior tibialis), right arm, and right ankle. The right ABI will be calculated by dividing the higher-pressure measurement from the right ankle (dorsalis pedis or posterior tibialis) by the higher brachial pressure (right or left side). The left ABI will be calculated using a similar method. The lower

ratio from either side will be considered as the participant's ABI [27].

To evaluate the random blood glucose levels, blood samples will be obtained from the capillary of the index finger for each patient. Subsequently, the Accu-Chek Active glucometer, a device manufactured in Germany, will be used to measure the samples, and the recorded values will be documented [28].

Statistical Analyses

The demographic characteristics of all participants will be summarized using descriptive statistics, such as means (SDs), frequencies, and ranges, which will be presented in a tabular form. Statistical analysis of the data will be performed using the SPSS statistical software (version 2, SPSS Inc). $P<.05$ will be considered statistically significant. The normality of the data will be assessed using the Kolmogorov-Smirnov test. Numerical variables will be presented as mean (SD) or median (IQR) values, while categorical variables will be presented as frequency (percentages). To determine differences in numerical variables between the therapeutic cookies and placebo groups, independent sample *t* tests or Mann-Whitney *U* tests will be used. The same tests will also be used to compare alterations in outcome variables between the 2 groups. For within-group comparisons, paired-sample *t* tests or the nonparametric Wilcoxon test will be used. To account for the effects of confounding factors, a general linear model will be applied. In addition, analysis of covariance will be used to account for the effects of confounding factors when appropriate.

Ethical Considerations

Prior to the commencement of this study, ethical review and approval were obtained from the local ethical committee of the Public Health Faculty of Universitas Hasanuddin, Makassar, Indonesia (approval number 10973/UN4.14.1/TP.01.02/2023). This study adheres to all applicable ethical guidelines and regulations governing research involving human subjects.

Informed consent was obtained orally from all participants involved in the primary and data collection. In the case of secondary analyses of research data, the original informed consent, as approved by the institutional review board, explicitly allowed for secondary analyses without the need for additional consent. Participants were informed that their data would be used for research purposes beyond the initial study.

The privacy and confidentiality of participants in this research were rigorously protected. All data collected were anonymized or deidentified to ensure the confidentiality of participants. Any personal identifying information was removed, and data were stored securely to prevent unauthorized access.

Participants received compensation in the form of monetary compensation for their time and participation. The compensation amount was set at IDR 100,000/week (US $7-8/week) and was disclosed to participants during the informed consent process.

The study has been registered on the Thai Clinical Trials Registry website (TCTR20230502001). Any changes to the study protocol will be communicated to the Trials journal.

Results

The recruitment and testing phase started in January 2024. The study is scheduled to be completed by the end of March 2024. Data analysis will commence in April 2024, and the publication of the results is anticipated in the same year (2024).

Discussion

Expected Outcomes

This study focuses on the significant issue of DFUs in patients with diabetes and the importance of preventing DFUs and associated amputations. DFUs affect approximately 6.4% of the global diabetic population [29], reduce quality of life, prolong hospital stays, and lead to a considerable number of lower limb amputations globally each year [30]. Notably, peripheral neuropathy, the most prevalent type of diabetic neuropathy, plays a critical role in the development of DFUs due to its impact on sensory function and increased susceptibility to ulcers [31].

In the realm of diabetic neuropathy, MMP-9 is considered crucial in its progression and holds a potential target for treatment purposes [32]. Furthermore, it is important to acknowledge that elevated blood sugar levels and insulin resistance in diabetes contribute to the generation of ROS, intensifying the complications associated with the disease [33]. The activity of MMP-9 is heightened in individuals with diabetes, partially due to increased production by vascular endothelial cells and the influence of ROS [33].

MMP-9 plays a role in increasing tissue inflammation, which is one of the contributing factors to diabetic neuropathy [32]. By reducing MMP-9 activity, we can decrease inflammation that harms peripheral nerves. MMP-9 can damage blood vessel walls, leading to impaired blood circulation to nerves [34]. Reducing vascular damage can enhance blood flow to nerves, aiding in the prevention of neuropathy. Additionally, MMP-9 can harm the extracellular matrix surrounding nerve cells. If MMP-9 is reduced, the extracellular matrix may be better preserved, offering improved protection against nerve damage. Excessive MMP-9 activity has been linked to apoptosis or nerve cell death [35]. By reducing MMP-9 activity, we can help safeguard nerve cells from death, which contributes to neuropathy. Furthermore, MMP-9 can contribute to nerve degeneration and loss of nerve function. Lowering MMP-9 can assist in slowing down or halting this degenerative process [36].

The main interest of this study is the concept of diabetic-friendly cookies, which can stimulate insulin production in the body by boosting the beta pancreas and decreasing the glycemic index through the mechanism of MMP-9 reduction. To further support the reduction in glycemic index and prevent DFU, the suitable herbal ingredients for combination in these cookies are Golden Rice and *P. crocatum*. They are known for their safety and therapeutic activities, such as anti-inflammatory effects, wound healing activities, antibacterial properties, antioxidant effects, and antihyperglycemic effects. The oral consumption of *P. crocatum* and Golden Rice extracts has been proven to be safe in humans. A functional beverage containing *P. crocatum* was

developed, demonstrating significant antioxidant and antidiabetic properties, and it was acceptable by consumers [37]. A recent study has also identified the use of *P. crocatum* as a healthy food and drink option for reducing blood sugar levels in patients with diabetes mellitus [38].

The reduction of MMP-9 as the study objective may not be sufficient to completely prevent diabetic neuropathy, as this disease is highly complex and involves numerous factors. However, reducing MMP-9 can be a potentially helpful step in mitigating the risk and impact of diabetic neuropathy, particularly when combined with other appropriate treatment approaches.

This study explores the biological mechanisms underlying diabetic neuropathy and the potential role of MMP-9, providing valuable insights into the pathophysiology of DFUs and potential therapeutic targets. The safety and acceptance of *P. crocatum* and Golden Rice extracts in humans, as demonstrated in previous studies, support the feasibility of incorporating these ingredients into dietary interventions to prevent DFUs.

Although this study delves into biological mechanisms and potential therapeutic interventions, the translation of these laboratory findings into clinical applications may require further research and clinical trials. The study may have limitations regarding the generalizability of its findings. It is essential to acknowledge that dietary interventions may have varying effects on individuals with different demographics, comorbidities, and genetic factors. The study duration is also considered a limitation, as it does not cover a long-term assessment of the effects of cookies and herbal ingredients.

Conclusions

In conclusion, the findings of this study hold the potential to significantly influence the strategies used by health care practitioners in enhancing diabetes self-management, particularly in the domain of therapeutic snacking, for patients diagnosed with diabetes mellitus. Considering the substantial burden of DFUs on patients, health care systems, and society, it is crucial to focus on preventing DFUs and amputations. Exploring potential therapeutic targets like MMP-9 and using natural ingredients like *P. crocatum* in combination with other diabetes-friendly products may provide promising avenues for preventing DFUs and improving the outcomes for patients with diabetes. Further research and clinical trials would be necessary to validate the efficacy and safety of such interventions. These insights can inform the selection of strategies for health care practitioners to enhance diabetes self-management, thereby benefiting patients with diabetes mellitus.

Acknowledgments

This research was funded by the Research and Community Service Institute of Hasanuddin University. However, the institution had no role in the study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication.

The authors would like to express their gratitude to all participants for their valuable contributions.

Data Availability

The data sets generated and analyzed during this study are not publicly available due to patient confidentiality concerns but are available from the corresponding author upon reasonable request. All requests will be subject to review and approval on a case-by-case basis. We are dedicated to making the data available, where possible, while ensuring the protection of participants' confidentiality and privacy.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT Checklist.
[PDF File (Adobe PDF File), 115 KB - resprot_v13i1e49940_app1.pdf]

Multimedia Appendix 2
Consort checklist.
[PDF File (Adobe PDF File), 1194 KB - resprot_v13i1e49940_app2.pdf]

References

1. Jeffcoate WJ, Vileikyte L, Boyko EJ, Armstrong DG, Boulton AJM. Current challenges and opportunities in the prevention and management of diabetic foot ulcers. Diabetes Care 2018 Apr;41(4):645-652. [doi: 10.2337/dc17-1836] [Medline: 29559450]
2. Armstrong DG, Boulton AJM, Bus SA. Diabetic foot ulcers and their recurrence. N Engl J Med 2017 Dec 15;376(24):2367-2375. [doi: 10.1056/NEJMra1615439] [Medline: 28614678]

3. Van Netten JJ, Woodburn J, Bus SA. The future for diabetic foot ulcer prevention: a paradigm shift from stratified healthcare towards personalized medicine. Diabetes Metab Res Rev 2020 Mar 16;36 Suppl 1(S1):e3234. [doi: 10.1002/dmrr.3234] [Medline: 31944530]
4. Juster-Switlyk K, Smith AG. Updates in diabetic peripheral neuropathy. F1000Res 2016 Apr 25;5:738 [FREE Full text] [doi: 10.12688/f1000research.7898.1] [Medline: 27158461]
5. Dee T, Sukartini T, Probowati R. Factors associated with foot ulcer among diabetic patients article info. IJNHS 2020;3(3):358-363. [doi: 10.35654/ijnhs.v3i3.222]
6. Deng L, Du C, Song P. Molecular mechanisms of dietary bioactive compounds in redox balance and metabolic disorders. Oxid Med Cell Longev 2021 Jun 01:1-11 [FREE Full text]
7. Matsuoka Y, Furutani K, Lee KB, Ge X, Ji R. Inhibition of diabetic neuropathic pain by intrathecal and intravenous administration of MMP-9 monoclonal antibody in mice. J Pain 2023 Apr;24(4):46. [doi: 10.1016/j.jpain.2023.02.141]
8. Ovaditya S, Brilliantika S, Chodidjah C, Sumarawati T. View of the effect of curcuma longa on fasting blood glucose, MMP-9 and IFN-? in diabetes mellitus: an experimental study. Bali Medical Journal 2022 Dec 27;11(3):1996-2002 [FREE Full text] [doi: 10.15562/bmj.v11i3.3648]
9. Kaur S, Pandhi P, Dutta P. Painful diabetic neuropathy: an update. ANS 2011 Aug 19;18(4):1-7. [doi: 10.5214/ans.0972.7531.1118409]
10. Papachristoforou E, Lambadiari V, Maratou E, Makrilakis K. Association of glycemic indices (hyperglycemia, glucose variability, and hypoglycemia) with oxidative stress and diabetic complications. J Diabetes Res 2020 Oct 12;2020:1-17 [FREE Full text] [doi: 10.1155/2020/7489795] [Medline: 33123598]
11. Das P, Adak S, Lahiri Majumder A. Genetic manipulation for improved nutritional quality in rice. Front Genet 2020 Jul 24;11:1-19 [FREE Full text] [doi: 10.3389/fgene.2020.00776] [Medline: 32793287]
12. Li HX, Widowati W, Azis R, Yang SY, Kim YH, Li W. Chemical constituents of the Piper crocatum leaves and their chemotaxonomic significance. Biochem Syst Ecol 2019 Oct;86:103905. [doi: 10.1016/j.bse.2019.05.013]
13. Ginting CN, Lister INE, Girsang E, Widowati W, Yusepany DT, Azizah AM, et al. Hepatotoxicity prevention in Acetaminophen-induced HepG2 cells by red betel (Ruiz and Pav) extract from Indonesia via antioxidant, anti-inflammatory, and anti-necrotic. Heliyon 2021 Jan;7(1):e05620 [FREE Full text] [doi: 10.1016/j.heliyon.2020.e05620] [Medline: 33474504]
14. Setyawati A, Wahyuningsih MSH, Nugrahaningsih DAA, Effendy C, Fneish F, Fortwengel G. Saudi J Biol Sci 2021 Dec;28(12):7257-7268 [FREE Full text] [doi: 10.1016/j.sjbs.2021.08.039] [Medline: 34867030]
15. Kusuma S, Mita S, Mutiara A. Antimicrobial lotion containing red Piper betle leaf (Piper crocatum Ruiz and Pav) ethanolic extract for topical application. Natl J Physiol Pharm Pharmacol 2017:1. [doi: 10.5455/njppp.2018.8.1042115112017]
16. Fatmawaty F, Anggreni NGM, Fadhil N, Prasasty VD. Potential In vitro and in vivo antioxidant activities from Piper Crocatum and Persea Americana leaf extracts. Biomed Pharmacol J 2019 Apr 9;12(2):661-667. [doi: 10.13005/bpj/1686]
17. Saputra M, Yuniarti E, Sumarmin R. EKSAKTA. URL: https://ocs.unud.ac.id/index.php/buletinvet/article/view/8899/6693 [accessed 2022-09-08]
18. Jones JI, Nguyen TT, Peng Z, Chang M. Targeting MMP-9 in diabetic foot ulcers. Pharmaceuticals (Basel) 2019 May 22;12(2):79 [FREE Full text] [doi: 10.3390/ph12020079] [Medline: 31121851]
19. Ünal A, Baykal O, Öztürk N. Comparison of matrix metalloproteinase 9 and 14 levels in vitreous samples in diabetic and non-diabetic patients: a case control study. Int J Retina Vitreous 2022 Jun 21;8(1):44 [FREE Full text] [doi: 10.1186/s40942-022-00394-0] [Medline: 35729613]
20. Khorshidi M, Sayyari A, Olang B, Alaei MR, Shab-Bidar S, Khalili M, et al. Study protocol of a randomized controlled clinical trial investigating the effects of omega-3 supplementation on endothelial function, vascular structure, and metabolic parameters in adolescents with type 1 diabetes. Trials 2021 Dec 27;22(1):953 [FREE Full text] [doi: 10.1186/s13063-021-05930-1] [Medline: 34961564]
21. Olawoye B, Gbadamosi SO, Otemuyiwa IO, Akanbi CT. Gluten-free cookies with low glycemic index and glycemic load: optimization of the process variables via response surface methodology and artificial neural network. Heliyon 2020 Oct;6(10):e05117 [FREE Full text] [doi: 10.1016/j.heliyon.2020.e05117] [Medline: 33083603]
22. Arfian N, Setyaningsih WAW, Romi MM, Sari DCR. Heparanase upregulation from adipocyte associates with inflammation and endothelial injury in diabetic condition. BMC Proc 2019 Dec 16;13(Suppl 11):17 [FREE Full text] [doi: 10.1186/s12919-019-0181-x] [Medline: 31890010]
23. Dube S, Hulke S, Wakode S, Khadanga S, Thakare A, Bharshankar R, et al. Effectiveness of Semmes Weinstein 10 gm monofilament in diabetic peripheral neuropathy taking nerve conduction and autonomic function study as reference tests. J Family Med Prim Care 2022 Oct;11(10):6204-6208 [FREE Full text] [doi: 10.4103/jfmpc.jfmpc_195_22] [Medline: 36618173]
24. Paz C, Dioquino C, Antoinette M. Usefulness of monofilament testing for detecting peripheral neuropathy I. Acta Med Philipp 2009 Jun 01;43(3):4-8 [FREE Full text]
25. McIllhatton A, Lanting S, Lambkin D, Leigh L, Casey S, Chuter V. Reliability of recommended non-invasive chairside screening tests for diabetes-related peripheral neuropathy: a systematic review with meta-analyses. BMJ Open Diabetes Res Care 2021 Dec 24;9(2):e002528 [FREE Full text] [doi: 10.1136/bmjdrc-2021-002528] [Medline: 34952841]

26. Dewi EM, Ramadhan G, Parlindungan R, Iryani L, Yuwono T. Measurement of ankle brachial index with oscillometric method for early detection of peripheral artery disease. JRE 2022 Jul 30;18(2):80-85 [FREE Full text] [doi: 10.17529/jre.v18i2.25758]
27. Setyawati A, Sangkala MS, Malasari S, Jafar N, Sjattar EL, Syahrul S, et al. Virgin coconut oil: a dietary intervention for dyslipidaemia in patients with diabetes mellitus. Nutrients 2023 Jan 21;15(3):564 [FREE Full text] [doi: 10.3390/nu15030564] [Medline: 36771272]
28. Katz LB, Stewart L, Guthrie B, Cameron H. Patient satisfaction with a new, high accuracy blood glucose meter that provides personalized guidance, insight, and encouragement. J Diabetes Sci Technol 2020 Mar 02;14(2):318-323 [FREE Full text] [doi: 10.1177/1932296819867396] [Medline: 31375031]
29. Zhang P, Lu J, Jing Y, Tang S, Zhu D, Bi Y. Global epidemiology of diabetic foot ulceration: a systematic review and meta-analysis. Ann Med 2017 Mar 03;49(2):106-116. [doi: 10.1080/07853890.2016.1231932] [Medline: 27585063]
30. Bekele F, Kelifa F, Sefera B. A males foot is being shot by an ulcer, not a gunshot! the magnitude and associated factors of diabetic foot ulcer among diabetes mellitus patients on chronic care follow-up of southwestern Ethiopian hospital: A cross-sectional study. Ann Med Surg (Lond) 2022 Jul;79:104003. [doi: 10.1016/j.amsu.2022.104003] [Medline: 35860152]
31. Volmer-Thole M, Lobmann R. Neuropathy and diabetic foot syndrome. Int J Mol Sci 2016 Jun 10;17(6):917 [FREE Full text] [doi: 10.3390/ijms17060917] [Medline: 27294922]
32. Deng X, Ma P, Wu M, Liao H, Song X. Role of matrix metalloproteinases in myelin abnormalities and mechanical allodynia in rodents with diabetic neuropathy. Aging and disease 2021;12(7):1808. [doi: 10.14336/ad.2021.0126]
33. Oguntibeju O. Type 2 diabetes mellitus, oxidative stress and inflammationxamining the links. Int J Physiol Pathophysiol Pharmaco 2019;11(3):45-63 [FREE Full text] [Medline: 31333808]
34. Cabral-Pacheco GA, Garza-Veloz I, Castruita-De la Rosa C, Ramirez-Acuña JM, Perez-Romero BA, Guerrero-Rodriguez JF, et al. The roles of matrix metalloproteinases and their inhibitors in human diseases. Int J Mol Sci 2020 Dec 20;21(24):9739 [FREE Full text] [doi: 10.3390/ijms21249739] [Medline: 33419373]
35. Hamdi T, Lelo A. What is the function of Matrix Metalloproteinase-2 and Matrix Metalloproteinase-9 in pain processes? J Med Soc 2022 Dec 21;2(2):1-5 [FREE Full text] [doi: 10.1007/springerreference_39046]
36. Behl T, Kaur G, Sehgal A, Bhardwaj S, Singh S, Buhas C, et al. Multifaceted role of matrix metalloproteinases in neurodegenerative diseases: pathophysiological and therapeutic perspectives. Int J Mol Sci 2021 Jan 30;22(3):1413 [FREE Full text] [doi: 10.3390/ijms22031413] [Medline: 33573368]
37. Safithri M, Kurniawati A, Suminto S. Formula of Piper crocatum, Cinnamomum burmanii, Zingiber officinale extracts as a functional beverage for diabetics. Int Food Res J 2016:1123-1130 [FREE Full text]
38. Sakinah N, Sasilia N, Amanda Z, Abdina K. Utilization of red betel leaf(piper crocatum) as healthy food and drink to reduce blood sugar level in diabetes mellitus patients. Researchgate. 2018 May 01. URL: http://tinyurl.com/mryeynnn [accessed 2024-01-18]

Abbreviations

ABI: ankle-brachial index
DFU: diabetic foot ulcer
MMP-9: matrix metalloproteinase-9
***Piper crocatum*:** *P. crocatum*
ROS: reactive oxygen species
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

Edited by A Mavragani; submitted 15.06.23; peer-reviewed by S Sadler, C Portugal; comments to author 22.09.23; revised version received 15.10.23; accepted 01.11.23; published 29.02.24.

Please cite as:
Setyawati A, Saleh A, Tahir T, Yusuf S, Syahrul S, Aminuddin A, Raihan M, Jafar N, Hamzah H, Arfian N
Matrix Metalloproteinase-9 Testing of Golden Rice Cookies With Piper Crocatum Active Extract for Preventing Foot Ulcers in Patients With Diabetes: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2024;13:e49940
URL: https://www.researchprotocols.org/2024/1/e49940
doi:10.2196/49940
PMID:38422498

Protocol

Improving Health Professional Recognition and Response to Child Maltreatment and Intimate Partner Violence: Protocol for Two Mixed Methods Pilot Randomized Controlled Trials

Melissa Kimber[1,2], BA/BSW, MSW, PhD; Elizabeth Baker-Sullivan[1], HBSc; Donna E Stewart[3,4], CM, MD; Meredith Vanstone[5], PhD

[1]Offord Centre for Child Studies, Department of Psychiatry & Behavioural Neurosciences, McMaster University, Hamilton, ON, Canada

[2]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada

[3]Department of Psychiatry, University of Toronto, Toronto, ON, Canada

[4]Centre for Mental Health, University Health Network, Toronto, ON, Canada

[5]Department of Family Medicine, McMaster University, Hamilton, ON, Canada

Corresponding Author:
Melissa Kimber, BA/BSW, MSW, PhD
Offord Centre for Child Studies
Department of Psychiatry & Behavioural Neurosciences
McMaster University
WHC 120
1280 Main Street West
Hamilton, ON, L8S 4K1
Canada
Phone: 1 905 525 9140 ext 27220
Email: kimberms@mcmaster.ca

Abstract

Background: The optimal educational approach for preparing health professionals with the knowledge and skills to effectively recognize and respond to family violence, including child maltreatment and intimate partner violence, remains unclear. The Violence, Evidence, Guidance, and Action (VEGA) Family Violence Education Resources is a novel intervention that can be completed via self-directed learning or in a workshop format; both approaches focus on improving health professional preparedness to address family violence.

Objective: Our studies aim to determine the acceptability and feasibility of conducting a randomized controlled trial to evaluate the effectiveness of the self-directed (experimental intervention) and workshop (active control) modalities of VEGA, as an adjunct to standard education, to improve learner (*Researching the Impact of Service provider Education [RISE] with Residents*) and independent practice (*RISE with Veterans*) health professional preparedness, knowledge, and skills related to recognizing family violence in their health care encounters.

Methods: The *RISE with Residents* and *RISE with Veterans* research studies use embedded experimental mixed methods research designs. The quantitative strand for each study follows the principles of a pilot randomized controlled trial. For *RISE with Residents*, we aimed to recruit 80 postgraduate medical trainees; for *RISE with Veterans*, we intended to recruit 80 health professionals who work or have worked with Veterans (or their family members) of the Canadian military or the Royal Canadian Mounted Police in a direct service capacity. Participants complete quantitative assessments at baseline, after intervention, and at 3-month follow-up. A subset of participants from each arm also undergoes a qualitative semistructured interview with the aim of describing participants' perceptions of the value and impact of each VEGA modality, as well as research burden. Scores on potential outcome measures will be mapped to excerpts of qualitative data via a mixed methods joint display to aid in the interpretation of findings.

Results: We consented 71 individuals to participate in the *RISE with Residents* study. Data collection was completed on August 31, 2023, and data are currently being cleaned and prepared for analysis. As of January 15, 2024, we consented 34 individuals in the *RISE with Veterans* study; data collection will be completed in March 2024. For both studies, no data analysis had taken place at the time of manuscript submission. Results will be disseminated through peer-reviewed publications; academic conferences; and posting and sharing of study summaries and infographics on social media, the project website, and via professional network listserves.

Conclusions: Reducing the impacts of family violence remains a pressing public health challenge. Both research studies will provide a valuable methodological contribution about the feasibility of trial methods in health professions education focused on family violence. They will also contribute to education science about the differences in the effectiveness of self-directed versus facilitator-led learning strategies.

Trial Registration: ClinicalTrials.gov NCT05490121, https://clinicaltrials.gov/study/NCT05490121; ClinicalTrials.gov NCT05490004, https://clinicaltrials.gov/study/NCT05490004

International Registered Report Identifier (IRRID): DERR1-10.2196/50864

(JMIR Res Protoc 2024;13:e50864) doi:10.2196/50864

KEYWORDS

medical education; health professions education; child maltreatment; intimate partner violence; mixed methods; pilot trial; qualitative description; family violence

Introduction

Background

The prevention of family violence, which includes intimate partner violence (IPV) and child maltreatment, remains a global public health priority. IPV encompasses a range of behaviors by a current or former romantic or sexual partner that causes or can cause physical, psychological, or sexual harm, including physical assault or violence, sexual coercion or assault, threats of harm, stalking or surveillance, and verbal degradation or humiliation [1]. Child maltreatment refers to adverse caregiver or parent behavior, including physical, sexual, or emotional abuse; physical or emotional neglect; coercive control; and exposure to IPV between adult caregivers, which result in actual or potential physical or emotional harm to the child. Globally, up to 1 in 3 children are exposed to at least 1 form of maltreatment before the age of 18 years [2-4]. Similarly, 27% of ever-partnered women between the ages of 15 and 29 years will experience IPV in their lifetime, with 24% of women aged 15-19 years and 26% of women aged 19-24 years having experienced IPV before the age of 15 years [5]. The literature details a significant and positive association between exposure to child maltreatment and increased vulnerability to IPV victimization over the life course [6,7]. In addition, a fulsome and consistent body of evidence demonstrates that exposure to child maltreatment or IPV is associated with a range of health-risk behaviors and negative health outcomes, including significantly elevated risk for early-onset smoking and alcohol use, teen pregnancy, underimmunization, obesity, heart disease, chronic pain conditions, substance abuse, suicide attempts, posttraumatic stress disorder, eating disorders, depression, anxiety, among others [1,8-10]. Importantly, the prevalence of child maltreatment and IPV in families of Active Duty and Veteran service members is even higher. For example, nearly 63% of Active Duty and Veteran members of the Canadian Armed Forces (CAF) report exposure to maltreatment in childhood [11], and upward of 25% of Active Duty or Veteran members of the CAF (or whose partner is a member or a Veteran of the CAF) self-report IPV victimization or perpetration in their lifetime [12-14]. Among this subgroup of the population, a history of child maltreatment or IPV exposure is also associated with a range of physical and mental health disorders, which can be exacerbated by deployment-related traumatic experiences, including military sexual trauma; receipt of incoming artillery, rocket, or mortar fire; or knowing someone seriously injured or killed while deployed [11,15].

Critically, a growing compilation of clinical guidance and guidelines indicates that the probability for negative health outcomes related to family violence exposure, including child maltreatment and IPV, can be attenuated via early interaction with a health care professional that is considerate and who prioritizes not only physical and emotional safety in the health care encounter but also the broader social, psychological, and physical health needs of an exposed patient [4,16-20]. For this reason, health professionals have been identified as having an essential role in family violence prevention via recognizing and responding to this exposure and its associated sequelae in their health care practice. Unfortunately, several studies detail uniform challenges to family violence recognition and response across the health professions, including limited formal curriculum during preservice training, discomfort and a lack of confidence related to asking about and responding to family violence disclosures, and the perception that there is insufficient time to adequately address family violence disclosures in health care practice [21]. Paralleling these barriers is a dearth of evidence regarding how to best prepare health professionals with the knowledge and skills to effectively recognize and respond to suspected or disclosed family violence exposures in health care contexts [21,22]. It is also unclear whether family violence education efforts should be optimally targeted to preservice versus in-service health professionals, nor is it clear the extent to which repeated exposure to family violence curriculum is necessary to achieve and maintain professional competencies in this area.

Broadly, educational interventions focusing on family violence, which have been evaluated in undergraduate, postgraduate, and continuing education contexts, vary in their instructional approaches and often fail to consider active controls in their research designs [22-27]. In addition, there has been limited emphasis on developing and evaluating interventions that address the complex overlap between IPV, children's exposure to IPV, and other forms of child maltreatment [28,29]. Given the prevalence, overlap, and health-related burdens of child maltreatment, IPV, and children's exposure to IPV, there is an urgent need to identify empirically supported educational interventions that adequately prepare the health professionals to care for individuals and families impacted by all forms of family violence. Additionally, the field of health professions

education stands to benefit from research studies that provide evidence for the optimal educational approach (eg, self-directed learning vs facilitator-based approaches) to improve health professionals' knowledge and skills in complex areas, such as family violence. This methodological contribution can also offer guidance on whether the optimal educational approach varies according to the health professional's status as a learner or an independent practitioner.

Aims

The objective of our 2 complementary studies are to determine the acceptability and feasibility of conducting a randomized controlled trial (RCT) to evaluate the effectiveness of the self-directed (experimental intervention) and workshop (active control) modalities of the Violence, Evidence, Guidance, and Action (VEGA) Family Violence Education Resources [30], as an adjunct to standard education, to improve learner (*Researching the Impact of Service provider Education [RISE] with Residents*) and independent practice (*RISE with Veterans*) health professional preparedness, knowledge, and skills related to recognizing family violence in their health care encounters. Detailed information about the VEGA Family Violence Education Resources (hereafter referred to as "VEGA") is available on the web [31] and in the *Methods* section. Briefly, VEGA was developed based on systematic reviews and consultations with members of 22 national health care and social service organizations in Canada [30]. VEGA is a web-based suite of resources that uses a participatory, encounter-focused curriculum across 4 learning modules that focus on the following areas of family violence: (1) the epidemiology of child maltreatment, IPV, and children's exposure to IPV in Canada; (2) evidence-informed strategies for safely recognizing and responding to (a) child maltreatment and (b) IPV (including children's exposure to IPV) in health care encounters; and (3) principles for ensuring physical and emotionally safe health care encounters for family violence discussions [30]. VEGA can be completed as a self-directed educational activity (ie, self-directed VEGA) via completion of the web-based modules at the learner's own pace, or as a remote or face-to-face workshop (ie, workshop VEGA). VEGA workshops are delivered by trained facilitators who are also regulated and practicing health care professionals; both self-directed VEGA and workshop VEGA take approximately 3 hours to complete [21,30].

Methods

Study Design

The *RISE with Residents* and *RISE with Veterans* research studies use quantitatively dominant, embedded experimental mixed methods research design ("QUAN(qual)") [32]. The use of this design allows for the measurement of important acceptability and feasibility metrics related to enrollment, retention, attrition, and data completeness and the generation of exploratory estimates of the education effect for both VEGA modalities. This design also allows for the systematic collection of qualitative data to provide important contextual information regarding the tenability of a full RCT, as well as a description of how VEGA modalities influence any measured changes in health professional preparedness, knowledge, and skills related to recognizing and responding to family violence. Given the cost and complexity of implementing RCTs, as well as well-documented challenges related to recruiting and retaining health professionals in clinical and education research [33-35], pilot randomized studies that allow for responsive amendments to recruitment, retention, and data collection are an imperative proviso to reduce the possibility of failed or incomplete phase-3 RCTs [36-38].

Quantitative Strand of Data Collection

Quantitative Design and Participants

The quantitative research design for both studies follows the principles of a 2-armed pilot RCT [37,38]. Figures 1 and 2 detail the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) flow diagrams for *RISE with Residents* and *RISE with Veterans*, respectively [39,40]. For *RISE with Residents*, we aimed to recruit a voluntary sample of 80 participants from postgraduate medical residency programs in psychiatry or pediatrics in Ontario, Canada. Directors of each program were asked to circulate recruitment-related materials to their respective program residents, requesting that interested individuals contact the research team to determine eligibility and complete consenting procedures. For *RISE with Veterans*, we aimed to recruit a voluntary sample of 80 health professionals who currently work or have worked in a direct service capacity with Veterans of the Canadian military or the Royal Canadian Mounted Police (RCMP), or their family members, to participate. Directors of Veteran-serving programs, agencies, and organizations had the opportunity to meet with members of the research team to discuss the components of the study and were asked to distribute recruitment materials to potentially eligible staff. Recruitment materials requested that those who were interested in participating contact the research team.

Figure 1. RISE with Residents SPIRIT flow diagram. RISE: Researching the Impact of Service provider Education; SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials; VEGA: Violence, Evidence, Guidance, and Action.

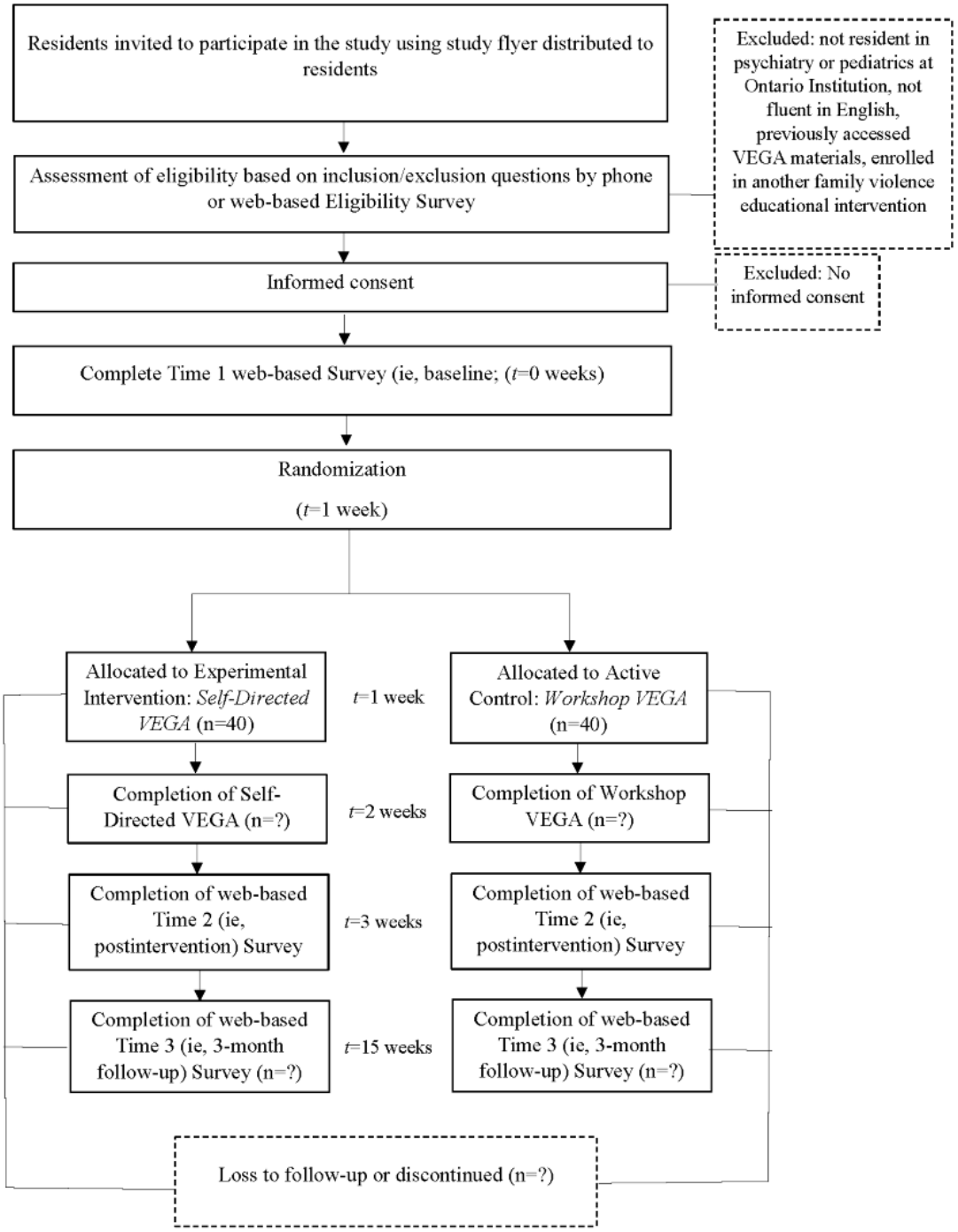
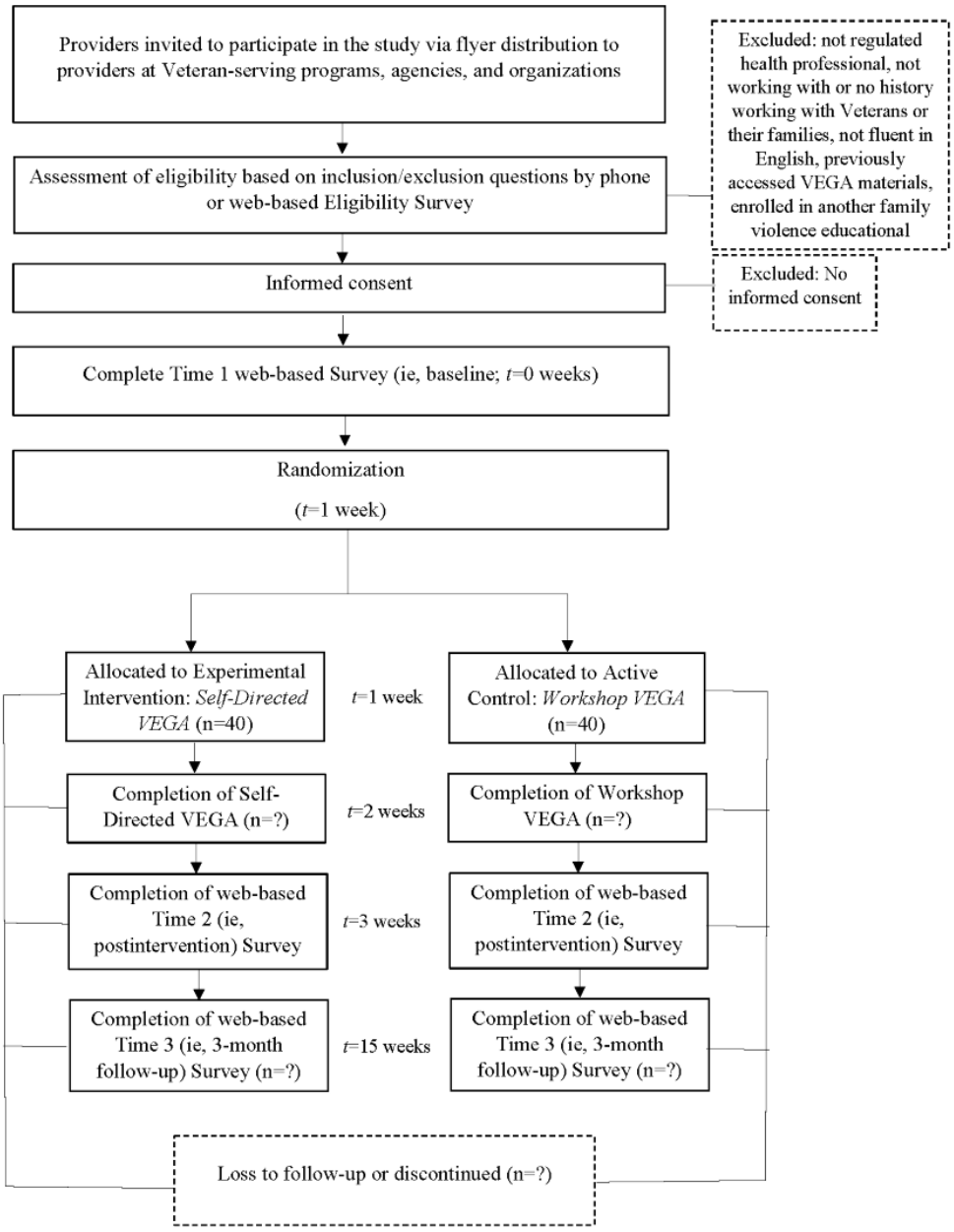


Figure 2. RISE with Veterans SPIRIT flow diagram. RISE: Researching the Impact of Service provider Education; SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials; VEGA: Violence, Evidence, Guidance, Action.



Eligibility Criteria

Eligibility screening was completed over the phone with the study research coordinator (RC) or electronically via REDCap (Research Electronic Data Capture; Vanderbilt University) using the eligibility criteria outlined in Textbox 1. At this time, we also collected sociodemographic characteristics of participants, including age, sex at birth, and self-identified gender. For *RISE with Residents*, we also included information about their residency program; *RISE with Veterans* additionally asked questions about the organization the participants work for, whether they work directly with Veterans of the military or the RCMP, or their family members, and if the latter, whether consent is required by the Veteran for the participant to provide services to the Veteran's family member. We obtained consent from potential participants to keep their responses to the screening measures in cases they were ineligible or did not end up participating in the study. This was for the purpose of comparing those who end up participating with those who do not end up participating to understand if our criteria are systematically excluding any groups. After completing screening, individuals were informed of their eligibility to participate and underwent an electronic informed consent process to participate in the remainder of research activities. Potential participants were provided the option to speak with a member of the research team to review any questions about the consent procedures and research process.

Textbox 1. Eligibility criteria.

Inclusion criteria

- *Researching the Impact of Service provider Education (RISE) with Residents*
  - Physician resident enrolled in a postgraduate medical residency program in psychiatry or pediatrics within Ontario, Canada
  - Willing and able to provide informed written consent and complete all project activities in English
- *RISE with Veterans*
  - 18 years of age or older
  - Regulated health care or social service professional
  - Working with military or Royal Canadian Mounted Police (RCMP) Veterans, or military or RCMP Veteran's family members in a direct service capacity at least 1 day per week

    OR

    Have 2 years of experience working with military or RCMP Veterans, or their family members, in a direct service capacity

    OR

    Have worked with 15 or more clients or patients who were either military or RCMP Veterans, or their family members, in a direct service capacity
  - Willing and able to provide informed written consent and complete all project activities in English

Exclusion criteria

- *RISE with Residents*
  - Have previously accessed the Violence, Evidence, Guidance, and Action (VEGA) web-based or workshop materials
  - Are currently enrolled in or expected to enroll in any other educational intervention focused on family violence (intimate partner violence [IPV], child maltreatment, childhood exposure to IPV) within the study time period
- *RISE with Veterans*
  - Have previously accessed the VEGA materials
  - Are currently enrolled in or expected to enroll in any other educational intervention focused on family violence (IPV, child maltreatment, or childhood exposure to IPV) within the study time period

Randomization and Concealment

Randomization occurred after consent has been obtained and the web-based baseline survey (ie, time 1 survey, see below) is complete. To reduce the possibility of "availability bias," we required the accumulation of 20 consenting participants who indicated their availability to attend a VEGA workshop before randomization, as each VEGA workshop requires a minimum of 10 participants. The cohort of 20 consenting participants were then randomly assigned to the experimental (ie, self-directed VEGA) or active control (ie, workshop VEGA) condition using stratified block randomization [41] with a block size of 4 (blocking factor of 2), using a third-party, internet-based randomization service, Randomize.net. For *RISE with Residents*, randomization was stratified based on two variables: (1) sex at birth (female, male, intersex, or prefer not to answer) and (2) discipline (pediatrics vs psychiatry). For *RISE with Veterans*, randomization was stratified based on sex at birth only. Sex at birth, as opposed to gender identity, was selected as the stratification variable because of a limited number of categories needed to achieve balance across trial arms. The analysis section outlines our proposed approach to disaggregate sex- and gender-based data after the conclusion of both studies.

Masking

Given the nature of experimental and control arms, it is impossible to conceal allocation status from participants, as well as the facilitators of the active control arm (ie, workshop VEGA). Participants were informed of their allocation status by the RC. The RC did not reveal participant allocation status to the study research assistant, the latter of whom was responsible for ensuring quantitative data collection. Participants were also encouraged not to inform the research assistant of their allocation status.

Intervention

VEGA Family Violence Education Resources

Time for completion of self-directed VEGA or workshop VEGA is approximately 3 hours, and pedagogical elements for both approaches have been informed by education scholarship (see Table 1) [42-51]. Participants had or have the option of completing self-directed VEGA in either English or French as the VEGA website offers the content in both languages. Workshop VEGA is delivered in English only in a remote or in-person workshop format by trained facilitators who are regulated health professionals. VEGA workshops are

recommended to have a 10:1 participant-to-facilitator ratio and are standardized via the use of a flexibly structured facilitator guide [30].

Table 1. Pedagogical elements of self-directed VEGA (ie, experimental arm) and workshop VEGA (ie, active control arm) educational approaches.

Pedagogical elements	Self-directed VEGA[a] (experimental arm)	Workshop VEGA (active control arm)
Didactic material [48]	Asynchronous reading	Synchronous lecturing with 2 facilitators
Deliberate practice [49,50]	Case-based animated simulations	Case-based role play
Enabling learning tools [51]	Remote patients, clinical handbook, clinical scripts	Remote patients, clinical handbook, clinical scripts
Test-enhanced learning [46]	Individual multiple-choice questions with response feedback	Group-based polling (ie, multiple-choice) and feedback

[a]VEGA: Violence, Evidence, Guidance, and Action.

Experimental Arm (Self-Directed VEGA)

If a participant is randomized to the experimental arm, they will be or were asked to complete self-directed VEGA at their convenience, within 1 week of being informed of their allocation status. To complete the intervention, individuals are asked to register their access to the VEGA Resources and review and complete all module activities at their own pace during the weeklong intervention period [30].

Active Control Arm (Workshop VEGA)

If a participant is randomized to the active control arm, they will be or were informed that they need to attend a remote VEGA workshop. Because of COVID-19 restrictions in place at the outset of both studies, VEGA workshops take place via Zoom and are delivered by 2 trained facilitators. Workshops include 10 to 20 participants, keeping the recommended 10:1 participant-to-facilitator ratio, and last 3 hours [30].

Intervention Adherence

Intervention adherence is monitored by the RC. The RC has received or will receive attendance reports for participants allocated to VEGA workshops from the VEGA project team, who will also provide the research team confirmation of whether self-directed participants completed the “Self-Declaration of Module Completion Form” embedded within the self-directed VEGA website. Self-directed VEGA participants receive email reminders from the RC every 2 days to complete the modules within the intervention window [30].

Data Collection

The primary outcomes for the *RISE with Residents* and *RISE with Veterans* research studies are related to the acceptability and feasibility of RCT implementation. To this end, the RC tracked or is tracking the number of individuals for each study who (1) agreed to be screened, (2) are eligible for participation, and (3) enroll. We are also recording the number of (4) emails or phone calls needed to arrange all research assessments and the number of participants who (5) drop out, (6) could not be reached for follow-up, (7) complete the interventions, and (8) partially complete versus fully complete secondary outcome research assessments. As an indicator of feasibility, we are also recording the total time to complete all secondary outcome research assessments and track the number of protocol amendments (if any) and their rationale. Acceptability and feasibility metrics will be matrixed alongside sociodemographic characteristics (sex at birth, gender, age, etc) of screened and consented participants.

Table 2 details the list the measures that are being used to assess the secondary (ie, education-related) outcomes and their correlates in the *RISE with Residents* and *RISE with Veterans* research projects and their respective overlap. The research assistant is administering research assessments of family violence knowledge and skills via REDCap to participants in both studies at 3 time points: the week before they begin their VEGA intervention (time 1), posteducation (ie, postintervention; time 2), and 3 months after the time 1 survey is completed (time 3). Participants are being asked to complete the surveys within 1 week, from the date they are initially sent, on their own time. Each assessment takes approximately 30 minutes to complete.

Table 2. Quantitative research assessments for *RISE with Residents* and *RISE with Veterans*.

Measure	*RISE*[a] *with Residents*			*RISE with Veterans*		
	Baseline	Postedu-cation	3-month follow-up	Baseline	Postedu-cation	3-month follow-up
Adapted Brief Individual Readiness to Change Scale (BIRCS) [52]: The original BIRCS was developed by Goldman [52] to assess health professional readiness to learn and implement new evidence-based practices in the field of addictions; respondents were asked to indicate on a 5-point Likert scale the extent to which they disagreed (0=strongly disagree) or agreed (4=strongly agree) with 5 statements about their use of "direct service techniques that are based on research" (eg, I believe I have the skills to use them; I believe I have the flexibility to use them). For the purposes of our research, we adapted the items to be specific to child maltreatment, added 2 items (eg, "I believe I have the knowledge to recognize and respond to all forms of child maltreatment in my practice"; "I am motivated to learn about child maltreatment"), and replicated the set of items for intimate partner violence (IPV) (ie, BIRCS—Child Maltreatment; BIRCS—IPV). After reverse scoring 1 item, the mean score of the responses for each scale is used to interpret the results, with a higher mean score indicative of a greater readiness to make practice changes related to child maltreatment or IPV.	✓	—[b]	—	✓	—	—
Adapted Child Maltreatment Vignette Scale (CMVS) [53,54]: For the original CMVS, respondents are prompted to review 14 distinct analog vignettes that depict a range of signs and symptoms of child maltreatment exposure. On completing their review of each vignette, participants are asked to indicate their responses to four items: (1) "is this child being maltreated" (yes/no); (2) "please indicate how confident you are in your response (50%-100%, your answer must be between 50% and 100%)"; (3) "would you report this case to children's services?" (yes/no); and (4) "please indicate how confident you are in your response (50%-100%, your answer must be between 50% and 100%)." With permission from the original authors, the measure was adapted to the Canadian context via removing 1 scenario from the measure (due to concerns about multiple maltreated children), amending physician-focused language to "health professional" and changing (1) for each vignette to "for any child/youth in this scenario, do you have a reason to suspect child maltreatment?" (yes/no) and changing (3) for each vignette to "would you report this case to Child Welfare Services?" (yes/no). Adaptations were made in consultation with clinical experts in child maltreatment impact assessment at a tertiary care center in Ontario, Canada. Responses to (1) and (3) for each vignette will be scored as either correct ("1") or incorrect ("0") as predetermined, a priori; a mean "knowledge and skill accuracy" score is generated for analysis, with higher scores indicative of greater knowledge and skill accuracy related to child maltreatment.	✓	✓	✓	✓	✓	✓
Mandatory Reporting Self-Efficacy Scale (MRSES) [55]: The MRSES is a 7-item measure that asks respondents to indicate the extent to which they perceive their ability to implement a series of behaviors related to mandatory reporting of child maltreatment. Response options for each item are anchored on a scale from 0 to a 100, with statements at 0, 50, and 100 indicating "cannot do at all (0)," "moderately can do (50)," and "highly certain can do (100)." A total score is generated by summing items across the scale for each participant, with higher scores indicative of greater self-efficacy related to recognizing and reporting suspected child maltreatment.	✓	✓	✓	✓	✓	✓

Measure	*RISE*[a] *with Residents*			*RISE with Veterans*		
	Baseline	Postedu-cation	3-month follow-up	Baseline	Postedu-cation	3-month follow-up
Adapted Preparedness Subscale of the Physician Readiness to Manage Intimate Partner Violence Survey (PREMIS) [56,57]: The PREMIS is a 67-item self-report tool that was developed to assess physician management of IPV across 10 subscales. The Preparedness Subscale asks respondents to indicate the extent to which they feel prepared to address various aspects of IPV recognition and response when working with their clients across 11 items; these aspects include the conduct of safety assessments, asking appropriate questions about IPV, responding to IPV disclosures, among others. Response options are on a 7-point Likert scale ranging from "not prepared" (1) to "quite well prepared" (7), and items are averaged to generate a mean score for practitioner preparedness, with higher scores indicative of generally greater preparedness to recognize and respond to IPV. Preparedness items were adapted to focus on child maltreatment, allowing our team to determine participant preparedness to recognize and respond to both IPV and child maltreatment in their practice encounters.	✓	—	✓	✓	✓	✓
Adapted Knowledge Subscale of the Physician Readiness to Manage Intimate Partner Violence Survey (PREMIS) [56,57]: The knowledge subscale of the PREMIS assesses the accuracy of participants actual knowledge about IPV against a set of multiple-choice, matching, and true-or-false questions capturing information about IPV signs and symptoms and risk factors that are informed by the current literature. A total score of correct items is used to represent actual IPV knowledge, with higher scores indicative of greater knowledge.	—[b]	—	—	✓	✓	✓
Adapted Opinions and Self-Efficacy Subscale of the Physician Readiness to Manage Intimate Partner Violence Survey (PREMIS) [56,57]. The opinions (24 items) and self-efficacy (3 items) subscale of the PREMIS assesses participants' agreement with statements capturing thoughts and beliefs related to recognizing and managing IPV in clinical practice. Response options are on a 7-point Likert scale ranging from "strongly disagree" (1) to "strongly agree" (7); items are averaged to generate a mean score for opinions and self-efficacy, with higher scores indicative of generally positive opinions and self-efficacy to recognize and manage IPV in practice. Developed in the United States, the original scale contained an item related to state-specific reporting of "IPV, elder abuse, and child abuse"; this item was removed for our studies to reduce redundancy with other measures and to reduce measurement burden. Self-efficacy items were asked at all time points in the study, with opinions items asked at baseline and 3-month follow-up.	—	—	—	✓	✓[c]	✓
Thoughts and Beliefs about Role Responsibility to Recognize and Respond to Family Violence (TBR-FV) [21]. The TBR-FV is a measure created by our research team that captures participants' perceived professional responsibility related to recognizing and responding to IPV and child maltreatment in their health professional encounters. The generation of this measure was informed by a mixed methods program of research evaluating health professions education in family violence [21].	✓	—	—	✓	—	—
Healthcare Provider Attitudes toward Child Maltreatment Reporting Scale (HPA-CMRS) [58,59]: The HPA-CMRS is a 26-item psychometrically validated scale that asks respondents to indicate the extent to which they agree with statements that capture attitudes and beliefs regarding the reporting of child maltreatment to child protective services. Items are rated on a 5-point Likert scale ranging from "0" (strongly disagree) to "4" (strongly agree) and summed to produce a total score, with higher total scores indicative of more positive attitudes and beliefs toward the reporting of child maltreatment.	✓	—	✓	—	—	—
Adapted Version of the Achievement Goals for Work Domain (AGWD) [60,61]: The AGWD is a 23-item, psychometrically validated measure of work-related achievement goals that map onto the 4 goal orientations described by Achievement Goal Theory. Respondents are asked to indicate their agreement with 22 statements that follow the stem of "In residency, my goal is..." Response options range from "1" (strongly disagree) to "7" (strongly agree), and responses are summed to generate a total score for each subscale corresponding to each type of goal orientation; higher scores are more indicative of the respondent's affinity to that goal orientation.	✓	—	—	—	—	—

Measure	*RISE*[a] *with Residents*			*RISE with Veterans*		
	Baseline	Posteducation	3-month follow-up	Baseline	Posteducation	3-month follow-up
Sociodemographics (current age, sex at birth, current gender identity, race, child maltreatment training history, IPV training history, etc)	✓	—	—	✓	—	—

[a]RISE: Researching the Impact of Service provider Education.

[b]Not applicable.

[c]Only the self-efficacy items will be administered at this time point.

Sample Size

A sample size of 80 participants (40 per arm) for each study was selected based on the recommendations of Whitehead et al [62] and Norman et al [63]. Based on these guidelines, a sample of 40 participants randomly allocated to each intervention arm would provide, at minimum, 80% power to detect a moderate (0.5 SD to 0.6 SD) effect size, which is indicative of a clinically significant change. In following this algorithm, our team will be able to consider the needed recruitment and retention rates to successfully implement a definitive education trial.

Qualitative Strand of Data Collection

Qualitative Design and Participants

The qualitative portion of both studies is guided by the principles of qualitative description, which is a flexible yet rigorous approach to conducting qualitative health research that has clinical and practical relevance [64]. Qualitative description is being used to expand and extend what we learn about acceptability and feasibility of implementing the experimental and active control interventions and associated research activities, as well as capture the perceived value and impact of VEGA's educational modalities, using the language of participants. Given that the qualitative data will complement the quantitative strand of data collection, we used purposive criterion sampling [65] to select a subsample of the participants from the active control and experimental arms of each study (n=60; 15 per arm, per study) to participate in a one-on-one semistructured interview with an unmasked member of the research team. For *RISE with Residents*, recruitment of qualitative participants is stratified by resident discipline and residency year, whereas for *RISE with Veterans*, qualitative recruitment is stratified by participants' sex at birth (male vs female).

Data Collection

Individual semistructured interviews take place after intervention completion. Interviews are up to 60 minutes in length and conducted via Zoom using the audio function only (or by phone, if the participant prefers). Interviews are being audio-recorded and transcribed verbatim to ensure data integrity. A semistructured interview guide of 5 to 7 key questions and probes is used to guide interview experiences. Field notes completed by the interviewer document interview observations that may be relevant to analysis.

Quantitative and Qualitative Data Analysis and Integration

On the completion of data cleaning, descriptive statistics (means, SDs, relevant quantiles, and proportions) will be used to compare VEGA modalities with respect to measures taken at baseline to ensure that groups do not significantly differ on sociodemographic characteristics [66]. The proportion of participants who met eligibility requirements, who enrolled, who were lost to follow-up, and who completed all quantitative secondary outcome assessments will be calculated. Assuming a normal distribution, standardized effect estimates for each of our educational outcomes in the form of Cohen *d* will be calculated for postintervention and 3-month follow-up time points. These data will be analyzed using intention-to-treat analysis. Depending on acceptability and feasibility outcomes, sample size calculations for a proposed RCT will be generated using the effect size and variance estimates from the posteducation change data for the selected outcome measures. Although forced-choice frameworks in REDCap reduce the proportion of missing data at the item level, missing follow-up data will be addressed using imputation procedures, where appropriate [67].

Transcripts of qualitative interviews, as well as associated field notes, are being exported into and managed in NVivo (Lumivero). On completion of both studies, transcripts will be analyzed using reflexive thematic analysis [68] and the constant comparison technique, which will allow for the identification codes, categories, and themes related to implementing and evaluating both VEGA modalities among health professionals in a postgraduate training (ie, learner) and independent practice setting. After conducting separate quantitative and qualitative analyses, quantitative and qualitative data will be integrated for interpretation via a mixed methods joint display [69]. Quantitative acceptability and feasibility metrics will be mapped to excerpts of qualitative data on perceived acceptability or educational burden; this joint display will support a comprehensive interpretation of the extent to which definitive trials examining VEGA in our sample populations are tenable. A separate joint display will cross-tabulate scores on secondary outcome measures with qualitative excerpts of VEGA's perceived value and impact for improving health professional knowledge and skills in family violence.

Ethical Considerations, Protocol Deviations and Amendments

Risks associated with the *RISE with Residents* and *RISE with Veterans* studies are minimal. All de-identified data are being stored on a secure server at McMaster University, as approved

by the Hamilton Integrated Research Ethics Board (HiREB). Any identifying data will be destroyed on completion of both studies. Only the research team has access to study-related data; anyone outside of the research team who wishes to analyze the data can request to do so via formal secondary data analysis approval procedures administered via the HiREB. Anticipated adverse events that are relevant to this study include those related to participant safety and well-being and include (1) participants' own experiences with IPV or child maltreatment, which may raise or contribute to distress during the educational intervention or during research activities, and (2) participants' experiences with providing care to patients who have experienced IPV or child maltreatment, which may be distressing. Anticipated adverse events that are not serious are discussed, as needed by research staff, with the principal investigator if the nature of the adverse event is considered to signal unresolved risk to the participant. VEGA workshop facilitators are regulated health professionals with significant training and expertise in distress protocols. As per our protocols, emergency medical services are alerted as required if there is concern about imminent risk to life of an adult or safety of a child. The principal investigator, who is a registered social worker and psychotherapist, continues to follow regulated reporting requirements as necessary and determine whether other steps are needed to mitigate any risks to participants. Given that the purposes of both studies are to determine acceptability and feasibility of RCT implementation, a detailed accounting of any adverse events, research protocol deviations, and amendments continues to be tracked and documented by the RC, in collaboration with the principal investigator. Given the emphasis of both studies on the acceptability and feasibility of proposed RCT procedures, a data monitoring committee has not been established; however, findings from the present studies will inform the development of a data monitoring committee should results indicate that pursuit of a full RCT is acceptable and feasible.

Ethics Review

The *RISE with Residents* and *RISE with Veterans* research projects have been approved for human research by the HiREB, affiliated with McMaster University in Ontario, Canada. The associated project approvals are HiREB #14381 (*RISE with Residents*) and HiREB #14243 (*RISE with Veterans*), respectively. All research procedures will be performed in accordance with the relevant guidelines and regulations of the HiREB and Tri Council Policy Statement on the Ethical Conduct for Research Involving Humans. In both studies, informed consent for study participation is obtained from all participants.

Results

Study Timeline

The *RISE with Residents* and *RISE with Veterans* studies were registered and posted to ClinicalTrials.gov on August 5, 2022. As of January 15, 2024, we consented 71 individuals to participate in the *RISE with Residents* study and data are currently being cleaned and prepared for analysis. A total of 6 amendments were submitted to the HiREB throughout the duration of the *RISE with Residents* data collection period; no adverse events were reported by research participants. For the *RISE with Veterans* study, as of January 15, 2024, we have consented 34 individuals to participate in the study and data collection will be completed in March 2024. At the time of writing (January 2024), 7 amendments were submitted to the HiREB and no adverse events have been reported by research participants.

Dissemination Plan

In addition to the open-access publication of our research protocol, our team has identified several strategies that will accelerate the translation of our findings into education guidelines, practice, and scholarship. First, we will publish study findings for both the *RISE with Residents* and *RISE with Veterans* studies in open-access, peer-reviewed journals according to reporting guidelines for mixed methods [70], pilot trial [71], and education studies [72]. Second, end-of-grant knowledge translation will involve the preparation of 1-page infographics and curriculum recommendations for project funders at the Royal College of Physicians and Surgeons of Canada, the Atlas Institute for Veterans and their Families, and our network of health professions associations; representatives from each association generously disseminate our knowledge translation products via posts to their website, social media channels, and listserve platforms. Finally, we will present our findings at national and international conferences focused on health professions education and education scholarship.

Discussion

Key Findings

The *RISE with Residents* and *RISE with Veterans* research studies aim to determine the acceptability and feasibility of conducting an RCT to evaluate the effectiveness of the self-directed (experimental intervention) and workshop (active control) modalities of the VEGA Family Violence Education Resources [30], as an adjunct to standard education, to improve learner (*RISE with Residents*) and independent practice (*RISE with Veterans*) health professional preparedness, knowledge, and skills related to recognizing family violence in their health care encounters. We compare these 2 educational modalities for 2 key reasons. First, evidence indicates that self-directed education may be as effective as traditional education methods for improving knowledge and skills among health professionals, especially when self-directed methods incorporate active learning strategies [73,74]. Given that VEGA is a free, online, and brief intervention, determining the extent to which self-directed education yields improved preparedness, knowledge, and skills among learner and independently practicing health professionals, as an adjunct to formal curriculum, could (1) widely (and rapidly) shift the preparation of Canadian health professionals to effectively recognize and respond to family violence without requiring formal curricular changes and (2) meaningfully contribute to our understanding about effective postgraduate and continuing education strategies, which has education implications beyond family violence and the VEGA intervention.

Second, the comparison of educational modalities in our respective studies minimizes the variability that could not be

accounted for if VEGA were compared with a non-VEGA control; this includes variability related to intervention content and emphasis, student enthusiasm, among others. RCTs in education scholarship have been controversial because they typically average too many variables to yield any real insights [75,76]. This is particularly true when an intervention is compared with a passive control or an active control that is focused on a separate subject. By keeping the content standard, varying only the educational modality, and placing emphasis on evaluating the acceptability and feasibility of an RCT, both studies address each of these important issues [77-79].

Strengths and Limitations

A particular strength of the *RISE with Residents* and *RISE with Veterans* research studies lies in their emphasis on postgraduate and continuing education contexts. It is possible that family violence education may be especially impactful in the postgraduate training period given the need to (1) understand that children, youths, and adults can present with signs and symptoms of all types of family violence in every health professional subspecialty and (2) demonstrate competencies related to the scope of one's professional responsibilities (eg, mandatory reporting) and the purview of one's clinical practice, including when and how to make appropriate treatment referrals to prevent or reduce mental or physical health impairment. To this end, the results of the *RISE with Residents* and *RISE with Veterans* studies provide a valuable methodological contribution about the feasibility and acceptability of trial methods in postgraduate and continuing education focused on family violence in the Canadian context; it will also contribute new knowledge to education science about the differences between the effectiveness of self-directed versus facilitator-led learning strategies at different stages of the learning trajectory, more broadly.

The limitations of the *RISE with Residents* and *RISE with Veterans* research studies are influenced by the scope of the available literature on effective interventions for preventing family violence and mitigating associated harms, more generally. For example, it is important to note that IPV occurs in all countries, cultures, religions, and socioeconomic groups in the world. However, generally speaking, IPV is a gendered phenomenon; cisgender and transgender women and girls are disproportionately affected by IPV. Yet, increasing evidence indicates that IPV may be perpetrated by men toward women and by women toward men and occur in same-sex, gender, and sexually diverse relationships [10]. IPV may materialize in marital relationships, common-law relationships, cohabitation, or any intimate relationship including dating and casual sexual relationships across the age spectrum [10]. Yet, most epidemiological and intervention data related to IPV and its prevention have been collected in the context of cisgender, heterosexual adult relationships; thus, the information contained in VEGA is largely informed by that lens. Similarly, information regarding evidence-based approaches, practices, and programs for individuals who use violence (ie, perpetrators of IPV or child maltreatment) is limited. This limitation is also reflected in the evidence reviews and available guidance for working with perpetrators contained within the VEGA education modalities [10,80-82]. Finally, and methodologically, our quantitative measures rely on learner and independent practitioner self-report, which can be prone to bias. However, our selected measures have undergone psychometric scrutiny and heavily rely on a behavioral intention framework, which is consistent with the concept of self-efficacy (ie, beliefs about capabilities)—a construct with moderate-to-strong associations with provider behavior change [83,84].

Conclusions

We expect that the *RISE with Residents* and *RISE with Veterans* research studies will provide critical evidence related to the acceptability and tenability of evaluating VEGA in postgraduate and continuing education settings. Both studies will also provide foundational estimates of intervention impact among 2 distinct populations. To this end, the findings have broader implications for the possibility of improving the preparation of health professionals to be able to recognize and respond to family violence in their care encounters safely and effectively. The generated effect estimates will serve as benchmarks for replication and, more specifically, the design of adequately powered and methodologically robust evaluations of the VEGA and other family-violence focused educational interventions over the long term.

Acknowledgments

For *RISE with Residents* and *RISE with Veterans*, a Letter of Permission from McMaster University was provided to evaluate the Violence, Evidence, Guidance, Action (VEGA) Family Violence Education Resources. We acknowledge the support of Dr Harriet MacMillan, who is the lead of the VEGA Project, to undertake this work and appreciate Dr MacMillan acting as the VEGA Advisor for the *RISE with Residents* and *RISE with Veterans* research projects. We would also like to acknowledge the input of Fardous Hosseiny, MaryAnn Notarianni, Ashlee Mulligan, and Catherine Virelli of the Atlas Institute for Veterans and Families on the *RISE with Veterans* recruitment procedures. *RISE with Residents* is funded by a 2021 Medical Education Research Grant from the Royal College of Physicians and Surgeons of Canada (award reference number: 21/MERG-05). *RISE with Veterans* is funded by the Atlas Institute for Veterans and Families (formerly the Centre for Excellence for PTSD and Related Mental Health Conditions; agreement number: 2021-0630). The views expressed in this paper do not necessarily represent the views of the Royal College of Physicians and Surgeons of Canada, nor the Atlas Institute for Veterans and Families. The Royal College of Physicians and Surgeons of Canada and the Atlas Institute for Veterans and Families were not involved in the design of these studies, nor were they involved in the writing of this manuscript.

Data Availability

To protect human privacy, data are not publicly available. Should researchers wish to complete secondary analysis of the *RISE with Residents* and *RISE with Veterans* research data, they may formally apply with a request to do so via the Hamilton Integrated Research Ethics Board (HiREB).

Authors' Contributions

MK, EBS, DES, and MV were all involved in the development of this protocol. MK drafted this manuscript. All authors were involved in the critical revision of the paper for intellectual content and its final approval before submission. All authors read and approved the final manuscript. Generative AI was not used for writing any portion of this manuscript.

Conflicts of Interest

None declared.

References

1. Stewart DE, MacMillan H, Kimber M. Recognizing and responding to intimate partner violence: an update. Can J Psychiatry 2021 Jan;66(1):71-106 [FREE Full text] [doi: 10.1177/0706743720939676] [Medline: 32777936]
2. Moody G, Cannings-John R, Hood K, Kemp A, Robling M. Establishing the international prevalence of self-reported child maltreatment: a systematic review by maltreatment type and gender. BMC Public Health 2018 Oct 10;18(1):1164 [FREE Full text] [doi: 10.1186/s12889-018-6044-y] [Medline: 30305071]
3. Stoltenborgh M, Bakermans‐Kranenburg M, Alink LRA, van IJzendoorn MH. The prevalence of child maltreatment across the globe: review of a series of meta‐analyses. Child Abuse Review 2014 Oct 20;24(1):37-50. [doi: 10.1002/car.2353]
4. World Health Organization. Responding to Child Maltreatment: A Clinical Handbook for Health Professionals. Geneva: World Health Organization; 2022.
5. Sardinha L, Maheu-Giroux M, Stöckl H, Meyer SR, García-Moreno C. Global, regional, and national prevalence estimates of physical or sexual, or both, intimate partner violence against women in 2018. Lancet 2022;399(10327):803-813 [FREE Full text] [doi: 10.1016/S0140-6736(21)02664-7] [Medline: 35182472]
6. Herrenkohl TI, Fedina L, Roberto KA, Raquet KL, Hu RX, Rousson AN, et al. Child maltreatment, youth violence, intimate partner violence, and elder mistreatment: a review and theoretical analysis of research on violence across the life course. Trauma Violence Abuse 2022;23(1):314-328 [FREE Full text] [doi: 10.1177/1524838020939119] [Medline: 32723166]
7. Karsberg S, Bramsen RH, Lasgaard M, Elklit A. The association between distinct categories of child abuse experiences and dating violence in early adolescence. J Fam Viol 2018;34(3):165-176. [doi: 10.1007/s10896-018-9979-y]
8. Teicher MH, Gordon JB, Nemeroff CB. Recognizing the importance of childhood maltreatment as a critical factor in psychiatric diagnoses, treatment, research, prevention, and education. Mol Psychiatry 2022;27(3):1331-1338 [FREE Full text] [doi: 10.1038/s41380-021-01367-9] [Medline: 34737457]
9. Vizard E, Gray J, Bentovim A. The impact of child maltreatment on the mental and physical health of child victims: a review of the evidence. BJPsych Adv 2021;28(1):60-70 [FREE Full text] [doi: 10.1192/bja.2021.10]
10. Oram S, Fisher HL, Minnis H, Seedat S, Walby S, Hegarty K, et al. The Lancet Psychiatry Commission on intimate partner violence and mental health: advancing mental health services, research, and policy. Lancet Psychiatry 2022;9(6):487-524 [FREE Full text] [doi: 10.1016/S2215-0366(22)00008-6] [Medline: 35569504]
11. Afifi TO, Sareen J, Taillieu T, Stewart-Tufescu A, Mota N, Bolton SL, et al. Association of child maltreatment and deployment-related traumatic experiences with mental disorders in active duty service members and veterans of the Canadian Armed Forces. Association de la maltraitance des enfants et des expériences traumatisantes liées au déploiement avec les troubles mentaux chez les membres du service actif et les anciens combattants des Forces Armées Canadiennes. Can J Psychiatry 2021;66(11):961-970 [FREE Full text] [doi: 10.1177/0706743720987086] [Medline: 33472392]
12. Cowlishaw S, Freijah I, Kartal D, Sbisa A, Mulligan A, Notarianni M, et al. Intimate partner violence (IPV) in military and veteran populations: a systematic review of population-based surveys and population screening studies. Int J Environ Res Public Health 2022;19(14):8853 [FREE Full text] [doi: 10.3390/ijerph19148853] [Medline: 35886702]
13. Kwan J, Sparrow K, Facer-Irwin E, Thandi G, Fear NT, MacManus D. Prevalence of intimate partner violence perpetration among military populations: a systematic review and meta-analysis. Aggress Violent Behav 2020;53:101419 [FREE Full text] [doi: 10.1016/j.avb.2020.101419] [Medline: 32714067]
14. Zamorski MA, Wiens-Kinkaid ME. Cross-sectional prevalence survey of intimate partner violence perpetration and victimization in Canadian military personnel. BMC Public Health 2013;13:1019 [FREE Full text] [doi: 10.1186/1471-2458-13-1019] [Medline: 24165440]
15. Afifi TO, Taillieu T, Zamorski MA, Turner S, Cheung K, Sareen J. Association of child abuse exposure with suicidal ideation, suicide plans, and suicide attempts in military personnel and the general population in Canada. JAMA Psychiatry 2016;73(3):229-238 [FREE Full text] [doi: 10.1001/jamapsychiatry.2015.2732] [Medline: 26817953]
16. Feder G, Wathen CN, MacMillan HL. An evidence-based response to intimate partner violence: WHO guidelines. JAMA 2013;310(5):479-480. [doi: 10.1001/jama.2013.167453] [Medline: 23925614]

17. World Health Organization. Health Care for Women Subjected to Intimate Partner Violence or Sexual Violence: A Clinical Handbook. Geneva, Switzerland: World Health Organization; 2014.
18. World Health Organization. Responding to Children and Adolescents Who Have Been Sexually Abused: WHO Clinical Guidelines. Geneva: World Health Organization; 2017.
19. World Health Organization. World Health Organization Guidelines for the Health Sector Response to Child Maltreatment. Geneva, Switzerland: World Health Organization; 2019.
20. Child maltreatment: when to suspect maltreatment in under 18s. National Institute for Health and Care Excellence (NICE). 2017. URL: https://www.nice.org.uk/guidance/cg89 [accessed 2024-03-04]
21. Kimber M, Vanstone M, Dimitropoulos G, Collin-Vézina D, Stewart D. Researching the Impact of Service provider Education (RISE) Project—a multiphase mixed methods protocol to evaluate implementation acceptability and feasibility. Pilot Feasibility Stud 2022 Jul 02;8(1):135 [FREE Full text] [doi: 10.1186/s40814-022-01096-y] [Medline: 35780156]
22. Kalra N, Hooker L, Reisenhofer S, Di Tanna GL, García-Moreno C. Training healthcare providers to respond to intimate partner violence against women. Cochrane Database Syst Rev 2021;5(5):CD012423 [FREE Full text] [doi: 10.1002/14651858.CD012423.pub2] [Medline: 34057734]
23. Turner W, Hester M, Broad J, Szilassy E, Feder G, Drinkwater J, et al. Interventions to improve the response of professionals to children exposed to domestic violence and abuse: a systematic review. Child Abuse Rev 2017;26(1):19-39 [FREE Full text] [doi: 10.1002/car.2385] [Medline: 28392674]
24. Hamberger LK. Preparing the next generation of physicians: medical school and residency-based intimate partner violence curriculum and evaluation. Trauma Violence Abuse 2007;8(2):214-225. [doi: 10.1177/1524838007301163] [Medline: 17545575]
25. Zaher E, Keogh K, Ratnapalan S. Effect of domestic violence training: systematic review of randomized controlled trials. Can Fam Physician 2014;60(7):618-624, e340 [FREE Full text] [Medline: 25022633]
26. Sawyer S, Coles J, Williams A, Williams B. A systematic review of intimate partner violence educational interventions delivered to allied health care practitioners. Med Educ 2016;50(11):1107-1121. [doi: 10.1111/medu.13108] [Medline: 27762036]
27. Divakar U, Nazeha N, Posadzki P, Jarbrink K, Bajpai R, Ho AHY, et al. Digital education of health professionals on the management of domestic violence: systematic review and meta-analysis by the Digital Health Education Collaboration. J Med Internet Res 2019;21(5):e13868 [FREE Full text] [doi: 10.2196/13868] [Medline: 31124462]
28. Chamberland C, Fallon B, Black T, Trocmé N. Emotional maltreatment in Canada: prevalence, reporting and child welfare responses (CIS2). Child Abuse Negl 2011;35(10):841-854. [doi: 10.1016/j.chiabu.2011.03.010] [Medline: 21820176]
29. Hester M. The three planet model: towards an understanding of contradictions in approaches to women and children's safety in contexts of domestic violence. Br J Soc Work 2011;41(5):837-853. [doi: 10.1093/bjsw/bcr095]
30. VEGA Family Violence Education Resources. VEGA Family Violence Project. URL: https://vegaproject.mcmaster.ca/ [accessed 2024-09-27] Used with Permission from (c) 2020 VEGA Project, McMaster University. VEGA Family Violence Education Resources
31. VEGA Family Violence Project. McMaster University. URL: https://vegaproject.mcmaster.ca/home/ [accessed 2024-02-09]
32. Creswell JW, Clark VLP. Designing and Conducting Mixed Methods Research, Third Edition. Los Angeles: SAGE; 2018.
33. Browne S, Dooley S, Geraghty A, Castro PD, Reynolds C, Perrotta C, et al. Reflections on recruiting healthcare professionals as research participants: learning from the ONSPres study. HRB Open Res 2022;5:47 [FREE Full text] [doi: 10.12688/hrbopenres.13499.1] [Medline: 36091186]
34. Brakey HR, Martinez JM, Sussman AL, McWethy MM, Martinez J, Cordova CN, et al. Use of a community engagement and research core model to enhance primary care provider recruitment: a case example. J Clin Transl Sci 2023;7(1):e11 [FREE Full text] [doi: 10.1017/cts.2022.505] [Medline: 36755529]
35. Bruneau J, Moralejo D, Donovan C, Parsons K. Recruitment of healthcare providers into research studies. Can J Nurs Res 2021;53(4):426-432. [doi: 10.1177/0844562120974911] [Medline: 33573391]
36. Sandars J, Cecilio-Fernandes D, Patel R, Gandomkar R. Avoid 'running before we can walk' in medical education research: the importance of design and development research. Med Teach 2021;43(11):1335-1336. [doi: 10.1080/0142159X.2020.1854452] [Medline: 33272071]
37. Eldridge SM, Lancaster GA, Campbell MJ, Thabane L, Hopewell S, Coleman CL, et al. Defining feasibility and pilot studies in preparation for randomised controlled trials: development of a conceptual framework. PLoS One 2016;11(3):e0150205 [FREE Full text] [doi: 10.1371/journal.pone.0150205] [Medline: 26978655]
38. Thabane L, Ma J, Chu R, Cheng J, Ismaila A, Rios LP, et al. A tutorial on pilot studies: the what, why and how. BMC Med Res Methodol 2010;10:1 [FREE Full text] [doi: 10.1186/1471-2288-10-1] [Medline: 20053272]
39. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med 2013;158(3):200-207 [FREE Full text] [doi: 10.7326/0003-4819-158-3-201302050-00583] [Medline: 23295957]
40. Chan AW, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ 2013;346:e7586 [FREE Full text] [doi: 10.1136/bmj.e7586] [Medline: 23303884]

41. Broglio K. Randomization in clinical trials: permuted blocks and stratification. JAMA 2018;319(21):2223-2224. [doi: 10.1001/jama.2018.6360] [Medline: 29872845]
42. Adams NE. Bloom's taxonomy of cognitive learning objectives. J Med Libr Assoc 2015;103(3):152-153 [FREE Full text] [doi: 10.3163/1536-5050.103.3.010] [Medline: 26213509]
43. Armson H, Elmslie T, Roder S, Wakefield J. Is the cognitive complexity of commitment-to-change statements associated with change in clinical practice? an application of Bloom's taxonomy. J Contin Educ Health Prof 2015;35(3):166-175. [doi: 10.1002/chp.21303] [Medline: 26378422]
44. Su WM, Osisek PJ. The revised Bloom's taxonomy: implications for educating nurses. J Contin Educ Nurs 2011;42(7):321-327. [doi: 10.3928/00220124-20110621-05] [Medline: 21707023]
45. Kolb AY, Kolb DA. Experiential learning theory as a guide for experiential educators in higher education. ELTHE 2022;1(1):38 [FREE Full text] [doi: 10.46787/elthe.v1i1.3362]
46. Larsen DP, Butler AC, Roediger HL. Test-enhanced learning in medical education. Med Educ 2008;42(10):959-966 [FREE Full text] [doi: 10.1111/j.1365-2923.2008.03124.x] [Medline: 18823514]
47. McLean SF. Case-based learning and its application in medical and health-care fields: a review of worldwide literature. J Med Educ Curric Dev 2016;3:JMECD.S20377 [FREE Full text] [doi: 10.4137/JMECD.S20377] [Medline: 29349306]
48. Jordan J, Jalali A, Clarke S, Dyne P, Spector T, Coates W. Asynchronous vs didactic education: it's too early to throw in the towel on tradition. BMC Med Educ 2013;13(1):105 [FREE Full text] [doi: 10.1186/1472-6920-13-105] [Medline: 23927420]
49. Ericsson KA. Deliberate practice and acquisition of expert performance: a general overview. Acad Emerg Med 2008;15(11):988-994 [FREE Full text] [doi: 10.1111/j.1553-2712.2008.00227.x] [Medline: 18778378]
50. Akl EA, Pretorius RW, Sackett K, Erdley WS, Bhoopathi PS, Alfarah Z, et al. The effect of educational games on medical students' learning outcomes: a systematic review: BEME guide no 14. Med Teach 2010;32(1):16-27. [doi: 10.3109/01421590903473969] [Medline: 20095770]
51. Consorti F, Mancuso R, Nocioni M, Piccolo A. Efficacy of virtual patients in medical education: a meta-analysis of randomized studies. Comput Educ 2012;59(3):1001-1008. [doi: 10.1016/j.compedu.2012.04.017]
52. Goldman GD. Initial validation of a Brief Individual Readiness for Change Scale (BIRCS) for use with addiction program staff practitioners. J Soc Work Pract Addict 2009;9(2):184-203. [doi: 10.1080/15332560902858596]
53. Pelletier HL. The Efficacy of Educating Medical Students on How to Identify and Report Suspected Child Maltreatment. Ann Arbor, MI: Doctoral Dissertation, University of Toledo; 2014.
54. Pelletier HL, Knox M. Incorporating child maltreatment training into medical school curricula. J Child Adolesc Trauma 2017;10(3):267-274 [FREE Full text] [doi: 10.1007/s40653-016-0096-x] [Medline: 29026450]
55. Ayling NJ. Measuring Early Childhood Educators' Self-Efficacy for Mandatory Reporting of Child Maltreatment. Masters Thesis. Queensland: Queensland University of Technology; 2019.
56. Short LM, Alpert E, Harris JM, Surprenant ZJ. A tool for measuring physician readiness to manage intimate partner violence. Am J Prev Med 2006;30(2):173-180 [FREE Full text] [doi: 10.1016/j.amepre.2005.10.009] [Medline: 16459217]
57. Connor PD, Nouer SS, Mackey STN, Tipton NG, Lloyd AK. Psychometric properties of an intimate partner violence tool for health care students. J Interpers Violence 2011;26(5):1012-1035. [doi: 10.1177/0886260510365872] [Medline: 20587479]
58. Singh S, Knox M, Pelletier H. Exploratory factor analysis and psychometric evaluation of the healthcare provider attitudes toward child maltreatment reporting scale. Child Health Care 2016;46(4):356-365. [doi: 10.1080/02739615.2016.1193807]
59. Walsh K, Rassafiani M, Mathews B, Farrell A, Butler D. Exploratory factor analysis and psychometric evaluation of the teacher reporting attitude scale for child sexual abuse. J Child Sex Abus 2012;21(5):489-506. [doi: 10.1080/10538712.2012.689423] [Medline: 22994689]
60. Baranik LE, Barron KE, Finney SJ. Measuring goal orientation in a work domain. Educ Psychol Meas 2007;67(4):697-718. [doi: 10.1177/0013164406292090]
61. Daniels L, Daniels V. Internal medicine residents' achievement goals and efficacy, emotions, and assessments. Can Med Educ J 2018;9(4):e59-e68 [FREE Full text] [Medline: 30498544]
62. Whitehead AL, Julious SA, Cooper CL, Campbell MJ. Estimating the sample size for a pilot randomised trial to minimise the overall trial sample size for the external pilot and main trial for a continuous outcome variable. Stat Methods Med Res 2016;25(3):1057-1073 [FREE Full text] [doi: 10.1177/0962280215588241] [Medline: 26092476]
63. Norman GR, Sloan JA, Wyrwich KW. The truly remarkable universality of half a standard deviation: confirmation through another look. Expert Rev Pharmacoecon Outcomes Res 2004;4(5):581-585. [doi: 10.1586/14737167.4.5.581] [Medline: 19807551]
64. Bradshaw C, Atkinson S, Doody O. Employing a qualitative description approach in health care research. Glob Qual Nurs Res 2017;4:2333393617742282 [FREE Full text] [doi: 10.1177/2333393617742282] [Medline: 29204457]
65. Luciani M, Campbell K, Tschirhart H, Ausili D, Jack SM. How to design a qualitative health research study. part 1: design and purposeful sampling considerations. Prof Inferm 2019;72(2):152-161. [Medline: 31550432]
66. Welch V, Doull M, Yoganathan M, Jull J, Boscoe M, Coen SE, et al. Reporting of sex and gender in randomized controlled trials in Canada: a cross-sectional methods study. Res Integr Peer Rev 2017;2(1):15 [FREE Full text] [doi: 10.1186/s41073-017-0039-6] [Medline: 29451565]

67. McNeish D. Missing data methods for arbitrary missingness with small samples. J Appl Stat 2016;44(1):24-39 [FREE Full text] [doi: 10.1080/02664763.2016.1158246]
68. Crowe M, Inder M, Porter R. Conducting qualitative research in mental health: thematic and content analyses. Aust N Z J Psychiatry 2015;49(7):616-623. [doi: 10.1177/0004867415582053] [Medline: 25900973]
69. Guetterman TC, Fetters MD, Creswell JW. Integrating quantitative and qualitative results in health science mixed methods research through joint displays. Ann Fam Med 2015;13(6):554-561 [FREE Full text] [doi: 10.1370/afm.1865] [Medline: 26553895]
70. O'Cathain A, Murphy E, Nicholl J. The quality of mixed methods studies in health services research. J Health Serv Res Policy 2008;13(2):92-98. [doi: 10.1258/jhsrp.2007.007074] [Medline: 18416914]
71. Thabane L, Lancaster G. A guide to the reporting of protocols of pilot and feasibility trials. Pilot Feasibility Stud 2019;5(1):37 [FREE Full text] [doi: 10.1186/s40814-019-0423-8] [Medline: 30858987]
72. Ogrinc G, Armstrong GE, Dolansky MA, Singh MK, Davies L. SQUIRE-EDU (Standards for Quality Improvement Reporting Excellence in Education): publication guidelines for educational improvement. Acad Med 2019;94(10):1461-1470 [FREE Full text] [doi: 10.1097/ACM.0000000000002750] [Medline: 30998575]
73. Murad MH, Coto-Yglesias F, Varkey P, Prokop LJ, Murad AL. The effectiveness of self-directed learning in health professions education: a systematic review. Med Educ 2010;44(11):1057-1068 [FREE Full text] [doi: 10.1111/j.1365-2923.2010.03750.x] [Medline: 20946476]
74. Harris N, Bacon CEW. Developing cognitive skills through active learning: a systematic review of health care professions. Athl Train Educ J 2019;14(2):135-148 [FREE Full text] [doi: 10.4085/1402135]
75. Norman G. RCT = results confounded and trivial: the perils of grand educational experiments. Med Educ 2003;37(7):582-584. [doi: 10.1046/j.1365-2923.2003.01586.x] [Medline: 12834412]
76. Berliner DC. Comment: educational research:the hardest science of all. Educ Res 2016;31(8):18-20. [doi: 10.3102/0013189x031008018]
77. Cook DA, Levinson AJ, Garside S, Dupras DM, Erwin PJ, Montori VM. Internet-based learning in the health professions: a meta-analysis. JAMA 2008;300(10):1181-1196. [doi: 10.1001/jama.300.10.1181] [Medline: 18780847]
78. Norman G. The end of educational science? Adv Health Sci Educ Theory Pract 2008;13(4):385-389. [doi: 10.1007/s10459-008-9139-x] [Medline: 18941917]
79. Sullivan GM. Getting off the "gold standard": randomized controlled trials and education research. J Grad Med Educ 2011;3(3):285-289 [FREE Full text] [doi: 10.4300/JGME-D-11-00147.1] [Medline: 22942950]
80. Guidance for recognizing and responding safely to intimate partner violence. VEGA Family Violence Education Resources. Hamilton, Ontario: McMaster University; 2019. URL: https://vegaeducation.mcmaster.ca/files/en/ipv/Guidance-for-Recognizing-and-Responding-Safely-to-IPV.pdf [accessed 2024-02-09]
81. Guidance for recognizing and responding safely to child maltreatment. VEGA Family Violence Education Resources. Hamilton, Ontario: McMaster University; 2019. URL: https://vegaeducation.mcmaster.ca/files/en/cm/Guidance-for-Recognizing-and-Responding-Safely-to-Child-Maltreatment.pdf [accessed 2024-02-09]
82. Guidance for recognizing and responding safely to children's exposure to intimate partner violence. VEGA Family Violence Education Resources. Hamilton, Ontario: McMaster University; 2019. URL: https://vegaeducation.mcmaster.ca/files/en/ceipv/Guidance-for-Recognizing-and-Responding-Safely-to-CEIPV.pdf [accessed 2024-02-09]
83. Eccles MP, Hrisos S, Francis J, Kaner EF, Dickinson HO, Beyer F, et al. Do self- reported intentions predict clinicians' behaviour: a systematic review. Implement Sci 2006;1(1):28 [FREE Full text] [doi: 10.1186/1748-5908-1-28] [Medline: 17118180]
84. Godin G, Bélanger-Gravel A, Eccles M, Grimshaw J. Healthcare professionals' intentions and behaviours: a systematic review of studies based on social cognitive theories. Implement Sci 2008;3(1):36 [FREE Full text] [doi: 10.1186/1748-5908-3-36] [Medline: 18631386]

Abbreviations

CAF: Canadian Armed Forces
HiREB: Hamilton Integrated Research Ethics Board
IPV: intimate partner violence
RC: research coordinator
RCMP: Royal Canadian Mounted Police
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
RISE: Researching the Impact of Service provider Education
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
VEGA: Violence, Evidence, Guidance, and Action

Edited by A Mavragani; submitted 14.07.23; peer-reviewed by A Arbabisarjou, S Etches; comments to author 20.12.23; revised version received 24.01.24; accepted 05.02.24; published 21.03.24.

Please cite as:
Kimber M, Baker-Sullivan E, Stewart DE, Vanstone M
Improving Health Professional Recognition and Response to Child Maltreatment and Intimate Partner Violence: Protocol for Two Mixed Methods Pilot Randomized Controlled Trials
JMIR Res Protoc 2024;13:e50864
URL: https://www.researchprotocols.org/2024/1/e50864
doi:10.2196/50864
PMID:38512307

Protocol

Heat and Acupuncture to Manage Osteoarthritis of the Knee (HARMOKnee): Protocol for an Effectiveness-Implementation Hybrid Randomized Controlled Trial

Bryan Yijia Tan[1], MBBS, MRCS, MMed; Chun Yue Tan[1], Dip; Tong Leng Tan[2], MMED; Su-Yin Yang[3], PhD; Gillian Long Szu Chew[1], BD; Siang Ing Tan[4], PhD; Yu Chun Chua[4], BD; Yew Wai Yan[4], BD; Derrick Bing Quan Soh[4], BD; Tong Hwee Goh[5,6], Dip; Pu Jue Ng[5,6], PhD; Yee Teck Ng[5], BD; Swee Boey Kuan[5], BD; Bo Siang Teo[5], BD; Keng He Kong[7], PhD; Michelle Jessica Pereira[8], PhD; Hui Ping Ng[5,6], BSc, MMSc

[1]Department of Orthopaedic Surgery, Woodlands Health, National Healthcare Group, Singapore, Singapore

[2]Department of Orthopaedic Surgery, Tan Tock Seng Hospital, National Healthcare Group, Singapore, Singapore

[3]Psychology Service, Woodlands Health, Singapore, Singapore

[4]Complementary Integrative Medicine, Tan Tock Seng Hospital, National Healthcare Group, Singapore, Singapore

[5]Traditional Chinese Medicine Pain Management, Medical Department, Singapore Chung Hwa Medical Institution, Singapore, Singapore

[6]Teaching Department, Singapore College of Traditional Chinese Medicine, Singapore, Singapore

[7]Rehabilitation Centre, Tan Tock Seng Hospital, National Healthcare Group, Singapore, Singapore

[8]Health Services and Outcomes Research, National Healthcare Group, Singapore, Singapore

Corresponding Author:
Bryan Yijia Tan, MBBS, MRCS, MMed
Department of Orthopaedic Surgery
Woodlands Health
National Healthcare Group
17 Woodlands Dr 17
Singapore, 737628
Singapore
Phone: 65 90057277
Email: bryan_tan@wh.com.sg

Abstract

Background: Knee osteoarthritis (KOA) is one of most prevalent and fastest-growing causes of pain, impaired mobility, and poor quality of life in the rapidly aging population worldwide. There is a lack of high-quality evidence on the efficacy of traditional Chinese medicine (TCM), particularly acupuncture, and a lack of KOA practice guidelines that are tailored to unique population demographics and tropical climates.

Objective: Our HARMOKnee (Heat and Acupuncture to Manage Osteoarthritis of the Knee) trial aims to address these gaps by evaluating the short- and medium-term clinical and cost-effectiveness of acupuncture with heat therapy in addition to standard care, compared to standard care alone. Through a robust process and economic evaluation, we aim to inform evidence-based practice for patients with KOA to facilitate the large-scale implementation of a comprehensive and holistic model of care that harmonizes elements of Western medicine and TCM. We hypothesize that acupuncture with heat therapy as an adjunct to standard care is clinically more effective than standard care alone.

Methods: A multicenter, pragmatic, parallel-arm, single-blinded, effectiveness-implementation hybrid randomized controlled trial will be conducted. We intend to recruit 100 patients with KOA randomized to either the control arm (standard care only) or intervention arm (acupuncture with heat therapy, in addition to standard care). The inclusion criteria are being a community ambulator and having primary KOA, excluding patients with secondary arthritis or previous knee replacements. The primary outcome measure is the Knee Osteoarthritis Outcome Score at 6 weeks. Secondary outcome measures include psychological, physical, quality of life, satisfaction, and global outcome measures at 6, 12, and 26 weeks. A mixed method approach through an embedded process evaluation will facilitate large-scale implementation. An economic evaluation will be performed to assess financial sustainability.

Results: Patient enrollment has been ongoing since August 2022. The recruitment process is anticipated to conclude by July 2024, and the findings will be analyzed and publicized as they are obtained. As of November 6, 2023, our patient enrollment stands at 65 individuals.

Conclusions: The findings of our HARMOKnee study will contribute substantial evidence to the current body of literature regarding the effectiveness of acupuncture treatment for KOA. Additionally, we aim to facilitate the creation of standardized national guidelines for evidence-based practice that are specifically tailored to our unique population demographics. Furthermore, we seek to promote the adoption and integration of acupuncture and heat therapy into existing treatment models.

Trial Registration: ClinicalTrials.gov NCT05507619; https://clinicaltrials.gov/study/NCT05507619

International Registered Report Identifier (IRRID): DERR1-10.2196/54352

(JMIR Res Protoc 2024;13:e54352) doi:10.2196/54352

KEYWORDS

knee osteoarthritis; acupuncture; heat therapy; effectiveness-implementation hybrid study; randomized controlled trial; RCT

Introduction

Knee osteoarthritis (KOA) is an age-related degeneration representing “wear and tear” of the knee joint, and it is one of the most prevalent and fast-growing causes of pain, impaired mobility, and poor quality of life (QOL) in the rapidly aging population worldwide [1]. The 2019 Global Burden of Disease Study reported that the knee is the joint most frequently affected by osteoarthritis, with a prevalence of approximately 365 million, followed by the hand and the hip [2].

Acupuncture is the most prevalent form of traditional medicine practice, with 183 of 202 (90.5%) surveyed countries recognizing its use, as reported by the World Federation of Acupuncture-Moxibustion Societies [3]. A bibliometric analysis reported that of 2189 positive recommendations for the use of acupuncture, about 68% were associated with 107 pain indications [4].

A review of 10 randomized controlled trials (RCTs) concluded that acupuncture is an effective treatment for KOA-related pain and physical dysfunction [5]. However, major updated clinical guidelines from the American Academy of Orthopaedic Surgeons, Joint Surgery Branch of the Chinese Orthopaedic Association, American College of Rheumatology/Arthritis Foundation, and others still consider acupuncture treatment to be insufficient, limited, conditional, or unrecommended for KOA [6]. A review highlighted the lack of evidence supporting the efficacy and cost-effectiveness of acupuncture in osteoarthritis due to poor methodological quality, significant heterogeneity, inadequate reporting of acupuncture treatment details, small sample sizes, and high placebo responses in studies [7].

The primary aim of our study is to evaluate the short- and medium-term clinical effectiveness of acupuncture, part of traditional Chinese medicine (TCM), with far-infrared heat therapy in addition to standard care, compared to standard care alone. The secondary aims include (1) performing a process evaluation to understand the context and identify mechanisms of impact that will inform large-scale implementation of the intervention and (2) performing an economic evaluation to assess the cost-effectiveness of the intervention. We hypothesize that acupuncture with heat therapy as an adjunct to standard care is clinically more effective than standard care alone.

Methods

Design

The study is an effectiveness-implementation hybrid trial, which combines effectiveness and implementation components [8,9]. This will be a type 1 hybrid trial where the emphasis and primary aim is to evaluate the effectiveness of acupuncture with far-infrared heat therapy as an adjunct to standard care through a pragmatic RCT under real-world conditions, and its secondary aim is to understand the context of implementation through a mixed-method, process-oriented approach. The pragmatic nature of the study was guided by the Pragmatic Explanatory Continuum Indicator Summary (PRECIS-2) tool [10].

The study will be conducted as a multicenter, pragmatic, parallel-arm, single-blinded RCT using a mixed method approach comparing the clinical effectiveness of acupuncture with far-infrared heat therapy as an adjunct to standard care and standard care alone. The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) [11] and the Osteoarthritis Research Society International (OARSI) clinical trial recommendation on the design and conduct of clinical trials for KOA [12] guided the development of the trial protocol. To ensure clear reporting of acupuncture treatment details, Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) reporting guidelines [13] will also be followed. The findings of the trial will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) 2010 [14] guidelines for reporting parallel-group randomized trials. The study will use an explanatory sequential mixed method design where the qualitative data from interviews will be used to interpret and provide context for the quantitative results.

Participants

We will recruit patients based on the eligibility criteria outlined in Textbox 1.

Textbox 1. Eligibility criteria.

Inclusion criteria

- National Institute of Health and Care Excellence (NICE) clinical criteria for knee osteoarthritis (KOA) [5]:
  - Being aged 45 years or older
  - Having activity-related joint pain
  - Having either no morning joint-related stiffness or morning stiffness that lasts no longer than 30 minutes
- Being a community ambulator with or without walking aid

Exclusion criteria

- Alternative diagnosis to KOA, such as referred pain from the spine or hip
- Other forms of arthritis, such as inflammatory arthritis
- Inability to comply with study protocol (eg, due to dementia)
- Previous knee arthroplasty
- Being a wheelchair user
- Medical conditions that would medically interfere with study involvement, such as decompensated heart failure, stroke, and end-stage renal failure
- Allergies to metal (needles)

Components of the Study

The Heat and Acupuncture to Manage Osteoarthritis of the Knee (HARMOKnee) study will have three components: (1) an RCT, (2) an economic evaluation, and (3) a process evaluation.

Component 1: RCT

This RCT will be administered in accordance with the STRICTA guidelines, an extension of the CONSORT statement designed to enhance the quality of clinical trials of acupuncture [13].

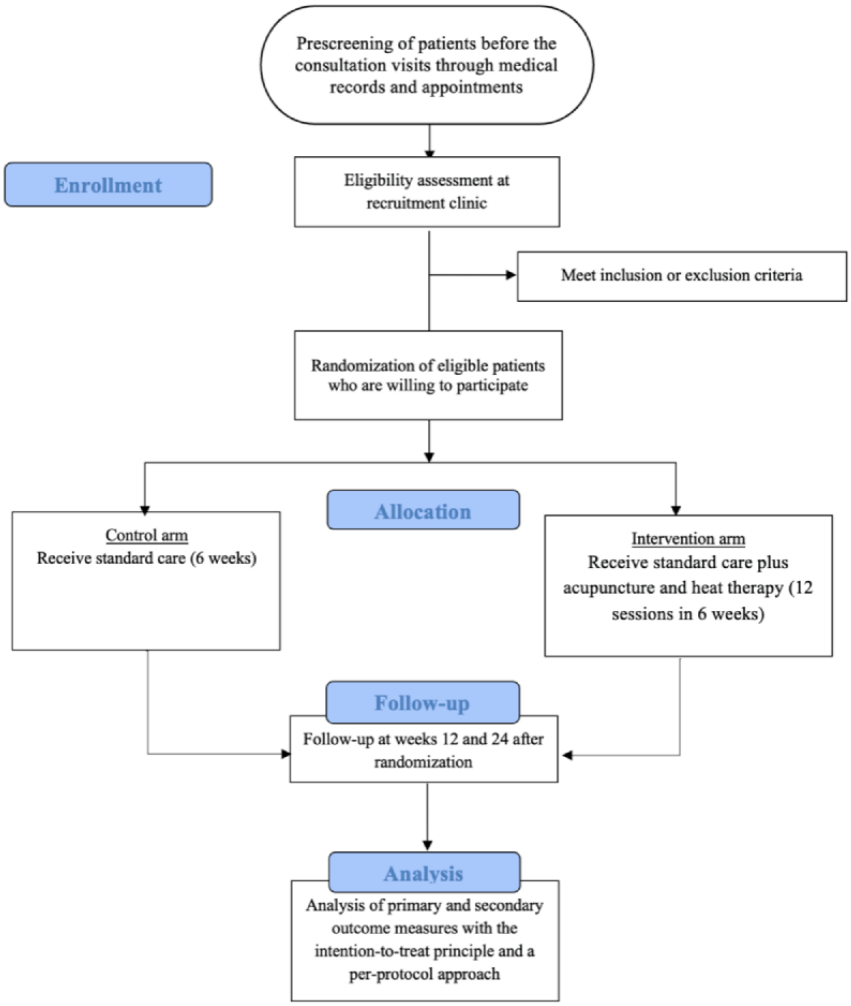
Trial Procedure and Recruitment

By using the hospital's electronic medical records and appointment system, patients who are referred to the orthopedic surgery outpatient clinic at a tertiary hospital in Singapore will be screened based on the eligibility criteria prior to their actual consultation visit. During the clinic visit, potential patients will be invited to participate in the study if they meet all the inclusion and exclusion criteria. A research assistant will share details of the study with patients who are interested. Written informed consent will be obtained for those who subsequently agree to join the trial. The reasons for rejection to participate will be recorded. Each consenting participant will be asked to complete the baseline measures. Patients will then be randomized into the control arm or the intervention arm. Considering previous studies [15,16], patients who have received TCM treatment within 1 week prior to the trial will be subject to a 2-week washout period, counting from their last TCM treatment date. They will be requested to stop any form of acupuncture before beginning the trial. For this group of patients, randomization and baseline measures will be performed after the wash-out period. Participants are allowed to take any analgesics as needed throughout the study duration, and this will be recorded. All medications (prescription and over the counter), vitamin and mineral supplements, and herbs taken by the participant will be documented. Data collection will be done at baseline and weeks 6, 12, and 26. The research assistant will follow up with the participants regularly to ensure study completion. Figures 1 and 2 illustrate the study schedule of enrollment, interventions, and outcome measurements according to the SPIRIT guidelines and the CONSORT flowchart, respectively.

Figure 1. Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) figure of the study schedule. TCM: traditional Chinese medicine.

		Study period										
	Description	Enrollment/ baseline	Allocation	Postallocation (week)							Closeout	Remarks
Timepoint		$-t_1$	0	1	2	3	4	5	6	12	24	
Enrollment												
Eligibility screen		✓										
Informed consent		✓										
Allocation			✓									
Interventions												
Intervention arm	Standard care + acupuncture with heat therapy			←	—	—	—	—	→			2 sessions per week
Control arm	Standard care			←	—	—	—	—	→			
Assessments												
1. Baseline measures	Demographics	✓										
	Height and weight	✓								✓	✓	
2. Primary outcome	Knee Osteoarthritis Outcome Score	✓							✓	✓	✓	
3. Secondary outcomes	EQ-5D-5L	✓							✓	✓	✓	
	Patient Health Questionnaire-4	✓							✓	✓	✓	
	Pain, Enjoyment of Life and General Activity Scale	✓							✓	✓	✓	
	Global Perceived Effect								✓	✓	✓	
	Patient Acceptable Symptom State								✓	✓	✓	
	Medication use	✓							✓	✓	✓	
	Cost Questionnaire	✓								✓	✓	
	Functional assessment	✓								✓	✓	
	Knee Osteoarthritis TCM Evaluation			✓			✓		✓			Prior to first and seventh session and after twelfth session
	Knee Osteoarthritis Visual Analog Scale; Range of Motion Evaluation			✓	✓	✓	✓	✓	✓			Pre- and posttreatment

Figure 2. Consolidated Standards of Reporting Trials (CONSORT) flowchart of the study.



Randomization and Concealment of Allocation

Patients who consent to participate will be randomized in a 1:1 allocation ratio to intervention or standard care using a stratified, permuted, block randomization method (block sizes of 4, 6, and 8). Stratification is based on gender with a female to male ratio of 2:1. The unbalance ratio was based on the World Health Organization's estimate of the prevalence of symptomatic osteoarthritis for people aged 60 years or older, among whom the prevalence of women is almost double that of men (male vs female: 9.6% vs 18%) [17]. The allocation sequence is generated by an independent statistician a priori using Stata (version 16.1; StataCorp) and will be kept concealed from the study team. Randomization will be done using the REDCap (Research Electronic Data Capture; Vanderbilt University) randomization module based on the allocation sequence; allocation will be locked once assigned. Randomization and intervention allocation will only be performed by the study team after the patient is counselled fully about the study and provides informed consent.

Intervention: Acupuncture Plus Heat Therapy and Standard Care

After reviewing international literature and engaging with local TCM experts, this clinical intervention was designed in accordance with local practice. The intervention involves acupuncture with far-infrared heat therapy in addition to standard care, which will be administered by qualified TCM practitioners from Tan Tock Seng Hospital's Complementary Integrative Medicine Clinic (CIMC) and Singapore Chung Hwa Medical Institution (SCHMI), who have full registration with the Traditional Chinese Medicine Practitioners' Board and a minimum of 3 years of acupuncture practice. Before the commencement of the trial, all the acupuncturists from the participating institutions will undergo training on acupoint locations and needling methods to ensure standardization of acupuncture techniques in accordance to the acupuncture protocol that was developed by consensus among all the senior acupuncturists participating in this trial. The treatment protocol and rationale are elaborated below.

Our study aims to evaluate the therapeutic effectiveness of acupuncture combined with far-infrared heat therapy in addition to standard care, compared to standard care alone. To achieve this purpose, we have not included sham acupuncture as an inactive control in our study design. There are controversies about the validity of sham acupuncture. A study found that sham acupuncture may produce comparable effects on biomarkers as *verum* acupuncture, which suggests that sham acupuncture, being an inactive intervention akin to a placebo, should be reevaluated [18]. Additionally, heat therapy will yield beneficial

outcomes in the treatment, regardless of whether *verum* or sham acupuncture is used.

Acupuncture Intervention Rationale

Although the 2007 Singapore Ministry of Health clinical guidelines for KOA recommend electroacupuncture as an adjunct therapy, anecdotal input from our local subject matter experts suggests that some patients are afraid of electrical stimulation and that it is generally less well tolerated due to the pain of electrical stimulation. Studies have also shown that even though electroacupuncture has advantages compared to standard care, acupuncture with heat therapy, a more tolerable option, possesses similar efficacy as electroacupuncture when combined with the usual pharmacotherapies [19]. Therefore, we chose to evaluate acupuncture with heat therapy to establish its clinical effectiveness as an adjunctive therapy in the management of KOA, with long-term implementability a key consideration.

Upon careful review of the evidence-based Guidelines of Clinical Practice with Acupuncture and Moxibustion for KOA [20] and the intervention protocols of several acupuncture RCTs that examined patients with KOA (Multimedia Appendix 1, Figure S1 [10, 21-29]), acupoints that were previously reported to be effective in pain relief and improving knee flexibility were identified.

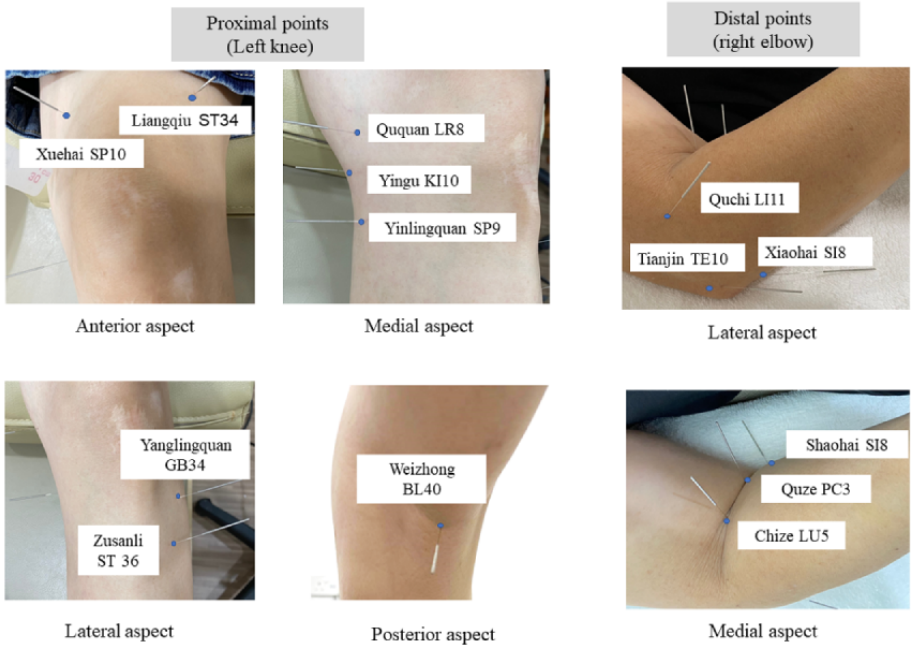
Guided by international evidence in consultation with the local TCM collaborators, a consensus on a set of proximal and distal acupoints based on TCM meridian differentiation was reached (Multimedia Appendix 1, Figure S2 [30,31]).

Acupoint Selection

In total, 14 needle insertions will be made on a fixed set of proximal and distal acupoints for each patient per session (Figure 3).

Distal acupoints will be applied on the opposite elbow [32] to increase the analgesic efficacy according to contralateral collateral needling (缪刺) from *Huang Di Nei Jing* (*Yellow Emperor's Inner Classic* in English). It is a therapy where the right side is acupunctured if the left side is diseased and vice versa; the upper side is acupunctured if the below is diseased and vice versa. Studies have shown that contralateral collateral needling unblocks collaterals and is potentially more effective than conventional acupuncture for some conditions, including hemiplegia following acute ischemic stroke, cervical shoulder pain, insomnia, and KOA [33-35]. From a pragmatic perspective, patients with bilateral knee pain will only receive acupuncture on the most painful knee and the opposite elbow. This practice is supported with evidence that suggests unilateral acupuncture is equally as effective as bilateral acupuncture in increasing function and reducing the pain associated with KOA [36].

Figure 3. Proximal and distal acupoints.

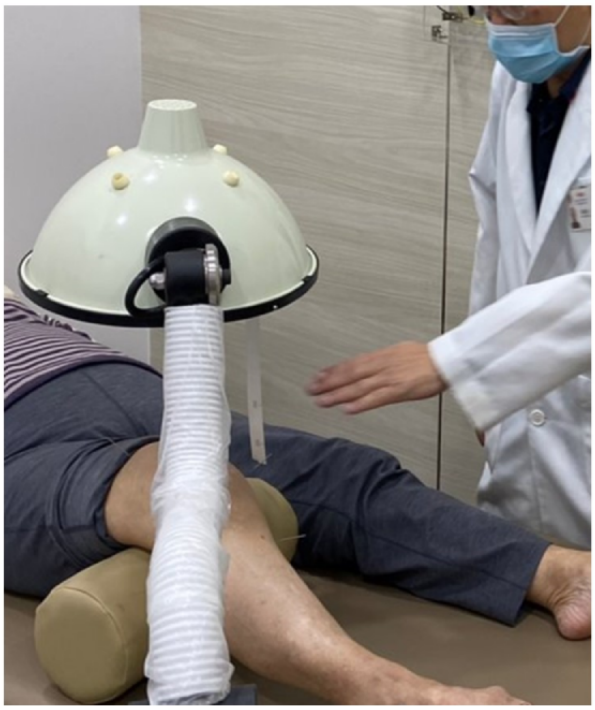


Treatment Regimen

The patient will be treated in a supine position with pillows under both knees. After a standard disinfection procedure, a 30 × 40–mm disposable stainless steel acupuncture needle (YangTzeKing Impex S Pte Ltd) will be inserted according to the location defined; the direction of insertion and the safe depth range are specified in Multimedia Appendix 1, Figure S2 [21, 30,31]. Basic manipulations such as lifting and thrusting, twirling, and rotating are applied until the needling sensation (*de-qi*) is obtained. After *de-qi* is obtained, uniform reinforcing-reducing (平补平泻) manipulations are applied. The needles will be retained for 30 minutes (except for weizhong [BL40], where the needle is removed immediately after the needling sensation is obtained), whereupon 2 manipulations will be applied at 10-minute intervals before needle removal. During needle retention, far-infrared heat therapy will be applied at the lateral, medial, and anterior sides of the knee for 10 minutes each for a total of 30 minutes while maintaining a 30-cm safety distance (Figure 4). The treated region will be observed

and checked for redness at 10-minute intervals to prevent burn injury. A total of 12 acupuncture sessions will be administered twice a week for 6 weeks in addition to standard care. A minimum of 50% attendance (6 of 12 sessions) is required to qualify as completing the study treatment. There are no make-up sessions should the patient miss the scheduled appointment. Total numbers and dates of attended and missed sessions will be recorded for analysis purposes. The study intervention will be conducted at TTSH, CIMC, or SCHMI. The patients are allowed to indicate their preference for the treatment location at the start of the intervention and must attend at the selected location throughout the 6-week intervention. Each TCM session takes approximately 40 minutes, involving acupuncture and heat therapy. Safety precautions will also be exercised to ensure the safety of the patients. Generally, acupuncture is safe and has a low risk of adverse events [37]. However, since the most common adverse events are subcutaneous hematomas and hemorrhages at the site of needling [37], the TCM practitioner will take extra precaution if patients indicate during informed consent that they are taking antiplatelets or anticoagulants. All adverse events that occur during the treatment will be documented.

Figure 4. Heat therapy applied during acupuncture.



Standard Care

Standard care generally constitutes simple lifestyle advice, analgesia, and a referral to the outpatient physiotherapist. The physiotherapist conducts an assessment and recommends a variety of lifestyle modifications and exercise therapy. Any other treatment or the involvement of allied health professionals, such as dieticians, will take place at the discretion of the managing physician. The patients in the standard care group will be discouraged from seeking acupuncture treatment for 6 to 8 weeks after randomization. However, if they do so, it will be noted and accounted for in the analysis.

Withdrawal Criteria

The study intervention may be discontinued under the following circumstances: (1) a serious adverse event arises from the intervention, (2) a participant opts for total knee replacement, (3) a participant is unable to continue the study (eg, because of the sudden onset of any medical condition that prohibits continuing the study), and (4) a collaborator withdraws due to unforeseen circumstances. The participants may also withdraw voluntarily from the study intervention for any reason.

Outcome Measures

The choice of outcome measures is based on the OARSI guidelines for lifestyle diet and exercise clinical trials in osteoarthritis [38]. The recommended core outcomes include pain, physical function, and global patient assessment. Additional outcomes include health-related QOL and global physician assessment. Outcome measures will be collected at baseline (pretreatment), week 6, week 12, and week 26. The primary end point in this study is the Knee Osteoarthritis Outcome Score (KOOS-12) at week 6. KOOS-12 is a specialized tool designed to evaluate patients' knee condition, and it assesses the short- and long-term effects of knee injuries [39]. It reduces respondent burden by 70% from the original KOOS while providing scale scores for knee-specific pain, function, and QOL, along with a summary measure of overall knee impact [40]. The KOOS score has been validated in Singapore [39,41].

Baseline measures such as demographics, socioeconomic status, medical comorbidities, knee symptoms, radiographic severity, height, and weight will be collected.

Additionally, after considering the progression and severity of KOA as defined in TCM clinical guidelines published in China (Multimedia Appendix 1, Figure S3), 2 evaluation forms have been designed. The Knee Osteoarthritis TCM Evaluation Form (Multimedia Appendix 1, Figure S4) was specifically created to integrate the KOOS-12 knee survey with questions based on TCM syndrome differentiation for KOA. This will enable the investigators to assess the efficacy of the treatment by analyzing syndrome differentiation. This form will be administered at week 1 (start of treatment, before the first acupuncture session), week 4 (midtreatment, before the seventh acupuncture session) and week 6 (end of treatment, after the 12th or last acupuncture session). The Knee Osteoarthritis Visual Analog Scale and Range of Motion Evaluation Form (Multimedia Appendix 1, Figure S5) will be administered before and after each of the 12 biweekly acupuncture sessions over 6 weeks.

Clinical data (glycated hemoglobin, blood pressure, and other chronic disease parameters) and operational and cost data (health care use) will also be obtained through the health care administrative databases for economic evaluation.

Outcome Assessment and Blinding

Except for the TCM evaluation forms (Multimedia Appendix 1, Figures S4 and S5), the remaining outcome measures will be measured by blinded outcome assessors. All outcome assessors will receive training prior to study initiation to ensure good inter- and intraobserver reliability, particularly for the functional performance testing. Patients will be instructed not to reveal their allocation to the outcome assessors. Outcome assessment will be conducted at the TTSH physiotherapy clinic. Unblinding will be carefully considered and justified in each case of medical emergency or clinical treatment decisions that require the intervention to be known, following the study protocol and ethical guidelines.

Sample Size Calculation

The sample size needed to find a 10-point difference for KOOS-12 (the primary outcome) between the intervention and control arms with a power of 90%, a *P* value of .05 (2-sided) and an SD of 14 is n=42. The 10-point difference is based on the minimal clinical important difference for KOOS [42]. The anticipated baseline and SD are based on studies done in similar populations. Accounting for a 20% drop-out rate, a total of 100 patients will be needed for the study.

Data Analysis Plan

Results will be analyzed by the intention-to-treat principle. However, data will also be analyzed by a per-protocol approach to account for protocol violations, such as patients who were deemed not compliant to treatment or patients who underwent a surgical procedure of the knee due to treatment failure during the study. Descriptive frequency analysis will be used for baseline characteristics. For continuous variables, the mean and SD will be reported and for categorical variables, the frequencies and percentages will be reported. Between-group comparisons of change from baseline to the 26-week follow-up in the primary and secondary continuous outcomes will be analyzed using a generalized linear mixed model (GLMM). Testing for normality of distributions of outcomes will be based both on the Shapiro-Wilks test and a visual analysis of the histogram plot. Categorical secondary outcomes will be analyzed using the ordinal logistic regression function under the GLMM. A 2-sided *P* value less than .05 will be considered statistically significant. An analysis will be done on the nature of the missing data to determine if the data are missing at random or a systemic bias is present resulting from the missing data.

Data Management

All data will be monitored by the principal investigator and the study team independently of the study sponsor. Data quality measures include queries to identify outliers and missing data. A unique identifier will be assigned to each patient after enrollment to ensure patient confidentiality. Data will be collected and stored on the REDCap system, which is a widely used and secure web application for clinical data management in research. REDCap is password protected, and access rights to the study database are only granted to authorized people. Physical study files will be stored under lock and key.

Safety Monitoring Plan

A safety monitoring review will be done quarterly. Data monitored include serious adverse events and research-related events such as pain, burn, or any other adverse events that may arise due to the conduct of study activities. Safety monitoring reviews will be done by the principal investigator and the co–principal investigator of the study team. The study may be stopped by the principal investigator if serious safety concerns emerge. In the event that a critical adverse event occurs and a decision must be made to terminate the study, interim analyses will be conducted by an independent statistician.

Adverse events and other unanticipated effects of the intervention will be spontaneously reported by the acupuncturists. All reporting will be collected and assessed by the study team. Unanticipated problems involving risk to participants or other events will be reported to the institutional review board.

Confidentiality of Data and Patient Records

Only authorized study personnel will have access to the secured cabinet(s) or room(s) where hard-copy data will be stored. The electronic data will be stored on a password-protected desktop computer, laptop, and external HDD. The databases will not include subject identifiers, and the data relating subject identifiers to subject identification codes will be stored separately.The research data will only be accessible to the study team (including principal investigators, co-investigators, research coordinators, and statisticians). The anonymized and password-protected sharing of research data will be allowed with external institutions.

Ancillary and Posttrial Care

Enrolled participants are covered by indemnity for unexpected negligent harm due to the trial procedure.

Dissemination Plan

We anticipate that it will take between 3 and 4 months to compile the final results for the appropriate journal. The study results will be made available to the participating physicians

and the medical and TCM practitioner community via academic publication.

Component 2: Economic Evaluation

An economic evaluation will be conducted in tandem. The Panel on Cost-Effectiveness in Health and Medicine recommends the use of a societal perspective to ensure that potentially important indirect costs, such as productivity and caregiver cost, are not omitted [43]. The study will be conducted from a societal perspective to determine the cost-effectiveness of the intervention [43].

The cost data will be collected via hospital administrative databases and patient-reported questionnaires to estimate direct medical, direct nonmedical, and indirect costs based on the validated OA Cost and Consequences Questionnaire (OCC-Q), which has been adapted to the Singapore context. The OCC-Q will be administered at baseline, 12 weeks, and 26 weeks.

The primary measure of health benefit will be quality of life years measured using the EQ-5D [44]. The incremental cost-effectiveness ratio over the trial period of acupuncture with heat therapy in conjunction with standard care compared to standard care only will be determined.

Results from the economic evaluation will be reported based on the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement [45].

Component 3: Process Evaluation

The process evaluation will be embedded within the trial. The process evaluation is crucial in understanding the functioning of an intervention by examining its implementation, mechanisms of impact and contextual factors, and use of evaluation to understand how interventions work in practice. This is vital in building an evidence base that informs policy and practice. The Medical Research Council guidelines for the conduct of process evaluations [45] will be used to design the process evaluation.

The focus will be on fidelity of actual delivery, context, and mechanisms of impact with the goal of eventual large-scale implementation. Context includes anything external to the intervention that may act as a barrier or facilitator to its implementation. The examination of mechanisms of impact seeks to identify the potential causal pathways that resulted in the changes seen.

Ethical Considerations

Ethics approvals were obtained from the National Healthcare Group Domain Specific Review Board (2021/01106) and Parkway Independent Ethics Committee (PIEC/2022/022), which oversee human research studies in the participating centers. This study will be conducted in accordance with the ethical principles in the Declaration of Helsinki, International Council for Harmonisation Good Clinical Practice guidelines, and it is consistent with the applicable regulatory requirements of the Human Biomedical Research Act in Singapore. Written informed consent will be obtained from all participants who agree to join the study after screening. A translator and an impartial witness will be present throughout the consent process if a participant is unable to understand English. All study documents were deidentified and research data will be anonymized and password-protected to ensure privacy and confidentiality. This trial is covered under the National Clinical Trials Insurance.

Results

Patient enrollment has been ongoing since August 2022. The recruitment process is anticipated to conclude by July 2024, and the findings will be analyzed and publicized as they are obtained. As of November 6, 2023, our patient enrollment stands at 65 individuals.

Discussion

Overview

TCM has been growing in popularity as a viable treatment option for KOA in recent times. Systematic reviews have suggested that TCM has potential effectiveness in terms of pain relief and functional improvement and leads to few adverse events [46]. However, there have been significant concerns raised about the quality of evidence, with significant methodological flaws in many of the studies and a high risk of bias. Acupuncture in particular has had a fairly large base of evidence, but an overview of the various systematic reviews on the effectiveness and safety of acupuncture in KOA suggested while it has advantages in KOA, there is a significant risk of bias and reporting deficiencies that needs to be addressed [47].

In addition, there is little evidence for TCM treatment of KOA that is tailored to the unique demographics of populations in tropical climates. Many local practitioners often refer to China's Clinical Guidelines of Acupuncture and Moxibustion for KOA, published in 2015 [20]. The guidelines include treatment options based on various TCM syndrome classifications, such as liver and kidney yin deficiency with blood stasis in tendons, spleen and kidney deficiency with dampness in the joint, and kidney yang deficiency with phlegm and blood stasis syndromes. Each syndrome delineates a distinct pattern of symptoms. A local study highlighted a significant difference in the syndrome differentiation for KOA (Multimedia Appendix 1, Figure S6 [48]), with a very high proportion (51%) of patients with KOA in Singapore experiencing the spleen and kidney deficiency with dampness in joint syndrome type, as compared to a mere 4.2% of patients with KOA in China [48,49]. The guidelines from China therefore may not be suited to Singapore's unique patient demographics.

Our HARMOKnee study aims to (1) add high-quality evidence for acupuncture treatment for KOA to the existing literature on a broader scale; (2) support the development of locally standardized national evidence-based practice guidelines tailored to our unique population demographics; (3) support the implementation and integration of acupuncture and heat therapy into current treatment models supported by process and economic evaluations; and (4) establish a foundation for the development of an integrated model of care that harmonizes both Western and Eastern care components.

Strengths and Limitations

One of the major strengths of our HARMOKnee study is that it follows the gold standard for research design: an RCT. The RCT design guarantees that the research uses a rigorous methodology and controls for potential confounding variables. The likelihood of bias can be reduced through allowing more precise assessment of the intervention's efficacy. This study also adheres to the STRICTA guidelines, which provide a standardized framework for reporting acupuncture trials. All relevant data will be reported, thereby enhancing the study's transparency and reproducibility. Moreover, this effectiveness-implementation hybrid study has incorporated an implementation component with the clinical effectiveness assessment. Its benefits include allowing the researchers to maximize the efficiency of their research while collecting data on both effectiveness and implementation, thereby identifying gaps in implementation and increasing the likelihood that the interventions will be effectively implemented and disseminated in real-world settings.

Limitations include the use of a pragmatic study design to mimic real-world conditions as closely as possible. This has an impact in terms of what treatment the control arm receives and how the intervention is delivered. Considerations to ensure intervention delivery fidelity have been incorporated, including standardization and training among acupuncturists. In addition, the treatment that the control arm receives will be meticulously recorded as part of the cost questionnaire and will be included in the analysis. Second, due to logistical and funding limitations, we are only able to include a follow-up period of up to 26 weeks. This will not allow us to establish the long-term effectiveness of this intervention.

Conclusions

The findings of our HARMOKnee study will contribute substantial evidence to the current body of literature regarding the effectiveness of acupuncture treatment for KOA. Additionally, we aim to facilitate the creation of standardized national guidelines for evidence-based practice that are specifically tailored to our unique population demographics. Furthermore, we seek to promote the adoption and integration of acupuncture and heat therapy into existing treatment models.

Acknowledgments

The authors would like to thank the Singapore Ministry of Health for support through the TCM Research Grant (TCMRG-5-NHG-01). The funders played no role in the study's design, data collection and analysis, publication decision, or manuscript preparation.

Data Availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to restrictions on information that could compromise the privacy of research participants.

Authors' Contributions

BYT was the principal investigator. TLT and HPN were the site investigators. All authors participated in the study methodology design and reviewed and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
HARMOKnee Study Protocol.
[PDF File (Adobe PDF File), 419 KB - resprot_v13i1e54352_app1.pdf]

References

1. Cui A, Li H, Wang D, Zhong J, Chen Y, Lu H. Global, regional prevalence, incidence and risk factors of knee osteoarthritis in population-based studies. EClinicalMedicine 2020 Dec;29-30:100587 [FREE Full text] [doi: 10.1016/j.eclinm.2020.100587] [Medline: 34505846]
2. Long H, Liu Q, Yin H, Wang K, Diao N, Zhang Y, et al. Prevalence trends of site-specific osteoarthritis from 1990 to 2019: findings from the Global Burden of Disease Study 2019. Arthritis Rheumatol 2022 Jul;74(7):1172-1183 [FREE Full text] [doi: 10.1002/art.42089] [Medline: 35233975]
3. WHO traditional medicine strategy 2014-2023. World Health Organization. 2013. URL: https://www.who.int/publications/i/item/9789241506096 [accessed 2024-03-06]
4. Birch S, Lee MS, Alraek T, Kim T. Overview of treatment guidelines and clinical practical guidelines that recommend the use of acupuncture: a bibliometric analysis. J Altern Complement Med 2018 Aug;24(8):752-769. [doi: 10.1089/acm.2018.0092] [Medline: 29912569]

5. Selfe TK, Taylor AG. Acupuncture and osteoarthritis of the knee: a review of randomized, controlled trials. Fam Community Health 2008;31(3):247-254 [FREE Full text] [doi: 10.1097/01.FCH.0000324482.78577.0f] [Medline: 18552606]
6. Luo X, Liu J, Li Q, Zhao J, Hao Q, Zhao L, et al. Acupuncture for treatment of knee osteoarthritis: A clinical practice guideline. J Evid Based Med 2023 Jun;16(2):237-245. [doi: 10.1111/jebm.12526] [Medline: 36999342]
7. Acupuncture for adults with low back pain and neck pain. Agency for Care Effectiveness. 2020. URL: https://www.ace-hta.gov.sg/healthcare-professionals/ace-technology-guidances/details/acupuncture-for-adults-with-low-back-pain-and-neck-pain [accessed 2021-06-01]
8. David HP, Nhan TT, Taghreed A. Implementation Research in Health: A Practical Guide. Geneva, Switzerland: World Health Organization; 2013:45-47.
9. Curran GM, Bauer M, Mittman B, Pyne JM, Stetler C. Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact. Med Care 2012 Mar;50(3):217-226 [FREE Full text] [doi: 10.1097/MLR.0b013e3182408812] [Medline: 22310560]
10. Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 tool: designing trials that are fit for purpose. BMJ 2015 May 08;350:h2147 [FREE Full text] [doi: 10.1136/bmj.h2147] [Medline: 25956159]
11. Chan A, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med 2013 Feb 05;158(3):200-207 [FREE Full text] [doi: 10.7326/0003-4819-158-3-201302050-00583] [Medline: 23295957]
12. McAlindon TE, Driban JB, Henrotin Y, Hunter DJ, Jiang G, Skou ST, et al. OARSI Clinical Trials Recommendations: Design, conduct, and reporting of clinical trials for knee osteoarthritis. Osteoarthritis Cartilage 2015 May;23(5):747-760 [FREE Full text] [doi: 10.1016/j.joca.2015.03.005] [Medline: 25952346]
13. MacPherson H, Altman DG, Hammerschlag R, Youping L, Taixiang W, White A, STRICTA Revision Group. Revised STandards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA): extending the CONSORT statement. PLoS Med 2010 Jun 08;7(6):e1000261 [FREE Full text] [doi: 10.1371/journal.pmed.1000261] [Medline: 20543992]
14. Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, Consolidated Standards of Reporting Trials Group. CONSORT 2010 Explanation and Elaboration: Updated guidelines for reporting parallel group randomised trials. J Clin Epidemiol 2010 Aug;63(8):e1-37 [FREE Full text] [doi: 10.1016/j.jclinepi.2010.03.004] [Medline: 20346624]
15. Li J, Liu C, Zhang N, Yan C, Tu J, Wang L, et al. Neurological and psychological mechanisms of the specific and nonspecific effects of acupuncture on knee osteoarthritis: study protocol for a randomized, controlled, crossover trial. Trials 2020 Nov 30;21(1):989 [FREE Full text] [doi: 10.1186/s13063-020-04908-9] [Medline: 33256796]
16. Lv Z, Shen L, Zhu B, Zhang Z, Ma C, Huang G, et al. Effects of intensity of electroacupuncture on chronic pain in patients with knee osteoarthritis: a randomized controlled trial. Arthritis Res Ther 2019 May 14;21(1):120 [FREE Full text] [doi: 10.1186/s13075-019-1899-6] [Medline: 31088511]
17. Murray CJL, Lopez AD. The Global Burden of Disease: a Comprehensive Assessment of Mortality and Disability From Diseases, Injuries, and Risk Factors in 1990 Projected to 2020. Geneva, Switzerland: World Health Organization; 1996:1-40.
18. Kim T, Lee MS, Birch S, Alraek T. Plausible mechanism of sham acupuncture based on biomarkers: a systematic review of randomized controlled trials. Front Neurosci 2022;16:834112 [FREE Full text] [doi: 10.3389/fnins.2022.834112] [Medline: 35185461]
19. Zhang L, Yuan H, Zhang L, Li J, Li H. Effect of acupuncture therapies combined with usual medical care on knee osteoarthritis. J Tradit Chin Med 2019 Feb;39(1):103-110 [FREE Full text] [Medline: 32186030]
20. China Association of Acupuncture and Moxibustion. 循证针灸临床实践指南膝骨关节炎 [Xun zheng zhen jiu lin chuang shi jian zhi nan xi gu guan jie yan; Evidence-based Guidelines of Clinical Practice with Acupuncture and Moxibustion for Knee Osteoarthritis]. Beijing, China: China Press of Traditional Chinese Medicine; 2015.
21. Lin LL, Li YT, Tu JF, Yang JW, Sun N, Zhang S, et al. Effectiveness and feasibility of acupuncture for knee osteoarthritis: a pilot randomized controlled trial. Clin Rehabil 2018 Dec;32(12):1666-1675. [doi: 10.1177/0269215518790632] [Medline: 30037276]
22. Tu JF, Yang JW, Lin LL, Wang TQ, Du YZ, Liu ZS, et al. Efficacy of electro-acupuncture and manual acupuncture versus sham acupuncture for knee osteoarthritis: study protocol for a randomised controlled trial. Trials 2019 Jan 25;20(1):79 [FREE Full text] [doi: 10.1186/s13063-018-3138-x] [Medline: 30683147]
23. Luo X, Hou XS, Tian ZY, Meng X, Li SM, Bai P. [Randomized controlled clinical trial of acupuncture treatment for knee osteoarthritis in the early stage]. Zhen Ci Yan Jiu 2019 Mar 25;44(3):211-215. [doi: 10.13702/j.1000-0607.180677] [Medline: 30945505]
24. Foster NE, Thomas E, Barlas P, Hill JC, Young J, Mason E, et al. Acupuncture as an adjunct to exercise based physiotherapy for osteoarthritis of the knee: randomised controlled trial. BMJ 2007 Sep 01;335(7617):436 [FREE Full text] [doi: 10.1136/bmj.39280.509803.BE] [Medline: 17699546]
25. Qiu JQ, Liu SR, Lin QL, Li MJ, Zhuang JX, Wu GW. [Acupuncture combined with cinesiotherapy cupping for knee osteoarthritis with stagnation and blood stasis syndrome: a randomized controlled trial]. Zhongguo Zhen Jiu 2019 May 12;39(5):462-466. [doi: 10.13703/j.0255-2930.2019.05.002] [Medline: 31099214]

26. Williamson L, Wyatt MR, Yein K, Melton JTK. Severe knee osteoarthritis: a randomized controlled trial of acupuncture, physiotherapy (supervised exercise) and standard management for patients awaiting knee replacement. Rheumatology (Oxford) 2007 Sep;46(9):1445-1449. [doi: 10.1093/rheumatology/kem119] [Medline: 17604311]
27. Tang L, Jia P, Zhao L, Kang D, Luo Y, Liu J, et al. Acupuncture treatment for knee osteoarthritis with sensitive points: protocol for a multicentre randomised controlled trial. BMJ Open 2018 Oct 02;8(10):e023838 [FREE Full text] [doi: 10.1136/bmjopen-2018-023838] [Medline: 30282686]
28. Lin LL, Tu JF, Shao JK, Zou X, Wang TQ, Wang LQ, et al. Acupuncture of different treatment frequency in knee osteoarthritis: a protocol for a pilot randomized clinical trial. Trials 2019 Jul 11;20(1):423 [FREE Full text] [doi: 10.1186/s13063-019-3528-8] [Medline: 31296249]
29. Chen LX, Mao JJ, Fernandes S, Galantino ML, Guo W, Lariccia P, et al. Integrating acupuncture with exercise-based physical therapy for knee osteoarthritis: a randomized controlled trial. J Clin Rheumatol 2013 Sep;19(6):308-316 [FREE Full text] [doi: 10.1097/RHU.0b013e3182a21848] [Medline: 23965480]
30. Liang F, Wang H. Acupuncture and Moxibustion. Beijing, China: China Press of Traditional Chinese Medicine; 2016.
31. Deadman P, Baker K, Al-Khafaji M. A Manual of Acupuncture. Beijing, China: Journal of Chinese Medicine Publications; 2007.
32. Jin XZ, Jin GY, Gao Y. 远端取穴取血法治疗中老年鹤膝风的临床观察 [Yuan duan qu xue qu xie fa zhi liao zhong lao nian he xi feng de lin chuang guan cha; Clinical observation of distal point acupuncture treatment of knee osteoarthritis in elderly]. Guangming J Chin Med 2016;31(8):1133-1134 [FREE Full text]
33. Gao H, Li X, Gao X, Ma B. Contralateral needling at unblocked collaterals for hemiplegia following acute ischemic stroke. Neural Regen Res 2013 Nov 05;8(31):2914-2922 [FREE Full text] [doi: 10.3969/j.issn.1673-5374.2013.31.004] [Medline: 25206612]
34. Li S, Li R, Guo J. 巨刺法应用举隅 [Examples of application of contra-part needling]. World J Acupunct Moxibustion 2020 Dec;30(4):307-310 [FREE Full text] [doi: 10.1016/j.wjam.2020.11.007]
35. Wang ZD, Jiang XY. 巨刺法结合"膝痹八针"治疗膝骨性关节炎1例 [Ju ci fa jie he xi bi ba zhen zhi liao xi gu xing guan jie yan 1 li; Contra part needling combined with knee needling for treatment of knee osteoarthritis: 1 case study]. Guangxi J Tradit Chin Med 2020;43(5):52-53.
36. Tillu A, Roberts C, Tillu S. Unilateral versus bilateral acupuncture on knee function in advanced osteoarthritis of the knee--a prospective randomised trial. Acupunct Med 2001 Jun;19(1):15-18. [doi: 10.1136/aim.19.1.15] [Medline: 11471577]
37. Zhao L, Zhang F, Li Y, Wu X, Zheng H, Cheng L, et al. Adverse events associated with acupuncture: three multicentre randomized controlled trials of 1968 cases in China. Trials 2011 Mar 24;12:87 [FREE Full text] [doi: 10.1186/1745-6215-12-87] [Medline: 21435214]
38. Allen KD, Bierma-Zeinstra SMA, Foster NE, Golightly YM, Hawker G. OARSI Clinical Trials Recommendations: design and conduct of implementation trials of interventions for osteoarthritis. Osteoarthritis Cartilage 2015 May;23(5):826-838 [FREE Full text] [doi: 10.1016/j.joca.2015.02.772] [Medline: 25952353]
39. Tan BY, Ding BTK, Pereira MJ, Skou ST, Thumboo J, Car J. Collaborative model of care between orthopaedics and allied healthcare professionals trial (CONNACT) - a feasibility study in patients with knee osteoarthritis using a mixed method approach. BMC Musculoskelet Disord 2020 Sep 04;21(1):592 [FREE Full text] [doi: 10.1186/s12891-020-03611-9] [Medline: 32887594]
40. Gandek B, Roos E, Franklin P, Ware J. A 12-item short form of the Knee injury and Osteoarthritis Outcome Score (KOOS-12): tests of reliability, validity and responsiveness. Osteoarthritis Cartilage 2019 May;27(5):762-770 [FREE Full text] [doi: 10.1016/j.joca.2019.01.011] [Medline: 30716536]
41. Tan BY, Goh ZZS, Lim CJ, Pereira MJ, Yang S, Tan KG, et al. Singapore KneE osTeoarthritis CoHort (SKETCH): protocol for a multi-centre prospective cohort study. BMC Musculoskelet Disord 2023 Feb 07;24(1):104 [FREE Full text] [doi: 10.1186/s12891-023-06207-1] [Medline: 36750930]
42. Roos E. 30 years with the Knee injury and Osteoarthritis Outcome Score (KOOS). Osteoarthritis Cartilage 2023 Oct 12:1-9 [FREE Full text] [doi: 10.1016/j.joca.2023.10.002] [Medline: 37838308]
43. Sanders GD, Neumann PJ, Basu A, Brock DW, Feeny D, Krahn M, et al. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: second panel on cost-effectiveness in health and medicine. JAMA 2016 Sep 13;316(10):1093-1103. [doi: 10.1001/jama.2016.12195] [Medline: 27623463]
44. EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy 1990 Dec;16(3):199-208. [doi: 10.1016/0168-8510(90)90421-9] [Medline: 10109801]
45. Husereau D, Drummond M, Augustovski F, de Bekker-Grob E, Briggs AH, Carswell C, CHEERS 2022 ISPOR Good Research Practices Task Force. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) statement: updated reporting guidance for health economic evaluations. BMJ 2022 Jan 11;376:e067975 [FREE Full text] [doi: 10.1136/bmj-2021-067975] [Medline: 35017145]
46. Yang M, Jiang L, Wang Q, Chen H, Xu G. Traditional Chinese medicine for knee osteoarthritis: An overview of systematic review. PLoS One 2017;12(12):e0189884 [FREE Full text] [doi: 10.1371/journal.pone.0189884] [Medline: 29267324]

47. Li J, Li Y, Luo L, Ye J, Zhong DL, Xiao QW, et al. The effectiveness and safety of acupuncture for knee osteoarthritis: An overview of systematic reviews. Medicine (Baltimore) 2019 Jul;98(28):e16301 [FREE Full text] [doi: 10.1097/MD.0000000000016301] [Medline: 31305415]
48. Cai H. Xin jia po xi guan gu xing guan jie yan (KOA) zhong yi zheng xing fen bu yan jiu [TCM syndrome distribution study of knee osteoarthritis in Singapore]. Tong Ji Yi Yao J 2018;6:9-12 [FREE Full text]
49. Li ZF, Peng JY, Liu WC, Wu Y, Gu LL, Fan YS. 昆明市膝骨关节炎中医证候研究 [Kun ming shi xi gu guan jie yan zhong yi zheng hou yan jiu; Research study on the syndrome differentiation of knee osteoarthritis in Kunming province]. J Tradit Chin Orthop Trauma 2014;26(06):24-27.

Abbreviations

CHEERS: Consolidated Health Economic Evaluation Reporting Standards
CIMC: Complementary Integrative Medicine Clinic
CONSORT: Consolidated Standards of Reporting Trials
GLMM: generalized linear mixed model
HARMOKnee: Heat and Acupuncture to Manage Osteoarthritis of the Knee
KOA: knee osteoarthritis
KOOS-12: Knee Osteoarthritis Outcome Score
OARSI: Osteoarthritis Research Society International
OCC-Q: OA Cost and Consequences Questionnaire
PP: per-protocol
PRECIS-2: Pragmatic Explanatory Continuum Indicator Summary
QOL: quality of life
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SCHMI: Singapore Chung Hwa Medical Institution
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
STRICTA: Standards for Reporting Interventions in Clinical Trials of Acupuncture
TCM: traditional Chinese medicine

Edited by A Mavragani; submitted 07.11.23; peer-reviewed by J Li; comments to author 20.01.24; revised version received 22.01.24; accepted 24.01.24; published 03.04.24.

Please cite as:
Tan BY, Tan CY, Tan TL, Yang SY, Chew GLS, Tan SI, Chua YC, Yan YW, Soh DBQ, Goh TH, Ng PJ, Ng YT, Kuan SB, Teo BS, Kong KH, Pereira MJ, Ng HP
Heat and Acupuncture to Manage Osteoarthritis of the Knee (HARMOKnee): Protocol for an Effectiveness-Implementation Hybrid Randomized Controlled Trial
JMIR Res Protoc 2024;13:e54352
URL: https://www.researchprotocols.org/2024/1/e54352
doi:10.2196/54352
PMID:38568718

Protocol

Assessing the Effectiveness of a Multicomponent Intervention on Hand Hygiene and Well-Being in Primary Health Care Centers and Schools Lacking Functional Water Supply in Protracted Conflict Settings: Protocol for a Cluster Randomized Controlled Trial

Anaïs Galli[1,2], BA, BSc, MSc; Yaman Ma'ani Abuzahra[1,2,3], PharmB, MSc; Carola Bänziger[4], BSc, MSc; Aboubacar Ballo[5], BA, MA; Max N D Friedrich[6], BSc, MSc, PhD; Karin Gross[1,2], BSc, MSc, PhD; Miriam Harter[6], BSc, MSc, PhD; Jan Hattendorf[1,2], BSc, MSc, PhD; Maryna Peter[4], BSc, MSc, PhD; Andrea Tamas[6], BSc, MSc, PhD; Branwen N Owen[1,2], BSc, MSc, PhD; Mirko S Winkler[1,2], BSc, MSc, PhD, DTM&H, Prof Dr

[1]Department of Epidemiology and Public Health, Swiss Tropical and Public Health Institute, Allschwil, Switzerland

[2]Faculty of Natural Sciences, University of Basel, Basel, Switzerland

[3]Faculty of Medicine and Health Sciences, An-Najah National University, Nablus, Occupied Palestinian Territory

[4]Institute for Ecopreneurship, University of Applied Sciences and Arts, Northwestern Switzerland (FHNW), Muttenz, Switzerland

[5]WASH Regional Department Africa, Terre des hommes, Bamako, Mali

[6]Ranas, Zurich, Switzerland

Corresponding Author:
Anaïs Galli, BA, BSc, MSc
Department of Epidemiology and Public Health
Swiss Tropical and Public Health Institute
Kreuzstrasse 2
Allschwil, 4123
Switzerland
Phone: 41 612849252
Email: anais.galli@swisstph.ch

Abstract

Background: Hand hygiene is crucial in health care centers and schools to avoid disease transmission. Currently, little is known about hand hygiene in such facilities in protracted conflict settings.

Objective: This protocol aims to assess the effectiveness of a multicomponent hand hygiene intervention on handwashing behavior, underlying behavioral factors, and the well-being of health care workers and students. Moreover, we report our methodology and statistical analysis plan transparently.

Methods: This is a cluster randomized controlled trial with 2 parallel arms taking place in 4 countries for 1 year. In Burkina Faso and Mali, we worked in 24 primary health care centers per country, whereas in Nigeria and Palestine, we focused on 26 primary schools per country. Facilities were eligible if they were not connected to a functioning water source but were deemed accessible to the implementation partners. Moreover, health care centers were eligible if they had a maternity ward and ≥5 employees, and schools if they had ≤7000 students studying in grades 5 to 7. We used covariate-constrained randomization to assign intervention facilities that received a hardware, management and monitoring support, and behavior change. Control facilities will receive the same or improved intervention after endline data collection. To evaluate the intervention, at baseline and endline, we used a self-reported survey, structured handwashing observations, and hand-rinse samples. At follow-up, hand-rinse samples were dropped. Starting from the intervention implementation, we collected longitudinal data on hygiene-related health conditions and absenteeism. We also collected qualitative data with focus group discussions and interviews. Data were analyzed descriptively and with random effect regression models with the random effect at a cluster level. The primary outcome for health centers is the handwashing rate, defined as the number of times health care workers performed good handwashing practice with soap or alcohol-based handrub at one of the World Health Organization 5 moments for hand hygiene, divided by the number of moments

for hand hygiene that presented themselves during the patient interaction within an hour of observation. For schools, the primary outcome is the number of students who washed their hands before eating.

Results: The baseline data collection across all countries lasted from February to June 2023. We collected data from 135 and 174 health care workers in Burkina Faso and Mali, respectively. In Nigeria, we collected data from 1300 students and in Palestine from 1127 students. The endline data collection began in February 2024.

Conclusions: This is one of the first studies investigating hand hygiene in primary health care centers and schools in protracted conflict settings. With our strong study design, we expect to support local policy makers and humanitarian organizations in developing sustainable agendas for hygiene promotion.

Trial Registration: ClinicalTrials.gov NCT05946980 (Burkina Faso and Mali); https://www.clinicaltrials.gov/study/NCT05946980 and NCT05964478 (Nigeria and Palestine); https://www.clinicaltrials.gov/study/NCT05964478

International Registered Report Identifier (IRRID): DERR1-10.2196/52959

(JMIR Res Protoc 2024;13:e52959) doi:10.2196/52959

KEYWORDS

water, sanitation, and hygiene; WASH; hand hygiene; impact evaluation; conflict settings; behavior change; handwashing; students; handwashing stations; primary schools, primary health care facilities; humanitarian crisis; mobile phone

Introduction

Background

Globally, approximately 3% of deaths and 5% of disability-adjusted life years are attributable to the effects of a lack of safe water, sanitation, and hygiene (WASH) [1]. More than half of WASH-attributable deaths occur in sub-Saharan Africa [1].

Hand hygiene is crucial to sustaining individual and community health. Pathogens can easily be transmitted from contaminated hands to other people's hands, eyes, and mouths [2]. Inadequate hand hygiene can therefore increase the risk for transmission of diarrheal, respiratory, and skin diseases [3-5].

In 2022, a quarter of people worldwide [6] and three-quarters of people living in sub-Saharan Africa [7] lacked access to basic hygiene, defined as having a functioning handwashing station on the premises with water and soap. Hand hygiene is of particular importance in health care centers and schools (which we collectively refer to here as facilities) because populations considered vulnerable frequent them. In these facilities, pathogens can spread easily over health care workers' or students' hands [8,9]. In health care centers, basic hygiene means additionally that the handwashing station needs to be at the point of care and within 5 m of toilets, while it can be equipped with hand sanitizer instead of soap [10]. Access to basic hygiene in both facility types is low. Only three-fifths of schools worldwide [11] and two-fifths of health care centers at the point of care in low- and middle-income countries [10] are estimated to have access to basic hygiene services. Handwashing stations are half as common in primary health care centers compared to secondary and tertiary health care centers [12].

In fragile and conflict settings, sanitation infrastructure is often overburdened, water quality is poor, and water quantity is insufficient [13,14]. Water is thus primarily used for drinking and cooking, and hygiene and sanitation needs become secondary [15,16]. Basic hygiene access in health care centers and schools is therefore of even greater importance. There are little data on handwashing practices in these facilities, although the United Nations Children's Fund estimates that >50% of children without basic hygiene at school live in fragile or conflict contexts [17]. Such facilities are often excluded from hand hygiene investigations during crises, despite the increased risk of infections [18,19]. Furthermore, collecting baseline data and following monitoring and evaluation activities of hand hygiene usually have a low priority in these facilities [14,18,19].

Objectives

Our study is embedded in the hands4health (h4h) project as an effectiveness evaluation component. The project is funded by the Swiss Agency for Development and Cooperation and led by 10 partners from academia, nongovernmental organizations, and the private sector [20] in close collaboration with the ministries of health (MoHs), ministries of education (MoEs), and other key stakeholders of the project countries, Burkina Faso, Mali, Nigeria, and Palestine (refer to Multimedia Appendix 1 for the project consortium overview). The h4h project has the overarching objective of increasing hygiene in primary health care centers and schools without any functional water supply in the context of protracted conflict settings. The h4h consortium developed a systematic approach with a multicomponent hand hygiene intervention (MCHHI; refer to the Intervention and Control subsection) to improve the health of patients, health care providers, students, and teachers by improving their hand hygiene and water infrastructure. Our study aims to evaluate the effectiveness of the h4h MCHHI on the hand hygiene of health care workers and students by achieving objectives 1 to 4 (Textbox 1). All our objectives will be assessed using a cluster randomized controlled trial (cRCT) design because the MCHHI is implemented at cluster level (ie, health care center or school). By publishing this protocol, we aim to transparently report our study design, methods, and statistical analysis plan. Consequently, we intend to avoid duplicate studies, coordinate research efforts, and demonstrate our accountability to report the results in a timely manner.

Textbox 1. The hands4health (h4h) study aim with the more specific objectives 1 to 4.

Evaluate the effectiveness of the h4h multicomponent hand hygiene intervention (MCHHI) on the hand hygiene of health care workers and students

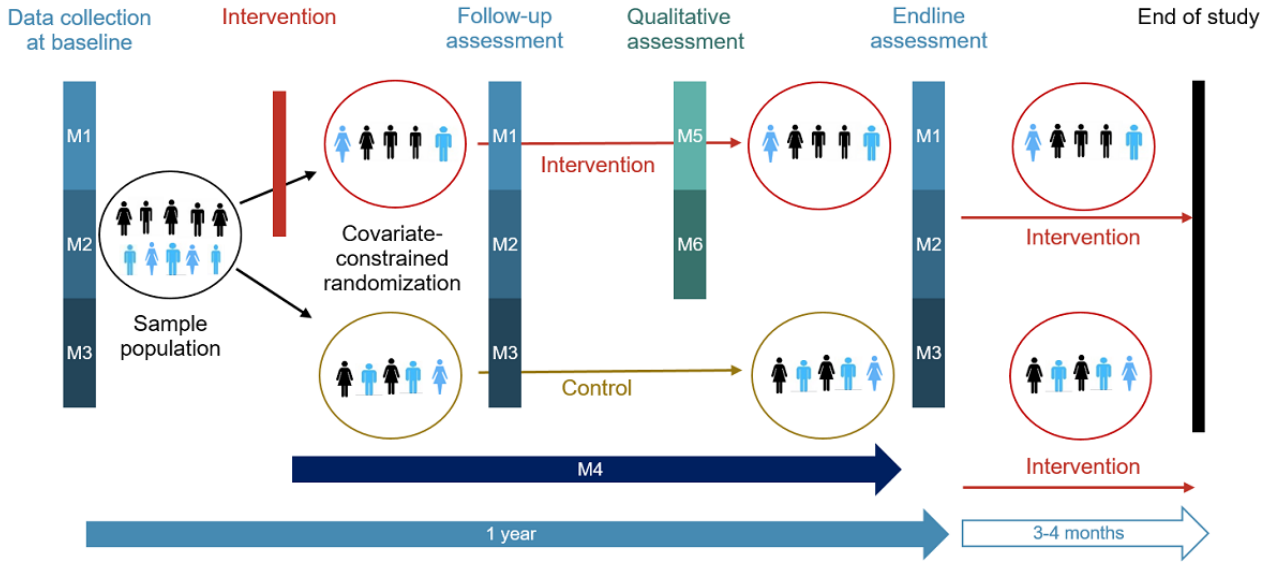
- Objective 1: assess the effectiveness of the h4h MCHHI on the hygiene-related risks, attitudes, norms, abilities, and self-regulation (RANAS) behavioral factors; handwashing behavior; and well-being of health care workers and students.
- Objective 2: assess the hygiene-related RANAS behavioral factors, handwashing practices, and well-being of health care workers and students at baseline.
- Objective 3: assess the perceived effectiveness of the h4h MCHHI on the health and well-being of health care workers and students in the intervention facilities.
- Objective 4 (exploratory): assess the effectiveness of the h4h MCHHI on the predefined health conditions and absenteeism of health care workers and students (objective 4 is exploratory because we did not take it into account during the sample size calculation; therefore, the sample size might be too small to detect a difference in the incidence of hygiene-related health conditions between the 2 study arms; however, as patient information remains anonymous, and the data collection does not add a big burden to the implementation partners, we decided to include this objective).

Methods

Study Design

We are conducting a parallel cRCT in 4 countries (Burkina Faso, Mali, Nigeria, and Palestine) with 2 study arms per country (Figure 1). For the cRCT, we collected baseline data in 24 primary health care centers per country (March to May 2023 in Burkina Faso and Mali) and 26 schools per country (February to June 2023 in Nigeria and Palestine). The data collection included hand hygiene observations; a survey about hand hygiene-related risks, attitudes, norms, abilities, and self-regulation (RANAS) behavioral factors as well as practices and well-being; and microbiological analyses of hand-rinse samples. The project partners implemented the h4h MCHHI in 12 randomly assigned primary health care centers and 13 randomly assigned schools per country. One to 2 months after the implementation of the intervention, we conducted follow-up data collection in both study arms where we repeated the observations and the survey, plus additional qualitative data in the respective intervention arms (November to December 2023 in all 4 countries). One year after baseline, we collect endline data in both study arms, including the same types of quantitative data as in the baseline data collection period (February to April 2024 in Burkina Faso and Mali and May-June 2024 in Nigeria and Palestine).

Figure 1. Overview of the hands4health study design, including the data collection methods M1 to M6. M1: module 1 (risks, attitudes, norms, abilities, and self-regulation and well-being survey); M2: module 2 (structured observation); M3: module 3 (hand-rinse samples); M4: module 4 (diary approach); M5: module 5 (focus group discussions); and M6: module 6 (key informant interviews).



We use a mixed methods design [21,22]. By collecting qualitative data before the start of the cRCT and during the cRCT, we assess WASH-related needs and perceptions about the effectiveness of our intervention on the health and well-being of our study population. By collecting quantitative data about WASH-related health determinants such as the prevalence of handwashing and RANAS behavioral factors, we will assess the effectiveness of the h4h MCHHI on our study population's hand hygiene and well-being.

Our study design is based on previous h4h project activities. First, the project coordination partner commissioned 2 reviews on current tools used for WASH infrastructure in health care centers and schools [23]. Second, the main local implementation partners used a Facility Evaluation Tool for Water, Sanitation, and Hygiene in Institutions (FACET) to assess the WASH

infrastructure of the facilities in the study regions [24]. Third, the project coordination partners led a theory of change approach [25]. The theory of change aims to understand the complexity of the WASH system in the study countries to identify key stakeholders, problems, and starting points for potential solutions. The partners conducted various workshops and interviews with stakeholders and project staff to support this process. Fourth and last, we collected qualitative data with focus group discussions (FGDs) to investigate the local perceptions and needs of hygiene in the pilot facilities. The project consortium then used all this information to develop the h4h MCHHI for each country (refer to Multimedia Appendix 2 [26-37]).

Setting

This study focuses on primary health care centers in rural areas of Burkina Faso and Mali and primary schools in Nigeria and Palestine from 2021 to 2024 (Table 1). All 4 countries involved in this study are subject to protracted conflicts. In the West African countries, jihadists and other radical groups have been terrorizing the population, leading to a rise in internally displaced persons, while Palestine has been under Israeli military occupation for 56 years [38-41]. All targeted facilities in our study regions suffer severe water shortages and a lack of WASH infrastructure and maintenance activities. Moreover, most facilities expect being overcrowded in the near future due to a rise in internally displaced persons. In Maiduguri, Borno State, Nigeria, the schools are already overcrowded, with an average of 101 students per elementary class [42].

Table 1. Description of the country settings of the hands4health project.

	Burkina Faso	Mali	Nigeria	Palestine
Cluster type	Primary health care centers	Primary health care centers	Primary schools	Primary schools
Clusters (n=100), n (%)	24 (24)	24 (24)	26 (26)	26 (26)
Geographic region	West Africa	West Africa	West Africa	Middle East
Country region	Boucle du Mouhon	Ségou and San	Borno State	West Bank
Districts	Dédougou and Boromo	Macina, Markala, San, and Tominian	Maiduguri	Hebron
Reasons for instability	Occupation by jihadist and other radical groups; 2 coups d'états and a political crisis	Occupation by jihadist and other radical groups; 2 coups d'états	Boko Haram insurgency	Israeli military occupation
Internally displaced people per country, n	2.06 million[a]	375,500[b]	2.2 million[c]	N/A[d]

[a]Burkina Faso: Aperçu des personnes déplacées internes (Overview of internally displaced persons; United Nations Office for the Coordination of Humanitarian Affairs [OCHA]; March 31, 2023) [43].

[b]Mali: Tableau de bord humanitaire (Humanitarian dashboard; OCHA; April 30, 2023) [44].

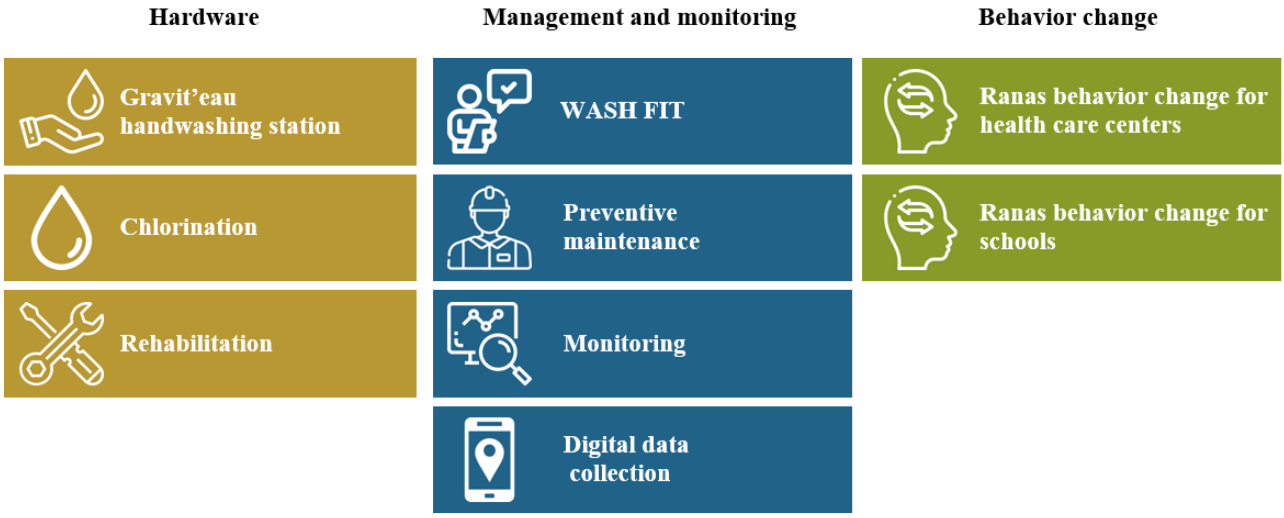
[c]Nigeria: Situation Report (OCHA; July 18, 2023) [45].

[d]N/A: not applicable.

Intervention and Control

The MCHHI varies by study country because it was adapted to each country's needs, local acceptability of intervention components, and tools available for health care centers or schools (refer to Multimedia Appendix 2 for a detailed description). The intervention components, covering hardware, management and monitoring, and behavior change are depicted in Figure 2. In terms of hardware, a handwashing station that recycles water, called Gravit'eau, was locally built and adapted in terms of height and size of basin to the type of institution (ie, health care center or school) in the African countries. Per health care center, 2 individual stations were installed and positioned according to the health care provider's wishes. In Nigeria, 2 stations were placed near 4 to 6 classrooms and toilet areas serving our selected sample of 50 students in each school. In Palestine, recycled water was not culturally accepted. Therefore, instead of receiving a station, we supported the schools with infrastructure rehabilitation work. Facilities in the control arm will receive the intervention once the cRCT is completed. Any viable potential improvements identified during the trial will be implemented.

Figure 2. The hands4health multicomponent hand hygiene intervention components implemented in at least one of the study countries grouped according to hardware (yellow), management and monitoring (blue), and behavior change (green). The icons were sourced from Freepik. RANAS: risks, attitudes, norms, abilities, and self-regulation; WASH FIT: Water and Sanitation for Health Facility Improvement Tool.



Recruitment and Eligibility

Primary Health Care Centers

We selected the primary health care centers with the support of the local implementation partners. They conducted a FACET survey in 179 centers in Burkina Faso and 60 centers in Mali. From these centers, we selected a subset based on the following inclusion criteria: at the time of the FACET survey, the facility (1) did not have any water source directly connected to the building, (2) had a maternity ward, (3) had at least 5 employees, and (4) was impacted by insecurity but was still deemed accessible to the implementation partners. Of the centers meeting these criteria, the implementation partners chose 48 (n=24, in each country) that were most likely to remain accessible for at least 1 year.

As study participants in the health care centers at baseline, we invited all health care workers who met the inclusion criteria and were present at the time of data collection for the quantitative data collection. The inclusion criteria for the quantitative data collection were as follows: health care workers (1) aged at least 18 years and (2) in direct physical contact with patients. The exclusion criteria were as follows: health care workers (1) whose primary occupation does not involve the health care center of the h4h project, (2) who have a skin condition that precludes the use of soap or alcohol-based handrub, and (3) who refuse to participate. All recruited participants received a unique ID. The same eligibility criteria will apply for the follow-up (1-2 months after the intervention) and endline (12 months from the baseline) data collection.

As part of the quantitative data collection in health care centers, we conducted structured observations during patient consultations. The patients needed to fulfill the following inclusion criteria: (1) aged at least 18 years or being accompanied by a legal guardian aged ≥18 years; and (2) visiting the facility for a physical examination, injections or vaccinations, or a blood test. We did not observe sensitive procedures such as giving birth.

Participants for the qualitative data collection at follow-up will be recruited from those who participated in the quantitative baseline data collection. In addition, we will seek to recruit others working in the intervention centers, such as hygiene technicians or people working in administrative positions, as well as stakeholders within the community, state, region, or country of the intervention whose position is related to WASH in health care centers.

Primary Schools

The MoE in Nigeria and Palestine identified 51 and 50 schools, respectively, as being greatly in need of WASH infrastructure. The implementation partners conducted a FACET survey in each of these schools before the start of this study. From these 101 schools, we selected 52 (51.5%; n=26, in each country) based on the following inclusion criteria: at the time of the FACET survey, the school (1) was deemed accessible to the implementation partners, (2) lacked a functional water source, and (3) had ≤7000 students studying in grades 5 to 7.

For the baseline data collection, we selected 50 eligible students aged 10 to 12 years from 1 or 2 classes from each school using random sampling. If a school had a single class consisting of ≥50 students within our target age group, we selected our sample from this class. However, if no class in our target age group had ≥50 students, we randomly selected 2 classes from within the target age group and selected our sample from these classes. For the different data collection modules, we randomly selected subsets from the 50 previously selected students (Figure 1). The inclusion criteria for both quantitative and qualitative data collection were as follows: (1) aged 10 to 12 years and (2) registered at the school for the duration of the study period (1 year). The exclusion criteria included (1) not providing signed consent (for the guardians) and assent form (for the students), (2) having a medical condition that prevents them from washing their hands, (3) having unexplained intermittent attendance in school (school teachers were consulted, and the school's absenteeism records were checked), and (4) not being in the same school for the course of the study (1 year). The same 50 students will be revisited for the follow-up (1-2 months after

the intervention) and endline (12 months from the baseline) data collection.

In addition to the data collected from students, we will collect qualitative data from teachers and key stakeholders at follow-up. The eligibility criteria for teachers are as follows: (1) aged ≥18 years, (2) permanent employee in one of the intervention schools, and (3) teaching one of the classes included in the intervention. The exclusion criterion is refusal to participate. Key stakeholders will be identified through purposeful sampling, primarily through consultation with the local implementation partners. Key stakeholders will be eligible for inclusion in the study based on the following criteria: (1) they occupy a role within the community, state, or region of the study that is associated with WASH in schools (eg, teachers and school principals or people working in any of the organizations that are part of the WASH cluster, such as the MoE or MoH); and (2) they are aged ≥18 years. The exclusion criterion is refusal to participate.

Ethical Considerations

All our study protocols were approved by the Ethikkommission Nordwest- und Zentralschweiz (Ethics Committee for Northwestern and Central Switzerland; AO_2023-00004 and AO_2023-00047) and the ethics boards in each project country: (1) the Comité d'Ethique pour la Recherche en Santé (Ethics Committee for Health Research) in Burkina Faso (2023-02-020), (2) the National Institute of Public Health in Mali (05/2023/CE-INSP), (3) the National Health Research Ethics Committee in Nigeria (21/2023), and (4) the institutional review board of An-Najah National University in Palestine (H Sp. Feb. 2023/18). Study participants in the health care centers and legal guardians of schoolchildren gave written informed consent to participate in this study, whereas schoolchildren gave oral assent. For structured observations, the local implementation partners obtained consent in both facility types before the baseline observations. At the health care center level, consent was obtained from the director of the center for the duration of the study period. In addition, oral consent was obtained from the patients who visited the centers at the time of the observations. Similarly, at the school level, consent was secured from the school administration and from the parents of the participating students. All participants received a unique ID that was coded and will be completely anonymized by the end of this study. Our study protocols for health care centers and schools are registered in ClinicalTrials.gov (NCT05946980 and NCT05964478). We report our study in line with the CONSORT (Consolidated Standards of Reporting Trials) statement: extension to cluster randomized trials [46].

Randomization

We used covariate-constrained randomization to allocate facilities into the control and intervention arms. This methodology, also referred to as restricted randomization, was first suggested by Moulton [47] to minimize the risk of baseline imbalances. These issues are usually more prominent in cRCTs due to the relatively low number of randomized units.

A statistician who was not involved in any h4h field activities performed the covariate-constrained randomization after baseline data collection following these steps: (1) definition of a set of maximum imbalance criteria for several important baseline characteristics, (2) generation of a list of all potential allocation sequences that satisfy these criteria, (3) verification of the independence of units, and (4) random selection of one of the valid sequences as the final allocation.

For health care facilities in Mali and Burkina Faso, we defined the following four constraints: (1) proportions of health care facilities with shortages in water sources should be perfectly balanced, (2) a difference in the proportion of secure facilities of <10 percentage points, (3) a difference in the mean proportions of the population living within 5 km of <10 percentage points, and (4) a difference in the mean proportions of accurate handwashing in each facility of <3 percentage points. In Mali and Burkina Faso, 248,574 and 767,792 potential allocation sequences, respectively, satisfied all 4 criteria.

For schools in Palestine, we first stratified the clusters before applying the restricted randomization. This stratification was based on two key parameters: (1) the directorate in which the school is located; and (2) the school's geographic location, categorized as city, town, or village. After stratification, the allowed allocation sequences had to satisfy the following criteria: (1) balanced administrative areas for schools across both arms, (2) balanced sex, (3) a difference of ≤33% points in the proportions of schools connected to a water network across the arms, (4) a difference of ≤33% percentage points in the proportions of schools with consistent access to water, (5) a difference of <50 in the mean numbers of students across the arms, (6) a difference of <0.2 in the mean grades across the arms, and (7) a difference of <50 in the mean ratios of the number of handwashing stations to the total number of students across the arms. In total, 394 potential allocation sequences satisfied all criteria.

For Nigeria, we defined the following criteria: (1) similar proportions of schools with no currently available water source, (2) similar proportions of schools with <2 days of water availability, (3) similar proportions of schools located in a village as opposed to a city or town, and (4) similar proportions of primary schools in comparison to mixed primary and secondary schools. Other variables allowed a certain degree of imbalance but still required consideration to ensure appropriate balance. These included (1) a difference of ≤200 students in the average student numbers per school between the study arms, (2) a difference of ≤25 percentage points in the proportions of schools with water network connections across the arms, and (3) a difference of ≤25 percentage points in the proportions of schools with water availability for 3 to 5 days a week across the arms. Of all potential allocation sequences, 57,054 satisfied all criteria.

Blinding

To reduce selective counting of colony-forming units (CFUs) of bacteria in the hand-rinse samples collected at baseline, the laboratory workers assessing the number of CFUs were blinded. The data collectors delivered the coded samples to the laboratory workers. From the identification code of the samples, the laboratory workers could not derive whether the sample was collected in an intervention facility or a control facility. The

laboratory workers will be blinded again at endline data collection.

Quantitative Methods

We collected quantitative data with four different modules: (1) module 1 (RANAS and well-being survey), (2) module 2 (structured handwashing observations), (3) module 3 (microbiological analysis of hand-rinse samples), and (4) module 4 (diary approach for predefined health conditions).

Module 1: RANAS and Well-Being Survey

We started the survey by asking participants about sociodemographic information, followed by knowledge questions about hand hygiene and self-reported hand hygiene practices (for detailed descriptions of the variables, refer to Multimedia Appendix 3). The survey proceeded with questions to measure the RANAS behavioral factors, such as perceptions of costs and benefits of consistent hand hygiene, social norms, and ability beliefs, on 5-point Likert scales to measure frequencies, magnitudes, and degrees [27]. Questions about the hygiene infrastructure in the facilities followed this section. In health care centers, there were additional survey items on the quality of care, and in schools, on student well-being. Well-being was assessed with the KINDL tool (Kinder Lebensqualität Fragebogen, Children's Quality of Life Questionnaire), which was developed specifically to measure health-related quality of life in children and adolescents by assessing different domains of well-being [48].

We conducted the survey with all participating primary health care workers and a randomly chosen subset of 25 students per school at baseline and will repeat at follow-up (1-2 months after the intervention) and endline (12 months from the baseline). The survey will be interviewer administered using Open Data Kit Central software (version 2022.3.1) on Android tablets or smartphones.

Module 2: Structured Handwashing Observations

Structured handwashing observations are considered the gold standard method to assess handwashing behavior [12,49]. We conducted the observations with primary health care workers and schoolchildren at baseline and will repeat these observations at follow-up and endline. Due to structural differences in health care centers and schools, we chose 2 different observation approaches for the 2 facility types.

In primary health care centers, staff members from the implementation partner or the regional MoH were trained by the first author (AG) as observers for the baseline data collection. Observers usually worked in the health care centers in a different role, and they visited the facility under the pretext of performing their usual role and did not declare that they were observing handwashing. Hence, the handwashing observations were conducted covertly. The observers were equipped with an observation tool programmed in Open Data Kit Central (version 2022.3.1) on their smartphone. During their visit, they spent 1 hour in each unit to record all hand hygiene actions taken by the health care providers, as well as their handwashing techniques [50]. The same observation process will be repeated at follow-up and endline.

In schools, student handwashing was observed by implementation partners who were trained by the second author (YA). To aid the identification of participating students, all children were given badges, with 1 color for those participating and another for those not participating. The students were told that the color assignment was random. The implementation partners observed each student's handwashing practices across a variety of occasions, including the 2 critical moments: before eating and after using the toilet (among others, eg, after eating and after playing). To observe handwashing before eating, we involved the students in an experiment. We engaged the children in a 30-minute painting activity, after which the children were rewarded with a popcorn snack and granted a 15-minute break to enjoy it together. This created an opportunity to observe whether the children washed their hands before eating the snack. Observers did not reveal their intention of observing handwashing throughout the time of the data collection. In Nigeria, we additionally observed the children for 3 hours. The observation started at 9 AM (60 minutes before the breakfast break) and ended at noon (90 minutes after the break). Four observers were stationed near all available water points and toilets. Using a paper-based observation tool, the observers recorded all participating students who washed their hands and whether they did so before eating, after using the toilet, or at another time point. In addition, any participating student observed using the toilet who did not wash their hands was also recorded.

Observers then cross-checked their results to eliminate instances of duplicate observations for the same students. They merged observations made at different critical times or water points for the same student and confirmed whether those who used the toilet also washed their hands, particularly in scenarios where toilets were situated at a considerable distance from the water points. After this cross-checking process, the data were transferred to Open Data Kit Central (version 2023.3.1) for analysis and storage. These observations yielded a dichotomous measure: whether handwashing occurred at each critical event. However, options such as "not visible" or "soap or water was not available" were included to account for potential complications. If feasible, we observed the handwashing steps of students who washed their hands. Observations will be repeated in schools at follow-up and endline.

Module 3: Microbiological Analysis of Hand-Rinse Samples

We collected hand-rinse samples of all participating health care workers and a randomly selected subset of 12 students at baseline with a modified glove juice method as described by Pickering et al [51]. We asked the participants to insert their hand into a Whirl-Pak bag (Nasco Sampling LLC; sizes 2041 mL and 7120 mL for adults and children, respectively), filled with 350 mL of bottled drinking water without chlorine. The participants were asked to shake their hand in the water and rub their thumb and fingers together for 15 seconds, and then the sample collector massaged the participant's hand through the bag for another 15 seconds [51]. Afterward, we repeated the procedure with the other hand.

We kept the Whirl-Pak bags containing the samples on ice in an isolation box and processed them within 8 hours of sampling [51]. We used membrane filtration to detect CFUs of *Escherichia coli* and total coliforms. In a field laboratory, we passed 100 mL of the bag's content through the filter paper, which we then placed on Nissui Compact Dry EC plates (Shimadzu Diagnostics Europe) to incubate them at 35 °C −0.5 °C to +0.5 °C for a duration of 24 hours [51]. For quality control, we carried out a duplicate filtration of every 10th sample and a negative control, only containing the bottled water, each day.

We calculated the lower detection limit of CFUs by dividing 1 CFU per plate by the filtrate volume and then multiplying it by the total Whirl-Pak volume of 350 mL. We calculated the upper detection limit by dividing 301 CFUs per plate by the filtrate volume and then multiplying it by the Whirl-Pak volume. We normalized and $\log_{10}$-transformed the CFUs per hand for the statistical analysis [51]. We will repeat the same hand-rinse sampling procedure again at follow-up and endline.

Module 4: Diary Approach for Predefined Health Conditions

Using a diary approach, we will ask health care center directors to collect longitudinal data on the hygiene-related health conditions of patients. These conditions include maternal and neonatal mortality, stillbirths, postpartum endometritis, neonatal sepsis, umbilical cord infections, and infections of wounds after treatment. For each relevant health condition among patients, the director will be asked to report the date of diagnosis, and if known, the duration of the condition, the etiology, and ultimate outcome (eg, recovery or death). Detailed descriptions of the health conditions are presented in Multimedia Appendix 4 [52].

Similarly, hygiene-related absences of all participating health care workers and the 50 students will be reported during the period after the intervention until the endline data collection in both study arms. For absenteeism in health care centers or schools, the person responsible will record the event, the number of days absent, and the reason for the absence. We define absenteeism as hygiene related if the facility worker or student experienced diarrheal diseases (including cholera), respiratory tract infections (including tuberculosis, COVID-19, and influenza), bacterial infections of the skin and eyes (including trachoma), and newly diagnosed HIV and hepatitis B or C. The diary will consist of 1 table per month containing all different health conditions and subcategories. No personal information will be recorded in this module.

Outcomes

Primary Outcome

Due to the difference in settings, health care centers and schools have different primary outcomes. In health care centers, the primary outcome is the handwashing rate, defined as the number of times each health care worker performs good handwashing practice with soap or alcohol-based handrub at one of the World Health Organization (WHO) 5 moments for hand hygiene [53], divided by the number of moments for hand hygiene that presented themselves during the patient interaction. The handwashing rate was assessed by structured handwashing observations over 1 hour per unit in a health care center. The 5 moments for hand hygiene are defined by the WHO as follows:

1. Before touching a patient
2. Before clean or aseptic procedures
3. After risk or exposure to body fluids
4. After touching a patient
5. After touching a patient's surroundings

In schools, the primary outcome is the number of participating students who wash their hands before eating. This number was collected using structured handwashing observations after students were given a snack after their participation in a painting activity. We selected this outcome because it allows for an objective assessment across all participating students, given that all were presented with this handwashing opportunity during the course of the experiment.

Secondary Outcomes

The most important secondary outcomes in both settings are as follows:

1. Self-reported handwashing practice on a Likert scale ranging from *almost never* to *almost always* (in health care centers: for each of the 5 moments for hand hygiene; in schools: before eating and after using the toilet)
2. The $\log_{10}$-transformed number of total coliforms and *E. coli* CFUs per hand before handwashing
3. RANAS behavioral factors measured on a 5-point Likert scale
4. Hygiene-related absenteeism and health conditions, which are summarized in Multimedia Appendix 4; the sum of each outcome variable will be used separately per facility (cluster) as a measure for statistical analysis, and health conditions will be reassessed with local experts in the respective countries to ensure feasibility before the start of the intervention

Secondary outcomes only applying to the school setting are as follows:

1. Good handwashing practice defined as the number of students who wash their hands after using the toilet (assessed by structured handwashing observation)
2. Self-reported well-being of students assessed using the KINDL tool [48], with responses given on a Likert scale ranging from *almost never* to *almost always*

Statistical Analysis

Sample Size Calculation

We ran a series of simulations using R software (version 4.1.3; R Foundation for Statistical Computing) to determine the required sample size for health care centers. For the simulations, we assumed 6 staff members per health care center, a mean number of 5 (SD 5) times a person was supposed to wash their hands, and an intracluster correlation coefficient of 0.15; we needed to enroll 10 health care centers in each trial arm to detect a difference of 15 percentage points in the proportions of handwashing during the 5 critical moments for handwashing (30% control vs 45% intervention) with 81% power at a 2-tailed 5% significance level. To account for potential loss to follow-up,

we enrolled 24 health care centers per country in Burkina Faso and Mali.

Within schools, we assessed the number of clusters (schools) and students per school with simulations using R. We aimed for a power of 80% at the 95% CI and anticipated an intraclass correlation coefficient of 0.2. In the simulation, we assumed a prevalence of handwashing before eating of 20% in control schools versus 45% in intervention schools after 1 year from the baseline. On the basis of this assumption, we needed 13 schools per trial arm with 50 students per school. However, the number of students assessed for different modules will differ throughout the study due to capacity limitations of assessing the 50 students included in each school.

Statistical Methods

We summarized baseline characteristics using descriptive statistics (Textbox 2). We will investigate the difference in the observed proportions of always handwashing at the 5 critical moments as defined by the WHO for primary health care centers and of the number of participants who wash their hands before eating for primary school students between the 2 study arms at follow-up using random effect logistic regression models. We will only include the intervention as a predictor in the primary analysis. For the primary analysis, we will use the available case population of health care workers and students, which will be analyzed according to the intent-to-treat principles.

Textbox 2. Statistical methods used for the analysis of the results of the different quantitative modules of the hands4health study.

Modules and statistical methods

- Risks, attitudes, norms, abilities, and self-regulation and well-being survey (module 1)
  - Descriptive statistics
  - Random effect linear regression modeling
  - Random effect logistic regression modeling
- Structured handwashing observations (module 2)
  - Random effect logistic regression modeling
- Microbiological analysis of hand-rinse samples (module 3)
  - Random effect negative binomial regression modeling
- Diary approach for predefined health conditions (module 4)
  - Descriptive analysis with the sum of each outcome variable calculated separately per facility
  - Random effect linear regression modeling

Qualitative Methods and Analysis

Before the baseline data collection and at follow-up, we supplement our quantitative methods with two modules of qualitative methods: (1) module 5 (FGDs) and (2) module 6 (key informant interviews [KIIs]).

Module 5: FGDs

FGDs offer a practical way to gather insights more efficiently than other qualitative methods [54,55]. Before the onset of the study, the local implementation partners with experience in qualitative data collection collected data through FGDs involving health care workers, students, and teachers. These FGDs helped us to gain insight into the hygiene-related needs as well as the acceptability of our intervention among health care workers and students. We let the groups vote for their most urgent hygiene-related needs as well as the potential positive and negative impacts of our intervention. After counting and discussing the votes during the FGD, the project consortium adapted the country-specific interventions, and we identified what we needed to include in the quantitative data collection.

We collect data with FGDs again since January 2024 and will continue this data collection until April 2024 with the same trained implementation partners for health care workers and students to assess the perceived effectiveness and potential improvements of the h4h intervention. In addition, we will conduct FGDs with teachers from the schools in the intervention arm. We will train the team containing at least 1 moderator and 1 observer or notetaker before data collection. If the security situation allows, AG or YA will join the team. We will use a field research journal throughout the study to take structured notes and observations of the FGDs. We will audio record and transcribe the discussions and then translate into French or English for further analysis.

All health care workers in the intervention centers will be invited to participate in FGDs.

In health care centers, we will take into account the structures of hierarchy and gender when building mini groups of 3 to 4 participants to allow participants the greatest possible freedom of speech. We chose to have mini groups because the health care workers who participate are expected to have a high expertise in hand hygiene. Usually, the higher the expertise of participants, the smaller the group can be [54]. Depending on the hierarchical levels, 1 to 4 FGDs will take place per facility. We expect to conduct a maximum of 20 FGDs per country (fewer if we reach saturation beforehand) [55].

In schools, we will select students from each class in the intervention arm, in consultation with the school administration. We will conduct FGDs with 5 to 10 boys and girls separately until saturation is reached (or up to the maximum of 5 FGDs with each sex) and 5 FGDs with teachers [55]. KIIs may be conducted instead of FGDs if we do not have enough participants to form groups in both facility types.

Module 6: KIIs

Aiming to further explore issues arising from the FGDs and to understand perceptions of the intervention, we will conduct KIIs with other stakeholders who influence the project's intervention areas, such as representatives of the MoH and MoE as well as local majors. We have identified some of these key informants through the theory of change approach, while others will be suggested by local partners. Here, we chose individual interviews rather than FGDs so that the stakeholder's status does not influence other participants' freedom of speech [55].

If necessary and appropriate, we may carry out interviews on the web, in French or English. Local project partners with experience in interviewing will conduct stakeholder interviews until saturation is reached [55]. We will apply the same steps of audio recording, transcription, and translation for the KIIs as for the FGDs.

We will analyze FGD and KII transcripts as well as field and observation notes using the framework method [56] with MAXQDA software (VERBI GmbH) with at least 1 local partner per country with qualitative expertise.

Triangulation of Results

We triangulate our results throughout the study. Qualitative data from the pilot phase informed our quantitative data collection at baseline. Moreover, questions identified during the quantitative baseline and follow-up data collection will guide our qualitative FGDs and KIIs, which can then be used to better understand our results from the endline data collection By triangulating the results, we will be able to validate them, find discrepancies, and increase our understanding of why certain quantitative results emerged [21,22]. In addition, we might identify new research gaps and potential solutions to issues that we identified during the study period.

Results

The baseline data collection of this study started in February 2023 and ended in June 2023. In Burkina Faso, we conducted 95 RANAS surveys, observed 82 participants, and collected 99 hand-rinse samples in 24 primary health care centers. In Mali, we conducted 105 RANAS surveys, observed 111 participants, and collected 100 hand-rinse samples in 24 primary health care centers. As of March 2024, the analysis of the baseline results in health care centers is completed and a manuscript will be submitted within the same month for publication. In Nigeria, we conducted 640 RANAS surveys, observed 1300 participants, and collected 369 hand-rinse samples in 26 primary schools. In Palestine, we conducted 646 RANAS surveys and observed 1127 participants in 26 primary schools. We did not collect hand-rinse samples in Palestine because the method was deemed culturally inappropriate by the MoE. As of March 2024, data analysis for schools is ongoing. Follow-up data collection took place from November to December 2023 in 24 health care centers in Burkina Faso and Mali, respectively and in 26 schools in Nigeria. Due to the crisis in Palestine, follow-up activities were suspended. As of March 2024, data analysis remains ongoing. Qualitative data collection started in Burkina Faso in January 2024 and is planned to start in Mali and Nigeria in March 2024. Endline data collection started in Mali in February 2024 and will be completed in all countries by June 2024. We will publish more results investigating data collected during the follow-up, qualitative, and endline data collection in the year 2024. Project funding is guaranteed until December 2024.

Discussion

Summary

By implementing a mixed methods approach within a cRCT study design with multiple stakeholders from academia, the private sector, humanitarian organizations, and MoHs and MoEs, we aim to better understand the complex situations in our 4 project countries. We used mixed methods to generate much-needed quantitative data about the WASH infrastructure and behavior in primary health care centers and schools in regions where such data are usually very scarce. At the same time, the qualitative data help to better understand the reasons behind the effectiveness of our intervention and to capture intricacies missed with quantitative data collection. In our opinion, conducting research across disciplines is crucial in humanitarian crisis contexts to guarantee ethical and beneficial outcomes, which policy makers can then use locally.

Research in Conflict Settings

The demand for research in conflict settings is increasing to support evidence-based interventions and impact evaluations [49]. Unfortunately, this type of research is still rare and the quality of existing studies poor [57]. Apart from obvious challenges such as the researchers' and participants' security as well as political instability, additional difficulties might hinder research in these settings [58]. These difficulties include a lack of data, determining the study population, knowing the baseline health status of the study population, displacement of the study population, and issues with logistics [58]. We tried to respond to these difficulties by involving local actors from humanitarian and governmental organizations and the facilities from the project outset. However, the rapidly changing political and security situations in the project countries make it difficult to plan ahead.

Strengths and Limitations

Our study has some noteworthy strengths: first, with the cRCT, we use the study design with the highest level of evidence [59]. Second, by using mixed methods, we can further strengthen our results by triangulation. Third, the design of the MCHHI is data driven and hence well adapted to promoting sustainability in the contexts in which it was implemented. Fourth, one of the core strengths of this study lies within our inter- and transdisciplinary teams and consortium. By including the humanitarian sector, local authorities, health care personnel, teachers, and students early in the process through regular

meetings, the theory of change workshops, and FGDs, we expect to address real needs with our research. Throughout the process of developing the study protocol, we kept consulting with our partners through regular remote meetings and several in-person workshops in the respective countries. This close exchange throughout the project enabled us to rigorously and continuously evaluate the situation in the unstable settings we worked in. Fifth, by conducting this project in 4 different countries, we can gain valuable insights into how the h4h MCHHI needs to be adapted to different contexts and how it can be made more readily available for future interventions in other regions. Finally, we address big data gaps with this study. In Burkina Faso and Mali, the current MoHs actively want to strengthen hygiene, water, and sanitation in health care. However, they lack data about hand hygiene and WASH infrastructure in primary health care to inform their campaigns. This study can inform them directly about current practices and how they can or cannot be influenced with our proposed MCHHI. In schools, the respective MoEs have expressed a keen interest in this study. The findings, which clarify student hand hygiene, are anticipated to be of considerable value. These insights will not only inform about the intervention's impact but will also guide the MoEs in scaling the intervention across a broader spectrum. By identifying the strengths and weaknesses of the intervention, they can further enhance and replicate the successful aspects while avoiding any identified shortcomings.

Despite the strengths, our study has some limitations. First, we could not choose facilities completely at random. They needed a high probability of remaining accessible to the local partners. Therefore, our results are not fully generalizable and might miss some of the people considered most vulnerable and inaccessible. Second, due to the nature of this study, we could not blind the participants, our implementation partners, or the people conducting the statistical analysis. Therefore, a nonblinding bias cannot be excluded. Third, to maintain a balance between achieving a sample size of institutions for a high enough statistical power and having a sufficient budget to implement hardware interventions in all these institutions, 2 Gravit'eau stations per institution were implemented. In health care centers, we expect an average of 3 health care workers using 1 station and, if accessible to patients, approximately 20 patients per day. In schools, the stations were designed to accommodate up to 100 individuals per hour. Judging from the station's strategic positioning, we estimate that 250 to 300 students will be using 1 station during a school day. Fourth, we expect a high social desirability bias in the self-reported handwashing and hygiene behavior data. We anticipate having a more realistic and objective view of handwashing and hygiene behavior by complementing the survey data with observation and hand-rinse data. Fifth, the structured observations might be subject to a Hawthorne effect [60]. We aim to counteract this effect by conducting the observations covertly before the official beginning of the study. In health care centers, we chose implementation partners and MoH staff who regularly visit the centers for other supervision activities unrelated to handwashing. This might still change the participants' behavior, but we expect they did not focus too much on handwashing. We had to inform the head of health care centers before the observations for ethical reasons. Therefore, the possibility that the participants knew why they were observed remains.

Conclusions

To our knowledge, this is one of the most innovative studies to investigate the effectiveness of an MCHHI on the health determinants of beneficiaries in primary health care centers and schools. With our sound inter- and transdisciplinary methodological approach, we expect to generate results and conclusions that can sustainably impact local policy makers and the humanitarian sector working in the project countries and beyond.

Acknowledgments

The authors want to express their utmost gratitude to the Swiss Agency for Development and Cooperation, which funded and supported the hands4health project (7F-l 0345.03.01), with special thanks to Nathalie Wyzer. The authors would also like to thank Bruno Pascual and Sébastien Mercier, their partners from Terre des hommes, Lausanne, Switzerland, as well as the Terre des hommes country offices in Burkina Faso (Kamboulbé Dah, Ibrahim Simia, Dramane Zongo, Salifou Ouedraogo, Dieudonné Belembaongo, Alimata Tall, Philip Parfait, Julien George, and Paolo Pennati), Mali (Hassane Dembélé, Issa Bagayogo, Modibo Traoré, Saran Samaké, Dramane Keïta, Jean-Paul Elle Sibiri Somboro, and Françis Ntéssani), and Nigeria (Zainab Abdulkarim, Usman Kolo, and Muhammad Shuaibu) for supporting them throughout the development and implementation of this study with their expertise and experience. In the same way, the authors are grateful to their partners from Cesvi (Roberto Turcato, Issa Younan, and Ola Sa'o) and the Palestine Polytechnic University (Hasan Abusalha, Maher Ja'bari, and Safa Sultan). The authors want to express their deep gratitude to the regional and national Ministries of Health in Burkina Faso (Valentin Ouedraogo, Martine Kaboré, Oussény Sankara, Malick Nayété, and Houssen Koanda) and Mali (Mamadou Keïta), the Ministry of Education in Palestine (Ahmad Salah, Amjad Hemaidat, Razan Salah, and Wissam Nakhleh), and Ministry of Education—The Borno State Universal Basic Education Board in Nigeria, which actively support their project. The authors thank all data collectors who worked with Terre des hommes and Cesvi for their great efforts and courage to work in these challenging settings. The authors highly appreciate the support of Marco Verber, formerly from the University of Applied Sciences and Arts Northwestern Switzerland, for his technical and project management knowledge, and Anna Gamma, formerly from Ranas Ltd, for her expertise in behavior change. Finally, the authors would like to thank Skat Foundation for its lead in the theory of change process and support for the qualitative data collection (Matthias Saladin, Bertha Camacho, Rena Salzmann, and Meleesa Naughton) and Fabian Peter, cofounder of Gravit'eau, who supported the implementation teams with the construction of the handwashing stations.

Authors' Contributions

MSW is the principal investigator of all impact evaluation research activities of the hands4health study. AG and YMA are responsible for the study design, ethics approval, trial registration, fieldwork supervision, and data analysis. JH was the main statistical adviser, supported by BNO, and KG was the main adviser for the qualitative study design. AB is a focal point of the implementation partner and advised during the process of developing the study protocol, supported all implementation activities, and leads the Water and Sanitation for Health Facility Improvement Tool intervention. MH, MNDF, and AT developed the risks, attitudes, norms, abilities, and self-regulation survey and led the whole RANAS approach. CB and MP developed all infrastructure-related tools and were involved in the overall project management. AG, YMA, BNO, and MSW drafted the manuscript. CB, AB, MNDF, MH, JH, KG, MP, and AT revised the manuscript.

Conflicts of Interest

AT, MNDF, and MH are cofounders of Ranas Ltd. However, Ranas Ltd has no patents, products in development, or marketed products associated with this research. MP is a cofounder of Gravit'eau. However, Gravit'eau is a nonprofit organization that does not promote the handwashing stations with marketing. All other authors declare no other conflicts of interest.

Multimedia Appendix 1
The hands4health consortium.
[PDF File (Adobe PDF File), 435 KB - resprot_v13i1e52959_app1.pdf]

Multimedia Appendix 2
The hands4health multicomponent hand hygiene intervention.
[PDF File (Adobe PDF File), 552 KB - resprot_v13i1e52959_app2.pdf]

Multimedia Appendix 3
Description of the variables of the risks, attitudes, norms, abilities, and self-regulation and well-being survey.
[PDF File (Adobe PDF File), 446 KB - resprot_v13i1e52959_app3.pdf]

Multimedia Appendix 4
Details of hygiene-related absenteeism and health conditions.
[PDF File (Adobe PDF File), 425 KB - resprot_v13i1e52959_app4.pdf]

References

1. Safer water, better health. World Health Organization. 2019. URL: https://www.who.int/publications/i/item/9789241516891 [accessed 2024-03-05]
2. Aiello AE, Coulborn RM, Perez V, Larson EL. Effect of hand hygiene on infectious disease risk in the community setting: a meta-analysis. Am J Public Health 2008 Aug;98(8):1372-1381. [doi: 10.2105/AJPH.2007.124610] [Medline: 18556606]
3. Freeman MC, Stocks ME, Cumming O, Jeandron A, Higgins JP, Wolf J, et al. Hygiene and health: systematic review of handwashing practices worldwide and update of health effects. Trop Med Int Health 2014 Aug;19(8):906-916 [FREE Full text] [doi: 10.1111/tmi.12339] [Medline: 24889816]
4. Ejemot RI, Ehiri JE, Meremikwu MM, Critchley JA. Hand washing for preventing diarrhoea. Cochrane Database Syst Rev 2008 Jan 23(1):CD004265. [doi: 10.1002/14651858.CD004265.pub2] [Medline: 18254044]
5. Rabie T, Curtis V. Handwashing and risk of respiratory infections: a quantitative systematic review. Trop Med Int Health 2006 Mar;11(3):258-267 [FREE Full text] [doi: 10.1111/j.1365-3156.2006.01568.x] [Medline: 16553905]
6. The sustainable development goals report 2021. United Nations. 2021. URL: https://unstats.un.org/sdgs/report/2021/#:~:text=As%20the%20pandemic%20continues%20to,into%20extreme%20poverty%20in%202020 [accessed 2024-03-05]
7. Joint Monitoring Programme for Water Supply, Sanitation and Hygiene. Hygiene. World Health Organization & United Nations Children's Fund. URL: https://washdata.org/monitoring/hygiene [accessed 2022-06-10]
8. Gould DJ, Moralejo D, Drey N, Chudleigh JH, Taljaard M. Interventions to improve hand hygiene compliance in patient care. Cochrane Database Syst Rev 2017 Sep 01;9(9):CD005186 [FREE Full text] [doi: 10.1002/14651858.CD005186.pub4] [Medline: 28862335]
9. Mbakaya BC, Lee PH, Lee RL. Hand Hygiene Intervention Strategies to Reduce Diarrhoea and Respiratory Infections among Schoolchildren in Developing Countries: A Systematic Review. Int J Environ Res Public Health 2017 Apr 01;14(4):371-385 [FREE Full text] [doi: 10.3390/ijerph14040371] [Medline: 28368323]
10. WASH in health care facilities: global baseline report 2019. World Health Organization & United Nations Children's Fund. 2019. URL: https://www.who.int/publications/i/item/9789241515504 [accessed 2024-03-05]

11. Progress on drinking water, sanitation and hygiene in schools: 2000-2021 data update. World Health Organization & United Nations Children's Fund. 2022. URL: https://www.who.int/publications/m/item/progress-on-drinking-water--sanitation-and-hygiene-in-schools--2000-2021-data-update [accessed 2024-03-05]
12. Water, sanitation, hygiene and health: a primer for health professionals. World Health Organization. 2019. URL: https://www.who.int/publications/i/item/WHO-CED-PHE-WSH-19.149 [accessed 2024-03-05]
13. Sphere Association. The Sphere Handbook: Humanitarian Charter and Minimum Standards in Humanitarian Response. Geneva, Switzerland: Sphere Association; 2018.
14. Vujcic J, Blum L, Ram PK. Strategies and challenges to handwashing promotion in humanitarian emergencies. University at Buffalo. 2014. URL: https://globalhandwashing.org/wp-content/uploads/2015/03/Hand-hygiene-in-emergencies-experts-perspectives-University-at-Buffalo-report.pdf [accessed 2024-03-05]
15. Brown J, Cavill S, Cumming O, Jeandron A. Water, sanitation, and hygiene in emergencies: summary review and recommendations for further research. Waterlines 2012 Jan;31(1-2):11-29. [doi: 10.3362/1756-3488.2012.004]
16. Ramos M, Benelli P, Irvine E, Watson J. WASH in emergencies problem exploration report - handwashing. Humanitarian Innovation Fund. 2016. URL: https://www.susana.org/en/knowledge-hub/resources-and-publications/library/details/2974# [accessed 2024-03-05]
17. Schools ill-equipped to provide healthy and inclusive learning environments for all children. World Health Organization & United Nations Children's Fund. 2022. URL: https://www.unicef.org/rosa/press-releases/schools-ill-equipped-provide-healthy-and-inclusive-learning-environments-all [accessed 2023-08-09]
18. Als D, Meteke S, Stefopulos M, Gaffey MF, Kamali M, Munyuzangabo M, et al. Delivering water, sanitation and hygiene interventions to women and children in conflict settings: a systematic review. BMJ Glob Health 2020 Jul;5(Suppl 1):e002064 [FREE Full text] [doi: 10.1136/bmjgh-2019-002064] [Medline: 32641288]
19. Domini M, Guidotti S, Lantagne D. Temporal analysis of water, sanitation, and hygiene data from knowledge, attitudes, and practices surveys in the protracted humanitarian crisis in Myanmar. J Water Sanit Hyg Dev 2020;10(4):806-817. [doi: 10.2166/washdev.2020.025]
20. Hand hygiene, water quality and sanitation in primary health care facilities and schools not connected to functional water supply systems. hands4health. URL: https://hands4health.dev/ [accessed 2024-03-18]
21. Hussein A. The use of triangulation in social sciences research: can qualitative and quantitative methods be combined? J Comp Soc Work 2009;4(1):106-117. [doi: 10.31265/jcsw.v4i1.48]
22. Bekhet AK, Zauszniewski JA. Methodological triangulation: an approach to understanding data. Nurse Res 2012 Nov 22;20(2):40-43. [doi: 10.7748/nr2012.11.20.2.40.c9442] [Medline: 23316537]
23. Skat Foundation. Mapping of existing WASH in HCF tools & approaches. WASH in Health Care Facilities. 2021. URL: https://www.washinhcf.org/resource/mapping-of-existing-wash-in-hcf-tools-approaches/ [accessed 2023-06-09]
24. Schelbert V, Renggli S, Füllemann N, Mercier S, Brogan J. Manual: facilitiy evaluation tool for WASH in institutions (FACET). WHO / UNICEF Joint Monitoring Programme for water supply, sanitation and hygiene. URL: https://www.eawag.ch/en/department/sandec/projects/sesp/facet/ [accessed 2024-03-05]
25. Deutsch L, Belcher B, Claus R, Hoffmann S. Leading inter- and transdisciplinary research: Lessons from applying theories of change to a strategic research program. Environmental Science & Policy 2021 Jun;120:29-41 [FREE Full text] [doi: 10.1016/j.envsci.2021.02.009]
26. Water and sanitation for health facility improvement tool (WASH FIT): a practical guide for improving quality of care through water, sanitation and hygiene in health care facilities. World Health Organization & United Nations Children's Fund. URL: https://www.who.int/publications/i/item/9789241511698 [accessed 2024-03-05]
27. Mosler HJ. A systematic approach to behavior change interventions for the water and sanitation sector in developing countries: a conceptual model, a review, and a guideline. Int J Environ Health Res 2012;22(5):431-449. [doi: 10.1080/09603123.2011.650156] [Medline: 22292899]
28. The handwashing station. Gravit'eau. 2022. URL: https://www.graviteau.ch/handwashing-station [accessed 2022-06-13]
29. CUBE mini filter. Martin Membrane Systems. 2023. URL: https://www.martin-membrane.de/en/products/drinkable-water [accessed 2023-09-13]
30. Ajzen I. The theory of planned behavior. Organ Behav Hum Decis Process 1991 Dec;50(2):179-211. [doi: 10.1016/0749-5978(91)90020-T]
31. Cialdini RB. Descriptive Social Norms as Underappreciated Sources of Social Control. Psychometrika 2007 Jun 12;72(2):263-268 [FREE Full text] [doi: 10.1007/s11336-006-1560-6]
32. Schwarzer R. Modeling Health Behavior Change: How to Predict and Modify the Adoption and Maintenance of Health Behaviors. Applied Psychology 2008 Jan 30;57(1):1-29. [doi: 10.1111/j.1464-0597.2007.00325.x]
33. Contzen N, Mosler HJ. Impact of different promotional channels on handwashing behaviour in an emergency context: Haiti post-earthquake public health promotions and cholera response. J Public Health 2013 Jun 30;21(6):559-573. [doi: 10.1007/s10389-013-0577-4]
34. Contzen N, Inauen J. Social-cognitive factors mediating intervention effects on handwashing: a longitudinal study. J Behav Med 2015 Dec;38(6):956-969. [doi: 10.1007/s10865-015-9661-2] [Medline: 26243641]

35. Seimetz E, Boyayo AM, Mosler HJ. The Influence of Contextual and Psychosocial Factors on Handwashing. Am J Trop Med Hyg 2016 Jun 01;94(6):1407-1417 [FREE Full text] [doi: 10.4269/ajtmh.15-0657] [Medline: 27139449]
36. Gamma AE, Slekiene J, von Medeazza G, Asplund F, Cardoso P, Mosler HJ. Contextual and psychosocial factors predicting Ebola prevention behaviours using the RANAS approach to behaviour change in Guinea-Bissau. BMC Public Health 2017 May 15;17(1):446 [FREE Full text] [doi: 10.1186/s12889-017-4360-2] [Medline: 28506274]
37. Friedrich MN, Kappler A, Mosler HJ. Enhancing handwashing frequency and technique of primary caregivers in Harare, Zimbabwe: a cluster-randomized controlled trial using behavioral and microbial outcomes. Soc Sci Med 2018 Jan;196:66-76. [doi: 10.1016/j.socscimed.2017.10.025] [Medline: 29128787]
38. Bell M, Card K. Maiduguri: city scoping study. Manchester: African Cities Research Consortium, University of Manchester. URL: https://www.gov.uk/research-for-development-outputs/maiduguri-city-scoping-study [accessed 2024-03-05]
39. The question of Palestine. United Nations. 2023. URL: https://www.un.org/unispal/history/ [accessed 2024-03-05]
40. The world Factbook - Mali Africa. Central Intelligence Agency. 2023. URL: https://www.cia.gov/the-world-factbook/countries/mali/ [accessed 2023-06-08]
41. The world Factbook - Burkina Faso Africa. Central Intelligence Agency. URL: https://www.cia.gov/the-world-factbook/countries/burkina-faso/ [accessed 2023-06-08]
42. Annual school cencus report 2018/2019. Borno State Ministry of Education. 2018. URL: https://medu.bornostate.gov.ng/wp-content/uploads/2023/01/Borno-18_19-ASC-Report-4_10_20-V2-1.pdf [accessed 2024-03-05]
43. Burkina Faso: Aperçu des personnes déplacées internes. United Nations Office for the Coordination of Humanitarian Affairs. URL: https://www.unocha.org/publications/report/burkina-faso/burkina-faso-apercu-des-personnes-deplacees-internes-28-fevrier-2023 [accessed 2024-03-05]
44. Mali : tableau de bord Accès humanitaire (décembre 2023). United Nations Office for the Coordination of Humanitarian Affairs. 2023. URL: https://www.unocha.org/publications/report/mali/mali-tableau-de-bord-acces-humanitaire-decembre-2023 [accessed 2023-04-30]
45. Nigeria: situation report. United Nations Office for the Coordination of Humanitarian Affairs. URL: https://reports.unocha.org/en/country/nigeria [accessed 2024-03-05]
46. Campbell MK, Piaggio G, Elbourne DR, Altman DG, CONSORT Group. Consort 2010 statement: extension to cluster randomised trials. BMJ 2012 Sep 04;345:e5661. [doi: 10.1136/bmj.e5661] [Medline: 22951546]
47. Moulton LH. Covariate-based constrained randomization of group-randomized trials. Clin Trials 2004;1(3):297-305. [doi: 10.1191/1740774504cn024oa] [Medline: 16279255]
48. Ravens-Sieberer U, Bullinger M. Assessing health-related quality of life in chronically ill children with the German KINDL: first psychometric and content analytical results. Qual Life Res 1998 Jul;7(5):399-407. [doi: 10.1023/a:1008853819715] [Medline: 9691720]
49. Hofmann CA, Roberts L, Shoham J, Harvey P. Measuring the impact of humanitarian aid: a review of current practice. The Overseas Development Institute. 2004. URL: https://odi.org/en/about/our-work/measuring-the-impact-of-humanitarian-aid-a-review-of-current-practice/ [accessed 2024-03-05]
50. WHO guidelines on hand hygiene in health care: first global patient safety challenge - clean care is safer care. World Health Organization. 2009. URL: https://www.who.int/publications/i/item/9789241597906 [accessed 2024-03-05]
51. Pickering AJ, Boehm AB, Mwanjali M, Davis J. Efficacy of waterless hand hygiene compared with handwashing with soap: a field study in Dar es Salaam, Tanzania. Am J Trop Med Hyg 2010 Feb;82(2):270-278 [FREE Full text] [doi: 10.4269/ajtmh.2010.09-0220] [Medline: 20134005]
52. Seale AC, Mwaniki M, Newton CR, Berkley JA. Maternal and early onset neonatal bacterial sepsis: burden and strategies for prevention in sub-Saharan Africa. Lancet Infect Dis 2009 Jul;9(7):428-438 [FREE Full text] [doi: 10.1016/S1473-3099(09)70172-0] [Medline: 19555902]
53. Hand hygiene in outpatient and home-based care and long-term care facilities: a guide to the application of the WHO multimodal hand hygiene improvement strategy and the “my five moments for hand hygiene” approach. World Health Organization. 2020. URL: https://www.who.int/publications/i/item/9789241503372 [accessed 2024-03-05]
54. Eeuwijk P, Angehrn Z. How to … conduct a focus group discussion (FGD): methodological manual. Swiss Tropical and Public Health Institute/Swiss TPH. 2017. URL: https://www.swisstph.ch/fileadmin/user_upload/SwissTPH/Topics/Society_and_Health/Focus_Group_Discussion_Manual_van_Eeuwijk_Angehrn_Swiss_TPH_2017_2.pdf [accessed 2024-03-05]
55. Mack N, Woodsong C, MacQueen KM, Guest G, Namey E. Qualitative research methods: a data collector's field guide. Family Health International, US Aid. 2005. URL: https://www.fhi360.org/sites/default/files/media/documents/Qualitative%20Research%20Methods%20-%20A%20Data%20Collector's%20Field%20Guide.pdf [accessed 2024-03-05]
56. Gale NK, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. BMC Med Res Methodol 2013 Sep 18;13:117 [FREE Full text] [doi: 10.1186/1471-2288-13-117] [Medline: 24047204]
57. Blanchet K, Ramesh A, Frison S, Warren E, Hossain M, Smith J, et al. Evidence on public health interventions in humanitarian crises. Lancet 2017 Nov;390(10109):2287-2296. [doi: 10.1016/s0140-6736(16)30768-1]

58. Leresche E, Truppa C, Martin C, Marnicio A, Rossi R, Zmeter C, et al. Conducting operational research in humanitarian settings: is there a shared path for humanitarians, national public health authorities and academics? Confl Health 2020;14:25 [FREE Full text] [doi: 10.1186/s13031-020-00280-2] [Medline: 32435274]
59. Canadian Task Force on the Periodic Health Examination. The periodic health examination. Can Med Assoc J 1979 Nov 03;121(9):1193-1254 [FREE Full text] [Medline: 115569]
60. Adair JG. The Hawthorne effect: a reconsideration of the methodological artifact. J Appl Psychol 1984;69(2):334-345. [doi: 10.1037//0021-9010.69.2.334]

Abbreviations

CFU: colony-forming unit
CONSORT: Consolidated Standards of Reporting Trials
cRCT: cluster randomized controlled trial
FACET: Facility Evaluation Tool for Water, Sanitation, and Hygiene in Institutions
FGD: focus group discussion
h4h: hands4health
KII: key informant interview
MCHHI: multicomponent hand hygiene intervention
MoE: ministry of education
MoH: ministry of health
RANAS: risks, attitudes, norms, abilities, and self-regulation
WASH: water, sanitation, and hygiene
WHO: World Health Organization

Edited by A Mavragani; submitted 20.09.23; peer-reviewed by N Amin; comments to author 25.01.24; revised version received 06.02.24; accepted 07.02.24; published 03.04.24.

Please cite as:
Galli A, Ma'ani Abuzahra Y, Bänziger C, Ballo A, Friedrich MND, Gross K, Harter M, Hattendorf J, Peter M, Tamas A, Owen BN, Winkler MS
Assessing the Effectiveness of a Multicomponent Intervention on Hand Hygiene and Well-Being in Primary Health Care Centers and Schools Lacking Functional Water Supply in Protracted Conflict Settings: Protocol for a Cluster Randomized Controlled Trial
JMIR Res Protoc 2024;13:e52959
URL: https://www.researchprotocols.org/2024/1/e52959
doi:10.2196/52959
PMID:38569182

Protocol

Effectiveness of Sensitization Campaigns in Reducing Leprosy-Related Stigma in Rural Togo: Protocol for a Mixed Methods Cluster Randomized Controlled Trial

Dominik Jockers[1], MA; Akila Wimima Bakoubayi[2], MD; Kate Bärnighausen[1], PhD; P'tanam P'kontème Bando[2]; Stefanie Pechar[3], MA; Teresia Wamuyu Maina[1], MA; Jonas Wachinger[1], MA; Mark Vetter[4], PhD; Yawovi Djakpa[2], MA; Bayaki Saka[5], MD; Piham Gnossike[6], MD; Nora Maike Schröder[1]; Shuyan Liu[7], PhD; Denis Agbenyigan Yawovi Gadah[2], MPH; Christa Kasang[8], PhD; Till Bärnighausen[1], PhD

[1]Heidelberg Insititute of Global Health, Faculty of Medicine and University Hospital, Heidelberg University, Heidelberg, Germany

[2]German Leprosy and Tuberculosis Relief Association, Lomé, Togo

[3]Public Health and Prevention, Technical University of Munich, Munich, Germany

[4]Geovisualization, Technical University of Applied Sciences Würzburg-Schweinfurt, Würzburg, Germany

[5]Department of Dermatology, Tsévié Hospital, University of Lomé, Lomé, Togo

[6]National Programme for Neglected Tropical Diseases, Lomé, Togo

[7]Department of Psychiatry and Psychotherapy (Campus Charité Mitte), Charité – Universitätsmedizin Berlin, Berlin, Germany

[8]German Leprosy and Tuberculosis Relief Association, Würzburg, Germany

Corresponding Author:
Dominik Jockers, MA
Heidelberg Insititute of Global Health
Faculty of Medicine and University Hospital
Heidelberg University
INF 130.3
Heidelberg, 69120
Germany
Phone: 49 6221560
Email: dominik.jockers@uni-heidelberg.de

Abstract

Background: In the global strategy to eliminate leprosy, there remains a need for early case detection to successfully interrupt transmissions. Poor knowledge about leprosy and leprosy-related stigma are key drivers of delayed diagnosis and treatment. Sensitization campaigns to inform and increase awareness among the general population are an integral part of many national neglected tropical disease programs. Despite their importance, the effectiveness of such campaigns has not been rigorously studied in the West African context. A multilingual rural setting with low health literacy in this region presents challenges to the potential impact of sensitization campaigns.

Objective: The primary objective of this study is to assess the causal effect of common practice community sensitization campaigns on leprosy-related knowledge and stigma at the community level and among community health volunteers. Additionally, we will test the potential of novel educational audio tools in the 15 most prominent local languages to overcome literacy and language barriers and amplify sensitization campaigns.

Methods: We will conduct a cluster randomized controlled trial using a sequential mixed methods approach in 60 rural communities across all regions of Togo, West Africa. The study features 2 intervention arms and 1 control arm, with intervention and control assignments made at the community level through randomization. Communities in intervention arm 1 will receive a sensitization campaign in line with the current Togolese national neglected tropical disease program. Communities in intervention arm 2 will receive the same sensitization campaign along with educational audio tools distributed to community households. The control arm will receive no intervention before data collection. Quantitative outcome measures on knowledge and stigma will be collected from a random sample of 1200 individuals. Knowledge will be assessed using the 9-item standardized Knowledge, Attitudes, and Practices Questionnaire. Stigma will be measured using the 7-item Social Distance Scale and the 15-item Explanatory Model Interview Catalogue Community Stigma Scale. We will estimate intention-to-treat effects at the individual level, comparing

the outcomes of the intervention and control arms. In an accompanying qualitative component, we will conduct in-depth interviews with community members, community health volunteers, and health care workers in both treatment arms and the control arm to explore intervention and stigma-related experiences.

Results: This paper describes and discusses the protocol for a mixed methods cluster randomized controlled trial. Data collection is planned to be completed in June 2024, with ongoing data analysis. The first results are expected to be submitted for publication by the end of 2024.

Conclusions: This trial will be among the first to test the causal effectiveness of community-based sensitization campaigns and audio tools to increase knowledge and reduce leprosy-related stigma. As such, the results will inform health policy makers, decision-makers, and public health practitioners designing sensitization campaigns in rural multilingual settings.

Trial Registration: German Clinical Trials Register DRKS00029355; https://drks.de/search/en/trial/DRKS00029355

International Registered Report Identifier (IRRID): DERR1-10.2196/52106

(JMIR Res Protoc 2024;13:e52106) doi:10.2196/52106

KEYWORDS

audio; community health worker; information campaign; knowledge, attitude, and practices; language; leprosy-related stigma; qualitative and quantitative research; stigma intervention; Togo; West Africa

Introduction

Overview

Leprosy is a communicable neglected tropical disease (NTD) caused by *Mycobacterium leprae*. In 2022, more than 140,000 cases were reported globally, mainly in Southeast Asia, Africa, and the Americas [1]. Across sub-Saharan African countries, leprosy is found in endemic pockets and is most common among the rural poor [2,3]. Despite effective antibiotic treatment being widely available, new cases of leprosy continue to occur in Togo [4]. In line with experiences in other countries, a significant number of hidden cases is expected [1,5,6]. In its global strategy to eliminate leprosy, the World Health Organization emphasizes the need for early case detection to successfully interrupt transmissions. Additionally, as an independent objective, the need to reduce stigma is emphasized to further alleviate the burden of the disease [7].

Leprosy is a highly stigmatized disease, mainly due to low understanding and knowledge about the disease itself, including misconceptions regarding transmission and treatment [8-10]. While knowledge and stigma are distinct constructs, they often interact. Consequently, a lack of knowledge about the disease can foster false beliefs that may contribute to the stigmatization of patients. However, even with increased understanding of the disease, stigmatizing attitudes can persist [8]. This stigma contributes to patients' hesitation to seek care [10], as well as delayed diagnosis and treatment [11,12]. As a consequence, a delayed or missed diagnosis of leprosy often results in irreversible disabilities causing permanent visible impairments [13], which in turn reinforce stigma and discrimination [14].

Existing sensitization campaigns aim to create awareness and improve understanding of leprosy among the general population and ultimately achieve early case detection and treatment [15]. Common practice leprosy sensitization campaigns include information on the disease itself, transmission, incubation, development, and potential treatment. Group discussions, leaflets, and positive testimonies of people successfully cured are used to overcome potential entrenched misconceptions among the population. Although there is a comprehensive body of literature on conceptualizing the drivers and consequences of health-related stigma [8,16-20], the effectiveness assessment of interventions targeting leprosy-related stigma are rare. A nonrandomized intervention study in India found health posters and focus group discussions to be associated with improved leprosy-related knowledge and reduced stigma [21]. A before-and-after study in Indonesia also showed leprosy sensitization campaigns to be associated with a reduction of stigma [22]. To the best of our knowledge, the effectiveness of leprosy-related stigma interventions has not been studied in the West African context.

Togo has a literacy rate of 67%, and aside from French being the official working language, 49 local languages are widely spoken [23]. Especially in rural communities, local languages are often the predominant mother tongue. Several scholars have shown the impact of language on education outcomes in the multilingual sub-Saharan African context [24-26]. As such, literacy and language barriers are challenging to the potential effectiveness of one-time sensitization campaigns to build comprehensive knowledge and reduce stigma.

In this study, we assess the effectiveness of community-based sensitization campaigns in increasing leprosy-related knowledge and reducing stigma among the target populations in rural Togo. The common practice sensitization campaigns are carried out by the Togolese National NTD program. The campaigns are building on the inclusion of local health care workers (HCWs) and community health volunteers (CHVs) to mobilize community members and convey knowledge. Furthermore, we will establish the effectiveness of novel audio-based tools that provide target populations with information in local languages to overcome language barriers and increase the effectiveness of sensitization campaigns.

We will conduct a mixed methods cluster randomized controlled trial (cRCT) study in 60 rural communities in Togo.

Study Objectives

The main objective of this study is to assess the effectiveness of community-based sensitization campaigns to increase leprosy-related knowledge and reduce stigma. Our results will

inform national policy and decision makers, as well as stakeholders delivering health services and sensitization campaigns.

Specific research objectives are to (1) establish the effectiveness of community-level sensitization campaigns and local language audio tools to increase knowledge and decrease stigma related to leprosy among community members; (2) determine the effects of leprosy training for CHVs (knowledge on diagnosis, treatment, and prevention); and (3) elucidate the mechanisms and experiences of sensitization interventions among community members, HCWs, and CHVs.

Trial Design

We will use a cRCT using a sequential mixed methods design by collecting and analyzing quantitative and qualitative data. The trial will have 2 intervention arms that are randomly assigned across 60 study communities. Intervention arm 1 will receive the sensitization campaign (common practice by the national NTD program). Intervention arm 2 will receive the sensitization campaign (a common practice by the national NTD program) accompanied by audio tools. Control arm will receive no sensitization campaign exposure before endline data collection.

Communities assigned to the control arm will receive intervention arm 1 after data collection to ensure that all communities will receive common practice sensitization campaigns by the end of the study period.

Conceptual Framework

We use the universal health-related stigma and discrimination framework proposed by Stangl et al [27] to guide our understanding of leprosy-related stigma. Stigma is understood as an attribute discrediting the patient, enabling discrimination, and eventually limiting the opportunities of the affected persons [16,18]. The stigma and discrimination framework describes 4 different stages of health-related stigma: the first stage includes drivers and facilitators of stigma, followed by stigma marking to either health conditions or characteristics of affected groups in the second stage. Once stigma marking takes place, the third phase represents the manifestation of stigma, with experience and anticipation of stigma and stigmatizing behavior. Eventually, the manifestation of stigma affects several outcomes in the fourth stage at the individual level for affected persons and at the institutional level, manifesting as discriminating laws and guidelines. Following Stangl et al [27], the first 3 stages are key areas of applied research and interventions aiming at health-related stigma reduction.

In the context of leprosy, potential drivers of stigma are the fear of infection, social exclusion, and devaluation [8]. Misconceptions of leprosy, such as infection being a consequence of committed sins or social misconduct, can also drive stigma [28,29]. Facilitators of stigma are characteristics of affected groups such as low socioeconomic status or low educational background [8,30]. Leprosy-related stigma is commonly expressed by the loss of the social status, reputation, and self-esteem of affected persons. Patients are often socially isolated and face difficulties achieving socially desirable goals such as marriage [31]. Stigma manifestation also includes the anticipation and internalization of stigma [20]. As a consequence of stigma, early symptoms are often concealed, and delays in diagnosis lead to treatment being initiated at a disease stage where permanent, visible impairments and irreversible disabilities already occur.

While we acknowledge that education alone is never as effective as a combination of strategies for stigma reduction [8,32,33], the interventions in this study are designed to primarily target underlying causes and drivers of stigma by addressing knowledge and beliefs about leprosy at the community level. Additionally, the interventions also engage community members in activities aimed directly at reducing stigma. Through the inclusion of audio tools for information dissemination, we aim to acknowledge potential stigma facilitators, such as low literacy rates, in affected groups [30]. Offering learning content in local languages (rather than French), the audio tools could potentially improve campaign effectiveness by increasing self-efficacy through the ability to participate in the intervention as well as being able to understand the content [24-26]. Additionally, our trainings for CHVs and health facility staff in our intervention arms aim to reduce stigma at the organizational and institutional level (for example, avoiding segregation of patients) [15].

Methods

Study Setting and Implementation Partner

This study will be conducted in rural communities in Togo, West Africa. Study communities have been selected from the national NTD database. A community is considered eligible if it is located in a rural area and if at least one leprosy case has been reported in the national register between 2010 and 2020. A community has been classified as rural if its population (aged 18 years and older) did not exceed 1500 individuals based on remote censoring data [34]. Selected study sites span all 6 regions of Togo, yet districts bordering Burkina Faso were excluded due to security concerns. Between 2010 and 2014, 2630 new cases of leprosy were recorded by the Togolese National Leprosy/Buruli Ulcer Control Program. Nonetheless, a high number of undetected cases are expected [5,6]. To increase awareness, promote active case finding, and facilitate access to leprosy treatment, the Togolese National NTD program is working closely with the international nongovernment organization German Leprosy and Tuberculosis Relief Association (DAHW). The main activities of the collaboration include the implementation of skin screening campaigns in particularly vulnerable communities at risk of leprosy. During campaigns, individuals can receive professional skin screenings by dermatologists and appropriate treatment if needed. To increase help-seeking and prevent stigmatization of diagnosed patients, skin screening camps are preceded by a sensitization campaign on general skin diseases and leprosy in particular. Mobilization for sensitization campaigns and skin screenings is typically done by the respective HCWs and CHVs. Where HCWs are trained staff working from health facilities, CHVs received basic training and are voluntarily providing health services within their communities. The sensitization campaigns implemented by the National NTD program and the DAHW form the basis of the intervention to be evaluated in this study,

and study team members include representatives of the Togolese National NTD program and the DAHW to facilitate data collection and implementation.

Intervention Description

The sensitization campaigns in intervention arms 1 and 2 will be carried out in three steps: (1) planning, (2) social mobilization, and (3) implementation. The planning of sensitization and skin screening activities will be done in collaboration with influential forces in the community (eg, traditional chiefs, religious leaders, school principals, CHVs). Choices regarding the date, time, and place of the activity will be made in collaboration with the local opinion leaders. The social mobilization will entail the mobilization of all influential forces in the community to encourage individuals and families to participate in the activity.

On the day of the implementation of the sensitization activities, community members will be invited to educational sessions. The CHVs will give key information on skin-related NTDs, including leprosy. HCWs will support the CHVs to ensure the accuracy of the information and message given out. Topics covered will be clinical signs, symptoms, treatment, environmental aspects conducive to the contraction of the disease, methods of prevention, management, and prevention of disabilities. The knowledge dissimilation will be done with the help of posters, images of leprosy, and the screening of a documentary film on skin-related NTDs, followed by community debates. In addition, community members are actively involved in activities aimed at reducing stigmatizing attitudes and behaviors toward individuals affected by leprosy. Community leaders play a pivotal role in developing strategies to transform community norms that contribute to the stigma surrounding leprosy patients.

After the sensitization stage, consultations will take place for the screening of cutaneous dermatoses. In a private area, health staff will individually assess people who presents with a lesions, sores, or stains on the body. First aid will be offered by health professionals to any person who presents with a skin disorder, and individuals diagnosed with leprosy will be referred to the health facility for treatment initiation and follow-up consultations.

In intervention arm 2, in addition to the activities described above, the CHVs will offer audio tools to households in the study communities. The solar powered tools will contain the learning content of the campaign in audio form [35]. The content will be translated into the 15 most prominent local languages of the communities in intervention arm 2. The tools will remain within the community until endline data collection (approximately 2 months) to allow repetitive learning for all household members.

Implementation

This study is a cRCT, with the randomization unit being the administrative communities. We stratified the random assignment by administrative regions in Togo (Maritime, Plateaux, Central, Kara, and Savanes) to ensure representation of all intervention and control arms across all regions. Since the sensitization campaigns are carried out at the community level and are targeted at the whole community population, cluster randomization was the natural choice of study design. Participation in the sensitization campaign is voluntary, open to all community members, and does not imply participation in the study as such. Survey participants will be recruited from the general community population, irrespective of their participation in the sensitization campaigns.

We used computer-generated random numbers for intervention arm assignment. We set a random seed to 585,506 in Stata (StataCorp) to execute a replicable and random intervention arm assignment. Misfits at the regional level have been balanced at the global level.

Quantitative data have been collected at baseline in all 60 communities and will be complemented with an endline survey 2 months after intervention implementation. Primary outcomes will be collected in all intervention arms before and after intervention.

Baseline data collection took place in March 2023, and endline survey data and qualitative data are planned to be collected in November 2023. Training of health volunteers and professionals and the implementation of campaigns will take place between August and September 2023.

Eligibility Criteria

As described above, intervention participation is voluntary, open to all community members, and does not imply participation in the survey as such. Eligibility criteria for survey participation vary by study component.

Quantitative Study Component

People aged 18 years and older who are resident of the respective community. All CHVs serving a study community and aged 18 years and older will be eligible to participate in the survey.

Qualitative Study Component

People aged 18 years and older and are residents of the respective community. We will also purposefully select some patients with leprosy. CHVs and HCWs serving a target study community and aged 18 years and older will be eligible to participate in the study.

Outcome Measures

Quantitative End Points

Our primary outcomes to assess leprosy-related knowledge among community members will be based on the standardized Knowledge, Attitudes, and Practices Questionnaire adapted to leprosy. We will assess different forms and perceptions of leprosy-related stigma using the Social Distance Scale, asking for individuals own stigmatizing attitudes. Further, we will ask about the perceived attitudes and behaviors in the community using the Explanatory Model Interview Catalogue (EMIC). Individuals not affected by leprosy will receive the Community Stigma Scale. Affected individuals will receive questions related to their experience with stigma. In addition, we will assess a number of secondary outcomes, such as the Participation Scale. The primary and secondary outcomes are shown in Textbox 1.

Textbox 1. Primary and secondary outcomes.

Primary outcomes

- 15-item Knowledge, Attitudes and Practices Questionnaire [36].
- 7-item Social Distance Scale [36].
- 15-item Explanatory Model Interview Catalogue Community Stigma Scale for persons not affected and Explanatory Model Interview Catalogue for persons affected [37].

Secondary outcomes

- 18-item Participation Scale [38].
- 10-item Rosenberg Self-Esteem Scale [39].
- 3-item University of California, Los Angeles Loneliness Scale [40].
- 2-item Patient Health Questionnaire [41].
- 2-item Generalized Anxiety Disorder Scale [42].
- 3-item Alcohol Use Disorders Identification Test for Consumption [43].

Qualitative End Points

We will explore the needs, preferences, and understanding of HCWs and CHVs regarding training on leprosy treatment and care. With in-depth interviews (IDIs) and shared walks, we will build place-based data, examine the practices and perceptions of HCWs and CHVs relating to pathways to treatment and care, and analyze how stigma may mediate these pathways. Additionally, our IDIs with community members will explore cultural norms and beliefs around health seeking and treatment for leprosy and examine perceptions and experiences regarding the sensitization campaign.

Areas of particular interest are (1) understanding the perceptions of HCWs and CHVs regarding the use and appropriateness of the training received on leprosy treatment and care; (2) understanding the perceptions of HCWs and CHVs regarding stigma, diagnosis, treatment, and care of leprosy; and (3) understanding community perceptions regarding the sensitization campaign, the audio tool, and the diagnosis, treatment, and care of leprosy.

Sample Size

Quantitative Sample Size

We conducted a power calculation for our primary end points to determine the required sample size. The power calculation considers the study design of randomized intervention assignment across clusters (communities). To reach a power of 80% in detecting an effect size of 10 percentage points at a significance level of 5% (SD 30, intracluster correlation coefficient=0.05), a sample of a minimum of 15 individuals in each community is given a fixed number of 60 clusters. This leads to an overall required sample size of 900 individuals. To account for potential complications, we targeted a sample size of 1200 individuals. Baseline data collection took place in March 2023, with 1200 individuals successfully interviewed.

Qualitative Sample Size

To determine the qualitative sample size, we follow the principle of achieving data saturation, which ensures that reoccurring themes are exhausted [44]. With a study that uses IDIs and shared walks—with a relatively focused research question—saturation should occur at approximately 20 interviews or with 20 participants. Therefore, we aim to conduct 5-10 IDIs with HCWs in each of the intervention and control arms (15-30 in total) and 10-15 IDIs with community members in each of the intervention and control arms (30-45 in total).

Recruitment and Data Collection

Over the course of the study, we will integrate several rounds of quantitative and qualitative data collection with community members, CHVs, and HCWs. For an overview of all data collection instruments, see Table 1.

Table 1. Data collection instruments of a mixed methods cluster randomized controlled trial to assess the effectiveness of leprosy sensitization campaigns in rural Togo. A summary of study instruments, respondents, and procedures. Data collection and intervention implementation will take place between March 2023 and June 2024.

Data collection type and instrument	Population and recruitment					Sample size	Estimated duration (minutes)	Timing of data collection
	Population	Observation unit	Sampling unit	Sampling method	Eligibility			
Quantitative								
Survey baseline	Community members of all 60 study communities	Individual	Households	Random selection	Adult men and women aged ≥18 years, preferably household head and spouse	1200	20	Before Intervention
Survey endline	Community members of all 60 study communities	Individual	Households	Random selection	Adult men and women aged ≥18 years, preferably household head and spouse	1200	30	After Intervention
Survey CHV[a]	CHVs of all intervention communities	Individual	Community	Census (intervention arm 1 and 2)	CHV of study community	40	20	After Intervention
Qualitative								
In-depth interview cover sheet	HCWs[b], CHVs and community	Individual	Community	Purposive	Adult men and women aged ≥18 years and HCW, CHV or community member in the respective communities that provide written informed consent	45-75	N/A[c]	During intervention
In-depth interview guide	HCWs and CHVs	Individual	Community	Purposive	Adult men and women aged ≥18 years and HCW, CHV or community member in the respective communities that provide written informed consent	15-30	45-60	During intervention
Shared walk guide	HCWs and CHVs	Individual	Community	Purposive	Adult men and women aged ≥18 years and HCW, CHV or community member in the respective communities that provide written informed consent	15-20	N/A	During intervention
In-depth interview guide	Community members	Individual	Community	Purposive	Adult men and women aged ≥18 years that identify as a community member in the respective communities and provide written informed consent	30-45	45-60	During intervention

[a]CHV: community health volunteer.

[b]HCW: health care worker.

[c]N/A: not applicable.

Quantitative Survey Participants

At baseline, before intervention implementation, community members were sampled through a random selection of households in all 60 study communities. In each community, 10 households were selected following a random walk procedure adjusted to the local context of widely spread farmsteads [45]. In each selected household, one female and one male household member were interviewed, preferably the household head and respective spouse or husband. For the endline survey, the same individuals will be interviewed. All CHVs will be selected for a quantitative survey during the endline data collection.

Qualitative Interview and Shared Walk Participants

We will conduct IDIs with 5-10 HCWs and CHVs in each of the intervention and control arms. In this phase, we will also invite selected 15-20 IDI respondents to participate in a "shared walk" to walk through their community and show research assistants (RAs) where their work takes place, what locational influences there are on their work, and how they feel anything influences their work in relation to leprosy. We will also conduct IDIs with community members in each of the intervention and control arms (30-45 members in total) to understand (depending on the intervention assignment) their perceptions of the services being offered, the sensitization campaign, and their feelings and experiences regarding leprosy.

A total of 3 RAs will conduct the IDIs and shared walks using standardized instruments. These include a participant information sheet, a consent form, a cover sheet, and interview guides (Table 1). Cover sheets will capture sociodemographic data, including sex, age, employment status, children, partner status, and religion. Cover sheets also include a section for RAs to make reflexive and observational notes. Written informed consent will be obtained from all study participants before beginning interviews. Depending on the preference of the participants, IDIs will be conducted one-on-one in a local language or French and will be audio-recorded. Participants in the IDIs will be asked broad, open-ended questions regarding topics such as the training, the intervention and audio tool, stigma, and perceptions of leprosy. IDIs will be designed to elicit personal responses and then lead to more in-depth and specific narrative-building questions. RAs will probe themes that seem to be of relevance to the participant or that are identified as important recurring themes through the debriefing process.

The "shared walk" will follow the tenets of the docent method defined by Chang [46] to provide more place-based data. The participants decide the route and duration of the walk. The RA will ask the participant to show them locations on the walk that are of significance to them for any reason, but will also ask the participant to show locations that are of particular relevance for the work they do and where significant events (such as education or outreach) take place. Each participant is considered to be an expert guide. The participant is the educator, while the RA is the person who needs to learn from and follow the lead of the participant. These walks will be audio recorded and can be supported by photos if the participant wishes to take them. Any photographs submitted in which it is possible to identify individuals will be anonymized.

Data Analysis

Quantitative Analysis

Our primary analysis will be based on intention-to-treat at the individual level using linear regression comparing the outcomes of intervention and control arms. We will measure our primary outcomes in terms of absolute scores and as a percentage of the total possible score. We will use adjusted standard errors for clustering at the community level, our unit of randomization [47]. We will control for a number of baseline covariates, including gender, age, and education, among others.

Qualitative Analysis

Analysis will begin in the field with systematic debriefings. Debriefings are daily meetings with RAs and are designed to identify where interview questions are gaining in-depth responses and where questions need to be changed or refined [48]. Debriefings will also allow the research team to gain a superficial understanding of the main topics arising from the interviews and the shared walks, so that an initial codebook can be developed [48]. Once all data have been collected, IDIs will be translated, transcribed, and managed using NVivo (version pro 12; QSR International) [49]. We will follow a reflexive thematic analysis approach using the recursive 6 stages of analysis as defined by Braun and Clarke [50]. Data analysts will independently read and re-read transcripts for data familiarization. Transcripts will then be inductively analyzed in blocks of 5, and codes will be reviewed to identify similarities or divergence of ideas. This process will be followed until the coding is complete. The main codes will be presented to the study team to decide where reoccurring codes could build our core themes. After revising the codebook, we will develop a thematic scheme that will be presented to the study team, refined, named, and finalized for interpretation and writing.

Our mixed methods process will follow a sequential approach where we begin with quantitative data collection and analysis and, upon completion, start the qualitative component [51]. We assume that the quantitative data will allow us to develop more focused qualitative questions and that the qualitative data will help us to address any gaps in information that we cannot explain through the quantitative results. Further mixing of the 2 methods will occur during the data analysis of both data sets, when we will combine the qualitative and quantitative to present our findings to support the interpretation of the results. As such, we envision the shared walk data to allow us to identify potential intervention improvements with respect to the information provided, the dissemination of this information, and, in particular, participant understanding of the audio tool.

Ethical Considerations

This study was approved by the Togolese Bioethics Committee for Health Research (025/2022) and the Ethics Commission of the Medical Faculty Heidelberg (S-670/2022), Germany. Before consent, information about the study will be provided (verbal or written). All participants will give (verbal or written) informed consent to participate in the research. Participants will not receive compensation for their participation. The data will be deidentified before analysis and securely stored in a password-protected file and on a password-protected computer. Any photographs submitted during qualitative data collection, in which it is possible to identify individuals, will be anonymized. The trial is registered at the German Clinical Trials Register (DRKS-ID: DRKS00029355).

Results

Data collection started in March 2023 and is planned to be completed in June 2024, with ongoing data analysis. Analysis of the quantitative baseline data has been initiated, and results are planned to be submitted for peer-reviewed publication in the second quarter of 2024. The first quantitative endline and qualitative results are expected to be submitted for publication by the end of 2024.

Discussion

We will use the mixed methods cRCT to measure the causal effect of community sensitization campaigns and audio tools distributed to households on knowledge and stigma related to leprosy. The setting of this study is rural communities in Togo, West Africa. Our nested qualitative components, involving interviews and shared walks with community members and local stakeholders such as CHVs and HCWs, will explore the implementation of the intervention and contextualize the

quantitative results of the trial, while also helping to further characterize the mechanisms through which sensitization campaigns and audio tools affect leprosy-related knowledge and stigma.

The contribution of this study to the literature will be 3-fold. First, we will provide causal evidence on the effectiveness of sensitization campaigns on community-level leprosy-related knowledge and stigma. The literature on this is limited, especially in the West African context. Second, we will test novel audio tools for information dissemination to amplify potential campaign effects. The tools are designed to overcome literacy and language barriers in a multilingual context. Third, our results will contribute to the general understanding of leprosy-related stigma in the West African context. The qualitative and quantitative findings will inform policy makers and public health agents to effectively tailor and implement sensitization campaigns, particularly in challenging rural settings.

A potential limitation of this study is the fact that quantitative stigma indicators are self-reported by community members; this outcome might be affected by social-desirability bias. We will test intervention effects on the respondent's knowledge of the disease, which is a key driver of stigma and not prone to social desirability bias. Further, qualitative IDIs with unaffected and affected community members will allow us to triangulate quantitative findings on stigma.

This cRCT serves to provide rigorous scientific evidence about the causal effectiveness of 2 particular interventions in the broader field of health-related stigma interventions and multilingual low-literacy settings. The results will be beneficial for policy makers and public health agents to guide sensitization campaigns and inform them about the potential of audio tools to complement common practice.

Acknowledgments

This study has been externally reviewed and funded following a competitive grant application and review process by the Academic (Hospital Partnerships Funding Line Academic) program carried out by the Deutsche Gesellschaft für Internationale Zusammenarbeit GmbH. The funders had no role in the design, data collection, analysis, interpretation of data, or manuscript writing.

Data Availability

The final data set used and analyzed for this study will be available from the corresponding author on reasonable request.

Authors' Contributions

DJ, AWB, KB, NMS, DAYG, CK, and TB were responsible for the overall conceptualization of the study design. DJ led the design of the quantitative study components. KB led the design and writing of the qualitative study components and edited the protocol paper. DJ led the writing of the protocol paper. DAYG and AWB oversaw the Togolese ethics approval process and set up the local study implementation systems. DJ oversaw the German ethics approval process. CK and MV are grant holders. JW advised on the qualitative study design and edited the protocol paper. TWM advised on the qualitative study design. SL advised on the quantitative study design. SP supported the quantitative data collection and survey design. DJ conducted the power calculations. AWB, PPB, BS, PG and DAYG provided technical input and contributed with local context expertise and implementation in Togo. TB advised on the quantitative study design and sample size calculation. All authors have read and approved of the final version of the manuscript.

Conflicts of Interest

None declared.

References

1. Global leprosy (Hansen disease) update, 2021: moving towards interruption of transmission. Wkly Epidemiol Rec 2022;97(36):429-450 [FREE Full text]
2. Hotez PJ, Kamath A. Neglected tropical diseases in Sub-Saharan Africa: review of their prevalence, distribution, and disease burden. PLoS Negl Trop Dis 2009;3(8):e412 [FREE Full text] [doi: 10.1371/journal.pntd.0000412] [Medline: 19707588]
3. Schreuder PAM, Noto S, Richardus JH. Epidemiologic trends of leprosy for the 21st century. Clin Dermatol 2016;34(1):24-31. [doi: 10.1016/j.clindermatol.2015.11.001] [Medline: 26773620]
4. Leprosy - leprosy registered prevalence rate per 1 000 000 population. World Health Organization. 2021. URL: https://www.who.int/data/gho/indicator-metadata-registry/imr-details/5299 [accessed 2023-07-20]
5. Kombate K, Teclessou JN, Saka B, Tabe-Djato GL, Akakpo AS, Mouhari-Toure A, et al. [Leprosy in Togo: retrospective study of 2630 cases over 15 years]. Our Dermatol Online 2017;8(Suppl. 1):10-14 [FREE Full text] [doi: 10.7241/ourd.2017s.3]
6. Salgado CG, Barreto JG, da Silva MB, Frade MAC, Spencer JS. What do we actually know about leprosy worldwide? Lancet Infect Dis 2016;16(7):778. [doi: 10.1016/S1473-3099(16)30090-1] [Medline: 27352757]
7. Towards Zero Leprosy: Global Leprosy (Hansen's Disease) Strategy 2021–2030. Geneva: World Health Organization; 2021.

8. Sermrittirong S, Van Brakel WH. Stigma in leprosy: concepts, causes and determinants. Lepr Rev 2014;85(1):36-47. [Medline: 24974441]
9. Van't Noordende AT, Lisam S, Ruthindartri P, Sadiq A, Singh V, Arifin M, et al. Leprosy perceptions and knowledge in endemic districts in India and Indonesia: differences and commonalities. PLoS Negl Trop Dis 2021;15(1):e0009031 [FREE Full text] [doi: 10.1371/journal.pntd.0009031] [Medline: 33476343]
10. Barrett R. Self-mortification and the stigma of leprosy in Northern India. Med Anthropol Q 2005;19(2):216-230. [doi: 10.1525/maq.2005.19.2.216] [Medline: 15974328]
11. Dharmawan Y, Fuady A, Korfage I, Richardus JH. Individual and community factors determining delayed leprosy case detection: a systematic review. PLoS Negl Trop Dis 2021;15(8):e0009651 [FREE Full text] [doi: 10.1371/journal.pntd.0009651] [Medline: 34383768]
12. Nicholls PG, Wiens C, Smith WCS. Delay in presentation in the context of local knowledge and attitude towards leprosy: the results of qualitative fieldwork in Paraguay. Int J Lepr Other Mycobact Dis 2003;71(3):198-209. [doi: 10.1489/1544-581X(2003)71<198:DIPITC>2.0.CO;2] [Medline: 14608815]
13. Srinivas G, Muthuvel T, Lal V, Vaikundanathan K, Schwienhorst-Stich EM, Kasang C. Risk of disability among adult leprosy cases and determinants of delay in diagnosis in five states of India: a case-control study. PLoS Negl Trop Dis 2019;13(6):e0007495 [FREE Full text] [doi: 10.1371/journal.pntd.0007495] [Medline: 31247040]
14. Adhikari B, Kaehler N, Chapman RS, Raut S, Roche P. Factors affecting perceived stigma in leprosy affected persons in Western Nepal. PLoS Negl Trop Dis 2014;8(6):e2940 [FREE Full text] [doi: 10.1371/journal.pntd.0002940] [Medline: 24901307]
15. Heijnders M, Van Der Meij S. The fight against stigma: an overview of stigma-reduction strategies and interventions. Psychol Health Med 2006;11(3):353-363. [doi: 10.1080/13548500600595327] [Medline: 17130071]
16. Goffman E. Stigma: Notes on the Management of Spoiled Identity. Englewood Cliffs, NJ: Prentice-Hall; 1963.
17. Hofstraat K, van Brakel WH. Social stigma towards neglected tropical diseases: a systematic review. Int Health 2016;8(Suppl 1):i53-i70 [FREE Full text] [doi: 10.1093/inthealth/ihv071] [Medline: 26940310]
18. Link BG, Phelan JC. Conceptualizing stigma. Annu Rev Sociol 2001;27(1):363-385. [doi: 10.1146/annurev.soc.27.1.363]
19. Thornicroft G, Rose D, Kassam A, Sartorius N. Stigma: ignorance, prejudice or discrimination? Br J Psychiatry 2007;190(3):192-193 [FREE Full text] [doi: 10.1192/bjp.bp.106.025791] [Medline: 17329736]
20. Weiss MG. Stigma and the social burden of neglected tropical diseases. PLoS Negl Trop Dis 2008;2(5):e237 [FREE Full text] [doi: 10.1371/journal.pntd.0000237] [Medline: 18478049]
21. van 't Noordende AT, Lisam S, Singh V, Sadiq A, Agarwal A, Hinders DC, et al. Changing perception and improving knowledge of leprosy: an intervention study in Uttar Pradesh, India. PLoS Negl Trop Dis 2021;15(8):e0009654 [FREE Full text] [doi: 10.1371/journal.pntd.0009654] [Medline: 34424909]
22. Peters RMH, Dadun, Zweekhorst MBM, Bunders JFG, Irwanto, van Brakel WH. A cluster-randomized controlled intervention study to assess the effect of a contact intervention in reducing leprosy-related stigma in Indonesia. PLoS Negl Trop Dis 2015;9(10):e0004003 [FREE Full text] [doi: 10.1371/journal.pntd.0004003] [Medline: 26485128]
23. Literacy rate, adult total (% of people ages 15 and above) - Togo. World Bank. 2023. URL: https://data.worldbank.org/indicator/SE.ADT.LITR.ZS?locations=TG [accessed 2023-06-02]
24. Laitin DD, Ramachandran R, Walter SL. The legacy of colonial language policies and their impact on student learning: evidence from an experimental program in Cameroon. Econ Dev Cult Change 2019;68(1):239-272 [FREE Full text] [doi: 10.1086/700617]
25. Taylor S, von Fintel M. Estimating the impact of language of instruction in South African primary schools: a fixed effects approach. Econ Educ Rev 2016;50:75-89. [doi: 10.1016/j.econedurev.2016.01.003]
26. Eriksson K. Does the language of instruction in primary school affect later labour market outcomes? Evidence from South Africa. Econ Hist Dev Reg 2014;29(2):311-335. [doi: 10.1080/20780389.2014.955272]
27. Stangl AL, Earnshaw VA, Logie CH, van Brakel W, Simbayi LC, Barré I, et al. The health stigma and discrimination framework: a global, crosscutting framework to inform research, intervention development, and policy on health-related stigmas. BMC Med 2019;17(1):31 [FREE Full text] [doi: 10.1186/s12916-019-1271-3] [Medline: 30764826]
28. Ebenso B, Newell J, Emmel N, Adeyemi G, Ola B. Changing stigmatisation of leprosy: an exploratory, qualitative life course study in Western Nigeria. BMJ Glob Health 2019;4(2):e001250 [FREE Full text] [doi: 10.1136/bmjgh-2018-001250] [Medline: 30997168]
29. Opala J, Boillot F. Leprosy among the Limba: illness and healing in the context of world view. Soc Sci Med 1996;42(1):3-19. [doi: 10.1016/0277-9536(95)00026-7] [Medline: 8745104]
30. Pescarini JM, Strina A, Nery JS, Skalinski LM, de Andrade KVF, Penna MLF, et al. Socioeconomic risk markers of leprosy in high-burden countries: a systematic review and meta-analysis. PLoS Negl Trop Dis 2018;12(7):e0006622 [FREE Full text] [doi: 10.1371/journal.pntd.0006622] [Medline: 29985930]
31. van Brakel WH, Sihombing B, Djarir H, Beise K, Kusumawardhani L, Yulihane R, et al. Disability in people affected by leprosy: the role of impairment, activity, social participation, stigma and discrimination. Glob Health Action 2012;5(1):18394 [FREE Full text] [doi: 10.3402/gha.v5i0.18394] [Medline: 22826694]

32. Haverkort E, van ‘t Noordende AT. Health workers’ perceptions of leprosy and factors influencing their perceptions in endemic countries: a systematic literature review. Lepr Rev 2022;93(4):332-347 [FREE Full text] [doi: 10.47276/lr.93.4.332]
33. Arba IF, Hidayati AN, Soetjipto S, Damayanti. Stigma towards leprosy: a systematic review. J Pak Assoc Dermatol 2021;31(2):250-261.
34. Togo 100m population. WorldPop. URL: https://hub.worldpop.org/geodata/summary?id=6438 [accessed 2024-03-21]
35. Unlocking knowledge for everyone, everywhere. Audiopedia. 2023. URL: https://www.audiopedia.org/Main_Page [accessed 2023-06-14]
36. van ’t Noordende AT, van Brakel WH. Towards a cross-neglected tropical disease perception study toolkit: a prototype toolkit developed in the field of leprosy. Lepr Rev 2021;92(2):170-181 [FREE Full text] [doi: 10.47276/lr.92.2.170]
37. Weiss MG, Doongaji DR, Siddhartha S, Wypij D, Pathare S, Bhatawdekar M, et al. The Explanatory Model Interview Catalogue (EMIC): contribution to cross-cultural research methods from a study of leprosy and mental health. Br J Psychiatry 1992;160:819-830. [doi: 10.1192/bjp.160.6.819] [Medline: 1617366]
38. van Brakel WH, Anderson AM, Mutatkar RK, Bakirtzief Z, Nicholls PG, Raju MS, et al. The participation scale: measuring a key concept in public health. Disabil Rehabil 2006;28(4):193-203. [doi: 10.1080/09638280500192785] [Medline: 16467054]
39. Rosenberg M. Society and the Adolescent Self-Image. Middletown, CT: Wesleyan University Press; 1989.
40. Russell DW. UCLA Loneliness Scale (Version 3): reliability, validity, and factor structure. J Pers Assess 1996;66(1):20-40. [doi: 10.1207/s15327752jpa6601_2] [Medline: 8576833]
41. Kroenke K, Spitzer RL, Williams JBW. The Patient Health Questionnaire-2: validity of a two-item depression screener. Med Care 2003;41(11):1284-1292. [doi: 10.1097/01.MLR.0000093487.78664.3C] [Medline: 14583691]
42. Kroenke K, Spitzer RL, Williams JBW, Monahan PO, Löwe B. Anxiety disorders in primary care: prevalence, impairment, comorbidity, and detection. Ann Intern Med 2007;146(5):317-325. [doi: 10.7326/0003-4819-146-5-200703060-00004] [Medline: 17339617]
43. Bush K, Kivlahan DR, McDonell MB, Fihn SD, Bradley KA. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test. Arch Intern Med 1998 Sep 14;158(16):1789-1795 [FREE Full text] [doi: 10.1001/archinte.158.16.1789] [Medline: 9738608]
44. Fusch PI, Ness LR. Are we there yet? Data saturation in qualitative research. Qual Rep 2015;20(9):1408-1416. [doi: 10.46743/2160-3715/2015.2281]
45. Bauer JJ. Selection errors of random route samples. Sociol Methods Res 2014;43(3):519-544. [doi: 10.1177/0049124114521150]
46. Chang JS. The docent method: a grounded theory approach for researching place and health. Qual Health Res 2017;27(4):609-619. [doi: 10.1177/1049732316667055] [Medline: 27634293]
47. Abadie A, Athey S, Imbens GW, Wooldridge J. When should you adjust standard errors for clustering? Working paper 24003. National Bureau of Economic Research. 2017. URL: https://www.nber.org/system/files/working_papers/w24003/w24003.pdf [accessed 2024-03-21]
48. McMahon SA, Winch PJ. Systematic debriefing after qualitative encounters: an essential analysis step in applied qualitative research. BMJ Glob Health 2018;3(5):e000837 [FREE Full text] [doi: 10.1136/bmjgh-2018-000837] [Medline: 30233833]
49. Tenny S, Brannan JM, Brannan GD. Qualitative study. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2022.
50. Braun V, Clarke V. Reflecting on reflexive thematic analysis. Qual Res Sport Exerc Health 2019;11(4):589-597. [doi: 10.1080/2159676x.2019.1628806]
51. Cameron R. A sequential mixed model research design: design, analytical and display issues. Int J Mult Res Approaches 2014;3(2):140-152. [doi: 10.5172/mra.3.2.140]

Abbreviations

CHV: community health volunteer
cRCT: cluster randomized controlled trial
DAHW: German Leprosy and Tuberculosis Relief Association
EMIC: Explanatory Model Interview Catalogue
HCW: health care worker
IDI: in-depth interview
NTD: neglected tropical disease
RA: research assistant

Edited by A Mavragani; submitted 23.08.23; peer-reviewed by E Eschliman; comments to author 25.01.24; revised version received 14.02.24; accepted 22.02.24; published 18.04.24.

Please cite as:
Jockers D, Bakoubayi AW, Bärnighausen K, Bando PP, Pechar S, Maina TW, Wachinger J, Vetter M, Djakpa Y, Saka B, Gnossike P, Schröder NM, Liu S, Gadah DAY, Kasang C, Bärnighausen T
Effectiveness of Sensitization Campaigns in Reducing Leprosy-Related Stigma in Rural Togo: Protocol for a Mixed Methods Cluster Randomized Controlled Trial
JMIR Res Protoc 2024;13:e52106
URL: https://www.researchprotocols.org/2024/1/e52106
doi:10.2196/52106
PMID:38635983

Protocol

Needs and Experiences With Health Care Providers of Adult Rare Disease Patients and Caregivers of People With Rare Diseases: Protocol for a Qualitative Study

Tina Černe[1], MSc; Eva Turk[2,3], MBA, PhD; Spela Mirosevic[1], MSc, PhD; Danica Rotar Pavlič[1], MD, PhD

[1]Deparment of Family Medicine, Univeristy of Ljubljana, Ljubljana, Slovenia

[2]Center for Digital Health and Social Innovation, Department of Health Sciences, Univerisity of St. Pölten, St. Pölten, Austria

[3]Medical Faculty, University of Maribor, Maribor, Slovenia

Corresponding Author:
Tina Černe, MSc
Deparment of Family Medicine
Univeristy of Ljubljana
Poljanski nasip 58
Ljubljana, 1000
Slovenia
Phone: 386 041920083
Email: tina.cerne@mf.uni-lj.si

Abstract

Background: Rare diseases in Europe are defined as diseases with a prevalence of less than 5 per 10,000 people. Despite their individual rarity, the total number of rare diseases is considerable. Rare diseases are often chronic and complex, affecting physical, mental, and neurological health. People with rare diseases face challenges such as delayed diagnosis, limited medical support, and financial burden. Caregivers, usually family members, bear significant physical and emotional burdens. Understanding the experiences of patients with rare disease and their caregivers is critical to effective care, but this is still underresearched. Better support and understanding of the challenges faced by both patients and caregivers is clearly needed. Our study will explore the experiences and needs of people with rare diseases and caregivers of people with rare diseases in relation to accessing health services.

Objective: This study aims to explore the experiences of patients with rare disease and their caregivers with Slovenian health care providers and to create a theoretical model of needs and experiences.

Methods: This is a qualitative thematic analysis study, using the codebook approach. The study will conduct semi–open-ended interviews to understand the experiences and needs of people with rare diseases and caregivers of people with rare diseases in relation to accessing health services. The interview questions will be based on an extensive literature review. Data from the interviews will be analyzed using thematic analysis to identify patterns and build a thematic map. Data will be analyzed by at least 2 coders. To ensure reliability, respondent validation will be conducted and negative cases investigated. Any discrepancies will be resolved by consulting the entire research team until a consensus is reached.

Results: This study was not specifically funded. However, author TČ is supported by grant number P3-0339 from the Slovenian Agency for Research and Innovation. This study was approved by the Medical Ethics Committee of the Republic of Slovenia (0120-47/2022/3), and recruitment is expected to begin in May 2024, with data analysis results anticipated by the end of 2025.

Conclusions: This study will fill an important research gap in Slovenia by exploring the needs and experiences of people living with rare diseases and their caregivers. The results will contribute to the broader field of rare diseases and add knowledge that can inform future research processes and intervention strategies. It also aims to identify neglected areas that have a significant impact on the lives of people with rare diseases. This study is important not only because it addresses the immediate needs of the Slovenian rare disease community, but also because it contributes to a discussion on patient-centered care, health policy design, and the inclusion of psychosocial components in health care.

International Registered Report Identifier (IRRID): PRR1-10.2196/53362

(JMIR Res Protoc 2024;13:e53362) doi:10.2196/53362

KEYWORDS

rare diseases; patients; caregivers; needs; barriers; access to health care

Introduction

Rare Diseases in Europe and Slovenia

In Europe, rare diseases are defined as diseases with a prevalence of less than 5 per 10,000 people in the population [1]. While individual disease incidence is small, the collective number of all types of rare diseases is large [2]. The estimated number of rare diseases is currently between 6000 and 8000 [3]. They are usually chronic and complex and are associated with physical, mental, or neurological disorders. The psychosocial and emotional impact on affected individuals and families is significant and often exacerbated by a lack of adequate community support and services [4].

Health Care Needs of Patients With Rare Disease

Rare diseases, due to their multisystemic nature and associated cognitive and developmental challenges, manifest a wide range of symptoms, resulting in diverse health care needs. Managing these symptoms necessitates the involvement of various health care professionals, the use of medical devices, and "orphan drugs" [5]—specialized medicinal products developed to treat, diagnose, or prevent specific rare diseases [6].

Challenges Faced by Patients With Rare Disease and Caregivers

Rare diseases present numerous challenges, not only for those directly affected but also for their caregivers. These challenges include delayed diagnosis, difficulties accessing health care, and the financial burden of medical treatment [7]. Caregivers of individuals with rare diseases, who are often parents or spouses, shoulder a substantial physical and emotional burden without receiving financial compensation [8]. Their responsibilities encompass providing transportation, running errands, offering emotional support, monitoring symptoms, and performing additional household tasks [9,10]. Many caregivers are forced to reduce or quit their jobs due to these caregiving responsibilities, leading to additional financial strain [11]. The caregivers' physical and mental well-being directly impacts the level of care they can provide to patients with rare diseases [2].

Research Gap in Slovenia

In Slovenia, rare diseases pose a significant public health concern and represent a considerable challenge for the health care system [12]. It is roughly estimated that around 150,000 patients are affected by rare diseases in Slovenia [13], which emphasizes the importance of addressing this issue [14]. Recently, a register of rare, nonmalignant diseases was established in the Republic of Slovenia, which should provide valuable insights into this topic. While some studies have been conducted, such as the one by Halec et al [15] on the impact of rare diseases on an individual's quality of life, and others by Stanimirović et al [12-14] focusing on systems development and strategies to improve care for patients with rare disease, there remains a notable absence of research centered on the experiences and needs of patients with rare disease and their caregivers in Slovenia.

Addressing Research Gap by This Qualitative Study

In Slovenia, there is little research on the experiences of caregivers of people with rare diseases, especially compared with the studies on caregivers worldwide. While studies often focus on specific diseases and their pathophysiology [8], a comprehensive exploration of the experiences of both patients and caregivers is crucial for health care providers. Such insights can aid in developing treatments and support services that align with the unique challenges faced by this population [16].

Preliminary findings of a scoping review [17] and discussions with representatives of various rare disease associations highlight the pressing need for better support and understanding of such issues and that there is a lack of knowledge in the field about the challenges experienced by caregivers and people with rare diseases. The Ministry of Health states in the work plan in the field of rare diseases in the Republic of Slovenia for the period 2021-2030 that it would be useful to research the needs of patients with rare diseases in Slovenia, with special attention to social aspects, palliative care, psychological support, and economic aspects [18]. There is, therefore, a need to identify clear areas for change to help researchers, health care providers, and health policy makers develop, plan, and facilitate better services. The establishment of the rare non-malignant diseases registry of the Republic of Slovenia [19] and the development of a more comprehensive rare disease ecosystem [14] are important steps, but qualitative research focusing on the experiences of people living with rare diseases will complement these efforts and provide valuable insights.

Potential Contributions of This Study

This research study holds the potential to contribute significantly to science and the rare disease community in Slovenia by providing a better understanding of the human dimension, which is essential for developing patient-centered policies that consider the psychosocial, emotional, and practical challenges faced by people with rare diseases and their caregivers; identifying gaps in access to health services and psychosocial support; offering insights into priority areas for action that can guide policy makers; and filling a critical research gap in Slovenia by adding valuable knowledge to the rare disease field.

By addressing these aspects, this study has the potential to make a substantial and unique contribution to both the scientific community and the rare disease community in Slovenia.

Objectives

The primary aim of the study is to explore the needs and experiences of adults with rare diseases and caregivers of people with rare diseases with health care service providers in Slovenia. The secondary aim is to identify gaps in access to health care services and psychosocial support.

The objectives of the research are as follows: (1) to gain insights into the needs and experiences of adults with rare diseases with health care providers in Slovenia; (2) to gain insight into the needs and experiences of caregivers of people with rare diseases

with health care service providers in Slovenia; and (3) based on the obtained data, develop a thematic map of experiences and needs.

Research Questions

Our research questions are as follows: (1) What are the needs and experiences of adults with rare diseases in relation to health care providers in Slovenia? (2) What are the needs and experiences of caregivers of people with rare diseases in relation to health care providers in Slovenia?

Methods

The reporting of this study follows the guidelines of the Consolidated Criteria for Reporting Qualitative Studies in the areas that can be applied to a protocol [20].

Research Team and Reflexivity

In this qualitative research study, the interviews will be conducted by TČ, who has a master degree in psychology and is currently working as a researcher. TČ has previous experience with interviews and has spent over a year researching rare diseases and access to health care. Informal discussions were held with representatives of rare disease associations in Slovenia before the study began. These discussions served to develop an initial understanding of the challenges faced by the rare disease community. The main goal was to create a basic knowledge base and gain deeper insights into the problems faced by people living with rare diseases and their caregivers. Participants were informed that the study was part of a doctoral degree pursuit. Disclosure of this information provided transparency regarding the academic aims of the researcher and the context in which the study was conducted. The motivation for the research is rooted in the identified lack of comprehensive studies in this area and emphasizes a commitment to contribute meaningful knowledge to better support people living with rare diseases.

Study Design—Theoretical Framework

The study uses a conceptual framework based on the biopsychosocial model of health [21], which recognizes the interconnectedness of biological, psychological, and social factors associated with rare diseases [22,23]. The biopsychosocial model requires a multidisciplinary approach [24] and emphasizes the importance of a dynamic and empathetic dyadic relationship between clinicians and patients [25]. This approach includes examining various health-related factors, such as access to psychological support, impact on mental health, social support (family support, self-help groups or networks, and help from caregivers), availability of health care services, and financial resources for health-related needs. By applying the biopsychosocial model, this study aims to provide a comprehensive understanding of the unique experiences of people living with rare diseases and, based on this, make recommendations to improve health care services for people living with rare diseases.

The study follows the approach of qualitative thematic analysis [20]. Given the larger scope of our study and the expected high number of participants, we deliberately chose a “codebook” thematic analysis approach [26]. This structured approach aligns with the pragmatic demands of applied research offering a systematic and organized framework for handling a large volume of qualitative data [26]. We will use a structured coding framework to develop and document the analysis [27]. The codebook developed inductively after (some) data familiarization and coding will serve as a tool to guide data coding and a way of mapping or charting the coded data [26]. Themes that will be developed at an early stage after familiarization, will later be refined or new themes developed based on the subsequent inductive data engagement and analytical process [27].

In the final phase of the analysis, the identified themes generated from the coded data will be used to create a thematic map, and the results will be compared with the existing and new data to assess their relevance and reliability [26].

Participant Selection

Participants will be selected through purposive and snowball sampling. Participants will be invited by the research team by email or telephone. Email invitations will be sent by the research team using contact details from a public database of the National Contact Point for Rare Diseases, to which individuals have previously given consent to be contacted. We will also ask participants to invite other people with rare diseases and caregivers of people with rare diseases to participate in the study by using snowball sampling.

We will use snowball sampling, as it is difficult to identify and reach people with rare diseases and their caregivers. We will start with an initial group of participants contacted through the National Contact Point for Rare Disease, conduct interviews, and collect data, followed by an explanation of the snowball sampling process. We will ask the initial participants to provide us with their contact details or to facilitate communication with those who are eligible and willing to participate in the study.

In addition, the research team will contact the pediatric clinic and collaborate with the doctors in the Department of Family Medicine by email. The email will include a presentation of the study explaining the purpose, methodology, potential benefits, and the importance of participation in identifying suitable participants, as well as relevant study documents such as an information leaflet, consent forms, and contact details of the research team. These documents will serve as a reference for the pediatric clinic to inform eligible participants about the study. Approval and cooperation from the relevant authorities at the pediatric clinic will be obtained before contact is made. The aim of contacting the pediatric clinic is to invite eligible caregivers of people with rare diseases to participate in the study, and the aim of contacting the Department of Family Medicine is to invite adult patients with rare diseases.

To avoid overrepresentation of a particular rare disease in the sample, we will follow the guideline that for each rare disease included, a maximum of 2 participants (either the adult patient or the caregiver) will be included.

Sample Size

Braun and Clarke [28] suggest that studies of experiences and needs collected through interviews require a sample size of 15

to 30 people in order to effectively uncover patterns while maintaining a focus on individual experiences.

Considering the concept of information power, which suggests that a broader study aim, a less specific combination of participants for the research question, and the inclusion of cross-case analysis may require a larger sample size, we decided on a target sample size of at least 40 participants [29]. This includes 20 adults with rare diseases and 20 caregivers of people with rare diseases. As Malterud et al [29] suggest, the appraisal of information power will be repeated during the process, supported by an initial analysis. After the first 3 interviews, an initial review of the data will be done and first suggestions of relevant theory will be made [29].

We will also try to identify and document the reasons for nonparticipation, which will contribute to the transparency and reliability of the study.

Setting

This study is being conducted in Slovenia. It includes health care providers at all 3 levels of health care (primary, secondary, and tertiary care). Data will be collected either in our research offices or participants will have the option of a home visit or digital interview. As caregivers of people with rare diseases may have ongoing care needs [30], we decided to offer them the option of a home visit or digital interview. This gives participants the opportunity to take part at a time and place that is convenient or safe for them [31]. The individual interviews with adults diagnosed with a rare disease will be conducted independently. Caregivers will have the option to participate in the interviews either separately or, if they prefer, together with the person they care for. This flexibility aims to accommodate the preferences and comfort levels of both participants and caregivers.

Description of Sample

We will include adult patients with rare diseases and caregivers of people with rare diseases in our study. It is important to emphasize that our research will focus on rare, nonmalignant diseases. To determine the rarity of the disease, we will use the European definition of rare diseases, according to which rare diseases are categorized as those that affect less than 5 in 10,000 people in the population. To ensure a comprehensive representation of experiences, we aim to include people with different rare diseases. In addition, our sample will indirectly include people with impaired decision-making capacity, such as those with developmental or cognitive impairments, by involving their caregivers. This decision is in line with ethical considerations, as we recognize that it is difficult for people with developmental disabilities to give fully informed consent due to the nature of their condition. Involving caregivers is seen as an ethical strategy to ensure a full understanding of the research topic while upholding the principles of respect and protection of vulnerable populations. Caregivers can be family members, spouses, unmarried partners, close friends, or other people with direct caring responsibilities. To account for possible regional differences in access to health care and support services, our study will include participants from all 9 health regions of Slovenia. The inclusion criteria extend to people who are directly responsible for people diagnosed with a rare disease.

Data Collection

Separate interview guides will be used to explore the perspectives of adult patients with rare disease and their caregivers. The interview questions were formulated based on a literature review and will be pilot-tested to ensure clarity and effectiveness in data collection. The questions formulated for the interviews are also based on the biopsychosocial model of health [21]. In line with the biopsychosocial model, our interview questions refer not only to biological factors but also to psychological and social dimensions (how the rare disease affects the participants' social life and how these conditions influence psychological well-being and social interactions). If subsequent interviews reveal significant topics not covered previously, already interviewed participants may be contacted for additional exploration of those specific areas. Audio recording will be used to capture interviews, ensuring accurate and complete data representation. Participants will be informed about the recording, and explicit consent will be obtained. Field notes will be taken during or after interviews to document contextual information and observations that may enhance the understanding of participants' experiences. The duration of interviews will be based on the natural flow of the conversation, allowing participants to express themselves fully. Specific timeframes will be tailored to individual preferences and needs. As part of the respondent validation process, we plan to present the results of the study to participants and ask for their feedback and comments. While we will not necessarily provide full transcripts, this approach will ensure that participants have the opportunity to validate the results of the study and contribute to their interpretation.

The sociodemographic questionnaire will collect the following data: age, gender, marital status, education level, employment status, relationship to caregiver (caregiver questionnaire), monthly income, housing situation, rare disease diagnosis, year of diagnosis, duration of symptoms, impact of the disease on daily life, nature of costs associated with the rare disease, frequency of medical visits and difficulties in accessing health care services, and the participants' support networks.

Data Analysis

Two researchers will code and compare the data. The coding process will be a collaborative effort to ensure reliability and validity. Themes will be derived through a process. First, a series of initial themes will be developed based on the interview guide and existing literature. Coding will be conducted to provide evidence for these initial themes and to identify additional themes derived from the data. The themes and codes will be refined after the initial coding phase through the development and refinement of a coding template. The final phase of coding will be guided by the final template for theme development. We will use the NVivo program (Lumivero), for coding, editing, and structuring the data. We will also carry out respondent validation, that is, we will present results to the participants and ask them for comments [32]. We will also enrich the data obtained by examining so-called negative cases that deviate from the patterns that otherwise emerge through

data saturation [33]. By examining these cases, we will increase the reliability of the research and gain better insight into the strengths and weaknesses of the research [33].

Eligibility Criteria

The eligibility criteria for this study are listed in Textbox 1.

Textbox 1. The eligibility criteria for this study.

Inclusion criteria for adults with a rare disease

- Aged 18 years or older with a confirmed diagnosis of a rare disease
- Written consent to participate in the study of a person with a rare disease
- Persons who use health services in Slovenia
- Willingness to comply with the study protocol

Exclusion criteria for adults with a rare disease

- Inability to meet the requirements of the study (Participants with severe cognitive impairment or intellectual disabilities will be included in the study indirectly through their caregivers. As qualitative research relies on participants' ability to articulate their experiences, cognitive impairment may limit meaningful participation).
- Unwillingness to meet the demands of the study
- Refusal to fulfill the requirements of the study (refusal to actively participate in the in-depth interviews, to complete a sociodemographic questionnaire, and to consent to data collection)
- Persons who are unable to communicate in Slovene or who are not able to sufficiently understand and express themselves in Slovene will be excluded from the study

Inclusion criteria for caregivers of people with a rare disease

- Family caregivers who directly care for a person with a confirmed diagnosis of a rare disease. Family caregivers are usually relatives (often the patient's parents or spouse) who take on most of the physical and emotional burden of caring for the patient without receiving financial compensation (with the exception of family caregivers who receive payment in the form of social benefits) [34]. They carry out the tasks of monitoring, interpreting, making decisions, taking action, making adjustments, providing care, accessing resources, working with the sick person, and negotiating with the health system [35]
- Written consent to participate in a study of the caregiver of a person with a rare disease

Exclusion criteria for caregivers of people with a rare disease

- Unwillingness to comply with the requirements of the study (refusal to actively participate in in-depth interviews, to complete a sociodemographic questionnaire, and to consent to data collection)
- Inability to meet the study requirements (lack of cognitive ability to participate in the study, such as severe cognitive impairment, Alzheimer disease, or intellectual disability)
- Persons who have not reached the legal age of adulthood in Slovenia (younger than 18 years) will be excluded from the study
- Persons with whom it is not possible to communicate in the Slovene language or who are not able to understand and express themselves sufficiently in the Slovene language will be excluded from the survey
- Persons who provide care in the context of an employment relationship and who are not close persons to the person they are caring for (eg, paid home caregivers or home help, persons employed in social care institutions) will be excluded

Ethical Considerations

The medical ethics committee of the Republic of Slovenia considers the research to be ethically justifiable. The commission notes that all necessary documentation has been included, the statement is written in a way that is understandable for the participants, the security of data storage is guaranteed, and the anonymization of responses is ensured. The document bears the number 0120-47/2022/3. Explicit informed consent will be obtained from all participants. This comprehensive process will ensure participant understanding, adherence to ethical principles, and compliance with the statement approved by the medical ethics committee. The data collected as part of this study will be stored securely in both physical and electronic form, with access to the data restricted to those directly involved in the research. The electronic data will be anonymized by assigning identification codes and stored in a special database located on the premises of the Department of Family Medicine at the Faculty of Medicine in Ljubljana. Before the data are stored in the database, an anonymized version of the research data is created in order to preserve its usefulness while ensuring the confidentiality of the participants. Data protection is ensured by secure passwords, and passwords are stored separately. Participants will not receive any financial or nonmonetary compensation for their participation in this study.

Results

This study was not specifically funded. However, the author TČ is funded by the Slovenian Agency for Research and Innovation under grant number P3-0339. Data collection through

semistructured interviews for the study is scheduled to begin in May 2024 and is expected to be completed on 30 December 2024.

Discussion

Principal Results

This study aims to gain a deeper understanding of the needs and experiences of people living with rare diseases and their caregivers when interacting with health care providers in Slovenia and to shed light on the gap between them. The results of the research will be presented in a thematic map of the needs and experiences of people living with rare diseases and their caregivers. The thematic map will serve as a visual representation that will provide an overview of the interconnected themes identified in the analysis and improve our understanding of the complex relationships between the needs and experiences of the target groups. As identified in the exploratory phase of our research, we spoke informally with representatives of rare disease associations in Slovenia to understand the challenges faced by this community. They highlighted key issues, including the need for psychological support, gaps in palliative care for children, concerns about the attitudes of health care providers, and gaps in respite care. In addition, they highlighted issues around delays in diagnosis, poor communication with health care professionals, stigmatization, lack of information, and poorly coordinated care. Ongoing research will shed further light on these issues and contribute to a comprehensive understanding of the gap between needs and available services. We expect to gain a deeper understanding of the barriers to accessing health services, the impact of these barriers on disease progression, and their psychosocial consequences. We expect participants to express their needs in terms of support services and to give examples of good practices that can later be used for better planning of health services. We hope that the results will also point to previously overlooked areas that have a significant impact on the lives of people significantly affected by rare diseases. Based on the results, we will make recommendations to improve health services for people with rare diseases.

Limitations

A potential challenge of this study arises from the diversity of rare diseases included. Given the uniqueness of each rare disease, it might be difficult to identify commonalities in experiences and needs. While a national register for rare diseases has recently been established in Slovenia, our main resource remains a web-based website that serves as a national contact point for rare diseases. This website lists various associations. Our approach to recruiting participants is a purposive sampling combined with a snowball approach. However, a potential limitation is that individuals who are more involved in supportive communities may be overrepresented in our sample. Consequently, those who are less proactive in seeking the support they need might be underrepresented. To mitigate this bias, we try to use the snowball principle to recruit people who do not belong to these associations and contact participants through doctors. However, it is important to be aware that using the snowball principle may also have a disadvantage. This method could lead to limited diversity among our informants, which could limit the range of perspectives and experiences we can capture [36].

Another challenge is that the study focuses primarily on experiences and needs related to access to health services. However, patients with rare diseases and caregivers of people with rare diseases may face challenges and needs beyond health care, such as education and employment. These aspects may not be fully explored in the study.

Comparison With Prior Work

Previous research has shown that participants have a significant need for information, particularly in relation to psychological and health care aspects [22,37]. In particular, the Depping study highlights the importance of personalized information and the desire for better access to experts and treatments within the health care system [22].

In line with the aims of our study, we found that caregivers and patients often encountered health care professionals whom they perceived as lacking the necessary knowledge and understanding of them or (in the case of caregivers) the person they were caring for [22,37-40]. Consequently, they saw a noticeable gap in their access to vital and necessary care, emphasizing the urgency of better training for health care providers [22,37-40].

Our study protocol represents a step forward in capturing the specific needs and experiences of people living with rare diseases and their caregivers in Slovenia and differs from previous large-scale surveys, such as the comprehensive study conducted in the United States [40]. In contrast to these large-scale initiatives, our focus is tailored to the Slovenian health care landscape and provides a local understanding of the challenges faced by this population. By focusing on the specific context of Slovenia, our study aims to fill existing gaps and contribute valuable insights to the current state of knowledge in rare disease research.

Conclusions

This study will fill an important research gap in Slovenia by exploring the needs and experiences of people living with rare diseases and their caregivers. The results will contribute to the broader field of rare diseases and add knowledge that can inform future research processes and intervention strategies. It also aims to identify neglected areas that have a significant impact on the lives of people with rare diseases. This study is important not only because it addresses the immediate needs of the Slovenian rare disease community, but also because it contributes to a discussion on patient-centered care, health policy design, and the inclusion of psychosocial components in health care.

Acknowledgments

The study was funded by the Slovenian Agency for Research and Innovation (grant P3-0339).

Data Availability

The data sets generated or analyzed during this study are not publicly available due to confidentiality and ethical considerations but are available from the corresponding author on reasonable request.

Authors' Contributions

TČ contributed to the conceptualization and methodology of the project. DRP, ET, and ŠM provided supervision.

Conflicts of Interest

None declared.

References

1. Requena-Méndez A, Bisoffi Z, Vives-Corrons J, Gascon J, Plasència A. European expert network on rare communicable diseases and other rare diseases linked to mobility and globalisation focused on health care provision (EURaDMoG): a feasibility study. Orphanet J Rare Dis 2020 Oct 16;15(1):291-291 [FREE Full text] [doi: 10.1186/s13023-020-01534-1] [Medline: 33066818]
2. Vitale SA. Individual and family issues surrounding a rare disease. Clin Nurs Stud 2017 Aug;6(1):45 [FREE Full text] [doi: 10.5430/cns.v6n1p45]
3. Putzeist M, Mantel-Teeuwisse AK, Wied CC, Hoes AW, Leufkens HGM, de Vrueh RLA. Drug development for exceptionally rare metabolic diseases: challenging but not impossible. Orphanet J Rare Dis 2013;8:179 [FREE Full text] [doi: 10.1186/1750-1172-8-179] [Medline: 24237580]
4. Kole A, Faurisson F. The Voice of 12,000 Patients: Experiences and Expectations of Rare Disease Patients on Diagnosis and Care in Europe. Paris, France: Eurordis; 2009.
5. Zurynski Y, Frith K, Leonard H, Elliott E. Rare childhood diseases: how should we respond? Arch Dis Child 2008;93(12):1071-1074. [doi: 10.1136/adc.2007.134940] [Medline: 18684747]
6. Stedman TL. Stedman's Medical Dictionary. Philadelphia, PA: Lippincott Williams & Wilkins; 2000.
7. Stoller JK. The challenge of rare diseases. Chest 2018;153(6):1309-1314 [FREE Full text] [doi: 10.1016/j.chest.2017.12.018] [Medline: 29325986]
8. Breneol S, Belliveau J, Cassidy C, Curran JA. Strategies to support transitions from hospital to home for children with medical complexity: a scoping review. Int J Nurs Stud 2017;72:91-104. [doi: 10.1016/j.ijnurstu.2017.04.011] [Medline: 28521207]
9. Bakas T, Lewis RR, Parsons JE. Caregiving tasks among family caregivers of patients with lung cancer. Oncol Nurs Forum 2001;28(5):847-854. [Medline: 11421144]
10. Stenberg U, Ruland CM, Miaskowski C. Review of the literature on the effects of caring for a patient with cancer. Psychooncology 2010;19(10):1013-1025. [doi: 10.1002/pon.1670] [Medline: 20014159]
11. Lilly MB, Laporte A, Coyte PC. Labor market work and home care's unpaid caregivers: a systematic review of labor force participation rates, predictors of labor market withdrawal, and hours of work. Milbank Q 2007;85(4):641-690 [FREE Full text] [doi: 10.1111/j.1468-0009.2007.00504.x] [Medline: 18070333]
12. Stanimirovic D, Murko E, Battelino T, Groselj U, Tansek MZ. Towards a comprehensive strategy for the management of rare diseases in Slovenia: outlining an IT-enabled ecosystemic approach. Int J Environ Res Public Health 2021;18(23):12395 [FREE Full text] [doi: 10.3390/ijerph182312395] [Medline: 34886121]
13. Stanimirović D, Murko E. Register redkih bolezni: sistemska izhodišča in razvojne usmeritve. Slovensko društvo za medicinsko informatiko 2018;22(1-2):9-21 [FREE Full text]
14. Stanimirovic D, Murko E, Battelino T, Groselj U. Development of a pilot rare disease registry: a focus group study of initial steps towards the establishment of a rare disease ecosystem in Slovenia. Orphanet J Rare Dis 2019;14(1):172 [FREE Full text] [doi: 10.1186/s13023-019-1146-x] [Medline: 31288838]
15. Halec B, Žunkovic O, Pinteric GH, Lorber M. Kakovost življenja oseb s Pompejevo boleznijo. Zbornica zdravstvene nege 2021;55(1):16-23 [FREE Full text] [doi: 10.14528/snr.2021.55.1.3048]
16. Fleurence R, Selby JV, Odom-Walker K, Hunt G, Meltzer D, Slutsky JR, et al. How the patient-centered outcomes research institute is engaging patients and others in shaping its research agenda. Health Aff (Millwood) 2013;32(2):393-400. [doi: 10.1377/hlthaff.2012.1176] [Medline: 23381533]
17. Černe T, Zaletelj KL, Turk E, Pavlič DR. Experiences of quality of life and access to health services among rare disease caregivers: a scoping review. Orphanet J Rare Dis 2024 Unpublished manuscript(forthcoming).
18. Nacrt dela na podrocju redkih bolezni v Republiki Sloveniji za obdobje od leta 2021 do 2030. Ministrstvo za zdravje.: Ministrstvo za zdravje URL: https://www.gov.si/teme/redke-bolezni/ [accessed 2023-08-28]

19. Lovrečić L, Babić Božović I. Evropske referencne mreže v Sloveniji. Novosti na podrocju redkih bolezni;. Evropska komisija.: Združenje za medicinsko genetiko, Slovensko zdravniško društvo; 2023. URL: https://www.dlib.si/details/URN:NBN:SI:doc-HFSD25A0?&language=eng [accessed 2024-04-03]
20. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. Int J Qual Health Care 2007;19(6):349-357 [FREE Full text] [doi: 10.1093/intqhc/mzm042] [Medline: 17872937]
21. Kusnanto H, Agustian D, Hilmanto D. Biopsychosocial model of illnesses in primary care: a hermeneutic literature review. J Family Med Prim Care 2018;7(3):497-500 [FREE Full text] [doi: 10.4103/jfmpc.jfmpc_145_17] [Medline: 30112296]
22. Depping MK, Uhlenbusch N, von Kodolitsch Y, Klose HFE, Mautner VF, Löwe B. Supportive care needs of patients with rare chronic diseases: multi-method, cross-sectional study. Orphanet J Rare Dis 2021;16(1):44 [FREE Full text] [doi: 10.1186/s13023-020-01660-w] [Medline: 33482869]
23. Pelentsov LJ, Laws TA, Esterman AJ. The supportive care needs of parents caring for a child with a rare disease: a scoping review. Disabil Health J 2015;8(4):475-491 [FREE Full text] [doi: 10.1016/j.dhjo.2015.03.009] [Medline: 25959710]
24. Chambers JB, Marks EM, Russell V, Hunter MS. A multidisciplinary, biopsychosocial treatment for non-cardiac chest pain. Int J Clin Pract 2015;69(9):922-927 [FREE Full text] [doi: 10.1111/ijcp.12533] [Medline: 25363358]
25. Adler HM. Toward a biopsychosocial understanding of the patient-physician relationship: an emerging dialogue. J Gen Intern Med 2007;22(2):280-285 [FREE Full text] [doi: 10.1007/s11606-006-0037-8] [Medline: 17357001]
26. Braun V, Clarke V. Thematic Analysis: A Practical Guide. Los Angeles: SAGE Publications; 2021.
27. Braun V, Clarke V. One size fits all? what counts as quality practice in (reflexive) thematic analysis? Qual Res Psychol 2020;18(3):328-352. [doi: 10.1080/14780887.2020.1769238]
28. Braun V, Clarke V. Successful Qualitative Research: A Practical Guide for Beginners. Los Angeles: SAGE Publications; 2013.
29. Malterud K, Siersma VD, Guassora AD. Sample size in qualitative interview studies: guided by information power. Qual Health Res 2016;26(13):1753-1760. [doi: 10.1177/1049732315617444] [Medline: 26613970]
30. Anderson M, Elliott EJ, Zurynski YA. Australian families living with rare disease: experiences of diagnosis, health services use and needs for psychosocial support. Orphanet J Rare Dis 2013;8:22 [FREE Full text] [doi: 10.1186/1750-1172-8-22] [Medline: 23398775]
31. Pocock T, Smith M, Wiles J. Recommendations for virtual qualitative health research during a pandemic. Qual Health Res 2021;31(13):2403-2413. [doi: 10.1177/10497323211036891] [Medline: 34384307]
32. Torrance H. Triangulation, respondent validation, and democratic participation in mixed methods research. J Mix Methods Res 2012;6(2):111-123. [doi: 10.1177/1558689812437185]
33. Hanson A. Negative case analysis. In: Matthes J, Davis C, Potter R, editors. The International Encyclopedia of Communication Research Methods. Hoboken, NJ: Wiley; 2017:1-2.
34. Wang C, Yan J, Chen J, Wang Y, Lin YC, Hu R, et al. Factors associated with quality of life of adult patients with acute leukemia and their family caregivers in China: a cross-sectional study. Health Qual Life Outcomes 2020;18(1):8 [FREE Full text] [doi: 10.1186/s12955-020-1269-8] [Medline: 31910863]
35. Schumacher KL, Stewart BJ, Archbold PG, Dodd MJ, Dibble SL. Family caregiving skill: development of the concept. Res Nurs Health 2000;23(3):191-203. [doi: 10.1002/1098-240x(200006)23:3<191::aid-nur3>3.0.co;2-b] [Medline: 10871534]
36. Taylor SJ, Bogdan R. Introduction to Qualitative Research Methods: A Guidebook and Resource, 3rd Edition. Hoboken, NJ: John Wiley & Sons Inc; 1998.
37. Pelentsov LJ, Fielder AL, Esterman AJ. The supportive care needs of parents with a child with a rare disease: a qualitative descriptive study. J Pediatr Nurs 2016;31(3):e207-e218. [doi: 10.1016/j.pedn.2015.10.022] [Medline: 26651231]
38. Agazio E, Salerno P, Mirabella F, Gnessi F, Mastroiacovo P, Morosini P, et al. Accessibilità e qualita dei servizi socio-sanitari italiani per i pazienti con malattie rare: il parere delle associazioni. [accessibility and quality to health social services in Italy for the patients with rare diseases: the opinion of associations]. Ann Ig 2005;17(2):121-128. [Medline: 16676732]
39. Zurynski Y, Deverell M, Dalkeith T, Johnson S, Christodoulou J, Leonard H, et al. Australian children living with rare diseases: experiences of diagnosis and perceived consequences of diagnostic delays. Orphanet J Rare Dis 2017;12(1):68 [FREE Full text] [doi: 10.1186/s13023-017-0622-4] [Medline: 28399928]
40. Bogart K, Hemmesch A, Barnes E, Blissenbach T, Beisang A, Engel P, Chloe Barnes Advisory Council on Rare Diseases. Healthcare access, satisfaction, and health-related quality of life among children and adults with rare diseases. Orphanet J Rare Dis 2022;17(1):196 [FREE Full text] [doi: 10.1186/s13023-022-02343-4] [Medline: 35549731]

Edited by A Mavragani; submitted 04.10.23; peer-reviewed by G Rouleau, C Myhre Jensen, K Ayers; comments to author 24.01.24; revised version received 12.02.24; accepted 01.03.24; published 22.04.24.

Please cite as:
Černe T, Turk E, Mirosevic S, Rotar Pavlič D
Needs and Experiences With Health Care Providers of Adult Rare Disease Patients and Caregivers of People With Rare Diseases: Protocol for a Qualitative Study
JMIR Res Protoc 2024;13:e53362
URL: https://www.researchprotocols.org/2024/1/e53362
doi:10.2196/53362
PMID:38648088

Protocol

Marital Self-Disclosure Intervention for the Fear of Cancer Recurrence in Chinese Patients With Gastric Cancer: Protocol for a Quasiexperimental Study

Haiyan Zhao[1], BD; Ye Zhou[2], PhD; Chong Chin Che[3], PhD; Mei Chan Chong[3], PhD; Yu Zheng[1], MD; Yuzhu Hou[1], MD; Canjuan Chen[1], BD; Yantao Zhu[1], BD

[1]Nursing Department, Jingjiang People's Hospital, Taizhou, China

[2]Chinese Nursing Journals Publishing House Co, Ltd, Beijing, China

[3]Department of Nursing Science, Faculty of Medicine, Universiti Malaya, Kuala Lumpur, Malaysia

Corresponding Author:
Ye Zhou, PhD
Chinese Nursing Journals Publishing House Co, Ltd
28/F, Tower C, Chengming Building
Xizhimen South Street, Xicheng District
Beijing, 806054
China
Phone: 86 18801155781
Email: yeyecrystal@126.com

Abstract

Background: Patients with gastric cancer experience different degrees of fear of cancer recurrence. The fear of cancer recurrence can cause and worsen many physical and psychological problems. We considered the “intimacy and relationship processes in couples’ psychosocial adaptation” model.

Objective: The study aims to examine the effectiveness of a marital self-disclosure intervention for improving the level of fear of cancer recurrence and the dyadic coping ability among gastric cancer survivors and their spouses.

Methods: This is a quasiexperimental study with a nonequivalent (pretest-posttest) control group design. The study will be conducted at 2 tertiary hospitals in Taizhou City, Jiangsu Province, China. A total of 42 patients with gastric cancer undergoing chemotherapy and their spouses will be recruited from each hospital. Participants from Jingjiang People’s Hospital will be assigned to an experimental group, while participants from Taizhou People’s Hospital will be assigned to a control group. The participants in the experimental group will be involved in 4 phases of the marital self-disclosure (different topics, face-to-face) intervention. Patients will be evaluated at baseline after a diagnosis of gastric cancer and reassessed 2 to 4 months after baseline. The primary outcome is the score of the Fear of Progression Questionnaire-Short Form (FoP-Q-SF) for patients. The secondary outcomes are the scores of the FoP-Q-SF for partners and the Dyadic Coping Inventory.

Results: Research activities began in October 2022. Participant enrollment and data collection began in February 2023 and are expected to be completed in 12 months. The primary results of this study are anticipated to be announced in June 2024.

Conclusions: This study aims to assess a marital self-disclosure intervention for improving the fear of cancer recurrence in Chinese patients with gastric cancer and their spouses. The study is likely to yield desirable positive outcomes as marital self-disclosure is formulated based on evidence and inputs obtained through stakeholder interviews and expert consultation. The study process will be carried out by nurses who have received psychological training, and the quality of the intervention will be strictly controlled.

Trial Registration: ClinicalTrials.gov NCT05606549; https://clinicaltrials.gov/study/NCT05606549

International Registered Report Identifier (IRRID): DERR1-10.2196/55102

(JMIR Res Protoc 2024;13:e55102) doi:10.2196/55102

KEYWORDS

fear of cancer recurrence; dyadic coping ability; gastric cancer; intervention; nursing; protocol; psychological; marital self-disclosure

Introduction

In 2020, there were 1,089,103 new cases of gastric cancer and 768,793 deaths worldwide, accounting for 5.6% and 7.7% of the total incidences and deaths, respectively [1]. The standardized morbidity and mortality rates were 11.1/100,000 and 7.7/100,000, respectively, and the cumulative morbidity and mortality risks of those aged 0 to 74 years were 1.31% and 0.90%, respectively. Gastric cancer ranks second in terms of cancer incidence and mortality in China, with 679,000 cases and 498,000 deaths, followed by lung cancer (733,000 deaths) [2]. The disability-adjusted life years associated with gastric cancer in China is 9.825 million person-years, accounting for 44.21% of the gastric cancer cases globally [3].

Advancements in postoperative chemotherapy for gastric cancer have led to an increase in the 5-year survival rate of patients to 68% [4]. Although surgery and combined chemotherapy have improved the survival of patients to a certain extent, the high postoperative recurrence rate and metastatic rate, as adverse psychological events, have a tremendous psychological burden on patients [4]. The fear of cancer recurrence, which first appeared in the subject of oncologic psychology, has particular specificity and independence, which is different from other mental and psychological diseases [5]. Studies reported that about 72% of patients experienced various degrees of fear of cancer recurrence during cancer, of which about 46% were mild or moderate and about 7% were severe [6]. To our knowledge, to date, there have been no psychological intervention studies explicitly targeting the fear of cancer recurrence in Chinese patients with gastric cancer, and only 1 study has conducted a cross-sectional survey of cancer recurrence fear in patients with gastric cancer, which ignored the effect on spouses [7]. However, a spouse's high fear of cancer recurrence can affect the spouse's physical and mental health and further jeopardize the patient's health [8]. Therefore, designing a brief, practical, and feasible intervention to alleviate the fear of cancer recurrence in Chinese patients with gastric cancer and their spouses is critical.

Researchers, patients with cancer, representatives of patient rights, policymakers, and oncology psychologists from many countries reached an expert consensus, which defined the fear of cancer recurrence as "fears and concerns of patients with cancer regarding possible future cancer recurrence and/or metastasis and/or progression" [9]. The primary manifestations of high-level fear of cancer recurrence have been explained as follows: "highly focused, highly concerned, persistent, hypervigilant of physical symptoms and present for at least 3 months" [10].

The treatment cycle of advanced gastric cancer is long, and the recurrence rate is high. Although the progress of medical technology and the resection rate of advanced gastric cancer have increased, the high postoperative recurrence rate and metastatic rate, as adverse life events, have a tremendous psychological impact on patients [11]. Adverse reactions, such as nausea, vomiting, dry mouth, constipation, and bone marrow suppression, aggravate the psychological burden of patients, making them more fearful of the recurrence and progression of the disease [12].

Several studies [12-14] showed that the level of fear of cancer recurrence (as measured by the Fear of Progression Questionnaire-Short Form [FoP-Q-SF]) among patients with gastric cancer (120-170 cases) was middle to high (score of 35.43-42.3 points), the physical health dimension score was 18.09 (SD 4.52), and the social family dimension score was 17.34 (SD 6.34). The scores of the fear of cancer recurrence were higher in patients with gastric cancer than in patients with breast cancer [15] and early-stage prostate cancer [16]. A previous study [17] found that Chinese patients with gastric cancer have less knowledge of the fear of cancer recurrence. High levels of fear of cancer recurrence seriously affect the health of patients with gastric cancer, resulting in a series of dysfunctional behaviors, including avoidance behavior, hypervigilance of symptoms, and inability to plan for the future, which can reduce quality of life, and at the same time, the unmet supportive needs of cancer patients can lead to lower treatment compliance. These effects can persist for months or even years after treatment, and in severe cases, they can lead to anxiety disorders, posttraumatic stress symptoms, and depression [18].

In the relationship intimacy model of couples' adaptation to cancer by Manne et al [19], the authors emphasized that self-disclosure in relationship-enhancing behaviors is the primary factor affecting the psychological adjustment of cancer patients and their spouses and plays a positive role in the face of cancer. Marriage psychoeducation can help couples understand the value of communicating with each other, provide emotional and problem-focused support, help in the takeover of a spouse's responsibilities and tasks when one spouse is stressed, and help couples work together to cope when both partners are stressed [20]. In the long run, improvements in dyadic coping are more likely to increase relationship satisfaction than improvements in communication skills [21]. In short, dyadic coping is strongly associated with relationship satisfaction. Therefore, incorporating dyadic coping into a relationship enhancement program may benefit couples' relationships [22].

Emotional disclosure is a core component of marital emotional support, and it involves expressing feelings, ideas, and opinions to each other [23]. Couple discussion of cancer-related distress may help spouses understand the needs of patients and provide more effective support. Married patients with cancer tend to rate their spouses as their most important confidant. However, patients with cancer often feel constrained in talking about their concerns with their spouses, and partners often withdraw or distance themselves from the emotional distress of patients [24]. These avoidance patterns are present even in couples with satisfying relationships. The inability of patients to talk openly with their spouses about their cancer-related concerns may reduce the ability of couples to cope with stress and compromise the quality of the patient-partner relationship and the patient's psychological adjustment.

Multiple linear regression analysis results showed that the self-disclosure and intimacy of patients influenced their fear of cancer recurrence [8]. To date, most intervention studies focused

on the impact of self-disclosure on the psychological aspect of patients, and they ignored the role of their spouses regarding the psychological state [25-27] and failed to treat patients and their spouses as a whole [12]. Given the vast differences between Western countries and China in terms of race; cultural background; religious beliefs; economic development; and the adaptability and accuracy of the related theory, evaluation scale, and influencing factor analysis, the study results based on Western cultural background cannot be directly applied to the Chinese population. Research on spousal disease communication has primarily focused on patients recovering from breast cancer, lung cancer, and even prostate cancer [28,29]. The treatment cycle for advanced gastric cancer is extended, and the recurrence rate is high, which can intensify the psychological burden on patients [12]. During chemotherapy, patients with gastric cancer encounter numerous dietary restrictions and potential complications, such as nausea and vomiting, heartburn, and acid reflux, resulting in a loss of appetite for food [30]. In Chinese culture, it is believed that food is of utmost importance to people. Being unable to eat or having no appetite is a sign of worsening disease, which further exacerbates both the psychological and physical burdens of patients. No research has been performed on the spousal communication of patients with gastric cancer. Additionally, the research findings of other types of cancers cannot be generalized to patients with gastric cancer, and it is necessary to implement targeted psychological intervention measures for Chinese patients with gastric cancer.

The main objective of this study is to assess a marital self-disclosure intervention that is suitable and feasible based on Chinese culture and clinical practice, focuses on the fear of cancer recurrence, guides patients to adjust to a positive attitude through couple self-disclosure, and improves cancer recurrence fear and the marital relationship with their spouses. If the intervention is proven to be effective, the intervention can be adopted as a practical strategy of psychological care for patients with gastric cancer in China.

Methods

Aim

This study aims to develop a marital self-disclosure intervention and evaluate the effectiveness of this intervention for improving the fear of cancer recurrence and the dyadic coping ability in Chinese patients with gastric cancer and their spouses. The trial was registered in November 2022 at ClinicalTrials.gov (NCT05606549).

Hypotheses

The main hypothesis is as follows: Compared with the control group, participants (patients with gastric cancer and their spouses) in the experimental group show lower scores on the FoP-Q-SF after the intervention.

The secondary hypothesis is as follows: Compared with the control group, participants (patients with gastric cancer and their spouses) in the experimental group show improvements in the dyadic coping ability measured by the Dyadic Coping Inventory (DCI) after the intervention.

Theoretical Framework

Manne and Badr [31] believed that it is necessary to not only evaluate the psychological adaptation process of patients in the face of cancer, but also evaluate their spouses. On the basis of summarizing multiple theories, such as the resource theory and social cognition theory, Manne proposed the relationship intimacy model of couple adaptation to cancer [32]. This model divides the factors that affect psychological adaptation into 2 parts: relationship-enhancing behaviors and relationship-compromising behaviors. Relationship-enhancing behaviors, including reciprocal self-disclosure, partner responsiveness, and relationship engagement, have a positive effect on intimacy and psychological adaptation, and intimacy also has a positive effect on psychological adaptation. Relationship-compromising behaviors, including avoidance, criticism, and pressure withdrawal, have a negative effect on intimacy and psychological adaptation. In this model, Manne et al [19] emphasized that reciprocal self-disclosure in relationship-enhancing behaviors is the primary factor affecting the psychological adaptation of patients with cancer and their spouses, and plays a positive role in the face of cancer stressors. This model provides a theory basis for this study to analyze the effect of marital self-disclosure on the fear of cancer recurrence and dyadic coping ability from a binary perspective.

Methodology and Design

A quasiexperimental study with a nonequivalent (pretest-posttest) control group design will be used to examine the effect of marital self-disclosure on the fear of cancer recurrence and dyadic coping ability among patients with gastric cancer and their spouses. The study will be conducted at 2 tertiary hospitals in Taizhou City, Jiangsu Province, China. Considering the time constraints, sample availability, and prevention of contamination, the research will be conducted in the oncology departments (digestive system) of 2 hospitals. The 2 hospitals will be assigned randomly. A total of 42 patients with gastric cancer undergoing chemotherapy and their spouses will be recruited from each hospital. Eligible patients with gastric cancer undergoing chemotherapy who agree to participate and sign the informed consent form will be included in this research. Participants from Jingjiang People's Hospital will be assigned to the experimental group, while participants from Taizhou People's Hospital will be assigned to the control group. Patients with gastric cancer share similar characteristics, such as demographics, treatment, and nursing care plans. The treatment methods refer to the "Guidelines for Diagnosis and Treatment of Gastric Cancer" [32]. The chemotherapy scheme is selected according to the patient's actual situation, which is predicted for 4 to 6 cycles. The study includes 4 stages of face-to-face interventions. The researchers will take measurements at 3 time points: baseline and 2 and 4 months postintervention.

Study Setting and Recruitment

The study will recruit patients and their spouses who are interested in the study. The nurse practitioners will inform the researchers of the patients' interest, and the researchers will explain the research methods and requirements, and the ethical information in detail to the patients. Nurse practitioners from

the Oncology Department of the 2 hospitals will screen the eligible patients based on the inclusion criteria and will inform the patients and their spouses about the study. The patients who agree to participate will sign a written informed consent form.

Participants

Inclusion Criteria

Patients

The inclusion criteria for patients are as follows: (1) the disease meets the diagnostic criteria of the "Guidelines for Diagnosis and Treatment of Gastric Cancer" [32], the preoperative gastroscopy and pathological diagnosis indicate advanced gastric cancer, and the postoperative pathological classification is type II, III, or IV; (2) age ≥18 years and ability to write and communicate effectively; (3) the main caregiver is their spouse; (4) clear consciousness and no understanding barriers; and (5) written informed consent to participate in this study.

Spouses

The inclusion criteria for spouses are as follows: (1) age ≥18 years and ability to write and communicate effectively; (2) the main caregiver is the spouse; (3) clear consciousness and no understanding barriers; and (4) informed consent to participate in this study.

Exclusion Criteria

Patients

The exclusion criteria for patients are as follows: (1) another diagnosis of gastric cancer or another type of cancer, with severe complications, such as gastrointestinal obstruction and perforation; (2) received or is currently receiving psychotherapy from a psychiatrist or psychologist; (3) cognitive impairment or mental impairment; and (4) severe visual, hearing, and speech impairments.

Spouses

The exclusion criteria for spouses are as follows: (1) presence of serious physical diseases or acute diseases, such as cancer, stroke, and cardiovascular or cerebrovascular diseases; (2) received or is currently receiving psychotherapy from a psychiatrist or psychologist; (3) cognitive impairment or mental impairment; and (4) severe visual, hearing, and speech impairments.

Sample Size

The sample size will be calculated using the following formula for sample size based on the study by Charan and Biswas [33]: sample size = 2 (SD) 2 × (Zα/2 + Zβ)2 / D2. It is based on the FoP-Q-SF (primary outcome) from a previously published study [15]. It showed a 95% power to detect a mean difference of 2.88 points between the control and experimental intervention groups in 61 Chinese patients with breast cancer. Statistical significance will be calculated to achieve a statistical power of 0.9 at a 5% significance level for 70 participants in each group. A 2-tailed test will be used to test the hypothesis. The sample size of each dependent variable is 35. To address dropout, an additional 20% is added to the calculation. As a result, the sample size for the experimental and control groups is 42. Consecutive sampling will be used in this study.

Study Interventions

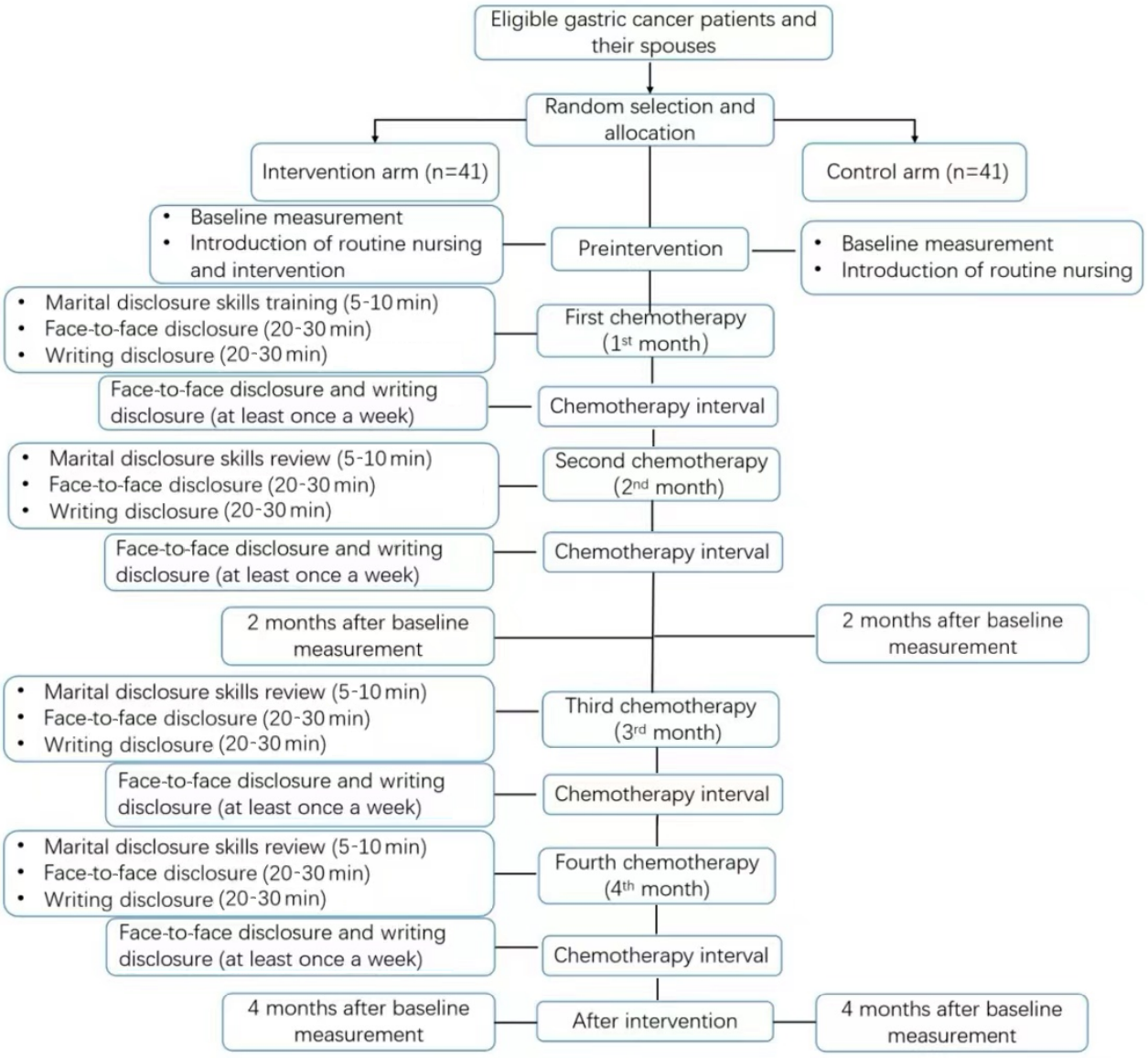
Control Intervention

Participants in the control group will only receive routine nursing care [34]. When patients are admitted to the hospital, apart from routine nursing related to patient treatment, nurses will provide a booklet to patients about gastric cancer and treatment introduction, adverse reactions of chemotherapy, nutrition management, exercise guidance, psychological support (eg, relaxation and music), and life guidance during chemotherapy. In addition, the researchers will contact patients by phone or WeChat every week and send relevant health education messages to reduce the dropout rate. The nurses will not provide patients with any training in communication skills and will not actively encourage couples to discuss cancer-related thoughts and feelings.

Experimental Intervention

The marital self-disclosure intervention is divided into 4 stages. Each stage will be divided into the chemotherapy and hospitalization phase and the interval and home phase. Both phases include verbal and written disclosures, and the intervention will be conducted in 16 weeks. The flowchart of the trial is shown in Figure 1.

Figure 1. Flowchart of the trial. The primary outcome is the score of the Fear of Progression Questionnaire-Short Form (FoP-Q-SF) for patients. The secondary outcomes are the scores of the FoP-Q-SF for partners and the Dyadic Coping Inventory.



Phase 1: Development of the Marital Self-Disclosure Intervention

A previous systematic study [35] by our team found that the most common methods of couple communication are one-on-one and face-to-face communication. They should accept training in marital communication methods before marital self-disclosure, such as how to incorporate the materials from the course into their daily lives through the communication skills learned [36], the strategies for expressing their thoughts and feelings about cancer, and the strategies for accepting and affirming each other's feelings and opinions [23]. Psychological evaluation indicators are stable, and no significant changes are observed in frequent evaluations [15]. Therefore, 3 to 5 weeks per session can obtain a trend change in the index and will not lead to patient evaluation fatigue, which involves better evaluation frequency. Patients with cancer become unwell due to chemotherapy, and short-term interventions (3-6 stages, 40-60 minutes each step) increase memory and application of what couples have learned and increase patient confidence and motivation to manage their disease [37]. In situations where disclosure to a partner becomes challenging or problematic, individuals may gain some benefit from writing a disclosure diary [15,38,39]. The researchers have developed and designed the intervention. The literature mentions the disclosure needs of cancer couples and the changes in cancer patients' fear of recurrence during chemotherapy, and provides information on the interview framework, objectives, benefits, mechanisms, and strategies to implement marital self-disclosure. To further improve the marital self-disclosure intervention, the researchers will conduct in-depth interviews with 3 patients with gastric cancer and their spouses to explore the experiences and needs of marital communication. Furthermore, 6 nurses from the oncology ward will be interviewed to explore the intervention preference and obtain their suggestions for the content of marital self-disclosure. The findings of in-depth interviews will be used to improve the frame, stage, time, and disclosure process of marital self-disclosure.

Phase 2: Panel Evaluation by Experts

An expert panel will be invited to provide expert inputs for developing the marital self-disclosure intervention. The expert selection criteria are as follows: (1) medical staff specializing in oncology, the gastrointestinal system, and psychology; (2) educational background of a bachelor's degree or above; (3) deputy senior title in a medical or nursing position or above; (4) rich experience in the above fields and ability to provide professional advice and guidance for this research; (5) working experience of more than 10 years; and (6) willingness to participate in this study. A total of 12 experts will be selected. Before the consultation, the research background and methods will be explained to the experts to obtain support and cooperation.

The contents and methods of marital self-disclosure are derived from the 2 phases mentioned above.

Chemotherapy and Hospitalization

The intervention time during hospitalization is the first day after chemotherapy, and the intervention is used once per chemotherapy for a total of 4 times for 45 to 70 minutes each time. The intervention includes verbal and written disclosures. The researcher will preside over the marital self-disclosure process and introduce it to patients with gastric cancer and their spouses (definitions of dyadic coping ability, marital self-disclosure, benefits, stages, process, techniques, and time). Both the patient and their spouse will take turns as speakers and listeners, and receive training or undergo review on marital self-disclosure skills for 5 to 10 minutes each time. The training or review details are shown in Table 1. The training will focus on emphasizing the strengths of dyadic coping and distinguishing between problem-solving and supportive communication. Couples will be encouraged to spend more time understanding each other through supportive communication rather than directly addressing communication issues. Couples will practice marital self-disclosure skills through 4 revealing themes. Couples will be encouraged to express their fear of cancer recurrence. When partners disclose information, supporters should allow the speakers to fully express their feelings and should respond positively to the messages of the speakers, showing empathy for them and acknowledging their points of view.

Each stage has different revealing goals, and the disclosure outline set according to the goals differs. The goals of the personal emotional expression stage are to reveal the person's thoughts and feelings after the illness, reveal the person's concerns about the progression of the disease, and express other emotions. The goals of the social cognition expression stage are to disclose the impact of cancer on family or social functioning after the illness, reveal the couple's specific concerns about the progression of the disease, and express other emotions. The goals of the benefit discovery stage are to disclose the benefits of couples from the experience of illness, reveal positive emotions after the illness, and reveal positive changes that have occurred in their life during treatment. The outlook to the future stage aims to disclose the couple's plans, reveal the couple's needs, formulate a cancer recurrence prevention plan, and express other emotions. The patient with gastric cancer and their spouse will disclose information to each other according to the disclosure outline (20-30 minutes) at each stage. When one party is disclosing information, the other party is required to listen actively. After the verbal disclosure, the patient will participate in a written disclosure based on the given topics for 20 to 30 minutes each time. During the written disclosure, the researcher and the patient's spouse are required to maintain silence and respond to the patient timely if there are any questions. After writing, the researcher will take back the notebook. The disclosure topics of the 4 stages are described in detail in Table 2.

Table 1. Disclosure training of the speaker and listener.

Disclosure request	Description
Disclosure request of the speaker	• Share a topic-related experience that evokes strong emotions • Follow your heart and express your thoughts sincerely • Tell your partner about the experience in as much detail as possible, including the event itself and psychological feelings • Do not talk too much at one time; pause occasionally to give your partner a chance to show understanding and support
Disclosure request of the listener	• Try to stand in your partner's role and understand their experience • Avoid immediately solving the problem or giving advice, focus the conversation on how your partner feels, reveal your thoughts when necessary, and facilitate the expression of your partner • Listen reflectively, summarize what your partner has said, pay attention to your tone of voice, maintain eye contact, and nod your head to show understanding

Table 2. Marital self-disclosure topics.

Theme and aspects	Description
First chemotherapy: personal emotional expression	
Verbal disclosure goals (couple)	• Reveal the person's thoughts and feelings after the illness • Reveal the person's concerns about the progression of the disease • Express other emotions
Disclosure outline	• How have you felt since (your partner) became ill? • Are you worried about the progression of the disease? What are the specific aspects? • What other emotions did you experience during the treatment?
Written disclosure (patient)	• Please write down your inner thoughts and feelings during the illness and how they affect you
Second chemotherapy: social cognition expression	
Verbal disclosure goals (couple)	• Disclose the impact of cancer on family or social functioning after the illness • Reveal the couple's specific concerns about the progression of the disease • Express other emotions
Disclosure outline	• What impact does the illness (of your partner) have on your family, work, and social interactions? • Are you worried about the progression of the disease? What are the specific aspects? • What other emotions did you experience during the treatment?
Written disclosure (patient)	• Please write down the couple's specific concerns during the illness and how they affect you
Third chemotherapy: benefit discovery	
Verbal disclosure goals (couple)	• Disclose the benefits for couples from the experience of the illness • Reveal the positive emotions after the illness • Reveal the positive changes that have occurred in your life during treatment
Disclosure outline	• Did you benefit from the experience of being sick? What are the specific aspects? What are the good influences on you? • What positive emotions did you experience after (your partner) got sick? • What positive changes have you made during the (partner) treatment?
Written disclosure (patient)	• Please write down the positive changes and emotions that you have experienced from the illness
Fourth chemotherapy: outlook to the future	
Verbal disclosure goals (couple)	• Disclose the future plans of the couple • Reveal the needs of the couple and formulate a cancer recurrence prevention plan • Express other emotions
Disclosure outline	• What are your plans for the future? • What other needs do you have for preventing disease recurrence and what are your plans to prevent the recurrence of the disease? • What other emotions did you experience during the treatment?
Written disclosure (patient)	• Please summarize and write about your cancer recurrence prevention plan and hopes for the future

Chemotherapy Interval and Homework

With regard to homework requirements, couples will determine the time of disclosure according to the actual situation. The verbal and written disclosures will be conducted at least once a week for 20 to 30 minutes each time. The disclosure outline during the chemotherapy interval is the same as that during the chemotherapy. At the end of every stage, a notebook will be provided to the patient, and the patient will be required to complete homework after chemotherapy.

Phase 3: Marital Self-Disclosure Intervention Workshop for Facilitators

First, 2 oncology nurses with strong nursing and communication skills will gain the trust of patients, screen patients who met the inclusion and exclusion criteria, ask them whether they are willing to participate in this study, and assist the consenting patients in signing the informed consent form. Second, participants in the experimental group will receive the marital self-disclosure intervention delivered by 2 communication-led nurses who have master's degrees in nursing and who are

certified psychological counselors. The communication-led nurse will (1) prevent negative interactions; (2) use the checklist to facilitate the disclosures of patients and their spouses; (3) ensure that the communication does not deviate from the outline; and (4) guide the disclosure content to focus on the speaker's experience. Furthermore, the research nurse will (1) add the WeChat ID of the patient or spouse; (2) provide weekly WeChat reminders; and (3) require the patient or spouse to take photos, upload data, and check in regarding the disclosure execution status and disclosure diary through WeChat. If patients have any nursing or treatment questions, they can consult the research nurse through WeChat. For patients who do not have WeChat, the nurse will follow-up on the implementation status through telephone contact. Moreover, the nurse will record the reasons for patient dropout.

Instruments and Measures

Sociodemographic and Clinical Variables

Variables include the demographic information of patients with gastric cancer and their spouses, including age, gender, education level, employment status, family per capita monthly income, duration of the marriage, and fertility status (couple). In addition, information on clinical variables, including pathological classification, tumor stage, treatment type, and time since cancer diagnosis (patient), will be collected.

Fear of Cancer Recurrence for Patients

The FoP-Q-SF is a 1-dimensional scale based on the Fear of Progression Questionnaire (FoP-Q). The FoP-Q-SF for patients includes 12 items, which are rated on a 5-point Likert scale (1 point indicating "never" and 5 points indicating "always"), with a total score ranging from 12 to 60 and with higher scores indicating higher fear of disease progression [40]. Wu et al [41] translated the scale into Chinese and tested its reliability and validity. The authors found that the Cronbach α coefficient of the total scale was 0.886 and the Guttman split-half coefficient was 0.855. Moreover, the Cronbach α coefficients of the 2 extracted common factors were 0.836 and 0.804, respectively, and the Guttman split-half coefficients were 0.806 and 0.828, respectively, which indicated good content consistency and met the requirements of psychometrics.

Fear of Cancer Recurrence for Partners

The FoP-Q-SF for partners was developed by Zimmermann et al [42] based on the structure of the FoP-Q-SF scale to assess the degree of partners' fear of disease progression in patients. The FoP-Q-SF for partners includes 12 items, which are rated on a 5-point Likert scale (1 point indicating "never" and 5 points indicating "always"), with a total score ranging from 12 to 60 and with higher scores indicating higher fear of their spouses' disease progression. The Cronbach α coefficient of the scale was 0.88. Wu et al [41] translated the scale into Chinese and tested its reliability and validity. The authors found that the Cronbach α coefficient of the total scale was 0.834 and the Guttman split-half coefficient was 0.818. The Cronbach α coefficients of the 2 extracted common factors were 0.835 and 0.699, respectively, and the Guttman split-half coefficients were 0.774 and 0.721, respectively, which indicated good content consistency and met the requirements of psychometrics.

Dyadic Coping Ability

The DCI based on the system interaction model was initially developed by Bodenmann [43], which included 6 dimensions (55 items) and used a 5-point Likert scale. After further improvement, the DCI [44] was revised to 37 items and was measured on a 5-point Likert scale ranging from 1 (not at all/very rarely) to 5 (very often). To assess the stress and coping behaviors of couples, the DCI includes 5 subscales for the patient and a corresponding subscale for the partner: (1) stress communication by self; (2) emotion-focused supportive dyadic coping by self; (3) problem-focused supportive dyadic coping by self; (4) delegated dyadic coping by self; and (5) negative dyadic coping by self. The DCI also assesses 2 common dyadic coping behaviors: emotion-focused common dyadic coping and problem-focused common dyadic coping. Xu et al [45] translated this questionnaire into Chinese. The Cronbach α coefficient was 0.73.

Outcome Assessment

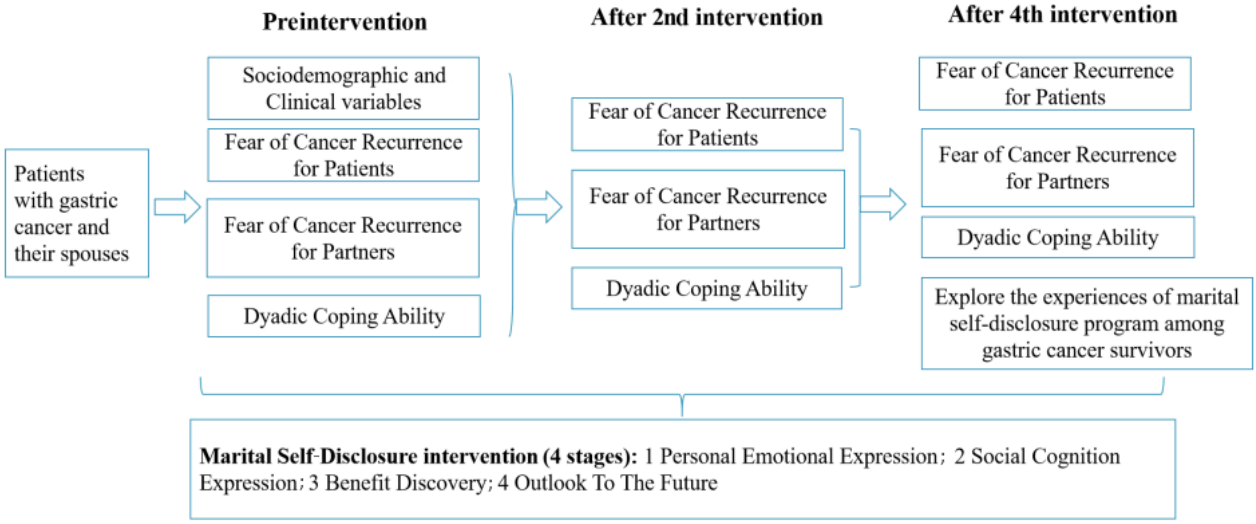
Permission to adopt the 3 questionnaires has been obtained from the original researchers. A trained researcher will assess the outcomes, including sociodemographic variables and psychosocial variables. The sociodemographic variables include demographic and clinical characteristics. The psychosocial variables include fear of cancer recurrence for patients, fear of cancer recurrence for partners, and dyadic coping ability. The psychosocial variables will be repeatedly collected at 3 time points: baseline, after the second session of the intervention (nearly 2 months after baseline), and after the last intervention (almost 4 months after baseline). The control group will be reassessed at the same intervals. Furthermore, participants in the experimental group will be assessed to determine their experiences with the intervention after the last intervention session (Table 3). The conceptual framework is shown in Figure 2.

Table 3. Study measures.

Variable	Outcome (measure)	Time point		
		Baseline	2 months after baseline (after the second intervention)	4 months after baseline (after the fourth intervention)
Inclusion criteria	Sociodemographic and clinical information	Yes	No	No
Primary outcome	FoP-Q-SF[a] for patients	Yes	Yes	Yes
Secondary outcome	FoP-Q-SF for partners and Dyadic Coping Inventory	Yes	Yes	Yes
Intervention experience	In-depth interview	No	No	Yes

[a]FoP-Q-SF: Fear of Progression Questionnaire-Short Form.

Figure 2. Conceptual framework.



Data Collection and Compensation

Upon agreeing to participate in the study, participants will be required to complete a paper-based baseline survey questionnaire. Participants in the intervention group will have the option to receive the marital self-disclosure intervention directly after completing the survey, while participants in the control group will only receive routine care. Both groups of participants will be tracked for a duration of 16 weeks after recruitment, and data will be collected at 3 time points: baseline and 2 and 4 months postintervention.

To ensure participant confidentiality, information collection will be restricted to face-to-face communication and a paper-based questionnaire. Birth dates or participant addresses will not be collected. All data will be stored on secure internal platforms of Hospitals A and B. At the end of the study period, only researchers will have access to the data set.

At each time point, the research team will contact participants via phone or WeChat, according to their preferences. Participants will be notified of upcoming follow-up studies and will be assisted in completing subsequent survey questionnaires. Upon completing each survey, they will receive small gifts, such as a hand sanitizer. Recruitment is expected to last for 12 months, with an additional 16 weeks needed for follow-up with all recruited participants to complete data collection. Data analysis will commence at the end of recruitment.

Allocation and Blinding

This study will recruit an equal number of patients with gastric cancer and their spouses. Participants from Jingjiang People's Hospital will be assigned to the experimental group, while participants from Taizhou People's Hospital will be assigned to the control group. As the study involves a face-to-face psychological intervention, participants and personnel will be unblinded, but the outcome assessment will be blinded. Participant data will be anonymized using individual participant codes, and the database will not contain participant identifiers (eg, birth dates and case numbers).

Data Analysis

Statistical analysis will be conducted using IBM SPSS 21.0 (IBM Corp). The level of statistical significance will be set as α=.05. Descriptive statistics will be used to describe the sociodemographic and psychosocial variables, including percentages, means, and standard deviations. For comparing the baseline characteristics of the 2 groups, the Student *t* test or Mann-Whitney *U* test will be used for quantitative variables and the chi-square test will be used for categorical variables. Two-way repeated-measures ANOVA will be performed to determine the presence of a significant change in the fear of cancer recurrence and DCI in the intervention and control groups in order to analyze the effects of the intervention and compare the control group with the experimental group at baseline and 2 and 4 months postintervention. This analysis will be performed

on an intention-to-treat basis. A *P*-value of <.05 will be considered statistically significant for differences between the 2 groups.

Ethical Considerations

The study protocol has been approved by the ethics committees of Jingjiang People's Hospital and Taizhou People's Hospital (TZRY-LL-AF/SQ-018-3.0 and KY 2022-167-01). A cover letter will be provided to guarantee human rights and ethical transparency, and inform the participants about the aims and benefits of this study. Participants will be informed that they can voluntarily participate and withdraw from the study without any impact on their treatment or nursing care. If they agree to participate, they will be required to sign an informed consent form with detailed information concerning the goals and procedures of the intervention. The data of this research will be kept confidential and anonymous. The trial was registered in November 2022 at ClinicalTrials.gov (NCT05606549).

Results

The research activities for this study commenced in October 2022. Participant recruitment and data collection began in February 2023, with the expectation of completion within 12 months (by December 2024). As of October 30, 2023, a total of 97 gastric cancer patients and their spouses have been recruited, and all baseline data have been collected. Once sufficient participants are recruited, subsequent measures will be performed and data analysis will commence. The primary results of this study are anticipated to be announced in June 2024.

Discussion

Marital Self-Disclosure Intervention and Protocol Design

Improvement of the fear of cancer recurrence and dyadic coping ability in patients with gastric cancer is necessary. To date, few psychological interventions effectively manage the fear of cancer recurrence in patients with gastric cancer. This is the first and only intervention with the explicit aim of improving the fear of cancer recurrence in Chinese patients with gastric cancer. The intervention focuses on personal emotional expression, social cognition expression, benefit discovery, and outlook to the future, with a further focus on the fear of cancer recurrence. This study will provide evidence of the effectiveness of the marital self-disclosure protocol for improving the fear of cancer recurrence compared with routine nursing care.

There are several advantages of the marital self-disclosure intervention. First, the study involves a long-term intervention that spans from the participant's diagnosis of gastric cancer until the end of chemotherapy. In a preview study, among patients with gastric cancer in the first, third, and sixth chemotherapy stages, greater family support was associated with a lower fear of cancer recurrence [7]. Therefore, early and lasting intervention is essential.

Second, the study considers the marital factors related to the fear of cancer recurrence and has developed relevant communication topics in each phase. The husband and wife will be trained in marital self-disclosure, and formal disclosure will be made after both husband and wife have mastered the method of disclosure. Moreover, before each phase, the couple will review the method of disclosure again so that the couple can fully grasp the method of disclosure and return it as a homework exercise, making the research results more credible. Finally, this study combines written and verbal representations to facilitate better participant expression of concerns regarding the fear of cancer recurrence.

Third, the study is based on not only a literature review but also Chinese cultural background, clinical practice, and stakeholder input to design a feasible intervention for Chinese patients with gastric cancer.

Fourth, the marital self-disclosure intervention will be designed for implementation by nurses, and it may appeal to nurses who seek flexibility and dynamism in their work. The intervention will train nurses to teach patients and their spouses to use the theory of respect, empathy, and positive attention in emotional communication and marital interaction. Stable, friendly, and trusting relationships will be built between nurses and patients.

Limitations

This study has some minor limitations. First, this study involves a long-term intervention, and some participants may not complete the study owing to loss of follow-up or physical deterioration during treatment. Second, missing data may influence the results and must be addressed statistically. To overcome this bias, a 20% attrition rate will be included in the sample size calculation, and an intention-to-treat analysis will be performed during the data analysis. Finally, this study will only include patients during chemotherapy.

Conclusion

This is the first attempt to develop a brief and feasible intervention to manage the fear of cancer recurrence in Chinese patients with gastric cancer. If the marital self-disclosure intervention is effective, it will be implemented at the hospital. This brief and focused intervention will be integrated to enhance clinical practice. Even with null results, participants with gastric cancer and their spouses will obtain more comprehensive self-care nursing knowledge. Furthermore, investigators will obtain a large amount of data to analyze the fear problems of patients with gastric cancer.

Acknowledgments

This research was funded by Taizhou Traditional Chinese Medicine Technology Development Project (grant number: TZ202106).

Authors' Contributions

HZ, Y Zhou, Y Zheng, YH, CC, and Y Zhu substantially contributed to conception and design, acquisition of data, and analysis and interpretation of data. HZ, Y Zhou, CCC, and MCC were involved in drafting the manuscript or revising it critically for important intellectual content. Y Zhou, CCC, and MCC provided final approval to the manuscript. Y Zhou agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of Interest

None declared.

References

1. Akbari A, Ashtari S, Tabaiean S, Mehrdad-Majd H, Farsi F, Shojaee S, et al. Overview of epidemiological characteristics, clinical features, and risk factors of gastric cancer in Asia-Pacific region. Asia Pac J Clin Oncol 2022 Dec;18(6):493-505 [FREE Full text] [doi: 10.1111/ajco.13654] [Medline: 35073453]
2. Xia C, Dong X, Li H, Cao M, Sun D, He S, et al. Cancer statistics in China and United States, 2022: profiles, trends, and determinants. Chin Med J (Engl) 2022 Mar 09;135(5):584-590 [FREE Full text] [doi: 10.1097/CM9.0000000000002108] [Medline: 35143424]
3. Bray F, Ferlay J, Soerjomataram I, Siegel R, Torre L, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018 Nov;68(6):394-424 [FREE Full text] [doi: 10.3322/caac.21492] [Medline: 30207593]
4. Waters E, Kincaid C, Kaufman A, Stock M, Peterson L, Muscanell N, et al. Concerns about unintended negative consequences of informing the public about multifactorial risks may be premature for young adult smokers. Br J Health Psychol 2014 Nov;19(4):720-736 [FREE Full text] [doi: 10.1111/bjhp.12069] [Medline: 24118369]
5. Thewes B, Bell M, Butow P, Beith J, Boyle F, Friedlander M, Members of the FCR Study Advisory Committee. Psychological morbidity and stress but not social factors influence level of fear of cancer recurrence in young women with early breast cancer: results of a cross-sectional study. Psychooncology 2013 Dec;22(12):2797-2806 [FREE Full text] [doi: 10.1002/pon.3348] [Medline: 24038525]
6. Simard S, Savard J, Ivers H. Fear of cancer recurrence: specific profiles and nature of intrusive thoughts. J Cancer Surviv 2010 Dec;4(4):361-371 [FREE Full text] [doi: 10.1007/s11764-010-0136-8] [Medline: 20617394]
7. Sicheng D. Fear of disease progression and its influencing factors in patients with advanced gastric cancer after chemotherapy. Anhui Province, China: Anhui Medical University; 2020.
8. Fan W. A binary interaction study of self-disclosure and fear of recurrence in breast cancer patients and spouses. Hebei Province, China: Hebei University; 2021.
9. Lebel S, Ozakinci G, Humphris G, Mutsaers B, Thewes B, Prins J, University of Ottawa Fear of Cancer Recurrence Colloquium attendees. From normal response to clinical problem: definition and clinical features of fear of cancer recurrence. Support Care Cancer 2016 Aug;24(8):3265-3268 [FREE Full text] [doi: 10.1007/s00520-016-3272-5] [Medline: 27169703]
10. Mutsaers B, Butow P, Dinkel A, Humphris G, Maheu C, Ozakinci G, et al. Identifying the key characteristics of clinical fear of cancer recurrence: An international Delphi study. Psychooncology 2020 Mar;29(2):430-436 [FREE Full text] [doi: 10.1002/pon.5283] [Medline: 31713279]
11. Zhao G, Li C, Li J, Balluz L. Physical activity, psychological distress, and receipt of mental healthcare services among cancer survivors. J Cancer Surviv 2013 Mar;7(1):131-139 [FREE Full text] [doi: 10.1007/s11764-012-0254-6] [Medline: 23184465]
12. Wang D, Zheng W, Yan T, Duan H, Hou S, Wang D. The fear of recurrence and its correlation with depression in patients with gastric cancer. Modern Preventive Medicine 2018;45(20):3824-3827.
13. Liu J, Fu Z, Cui H. Correlation between coping style and fear of disease progression in patients with postoperative chemotherapy for gastric cancer. China Laboratory Diagnostics 2022;26(2):194-198.
14. He B, Li Y, Hong Y. Role of mental resilience in fear of cancer recurrence in patients undergoing radical gastrectomy: An understanding of moderating effects of social support. WCJD 2020 Jan 8;28(1):33-38. [doi: 10.11569/wcjd.v28.i1.33]
15. Zhang X, Zhang L, Jia Z, Cheng Y. Application and effect evaluation of marital self-disclosure intervention on the fear of cancer recurrence in young breast cancer patients. Chinese Journal of Nursing 2019;54(11):1610-1614 [FREE Full text]
16. Carlson L, Rouleau C, Speca M, Robinson J, Bultz B. Brief supportive-expressive group therapy for partners of men with early stage prostate cancer: lessons learned from a negative randomized controlled trial. Support Care Cancer 2017 Apr;25(4):1035-1041 [FREE Full text] [doi: 10.1007/s00520-016-3551-1] [Medline: 28064386]
17. Zhao MH, Ma X. The Psychological Status of Fear of Cancer Recurrence in Patients with Advanced Gastric Cancer after Chemotherapy and Its Effect on Quality of Life and Follow-up Outcomes. Chinese Journal of Social Medicine 2023;40(2):192-195 [FREE Full text]

18. Porter L, Baucom D, Keefe F, Patterson E. Reactions to a partner-assisted emotional disclosure intervention: direct observation and self-report of patient and partner communication. J Marital Fam Ther 2012 Jun;38 Suppl 1:284-295 [FREE Full text] [doi: 10.1111/j.1752-0606.2011.00278.x] [Medline: 22765340]
19. Manne S, Ostroff J, Rini C, Fox K, Goldstein L, Grana G. The interpersonal process model of intimacy: the role of self-disclosure, partner disclosure, and partner responsiveness in interactions between breast cancer patients and their partners. J Fam Psychol 2004 Dec;18(4):589-599 [FREE Full text] [doi: 10.1037/0893-3200.18.4.589] [Medline: 15598164]
20. Kayser K, Watson L, Andrade J. Cancer as a "we-disease": Examining the process of coping from a relational perspective. Families, Systems, & Health 2007 Dec;25(4):404-418 [FREE Full text] [doi: 10.1037/1091-7527.25.4.404]
21. Bodenmann G, Bradbury TN, Pihet S. Relative Contributions of Treatment-Related Changes in Communication Skills and Dyadic Coping Skills to the Longitudinal Course of Marriage in the Framework of Marital Distress Prevention. Journal of Divorce & Remarriage 2008 Dec 29;50(1):1-21. [doi: 10.1080/10502550802365391]
22. Falconier M, Jackson J, Hilpert P, Bodenmann G. Dyadic coping and relationship satisfaction: A meta-analysis. Clin Psychol Rev 2015 Dec;42:28-46 [FREE Full text] [doi: 10.1016/j.cpr.2015.07.002] [Medline: 26295276]
23. Porter L, Keefe F, Baucom D, Hurwitz H, Moser B, Patterson E, et al. Partner-assisted emotional disclosure for patients with gastrointestinal cancer: results from a randomized controlled trial. Cancer 2009 Sep 15;115(18 Suppl):4326-4338 [FREE Full text] [doi: 10.1002/cncr.24578] [Medline: 19731357]
24. Northouse L, Mood D, Templin T, Mellon S, George T. Couples' patterns of adjustment to colon cancer. Soc Sci Med 2000 Jan;50(2):271-284 [FREE Full text] [doi: 10.1016/s0277-9536(99)00281-6] [Medline: 10619695]
25. Rabin C. Cancer-Related Self-Disclosure in the Workplace/School by Adolescent and Young Adult Cancer Survivors. J Adolesc Young Adult Oncol 2020 Aug;9(4):528-533 [FREE Full text] [doi: 10.1089/jayao.2019.0159] [Medline: 32255699]
26. Rafii F, Momeni M, Taleghani F. Symptom Disclosure Process Among Iranian Women With Self-discovered Breast Cancer. Cancer Nurs 2022 Jul 13;45(1):21-30 [FREE Full text] [doi: 10.1097/NCC.0000000000000861] [Medline: 32657898]
27. Zhang M. Construction of a self-disclosed benefit discovery intervention program for breast cancer patients. Anhui Province, China: Anhui Medical University; 2019.
28. Çömez S, Karayurt Ö. The effect of web-based training on life quality and spousal adjustment for women with breast cancer and their spouses. Eur J Oncol Nurs 2020 Aug;47:101758 [FREE Full text] [doi: 10.1016/j.ejon.2020.101758] [Medline: 32659714]
29. Zhihong N, Jun'e L, Yali S, Yue Z, Shenshen Y, Hui Q. Couples communication intervention for spouses of breast cancer patients: a randomized trial. Chinese Nursing Management 2019;19(5):682-687 [FREE Full text]
30. Qiuju T. Construction of oral nutrition nursing practice program for home-based patients after gastric cancer. Shanghai, China: Shanghai Jiao Tong University; 2022.
31. Manne S, Badr H. Intimacy and relationship processes in couples' psychosocial adaptation to cancer. Cancer 2008 Jun 01;112(11 Suppl):2541-2555 [FREE Full text] [doi: 10.1002/cncr.23450] [Medline: 18428202]
32. Department of Medical Affairs. Standard for the diagnosis and treatment of gastric cancer (2018 edition). Chinese Journal of Digestive Diseases and Imaging (Electronic Edition) 2019;9(03):118-144.
33. Charan J, Biswas T. How to calculate sample size for different study designs in medical research? Indian J Psychol Med 2013 Apr;35(2):121-126 [FREE Full text] [doi: 10.4103/0253-7176.116232] [Medline: 24049221]
34. Yongyi C. Oncology specialist nursing. Hunan Province, China: Hunan Science and Technology Press; 2010.
35. Zhou Y, Che C, Chong M, Zhao H, Lu Y. Effects of marital self-disclosure on marital relationship and psychological outcome for cancer patients: a systematic review. Support Care Cancer 2023 May 30;31(6):361 [FREE Full text] [doi: 10.1007/s00520-023-07826-z] [Medline: 37249639]
36. Duan SQ, Zhang L, Dou A. Effects of binary coping intervention on patients and their spouses after breast cancer surgery. Journal of Nursing 2022;37(04):71-74.
37. van Vugt M, de Wit M, Bader S, Snoek FJ. Does low well-being modify the effects of PRISMA (Dutch DESMOND), a structured self-management-education program for people with type 2 diabetes? Prim Care Diabetes 2016 Apr;10(2):103-110. [doi: 10.1016/j.pcd.2015.06.008] [Medline: 26186886]
38. Yucel E, Zhang S, Panjabi S. Health-Related and Economic Burden Among Family Caregivers of Patients with Acute Myeloid Leukemia or Hematological Malignancies. Adv Ther 2021 Oct;38(10):5002-5024 [FREE Full text] [doi: 10.1007/s12325-021-01872-x] [Medline: 34499319]
39. Boyd RL, Ashokkumar A, Seraj S, Pennebaker JW. The development and psychometric properties of LIWC-22. Austin, TX: University of Texas at Austin; 2022.
40. Kwakkenbos L, van den Hoogen FHJ, Custers J, Prins J, Vonk MC, van Lankveld WGJM, et al. Validity of the Fear of Progression Questionnaire-Short Form in patients with systemic sclerosis. Arthritis Care Res (Hoboken) 2012 Jun 25;64(6):930-934 [FREE Full text] [doi: 10.1002/acr.21618] [Medline: 22262505]
41. Wu QY, Ye ZX, Li L, Liu P. Sinicization and reliability and validity analysis of the simplified scale of fear of disease progression in cancer patients. Chinese Journal of Nursing 2015;50(12):1515-1519.
42. Zimmermann T, Herschbach P, Wessarges M, Heinrichs N. Fear of progression in partners of chronically ill patients. Behav Med 2011 Jul;37(3):95-104. [doi: 10.1080/08964289.2011.605399] [Medline: 21895427]
43. Bodenmann G. Stress and coping in couples. Göttingen, Germany: Hogrefe; 2000.

44. Bodenmann G, Randall AK. Common factors in the enhancement of dyadic coping. Behav Ther 2012 Mar;43(1):88-98. [doi: 10.1016/j.beth.2011.04.003] [Medline: 22304881]
45. Xu F, Hilpert P, Randall A, Li Q, Bodenmann G. Validation of the Dyadic Coping Inventory with Chinese couples: Factorial structure, measurement invariance, and construct validity. Psychol Assess 2016 Aug;28(8):e127-e140 [FREE Full text] [doi: 10.1037/pas0000329] [Medline: 27183045]

Abbreviations

DCI: Dyadic Coping Inventory
FoP-Q-SF: Fear of Progression Questionnaire-Short Form

Edited by A Mavragani; submitted 02.12.23; peer-reviewed by Z Ping, L Kouying; comments to author 07.02.24; revised version received 09.03.24; accepted 11.03.24; published 29.04.24.

Please cite as:
Zhao H, Zhou Y, Che CC, Chong MC, Zheng Y, Hou Y, Chen C, Zhu Y
Marital Self-Disclosure Intervention for the Fear of Cancer Recurrence in Chinese Patients With Gastric Cancer: Protocol for a Quasiexperimental Study
JMIR Res Protoc 2024;13:e55102
URL: https://www.researchprotocols.org/2024/1/e55102
doi:10.2196/55102
PMID:38684089

Protocol

Motor Effects of Intervention With Transcranial Direct Current Stimulation for Physiotherapy Treatment in Children With Cerebral Palsy: Protocol for a Randomized Clinical Trial

Anna Izabel Cangussu[1,2*], MSc; Beatriz Lucarini[1*], GME; Igor de Freitas Melo[1*], GME; Paula Araújo Diniz[1*], GME; Marisa Mancini[3], PhD; Bernardo de Mattos Viana[1,4*], PhD; Marco Aurélio Romano-Silva[1,4], MD, PhD; Débora Marques de Miranda[1,4,5], MD, PhD

[1]Faculdade de Medicina da Universidade Federal de Minas Gerais, Federal University of Minas Gerais, Belo Horizonte, Brazil

[2]Instituto Nacional de Ciência e Tecnologia de Medicina Molecular, Universidade Federal de Minas Gerais, Belo Horinzote, Brazil

[3]Departament of Occupational Therapy, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil

[4]Instituto Nacional de Ciência e Tecnologia Neurotech R, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil

[5]Departamento de Pediatria, Faculdade de Medicina, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil

[*]these authors contributed equally

Corresponding Author:
Anna Izabel Cangussu, MSc
Faculdade de Medicina da Universidade Federal de Minas Gerais
Federal University of Minas Gerais
Avenida Professor Alfredo Balena
190 - Santa Efigênia
Belo Horizonte, 30130-100
Brazil
Phone: 55 3134099670
Email: anna_izabel@yahoo.com.br

Abstract

Background: Children diagnosed with cerebral palsy (CP) often experience various limitations, particularly in gross motor function and activities of daily living. Transcranial direct current stimulation (tDCS) is a noninvasive brain stimulation technique that has been used to improve movement, gross motor function, and activities of daily living.

Objective: This study aims to evaluate the potential additional effects of physiotherapy combined with tDCS in children with CP in comparison with physiotherapy only.

Methods: This is a 2-arm randomized controlled trial that will compare the effects of tDCS as an adjunctive treatment during rehabilitation sessions to rehabilitation without tDCS. Children with CP classified by the Gross Motor Function Classification System as levels I and II will be randomly assigned to either the sham + rehabilitation group or the tDCS + rehabilitation group. The primary outcome will be the motor skills assessed using the Gross Motor Function Measure domain E scores, and the secondary outcome will be the measurement scores of the children's quality of life. The intervention will consist of a 10-day stimulation protocol with tDCS spread over 2 weeks, with stimulation or sham tDCS administered for 20 minutes at a frequency of 1 Hz, in combination with physiotherapy. Physical therapy exercises will be conducted in a circuit based on each child's baseline Gross Motor Function Measure results. The participants' changes will be evaluated and compared in both groups. Intervenient features will be tested.

Results: Data collection is ongoing and is expected to be completed by January 2025. A homogeneous sample and clear outcomes may be a highlight of this protocol, which may allow us to understand the potential use of tDCS and for whom it should or should not be used.

Conclusions: A study with good evidence and clear outcomes in children with CP might open an avenue for the potential best use of neurostimulation.

Trial Registration: Brazilian Registry of Clinical Trials RBR-104h4s4y; https://tinyurl.com/47r3x2e4

International Registered Report Identifier (IRRID): PRR1-10.2196/52922

(JMIR Res Protoc 2024;13:e52922) doi:10.2196/52922

KEYWORDS

cerebral palsy; tDCS; motor; development; randomized clinical trial; RCT; clinical trial; randomized; transcranial direct current stimulation; stimulation; children; child; brain stimulation; physical therapy; quality of life; researchers; researcher; neurological injuries; injury; injuries; gait; patient; patients

Introduction

Cerebral palsy (CP) is a prevalent cause of physical disability among children, with reported incidence rates ranging from 2.0 to 2.5 per 1000 live births in developed countries, and even higher in low and middle-income countries, reaching up to 7 per 1000 live births [1]. The treatment goals for CP primarily focus on improving motor function and promoting independence in activities of daily living, as well as enhancing quality of life (QoL) [2]. Despite the efforts made in this area, the heterogeneous clinical presentations and responses to interventions pose a challenge in generalizing information about the effectiveness of specific treatment methods [2]. Guidance from the Cochrane Collaboration in 2019 suggests there is a need to standardize the outcomes studied in interventions, to provide functional and informative results and guide the selection of the most effective interventions and an effective individualized treatment [3].

Children with CP have difficulties in balance, motor function, and movement coordination. Physical therapy is used to improve these disabilities. Transcranial direct current stimulation (tDCS) is a complementary intervention that has been shown to enhance balance and improve movement coordination and gross motor function in children with CP [2,4,5]. There is a difference in oscillation speed when associating tDCS with virtual reality [5]. De Almeida Carvalho Duarte et al [2] have shown that children with CP subjected to 5 sessions of treadmill training stimulated with tDCS for 2 weeks with stimulation in M1 for 20 minutes exhibited improvements in temporal functional mobility, such as gait. The results were still maintained 1 month after the intervention. Balance and functional performance seem improved in children with CP after 5 sessions of tDCS anodal stimulation of the motor cortex plus treadmill training for 2 consecutive weeks.

Just 1 session of tDCS realized in the M1 region for 20 minutes in a group of children with CP showed a momentary increase in cortex activation with a direct influence on motor control and an improvement in gait and balanced outcomes [6]. Permanent effects in the population submitted to tDCS with clinical effects were observed in promoting functional improvement in children with CP [2,4].

According to the previous results, we hypothesized that tDCS use might improve specific motor skills and positively impact QoL in a more homogeneous population with CP. This study was designed to examine the impact of the combination of tDCS and conventional rehabilitation exercises on the improvement of gross motor function in children with CP classified as level I and II in the Gross Motor Function Classification System (GMFCS). The primary outcome measure will be assessed using the scores of the Gross Motor Function Measure (GMFM) dimension E and the secondary outcome is the children's QoL.

According to Castelli and Fazzi [7], rehabilitation is a complex process that aims to promote the best possible participation and QoL for the child and the family. Rehabilitation for children with CP must be timely, intensive, and family-centered [7]. Despite the importance of understanding the effects on children's QoL, QoL is not commonly measured.

Castelli and Fazzi [7] recommend intensive rehabilitation with trained professionals and a multidisciplinary team focused on the child's functional improvement. Rehabilitation is one of the main parts as it involves performing functional assessments, establishing a functional prognosis, constructing a rehabilitation plan, and promoting a multidisciplinary approach [7].

Methods

This study is a single-blind randomized controlled trial (RCT). The participants will be blinded to the treatment allocation during the trial, but the researchers conducting this study will be aware of the treatment allocation. This study will conform to the CONSORT (Consolidated Standards of Reporting Trial) guidelines for nonpharmacological interventions. This study has been approved by the ethics committee in research.

Recruitment

All patients with CP who meet the previously described criteria for inclusion will be invited to participate in this study which will be realized in the Molecular Medicine Center of the Universidad Federal de Minas Gerais in Brazil.

Sample Size

The sample size was calculated using G* Power software (version 3.1; Universität Düsseldorf) [8]. Considering an effect size of 0.5, power of 0.95, and probability of type I error (α) of 5%, the total sample size should be 176 volunteers, with 2 groups of 88 volunteers. The impact of the intervention will be evaluated in the pilot phase to determine a more accurate estimate of the population sample size. The participants will be included from July 2023 to July 2024. After the end of the intervention, the data collected will be separated into groups, these being the intervention group (IG) and the control group (CG). We will carry out the analysis of the pre- and postintervention GMFM variables and the Pediatric Quality of Life Inventory (PedsQL). We will carry out the analysis between groups (CG and IG) and between individuals in the same group, and will compare participants with themselves, to quantify and describe the results. Analysis of covariance will be chosen to observe preexisting differences between groups, allowing for comparison of postintervention scores while controlling for baseline scores.

Participants and Eligibility Criteria

The participants in this study will be recruited through advertisements at clinics and the intervention will take place at the Molecular Medicine Center of the Universidade Federal de Minas Gerais in Brazil. To be eligible, participants must have a medical diagnosis of CP, be classified as GMFCS I or II, be aged between 8 and 12 years, be able to walk independently, and be able to understand commands. Exclusion criteria include other neurological conditions, recent history of surgery, uncontrolled epilepsy, a cranial metallic implant, and the use of a hearing aid. The waiting list group will have access granted afterwards based on the evidence.

Ethical Considerations

This study was evaluated and approved by the local ethical board at Universidade Federal de Minas Gerais (50504021.0.0000.5149). All participants and their guardians will be informed about the research protocols and will be required to sign the free and informed consent form and the free and clarified assent form. Participation will only be allowed when both the child and parent have agreed to participate. All data will be handled as anonymous. Following the national law, participation in the intervention must be voluntary and reimbursement will be available only for research-related transportation.

Measures

Overview

Both instruments will be used with all participants before and after the interventions to assess whether there was a significant improvement in gross motor movement according to the E domain of the GMFM or in QoL.

About GMFCS

This is a scale used to classify the level of impairments of the gross motor function of the CP population [9]. GMFCS allows us to classify functionality about walking, sitting, and standing [8]. It classifies gross motor function into 5 levels, as follows: level I: no access; level II: walks with limitation; level III: walks using a manual mobility device (such as a Canadian crutch, walker, or cane); level IV: self-mobility with a limitation (such as using a regular or automatic wheelchair); level V: patient transported via manual wheelchair by a responsible person. Initially, the entire sample will be evaluated using this instrument [10].

About GMFM

This instrument evaluates quantitatively the change in gross motor function in children with CP. The evaluation has five dimensions: dimension A, bed and roll; dimension B, sitting; dimension C, crawling and kneeling; dimension D, standing; and dimension E), walking, running, and jumping [11]. The scoring system is as follows: a score of zero is assigned if the individual is unable to start the activity, a score of 1 is assigned if the individual starts the activity, a score of 2 is assigned if the individual starts the activity but only completes half of it, and a score of 3 is assigned if the activity is completed. The scores for each dimension should be calculated separately by summing the scores for that dimension and dividing by the total score for that dimension [11].

In the end, the scores for each dimension should be multiplied by 100 to find the percentage that the child achieved in each dimension. Finally, the percentages for all dimensions should be added and divided by 5 (the number of dimensions evaluated), yielding the percentage that the child scored in the GMFM (dimension E). This method is based on the techniques of Luciana Ventura De Pina, PhD and Ana Paula Cunha Loureiro, PhD [12]. Both scales, the GMFM and the GMFCS, have been validated for use with children with CP. The GMFM assesses gross motor function and the GMFCS stratifies the functional level of children with CP. The Gross Motor Ability Estimator (GMAE) program will be used to analyze the GMFM results.

About PedsQL

The PedsQL is a multidimensional tool to measure health-related QoL in children and adolescents. It is a practical scale on the dimensions of health outlined by the World Health Organization, with questions related to the frequency of problems faced in the last month. The 23 item-PedsQL has 8 items for physical functioning; 5 for social functioning; 5 for emotional functioning; and 5 for school functioning, with 15 on patients' psychosocial health.

tDCS Intervention

Overview

The IG will receive 10 sessions of tDCS with a frequency of 5 daily sessions per week, over a period of 2 weeks. The stimulation will be administered during rehabilitation sessions. The electrodes will be 35-cm^2 sponges moistened with normal saline (0.9% NaCl solution). The stimulation will consist of anodal stimulation in the primary motor cortex (M1) and cathodal stimulation in the supraorbital region on the contralateral side, at an intensity of 1 mA and a duration of 20 minutes at a steady-state level, with a ramp-up and ramp-down of 4 seconds. The stimulation will be combined with specific exercises in a circuit format to target dimensions D and E of the GMFM [13]. CG will undergo 10 sessions of sham tDCS associated with rehabilitation activities 5 times per week, for a total of 2 weeks. Activities that target dimension E of the GMFM will be organized as a circuit including running, walking, and jumping. Any change to the trial will be informed along with the reason for the change.

Safety

The device used, tDCS Soterix Medical (Soterix Medical Inc), model number 1300-A and serial number 13ITC0619005, is approved by the Food and Drug Administration for use as an experimental device and some for clinical purposes (ANVISA-80969860041). Further, 3.5-cm^2 electrodes will be used. Bikson et al [13], prove if the purpose is to modulate neurophysiological measures for resting motor cortex stimulation in healthy young people (1 mA intensity), tDCS for 4 seconds induces acute excitability alterations.

Krishnan et al [14] demonstrated adequate safety of tDCS in children and adolescents. Well-accepted threshold of tDCS current density is <142.9 A/m^2 or 14.29 mA/cm^2. Each patient will undergo a thorough health assessment and medications in use will be registered as well as all health conditions. Cardiac frequency, blood pressure, temperature, respiration, clinical assessment of mental and functional status, and physical examination will be measured [15]. Any apparent side effects will be registered, and all changes to the study will be described so that individuals have the option to interrupt the trial; the trial may also be suspended.

Adverse Effects

Adverse effects will be assessed using the tDCS adverse effects questionnaire [16]. The dropout rate will be reported, and dropout reasons will be stated [15]. tDCS is generally well-tolerated with no serious adverse events [14]. The effects reported are rare, mild, and transient, with "redness," "slight tingling," "itching," and "burning sensation" as the most reported events. The intensity of current, density, and electrode size will be optimized to modulate the tingling and itch perception during transcranial stimulation. Furthermore, we will not pass the well-accepted threshold of tDCS current density (<142.9 A/m^2 or 14.29 mA/cm^2) [14].

Allocation

Participants will be randomly assigned to tDCS groups with a 1:1 allocation as per a computer-generated randomization schedule stratified by the patient's age using 5 permuted blocks of 6 participants.

Implementation

All participants will be randomized, and the randomization will be performed by the researcher who will carry out an intervention; the others will not know which group the participant is in. This member will upload the randomization results to the institution's REDCap (Research Electronic Data Capture) database [17]. The researcher who will perform a physiotherapeutic intervention and the researcher who will apply the assessments and questionnaires will not have information about group allocation.

Blinding

This will be a double-blinded study; during this study, the participants will be seen by three different teams: (1) the researcher who performs the assessment and questionnaires, (2) the neuromodulation team who apply the tDCS, and (3) the physiotherapist who performs the physiotherapy exercises. There will be no members working simultaneously on both teams. The results of randomization will only be available to the neuromodulation member responsible for the intervention, and the scales' results will only be available to the researcher who performed the assessment and questionnaires. The results will be held in a different project in REDCap and will be available only to the researcher who makes the assessment and questionnaires.

Emergency Unblinding

Emergency unblinding will be available under the determination of this study staff, in case of safety concerns related to the intervention.

Interventions: Participants

Initially, we will explain to the child how the intervention process will be carried out. The electrodes will be moistened in saline solution and will be placed on the participant's head, which may cause slight discomfort as it will wet the child's head, and, to minimize this discomfort, we will frequently dry their face. Associated with this, the child will perform physical therapy exercises.

CGs for tDCS will receive placebo stimulation for 30 seconds, for 10 sessions to give the child an initial feeling of stimulation. Associated with the placebo, the child will perform physical therapy exercises, focusing on the demands of the GMFM dimension E. The tDCS intervention will receive a current of 1 mA, for 20 minutes, for 10 sessions also associated with physical therapy exercises, focusing on the demands of the GMFM dimension E.

The intervention lasts from 25 to 35 minutes with each participant and will have a researcher exclusively dedicated to it during the intervention period for data collection. There will be 5 sessions with each participant per week over 2 consecutive weeks, with sessions taking place on weekdays and not weekends. All included participants will complete 10 sections of physiotherapy with or without tDCS stimulation. The tDCS device contains 2 electrodes, an anode, and a cathode, in the form of 2 nonmetallic sponges measuring 5×5 cm^2, moistened with saline solution. The anode will be positioned on the M1 of the participant's dominant hemisphere, according to the 10-20 System EEG, while the cathode will be placed on the supraorbital region of the region contralateral to the anode. In the case of the experimental group, a current will be applied to M1 for 20 minutes for neurorehabilitation.

After 10 sessions, the GMFM test will be repeated with each patient along with the PedsQL. Further, 1 researcher will carry out the intervention or the placebo with tDCS and the other researcher will evaluate the results blindly, without knowing which group is the intervention and which is the control. The use of the equipment and the evaluation will be carried out in different rooms to guarantee the researchers' blindness. Only the researcher in charge of using the tDCS will be aware of the allocation of children between experimental and CGs.

It is worth noting that the patients in the CGs learned, at the end of this study, the intervention that had the best effect on their motor function, respecting this study's ethical perspective that all children should receive the best treatment.

Results

There is a compelling need to tailor medical approaches more precisely, catering to individual differences. Achieving successful outcomes requires studies that use informative measures, robust evidence, and are applicable across diverse demographics.

In this proposal, we emphasize the importance of incorporating targeted and universally recognized outcomes, specifically focusing on motor skills impacted by the disorder. These skills are universally acknowledged and play a fundamental role in an individual's daily life. Additionally, we are examining how these interventions influence the overall QoL for affected individuals. Data collection is ongoing and is expected to be completed by January 2025.

Moreover, our study aims to optimize treatment efficacy by exposing participants to multiple sessions. This strategy is designed to fine-tune the intervention's impact, building upon a baseline established using the most credible rehabilitation practices available for this condition.

RCTs are not commonly conducted in pediatric populations, leading to a lack of dedicated information specific to this demographic's unique needs and responses. Addressing this gap is crucial to better understand how interventions impact children with this condition.

Discussion

A randomized controlled protocol using an additional tDCS was designed to improve specific motor skills and positively impact QoL in a homogeneous population with CP. This study aims to examine the impact of the combination of conventional rehabilitation exercises on the improvement of gross motor function in children with CP classified as level I and II in the GMFCS. The primary outcome was assessed using the scores of the GMFM dimension E and children's QoL as the secondary outcome. tDCS seems to improve balance, gross motor function, and gait in children with CP [2,4-7]. Mixed and heterogeneous outcomes of varied motor skills made it difficult to understand who and in what conditions individuals may benefit from tDCS complementary use.

To address this issue, the specific protocol proposed focuses on a homogeneous population of children with CP who have preserved walking skills and will evaluate them for motor features and QoL. By using the GMFCS and GMFM to classify and map the skills and their changes, we aim to improve the evidence, since there is a clear outcome that can be measured, and optimize treatment for a personalized medicine approach in the heterogeneity of CP. Our goal is to gather evidence for a stratified population of children with lower locomotion restrictions, as suggested by de Almeida Carvalho Duarte et al [2], who highlighted the importance of studying more homogeneous populations in the field of CP to better understand gains in the functional independence of these children. This will allow us to know the treatment effect size and for whom it should be a good choice.

The costs and presence of adverse effects will be features considered to reveal the individual cost-effect balance [16], and dropout rates will indicate any potential reason for dropping out [15].

Stimulation has been done on the M1 motor area in children with GMFCS I, II, and III [18]. Children with GMFCS III compared with children classified as I and II present an important difference in the use of aid devices. Children with GMFCS levels I and II are very functional, running and walking independently and having fewer limitations, while children with GMFCS III need an assistive device, such as walker assistance. In places with ramps, they may not be able to go up and down, due to the difficulty in controlling their movements independently. In De Moura et al's [4] meta-analysis, the difference in results was attributed to a high level of heterogeneity, potentially compromising the generalization of results and the understanding of who and in what conditions children would benefit from the use of tDCS. This protocol evaluated TDCS stimulation on the motor standardized measure and QoL outcomes.

Besides the efforts on RCT protocols, there are always the limits related to the artificial scenario observed in RCTs; many things are controlled and compared that differ from natural scenarios. However, the limitation in heterogeneity considering the differences in functional classification in motor skills may be an interesting strategy to decrease heterogeneity and truly understand the role of TDCS in the improvement of motor skills. Reporting quality, including sample size, control characteristics, important outcomes, and the methodology of intervention training and delivery may help in building a body of literature with better evidence [19,20].

QoL and health-related QoL are increasingly being considered therapeutic goals [19]. In the past decades, QoL has been defined as well-being across various domains and has become an important treatment goal, especially in diseases like CP [19]. Many studies have observed that parents report lower QoL for their children with CP than the children themselves report [19]. The emotional and social domains were evaluated equally for children and parents [19]. Furthermore, parents of children with severe impairment often report better QoL in the psychosocial domain [19]. Consistent findings suggest that children with CP can adapt well to their activity limitations and may have a satisfactory QoL despite deficits [19]. Improving QoL represents a crucial treatment objective for children with CP, necessitating precise measurement and targeted interventions aimed at achieving this outcome [19]. In conclusion, CONSORT-based report protocols based on homogeneous sampling and using relevant outcomes seem necessary to improve the evidence for personalized medicine, especially for the pediatric population.

Acknowledgments

This study received funding from the Conselho Nacional de Pesquisa (CNPq) Inct Neurotech-R (INCT CNPq406935/2022-0).

Conflicts of Interest

None declared.

References

1. Sadowska M, Sarecka-Hujar B, Kopyta I. Cerebral palsy: current opinions on definition, epidemiology, risk factors, classification and treatment options. Neuropsychiatr Dis Treat 2020;16:1505-1518 [FREE Full text] [doi: 10.2147/NDT.S235165] [Medline: 32606703]
2. de Almeida Carvalho Duarte N, Grecco LAC, Galli M, Fregni F, Oliveira CS. Effect of transcranial direct-current stimulation combined with treadmill training on balance and functional performance in children with cerebral palsy: a double-blind randomized controlled trial. PLoS One 2014;9(8):e105777 [FREE Full text] [doi: 10.1371/journal.pone.0105777] [Medline: 25171216]
3. Cumpston M, Li T, Page MJ, Chandler J, Welch VA, Higgins JP, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Database Syst Rev 2019;10(10):ED000142 [FREE Full text] [doi: 10.1002/14651858.ED000142] [Medline: 31643080]
4. de Moura MCDS, Hazime FA, Aparicio LVM, Grecco LAC, Brunoni AR, Hasue RH. Effects of transcranial Direct Current Stimulation (tDCS) on balance improvement: a systematic review and meta-analysis. Somatosens Mot Res 2019;36(2):122-135. [doi: 10.1080/08990220.2019.1624517] [Medline: 31181963]
5. Lazzari RD, Politti F, Belina SF, Grecco LAC, Santos CA, Dumont AJL, et al. Effect of transcranial direct current stimulation combined with virtual reality training on balance in children with cerebral palsy: a randomized, controlled, double-blind, clinical trial. J Mot Behav 2017;49(3):329-336. [doi: 10.1080/00222895.2016.1204266] [Medline: 27644454]
6. Grecco LAC, Duarte NAC, Zanon N, Galli M, Fregni F, Oliveira CS. Effect of a single session of transcranial direct-current stimulation on balance and spatiotemporal gait variables in children with cerebral palsy: a randomized sham-controlled study. Braz J Phys Ther 2014;18(5):419-427 [FREE Full text] [doi: 10.1590/bjpt-rbf.2014.0053] [Medline: 25372004]
7. Castelli E, Fazzi E, SIMFER-SINPIA Intersociety Commission. Recommendations for the rehabilitation of children with cerebral palsy. Eur J Phys Rehabil Med 2016;52(5):691-703 [FREE Full text] [Medline: 26629842]
8. Faul F, Erdfelder E, Buchner A, Lang AG. Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. Behav Res Methods 2009;41(4):1149-1160 [FREE Full text] [doi: 10.3758/BRM.41.4.1149] [Medline: 19897823]
9. Vitrikas K, Dalton H, Breish D. Cerebral palsy: an overview. Am Fam Physician 2020;101(4):213-220 [FREE Full text] [Medline: 32053326]
10. Rethlefsen SA, Ryan DD, Kay RM. Classification systems in cerebral palsy. Orthop Clin North Am 2010;41(4):457-467. [doi: 10.1016/j.ocl.2010.06.005] [Medline: 20868878]
11. Russel DJ, Wright M, Rosenbaum PL, Avery LM. Gross Motor Function Measure (GMFM-66 and GMFM-88) User's Manual. London, UK: Mac Keith Press; 2021.
12. Klatchoian DA, Len CA, Terreri MTRA, Silva M, Itamoto C, Ciconelli RM, et al. Qualidade de vida de crianças e adolescentes de São Paulo: confiabilidade e validade da versão brasileira do questionário genérico Pediatric Quality of Life InventoryTM versão 4.0. J Pediatr (Rio J) 2008;84(4):308-315. [doi: 10.1590/S0021-75572008000400005]
13. Bikson M, Grossman P, Thomas C, Zannou AL, Jiang J, Adnan T, et al. Safety of transcranial direct current stimulation: evidence based update 2016. Brain Stimul 2016;9(5):641-661 [FREE Full text] [doi: 10.1016/j.brs.2016.06.004] [Medline: 27372845]
14. Krishnan C, Santos L, Peterson MD, Ehinger M. Safety of noninvasive brain stimulation in children and adolescents. Brain Stimul 2015;8(1):76-87 [FREE Full text] [doi: 10.1016/j.brs.2014.10.012] [Medline: 25499471]
15. Buchanan NT, Perez M, Prinstein MJ, Thurston IB. Upending racism in psychological science: strategies to change how science is conducted, reported, reviewed, and disseminated. Am Psychol 2021;76(7):1097-1112. [doi: 10.1037/amp0000905] [Medline: 34990171]
16. Brunoni AR, Amadera J, Berbel B, Volz MS, Rizzerio BG, Fregni F. A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. Int J Neuropsychopharmacol 2011;14(8):1133-1145 [FREE Full text] [doi: 10.1017/S1461145710001690] [Medline: 21320389]
17. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: building an international community of software platform partners. J Biomed Inform 2019;95:103208 [FREE Full text] [doi: 10.1016/j.jbi.2019.103208] [Medline: 31078660]
18. Grecco LAC, Oliveira CS, de Almeida Carvalho Duarte N, Lima VLCC, Zanon N, Fregni F. Cerebellar transcranial direct current stimulation in children with ataxic cerebral palsy: a sham-controlled, crossover, pilot study. Dev Neurorehabil 2017;20(3):142-148. [doi: 10.3109/17518423.2016.1139639] [Medline: 27003795]
19. Aran A. Quality of life in children with cerebral palsy. In: Preedy VR, Watson RR, editors. Handbook of Disease Burdens and Quality of Life Measures. New York, NY: Springer; 2010:2453-2468.
20. Horr T, Messinger-Rapport B, Pillai JA. Systematic review of strengths and limitations of randomized controlled trials for non-pharmacological interventions in mild cognitive impairment: focus on Alzheimer's disease. J Nutr Health Aging 2015;19(2):141-153 [FREE Full text] [doi: 10.1007/s12603-014-0565-6] [Medline: 25651439]

Abbreviations

CG: control group

CP: cerebral palsy
GMFCS: Gross Motor Function Classification System
GMFM: Gross Motor Function Measure
IG: intervention group
PedsQL: Pediatric Quality of Life Inventory
QoL: quality of life
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
tDCS: transcranial direct current stimulation

Edited by A Mavragani; submitted 20.09.23; peer-reviewed by D Hohenschurz-Schmidt, X Zhang; comments to author 11.12.23; revised version received 27.12.23; accepted 20.01.24; published 30.04.24.

Please cite as:
Cangussu AI, Lucarini B, Melo IDF, Diniz PA, Mancini M, Viana BDM, Romano-Silva MA, Miranda DMD
Motor Effects of Intervention With Transcranial Direct Current Stimulation for Physiotherapy Treatment in Children With Cerebral Palsy: Protocol for a Randomized Clinical Trial
JMIR Res Protoc 2024;13:e52922
URL: https://www.researchprotocols.org/2024/1/e52922
doi:10.2196/52922
PMID:38687586

Protocol

Effect of Rural Trauma Team Development on the Outcomes of Motorcycle Accident–Related Injuries (Motor Registry Project): Protocol for a Multicenter Cluster Randomized Controlled Trial

Herman Lule[1], MMed, MBChB; Micheal Mugerwa[1], MSc; Robinson Ssebuufu[2], MMed, MBChB; Patrick Kyamanywa[3], MMed, MBChB, MPH, MBA; Till Bärnighausen[4], MD, MSc, ScD; Jussi P Posti[5], MD, PhD; Michael Lowery Wilson[4], MBA, MPH, PhD

[1]Injury Epidemiology and Prevention (IEP) Research Group, Turku Brain Injury Centre, Department of Clinical Neurosciences, Turku University Hospital and University of Turku, Turku, Finland

[2]Department of Surgery, Mengo Hospital, Kampala, Uganda

[3]Mother Kevin Postgraduate Medical School, Uganda Martyr's University, Nkozi, Uganda

[4]Heidelberg Institute of Global Health (HIGH), University Hospital and University of Heidelberg, Heidelberg, Germany

[5]Neurocentre, Department of Neurosurgery and Turku Brain Injury Centre, Turku University Hospital and University of Turku, Turku, Finland

Corresponding Author:
Herman Lule, MMed, MBChB
Injury Epidemiology and Prevention (IEP) Research Group
Turku Brain Injury Centre, Department of Clinical Neurosciences
Turku University Hospital and University of Turku
Turun Yliopisto
Turku, FI-20014
Finland
Phone: 358 465699821
Email: helule@utu.fi

Abstract

Background: Injury is a global health concern, and injury-related mortality disproportionately impacts low- and middle-income countries (LMICs). Compelling evidence from observational studies in high-income countries shows that trauma education programs, such as the Rural Trauma Team Development Course (RTTDC), increase clinician knowledge of injury care. There is a dearth of such evidence from controlled clinical trials to demonstrate the effect of the RTTDC on process and patient outcomes in LMICs.

Objective: This multicenter cluster randomized controlled clinical trial aims to examine the impact of the RTTDC on process and patient outcomes associated with motorcycle accident–related injuries in an African low-resource setting.

Methods: This is a 2-arm, parallel, multi-period, cluster randomized, controlled, clinical trial in Uganda, where rural trauma team development training is not routinely conducted. We will recruit regional referral hospitals and include patients with motorcycle accident–related injuries, interns, medical trainees, and road traffic law enforcement professionals. The intervention group (RTTDC) and control group (standard care) will include 3 hospitals each. The primary outcomes will be the interval from the accident to hospital admission and the interval from the referral decision to hospital discharge. The secondary outcomes will be all-cause mortality and morbidity associated with neurological and orthopedic injuries at 90 days after injury. All outcomes will be measured as final values. We will compare baseline characteristics and outcomes at both individual and cluster levels between the intervention and control groups. We will use mixed effects regression models to report any absolute or relative differences along with 95% CIs. We will perform subgroup analyses to evaluate and control confounding due to injury mechanisms and injury severity. We will establish a motorcycle trauma outcome (MOTOR) registry in consultation with community traffic police.

Results: The trial was approved on August 27, 2019. The actual recruitment of the first patient participant began on September 01, 2019. The last follow-up was on August 27, 2023. Posttrial care, including linkage to clinical, social support, and referral services, is to be completed by November 27, 2023. Data analyses will be performed in Spring 2024, and the results are expected to be published in Autumn 2024.

Conclusions: This trial will unveil how a locally contextualized rural trauma team development program impacts organizational efficiency in a continent challenged with limited infrastructure and human resources. Moreover, this trial will uncover how rural trauma team coordination impacts clinical outcomes, such as mortality and morbidity associated with neurological and orthopedic injuries, which are the key targets for strengthening trauma systems in LMICs where prehospital care is in the early stage. Our results could inform the design, implementation, and scalability of future rural trauma teams and trauma education programs in LMICs.

Trial Registration: Pan African Clinical Trials Registry (PACTR202308851460352); https://pactr.samrc.ac.za/TrialDisplay.aspx?TrialID=25763

International Registered Report Identifier (IRRID): DERR1-10.2196/55297

(JMIR Res Protoc 2024;13:e55297) doi:10.2196/55297

KEYWORDS

randomized controlled trial; medical education; trauma team; trauma registry; rural health; global health; team development; Africa; rural; trauma; motorcycle injury; multicenter cluster randomized controlled clinical trial; injury; accident; low- and middle-income countries; patient outcomes; education program

Introduction

Background

Transport-related injuries are a global public health threat and are anticipated to rank fifth in the global burden of disease by 2030 [1]. Evidence suggests that 90% of the transport-related crash mortality burden disproportionately occurs in low- and middle-income countries (LMICs), such as those in Africa [1], despite concerns of underreporting [2]. The main causes of injury-related mortality in Africa are road traffic accidents [3], which have serious economic consequences. According to Ryan-Coker et al [4], despite high poverty levels and minimal access to insurance and social protection schemes in Africa, which imply out of pocket expenditure, road traffic accidents cost US $119-$178 per injury and US $486-$12,845 per hospitalization, resulting in a gross domestic product (GDP) loss of 0.8%-9%.

Uganda is one of the LMICs in Africa with a high road traffic injury burden [5]. Our recent studies showed that most fatal injuries in Uganda result from motorized 2-wheeler and car collisions, contributing to 52.6%-64.7% of orthopedic and traumatic brain injuries [6-8]. Further, the majority (74%) of Uganda's population lives in rural areas [9], which could partly explain the high injury-related mortality rates. Research has shown that the risk of trauma-related deaths in rural areas increases with remoteness owing to health care disparities, such as large commute distances, scarce resources, delays in referral, and lack of skilled trauma care providers, as well as population-specific and contextual challenges, such as poverty and impassable road networks [10].

Uganda lacks universal access to trauma care and injury surveillance systems owing to limited health care funding. Thus, Uganda has made sluggish progress toward attaining the sustainable development goal (SDG3) for universal health care coverage [11]. As such, in terms of the level of specialty care, the ratio of surgeons to patients is 0.7:25,000 as interns and medical trainees represent the largest proportion of Uganda's health workforce [12,13].

Research has shown than more than half of the trauma patients in Uganda do not receive first aid prior to hospital arrival [6,7]. Moreover, most of these patients arrive at dedicated trauma centers much later than the recommended limit of 1 hour, and they are transported by either public vehicles, such as motorcycles [8], or police vans, without any focus on key factors, such as changes in blood pressure and oxygen circulation, which could lead to death, during transit [7,14]. These aspects have 3 important implications. First, strengthening the capacity for injury care among lay frontline workers. Second, stabilizing patients at rural regional trauma centers prior to transfer. Third, ensuring closed-loop communication between primary (level 3) and tertiary (level 1) trauma centers to enable safely coordinated referrals and adequate preparation at the receiving hospitals prior to patient transfer.

The key challenge that needs to be addressed in Ugandan rural settings is the lack of a formal prehospital care system as evidenced by emergency evacuation and transfer of trauma patients by untrained police staff [14]. Further, there is an immense need to redress the weak immediate care response after an accident as medical trainees are the first point of contact after an accident as opposed to specialists [12]. We will attempt to fix these challenges at the community level and at level 3 rural trauma centers by creating and providing training capacity for rural trauma networks between traffic police and medical interns or trainees at regional referral hospitals.

Rationale

Evidence from 2 systematic reviews has shown that trauma education programs have the potential to improve skill acquisition and knowledge retention among health professionals; however, with regard to LMICs, most of these programs have not been locally contextualized and have been largely assessed based on their theoretical merit rather than their clinical impact on patients [15,16]. A recent observational study in Portugal showed that the European trauma course (ETC) improved self-efficacy and organization skills in individual routine practice, but the authors mentioned that future investigations should be conducted to examine the effect of the training on trauma outcomes [17]. This European study and systematic reviews in LMICs have recommended high-caliber epidemiological studies to evaluate the effects of such educational programs on process outcomes, such as

organizational efficiency, and on patient outcomes, such as morbidity and mortality [15,16,18].

Except for an ongoing pilot trial comparing a primary trauma course (PTC) to advanced life support (ATLS) and routine care in India [19], trauma education programs in LMICs have mostly been evaluated based on nonrandomized studies, limiting their clinical uptake [15]. Moreover, most programs limit the course participants to qualified hospital-based medical providers [18], although interns, medical and allied health trainees, and road traffic law enforcement professionals are the most readily available frontline workers for managing injured patients in LMICs [14]. Inclusive planning while leveraging services that have no trauma designation, such as police services, is critical for expanding and strengthening complex rural trauma systems to improve injury reporting [2].

Locally contextualized trauma training has been identified as one of the most crucial steps for operationalizing nonfunctional rural trauma networks [10]. However, in a scoping review by Brown et al [18], only 12 out of 34 trauma courses in LMICs had been contextualized to suite low-income settings. Moreover, a cautiously executed integrative literature review on the challenges faced by trauma systems recommended that the next step for future research should be an examination of how trauma training impacts the outcomes of patients in remote environments [10]. This multicenter cluster randomized controlled trial will address this gap by examining the effect of the locally contextualized Rural Trauma Team Development Course (RTTDC) of the American College of Surgeons [20] on process and patient outcome measures in Ugandan trauma centers. The trial will focus on musculoskeletal and neurological injuries, which have been recently identified as the most important targets for strengthening health systems in rural Uganda [8], and it has been developed in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines for reporting outcomes in trial protocols [21].

Objectives

Broad Objective

The main objective of this trial is to determine the effect of RTTDC training on the time efficiency of the clinical process and the patient-centered outcomes of motorcycle accident–related injuries.

Specific Objectives

The specific objectives are to (1) determine the effect of RTTDC training on the time interval from the accident to hospital admission and the time interval from the referral decision to hospital discharge (primary outcomes) and (2) determine the effect of RTTDC training on the outcomes of neurological and musculoskeletal injuries (secondary outcomes).

Null Hypothesis

The null hypothesis of this trial is that RTTDC training has no effect on the time efficiency of the clinical process and the outcomes of orthopedic and neurological injuries.

Methods

Trial Design

This will be a pragmatic, 2-arm, parallel, multi-period, cluster randomized, controlled, clinical trial with 1 intervention (RTTDC) arm and 1 control (standard care) arm. The trial was set to start in 2019 but was delayed owing to the COVID-19 pandemic, and the subsequent prioritization of COVID-19–related studies by trial registers and target journals led to the delayed publication of this protocol.

This trial will embrace simultaneous cluster randomization, which is an ideal method for evaluating community-level interventions and overcoming ethical constraints that make randomization at the individual level impractical while avoiding probable contamination between the control and treatment groups [22]. Moreover, simultaneous randomization will enable timely operationalization and concurrent participant enrollment as all the outcomes will be measured as final values and there are no foreseen plans for study modifications in accordance with Esserman et al [23]. This arrangement is based on the fact that our previous studies have already provided insights on the likely rates of loss to follow-up and baseline mortality in our target trauma population and have informed the feasibility and relevance of collecting the intended primary and secondary outcomes [6,7].

Study Setting

This study will be conducted in 6 specialized teaching and regional referral hospitals in Uganda, including Kiryandongo, Jinja, Hoima, Fort Portal, Mubende, and Kampala International University Hospital. These facilities have similar characteristics and serve as teaching, residency, and internship sites for undergraduate and graduate medical doctors and nurses. The hospitals offer 24/7 emergency surgical services for trauma patients through multidisciplinary teams of orthopedic, general, and visiting neurosurgeons, as well as imaging, rehabilitation, and physiotherapy. Each surgical department in these facilities is typically composed of about 1-4 faculty members, 2-4 specialty residents often referred to as senior house officers, 4-6 interns, and 10-30 undergraduate medical trainees.

These facilities are suited for this study as they serve both rural populations and populations in newly created populous cities that are still struggling with urban planning. Uganda is the 8th most populous country in Africa and the 30th most populous country in the world [9], and its trauma surveillance systems are in the infancy stage with weak preaccident and postaccident responses [6,12]. Despite efforts made in the past decade by the Ugandan government to address the unmet need for trauma care through infrastructure development, such as equipping operating theaters and intensive care units (ICUs) in public hospitals, limited standardized preservice and in-service trauma training, prehospital delays, and human resource constraints still contribute to preventable trauma mortalities [14]. To guarantee the quality of data for this project, a prospective motorcycle trauma outcome registry (MOTOR) will be piloted at the participating 6 regional referral hospitals in parallel with this trial.

Eligibility Criteria

Inclusion Criteria

Study Sites

We will include level 3 trauma centers that are teaching hospitals; are staffed with medical trainees, interns, surgery residents, and consultants; and offer 24/7 emergency surgical care with access to blood banks, ultrasound scans, X-ray scans, and computed tomography (CT) scans as locally available or outsourced services.

Trainee Participants

We will include third-year or fifth-year medical or allied health students, interns, or specialty residents in surgery and traumatology clinical rotations who stay at the hospital of attachment for at least 2 months. Medical students may only rotate to a different hospital without crossing the study arm. In addition, we will include road traffic law enforcement professionals concerned with the evacuation of trauma patients from accident scenes.

Patient Participants

We will include patients who sustain motorcycle accident–related injuries and present to the study sites within 24 hours following the accident, as defined in a previous study [6]. These will include passengers on motorcycles, motorcycle riders, pedestrians or cyclists hit by motorcycles, and patients experiencing motorcycle-motorcycle collisions, motorcycle-static object collisions, or motorcycle-car collisions.

Exclusion Criteria

Study Sites

We will exclude trauma centers that do not offer placements and teaching facilities for students, interns, and residents.

Trainee Participants

We will exclude medical students who have not commenced their surgery clinical rotation and those not directly involved with the care of trauma patients at the time of the training, as trainee medical participants are expected to have already been introduced to surgery, emergency trauma resuscitation concepts, and trauma clinical scenarios through clerkships onto which we will be building the rural trauma team concept.

Patient Participants

We will exclude pregnant women, neonates, and infants aged 0-23 months owing to the known teratogenic effects of radiation in this population, as trauma evaluation in this study will involve obtaining radiographs for orthopedic injuries and CT scans for neurological injuries. Patients with documented stroke will also be excluded, as the study outcomes involve assessment for functional, physical, and neurological disabilities directly attributable to trauma. Moreover, mentally incapacitated patients who have no legally authorized representatives to sign an informed consent form and patients who die before hospital arrival or before imaging results are obtained will be excluded. Patients who are passengers in a car or drivers in a car at the time of the accident will be excluded, as the protective casing of the car body would make these patients less vulnerable to direct impacts compared with pedestrians, cyclists, or passengers on motorcycles. In addition, elderly patients older than 80 years will be excluded owing to their increased risk of fragility fractures that could misrepresent the severity of trauma. This cutoff age was used based on a systematic review by Tsuda et al [24], which documented a mean age of 80 years for long bone fragility fractures owing to increased muscle weakness, balance disorders, visual impairment, and dementia that predispose elderly people to falls. The number of ineligible participants and the reasons for their exclusion will be recorded in both arms in the consolidated standards of reporting trials flow diagram.

Ethical Considerations

Research Approval

Prior to recruitment, this study has been approved and registered by the research and ethics committees of the Uganda National Council for Science and Technology (reference number: SS 5082) and Mbarara University of Science and Technology (reference number: MUREC 1/7; 05/5-19).

Consent to Participate

Written informed consent will be obtained from all study participants or their legally authorized representatives prior to participation. The official informed consent form documents for Mbarara University of Science and Technology will be adopted for this purpose. Both trainee and patient participant informed consent documents are provided in Multimedia Appendix 1 and Multimedia Appendix 2, respectively. The ethical committees ruled that trainees involved in the data collection process at control centers do not need to provide any consent as this study will neither directly affect their practices nor collect their personal data.

Collection of Informed Consent

All participants or their legally authorized representatives (for minors and unconscious patients) will endorse a predesignated consent form document with their signatures in the presence of the principal investigator or research assistants (surgery specialty residents).

Additional Consent Provisions for the Collection and Use of Participant Data and Biological Specimens

There will be no biological specimens retained for this study. The informed consent form documents will have provisions for consenting to follow-up and the use of data for approved ancillary studies, and for permission to archive the anonymized data in a public data repository.

Consent for Publication

This manuscript does not contain any identifying individual participant information or images; thus, consent for publication is not applicable.

Privacy and Confidentiality Protection

To protect participants' confidentiality before, during, and after the trial, all hard copy data collection items will be kept under lock and key and will bear unique nonidentifying codes. Soft copies will be kept in password-protected computers, with a second-layer protection login password required for REDCap,

which will be only accessible to the study team. The final data sets will be anonymized prior to archiving and publication. Hard copies of the data will be destroyed 6 months after completion of the trial.

Compensation Type and Amount for Participants

Participation in this trial will be voluntary. However, transport reimbursement of 20,000 Ugandan shillings (US $5.0) will be provided to participants turning up for research follow-up appointments outside of their routine hospital visits. Moreover, time compensation of 10,000 Ugandan shillings (US $2.5) will be provided.

Interventions

Explanation for the Choice of Comparators

The intervention for this trial is based on the fourth edition of the RTTDC of the American College of Surgeons [20], which will be delivered to medical trainees, interns, and traffic law enforcement professionals at the 3 intervention study centers (intervention group). Specialty surgical residents will be trained as faculty who will later serve as trainers since they directly supervise interns and undergraduate medical students in Ugandan settings. The research and ethics committees approved training residents as opposed to specialists to avoid constraining the scarce specialized human resource as this is a trainee-capacity building trauma education program. Moreover, consultants rarely attend to trauma patients for immediate resuscitation as the first point of contact in Ugandan settings. The patient participants at intervention sites will be those with motorcycle accident–related injuries at any of the study sites. The comparator in this trial is a control group of hospitals that will offer standard care to eligible patients, without their care providers receiving the RTTDC training intervention.

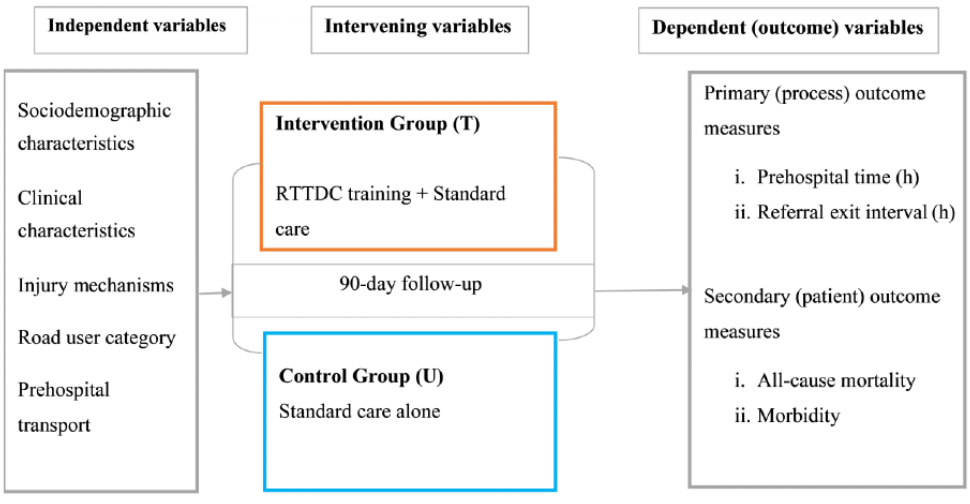
Intervention Description

The 2-day RTTDC interventional training will be conducted in designated spacious multimedia surgical simulation conference rooms at the study sites randomized to the intervention arm and will be delivered in the described standard format [20]. This training model is the most appropriate for Uganda, with its health worker to patient ratio of 1:25,000 and its large population of 48 million [12]. The model dwells on team concepts to improve coordination and efficiency of the existing “skeletal” health structure in the rural environment. We hope to train a total of 66 road traffic police officers, 12 specialty residents, 30 intern doctors, 140 fifth-year medical students, and 264 third-year medical students. These figures have been determined based on the average annual number of traffic police officers and trainees at the respective regional police headquarters and hospitals [25].

Our target is to train at least 80% of each cohort of eligible trainees identified every 1-5 months within the surgery department during the 4-year study period until the required trainee and patient participant sample sizes are attained. If trainees drop out prior to completion of data collection, compensations will be made to maintain the criterion during the next cohort of surgical rotation trainee intake. The details of how the training will be conducted have been provided elsewhere [25]. The research core team has agreed that trainee participants who score more than 60% in posttraining trauma-based multiple-choice questions (MCQs) at the intervention sites will be retained to form a rural trauma team network, which will constitute multiple local 6-member trauma committees of first responders with defined roles (ie, each team having 5 medical trainees and 1 contact road traffic officer).

To enable an active “alarm” activation criterion for the trauma committees, closed-loop communication, and a smooth “handover” process from police officers to medical trainees prior to patient transfer, the trained traffic officers on highways will serve as focal contact persons for the rural trauma teams from the parish (subcounty) level. In the event of a road traffic accident, teammates will freely contact each other both within and across teams to coordinate evacuation, consultation, referral, and arrival at recipient centers, with the support of trained interns and surgery residents as team leaders. Weekly audit meetings will be conducted remotely via Zoom (Zoom Video Communications) to discuss team challenges, otherwise a trained surgery resident will be available 24/7 to advise on referrals, transfers, and treatments in liaison with consultants who may be physically or remotely available. The control hospitals in this trial will be allowed to provide routine standard care without the RTTDC intervention as summarized in Figure 1.

Figure 1. Conceptual framework summarizing the intervention and the interaction of variables. RTTDC: Rural Trauma Team Development Course.



Criteria for Discontinuing or Modifying the Allocated Intervention

The fourth edition of the RTTDC will be delivered in its standardized form [20] without any modifications.

Strategies to Improve Adherence to the Intervention

The RTTDC is the intervention; thus, participants who do not attend all the modules and complete the posttraining MCQs will be excluded. Adherence to teachings in the RTTDC among care providers during clinical practice, such as the time taken from referral decision to execution and improper closed-loop communication leading to loss to follow-up, will be assessed as process measure outcomes.

Relevant Concomitant Care Permitted or Prohibited During the Trial

The baseline quality of care given to trauma patients at each of the participating 6 hospitals is based on the regulations of the Uganda Medical and Dental Practitioners Council (UMDPC), which regulates medical practice, and the National Council for Higher Education (NCHE), which regulates both undergraduate and graduate surgical curricula [26]. The councils require that graduating doctors undergo clinical rotations in surgery and traumatology, perform clerking activities, and present and document trauma scenarios in patient case files.

In addition, medical graduates should demonstrate the ability to initiate emergency resuscitation in accordance with advanced trauma life support protocols [27], such as execution of primary and secondary surveys; carefully discern, request, and comprehend the necessary imaging and laboratory investigations in trauma; acknowledge self-knowledge and resource limitations; and consult or refer patients whose surgical care demands exceed their own skills or the local trauma capacity. Further, upon graduation, Ugandan doctors are required to obtain a minimum of 48 hours of continuous professional development points annually to maintain their licensure.

In terms of the standards of care, both intervention and control facilities have medical trainees, interns, specialty residents, and specialists who provide care for injured patients. The care typically involves receiving trauma patients who may be brought by staffed ambulances, police officers, or public means to accident and emergency units, and these patients may be received by trainees, interns, or surgical residents. These cadres open case files; initiate immediate care through horizontal consultation; request X-ray scans, CT scans, and laboratory workup; and plan definitive care or referral in liaison with a senior surgical resident and in consultation with a multidisciplinary team of specialists on call. As such, procedures, such as surgical suturing and toileting, limb fracture casting and immobilization, and chest tube insertion, are often performed by interns. More demanding procedures, such as splenectomy, external fixation of fractures, and burr holes, are usually performed by specialty residents after notification of the consultant on duty, whereas major cases of polytrauma warrant the decision of the consultant specialist on call before the patient is taken to the operating room.

Imaging and blood transfusion services are often freely available at emergence units as government services but may be outsourced from private hospitals at a cost owing to long waiting times or service maintenance for CT scanners and X-ray machines. Finally, in terms of patient disposition, patients with minor injuries requiring surgery under local anesthesia are discharged on the same day. Moreover, patients with major trauma requiring conservative treatment, such as closed fractures, are treated in surgical wards, whereas those who are deeply unconscious or require critical care after major operations are admitted to the ICU until they are fit for care in general surgical wards prior to discharge. Alternatively due to overcrowding, often with higher bed occupancy rates exceeding the predetermined bed capacity, patients with major trauma may be referred to other centers, and the common reasons for referral include further neurosurgical evaluation with magnetic resonance imaging or further evaluation by a neurosurgeon, need for multiple specialty care and rehabilitation, and need for ICU admission elsewhere when local ICU beds are limited.

Provisions for Posttrial Care

Any participants requiring further care beyond the 90-day follow-up will be linked to their attending clinicians during an additional 3-month period after completion of the trial. There will be no compensation other than transport reimbursement for participants visiting solely for study follow-up outside routine clinical visits as this study was considered minimal risk by the approving research ethics committees. The principal investigator will refund the cost of imaging when the request is approved by attending surgeons and radiologists in cases where the services are unavailable free of charge.

Outcomes

This trial will examine both process measures and patient outcomes. The primary (process) outcomes of this trial will involve comparisons of (1) the time interval from the accident to hospital admission and (2) the time interval from the referral decision to hospital discharge between patients with motorcycle accident–related injuries presenting to the intervention centers and those presenting to the control centers.

The secondary (patient) outcomes of this trial will involve comparisons of (1) all-cause mortality at 90 days from the time of injury and (2) morbidity of motorcycle accident–related orthopedic and neurological injuries between patients presenting to the intervention centers and those presenting to the control centers. The morbidity of orthopedic injuries will be measured based on the Trauma Expectation Factor Score (TEFS) at admission and the Trauma Outcome Measure Score (TOMS) at 90 days as reported to outcome assessors [28]. On the other hand, for neurological injuries, the Glasgow Coma Scale (GCS) at admission and Glasgow Outcome Scale (GOS) at 90 days will be used as documented by the attending clinicians [29].

The tertiary outcomes will involve the effects of the training on provider knowledge based on pretraining and posttraining trauma-related MCQ scores and the barriers to injury care faced by providers during execution of definitive treatment. These will be determined in 2 ancillary studies that have been approved as part of this trial, and the protocols have been detailed

elsewhere [25]. A summary of all outcomes and their case definitions, specific measurement variables, analysis metrics, methods of aggregation, and time points has been provided in Multimedia Appendix 3.

The patient outcomes were selected based on their validity and relevance in previous studies [7,30]. Further, level III evidence suggests that prolonged prehospital times may be associated with increased mortality among trauma patients [31]. However, it is unclear how these results relate to time-sensitive orthopedic and neurological injuries in LMICs that lack formal coordinated prehospital systems [32]. Thus, our process outcome measure variables were selected within the context of evidence-based practice. This practice stipulates that in accordance with the golden hour rule, a major trauma patient should be in the right place within 60 minutes following injury, otherwise there is a risk of mortality or morbidity [33].

These variables align well with the proposed global surgery framework to improve national surgical, obstetric, and anesthesia care provider plans [34]. In addition, the variables expand on outcomes for trauma-informed interventions [35]. All outcomes will be measured as final values but will be discussed in relation to the baseline established in our prior feasibility studies [7,30]. The comparisons of outcomes will be made at both individual and cluster levels, using mixed effects regression models.

Participant Timeline

Initially, cluster randomization of the trauma centers will be performed 3 weeks prior to commencement of the training to determine which centers will receive the training. Potential participants for the training will be screened for eligibility by the hospital and study administrators 2 weeks prior to the training, and eligible trainee participants will be consented and assigned to “rural trauma teams” of 6 members on the first day of the training, during which they will complete a pretraining questionnaire involving trauma-based MCQs. Subsequently, trainee participants will be followed up at 90 days (3 months) to complete posttraining MCQs. The first eligible patient participants at both control and intervention sites will be enrolled concurrently through a motorcycle trauma outcome registry (MOTOR) that will run parallel to the trial.

Informed consent, baseline sociodemographic and clinical characteristics, and prehospital intervals will be obtained at admission, and the GCS score will be determined. The TEFS will be obtained during the first week of admission or prior to discharge on the assumption that patients would have received their definitive surgical intervention or would have been referred for further care during this period. Further, the GOS score, all-cause mortality rate, and TOMS will be obtained at the 90-day follow-up. The GCS will be used to assess the level of traumatic brain injury in the acute phase, whereas the GOS will be used to determine neurological outcomes within the context of the level of independence at a later phase of traumatic brain injury [29]. On the other hand, the TOMS will be used to assess patient-reported trauma outcomes with reference to their expectations (TEFS) at the time of the trauma intervention in relation to the levels of pain, physical function, disability, injury treatment satisfaction, and overall satisfaction [28,30]. Throughout the study period, any individual patient barriers encountered during the pathway to execution of definitive injury care will be documented as summarized in the timeline presented in Multimedia Appendix 4.

Sample Size

To estimate the sample size, we used the open-source R Shiny application for cluster randomized controlled trials with a parallel design and discrete time decay correlation structures for multiple periods [36] available at [37]. Further, we assumed *t*-distribution due to plans for small sample corrections at the analysis stage in accordance with the report by Rutterford et al [38]. The study was approved for 4 years, but the core research team foresaw it feasible to actively collect data for a period of 3 years considering university semester breaks, public holidays, and unexpected events, such as COVID-19–related interruptions, which led to suspension of the trial for 12 months from March 2020 to March 2021. The 3 years (36 months) would yield 12 study periods given the planned training of cohorts of medical students on a 3-monthly basis in accordance with the average duration of internship deployment by the Ugandan Ministry of Health (1-5 months) and the average duration of surgery clinical rotation for university medical students (2 months).

Fixing the study power at 80% for a parallel cluster randomized trial with different cross-sections, considering a discrete time decay period of every 3 months for a total of 12 periods, and assuming correlations to decay with each period, we explored the minimum number of patient participants (cluster size) required per period using the R Shiny application [36]. Assuming a significance level of .05, a within-period intraclass correlation coefficient (ICC) of 0.02 (lower extreme: 0.01, upper extreme: 0.05), and a cluster autocorrelation coefficient (CAC) (ratio of between-period ICC to within-period ICC) of 0.8; allowing for varying cluster sizes with a coefficient of variation of 0.5; and considering a mean difference of 1.02 hours in prehospital transfer time and a pooled standard deviation of 1.64 hours as continuous outcomes reported in a previous observational study from the United States [39], the upper ICC and base CAC plateaued between 5 and 10 participants (Figure 2).

Considering a maximum of 10 participants per cluster period, an 80% power could be attained (Figure 3) and could be met with a total of 3 clusters per arm (Figure 4). This indicates a total of 6 study centers (clusters) drawn from a pool of 17, which reasonably represents 35.3% of Uganda’s regional referral hospitals.

Figure 2. Reduction in the number of clusters required with an increase in the cluster-period size at a fixed power of 0.8. CAC: cluster autocorrelation coefficient; ICC: intraclass correlation coefficient.

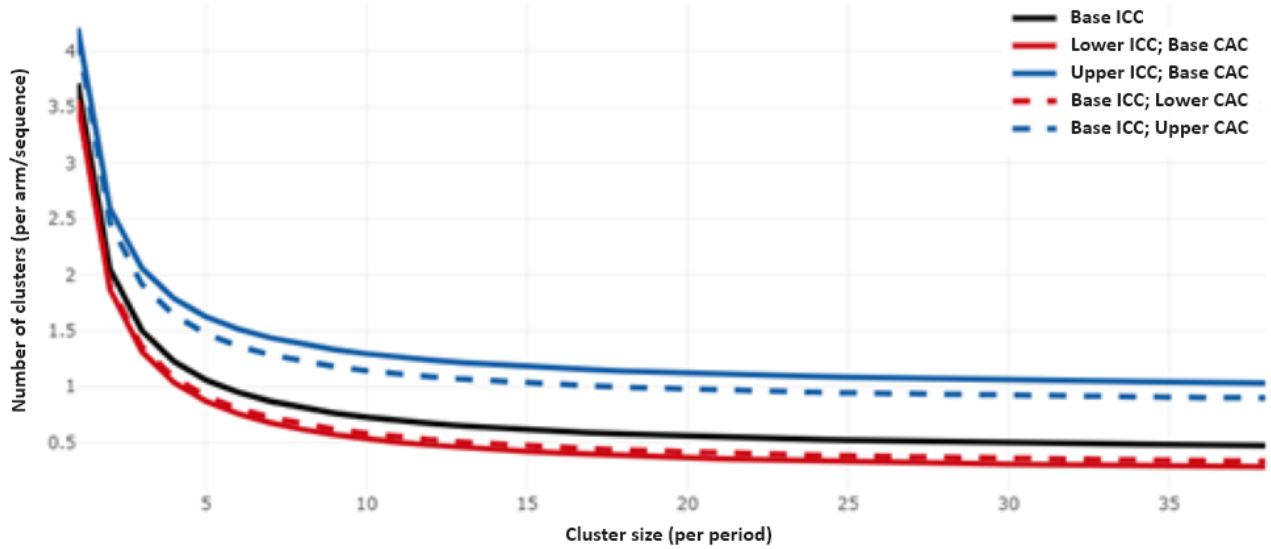


Figure 3. Cluster-period size of 10 meeting the required power of 0.8 for 12 periods. CAC: cluster autocorrelation coefficient; ICC: intraclass correlation coefficient.

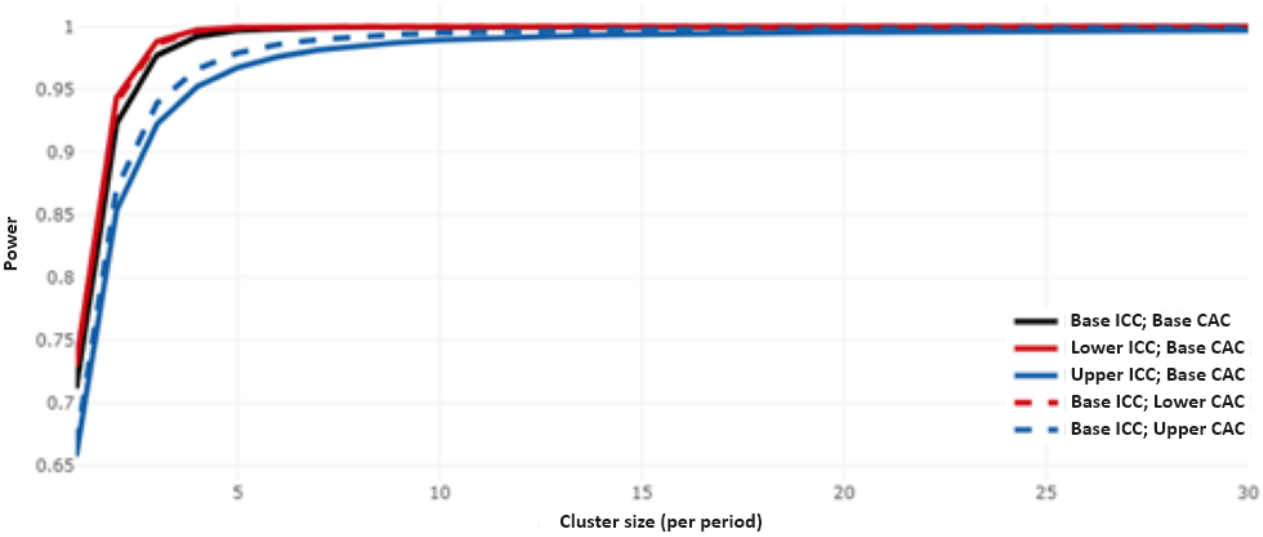
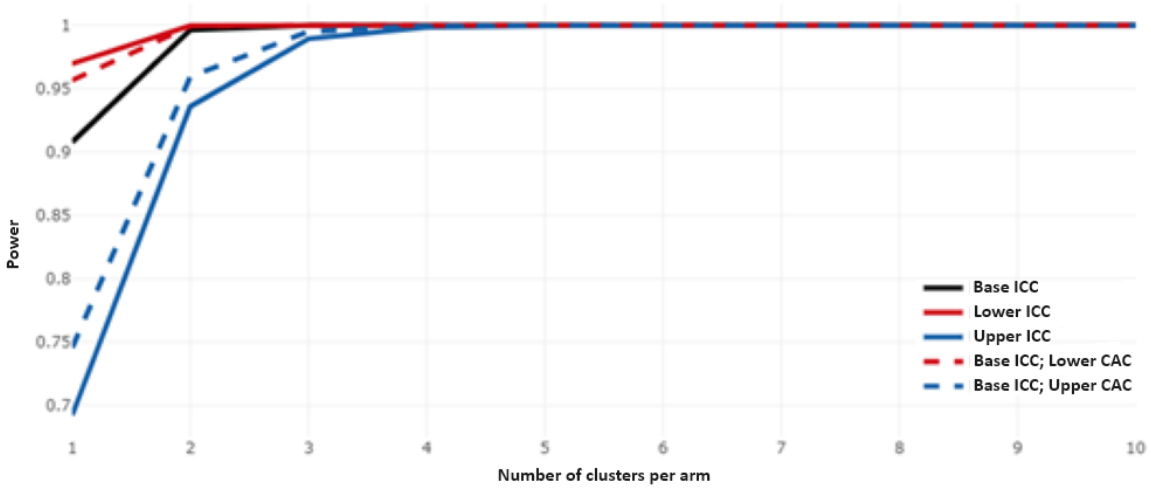


Figure 4. Three clusters per arm meeting the minimum required power of 0.8 for 12 periods. CAC: cluster autocorrelation coefficient; ICC: intraclass correlation coefficient.



The sample required per arm is calculated as follows: 10 participants per cluster period multiplied by 12 cluster periods multiplied by 3 clusters, yielding a total of 360 participants. The total sample required for 2 arms would be 720. However, we inflated the sample and variance to cater to the clustering design effect based on the assumption that this increases the statistical power in accordance with the repost by Hemming et al [36]. Thus, the derived sample size (s) is calculated using the following formula:

$$s = n (1 + [m - 1] \rho) \quad \textbf{(1)}$$

where s is the required sample size, m is the cluster size per period (ie, 10), and ρ is the within-period ICC (0.02).

This formula yields a total of 850 participants.

We will add a rate of loss to follow-up of 18% assuming the worst scenario based on our previous dropout rate of 9% in a feasibility study [7]. Therefore, the final sample will include approximately 1003 participants. Assuming an equal allocation ratio of 1:1, there will be 502 participants per arm and about 168 individuals per cluster. This sample is deemed feasible considering the high trauma burden in Uganda. According to a study at one of the Ugandan rural regional referral hospitals, a total of 900 motorcycle accident–related injuries were recorded during a 3-year period, of which 30.9% (278/900) and 15.8% (142/900) of patients sustained musculoskeletal and neurological injuries, respectively [8]. We will not compute sample sizes for each individual secondary outcome as previous studies have not reported any difference in mortality [40].

Recruitment

The training will be advertised by hospital administrators, class representatives, and regional traffic law enforcement leaders, and course participants will be recruited by the principal investigator and the respective hospital administrators. The patient participants will be recruited by dedicated project officers at the accident and emergency departments.

Assignment of Interventions: Allocation

Sequence Generation

We will perform cluster randomization for a permuted block size of 6 hospitals (clusters) using an open-source simulation software [41], with seed numbers that will be kept confidential to the offsite study administrator. A list of 6 random codes will be generated to assign hospitals to the intervention or control group. As we plan to perform analyses at both the individual level and treatment arm level, we will not add any stratification factors in the simulation model.

Concealment Mechanism

The allocation sequence and assignment codes will be generated by and kept secret by an offsite study administrator. Both outcome assessors and patient participants will be blinded to the treatment allocation.

Implementation

Trainee participants will be enrolled by the respective university hospital administrators, whereas patient participants will be enrolled by project medical officers at the respective study sites, who will serve as outcome assessors.

Assignment of the Intervention: Blinding

Who Will Be Blinded

Trial patient participants and outcome assessors will be blinded using blocked allocation sequence codes.

Procedure for Unblinding if Needed

Unblinding will only be permissible in the likely occurrence of adverse events among the study participants, which can be directly attributed to the study intervention. Such events will be discussed with the attending physicians. Otherwise, the allocation codes will only be revealed to the biostatistician at the time of interim analysis when half of the sample size is recruited. At this point, unblinding the biostatistician is considered more beneficial to inform termination or continuation of the trial, which outweighs the perceived fear of unknown bias [42].

Data Collection and Management

Plans for Assessment and Collection of Outcomes

Data collection will start simultaneously at all the study sites. Medical officers (blinded outcome assessors) with a minimum qualification of Bachelor of Medicine and Bachelor of Surgery (MBChB) and at least 2 years of clinical experience will prospectively collect data through clinical observations, interviews, home visits, and extraction from hospital and police records. All outcome assessors must be willing to undertake a 1-day budgeted training in the use of data collection tools for this trial and the World Health Organization (WHO) ICD-10 online coding module. The data will be collected daily as medical trainees and interns will attend clinical rotations every day. Upon obtaining informed consent, the venue for data collection, including follow-up information, will be at accident and emergence departments during admission, surgical wards, and outpatient clinics, as well as through home visits and phone calls to patients, care takers, or recipient hospital physicians in the case of referrals.

The study variables will include sociodemographic and clinical variables, such as sex, age, injury mechanisms, including nature of collision and road user category, time of injury, prehospital transit time, prehospital care, mode of arrival, vital signs, nature of physical injuries, radiological findings, and injury severity based on the GCS score and Kampala Trauma Score (KTS) [43]. In addition, data on the nature of the treatment administered; need for referral; referral-exit interval; and outcomes, including the TOMS, GOS score, mortality, and time from injury to death, will be obtained. The data collection tools that will be used in this trial, such as the GCS, GOS, TEFS, TOMS, and KTS, have been shown to demonstrate excellent criterion internal validity, consistence, and reproducibility in previous studies [28,29,43,44].

Further, the tools are recognized for their high interrater reliability, sensitivity to change, and ability to be used as continuous or categorical variables in validation studies [28,29,43,44]. The baseline TEFS, GCS score, and KTS will

be added as covariates whose interaction and confounding will be assessed and controlled since the inclusion of baseline values of outcomes as covariates is arguably one of the strongest factors to reduce ICC estimates [45]. The difference in distribution of baseline characteristics will be compared using means (SDs), medians (IQRs), and ranges for quantitative data; otherwise, frequencies and percentages will be used for categorical variables. All data collection forms for this trial and detailed definitions of assessment tools for patient and trainee participants are available in Multimedia Appendix 5 and Multimedia Appendix 6, respectively.

Plans to Promote Participant Retention and Complete Follow-Up

Coffee breaks will be facilitated during training to optimize participation. Phone and email contacts will be obtained from all medical trainees and law enforcement professionals. In addition, 2 phone contacts will be obtained for each patient participant at the time of enrollment at accident and emergency departments (ie, the patient and their next of kin or legally authorized representative who will in turn be provided with the phone contact of the study nurse coordinators for the purpose of follow-up). Automated reminders will be sent to data collection assistants through mobile phones and the research electronic data capture (REDCap) platform.

Where applicable, home visits will be conducted for participants who are unable to turn up for appointments because of their disability. Transport costs will be reimbursed for traffic law enforcement professionals and patient participants turning up for appointments outside of the routine hospital visits. Participants will be considered as lost to follow-up if they are untraceable by phone, clinic appointment, or home visit. Data on the baseline sociodemographic and clinical characteristics of those lost to follow-up or those who discontinue because of a breach of the intervention protocol will be retained for comparisons between groups, but the data of those who withdraw their consent will be deleted.

Patient and Public Involvement

Using semistructured questionnaires and semistructured interviews, a 1-day consultative meeting will be conducted at each study site with chief residents, heads of interns, patient caregivers, student representatives, and regional traffic police commanders in the month preceding study commencement to discuss their perceived barriers to injury care in order to uncover themes for potential sources of delays ranging from accident scene discovery, evacuation, and prehospital transportation to emergency care, which shaped the final data collection tools.

During this engagement, trainee and caregiver representatives will provide insights on the feasibility of the outcome assessment tools and the time commitment required to respond to the questionnaire, which will inform the data collection time points of day 1, the first week, and day 90. This strategy will strike a balance regarding the feasibility of maximizing response rates and obtaining data while not overloading the already scarce human resources of traffic law enforcement, and trainees and clinicians at accident and emergency departments. Further engagements will be made during RTTDC training sessions and audit meetings, during which bidirectional feedback will be provided on team performance, challenges with individual team dynamics, and proposed areas of improvement to help shape future training. The results of patient and public engagement will be reported in an ancillary study on the barriers to injury care.

Data Management

Due to expected network breakdowns in rural centers, data will be collected in hard copies, coded, and entered into the REDCap secure virtual network hosted by the University of Turku. Data entry will be performed by outcome assessors who will be issued with a confidential login password for REDCap. Later, the data will be exported to Stata version 15.0 (StataCorp) for analysis. The REDCap software was preferred owing to its presumed secure web-based intuitive interface for validated data capture, offering an additional advantage to prohibit dual entry, restrict values, calibrate data ranges, and retrieve audit trails for tracking data manipulation [46]. Further, the software permits seamless data export and download procedures that are compatible with Stata, while allowing for data integration and interoperability with external sources [47]. Any data errors will be resolved during weekly audit meetings in reference to the online codebook with a visible description of variables accessible to the principal investigator and all outcome assessors.

Plans for Collection, Laboratory Evaluation, and Storage of Biological Specimens for Genetic or Molecular Analysis

There are no plans to collect any biological laboratory specimens for storage or for genetic or molecular analysis in this trial.

Statistical Methods

Statistical Methods for Primary and Secondary Outcomes

Primary (Process) Outcomes

The primary (process) outcomes of (1) the time interval from the accident to hospital admission and (2) the time interval from the referral decision to hospital discharge will be compared between the intervention and control groups using a 2-sample *t* test if the data are normally distributed or a 2-sample Wilcoxon rank sum test if the data are not normally distributed. The normality of distribution will be assessed using the Shapiro-Wilks test, whereas the equality of variance will be determined using the Levene test. A difference in means of 60 minutes (1 hour) will be considered clinically meaningful in accordance with the golden hour principle [33].

Secondary (Patient) Outcomes

For assessing the morbidity of musculoskeletal injuries, the validated 10-item TEFS will be used at baseline and the 10-item TOMS will be used at 90 days [30]. The mean difference in the TEFS and TOMS will be compared between the intervention and control groups using the 2-sample *t* test. Further, the TOMS will be dichotomized into favorable (TOMS ≥ TEFS) and unfavorable (TOMS < TEFS) outcomes in accordance with previous studies [30]. The difference in these proportions between the intervention and control groups will be compared

using the adjusted chi-square test if the expected count is >5 or the Fisher exact test at 95% CI otherwise.

Further, subgroup analyses will be performed to determine and control for factors that could be associated with an unfavorable TOMS, using individual-level between-within mixed effects regression models, which inherently overcome the effect of smaller clusters and permit adjustment for covariates in a single stage, assuming equal allocation. The fixed effect variables will be the treatment arms (intervention vs control) as the unit of analysis, with the odds ratios (ORs) and their corresponding 95% CIs as direct estimates of the effect size. The covariates will include age, sex, education level, occupation, employment status, marital status, commute distance, road user category, injury severity score based on the KTS, presence or absence of fracture, nature of fracture if present, number of serious injuries, and treatment (surgical vs conservative).

For assessing the morbidity of neurological injuries, the validated GOS will be used at 90 days after injury. The mean difference in the GOS score will be compared between the intervention and control groups using the 2-sample *t* test. Further, the GOS score will be dichotomized into favorable (GOS score of 4 or 5) and unfavorable (GOS score of 3, 2, or 1) outcomes in accordance with previous studies [7]. The difference in proportions between the intervention and control groups will be compared using the adjusted chi-square test if the expected count is >5 or the Fisher exact test at 95% CI otherwise.

For all-cause mortality, the difference in proportions of all deaths at 90 days after injury will be compared between the intervention and control groups using the chi-square test if the expected count is >5 or the Fisher exact test at 95% CI otherwise. Lastly, we will conduct subgroup analyses to determine and control for factors associated with all-cause mortality using individual- and cluster-level between-within mixed effects regression models. The covariates will include age, sex, injury mechanism (including helmet use), mode of arrival, prehospital interval, referral decision to hospital discharge interval (dichotomized as ≤1 hour or >1 hour), prehospital first aid status, comorbidities, injury severity score based on the GCS at baseline, multiplicity of injuries, head and brain CT-based diagnosis, and neurosurgical intervention.

These variables have been found to influence outcomes following neurological trauma in previous studies [7]. All variables will be analyzed for confounding and effect modification using Mantel-Haenszel statistics to probe necessary interaction terms. Variables with *P* values of ≤0.2 in the bivariate analysis will be included in the multivariate analysis. The median (IQR) of the time to the event, that is, from the accident to death (in days), will be stratified by treatment arm, and the difference will be compared using the Wilcoxon 2-sample test. All analyses will be performed using Stata 15.0, and where appropriate, graphics, such as box plots, will be used to visualize the data.

Interim Analyses

The Uganda National Council for Science and Technology accessed a preliminary report of the interim analysis, which was performed on August 28, 2022, when half of the sample size (n=500) was attained, and at its discretion, it recommended continuation of the study. The requisite characteristics for early termination set by the ethics committee included the occurrence of an index patient-reported adverse outcome definitely attributable to the study in accordance with the framework described by Okoniewska et al [48].

Methods for Additional Analyses

Subgroup analyses will be performed for (1) varying road user categories (pedestrian, passenger, and motorcyclist); (2) injury mechanisms (motorcycle-motorcycle accident, motorcycle-pedestrian accident, motorcycle-static object accident, and motorcycle-car accident); (3) varying injury severities (mild, moderate, or severe based on the KTS and GCS); and (4) multiplicity of serious injuries (one or multiple). To determine the training-effect heterogeneity across time periods, we will use an extension of Hussey and Hughes fixed effects model [49] for determining whether the intervention effect differs for each training period as summarized in the schematic representation of the study design (Multimedia Appendix 7).

For the ancillary study on provider outcomes, the difference in pretraining and posttraining mean scores will be computed with 95% CIs if the data are normally distributed; otherwise, the difference in median and IQR will be reported. For the qualitative ancillary study on the perceived barriers to injury care, directed content analysis of themes of transcribed data will be collated manually and presented as percentages.

Methods in Analysis to Handle Protocol Nonadherence and Any Statistical Methods to Handle Missing Data

We will impute values for participants with missing end points, such as those lost to follow-up, those who withdraw consent, and those who crossover. The baseline sociodemographic and clinical characteristics of such participants will be compared between the intervention and control groups. For individual participants, crossover from the intervention group to the control group or vice versa for any reason will result in ultimate discontinuation from the trial.

Plans to Provide Access to the Full Protocol, Participant-Level Data, and Statistical Code

The full protocol will be published open access, and anonymized participant-level data sets and statistical codes will be shared publicly through a permanent weblink that will be provided by the publishing journal. Since the primary country of recruitment, which approved and registered the study prior to recruitment, lacks a publicly available electronic research register, this protocol has been retrospectively registered with the WHO-approved Pan African Clinical Trials Registry (PACTR202308851460352).

Oversight and Monitoring

Composition of the Coordinating Center and Trial Steering Committee

The principal investigator and a central study administrator will form a steering committee that will run the day-to-day activities

of the trial. The trial will have 2 onsite overseers and 2 off-site supervisors. In addition, the principal investigator will provide organizational support to rural trauma teams at the intervention study centers through weekly audit meetings. Each of the rural trauma teams is composed of a road traffic law enforcement professional, a third-year medical student, a fifth-year medical student, an intern doctor or nurse, and a specialty surgery resident.

Composition of the Data Monitoring Committee, and Its Role and Reporting Structure

The research and ethics committee of Mbarara University of Science and Technology is the designated independent data monitoring committee that will oversee this trial (reference number: MUREC 1/7; 05/5-19). The committee reports directly to the Uganda National Council for Science and Technology. The council, at its discretion, can recommend continuation, amendments, or termination of the trial at any time.

Adverse Event Reporting and Harms

Immediate medical concerns from participants will be reported to their attending clinicians. Any reported adverse events and other unintended effects of trial interventions or trial conduct will be reported to the trial monitoring committee. Patient-reported adverse outcomes resulting from the intervention (study) rather than biological injury progression will be captured during the follow-up interviews and evaluated on a 5-point Likert scale in accordance with the framework described by Okoniewska et al [48] as follows: (1) no evidence that the event is due to the intervention, (2) little evidence that the event is due to the intervention, (3) the event is possibly due to the intervention but most likely due to injury, (4) the event is more likely due to the intervention than injury, and (5) the event is definitely due to the intervention. Case files with 4 to 5 points will be forwarded for external auditing in surgery departmental meetings to ascertain if the adverse event was preventable, ameliorable, or neither.

Frequency and Plans for Auditing Trial Conduct

The trial monitoring committees will independently conduct annual and impromptu audits and may choose to extend or terminate the trial at any time. Such situations that could warranty termination include adverse events directly attributable to the intervention. The investigators will submit annual progress reports to the committees each year as part of continuing review.

Plans for Communicating Important Protocol Amendments to Relevant Parties

Any protocol amendments will be submitted to the data monitoring committee. Any approved amendments will be communicated to the Uganda National Council for Science and Technology and trial participants, and will be updated in the registries within 5 working days following approval.

Ancillary Studies

This trial has been approved with 2 ancillary studies. The first is a study to assess the effect of the RTTDC on provider knowledge, and the second is a qualitative study to assess the barriers to injury care as perceived by traffic police, medical trainee frontline workers, and individuals encountered in the real-time management of patient participants. The data collection team for the qualitative study will be surgery residents at the 6 regional referral hospitals who will be blinded to the cluster or treatment allocation. The results of the ancillary studies will be collected and analyzed separately and will be concealed from the trial team until the analysis of the main clinical trial findings is nearly complete. We hope that the findings of the ancillary studies will complement and inform the interpretation of the trial findings.

Dissemination Plans

Participants of the RTTDC training will receive feedback after the posttest questionnaire evaluation. Patient participants will be advised on the next plans of management during follow-up calls or through outpatient consultations. Before presentation of the study findings at scientific conferences and publication in peer-reviewed journals, copies of the findings in final bound reports will be submitted to the main libraries of the participating hospitals, the departments of surgery, and the internal review boards of Mbarara University of Science and Technology, Kampala International University, and Uganda National Council for Science and Technology.

The implications of the findings will be shared with authorities, including intern and medical student associations, district health officers, hospital directors, regional traffic police commanders, and chairpersons of the motorcycle riders' associations in the respective regions, as well as with the rural trauma networks of first responders. Priority will be made to present the preliminary findings at an international conference hosted in Uganda and at the annual world safety conference. Anonymized participant data sets from this trial will be archived on a publicly accessible permanent weblink that will be provided by the publishing journal within 12 months from the actual date of completion of the trial.

Results

The trial was approved on August 27, 2019. The actual recruitment of the first patient participant began on September 01, 2019. The last follow-up was on August 27, 2023. Posttrial care, including linkage to clinical, social support, and referral services, is to be completed by November 27, 2023. Data analyses will be performed in Spring 2024, and the results are expected to be published in Autumn 2024.

Discussion

Study Implications and Future Directions

This trial is meant to compare (1) the time interval from the accident to hospital admission, (2) the time interval from the referral decision to hospital discharge, (3) the all-cause mortality, and (4) the morbidity of patients with motorcycle accident–related orthopedic and neurological injuries between RTTDC (intervention) and standard care (control) study centers in Uganda, Africa.

This study is anticipated to reveal the overall impact of the rural trauma team development and training on the clinical process time efficiency and patient-centered outcomes of

musculoskeletal and neurological injuries in controlled clinical settings, using validated injury severity scores [43] and trauma outcome and process measures [29,30]. The findings will add value to the emerging evidence from previous nonrandomized studies in high-income countries, which have evaluated the RTTDC. The available evidence suggests that the RTTDC potentially reduces the prehospital interval [50] and referral decision time [50], and enhances trauma team role identity, but has no perceived impact on mortality reduction [51]. It remains unclear how these findings relate to LMICs whose trauma care systems are still in the infancy stage.

Study Limitations

Despite the strengths of this trial, we anticipate some limitations. First, while the authors are ambitious to assume that the study centers are homogeneous, the heterogeneity among the 6 participating regional referral hospitals could cause bias and affect study estimates. Further, the relatively smaller number of clusters could affect the power of the study. However, randomization of 6 out of the 17 trauma centers is within the ethical constraints as this sample already represents 35.3% of Uganda's regional referral hospitals. To overcome the statistical power bias limitation, the sample size is inflated for individual randomization to cater to the design effects in accordance with the report by Hooper et al [45]. Moreover, we plan to use mixed effects regression models, which permit adjustments for covariates at both the cluster and individual levels in a single-stage approach, and plan to use the *t* test, which is robust in terms of normality deviations. According to Borhan et al [52], mixed effects models are deemed suitable for smaller clusters in situations where the primary outcomes are continuous, which is the case in this trial. Further, we hope that the ancillary studies with mixed methods will add value to the overall interpretation of the trial results by providing data from individuals outside the health sector, such as traffic law enforcement professionals.

Conclusion

Existing systematic reviews on trauma education programs in LMICs have identified a critical gap with regard to a lack of robust epidemiological studies that assess the effect of such interventions on patient outcomes within the low-resource context [16]. By relying on the strength of local needs contextualization to extend the training to nontrauma specialists, such as traffic law enforcement professionals, the results of this trial could inform the design, implementation, and scalability of rural trauma team development in similar low-resource settings. To the best of our knowledge, this is the first cluster randomized controlled trial using prospectively collected data to compare the effects of RTTDC training and standard care on patient outcomes and process measures in LMICs.

Acknowledgments

The authors are grateful to the staff of the research and ethics committee of Mbara University of Science and Technology for their technical and ethical guidance during the early phases of this project design. Generative artificial intelligence was not used in writing any portion of this manuscript. This study did not receive any external funding. Author HL received a personal research loan from the Uganda Medical Association to support this study. Author JPP is supported by the Academy of Finland (grant number: 17379) and the Maire Taponen Foundation. The sponsors did not have any role in the design or writing of the protocol, or the decision to submit the protocol for publication.

Data Availability

The anonymized data sets arising from this study will be archived and made publicly available through a permanent weblink to a repository that will be provided by the publishing peer-reviewed journal.

Authors' Contributions

HL is the principal investigator and has contributed to conceptualization, data curation, investigation, methodology, project administration, resources, and writing of the original draft. HL and MM have contributed to formal analysis, software, and visualization. RS, PK, TB, JPP, and MLW have contributed to validation, writing–review, and editing. TB, JPP, and MLW have contributed to supervision and funding acquisition. All authors have read and approved the final manuscript. We plan to include a blinded external biostatistician to validate the final data analyses, and this person will be included as a co-author for the resulting manuscripts.

Conflicts of Interest

JPP has received funding from the Academy of Finland (grant 17379). The authors have no further interests to declare.

Multimedia Appendix 1
Informed consent form for rural trauma team development course participants.
[DOCX File , 37 KB - resprot_v13i1e55297_app1.docx]

Multimedia Appendix 2
Informed consent form for patient participants.

[DOCX File , 37 KB - resprot_v13i1e55297_app2.docx]

Multimedia Appendix 3
Outcome measurement variables and their analysis metrics.
[DOCX File , 19 KB - resprot_v13i1e55297_app3.docx]

Multimedia Appendix 4
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) table showing the study timelines.
[DOCX File , 18 KB - resprot_v13i1e55297_app4.docx]

Multimedia Appendix 5
Patient participant data collection tool for the motorcycle trauma registry.
[PDF File (Adobe PDF File), 63 KB - resprot_v13i1e55297_app5.pdf]

Multimedia Appendix 6
Trauma care frontline worker and public engagement trainee data collection tool.
[DOCX File , 52 KB - resprot_v13i1e55297_app6.docx]

Multimedia Appendix 7
Schematic representation of the study design.
[DOCX File , 16 KB - resprot_v13i1e55297_app7.docx]

References

1. Wan R, Xia J, Duan F, Min L, Liu T. Global burden and trends of transport injuries from 1990 to 2019: an observational trend study. Inj Prev 2023 Oct 07;29(5):418-424. [doi: 10.1136/ip-2023-044915] [Medline: 37549986]
2. Chang F, Huang H, Schwebel D, Chan A, Hu G. Global road traffic injury statistics: Challenges, mechanisms and solutions. Chin J Traumatol 2020 Aug;23(4):216-218 [FREE Full text] [doi: 10.1016/j.cjtee.2020.06.001] [Medline: 32680705]
3. Vissoci JRN, Shogilev DJ, Krebs E, Andrade LD, Vieira IF, Toomey N, et al. Road traffic injury in sub-Saharan African countries: A systematic review and summary of observational studies. Traffic Inj Prev 2017 Oct 03;18(7):767-773. [doi: 10.1080/15389588.2017.1314470] [Medline: 28448753]
4. Ryan-Coker MFD, Davies J, Rinaldi G, Hasselberg M, Marke DH, Necchi M, et al. Economic burden of road traffic injuries in sub-Saharan Africa: a systematic review of existing literature. BMJ Open 2021 Sep 15;11(9):e048231. [doi: 10.1136/bmjopen-2020-048231] [Medline: 34526339]
5. Muni KM, Ningwa A, Osuret J, Zziwa EB, Namatovu S, Biribawa C, et al. Estimating the burden of road traffic crashes in Uganda using police and health sector data sources. Inj Prev 2020 Mar 30;27(3):208-214. [doi: 10.1136/injuryprev-2020-043654] [Medline: 32229535]
6. Lule H, Ssebuufu R, Xaviour OF. Prehospital Factors Associated with Injury Severity of Motorcycle Related Femoral Fractures at Mbarara and Kampala International University Teaching Hospitals in Uganda. IOSR Journal of Dental and Medical Sciences 2017;16(8):79-92 [FREE Full text] [doi: 10.9790/0853-1608107992]
7. Ssebakumba MK, Lule H, Olweny F, Mabweijano J, Kiryabwire J. Thirty-day clinical outcome of traumatic brain injury patients with acute extradural and subdural hematoma: a cohort study at Mulago National Referral Hospital, Uganda. Egypt J Neurosurg 2020 Jan 23;35(1):1-12. [doi: 10.1186/S41984-020-0073-4]
8. Zheng DJ, Sur PJ, Ariokot MG, Juillard C, Ajiko MM, Dicker RA. Epidemiology of injured patients in rural Uganda: A prospective trauma registry's first 1000 days. PLoS One 2021 Jan 22;16(1):e0245779. [doi: 10.1371/journal.pone.0245779] [Medline: 33481891]
9. National Population and Housing Census 2014. Uganda Bureau of Statistics. 2016. URL: https://www.ubos.org/wp-content/uploads/publications/03_20182014_National_Census_Main_Report.pdf [accessed 2024-04-23]
10. Morgan J, Calleja P. Emergency trauma care in rural and remote settings: Challenges and patient outcomes. Int Emerg Nurs 2020 Jul;51:100880 [FREE Full text] [doi: 10.1016/j.ienj.2020.100880] [Medline: 32622226]
11. Aftab W, Siddiqui FJ, Tasic H, Perveen S, Siddiqi S, Bhutta ZA. Implementation of health and health-related sustainable development goals: progress, challenges and opportunities - a systematic literature review. BMJ Glob Health 2020 Aug 26;5(8):e002273. [doi: 10.1136/bmjgh-2019-002273] [Medline: 32847825]
12. Walker I, Obua A, Mouton F, Ttendo S, Wilson I. Paediatric surgery and anaesthesia in south-western Uganda: a cross-sectional survey. Bull World Health Org 2010 Dec 1;88(12):897-906. [doi: 10.2471/blt.10.076703]
13. Ogei E, Lewis C. Medical Training in Uganda: A Critical but Neglected Part of the Healthcare System. Cureus 2023 Jun;15(6):e40044. [doi: 10.7759/cureus.40044] [Medline: 37425588]

14. Ningwa A, Muni K, Oporia F, Kalanzi J, Zziwa EB, Biribawa C, et al. The state of emergency medical services and acute health facility care in Uganda: findings from a National Cross-Sectional Survey. BMC Health Serv Res 2020 Jul 09;20(1):634. [doi: 10.1186/s12913-020-05508-8] [Medline: 32646519]
15. Kadhum M, Sinclair P, Lavy C. Are Primary Trauma Care (PTC) courses beneficial in low- and middle-income countries - A systematic review. Injury 2020 Feb;51(2):136-141. [doi: 10.1016/j.injury.2019.10.084] [Medline: 31679834]
16. Livergant RJ, Demetrick S, Cravetchi X, Kung JY, Joos E, Hawes HG, et al. Trauma Training Courses and Programs in Low- and Lower Middle-Income Countries: A Scoping Review. World J Surg 2021 Dec 05;45(12):3543-3557. [doi: 10.1007/s00268-021-06283-1] [Medline: 34486080]
17. Neutel E, Kuhn S, Driscoll P, Gwinnutt C, Moreira Z, Veloso A, et al. Does participation in the European Trauma Course lead to new behaviours and organisational change? A Portuguese experience. BMC Med Educ 2023 Jun 06;23(1):415. [doi: 10.1186/s12909-023-04322-0] [Medline: 37280631]
18. Brown HA, Tidwell C, Prest P. Trauma training in low- and middle-income countries: A scoping review of ATLS alternatives. Afr J Emerg Med 2022 Mar;12(1):53-60. [doi: 10.1016/j.afjem.2021.11.004] [Medline: 35070655]
19. Gerdin Wärnberg M, Berg J, Bhandarkar P, Chatterjee A, Chatterjee S, Chintamani C, Trauma life support training Effectiveness Research Network (TERN) collaborators. A pilot multicentre cluster randomised trial to compare the effect of trauma life support training programmes on patient and provider outcomes. BMJ Open 2022 Apr 18;12(4):e057504. [doi: 10.1136/bmjopen-2021-057504] [Medline: 35437251]
20. Rural Trauma Team Development Course. The American College of Surgeons. URL: https://www.facs.org/quality-programs/trauma/education/rural-trauma-team-development-course/ [accessed 2024-03-10]
21. Butcher NJ, Monsour A, Mew EJ, Chan A, Moher D, Mayo-Wilson E, et al. Guidelines for Reporting Outcomes in Trial Protocols: The SPIRIT-Outcomes 2022 Extension. JAMA 2022 Dec 20;328(23):2345-2356. [doi: 10.1001/jama.2022.21243] [Medline: 36512367]
22. Schmidt W. Randomised and non-randomised studies to estimate the effect of community-level public health interventions: definitions and methodological considerations. Emerg Themes Epidemiol 2017 Sep 7;14(1):9. [doi: 10.1186/s12982-017-0063-5] [Medline: 28912825]
23. Esserman D, Allore HG, Travison TG. The Method of Randomization for Cluster-Randomized Trials: Challenges of Including Patients with Multiple Chronic Conditions. Int J Stat Med Res 2016 Jan 08;5(1):2-7. [doi: 10.6000/1929-6029.2016.05.01.1] [Medline: 27478520]
24. Tsuda T. Epidemiology of fragility fractures and fall prevention in the elderly: a systematic review of the literature. Curr Orthop Pract 2017 Nov;28(6):580-585. [doi: 10.1097/BCO.0000000000000563] [Medline: 29177024]
25. Lule H, Mugerwa M, SSebuufu R, Kyamanywa P, Posti J, Wilson M. Rural trauma team development training amongst medical trainees and traffic law enforcement professionals in a low-income country: a protocol for a prospective multicenter interrupted time series. Int J Surg Protoc 2024 Mar;28(1):12-19. [doi: 10.1097/SP9.0000000000000013] [Medline: 38433864]
26. Kiguli S, Mubuuke R, Baingana R, Kijjambu S, Maling S, Waako P, et al. A consortium approach to competency-based undergraduate medical education in Uganda: process, opportunities and challenges. Educ Health (Abingdon) 2014;27(2):163-169. [doi: 10.4103/1357-6283.143774] [Medline: 25420979]
27. ATLS Subcommittee, American College of Surgeons' Committee on Trauma, International ATLS Working Group. Advanced trauma life support (ATLS®): the ninth edition. J Trauma Acute Care Surg 2013 May;74(5):1363-1366. [doi: 10.1097/TA.0b013e31828b82f5] [Medline: 23609291]
28. Suk M, Daigl M, Buckley RE, Paccola CAJ, Lorich DG, Helfet DL, et al. TEFTOM: A Promising General Trauma Expectation/Outcome Measure-Results of a Validation Study on Pan-American Ankle and Distal Tibia Trauma Patients. ISRN Orthop 2013 Feb 28;2013:801784-801711. [doi: 10.1155/2013/801784] [Medline: 24967116]
29. McMillan T, Wilson L, Ponsford J, Levin H, Teasdale G, Bond M. The Glasgow Outcome Scale - 40 years of application and refinement. Nat Rev Neurol 2016 Aug 15;12(8):477-485. [doi: 10.1038/nrneurol.2016.89] [Medline: 27418377]
30. Fang C, Platz A, Müller L, Chandy T, Luo C, Vives JMM, et al. Evaluation of an expectation and outcome measurement questionnaire in ankle fracture patients: The Trauma Expectation Factor Trauma Outcomes Measure (TEFTOM) Eurasia study. J Orthop Surg (Hong Kong) 2020 Jan 09;28(1):2309499019890140. [doi: 10.1177/2309499019890140] [Medline: 31916492]
31. Waalwijk JF, van der Sluijs R, Lokerman RD, Fiddelers AA, Hietbrink F, Leenen LP, Pre-hospital Trauma Triage Research Collaborative (PTTRC). The impact of prehospital time intervals on mortality in moderately and severely injured patients. J Trauma Acute Care Surg 2022 Mar 01;92(3):520-527. [doi: 10.1097/TA.0000000000003380] [Medline: 34407005]
32. Bhattarai HK, Bhusal S, Barone-Adesi F, Hubloue I. Prehospital Emergency Care in Low- and Middle-Income Countries: A Systematic Review. Prehosp Disaster Med 2023 Aug 26;38(4):495-512. [doi: 10.1017/S1049023X23006088] [Medline: 37492946]
33. Rogers FB, Rittenhouse KJ, Gross BW. The golden hour in trauma: dogma or medical folklore? Injury 2015 Apr;46(4):525-527. [doi: 10.1016/j.injury.2014.08.043] [Medline: 25262329]
34. Roa L, Jumbam D, Makasa E, Meara J. Global surgery and the sustainable development goals. Br J Surg 2019 Jan;106(2):e44-e52. [doi: 10.1002/bjs.11044] [Medline: 30620060]

35. Han H, Miller HN, Nkimbeng M, Budhathoki C, Mikhael T, Rivers E, et al. Trauma informed interventions: A systematic review. PLoS One 2021 Jun 22;16(6):e0252747. [doi: 10.1371/journal.pone.0252747] [Medline: 34157025]
36. Hemming K, Kasza J, Hooper R, Forbes A, Taljaard M. A tutorial on sample size calculation for multiple-period cluster randomized parallel, cross-over and stepped-wedge trials using the Shiny CRT Calculator. Int J Epidemiol 2020 Jun 01;49(3):979-995. [doi: 10.1093/ije/dyz237] [Medline: 32087011]
37. Shiny CRT Calculator. Cluster RCTs. URL: https://clusterrcts.shinyapps.io/rshinyapp/ [accessed 2024-04-26]
38. Rutterford C, Copas A, Eldridge S. Methods for sample size determination in cluster randomized trials. Int J Epidemiol 2015 Jun 13;44(3):1051-1067. [doi: 10.1093/ije/dyv113] [Medline: 26174515]
39. Malekpour M, Neuhaus N, Martin D, Widom K, Rapp M, Leonard D, et al. Changes in rural trauma prehospital times following the Rural Trauma Team Development Course training. Am J Surg 2017 Feb;213(2):399-404. [doi: 10.1016/j.amjsurg.2016.06.015] [Medline: 27575601]
40. Dennis B, Vella M, Gunter O, Smith M, Wilson C, Patel M, et al. Rural Trauma Team Development Course decreases time to transfer for trauma patients. J Trauma Acute Care Surg 2016 Oct;81(4):632-637. [doi: 10.1097/TA.0000000000001188] [Medline: 27438684]
41. Create a randomisation list. Sealed Envelope. URL: https://www.sealedenvelope.com/simple-randomiser/v1/lists [accessed 2024-04-11]
42. Iflaifel M, Partlett C, Bell J, Cook A, Gamble C, Julious S, et al. Blinding of study statisticians in clinical trials: a qualitative study in UK clinical trials units. Trials 2022 Jun 27;23(1):535. [doi: 10.1186/s13063-022-06481-9] [Medline: 35761345]
43. Rosenkrantz L, Schuurman N, Hameed MS, Boniface R, Lett R. The Kampala Trauma Score: A 20-year track record. J Trauma Acute Care Surg 2022 Jun 01;92(6):e132-e138. [doi: 10.1097/TA.0000000000003567] [Medline: 35195097]
44. Jennett B, Snoek J, Bond MR, Brooks N. Disability after severe head injury: observations on the use of the Glasgow Outcome Scale. J Neurol Neurosurg Psychiatry 1981 Apr 01;44(4):285-293. [doi: 10.1136/jnnp.44.4.285] [Medline: 6453957]
45. Hooper R, Bourke L. Cluster randomised trials with repeated cross sections: alternatives to parallel group designs. BMJ 2015 Jun 08;350(jun08 8):h2925-h2925. [doi: 10.1136/bmj.h2925] [Medline: 26055828]
46. Harris P, Taylor R, Minor B, Elliott V, Fernandez M, O'Neal L, REDCap Consortium. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform 2019 Jul;95:103208 [FREE Full text] [doi: 10.1016/j.jbi.2019.103208] [Medline: 31078660]
47. Harris P, Taylor R, Thielke R, Payne J, Gonzalez N, Conde J. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009 Apr;42(2):377-381 [FREE Full text] [doi: 10.1016/j.jbi.2008.08.010] [Medline: 18929686]
48. Okoniewska B, Santana MJ, Holroyd-Leduc J, Flemons W, O'Beirne M, White D, et al. A framework to assess patient-reported adverse outcomes arising during hospitalization. BMC Health Serv Res 2016 Aug 05;16(a):357. [doi: 10.1186/s12913-016-1526-z] [Medline: 27494991]
49. Hemming K, Taljaard M, Forbes A. Analysis of cluster randomised stepped wedge trials with repeated cross-sectional samples. Trials 2017 Mar 04;18(1):101. [doi: 10.1186/s13063-017-1833-7] [Medline: 28259174]
50. Bauman ZM, Khan H, Raposo-Hadley A, Daubert T, Hamill ME, Kemp K, et al. Rural Trauma Team Development Course Positively Impacts its Desired Objectives. Am Surg 2024 Jan 13:31348241227205. [doi: 10.1177/00031348241227205] [Medline: 38217436]
51. Bauman ZM, Loftus J, Hodson A, Farrens A, Shostrom V, Summers J, et al. Rural Trauma Team Development Course Instills Confidence in Critical Access Hospitals. World J Surg 2020 May;44(5):1478-1484. [doi: 10.1007/s00268-019-05359-3] [Medline: 31894357]
52. Borhan S, Ma J, Papaioannou A, Adachi J, Thabane L. Performance of methods for analyzing continuous data from stratified cluster randomized trials - A simulation study. Contemp Clin Trials Commun 2023 Jun;33:101115. [doi: 10.1016/j.conctc.2023.101115] [Medline: 37397432]

Abbreviations

CAC: cluster autocorrelation coefficient
CT: computed tomography
GCS: Glasgow Coma Scale
GOS: Glasgow Outcome Scale
ICC: intraclass correlation coefficient
ICU: intensive care unit
KTS: Kampala Trauma Score
LMIC: low- and middle-income country
MCQs: multiple-choice questions
RTTDC: Rural Trauma Team Development Course
TEFS: Trauma Expectation Factor Score

TOMS: Trauma Outcome Measure Score
WHO: World Health Organization

Edited by A Mavragani; submitted 08.12.23; peer-reviewed by C Sandberg; comments to author 21.02.24; accepted 26.02.24; published 07.05.24.

Please cite as:
Lule H, Mugerwa M, Ssebuufu R, Kyamanywa P, Bärnighausen T, Posti JP, Wilson ML
Effect of Rural Trauma Team Development on the Outcomes of Motorcycle Accident–Related Injuries (Motor Registry Project): Protocol for a Multicenter Cluster Randomized Controlled Trial
JMIR Res Protoc 2024;13:e55297
URL: https://www.researchprotocols.org/2024/1/e55297
doi:10.2196/55297
PMID:

Protocol

Leveraging Community Health Workers and a Responsive Digital Health System to Improve Vaccination Coverage and Timeliness in Resource-Limited Settings: Protocol for a Cluster Randomized Type 1 Effectiveness-Implementation Hybrid Study

Lavanya Vasudevan[1,2*], CPH, MPH, PhD; Jan Ostermann[2,3*], PhD; Nathan Thielman[2,4], MD, MPH; Joy Noel Baumgartner[5], PhD; David Solomon[6], MD; Anna Mosses[6], MD; Amy Hobbie[2], MPH; Nicole L Hair[3], PhD; Chen Liang[3], PhD; Marco van Zwetselaar[7], MSc; Sayoki Mfinanga[6], MD, PhD; Esther Ngadaya[6*], MD, PhD

[1]Hubert Department of Global Health, Rollins School of Public Health, Emory University, Atlanta, GA, United States

[2]Duke Global Health Institute, Duke University, Durham, NC, United States

[3]Department of Health Services Policy & Management, Arnold School of Public Health, University of South Carolina, Columbia, SC, United States

[4]Department of Medicine, Duke University, Durham, NC, United States

[5]School of Social Work, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States

[6]National Institute for Medical Research, Muhimbili Research Centre, Dar es Salaam, United Republic of Tanzania

[7]Zwets IT, Harskamp, Netherlands

[*]these authors contributed equally

Corresponding Author:
Jan Ostermann, PhD
Department of Health Services Policy & Management
Arnold School of Public Health
University of South Carolina
915 Greene St, Discovery 351
Columbia, SC, 29208
United States
Phone: 1 8037778747
Email: jano@mailbox.sc.edu

Abstract

Background: Tanzania is 1 of 20 countries where the majority of unvaccinated and undervaccinated children reside. Prior research identified substantial rural-urban disparities in the coverage and timeliness of childhood vaccinations in Tanzania, with children in rural settings being more likely to receive delayed or no vaccinations. Further research is necessary to identify effective and scalable interventions that can bridge rural-urban gaps in childhood vaccination while accounting for multifaceted barriers to vaccination.

Objective: This protocol describes a type 1 effectiveness-implementation hybrid study to evaluate Chanjo Kwa Wakati (*timely vaccination* in Kiswahili), a community-based digital health intervention to improve vaccination timeliness. The intervention combines human resources (community health workers), low-cost digital strategies (electronic communication, digital case management, and task automation), a vaccination knowledge intervention, and insights from behavioral economics (reminders and incentives) to promote timely childhood vaccinations.

Methods: The study will be conducted in 2 predominantly rural regions in Tanzania with large numbers of unvaccinated or undervaccinated children: Shinyanga and Mwanza. Forty rural health facilities and their catchment areas (*clusters*) will be randomized to an early or delayed onset study arm. From each cluster, 3 cohorts of mother-child dyads (1 retrospective cohort and 2 prospective cohorts) will be enrolled in the study. The timeliness and coverage of all vaccinations recommended during the first year of life will be observed for 1200 children (n=600, 50% intervention group children and n=600, 50% nonintervention group children). The primary effectiveness outcome will be the timeliness of the third dose of the pentavalent vaccine (Penta3). Quantitative surveys, vaccination records, study logs, fidelity checklists, and qualitative interviews with mothers and key informants will inform the 5 constructs of the reach, effectiveness, adoption, implementation, and maintenance (RE-AIM) framework. The results will be used to develop an implementation blueprint to guide future adaptations and scale-up of Chanjo Kwa Wakati.

Results: The study was funded in August 2022. Data collection is expected to last from February 2024 to July 2027.

Conclusions: This study will address the lack of rigorous evidence on the effectiveness of community-based digital health interventions for promoting vaccination coverage and timeliness among children from sub-Saharan Africa and identify potential implementation strategies to facilitate the deployment of vaccination promotion interventions in low- and middle-income countries.

Trial Registration: ClinicalTrials.gov NCT06024317; https://www.clinicaltrials.gov/study/NCT06024317

International Registered Report Identifier (IRRID): PRR1-10.2196/52523

(JMIR Res Protoc 2024;13:e52523) doi:10.2196/52523

KEYWORDS

childhood vaccinations; timeliness; vaccine hesitancy; digital health; community health workers; Tanzania; low- and middle-income countries; SMS; reminder; conditional incentive

Introduction

Background

Globally, the number of children missing their first dose of the diphtheria-pertussis-tetanus (DPT) vaccine rose from 19 million in 2019 to 25 million in 2021 [1,2]. The vast majority (14.2 million, 78%) of such *zero-dose* children reside in 20 countries, including Tanzania [3]. As in other low- and middle-income countries (LMICs), substantial rural-urban disparities in routine childhood vaccination exist in Tanzania, with vaccination rates being lower in rural areas than in urban areas [4]. Using data from the 2015-2016 Tanzanian Demographic and Health Survey, we demonstrated gaps in vaccination coverage (receipt of each recommended vaccine dose by age 1 y) and timeliness (receipt of each vaccine dose within 28 d of the recommended age) for Tanzanian children [4]. The coverage of the first dose of the pentavalent vaccine (Penta1, which includes antigens of DPT, *Hemophilus influenzae*, and hepatitis B) was 79.4% nationally in this analysis, with the remaining 21% of children classified as zero dose [4]. We documented receipt of the third dose of the pentavalent vaccine (Penta3) in even fewer children (72.7%), suggesting dropouts in the multidose vaccine series. Finally, rural children had lower timeliness of vaccination (47.8% delayed for Penta3) than urban children (24.2% delayed for Penta3). New interventions are needed to reduce the number of children who are zero dose, receive delayed vaccines, or drop out and to close the rural-urban gap in vaccination [4,5]. Such interventions must consider multifaceted barriers to vaccination and variations in the availability of human resources and infrastructure in rural areas.

In prior research in southern Tanzania, we identified challenges with the availability of, and access to, vaccination services, including challenges with distance and transportation to health facilities, temporary nonavailability of vaccines owing to a lack of reliable refrigeration at health facilities, and vaccine wastage policies that prevented the use of multidose vials when clinics had low volumes of children to be vaccinated [6]. Service unreliability and lack of communication about service interruptions were noted as causes of frustration among mothers of vaccine-eligible children [6]. Our research also identified vaccine hesitancy owing to vaccine-related knowledge gaps and concerns. In general, rural mothers reported more vaccine-related knowledge gaps and concerns than urban mothers [6]. Despite challenges, vaccination intention was high among mothers, and conditional incentives were identified as a potential *nudge* to increase vaccination timeliness [7,8]. In addition, a community health worker (CHW)–delivered knowledge intervention was piloted and determined to be feasible to implement in rural areas. On the basis of the findings of this formative research and other published reports [9], we designed Chanjo Kwa Wakati (*timely vaccination* in Kiswahili, the most commonly spoken language in Tanzania), a community-based digital health intervention to improve childhood vaccination coverage and timeliness. The intervention seeks to combine human resources (CHWs), low-cost digital strategies (electronic communication, digital case management, and process automation), a vaccination knowledge intervention (counseling scripts addressing specific knowledge gaps), and insights from behavioral economics (reminders and incentives) to promote timely childhood vaccination.

Objectives

This protocol describes our planned evaluation of the implementation and impact of Chanjo Kwa Wakati. The study seeks to contribute evidence to the literature in 3 key ways. First, although many studies have evaluated mobile phone–based reminders for promoting childhood vaccinations [10], evidence is lacking [9] for more complex community-based digital health interventions that target multifaceted barriers to vaccinations, such as those identified in our prior research [4,6,7]. Second, few community-based digital health interventions for promoting childhood vaccination have been evaluated using rigorous randomized controlled study designs, especially in sub-Saharan African countries and in rural areas [11-15]. Third, evidence on implementation strategies associated with deploying community-based digital health interventions in LMICs is limited but critically important for supporting scale-up in the context of highly resource-constrained national health systems. To bridge these gaps in the literature, we will use a type 1 effectiveness-implementation hybrid study [16,17] to evaluate the effectiveness of Chanjo Kwa Wakati in improving the timeliness of childhood vaccinations in rural areas in Tanzania and identify strategies that support its implementation. The detailed protocol of the study is presented in the following sections.

Methods

Study Overview and Aims

This type 1 effectiveness-implementation hybrid study [16,17] uses a cluster randomized trial to evaluate intervention effectiveness and mixed methods to describe implementation outcomes. A cluster randomized design was chosen because the delivery of the intervention is organized at the cluster level. In addition, there are ethical concerns with the randomization of intervention activities, including incentives, at the individual level in rural communities in Tanzania. The evaluation of the Chanjo Kwa Wakati intervention will be guided by the reach, effectiveness, adoption, implementation, and maintenance (RE-AIM) framework. The methods used in this study are described in accordance with the CONSORT (Consolidated Standards of Reporting Trials) checklist for cluster randomized studies (Multimedia Appendix 1). The study aims and hypotheses are described in the following subsections.

Aim 1

The first aim is to evaluate the effectiveness of Chanjo Kwa Wakati for increasing the timeliness of childhood vaccinations due by age 1 year compared with the standard of care. The effectiveness of Chanjo Kwa Wakati will be evaluated in a cluster randomized trial with 1200 mother-child dyads enrolled from the catchment areas of 40 rural health facilities (*clusters*) in 2 regions in Tanzania. Clusters will be randomized into an early or delayed onset study arm. The intervention will target the mother-child dyad; outcomes will be assessed at the child level. Our hypothesis is that Chanjo Kwa Wakati is effective for increasing the timeliness of childhood vaccinations due by age 1 year compared with the standard of care. The primary outcome measure used to evaluate intervention effectiveness will be a continuous measure of the timeliness of the third dose of the pentavalent vaccine (Penta3), due at age 14 weeks, and determined using the birth and vaccination dates abstracted from official vaccination cards issued for the child. A secondary outcome will be a binary measure of timeliness, defined as receipt of Penta3 within 28 days of the due date. Other outcomes measures include the timeliness and coverage of all other vaccine doses due by age 1 year.

Aim 2

The second aim is to evaluate the implementation factors associated with variation in intervention effectiveness and develop an implementation blueprint for intervention scale-up to other settings. Study logs, fidelity checklists, quantitative surveys, and qualitative interviews with mothers and key informants will be used to inform other constructs of the RE-AIM framework, specifically reach, adoption, implementation, and maintenance. Two key implementation outcomes of interest are participants' reports of the receipt of intervention components (intervention fidelity) and their reports of intervention acceptability. Analyses of variation in intervention implementation at the cluster level and systematic variation in the effectiveness for aim 1 outcomes across children will guide the future optimization of Chanjo Kwa Wakati. The results will be used to develop an implementation blueprint to guide future adaptations and scale-up of Chanjo Kwa Wakati.

Study Setting

The study will be conducted in 4 rural districts in Mwanza and Shinyanga regions in Tanzania. Both regions have large numbers of unvaccinated or undervaccinated children. The populations of Mwanza and Shinyanga region were estimated to be 3,699,872 and 2,241,299, respectively [18]. In 2022, only 56% of children aged 12 to 23 months in Mwanza region and 32.2% of children in Shinyanga region were estimated to have received all basic vaccinations, including one dose of Bacillus Calmette-Guerin vaccine, 3 doses of polio vaccine, 3 doses of DPT-containing vaccine, and one dose of measles-containing vaccine [19]. Fewer children aged 12-23 month were considered fully vaccinated according to the national vaccination schedule shown in Table 1 (32.8% in Mwanza and 2.5% in Shinyanga) [19]. Notably, 3.3% of children aged 12-23 months in Mwanza and 14.5% in Shinyanga were reported to have received no vaccinations. [19].

Table 1. Routine childhood immunizations recommended in Tanzania before age 1 year.

Antigen	Age at vax due date
Bacillus Calmette-Guerin (BCG) and oral polio vaccine (OPV) 0	At birth or first contact
OPV1; pentavalent vaccine comprising antigens of diphtheria, pertussis, tetanus, *Hemophilus influenza* B, and hepatitis B (Penta) 1; pneumococcal vaccine (PCV) 1; and rotavirus vaccine (Rota) 1	6 weeks
OPV2, Penta2, PCV2, and Rota2	10 weeks
OPV3, Penta3, PCV3, and injectable polio vaccine (IPV)	14 weeks
Measles and rubella 1	9 months

Intervention Components

Chanjo Kwa Wakati focuses on individual-level barriers to timely vaccination to complement the Tanzanian government's efforts to strengthen vaccination systems and reduce structural barriers [20]. Chanjo Kwa Wakati comprises the following individual-level intervention components: a vaccination knowledge intervention, reminders about upcoming vaccination due dates, service notifications, and conditional incentives for timely vaccination (Table 2). The intervention's target population is the mother-child dyad from the time of pregnancy (third trimester) until the child is aged 1 year. Intervention activities are targeted toward the mother, whereas the timeliness of Penta3 (primary outcome) and other vaccinations recommended before age 1 year (secondary outcomes; Table 1) is assessed for the child.

Table 2. The Chanjo Kwa Wakati intervention.

Timing	Activities	Detailed description of activities
Last trimester of pregnancy	• Enrollment • Registration in digital health system • Knowledge intervention • Baseline assessment[a]	• Informed consent[a] • Register pregnancy and phone numbers in the digital health system • Identify knowledge gaps for an individualized knowledge intervention based on a study by Vasudevan et al [6] • Assess postintervention change in vaccination knowledge and attitudes as well as potential correlates of coverage and timeliness[a]
≤4 wk after the date of delivery	• CHW[b] phone call or home visit	• Ascertain date and place of birth as well as the receipt of vaccinations due at birth • Register the birth, record the 6-wk vaccination due date, and update phone numbers in the digital health system
Before each vaccination due date (6, 10, and 14 wk, and 9 mo)	• SMS text message reminders with incentive offers • Backup: CHW phone calls or home visits • Knowledge intervention	• Messages are sent to the mother and vaccine advocates 7 d and 1 d before each vaccination • Messages are individualized and account for information on service interruptions • Messages include conditional incentive offers • Individualized knowledge intervention focused on vaccinations due at an upcoming visit
≤1 wk after each vaccination due date	• CHW phone call or home visit	• Verify vaccination status and date against vaccination card and issue incentive as appropriate • Update vaccination due dates (and thus reminders) as necessary
12-15 mo after birth	• Follow-up assessment[a]	• Validate vaccination coverage and dates using vaccination cards[a] • Issue incentive as appropriate

[a]Research activity. All other activities are intervention activities.

[b]CHW: community health worker.

Individualized Knowledge Intervention

The knowledge intervention consists of 9 true or false statements that assess key knowledge gaps about childhood vaccinations. A brief counseling script is provided with each statement that will be read out by the CHW after an incorrect response. Statements are based on prior research in Tanzania [6]. Statements and counseling scripts were tested extensively for content, comprehension, and cultural appropriateness with national key informants from Tanzania's Immunization and Vaccines Development program, regional and district health officials, CHWs, and pregnant women from rural Tanzania. In addition to the in-person individualized vaccination education provided by CHWs, SMS text message–based vaccination promotion messages, sent via the Chanjo Kwa Wakati digital health system, will be individualized to each participant's knowledge gaps and aligned with the child's vaccination schedule.

Vaccination Reminder Messages

CHWs will verify the due date for the next vaccination using the child's vaccination card and update the child's information in the Chanjo Kwa Wakati digital health system. The system will automatically schedule SMS text message reminders to be sent 7 days and 1 day before each vaccination due date. The SMS text messages will include the name of the intended recipient, the child's name, the vaccination due date, and other relevant information.

Service Notifications

In the event of stockouts or service nonavailability, SMS text messages with relevant information will be sent to mothers whose children are due for vaccination.

Incentive Offers

Conditional incentive offers will be specific to each child's vaccination schedule. In our prior work [7,8], we identified a set of incentives (eg, pharmacy vouchers and birth certificates) that are likely to be acceptable to mothers. The specific incentives, their value, conditionality, and the timing of disbursement will be determined in discussion with local key informants.

Implementation Strategies

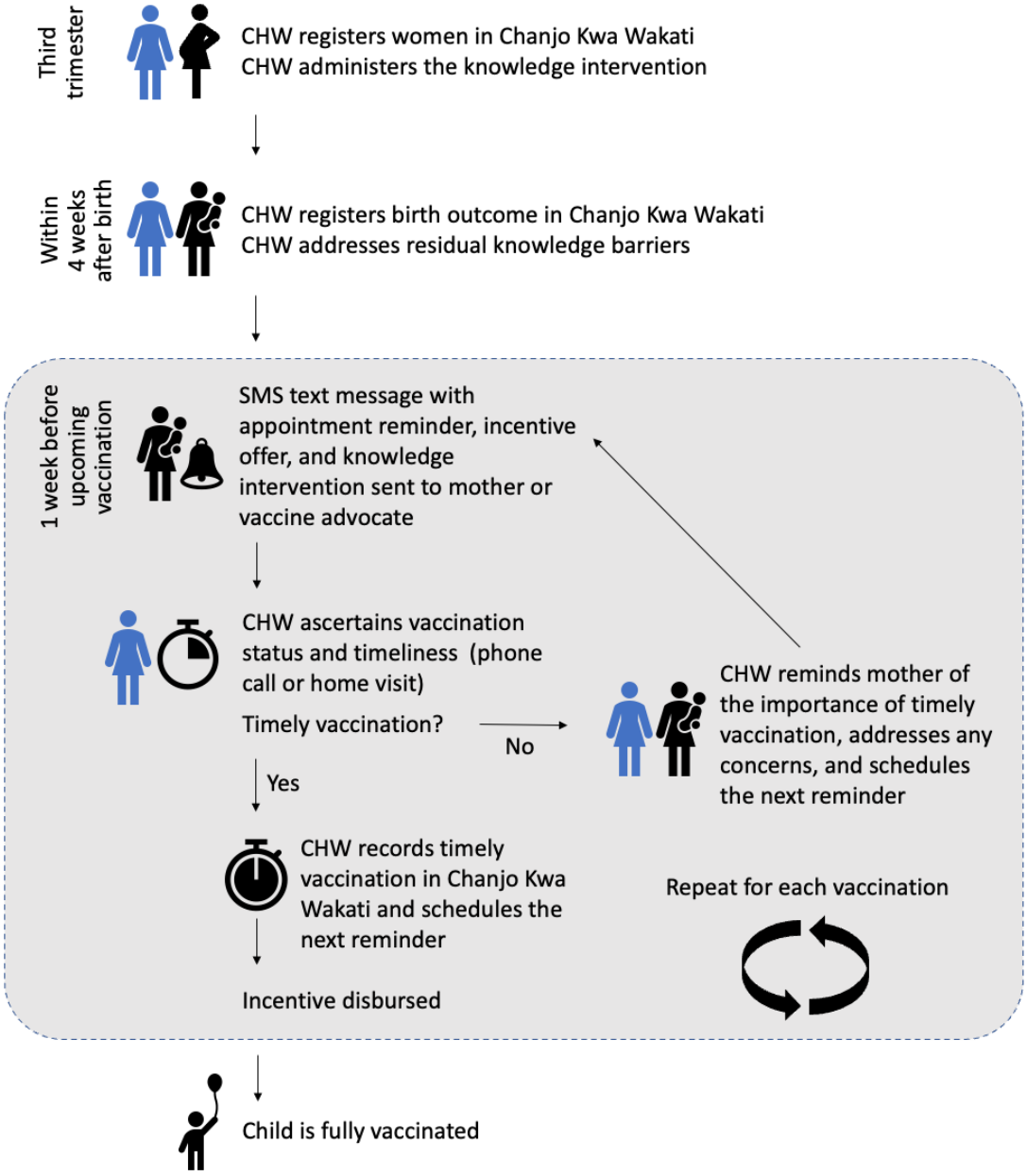
Relevant implementation strategies will be identified in collaboration with local key informants, and a detailed logic model will be developed to guide study activities.

Intervention Activities

Figure 1 describes the sequence of intervention activities. Pregnant women, enrolled in their third trimester, will receive a home visit from a CHW before the birth of their child, be registered with the Chanjo Kwa Wakati digital health system, and receive an individualized knowledge intervention to screen and counsel for common knowledge gaps and concerns about routine childhood vaccinations. After the birth of the child, the

mother will receive individualized SMS text message reminders for upcoming vaccinations, messages aimed at mitigating persistent vaccination knowledge gaps, service notifications (eg, related to stockouts or service nonavailability), and conditional economic incentive offers aimed at encouraging timely vaccinations. CHWs will use the digital health system for work planning, recording vaccination dates and due dates, and following up on missed vaccination appointments and backstop the digital health system with phone calls and in-person visits as needed for vaccination reminders and assessing and addressing mothers' knowledge gaps.

Figure 1. Sequence of intervention activities. CHW: community health worker.



Study Population

Sampling Area

The sampling area comprises 2 rural districts in Mwanza region and 2 rural districts in Shinyanga region, selected based on district-level information about vaccination rates, logistical considerations, and input from key informants.

Cluster Eligibility

Twenty clusters will be selected in each region for a total of 40 clusters. Clusters are defined as the catchment area of eligible health facilities in the sampling area. Eligible health facilities include public and public-designated (private not-for-profit facilities that serve the functions of public health facilities) hospitals, health centers, and dispensaries. Facilities must be operational, offer routine prenatal care and childhood vaccination services, have at least 2 active CHWs operating in the catchment area, and have reported at least 100 pregnancies or births in the year before study implementation. Eligibility will be determined initially using administrative data obtained from district offices and verified using surveys with health facilities.

Study Participants, Eligibility, and Recruitment

The study population will include 3 groups of participants.

Cross-Sectional Retrospective Cohort

This cohort (n=400) will be used for retrospective assessments of children's vaccination records during their first year of life. Eligible participants will be mothers or legal guardians (henceforth referred to as *mothers*) of children aged 12 to 23 months, aged ≥15 years, and residing in the sampling area since the birth of the child.

Before recruiting this cohort, CHWs, with help from local key informants (eg, village leaders, health care providers, and traditional birth attendants), will compile a list of children aged 12 to 23 months residing in each cluster. The lists will be randomized, and mothers will be approached by the research team for eligibility determination, informed consent, and enrollment until 10 mother-child dyads from each cluster are enrolled into the study. Up to 40 additional women, who are not necessarily living in the study area but meet the other eligibility criteria, may be enrolled to pilot-test the study instruments.

Longitudinal Prospective Cohort

This cohort (n=800) will be used for prospective assessments of children's vaccination records during their first year of life. Eligible participants will be pregnant women in their last trimester of pregnancy, aged ≥15 years, residing in the sampling area, and expected to reside in the sampling area until the child reaches age 1 year.

Before recruiting this cohort, CHWs, with help from local key informants (eg, village leaders, health care providers, and traditional birth attendants) will compile a list of pregnant women residing in each cluster. The lists will be randomized, and pregnant women will be approached by the research team for eligibility determination, informed consent, and enrollment until 10 pregnant women from each cluster are enrolled into the study. One additional eligible woman will be enrolled from each cluster during each prospective enrollment round to account for loss to follow-up (refer to the *Retention* subsection).

Participants in Qualitative Feedback

This group will be used to obtain feedback on the RE-AIM constructs. Eligible participants will be key informants at the national, regional, or local levels (target: n=12), health providers from participating facilities who are responsible for childhood vaccinations (target: n=40, approximately 1/cluster), CHWs in study clusters (target: n=80, approximately 2/cluster), and women enrolled in the prospective cohort (target: n=60).

To recruit these participants in qualitative work, a combination of purposive and snowball sampling strategies will be used. The numbers of participants represent target numbers; additional participants will be enrolled if saturation is not reached. Key informants, including policy makers, decision makers, and implementers at the national, regional, or local levels (eg, officials from Tanzania's Immunization and Vaccines Development program as well as regional, district, and local health officials) will be asked to participate in qualitative interviews on implementation factors and to recommend other individuals who can provide relevant information. Health providers who are responsible for childhood vaccinations will be enrolled from participating health facilities. CHWs will be enrolled from participating clusters. Women will be purposively selected from the prospective cohort based on data collected during enrollment or follow-up surveys, study logs, or the digital health system during study implementation.

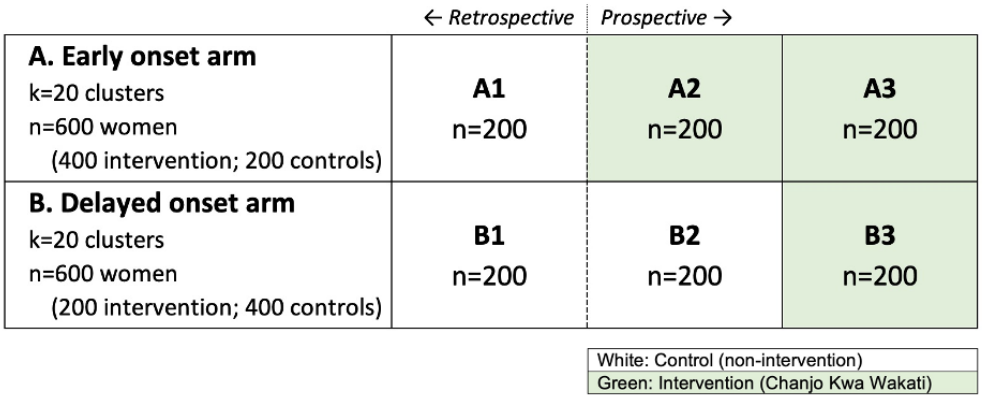
Study Design

Cluster Randomized Trial Design

Forty rural health facilities and their catchment areas (*clusters*), 20 per region, will be randomized to an (A) early or (B) delayed onset study arm (Figure 2). From each cluster, 3 cohorts of 10 mother-child dyads (1 retrospective cohort and 2 prospective cohorts) will be enrolled into the study. For the retrospective cohort, 400 mothers of children aged 12 to 23 months (10/cluster) will be enrolled as a cross-sectional sample for retrospective assessments of children's vaccination records during the first year of life. These cohorts, denoted by A1 and B1, will be part of the care-as-usual control group. For the longitudinal prospective cohort, 800 pregnant women in their last trimester of pregnancy will be enrolled during 2 rounds of enrollment (10 women/enrollment round/cluster) for prospective assessments of their children's vaccination records during the first year of life. These cohorts are denoted by A2, A3, B2, and B3. In the first round of enrollment, 200 (50%) of the 400 prospective participants (those enrolled from early onset clusters; A2) will receive the intervention, and the other 200 (50%) participants (B2) will be part of the care-as-usual control group. In the second round of enrollment, all 400 participants (A3 and B3) will receive the intervention. In total, vaccination uptake and timeliness will be observed for 1200 children (n=600, 50% intervention group children and n=600, 50% nonintervention group children) during their first year of life. The nonintervention group children represent the *care-as-usual* control group in the trial.

The trial design, which analytically resembles a difference-in-difference design, allows for an analysis of the effectiveness of the intervention even in the context of contemporaneous changes in the rate and timeliness of vaccinations at the national level (eg, through national vaccination campaigns or changes in the vaccination schedule).

Figure 2. Design of the 2-arm cluster randomized trial (n=1200).



Evaluation Framework

The evaluation of the Chanjo Kwa Wakati intervention will be guided by the RE-AIM framework. Quantitative survey data will be the primary source of information for the analysis of the effectiveness of the intervention. These data will be complemented by study logs, fidelity checklists, and qualitative interviews with Tanzanian key informants, facility-based health workers, CHWs, and mothers to assess the acceptability, reach, and fidelity of Chanjo Kwa Wakati, as well as factors that may inform sustainability and scalability in the future.

Outcomes Assessments

Vaccination outcomes are described in Table 3. Vaccination coverage and dates will be ascertained for each study child using government-issued vaccination cards, which will be photographed, scanned, or copied and entered by research staff. For the retrospective cohort, the enrollment survey will assess vaccination outcomes for the child; their participation will end after the enrollment survey. Outcome data for the prospective cohort will be collected during an endline survey 12 to 15 months after the birth of the child. All vaccination doses of all vaccination series will be tracked. For women who cannot provide vaccination cards at the time of the survey, consent will be sought to access their children's paper-based or electronic vaccination records at their local health facility.

Table 3. Outcome measures for the cluster randomized controlled trial.

Outcome measure	Type	Source
Timeliness of the third dose of the pentavalent vaccine, Penta3 (number of days delayed)	Primary	Vaccination cards
Timeliness of Penta3 (≤28 days delayed)	Secondary	Vaccination cards
Timeliness of all other vaccine doses recommended by age 1 y (number of days delayed)	Other	Vaccination cards
Coverage of all vaccine doses recommended by age 1 y	Other	Vaccination cards

Study Procedures

Cluster Randomization

In each district, all eligible health facilities will be assigned random IDs. Random IDs will be generated using a random number generator in Stata (version ≥16; StataCorp LLC) with a fixed seed to ensure reproducibility. In each district, the 10 clusters with the smallest random IDs will be allocated to either the early onset arm (odd ranks) or delayed onset arm (even ranks). Facilities that are not willing to participate or are deemed ineligible will be replaced with the next odd- or even-ranked facility, respectively. If the distributions of key characteristics of clusters (eg, the number of pregnant women/y, the number of births/y, the percentage of home births, vaccination coverage, and the number of days vaccinations are offered each wk) differ significantly between study arms, a covariate-constrained randomization [21,22] approach will be used to maximize the balance of these characteristics across study arms.

Blinding

Owing to the nature of the intervention, there will be no blinding of investigators, implementers (CHWs), data collectors, or participants.

Enrollment

Participants may be enrolled at their homes, health facilities, or other mutually agreed-upon locations. The potential risks and benefits of research participation will be carefully explained during the informed consent process (refer to the *Ethical Considerations* subsection). To maximize the reach of the intervention, participants without mobile phones will be able to designate a vaccine advocate of their choice to receive mobile phone–based messages.

Retention

Retention only applies to the prospective cohort. To ensure the retention of study participants, extensive contact information, including the names and mobile phone numbers of both parents, vaccine advocates, and other contacts, as well as expectations for the place of delivery, travel plans after birth, and GPS

coordinates of homes will be documented at enrollment. In the event of child death, maternal death, or participant withdrawal, intervention activities related to the mother-child dyad will be suspended, and the dyad will be withdrawn from the study. In the event of child relocation or family travel during study activities, efforts will be made to collect outcomes data for the child using a combination of mobile phone–based surveys; a review of the child's records at the local health facility; and proxy reports from the father, other legal guardians, or other informants. As the intervention involves local CHWs, for participants relocating outside their cluster for the remainder of the study period, intervention activities will stop after relocation.

Data Collection

Overview

Trained research assistants will conduct enrollment and data collection in Kiswahili. Survey instruments will be developed in English, translated into Kiswahili, and back-translated into English. The development of the surveys will be informed by prior surveys [6,8].

Enrollment Survey

All participants will complete an enrollment survey. The survey will last approximately 45 minutes and assess knowledge and attitudes, sociodemographic characteristics of participants and their households, access barriers, digital literacy, residual knowledge gaps, and other correlates of vaccine uptake and timeliness. The mother's engagement in prenatal care will be assessed via self-report and scanned prenatal care cards. For retrospective participants, the enrollment survey will also assess vaccination uptake and timeliness (Table 3), whereas for prospective participants, extensive contact information will be collected (refer to the *Retention* subsection).

Follow-Up Survey

Prospective participants will complete a follow-up survey 12 to 15 months after their child's birth. The survey will last approximately 30 minutes. The primary purpose of the follow-up survey is to collect data on vaccination outcomes (Table 3). The follow-up survey will include the knowledge intervention that addresses each woman's vaccination-specific knowledge gaps and assess vaccination attitudes and experiences with vaccine uptake and timeliness during the study period. The follow-up survey will also be used to update information on mothers' engagement in prenatal care via self-report and scanned prenatal care cards. For intervention group women, the follow-up survey will also assess implementation measures, experiences with the intervention, and the acceptability and perceived efficacy of Chanjo Kwa Wakati.

Facility Survey

During the enrollment and follow-up work, we will conduct a survey of the health facility in each cluster. The purpose of the facility survey is to assess the implementation context. The survey will collect service information (eg, information on vaccine stockouts and facility closures), procedural knowledge (eg, vaccination dates, scheduling, and rescheduling), and contact information.

Qualitative Data

In-depth interviews (IDIs) will elucidate wide-ranging feedback on all constructs of the RE-AIM framework. IDIs will be conducted by local trained study staff in English or Kiswahili. Study staff will follow a semistructured interview guide. IDIs will be recorded to facilitate transcription and data analysis. Depending on the availability of the participants, IDIs may be conducted by phone or in person. IDIs are expected to last 45 to 60 minutes.

Statistical Power

The aim 1 cluster randomized trial will include 1200 women, enrolled from 40 different clusters, across 3 distinct enrollment phases, with 10 women enrolled from each cluster in each phase. This equates to k=120 statistical clusters with n=10 women per cluster. Half of these clusters (k=60/120, 50%; n=600/1200, 50%) will be allocated to the intervention arm and half to the control arm. Assuming that the primary outcome—the timeliness of the Penta3 vaccine—has an SD of 28 days, the power of the trial to detect an intervention-related difference of 7 days is 0.95 with an intracluster correlation coefficient of 0.05; the power is 0.88 with an intracluster correlation coefficient of 0.10.

The aim 2 qualitative formative work will yield data from IDIs with key informants (n=12), facility-based health workers (up to n=40), CHWs (up to n=80), and mothers (up to n=60). Prior research suggests that thematic saturation can be achieved with 12 interviews, with metathemes presenting as early as 6 interviews [23-25]. Thus, these proposed sample sizes should be sufficient to achieve thematic saturation of implementation barriers and residual barriers to timely and equitable vaccinations, as well as to identify any regional variation in reasons for delayed vaccinations.

Data Analysis

Quantitative Analysis of Intervention Effectiveness

The primary outcome measure of interest will be a continuous measure of vaccination timeliness, expressed as the delay, in days, between the vaccination due date and the date on which the vaccination was received for the third dose of the pentavalent vaccine, Penta3, due at age 14 weeks (Table 1). The secondary and other outcome measures include the timeliness and coverage of all vaccine doses recommended by age 1 year. Owing to the randomization, a comparison of mean outcomes between participants in the intervention group and those in the nonintervention group yields an unbiased estimate of the effect of the intervention.

To control for variation in sociodemographic characteristics across participants, seasonal effects, and other potential correlates of vaccination timeliness, outcomes will also be analyzed in a multivariable regression framework using accelerated failure time models with the completed vaccination dose as the failure event, age in days describing time to failure, and membership in the intervention versus control groups as the primary covariate of interest.

Robust SEs will be estimated to account for the clustering of observations across mother-child dyads enrolled from the same geographic clusters at the same time.

Analysis of Implementation Outcomes

We will generate summary measures (eg, means) for continuous data and use proportions to summarize categorical data. For outcomes assessed using validated measures (eg, the Acceptability of Intervention Measure [26]), we will present composite scale scores. Qualitative implementation outcomes will be analyzed as described below.

Analysis of Qualitative Data and Integration With Quantitative Data

Thematic analyses will be facilitated by qualitative software (eg, NVivo [Lumivero]) and a codebook made up of a priori and emergent structural codes based on the interview guide and 4 interrelated steps: reading, coding, data display, and data reduction [27]. The data will be used to fully map the Chanjo Kwa Wakati process from the perspectives of the mother and the CHW and characterize the opportunities and limitations of using digital and in-person resources to support vaccination timeliness. Using convergent mixed methods, we will use joint displays and narrative integration to connect the quantitative and qualitative data [28-30].

Analysis of Systematic Variation in Effectiveness

Extensive sensitivity analysis for the aim 1 primary and secondary outcomes analyses will characterize variation in intervention effectiveness with population, setting, and implementation factors. Variation in intervention effectiveness will be evaluated using interactions between geographic, maternal, or child characteristics and the intervention variable. Statistically significant parameters on interaction terms are indicative of differential intervention effects for different subgroups. To account for variation in implementation, sensitivity analysis will include per-protocol (as-treated) and intention-to-treat analyses in which a vector of variables describing the fidelity of the different intervention components will be used in place of the binary intervention variable.

Missing Data

The *Study Limitations and Adaptations* subsection in the *Discussion* section discusses considerations regarding missing data on outcomes and covariates and their handling in the analyses.

Ethical Considerations

The study protocol, informed consent forms, and procedures have been reviewed and approved by the Health Sciences South Carolina Institutional Review Board (the reviewing institutional review board [IRB]; Pro00120675) and the ethics review committee of the National Institute for Medical Research in Tanzania (NIMR/HQ/R.8a/Vol.IX/4242), as well as the relying IRBs at Duke University (Pro00111772), Emory University (STUDY00005518), and the University of North Carolina at Chapel Hill. Informed consent will be sought from all study participants.

To maintain confidentiality, interviewers will conduct the consent process in a private space or in a mutually agreed-upon location where other people are not present. The interviewers will read out the consent form to potential participants and answer any questions. The potential risks and benefits of participation as well as the details of data confidentiality and use will be carefully explained in culturally appropriate and understandable language. Participants can refuse to participate and will only be consented after the research staff is satisfied that they understand all substantive provisions of the informed consent document. Persons with obvious psychological or psychiatric disorders that preclude informed consent will be excluded. Participants will be asked to provide written consent. They will be provided with a copy of the consent form. Informed consent documents will be developed in English, translated into Kiswahili, and back-translated into English.

Participants in the trial will be aged ≥15 years and either pregnant in their last trimester of pregnancy or mothers or legal guardians of children aged 12 to 23 months. For adolescents aged 15 to 17 years who are pregnant or mothers of children aged 12 to 23 months and are otherwise eligible to participate in the study, we obtained a waiver of parental consent. Tanzanian national policy indicates that adolescents aged <18 years who are sexually active and pregnant have the right to access reproductive health services (eg, HIV testing, care, and treatment [31], as well as family planning [32]) without parental or spousal consent, and they can make associated medical decisions on their own behalf. Given that these adolescents have this *adult* right to medical decision-making, we posit that they are also able to consent to research participation for themselves without parental or spousal consent. Risks from participation in this study are considered commensurate with ordinary daily life.

Protocol amendments will be submitted to the relevant IRBs for approval before implementation. Adverse events will be reported to the ethics review committee of the National Institute for Medical Research in Tanzania and the US-based IRBs.

Participants will be compensated for the time they spend participating in study activities. Ethically and culturally appropriate compensation will be established in collaboration with community advisers and other key informants. Subject to IRB approval and discussions with key informants, incentive amounts may be adjusted during the study period to account for exchange rate fluctuations and cost-of-living increases.

Results

Results are pending. The study was funded in August 2022. Data collection is expected to last from February 2024 to July 2027.

Discussion

Relevance

The Chanjo Kwa Wakati intervention and proposed evaluation are aligned with the strategic priorities of the Immunization Agenda 2030 and Tanzanian priorities for digital health and community health workforce development [33,34]. Specifically, our study builds on a Tanzanian digital health investment road map [35] to digitize health care data and is in line with Tanzania's 2020 National Operational Guideline for Community-Based Health Care Services, which seeks to build a strong community health workforce for health promotion,

including for child health [36]. The relevance of our study extends beyond rural Tanzania. The low-cost strategies developed and evaluated in this study are applicable to other rural contexts where some populations are less likely to be vaccinated, experience poor vaccine access, or express low confidence in vaccinations, and our study may inform the development and implementation of multipronged programs to promote timely vaccinations in such settings.

Contributions to the Literature

Our study is expected to make several important contributions to the scientific literature on digital health and vaccination interventions. First, numerous studies have documented low timeliness of vaccinations for children from LMICs, with a disproportionate burden for rural children [4,6,37-41]. Our study is significant because it seeks to evaluate an intervention for promoting vaccination timeliness for rural children. Second, lay health care workers such as CHWs play a critical role in delivering health services in LMICs. Our study will use a hybrid digital and in-person approach and contribute evidence on effective and scalable strategies for supporting lay health workers with digital health tools to promote childhood vaccination equity. Third, although many studies have evaluated mobile phone–based reminders for promoting childhood vaccinations [10], evidence is lacking for community-based systems that target multifaceted barriers to vaccinations. Our study will contribute data on the effectiveness of a community-based digital health intervention to promote equitable and timely vaccination in LMICs. Fourth, research studies support the use of screening tools to identify vaccination knowledge gaps and deliver targeted interventions to combat vaccine hesitancy. Our study will integrate CHW outreach and mobile phone–based vaccination education to bridge gaps in vaccination knowledge, respond to parental concerns, and reduce hesitancy. Finally, our study will contribute evidence on strategies to bridge the *digital divide* in rural areas and the *gender gap* in mobile phone access by using a combined digital and in-person approach.

Study Limitations and Adaptations

Unknown Number of Eligible Women per Cluster

Although we estimate that 20 clusters per region are required to reach our enrollment targets for the cross-sectional and longitudinal samples, neither the number of eligible women per cluster nor the number of refusals are known a priori. If the sample size across clusters is too small, sampling may be extended to additional clusters until sample size targets have been reached in each region and study arm.

Randomization

If the distributions of key characteristics of clusters vary greatly between the initially specified study arms (based on randomized IDs), a covariate-constrained randomization approach may be used that maximizes the balance across study arms in the distribution of key characteristics of clusters.

Spillover and Contamination

Cluster randomization is expected to minimize spillover effects; however, contamination may exist for participants living at the boundaries between intervention and nonintervention clusters. Sensitivity analyses will evaluate potential spillover effects by including geographic proximity to an intervention cluster as a covariate for the nonintervention group women in our models.

External Events

A potential threat to validity stems from the possibility of a local vaccination campaign or selective stockouts among subsets of clusters during follow-up. Given our collaboration with regional and national stakeholders, enrollment from multiple clusters, multiple vaccination time points for each participant, and the robust design, the likelihood and potential impact of such external events on our findings is low. The effects of stockouts on timeliness will be assessed in the *per-protocol* sensitivity analysis.

Missing Data

If vaccination cards are missing for >10% of the cross-sectional sample, and their vaccination information cannot readily be ascertained from records at the local health facility, enrollment into the cross-sectional cohort will continue until key outcome measures can be ascertained for the target number of 400 mothers. This may include the expansion of enrollment to additional clusters. Enrollment into the longitudinal cohort will be increased proportionately. Missing data on other characteristics will be addressed using full information maximum likelihood estimation or sensitivity analyses [42-45].

Mobile Phone Access and Use

In the target population, mobile phone access and use is not universal, and mobile phones may be shared within households. Chanjo Kwa Wakati is specifically designed to compensate for gaps in mobile phone ownership and coverage, including through the designation of vaccine advocates who will receive reminders and in-person outreach by CHWs to those who are not reached by mobile phone.

Sustainability of Reminders and Incentives

Reminder messages and incentive offers, which were informed by our prior work, will be carefully reviewed by investigators and key informants to ensure their ethical implementation and sustainability for a scaled-up intervention.

Generalizability

To assess the generalizability of the study's context and findings, study data and the relationships among key variables of interest will be compared with information in publicly available survey data and administrative data sources.

Interpretation and Dissemination

If successful, this study will contribute data on the effectiveness and implementation of the Chanjo Kwa Wakati intervention that engages recent mothers to increase the timeliness and coverage of routine childhood vaccinations in rural Tanzania. Key findings will be presented in peer-reviewed manuscripts, presentations at national and international conferences, and media outlets. Policy and programmatic recommendations will be developed in collaboration with key informants and decision makers at the national, regional, and district levels.

Acknowledgments

The authors would like to thank the Duke Global Health Institute Research Design & Analysis Core staff for their input on cluster randomization and sample size calculations. The research reported in this publication was supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development of the National Institutes of Health (R01HD110844). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Data Availability

The data from this study will be available from the National Institute for Medical Research, Muhimbili Research Centre, Dar es Salaam, Tanzania, but restrictions apply that are governed by consent forms and data transfer agreements. Data may be made available by the authors upon reasonable request and with the permission of the National Medical Research Review Committee of the National Institute for Medical Research, Tanzania. The open-source digital health system will be made available to interested researchers and practitioners.

Authors' Contributions

LV, JO, and EN designed the study with critical input from JNB, NT, DS, MvZ, and AH. LV and JO wrote the first draft, and EN, JNB, NT, DS, MvZ, and AH contributed to revisions. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT (Consolidated Standards of Reporting Trials) 2010 checklist of information to include when reporting a cluster randomized trial.
[DOCX File , 36 KB - resprot_v13i1e52523_app1.docx]

Multimedia Appendix 2
Peer-review report: Clinical Informatics and Digital Health Study Section, Healthcare Delivery and Methodologies Integrated Review Group, Center for Scientific Review, National Institutes of Health.
[PDF File (Adobe PDF File), 155 KB - resprot_v13i1e52523_app2.pdf]

References

1. Peck M, Gacic-Dobo M, Diallo MS, Nedelec Y, Sodha SV, Wallace AS. Global routine vaccination coverage, 2018. MMWR Morb Mortal Wkly Rep 2019 Oct 25;68(42):937-942 [FREE Full text] [doi: 10.15585/mmwr.mm6842a1] [Medline: 31647786]
2. Immunization. United Nations International Children's Emergency Fund. URL: https://www.unicef.org/immunization [accessed 2023-11-29]
3. Message by the director of the department of immunization, vaccines and biologicals at WHO - December 2022. World Health Organization. 2022 Dec 6. URL: https://www.who.int/news/item/06-12-2022-message-by-the-director-of-the-department-of-immunization--vaccines-and-biologicals-at-who---december-2022 [accessed 2023-11-29]
4. Yelverton V, Hair NL, Ghosh SH, Mfinanga SG, Ngadaya E, Baumgartner JN, et al. Beyond coverage: rural-urban disparities in the timeliness of childhood vaccinations in Tanzania. Vaccine 2022 Sep 02;40(37):5483-5493 [FREE Full text] [doi: 10.1016/j.vaccine.2022.07.020] [Medline: 35961796]
5. Cobos Muñoz D, Monzón Llamas L, Bosch-Capblanch X. Exposing concerns about vaccination in low- and middle-income countries: a systematic review. Int J Public Health 2015 Nov 23;60(7):767-780. [doi: 10.1007/s00038-015-0715-6] [Medline: 26298444]
6. Vasudevan L, Baumgartner JN, Moses S, Ngadaya E, Mfinanga SG, Ostermann J. Parental concerns and uptake of childhood vaccines in rural Tanzania - a mixed methods study. BMC Public Health 2020 Oct 20;20(1):1573 [FREE Full text] [doi: 10.1186/s12889-020-09598-1] [Medline: 33081744]
7. Ostermann J, Hair NL, Moses S, Ngadaya E, Godfrey Mfinanga S, Brown DS, et al. Is the intention to vaccinate enough? Systematic variation in the value of timely vaccinations and preferences for monetary vs non-monetary incentives among pregnant women in southern Tanzania. Vaccine X 2023 Apr;13:100266 [FREE Full text] [doi: 10.1016/j.jvacx.2023.100266] [Medline: 36814594]

8. Ostermann J, Vasudevan L, Baumgartner JN, Ngadaya E, Mfinanga SG. Do mobile phone-based reminders and conditional financial transfers improve the timeliness of childhood vaccinations in Tanzania? Study protocol for a quasi-randomized controlled trial. Trials 2019 Jul 04;20(1):397 [FREE Full text] [doi: 10.1186/s13063-019-3430-4] [Medline: 31272487]
9. Oyo-Ita A, Wiysonge CS, Oringanje C, Nwachukwu CE, Oduwole O, Meremikwu MM. Interventions for improving coverage of childhood immunisation in low- and middle-income countries. Cochrane Database Syst Rev 2016 Jul 10;7(7):CD008145 [FREE Full text] [doi: 10.1002/14651858.CD008145.pub3] [Medline: 27394698]
10. Yunusa U, Garba SN, Umar AB, Idris SH, Bello UL, Abdulrashid I, et al. Mobile phone reminders for enhancing uptake, completeness and timeliness of routine childhood immunization in low and middle income countries: a systematic review and meta-analysis. Vaccine 2021 Jan 08;39(2):209-221 [FREE Full text] [doi: 10.1016/j.vaccine.2020.11.043] [Medline: 33277058]
11. Atkinson KM, Wilson K, Murphy MS, El-Halabi S, Kahale LA, Laflamme LL, et al. Effectiveness of digital technologies at improving vaccine uptake and series completion - a systematic review and meta-analysis of randomized controlled trials. Vaccine 2019 May 21;37(23):3050-3060 [FREE Full text] [doi: 10.1016/j.vaccine.2019.03.063] [Medline: 31036457]
12. Chen L, Du X, Zhang L, van Velthoven MH, Wu Q, Yang R, et al. Effectiveness of a smartphone app on improving immunization of children in rural Sichuan Province, China: a cluster randomized controlled trial. BMC Public Health 2016 Aug 31;16(1):909 [FREE Full text] [doi: 10.1186/s12889-016-3549-0] [Medline: 27581655]
13. Modi D, Dholakia N, Gopalan R, Venkatraman S, Dave K, Shah S, et al. mHealth intervention "ImTeCHO" to improve delivery of maternal, neonatal, and child care services-A cluster-randomized trial in tribal areas of Gujarat, India. PLoS Med 2019 Oct;16(10):e1002939 [FREE Full text] [doi: 10.1371/journal.pmed.1002939] [Medline: 31647821]
14. Prinja S, Nimesh R, Gupta A, Bahuguna P, Gupta M, Thakur JS. Impact of m-health application used by community health volunteers on improving utilisation of maternal, new-born and child health care services in a rural area of Uttar Pradesh, India. Trop Med Int Health 2017 Jul;22(7):895-907 [FREE Full text] [doi: 10.1111/tmi.12895] [Medline: 28510997]
15. Uddin MJ, Shamsuzzaman M, Horng L, Labrique A, Vasudevan L, Zeller K, et al. Use of mobile phones for improving vaccination coverage among children living in rural hard-to-reach areas and urban streets of Bangladesh. Vaccine 2016 Jan 04;34(2):276-283 [FREE Full text] [doi: 10.1016/j.vaccine.2015.11.024] [Medline: 26647290]
16. Curran GM, Bauer M, Mittman B, Pyne JM, Stetler C. Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact. Med Care 2012 Mar;50(3):217-226 [FREE Full text] [doi: 10.1097/MLR.0b013e3182408812] [Medline: 22310560]
17. Curran GM, Landes SJ, McBain SA, Pyne JM, Smith JD, Fernandez ME, et al. Reflections on 10 years of effectiveness-implementation hybrid studies. Front Health Serv 2022 Dec 8;2:1053496 [FREE Full text] [doi: 10.3389/frhs.2022.1053496] [Medline: 36925811]
18. Administrative units population distribution report. The United Republic of Tanzania, Ministry of Finance and Planning, Tanzania National Bureau of Statistics and President's Office - Finance and Planning, Office of the Chief Government Statistician, Zanzibar. 2022 Dec. URL: https://www.nbs.go.tz/nbs/takwimu/Census2022/Administrative_units_Population_Distribution_Report_Tanzania_volume1a.pdf [accessed 2023-11-29]
19. Tanzania demographic and health survey and malaria indicator survey (TDHS-MIS) 2022. Ministry of Health, Dodoma, Ministry of Health, Zanzibar, National Bureau of Statistics, Dodoma, Office of the Chief Government Statistician, Zanzibar, The DHS Program, ICF, Rockville, Maryland, USA. 2022 Sep. URL: https://dhsprogram.com/pubs/pdf/FR382/FR382.pdf [accessed 2023-11-29]
20. Mvundura M, Di Giorgio L, Vodicka E, Kindoli R, Zulu C. Assessing the incremental costs and savings of introducing electronic immunization registries and stock management systems: evidence from the better immunization data initiative in Tanzania and Zambia. Pan Afr Med J 2020 Feb 12;35(Suppl 1):11 [FREE Full text] [doi: 10.11604/pamj.supp.2020.35.1.17804] [Medline: 32373262]
21. Yu H, Li F, Gallis J, Turner E. cvcrand: a package for covariate-constrained randomization and the clustered permutation test for cluster randomized trials. R J 2019;11(2):191-204. [doi: 10.32614/rj-2019-027]
22. Gallis JA, Li F, Yu H, Turner EL. cvcrand and cptest: commands for efficient design and analysis of cluster randomized trials using constrained randomization and permutation tests. Stata J 2018 Jun 01;18(2):357-378 [FREE Full text] [doi: 10.1177/1536867x1801800204] [Medline: 34413708]
23. Namey E, Guest G, McKenna K, Chen M. Evaluating bang for the buck: a cost-effectiveness comparison between individual interviews and focus groups based on thematic saturation levels. Am J Eval 2016 Jul 09;37(3):425-440. [doi: 10.1177/1098214016630406]
24. Guest G, Bunce A, Johnson L. How Many Interviews Are Enough?: An Experiment with Data Saturation and Variability. Field Methods 2006;18(1):59-82. [doi: 10.1177/1525822x05279903]
25. Mack N, Woodsong C, MacQueen KM, Guest G, Namey E. Qualitative Research Methods: A Data Collector's Field Guide. Durham, NC: Family Health International; Jan 2005.
26. Weiner BJ, Lewis CC, Stanick C, Powell BJ, Dorsey CN, Clary AS, et al. Psychometric assessment of three newly developed implementation outcome measures. Implement Sci 2017 Aug 29;12(1):108 [FREE Full text] [doi: 10.1186/s13012-017-0635-3] [Medline: 28851459]

27. Ulin PR, Robinson ET, Tolley EE. Qualitative Methods in Public Health: A Field Guide for Applied Research. Hoboken, NJ: John Wiley & Sons; 2004.
28. Creswell JW, Plano Clark VL. Designing and Conducting Mixed Methods Research Third Edition. Thousand Oaks, CA: SAGE Publications, Inc; Sep 2017.
29. Fetters MD, Curry LA, Creswell JW. Achieving integration in mixed methods designs-principles and practices. Health Serv Res 2013 Dec;48(6 Pt 2):2134-2156 [FREE Full text] [doi: 10.1111/1475-6773.12117] [Medline: 24279835]
30. Guetterman TC, Fetters MD, Creswell JW. Integrating quantitative and qualitative results in health science mixed methods research through joint displays. Ann Fam Med 2015 Nov 09;13(6):554-561 [FREE Full text] [doi: 10.1370/afm.1865] [Medline: 26553895]
31. National comprehensive guidelines on HIV testing services. The United Republic of Tanzania Ministry of Health National Aids Control Programme. 2019 Dec. URL: https://nacp.go.tz/download/national-comprehensive-guidelines-on-hiv-testing-services/ [accessed 2023-11-29]
32. National family planning guidelines and standards. The United Republic of Tanzania Ministry of Health and Social Welfare. 2013. URL: https://www.prb.org/wp-content/uploads/2018/05/National-Family-Planning-Guidelines-and-Standards-2013.Tanzania.pdf [accessed 2023-11-29]
33. World HO. WHO and UNICEF warn of a decline in vaccinations during COVID-19. World Health Organization. 2020 Jul 15. URL: https://www.who.int/news/item/15-07-2020-who-and-unicef-warn-of-a-decline-in-vaccinations-during-covid-19 [accessed 2023-11-29]
34. Immunization services begin slow recovery from COVID-19 disruptions, though millions of children remain at risk from deadly diseases – WHO, UNICEF, Gavi. United Nations International Children's Emergency Fund. 2021 Apr 26. URL: https://www.unicef.org/press-releases/immunization-services-begin-slow-recovery-covid-19-disruptions-though-millions [accessed 2023-11-29]
35. Tanzania digital health investment road map 2017-2023. Government of Tanzania and PATH. URL: https://media.path.org/documents/Tanzania_Digital_Health_Investment_Road_Map.2017_to_2023.pdf [accessed 2023-11-29]
36. National operational guideline for community-based health services, 2021. The United Republic of Tanzania Ministry of Health. 2021. URL: https://hssrc.tamisemi.go.tz/storage/app/uploads/public/636/259/2d6/6362592d642dd250982263.pdf [accessed 2023-11-29]
37. Le Polain de Waroux O, Schellenberg JR, Manzi F, Mrisho M, Shirima K, Mshinda H, et al. Timeliness and completeness of vaccination and risk factors for low and late vaccine uptake in young children living in rural southern Tanzania. Int Health 2013 Jun 10;5(2):139-147. [doi: 10.1093/inthealth/iht006] [Medline: 24030114]
38. Clark A, Sanderson C. Timing of children's vaccinations in 45 low-income and middle-income countries: an analysis of survey data. Lancet 2009 May 02;373(9674):1543-1549. [doi: 10.1016/S0140-6736(09)60317-2] [Medline: 19303633]
39. Akmatov MK, Kretzschmar M, Krämer A, Mikolajczyk RT. Timeliness of vaccination and its effects on fraction of vaccinated population. Vaccine 2008 Jul 23;26(31):3805-3811. [doi: 10.1016/j.vaccine.2008.05.031] [Medline: 18565626]
40. Akmatov MK, Mikolajczyk RT. Timeliness of childhood vaccinations in 31 low and middle-income countries. J Epidemiol Community Health 2012 Jul;66(7):e14. [doi: 10.1136/jech.2010.124651] [Medline: 21551179]
41. Vasudevan L, Labrique AB, Mehra S, Wu L, Levine O, Feikin D, et al. Maternal determinants of timely vaccination coverage among infants in rural Bangladesh. Vaccine 2014 Sep 22;32(42):5514-5519. [doi: 10.1016/j.vaccine.2014.06.092] [Medline: 25132336]
42. Little RJ. A test of missing completely at random for multivariate data with missing values. J Am Stat Assoc 1988 Dec;83(404):1198-1202. [doi: 10.1080/01621459.1988.10478722]
43. Little RJ, Rubin DB. The analysis of social science data with missing values. Sociol Methods Res 2016 Jun 30;18(2-3):292-326. [doi: 10.1177/0049124189018002004]
44. Little RJ, Wang Y. Pattern-mixture models for multivariate incomplete data with covariates. Biometrics 1996 Mar;52(1):98-111. [doi: 10.2307/2533148]
45. Wang R, Sedransk J, Jinn JH. Secondary data analysis when there are missing observations. J Am Stat Assoc 1992 Dec;87(420):952-961. [doi: 10.1080/01621459.1992.10476249]

Abbreviations

CHW: community health worker
CONSORT: Consolidated Standards of Reporting Trials
DPT: diphtheria-pertussis-tetanus
IDI: in-depth interview
IRB: institutional review board
LMICs: low- and middle-income countries
OPV: oral polio vaccine
RE-AIM: reach, effectiveness, adoption, implementation, and maintenance

Edited by A Mavragani; submitted 12.09.23; this is a non–peer-reviewed article;accepted 26.10.23; published 12.01.24.

Please cite as:
Vasudevan L, Ostermann J, Thielman N, Baumgartner JN, Solomon D, Mosses A, Hobbie A, Hair NL, Liang C, van Zwetselaar M, Mfinanga S, Ngadaya E
Leveraging Community Health Workers and a Responsive Digital Health System to Improve Vaccination Coverage and Timeliness in Resource-Limited Settings: Protocol for a Cluster Randomized Type 1 Effectiveness-Implementation Hybrid Study
JMIR Res Protoc 2024;13:e52523
URL: https://www.researchprotocols.org/2024/1/e52523
doi:10.2196/52523
PMID:38214956

Protocol

Testing an Evidence-Based Self-Help Program for Infertility-Related Distress: Protocol for a Randomized Controlled Trial

Jennifer L Gordon[1], PhD; Megan M L Poulter[1], BA; Ashley A Balsom[1], MA; Tavis S Campbell[2], PhD

[1]Department of Psychology, University of Regina, Regina, SK, Canada

[2]Department of Psychology, University of Calgary, Calgary, SK, Canada

Corresponding Author:
Jennifer L Gordon, PhD
Department of Psychology
University of Regina
3737 Wascana Parkway
Regina, SK, S4S 0A2
Canada
Phone: 1 306 585 4389
Email: jennifer.gordon@uregina.ca

Abstract

Background: Infertility—the inability to achieve pregnancy despite ≥12 months of focused attempts to conceive—is experienced by 1 in 6 couples. Women typically carry a disproportionate share of the psychological burden associated with infertility, experiencing poor quality of life, and 30%-40% experiencing depressive mood or anxiety. Unfortunately, currently available psychological interventions targeting infertility-related distress are associated with modest effects.

Objective: Our team, in collaboration with patient advisors, has designed a self-help intervention for infertility-related distress involving 7 weekly 10-minute videos addressing the cognitive, behavioral, and interpersonal challenges associated with infertility, delivered through a mobile app. A feasibility study suggests that it is well accepted and highly effective in reducing symptoms of anxiety and depressed mood among distressed individuals dealing with infertility. This study represents the next step in this line of research: a fully powered randomized controlled trial comparing the intervention to a waitlist control group.

Methods: We will recruit 170 individuals struggling to become pregnant in Canada or the United States to be randomized to our 7-week self-help program or a treatment-as-usual condition. The primary outcome will be fertility quality of life, while secondary outcomes will include depressive symptoms, anxious symptoms, and relationship quality, assessed before and after the program as well as biweekly for 16 weeks following completion of the program. Self-reported health care use and the presence of diagnosed mood and anxiety disorders, assessed through a structured psychiatric interview, will also be assessed immediately following the intervention and at the 16-week follow-up assessment. Treatment adherence and retention will also be recorded throughout the intervention. Multilevel modeling will compare the intervention arm to the treatment-as-usual condition in terms of all continuous outcomes across the 9 measurement points. Logistic regression will be used to assess the occurrence of mood and anxiety disorders in the 2 treatment arms at the posttreatment assessment as well as at the 16-week follow-up. Sensitivity analyses will examine potential treatment moderators: membership in the LGBTQIA+ (lesbian, gay, bisexual, transgender, queer, intersex, and asexual) communities, baseline fertility quality of life, cultural background, disability status, and pursuit of conception through medical intervention.

Results: We expect our intervention to be more effective than treatment-as-usual in improving all mental health parameters assessed and decreasing health care use related to both mental and reproductive health. Effects are expected to be larger with decreasing baseline quality of life and equally effective regardless of membership in the LGBTQIA+ communities, cultural background, or disability status.

Conclusions: If our intervention is successful, this would suggest that it should be scaled up and made publicly available. The availability of this program would fill an important gap in light of the high rates of psychopathology among those experiencing infertility and considering the current lack of effective psychotherapy approaches for infertility.

Trial Registration: Clinicaltrials.gov NCT06006936; https://classic.clinicaltrials.gov/ct2/show/NCT06006936

International Registered Report Identifier (IRRID): PRR1-10.2196/52662

(JMIR Res Protoc 2024;13:e52662) doi:10.2196/52662

KEYWORDS

anxiety; cognitive-behavior therapy; depression; infertility; infertility-related distress; mHealth

Introduction

Overview

The Canadian Community Health Survey reveals that 16% of Canadian reproductive-aged couples are currently infertile [1], defined as being unable to achieve pregnancy despite ≥12 months of focused attempts to conceive. Although male- and female-factor infertility are equally prevalent, women bear the brunt of the infertility-related burden as treatments require that women monitor their menstrual cycles, attend near-daily ultrasounds, self-inject gonadotropins, and undergo invasive and painful procedures. Women who travel for fertility treatments face additional psychosocial burdens, including schedule disruptions, time off work, and coordination of care among multiple health care providers. It is therefore not surprising that women carry a disproportionate share of the psychological burden associated with infertility, with infertile women consistently reporting lower self-esteem, more instances of depressed mood and anxiety, and lower life satisfaction than their male partners [2]. Lesbian couples pursuing sperm donation experience similar distress, with the intended pregnant individual being at higher risk for depression and anxiety relative to their partner [3].

Around 30%-40% of women presenting for the evaluation of infertility report clinical symptoms of depressed mood and/or anxiety [4-7]. In addition, research from our team [8] suggests that the COVID-19 pandemic has exacerbated distress amid fertility treatment suspensions and delays. Untreated symptoms of depressed mood and anxiety among women with infertility may, in turn, reduce the likelihood of achieving pregnancy, given that psychological burden is the most commonly cited reason for prematurely discontinuing fertility treatments [9]. In a study of 450 couples who were offered 3 government-funded in vitro fertilization (IVF) cycles, 54% did not complete all 3 cycles despite not achieving pregnancy, with "psychological burden" being the primary reason for discontinuing IVF [10]. It is critical that women with infertility who are distressed receive effective mental health treatment to reduce distress and improve conception rates.

Despite high rates of distress among women with infertility, currently available psychological interventions are often ineffective or associated with relatively small benefits. In our recent systematic review of psychological interventions for infertility-related distress [11], we observed that typical interventions are associated with a small beneficial effect on anxiety but a nonsignificant effect on depressive mood, marital quality, or quality of life. Our conclusions confirm findings from a previous meta-analysis [12] and those of a recent review [13] concluding that "a new intervention (targeting infertility-related distress) should be developed."

Intervention Development

This trial seeks to test the efficacy of a novel infertility-specific intervention. In developing a treatment that is designed to improve upon the limitations of current approaches, we have used a methodical and evidence-based framework in designing and refining our intervention, using the Medical Research Council [14] and National Institute of Health's ORBIT Model [15] for trial design interventions as guides. Specifically, we have completed the following milestones to date: (1) completed a systematic review of available interventions, (2) conducted a needs-based assessment using qualitative research methods, (3) carried out an evaluation of potential intervention components, and (4) performed a preliminary test of the acceptability and effect of our newly developed intervention. These steps are described in greater detail below.

Systematic Review and Meta-Analysis

As a starting point, we conducted a systematic review and meta-analysis of psychological interventions for infertility [11,16], which included an examination of treatment moderators such as psychotherapeutic approach (eg, mindfulness-based approaches vs cognitive behavioral therapy) and therapy format (eg, self-administered vs group). This process not only confirmed that currently available interventions were largely ineffective but also revealed that neither therapeutic approach nor format significantly impact treatment benefits.

Qualitative Needs Assessment

Our team then used semistructured interviews with women with infertility and mental health professionals specializing in infertility to identify the unique aspects of infertility-related distress [17]. Table 1 depicts the themes and subthemes identified. Unique features include the avoidance of infertility reminders (eg, pregnant women and children), excessive cognitive and behavioral focus on one's infertility to the exclusion of previously enjoyed activities, and negative interactions with loved ones perceived as insensitive.

Table 1. Themes and subthemes of infertility-related distress identified through a qualitative research project by our team [17].

Theme 1: anxiety	Theme 2: mood disturbance	Theme 3: threat to self	Theme 4: threat to couple	Theme 5: weakened social support
Anxious rumination	Emotional lability	Unmet expectations for self and one's future	Differences in coping	Strained romantic relationship
Avoidance of infertility reminders	Helplessness	Shame	Sexual dysfunction	Social stigma
Narrowed focus on infertility-related activities	Emotional exhaustion	Self-blame	Financial stress	Social isolation
Excessive information seeking	N/A[a]	N/A	Disagreement on next steps	Dismissal by health care providers

[a]N/A: not applicable.

In addition to identifying clear psychological targets for our intervention, this study also aimed to clarify which interventions were currently being used by practicing clinicians. Our findings indicated a near-universal use of an eclectic and unstructured approach associated with the widely held opinion that no existing therapeutic approach sufficiently addresses all of the biopsychosocial factors contributing to infertility-related distress.

Evaluation of Potential Intervention Components

The next step in our intervention development was to identify and consider all candidate techniques that might effectively target the psychological challenges identified as being common in infertility. To do so, we identified all of the psychotherapeutic approaches endorsed by the American Psychological Association's Clinical Section as being evidence-based for the treatment of anxiety, mood disorders, relationship difficulties, and chronic illness. The 5 identified approaches were then further broken down into their component procedures, resulting in a total of 14 different psychological techniques. In collaboration with a panel of patient advisors and using lay language, we described how each of these techniques would look when applied to infertility-related distress and what their purpose would be. We then surveyed a total of 644 women from online infertility-specific support groups [18], asking them to rate the perceived usefulness of each of the 14 techniques while asking them to identify up to 5 that were "most liked" and "most hated." Participants were also given the opportunity to provide written feedback on each of the techniques, such as how they might be better tailored to infertility. We then presented the results of this survey to our panel of patient advisors and collaboratively decided on the content of our intervention. We decided on 6 core modules plus a bonus module, the content of which is described in Textbox 1 [18].

Textbox 1. Chosen modules based on a survey of 644 women with infertility [18] and collaboration with patient advisors. Mean helpfulness ratings for each module, as assessed in a feasibility study of 21 women, are shown.

Modules and focus

- Cognitive restructuring: identifying and challenging the extreme negative thoughts that contribute to a depressive and anxious mood (eg, "In vitro fertilisation will never work").
- Challenging core beliefs: identifying and challenging unhelpful deep-seated beliefs about themselves, other people, and the world that are perhaps not based on reality (eg, "nothing ever works out for me"). It involves looking for patterns in one's thinking from the first module.
- Behavioral activation: identifying activities that have been dropped or engaged in less because of an increased focus on infertility. Aim to reintegrate these previously enjoyed activities into their day-to-day lives.
- Sharing your grief: learning about different styles of coping and how clashes in coping styles can lead to conflict within a couple. The individual is instructed on how to engage their partner in a structured conversation about how each can help the other in times of grief, such as following a negative pregnancy test.
- Strengthening your relationship (bonus module): provides evidence-based information about how to better connect with one's partner in general. Was offered along with Module 4 for those experiencing relationship distress.
- Living your values (ie, stopping avoidance): reflecting on one's overarching life values and considering how one's daily actions align with those values. Indirectly addresses avoidance that is common among individuals with infertility (eg, withdrawing from friends and family and avoiding children and pregnant women). Encourages the individual to consider ways in which they can reduce avoidance without worsening their distress.
- Summary or wrap up: providing an overview of the program's content and encouraging the individual to reflect on what's been accomplished as well as areas for further development.

When it came time to decide on the format of our intervention, a self-help internet-delivered intervention was chosen for several reasons. First, the findings from our systematic review indicate that self-administered interventions are as effective in improving mental health as other, more costly formats. Second, when asked what format a new intervention should take, 71% (15/21) of women from our needs assessment qualitative study responded that it should be self-delivered through the internet. Third, we reasoned that this format could be most effectively scaled up and made accessible to diverse populations of women and in

regions with limited access to psychological services. Thus, in close collaboration with our patient advisors, each module was translated into a 10-minute PowerPoint (Microsoft Corp) slideshow with professional voiceover. A mobile app was then developed to increase accessibility to the modules.

Preliminary Testing of Our New Infertility-Specific Intervention

With a new program developed and fully vetted in consultation with our patient advisory panel, we conducted a pilot study of 21 women recruited through local support groups, assessing intervention acceptability [19]. All participants exhibited clinically significant levels of infertility-related distress, as indicated by a Fertility Quality of Life Scale (FertiQoL) score ≤52 [20]. Enrolled through a Zoom (Zoom Video Communications)-administered enrollment session, participants received 1 module per week through email and were asked to view the 10-minute slideshow within 24 hours of receipt. Midweek, they received an email reminder of the homework assignment, encouraging them to apply their homework assignment throughout the week. At the end of each week, participants were asked to rate the extent to which the module and homework were perceived as helpful in lowering their distress (0-10). At baseline and each week, participants completed the Generalized Anxiety Disorder-7 (GAD-7) and 9-item Patient Health Questionnaire (PHQ-9); the FertiQoL was completed at baseline and after the intervention. Each week and in an interview at the end of the study, participants provided written and verbal feedback, respectively, on the intervention.

Of the 21 women enrolled in the study, 2 became pregnant and were removed from the program prematurely (all outcomes assessed until the point of pregnancy were analyzed). Of the remaining 19 women, 15 completed all 6 modules, and 4 completed a portion of the program. Data from all 19 women were included in the analysis. The average helpfulness rating of each module was found to be 7.4 or above out of 10. Fertility quality of life increased by an average of 12 points out of 100, translating to a Cohen *d*=0.9. Large reductions in both mean symptoms of anxiety and depressed mood were observed (pre-to-post Cohen *d*=–1.2 and –1.3, respectively, where effects above 0.8 are considered large), corresponding with clinically meaningful improvements. In addition, 85% of participants experienced a clinically significant decline in either anxious or depressive symptoms (defined as a change of 4 points on the GAD-7 [21] and 5 points on the PHQ-9 [22]).

While the intervention was successful, areas for improvement were identified. For example, homework assignments were modified to include examples of completed homework. Participants reported that our “bonus” relationship module deserved to be a core part of the program, extending it to a total of 7 weeks.

The Current Trial

Over the last 3 years, our team has carefully designed a self-help intervention for infertility-related distress that is patient-informed and developed using best practices in intervention design. Results from this feasibility study suggest that it is well accepted and effective in increasing quality of life and reducing symptoms of depressed mood and anxiety among women with infertility-related distress. The proposed project, a sufficiently powered randomized controlled trial comparing the intervention to a treatment-as-usual control group, is the next step in this line of inquiry. It is hypothesized that the intervention will result in greater increases in fertility quality of life and relationship quality as well as decreases in symptoms of depressed mood and anxiety relative to a treatment-as-usual condition, and that these improvements will be maintained over a 16-week follow-up assessment period.

If the proposed trial confirms that the intervention is effective in improving quality of life and mental health symptoms among those with infertility, our next step will be to make this program widely available to women, including making the intervention available through YouTube and engaging our collaborating knowledge users and partner organizations to promote it widely. We will also aim to tailor the program for diverse and marginalized underserved groups.

Methods

Trial Design

The proposed research is a single-blind randomized controlled trial comparing the above-described self-help program to a waitlist control condition. As the project requires no in-person contact, we will recruit women living throughout Canada and the United States. Fertility quality of life, infertility-related distress, symptoms of depressed mood and anxiety, and relationship quality will be assessed before and after the program, as well as every other week for 16 weeks.

Treatment Conditions

Intervention Condition

Participants will be given access to a 10-minute module video per week through a mobile app created for this trial. Midweek, participants will receive an automated email reminder of the homework assignment for that week, encouraging them to incorporate the homework into their daily lives. Participants will be permitted to engage in any other psychological interventions they wish but will be asked to report other psychological interventions accessed at the end of their participation.

Treatment-As-Usual Control Condition

Participants assigned to the control condition will be instructed to continue their pursuits to conceive without accessing the self-help program. They will be permitted to access other psychological resources that are available to them, though, like the intervention condition, they will be asked to report any treatments accessed in the postintervention survey. They will complete the outcome measures at the same time as participants in the treatment condition. Following completion of the study, the control group will be offered the program in the same manner as the treatment group.

In the original funded grant protocol, we had proposed a waitlist control condition in which participants were not permitted to access other mental health services; however, we have since changed the control condition to treatment-as-usual in order to

more accurately estimate the real-world effectiveness of the treatment. This change also allows us to open the trial to individuals reporting suicidal ideation because these participants will likely require additional mental health services while participating in the current trial.

Randomization Scheme

The Clinical Research Support Unit at the University of Saskatchewan will create the randomization scheme and provide the principal investigator with opaque envelopes containing treatment assignments, ensuring that the research team has no control over the assignments. Randomization will take place at the end of each enrollment session, after the baseline surveys have been completed, and will be stratified based on whether a woman is undergoing fertility treatments or attempting to conceive without medical intervention, as this will be a potential moderating variable.

Protecting Against Sources of Bias

A number of strategies will be used to protect against bias. First, the trial will be registered with clinicaltrials.org before any data collection commences. Second, as described above, the randomization scheme will be created by a third party, and the study research assistants will be instructed to strictly adhere to the randomization protocol without exception. Third, though it is not possible to maintain full blinding of either the participant or research team given the nature of the intervention, all outcomes will be collected by a research assistant who is blind to the participant's treatment allocation. Fourth, an intent-to-treat approach will be taken in analyzing the results—every effort will be made to continue to collect outcome data on all participants, regardless of whether participants dropped out of the intervention early or not. Final, we will follow the CONSORT-SPI (Consolidated Standards of Reporting Trials for Social and Psychological Intervention Trials) reporting guidelines [23] in reporting the results of the trial, strictly adhering to the original trial protocol. Any deviations will be clearly described and justified.

Participants

Inclusion and Exclusion Criteria

Based on our sample size calculations, we will recruit 170 women, recruited through the web. The inclusion criteria will include the following: is infertile as defined as either actively attempting to conceive for ≥12 months without success or is currently undergoing fertility treatments (eg, ovulation induction medication, IVF, and intrauterine insemination). This definition ensures that this study is inclusive of both individuals who cannot afford fertility treatments and women who are in same-sex couples and cannot conceive naturally. Though the original funded protocol excluded individuals reporting active suicidal ideation, those already receiving psychotherapy, and those with high levels of fertility-related quality of life (FertiQoL above 70), we have since decided to remove these exclusion criteria in order to closely estimate the program's anticipated real-world effectiveness. Rather than exclude individuals based on baseline quality of life, we will perform secondary analyses, considering baseline quality of life as a treatment moderator.

Sex and Gender Considerations

In light of research finding that the intended pregnant individual experiences the most distress in the context of infertility, we will only recruit individuals who have a uterus. However, we will ensure that this study is welcoming to individuals of all gender identities and sexual orientations, as this study will aim to contribute to current knowledge surrounding the psychological experiences of individuals from minority genders, and sexual groups experiencing infertility. This study materials including advertisements, will use inclusive language. Advertisements will not use the word "woman" but instead "individuals attempting to get pregnant but experiencing infertility." The intervention itself has also been designed with inclusive language, a gender-neutral design, and pictures of individuals from diverse backgrounds and sexual orientations. To ensure adequate diversity among our participants, we will advertise on subreddits specifically targeting members of the LGBTQIA+ (lesbian, gay, bisexual, transgender, queer, intersex, and asexual) community.

Participant Screening and Enrollment

Prospective participants will be emailed the link to a web-based eligibility survey. If found to be eligible, they will be asked to provide their contact information, and a research assistant will contact them to schedule an enrollment session through videoconference.

During the Zoom-facilitated remote enrollment session, eligibility will be confirmed, a brief introductory video explaining the study and intervention will be presented, and consent will be obtained. An enrollment session in which visual contact is made will ensure that our recruited participants are not simply "bots" posing as eligible participants. During the session, participants will complete the baseline questionnaires through a link emailed to them by the research assistant. Upon completion of the questionnaires, the research assistant will open an opaque envelope, revealing the participant's random assignment to either the treatment or control condition. The research assistant will then ask the participant which day of the week they would like to receive their weekly module video (if assigned to the treatment condition) or weekly outcomes survey (if assigned to the control condition).

Participant Safety

Participants endorsing suicidal ideation on question 9 of the PHQ-9 at baseline will be permitted to participate in the study but will be informed that their level of risk will be reassessed weekly. Specifically, each week, they will receive a survey question, "Please pick out the one statement that best described how you have been feeling during the past week, including today: (A) I don't have any thoughts of killing myself. (B) I have thoughts of killing myself, but I would not carry them out. (C) I would like to kill myself, or (D) I would kill myself if I had the chance." If participants choose either C or D, a message including contact information for 2 suicide hotlines will appear. As well, an automatic notification will be sent to the study therapist, flagging the response. They will then follow up with the participant immediately by phone, at most within 24 hours.

If participants endorse A or B, they will simply be allowed to continue with the program.

In addition, the presence of active suicidal ideation (presence of a plan or intent) will be assessed by the researcher during the Zoom-facilitated enrollment session. Those endorsing active suicidal ideation will be referred to additional in-person mental health resources available in their geographic area. They will be given access to the program for their own benefit but will not be enrolled in the study.

Primary and Secondary Outcomes

Overview

Self-reported psychological outcomes will be assessed immediately postintervention (ie, at the end of the 7th week) and every 2 weeks for 16 weeks. Mood and anxiety disorders will be assessed immediately postintervention as well as 16 weeks postintervention. Finally, health care use will be assessed at postintervention week 16. The control group will follow an identical outcome assessment schedule.

Demographic and Medical Information

Age, ethnicity, gender identity, sexual orientation, marital and parental status, years of education, income, occupation, reproductive health history, and medications will be assessed using a survey created for this study.

Primary Outcome

Fertility-related quality of life was assessed using the 24-item Core FertiQoL [24], yields 4 subscales: mind-body, relational, social, and emotional. High scores on the FertiQoL scale indicate a better quality of life. It is the most widely used infertility-specific measure of quality of life [25] and has been well validated in multiple studies [20]. This primary outcome was chosen in collaboration with our patient advisors as it provides an integrated measure of the emotional, physical, and interpersonal impacts of infertility.

Secondary Outcomes

Secondary outcomes will include depressive and anxious symptoms, instances of mood and anxiety disorders, relationship quality, and health care use. Treatment adherence and acceptability will also be assessed.

Depressive Symptoms

Self-reported symptoms will be assessed using the PHQ-9 [26], a 9-item measure assessing symptoms in the last 2 weeks that closely parallels the criteria for major depressive disorder as defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) [27]. Internal consistency coefficient (ICC) has been estimated at α=.89 and test-retest reliability at r=0.84. The PHQ-9 has been shown to be superior to other questionnaires in detecting changes in depressive mood following treatment [28]. Participants endorsing suicidal ideation on item 9 of the PHQ-9 will be required to answer a weekly question.

Anxious Symptoms

Self-reported symptoms will be assessed using the GAD-7 [29], a 7-item measure that asks about symptoms in the last 2 weeks and closely parallels the DSM-5 criteria for generalized anxiety disorder. ICC is α=.92. The GAD-7 has been shown to be superior to other questionnaires in detecting change in anxious mood following treatment [30].

Mood and Anxiety Disorders

These will be assessed using NetSCID (TeleSage), the computerized version of the Structured Clinical Interview for the DSM-5 (SCID). Though the originally funded protocol proposed to use the Primary Care Evaluation of Mental Disorders (PRIME-MD), we decided to switch to the SCID because of the availability of the computerized version of this interview. The SCID is also the gold standard assessment for psychiatric diagnoses.

Relationship Quality

Relationship quality will be measured through the 7-item Relationship Assessment Scale. Internal consistency among individuals with infertility has been found to be high, with α=.83 [31].

Health Care Use

The questionnaire on health care consumption and productivity losses for patients with a psychiatric disorder will be administered 16 weeks following the intervention, asking participants to report on health care use in the last 4 months. This survey has shown good agreement with hospital- and employer-confirmed data. An additional section has been added to specifically ask about the receipt of fertility treatments.

Treatment Adherence

The total number of minutes spent accessing each moule video will be tracked through the mobile app. Homework completion between the weekly module videos will be tracked using Qualtrics, a web-based survey platform that facilitates scheduled survey distribution, notifications, and reminders. Homework compliance will be further measured at the end of each week through the 12 items contained within the Homework Rating Scale, which assesses comprehension of homework assignments as well as effort spent on assignments [32].

Treatment Acceptability

The Credibility Expectancy Questionnaire [33] will be administered at baseline to assess participants' initial expectations about the intervention. Postintervention, the Treatment Acceptability and Adherence Scale [34] will be used to assess treatment acceptance. The Negative Effects Questionnaire [35] will assess any potential adverse events perceived to be related to the intervention. Final, participants will be invited to provide written feedback about any of the modules or the program as a whole, including suggestions for further improvement and refinement.

Outcomes Assessment

A research assistant who is blinded to the participant's treatment condition will email the participant a link to a web-based survey containing the outcome measures. If a participant fails to complete the survey within 48 hours of receipt, they will receive up to 3 reminders through email, voicemail, and SMS text messaging. Though participants will not be compensated for

completing the intervention, they will be compensated US/CAD $10 (or its equivalent depending on their location) for each postintervention survey completed (postintervention +8 biweekly follow-up surveys) and an additional US/CAD $20 for each of the 2 postintervention interviews, for a maximum total of US/CAD $130, to maximize the chances that even those participants who abandoned the intervention prematurely will complete the outcome surveys.

Statistical Analyses

Descriptive statistics will examine treatment acceptability outcomes as well as the trial recruitment rate. A 2-tailed *t* test will be used to compare the treatment arms in terms of baseline characteristics, assessing randomization success. A mixed model design using the MIXED procedure in SAS (version 9.4; SAS Institute) applying an intent-to-treat approach will compare the intervention arm to the waitlist control group in terms of FertiQoL, PHQ-9, GAD-7, Copenhagen Multi-Center Psychosocial Infertility Fertility Problem Stress Scale, and Relationship Assessment Scale (RAS) score across the 9 outcome measurement points (ie, at the end of intervention week 7 and biweekly for 16 weeks). Each outcome will be examined in a separate model; subject will be treated as a random effect, and the treatment assignment will be treated as a fixed effect. A repeated statement will identify assessment week as a repeated measure factor. Baseline levels of the outcome will be included as a covariate. This method has been shown to provide optimal statistical power relative to measuring pre- and postintervention outcome change [36]. In using all available data, a mixed model design has also been shown to outperform ad hoc approaches, such as the last-outcome-carried-forward approach [37].

In addition to examining the main effect of treatment assignment on outcomes, the interaction between assignment and assessment week will be examined to determine whether outcomes are maintained across the 9 postintervention measurements. Sensitivity analyses will use a similar approach to examine potential treatment moderators: membership in the LGBTQIA+ communities, baseline FertiQoL score, cultural background, disability status, and pursuit of conception through medical intervention.

The LOGISTIC procedure will assess the occurrence of mood (major or minor depressive episode or persistent depressive disorder) and/or anxiety disorders (generalized anxiety disorder, social anxiety disorder, or panic disorder) in the 2 treatment arms at the posttreatment assessment as well as at the 16-week follow-up.

To limit the family-wise error rate, the Benjamin and Hochberg [38] false discovery rate correction will be applied to all analyses.

Power Calculations

Power calculations were performed using G*Power (Axel Buchner) and are focused on the primary outcome, infertility-related quality of life. Based on SDs observed in the population of distressed women with infertility [18], setting α at .05 and power at 80%, a total of 128 participants would be needed to detect a moderate effect size (Cohen f=0.25), equivalent to a 6-point difference on the FertiQoL (out of 100) between 2 arms. To allow for a 25% (42/170) dropout rate, we will recruit 170 participants (85 per arm), in line with average completion rate of 82% observed in our meta-analysis of psychological interventions for infertility-related distress and allowing for additional drop-out given considering the 16-week follow-up.

Planned Recruitment Rate

We propose to complete the trial within 2 years. The timeline relies on a recruitment rate of 3 participants per week, which we consider to be a highly conservative estimate of what is possible based on our previous experience successfully recruiting participants from this population.

Through our experience in our preliminary work, we have determined that the most successful strategy for recruiting the target population is to advertise through online infertility support or special interest groups—this will therefore be the primary method used to recruit for this study. We have found these groups to be very willing to share our research, and their members are extremely receptive as well as highly likely to be eligible to participate. We have also had great success in recruiting individuals from LGBTQIA+ communities attempting to conceive through IVF. In an ongoing study specifically targeting this population, we approached a pair of social media influencers (a lesbian couple who regularly share their experiences of undergoing IVF) who enthusiastically shared our project with their followers. Within 2 days, we had received over 400 entries in our eligibility survey.

In addition to providing large pools of highly engaged, eligible participants, one important advantage of web-based recruitment is that samples tend to be much more diverse in terms of race, education, and income relative to studies that recruit through fertility clinics, the patients for which are disproportionately high-income. While web-based recruitment can increase the risk of recruiting noneligible individuals posing as eligible participants, the use of a face-to-face Zoom enrollment session greatly reduces this risk. Our research team is also experienced in identifying suspicious survey responses.

Ethical Considerations

This study has been reviewed and approved by the University of Regina Ethics Board (REB #2023-210) as well as registered on ClinicalTrials.gov (NCT06006936). All prospective participants will provide informed written consent before enrolling in the trial.

To protect participant confidentiality, all participant data, including both interview data and questionnaire data, will be saved under ID numbers only, with no identifying information attached. Only the research team will have access to the collected survey data. The team will maintain a document associating participant names with their anonymous subject numbers. This document will be password-protected, opened only on encrypted devices, and stored separately from the rest of the data.

Participants will receive US $10 for each postintervention and follow-up survey completed and US $20 for each of the 2 postintervention interviews, for a maximum total of US $130.

Results

Recruitment will begin in January 2024 and continue for approximately 1.5 years. All data are expected to be collected by January 2026. Results will be uploaded on the ClinicalTrials.gov website shortly thereafter.

Discussion

Significance of the Study

It is expected that participants assigned to the Coping with Infertility program will exhibit improved fertility quality of life as well as depressive and anxious symptoms, with moderate to large effect sizes. We also expect rates of clinical mood and anxiety disorders as well as self-reported health care use to be lower among participants randomized to the treatment arm. Baseline fertility quality of life is furthermore expected to moderate the effect of treatment such that effect sizes will increase with decreasing baseline fertility quality of life. Based on the pilot study results, we expect adherence and retention to be favorable. If our hypotheses are confirmed, these findings would suggest that the Coping with Infertility program is more effective than currently available psychological interventions for infertility. Indeed, a recent meta-analysis by our team identified 58 randomized controlled trials testing psychological interventions for infertility and found that, with the exception of trials conducted in the Middle East, interventions were associated with only small psychological benefits, highlighting the need for more effective interventions [16]. The self-help nature of the Coping with Infertility program also likely makes it more cost-effective than individual psychotherapy, which typically costs US $100-$200 per session.

If our intervention proves effective, we will aim to make our mobile app publicly available through the Apple Store and Google Play Store. Decreased health care use in the treatment arm relative to the treatment-as-usual arm would provide a strong rationale for seeking government funding to upkeep the Coping with Infertility mobile app, which would allow us to make the program available free of charge. We would provide flyers and posters to fertility clinics across North America, to be posted in clinic waiting rooms and physician offices. We will reach out to relevant professional societies and nonprofit organizations, asking them to include the app as a mental health resource listed on their website. Online forums relevant to infertility will also be contacted and asked to share information related to the app. A YouTube channel will be created to house all of the weekly module videos along with a professionally produced animated explainer video introducing the intervention and describing the results from the trial supporting its efficacy. Final, we will publish our findings in open-access journal articles in respected scientific journals.

In addition to disseminating the Coping with Infertility program as a stand-alone intervention, it may also be worthwhile to pair it with other traditional mental health resources. For example, future research pairing the Coping with Infertility program with infertility support groups, or with individual psychotherapy may help target a broader audience of individuals experiencing infertility-related distress who wish to benefit from peer or therapist support. Translating the content of the program into a workbook format may also appeal to a subset of the target population.

Limitations

First, access to the Coping with Infertility program is contingent upon internet access; research participants may therefore not include individuals who do not have such access, such as those who cannot afford internet access or those living in remote communities. Second, due to the nature of the intervention, it is impossible to conduct this trial as a double-blind, randomized trial. Third, health care use will be self-reported and therefore may not capture use as accurately as hospital and clinic records.

Conclusions

This study will test a self-help program for infertility-related distress through a mobile app. If the intervention proves effective, it will provide a highly cost-effective and accessible mental health resource for those struggling with the mental health impacts of infertility. This will fill an important gap in light of high rates of psychopathology among those experiencing infertility and considering the current lack of effective psychotherapy approaches for infertility.

Acknowledgments

The authors would like to thank Canadian Institutes of Health Project Grant (#PJT186221) for the funding to complete this trial.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the Canadian Institutes of Health Research.
[PDF File (Adobe PDF File), 80 KB - resprot_v13i1e52662_app1.pdf]

References

1. Bushnik T, Cook JL, Yuzpe AA, Tough S, Collins J. Estimating the prevalence of infertility in Canada. Hum Reprod 2012;27(3):738-746 [FREE Full text] [doi: 10.1093/humrep/der465] [Medline: 22258658]

2. Bromham DR, Bryce FC, Balmer B, Wright S. Psychometric evaluation of infertile couples. (Preliminary findings.). J Reprod Infant Psychol 1989;7(4):195-202. [doi: 10.1080/02646838908403594]
3. Stanger S. Exploring the Experiences of Members of 2SLGBTQIA+ Communities Pursuing Third-Party Reproduction [Honours Thesis]. Regina, Saskatchewan: University of Regina; 2022. URL: https://ourspace.uregina.ca/items/bd3716b4-3966-4df3-a79f-9f8e6ee66e99 [accessed 2023-12-08]
4. Chen TH, Chang SP, Tsai CF, Juang KD. Prevalence of depressive and anxiety disorders in an assisted reproductive technique clinic. Hum Reprod 2004;19(10):2313-2318 [FREE Full text] [doi: 10.1093/humrep/deh414] [Medline: 15242992]
5. Nelson CJ, Shindel AW, Naughton CK, Ohebshalom M, Mulhall JP. Prevalence and predictors of sexual problems, relationship stress, and depression in female partners of infertile couples. J Sex Med 2008;5(8):1907-1914 [FREE Full text] [doi: 10.1111/j.1743-6109.2008.00880.x] [Medline: 18564149]
6. Kee BS, Jung BJ, Lee SH. A study on psychological strain in IVF patients. J Assist Reprod Genet 2000;17(8):445-448 [FREE Full text] [doi: 10.1023/a:1009417302758] [Medline: 11062855]
7. Volgsten H, Svanberg AS, Ekselius L, Lundkvist O, Poromaa IS. Prevalence of psychiatric disorders in infertile women and men undergoing in vitro fertilization treatment. Hum Reprod 2008;23(9):2056-2063 [FREE Full text] [doi: 10.1093/humrep/den154] [Medline: 18583334]
8. Gordon JL, Balsom AA. The psychological impact of fertility treatment suspensions during the COVID-19 pandemic. PLoS One 2020;15(9):e0239253 [FREE Full text] [doi: 10.1371/journal.pone.0239253] [Medline: 32946479]
9. Domar AD. Impact of psychological factors on dropout rates in insured infertility patients. Fertil Steril 2004;81(2):271-273 [FREE Full text] [doi: 10.1016/j.fertnstert.2003.08.013] [Medline: 14967355]
10. Olivius C, Friden B, Borg G, Bergh C. Why do couples discontinue in vitro fertilization treatment? A cohort study. Fertil Steril 2004;81(2):258-261 [FREE Full text] [doi: 10.1016/j.fertnstert.2003.06.029] [Medline: 14967352]
11. Bright K, Dube L, Hayden KA, Gordon JL. Effectiveness of psychological interventions on mental health, quality of life and relationship satisfaction for individuals and/or couples undergoing fertility treatment: a systematic review and meta-analysis protocol. BMJ Open 2020;10(7):e036030 [FREE Full text] [doi: 10.1136/bmjopen-2019-036030] [Medline: 32690514]
12. Frederiksen Y, Farver-Vestergaard I, Skovgård NG, Ingerslev HJ, Zachariae R. Efficacy of psychosocial interventions for psychological and pregnancy outcomes in infertile women and men: a systematic review and meta-analysis. BMJ Open 2015;5(1):e006592 [FREE Full text] [doi: 10.1136/bmjopen-2014-006592] [Medline: 25631310]
13. Ying L, Wu LH, Loke AY. The effects of psychosocial interventions on the mental health, pregnancy rates, and marital function of infertile couples undergoing in vitro fertilization: a systematic review. J Assist Reprod Genet 2016;33(6):689-701 [FREE Full text] [doi: 10.1007/s10815-016-0690-8] [Medline: 26979745]
14. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new medical research council guidance. Int J Nurs Stud 2013;50(5):587-592 [FREE Full text] [doi: 10.1016/j.ijnurstu.2012.09.010] [Medline: 23159157]
15. Czajkowski SM, Powell LH, Adler N, Naar-King S, Reynolds KD, Hunter CM, et al. From ideas to efficacy: the ORBIT model for developing behavioral treatments for chronic diseases. Health Psychol 2015;34(10):971-982 [FREE Full text] [doi: 10.1037/hea0000161] [Medline: 25642841]
16. Dube L, Bright K, Hayden KA, Gordon JL. Efficacy of psychological interventions for mental health and pregnancy rates among individuals with infertility: a systematic review and meta-analysis. Hum Reprod Update 2023;29(1):71-94. [doi: 10.1093/humupd/dmac034] [Medline: 36191078]
17. Dube L, Nkosi-Mafutha N, Balsom AA, Gordon JL. Infertility-related distress and clinical targets for psychotherapy: a qualitative study. BMJ Open 2021;11(11):e050373 [FREE Full text] [doi: 10.1136/bmjopen-2021-050373] [Medline: 34753757]
18. Gordon JL, Lybeck S, Dube L. Which psychotherapy techniques do women prefer for the treatment of infertility-related distress? 2021 Presented at: Annual Meeting of the Canadian Fertility and Andrology Society; 2021; Vancouver, Canada.
19. Poulter M, Sander B, Gordon JL. Pilot trial of a new self-directed psychological intervention for infertility-related distress. 2023 Presented at: Annual meeting of the Canadian Psychological Association; 2023; Toronto, ON.
20. Koert E, Takefman J, Boivin J. Fertility quality of life tool: update on research and practice considerations. Hum Fertil (Camb) 2021;24(4):236-248. [doi: 10.1080/14647273.2019.1648887] [Medline: 31387469]
21. Toussaint A, Hüsing P, Gumz A, Wingenfeld K, Härter M, Schramm E, et al. Sensitivity to change and minimal clinically important difference of the 7-item Generalized Anxiety Disorder Questionnaire (GAD-7). J Affect Disord 2020;265:395-401 [FREE Full text] [doi: 10.1016/j.jad.2020.01.032] [Medline: 32090765]
22. Löwe B, Unützer J, Callahan CM, Perkins AJ, Kroenke K. Monitoring depression treatment outcomes with the patient health questionnaire-9. Med Care 2004;42(12):1194-1201. [doi: 10.1097/00005650-200412000-00006] [Medline: 15550799]
23. Grant S, Mayo-Wilson E, Montgomery P, Macdonald G, Michie S, Hopewell S, et al. CONSORT-SPI 2018 explanation and elaboration: guidance for reporting social and psychological intervention trials. Trials 2018;19(1):406 [FREE Full text] [doi: 10.1186/s13063-018-2735-z] [Medline: 30060763]
24. Boivin J, Takefman J, Braverman A. The Fertility Quality of Life (FertiQoL) tool: development and general psychometric properties. Hum Reprod 2011;26(8):2084-2091 [FREE Full text] [doi: 10.1093/humrep/der171] [Medline: 21665875]

25. Kitchen H, Aldhouse N, Trigg A, Palencia R, Mitchell S. A review of patient-reported outcome measures to assess female infertility-related quality of life. Health Qual Life Outcomes 2017;15(1):86 [FREE Full text] [doi: 10.1186/s12955-017-0666-0] [Medline: 28449717]
26. Löwe B, Kroenke K, Herzog W, Gräfe K. Measuring depression outcome with a brief self-report instrument: sensitivity to change of the Patient Health Questionnaire (PHQ-9). J Affect Disord 2004;81(1):61-66 [FREE Full text] [doi: 10.1016/S0165-0327(03)00198-8] [Medline: 15183601]
27. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-5®). Washington, D.C: American Psychiatric Pub; 2013.
28. Titov N, Dear BF, McMillan D, Anderson T, Zou J, Sunderland M. Psychometric comparison of the PHQ-9 and BDI-II for measuring response during treatment of depression. Cogn Behav Ther 2011;40(2):126-136. [doi: 10.1080/16506073.2010.550059] [Medline: 25155813]
29. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006;166(10):1092-1097 [FREE Full text] [doi: 10.1001/archinte.166.10.1092] [Medline: 16717171]
30. Dear BF, Titov N, Sunderland M, McMillan D, Anderson T, Lorian C, et al. Psychometric comparison of the generalized anxiety disorder scale-7 and the Penn State Worry Questionnaire for measuring response during treatment of generalised anxiety disorder. Cogn Behav Ther 2011;40(3):216-227. [doi: 10.1080/16506073.2011.582138] [Medline: 21770844]
31. Maroufizadeh S, Omani-Samani R, Almasi-Hashiani A, Navid B, Sobati B, Amini P. The Relationship Assessment Scale (RAS) in infertile patients: a reliability and validity study. Middle East Fertil Soc J 2018;23(4):471-475 [FREE Full text] [doi: 10.1016/j.mefs.2018.04.001]
32. Kazantzis N, Deane F, Ronan K. Assessment of Homework Completion. In: Kazantzis N, Deane F, Ronan K, L'Abate L, editors. Using Homework Assignments in Cognitive Behavior Therapy. New York, NY: Routledge Taylor & Francis Group; 2005:50-60.
33. Devilly GJ, Borkovec TD. Psychometric properties of the credibility/expectancy questionnaire. J Behav Ther Exp Psychiatry 2000;31(2):73-86. [doi: 10.1016/s0005-7916(00)00012-4] [Medline: 11132119]
34. Milosevic I, Levy HC, Alcolado GM, Radomsky AS. The treatment acceptability/adherence scale: moving beyond the assessment of treatment effectiveness. Cogn Behav Ther 2015;44(6):456-469. [doi: 10.1080/16506073.2015.1053407] [Medline: 26091250]
35. Rozental A, Kottorp A, Forsström D, Månsson K, Boettcher J, Andersson G, et al. The negative effects questionnaire: psychometric properties of an instrument for assessing negative effects in psychological treatments. Behav Cogn Psychother 2019;47(5):559-572 [FREE Full text] [doi: 10.1017/S1352465819000018] [Medline: 30871650]
36. Twisk J, Bosman L, Hoekstra T, Rijnhart J, Welten M, Heymans M. Different ways to estimate treatment effects in randomised controlled trials. Contemp Clin Trials Commun 2018;10:80-85 [FREE Full text] [doi: 10.1016/j.conctc.2018.03.008]
37. Mazumdar S, Liu KS, Houck PR, Reynolds CF. Intent-to-treat analysis for longitudinal clinical trials: coping with the challenge of missing values. J Psychiatr Res 1999;33(2):87-95 [FREE Full text] [doi: 10.1016/s0022-3956(98)00058-2] [Medline: 10221740]
38. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc 2018;57(1):289-300. [doi: 10.1111/j.2517-6161.1995.tb02031.x]

Abbreviations

CONSORT-SPI: Consolidated Standards of Reporting Trials for Social and Psychological Intervention Trials
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
FertiQoL: Fertility Quality of Life Scale
GAD-7: Generalized Anxiety Disorder-7
ICC: internal consistency coefficient
IVF: in vitro fertilization
LGBTQIA+: lesbian, gay, bisexual, transgender, queer, intersex, and asexual
PHQ-9: 9-item Patient Health Questionnaire
PRIME-MD: Primary Care Evaluation of Mental Disorders
SCID: Structured Clinical Interview for the DSM-5

Edited by A Mavragani; submitted 12.09.23; this is a non–peer-reviewed article;accepted 23.11.23; published 18.01.24.

Please cite as:
Gordon JL, Poulter MML, Balsom AA, Campbell TS
Testing an Evidence-Based Self-Help Program for Infertility-Related Distress: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2024;13:e52662
URL: https://www.researchprotocols.org/2024/1/e52662
doi:10.2196/52662
PMID:38236638

Protocol

Effects of a Powered Ankle-Foot Prosthesis and Physical Therapy on Function for Individuals With Transfemoral Limb Loss: Rationale, Design, and Protocol for a Multisite Clinical Trial

Jason T Maikos[1*], PhD; Alison L Pruziner[2,3,4*], PT, DPT; Brad D Hendershot[2,3,5*], PhD; David V Herlihy[6*], BS; John M Chomack[6*], MS; Michael J Hyre[6*], MS, CAPM; Samuel L Phillips[7*], PhD, CP; Alexis N Sidiropoulos[1*], PhD; Christopher L Dearth[2,3,5*], PhD; Leif M Nelson[1,3,4*], PT, DPT

[1]Veterans Affairs New York Harbor Healthcare System, New York, NY, United States

[2]Walter Reed National Military Medical Center, Bethesda, MD, United States

[3]Extremity Trauma and Amputation Center of Excellence, Falls Church, VA, United States

[4]National Veterans Sports Programs and Special Events, Department of Veterans Affairs, Washington, DC, United States

[5]Uniformed Services University of the Health Sciences, Bethesda, MD, United States

[6]The Narrows Institute for Biomedical Research and Education, Brooklyn, NY, United States

[7]James A. Haley Veterans' Hospital, Tampa, FL, United States

[*]all authors contributed equally

Corresponding Author:
Jason T Maikos, PhD
Veterans Affairs New York Harbor Healthcare System
423 E. 23rd Street
New York, NY, 10010
United States
Phone: 1 2126867500 ext 7482
Email: jason.maikos@va.gov

Abstract

Background: Powered ankle-foot prosthetic devices can generate net positive mechanical work during gait, which mimics the physiological ankle. However, gait deviations can persist in individuals with transfemoral limb loss because of habit or lack of rehabilitation. Prosthetic research efforts favor the design or evaluation of prosthetic componentry and rarely incorporate any type of rehabilitation, despite evidence suggesting that it is critical for minimizing gait imbalances. Given the accelerated rate of innovation in prosthetics, there is a fundamental knowledge gap concerning how individuals with transfemoral limb loss should learn to correctly use powered ankle-foot devices for maximum functional benefit. Because of the recent advances in prosthetic technology, there is also a critical unmet need to develop guidelines for the prescription of advanced prosthetic devices that incorporate both physical and psychological components to identify appropriate candidates for advanced technology.

Objective: The primary goal of this investigation is to examine the roles of advanced prosthetic technology and a device-specific rehabilitative intervention on gait biomechanics, functional efficacy, and pain in individuals with transfemoral limb loss. The secondary goal is to develop preliminary rehabilitation guidelines for advanced lower limb prosthetic devices to minimize gait imbalances and maximize function and to establish preliminary guidelines for powered ankle-foot prosthetic prescription.

Methods: This prospective, multisite study will enroll 30 individuals with unilateral transfemoral limb loss. At baseline, participants will undergo a full gait analysis and assessment of function, neurocognition, cognitive load, subjective preferences, and pain using their current passive prosthesis. The participants will then be fitted with a powered ankle-foot device and randomized into 2 equal groups: a powered device with a device-specific rehabilitation intervention (group A) or a powered device with the current standard of practice (group B). Group A will undergo 4 weeks of device-specific rehabilitation. Group B will receive the current standard of practice, which includes basic device education but no further device-specific rehabilitation. Data collection procedures will then be repeated after 4 weeks and 8 weeks of powered ankle use.

Results: This study was funded in September 2017. Enrollment began in September 2018. Data collection will conclude by March 2024. The initial dissemination of results is expected in August 2024.

Conclusions: The projected trends indicate that the number of individuals with limb loss will dramatically increase in the United States. The absence of effective, evidence-based interventions may make individuals with transfemoral limb loss more susceptible

to increased secondary physical conditions and degenerative changes. With this expected growth, considerable resources will be required for prosthetic and rehabilitation services. Identifying potential mechanisms for correcting gait asymmetries, either through advanced prosthetic technology or rehabilitative interventions, can provide a benchmark for understanding the optimal treatment strategies for individuals with transfemoral limb loss.

Trial Registration: ClinicalTrials.gov NCT03625921; https://clinicaltrials.gov/study/NCT03625921

International Registered Report Identifier (IRRID): DERR1-10.2196/53412

(JMIR Res Protoc 2024;13:e53412) doi:10.2196/53412

KEYWORDS

amputation; limb loss; physical therapy; powered prosthetic ankle-foot device; lower extremity

Introduction

Background

There are approximately 1.9 million Americans with limb loss today, with an estimated 185,000 people who undergo an amputation procedure each year [1]. Over the last 2 decades, the Department of Veterans Affairs (VA) and the Department of Defense (DoD) have experienced an increase in the number of veterans and service members with lower limb loss [2]. Since the start of the most recent conflicts, more than 1700 service members have experienced combat-related limb loss, with the vast majority of these traumatic amputations of the lower limb [2-4]. VA, the largest integrated health care network in the United States, serves this unique population after their separation from active duty and provides care for an additional 41,000 veterans with lower limb loss [5]. Transfemoral limb loss, the second most common level of lower limb loss, accounts for one-fifth of the total limb loss population in the United States [6]. With this already large population expected to grow, effective outcomes-based clinical practice will be necessary to improve mobility, decrease long-term disability, and provide a higher quality of life.

Abnormal Gait Mechanics for Individuals With Transfemoral Limb Loss

Individuals with transfemoral limb loss have unique functional challenges owing to the loss of the knee and ankle joints [7-9]. Gait mechanics of individuals with transfemoral limb loss have been extensively investigated, with abnormalities typically characterized by asymmetries in stance phase biomechanics [10-13]. Individuals with transfemoral limb loss exhibit increased ipsilateral hip extensor activity and hip power, which is thought to be compensation for the lack of ankle power normally provided by the gastroc-soleus complex [14]. Consequently, compensatory mechanisms at joints proximal to the level of limb loss are often used to replace the function normally delivered by the muscles surrounding the ankle joint [12]. Individuals with unilateral transfemoral limb loss also tend to walk with longer stance times on the intact versus prosthetic limb [10], which can lead to a corresponding asymmetrical load distribution [15]. These asymmetrical joint forces place greater demands on the intact limb, which may explain the higher prevalence of musculoskeletal injuries, pain, and joint degeneration of the intact limb compared with uninjured individuals [16,17]. Significant among these secondary conditions is pain, specifically in the intact knee and lower back. In a study of experienced prosthesis users, knee pain in the intact limb was the primary complaint of 75% of individuals with transfemoral limb loss [18]. In a sample of 63 male veterans with traumatic lower limb loss, individuals with transfemoral limb loss were 5 times more likely to have intact knee pain compared with neurotypical participants [16]. Among individuals with lower limb loss (both transtibial and transfemoral), 71% reported back pain within the previous month, but individuals with transfemoral versus transtibial limb loss were significantly more likely to have greater pain intensity [19]. Chronic, persistent pain can lead to limitations in function. There is a significant need to explore the effects of advanced prosthetic technologies and rehabilitative interventions on pain reduction, function, and biomechanics.

Biomimetic Prosthetic Technology

New technologies in lower limb prostheses have attempted to combat gait pathologies by generating biomimetic ankle power through spring-clutch mechanisms or advanced sensor and actuator technology [20]. Recent advances in microelectronics, battery technologies, and the development of several new types of actuators [21,22] have ushered in the development of powered lower limb prostheses that can better replicate the positive work phases of the ankle through the use of actuators, motors, or pneumatic muscles [23-27].

The Empower (Ottobock Inc), which uses a series-elastic actuator and a carbon-composite footplate, is currently the only commercially available powered ankle-foot device [28,29]. The Empower has been investigated in the population of individuals with transtibial limb loss, but it has yet to be fully investigated in individuals with transfemoral limb loss [30-33]. In a study of individuals with transtibial limb loss, the use of a powered versus passive ankle-foot device reduced the peak resultant force and knee adduction moment on the unaffected leg during level ground walking, potentially limiting the risk of secondary musculoskeletal comorbidities [31]. Individuals with transtibial limb loss using the same powered ankle-foot device had improved ankle power, greater net trailing limb step-to-step transition work, and a lower metabolic rate compared with a passive energy storing and returning ankle-foot prosthesis during level ground ambulation [32].

Although biomimetic prosthetic devices can better approximate biological ankle biomechanics, residual gait deviations can persist, either because of habit or a lack of proper rehabilitative training. For example, despite greater ankle power generation with powered ankle-foot device use, individuals with transtibial

limb loss can still walk with compensatory strategies at the proximal joints, which can be attributed to the introduction of new interlimb asymmetries from the uniarticular function of the device [30]. Therefore, device-specific rehabilitation may be needed to minimize or correct the reported deficiencies. Similarly, in the absence of an evidence-based rehabilitation program to correct or minimize preexisting gait asymmetries, instrumented gait analyses that assess the biomechanical function of prosthetic devices may be more likely to quantify the physical gait deviations developed through habit or lack of training rather than device-specific attributes [34]. Therefore, it may be more accurate to postulate that powered ankle-foot devices, through the generation of normative ankle power during push off, offer an opportunity to minimize gait deviations and normalize prosthetic function but not without the incorporation of a rehabilitation program to train prosthesis users to reduce existing gait deviations.

Prosthetic Rehabilitation Programs

The current state of prosthetic research efforts appears to favor the design and evaluation of prosthetic componentry, particularly with respect to gait mechanics, and rarely incorporates or reports any type of physical therapy (PT) program or device-specific training [34]. Given the accelerated rate of technological innovation in prosthetic devices, there is a fundamental knowledge gap concerning how individuals with lower limb loss should learn to correctly use this advanced, powered technology for maximum benefit. However, previous investigations have examined the effectiveness of rehabilitation protocols on the outcomes of individuals with transfemoral limb loss who used passive prosthetic devices. Prosthetic gait training based on proprioceptive feedback for individuals with transfemoral limb loss was more effective for improved weight-bearing and temporal-spatial parameters than traditional gait training [35]. Sjodahl et al [36] used instrumented gait analysis to measure the gait parameters of individuals with unilateral transfemoral limb loss before and after a training program and reported improved walking speed and sagittal plane hip kinematic symmetry after training. However, the authors also reported increases in compensatory strategies for the intact limb, including an increase in the intact knee extension moment. Virtual reality–based gait training with real-time biomechanical feedback improved frontal plane hip, pelvis, and trunk motion during level ground walking [37]. Currently, there have been no published studies detailing the effects of a device-specific rehabilitation program on the biomechanical or functional outcomes of individuals with transfemoral limb loss who use a powered ankle-foot prosthesis. In this investigation, this knowledge gap will be addressed, and a benchmark to understand optimal treatment strategies will be provided for individuals with transfemoral limb loss to minimize gait impairments.

Summary

The development of evidence-based health care practices is critical to maximizing prosthetic and health outcomes in the growing population of individuals with transfemoral limb loss. Identifying potential mechanisms for correcting gait asymmetries, through advanced prosthetic technology, rehabilitative interventions, or both, can provide a benchmark to better understand the optimal treatment strategies for individuals with transfemoral limb loss. Despite research suggesting that an evidence-based rehabilitation program that incorporates prosthetic gait training is a critical factor in minimizing compensatory mechanisms [38-40], most prosthetic device protocols fail to incorporate any type of significant rehabilitation or device-specific training. Therefore, this investigation will be the first to elucidate the effects of an advanced powered prosthesis and the role of rehabilitative interventions on gait biomechanics, performance, and pain in individuals with transfemoral limb loss.

Study Objectives

The overarching goal of this investigation is to examine the roles of advanced prosthetic technology and a device-specific rehabilitative intervention in individuals with transfemoral limb loss. The central hypothesis is that powered plantarflexion, coupled with an evidence-based, device-specific PT intervention, will improve biomechanical outcomes, which will correlate with decreased pain and improved functional performance. The objectives of this investigation are as follows:

1. To examine the biomechanical and functional efficacy of a powered prosthesis compared with a passive prosthesis for individuals with transfemoral limb loss
2. To determine the effects of a powered prosthetic ankle-foot device and a PT intervention on lower extremity kinematic and kinetic patterns, functional efficacy, and pain in individuals with transfemoral limb loss
3. To develop preliminary rehabilitation guidelines for a powered ankle-foot device to minimize gait imbalances and maximize function, as well as to establish preliminary guidelines for powered ankle-foot prosthetic prescription

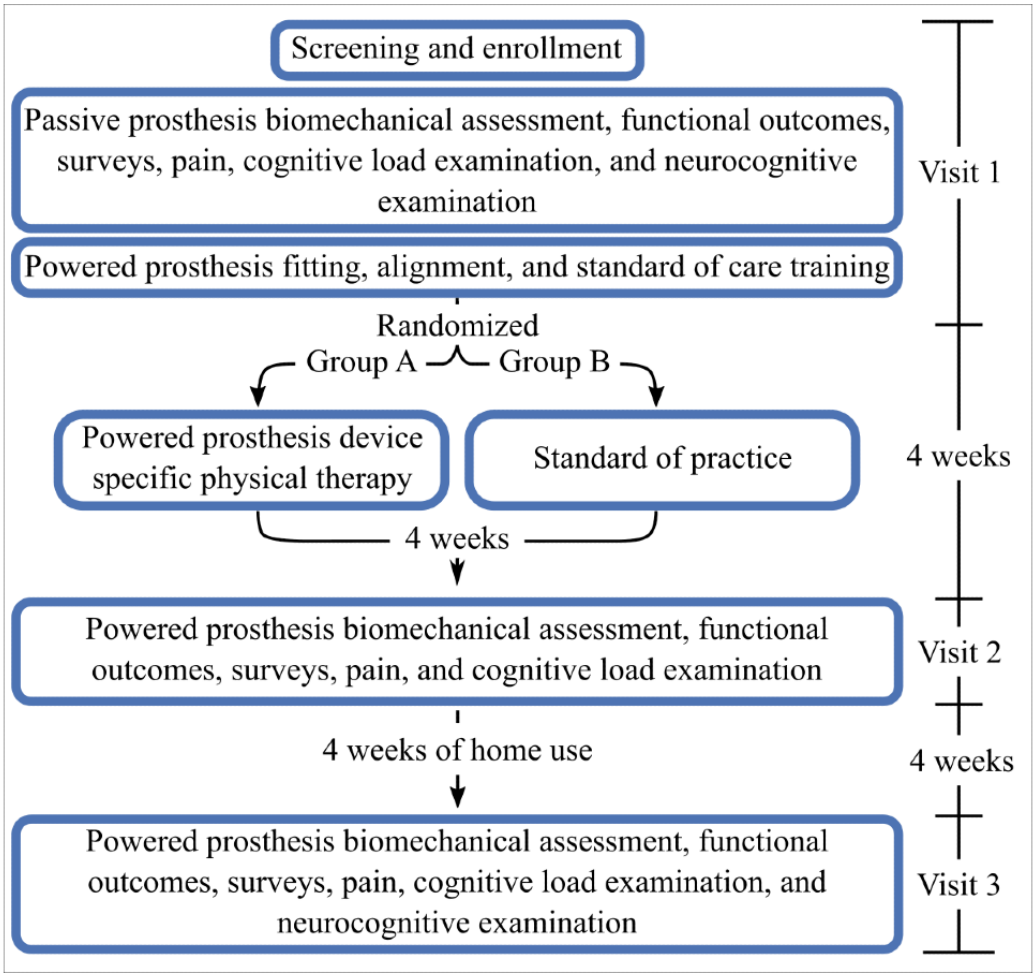
Methods

Study Overview

This investigation will be a prospective, multisite study including VA New York Harbor Healthcare System (VANYHHS), James A. Haley Veterans' Hospital (JAHVH), and Walter Reed National Military Medical Center (WRNMMC). Enrollment began in September 2018, and data collection is expected to conclude in 2024. Briefly, 30 individuals with transfemoral limb loss are expected to be enrolled equally across the 3 sites. For all participants, a full biomechanical gait analysis, functional measures, surveys, neurocognitive assessment, cognitive load assessment, and pain assessment will be captured at baseline with their clinically prescribed passive energy storing and returning ankle-foot prosthesis. The participants will be fitted with a powered ankle-foot device (Empower) and then be evaluated for safe use. The participants will then be randomly assigned into 2 groups: a powered ankle-foot device with a 4-week, 8-session device-specific PT intervention (group A) or a powered ankle-foot device with the current standard of practice (group B), which includes basic device education and training provided by the study prosthetist (outlined in the Powered Ankle-Foot Device Standard of Practice section), but no device-specific PT intervention. Group A will then undergo 4 weeks of

device-specific rehabilitation, while group B will not receive any further PT. All participants will then undergo a full gait analysis as well as assessments of function, subjective preferences, neurocognition, cognitive load, and pain after 4 weeks and 8 weeks of powered ankle-foot device use (Figure 1). A comparison between the 2 groups will help evaluate the efficacy of a powered versus passive prosthesis, as well as elucidate the contribution of device-specific effects to rehabilitation-specific effects for individuals with transfemoral limb loss.

Figure 1. Participant timeline of activities.



Participants

A convenience sample of 30 individuals with unilateral transfemoral limb loss will be recruited for this study (Textbox 1 shows the inclusion and exclusion criteria). All participants will consent to participate before participating in any study activities. The participants will be randomly stratified into 2 study arms: group A, a powered ankle-foot device with device-specific PT (15/30, 50%), and group B, a powered ankle-foot device with standard of practice (15/30, 50%), which includes basic device education and training but no device-specific PT intervention. Recruitment of participants will be on a first-come, first-serve basis among the patients of VANYHHS, JAHVH, and WRNMMC. The participants will be recruited through the VANYHHS, JAHVH, and WRNMMC rehabilitation and prosthetic clinics. All participants will have experience using a microprocessor knee and will currently use a passive-elastic ankle-foot prosthesis.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Unilateral transfemoral limb loss because of any etiology
- Use of a microprocessor knee with >6 months of experience
- ≤8 limb loss–related physical therapy sessions in the previous 6 months
- Aged at least 18 years
- Score of ≥33 on the Amputee Mobility Predictor, corresponding to a high K2 or above ambulator
- Able to walk a minimum of 30 meters without an assistive device
- Able to walk on a treadmill for 5 minutes at self-selected speed with or without the use of handrails

Exclusion criteria

- Inability to tolerate the wearing of a socket or a poorly fitting socket
- Conditions of the intact limb prohibit prosthesis use (eg, ulcers, sores, skin breakdown, burns, poor skin coverage, contractures, and severe heterotopic ossification)
- The length of the residual limb prohibits socket or prosthesis fitting
- Cognitive deficits or a mental health pathology limiting the ability to participate fully in the study or any deficit deemed by the principal investigator to be detrimental to the completion of the study
- Significant comorbidity, which would interfere with the study (eg, neuropathy, uncontrolled diabetes, receiving dialysis, insensate feet, severe phantom pain, or a history of skin ulcers)
- Severe circulatory problems, including peripheral vascular disease and pitting edema
- Pregnant women in the second trimester or beyond or women who will be in the second trimester within the enrollment period
- Weigh >130 kg at screening
- Use of nonprescribed opioids or overuse of any prescription drugs
- Major upper limb loss
- Currently uses a powered ankle-foot prosthesis as a primary prosthesis or used a powered ankle-foot device as a primary prosthesis in the previous 6 months
- Any cardiopulmonary, metabolic, or integumentary diagnosis where walking for 15 minutes is contraindicated

Ethical Considerations

This study was approved by the following institutional review boards (IRBs): VANYHHS IRB (1643), WRNMMC IRB (WRNMMC-2018-0167), and the University of South Florida IRB, which is the IRB of record for JAHVH (IRB STUDY000870). The oversight and protection of human participants was also approved by the US Army Medical Research and Development Command Office of Human Research Oversight (E04081). All participants will provide informed consent before participating in any study activities.

Baseline Visit

Informed Consent, Enrollment, and Randomization

Informed consent for each potential participant will be conducted in person in a private room. The site-principal investigator or qualified designee will explain the study protocol in detail. The participants will be asked to consent to randomization of the treatment group, either to be fit with the powered ankle-foot device and receive device-specific PT (group A) or to be fit with the powered ankle-foot device and receive the current standard of practice that does not include device-specific PT (group B). The participants will be asked to make a commitment to be available for all study-related activities. The individuals will be given adequate time to review and comprehend all information about the study before agreeing to participate, minimizing the possibility of coercion and undue influence. After the study has been explained and consent has been given, the participants will be randomized into the 2 groups using a computer-generated algorithm that block randomizes participants into each group at each site.

Baseline Data Capture

Regardless of the group assignment, all participants will undergo baseline data capture using their current passive energy storing and returning prosthesis. The study prosthetist will ensure proper fit and alignment of the prosthesis before any data collection. Once fit and alignment are confirmed, the participants will complete 3 surveys: an assessment of quality of life, the Prosthesis Evaluation Questionnaire (PEQ), and the PEQ Addendum. Then, pain, cognitive load, neurocognition, biomechanical gait analysis, and functional outcomes will be captured at baseline for all participants on their current passive energy storing and returning prosthesis.

Quality-of-Life Assessment

A single-item assessment will ask the participants to rate their quality of life over the past 4 weeks on a 100-mm visual analog scale.

Assessment With PEQ

The PEQ is a self-reported visual analog–style questionnaire for people with lower limb loss who use a prosthesis to evaluate the prosthesis and life with the prosthesis. The PEQ is organized into 9 domains that may be used independently to measure a specific domain of interest. Domains of utility, appearance, sounds, residual limb health, and ambulation will be used in this investigation. In addition, the PEQ contains items beyond the domains that can be evaluated individually, including questions on satisfaction, pain, and transfers that will be used in this study [41].

Assessment With PEQ Addendum

The PEQ Addendum asks 2 open-ended questions assessing any falls or stumbles that the participant may have experienced over the previous 4 weeks [42].

Pain Assessment

Participants will complete the Patient-Reported Outcomes Measurement Information System Pain Interference Scale 8a, which is a self-report survey that assesses the extent to which pain interferes with physical, psychosocial, cognitive, emotional, and recreational activities [43].

Neurocognitive and Cognitive Load for Prosthesis Use

Prosthesis use requires physical capabilities and the cognitive capacity to learn new techniques across different situations and environments. These skills include spatial organization, memory, attention, and visuospatial function [44]. Powered ankle-foot devices can be more complex than passive devices and may require certain levels of neurocognition and cognitive load for ambulation, especially for higher-level functional tasks. Diabetes and peripheral vascular disease, the most prevalent causes of lower limb loss, are linked to declining neurocognition [45,46]. Importantly, diminished neurocognitive function is not often observed until late in the rehabilitation process (well after prosthetic prescription) [47], which can result in the mismanaged use of staff and patient time and prosthetic resources. If certain levels of neurocognitive abilities correlate with successful prosthetic outcomes with the powered prosthesis, neurocognitive assessment (before prosthetic prescription) can potentially aid in the selection of appropriate candidates for advanced technology.

Cognitive Load Assessment

Cognitive load assessments will be performed at baseline using the passive energy storing and returning ankle-foot prosthesis. Before any cognitive load testing, a self-selected walking speed will be established via treadmill walking. The participants will be encouraged to walk unsupported on the treadmill, if possible. The treadmill console will be covered to prevent number distractions, and the participants will be reminded to hold their gaze straight ahead. To determine the self-selected speed, the participants will begin walking on the treadmill at a comfortable speed in the absence of any additional cognitive load. The treadmill will then be increased by 0.09 m/s every 10 seconds until the participant verbalizes their preferred speed. To avoid quick trigger responses, the speed will be increased by 0.18 m/s and then subsequently lowered by 0.04 m/s every 5 seconds until the participant verbalizes their preferred speed. If the final speed does not match the initial speed, this procedure will be repeated until the participant matches the preferred walking speed.

Cognitive load testing consists of five 1-minute standardized cognitive tasks: 1 serial subtraction task, 3 controlled oral word association tasks, and 1 category task. These tasks consist of auditory and verbal cognitive measures to simulate real-world conditions. Visual tasks will not be used to avoid measures that require reading while walking. The participants will complete each cognitive task while walking on a treadmill at the previously noted self-selected speed. The directions will be read to each participant to ensure protocol consistency. The number of correct answers will be determined for each 1-minute test using a digital voice recorder and paper recordings to ensure accurate documentation of the participants' answers. The participants will complete a practice trial before each task initiation to ensure complete comprehension. The participants will also be allowed to rest between cognitive tests as needed. The cognitive tasks are as follows:

- Serial subtraction: Serial subtraction is a mental arithmetic task [48]. The participants are given a random 3-digit number and asked to continually subtract 3 while they walk for 1 minute. The number of errors will be calculated. The participants are not penalized for multiple errors if 1 error was made; however, they continued sequentially thereafter.
- Controlled Oral Word Association Test: This measure consists of 3 tests that measure verbal phonemic fluency and other neuropsychologic domains [49]. The participants will be asked to list words beginning with a certain letter while walking for 1 minute. The test is then repeated for 2 other letters. The total number of unique words for each letter will be documented.
- Category Test: The participants are asked to list words belonging to a certain category within 1 minute (eg, fruits or parts of a car). Category naming has shown validity and reliability [50]. The total number of unique words for each category will be documented.

After each cognitive load test, the participants will be asked to rate on a 0 to 10 scale (with 0 being "none" and 10 being "a great deal") their focus on walking, their focus on thinking of words or subtracting numbers, and their focus on distractions. This will provide information on the subjective experience of cognitive load.

Neurocognitive Assessment

Following the cognitive load assessment, the participants will take an electronic neurocognitive battery (CNS Vital Signs) [51]. The computerized neurocognitive assessment measures 5 domains (memory, psychomotor speed, reaction time, complex attention, and cognitive flexibility), is designed to be administered serially, and has demonstrated good test-retest

reliability. The neurocognitive assessment consists of the following 7 tests:

- Verbal memory: the participants are instructed to remember 15 words that are displayed 1 at a time every 2 seconds. The target words are then randomly mixed with 15 new words. The participants are instructed to press the space bar when a target word is displayed. This test is repeated at the end of the assessment with the same 15 target words randomly mixed with 15 new nontarget words.
- Visual memory: the participants are instructed to remember 15 geometric shapes that are shown 1 at a time every 2 seconds. The shapes are then randomly mixed with 15 new nontarget shapes. The participants are instructed to press the space bar when they identify a target shape. This test is repeated at the end of the neurocognitive assessment period.
- Finger tapping: the participants are instructed to tap the space bar with their right index finger as quickly as possible during the 10-second test. The test is then repeated with the left index finger.
- Symbol Digit Coding: this test consists of 8 digit-symbol pairs, followed by a list of digits. The participants are instructed to serially type numbers that correspond to the symbols during the 120-second test.
- Stroop test: in part 1 of the Stroop test, the participants are randomly shown the words "GREEN," "YELLOW," "RED," and "BLUE." These words are printed in black. The participants are instructed to press the space bar when they see one of these words. In part 2, the same words appear on the screen but are printed in different colors. The participant is instructed to press the space bar when the color presented matches the word (eg, the word "RED" is printed in red). In part 3, the same words are presented on the screen in different colors. The participants are then instructed to press the space bar when the color presented does not match the word (eg, the word "RED" is printed in green).
- Shifting Attention: in this test, 3 figures appear on the screen. There is a single figure at the top of the screen (either a circle or a square). At the bottom of the screen, 2 figures are presented (both a square and a circle). The figures are randomly mixed to be either red or blue. The participant is then instructed to match one of the corresponding bottom figures with the top figure by shape or color. However, the rules for matching by shape or color change at random. This test occurs for 90 seconds.
- Continuous performance test: during a 5-minute period, the participants are asked to press the spacebar when the letter *B* appears on the screen. The participants are further instructed not to respond to any other letters. The letters are presented at random.

Biomechanical Gait Analysis

Gait analyses will be performed at the biomechanics laboratories at VANYHHS, WRNMMC, and JAHVH. The VANYHHS laboratory is a 133-m^2 space comprising an 11-camera motion capture system (Qualisys, Inc) with 4 multiaxis force platforms (AMTI, Inc). At WRNMMC, the biomechanics laboratory is an 167-m^2 space comprising an 18-camera motion capture system (Qualisys, Inc) and 6 multiaxis force platforms (AMTI Inc). At JAHVH, the motion capture laboratory is a 74-m^2 space equipped with a 12-camera motion capture system (Vicon Inc) and 4 multiaxis force platforms (AMTI Inc). All 3 systems track the positions of passive reflective markers at a rate of 120 Hz, and force platforms sample ground reaction forces at a rate of 1200 Hz. Visual3D software (C-Motion Inc) will be used for the analysis of 3D motion capture data.

All laboratories in this investigation will follow recommendations provided by an interlab reliability study that was conducted between gait laboratories at the 3 military treatment facilities [52]. Specifically, all sites will use identical marker sets, identical anatomical segment definitions, and a single examiner at each site to conduct postprocessing of the respective data to reduce potential variability between the laboratories.

For all participants, biomechanical gait analysis will be performed at baseline using their prescribed energy storing and returning prostheses. All kinematic and kinetic biomechanical measures will be captured using an identical 6-degrees-of-freedom marker set. A custom, full-body passive reflective marker set will be placed on each participant, which tracks each segment independently, allowing for the accurate measurement of movements. As previously described [53], 78 markers will be placed or digitized on the head, trunk, pelvis, and extremities. Marker placements for the prosthetic limb will be matched to those of the intact leg or placed on the centers of rotation of the prosthetic ankle-foot and knee devices. The cluster technique will be used to minimize the surface-to-bone displacements for the thigh, shank, and upper arm–mounted markers [54]. Tracking clusters will be placed bilaterally on the thigh, the tibial crest, and the upper arm. Functional joints, adapted from Schwartz and Rozumalski [55], will also be calculated for the intact ankle and knee as well as bilaterally for the hips.

During each experimental session, the participants will separately walk at 3 speeds across an instrumented walkway until 5 acceptable trials for each foot at each speed are completed. Trials will be considered acceptable when a foot makes full contact with a force platform. Because kinetic outcome measures are speed-dependent, the participants will ambulate at 3 controlled speeds: 0.7, 1.0, and 1.3 m/s. These speeds were selected to represent a slow, moderate, and fast walking speed, respectively, for individuals with transfemoral limb loss. The order of speeds will be randomized for each data collection visit. Auditory feedback will be provided to the participant by the study team to ensure that all participants walk at the targeted speed (−5% to +5%). The main purpose of this session is to collect joint motion, force, torque, and power data at each walking speed. The ranges of motion; speeds and accelerations; and hip, knee, and ankle joint moments of force and generated and absorbed powers will be computed using inverse dynamics methods. Temporal-spatial parameters will also be recorded.

The reflective marker positions will be digitized using motion tracking software. A 15-segment rigid body model (head, trunk,

pelvis, bilateral upper and lower arms, hands, thighs, shanks, and feet) will be created based on the skin-mounted markers and functional joints. Local coordinate systems for each segment will be defined using the International Society of Biomechanics recommendations [56,57]. The data of 5 acceptable walking trials at each speed will be processed using Visual3D. Marker data will be filtered with a 6 Hz Butterworth low-pass filter. Raw analog data will be filtered using a second-order low-pass Butterworth filter with a 25-Hz cutoff frequency. Visual3D will be used to calculate temporal-spatial values, walking speed, and lower extremity kinematics and kinetics. Inverse dynamic analysis will be applied to the kinematics of the biomechanical model and to the location, magnitude, and direction of ground reaction forces acting on the foot to calculate lower extremity joint torques and powers, including ankle, knee, and hip power of the biological and prosthetic limb over the stance phase, as well as the frontal plane knee moments for the unaffected leg.

Functional Outcome Measures

The effects of the prosthetic devices and the rehabilitative intervention on physical performance will be evaluated using agility and mobility tests, including the 6-minute walk test (6MWT) [58], the Amputee Mobility Predictor with prosthesis (AMPpro) [59], and the Comprehensive High-Level Activity Mobility Predictor (CHAMP) [60]. By capturing the functional measures in each group, the effects of the ankle-foot device can be isolated from the rehabilitation effects on physical performance. These measures are as follows:

- 6MWT: the 6MWT measures the distance an individual can walk in 6 minutes without help or encouragement. It is a valid and reliable measure that correlates with physical function and has good interrater and intrarater reliability in individuals with lower limb loss [58].
- AMPpro: the AMPpro is a 21-item instrument designed to measure prosthetic mobility in individuals with lower limb loss [59].
- CHAMP: participants who attain a score of 37 or higher on the AMPpro will undergo the CHAMP, which consists of the following tasks:
    - Single limb stance: participants fold their arms across their chest and then lift their foot above a 15-cm cone or box. The test ends when the foot touches the ground again (or until 30 s) or if the arms uncross. This procedure is performed on both feet.
    - Edgren Sidestep Test: participants sidestep left and then right along a 5-meter line of cones (1 meter apart). The sidestep test lasts for 10 seconds.
    - T-Test: the T-Test measures forward, lateral, and backward walking (or running) and sidestepping in a T pattern.
    - Illinois Agility Test: this advanced agility test requires the participant to run or walk and change direction around multiple cones. Over 60 meters, participants perform 90° and 180° turns 11 times around multiple cones.

Powered Ankle-Foot Prosthesis Fitting

Following all baseline data collection procedures, all participants will then be fit with the Empower. Study prosthetists at VANYHHS, WRNMMC, and JAHVH are highly experienced in fitting all commercial microprocessor knees and the Empower. The study prosthetists will bench align the powered ankle-foot device onto the participant's existing microprocessor prosthetic knee and socket. Once the powered ankle-foot device is fitted and bench-aligned to the prosthetic knee and socket, dynamic alignment of the prosthetic knee and ankle will occur. Initially, the study prosthetist will ensure proper alignment of the microprocessor prosthetic knee with the Empower turned off. The Empower will still function (ie, articulate) with the power off but will not provide net positive plantarflexion torque. The microprocessor prosthetic knee software and prosthesis alignment will be adjusted during standing and walking tasks, as necessary, until the prosthetist and the participant are satisfied with the knee alignment. Once the microprocessor knee setup is completed, the Empower will be powered on and adjusted according to the manufacturer's specifications. Briefly, the participants will sequentially walk at 3 different speeds (slow, self-selected, and fast) while the stiffness and power delivery of the powered ankle-foot device is tuned [33]. If further dynamic adjustments to prosthetic knee alignment are necessary, these adjustments will be made at this point.

Powered Ankle-Foot Device Standard of Practice

Once a stable and comfortable alignment has been established, all participants will be educated by the study prosthetist on the proper use of the Empower, which includes battery handling and charging, understanding low battery indicators, considerations while driving with the Empower (if applicable), and avoidance of exposure to rain and water. Next, the participants will ascend and descend an Americans with Disabilities Act–compliant ramp under the supervision of the study physical therapist or prosthetist. The intent of ramp walking is to trigger the power for ascent but not during descent. Each participant will be given the opportunity to practice the ramp as often as necessary to ensure safe and comfortable use. The participants will then negotiate a standard staircase with handrails under the supervision of the study physical therapist or prosthetist to ensure that they can safely negotiate stairs using the Empower. Proper technique will consist of demonstrating the correct foot placement on each step to activate powered push off during ascent. Participants unable to ascend stairs in a step-over-step pattern will be shown the correct foot placement using a step-to gait pattern. For proper stair descent, participants will be shown the correct foot placement to initiate rollover and not trigger the power. Participants will be given time to practice stair ascent and descent. After stair and ramp ambulation, participants will be asked to demonstrate safe use of the Empower in different situations, including turning, varying speeds, sudden stops, obstacle avoidance, stepping over obstacles, and different surfaces. Once the physical therapist is satisfied that the participant has demonstrated safe use and all questions have been answered, the participant will be released home with the Empower. If the physical therapist feels that the progress is unsatisfactory, the participant will not take the Empower home and will be asked to return for continued

supervised use until the participant demonstrates safe use. The standard of practice to use the powered prosthesis is approximately 30 to 45 minutes after fitting and tuning.

Following the baseline visit, group A will undergo the device-specific PT program, whereas group B will not undergo any further training.

PT Program: Group A

Overview

Participants in group A will complete, on average, 8 PT sessions lasting 30 to 45 minutes each. The exact PT protocol and criteria for advancement are outlined by level in the subsequent section. In brief, level 1 of the PT plan will focus on education, strengthening through therapeutic exercises, and early neuromuscular reeducation. A home exercise program (HEP) will be initiated during the initial sessions and will progress along with the program. Level 2 will include gait training on level surfaces, sit-to-stand transitions, and ramp negotiation. Level 3 will include multidirectional training for both neuromuscular reeducation and gait and the introduction of stair ascent and descent. Training will conclude with level 4 where the previous skills will be further challenged and advanced gait skills, including ambulation on ramps and uneven surfaces, will be introduced. Participants must meet the outlined criteria before progressing through each level. Participants who do not meet the specified criteria will be offered additional PT sessions. The number of additional sessions will be recorded and used to refine the PT program for future use.

Level 1 (Sessions 1 and 2)

Level 1 (Table 1) includes initial evaluation, patient education, gait assessment, training to ensure safe use in the community, therapeutic exercises (including introduction of the HEP), and the initiation of early neuromuscular reeducation training.

Table 1. Level 1 device-specific physical therapy protocol.

Protocol	Description	Criteria for advancement to level 2
Level 1 (sessions 1 and 2)		
Evaluation	Assessment of prosthesis fit and gait to determine deficits	N/A[a]
Strengthening	Strengthening of transversus abdominis and multifidus, gluteus maximus, gluteus medius, and general trunk strengthening	Able to perform HEP[b] independently
Stretching	Address deficits from evaluation, including iliopsoas	Within normal limits for range of motion
Education	Explanation of function of powered ankle-foot device	Verbalizes understanding of function of powered ankle-foot device
Gait training	Safely negotiate level surface without increased falls or stumbles	Able to ambulate 46 meters without an assistive device independently on a flat, level surface; self-reported occurrence of stumbles or falls is no greater than baseline
Mobility training	Side stepping, backward stepping, and turns	Able to ambulate outdoors without increased falls or stumbles with or without an assistive device
Neuromuscular reeducation	Weight shifting and control over prosthesis, intact limb mobility (toes in and toes out, heel in and heel out) to promote weight shifting, static single limb balance training on prosthesis side with upper limb support, and anterior and posterior stepping exercises with the intact limb	Independent in HEP
HEP	Initiated with all therapeutic exercises outlined in level 1	Independent in HEP

[a]N/A: not applicable.

[b]HEP: home exercise program.

Level 2 (Sessions 3 and 4)

Level 2 (Table 2) will include the progression of therapeutic exercises through increased frequency, duration, and resistance.

All strengthening and stretching will be shifted to the HEP by the completion of level 2. Lumbar, abdominal, and closed kinetic chain lower extremity strengthening exercises will progress to more dynamic positions. Single limb stance progressions (neuromuscular reeducation) will include decreased upper limb support for stepping exercises and progressing to step touches with the intact limb. Upper limb support will progress from bilateral support to support provided only on the side of the prosthesis. Anterior and posterior stepping exercises will begin with the support of parallel bars while maintaining weight on the prosthesis.

Table 2. Level 2 device-specific physical therapy protocol.

Protocol	Description	Criteria for advancement to level 3
Level 2 (sessions 3 and 4)		
Evaluation	Reassessment as needed	N/A[a]
Strengthening	Progression to sitting, quadruped, planks, standing, and transitions	Independent in HEP[b]
Stretching	Primarily used for cooldown at completion of each session	Independent in HEP
Education	Description of HEP and purpose of each exercise	Verbalizes understanding of each exercise
Gait training	Improving step length symmetry (eg, verbal cueing to increase step length on nonprosthesis side) and improving rollover on prosthesis side (eg, resistive gait training with TheraBand)	Ability to trigger power in prosthetic foot during gait >50% of steps and increased gait symmetry with verbal cueing for step length as determined through observational gait analysis
Mobility training	Transfers (eg, stand-to-sit), and ramp negotiation	Able to maintain midline center of mass with stand-to-sit transfer
Neuromuscular reeducation	Intact limb mobility (eg, rolling ball under intact limb) to promote weight shifting, static single limb balance training on prosthesis side with minimally necessary upper limb support and stepping exercises (eg, step touches 15-20 cm step in parallel bars and step touches to a cone in the parallel bars)	Independent in HEP
HEP	Includes therapeutic exercises outlined in level 2	Independent in HEP

[a]N/A: not applicable.

[b]HEP: home exercise program.

Level 3 (Sessions 5 and 6)

At level 3 (Table 3), all strengthening will be performed exclusively in the HEP. PT will include neuromuscular reeducation progression, including multidirectional movements.

Stepping exercises will be performed with decreasing upper extremity support at a tolerance demonstrated by the participant maintaining an appropriate body position. Single limb stance activities will include perturbations, such as resistance with movements of a non–weight-bearing intact limb or standing on a foam pad or balance disc. Gait training will include multidirectional stepping with upper extremity support in the parallel bars. Resistive gait training will be introduced to promote proper mechanics for loading the prosthesis in stance and achieving maximal energy return at push off. In addition, manual proprioceptive neuromuscular facilitation will be performed to promote proper anterior pelvic rotation. Multidirectional ambulation will be progressed to outside of parallel bars.

Table 3. Level 3 device-specific physical therapy protocol.

Protocol	Description	Criteria for advancement
Level 3 (sessions 5 and 6)		
Evaluation	Reassessment as needed	N/A[a]
Strengthening	Review as needed	Independent in HEP[b]
Stretching	To be used for cooldown at session completion	Independent in HEP
Education	Gait training and purpose for improving symmetry	Verbalizes understanding of gait training
Gait training	Promoting gait initiation on prosthesis side with anterior pelvic rotation (ie, manual techniques to facilitate or initiate anterior pelvic rotation while in parallel bars with progression to anterior stepping on prosthesis side), relaxed upright posture with ambulation (ie, verbal cueing to keep chest upright), and resistive gait training with TheraBand and verbal cues for increased step length with intact limb	Demonstrates ability to trigger power with at least 80% accuracy during level ground ambulation and increased gait symmetry, including upright posture, step length, and toe break as determined through observational gait analysis
Mobility training	Ramp and stair negotiation	Hill Assessment Index score ≥6 (ie, step past more than half foot length, with assistive device)
Neuromuscular reeducation	Four-directional resistance exercise on intact side while maintaining single limb stance on prosthesis side, static single limb balance training on prosthesis side to be progressed to noncompliant surface (eg, foam), and progression of stepping exercises to increase time in single limb stand on the prosthesis	Able to maintain single limb stance on prosthesis side with or without an assistive device for 15 seconds
HEP	Includes therapeutic exercises in level 3	Independent in HEP

[a]N/A: not applicable.

[b]HEP: home exercise program.

Level 4 (Sessions 7 and 8)

At level 4 (Table 4), PT will include advanced neuromuscular reeducation and gait training, followed by a final PT evaluation.

Neuromuscular reeducation will include single limb squats in the parallel bars with upper extremity support, as needed. Gait training will continue resistive training on even surfaces, proprioceptive neuromuscular facilitation for pelvic rotation, verbal and tactile cueing for symmetrical and appropriate trunk rotation, and negotiation of uneven surfaces.

Individuals who do not meet the criteria to complete the PT program will be offered an additional 8 PT sessions after completion of the study.

Table 4. Level 4 device-specific physical therapy protocol.

Protocol	Description	Criteria for advancement
Level 4 (sessions 7 and 8)		
Evaluation	Re-evaluation at final session	N/A[a]
Strengthening	N/A	N/A
Stretching	To be used for cooldown at session completion	Independent in HEP[b]
Education	Importance of continuation of HEP	Verbalizes understanding
Gait training	Promoting gait initiation on prosthesis side with anterior pelvic rotation, manual techniques and verbal cues to promote increased trunk rotation and trunk rotation symmetry, verbal cueing for symmetrical arm swing and trunk rotation (eg, "relax your shoulders"), and resistive gait training with TheraBand and verbal cues for increased step length with the intact limb and relaxed upright posture	Demonstrates ability to trigger power with at least 90% accuracy for powered prosthetic foot and increased gait symmetry for trunk rotation and arm swing, as determined through observational gait analysis
Mobility training	Ascending and descending ramps and stairs	Stair Assessment Index score of at least 4 (with assistive device, step-to pattern) for ascending and descending stairs, and ambulates in the community without increased participant-reported stumbles or falls compared with baseline
Neuromuscular reeducation	Applied during HEP	Demonstrates increased gait symmetry for step length, push off, anterior pelvic rotation, upright posture, trunk rotation, and arm swing
HEP	Review HEP	Demonstrates independence in HEP

[a]N/A: not applicable.

[b]HEP: home exercise program.

Data Collection Visit 2

After completion of the device-specific PT program, all participants will undergo data collection on the powered ankle-foot prosthesis. The participants will repeat the quality-of-life assessment, subjective surveys, pain assessment, cognitive load assessment, biomechanical gait analysis, and functional measures using the powered ankle-foot prosthesis, as described in the baseline visit. Following visit 2, participants will keep the powered ankle-foot prosthesis for an additional 4 weeks of home use and community use but will not undergo any further device-specific training.

Data Collection Visit 3

After the final 4 weeks of powered ankle-foot prosthesis use, participants will undergo final data collection. Participants will repeat the quality-of-life assessment, subjective surveys, pain assessment, cognitive load measurements, neurocognitive assessment, biomechanical gait analysis, and functional measures, as described in the baseline visit. Following data collection, all participants will be refitted with their energy storing and returning ankle-foot devices, and the powered ankle-foot devices will be returned to the study staff.

Statistical Analysis

Across the study population, outcomes will be assessed with descriptive statistics and compared between each ankle-foot device category as well as by PT intervention (ie, device-specific PT and standard of care). Inferential statistics for ordinal data will be conducted with a repeated-measures Friedman test (α=.05) and a Dunn post hoc test at a 95% CI. To address which measures are the most sensitive to intervention type, a linear mixed-effects model will be used. Separate models will be used for each type of measure (pain, subjective, cognitive, neurocognitive, functional, and biomechanical), and measures that have a significant association with the intervention type in the presence of adjusting (control) variables will be determined. Pair-wise comparisons will be tested for significance using linear contrasts with a Tukey honestly significant difference or by applying a Bonferroni correction, where applicable. The following sections outline the specific analyses that will be performed for each study objective.

Planned Statistical Analysis for Biomechanical and Functional Outcomes

Although there are numerous biomechanical and physiological parameters that can be evaluated following gait analysis [61], this investigation will focus on the biomechanical parameters that are most relevant, commonly used, able to discriminate, and have specific clinical relevance for individuals with transfemoral limb loss. The primary biomechanical outcome measures will include measures of rollover shape, individual characteristics of the 3D ground reaction force, and ankle, knee, and hip joint angles, moments, and powers (on both the intact and affected limbs). To evaluate the load distribution of the medial and lateral knee compartments, the peak resultant ground reaction force, ground reaction force rate, peak knee external adduction moments, and knee external adduction moment rate will be compared between the baseline (passive energy storing and returning condition) and the powered condition at each follow-up visit.

Linear mixed-effects models will be used to identify statistically significant differences in gait temporal-spatial and biomechanical variables for all walking speeds. The fixed effects will be the average differences in gait biomechanical and temporal-spatial variables by prosthetic ankle type (powered vs passive). These models also estimate random effects because of differences in mean biomechanical variables across participants, as well as the random effects associated with minimized variability, as the participants will be tested with both prostheses. For example, a linear mixed-effects regression will be used to examine the relationship between the intact knee peak external adduction moment and the prosthetic ankle-foot condition. Peak intact knee external adduction moment will be the dependent variable, whereas ankle-foot condition will be the independent variable, and participant-by-ankle-foot condition will be modeled as random effects. Pair-wise comparisons will be tested for significance using linear contrasts with a Tukey honestly significant difference or by applying a Bonferroni correction, where applicable. In addition, linear mixed-effects regression will be used to determine the association between prosthetic peak ankle power and foot condition.

Planned Statistical Analysis for Pain Outcomes

The following parameters will be measured and statistically compared between baseline (energy storing and returning condition) and each follow-up visit with the powered ankle-foot prosthesis (weeks 4 and 8):

- Joint reaction forces on the lower back (L5 and S1) and contralateral (intact) knees
- PEQ pain scores
- Functional outcome measures (6MWT, AMPpro, and CHAMP)

Spearman correlations will be calculated to correlate data between pain and lower extremity kinematic and kinetic parameters of interest and pain and functional outcome values across the groups. Linear mixed-effects models will be used to identify statistically significant differences in pain scores and biomechanical variables listed in the previous section for all walking speeds. For example, a linear mixed-effects regression will be used to examine the relationship between peak reaction moments at L5 and S1 and pain for each prosthetic ankle-foot condition. Pair-wise comparisons will be tested for significance using linear contrasts with a Tukey honestly significant difference or by applying a Bonferroni correction, where applicable.

Multiple linear regression will be performed with PEQ pain as the dependent variable. Because of the large number of predictor variables in relation to the number of participants, penalized methods (eg, ridge regression or lasso) will be used to identify variables that contribute the most to the prediction model. Penalized methods add a tuning parameter to the regression model that shrinks the less important coefficients toward 0. Cross-validation will be used to select the best tuning parameter value [62]. The independent variables will be comprised of functional parameters (eg, peak joint reaction forces) and the condition (ankle-foot type and intervention).

Planned Statistical Analysis for Cognitive Load and Neurocognitive Outcomes

Linear mixed-effects models will be performed to examine the differences between the ankle-foot devices on cognitive performance, walking speed, and subjective responses to attention. The parameters in the linear effects model will include prosthetic ankle-foot type, PT intervention, and participants. Ankle-foot type, PT intervention, and cognitive performance will be treated as fixed effects, whereas participants will be treated as random. The total number of errors and the error rates for the cognitive task will be calculated, and the mean error rate will be determined for each cognitive task performed by each participant. Repeated-measures ANOVA will be used to compare the error rates for the 3 cognitive tasks. Fisher least significant difference test will be used to make post hoc comparisons.

For the neurocognitive battery, Pearson correlation coefficients (pair-wise 2-tailed) will be calculated for all variables of interest. Stepwise multiple regression will be performed with the neurocognitive scores (Neurocognitive Index, composite memory, cognitive flexibility, and complex attention scores) as the dependent variable. The independent variables will comprise functional outcomes, pain, and gait biomechanics, including asymmetry index.

Power Analysis and Sample Size Estimation

The sample size was based on a power analysis of 3 biomechanical measures (leading limb work, ground reaction force rate, and knee adduction moment rate) and 1 functional outcome (6MWT distance), and 1 subjective outcome (PEQ—utility) obtained from preliminary analyses, with all measurements obtained at baseline and 2 additional measurements over an 8-week period. The sample size was calculated for the group-by-time interaction, which tests the differences in change over time between the study groups. Assuming an α error rate of 5%, Table 5 presents the power achieved for each measurement for 30 participants, 15 (50%) in each group.

Table 5. Power analysis and sample size estimation.

Measure	Difference, mean (SD)	Power (N=30)
Leading limb work (J/kg)	0.03 (0.04)	85
Ground reaction force rate (N/kg/s)	15 (26.9)	82
Knee adduction moment rate (N m/kg/s)	1.1 (1.2)	98
6MWT[a] distance (m)	60 (61)	96
PEQ[b]—utility	8.4 (8.8)	96

[a]6MWT: 6-minute walk test.

[b]PEQ: Prosthesis Evaluation Questionnaire.

Results

This study was funded in September 2017, with enrollment beginning in September 2018. Data collection is expected to conclude by March 2024. Data analysis of the completed data set is expected to begin after final data collection. The initial dissemination of results is expected in August 2024, with subsequent publication of secondary analyses in December 2024.

Discussion

Expected Outcomes and Anticipated Principal Findings

After the completion of this research project, this investigation will have quantified the dependence of symmetrical lower limb gait biomechanics, physical function, and pain reduction on advanced prosthetic technology and device-specific rehabilitation. Furthermore, a device-specific treatment strategy designed to minimize impairments and maximize function will be evaluated. Finally, an objective measure of cognitive load and neurocognition to guide the prosthetic prescription of powered ankle-foot prostheses will be assessed. As such, the evidence-based outcomes obtained from this research investigation can be appropriately translated into clinical practice as well as drive the future of clinical care in this population.

VA provides care for veterans with limb loss of all generations, including the influx of service members with limb loss from the most recent conflicts [5]. Projected trends indicate that the overall number of individuals with limb loss will continue to increase dramatically, largely attributable to the aging population and the growing number of people with dysvascular disease and diabetes [1]. With this large population expected to grow, considerable resources will be required for rehabilitation and prosthetic services, driving limb loss care to become a high priority for VA. Effective outcomes-based clinical practice will be necessary to decrease long-term disabilities associated with prosthetic use and improve the quality of life. Therefore, it is the goal of this study to examine the effectiveness of a powered ankle-foot prosthesis and device-specific rehabilitation on gait biomechanics, performance, and pain in individuals with transfemoral limb loss. Results from this investigation will provide evidence-based outcomes that can be translated into successful strategies to minimize impairments and maximize function and may drive the evaluation of future advancements in prosthetic technology.

Dissemination Plan

The results of this investigation can help form evidence-based guidelines for individuals with transfemoral limb loss that can serve as a source for lower limb loss clinical practice guidelines. Dissemination of the results of this study within the DoD, VA, and the civilian health care systems will be performed in 3 ways. First, the results will be disseminated to the scientific and clinical community through traditional means, such as peer-reviewed submissions to professional conferences (eg, the Gait and Clinical Movement Analysis Society Annual Conference, the American Congress of Rehabilitation Medicine Annual Conference, and the Military Health System Research Symposium), targeted limb loss and rehabilitation publications (eg, *Archives of Physical Medicine and Rehabilitation*, *Gait & Posture*, and *Frontiers in Bioengineering and Biotechnology*), as well as sharing the data through large data repositories. Second, both VA and the DoD have national, interdisciplinary groups and committees that enable the national dissemination and adoption of best practices among different disciplines. For the VA and DoD limb loss care teams, the Extremity Trauma and Amputation Center of Excellence and the VA Amputation System of Care hold a bimonthly webinar series for clinicians, scientists, and researchers that is available across the entire DoD and VA health care network. This series allows research results to be presented to a large, diverse audience of researchers and health care professionals in limb loss care, which can directly influence the care provided to veterans and service members with limb loss. Finally, the outcomes will be disseminated directly to leaders in the prosthetics industry to provide real-world feedback on their products. The results provided to industry leaders can help in the evolution of lower extremity prosthetic components, which can then lead to improved devices for individuals with transfemoral limb loss.

Limitations

This investigation will not address the varied dosing, timing, frequency, and duration of the device-specific rehabilitation protocol. However, the frequency of PT visits and protocol timing will be evaluated for each participant, which can provide preliminary data for a future study to optimize the rehabilitation strategy. The heterogeneity of the sample population may also limit the generalizability of the outcomes to a more diverse population. In addition, the statistical analysis models will also adjust for specific parameters (eg, age, time since limb loss, and etiology of limb loss), which may limit the sample size and interpretability of the results. The type of microprocessor knee

used by each participant will not be prescribed and may be a confounding factor. This influence of the microprocessor knee type will be evaluated in the statistical models. Finally, a 4-week assessment following completion of the device-specific protocol may not be sufficient to evaluate any PT rebound effects or long-term changes in gait, specifically regarding the effectiveness of the acute PT intervention on gait biomechanics.

Acknowledgments

At Veterans Affairs New York Harbor Healthcare System, the authors would like to acknowledge Mr Michael Poppo for his assistance during data collection and processing; Mr Eric Baksh; Mr Kenneth Breuer; and Mr Eric Hubbs for their assistance in prosthesis fitting and alignment and Dr Cristina Parker, Dr Ellen Godwin, and Dr Jonathan Glasberg for conducting the rehabilitation program. At Walter Reed National Military Medical Center, the authors would like to acknowledge Mr Jonathan Gladish for his assistance during data collection and processing, Dr Ashley Knight for her assistance in project administration, and Dr Allison Symsack for helping develop the device-specific physical therapy program. At James A. Haley Veterans' Hospital, the authors would like to acknowledge Dr Meghan Kern and Dr Lisa Ballestrea for their assistance during data collection and participant training and Ms Anh Du for her assistance in prosthesis fitting and alignment. Finally, the authors would like to acknowledge the Narrows Institute for Biomedical Research and Education for their assistance in grant management. The Congressionally Directed Medical Research Programs, Orthotics, and Prosthetics Outcomes Research Program provided support (grant W81XWH-17-1-0568). This funding source had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Disclaimer

The views expressed in this paper are those of the authors and do not necessarily reflect the official policy of the departments of the Air Force, Army, Navy, Defense, Veterans Affairs, or the United States government. The identification of specific products or scientific instrumentation is considered an integral part of the scientific endeavor and does not constitute endorsement or implied endorsement on the part of the author, the Department of Veterans Affairs, the Department of Defense, or any component agency.

Data Availability

All data for this manuscript are included in this published paper. Final results will be available via a publicly available data repository.

Authors' Contributions

JTM, ALP, and LMN participated in conceptualization of the study. JTM, ALP, BDH, and CLD participated in methodology development. JTM, ALP, BDH, DVH, JMC, MJH, SLP, and ANS participated in data collection. JTM, ALP, BDH, DVH, JMC, MJH, SLP, ANS, CLD, and LMN participated in writing, editing, and review of the manuscript. JTM, BDH, MJH, and SLP participated in project administration. JTM, BDH, and SLP participated in supervision of the project and staff. JTM, ALP, CLD, and LMN participated in funding acquisition. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review summary statement.
[PDF File (Adobe PDF File), 121 KB - resprot_v13i1e53412_app1.pdf]

Multimedia Appendix 2
Peer-review response from the investigators.
[PDF File (Adobe PDF File), 126 KB - resprot_v13i1e53412_app2.pdf]

References

1. Ziegler-Graham K, MacKenzie EJ, Ephraim PL, Travison TG, Brookmeyer R. Estimating the prevalence of limb loss in the United States: 2005 to 2050. Arch Phys Med Rehabil 2008 Mar;89(3):422-429. [doi: 10.1016/j.apmr.2007.11.005] [Medline: 18295618]
2. Webster JB, Crunkhorn A, Sall J, Highsmith MJ, Pruziner A, Randolph BJ. Clinical practice guidelines for the rehabilitation of lower limb amputation. Am J Phys Med Rehabil 2019 May 13;98(9):820-829. [doi: 10.1097/phm.0000000000001213]

3. Fischer H. A guide to U.S. military casualty statistics: operation freedom's sentinel, operation inherent resolve, operation new dawn, operation Iraqi freedom, and operation enduring freedom. Congressional Research Service. 2015 Aug 7. URL: https://crsreports.congress.gov/product/details?prodcode=RS22452 [accessed 2023-04-18]
4. Farrokhi S, Perez K, Eskridge S, Clouser M. Major deployment-related amputations of lower and upper limbs, active and reserve components, U.S. Armed Forces, 2001-2017. MSMR 2018 Jul;25(7):10-16. [Medline: 30047274]
5. Healthcare inspection: prosthetic limb care in VA facilities. Department of Veterans Affairs Office of the Inspector General. 2012 Mar 8. URL: https://www.va.gov/oig/pubs/VAOIG-11-02138-116.pdf [accessed 2023-04-18]
6. Adams PF, Hendershot GE, Marano MA, Centers for Disease ControlPrevention/National Center for Health Statistics. Current estimates from the National Health Interview Survey, 1996. Vital Health Stat 10 1999 Oct(200):1-203 [FREE Full text] [Medline: 15782448]
7. Highsmith MJ, Kahle JT, Carey SL, Lura DJ, Dubey RV, Csavina KR, et al. Kinetic asymmetry in transfemoral amputees while performing sit to stand and stand to sit movements. Gait Posture 2011 May;34(1):86-91. [doi: 10.1016/j.gaitpost.2011.03.018] [Medline: 21524913]
8. Schaarschmidt M, Lipfert SW, Meier-Gratz C, Scholle HC, Seyfarth A. Functional gait asymmetry of unilateral transfemoral amputees. Hum Mov Sci 2012 Aug;31(4):907-917 [FREE Full text] [doi: 10.1016/j.humov.2011.09.004] [Medline: 22248566]
9. Hafner BJ, Smith DG. Differences in function and safety between Medicare Functional Classification Level-2 and -3 transfemoral amputees and influence of prosthetic knee joint control. J Rehabil Res Dev 2009;46(3):417-433 [FREE Full text] [Medline: 19675993]
10. Jaegers SM, Arendzen JH, de Jongh HJ. Prosthetic gait of unilateral transfemoral amputees: a kinematic study. Arch Phys Med Rehabil 1995 Aug;76(8):736-743. [doi: 10.1016/s0003-9993(95)80528-1] [Medline: 7632129]
11. Kaufman KR, Frittoli S, Frigo CA. Gait asymmetry of transfemoral amputees using mechanical and microprocessor-controlled prosthetic knees. Clin Biomech (Bristol, Avon) 2012 Jun;27(5):460-465 [FREE Full text] [doi: 10.1016/j.clinbiomech.2011.11.011] [Medline: 22221344]
12. Prinsen EC, Nederhand MJ, Rietman JS. Adaptation strategies of the lower extremities of patients with a transtibial or transfemoral amputation during level walking: a systematic review. Arch Phys Med Rehabil 2011 Aug;92(8):1311-1325. [doi: 10.1016/j.apmr.2011.01.017] [Medline: 21714957]
13. Bae TS, Choi K, Hong D, Mun M. Dynamic analysis of above-knee amputee gait. Clin Biomech (Bristol, Avon) 2007 Jun;22(5):557-566. [doi: 10.1016/j.clinbiomech.2006.12.009] [Medline: 17321021]
14. Seroussi RE, Gitter A, Czerniecki JM, Weaver K. Mechanical work adaptations of above-knee amputee ambulation. Arch Phys Med Rehabil 1996 Nov;77(11):1209-1214. [doi: 10.1016/s0003-9993(96)90151-3] [Medline: 8931539]
15. Nolan L, Wit A, Dudziñski K, Lees A, Lake M, Wychowañski M. Adjustments in gait symmetry with walking speed in trans-femoral and trans-tibial amputees. Gait Posture 2003 Apr;17(2):142-151. [doi: 10.1016/s0966-6362(02)00066-8] [Medline: 12633775]
16. Norvell DC, Czerniecki JM, Reiber GE, Maynard C, Pecoraro JA, Weiss NS. The prevalence of knee pain and symptomatic knee osteoarthritis among veteran traumatic amputees and nonamputees. Arch Phys Med Rehabil 2005 Mar;86(3):487-493. [doi: 10.1016/j.apmr.2004.04.034] [Medline: 15759233]
17. Struyf PA, van Heugten CM, Hitters MW, Smeets RJ. The prevalence of osteoarthritis of the intact hip and knee among traumatic leg amputees. Arch Phys Med Rehabil 2009 Mar;90(3):440-446. [doi: 10.1016/j.apmr.2008.08.220] [Medline: 19254609]
18. Mussman M, Altwerger W, Eisenstein J, Turturro A, Glockenberg A, Bubbers L. Contralateral lower extremity evaluation with a lower limb prosthesis. J Am Podiatry Assoc 1983 Jul;73(7):344-346. [doi: 10.7547/87507315-73-7-344] [Medline: 6875169]
19. Smith DG, Ehde DM, Legro MW, Reiber GE, del Aguila M, Boone DA. Phantom limb, residual limb, and back pain after lower extremity amputations. Clin Orthop Relat Res 1999 Apr;361(361):29-38. [doi: 10.1097/00003086-199904000-00005] [Medline: 10212593]
20. Segal AD, Zelik KE, Klute GK, Morgenroth DC, Hahn ME, Orendurff MS, et al. The effects of a controlled energy storage and return prototype prosthetic foot on transtibial amputee ambulation. Hum Mov Sci 2012 Aug;31(4):918-931 [FREE Full text] [doi: 10.1016/j.humov.2011.08.005] [Medline: 22100728]
21. Verrelst B, Van Ham R, Vanderborght B, Lefeber D, Daerden F, Van Damme M. Second generation pleated pneumatic artificial muscle and its robotic applications. Adv Robot 2012 Apr 02;20(7):783-805. [doi: 10.1163/156855306777681357]
22. Vanderborght B, Albu-Schaeffer A, Bicchi A, Burdet E, Caldwell DG, Carloni R, et al. Variable impedance actuators: a review. Robot Auton Syst 2013 Dec;61(12):1601-1614. [doi: 10.1016/j.robot.2013.06.009]
23. Versluys R, Lenaerts G, Van Damme M, Jonkers I, Desomer A, Vanderborght B, et al. Successful preliminary walking experiments on a transtibial amputee fitted with a powered prosthesis. Prosthet Orthot Int 2009 Dec;33(4):368-377. [doi: 10.3109/03093640902984587] [Medline: 19947821]
24. Sup F, Bohara A, Goldfarb M. Design and control of a powered transfemoral prosthesis. Int J Rob Res 2008 Mar 01;27(2):263-273 [FREE Full text] [doi: 10.1177/0278364907084588] [Medline: 19898683]
25. Sup F, Varol HA, Mitchell J, Withrow TJ, Goldfarb M. Preliminary evaluations of a self-contained anthropomorphic transfemoral prosthesis. IEEE/ASME Trans Mechatron 2009 Dec;14(6):667-676. [doi: 10.1109/tmech.2009.2032688]

26. Sup F, Varol HA, Mitchell J, Withrow TJ, Goldfarb M. Self-contained powered knee and ankle prosthesis: initial evaluation on a transfemoral amputee. In: Proceedings of the IEEE International Conference on Rehabilitation Robotics. 2009 Presented at: IEEE International Conference on Rehabilitation Robotics; June 23-26, 2009; Kyoto, Japan. [doi: 10.1109/icorr.2009.5209625]
27. Tran M, Gabert L, Hood S, Lenzi T. A lightweight robotic leg prosthesis replicating the biomechanics of the knee, ankle, and toe joint. Sci Robot 2022 Nov 23;7(72):eabo3996 [FREE Full text] [doi: 10.1126/scirobotics.abo3996] [Medline: 36417500]
28. Au SK, Herr H, Weber J, Martinez-Villalpando EC. Powered ankle-foot prosthesis for the improvement of amputee ambulation. In: Proceedings of the 29th Annual International Conference of the IEEE Engineering in Medicine and Biology Society. 2007 Presented at: 29th Annual International Conference of the IEEE Engineering in Medicine and Biology Society; August 22-26, 2007; Lyon, France. [doi: 10.1109/iembs.2007.4352965]
29. Au S, Berniker M, Herr H. Powered ankle-foot prosthesis to assist level-ground and stair-descent gaits. Neural Netw 2008 May;21(4):654-666. [doi: 10.1016/j.neunet.2008.03.006] [Medline: 18499394]
30. Ferris AE, Aldridge JM, Rábago CA, Wilken JM. Evaluation of a powered ankle-foot prosthetic system during walking. Arch Phys Med Rehabil 2012 Nov;93(11):1911-1918. [doi: 10.1016/j.apmr.2012.06.009] [Medline: 22732369]
31. Grabowski AM, D'Andrea S. Effects of a powered ankle-foot prosthesis on kinetic loading of the unaffected leg during level-ground walking. J Neuroeng Rehabil 2013 Jun 07;10(1):49 [FREE Full text] [doi: 10.1186/1743-0003-10-49] [Medline: 23758860]
32. Russell Esposito E, Aldridge Whitehead JM, Wilken JM. Step-to-step transition work during level and inclined walking using passive and powered ankle-foot prostheses. Prosthet Orthot Int 2016 Jun;40(3):311-319. [doi: 10.1177/0309364614564021] [Medline: 25628378]
33. Herr HM, Grabowski AM. Bionic ankle-foot prosthesis normalizes walking gait for persons with leg amputation. Proc Biol Sci 2012 Mar 07;279(1728):457-464 [FREE Full text] [doi: 10.1098/rspb.2011.1194] [Medline: 21752817]
34. Gailey RS, Gaunaurd I, Agrawal V, Finnieston A, O'Toole C, Tolchin R. Application of self-report and performance-based outcome measures to determine functional differences between four categories of prosthetic feet. J Rehabil Res Dev 2012;49(4):597-612 [FREE Full text] [doi: 10.1682/jrrd.2011.04.0077] [Medline: 22773262]
35. Yiğiter K, Sener G, Erbahçeci F, Bayar K, Ulger OG, Akdoğan S. A comparison of traditional prosthetic training versus proprioceptive neuromuscular facilitation resistive gait training with trans-femoral amputees. Prosthet Orthot Int 2002 Dec;26(3):213-217. [doi: 10.1080/03093640208726650] [Medline: 12562068]
36. Sjödahl C, Jarnlo GB, Söderberg B, Persson BM. Kinematic and kinetic gait analysis in the sagittal plane of trans-femoral amputees before and after special gait re-education. Prosthet Orthot Int 2002 Aug;26(2):101-112. [doi: 10.1080/03093640208726632] [Medline: 12227444]
37. Darter BJ, Wilken JM. Gait training with virtual reality-based real-time feedback: improving gait performance following transfemoral amputation. Phys Ther 2011 Sep;91(9):1385-1394. [doi: 10.2522/ptj.20100360] [Medline: 21757579]
38. Agrawal V, Gailey R, O'Toole C, Gaunaurd I, Dowell T. Symmetry in external work (SEW): a novel method of quantifying gait differences between prosthetic feet. Prosthet Orthot Int 2009 Jun;33(2):148-156. [doi: 10.1080/03093640902777254] [Medline: 19367518]
39. Agrawal V, Gailey RS, Gaunaurd IA, O'Toole C, Finnieston AA. Comparison between microprocessor-controlled ankle/foot and conventional prosthetic feet during stair negotiation in people with unilateral transtibial amputation. J Rehabil Res Dev 2013;50(7):941-950. [doi: 10.1682/jrrd.2012.05.0093]
40. Agrawal V, Gailey R, O'Toole C, Gaunaurd I, Finnieston A. Influence of gait training and prosthetic foot category on external work symmetry during unilateral transtibial amputee gait. Prosthet Orthot Int 2013 Oct;37(5):396-403. [doi: 10.1177/0309364612473501] [Medline: 23364890]
41. Legro MW, Reiber GD, Smith DG, del Aguila M, Larsen J, Boone D. Prosthesis evaluation questionnaire for persons with lower limb amputations: assessing prosthesis-related quality of life. Arch Phys Med Rehabil 1998 Aug;79(8):931-938. [doi: 10.1016/s0003-9993(98)90090-9] [Medline: 9710165]
42. Kahle JT, Highsmith MJ, Hubbard SL. Comparison of nonmicroprocessor knee mechanism versus C-Leg on Prosthesis Evaluation Questionnaire, stumbles, falls, walking tests, stair descent, and knee preference. J Rehabil Res Dev 2008 Dec 01;45(1):1-14 [FREE Full text] [doi: 10.1682/jrrd.2007.04.0054] [Medline: 18566922]
43. Revicki DA, Chen WH, Harnam N, Cook KF, Amtmann D, Callahan LF, et al. Development and psychometric analysis of the PROMIS pain behavior item bank. Pain 2009 Nov;146(1-2):158-169 [FREE Full text] [doi: 10.1016/j.pain.2009.07.029] [Medline: 19683873]
44. O'Neill BF, Evans JJ. Memory and executive function predict mobility rehabilitation outcome after lower-limb amputation. Disabil Rehabil 2009 Jul 21;31(13):1083-1091. [doi: 10.1080/09638280802509579] [Medline: 19280435]
45. Waldstein SR, Tankard CF, Maier KJ, Pelletier JR, Snow J, Gardner AW, et al. Peripheral arterial disease and cognitive function. Psychosom Med 2003;65(5):757-763. [doi: 10.1097/01.psy.0000088581.09495.5e] [Medline: 14508017]
46. Strachan MW, Deary IJ, Ewing FM, Frier BM. Is type II diabetes associated with an increased risk of cognitive dysfunction? A critical review of published studies. Diabetes Care 1997 Mar;20(3):438-445. [doi: 10.2337/diacare.20.3.438] [Medline: 9051402]

47. Coffey L, O'Keeffe F, Gallagher P, Desmond D, Lombard-Vance R. Cognitive functioning in persons with lower limb amputations: a review. Disabil Rehabil 2012 Mar 30;34(23):1950-1964. [doi: 10.3109/09638288.2012.667190] [Medline: 22458350]
48. Pellecchia GL. Postural sway increases with attentional demands of concurrent cognitive task. Gait Posture 2003 Aug;18(1):29-34. [doi: 10.1016/s0966-6362(02)00138-8] [Medline: 12855298]
49. Loonstra AS, Tarlow AR, Sellers AH. COWAT metanorms across age, education, and gender. Appl Neuropsychol 2010 Jun 07;8(3):161-166. [doi: 10.1207/s15324826an0803_5]
50. Lezak MD. Neuropsychological Assessment. New York, NY: Oxford University Press; 1995.
51. Gualtieri CT, Johnson LG. Reliability and validity of a computerized neurocognitive test battery, CNS Vital Signs. Arch Clin Neuropsychol 2006 Oct;21(7):623-643. [doi: 10.1016/j.acn.2006.05.007] [Medline: 17014981]
52. Kaufman K, Miller E, Kingsbury T, Russell Esposito E, Wolf E, Wilken J, et al. Reliability of 3D gait data across multiple laboratories. Gait Posture 2016 Sep;49:375-381. [doi: 10.1016/j.gaitpost.2016.07.075] [Medline: 27497755]
53. Maikos JT, Hendershot BD, Pruziner AL, Hyre MJ, Chomack JM, Phillips SL, et al. Criteria for advanced prosthetic foot prescription: rationale, design, and protocol for a multisite, randomized controlled trial. JMIR Res Protoc 2023 Apr 04;12:e45612 [FREE Full text] [doi: 10.2196/45612] [Medline: 37014672]
54. Lathrop RL, Chaudhari AM, Siston RA. Comparative assessment of bone pose estimation using point cluster technique and OpenSim. J Biomech Eng 2011 Nov;133(11):114503. [doi: 10.1115/1.4005409] [Medline: 22168744]
55. Schwartz MH, Rozumalski A. A new method for estimating joint parameters from motion data. J Biomech 2005 Jan;38(1):107-116. [doi: 10.1016/j.jbiomech.2004.03.009] [Medline: 15519345]
56. Wu G, Siegler S, Allard P, Kirtley C, Leardini A, Rosenbaum D, et al. ISB recommendation on definitions of joint coordinate system of various joints for the reporting of human joint motion--part I: ankle, hip, and spine. International Society of Biomechanics. J Biomech 2002 Apr;35(4):543-548. [doi: 10.1016/s0021-9290(01)00222-6] [Medline: 11934426]
57. Wu G, van der Helm FC, Veeger HE, Makhsous M, Van Roy P, Anglin C, et al. ISB recommendation on definitions of joint coordinate systems of various joints for the reporting of human joint motion--part II: shoulder, elbow, wrist and hand. J Biomech 2005 May;38(5):981-992. [doi: 10.1016/j.jbiomech.2004.05.042] [Medline: 15844264]
58. Brooks D, Hunter JP, Parsons J, Livsey E, Quirt J, Devlin M. Reliability of the two-minute walk test in individuals with transtibial amputation. Arch Phys Med Rehabil 2002 Nov;83(11):1562-1565. [doi: 10.1053/apmr.2002.34600] [Medline: 12422326]
59. Gailey RS, Roach KE, Applegate EB, Cho B, Cunniffe B, Licht S, et al. The amputee mobility predictor: an instrument to assess determinants of the lower-limb amputee's ability to ambulate. Arch Phys Med Rehabil 2002 May;83(5):613-627. [doi: 10.1053/apmr.2002.32309] [Medline: 11994800]
60. Gailey RS, Scoville C, Gaunaurd IA, Raya MA, Linberg AA, Stoneman PD, et al. Construct validity of Comprehensive High-Level Activity Mobility Predictor (CHAMP) for male servicemembers with traumatic lower-limb loss. J Rehabil Res Dev 2013;50(7):919-930. [doi: 10.1682/jrrd.2012.05.0100]
61. Sagawa YJ, Turcot K, Armand S, Thevenon A, Vuillerme N, Watelain E. Biomechanics and physiological parameters during gait in lower-limb amputees: a systematic review. Gait & Posture 2011 Apr;33(4):511-526. [doi: 10.1016/j.gaitpost.2011.02.003] [Medline: 21392998]
62. Tibshirani R. Regression shrinkage and selection via the lasso. J R Stat Soc Series B Stat Methodol 2018 Dec 05;58(1):267-288. [doi: 10.1111/j.2517-6161.1996.tb02080.x]

Abbreviations

6MWT: 6-minute walk test
AMPpro: Amputee Mobility Predictor with prosthesis
CHAMP: Comprehensive High-Level Activity Mobility Predictor
DoD: Department of Defense
HEP: home exercise program
IRB: institutional review board
JAHVH: James A. Haley Veterans' Hospital
PEQ: Prosthesis Evaluation Questionnaire
PT: physical therapy
VA: Veterans Affairs
VANYHHS: Veterans Affairs New York Harbor Healthcare System
WRNMMC: Walter Reed National Military Medical Center

Edited by A Mavragani; submitted 06.10.23; this is a non–peer-reviewed article;accepted 10.12.23; published 26.01.24.

Please cite as:
Maikos JT, Pruziner AL, Hendershot BD, Herlihy DV, Chomack JM, Hyre MJ, Phillips SL, Sidiropoulos AN, Dearth CL, Nelson LM
Effects of a Powered Ankle-Foot Prosthesis and Physical Therapy on Function for Individuals With Transfemoral Limb Loss: Rationale, Design, and Protocol for a Multisite Clinical Trial
JMIR Res Protoc 2024;13:e53412
URL: https://www.researchprotocols.org/2024/1/e53412
doi:10.2196/53412
PMID:38277197

Protocol

Physical Activity Intervention for Urban Black Women With Asthma: Protocol for a Randomized Controlled Efficacy Study

Ellen Davis[1], MS; Elizabeth Townsend[1]; Aero Cavalier[1], BA; Yi-Fan Chen[2], PhD; Dameka Edwards-Hart[1]; Spyros Kitsiou[3], PhD; Wiktoria Kowalczyk[1], BS; Iliana Mansur[1], BA; Ebere Okpara[4], BPharm; Karen Powell[1], BS, MHA; Valerie G Press[5], MD; Toni Ramirez[1], BS; Deborah Salvo[6], PhD; Lisa K Sharp[7,8], BSN, MA, PhD; Brittani Wright[1], BS; Sharmilee Maria Nyenhuis[1], MD

[1]Section of Allergy and Immunology, Department of Pediatrics, University of Chicago, Chicago, IL, United States

[2]Center for Research on Health Care Data Center, Department of Medicine, University of Pittsburgh, Pittsburgh, PA, United States

[3]Department of Biomedical and Health Information Sciences, University of Illinois Chicago, Chicago, IL, United States

[4]Department of Pharmacy, Systems, Outcomes and Policy, University of Illinois Chicago, Chicago, IL, United States

[5]Section of General Internal Medicine, Department of Medicine, University of Chicago, Chicago, IL, United States

[6]People, Health and Place Lab, Department of Kinesiology and Health Educations, University of Texas Austin, Austin, TX, United States

[7]Department of Biobehavioral Nursing Science, University of Illinois Chicago, Chicago, IL, United States

[8]Office of Research Facilitation, College of Nursing, University of Illinois Chicago, Chicago, IL, United States

Corresponding Author:
Sharmilee Maria Nyenhuis, MD
Section of Allergy and Immunology
Department of Pediatrics
University of Chicago
5837 S Maryland Ave
Chicago, IL, 60637
United States
Phone: 1 7738347121
Email: snyenhuis@bsd.uchicago.edu

Abstract

Background: Black women experience a higher prevalence of poor asthma outcomes and physical inactivity than their White counterparts. Black women comprise a particularly vulnerable group of patients with asthma, with some of the highest rates of asthma in adults, high health care use (emergency department visits and hospitalizations), and the highest crude asthma mortality rate of all race or ethnicity groups. Despite recommendations to engage in regular physical activity, fewer than 15% of Black women meet the 2008 National Physical Activity Guidelines, the lowest of all racial subgroups of adults. Given the connection between physical inactivity and poor asthma outcomes, addressing physical activity among Black women with asthma is imperative.

Objective: This 2-arm randomized controlled trial aims to (1) determine the efficacy of a lifestyle walking intervention on asthma control compared to an education (control) group over 24 weeks, (2) examine the maintenance effects of the lifestyle walking intervention on asthma control at 48 weeks, (3) explore the behavioral mediators (eg, self-efficacy, social support, self-regulation, and daily physical activity levels) and contextual moderators (eg, baseline asthma severity, neighborhood environment, comorbid conditions, and social determinants of health) that contribute to treatment responsiveness, and (4) assess the reach and implementation potential of the intervention.

Methods: The proposed study (ACTION [A Lifestyle Physical Activity Intervention for Minority Women with Asthma]) delivers a 24-week lifestyle walking intervention designed for and by urban Black women with asthma. Participants (n=224) will be recruited through 2 urban health care systems that care for a diverse Black population. Patients will be randomized to one of two groups: (1) ACTION intervention (group sessions, physical activity self-monitoring—Fitbit, and text-based support for step goal setting) or (2) education control (an individual asthma education session and SMS text messages related to asthma education). Outcome assessments will take place at baseline, 12, 24, and 48 weeks. The primary outcome is a change in asthma control from baseline to week 24 as assessed by the asthma control questionnaire-6 (ACQ-6). Secondary outcomes include asthma-related quality of life, health care use, and asthma exacerbations and behavioral outcomes such as self-efficacy, self-regulation, social support, and physical activity.

Results: This study was funded by the National Institute of Minority Health Disparities in August 2022. We pilot-tested our recruitment and intervention procedures and began recruitment in April 2023, with the enrollment of our first participant in May 2023. The anticipated completion of the study is April 2027.

Conclusions: This study will deliver a new approach to physical activity interventions in Black women with asthma and help to provide guidance for addressing physical activity within this subgroup. This study will also provide a potential framework for future studies in minoritized populations with other disease conditions associated with low levels of physical activity.

Trial Registration: ClinicalTrials.gov NCT05726487; https://clinicaltrials.gov/study/NCT05726487

International Registered Report Identifier (IRRID): DERR1-10.2196/55700

(JMIR Res Protoc 2024;13:e55700) doi:10.2196/55700

KEYWORDS

asthma; physical activity; lifestyle; Black women

Introduction

Background

Asthma is a serious global health problem affecting about 358 million people worldwide [1]. Black women comprise a particularly vulnerable group of patients with asthma, with the highest rates of asthma among adults (11.4%), high health care use (emergency department visits and hospitalizations), and the highest crude asthma mortality rate of all racial or ethnic groups [2,3]. There are multiple factors that contribute to this increased morbidity and mortality including, high rates of exposure to environmental pollution, and limited access to quality health care [4]. Low levels of physical activity (PA) are associated with worse asthma outcomes including higher health care use, poorer lung function, lower asthma control, and decreased exercise capacity [2]. Despite recommendations to engage in regular PA, fewer than 15% of Black women meet the 2008 National Physical Activity Guidelines, the lowest of all adult subgroups [5,6]. Given the connection between physical inactivity and poor asthma outcomes, there is a critical need for interventions to address low rates of PA among Black women with asthma.

Lifestyle PA interventions, such as walking, have been shown to be an effective and sustainable way to engage in regular PA. Research shows that people living with asthma prefer low-intensity activities such as walking, which has a low propensity to cause asthma symptoms [7-9]. Yet, only 2 randomized controlled trials (RCTs) of lifestyle PA (walking) interventions have focused on adults with asthma [10,11]. One occurs in a supervised research or academic setting and the other in the community setting. While both studies found improvements in asthma outcomes (asthma quality of life or asthma control), they were conducted predominantly in White women, and neither assessed the maintenance of effects on asthma control.

Research testing strategies to encourage Black women with asthma to increase their PA is a nascent area of study. While asthma is a known barrier to PA participation due to exercise-induced bronchoconstriction, contextual factors influencing PA engagement among people with asthma have also been identified. This includes previous negative experiences with the disease such as frequent asthma exacerbations; marked limitations in daily living due to asthma; and the effect of extreme weather, pollen, or pollution on asthma [10,12-14]. This is in addition to the many PA barriers urban Black women face, such as social and culturally based preferences for hair and body type, neighborhood characteristics (safety and walkability), family or caregiver responsibilities, and lack of role models or social support [5,15,16].

A Lifestyle Physical Activity Intervention for Minority Women With Asthma

Culturally tailored lifestyle PA interventions among Black women without asthma are more effective and sustainable than more generalized interventions [17]. However, similar interventions have not been applied to PA interventions in asthma. Using a theory-informed approach, A Lifestyle Physical Activity Intervention for Minority Women With Asthma (ACTION), was developed as one of the first culturally tailored lifestyle PA interventions for Black women with asthma. Pilot work demonstrated the feasibility and acceptability of the intervention and yielded preliminary findings of improvement in asthma outcomes and moderate PA [18]. This study takes the next step to examine the efficacy of a lifestyle walking program designed for Black women with asthma.

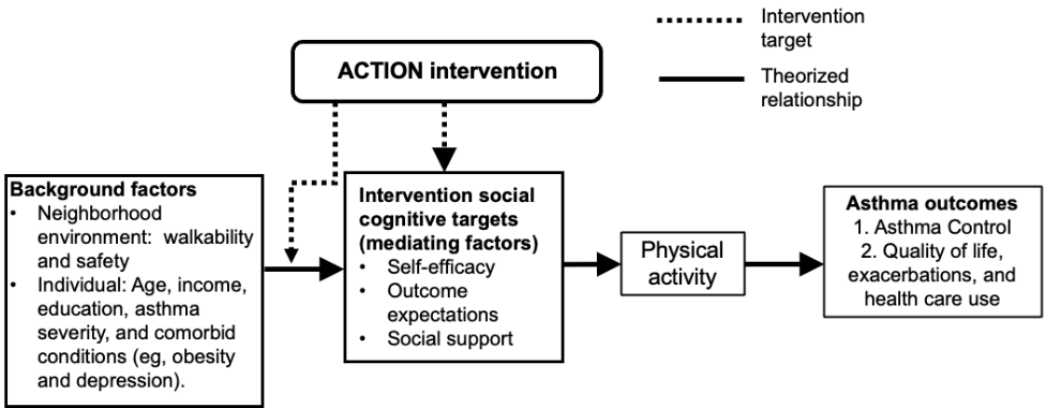
Conceptual Model

The conceptual model that guided this project is shown in Figure 1. Within the conceptual framework, explanatory relationships among various determinants of PA or factors that influence behavior, intervention strategies, and subsequent participant outcomes have been examined. Important contextual factors include individual demographics (age, income, and education), disease severity, comorbid conditions, and neighborhood environment. To explain motivation to become more physically active, the intrapersonal characteristics of self-efficacy (belief in one's ability to perform a behavior), social support, and self-regulation (the process of guiding one's own thoughts, behaviors, and feelings to reach goals) are used [19].

These intrapersonal characteristics can influence an intervention and thereby influence behavior change. The intervention is targeted to the characteristics of Black women with asthma, such as environmental safety factors, current health, and intrapersonal characteristics. The participant outcomes are those elements that are improved by exposure to the intervention, including PA and health outcomes. The framework specifies that participant outcomes are dynamically related; the greater

the tailoring of the intervention to the determinants of the behavior, the greater the likelihood of positive outcomes. Theoretical support for the core elements of the ACTION intervention is derived from social cognitive theory and augmented by self-regulation theory, which stems from social cognitive theory [19,20].

Figure 1. Conceptual framework. ACTION: A Lifestyle Physical Activity Intervention for Minority Women With Asthma.



Objectives and Aims

The proposed study has 3 aims involving a total of 224 sedentary urban Black women with asthma.

- Aim 1A is to determine the efficacy of ACTION intervention on asthma control. We will test the hypothesis that at 24 weeks, Black women with asthma who receive the intervention will have a greater improvement in asthma control (asthma control questionnaire [ACQ]) compared to women in the education control group (efficacy end point).
- Aim 1B is to examine the maintenance effects of the ACTION intervention on asthma control at 48 weeks. We will examine the long-term impact of the intervention on asthma control (eg, control and quality of life). We hypothesize the effects of ACTION on asthma outcomes will be maintained at 48 weeks.
- Aim 2 is to explore the behavioral mediators (eg, self-efficacy, social support, self-regulation, and daily PA levels) and contextual moderators (eg, baseline asthma severity, neighborhood environment, comorbid conditions, and social determinants of health) that contribute to treatment responsiveness. Mediation and moderation analyses will be performed with behavioral mediators and contextual moderators.
- Aim 3 is to assess the reach and implementation potential of ACTION. Reach will be measured by the number of potential participants (based on the recruitment pool) who are randomized into the study. Implementation potential will be measured using a mixed methods approach to identify important explanatory factors underlying the performance of the intervention components.

Methods

Project Overview

This study uses a theory-driven intervention (ACTION) to deliver a 24-week lifestyle PA intervention designed for and by urban Black women with asthma. Participants are recruited through 2 urban health care systems that care for a diverse urban Black population. Patients are randomized to one of two groups: (1) ACTION intervention (group sessions, PA self-monitoring, and text-based support for goal setting) or (2) education control (an individual asthma education session and text messages related to asthma education). Participants are followed for an additional 24 weeks after the intervention to assess for the maintenance of intervention effects on asthma health outcomes.

This efficacy study focuses on asthma outcomes, explores behavioral mechanisms of the intervention, and assesses factors that influence its reach and implementation potential.

Ethical Considerations

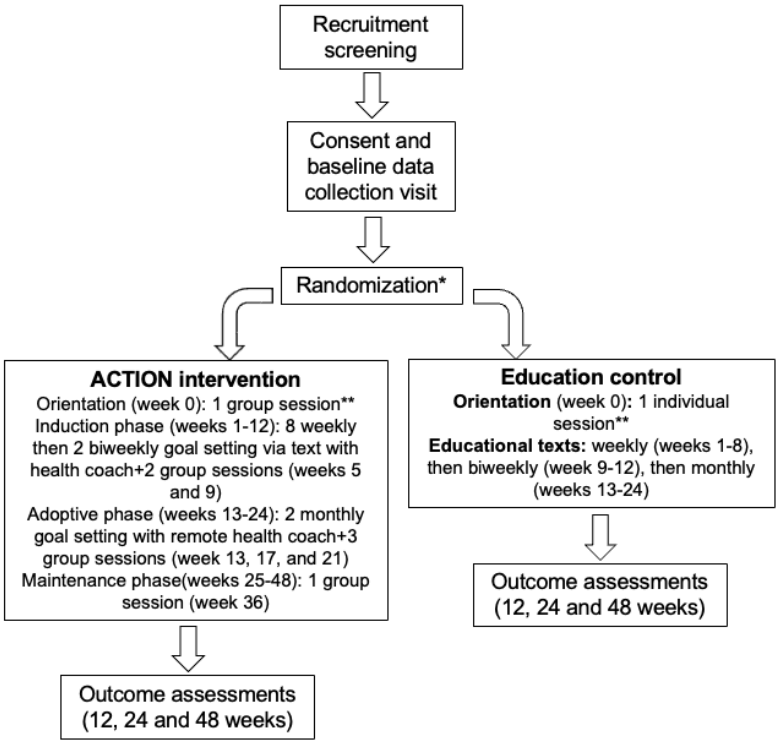
This study is conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines and approved by the relevant institutional review boards at the University of Chicago (22-0911). The University of Illinois Chicago and the University of Texas at Austin have ceded institutional review board reliance to the University of Chicago institutional review board. This study has been registered at ClinicalTrials.gov (NCT05726487).

Study Design

This is a 2-arm RCT enrolling participants at the University of Chicago and the University of Illinois at Chicago in which 224 Black women with asthma will be randomly assigned to an education control group or receive ACTION intervention for 24 weeks (Figure 2). The remaining 24 weeks is the maintenance phase, and participants in the intervention group will receive 1 booster group session at ~36 weeks. Assessments will occur at 0, 12, 24, and 48 weeks.

The primary efficacy end point is a change from baseline to week 24 asthma control as assessed by asthma control questionnaire-6. We hypothesize that ACTION will be superior to education control for improving asthma control by week 24. The 48-week time point is important for examining behavioral mediators, contextual moderators, and maintenance of intervention effects.

Figure 2. Study design. ACTION: A Lifestyle Physical Activity Intervention for Minority Women With Asthma. *Participant must return accelerometer and have adequate data (10 hours of data for 3 days or more) prior to randomization **Individual/Group sessions are in-person except group session 3 and 5 which are remote.



Participants and Eligibility

Recruitment

The primary recruitment strategy uses electronic health records to identify patients who meet the basic inclusion criteria: age≥18 years old, female, Black or African American, International Statistical Classification of Diseases, 10th Revision (ICD-10) diagnosis of asthma, and no ICD-10 diagnosis of chronic obstructive pulmonary disease (Textbox 1). An electronic health record data of patients meeting these criteria is obtained for each respective institution. Patient registries, in-clinic referrals, and flyers are also used as recruitment methods. Emails, SMS text messages, and postcards containing information about the study and a link to the eligibility screening survey are sent to randomly selected batches of potential participants.

Textbox 1. Inclusion and exclusion criteria for the study.

Inclusion criteria

- Self-identify as female and Black or African American
- Age≥18 years
- Physician diagnosed asthma that is suboptimally controlled based on Asthma Control Test (<20) or history in the past year of an asthma exacerbation (a need for systemic corticosteroids or hospital admission or emergency treatment for worsening asthma)
- Willing to enroll and provide written informed consent
- Willing to be randomized to 1 of the 2 study arms
- Has a smartphone or tablet with unlimited texting capabilities and uses text messaging at least daily

Exclusion criteria

- Plans to move from the Chicagoland area during the study period
- Unable to ambulate without the use of a wheelchair or scooter
- Currently pregnant, less than 3 months postpartum, or pregnancy anticipated during the study
- Significant medical (eg, unstable heart disease, uncontrolled high blood pressure, active cancer treatment in the past 1 year, and end-stage organ failure) or psychiatric (eg, active bipolar disorder and psychosis) comorbidities
- Diagnosis of chronic obstructive pulmonary disease (emphysema or chronic bronchitis) suggested by patient report of doctor diagnosis or smoking history (≥20 pack year history)
- A contraindication to exercise as indicated by the exercise assessment and screening tool unless written permission by a health care provider
- Participation in another structured physical activity program
- Asthma exacerbation, defined by an urgent care visit for asthma in the last 4 weeks, or the need for an acute course of systemic corticosteroids for asthma in the last 4 weeks
- Family or household member of another participant or staff member
- Inability to speak, read, or understand English
- Investigator discretion for safety or protocol adherence reasons

Eligibility Screening

Potential participants can self-screen using a REDCap (Research Electronic Data Capture; Vanderbilt University) eligibility screening form. This screener is accessed by scanning a QR code on this study's flyers and postcards or through a link that may be emailed or texted to potential participants. This survey is also verbally administered by the study staff over the phone.

If potential participants are immediately eligible, they are asked to schedule their baseline visit. Those who do not immediately meet the eligibility criteria or need medical clearance will be contacted by the study staff.

Baseline Assessment, Randomization, and Blinding

The baseline visit begins with the informed consent process facilitated by study staff. Participants are asked to complete study surveys (patient demographics, asthma demographics, Asthma Control Questionnaire, Asthma-related Quality of Life Questionnaire, Asthma Safety Measures, Adult Asthma Adherence Questionnaire, Patient Health Questionnaire Depression Scale Scored, PROMIS SF v 1.0-Sleep Disturb, SDQ-SA, PWMAQ, Exercise Self-Regulation, Self-efficacy for Walking Scale, Social Support for Walking Scale, Social Support and Exercise Survey, Active Where); baseline spirometry [21] and anthropometrics are obtained by trained study staff. Participants at 1 site are also asked to wear an accelerometer for 7 days.

Eligible participants will be randomized following recruitment and of all baseline measures, using stratified randomization in REDCap at each site after baseline data collection is complete. Stratification will be based on age (18-45 and 46+ years) and current BMI (≤25 and >25 kg/m^2). Blinding of participants is not feasible for this study. Participant's health care providers are blinded to group allocation.

Intervention

Overview

ACTION is a behavioral lifestyle intervention that promotes lifestyle PA in accordance with the current PA guidelines in the United States [17]. This intervention is a 24-week group lifestyle PA intervention consisting of 7 group sessions, PA self-monitoring, and text-based support for goal setting. The active period of the intervention is 24 weeks. Trained interventionists and remote health coaches deliver the intervention via a combination of in-person group walking sessions and text-based goal setting. Trained research staff provide a Fitbit for the participant and deliver the text messaging component of the intervention.

Group Sessions

Session 1

Participants attend an in-person or Health Insurance Portability and Accountability Act (HIPAA)–compliant audio or video

platform (eg, Zoom) group session on "Becoming Physically Active with Asthma." The group session includes a 45-minute asthma education session, based on the American Lung Association's Asthma Basics course, led by a Black, female asthma educator. Participants in the intervention group are given a manual with educational materials, which include information on increasing PA with asthma. Following the education content, each intervention group participant receives a Fitbit Charge 5 for self-monitoring of steps and heart rate. Specific step-by-step instructions on setup and use of the Fitbit monitor are provided with individual support as needed in the group setting. The study team reviews Specific Measurable Attainable Relevant and Time bound (SMART) goal setting [22], assesses text preferences, and sets individualized step goals based on their baseline PA levels.

Sessions 2-7

Women attend a 2-hour, in-person, or video remote group meeting at a convenient time during the induction or adoptive phases (weeks 0-24) and once during the maintenance phase (weeks 25-48). Participants from the individual sites are kept separate and do not attend group sessions together. Group session content is described in Textbox 2.

After 24 weeks of active intervention, participants randomized to ACTION no longer receive remote health coach text messages and attend monthly group sessions. A booster group session at 36 weeks will occur for the intervention group only.

Textbox 2. Content of ACTION (A Lifestyle Physical Activity Intervention for Minority Women With Asthma) group sessions.

Session 1 (week 0)

- Safely exercising with asthma: "Becoming Physically Active with Asthma"
- Receive Fitbit and discuss setting step goals

Sessions 2-7 (weeks 5,9,13, 17, 21, and 36)

- Video (10 minutes) on physical activity topics (eg, identifying realistic expectations for PA outcomes with asthma, handling personal and environmental problems that interfere with physical activity, and handling relapses)
- Group discussion and problem-solving (45 minutes)
- Group stretching and walking (20 minutes)

PA Tracking as an Intervention Component

Each intervention participant is given a Fitbit Charge 5 that counts steps per day, distance, active minutes (time spent in moderate to vigorous activity), sedentary time, and heart rate. Participants work with health coaches (as above) to set their step goals and monitor their PA on the Fitbit App. Participants are required to download the Fitbit app on their phone or tablet. The Fitbit mobile app and device require the creation of individual digital accounts with Google for all study participants. During the study, participants will use their study-created Google account to interact with the features of the Fitbit mobile app. Upon completion of the program, participants will be able to transfer their Fitbit device to an account using their personal Google login for continued use of the device.

Fitbit data are managed through iCardia. The iCardia platform [23] is used to remotely collect real-time PA data from study participants' Fitbit app and to send personalized SMS text messages to participants' cell phones (Figure 3). iCardia (University of Illinois at Chicago) is a secure password-protected system that comprises user-friendly visualization and data exportation tools, allowing key research personnel to view participants' Fitbit data in the form of graphs every time participants sync their wearable tracker with the Fitbit mobile app. Study participants do not have access to iCardia; they will only interact with the Fitbit mobile app and activity tracker. The SMS text messaging feature is integrated with the iCardia clinical dashboard and uses Twilio's application programming interface to send messages via the SMS protocol.

Figure 3. Screenshot of the iCardia platform.

Remote Health Coach and Individualized Step Goal Setting and Tracking

Study participants will work with the health coach through texts to set a SMART goal [22]. This will begin within 1 week of the completion of session 1. The process includes contingency planning (what if…). Goals will be set once a week for 8 weeks, every 2 weeks for weeks 9-12 sessions, and monthly through 24 weeks. We have set a realistic PA goal for intervention participants of 3000 steps per day of moderate intensity above each participant's baseline (based on Fitbit-based step counts per day), recognizing that baseline levels of activity will vary across individuals. Thirty minutes of walking at moderate intensity produces an estimated average of 3000 steps in most free-living adults [24]. Health coach texting will be managed through iCardia (described above). Health coaches can monitor Fitbit steps to evaluate goal attainment and send texts to support self-regulation via the text messaging protocol. The Fitbit data collected in iCardia will be used to generate process indicators but not as the primary measure to assess changes in health-enhancing PA (moderate to vigorous intensity physical activity [MVPA]). Health coaches will be sensitive to health status that may impact the ability to escalate steps. Weekly meetings will be conducted with health coaches to ensure texts are following the SMART goal framework and discuss any safety issues or questions.

Education Control Group

The education control group will receive (1) 1 group asthma education session similar to session 1 described above and (2) text messages with asthma facts and tips (see Table S1 in Multimedia Appendix 1). The asthma education session consists of a 45-minute video on basic asthma education based on American Lung Association's asthma basics content followed by a live Q&A with an asthma educator. The video was culturally tailored using feedback from stakeholders and includes a Black female asthma educator and other Black women with asthma. The SMS text messages with asthma facts and tips were also developed using feedback from stakeholders and will be delivered twice weekly (weeks 1-8), biweekly (weeks 9-12), and monthly (weeks 13-24). At the completion of the study, participants in the education control group will receive the study manual, a pedometer, and access to the videos presented in the ACTION intervention group sessions.

Measures

Asthma Measures

Asthma control will be measured using the validated ACQ [25]. Asthma quality of life will be measured using the mini-asthma quality of life measure, a well-validated survey [26]. Asthma exacerbation will be defined as the need for systemic corticosteroids, hospital admission, or emergency treatment for worsening asthma. This will be self-reported, and the time frame will be captured at 3- and 6-month time frames (Table S2 in Multimedia Appendix 2). Health care use is defined as the number of urgent care or emergency room or hospitalization visits. This will be self-reported, and the time frame will be in 3- and 6-month time frames (Table S2 in Multimedia Appendix 2). Spirometry will be performed using standard procedures at baseline, 24, and 48 weeks. Asthma severity will be assessed per the National Heart Lung and Blood Institute National Guidelines for Asthma management based on current asthma treatment [27].

PA Measures

Given that the intervention centers on increasing PA levels through walking, it is important to accurately assess the changes in health-enhancing PA among intervention and control participants throughout the study period. Health-enhancing PA

is defined as having MVPA and can occur in the domains of discretionary time, travel, home, or work [17]. Our intervention focuses on increasing overall MVPA levels by adding time spent in moderate-intensity PA during discretionary time, through walking. We will measure domain-specific PA through self-reported data for the full sample. We will also measure PA objectively in half of the sample, as this is a more cost-prohibitive assessment instrument.

Accelerometry

MVPA (minutes per day) at baseline (before randomization), 12, 24, and 48 weeks will be assessed objectively using accelerometry. During each assessment period, accelerometer data will be collected over 7 consecutive days using the ActiGraph wGT3X-BT activity monitor (ActiGraph, LLC), a small, triaxial piezoelectric accelerometer (4.6 cm×3.3 cm×1.5 cm; 19 g) that will be worn around the waist on an elastic belt. Accelerometry data will be collected using a standardized protocol. ActiGraph monitors have been extensively validated in laboratory and free-living conditions [28]. At the first data collection appointment, study staff will introduce the accelerometer and provide participants with verbal instructions and a package that includes (1) an initialized accelerometer, (2) detailed written wear instructions, (3) tracking log, (4) contact information, and (5) a padded prepaid trackable envelope to return the devices after concluding the 7-day wear period.

In the tracking log, participants will enter the (1) time they put the monitor on in the morning, (2) time removed it in the evening, and (3) time that the monitor was removed and replaced for ≥30 minutes throughout the day (eg, bathing or swimming activities). Raw triaxial data will be sampled at 40 Hz for 7 consecutive days. Once the accelerometer and tracking log are returned by the participant, data will be downloaded by the study staff and prepared for processing and analysis. Data will be processed using ActiLife software (ActiGraph) through a digitally matched filter, reintegrated up to a 60-s epoch, and screened for wear time using the Choi algorithm [29]. Weekly summary accelerometer estimates will be averaged (across days) for all participants with ≥4 valid days of ≥10 hours per day of wear time (minimum wear time to consider the data valid for analysis). If insufficient wear time is detected, the participant will be contacted and asked to rewear the device to provide valid data. Average accelerometer counts (per minute per day) will be calculated using summed daily counts detected over wear periods, and vector magnitude will be calculated as the square root of the sum of the squares obtained from each axis (ie, 3) of data. Time (ie, minutes per day) spent sedentary and in light-, moderate-, and vigorous-intensity physical will be estimated using Freedson cut points (for adults) based on triaxial data [30]. Data checks, including a descriptive analysis of the accelerometer estimates, will be performed quarterly.

Self-Reported Discretionary Time and Travel-Based PA

Self-report data adds rich context that accelerometers lack [31]. Our self-report measures will provide information on the domain (eg, recreational and transportation) of PA. These data will be important to quantify the effect of the intervention in increasing leisure-time walking (its main intention), as well as any potential unintended consequence in increasing or decreasing time spent on other types of activities. Participants will self-report PA using the Past Week Modifiable Activity Questionnaire (PWMAQ). The Modifiable Activity Questionnaire is a self-report instrument that assesses leisure PAs over the past 7 days [32,33]. The structure of the PWMAQ is similar to the Modifiable Activity Questionnaire and includes questions that quantify occupational activity (eg, sedentary, low, and high active occupations), active transport, and common sedentary behaviors. The PWMAQ includes information on 38 leisure-time PAs common among diverse adults. The PWMAQ has been shown to be a reliable and valid measure of PA compared to accelerometry and physical fitness [34,35].

Additional PA-Related Measures

Self-efficacy for walking, social support for exercise, and self-regulation will also be assessed as they constitute behavioral mediators for attaining increased PA levels, and the physiologic response to increases in PA, respectively. Details on these measures can be found in Table S3 in Multimedia Appendix 3.

Contextual Moderators

Contextual moderators will be collected at the in-person baseline data collection visit. The neighborhood environment will be assessed using a validated survey about neighborhood safety, crime, and areas to engage in PA [36]. Social determinants of health, including age, income, education level, marital status, and economic hardship will be assessed using validated questions that the principal investigator has used in prior studies. These have been chosen as they can impact PA levels [37,38]. The comorbid conditions of interest are obesity and depression as they are known to moderate PA levels and asthma outcomes [39,40]. Obesity is defined as a BMI ≥30 kg/m^2, and depression will be assessed by a validated depression questionnaire, Patient Health Questionnaire Depression Scale-8 [41].

Implementation Measures

We propose an explanatory sequential mixed methods design in which quantitative analyses are followed by qualitative analyses to maximize our understanding of the implementation of ACTION [42,43]. The quantitative data will include detailed process metrics and surveys, and qualitative data will include brief interviews with participants. Process metrics will be collected based on the number of participants screened and randomized. Surveys to assess the acceptability of the intervention components will be collected at the end of each group session and at the end of the intervention (after group session 6). Evaluations of the intervention will be conducted using open-ended questions with intervention participants at 24- and 48-week data collection visits. Questions will focus on aspects of the intervention they found helpful, barriers to engagement in each component of the intervention (eg, groups, remote health coach, and Fitbit), and suggestions for improvement. General prompts will be used to orient qualitative data descriptively on the core intervention components. The qualitative portion of the intervention will be conducted by trained and experienced data collectors at the end of the brief quantitative data collection, audio-recorded, and professionally transcribed.

Data Analysis Plan

Data will be analyzed based on the intent-to-treat principle in this multisite RCT. We will use descriptive statistics to describe the sample by intervention group, and any assumption behind each statistical method will be examined during the analysis. Missing data will be handled by each model's assumption or by using multiple imputation with a fully conditional specification approach, as appropriate [44]. A 2-sided *P* value less than .05 would be considered statistically significant, and the exact *P* value will be reported. All quantitative analyses will be conducted by using SAS (version 9.4; SAS Institute Inc) and R (version 4.0.2; R Core Team).

The primary research outcome for aim 1A is the differences in ACQ score between baseline and 24 weeks for aim 1A and between baseline and 48 weeks for aim 1B. This will be compared between education control and ACTION intervention groups first using 2 sample *t* test to examine the efficacy and the maintenance effect of the proposed intervention, respectively. Two-tailed statistical tests will be conducted throughout the entire analysis unless specified otherwise. A linear mixed model with a subject-level random intercept then will be built on the same outcome in its original scale having time (12 weeks vs baseline; 24 weeks vs baseline; 48 weeks vs baseline), group (ACTION vs education control), and their interaction as the main factors while adjusting for site, recruitment wave, and any imbalanced confounder [45]. This model will allow us to estimate the efficacy of the intervention through the interaction terms after controlling for confounders and subject dependence. Moreover, any missing data can be handled by this model under the missing at random assumption. The estimated coefficients on the mean scale of the outcome will be reported, along with their SEs, 95% CIs, and *P* values. The similar modeling approach mentioned above using generalized linear mixed models instead will be applied to secondary outcomes (asthma quality of life, health care use, and asthma exacerbations) as secondary analyses.

For aim 2, we will explore the potential mediation effects of multiple variables on the relationship between the intervention and clinical outcomes. That is, a portion of the intervention effect on an outcome may be going through the path via a mediator indirectly. Through mediation analysis, the direct effect, the indirect effect also known as the mediated effect, and their total effect will be measured using the approach by Yu et al [46,47] along with their CIs via bootstrapping. The multiple mediators of interest here include social support, self-regulation, self-efficacy, and PA, while the clinical outcomes of interest are the ACQ score and mini-AQLQ score. To avoid the problem of mediation analysis with cross-sectional data, we define the mediation relationship generally noted as *X-M-Y*, using X_{BL} as the exposure at baseline, $M_{j,24w}$ as the *j*th mediator at 12 weeks (j=1,…, 6), and $Y_{k,48w}$ as the *k*th outcome at 48 weeks (k=1,2) [48]. As a secondary analysis, multilevel mediation analysis using the method by Yu and Li [49] will also be considered. For moderation analysis, we will examine moderators including comorbid conditions (depression and obesity), social determinants of health (age, income, and education level), asthma severity (mild, moderate, and severe), and neighborhood environment (walkability and safety) by separately adding their interaction terms with the treatment group to the models mentioned for aim 1A to estimate their moderating effects on treatment responsiveness. We will focus on several plausible behavioral mechanisms. We anticipate improved PA will lead to improved asthma outcomes (control and quality of life) and a reduction in self-reported exacerbations and emergency health care use.

For aim 3, we will report process metrics, such as recruitment rate, monthly to assess reach overall, within key patient subgroups, and each site. Simple descriptive statistics and 95% CIs will be used to summarize measurement for reach and implementation potential at the end of the study. To identify participant characteristics (eg, age, income, and education level) or site-level factors that may be associated with reach, we will examine those associations using the chi-square test or Fisher exact test for categorical variables and the Kruskall-Wallis test for continuous variables. For analysis of qualitative data, the deidentified interview transcripts will be uploaded to the qualitative data software (eg, NVivo [OSR International] or Dedoose [University of California, Los Angeles]). Qualitative assistants will work with qualitative experts to code the data. All coders will initially read all 112 transcripts to become familiar with the data. Thematic interpretation will focus on individual, social, and structural factors associated with acceptability and reasons for variability in uptake and effectiveness of the intervention components. Ten transcripts will be independently coded by all coders. The codes will be reviewed and discussed collectively to develop a shared understanding of how the codes should be applied to the transcripts. This process of independent coding will be repeated ≥2 times until a consistent agreement is reached. Coded transcripts will be sorted to identify thematic groupings. The thematic groupings will be reviewed to identify emergent themes within each domain of the coding framework and quotes that best represent each domain.

Results

This project received funding in August 2022 and received institutional review board approval in July 2022. The first year of this project was focused on hiring and training staff, regulatory approvals, setting up data collection processes, and recruitment. We pilot-tested our recruitment and intervention procedures and began recruitment in April 2023. At the time of manuscript submission, 76 participants have been recruited. We anticipate study completion in 2027.

Discussion

Principal Findings

As one of the first lifestyle PA interventions in asthma to explore behavioral mechanisms, and the only focusing on a group most in need—Black women, this study is expected to contribute importantly to this very limited body of literature and offer useful insights for PA interventions in asthma. Our intervention focuses on walking as a lifestyle approach in urban Black women with asthma, which has been shown to be the preferred method of PA among Black women and people living with

asthma. Walking is affordable, accessible, and sustainable even for Black women residing in urban neighborhoods with high levels of crime or low-resourced neighborhoods. This approach to PA also considers activities done in leisure, household, transportation, and occupational roles. We also use a patient-centered perspective, which has yet to be used in developing PA interventions in adults with asthma. Modifications to the intervention leverage the high levels of technology use in this population while reducing the participant burden associated with in-person sessions [50]. Moreover, from a public health standpoint, interventions using technology-based platforms can provide researchers the ability to reach a large number of people at a relatively low cost, which ultimately leads to a greater public health impact.

Anticipated Challenges and Limitations

As this study will take place in the Midwest, there is a concern that the weather may have an impact on the ability to engage in walking during the winter and even summer months. The intervention addresses this through providing free or low-cost resources on where to exercise indoors during challenging weather. Furthermore, the study team tailors the text messages to local weather and air quality alerts. For example, during the Canadian wildfires in July 2023 when Chicago was experiencing the poorest air quality in the world, we cautioned participants to monitor the air quality index before going outdoors but also provided alternatives to walking outdoors. During our pilot, the participants requested more flexibility with the in-person sessions and have the option to remote in with a secure video platform, which we incorporated into this study. There may still be challenges in having participants attend all the in-person group sessions, but we will work with the participants to find an optimal time to attend, and if needed, allow for a hybrid group session model with some participants in-person and others virtual. Although not an issue in pilot work, it is possible that differential dropout across study groups may occur. To mitigate this concern, participants in the control arm will receive asthma education session text messages at a similar frequency as the intervention participants. In the pilot study, the asthma education session was valued by participants in the control arm. Nonetheless, should problems arise, coinvestigators and a recruitment or retention core will be engaged for input on changes to improve retention. Finally, the information gained from our implementation measures will be critical for revising the conceptual model and rethinking the choice of intervention components to be tested in future studies and will also inform theory development in implementation science.

Conclusions

The findings from this study will provide insight into the next steps for addressing PA in Black women with asthma. It will deliver a new approach to PA interventions in chronic lung diseases such as asthma and a better understanding of the underlying behavioral mechanisms among a high-risk underresearched population. This field is in its infancy and showing the short- and long-term efficacy of a culturally tailored lifestyle PA intervention in a vulnerable patient population, as well as identifying the behavioral mechanisms, are important and will be critical. This study will also set a standard for future studies in minority populations with other disease conditions associated with low levels of PA.

Acknowledgments

The authors thank the Clinical Research Staff at The University of Chicago and UI Health for conducting our study visits. The authors also thank Julissa Acevedo, Senior Systems Analyst, and REDCap Administrator at The University of Chicago for her continued guidance. This research was supported by the National Institute of Minority Health and Disparities under Award Number R01MD017277. The project described was also supported by the National Center for Advancing Translational Sciences, National Institutes of Health (NIH), through Grant Award Number UL1TR002003. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Authors' Contributions

ED and ET drafted and edited the manuscript. AC, YFC, DEH, SK, WK, IM, EO, KP, VGP, TR, DS, and BW reviewed and edited the manuscript. LKS assisted with study conceptualization and reviewed and edited the manuscript. SMN conceptualized the study and assisted with drafting and editing the manuscript. YFC drafted the statistical analysis plan.

Conflicts of Interest

SMN reports funding from National Institutes of Health (NIH), Asthma and Allergy Foundation of America, and receives consulting or royalty fees from GlaxoSmithKline, PRIME education, Wolters Kluwer, and Springer. VGP reports funding from the NIH and Agency for Healthcare Research and Quality and receives consulting fees from Humana regarding patient education programming.

Multimedia Appendix 1
Sample asthma education text messages.
[DOCX File , 16 KB - resprot_v13i1e55700_app1.docx]

Multimedia Appendix 2

Study procedures occurring at each time point.
[DOCX File , 16 KB - resprot_v13i1e55700_app2.docx]

Multimedia Appendix 3
Outcome measures and variables for A Lifestyle Physical Activity Intervention for Minority Women With Asthma (ACTION).
[DOCX File , 20 KB - resprot_v13i1e55700_app3.docx]

Multimedia Appendix 4
Peer-review report by the National Institute of Minority Health and Disparities.
[PDF File (Adobe PDF File), 145 KB - resprot_v13i1e55700_app4.pdf]

References

1. Reddel HK, Bacharier LB, Bateman ED, Brightling CE, Brusselle GG, Buhl R, et al. Global Initiative for Asthma Strategy 2021: executive summary and rationale for key changes. Eur Respir J 2022 Jan;59(1):2102730 [FREE Full text] [doi: 10.1183/13993003.02730-2021] [Medline: 34667060]
2. Akinbami LJ, Moorman JE, Bailey C, Zahran HS, King M, Johnson CA, et al. Trends in asthma prevalence, health care use, and mortality in the United States, 2001-2010. NCHS Data Brief 2012(94):1-8 [FREE Full text] [Medline: 22617340]
3. Morbidity and mortality weekly report. Centers for Disease Control and Prevention.: US Department of Health and Human Services; 2020. URL: https://wonder.cdc.gov/mmwr.html [accessed 2024-01-06]
4. Forno E, Celedon JC. Asthma and ethnic minorities: socioeconomic status and beyond. Curr Opin Allergy Clin Immunol 2009 Apr;9(2):154-160 [FREE Full text] [doi: 10.1097/aci.0b013e3283292207] [Medline: 19326508]
5. Wilbur J, Chandler P, Dancy B, Choi J, Plonczynski D. Environmental, policy, and cultural factors related to physical activity in urban, African American women. Women Health 2002;36(2):17-28. [doi: 10.1300/J013v36n02_02] [Medline: 12487138]
6. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics--2012 update: a report from the American Heart Association. Circulation 2012;125(1):e2-e220 [FREE Full text] [doi: 10.1161/CIR.0b013e31823ac046] [Medline: 22179539]
7. Mancuso CA, Sayles W, Robbins L, Phillips EG, Ravenell K, Duffy C, et al. Barriers and facilitators to healthy physical activity in asthma patients. J Asthma 2006;43(2):137-143. [doi: 10.1080/02770900500498584] [Medline: 16517430]
8. Ford ES, Heath GW, Mannino DM, Redd SC. Leisure-time physical activity patterns among US adults with asthma. Chest 2003;124(2):432-437. [doi: 10.1378/chest.124.2.432] [Medline: 12907526]
9. Avallone KM, McLeish AC. Asthma and aerobic exercise: a review of the empirical literature. J Asthma 2013;50(2):109-116. [doi: 10.3109/02770903.2012.759963] [Medline: 23252987]
10. Mancuso CA, Choi TN, Westermann H, Wenderoth S, Wells MT, Charlson ME. Improvement in asthma quality of life in patients enrolled in a prospective study to increase lifestyle physical activity. J Asthma 2013;50(1):103-107 [FREE Full text] [doi: 10.3109/02770903.2012.743150] [Medline: 23173979]
11. Boyd A, Yang CT, Estell K, Ms CT, Gerald LB, Dransfield M, et al. Feasibility of exercising adults with asthma: a randomized pilot study. Allergy Asthma Clin Immunol 2012;8(1):13 [FREE Full text] [doi: 10.1186/1710-1492-8-13] [Medline: 22863207]
12. Lee RE, Medina AV, Mama SK, Reese-Smith JY, O'Connor DP, Brosnan M, et al. Health is power: an ecological, theory-based health intervention for women of color. Contemp Clin Trials 2011;32(6):916-923 [FREE Full text] [doi: 10.1016/j.cct.2011.07.008] [Medline: 21782975]
13. Nyenhuis SM, Shah N, Ma J, Marquez DX, Wilbur J, Cattamanchi A, et al. Identifying barriers to physical activity among African American women with asthma. Cogent Med 2019;6(1):1582399 [FREE Full text] [Medline: 31754624]
14. Freitas PD, Passos NFP, Carvalho-Pinto RM, Martins MA, Cavalheri V, Hill K, et al. A behavior change intervention aimed at increasing physical activity improves clinical control in adults with asthma: a randomized controlled trial. Chest 2021;159(1):46-57. [doi: 10.1016/j.chest.2020.08.2113] [Medline: 32931821]
15. Joseph RP, Ainsworth BE, Keller C, Dodgson JE. Barriers to physical activity among African American women: an integrative review of the literature. Women Health 2015;55(6):679-699 [FREE Full text] [doi: 10.1080/03630242.2015.1039184] [Medline: 25909603]
16. Fleury J, Lee SM. The social ecological model and physical activity in African American women. Am J Community Psychol 2006;37(1-2):129-140. [doi: 10.1007/s10464-005-9002-7] [Medline: 16680541]
17. Piercy KL, Troiano RP, Ballard RM, Carlson SA, Fulton JE, Galuska DA, et al. The physical activity guidelines for Americans. JAMA 2018;320(19):2020-2028 [FREE Full text] [doi: 10.1001/jama.2018.14854] [Medline: 30418471]
18. Nyenhuis SM, Dixon AE, Ma J. Impact of lifestyle interventions targeting healthy diet, physical activity, and weight loss on asthma in adults: what is the evidence? J Allergy Clin Immunol Pract 2018;6(3):751-763 [FREE Full text] [doi: 10.1016/j.jaip.2017.10.026] [Medline: 29221919]

19. Clark NM, Gong M, Kaciroti N. A model of self-regulation for control of chronic disease. Health Educ Behav 2014;41(5):499-508 [FREE Full text] [doi: 10.1177/1090198114547701] [Medline: 25270175]
20. Bandura A. Health promotion by social cognitive means. Health Educ Behav 2004;31(2):143-164. [doi: 10.1177/1090198104263660] [Medline: 15090118]
21. Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, et al. Standardization of Spirometry 2019 update. An official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med 2019 Oct 15;200(8):e70-e88 [FREE Full text] [doi: 10.1164/rccm.201908-1590ST] [Medline: 31613151]
22. Smart M, Nabulsi N, Gerber B, Sharp LK. A qualitative evaluation of a pilot behavioral intervention technology program to promote walking in underserved populations. Ann Behav Med 2020;54:S1-S827. [doi: 10.1093/abm/kaaa009]
23. Kitsiou S, Thomas M, Marai GE, Maglaveras N, Kondos G, Arena R, et al. Development of an innovative mHealth platform for remote physical activity monitoring and health coaching of cardiac rehabilitation patients. : IEEE; 2017 Presented at: 2017 IEEE EMBS International Conference on Biomedical & Health Informatics (BHI); February 16-19, 2017; Orlando, FL, USA URL: https://ieeexplore.ieee.org/document/7897223 [doi: 10.1016/j.vetmic.2016.12.028]
24. Wilde BE, Sidman CL, Corbin CB. A 10,000-step count as a physical activity target for sedentary women. Res Q Exerc Sport 2001;72(4):411-414. [doi: 10.1080/02701367.2001.10608977] [Medline: 11770790]
25. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J 1999;14(4):902-907 [FREE Full text] [doi: 10.1034/j.1399-3003.1999.14d29.x] [Medline: 10573240]
26. Juniper EF, Guyatt GH, Cox FM, Ferrie PJ, King DR. Development and validation of the mini asthma quality of life questionnaire. Eur Respir J 1999;14(1):32-38 [FREE Full text] [doi: 10.1034/j.1399-3003.1999.14a08.x] [Medline: 10489826]
27. National Center for Health Statistics (US). Health, United States, 2007: With Chartbook on Trends in the Health of Americans. Hyattsville, MD: National Center for Health Statistics (US); 2007.
28. Ried-Larsen M, Brønd JC, Brage S, Hansen BH, Grydeland M, Andersen LB, et al. Mechanical and free living comparisons of four generations of the actigraph activity monitor. Int J Behav Nutr Phys Act 2012;9:113 [FREE Full text] [doi: 10.1186/1479-5868-9-113] [Medline: 22971175]
29. Choi L, Liu Z, Matthews CE, Buchowski MS. Validation of accelerometer wear and nonwear time classification algorithm. Med Sci Sports Exerc 2011;43(2):357-364 [FREE Full text] [doi: 10.1249/MSS.0b013e3181ed61a3] [Medline: 20581716]
30. Sasaki JE, John D, Freedson PS. Validation and comparison of ActiGraph activity monitors. J Sci Med Sport 2011;14(5):411-416. [doi: 10.1016/j.jsams.2011.04.003] [Medline: 21616714]
31. Prince SA, Cardilli L, Reed JL, Saunders TJ, Kite C, Douillette K, et al. A comparison of self-reported and device measured sedentary behaviour in adults: a systematic review and meta-analysis. Int J Behav Nutr Phys Act 2020;17(1):31 [FREE Full text] [doi: 10.1186/s12966-020-00938-3] [Medline: 32131845]
32. Kriska AM, Knowler WC, LaPorte RE, Drash AL, Wing RR, Blair SN, et al. Development of questionnaire to examine relationship of physical activity and diabetes in Pima Indians. Diabetes Care 1990;13(4):401-411 [FREE Full text] [doi: 10.2337/diacare.13.4.401] [Medline: 2318100]
33. Pereira MA, FitzerGerald SJ, Gregg EW, Joswiak ML, Ryan WJ, Suminski RR, et al. A collection of physical activity questionnaires for health-related research. Med Sci Sports Exerc 1997;29(6 Suppl):S1-S205. [Medline: 9243481]
34. Gabriel KP, McClain JJ, Lee CD, Swan PD, Alvar BA, Mitros MR, et al. Evaluation of physical activity measures used in middle-aged women. Med Sci Sports Exerc 2009;41(7):1403-1412 [FREE Full text] [doi: 10.1249/MSS.0b013e31819b2482] [Medline: 19516161]
35. Gabriel KP, McClain JJ, Schmid KK, Storti KL, Ainsworth BE. Reliability and convergent validity of the past-week modifiable activity questionnaire. Public Health Nutr 2011;14(3):435-442 [FREE Full text] [doi: 10.1017/S1368980010002612] [Medline: 20843404]
36. Cerin E, Saelens BE, Sallis JF, Frank LD. Neighborhood environment walkability scale: validity and development of a short form. Med Sci Sports Exerc 2006;38(9):1682-1691 [FREE Full text] [doi: 10.1249/01.mss.0000227639.83607.4d] [Medline: 16960531]
37. Bauman AE, Reis RS, Sallis JF, Wells JC, Loos RJF, Martin BW, Lancet Physical Activity Series Working Group. Correlates of physical activity: why are some people physically active and others not? Lancet 2012;380(9838):258-271. [doi: 10.1016/S0140-6736(12)60735-1] [Medline: 22818938]
38. Harley AE, Rice J, Walker R, Strath SJ, Quintiliani LM, Bennett GG. Physically active, low-income African American women: an exploration of activity maintenance in the context of sociodemographic factors associated with inactivity. Women Health 2014;54(4):354-372. [doi: 10.1080/03630242.2014.896440] [Medline: 24617833]
39. Cooley C, Park Y, Ajilore O, Leow A, Nyenhuis SM. Impact of interventions targeting anxiety and depression in adults with asthma. J Asthma 2022;59(2):273-287 [FREE Full text] [doi: 10.1080/02770903.2020.1847927] [Medline: 33176512]
40. Dixon AEN, Nyenhuis SN. Obesity and asthma. UptoDate, H. Hollingsworth, Editor. Waltham, MA: UptoDate; 2020. URL: https://www.uptodate.com/contents/obesity-and-asthma# [accessed 2024-01-06]
41. Kroenke K, Strine TW, Spitzer RL, Williams JBW, Berry JT, Mokdad AH. The PHQ-8 as a measure of current depression in the general population. J Affect Disord 2009;114(1-3):163-173. [doi: 10.1016/j.jad.2008.06.026] [Medline: 18752852]

42. Creswell JW, Klassen AC, Clark VLP, Smith KC. Best practices for mixed methods research in the health sciences. National Institutes of Health. 2011. URL: https://obssr.od.nih.gov/sites/obssr/files/Best_Practices_for_Mixed_Methods_Research.pdf [accessed 2024-01-06]
43. Creswell JW, Clark VLP. Designing and Conducting Mixed Methods Research. 2nd Edition. Thousand Oaks, CA: Sage Publications; 2011.
44. Van Buuren S, Brand JPL, Groothuis-Oudshoorn CGM, Rubin DB. Fully conditional specification in multivariate imputation. J Stat Comput Simul 2006;76(12):1049-1064. [doi: 10.1080/10629360600810434]
45. Brown H, Prescott R. Applied Mixed Models in Medicine, 3rd Edition. Hoboken, New Jersey: John Wiley & Sons; 2014.
46. Yu Q, Wu X, Li B, Scribner RA. Multiple mediation analysis with survival outcomes: with an application to explore racial disparity in breast cancer survival. Stat Med 2019;38(3):398-412 [FREE Full text] [doi: 10.1002/sim.7977] [Medline: 30255567]
47. Yu Q, Li B. Mma: an R package for mediation analysis with multiple mediators. JORS 2017;5(1):11 [FREE Full text] [doi: 10.5334/jors.160]
48. Fairchild AJ, McDaniel HL. Best (but oft-forgotten) practices: mediation analysis. Am J Clin Nutr 2017 Jun;105(6):1259-1271 [FREE Full text] [doi: 10.3945/ajcn.117.152546] [Medline: 28446497]
49. Yu Q, Li B. Third-variable effect analysis with multilevel additive models. PLoS One 2020;15(10):e0241072 [FREE Full text] [doi: 10.1371/journal.pone.0241072] [Medline: 33095796]
50. Joseph RP, Keller C, Adams MA, Ainsworth BE. Print versus a culturally-relevant Facebook and text message delivered intervention to promote physical activity in African American women: a randomized pilot trial. BMC Womens Health 2015 Mar 27;15:30 [FREE Full text] [doi: 10.1186/s12905-015-0186-1] [Medline: 25886945]

Abbreviations

ACQ: asthma control questionnaire
ACTION: A lifestyle Physical Activity Intervention for Minority Women With Asthma
HIPPA: Health Insurance Portability and Accountability Act
ICD-10: International Statistical Classification of Diseases, 10th Revision
MVPA: moderate-to-vigorous intensity physical activity
PA: physical activity
PWMAQ: Past Week Modifiable Activity Questionnaire
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SMART: Specific Measurable Attainable Relevant and Time bound

Edited by A Mavragani; submitted 21.12.23; this is a non–peer-reviewed article;accepted 22.12.23; published 07.02.24.

Please cite as:
Davis E, Townsend E, Cavalier A, Chen YF, Edwards-Hart D, Kitsiou S, Kowalczyk W, Mansur I, Okpara E, Powell K, Press VG, Ramirez T, Salvo D, Sharp LK, Wright B, Nyenhuis SM
Physical Activity Intervention for Urban Black Women With Asthma: Protocol for a Randomized Controlled Efficacy Study
JMIR Res Protoc 2024;13:e55700
URL: https://www.researchprotocols.org/2024/1/e55700
doi:10.2196/55700
PMID:38324365

Protocol

Telehealth Behavioral Intervention for Chronic Disease Self-Management in Adults With Physical Disabilities (My Health, My Life, My Way): Protocol for Intervention Fidelity and Dashboard Design for a Randomized Controlled Trial

Eric Evans[1*], PhD; Ayse Zengul[2*], MS; Tejaswini Subhash Chilke[3], MS; Amy Knight[4*], PhD; Amanda Willig[5], PhD; Andrea Cherrington[6], MD; Tapan Mehta[7*], PhD; Mohanraj Thirumalai[1], MS, MEng, PhD

[1]Department of Health Services Administration, School of Health Professions, University of Alabama at Birmingham, Birmingham, AL, United States

[2]Department of Nutrition Sciences, School of Health Professions, University of Alabama at Birmingham, Birmingham, AL, United States

[3]UAB Research Collaborative, School of Health Professions, University of Alabama at Birmingham, Birmingham, AL, United States

[4]Department of Neuroology, Heersink School of Medicine, University of Alabama at Birmingham, Birmingham, AL, United States

[5]Division of Infectious Disease, Heersink School of Medicine, University of Alabama at Birmingham, Birmingham, AL, United States

[6]Division of Preventive Medicine, Heersink School of Medicine, University of Alabama at Birmingham, Birmingham, AL, United States

[7]Department of Family and Community Medicine, Heersink School of Medicine, University of Alabama at Birmingham, Birmingham, AL, United States

[*]these authors contributed equally

Corresponding Author:
Mohanraj Thirumalai, MS, MEng, PhD
Department of Health Services Administration
School of Health Professions
University of Alabama at Birmingham
SHPB 590D
1716 9th Ave S
Birmingham, AL, 35233
United States
Phone: 1 2059347189
Email: mohanraj@uab.edu

Abstract

Background: Individuals with physical disabilities experience higher rates of chronic health conditions than individuals without physical disabilities. Self-management programs that use health coaching are effective at eliciting health behavior change in health outcomes such as goal setting, adherence, and health care use. Additionally, web-based resources such as telehealth-based technologies, including SMSS text messaging, web-based applications, and educational multimedia content, can complement health coaching to improve health-related behaviors and the use of health services. The complexity of studies using these resources requires a fidelity protocol to ensure that health behavior studies are administered properly.

Objective: The My Health, My Life, My Way fidelity protocol provides methods, strategies, and procedures of a multifaceted telehealth program for individuals with permanent physical disabilities and chronic health conditions. This health behavior study is a randomized controlled trial with four study arms: (1) scheduled coaching calls with gamified rewards, (2) no scheduled coaching calls with gamified rewards, (3) scheduled coaching calls with fixed rewards, and (4) no scheduled coaching calls with fixed rewards. To guide the fidelity protocol developed, we used the National Institutes of Health Behavior Change Consortium framework (NIH BCC).

Methods: The fidelity intervention protocol was developed by using the 5 primary domains provided by the NIH BCC: study design, provider training, treatment delivery, treatment receipt, and enactment of treatment skills. Following the NIH BCC guidelines and implementing social cognitive theory, this study is designed to ensure that all study arms receive equal treatment across conditions and groups. Health coaches and providers will be trained to deliver consistent health coaching, and thus participants will receive appropriate attention. Educational content will be developed to account for health literacy and comprehension of the material. Multiple fidelity intervention steps such as coaching call logs, regular content review, and

participant progress monitoring will translate to participants using the skills learned in their daily lives. Different monitoring steps will be implemented to minimize differences among the 4 treatment groups.

Results: My Health, My Life, My Way has been approved by the institutional review board and will begin enrollment in January 2024 and end in December 2024, with results reported in early 2025.

Conclusions: Intervention fidelity protocols are necessary to ensure that health behavior change studies can be implemented in larger real-world settings. The My Health, My Life, My Way fidelity protocol has used the guidelines by the NIH BCC to administer a telehealth intervention combined with health coaching for individuals with physical disabilities and chronic health conditions. This fidelity protocol can be used as a complementary resource for other researchers who conduct similar research using telehealth technologies and health coaching in real-world settings.

Trial Registration: ClinicalTrials NCT05481593; https://clinicaltrials.gov/study/NCT05481593

International Registered Report Identifier (IRRID): PRR1-10.2196/53410

(JMIR Res Protoc 2024;13:e53410) doi:10.2196/53410

KEYWORDS

chronic health conditions; telehealth; health coaching; self-management; intervention fidelity protocol

Introduction

Background

According to the US Centers for Disease Control and Prevention, nearly 60% of Americans currently live with a chronic health condition, such as diabetes, heart disease, or hypertension [1]. The prevalence of individual conditions varies and affects activities of daily living differently for each subpopulation. For example, nearly 10% of Americans live with a version of diabetes, including type 1, type 2, and prediabetes [2]. For heart disease, the most common form is coronary artery disease, which is prevalent in the United States in approximately 7% of the population [3]. For example, individuals with physical disabilities experience higher rates of chronic conditions than individuals without physical disabilities [4,5]. Different approaches have been used to manage chronic health conditions and their related symptoms. Prior research has shown that self-management programs, which refer to one's ability to care for their health, are able to promote positive self-care, increase physical activity, and monitor dietary behavior for individuals with chronic health conditions [6].

Different approaches have been used to provide mechanisms for individuals with chronic health conditions to successfully manage their health. Telehealth interventions have been used as effective strategies for self-management across a variety of chronic health conditions [7-10]. A primary benefit of using telehealth technologies for self-management is the convenience of engaging in programs at flexible times and locations, such as home settings [11,12]. Telehealth programs also provide benefits for clinicians and health care providers, that is, the ability to engage with patients remotely to provide adequate care and promote healthy behaviors. However, there are no accessible and inclusive telehealth programs for individuals with physical disabilities. The lack of inclusive programming for individuals with physical disabilities highlights barriers that this population experiences, including transportation and inadequate time to participate in telehealth interventions [13].

The lack of programming for individuals with physical disabilities demands an immediate remedy. Therefore, we are developing a telehealth program that includes a website with inclusive multimedia educational content combined with access to trained health coaches to provide optimal self-management programming to individuals with physical disabilities. As part of this intervention, we will use an artificial intelligence (AI)–assisted, customized lifestyle program to increase the overall fidelity of the intervention and optimize health coaching resources for telecoaching.

Reporting Fidelity

To ensure that a health behavior intervention is delivered as intended, it is necessary to develop fidelity protocols to minimize issues with protocol implementation. The complexity of telehealth interventions, the research designs used, and the multiple development teams (health coaches, technical staff, etc) introduce several challenges to maintaining overall study fidelity. Because variations exist in health behavior studies, guidelines have been developed to provide recommendations and strategies for using fidelity concepts in future projects. The National Institutes of Health Behavior Change Consortium (NIH BCC) published recommendations for implementing fidelity concepts for health behavior interventions. The specific areas covered by the NIH BCC include recommendations for study design, provider training, treatment delivery, treatment receipt, and enactment of treatment skills [14]. Therefore, we aim to use the guidelines set forth by the NIH BCC to describe and report the fidelity protocol for the My Health, My Life, My Way study. This intervention will use mobile health technology in conjunction with health coaching to create a comprehensive web-based self-management program for individuals with physical disabilities who experience chronic health conditions. Furthermore, the development of this protocol addresses the 5 domains of fidelity monitoring set forth by the NIH BCC and will provide valuable insight into reproducing future telehealth interventions.

Methods

Overview of the Study and Fidelity Protocol

The My Health, My Life, My Way study aims to optimize an AI, telehealth-based self-management program for individuals with physical disabilities and chronic conditions. This program

includes a telecoaching website where participants can communicate with health coaches through different communication mediums (ie, texting and phone calls), access customized, educational material related to their specific health conditions, and track health-related behaviors such as physical activity and nutrition. Additionally, the program aims to actively encourage positive lifestyle changes by incorporating features that promote healthy behaviors. These features encompass aiding users in creating well-balanced meal plans and encouraging regular physical activity. By integrating these elements, the program provides a comprehensive toolset for both fostering healthier habits and receiving expert guidance, ultimately contributing to participants' overall well-being.

Within the website system, AI-embedded technology will be implemented that will have access to an ingredient and recipe database system which will offer personalized dietary suggestions based on the participant's dietary preferences or restrictions, cooking resources, financial status, and cooking skills. Similarly, the system will be able to provide physical activity recommendations based on health status, preferred activities, and climate. Health coaches will have access to participants' web-based website to monitor and approve health behavior changes and goals set by the participants. Individuals will be able to communicate with the health coaches through multiple communication mediums, including smartphone apps, SMS text messaging, phone calls, and conversation agents (ie, Amazon Echo). Educational content provided on the website will be created and tailored to individuals with physical disabilities. The combination of these technologies, with a focus placed on the participant, will minimize the time, effort, and costs of using health coaching staff; promote adherence and regular use of the system; and ultimately promote health self-management.

The purpose of this study is to use the Multiphase Optimization Strategy to pilot-test and identify the optimal combination of intervention components that are effective in improving health-related quality of life in adults with physical disabilities and chronic health conditions. We will be using a pilot randomized controlled trial study design, in which 200 adults with physical disabilities and chronic health conditions will be randomized into 1 of 4 groups with 50 participants in each group: (1) scheduled coaching calls with gamified rewards, (2) scheduled coaching calls with independent rewards, (3) no scheduled coaching calls with gamified rewards, and (4) no scheduled coaching calls with independent rewards. Those not receiving scheduled coaching will be able to communicate with health coaches as needed to discuss health-related behaviors and goal setting. Participants will be able to communicate with the health coaches through communication methods such as SMS text messages, phone calls, and the telehealth website. Recruitment will be conducted nationally through web-based advertisements and social media accounts associated with the National Center on Health, Physical Activity and Disability, and ResearchMatch platform. Inclusion criteria include (1) 18 years of age or older; (2) diagnosis of heart disease, chronic lung disease, or type 2 diabetes; (3) living with a permanent physical disability such as spinal cord injury, spina bifida, multiple sclerosis, or stroke; (4) ability to converse and read English; and (5) smartphone or computer access.

Within the intervention, participants will be randomly assigned to 1 of 4 groups (Table 1). The total duration of the program is 24 weeks (6 months). Those receiving scheduling coaching calls will have weekly coaching calls with trained health coaches who will provide customized recommendations and education based on participant needs, including physical activity, nutrition, and other health-related topics. Those not receiving scheduled coaching calls will have the capability to contact health coaches through the telecoaching website, SMS text messages, or phone call to discuss similar health-related objectives. Participants will also receive a physical activity tracker (FitBit) to track activity during the program.

We incorporated the NIH BCC Treatment Fidelity recommendations to develop our fidelity protocol to monitor fidelity and ensure the external and internal validity of the intervention.

Table 1. Research design.

Gamification rewards	Coaching calls	
	Scheduled coaching calls	No scheduled coaching calls
Gamification-based rewards	Scheduled coaching calls with gamified rewards	No scheduled coaching calls with gamified rewards
Rewards independent of gamification	Scheduled coaching calls with rewards independent of gamification	No scheduled coaching calls with rewards independent of gamification

Ethical Considerations

The protocol for the My Health, My Life, My Way study was approved by the University of Alabama at Birmingham's institutional review board (300009485). Enrollment is expected to begin in January 2024 and study completion is expected to end in December 2024.

Study Design

Overview

The principles of the NIH BCC state that fidelity interventions must make certain that (1) appropriate theory and clinical practice are aligned with procedures and implementation, (2) treatment and dose across participants are equal, and (3) possible setbacks in intervention implementation are addressed. Textbox 1 provides the study design and monitoring plan for My Health, My Life, My Way.

Textbox 1. Fidelity of the study design and monitoring plan.

Goal

- Intervention will be congruent with the presented theory and practice
- Ensure equal treatment and dose are provided across and within all conditions
- Implementation setbacks are addressed

Description from National Institutes of Health Behavior Change Consortium

- Operationalize treatment to optimally reflect theoretical roots and precisely define variables most relevant to the "active ingredients" of the intervention
- Setbacks in implementation are addressed

Fidelity plan for My Health, My Life, My Way

- Monthly review of coaching call checklist
- Monthly review of coaching call logs
- Quarterly assessment of random coaching call audio recordings
- Quarterly assessment of education content provided to participants
- Weekly review of participant journals
- Monthly review of the telecoaching platform and events log
- Quarterly assessment of participant log-ins and time spent on the platform
- Weekly team meetings to discuss participant progress and protocol adherence

Presented Theory and Clinical Practices Are Congruent With Procedures and Implementation

My Health, My Life, My Way is grounded in Social Cognitive Theory and is designed to serve as a support system and communication platform among health coaches, participants with disabilities and their caregivers, and health care providers. The website will allow joint efforts for all parties to promote support among friends and family, regular physical activity and healthy dietary behaviors, and goal settings.

Equal Dose of Treatments Across Participants

As this study is a 2×2 factorial design, half of the participants will not receive scheduled coaching calls, while the other half will receive scheduled coaching calls. The duration and frequency of coaching calls for the scheduled group will be consistent to ensure an equal dose of calls. Those not receiving scheduled coaching calls will be able to contact the health coaches as needed during the study. For gamification elements, half of the participants will receive incremental rewards for engaging with the study. Such engagement includes but is not limited to (1) engaging with the telehealth website, (2) logging health behavior data, and (3) engaging with educational content. Half will receive independent rewards by performing similar tasks, thereby making the requirements for rewards equal across all participants. Additionally, all groups will be subject to the same data collection methods and study protocols.

Protocols for Setbacks in Implementation

All adverse events, emergencies, and issues with participant engagement and intervention will be collected and reported. We will track participant feedback and issues in adherence through the coaching logs and notes collected on the telehealth website, call logs, and staff logs.

Provider Training

All team members in the study have appropriate backgrounds and experiences in conducting every study activity. The multidisciplinary team includes technical, academic, and programmatic personnel who are able to perform all relevant tasks to ensure the successful completion of the My Health, My Life, My Way study. Academic staff include researchers who are charged with the overall administration of the program and trained health coaches who will engage with participants and provide relevant health-related content such as physical activity and nutrition. Technical staff are trained in developing the website that participants will use and will maintain the technological infrastructure through feedback from academic personnel and participants. Textbox 2 shows the strategies that we will use to monitor provider training based on the NIH BCC.

Textbox 2. Fidelity of provider training.

Goal

- Standardized training
- Ensure provider skill acquisition
- Minimize “drift” in provider skills
- Accommodate provider differences

Description from National Institutes of Health Behavior Change Consortium

- Similar training conducted by providers
- Providers trained using predetermined and defined criteria
- Reduce provider skill decay over time
- Ensure adequate training of providers with different levels of skills, experience, and background

Strategy used in My Health, My Life, My Way

- Health coaches will receive equal training through specified a curriculum
- Review and monitor coaching calls and call logs
- Evaluate audio recordings of coaching calls
- Collect audio recordings of coaching calls
- Regular team meetings to monitor participant progress and provider protocol adherence

Treatment Delivery

Overview

The NIH BCC provides guidance on how to ensure that interventions are delivered as intended. By using their guidance, we will address four concerns cited by the NIH BCC for treatment delivery: (1) controlling provider differences, (2) reducing differences within study groups, (3) ensuring adherence to study protocols, and (4) reducing contamination between study groups. Textbox 3 shows the strategies used in My Health, My Life, My Way.

Textbox 3. Fidelity strategy for treatment delivery.

Goal

- Control for provider differences
- Reduce differences within study groups
- Ensure adherence to the study protocol
- Reduce contamination between study groups

Description from National Institutes of Health Behavior Change Consortium

- Monitor and control for subject perceptions of nonspecific treatment effects (eg, warmth and credibility) across conditions
- Ensure that providers in the same condition are delivering the same intervention
- Ensure that the treatments are being delivered in the way in which they were conceived with regard to content and treatment dose
- Minimize contamination across treatment or control conditions, especially when implemented by the same provider

Strategies used in My Health, My Life, My Way

- Coaching call checklist
- Coaching call logs
- Audio recording of coaching calls
- Review of the telecoaching platform and its event log
- Team meetings to discuss participant progress and protocol adherence

Controlling Provider Differences

We have developed several strategies to monitor treatment delivery in the study. First, we have developed several coaching guides and scripts that will inform health coaches on what content to cover during coaching calls. We also plan to track the frequency of coaching calls through call logs. This will allow us to evaluate whether participants are receiving an equal number of coaching calls throughout the program. Next, we will collect audio recordings of coaching calls and randomly select calls to evaluate content delivery. The study team will conduct weekly team meetings to evaluate the progress of participants, health coaching curriculum, and protocol adherence.

Reducing Differences Within Treatment Groups

This study uses AI to enhance the fidelity of coaching sessions and minimize the effort required by health coaches to provide customized telecoaching. The program will use a telehealth website that will be an assistive tool for health coaches to deliver appropriate content to each participant during coaching call sessions. Health coaches will be provided standardized protocols and guidelines regardless of intervention group assignment. All educational content will be developed by experts to be inclusive of individuals with physical disabilities.

Regardless of group assignment, all procedures will be standardized to reduce differences within treatment groups. Coaches will focus on domains of health, including but not limited to physical activity, mindfulness, and nutrition. In these areas of health, the health coach will follow a progressive routine. For example, if a participant has a goal to increase physical activity participation, the health coach will start with lower activity goals with the ultimate aim of meeting physical activity guidelines of 150 minutes of aerobic activity per week. Similar approaches to nutrition and other health-related behaviors will be used. Although half of the participants will not receive scheduled coaching calls, those participants will be able to communicate with the health coaches through on-demand services through different communication methods regarding health behaviors they seek to improve. Health coaches will follow the same standardized protocols and guidelines for these participants as well.

Finally, the My Health, My Life, My Way telehealth website will include multimedia educational content (ie, videos, infographics, and SMS text messages) to deliver the intervention. All participants will have access to the material and can view them at their discretion.

Ensuring Adherence to Treatment Protocols

Health coaches will be given standardized checklists and protocols to ensure adherence to intervention treatment and delivery. The collection of call logs, monthly evaluation of audio recordings, and weekly team meetings will be conducted to further ensure that all protocols are regularly followed. All documents provided to the health coaches will serve as reminders to prepare for any coaching call and discuss relevant content with each participant.

Minimizing Contamination Between Conditions

All enrolled participants will be randomized into 1 of 4 groups (Table 1). Each group will have a developed protocol that will be given to the health coaches to use during the study duration. The coaches will use the same educational material that will be adapted for individuals with physical disabilities.

Receipt of Treatment

A primary element of the success of an intervention is its simplicity and applicability. The NIH BCC emphasizes treatment receipt, which involves assessing the degree to which participants understand the material provided to them and are able to perform health behavior–related skills during the intervention. My Health, My Life, My Way fidelity protocol seeks to achieve goals suggested by the NIH BCC (Textbox 4).

Textbox 4. Fidelity strategy for receipt of treatment.

Goal

- Ensure participant comprehension
- Ensure participant's ability to use cognitive skills
- Ensure participant's ability to perform behavioral skills

Description from National Institutes of Health Behavior Change Consortium

- Ensure that participants understand the information provided by the intervention
- Make sure that participants are able to use the cognitive skills taught in the intervention
- Make sure that participants are able to use behavioral skills taught in the intervention

Strategies used in My Health, My Life, My Way

- Use plain language for content with a target reading at fifth-grade reading level
- Review audio recordings of coaching calls
- Review participant website journals for physical activity, medication, and nutrition behaviors
- Review duration spent on the website by participants
- Conduct study team meetings to review participant progress in the intervention

It is estimated that 80 million US adults have low health literacy, which refers to the inability to listen effectively, read, understand, and interpret text and numerals related to health management, such as food labels, blood glucose measurements, and clinical instructions. Using plain language is important to increase health literacy for individuals with physical disabilities who experience chronic health conditions. As My Health, My Life, My Way is designed for populations with disability, we plan to use language at a fifth-grade reading level for all written content. Such modification to education material is necessary to increase participants' capacity to perform self-management skills.

My Health, My Life, My Way will incorporate principles of cognitive behavioral therapy to counsel participants on diet, exercise, and positive psychological behaviors like motivation and managing stress. Health coaches will use similar techniques derived from cognitive behavioral therapy to provide proper motivational interviewing that will assist participants in creating and following through on creating goals and implement strategies to meet those goals.

Enactment of Treatment Skills

The enactment of treatment skills refers to the ability to monitor and increase the capacity of participants to act on behavioral and cognitive skills in real-world settings that they learned during the study intervention [14]. Because we aim to promote long-term adherence to skills beyond the study duration, this program will use adapted and engaging content designed for individuals with physical disabilities in mind. Such content will include multimedia, textual, and graphical material and access through a telehealth website that will provide access to all content (Textbox 5).

Textbox 5. Fidelity strategy for the enactment of treatment skills.

Goal

- Ensure participant's use of cognitive skills
- Ensure participant's use of behavioral skills

Description from National Institutes of Health Behavior Change Consortium

- Ensure that participants use the cognitive skills provided at the intervention in appropriate life settings
- Ensure that participants actually use the behavioral skills provided in the intervention in appropriate life settings

Strategies used in My Health, My Life, My Way

- Review participant logs for physical activity, food, medication, etc
- Review the number of log-ins and time spent on the telehealth website
- Regular team meetings to assess participant progress and overall protocol adherence
- Review and monitor coaching notes collected during the intervention

My Health, My Life, My Way Telehealth Coaching Dashboard

This program provides a comprehensive telehealth coaching dashboard, a multifaceted solution designed to elevate participant engagement, communication, and monitoring within the realm of health and wellness. This dynamic platform seamlessly integrates 3 essential components. The telehealth coaching dashboard will serve as the pivotal interface enabling participants to establish effective and real-time communication with their designated health coaches. Through a variety of mediums such as SMS text message–based messaging and phone calls, participants can engage in meaningful conversations, seek guidance, and receive personalized support. For participant monitoring and tracking, the platform will offer robust capabilities for monitoring and tracking health-related behaviors, including physical activity, time spent on reading health-related contents, and watching minutes of exercise videos and nutritional choices. This helps health coaches to provide guidance to participants during health coaching sessions. Finally, the user interface for participants will receive an intuitive user interface tailored to their needs. This interface provides them with convenient access to an array of features, such as customized educational materials catering to their specific health conditions, exercise videos, and on-demand health coaching. Moreover, the interface empowers participants to log and manage their activities for promoting positive behavior changes, ranging from effective meal planning to encouraging regular physical activity through goal settings. Overall, through seamless communication channels, comprehensive monitoring tools, and a user-friendly interface, the telehealth coaching dashboard will empower participants to take charge of their health journey while receiving expert guidance and support. Figures 1-3 provide the samples of the telehealth coaching monitoring dashboard.

Figure 1. Sample fidelity monitoring dashboard screenshot—participant monitoring dashboard.

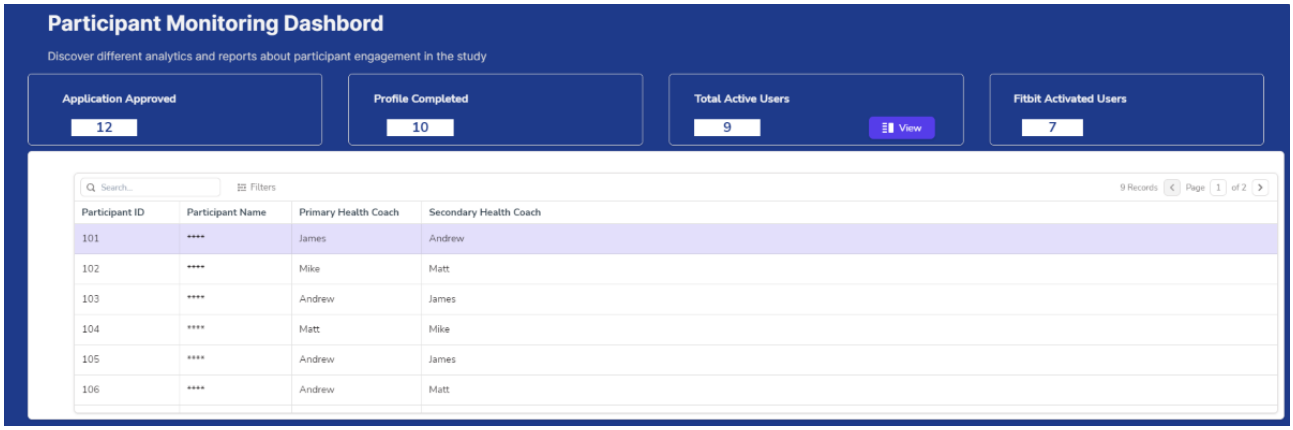


Figure 2. Sample fidelity monitoring dashboard screenshot—log-in analytics.

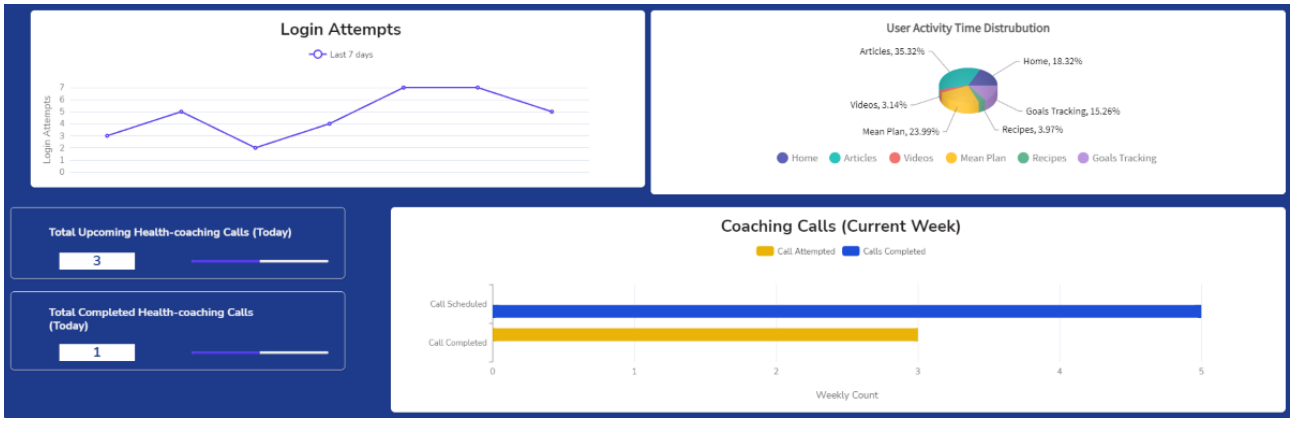
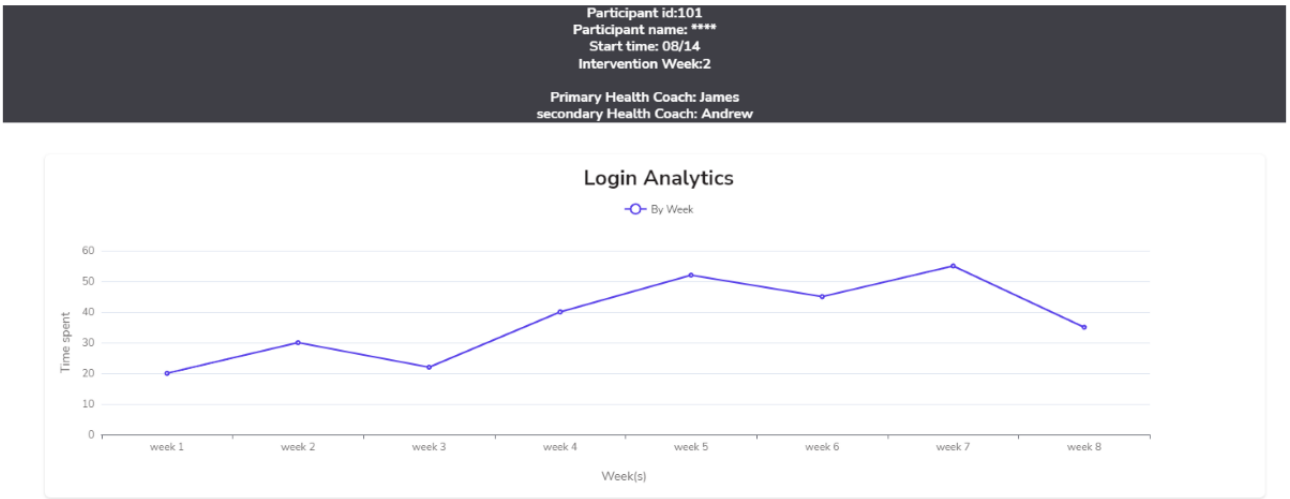


Figure 3. Sample fidelity monitoring dashboard screenshots —summary dashboard.



Results

Enrollment for the My Health, My Life, My Way program will begin in January 2024 and will end in December 2024. The results of this study will be reported in early 2025.

Discussion

The purpose of this paper was to outline and describe the intervention fidelity protocol for the My Health, My Life, My Way study. This randomized controlled trial aims to develop and evaluate a telehealth platform, which is paired with inclusive education content for individuals with physical disabilities who experience chronic health conditions. Intervention fidelity refers to mechanisms of monitoring the planned delivery of study interventions [14]. Maintaining strict fidelity throughout study interventions will minimize external influence on both participants and research team members. It will also ensure that results from the intervention are reflective of the participants' behaviors in real-world settings.

By using strategies provided by the NIH BCC, we developed an intensive fidelity intervention protocol addressing the 5 main

domains to monitor, assess, and enhance overall study fidelity. The NIH BCC has provided relevant guidelines and strategies for health behavior interventions to maintain both internal and external validity. Telehealth studies can positively impact self-management skills for individuals with chronic health conditions. The My Health, My Life, My Way program will be the first self-management program for individuals with physical disabilities and chronic health conditions. Because this program is conducted through the web, it has the capability to become accessible, inclusive, scalable, and sustainable. Therefore, by reporting the fidelity intervention protocol for My Health, My Life, My Way, this paper will inform future studies using telehealth technology and health coaching.

The 5 domains to maintain fidelity provided by the NIH BCC addressed in this paper include study design, provider training, treatment delivery, treatment receipt, and enactment of treatment skills. The fidelity monitoring protocol described here was developed in conjunction with a similar telehealth study using similar technology and health coaching for individuals with physical disabilities and diabetes [15,16]. Similar to that fidelity intervention protocol, a challenge of ensuring high fidelity is that My Health, My Life, My Way will use different technological platforms for different fidelity purposes. Examples include using the telehealth website, REDCap (Research Electronic Data Capture; Vanderbilt University) for data collection, and communication platforms for health coaches to engage with participants. Possible implementation setbacks will be addressed, and ongoing collaboration with the multidisciplinary team (ie, research staff, health coaches, and technical support) will reduce variations in fidelity monitoring.

Several steps in program implementation have been conducted prior to fidelity development and standardized protocols have been developed for future steps. In the context of health coaching, strict coaching session guidelines have been developed to reduce variation in conducting health coaching calls, which is a significant concern in telehealth interventions [17,18]. The development of AI that is embedded in our telecoaching website provides convergent communication capabilities that will reduce health coaching workload and need to aid in the personalization of self-management skills for participants. Other monitoring procedures have been created to evaluate the consistency of health coaching sessions, including audio recordings, call logs, and a review of the training used by the coaching team. Such procedures will enhance the internal validity of the protocol and contribute to the creation of effective, evidence-based telecoaching programs.

Acknowledgments

This study was funded by the National Institute on Disability, Independent Living, and Rehabilitation Research (90DPGE0017).

Conflicts of Interest

TM received consulting fees from Novo Nordisk, Heart Rythm ClinicalResearch Solutions, New Balance Foundation Obesity Prevention Center, and fees as an editor by The Obesity Society and PLOS One.

Multimedia Appendix 1
Peer review report from the National Institute on Disability, Independent Living, and Rehabilitation Research (NIDILRR).
[PDF File (Adobe PDF File), 374 KB - resprot_v13i1e53410_app1.pdf]

References

1. About chronic diseases. Centers for Disease Control and Prevention. URL: https://www.cdc.gov/chronicdisease/about/index.htm [accessed 2023-12-13]
2. Zimmet P, Alberti KG, Magliano DJ, Bennett PH. Diabetes mellitus statistics on prevalence and mortality: facts and fallacies. Nat Rev Endocrinol 2016;12(10):616-622. [doi: 10.1038/nrendo.2016.105] [Medline: 27388988]
3. Heart disease facts. Centers for Disease Control and Prevention. URL: https://www.cdc.gov/heartdisease/facts.htm [accessed 2023-12-13]
4. Behavioral risk factor surveillance system—2018 data. Centers for Disease Control and Prevention. 2019. URL: https://www.cdc.gov/brfss/ [accessed 2023-12-13]
5. Froehlich-Grobe K, Jones D, Businelle MS, Kendzor DE, Balasubramanian BA. Impact of disability and chronic conditions on health. Disabil Health J 2016;9(4):600-608. [doi: 10.1016/j.dhjo.2016.04.007] [Medline: 27216441]
6. Odnoletkova I, Goderis G, Nobels F, Fieuws S, Aertgeerts B, Annemans L, et al. Optimizing diabetes control in people with type 2 diabetes through nurse-led telecoaching. Diabet Med 2016;33(6):777-785. [doi: 10.1111/dme.13092] [Medline: 26872105]
7. Lee JA, Choi M, Lee SA, Jiang N. Effective behavioral intervention strategies using mobile health applications for chronic disease management: a systematic review. BMC Med Inform Decis Mak 2018;18(1):12 [FREE Full text] [doi: 10.1186/s12911-018-0591-0] [Medline: 29458358]
8. Whitehead L, Seaton P. The effectiveness of self-management mobile phone and tablet apps in long-term condition management: a systematic review. J Med Internet Res 2016;18(5):e97 [FREE Full text] [doi: 10.2196/jmir.4883] [Medline: 27185295]

9. Rush KL, Hatt L, Janke R, Burton L, Ferrier M, Tetrault M. The efficacy of telehealth delivered educational approaches for patients with chronic diseases: a systematic review. Patient Educ Couns 2018;101(8):1310-1321 [FREE Full text] [doi: 10.1016/j.pec.2018.02.006] [Medline: 29486994]
10. Polisena J, Coyle D, Coyle K, McGill S. Home telehealth for chronic disease management: a systematic review and an analysis of economic evaluations. Int J Technol Assess Health Care 2009;25(3):339-349. [doi: 10.1017/S0266462309990201] [Medline: 19619353]
11. Bull TP, Dewar AR, Malvey DM, Szalma JL. Considerations for the telehealth systems of tomorrow: an analysis of student perceptions of telehealth technologies. JMIR Med Educ 2016;2(2):e11 [FREE Full text] [doi: 10.2196/mededu.5392] [Medline: 27731865]
12. Edwards L, Thomas C, Gregory A, Yardley L, O'Cathain A, Montgomery AA, et al. Are people with chronic diseases interested in using telehealth? a cross-sectional postal survey. J Med Internet Res 2014;16(5):e123 [FREE Full text] [doi: 10.2196/jmir.3257] [Medline: 24811914]
13. Rimmer JH, Riley B, Wang E, Rauworth A, Jurkowski J. Physical activity participation among persons with disabilities: barriers and facilitators. Am J Prev Med 2004;26(5):419-425. [doi: 10.1016/j.amepre.2004.02.002] [Medline: 15165658]
14. Bellg AJ, Borrelli B, Resnick B, Hecht J, Minicucci DS, Ory M, et al. Enhancing treatment fidelity in health behavior change studies: best practices and recommendations from the NIH behavior change consortium. Health Psychol 2004;23(5):443-451. [doi: 10.1037/0278-6133.23.5.443] [Medline: 15367063]
15. Zengul A, Evans E, Hall A, Qu H, Willig A, Cherrington A, et al. Telehealth behavioral intervention for diabetes management in adults with physical disabilities: intervention fidelity protocol for a randomized controlled trial. JMIR Res Protoc 2021;10(9):e31695 [FREE Full text] [doi: 10.2196/31695] [Medline: 34505835]
16. Evans E, Zengul A, Hall A, Qu H, Willig A, Cherrington A, et al. Disability-inclusive diabetes self-management telehealth program: protocol for a pilot and feasibility study. JMIR Res Protoc 2021;10(9):e31689 [FREE Full text] [doi: 10.2196/31689] [Medline: 34505831]
17. Willard-Grace R, Chen EH, Hessler D, DeVore D, Prado C, Bodenheimer T, et al. Health coaching by medical assistants to improve control of diabetes, hypertension, and hyperlipidemia in low-income patients: a randomized controlled trial. Ann Fam Med 2015;13(2):130-138 [FREE Full text] [doi: 10.1370/afm.1768] [Medline: 25755034]
18. Sharma AE, Willard-Grace R, Hessler D, Bodenheimer T, Thom DH. What happens after health coaching? observational study 1 year following a randomized controlled trial. Ann Fam Med 2016;14(3):200-207 [FREE Full text] [doi: 10.1370/afm.1924] [Medline: 27184989]

Abbreviations

AI: artificial intelligence
NIH BCC: National Institutes of Health Behavior Change Consortium framework
REDCap: Research Electronic Data Capture

Edited by A Mavragani; submitted 05.10.23; this is a non–peer-reviewed article;accepted 23.11.23; published 12.02.24.

Please cite as:
Evans E, Zengul A, Subhash Chilke T, Knight A, Willig A, Cherrington A, Mehta T, Thirumalai M
Telehealth Behavioral Intervention for Chronic Disease Self-Management in Adults With Physical Disabilities (My Health, My Life, My Way): Protocol for Intervention Fidelity and Dashboard Design for a Randomized Controlled Trial
JMIR Res Protoc 2024;13:e53410
URL: https://www.researchprotocols.org/2024/1/e53410
doi:10.2196/53410
PMID:38345845

Protocol

A Digital Intervention to Improve Skin Self-Examination Among Survivors of Melanoma: Protocol for a Type-1 Hybrid Effectiveness-Implementation Randomized Trial

Sharon Manne[1], PhD; Carolyn J Heckman[1], PhD; Sara Frederick[1], MS; Alexis A Schaefer[1], MPH; Christina R Studts[2], PhD; Olga Khavjou[3], MA; Amanda Honeycutt[3], PhD; Adam Berger[1], MD; Hao Liu[1], PhD

[1]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, United States

[2]University of Colorado Anschutz Medical Campus, Aurora, CO, United States

[3]RTI International, Research Triangle Park, NC, United States

Corresponding Author:
Sharon Manne, PhD
Rutgers Cancer Institute of New Jersey
195 Little Albany St,
New Brunswick, NJ, 08901
United States
Phone: 1 (732) 357 7978
Email: mannesl@cinj.rutgers.edu

Abstract

Background: Although melanoma survival rates have improved in recent years, survivors remain at risk of recurrence, second primary cancers, and keratinocyte carcinomas. The National Comprehensive Cancer Network recommends skin examinations by a physician every 3 to 12 months. Regular thorough skin self-examinations (SSEs) are recommended for survivors of melanoma to promote the detection of earlier-stage, thinner melanomas, which are associated with improved survival and lower treatment costs. Despite their importance, less than a quarter of survivors of melanoma engage in SSEs.

Objective: Previously, our team developed and evaluated a web-based, fully automated intervention called mySmartSkin (MSS) that successfully improved SSE among survivors of melanoma. Enhancements were proposed to improve engagement with and outcomes of MSS. The purpose of this paper is to describe the rationale and methodology for a type-1 hybrid effectiveness-implementation randomized trial evaluating the enhanced MSS versus control and exploring implementation outcomes and contextual factors.

Methods: This study will recruit from state cancer registries and social media 300 individuals diagnosed with cutaneous malignant melanoma between 3 months and 5 years after surgery who are currently cancer free. Participants will be randomly assigned to either enhanced MSS or a noninteractive educational web page. Surveys will be collected from both arms at baseline and at 3, 6, 12, and 18 months to assess measures of intervention engagement, barriers, self-efficacy, habit, and SSE. The primary outcome is thorough SSE. The secondary outcomes are the diagnosis of new or recurrent melanomas and sun protection practices.

Results: Multilevel modeling will be used to examine whether there are significant differences in survivor outcomes between MSS and the noninteractive web page over time. Mixed methods will evaluate reach, adoption, implementation (including costs), and potential for maintenance of MSS, as well as contextual factors relevant to those outcomes and future scale-up.

Conclusions: This trial has the potential to improve outcomes in survivors of melanoma. If MSS is effective, the results could guide its implementation in oncology care and nonprofit organizations focused on skin cancers.

International Registered Report Identifier (IRRID): RR1-10.2196/52689

(JMIR Res Protoc 2024;13:e52689) doi:10.2196/52689

KEYWORDS

melanoma; cancer survivorship; skin self-examinations; digital interventions

Introduction

Background

More than 97,610 cases of cutaneous malignant melanomas will be diagnosed in the United States in 2023, making it the fifth most commonly diagnosed cancer. With incidence rates more than tripling from 1975 to 2020, the population of survivors of melanoma is estimated at >1 million. Among persons diagnosed with localized, regional, or distant-stage melanoma, the 5-year survival rates have improved in the last decade, with 99%, 65%, and 25% survival rates, respectively [1]. Improved survival and increased incidence have translated to an estimated annual treatment cost for melanoma of approximately US $2.5 billion [2].

Survivors of melanoma remain at risk of recurrence, second primary cancers, and keratinocyte carcinomas. Recurrence rates depend on tumor thickness and nodal involvement and range from 3% to 24% among persons with thinner lesions to 51% among persons with thicker lesions or lymph node involvement [3-5]. Recurrent or new primary melanomas occur most commonly during the first 5 years after diagnosis but can arise many years later [6,7]. Recurrent melanoma typically occurs at local or regional sites, and approximately half of distant recurrences present within the skin or lymph nodes [8,9]. Psychosocial morbidity is an issue for patients and survivors, with studies reporting higher anxiety and depressive symptoms than in the general population [10] and elevated anxiety about recurrence.

For survivors of melanoma, National Comprehensive Cancer Network guidelines recommend several actions, including skin examinations by a physician every 3 to 12 months and regular thorough skin self-examination (SSE) [11-13], which entails a deliberate, systematic inspection of all areas of the body using a mirror or the assistance of another person to examine hard-to-view areas [14]. Patient education about SSE by a health care professional is also recommended. Engagement in regular sun protection behavior is also recommended to reduce the risk of subsequent skin cancers as UV radiation from the sun is a contributing factor for melanoma and other skin cancers [2].

Limited data suggest that performance of SSE is associated with differential survival rates among patients with melanoma, and professional recommendations for regular SSE are supported by 3 research findings. First, more than half of recurrences and new primary melanomas are detected by survivors themselves [11,15,16]. Second, individuals who perform SSE are diagnosed with significantly earlier-stage melanomas than those who do not. Detection and treatment of recurrent disease and new primary cancers at earlier stages leads to improved survival, which is not accounted for by lead-time bias [17]. Third, melanomas identified through SSE are thinner than those found incidentally [16,18,19]. Retrospective studies suggest that individuals who perform SSE have lower tumor thickness. Thinner melanomas are associated with better survival [19-23]. Thus, promoting regular SSE will likely enhance the early detection of easier-to-treat recurrences and new primary cancers among survivors. For example, Robinson et al [24] found that 13.4% of patients in their SSE randomized controlled trial (RCT) developed a new melanoma over the 2-year follow-up. Patients in the SSE intervention condition detected 81% of these melanomas, approximately 34% of which were invasive, with only a 1% increase in physician visits. The costs of treating earlier- versus later-stage melanomas are significantly lower [25,26]. In summary, regular thorough SSE is recommended for survivors of melanoma and results in the detection of earlier-stage, thinner melanomas, which is associated with improved survival and lower treatment costs.

Despite its importance, engagement in regular, thorough SSE is low. Compliance rates with thorough SSE range between 7% and 17% among survivors of melanoma [14,20,22,27,28]. Studies document wide variation in SSE performance, with figures dependent upon the way that SSE is measured and the time frame for assessment. When patients are asked whether they have performed any form of SSE in the past 2 months, high rates of performance are observed (71.5%) [29]. SSE rates are higher when specifying any performance in the past year (84.3%) [30]. However, significantly lower rates are found if SSE is defined by its thoroughness. We reported that 13.7% of survivors checked 4 key areas and had someone assist them or used a mirror for hard-to-see areas [30]. Loescher et al [31] found that 16% of women and 7% of men examined each of the 7 designated body parts in the previous 2 months. Mujumdar et al [32] reported that 17% of survivors examined a minimum number of areas of the body (8 out of 9 areas) in the previous 2 months. In our recent work, 65% reported having conducted an SSE in the previous 2 months, but only 7.5% of the sample checked all 15 body parts. Hard-to-see areas were missed, including the scalp (37.9%), buttocks (40.4%), soles of the feet (41.6%), and genitals (44.4%). Less than half (46.2%) [33] reported using a mirror to view hard-to-see places, and only 39% reported asking for assistance. In total, 2% reported using a mole map to guide their most recent SSE.

A limited number of interventions have been evaluated to improve SSE among survivors of melanoma [24,34-37]. Existing interventions have used in-person, print, or web-based delivery modes. Several have demonstrated improvements in SSE [34,35]. Limitations of previous studies include lack of a comparison group [35]; being an in-person or partner-assisted intervention, which compromises the ability to disseminate it [24]; lack of inclusion of long-term outcomes [24]; lack of inclusion of SSE performance [36] as an outcome; and low intervention use and high dropout [35]. No existing intervention is fully automated and, thus, potentially cost-effective and highly scalable. To this end, our team developed and evaluated mySmartSkin (MSS), a web-based, fully automated intervention to improve SSE among survivors of melanoma. MSS is a behaviorally based program that is delivered via the internet, tailored to the user, and fully automated with no human clinical support. MSS was compared with usual care (UC) in an RCT of 430 survivors of melanoma from New Jersey [38,39]. The results indicated a beneficial impact of MSS versus UC on the performance of thorough SSE at all follow-ups up to 1 year [24,34-37]. Effect sizes were in the small to medium magnitude range for SSE, but these effects were not sufficiently strong to scale up for implementation in the existing form.

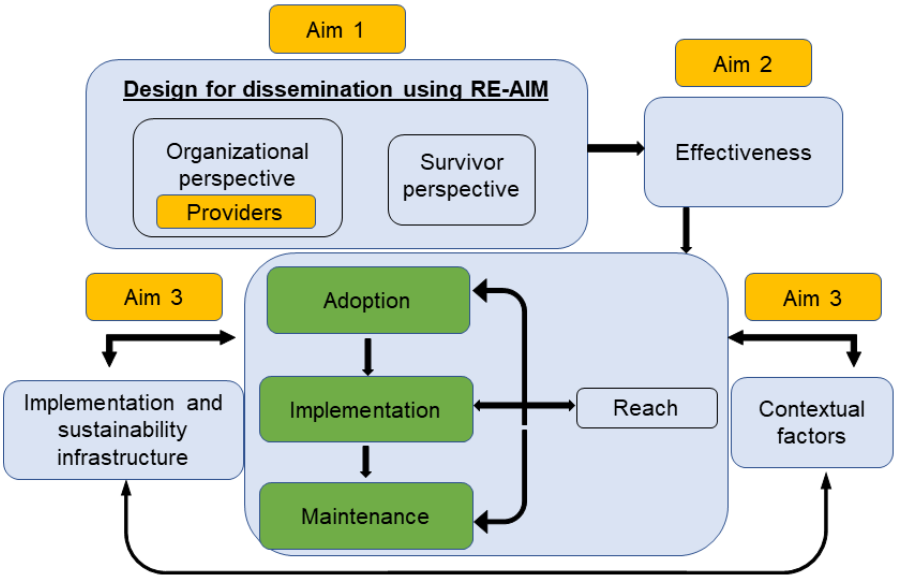
In addition to SSE, professional agencies recommend engagement in regular sun protection behaviors, such as staying in the shade, applying sunscreen with a sun protection factor of at least 30, and wearing protective clothing (eg, hats and long sleeves). Survivors of melanoma report engaging in higher levels of sun protection behaviors than the general population [40], but their sun protection behaviors do not meet the recommended guidelines [30,32,41]. To date, only 2 intervention studies have targeted improved sun protection behaviors among survivors of melanoma [34,38]. Bowen et al [34] reported significant improvements in some sun protection behaviors (eg, wearing sunglasses and staying in the shade). In our prior work [38], we evaluated the effects of MSS on sun protection behaviors, which was included as a component of the original intervention. The effects of MSS compared with UC on sun protection behaviors were only statistically significant at the 24-week follow-up in analyses that did not control for baseline sun protection behaviors or other potential covariates. Stronger and more consistent improvements in sun protection would be an important goal for future work.

Theoretical Frameworks

Previous empirical findings regarding factors associated with SSE [29,30,32,42,43] and sun protection, as well as the preventive health model (PHM) [44,45], inform the content of MSS. The PHM posits that the performance of preventive behaviors is influenced by background, affective, cognitive, and social factors. Background factors include sociodemographic characteristics, risk factors for skin cancer, medical history, and knowledge about melanoma. Affective factors include concerns about melanoma recurrence and distress about the diagnosis. Cognitive factors include perceived controllability of melanoma, self-efficacy, and benefits and barriers. Social normative factors include family and friend support and physician recommendations. In addition to our previous research on skin cancer risk reduction practices among family members of patients with melanoma [46,47], the PHM has been used successfully to understand and promote screening for colorectal and prostate cancer [44,48]. The original MSS focused on improving the perceived controllability of melanoma through the performance of comprehensive SSE; increasing the perceived benefits of SSE and sun protection; reducing barriers to SSE and sun protection; enhancing self-efficacy for SSE and sun protection; and enhancing family, friend, and physician support for sun protection.

A major challenge for intervention research is that most interventions that demonstrate a beneficial impact are not tested in effectiveness or dissemination trials and are not conducive to “real world” delivery or use. As a result, they do not penetrate the general population and, unfortunately, are not received by those who most need them [49]. Our work is guided by the Practical, Robust Implementation and Sustainability Model (PRISM), which extends the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) [50] framework to consider not only implementation outcomes but also multilevel contextual factors influencing implementation. *Reach* refers to the percentage and representativeness of persons exposed to a program. *Effectiveness* refers to the impact on key survivor-level outcomes. As MSS is a free-standing, recipient-facing intervention, *adoption* is defined as the proportion and representativeness of recipients (in this case, survivors) who adopt (ie, at least log into) the program. *Implementation* refers to the degree to which a program is delivered and received as intended. This is measured through costs, engagement, acceptability, feasibility, and appropriateness. *Maintenance* is the extent to which a program and its survivor-level effects are sustained over time. The integration of these models with the study’s aims is shown in Figure 1 [51-55]. In the proposed study, in aim 1, the goal of the iterative process of enhancing the MSS intervention using stakeholder feedback and usability testing is to improve RE-AIM outcomes, which will be assessed in aims 2 and 3. In aim 2, we focus on the effectiveness of the enhanced MSS, testing its effects on survivor-level outcomes, including clinical outcomes (eg, melanomas found). In aim 3, we address the remaining RE-AIM dimensions. In addition, to proactively identify barriers to and facilitators of future scale-up and widespread dissemination and implementation of MSS, we explore multilevel contextual factors identified by key stakeholders drawn from the PRISM domains of recipients, external environment, intervention design, and implementation and sustainability infrastructure. We anticipate that incorporating PRISM and RE-AIM throughout the study aims will ensure that the enhanced intervention is responsive to key stakeholder preferences and that we “design for dissemination” [56], recognizing potential barriers to and facilitators of future scale-up and informing our next stage of developing dissemination and implementation strategies to maximize the public health impact of MSS.

Figure 1. Integration of preventive health model and implementation frameworks with the study aims. RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance.



Study Objectives

Overview

The purpose of this type-1 hybrid effectiveness-implementation study is to evaluate the effectiveness of a web-based intervention, MSS, and explore its implementation and relevant contextual factors. A type-1 hybrid effectiveness-implementation approach requires the engagement of multilevel stakeholders throughout the research process, focus on evaluating the effectiveness of the enhanced MSS, and identification of critical factors that could promote or prevent wide-scale implementation. The study's 3 aims are guided by implementation frameworks and behavior change theories.

Aim 1

The first aim is to enhance MSS by collaborating with multilevel stakeholders. We will collaborate with stakeholders to enhance MSS through qualitative interviews and usability testing of potential intervention enhancements. Enhancements are based on empirically validated behavior change techniques (BCTs) and lessons learned from survivors' feedback in our previous study. We will use an iterative process that includes (1) key informant interviews with survivors, providers, and professional organization representatives regarding proposed enhancements; (2) conversion to an enhanced mobile-based delivery platform; (3) usability testing; and (4) iterative program refinements.

Aim 2

The second aim is to evaluate the effects of the enhanced MSS on thorough SSE (primary outcome) and examine its impact on the diagnosis of new or recurrent melanomas (secondary outcome) and sun protection practices (secondary outcome). We will conduct an RCT comparing MSS and a noninteractive educational web page with 300 survivors to test the intervention effects on these outcomes.

Aim 2 Hypothesis

We propose that MSS participants will be more likely to perform thorough SSE over the 18-month follow-up period. We will explore the impact of MSS on new or recurrent melanomas and sun protection behaviors. We anticipate diagnosing a greater number of earlier-stage melanomas and observing higher sun protection behaviors among those in MSS compared with those in UC.

Aim 3

The third aim is to assess selected implementation outcomes and identify factors relevant to future scale-up for widespread dissemination, implementation, and maintenance of MSS. We will use mixed methods to assess implementation outcomes and explore perspectives from survivors, care providers, and professional organizations to inform the selection of strategies to best disseminate and implement MSS on a broad scale. The subaims are as follows:

1. Aim 3a is to estimate program costs and assess the cost-effectiveness of MSS relative to control. We hypothesize that MSS costs will be higher than UC costs. We expect that MSS will be a more cost-effective strategy given its previous positive effects on SSE and the identification of new or recurrent melanoma. If our findings support this as expected, exploratory cost-effectiveness analyses from the health care and societal perspectives will be conducted using simulation models of melanoma-related costs, disease progression, and survival over 5- and 10-year analysis horizons.
2. Aim 3b is to examine the reach, adoption, implementation (ie, engagement, acceptability, appropriateness, and feasibility), and maintenance of MSS. For reach, we predict that the demographic characteristics of those exposed to MSS will not differ from those of the general population of survivors of melanoma. For adoption, we propose that the proportion of contacted and eligible survivors randomized to MSS who consent, complete the baseline questionnaire, and log into MSS will be equal to or greater

than the proportion in our previous efficacy trial. For engagement, we propose that 80% of MSS participants will log into the intervention at least once. For acceptability, we predict that MSS will be rated as highly acceptable. We do not have hypotheses regarding appropriateness, feasibility, and maintenance as these data will be evaluated in terms of future implementation of MSS should it have an impact on SSE and sun protection outcomes. For each of these implementation outcomes, we will assess the demographic characteristics of MSS participants to determine whether outcomes differ among survivors in specific subgroups (eg, by age, sex, race, ethnicity, and socioeconomic status).

3. Aim 3c is to identify and describe contextual factors experienced by multilevel stakeholders as key to scale-up and widespread implementation of MSS, including consideration of potential delivery settings, timing of delivery, and resources needed to promote its implementation.

Methods

Ethics Approval

Study procedures were approved by the Rutgers University institutional review board (IRB; protocol Pro2022000948).

Aim 1: Enhancements to the Existing Version of MSS Using Multilevel Stakeholders

Overview

This phase engages multilevel stakeholders in optimizing MSS by targeting multiple RE-AIM outcomes: effectiveness, adoption, implementation, and maintenance. Iterative enhancements will be made to MSS intended to increase the effects on SSE by increasing adoption, acceptability, appropriateness, feasibility, and maintenance. This process will include key informant interviews with survivors, health care delivery stakeholders, and professional organizations to inform the selection of enhancements from the potential theory-based strategies we identified based on the findings and survivor feedback from our previous RCT. This user-centered process will involve assessment of preferences regarding content (eg, "What are your thoughts on the option of uploading pictures of your moles?"), use (eg, "How useful would it be to log in to MSS three months after you complete it and what would you use it for?"), and preferred ways to motivate targeted behaviors (eg, "What are your thoughts about incentives such as free products?"). This phase of our design for dissemination approach will use an iterative process that includes (1) key informant interviews with survivors of melanoma and care providers to inform the selection of proposed theory-based enhancements, (2) conversion to a mobile-based intervention delivery platform incorporating selected enhancements, (3) usability testing with survivors who use the program for 1 month, and (4) program refinement.

Proposed Enhancements

The existing MSS content was guided by PHM and evidence-based BCTs. The original MSS included two categories of BCTs: (1) prompts (participants could set an email reminder to perform SSE on specific dates for the duration of study participation) and (2) planning (participants could set a goal related to SSE and select up to 2 action steps to address barriers). The other material primarily targeted SSE knowledge (eg, how to recognize a suspicious growth) and self-efficacy (building confidence in identifying suspicious growths), which were the mediators of MSS effects on SSE.

Our selection of proposed enhancements was guided by two goals: (1) to optimize engagement with MSS and (2) to increase sustained performance of SSE. A summary of enhancements is shown in Textbox 1. We focused on optimizing engagement as participants who used MSS more were more likely to perform SSE across the follow-up period, which we are now extending. Thus, increasing engagement with MSS should enhance its impact over time.

Textbox 1. Proposed enhancements to mySmartSkin (MSS).

Self-monitoring and performance feedback

- Upload pictures of moles each month on mole map
- Illustrate body parts checked each month
- Bar graph of completed skin self-examinations (SSEs) over time from baseline to 1 year on the MSS home page
- Monthly feedback on progress with SSE

Incentives for success

- Incentives for self-reported SSE, core completion, and SSE and sun protection goal setting: rulers, reminder stickers, sun hats, sunscreen, sun protection factor ChapStick, sun safety checklist magnet, calendars, hanging door signs with the ABCDEFs (asymmetry, border irregularity, color variation, diameter of >6 mm, evolving, and funny looking) of melanoma, sun umbrella, among others (up to 6 incentives)

Prompts

- Personalized text reminder delivered the day before SSE is due each month to perform it, with a link to the self-check program
- Tailored reminder of body parts to remember to check

Goals and planning

- Identification of personal barriers to SSE and sun protection behaviors
- Continued troubleshooting of ways to address SSE barriers and sun protection behaviors
- Regular personalized feedback and ability to track progress on SSE and sun protection goals

Social support

- Discuss the importance of support for change
- Identify someone to support SSE (eg, spouse) and how the patient would like to talk to and involve them
- Provide SSE information via email to authorized support person

To optimize initial engagement, we are implementing four enhancements: (1) enhancing participant-facing recruitment materials (eg, advertisements, emails, and study home page) by including narratives from survivors and oncologists about MSS and the importance of thorough SSE, (2) streamlining enrollment materials and processes (eg, screening and baseline surveys and instructions), (3) reaching out to participants who do not log into MSS by day 3 to provide a brief orientation session fostering ease of access (ie, review modules and topics and the importance of completing modules, show the participant how to log in, and discuss SSE benefits for finding recurrence early), and (4) informing participants about incentives for completion of each core and other tasks within the program.

To improve sustained SSE, we identified 6 categories of BCTs for the proposed enhancements [57]; we included (1) self-monitoring and performance feedback to improve self-efficacy (eg, uploading photos of moles and saving them to compare with the next SSE); (2) behavioral incentives (eg, provided for completing SSE); (3) additional prompts for SSE (eg, programmed reminders about missed areas of the body); (4) adding a more comprehensive approach to setting goals and planning, including continued troubleshooting of barriers; (5) including more content on receiving assistance and support from others in performing SSE (including the option to email an authorized support person about assisting with the participant's SSE); and (6) adding a goal-setting component that fosters habit formation and maintenance of behavior change. We created an in-depth goal-setting section that allows users to track their progress and make updates to their goals and progress over time. The goal-setting component is tailored based on the user's current SSE and sun protection behaviors, and the purpose of this component is to assist in the creation of a plan to improve both behaviors.

In terms of sun protection behaviors, we included a sun safety core with content categorized into chapters addressing (1) learning more about sun safety with topics such as risks of UV rays, risks of unprotected sun exposure, sunscreen education, how to avoid sunburns, and other sun protection behaviors; (2) assessing current sun protection behaviors; (3) increasing confidence in and motivation for sun protection; and (4) setting sun protection goals. A more detailed summary of the content of each core is provided in Table 1.

Table 1. Enhanced mySmartSkin intervention content.

Section	Key content	Interactive features
Tutorial	• Overview of navigation, sections, and features	• N/A[a]
Core 1: learn about spots	• Personal melanoma history • Skin cancer facts and figures • Melanoma risk factors • Risk of recurrence • Purpose of SSE[b] • How to conduct an SSE • The ABCDEFs[c] of melanoma • Your experience doing SSE • What to do when you find a suspicious spot • Importance of SSE and physician skin examinations • Confidence in checking spots	• Mole facts and fiction • ABCDEF-identifying challenge quiz • Suspicious or not mole challenge • Vignette and physician video and audio clips • SSE goal setting
Core 2: sun-safe behaviors	• Sun-safe behaviors • Risks of sun exposure • UV index • Types of sunscreen • Avoiding sunburns during outdoor activities • Risk assessment for outdoor activities • Sun-safe clothing • Limiting sun exposure • Increasing confidence and motivation for sun safety • Prioritizing sun-safe behaviors • SSE goal setting	• Sunscreen FAQs[d] • Sunscreen facts and fiction • Tanning facts and fiction • Assessing current tanning beliefs • Vignette and physician video or audio clips • Sun-safe behavior importance rating • Sun safety goal setting
MyStuff	• Goal summary • SSE progress tracker • Badges and prizes	• Goal progress tracker

[a]N/A: not applicable.

[b]SSE: skin self-examination.

[c]ABCDEF: asymmetry, border irregularity, color variation, diameter of >6 mm, evolving, and funny looking.

[d]FAQ: frequently asked question.

Key Informant Interviews to Gather Input on Enhancements

This phase of aim 1 has been completed. The procedures are described in the following sections, and the results are described later in the paper (see the *Results* section).

Sample

We planned to recruit 10 survivors of melanoma who had completed treatment within up to 3 years since diagnosis from the Rutgers Cancer Institute of New Jersey (CINJ) through new case ascertainment by research staff using electronic medical records. On the basis of our past experience in qualitative assessments, this sample was expected to provide thematic saturation of the data, although additional interviews could be conducted if needed.

Questionnaire

Following informed consent procedures, participants completed a brief demographic questionnaire before their interview began. Participants self-reported their age, sex or gender, race, ethnicity, education, current insurance coverage, school enrollment, employment, and marital status. Patients also reported current SSE practices.

Procedures

The project coordinator (AS) conducted the interviews, which were audio recorded with participant permission and approximately 45 minutes in duration. During the interviews, participants were shown prototypes and wireframe illustrations of the proposed enhancements. To ensure that feedback was gathered on all aspects of the MSS platform, interviewers highlighted different sections, including the goal-setting activity sequence and skin self-check body map. The semistructured interviews elicited feedback on the proposed enhancements. We included probes about enhancements based on stakeholders' positive, neutral, or negative reactions (eg, "What parts of the site did you think were most interesting and helpful?" and "What parts were less helpful or seemed less relevant to you?"). Phase 1 participants received US $50 for the interviews. These interviews were conducted in person at the CINJ or using videoconferencing software. The interviewer took field notes, and the interviews were transcribed verbatim.

Refining Enhancements

The study team reviewed the field notes and verbatim transcriptions of key informant interviews. The responses to each proposed enhancement were coded as positive, neutral, negative, or mixed. Although potential enhancements were based on findings from the previous RCT, suggestions from participants, BCTs, and proven ways to optimize engagement, if particular enhancements were perceived negatively by multiple stakeholders, we used these interviews to explore alternatives that would be more acceptable. For those enhancements with multiple negative or mixed comments, the team decided whether the issue could be addressed feasibly and crafted changes to the content and approach that were congruent with stakeholder feedback. The stakeholders in later interviews reviewed the changes made in response to feedback given in earlier interviews to provide confirmation on whether the issue was adequately addressed. The study team provided feedback to the web developer, Radiant (Radiant Creative Group LLC), throughout the interview process for changes to be incorporated in a timely manner.

Conversion to a Mobile-Based MSS Platform, Usability Testing, and Refinements With Multilevel Stakeholders

Stakeholder-informed enhancements to content and program features will be incorporated with the existing content and migrated to the mobile-based delivery platform in collaboration with Radiant. Testing will be conducted throughout the preproduction and production stages to ensure the suitability of the content for the intended audience. Weekly meetings with Radiant will be conducted to review uploaded content.

Usability Testing, Feedback, and Refinements

Testing will be accomplished by conducting focused interviews with up to 10 survivors of melanoma, 5 health care providers, and 5 organization representatives who will each receive US $100. Testing is modeled after a National Cancer Institute website design project [58]. The process will involve checking the content with participants for attractiveness, comprehension, acceptability, and persuasion. In addition, participants will be able to use MSS for approximately 1 week before the interview so that we can gather input on features that are planned over time, such as self-monitoring and performance feedback, incentives, and prompts. A series of questions and structured guides will be prepared in advance related to the elements to be evaluated.

In the set of interviews, all enhancements and engagement tools, including reminder prompts, will be activated, providing an opportunity to evaluate all components of the enhanced MSS. After that, we will set up a virtual meeting in which the participant will provide feedback about acceptability, ease of use or intuitiveness, and satisfaction. During this session, we will discuss the topic areas and review MSS using a shared screen to allow participants to react to each screen. Participants will be asked to provide feedback on features. These sessions will be digitally video recorded and transcribed, and AS will take notes. The data will be summarized and reviewed to determine further modifications to be made. These efforts will yield a set of understandable, acceptable, and appealing enhancements to MSS that are customized to the needs, capabilities, and preferences of patients with melanoma, providers, and organizational stakeholders. We will conduct weekly meetings that include Radiant and the study team to review and produce content. Once the final beta website has been agreed upon by the full research team, it will undergo extensive testing by Radiant to ensure that the programming is functioning correctly.

Aim 2: Evaluate Effects of MSS Versus a Noninteractive Educational Web Page on SSE

Overview

Phase 2 is a randomized effectiveness trial in which MSS will be tested in an RCT comprising 2 groups (MSS vs a noninteractive educational web page) and 5 assessments (baseline, 3 months, 6 months, 1 year, and 18 months) with 300 survivors of melanoma. The main goal is to evaluate the effects of MSS on thorough SSE and examine the impact on clinical outcomes (eg, diagnosed early-stage skin cancers).

Recruitment

Overview

We will recruit participants from 2 sources: state cancer registries and Facebook. This approach was adopted to prepare for dissemination by assisting the team in comparing the reach of the 2 methods of recruitment. This will foster our ability to determine future settings. The registries include all patients with melanoma in each state, which facilitates eventual generalizability. We chose NJ and CA registries because the 2 states are geographically disparate and sociodemographically diverse, and we have worked successfully with both registries on current projects (CA2219854 and CA221854). We chose Facebook as a second approach as the vast majority of Americans (84% in 2021) [59] use social media, with use steadily increasing each year. This strategy will reach a broad audience of survivors. In addition, many melanoma and skin cancer advocacy groups are active on social media, which will inform the potential for working with them on future dissemination.

Registries

We will recruit from the New Jersey State Cancer Registry (NJSCR) and the Cancer Registry of Greater California (CRGC). Owing to state laws, allowable recruitment procedures differ. NJSCR procedures entail case ascertainment, a letter to the physician, an address check, a letter mailed to the patient, up to 12 calls to verify that they received the letter, and the provision of verbal consent to send contact information to the CINJ. The CINJ reaches out to the patient to describe the study and send a link to the MSS website. We have enhanced the CRGC procedures to be as similar as possible to those of the NJSCR. The CRGC queries their database, confirms that the patient is alive, and checks this information with the provider. Case information is sent to the CINJ, a letter is sent explaining the study followed by up to 12 calls to the patient to obtain their email address, and a link to the study web page is emailed. The process takes approximately 2 months.

Facebook

We will use paid Facebook advertisements. We will work with a social media marketing company to develop keywords and advertisements targeting individuals with characteristics similar to those of survivors of melanoma (eg, older age). As noted previously, this approach has been successfully used in 2 previous and one current skin cancer–related intervention project [60-62]. This approach will also recruit a broader population of survivors of melanoma than the previous efficacy trial.

Eligibility

The eligibility for this trial is as follows:

1. Diagnosis of primary pathological stage-0 to stage-III cutaneous malignant melanoma
2. Being 3 months to 5 years after surgery
3. No current evidence of cancer
4. No adherence to thorough SSE [14] (ie, did not check the entire body at least once during the past 3 months)
5. Age of ≥18 years
6. Internet access
7. Ability to speak and read English
8. Ability to provide informed consent

The incidence is most common among non-Hispanic White individuals, who have an annual rate of 28 cases per 100,000 compared with 7 in American Indian or Alaska Native individuals; 5 in Hispanic individuals; and 1 in non-Hispanic Black, Asian, and Pacific Islander individuals (92.4% among non-Hispanic White individuals). Consistent with population rates, we will oversample minority groups from cancer registries to ensure a minimum of 7.6% racial and ethnic minority group survivor enrollment.

Sample

The projected sample size is 300. Participants will be recruited using 2 methods. Half of the sample will be recruited from 2 state cancer registries. We expect >10,000 eligible patients with melanoma from the 2 registries during our recruitment period. We will select a random sample from each diagnosis year to balance the year of diagnosis. The acceptance rate for the previous MSS study was 40.9%, but we anticipate a lower recruitment from the registry participants in this study based on our recent work with both CRGC and NJSCR patients (CA221854) [63]. Both cancer registries have a large number of survivors annually. Thus, we will randomly select a subset of cases from each of the retrospective 5-year time frames. The other half of the sample will be recruited via Facebook. We will use paid Facebook advertisements targeted at persons who follow skin cancer–related causes and organizations**.** We will end recruitment from each source when the required sample size is reached.

Enrollment, Randomization, Intervention Delivery, and Follow-Up Surveys

Potential participants recruited via registries will be asked for their email when they verbally consent to participate in the study. Staff will then email these potential participants the link to the study's web page. Participants recruited via social media advertisements will be automatically linked to the study web page when they click on the "learn more" part of the advertisement. Once on the web page, the following automated, completely web-based procedures will be used for enrollment. On the study's web page, there is a screening survey to determine eligibility. Potential participants will complete the eligibility screener. If eligible, the program automatically moves to the electronic consent. Once consent is obtained, the program automatically moves to the baseline survey. After survey completion, the program randomizes the participant to MSS or the comparison condition and automatically moves to either the MSS landing page or the comparison condition landing page. Randomization will be stratified according to disease stage and time since diagnosis (3 months-3 years and 4-5 years) and, then, within strata, block randomized using blocks of 20 participants overseen by the study statistician following standard operating procedures of the CINJ Biostatistics Shared Resource.

Participants who do not log into the MSS program by day 3 will be contacted by a study coordinator via SMS text message, email, or phone 3 times between days 3 and 10 to remind them about logging into MSS. Participants who log in but do not review core 1 by day 5 will be contacted 3 times via email, SMS text message, or calls to invite them to review core 1. These interactions will also serve as an orientation for the participants allowing them to ask any questions about the study or the intervention.

Survey Procedures

Participants will be prompted (via automated email, as well as via SMS text message, telephone, and mail, as necessary) to complete the following web-based surveys: follow-up 1 at 3 months after the baseline, follow-up 2 at 6 months after the baseline, follow-up 3 at 1 year after the baseline, and follow-up 4 at 18 months after the baseline. Participants who do not complete the surveys will be reminded as follows: (1) reminder email and SMS text message with a link to the survey if it is not returned after 1 week, (2) call with a voicemail if no contact is made and email with a link to the survey if it is not returned after 2 weeks, and (3) the same procedure as at 2 weeks if the survey is not returned after 3 weeks. Participants who do not return the survey after a month will be considered lost to follow-up at that time point. Our primary effectiveness analyses will focus on individuals' performance of thorough SSE at 18 months, which will ensure that all participants' SSE practices are assessed over a long time frame and increase the likelihood of detecting new or recurrent melanomas. Participants will receive incremental gift card amounts for each survey (maximum total of US $120).

Intervention Procedures

Participants will have a unique identifying user code and create a password to access the interventions. If users forget their password, they will provide a unique answer to a personal question and the database will return the forgotten password. If users forget both their user ID and password, they can contact the technical assistance hotline. In the previous study, navigation issues were rare. We anticipate that it will take participants approximately 1 hour to complete the entire MSS intervention once and approximately 15 minutes to complete the comparison

condition. Participants will have access to the interventions for 18 months.

Comparison Group

We chose a noninteractive educational web page comparison group for the following reasons: (1) the information incorporated is widely available to the public and used in dermatology and primary care, (2) the digital delivery method is similar to that of MSS, (3) it allows for a comparison of MSS effects with a minimal knowledge-based educational intervention, (4) it permits a comparison of MSS effects with the results of previous studies that used minimal comparison interventions, (5) it presents a standardized intervention rather than a variable treatment-as-usual intervention, (6) a no-intervention control would be unethical for this high-risk population, and (7) we considered using an intervention for another health issue (eg, nutrition) but anticipated that survivors of melanoma would be less likely to participate. We will create a static educational web page whose content will be based on freely available, accurate information relevant to melanoma, melanoma risk, and SSE. Possible topics include the warning signs of melanoma [64], the risk of recurrence among survivors of melanoma, and how to perform an SSE [65].

Aim 2 Measures

Covariates

Demographics

The demographic information collected will include age, sex, race, ethnicity, education, marital status, state of residence, employment, income, and insurance.

Clinical Characteristics

The clinical characteristics collected will be date of diagnosis, stage, and treatment received.

Melanoma Risk

The melanoma risk information collected will be eye color, natural hair and skin color, skin reactivity to the sun, freckling, moles, sunburn history, indoor UV tanning, and family history.

Environmental Factors

The environmental factors collected will be month of assessment, residential location, and average UV index at solar noon over the 3 months before each time point.

Primary Outcome Measure: Skin Self-Check Comprehensiveness

A full list of outcome measures and covariates is shown in Table 2. The primary outcome consists of the following items: (1) “Have you, or anyone else, not including a doctor or other healthcare professional, ever checked any part of your body for signs of skin cancer?” (yes or no), (2) “If yes, in the last three months, did you check your body for early signs of skin cancer?” (yes or no), and (3) “Doing a thorough skin check or skin self-examination means spending time looking at the skin systematically and deliberately. Please indicate whether you thoroughly checked each of the following areas of your body the last time you checked your body for early signs of skin cancer: Scalp, face, neck, shoulders, front of arms, back of arms, chest, stomach, upper back, lower back, front of legs, back of legs, bottom of feet, buttocks, and genitals” (yes or no for each). For all time points, comprehensiveness will be based on the total number of body parts checked among participants who conducted an SSE in the last 3 months. Participants who did not conduct an SSE in the last 3 months will be coded as 0 for this outcome.

Table 2. Aim 2 measures.

Measure	Baseline	Time 2	Time 3	Time 4	Time 5
Covariates					
Date of birth	✓				
Sex	✓				
Marital status	✓				
Race and ethnicity	✓				
Education	✓				
Insurance status	✓				
Employment status	✓				
Time since diagnosis	✓				
Month of assessment	✓	✓	✓	✓	✓
Residential location					
Average UV index at solar noon	✓	✓	✓	✓	✓
Outcomes					
Skin self-examination	✓	✓	✓	✓	✓
Sun protection behaviors	✓	✓	✓	✓	✓
Melanoma diagnosis, stage, thickness, and date		✓	✓	✓	✓
Clinician confirmation of cancer		✓	✓	✓	✓

Secondary Outcomes

Sun Protection Behaviors

Participants report how often they engage in 4 behaviors when outside on a sunny day: wearing sunscreen with a sun protection factor of ≥30, wearing a long-sleeved shirt, wearing a wide-brimmed hat, and staying in the shade [66]. Items are rated on a 5-point Likert scale (1=*never*; 5=*always*).

Clinical Outcomes

Participants report whether a new melanoma or other skin cancer was diagnosed and the stage, thickness, and date. Physician confirmation of this information will be collected.

Analyses of the Impact of MSS on SSE, Sun Protection, and Clinical Outcomes

Analyses of Thorough SSE and Sun Protection

Demographics and baseline variables will be compared between the 2 conditions using chi-square tests and ANOVAs for categorical and continuous variables, respectively. These variables, including outcomes, will also be compared by recruitment source. Missing data will be handled using multiple imputation with 50 imputed samples [67]. Tests of intervention effects on thorough SSE and sun protection will be conducted separately for each wave of postintervention data collection using logistic regression models that treat baseline SSE or sun protection, respectively, as a covariate. Given the large number of potential additional demographic and medical covariates, additional analyses will include the covariates that are significant predictors of the outcome.

Sample Size and Power

On the basis of our previous study, we expect follow-up survey completion rates between 80% and 93% at the 1-year time point and 80% to 85% at the 18-month time point, which will result in an expected final sample size of N=255. In the previous trial, thorough SSE occurred at a rate of approximately 30% in MSS at each time point, and effect sizes for conducting a thorough SSE ranged from w=0.29 (8 weeks) to w=0.21 (6 months). Given that the MSS intervention will be enhanced, we expect that the SSE rate will be higher (45%), which will result in approximately w=0.36. A sensitivity power analysis using G*Power indicated that a sample of N=255 will be able to detect an even smaller effect of w=0.22 with a 2-tailed test, Cronbach α of .05, and power of 0.95. Thus, the expected effect of w=0.36 with a sample size of N=255 will be detectable with a power of 0.99. Given that sun protection behavior is a secondary outcome, we are not powering the trial for this variable.

Analyses of the Impact of MSS on the Diagnosis of New or Recurrent Melanoma

The impact of MSS would be strengthened with data suggesting that survivors who use MSS detect suspicious growths and bring them to physicians for appropriate workup and diagnosis. Given the likely low recurrence rate over the 18 months that participants are followed for in this trial, the study is not powered for testing hypotheses on this end point. Rather, we will conduct an exploratory analysis to examine whether diagnoses differ between MSS and UC. Specifically, the number of diagnoses of earlier-stage new and recurrent melanoma at 18 months will be compared for the 2 conditions using either negative binomial regression models or binary logistic models depending on the distribution of new diagnoses (ie, if there are patients with more than one new diagnosis during the period).

If our findings show that more melanomas are detected in MSS, we will conduct exploratory cost-effectiveness analyses from the health care and societal perspectives by creating simulation models of melanoma-related costs, disease progression, and survival over 5- and 10-year analysis horizons from the start of the trial (aim 3a).

Aim 3: Implementation Outcomes and Contextual Factors Relevant to Future Scale-Up

Overview

The type-1 hybrid effectiveness-implementation approach allows us to obtain vital data to inform future scale-up, dissemination, and implementation. This aim has 3 parts. In aim 3a, we will assess the costs of delivery of MSS and the control condition website; if indicated by the results of aim 2, we will conduct cost-effectiveness analyses. In aim 3b, guided by RE-AIM, we will evaluate the implementation outcomes of MSS from the aim 2 effectiveness trial. In aim 3c, we will elicit actionable feedback on contextual factors relevant to future scale-up, dissemination, implementation, and maintenance from multilevel stakeholders, including survivors, providers, and representatives of organizations invested in melanoma survivorship care. Quantitative and qualitative data from aims 3a, 3b, and 3c will be analyzed and interpreted together to provide valuable insights and directions regarding implementation strategies needed to inform the scale-up and widespread implementation, focusing particularly on reach, adoption, implementation, and maintenance. The results of aim 3 as a whole will answer the following key questions: how can we increase the number of MSS users to maximize adoption? What dissemination channels are preferred to increase our reach to survivors? How can MSS be maintained to provide a sustainable intervention for survivors? What resources or adaptations are needed for organizations and practices to integrate MSS into their survivorship care offerings?

Aim 3a: Costs and Cost-Effectiveness

Assessment of Program Costs

The research team will track the costs of delivering both MSS and the noninteractive educational web page. Costs will first be estimated from a program perspective, capturing the explicit resources required to deliver and maintain the program after all start-up costs (eg, development and programming costs) have been incurred. Costs that are needed to deliver the intervention will be collected to inform the cost of scale-up, but any research-related costs that would not be required for standard program implementation will also be tracked. Sunk costs, which are one-time upfront costs, will be reported separately from ongoing program implementation costs. Program cost data will be collected using a modified version of previous cost surveys developed by the research team and adapted for several interventions [68-73]. The cost surveys capture all relevant labor- and non–labor-related inputs necessary to quantify costs. Labor costs for program staff time (via questionnaires) will be valued using actual or estimated wages. Nonlabor costs will be obtained from program billing records; these include materials and supplies used to support program and intervention activities and costs of facilities and contracted services. The feasibility of including the value of participant time spent on the intervention will also be explored, where participants' time will be valued using age- and sex-specific wage rates. In addition, if the results of the analysis in aim 2 indicate that more melanomas are found among MSS participants than among the educational web page arm participants, costs to the health care sector will be estimated. These include the costs of diagnosing and treating recurrent melanoma. Published estimates of stage-specific medical costs of melanoma will be used to calculate the treatment costs of melanoma by stage at detection [74-79]. To estimate costs from a societal perspective, the costs to each stakeholder group will be summed, including program implementation costs, costs to the health care sector, and the value of participants' time.

Cost Analysis

Total and incremental program costs will be estimated for each arm. Program development costs, a one-time capital investment, will be calculated separately from ongoing implementation costs, or the costs to maintain program delivery for the duration of the intervention. Analyses will distinguish between fixed costs, those that do not vary with enrollment rates (eg, server maintenance), and variable costs, which increase for each participant added. As most costs for MSS are expected to be fixed, the mean cost per participant will be driven largely by the number of enrolled participants. To explore the costs of scale-up, sensitivity analyses will be conducted regarding additional program dissemination efforts and variations in uptake rates. The primary cost-effectiveness analysis will evaluate the additional costs per thorough SSE completed for MSS versus educational web page participants over the 18-month trial. This analysis will be conducted from the program, health care sector (including program costs and costs of health care use for lesions detected), and societal (ie, health care sector plus participant costs) perspectives. The incremental cost-effectiveness of MSS relative to the educational web page will be determined as the difference in mean costs between the 2 arms divided by the difference in mean outcome changes [80,81].

Simulation Models of Melanoma-Related Costs, Disease Progression, and Survival

If the findings show that more melanomas are detected in early stages for the MSS arm relative to the educational web page arm as expected, secondary or exploratory cost-effectiveness analyses will be conducted from the health care sector and societal perspectives by creating statistical simulation models of melanoma-related costs and disease progression over 5- and 10-year analysis horizons from the start of the trial. Assuming the equivalent likelihood of a melanoma recurrence for MSS and educational web page participants, trial data on stage at diagnosis for melanomas detected during the trial (from aim 2) and published estimates of average stage at diagnosis for survivor recurrences in the general population will be used. Melanoma treatment costs beyond the trial period will be simulated for both arms, where the hypothesis is that MSS participants will have lower treatment costs than those in the educational web page arm as earlier detection requires less aggressive treatment. Mortality will also be simulated for both arms to create an effectiveness measure of simulated life years gained (LYGs) for MSS versus the educational web page

comparison group. To estimate LYGs, reductions in melanoma mortality for MSS versus the comparison group will be combined with life expectancy data [82]. As health-related quality of life among survivors of melanoma is similar to health-related quality of life in the general population, there will be no quality adjustment of LYGs as any differences across arms in quality-adjusted life years would be driven by differences in mortality [83-88]. The cost-effectiveness analysis will examine the total incremental costs of MSS compared with the educational web page arm. Incremental costs include program implementation costs (excluding sunk and research costs), health care use costs incurred during the trial and any melanoma treatment costs simulated to occur beyond the trial, and the value of patients' time to participate in the intervention. Incremental effectiveness will be calculated as LYGs for MSS compared with the educational web page arm. Base analyses will discount future costs and life years and use bootstrapping methods to generate 95% CIs for the incremental cost-effectiveness ratio. Sensitivity analyses will explore factors such as rates of detection of thin lesions through SSE, which may make MSS more cost-effective than the educational web page comparator.

Aims 3b and 3c: Exploration of Implementation Outcomes and Contextual Factors Relevant for Future Scale-Up

Sample

MSS Participants

All participants in the intervention trial assigned to MSS will complete surveys assessing specific implementation outcomes. A subset of MSS participants (n=30) will be purposively selected to participate in key informant interviews to reflect a diversity of MSS outcomes, MSS use, ratings of acceptability, and sociodemographic and clinical characteristics.

Additional Stakeholders

To ensure that we obtain a breadth of perspectives on the potential for scale-up, dissemination, widespread implementation, and maintenance of MSS, we will also identify and invite 20 individuals from multiple groups involved in melanoma treatment and survivorship to participate in key informant interviews. These stakeholders will include additional health care providers and representatives from the same organizations participating in aim 1. Participants in aim 3 key informant interviews will receive US $50 for completing the interviews, which will be conducted in person or via videoconferencing software.

Procedures, Measures, and Analyses

Overview

Aim 2 addresses the effectiveness of MSS. Aim 3a addresses the costs associated with delivering MSS, an important factor in the future potential scale-up of the intervention. In aims 3b and 3c, we use mixed methods to focus on the remaining RE-AIM outcomes and PRISM domains using data from the aim 2 RCT combined with surveys and stakeholder interviews.

Quantitative Implementation Outcomes and Analyses

As this is a type-1 hybrid effectiveness-implementation study, our analyses of implementation outcomes are primarily descriptive and meant to inform future planning for scale-up, dissemination, and implementation. Analyses of *Reach* will describe the proportion of contacted individuals who express interest by completing an eligibility survey. The clinical and sociodemographic characteristics of potential participants will be described and compared with those of the population of survivors of melanoma. Analysis of *Adoption* will describe the proportion of eligible participants who enter the intervention website (Table 3). Analyses of *Implementation* will describe the indicators listed in Table 3 and examine their variability by participant clinical characteristics, sociodemographic characteristics, and melanoma risk factors assessed in aim 2. We will also examine the variability in indicators of implementation by recruitment source (registry vs social media advertisements). The Acceptability of Intervention Measure (AIM) is a brief, quantitative measure of intervention acceptability that has demonstrated content and structural validity and test-retest reliability [89] as well as face validity [90]. Participants respond to 4 statements using 5-point Likert-type scales, with higher scores indicating higher acceptability. The AIM will be completed by MSS arm participants at the first follow-up. Acceptability ratings will be summarized using descriptive statistics and compared across clinical, sociodemographic, and risk factor groups.

Table 3. Aim 3 implementation measures.

Outcome	Definition	Measurement	Data source
Reach	• Proportion and representativeness of individuals who express interest in MSS[a]	• Proportion of contacted participants who complete an eligibility survey • Sociodemographic and medical characteristics of individuals who screen vs the population of survivors	• Recruitment and enrollment data • National survivor data set (eg, NHIS[b] and HINTS[c])
Adoption	• Proportion of individuals who begin an intervention	• Proportion of contacted participants who consent, complete baseline survey, and enter the intervention website	• MSS automated data
Engagement	• How much individuals use MSS	• Number of core modules completed • SSEs[d] performed with self-check program • Number of views of MSS • Use of each enhancement (incentives)	• MSS automated data
Program costs and cost-effectiveness	• Total and incremental costs of MSS vs comparison arm; cost-effectiveness of MSS	• Surveys and billing and invoicing documents	• Staff, service provider, and participant surveys; billing and invoicing, including payments; and published literature
Feasibility	• Perception that MSS is feasible for use, dissemination, and delivery	• Qualitative key informant interviews	• Health care providers and professional organizations
Acceptability	• Perception that MSS is satisfactory	• Acceptability of Intervention Measure • Qualitative key informant interviews	• Participant surveys • Survivors, providers, and organizations
Appropriateness	• Perception that MSS is an appropriate fit for intended use	• Qualitative key informant interviews	• Survivors, health care providers, and organizations
Maintenance	• Perceptions of the likelihood, needs, and resources for maintaining MSS delivery	• Qualitative key informant interviews	• Health care providers and organizations
PRISM[e] contextual factors	• Perceived contextual factors related to scale-up and D&I[f]	• Qualitative key informant interviews	• Survivors, health care providers, and organizations

[a]MSS: mySmartSkin.

[b]NHIS: National Health Interview Survey.

[c]HINTS: Health Information National Trends Survey.

[d]SSE: skin self-examination.

[e]PRISM: Practical, Robust Implementation and Sustainability Model.

[f]D&I: dissemination and implementation.

Qualitative Key Informant Interviews

Interviews will be conducted with stakeholders from each group (ie, participants, providers, and organizations) to assess the perceptions of potential barriers and facilitators to consider for future scale-up, widespread implementation, and maintenance. MSS participant interviews will be conducted within the month following their final follow-up during the aim 2 trial. Interviews with other stakeholders will be conducted following completion of the effectiveness trial during the final study year. Semistructured interview guides will include open-ended questions and probes regarding [91] implementation outcomes of feasibility, acceptability, and appropriateness of widespread implementation of MSS for survivors of melanoma. The potential for MSS maintenance will also be explored using open-ended questions and probes, including resources available and needed for the sustainability of the intervention from multiple stakeholder perspectives. In addition, we plan to focus on three PRISM domains: (1) organizational, provider, and patient perspectives on the intervention; (2) characteristics of the recipients of the intervention (survivors); and (3) implementation and sustainability infrastructure (if MSS were to be disseminated and supported by specific organizations outside the research context). To elicit perspectives on the 3 PRISM domains of interest to scale-up, dissemination, implementation, and maintenance, interview questions (as appropriate for each stakeholder group) will focus on (1) current approaches and practices relevant to the promotion of SSE; (2)

the benefits and shortcomings of the MSS intervention; (3) barriers to MSS use (for survivors and those who may suggest it as a resource); (4) possible strategies to disseminate MSS to survivors; (5) pros and cons of suggested dissemination channels and strategies; (6) the "fit" of MSS with the missions and objectives of providers, practices, and organizations; and (7) resources, infrastructure, and other factors needed to sustain MSS.

Qualitative Analyses of Implementation Outcomes

We will follow the guidelines established by the COREQ (Consolidated Criteria for Reporting Qualitative Research) for data collection, analysis, and reporting. The audio recordings of the interviews and focus groups will be transcribed verbatim, deidentified, and imported into the ATLAS.ti software (ATLAS.ti Scientific Software Development GmbH) for analysis. Directed content analysis will be used. This structured method allows researchers to specify constructs of interest a priori (eg, acceptability, feasibility, appropriateness, and PRISM domains) and obtain detailed descriptions or elaborations of them, classifying and coding themes within and across constructs [92]. The study investigators will develop a preliminary codebook for each stakeholder group. A primary and secondary coder will independently code and discuss an initial subset of interviews to explore thematic content and then merge and explore them for concordant and discordant coding. After refining the codebooks, they will recode the first set of transcripts and determine the interrater reliability. After achieving consistency, the coding process will continue. In total, 4 randomly selected transcripts will be identified for double coding and evaluation of discordant coding, followed by any needed modifications and recoding to achieve consensus. Once the initial coding has been completed, 10% of the sample (ie, 1-2 participants from each stakeholder group) will be randomly selected and invited to participate in a member-checking process to determine whether additional data collection is necessary and ensure that valid inferences are made through coding procedures [93]. Following any further corrections, the team will develop a summative grid of emergent themes across and within stakeholder groups.

Synthesis of Quantitative and Qualitative Data to Inform Scale-Up

Mixed methods data will be analyzed and integrated using a concurrent parallel design [94]. As described previously, each type of data (quantitative and qualitative) will initially be collected and analyzed separately. A mapping and matrix approach will facilitate the integration and interpretation of the results, and joint displays will present the integrated results, connecting qualitative themes with quantitative outcomes. The results will be summarized within and across stakeholder groups to allow for consideration of multilevel dissemination and implementation strategies needed for future scale-up, dissemination, implementation, and maintenance.

Data Safety and Monitoring

Before initiating this study, the Rutgers Scientific Review Board will review the study procedures to ensure their scientific merit, safety, legality, and technical feasibility per the established policy. The proposed procedures will then be reviewed for protection against risks by the Rutgers health sciences IRB. Adverse events will be reported through the Rutgers CINJ for processing as per the established policy. This policy includes specific timelines for reporting events that are stipulated by the IRB. In addition to the IRB, the Rutgers CINJ Protocol Monitoring Committee reviews all adverse events for investigator-initiated trials as they occur. The project coordinator, under the direct supervision of the principal investigator, will be responsible for reporting any adverse events that are documented on the safety or adverse events form or reported by the study interventionist. The Rutgers CINJ Protocol Monitoring Committee will oversee the validity and integrity of the data by conducting periodic audits of the study records. The committee is empowered to suspend or close studies with major deficiencies and provides direction to investigators in the development of corrective action plans to rectify and meet identified deficiencies. As part of the Protocol Monitoring Committee function, accrual is monitored for clinical trials. All clinical trials undergo a semiannual review by the Protocol Monitoring Committee, at which time accrual figures are reviewed. Specific accrual rates for each trial are required under protocol monitoring policy. The Rutgers CINJ uses an internal audit program to address retention of participants, adherence to protocol, and data completeness. This audit program is reviewed and governed by the Protocol Monitoring Committee. In addition, there is a Data Safety and Monitoring Advisory Board. This team will consist of a dermatologist, a psychologist, and a survivor of melanoma from the community. The board, along with the study principal investigators, will convene for an in-person or virtual meeting annually. The agenda of the annual meeting will be to review risk procedures, adverse event reporting, and quality assurance. The Data Safety and Monitoring Advisory Board will review any serious adverse events reported as well as investigator adherence to eligibility rules.

Results

To date, we have completed the first phase of aim 1; the remaining phases of this aim are currently in progress. The prototype and content for the MSS intervention were developed in collaboration with Radiant Inc. Following the procedures described in the *Methods* section, one set of stakeholder interviews was conducted with 5 survivors of melanoma who were shown the SSE body map component. A second set of stakeholder interviews was conducted with another sample of 5 survivors of melanoma who were shown the goal-setting module. Participants were shown the prototypes and wireframe. The responses were summarized in field notes, and we reviewed the notes and verbatim transcriptions of key informant interviews. Each proposed enhancement was coded as supportive, neutral, negative, or mixed. For those enhancements that had multiple negative or mixed comments, the team decided whether the issue could be addressed and crafted changes to the content and approach that were congruent with stakeholder feedback.

For the 2 sets of interviews, 19 patients were approached. Of these 19 patients, 10 (53%) were enrolled and 9 (47%) refused. The sample consisted of 50% (5/10) women and 50% (5/10)

men, ranging in age from 32 to 75 (mean 57, SD 14.55) years. They were primarily non-Hispanic White (9/10, 90%) individuals, with 10% (1/10) of the participants identifying as non-Hispanic Black. Most (9/10, 90%) were employed, and 50% (5/10) had a college degree or higher education. In total, 40% (4/10) had conducted a partial SSE in the last year, another 30% (3/10) had conducted a comprehensive SSE in the last year, and 30% (3/10) had not conducted an SSE in the last year.

A summary of the comments regarding design and navigation suggestions is provided in Multimedia Appendix 1. A summary of comments about content is shown in Table 4.

The team provided the recommended changes based on the feedback to the web developer. The interviewees in later interviews reviewed the changes made in response to feedback given in earlier interviews to provide confirmation on whether the issue was adequately addressed.

Table 4. Feedback regarding mySmartSkin (MSS) content and coding for phase 1.

Feedback	Coding	Team decision
Mixed reviews on the incentive options	Mixed	Changed incentive options based on feedback
MSS would be very helpful for survivorship care	Positive	—[a]
Wish MSS was available for public use	Positive	—
Content is thorough but quick to get through, which will motivate patients to use the app	Positive	—
Helps user feel in control of their health	Positive	—
Content seems overwhelming	Mixed	As some users felt that the content was manageable whereas others felt that it was overwhelming, we added a time estimate for each chapter so users will know how long it will take to complete so they can break the content into manageable sessions based on their own schedule.
Make the app more fun	Negative	Included gamification aspects such as badges and prizes that users can win
The importance of SSE[b] and MSS comes through in the content	Positive	—
Content is straightforward, direct, and concise	Positive	—
The app is visually pleasing	Positive	—
User likes the ability to make the text bigger	Positive	—
User likes the use of statistics to reinforce the importance of SSE	Positive	—
Want to share app with family and friends	Positive	—

[a]No decision made as feedback as positive.

[b]SSE: skin self-examination.

Discussion

Principal Findings

Once the analyses are completed, we anticipate that MSS participants will be more likely to perform thorough SSE and sun safety behaviors over the 18-month follow-up period and propose that there will be more earlier-stage melanomas diagnosed in MSS than in UC. In terms of the cost analysis, we expect that MSS will be a more cost-effective strategy given its greater effectiveness in increasing SSE and identifying new or recurrent melanoma. For the reach outcome, we predict that the demographic variables of survivors exposed to MSS will not differ from those of the general population of survivors of melanoma. For adoption, we propose that the proportion of contacted or eligible survivors randomized to MSS who consent, complete the baseline survey, and log into MSS will be equal to or greater than the proportion who adopted the intervention in our previous efficacy trial. For engagement, we propose that 80% of MSS participants will log into the intervention site at least once. For acceptability, we predict that MSS will be rated as highly acceptable, with mean acceptability ratings of ≥4 (out of 5) on the AIM.

Strengths, Limitations, and Unanticipated Problems

The study's strengths are the focus on both effectiveness and implementation through the type-1 hybrid approach; multilevel stakeholder engagement throughout the trial; a novel integration of RE-AIM, PRISM, and health behavior frameworks; the enhancement of a promising fully automated intervention; the scalability of this mobile or web-based intervention; the cost analysis; the longitudinal study design; and the inclusion of clinical outcomes. There are few interventions that have been evaluated to improve SSE among survivors of melanoma. No published intervention is fully automated, which represents a potentially cost-effective and scalable intervention delivery

method. This study will advance the science of cancer survivorship by optimizing a promising intervention for an underserved group of survivors and preparing for widespread dissemination and implementation. Few studies have focused on implementation science aspects of consumer-facing digital interventions. Our use of a type-1 hybrid effectiveness-implementation trial will inform not only our understanding of the effects and implementation of MSS but also our understanding of future large-scale dissemination of self-administered web-based interventions. By evaluating and modeling the clinical outcomes, cost, and cost-effectiveness of MSS, our work will provide information about the costs associated with possible implementation and value.

There are at least 2 limitations. First, some individuals will not use MSS despite its high dissemination. Second, SSE outcomes are measured through self-report. However, this weakness is mitigated by the fact that self-report measures have excellent reliability and validity [14,66,95-100] and self-report has been recommended as the most appropriate assessment approach for wide-scale skin cancer risk reduction research [101].

Future Directions

If effective, MSS could be disseminated and delivered via dermatologist practices, public health organizations such as the American Cancer Society, and nonprofit organizations focused on melanoma or in partnership with existing social media channels. Future research should evaluate potential dissemination and implementation strategies to reach survivors building upon what we will learn in this study about the contextual factors that may impede or promote the future reach, adoption, implementation, and maintenance of MSS.

Acknowledgments

This project was supported by the National Cancer Institute under R01CA265548 awarded to SM and CJH. Services, results, or products in support of the research project were generated by the Rutgers Cancer Institute of New Jersey Cancer Prevention and Outcomes Data Support Shared Resource. The authors acknowledge the following individuals for their valuable contributions to this project: Carolina Lozada, Lisa Paddock, and Radiant Inc.

Data Availability

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

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the Science of Implementation in Health and Healthcare Study Section Healthcare Delivery and Methodologies Integrated Review Group Center For Scientific Review (SIHH, USA).
[DOCX File , 17 KB - resprot_v13i1e52689_app1.docx]

References

1. Survival rates for melanoma skin cancer. American Cancer Society. URL: https://www.cancer.org/cancer/melanoma-skin-cancer/detection-diagnosis-staging/survival-rates-for-melanoma-skin-cancer-by-stage.html#references [accessed 2023-08-30]
2. Kao SY, Ekwueme DU, Holman DM, Rim SH, Thomas CC, Saraiya M. Economic burden of skin cancer treatment in the USA: an analysis of the Medical Expenditure Panel Survey Data, 2012-2018. Cancer Causes Control 2023 Mar 30;34(3):205-212. [doi: 10.1007/s10552-022-01644-0] [Medline: 36449145]
3. Francken AB, Accortt NA, Shaw HM, Colman MH, Wiener M, Soong SJ, et al. Follow-up schedules after treatment for malignant melanoma. Br J Surg 2008 Nov;95(11):1401-1407. [doi: 10.1002/bjs.6347] [Medline: 18844268]
4. Francken AB, Bastiaannet E, Hoekstra HJ. Follow-up in patients with localised primary cutaneous melanoma. Lancet Oncol 2005 Aug;6(8):608-621. [doi: 10.1016/S1470-2045(05)70283-7] [Medline: 16054572]
5. Leiter U, Buettner PG, Eigentler TK, Bröcker EB, Voit C, Gollnick H, et al. Hazard rates for recurrent and secondary cutaneous melanoma: an analysis of 33,384 patients in the German Central Malignant Melanoma Registry. J Am Acad Dermatol 2012 Jan;66(1):37-45. [doi: 10.1016/j.jaad.2010.09.772] [Medline: 21700361]
6. Christianson DF, Anderson CM. Close monitoring and lifetime follow-up is optimal for patients with a history of melanoma. Semin Oncol 2003 Jun;30(3):369-374. [doi: 10.1016/s0093-7754(03)00097-6] [Medline: 12870138]
7. NCCN clinical practice guidelines in oncology: melanoma; version 4.2011. National Comprehensive Cancer Network. URL: https://www.nccn.org/patientresources/patient-resources [accessed 2024-01-25]
8. Huang CL, Provost N, Marghoob AA, Kopf AW, Levin L, Bart RS. Laboratory tests and imaging studies in patients with cutaneous malignant melanoma. J Am Acad Dermatol 1998 Sep;39(3):451-463. [doi: 10.1016/s0190-9622(98)70324-x] [Medline: 9738782]

9. Lifchez SD, Kelamis JA. Melanoma: workup and surveillance. Clin Plast Surg 2010 Jan;37(1):55-63. [doi: 10.1016/j.cps.2009.08.004] [Medline: 19914458]
10. Lisy K, Lai-Kwon J, Ward A, Sandhu S, Kasparian NA, Winstanley J, et al. Patient-reported outcomes in melanoma survivors at 1, 3 and 5 years post-diagnosis: a population-based cross-sectional study. Qual Life Res 2020 Aug 05;29(8):2021-2027. [doi: 10.1007/s11136-020-02464-y] [Medline: 32140919]
11. Francken AB, Shaw HM, Accortt NA, Soong SJ, Hoekstra HJ, Thompson JF. Detection of first relapse in cutaneous melanoma patients: implications for the formulation of evidence-based follow-up guidelines. Ann Surg Oncol 2007 Jun 15;14(6):1924-1933. [doi: 10.1245/s10434-007-9347-2] [Medline: 17357855]
12. Wolff T, Tai E, Miller T. Screening for skin cancer: an update of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med 2009 Feb 03;150(3):194-198 [FREE Full text] [doi: 10.7326/0003-4819-150-3-200902030-00009] [Medline: 19189909]
13. NCCN Guidelines® insights - melanoma: cutaneous, version 2.2021. National Comprehensive Cancer Network. 2021. URL: https://education.nccn.org/node/89579 [accessed 2024-01-25]
14. Weinstock MA, Risica PM, Martin RA, Rakowski W, Smith KJ, Berwick M, et al. Reliability of assessment and circumstances of performance of thorough skin self-examination for the early detection of melanoma in the Check-It-Out Project. Prev Med 2004 Jun;38(6):761-765. [doi: 10.1016/j.ypmed.2004.01.020] [Medline: 15193896]
15. Moore Dalal K, Zhou Q, Panageas KS, Brady MS, Jaques DP, Coit DG. Methods of detection of first recurrence in patients with stage I/II primary cutaneous melanoma after sentinel lymph node biopsy. Ann Surg Oncol 2008 Aug 30;15(8):2206-2214. [doi: 10.1245/s10434-008-9985-z] [Medline: 18512102]
16. McPherson M, Elwood M, English DR, Baade PD, Youl PH, Aitken JF. Presentation and detection of invasive melanoma in a high-risk population. J Am Acad Dermatol 2006 May;54(5):783-792. [doi: 10.1016/j.jaad.2005.08.065] [Medline: 16635658]
17. Leiter U, Garbe C. Epidemiology of melanoma and nonmelanoma skin cancer--the role of sunlight. Adv Exp Med Biol 2008;624:89-103. [doi: 10.1007/978-0-387-77574-6_8] [Medline: 18348450]
18. De Giorgi V, Grazzini M, Savarese I, Gori A, Papi F, D'Errico A, et al. The impact of body area in melanoma self-detection: a retrospective study. Eur J Cancer Prev 2015 Jul;24(4):343-346. [doi: 10.1097/CEJ.0000000000000091] [Medline: 25325306]
19. Pollitt RA, Geller AC, Brooks DR, Johnson TM, Park ER, Swetter SM. Efficacy of skin self-examination practices for early melanoma detection. Cancer Epidemiol Biomarkers Prev 2009 Nov;18(11):3018-3023. [doi: 10.1158/1055-9965.EPI-09-0310] [Medline: 19861521]
20. Murali R, Haydu LE, Long GV, Quinn MJ, Saw RP, Shannon K, et al. Clinical and pathologic factors associated with distant metastasis and survival in patients with thin primary cutaneous melanoma. Ann Surg Oncol 2012 Jun;19(6):1782-1789. [doi: 10.1245/s10434-012-2265-y] [Medline: 22350600]
21. Berwick M, Armstrong BK, Ben-Porat L, Fine J, Kricker A, Eberle C, et al. Sun exposure and mortality from melanoma. J Natl Cancer Inst 2005 Feb 02;97(3):195-199. [doi: 10.1093/jnci/dji019] [Medline: 15687362]
22. Schneider JS, Moore DH2, Mendelsohn ML. Screening program reduced melanoma mortality at the Lawrence Livermore National Laboratory, 1984 to 1996. J Am Acad Dermatol 2008 May;58(5):741-749. [doi: 10.1016/j.jaad.2007.10.648] [Medline: 18068264]
23. Lo SN, Scolyer RA, Thompson JF. Long-term survival of patients with thin (T1) cutaneous melanomas: a Breslow thickness cut point of 0.8 mm separates higher-risk and lower-risk tumors. Ann Surg Oncol 2018 Apr 12;25(4):894-902. [doi: 10.1245/s10434-017-6325-1] [Medline: 29330716]
24. Robinson JK, Wayne JD, Martini MC, Hultgren BA, Mallett KA, Turrisi R. Early detection of new melanomas by patients with melanoma and their partners using a structured skin self-examination skills training intervention: a randomized clinical trial. JAMA Dermatol 2016 Sep 01;152(9):979-985 [FREE Full text] [doi: 10.1001/jamadermatol.2016.1985] [Medline: 27367303]
25. Gogebakan KC, Mukherjee K, Berry EG, Sonmez K, Leachman SA, Etzioni R. Impact of novel systemic therapies on the first-year costs of care for melanoma among Medicare beneficiaries. Cancer 2021 Aug 15;127(16):2926-2933 [FREE Full text] [doi: 10.1002/cncr.33515] [Medline: 33905529]
26. Serra-Arbeloa P, Rabines-Juárez Á, Álvarez-Ruiz MS, Guillén-Grima F. Cost of cutaneous melanoma by tumor stage: a descriptive analysis. Actas Dermosifiliogr 2017 Apr;108(3):229-236 [FREE Full text] [doi: 10.1016/j.ad.2016.09.010] [Medline: 27887672]
27. Duffecy J, Sanford S, Wagner L, Begale M, Nawacki E, Mohr DC. Project onward: an innovative e-health intervention for cancer survivors. Psychooncology 2013 Apr 21;22(4):947-951 [FREE Full text] [doi: 10.1002/pon.3075] [Medline: 22438297]
28. Regan MW, Reid CD, Griffiths RW, Briggs JC. Malignant melanoma, evaluation of clinical follow up by questionnaire survey. Br J Plast Surg 1985 Jan;38(1):11-14. [doi: 10.1016/0007-1226(85)90080-3] [Medline: 3967106]
29. Coups EJ, Manne SL, Stapleton JL, Tatum KL, Goydos JS. Skin self-examination behaviors among individuals diagnosed with melanoma. Melanoma Res 2016 Feb;26(1):71-76. [doi: 10.1097/CMR.0000000000000204] [Medline: 26426762]

30. Manne S, Lessin S. Prevalence and correlates of sun protection and skin self-examination practices among cutaneous malignant melanoma survivors. J Behav Med 2006 Oct 20;29(5):419-434. [doi: 10.1007/s10865-006-9064-5] [Medline: 16855870]
31. Loescher LJ, Harris RB, Lim KH, Su Y. Thorough skin self-examination in patients with melanoma. Oncol Nurs Forum 2007 Jan 2;33(3):633-637. [doi: 10.1188/06.onf.633-637]
32. Mujumdar UJ, Hay JL, Monroe-Hinds YC, Hummer AJ, Begg CB, Wilcox HB, et al. Sun protection and skin self-examination in melanoma survivors. Psychooncology 2009 Oct;18(10):1106-1115 [FREE Full text] [doi: 10.1002/pon.1510] [Medline: 19142859]
33. Manne SL, Heckman CJ, Kashy D, Lozada C, Gallo J, Ritterband L, et al. Prevalence and correlates of skin self-examination practices among cutaneous malignant melanoma survivors. Prev Med Rep 2020 Sep;19:101110 [FREE Full text] [doi: 10.1016/j.pmedr.2020.101110] [Medline: 32461880]
34. Bowen DJ, Burke W, Hay JL, Meischke H, Harris JN. Effects of web-based intervention on risk reduction behaviors in melanoma survivors. J Cancer Surviv 2015 Jun 26;9(2):279-286 [FREE Full text] [doi: 10.1007/s11764-014-0412-0] [Medline: 25425205]
35. Loescher LJ, Hibler E, Hiscox H, Quale L, Harris R. An internet-delivered video intervention for skin self-examination by patients with melanoma. Arch Dermatol 2010 Aug 16;146(8):922-923 [FREE Full text] [doi: 10.1001/archdermatol.2010.178] [Medline: 20713834]
36. Robinson JK, Gaber R, Hultgren B, Eilers S, Blatt H, Stapleton J, et al. Skin self-examination education for early detection of melanoma: a randomized controlled trial of internet, workbook, and in-person interventions. J Med Internet Res 2014 Jan 13;16(1):e7 [FREE Full text] [doi: 10.2196/jmir.2883] [Medline: 24418949]
37. Robinson JK, Turrisi R, Stapleton J. Efficacy of a partner assistance intervention designed to increase skin self-examination performance. Arch Dermatol 2007 Jan 01;143(1):37-41. [doi: 10.1001/archderm.143.1.37] [Medline: 17224540]
38. Coups EJ, Manne SL, Ohman Strickland P, Hilgart M, Goydos JS, Heckman CJ, et al. Randomized controlled trial of the mySmartSkin web-based intervention to promote skin self-examination and sun protection behaviors among individuals diagnosed with melanoma: study design and baseline characteristics. Contemp Clin Trials 2019 Aug;83:117-127 [FREE Full text] [doi: 10.1016/j.cct.2019.06.014] [Medline: 31255801]
39. Manne SL, Heckman CJ, Kashy DA, Ritterband LM, Thorndike FP, Lozada C, et al. Randomized controlled trial of the mySmartSkin web-based intervention to promote skin self-examination and sun protection among individuals diagnosed with melanoma. Transl Behav Med 2021 Jul 29;11(7):1461-1472 [FREE Full text] [doi: 10.1093/tbm/ibaa103] [Medline: 33904921]
40. Mayer D, Layman A, Carlson J. Sun-protection behaviors of melanoma survivors. J Am Acad Dermatol 2012 Jan;66(1):e9-10 [FREE Full text] [doi: 10.1016/j.jaad.2010.10.002] [Medline: 22177654]
41. Freiman A, Yu J, Loutfi A, Wang B. Impact of melanoma diagnosis on sun-awareness and protection: efficacy of education campaigns in a high-risk population. J Cutan Med Surg 2004 May 5;8(5):303-309. [doi: 10.1007/s10227-005-0009-3] [Medline: 15868284]
42. Bowen D, Jabson J, Haddock N, Hay J, Edwards K. Skin care behaviors among melanoma survivors. Psychooncology 2012 Dec 21;21(12):1285-1291. [doi: 10.1002/pon.2017] [Medline: 21780240]
43. Oliveria SA, Christos PJ, Halpern AC, Fine JA, Barnhill RL, Berwick M. Evaluation of factors associated with skin self-examination. Cancer Epidemiol Biomarkers Prev 1999 Nov;8(11):971-978. [Medline: 10566551]
44. Myers RE, Ross E, Jepson C, Wolf T, Balshem A, Millner L, et al. Modeling adherence to colorectal cancer screening. Prev Med 1994 Mar;23(2):142-151. [doi: 10.1006/pmed.1994.1020] [Medline: 8047519]
45. Bruce AF, Theeke L, Mallow J. A state of the science on influential factors related to sun protective behaviors to prevent skin cancer in adults. Int J Nurs Sci 2017 Jul 10;4(3):225-235 [FREE Full text] [doi: 10.1016/j.ijnss.2017.05.005] [Medline: 31406745]
46. Manne S, Jacobsen PB, Ming ME, Winkel G, Dessureault S, Lessin SR. Tailored versus generic interventions for skin cancer risk reduction for family members of melanoma patients. Health Psychol 2010 Nov;29(6):583-593 [FREE Full text] [doi: 10.1037/a0021387] [Medline: 21090893]
47. Manne SL, Coups EJ, Jacobsen PB, Ming M, Heckman CJ, Lessin S. Sun protection and sunbathing practices among at-risk family members of patients with melanoma. BMC Public Health 2011 Feb 21;11:122 [FREE Full text] [doi: 10.1186/1471-2458-11-122] [Medline: 21338483]
48. Myers RE, Hyslop T, Wolf TA, Burgh D, Kunkel EJ, Oyesanmi OA, et al. African-American men and intention to adhere to recommended follow-up for an abnormal prostate cancer early detection examination result. Urology 2000 May;55(5):716-720. [doi: 10.1016/s0090-4295(99)00588-9] [Medline: 10792087]
49. Proctor EK, Colditz GA, Brownson RC. Dissemination and Implementation Research in Health: Translating Science to Practice. New York, NY: Oxford University Press; 2012.
50. Glasgow RE, Vogt TM, Boles SM. Evaluating the public health impact of health promotion interventions: the RE-AIM framework. Am J Public Health 1999 Sep;89(9):1322-1327. [doi: 10.2105/ajph.89.9.1322] [Medline: 10474547]

51. Blackman KC, Zoellner J, Berrey LM, Alexander R, Fanning J, Hill JL, et al. Assessing the internal and external validity of mobile health physical activity promotion interventions: a systematic literature review using the RE-AIM framework. J Med Internet Res 2013 Oct 04;15(10):e224 [FREE Full text] [doi: 10.2196/jmir.2745] [Medline: 24095951]
52. Carnevale TD. Universal adolescent depression prevention programs: a review. J Sch Nurs 2013 Jun 26;29(3):181-195. [doi: 10.1177/1059840512469231] [Medline: 23269544]
53. Glasgow RE, Klesges LM, Dzewaltowski DA, Estabrooks PA, Vogt TM. Evaluating the impact of health promotion programs: using the RE-AIM framework to form summary measures for decision making involving complex issues. Health Educ Res 2006 Oct 15;21(5):688-694. [doi: 10.1093/her/cyl081] [Medline: 16945984]
54. Kessler RS, Purcell EP, Glasgow RE, Klesges LM, Benkeser RM, Peek CJ. What does it mean to "employ" the RE-AIM model? Eval Health Prof 2013 Mar 21;36(1):44-66. [doi: 10.1177/0163278712446066] [Medline: 22615498]
55. Klesges LM, Dzewaltowski DA, Glasgow RE. Review of external validity reporting in childhood obesity prevention research. Am J Prev Med 2008 Mar;34(3):216-223. [doi: 10.1016/j.amepre.2007.11.019] [Medline: 18312810]
56. Kwan BM, Brownson RC, Glasgow RE, Morrato EH, Luke DA. Designing for dissemination and sustainability to promote equitable impacts on health. Annu Rev Public Health 2022 Apr 05;43(1):331-353 [FREE Full text] [doi: 10.1146/annurev-publhealth-052220-112457] [Medline: 34982585]
57. Michie S, Richardson M, Johnston M, Abraham C, Francis J, Hardeman W, et al. The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. Ann Behav Med 2013 Aug;46(1):81-95 [FREE Full text] [doi: 10.1007/s12160-013-9486-6] [Medline: 23512568]
58. Atkinson NL, Massett HA, Mylks C, Hanna B, Deering MJ, Hesse BW. User-centered research on breast cancer patient needs and preferences of an internet-based clinical trial matching system. J Med Internet Res 2007 May 15;9(2):e13 [FREE Full text] [doi: 10.2196/jmir.9.2.e13] [Medline: 17513284]
59. Auxier B, Anderson M. Social media use in 2021. Pew Research Center. 2021 Apr 7. URL: https://www.pewresearch.org/internet/2021/04/07/social-media-use-in-2021/ [accessed 2021-06-24]
60. Manne S, Buller D, Devine K, Heckman C, Pagoto S, Frederick S, et al. Sun safe partners online: pilot randomized controlled clinical trial. J Med Internet Res 2020 Sep 17;22(9):e18037 [FREE Full text] [doi: 10.2196/18037] [Medline: 32673215]
61. Heckman CJ, Riley M, Khavjou O, Ohman-Strickland P, Manne SL, Yaroch AL, et al. Cost, reach, and representativeness of recruitment efforts for an online skin cancer risk reduction intervention trial for young adults. Transl Behav Med 2021 Oct 23;11(10):1875-1884 [FREE Full text] [doi: 10.1093/tbm/ibab047] [Medline: 34160622]
62. Manne S, Day A, Coups EJ, Kashy D. Sun safe partners: a pilot and feasibility trial of a couple-focused intervention to improve sun protection practices. Prev Med Rep 2018 Dec;12:220-226 [FREE Full text] [doi: 10.1016/j.pmedr.2018.10.010] [Medline: 30370209]
63. Manne S, Hudson S, Frederick S, Mitarotondo A, Baredes S, Kalyoussef E, et al. e-Health self-management intervention for oral and oropharyngeal cancer survivors: design and single-arm pilot study of empowered survivor. Head Neck 2020 Nov;42(11):3375-3388 [FREE Full text] [doi: 10.1002/hed.26403] [Medline: 32830404]
64. Melanoma warning signs. The Skin Cancer Foundation. URL: https://www.skincancer.org/skin-cancer-information/melanoma/melanoma-warning-signs-and-images [accessed 2023-09-01]
65. Self-exams save lives: how to do a skin check. The Skin Cancer Foundation. URL: https://www.skincancer.org/early-detection/self-exams [accessed 2023-09-01]
66. Glanz K, Yaroch AL, Dancel M, Saraiya M, Crane LA, Buller DB, et al. Measures of sun exposure and sun protection practices for behavioral and epidemiologic research. Arch Dermatol 2008 Feb;144(2):217-222. [doi: 10.1001/archdermatol.2007.46] [Medline: 18283179]
67. Lang KM, Little TD. Principled missing data treatments. Prev Sci 2018 Apr 4;19(3):284-294. [doi: 10.1007/s11121-016-0644-5] [Medline: 27040106]
68. Cho BH, Hicks KA, Honeycutt AA, Hupert N, Khavjou O, Messonnier M, et al. A tool for the economic analysis of mass prophylaxis operations with an application to H1N1 influenza vaccination clinics. J Public Health Manag Pract 2011;17(1):E22-E28. [doi: 10.1097/PHH.0b013e3181f87952] [Medline: 21135651]
69. Honeycutt AA, Khavjou OA, Bradley C, Neuwahl S, Hoerger TJ, Bellard D, et al. Intervention costs from communities putting prevention to work. Prev Chronic Dis 2016 Jul 28;13:E98 [FREE Full text] [doi: 10.5888/pcd13.150368] [Medline: 27468157]
70. Honeycutt AA, Khavjou OA, Jones DJ, Cuellar J, Forehand RL. Helping the noncompliant child: an assessment of program costs and cost-effectiveness. J Child Fam Stud 2015 Feb 7;24(2):499-504 [FREE Full text] [doi: 10.1007/s10826-013-9862-7] [Medline: 25642124]
71. Khavjou OA, Honeycutt AA, Hoerger TJ, Trogdon JG, Cash AJ. Collecting costs of community prevention programs: communities putting prevention to work initiative. Am J Prev Med 2014 Aug;47(2):160-165. [doi: 10.1016/j.amepre.2014.02.014] [Medline: 24746039]
72. Khavjou OA, Honeycutt AA, Yarnoff B, Bradley C, Soler R, Orenstein D. Costs of community-based interventions from the Community Transformation Grants. Prev Med 2018 Jul;112:138-144. [doi: 10.1016/j.ypmed.2018.04.025] [Medline: 29678616]

73. Yarnoff B, Khavjou O, Bradley C, Leis J, Filene J, Honeycutt A, et al. Standardized cost estimates for home visiting: pilot study of the home visiting budget assistance tool (HV-BAT). Matern Child Health J 2019 Apr 13;23(4):470-478. [doi: 10.1007/s10995-018-2657-0] [Medline: 30547353]
74. Kakushadze Z, Raghubanshi R, Yu W. Estimating cost savings from early cancer diagnosis. Data 2017 Sep 04;2(3):30. [doi: 10.3390/data2030030]
75. Guy JGJ, Zhang Y, Ekwueme DU, Rim SH, Watson M. The potential impact of reducing indoor tanning on melanoma prevention and treatment costs in the United States: an economic analysis. J Am Acad Dermatol 2017 Feb;76(2):226-233 [FREE Full text] [doi: 10.1016/j.jaad.2016.09.029] [Medline: 27939556]
76. Guy GPJ, Machlin SR, Ekwueme DU, Yabroff KR. Prevalence and costs of skin cancer treatment in the U.S., 2002-2006 and 2007-2011. Am J Prev Med 2015 Feb;48(2):183-187 [FREE Full text] [doi: 10.1016/j.amepre.2014.08.036] [Medline: 25442229]
77. Styperek A, Kimball AB. Malignant melanoma: the implications of cost for stakeholder innovation. Am J Pharm Benefits 2012;4(2):66-76.
78. Alexandrescu DT. Melanoma costs: a dynamic model comparing estimated overall costs of various clinical stages. Dermatol Online J 2009;15(11) [FREE Full text] [doi: 10.5070/D353f8q915]
79. SEER cancer statistics review (CSR). National Cancer Institute. URL: https://seer.cancer.gov/csr/ [accessed 2024-01-25]
80. Haddix AC, Teutsch SM, Corso PS. Prevention Effectiveness: A Guide to Decision Analysis and Economic Evaluation. Oxford, UK: Oxford University Press; 1996.
81. Neumann PJ, Sanders GD, Russell LB, Siegel JE, Ganiats TG. Cost-Effectiveness in Health and Medicine. Oxford, UK: Oxford University Press; 2016.
82. Arias E, Bastian B, Xu J, Tejada-Vera B. U.S. State life tables, 2018. National Vital Statistics Reports. 2021 Mar 11. URL: https://stacks.cdc.gov/view/cdc/101128 [accessed 2024-01-25]
83. Sampogna F, Paradisi A, Iemboli ML, Ricci F, Sonego G, Abeni D. Comparison of quality of life between melanoma and non-melanoma skin cancer patients. Eur J Dermatol 2019 Apr 01;29(2):185-191. [doi: 10.1684/ejd.2019.3523] [Medline: 31106760]
84. Blackford S, Roberts D, Salek MS, Finlay A. Basal cell carcinomas cause little handicap. Qual Life Res 1996 Apr;5(2):191-194. [doi: 10.1007/bf00434740]
85. Schlesinger-Raab A, Schubert-Fritschle G, Hein R, Stolz W, Volkenandt M, Hölzel D, et al. Quality of life in localised malignant melanoma. Ann Oncol 2010 Dec;21(12):2428-2435 [FREE Full text] [doi: 10.1093/annonc/mdq255] [Medline: 20494965]
86. Rhee JS, Matthews BA, Neuburg M, Smith TL, Burzynski M, Nattinger AB. Skin cancer and quality of life. Dermatol Surg 2004;30(4):525-529. [doi: 10.1097/00042728-200404000-00013]
87. Sampogna F, Tabolli S, Abeni D. Impact of different skin conditions on quality of life. G Ital Dermatol Venereol 2013 Jun;148(3):255-261. [Medline: 23670062]
88. Schubert-Fritschle G, Schlesinger-Raab A, Hein R, Stolz W, Volkenandt M, Hölzel D, et al. Quality of life and comorbidity in localized malignant melanoma: results of a German population-based cohort study. Int J Dermatol 2013 Jun;52(6):693-704. [doi: 10.1111/j.1365-4632.2011.05401.x] [Medline: 23432215]
89. Weiner BJ, Lewis CC, Stanick C, Powell BJ, Dorsey CN, Clary AS, et al. Psychometric assessment of three newly developed implementation outcome measures. Implement Sci 2017 Aug 29;12(1):108 [FREE Full text] [doi: 10.1186/s13012-017-0635-3] [Medline: 28851459]
90. De Marchis EH, Hessler D, Fichtenberg C, Adler N, Byhoff E, Cohen AJ, et al. Part I: a quantitative study of social risk screening acceptability in patients and caregivers. Am J Prev Med 2019 Dec;57(6 Suppl 1):S25-S37 [FREE Full text] [doi: 10.1016/j.amepre.2019.07.010] [Medline: 31753277]
91. Proctor E, Silmere H, Raghavan R, Hovmand P, Aarons G, Bunger A, et al. Outcomes for implementation research: conceptual distinctions, measurement challenges, and research agenda. Adm Policy Ment Health 2011 Mar 19;38(2):65-76 [FREE Full text] [doi: 10.1007/s10488-010-0319-7] [Medline: 20957426]
92. Hsieh HF, Shannon SE. Three approaches to qualitative content analysis. Qual Health Res 2005 Nov;15(9):1277-1288. [doi: 10.1177/1049732305276687] [Medline: 16204405]
93. Fielding NG, Fielding JL. Linking Data. Thousand Oaks, CA: SAGE Publications, Inc; Mar 13, 1986.
94. Creswell JW, Clark VL. Designing and Conducting Mixed Methods Research. Thousand Oaks, CA: SAGE Publications, Inc; 2007.
95. Weinstock MA, Martin RA, Risica PM, Berwick M, Lasater T, Rakowski W, et al. Thorough skin examination for the early detection of melanoma. Am J Prev Med 1999 Oct;17(3):169-175. [doi: 10.1016/s0749-3797(99)00077-x] [Medline: 10987631]
96. Glanz K, Schoenfeld ER, Steffen A. A randomized trial of tailored skin cancer prevention messages for adults: project SCAPE. Am J Public Health 2010 Apr;100(4):735-741 [FREE Full text] [doi: 10.2105/AJPH.2008.155705] [Medline: 20167900]

97. O'Riordan DL, Glanz K, Gies P, Elliott T. A pilot study of the validity of self-reported ultraviolet radiation exposure and sun protection practices among lifeguards, parents and children. Photochem Photobiol 2008 May;84(3):774-778 [FREE Full text] [doi: 10.1111/j.1751-1097.2007.00262.x] [Medline: 18179624]
98. O'Riordan DL, Nehl E, Gies P, Bundy L, Burgess K, Davis E, et al. Validity of covering-up sun-protection habits: association of observations and self-report. J Am Acad Dermatol 2009 May;60(5):739-744 [FREE Full text] [doi: 10.1016/j.jaad.2008.12.015] [Medline: 19278750]
99. Hillhouse J, Turrisi R, Jaccard J, Robinson J. Accuracy of self-reported sun exposure and sun protection behavior. Prev Sci 2012 Oct 27;13(5):519-531 [FREE Full text] [doi: 10.1007/s11121-012-0278-1] [Medline: 22855253]
100. Køster B, Søndergaard J, Nielsen JB, Olsen A, Bentzen J. Reliability and consistency of a validated sun exposure questionnaire in a population-based Danish sample. Prev Med Rep 2018 Jun;10:43-48 [FREE Full text] [doi: 10.1016/j.pmedr.2018.02.002] [Medline: 29552457]
101. Glanz K, Mayer JA. Reducing ultraviolet radiation exposure to prevent skin cancer methodology and measurement. Am J Prev Med 2005 Aug;29(2):131-142. [doi: 10.1016/j.amepre.2005.04.007] [Medline: 16005810]

Abbreviations

AIM: Acceptability of Intervention Measure
BCT: behavior change technique
CINJ: Cancer Institute of New Jersey
COREQ: Consolidated Criteria for Reporting Qualitative Research
CRGC: Cancer Registry of Greater California
IRB: institutional review board
LYG: life year gained
MSS: mySmartSkin
NJSCR: New Jersey State Cancer Registry
PHM: preventive health model
PRISM: Practical, Robust Implementation and Sustainability Model
RCT: randomized controlled trial
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance
SSE: skin self-examination
UC: usual care

Edited by A Mavragani; submitted 12.09.23; this is a non–peer-reviewed article;accepted 26.10.23; published 12.02.24.

Please cite as:
Manne S, Heckman CJ, Frederick S, Schaefer AA, Studts CR, Khavjou O, Honeycutt A, Berger A, Liu H
A Digital Intervention to Improve Skin Self-Examination Among Survivors of Melanoma: Protocol for a Type-1 Hybrid Effectiveness-Implementation Randomized Trial
JMIR Res Protoc 2024;13:e52689
URL: https://www.researchprotocols.org/2024/1/e52689
doi:10.2196/52689
PMID:38345836

Protocol

Telehealth Movement-to-Music With Arm-Based Sprint-Intensity Interval Training to Improve Cardiometabolic Health and Cardiorespiratory Fitness in Children With Cerebral Palsy: Protocol for a Pilot Randomized Controlled Trial

Byron Lai[1*], PhD; Robert A Oster[2*], PhD; Drew Davis[1*], MD; Larsen Bright[1*]; Gordon Fisher[3*], PhD; Jereme Wilroy[4*], PhD; Yumi Kim[4*], PhD; Raven Young[1*], BS; Ashley Wright[1*], BS; Tanvee Sinha[4*], BS; James H Rimmer[5*], PhD

[1]Division of Pediatric Rehabilitation Medicine, Department of Pediatrics, University of Alabama at Birmingham, Birmingham, AL, United States

[2]Division of Preventive Medicine, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, United States

[3]Department of Human Studies, University of Alabama at Birmingham, Birmingham, AL, United States

[4]Department of Physical Medicine and Rehabilitation, University of Alabama at Birmingham, Birmingham, AL, United States

[5]Dean's Office, School of Health Professions, National Center on Health, Physical Activity and Disability, Birmingham, AL, United States

[*]all authors contributed equally

Corresponding Author:
Byron Lai, PhD
Division of Pediatric Rehabilitation Medicine
Department of Pediatrics
University of Alabama at Birmingham
1720 University Blvd
Birmingham, AL, 35294
United States
Phone: 1 205 638 9790 ext 8
Email: byronlai@uab.edu

Abstract

Background: Children with mobility disabilities, including those with cerebral palsy, have limited options and limited time to exercise to manage their cardiometabolic health and cardiorespiratory fitness. Regular cardiovascular exercise during childhood is a critical health behavior for preventing health decline in adulthood. Thus, there is an urgent need for accessible, age-appropriate, convenient exercise modalities in this group. Sprint-intensity interval training (SIT), combined with telehealth procedures, may be ideal for children with disabilities. SIT includes repetitive bouts of maximal exercise effort combined with rest periods, which can be effective in eliciting comparable results to moderate-exercise training with very short training durations.

Objective: This phase 1 pilot feasibility randomized controlled trial aims to investigate the potential effects of a 12-week SIT program on indicators of cardiorespiratory fitness and cardiometabolic health among children with cerebral palsy. An ancillary aim is to evaluate the feasibility of the program through several process feasibility metrics.

Methods: This study uses a 2-armed parallel group design. A total of 50 physically inactive children with cerebral palsy (aged 6-17 years) will be randomly allocated into 1 of 2 groups: a 12-week SIT or a waitlist control group that continues habitual activity for 12 weeks. The SIT prescription includes 3 tele-supervised sessions per week with 30 repeated sequences of 4 seconds of maximal arm exercise, with active recovery, warm-up, and cooldown periods (for an approximately 20-minute total session). SIT includes guided videos with child-themed arm routines and music. The exercise sessions will be remotely supervised through a web-based videoconference application and include safety monitoring equipment. Outcomes are measured at pre- and postintervention (weeks 0 and 13, respectively). Health outcome measures include peak oxygen consumption (VO_2 peak), measured by a graded exercise test; high-sensitivity C-reactive protein and blood insulin, hemoglobin A_{1c}, triglycerides, and cholesterol using a finger stick dried blood spot test; blood pressure, using a sphygmomanometer; and body composition (total mass, total lean mass, tissue % lean, and tissue % fat) using dual x-ray absorptiometry. Feasibility will be evaluated by the following metrics: adverse events or problems experienced throughout the intervention related to participant safety; perceived enjoyment; and recruitment, enrollment, and attrition rates.

Results: Recruitment procedures started in November 2023. All data are anticipated to be collected by February 2025. Full trial results are anticipated to be analyzed and submitted for publication by March 2025. Secondary analyses of data will be subsequently published.

Conclusions: This trial tests an accessible and low-cost exercise program that leverages principles of high-intensity exercise to provide a convenient program for children with physical disabilities. Knowledge obtained from this study will inform the development of a larger trial for improving the cardiometabolic health, cardiorespiratory fitness, and well-being of children with physical disabilities.

Trial Registration: ClinicalTrials.gov NCT05619211; https://clinicaltrials.gov/study/NCT05619211

International Registered Report Identifier (IRRID): DERR1-10.2196/56499

(JMIR Res Protoc 2024;13:e56499) doi:10.2196/56499

KEYWORDS

disability; high-intensity; interval training; pediatrics; physical activity; telehealth

Introduction

Overview of Cerebral Palsy

Cerebral palsy (CP) is a clinical syndrome that results from a developmental brain injury and is prevalent in approximately 1 million people in the United States and 23 million people worldwide [1]. CP is characterized by disorders of movement and posture due to nonprogressive disturbances of the fetal or developing brain, which is often accompanied by disturbances of sensation, perception, cognition, communication, and behavior [2]. Secondary neurological conditions such as epilepsy, along with other musculoskeletal issues, are also found among people who are diagnosed with CP [2]. Recent innovations in treatments and technology have increased the survival rates of people with CP, resulting in a steadily growing population of adults with CP [3]. Health professionals can now focus on how to help empower young people with CP to live well with a disability, amid a variety of health conditions and socioecological challenges they face with community engagement in adulthood [4,5].

Adulthood and Cardiometabolic Risk

The transitory age between childhood and adulthood is a critical stage for health prevention interventions. As children with CP age into their 20s, they have a substantially increased risk of cardiovascular disease (CVD), related conditions, metabolic syndrome [6], and a 3-fold increased risk of CVD mortality compared to the general population [7-12]. The risk for these cardiometabolic diseases can be lowered by participation in regular moderate-intensity exercise [13-15]. However, recent studies demonstrate that children with CP do not engage in sufficient levels of exercise to obtain health-enhancing benefits, and these levels of exercise participation are far lower than those observed among children without CP [16-18]. Children with CP who exercise regularly are twice as likely to exercise as adults [16]. Consequently, there is a need to identify interventions that promote the early adoption of exercise as a behavior for preventing disease onset, particularly among children with CP who have a mobility disability and have the greatest risk of cardiometabolic disease [19].

Limited Aerobic Exercise Options for Mobility Disability

Conventional exercises that are known to improve cardiorespiratory fitness (eg, walking, running, and cycling) generally require long durations of training that [20] are unsuitable for a large majority of children with CP. As children transition into adulthood, approximately 27% will be unable to walk, 35% will experience decreased walking ability, and 9% will lose their ability to walk [21,22]. Children and adults with CP often experience secondary conditions, such as hemiparesis, fatigue, impaired balance, and joint pain, and these factors impede their mobility to walk or perform types of exercise (eg, cycle) for prolonged periods [22-25]. A recent scoping review demonstrated that a top research priority in the field of disability and exercise is to develop aerobic exercises that are inclusive of wheelchair users [26]. The standard options for exercise training methods require leg work or full body involvement. Aside from arm-ergometry or wheelchair propulsion, there are limited aerobic exercise modalities that are efficacious or effective for people who require seated training, particularly modalities that accommodate hemiparesis [26]. Of note, no randomized controlled trial of exercise has demonstrated a clinically meaningful improvement in cardiorespiratory risk factors in children with CP, likely due to a lack of a sufficient exercise dose [26].

Limited Generalizability of Research Interventions

A second notable limitation of published exercise interventions for CP is low rates of both recruitment and participation [26,27]. Despite over 30 years of research, including 49 published randomized controlled trials, the average sample size for a study was 30 [26]. Most participants were ambulatory, and wheelchair users were typically excluded from participation. These issues hinder the generalizability and transferability of study findings [26-30]. Moreover, low levels of participation in exercise trials were speculated to be due to the following barriers: (1) in-person supervision by a rehabilitation professional or exercise specialist, (2) on-site training at a laboratory or fitness facility, and (3) costly, specialized equipment [26,27]. The identification of an effective evidence-based modality that is inclusive of wheelchair users will require a protocol that can be replicated in a large trial that can provide confirmatory study findings.

Rationale for Sprint-Intensity Arm Exercise

High-intensity interval training (HIIT) has been studied as an effective dose of exercise that has a moderate to large effect on cardiorespiratory fitness and cardiometabolic health while requiring a lower duration of training compared with continuous moderate-intensity exercise [31,32]. Sprint-intensity interval training (SIT) is a form of HIIT that also emphasizes short bouts of exercise with maximum effort at or above a power output associated with a peak oxygen consumption (VO_2 peak) [33]. A meta-analysis [34] found that SIT has a moderate-to-large effect on VO_2 peak that is similar to both moderate-intensity [35,36] and HIIT exercise [33]. Regarding the mechanism, SIT is believed to use anaerobic energy pathways of type IIB muscle fibers, the fast-twitch glycolytic pathways, which are replenished through oxidative metabolism [37], primarily from the kidneys [38]. In other words, extremely short bouts of exercise at maximal intensity can be sustained through the use of lower-intensity aerobic energy pathways. Specifically, higher exercise intensities result in increased renal hypoxemia and, thus, greater production of the hormone erythropoietin. Erythropoietin initiates the production of red blood cells that enhance oxygen use of performing muscles [39] and, thus, VO_2 peak. SIT may further increase VO_2 peak through mitochondrial biogenesis and capillary density [37]. A higher VO_2 peak is linked with reduced risk for cardiometabolic disease [36,40], which is relevant among children with CP who generally have low levels of cardiorespiratory fitness [41]. HIIT with a treadmill has been found to be safe and effective in improving VO_2 peak among ambulatory children with CP [42]. To the best of our knowledge, no randomized controlled efficacy or effectiveness trial has examined a wheelchair-accessible SIT program among children with CP [26,27]. SIT with arm-cycling results in greater gains in VO_2 peak versus leg-cycling (eg, 52% vs 6% increase in VO_2 peak, respectively) [43], likely due to a higher proportion of fast muscle fibers in the arms [43], and this information holds great value for nonambulatory children who can use their arms for exercise.

Telehealth Interventions Foster Enrollment and Attendance

To address low participation, telehealth interventions are especially promising because they remove many of the geographic, environmental, and financial burdens associated with traveling and paying for community programs and classes [44]. Telehealth interventions are especially helpful in delivering health services to children because of reduced burden on the caregiver, who would otherwise have to miss work or other commitments to travel or allocate transportation for the child's appointment [44]. Transportation and time are substantial barriers to exercise participation among people with disabilities [5]. Studies have shown that overall ratings of caregivers toward telehealth appointments are highly positive, and most view telemedicine consultations as at least as effective as those on-site; caregivers had modest reductions in out-of-pocket costs and less missed work costs [45]. In addition, telehealth programs are believed to enhance adherence by providing a sense of accountability, which is created by performance monitoring and social bonds with trusted professionals, as explained by the Supportive Accountability Theory [46]. Home-based exercise programs that incorporate telecommunications and monitoring have achieved the largest sample sizes of people with disabilities [26,27,47]. It is important to note that telehealth interventions that aim to promote strong attendance to an exercise regimen will require remote behavioral coaching strategies to maintain participant engagement. One meta-analysis found that exercise interventions that include behavioral techniques have stronger effects on exercise behavior than those that do not have such techniques [48].

Study Rationale and Purposes

In consideration of exercise barriers (lack of time and transportation) and facilitators of engagement among children (enjoyable exercises and music), this study aims to test a program among children with CP that incorporates (1) age-appropriate prerecorded videos with movement-to-music exercises that are based on child-appropriate themes (eg, superheroes, sports, and pop music), (2) replicable cloud-based telemonitoring procedures, (3) behavioral tele-physical education supervision during exercise, and (4) SIT adapted for varying arm abilities.

Aims

This study has 3 aims, described in following sections.

Aim 1: Examine the Effects of a 12-Week Home-Based SIT Program on Cardiorespiratory Fitness (VO_2 Peak) Compared to a Waitlist Control Among 50 Children With CP

This study will compare pre-post changes in cardiorespiratory fitness between 2 study groups. One group will receive 12 weeks of home-based SIT (n=25), and the second group, waitlist control (WC; n=25), will resume their normal daily activities for 12 weeks. VO_2 peak is the cardiorespiratory outcome of interest, which will be assessed by a graded exercise test using an arm ergometer. We hypothesized that the immediate start group would achieve greater improvements in VO_2 peak versus WC.

Aim 2: Explore the Effect Estimates of SIT on Cardiometabolic Risk Indicators Versus WC

Cardiometabolic outcomes will include high-sensitivity C-reactive protein (hsCRP) and blood insulin, hemoglobin A_{1c} (HbA_{1c}), triglycerides, and cholesterol using a finger stick dried blood spot test, and blood pressure using a sphygmomanometer. Additionally, body composition (total mass, total lean mass, tissue % lean, and tissue % fat) will be measured using dual x-ray absorptiometry (DXA). We hypothesized that arm-based SIT would demonstrate greater improvements in outcomes versus WC.

Aim 3: Evaluate the Feasibility of Arm-SIT Among Children With CP

Feasibility will be measured by process feasibility metrics [49] to inform a larger efficacy or effectiveness trial. Variables will include (1) intervention adherence (class attendance and video minutes through cloud-based analytics), (2) safety (adverse events or problems experienced throughout the intervention

related to participant safety), (3) perceived enjoyment, and (4) engagement (recruitment, enrollment, and attrition rates).

Methods

Study Design and Overview

This phase 1, pilot feasibility randomized controlled trial will include a 2-armed parallel group design to examine the preliminary effects of 12 weeks of arm-based SIT on cardiorespiratory fitness compared to a WC that undergoes habitual activities for 12 weeks. The project will include 50 children with CP (n=25 per arm) and caregivers (n=50 parent-child dyads). One caregiver is required to participate by supporting their child's safety through the intervention and managing the child's exercise schedule. Participants will come to the laboratory for 2 total visits (baseline and week 13) to complete the data collection procedures. Participants will perform the intervention at home, with supervision by a research staff member through telecommunications.

Participants

Textbox 1 contains eligibility criteria for child participants.

Contraindications were informed by guidelines that were established by the American College of Sports Medicine [50] and the Pediatric Physical Medicine and Rehabilitation physician of the study team (DD).

Eligible caregivers will include parents or legal guardians of the child, who can commit sufficient time to support the child in their roles for the study and communicate in English. Caregivers who have complete blindness or deafness will be excluded from participation.

Textbox 1. Eligibility criteria for child participants.

Inclusion criteria

- medical diagnosis of cerebral palsy, as determined by the International Classification of Diseases–Tenth Revision codes
- age 6-17 years
- Gross Motor Function Classification System level 1 to 3 (as determined through participant screening, explained in the Screening and Recruitment section)
- medical clearance from a physician to participate in high-intensity exercise (using the attached medical screening form and explained in the intervention safety, monitoring, and response plan)
- access to a Wi-Fi internet connection in the home through a mobile phone or tablet computer
- a *z* score of ≤–3, indicative of high risk for fracture that could occur from torsion of spine

Exclusion criteria

- physically active (defined as >150 minutes per week of self-reported moderate to vigorous intensity exercise in a typical week)
- cannot use their arms for exercise
- Gross Motor Function Classification level of 4 to 5
- complete blindness or deafness
- pregnant
- uses a pacemaker
- has not been seen by a physician within the previous 12 months of their baseline visit
- uses a g-tube
- any past history of a contraindication to exercise testing: ischemia; myocardial infarction or other acute cardiac event; unstable angina; uncontrolled cardiac dysrhythmias; aortic stenosis; heart failure; pulmonary embolus or pulmonary infarction; myocarditis or pericarditis; aneurysm; low bone-mineral density of the spine (a *z* score of ≤–3, indicative of high risk for fracture that could occur from torsion of spine, determined at baseline data collection through the dual x-ray absorptiometry scan)

Participant Roles

Both the child and caregiver are considered participants in the study, and both will sign the informed consent or assent document.

The child's role in the study is to exercise, following along with exercise videos, 3 times per week for 12 weeks while being supervised through a videoconference web platform by a telecoach.

The caregiver's roles in the study are to (1) attend each videoconference exercise session with the child, (2) schedule and manage the child's exercise schedule, (3) support the safety of the child, and (4) achieve cardiopulmonary resuscitation (CPR) and automated external defibrillator (AED) certification through the Red Cross (certified by the principal investigator, BL, who is certified as a Red Cross CPR/AED instructor).

Screening and Recruitment

Screening for this study will occur in 3 phases. First, contact lists are screened for a medical diagnosis of CP based on the International Classification of Diseases, Tenth Revision (ICD-10) codes. Second, during the initial recruitment contact with a caregiver, research staff will screen participants based

on the study eligibility criteria. As noted previously, to enhance intervention safety, this study aims to enroll children with CP who have only mild to moderate mobility disability and have a low risk of adverse events from exercise. Therefore, the initial recruitment contact through telephone will include the Gross Motor Function Classification System (GMFCS) level [51], using the GMFCS Family Report Questionnaire [52-54]. This assessment will be asked over the phone to avoid wasting participants' time arriving at the laboratory and learning that they do not qualify for the study. Third, a physician (study physician or participants' physicians) will review the patient's medical record and screen the participant for contraindications to exercise testing and risks for participation in high-intensity exercise (based on the Medical Clearance Form, Multimedia Appendix 1). In summary, if an absolute contraindication is identified, the participant will be excluded or withdrawn from the study. If no absolute contraindication is identified, the physician will identify major and minor risks based on the latest information within the patient's medical record and then decide based on major and minor risks to clear the participant for high-intensity exercise training at home. To ensure that record review information is relevant, if the patient has not been seen in the past year, they will have to be seen before obtaining medical clearance and participating in the study.

Candidates will be prescreened and recruited primarily from medical and billing records from the Children's Hospital of Alabama. Medical and billing record databases will be prescreened for potentially eligible patients by patient diagnoses codes (ICD-10, Clinical Modification) related to CP. Contact lists will be generated from the databases. Specific methods of recruitment will include word of mouth and flyers, physician, and staff referrals, mailouts, and phone calls.

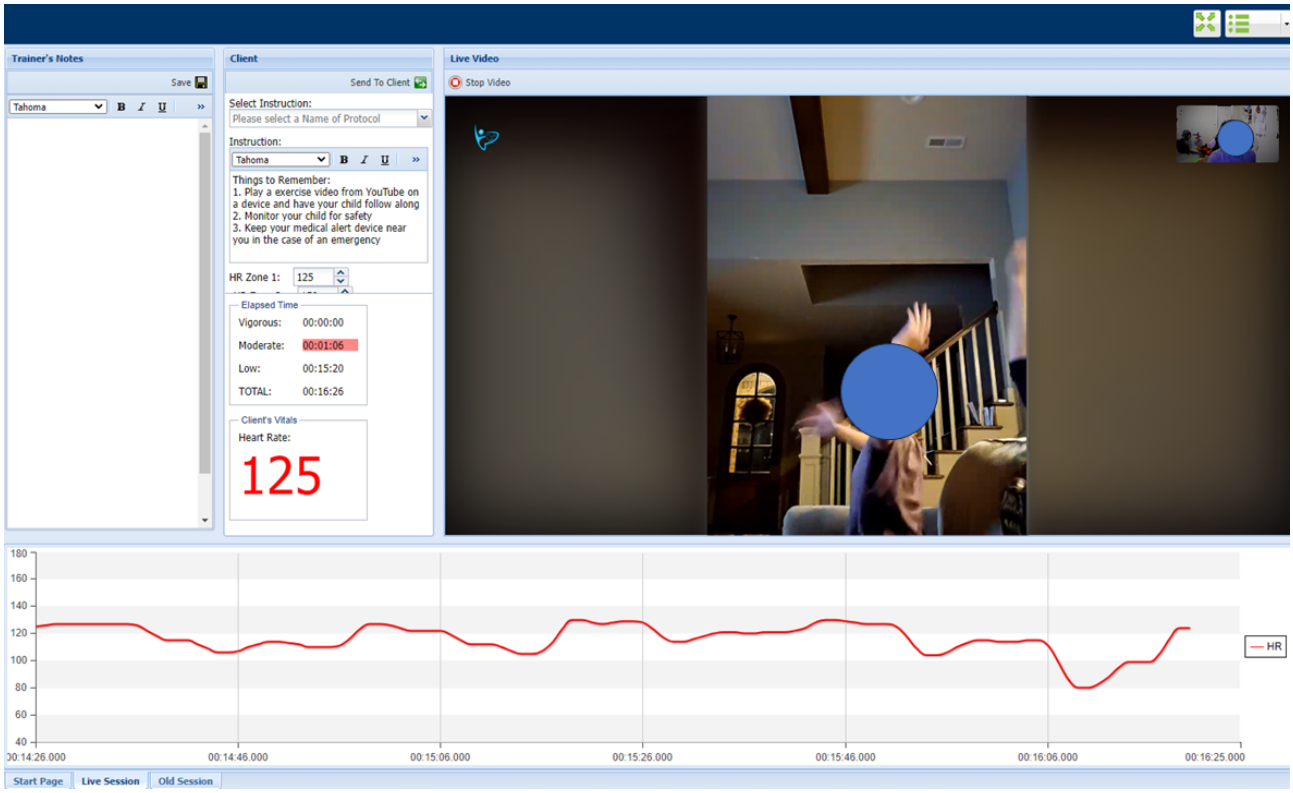
Randomization and Clinical Trial Considerations

Parent-child dyads will be randomized into 1 of 2 groups: arm-based SIT or WC (n=25 per group) with a 1:1 allocation ratio using a permuted block randomization approach. The randomization sequence was generated by the project statistician (RAO) using a computer-generated randomized permuted block design (SAS software, version 9.4; SAS Institute). The project statistician sent the randomization sequence to the database manager (RY) during the study preparation phase. The database manager will unfold the randomization sequence for successfully enrolled participants into 1 of the 2 groups. Study outcomes will be assessed by a research assistant, who will be blinded to group allocation (single-blinded trial design). Recruitment will occur primarily through the Children's Hospital of Alabama. All other activities will be conducted at the Human Performance Laboratory in the Wellness Health and Research Facility at the University of Alabama at Birmingham.

Equipment and Telehealth Monitoring Platform

The study will use a web-based platform with physiologic devices to support remote telehealth supervision of the intervention. The platform, referred to as TeleRehab, includes an Android app that is installed on a computer tablet with Bluetooth capability, which sends data and allows 2-way communications to a secure web server. This setup allows a user on an Android computer tablet to communicate in real time with a member of the research team on a desktop computer. Communication features include videoconference and SMS text messaging. Heart rate data are recorded and transmitted for real-time view by both the user and research staff using a heart rate device (Polar Sense). The heart rate device was placed on a headband and worn on the head to avoid disruption caused by the rapid and vigorous arm movements required for the exercise intervention. Based on internal testing among research staff (nonpublished findings), placement on the head may result in more accurate readings during intervention exercise than when the device was worn on the forearm or upper arm. The device instructions from the manufacturer state that the Polar Sense can be worn on the head, forearm, or upper arm. The TeleRehab app system was an upgraded version of one used previously in a telemonitored feasibility exercise study among people with spinal cord injury [55]. A demonstration of an exercise session in the TeleRehab web portal, as viewed by a telecoach, is displayed in Figure 1. Additional equipment to support the safety of the intervention exercise sessions will include: (1) a blood pressure monitor (Omron HEM-7200/BP7200, 5 Series); (2) a medical alert device (Monitored Medical Alert System), a necklace-worn device that allows 2-way communication between the user and the American District Telegraph (ADT) emergency response team, who is available at all hours of the day to provide remote support for obtaining local emergency response to the user; and (3) a defibrillator (Philips HeartStart OnSite AED Home). Participants will be trained to use all devices at baseline data collection.

Figure 1. Telecoach view of an exercise session with a participant through the TeleRehab app.



Procedures

Participants in the immediate start group will complete a 12-week exercise intervention with 2 data collection visits to the laboratory (pre- and postintervention; weeks 0 and 13, respectively). Participants in the control group will wait 12 weeks before starting the intervention, and they will also complete week 0 and week 13 data collection. Before arrival on a data collection visit, participants will be asked to fast for 10 to 12 hours overnight.

The first data collection visit (week 0) will include the following: (1) study briefing (purpose, procedures, roles, risks, and benefits), (2) informed consent and assent documentation, (3) study questionnaires, (4) cardiorespiratory fitness and cardiometabolic outcome measures, (5) Red Cross CPR and AED training for the caregiver, (6) ADT subscriber agreement form (to receive a medical alert device, shipped to the home from ADT), and (7) intervention or wait briefing (12-week prescription and equipment instructions).

The second data collection visit (week 13) will include (1) study questionnaires, (2) cardiorespiratory fitness and cardiometabolic outcome measures, and (3) debriefing (reviewing pre-post changes in outcomes) for the intervention group or intervention briefing for the control group.

Measures

Questionnaires

The study will include a demographic questionnaire of participant characteristics (eg, age, sex, and BMI) and the Godin Leisure-Time Exercise Questionnaire (GLTEQ). The GLTEQ [56] is a 3-item self-report questionnaire that is used to measure physical activity participation. The GLTEQ asks participants to report the number of times that low, moderate, and vigorous intensity of physical activity was performed for longer than 15 minutes in a typical week. The numbers reported for moderate and vigorous exercise intensity are then multiplied by 7 and 9, respectively, and summed for a score, which is referred to as the health contribution score. A health contribution score of <24 is classified as physically inactive, whereas a score of ≥24 is considered physically active [57]. There is evidence to support the GLTEQ as a valid and reliable measure of physical activity among adults with multiple sclerosis [58] and adolescents [59].

Cardiometabolic Outcomes

Aim 1 Primary Outcome: Peak Oxygen Consumption (VO_2 Peak)

The $V0_2$ peak will be measured during a graded exercise test on an arm ergometer using open-circuit spirometry with a metabolic cart (TruOne, ParvoMedics). Arm ergometers are considered the gold-standard modality for exercise testing among people with disabilities who use wheelchairs or cannot run or cycle for prolonged periods [60,61]. Arm ergometry has been suggested as a valid and reliable method for measuring VO_2 peak among children with CP with mild to moderate disability [62]. Before starting the test, participants rest for 3 minutes. They will then be instructed to maintain a pedaling cadence of 60 revolutions per minute. Resistance is increased every minute by 10 watts until the participant reaches volitional fatigue or achieves 3 of 5 criteria: age-predicted heart rate max of more than 85%; 17 or higher on the Borg rating of perceived exertion (RPE) 6-20 scale; respiratory exchange ratio of 1:1 or higher; plateau in oxygen consumption; volitional fatigue [63]; and subjective signs of exhaustion [64]. Heart rate and oxygen consumption will be measured continuously.

Aim 2 Outcomes: Indicators of Cardiometabolic Health

Cardiometabolic health will be measured through a dried blood spot test, a blood pressure cuff, and a DXA scan.

DXA Scan

DXA scan variables will include total mass, total lean mass, tissue % lean, and tissue % fat. Scans will be analyzed using CoreScan software (GE HealthCare).

Blood Pressure (mm Hg)

Blood pressure will be measured by a sphygmomanometer. Elevated blood pressure during childhood is associated with intermediate markers and hard outcomes of CVD in adulthood [65]. Small changes in blood pressure (–6.4 mm Hg systolic and –4 mm Hg diastolic pressure) can occur from endurance training interventions with durations of up to 12 weeks [66].

Dried Blood Spot Fingerstick Test

A dried blood spot fingerstick test (ZRT Laboratory) will be used to assess blood-related cardiometabolic profiles and include hsCRP, HbA_{1C}, fasting insulin, triglycerides, and cholesterol (total, low-density lipoprotein [LDL], and high-density lipoprotein [HDL]). Dried blood spot tests will be shipped for analysis to the ZRT Laboratory [67]. The ZRT Laboratory blood spot test has been conducted with children [68,69] and has demonstrated excellent validity with venous serum samples (eg, hsCRP, r=0.99; fasting insulin, r=0.93; fasting triglycerides, r=0.95) [67,70].

hsCRP (mg/L): C-reactive protein is a critical marker of inflammation that contributes to proinflammatory and prothrombotic elements of CVD risk. A single hsCRP measure is a strong predictor of myocardial infarction or coronary heart disease mortality, and several other diseases of the circulatory system in people without a history of such conditions [71]. Changes in hsCRP may occur from as early as 8-weeks of exercise [72].

HbA_{1c} (mmol/mol): HbA_{1c} is a measure of red blood cell mean hemoglobin glycation over the previous 3 months. A 1-month exercise intervention without a dietary component can expect a small to moderate effect [73].

Fasting Insulin (µIU/mL): High fasting insulin indicates the presence of insulin resistance, whether an individual shows glucose intolerance. Exercise interventions without a dietary component can expect a small beneficial change in fasting insulin levels after 1 month of training [73].

Fasting Triglycerides (mg/dL): A triglyceride level >150 mg/dL, is supported as an indicator of CVD risk [74,75]. Exercise interventions without a dietary component can expect a small beneficial change in triglyceride levels following 1 month of training [73], even among people with normal triglyceride levels [76].

Fasting Cholesterol (mg/dL): Abnormalities in the lipid profile, including high total cholesterol (TC), high LDL cholesterol, and low HDL cholesterol, are predictors of future CVD among young and middle-aged people [77,78]. Exercise interventions without a dietary component can expect a small effect after 1 month [73].

Aim 3 Intervention Feasibility

Feasibility will be measured using process metrics that will inform a larger trial [49]. Metrics will include adherence to the exercise prescription (measured through an attendance log managed by the telecoaches and TeleRehab cloud-analytics); technological issues; perceived enjoyment after completing the program will be assessed using the Physical Activity Enjoyment Scale (PACES) [79]; recruitment, enrollment, and attrition rates; and adverse events or problems experienced throughout the intervention.

Home-Based Intervention

The SIT intervention will be performed by participants at home and include 3 sessions of exercise per week for a total of 12 weeks. Each SIT session will include 30 repeated sequences of 4 seconds of maximal arm exercise [38], supplemented with active recovery periods of low-intensity posterior shoulder movements to prevent overuse of anterior muscles. Recovery will be gradually reduced from 30 seconds in week 1, 24 seconds in weeks 2-4, to 15 seconds in weeks 5-12 [38]. The total session duration changes from 24 minutes in week 1 to 16.5 minutes in weeks 6-12. Included in the total session duration are a 5-minute warmup and a 2-minute cooldown. A similar leg exercise protocol was found to be effective for raising VO_2 peak [38], and this dose may be optimal for achieving a high training volume while preventing fatigue due to muscle acidosis [38,80]. To achieve maximum intensity, participants are encouraged by the guidance in the videos to perform the 4-second bouts at their maximal effort. Regarding progression, resistance bands (low, medium, and heavy) will be gradually introduced into the exercises so that a participant will report a near maximum intensity (≥7 on the Borg RPE 0-10 scale; explained in detail in the next section) [81,82]. Children with CP from a home-based movement-to-music pilot intervention, from which this study protocol was based, reported that 20-minute videos would be ideal for their attention spans and busy school and care schedules [83]. Sessions will be guided by prerecorded videos that include an adapted exercise instructor (principal investigator BL) and a young adult actor with CP (LB; Figure 2).

Figure 2. Exercise video themes guided by a disability exercise specialist and a young adult with cerebral palsy.

Videos will include 5 themes that were requested by children with CP from our pilot: 3 themes related to superheroes, 1 theme for pop music, and 1 theme for sports. Each theme will include 3 sequential videos that coincide with the rest periods (1 video for week 1, 1 video for weeks 2-4, and 1 video for weeks 5-12), totaling 15 videos. Children with CP can choose to exercise with any themed video that corresponds to their exercise week. Videos include songs that relate to the video themes. Music tempo and volume coincide with sprint and recovery periods. Sprint training incorporates repetitive arm movements that relate to video themes (eg, Spiderman videos include web shooting, football, and arm running or passing). Participants are instructed by the 2 actors in the videos, who demonstrate and guide participants through the exercises. Videos include CP-specific adaptations to enhance engagement [83]: verbal cues, visualized movement adaptations for hemiparesis, slow and repetitive instructions, positive reinforcement, judgment-free atmosphere, and imagery. Videos will be archived within a YouTube playlist. The benefits of archiving videos within YouTube (as opposed to a custom-designed mobile or web application) are that videos are easily accessible on any device, many people are already familiar with YouTube, and this process can easily be replicated. Videos will include themes that are based on copyrighted material, which will only be used for research purposes to adhere to “fair use” for “education” and “research purposes” of the Fair Use Act Copyright Disclaimer, Section 107 of the Copyright Act 1976.

WC participants will be asked to maintain their habitual activity behavior for 12 weeks and then receive the SIT intervention. All participants will be asked to maintain their habitual diet and eating patterns.

Intervention Development

The SIT intervention was adapted from a clinical adult exercise program, referred to as movement-to-music [84]. The program originated from a clinical efficacy trial that demonstrated improvements in lower extremity function and fatigue among adults with mobility disabilities [84]. The success of movement-to-music led to its implementation in larger confirmatory trials among adults with disabilities [85-87]. In contrast, a pilot feasibility trial found that several aspects of movement-to-music required modification to enhance participant engagement among children with CP who had mobility disabilities [69]. Findings from that study informed the development of the present SIT program.

Telecoach and Fidelity

This study will test a high volume of supervised training to ensure children with CP achieve the desired intensity before testing a more scalable self-regulated protocol in a larger randomized controlled trial. All 3 of the weekly prescribed SIT sessions will be supervised through a Zoom (Zoom Video Communications) videoconference by a telecoach. The telecoach will support participants in maintaining maximal effort intensity by monitoring RPE and providing motivational support. Motivational strategies will include positive verbal encouragement to bolster exercise confidence (ie, self-efficacy) and performing the exercises with the participant to enhance learning through observation (ie, vicarious learning). These strategies are informed by social cognitive theory [88], and the research team has used these strategies in other trials [55,83,86,89]. To monitor exercise intensity, the telecoach will ask participants how hard they are working after every change in song (~5 minutes) throughout the session. If participants report <7 RPE, coaches or caregivers will provide positive

verbal encouragement to enhance motivation. Post session, participants will report an overall RPE for the entire bout to determine the need to add resistance bands. RPE has been found to be effective in controlling vigorous exercise intensity in people with spinal cord injury [90]. Since caregiver knowledge and attitude are determinants of participation [91-93], they will be asked to help manage the child's exercise schedule. The telecoach procedure was framed on supportive accountability theory: building a social relationship and bond with a trusted and knowledgeable health professional, with the inclusion of motivation strategies, can enhance intervention adherence [46].

Analyses

Statistical Power

The chosen sample size of 50 participants permits at least 20 in each of the 2 study groups at 12-week follow-up after allowing for up to 20% dropout (in each arm). Power calculations were performed using nQuery (version 8.7) for aims 1 and 2, and SAS (version 9.4) for aim 3.

For aims 1 and 2, baseline measurements will be compared with those obtained in week 13. We obtained estimates of the SD for VO_2 peak of 7.11 mL/kg/min [64], percent body fat (BF) of 8.5% [94], TC of 27.3 mg/dL [95], systolic blood pressure (SBP) of 14.0 mmHg [95], and diastolic blood pressure (DBP) of 11.7 mmHg [95]. With these assumptions and those of a 2-sided 2-group *t* test, an α of .05, and 20 participants per group, the study will have at least 80% power to detect between-group differences of at least 6.47 mL/kg/min in VO_2 peak, 7.7% BF, 24.9 mg/dL in TC, 12.8 mmHg in SBP, and 10.7 mmHg in DBP as being statistically significant (at any time point); with the previous assumptions and those of a 2-sided paired *t* test, an α of .05, and 20 participants, we will have at least 80% power to detect within-group changes of at least 4.70 mL/kg/min in VO_2 peak, 5.6% BF, 18.1 mg/dL in TC, 9.3 mmHg in SBP, and 7.8 mmHg in DBP as being statistically significant (between any 2 time points).

For aim 3, we anticipate adherence to the supervised exercise sessions of this study will be 75%, based on the 70% adherence found from our pilot, which had unsupervised sessions and videos that were not designed for adolescents. For an adherence rate of 75%, and assuming 40 participants in total, with 20 per study arm, complete the study, the corresponding exact binomial 95% CIs are 0.588-0.873) and 0.509-0.913.

Analyses

For all aims, data analyses will follow intent-to-treat principles. Descriptive statistics will be obtained and reported for study variables. The normality of data distribution of the continuous outcomes will first be confirmed using graphical techniques and tests of normality; continuous outcomes that deviate greatly from a normal distribution will be adjusted (eg, transformed) so that the data distribution approximates a normal distribution. All statistical tests will be 2-sided. Differences will be considered significant at $P<.05$. Statistical analysis will be performed using SAS software (version 9.4). Missing data that are not rectified through ongoing review of source documents may be managed with multiple imputations, and the influence of the missing data will be assessed with sensitivity analyses.

For aims 1 and 2, our primary method of analysis will be general linear mixed model techniques, such as mixed model repeated measures analyses, as there will be 2 study groups (SIT and WC) and 3 time points (baseline, 6 weeks, and 12 weeks). Post hoc analyses will be performed using the Tukey-Kramer multiple comparisons test. These models will allow us to assess the between-group effect, the within-group effect, and the group-by-time interaction. Covariates to be included in some models include age, sex, and GMFCS level. Analysis of categorical variables between groups will be performed using the chi-square test (or Fisher exact test, if needed). Pairwise correlations between study parameters will be assessed using Pearson (or Spearman, if needed) correlation analysis.

For aim 3, we will calculate adherence rates, adverse event rates, and other rates of interest and corresponding exact binomial 95% CIs. These rates will be calculated overall and stratified by the study group. Exploratory comparisons of rates between groups will be performed using the chi-square test (or Fisher exact test, if needed).

Ethical Considerations

The protocol and informed consent and assent forms were approved by the University of Alabama at Birmingham Institutional Review Board for Human Use (IRB-300008913) on January 12, 2023. Prospective participants provide written informed consent or assent documentation before participation in the study. Consent and assent forms are completed on the baseline data collection visit.

Before the enrollment of participants, this study was approved by the institutional review board of the university. Written informed consent documentation will be obtained from all participants before their engagement in the study. Participants will receive an electronic gift card that will be loaded for US $500 for each of the data collections completed, for a total of up to US $1000. The rationale for this value is to account for the commitment and time required of both the child and caregiver to complete the study. No artificial intelligence software or program was used in the writing of this manuscript.

Results

This study was approved by the university's institutional review board on January 12, 2023. The study was funded and initiated in May 2023, and the first participant was enrolled in October 2023. As of this manuscript submission on February 7, 2024, a total of 11 people have been enrolled in the study. The study's end date is April 30, 2025. The anticipated publication of the study findings will be in March 2025.

Discussion

Overview

This study will investigate the preliminary efficacy of a home-based, low-cost program for improving cardiorespiratory fitness and metabolic health that is child-appropriate for CP. A program that is short in duration, accessible for various physical

abilities, and can be accessed anywhere through the internet could benefit this population. CP is a low-prevalence disability group that is often geographically isolated from suitable clinics, specialists, and adapted exercise services. Moreover, children with CP have limited options for exercise that are evidenced to improve their health [26,27] and have experienced lower participation in exercise since the outbreak of the COVID-19 pandemic [96].

Strengths and Limitations

Considering that this program can be delivered entirely through an internet video cloud server, YouTube, it has the potential to be carried forward in a scale-up randomized controlled trial of exercise for children with CP. This is important, considering that the average sample size for a randomized controlled trial for children and youths with disabilities has been found to be 27 people, and one of the largest trials included 159 people [27], numbers that are certainly not representative of the diverse needs of children with CP [97]. Another strength of this study is the incorporation of child-appropriate themes and music. Music-based therapy has been found to have an effect on functional ability and goal attainment among children with CP [98]. Child-appropriate themes were requested by this age group and could enhance engagement in therapeutic exercise [83].

This is a preliminary study with a high focus on examining the safety of the intervention and its efficacy under carefully controlled conditions (supervised exercise sessions). Supervised training through telehealth communication provides a sense of accountability that enhances adherence to the intervention prescription [46]. Thus, this study assumes that participants will adhere strongly to the intervention exercise, and the research question is not whether they will perform the exercise; instead, the question focuses on how well they will enhance their health with strong attendance. Should this trial be successful, there will be a need to compare the effects of supervised exercise training versus self-regulated, asynchronous training, which will be the primary format in which prerecorded videos will be used in real-world settings. Supervised training is burdensome for both the research staff and participants.

An additional limitation of this study is the requirement for on-site data collection procedures, which warrants investigation. On-site visitations are difficult for children with CP and their caregivers due to difficulties with transportation and lack of time with busy school schedules, therapies, and daily activities [5,99]. There is a need to develop home-based data collection procedures that provide comparable results to those obtained from in-person testing. The blood spot test can be performed remotely by shipping blood spot test kits to the homes of children with CP. However, to the best of our knowledge, there is no home-based alternative method for measuring cardiorespiratory fitness or body composition imaging, particularly among people with mobility disabilities [20].

Conclusions

Should the findings of this study suggest that the program can improve cardiorespiratory fitness or cardiometabolic health, the study may discover an innovative and, most importantly, scalable method of exercise intervention among children with physical disabilities.

Acknowledgments

The research reported in this publication was supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development of the National Institutes of Health (award R21HD109358). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The laboratory equipment was also supported by the Human Performance Laboratory in the Wellness Health and Research Facility at the University of Alabama at Birmingham. The study team would like to thank the American District Telegraph for their professionalism and support in working with the university to support this study with contracted medical alert devices.

Data Availability

The data sets generated and analyzed during this study will be made publicly available at the completion of the study and can be obtained from the corresponding author on reasonable request.

Authors' Contributions

All authors contributed to the final draft of the manuscript and project design. BL and TS created the initial manuscript draft. All authors contributed to either the study design, the creation of the study videos, or procedures.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Medical clearance screening form.
[DOCX File , 17 KB - resprot_v13i1e56499_app1.docx]

Multimedia Appendix 2

CONSORT-eHEALTH checklist (V 1.6.2).
[PDF File (Adobe PDF File), 90 KB - resprot_v13i1e56499_app2.pdf]

Multimedia Appendix 3
Peer-review report from the National Institutes of Health (NIH).
[PDF File (Adobe PDF File), 1098 KB - resprot_v13i1e56499_app3.pdf]

References

1. Gulati S, Sondhi V. Cerebral palsy: an overview. Indian J Pediatr 2018;85(11):1006-1016. [doi: 10.1007/s12098-017-2475-1] [Medline: 29152685]
2. No authors listed. The definition and classification of cerebral palsy. Dev Med Child Neurol 2007;49(s109):1-44 [FREE Full text] [doi: 10.1111/j.1469-8749.2007.00001.x] [Medline: 17371509]
3. Mutch L, Alberman E, Hagberg B, Kodama K, Perat MV. Cerebral palsy epidemiology: where are we now and where are we going? Dev Med Child Neurol 1992;34(6):547-551. [doi: 10.1111/j.1469-8749.1992.tb11479.x] [Medline: 1612216]
4. Rimmer JH. Health promotion for people with disabilities: the emerging paradigm shift from disability prevention to prevention of secondary conditions. Phys Ther 1999;79(5):495-502. [Medline: 10331753]
5. Martin Ginis KA, Ma JK, Latimer-Cheung AE, Rimmer JH. A systematic review of review articles addressing factors related to physical activity participation among children and adults with physical disabilities. Health Psychol Rev 2016;10(4):478-494. [doi: 10.1080/17437199.2016.1198240] [Medline: 27265062]
6. Heyn PC, Tagawa A, Pan Z, Thomas S, Carollo JJ. Prevalence of metabolic syndrome and cardiovascular disease risk factors in adults with cerebral palsy. Dev Med Child Neurol 2019;61(4):477-483 [FREE Full text] [doi: 10.1111/dmcn.14148] [Medline: 30663044]
7. McPhee PG, Gorter JW, Cotie LM, Timmons BW, Bentley T, MacDonald MJ. Associations of non-invasive measures of arterial structure and function, and traditional indicators of cardiovascular risk in adults with cerebral palsy. Atherosclerosis 2015;243(2):462-465. [doi: 10.1016/j.atherosclerosis.2015.09.035] [Medline: 26520900]
8. Ryan JM, Peterson MD, Ryan N, Smith KJ, O'connell NE, Liverani S, et al. Mortality due to cardiovascular disease, respiratory disease, and cancer in adults with cerebral palsy. Dev Med Child Neurol 2019;61(8):924-928 [FREE Full text] [doi: 10.1111/dmcn.14176] [Medline: 30727025]
9. Mcphee PG, Claridge EA, Noorduyn SG, Gorter JW. Cardiovascular disease and related risk factors in adults with cerebral palsy: a systematic review. Dev Med Child Neurol 2019;61(8):915-923 [FREE Full text] [doi: 10.1111/dmcn.14028] [Medline: 30221763]
10. McPhee PG. Cardiovascular disease in cerebral palsy: shifting our focus from attention to prevention. Dev Med Child Neurol 2019;61(4):390-391 [FREE Full text] [doi: 10.1111/dmcn.14198] [Medline: 30761526]
11. van der Slot WMA, Roebroeck ME, Nieuwenhuijsen C, Bergen MP, Stam HJ, Burdorf A, et al. Cardiovascular disease risk in adults with spastic bilateral cerebral palsy. J Rehabil Med 2013;45(9):866-872 [FREE Full text] [doi: 10.2340/16501977-1185] [Medline: 23828200]
12. Peterson MD, Kamdar N, Hurvitz EA. Age-related trends in cardiometabolic disease among adults with cerebral palsy. Dev Med Child Neurol 2019;61(4):484-489 [FREE Full text] [doi: 10.1111/dmcn.13777] [Medline: 29704244]
13. Ryan JM, Crowley VE, Hensey O, Broderick JM, McGahey A, Gormley J. Habitual physical activity and cardiometabolic risk factors in adults with cerebral palsy. Res Dev Disabil 2014;35(9):1995-2002 [FREE Full text] [doi: 10.1016/j.ridd.2014.03.051] [Medline: 24864052]
14. Slaman J, Roebroeck M, van der Slot W, Twisk J, Wensink A, Stam H, et al. Can a lifestyle intervention improve physical fitness in adolescents and young adults with spastic cerebral palsy? A randomized controlled trial. Arch Phys Med Rehabil 2014;95(9):1646-1655. [doi: 10.1016/j.apmr.2014.05.011] [Medline: 25067790]
15. Thorpe D. The role of fitness in health and disease: status of adults with cerebral palsy. Dev Med Child Neurol 2009;51(Suppl 4):52-58 [FREE Full text] [doi: 10.1111/j.1469-8749.2009.03433.x] [Medline: 19740210]
16. Waltersson L, Rodby-Bousquet E. Physical activity in adolescents and young adults with cerebral palsy. Biomed Res Int 2017;2017:8080473 [FREE Full text] [doi: 10.1155/2017/8080473] [Medline: 29423412]
17. Rabani AS, Harries N, Namoora I, Al-Jarrah MD, Karniel A, Bar-Haim S. Duration and patterns of habitual physical activity in adolescents and young adults with cerebral palsy. Dev Med Child Neurol 2014;56(7):673-680 [FREE Full text] [doi: 10.1111/dmcn.12394] [Medline: 24506509]
18. Carlon SL, Taylor NF, Dodd KJ, Shields N. Differences in habitual physical activity levels of young people with cerebral palsy and their typically developing peers: a systematic review. Disabil Rehabil 2013;35(8):647-655. [doi: 10.3109/09638288.2012.715721] [Medline: 23072296]
19. McPhee PG, Gorter JW, Cotie LM, Timmons BW, Bentley T, MacDonald MJ. Descriptive data on cardiovascular and metabolic risk factors in ambulatory and non-ambulatory adults with cerebral palsy. Data Brief 2015;5:967-970 [FREE Full text] [doi: 10.1016/j.dib.2015.10.045] [Medline: 26759816]

20. Novak I, Hines M, Goldsmith S, Barclay R. Clinical prognostic messages from a systematic review on cerebral palsy. Pediatrics 2012;130(5):e1285-e1312. [doi: 10.1542/peds.2012-0924] [Medline: 23045562]
21. Andersson C, Mattsson E. Adults with cerebral palsy: a survey describing problems, needs, and resources, with special emphasis on locomotion. Dev Med Child Neurol 2001;43(2):76-82 [FREE Full text] [doi: 10.1017/s0012162201] [Medline: 11221908]
22. Opheim A, Jahnsen R, Olsson E, Stanghelle JK. Walking function, pain, and fatigue in adults with cerebral palsy: a 7-year follow-up study. Dev Med Child Neurol 2009;51(5):381-388 [FREE Full text] [doi: 10.1111/j.1469-8749.2008.03250.x] [Medline: 19207296]
23. Rimmer JH, Chen MD, Hsieh K. A conceptual model for identifying, preventing, and managing secondary conditions in people with disabilities. Phys Ther 2011;91(12):1728-1739 [FREE Full text] [doi: 10.2522/ptj.20100410] [Medline: 22003160]
24. Parkinson KN, Dickinson HO, Arnaud C, Lyons A, Colver A, SPARCLE group. Pain in young people aged 13 to 17 years with cerebral palsy: cross-sectional, multicentre European study. Arch Dis Child 2013;98(6):434-440 [FREE Full text] [doi: 10.1136/archdischild-2012-303482] [Medline: 23606716]
25. Alriksson-Schmidt A, Hägglund G. Pain in children and adolescents with cerebral palsy: a population-based registry study. Acta Paediatr 2016;105(6):665-670 [FREE Full text] [doi: 10.1111/apa.13368] [Medline: 26880375]
26. Lai B, Lee E, Kim Y, Matthews C, Swanson-Kimani E, Davis D, et al. Leisure-time physical activity interventions for children and adults with cerebral palsy: a scoping review. Dev Med Child Neurol 2021;63(2):162-171 [FREE Full text] [doi: 10.1111/dmcn.14751] [Medline: 33241561]
27. Lai B, Lee E, Wagatsuma M, Frey G, Stanish H, Jung T, et al. Research trends and recommendations for physical activity interventions among children and youth with disabilities: a review of reviews. Adapt Phys Activ Q 2020;37(2):211-234. [doi: 10.1123/apaq.2019-0081] [Medline: 32131052]
28. Ryan JM, Cassidy EE, Noorduyn SG, O'Connell NE. Exercise interventions for cerebral palsy. Cochrane Database Syst Rev 2017;6(6):CD011660 [FREE Full text] [doi: 10.1002/14651858.CD011660.pub2] [Medline: 28602046]
29. Reedman S, Boyd RN, Sakzewski L. The efficacy of interventions to increase physical activity participation of children with cerebral palsy: a systematic review and meta-analysis. Dev Med Child Neurol 2017;59(10):1011-1018 [FREE Full text] [doi: 10.1111/dmcn.13413] [Medline: 28318009]
30. Verschuren O, Peterson MD, Balemans ACJ, Hurvitz EA. Exercise and physical activity recommendations for people with cerebral palsy. Dev Med Child Neurol 2016;58(8):798-808 [FREE Full text] [doi: 10.1111/dmcn.13053] [Medline: 26853808]
31. Costigan SA, Eather N, Plotnikoff RC, Taaffe DR, Lubans DR. High-intensity interval training for improving health-related fitness in adolescents: a systematic review and meta-analysis. Br J Sports Med 2015;49(19):1253-1261. [doi: 10.1136/bjsports-2014-094490] [Medline: 26089322]
32. Ramos JS, Dalleck LC, Tjonna AE, Beetham KS, Coombes JS. The impact of high-intensity interval training versus moderate-intensity continuous training on vascular function: a systematic review and meta-analysis. Sports Med 2015;45(5):679-692. [doi: 10.1007/s40279-015-0321-z] [Medline: 25771785]
33. Rosenblat MA, Perrotta AS, Thomas SG. Effect of high-intensity interval training versus sprint interval training on time-trial performance: a systematic review and meta-analysis. Sports Med 2020;50(6):1145-1161. [doi: 10.1007/s40279-020-01264-1] [Medline: 32034701]
34. Gist NH, Fedewa MV, Dishman RK, Cureton KJ. Sprint interval training effects on aerobic capacity: a systematic review and meta-analysis. Sports Med 2014;44(2):269-279. [doi: 10.1007/s40279-013-0115-0] [Medline: 24129784]
35. Sun S, Zhang H, Kong Z, Shi Q, Tong TK, Nie J. Twelve weeks of low volume sprint interval training improves cardio-metabolic health outcomes in overweight females. J Sports Sci 2019;37(11):1257-1264. [doi: 10.1080/02640414.2018.1554615] [Medline: 30563431]
36. Cassidy S, Thoma C, Houghton D, Trenell MI. High-intensity interval training: a review of its impact on glucose control and cardiometabolic health. Diabetologia 2017;60(1):7-23 [FREE Full text] [doi: 10.1007/s00125-016-4106-1] [Medline: 27681241]
37. Gaitanos GC, Williams C, Boobis LH, Brooks S. Human muscle metabolism during intermittent maximal exercise. J Appl Physiol (1985) 1993;75(2):712-719. [doi: 10.1152/jappl.1993.75.2.712] [Medline: 8226473]
38. Satiroglu R, Lalande S, Hong S, Nagel MJ, Coyle EF. Four-second power cycling training increases maximal anaerobic power, peak oxygen consumption, and total blood volume. Med Sci Sports Exerc 2021;53(12):2536-2542 [FREE Full text] [doi: 10.1249/MSS.0000000000002748] [Medline: 34310498]
39. Mairbäurl H. Red blood cells in sports: effects of exercise and training on oxygen supply by red blood cells. Front Physiol 2013;4:332 [FREE Full text] [doi: 10.3389/fphys.2013.00332] [Medline: 24273518]
40. McMurray RG, Ainsworth BE, Harrell JS, Griggs TR, Williams OD. Is physical activity or aerobic power more influential on reducing cardiovascular disease risk factors? Med Sci Sports Exerc 1998;30(10):1521-1529 [FREE Full text] [doi: 10.1097/00005768-199810000-00009] [Medline: 9789853]
41. García CC, Alcocer-Gamboa A, Ruiz MP, Caballero IM, Faigenbaum AD, Esteve-Lanao J, et al. Metabolic, cardiorespiratory, and neuromuscular fitness performance in children with cerebral palsy: a comparison with healthy youth. J Exerc Rehabil 2016;12(2):124-131 [FREE Full text] [doi: 10.12965/jer.1632552.276] [Medline: 27162775]

42. Lauglo R, Vik T, Lamvik T, Stensvold D, Finbråten AK, Moholdt T. High-intensity interval training to improve fitness in children with cerebral palsy. BMJ Open Sport Exerc Med 2016;2(1):e000111 [FREE Full text] [doi: 10.1136/bmjsem-2016-000111] [Medline: 27900177]
43. Zinner C, Morales-Alamo D, Ørtenblad N, Larsen FJ, Schiffer TA, Willis SJ, et al. The physiological mechanisms of performance enhancement with sprint interval training differ between the upper and lower extremities in humans. Front Physiol 2016;7:426 [FREE Full text] [doi: 10.3389/fphys.2016.00426] [Medline: 27746738]
44. Langkamp DL, McManus MD, Blakemore SD. Telemedicine for children with developmental disabilities: a more effective clinical process than office-based care. Telemed J E Health 2015;21(2):110-114 [FREE Full text] [doi: 10.1089/tmj.2013.0379] [Medline: 25545598]
45. Harper DC. Telemedicine for children with disabilities. Child Health Care 2006;35(1):11-27. [doi: 10.1207/s15326888chc3501_3]
46. Mohr DC, Cuijpers P, Lehman K. Supportive accountability: a model for providing human support to enhance adherence to eHealth interventions. J Med Internet Res 2011;13(1):e30 [FREE Full text] [doi: 10.2196/jmir.1602] [Medline: 21393123]
47. Lai B, Young HJ, Bickel CS, Motl RW, Rimmer JH. Current trends in exercise intervention research, technology, and behavioral change strategies for people with disabilities: a scoping review. Am J Phys Med Rehabil 2017;96(10):748-761. [doi: 10.1097/PHM.0000000000000743] [Medline: 28398967]
48. Ma JK, Martin Ginis KA. A meta-analysis of physical activity interventions in people with physical disabilities: content, characteristics, and effects on behaviour. Psychol Sport Exerc 2018;37:262-273. [doi: 10.1016/j.psychsport.2018.01.006]
49. Tickle-Degnen L. Nuts and bolts of conducting feasibility studies. Am J Occup Ther 2013;67(2):171-176 [FREE Full text] [doi: 10.5014/ajot.2013.006270] [Medline: 23433271]
50. Liguori G, American College of Sports Medicine. ACSM's Guidelines for Exercise Testing and Prescription, Eleventh Edition. Philadelphia, PA: Wolters Kluwer Health; 2020.
51. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol 1997;39(4):214-223 [FREE Full text] [doi: 10.1111/j.1469-8749.1997.tb07414.x] [Medline: 9183258]
52. Morris C, Galuppi BE, Rosenbaum PL. Reliability of family report for the Gross Motor Function Classification System. Dev Med Child Neurol 2004;46(7):455-460 [FREE Full text] [doi: 10.1017/s0012162204000751] [Medline: 15230458]
53. Morris C, Kurinczuk JJ, Fitzpatrick R, Rosenbaum PL. Who best to make the assessment? Professionals' and families' classifications of gross motor function in cerebral palsy are highly consistent. Arch Dis Child 2006;91(8):675-679 [FREE Full text] [doi: 10.1136/adc.2005.090597] [Medline: 16638783]
54. Jewell AT, Stokes AI, Bartlett DJ. Correspondence of classifications between parents of children with cerebral palsy aged 2 to 6 years and therapists using the Gross Motor Function Classification System. Dev Med Child Neurol 2011;53(4):334-337 [FREE Full text] [doi: 10.1111/j.1469-8749.2010.03853.x] [Medline: 21166672]
55. Lai B, Rimmer J, Barstow B, Jovanov E, Bickel CS. Teleexercise for persons with spinal cord injury: a mixed-methods feasibility case series. JMIR Rehabil Assist Technol 2016;3(2):e8 [FREE Full text] [doi: 10.2196/rehab.5524] [Medline: 28582252]
56. Godin G, Shephard RJ. Leisure Time Exercise Questionnaire. APA PsycTests. 1997. URL: https://psycnet.apa.org/doiLanding?doi=10.1037%2Ft31334-000 [accessed 2023-02-06]
57. Amireault S, Godin G. The godin-shephard leisure-time physical activity questionnaire: validity evidence supporting its use for classifying healthy adults into active and insufficiently active categories. Percept Mot Skills 2015;120(2):604-622. [doi: 10.2466/03.27.PMS.120v19x7] [Medline: 25799030]
58. Sikes EM, Richardson EV, Cederberg KJ, Sasaki JE, Sandroff BM, Motl RW. Use of the Godin leisure-time exercise questionnaire in multiple sclerosis research: a comprehensive narrative review. Disabil Rehabil 2019;41(11):1243-1267. [doi: 10.1080/09638288.2018.1424956] [Medline: 29343122]
59. Zelener J, Schneider M. Adolescents and self-reported physical activity: an evaluation of the modified Godin leisure-time exercise questionnaire. Int J Exerc Sci 2016;9(5):587-598 [FREE Full text] [Medline: 29177023]
60. Larsen RT, Christensen J, Tang LH, Keller C, Doherty P, Zwisler AD, et al. A systematic review and meta-analysis comparing cardiopulmonary exercise test values obtained from the arm cycle and the leg cycle respectively in healthy adults. Int J Sports Phys Ther 2016;11(7):1006-1039 [FREE Full text] [Medline: 27999717]
61. Eerden S, Dekker R, Hettinga FJ. Maximal and submaximal aerobic tests for wheelchair-dependent persons with spinal cord injury: a systematic review to summarize and identify useful applications for clinical rehabilitation. Disabil Rehabil 2018;40(5):497-521. [doi: 10.1080/09638288.2017.1287623] [Medline: 28637157]
62. Brehm MA, Balemans ACJ, Becher JG, Dallmeijer AJ. Reliability of a progressive maximal cycle ergometer test to assess peak oxygen uptake in children with mild to moderate cerebral palsy. Phys Ther 2014;94(1):121-128 [FREE Full text] [doi: 10.2522/ptj.20130197] [Medline: 24029296]
63. Thompson PD, Arena R, Riebe D, Pescatello LS, American College of Sports Medicine. ACSM's new preparticipation health screening recommendations from ACSM's guidelines for exercise testing and prescription, ninth edition. Curr Sports Med Rep 2013;12(4):215-217 [FREE Full text] [doi: 10.1249/JSR.0b013e31829a68cf] [Medline: 23851406]

64. Balemans ACJ, Van Wely L, De Heer SJA, Van den Brink J, De Koning JJ, Becher JG, et al. Maximal aerobic and anaerobic exercise responses in children with cerebral palsy. Med Sci Sports Exerc 2013;45(3):561-568 [FREE Full text] [doi: 10.1249/MSS.0b013e3182732b2f] [Medline: 23034639]
65. Yang L, Magnussen CG, Yang L, Bovet P, Xi B. Elevated blood pressure in childhood or adolescence and cardiovascular outcomes in adulthood: a systematic review. Hypertension 2020;75(4):948-955 [FREE Full text] [doi: 10.1161/HYPERTENSIONAHA.119.14168] [Medline: 32114851]
66. Cornelissen VA, Smart NA. Exercise training for blood pressure: a systematic review and meta-analysis. J Am Heart Assoc 2013;2(1):e004473 [FREE Full text] [doi: 10.1161/JAHA.112.004473] [Medline: 23525435]
67. Kapur S, Kapur S, Zava D. Cardiometabolic risk factors assessed by a finger stick dried blood spot method. J Diabetes Sci Technol 2008;2(2):236-241 [FREE Full text] [doi: 10.1177/193229680800200210] [Medline: 19885348]
68. Larkin EK, Gebretsadik T, Koestner N, Newman MS, Liu Z, Carroll KN, et al. Agreement of blood spot card measurements of vitamin D levels with serum, whole blood specimen types and a dietary recall instrument. PLoS One 2011;6(1):e16602 [FREE Full text] [doi: 10.1371/journal.pone.0016602] [Medline: 21304997]
69. Lai B, Davis D, Young R, Kimani-Swanson E, Wozow C, Wen H, et al. The effects of virtual reality tele-exergaming on cardiometabolic indicators of health among youth with cerebral palsy: protocol for a pilot randomized controlled trial. JMIR Res Protoc 2022;11(8):e40708 [FREE Full text] [doi: 10.2196/40708] [Medline: 35976192]
70. Kapur S, Groves MN, Zava DT, Kapur S. Postprandial insulin and triglycerides after different breakfast meal challenges: use of finger stick capillary dried blood spots to study postprandial dysmetabolism. J Diabetes Sci Technol 2010;4(2):236-243 [FREE Full text] [doi: 10.1177/193229681000400202] [Medline: 20307382]
71. Bassuk SS, Rifai N, Ridker PM. High-sensitivity C-reactive protein: clinical importance. Curr Probl Cardiol 2004;29(8):439-493. [Medline: 15258556]
72. Ford ES. Does exercise reduce inflammation? Physical activity and C-reactive protein among U.S. adults. Epidemiology 2002;13(5):561-568 [FREE Full text] [doi: 10.1097/00001648-200209000-00012] [Medline: 12192226]
73. Snowling NJ, Hopkins WG. Effects of different modes of exercise training on glucose control and risk factors for complications in type 2 diabetic patients: a meta-analysis. Diabetes Care 2006;29(11):2518-2527 [FREE Full text] [doi: 10.2337/dc06-1317] [Medline: 17065697]
74. Singh AK, Singh R. Triglyceride and cardiovascular risk: a critical appraisal. Indian J Endocrinol Metab 2016;20(4):418-428 [FREE Full text] [doi: 10.4103/2230-8210.183460] [Medline: 27366705]
75. Lee JS, Chang PY, Zhang Y, Kizer JR, Best LG, Howard BV. Triglyceride and HDL-C dyslipidemia and risks of coronary heart disease and ischemic stroke by glycemic dysregulation status: the strong heart study. Diabetes Care 2017;40(4):529-537 [FREE Full text] [doi: 10.2337/dc16-1958] [Medline: 28122840]
76. Igarashi Y, Akazawa N, Maeda S. Effects of aerobic exercise alone on lipids in healthy East Asians: a systematic review and meta-analysis. J Atheroscler Thromb 2019;26(5):488-503 [FREE Full text] [doi: 10.5551/jat.45864] [Medline: 30381613]
77. Peters SAE, Singhateh Y, Mackay D, Huxley RR, Woodward M. Total cholesterol as a risk factor for coronary heart disease and stroke in women compared with men: a systematic review and meta-analysis. Atherosclerosis 2016;248:123-131. [doi: 10.1016/j.atherosclerosis.2016.03.016] [Medline: 27016614]
78. Ravnskov U, de Lorgeril M, Diamond DM, Hama R, Hamazaki T, Hammarskjöld B, et al. LDL-C does not cause cardiovascular disease: a comprehensive review of the current literature. Expert Rev Clin Pharmacol 2018;11(10):959-970 [FREE Full text] [doi: 10.1080/17512433.2018.1519391] [Medline: 30198808]
79. Kendzierski D, DeCarlo KJ. Physical activity enjoyment scale: two validation studies. J Sport Exerc Psychol 1991;13(1):50-64. [doi: 10.1123/jsep.13.1.50]
80. Buchheit M, Laursen PB. High-intensity interval training, solutions to the programming puzzle: part I: cardiopulmonary emphasis. Sports Med 2013;43(5):313-338. [doi: 10.1007/s40279-013-0029-x] [Medline: 23539308]
81. Williams N. The Borg Rating of Perceived Exertion (RPE) scale. Occup Med 2017;67(5):404-405 [FREE Full text] [doi: 10.1093/occmed/kqx063]
82. Borg G. Borg's Perceived Exertion and Pain Scales. Champaign, IL: Human Kinetics; 1988.
83. Lai B, Vogtle L, Young R, Craig M, Kim Y, Gowey M, et al. Telehealth movement-to-music to increase physical activity participation among adolescents with cerebral palsy: pilot randomized controlled trial. JMIR Form Res 2022;6(10):e36049 [FREE Full text] [doi: 10.2196/36049] [Medline: 36306154]
84. Young HJ, Mehta T, Herman C, Baidwan NK, Lai B, Rimmer JH. The effects of a Movement-to-Music (M2M) intervention on physical and psychosocial outcomes in people poststroke: a randomized controlled trial. Arch Rehabil Res Clin Transl 2021;3(4):100160 [FREE Full text] [doi: 10.1016/j.arrct.2021.100160] [Medline: 34977542]
85. Young HJ, Lai B, Mehta T, Thirumalai M, Wilroy J, Yates A, et al. The movement-to-music (M2M) study: study protocol for a randomized controlled efficacy trial examining a rhythmic teleexercise intervention for people with physical disabilities. Trials 2021;22(1):779 [FREE Full text] [doi: 10.1186/s13063-021-05751-2] [Medline: 34743701]
86. Rimmer JH, Mehta T, Wilroy J, Lai B, Young HJ, Kim Y, et al. Rationale and design of a scale-up project evaluating responsiveness to home exercise and lifestyle tele-health (SUPER-HEALTH) in people with physical/mobility disabilities: a type 1 hybrid design effectiveness trial. BMJ Open 2019;9(3):e023538 [FREE Full text] [doi: 10.1136/bmjopen-2018-023538] [Medline: 30928927]

87. Wilroy J, Kim Y, Lai B, Mehta T, Thirumalai M, Mintz M, et al. Scale up project evaluating responsiveness to home exercise and lifestyle tele-health (SUPER-HEALTH): preliminary findings. Arch Phys Med Rehabil 2022;103(12):e121 [FREE Full text] [doi: 10.1016/j.apmr.2022.08.752]
88. Bandura A. Health promotion by social cognitive means. Health Educ Behav 2004;31(2):143-164. [doi: 10.1177/1090198104263660] [Medline: 15090118]
89. Lai B, Bond K, Kim Y, Barstow B, Jovanov E, Bickel CS. Exploring the uptake and implementation of tele-monitored home-exercise programmes in adults with Parkinson's disease: a mixed-methods pilot study. J Telemed Telecare 2020;26(1-2):53-63 [FREE Full text] [doi: 10.1177/1357633X18794315] [Medline: 30134777]
90. Goosey-Tolfrey V, Lenton J, Goddard J, Oldfield V, Tolfrey K, Eston R. Regulating intensity using perceived exertion in spinal cord-injured participants. Med Sci Sports Exerc 2010;42(3):608-613 [FREE Full text] [doi: 10.1249/MSS.0b013e3181b72cbc] [Medline: 19952816]
91. Bloemen MAT, Backx FJG, Takken T, Wittink H, Benner J, Mollema J, et al. Factors associated with physical activity in children and adolescents with a physical disability: a systematic review. Dev Med Child Neurol 2015;57(2):137-148 [FREE Full text] [doi: 10.1111/dmcn.12624] [Medline: 25403649]
92. Verschuren O, Wiart L, Hermans D, Ketelaar M. Identification of facilitators and barriers to physical activity in children and adolescents with cerebral palsy. J Pediatr 2012;161(3):488-494. [doi: 10.1016/j.jpeds.2012.02.042] [Medline: 22494875]
93. Verschuren O, Ketelaar M, Gorter JW, Helders PJM, Uiterwaal CSPM, Takken T. Exercise training program in children and adolescents with cerebral palsy: a randomized controlled trial. Arch Pediatr Adolesc Med 2007;161(11):1075-1081. [doi: 10.1001/archpedi.161.11.1075] [Medline: 17984410]
94. Finbråten AK, Martins C, Andersen GL, Skranes J, Brannsether B, Júlíusson PB, et al. Assessment of body composition in children with cerebral palsy: a cross-sectional study in Norway. Dev Med Child Neurol 2015;57(9):858-864 [FREE Full text] [doi: 10.1111/dmcn.12752] [Medline: 25827868]
95. Barja S, Le Roy C, Sepúlveda C, Guzmán ML, Olivarez M, Figueroa MJ. Obesity and cardio-metabolic risk factors among children and adolescents with cerebral palsy. Nutr Hosp 2020;37(4):685-691 [FREE Full text] [doi: 10.20960/nh.03009] [Medline: 32686452]
96. Lai B, Wen H, Sinha T, Davis D, Swanson-Kimani E, Wozow C, et al. The impact of COVID-19 on the lifestyles of adolescents with cerebral palsy in the Southeast United States. Disabil Health J 2022;15(2):101263 [FREE Full text] [doi: 10.1016/j.dhjo.2021.101263] [Medline: 35000878]
97. McIntyre S, Goldsmith S, Webb A, Ehlinger V, Hollung SJ, McConnell K, et al. Global prevalence of cerebral palsy: a systematic analysis. Dev Med Child Neurol 2022;64(12):1494-1506 [FREE Full text] [doi: 10.1111/dmcn.15346] [Medline: 35952356]
98. Yanagiwara S, Yasuda T, Koike M, Okamoto T, Ushida K, Momosaki R. Effects of music therapy on functional ability in people with cerebral palsy: a systematic review. J Rural Med 2022;17(3):101-107 [FREE Full text] [doi: 10.2185/jrm.2022-014] [Medline: 35847757]
99. Shields N, Synnot AJ, Barr M. Perceived barriers and facilitators to physical activity for children with disability: a systematic review. Br J Sports Med 2012;46(14):989-997. [doi: 10.1136/bjsports-2011-090236] [Medline: 21948121]

Abbreviations

ADT: American District Telegraph
AED: automated external defibrillator
BF: body fat
CP: cerebral palsy
CPR: cardiopulmonary resuscitation
CVD: cardiovascular disease
DBP: diastolic blood pressure
DXA: dual x-ray absorptiometry
GLTEQ: Godin Leisure-Time Exercise Questionnaire
GMFCS: Gross Motor Function Classification System
HbA_{1c}: hemoglobin A_{1c}
HDL: high-density lipoprotein
HIIT: high-intensity interval training
hsCRP: high-sensitivity C-reactive protein
ICD-10: International Classification of Diseases–Tenth Revision
LDL: low-density lipoprotein
PACES: Physical Activity Enjoyment Scale
RPE: rating of perceived exertion
SBP: systolic blood pressure
SIT: sprint-intensity interval training

TC: total cholesterol
VO_2 peak: peak oxygen consumption
WC: waitlist control

Edited by A Mavragani; submitted 22.01.24; this is a non–peer-reviewed article;accepted 30.01.24; published 05.03.24.

Please cite as:
Lai B, Oster RA, Davis D, Bright L, Fisher G, Wilroy J, Kim Y, Young R, Wright A, Sinha T, Rimmer JH
Telehealth Movement-to-Music With Arm-Based Sprint-Intensity Interval Training to Improve Cardiometabolic Health and Cardiorespiratory Fitness in Children With Cerebral Palsy: Protocol for a Pilot Randomized Controlled Trial
JMIR Res Protoc 2024;13:e56499
URL: https://www.researchprotocols.org/2024/1/e56499
doi:10.2196/56499
PMID:38441939

Protocol

An mHealth Intervention to Address Depression and Improve Antiretroviral Therapy Adherence Among Youths Living With HIV in Uganda: Protocol for a Pilot Randomized Controlled Trial

Proscovia Nabunya[1*], PhD; Patricia Cavazos-Rehg[2*], PhD; James Mugisha[3*], PhD; Erin Kasson[2*], MSW; Olive Imelda Namuyaba[4*], BSc; Claire Najjuuko[5*], BSc; Edward Nsubuga[1*], BSc; Lindsey M Filiatreau[6*], PhD; Abel Mwebembezi[7*], PhD; Fred M Ssewamala[1*], PhD

[1]International Center for Child Health and Development, Brown School, Washington University in St. Louis, St. Louis, MO, United States

[2]Department of Psychiatry, School of Medicine, Washington University in St. Louis, St. Louis, MO, United States

[3]College of Health Sciences, Makerere University, Kampala, Uganda

[4]International Center for Child Health and Development Field Office, Masaka, Uganda

[5]Division of Computational & Data Sciences, McKelvey School of Engineering, Washington University in St. Louis, St. Louis, MO, United States

[6]Division of Infectious Diseases, School of Medicine, Washington University in St. Louis, St. Louis, MO, United States

[7]Reach the Youth, Kampala, Uganda

[*]all authors contributed equally

Corresponding Author:
Proscovia Nabunya, PhD
International Center for Child Health and Development
Brown School
Washington University in St. Louis
One Brookings Drive
Campus Box 1196
St. Louis, MO, 63130
United States
Phone: 1 3149359087
Email: nabunyap@wustl.edu

Abstract

Background: People living with HIV often struggle with mental health comorbidities that lower their antiretroviral therapy (ART) adherence. There is growing evidence that depression treatment may improve ART adherence and result in improved HIV outcomes. Given that mental health services are severely underequipped in low-resource settings, including in Uganda, new solutions to increase access to mental health care and close the treatment gap are urgently needed. This protocol paper presents the Suubi-Mhealth study, which proposed to develop a mobile health (mHealth) intervention for use among Ugandan youths (14-17 years) with comorbid HIV and depression, taking into account their unique contextual, cultural, and developmental needs.

Objective: The proposed study is guided by the following objectives: (1) to develop and iteratively refine an intervention protocol for Suubi-Mhealth based on formative work to understand the needs of youths living with HIV; (2) to explore the feasibility and acceptability of Suubi-Mhealth on a small scale to inform subsequent refinement; (3) to test the preliminary impact of Suubi-Mhealth versus a waitlist control group on youths' outcomes, including depression and treatment adherence; and (4) to examine barriers and facilitators for integrating Suubi-Mhealth into health care settings.

Methods: Youths will be eligible to participate in the study if they are (1) 14-17 years of age, (2) HIV-positive and aware of their status, (3) receiving care and ART from one of the participating clinics, and (4) living within a family. The study will be conducted in 2 phases. In phase 1, we will conduct focus group discussions with youths and health care providers, for feedback on the proposed intervention content and methods, and explore the feasibility and acceptability of the intervention. In phase II, we will pilot-test the preliminary impact of the intervention on reducing depression and improving ART adherence. Assessments will be conducted at baseline, 1-, 2-, and 6-months post intervention completion.

Results: Participant recruitment for phase 1 is completed. Youths and health care providers participated in focus group discussions to share their feedback on the proposed Suubi-Mhealth intervention content, methods, design, and format. Transcription and

translation of focus group discussions have been completed. The team is currently developing Suubi-Mhealth content based on participants' feedback.

Conclusions: This study will lay important groundwork for several initiatives at the intersection of digital therapeutics, HIV treatment, and mental health, especially among sub-Saharan African youths, as they transition through adolescence and into adult HIV care settings.

Trial Registration: ClinicalTrials.gov NCT05965245; https://clinicaltrials.gov/study/NCT05965245

International Registered Report Identifier (IRRID): DERR1-10.2196/54635

(JMIR Res Protoc 2024;13:e54635) doi:10.2196/54635

KEYWORDS

depression; adherence; mHealth; cognitive behavioral therapy; antiretroviral therapy; youth living with HIV; Uganda

Introduction

Overview

Globally, an estimated 39 million people were living with HIV in 2022; of these, 1.5 million were children <15 years [1]. Approximately 84% of new HIV infections among children <15 years occurred in sub-Saharan Africa (SSA) [1]. HIV disproportionately impacts children from poor and disadvantaged backgrounds, and the prevalence of HIV–related complications and mortality are highest among those struggling with poverty and deprivation [2,3]. Poor children living with HIV are more likely to experience compromised health, inconsistent antiretroviral therapy (ART) adherence, and elevated mental health difficulties, including depression, which increases the risk of HIV transmission [2,3]. In Uganda, the focus of this study and one of the SSA countries hardest hit by HIV, over 80,000 children (0-14 years) are living with HIV [4]. Improvements in access and use of HIV services, including testing, care, and availability of free ART have reduced child mortality [5] and resulted in an increased number of children now growing up with a highly stigmatizing and transmittable infection.

Depression is the most common psychiatric disorder among people living with HIV [6,7]. The prevalence of depression among people living with HIV is estimated to be as high as 63% in SSA [8]. Among young people, the prevalence of major depression is estimated between 16% and 40.8% [9]. Depression is associated with compounding and exacerbating negative HIV outcomes [10,11]. While high levels of ART adherence are necessary for young people to benefit individually from ART, as well as for reducing the risk of HIV transmission, depression has been found to significantly impede ART adherence [10,11]. Previous studies have found that patients with depression are nearly 3 times more likely to be nonadherent to medication regimens than patients without depression [12,13]. Depression can impact ART adherence through isolation from social support, impaired adaptive coping skills, apathy, forgetfulness, and hopelessness [14]. In addition, depression-related fatigue, low energy, inconsistent or lack of sleep, and loss of appetite may make it hard to take ART and attend medical appointments [15]. Indeed, due to limited ART adherence and associated medical complications, patients with depression have a higher risk of increased HIV viral load [16], rapid disease progression, and mortality relative to patients who are not depressed [17,18], making this a crucial population with which to intervene. Thus, failure to address the mental health needs of youths living with HIV, including depression, may lead to costly long-term consequences.

There is growing evidence that depression treatment may improve ART adherence and result in improved HIV outcomes [19,20]. Studies have shown that treating depression was associated with up to 83% higher odds of adhering to HIV treatment [19,21]. Among adults, improvements in cognitive processes have been shown to increase confidence and motivation to engage in HIV management behaviors [22,23]. However, few studies targeting the treatment of depression and evaluating the subsequent improvement in ART adherence have been conducted with adolescents [24], and even fewer studies have been conducted with populations from SSA [25]. Therefore, it is crucial to develop interventions for depression that are tailored to the needs of this specific population, given the prevalence of HIV in the region and the elevated risk factors and myriad barriers to care.

Youths are the lowest ART adherent age group and are at the highest risk of dropping out of ART care programs [26-28]. Poor ART adherence among youths is due, in part, to their transition from youth-focused care into adult-focused care that is less accommodating to the needs of this age group who are at the cusp of taking on new roles and responsibilities including their own disease management [29-31]. Moreover, insufficient staff training to support youths living with HIV during this period, lack of pediatric ART formulations in adult clinics, insufficient clinical monitoring, rigid scheduling that interferes with schooling, as well as loss of pediatric clinic relations with peers and clinical support staff all contribute to poor engagement in care during this transition period [27,28]. Indeed, studies indicate that this period in the life course is associated with a significant drop in ART adherence with up to 50% of youths discontinuing their HIV care entirely during this shift [32]. Thus, targeted interventions to improve retention and treatment outcomes during this period are critical.

Cognitive behavioral therapy (CBT) is a promising approach to reduce depression and improve ART adherence [33-35]. CBT is a form of psychotherapy that is focused on changing patterns of thinking and the associated behaviors [36]. CBT has a growing evidence base as an efficacious approach to reducing depressive symptoms and improving ART adherence among people living with HIV [24,33,37-39]. Moreover, evidence

supports the efficacy and effectiveness of CBT in reducing self-stigma for people with mental illness—one of the major barriers to treatment adherence [40,41]. Some key principles of CBT that specifically target ART adherence and depression include instruction for behavioral activation, cognitive restructuring that addresses negative automatic thoughts, problem-solving, and relaxation training [39,42,43]. Despite the promise of CBT, youths with depression living with HIV, particularly those in resource-constrained settings such as Uganda, are challenged by numerous barriers to treatment including lack of access to health care and a severe shortage of trained providers [43-45]. As such, there is a need for interventions developed to take into account these numerous treatment barriers and to structure intervention components and delivery methods to fill the gaps in the current system of traditional assessment and treatment access.

A mobile health (mHealth) intervention is a feasible approach for the delivery of interventions to youths with depression living with HIV in Uganda. Upwards of 85% of countries in SSA have accomplished a high level of mobile phone penetration [46]. According to the 2021 Uganda Communications Commission Report, over 70% of Ugandans own a mobile phone [47]. Indeed, several studies in Uganda have used mobile technology to deliver health interventions, including the promotion of correct HIV or AIDS knowledge and testing [48], improving patient-provider communication [49], increasing clinic attendance among individuals on ART [50], and improving HIV care [51].

However, none have focused on addressing depression among youths living with HIV. Moreover, in our own work in Uganda, 80% of youth indicate access to a mobile phone [52]. In neighboring Kenya, a mobile app tested to deliver individual counseling services and facilitate peer support among youth living with HIV documented positive experiences, peer network development, as well as benefits related to treatment adherence, stigma reduction, and mental and behavioral health [53]. Thus, given the many barriers to care experienced by Ugandan youths living with HIV, as well as the lack of access to trained providers [54,55], the proposed Suubi-Mhealth intervention is a viable and sustainable approach for treating depression treatment in this priority population.

This Suubi-Mhealth study will develop a mHealth intervention for use among Ugandan youth with comorbid HIV and depression, taking into account their unique contextual, cultural, and developmental needs. This mobile app will apply user-centered design methodologies we have used to develop and evaluate similar evidence-based digital therapies [56]. The study will be conducted in 2 phases and will be guided by the following specific aims:

1. Phase 1, aim 1: develop and iteratively refine an intervention protocol for Suubi-Mhealth based on formative work to understand the needs of youths with depression living with HIV (14-17 years).
2. Phase 1, aim 2: based on the results of aim 1, we will explore the feasibility and acceptability of Suubi-Mhealth for use with youths with depression living with HIV on a small scale to inform subsequent refinement for the larger phase of this project.
3. Phase 2, aim 1: pilot-test the preliminary impact of Suubi-Mhealth versus a waitlist control group, on reducing depression (primary outcome) and improving ART adherence, mental health functioning, quality of life, and lowering HIV stigma (secondary outcomes).
4. Phase 2, aim 2: qualitatively examine barriers and facilitators for integrating Suubi-Mhealth into health care settings.

Theoretical Frameworks Guiding the Study

The Suubi-Mhealth study is guided by two complementary frameworks: (1) the mHealth development and evaluation framework [57], and (2) PRISM (Practical, Robust Implementation, and Sustainability Model) [58]. The mHealth development and evaluation framework involves an iterative process for refining a mHealth intervention through integrating various information sources including published evidence, theory, and formative research with the target group [57]. Specifically, this process involves the following steps: (1) formative research to inform the development of the intervention content and regimen; (2) pretesting to determine the acceptability of the proposed intervention, improve and refine the intervention based on feedback; (3) pilot study to test intervention content and regimen as well as the process, including recruitment and data collection; (4) randomized control trial to test the effect of the intervention in comparison with a control group; (5) qualitative research to improve the intervention and implementation issues and methods; and (6) evaluation and implementation to determine the effect of the intervention once scaled up [57].

Similarly, PRISM is a comprehensive intervention development and implementation framework [58]. It emphasizes the following: (1) organizational perspectives on an intervention (eg, feasibility, adaptability, and barriers); (2) external environment (eg, community resources); (3) recipients' characteristics (youths, provider, and parent response); and (4) implementation and sustainability infrastructure (training and supervision supports). PRISM provides a framework to study the interaction of interventions with the characteristics of multilevel contexts or factors that may influence uptake, implementation, integration, and youths' outcomes (youths' responses, provider preparedness, motivation and fidelity, and community-level support).

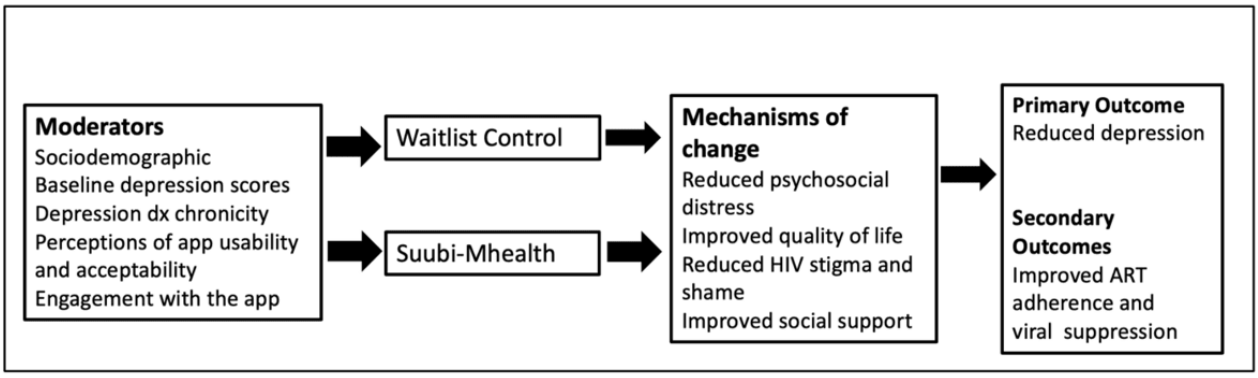
Methods

Study Overview

The overall goal of this study is to develop a mHealth intervention (Suubi-Mhealth) for use among Ugandan youths with comorbid HIV and depression, taking into account their unique contextual, cultural, and developmental needs. In phase 1 of the study, we will conduct 4 focus group discussions, each with 6-8 youths and 2 focus group discussions with health care providers, for feedback on the proposed intervention content and methods. Based on the results from focus group discussions, we will recruit 30 youths to engage with the Suubi-Mhealth app to explore its feasibility and acceptability so as to inform

subsequent refinement for the larger phase of this project. In phase 2, a total of 200 youth from 10 health clinics will be recruited, and randomly assigned to either the Suubi-Mhealth condition or waitlist control condition (5 clinics with 100 youths per condition), to pilot-test the preliminary impact of the intervention on reducing depression and improving ART adherence, mental health functioning, quality of life, and lowering HIV stigma. Upon intervention condition, we will qualitatively examine participants' intervention experiences, as well as barriers and facilitators for integrating Suubi-Mhealth into health care settings. The hypothesized relationships are provided in Figure 1 below.

Figure 1. Suubi-Mhealth conceptual model. ART: antiretroviral therapy.



Research Setting

The Suubi-Mhealth study will be implemented in the greater Masaka region located in Southern Uganda, with one of the highest HIV prevalence in the country [4]. Youths will be recruited from health clinics where the International Center for Child Health and Development (ICHAD), which will house the study, and our collaborating institution, Reach the Youth Uganda, operate. For phase 1, youths will be selected from 2 clinics within 1 district. These clinics will be excluded from phase 2. For phase 2, we will select 10 clinics based on size (total number of youth served) and health facility level (levels II, III, IV, or hospital) in each district. For a health clinic to be included in the study, it will have to be credited by the Uganda Ministry of Health to provide ART and have adolescent-friendly services, for example, adolescent clinic days. The procedures have been used in our other studies implemented in the study region [52,59,60].

Inclusion Criteria

Youths will be eligible to participate if they meet the following criteria: (1) 14-17 years of age with the cognitive ability to understand and comprehend the assenting process; (2) HIV-positive and aware of their status, that is, disclosed to; (3) receiving ART and care from one of the participating clinics; and (4) living within a family, including with extended family members (not in institutions). We will identify youths with depressive symptoms by administering the Patient Health Questionnaire-9 (PHQ-9) [61], which has been validated in rural settings in Uganda [62,63]. Youth scoring ≥10 on the PHQ-9 will be considered for enrollment. Youths will be excluded if they do not meet the inclusion criteria above or are unable to understand the informed consent process, or inability or unwillingness to commit to study completion. Health care providers will be recruited if they are working directly with youths living with HIV at their clinics and agree to participate in the study.

Participant Recruitment and Consent

Procedures tested in our previous and ongoing studies in the study region will be used [59,60,64,65]. Specifically, participants will be identified and recruited from health clinics that are currently collaborating with ICHAD and Reach the Youth in the study region. A list of eligible participants will be created from medical records. Health care providers will present the study to adult caregivers of eligible youth during adolescent clinic days. These are scheduled days when youths visit clinics for ART refills, counseling, and treatment check-ins. If caregivers are interested, verbal consent to be contacted by a research staff (who will be onsite) will be requested. Next, the adult caregiver and the youth will separately provide consent or assent for the youth to be screened. Youths who meet the inclusion criteria and their caregivers (separately) will undergo an informed consent process to participate in the study. The consent and assent forms will clearly state that the youth can withdraw from the study at any time, for any reason, with no explanation, and will not be penalized. Caregivers will sign the consent form consenting for their children to participate. Youths will sign an assent form. If either the youth or the caregiver refuses to participate, the youth will not be enrolled. Health care providers will go through the same process and sign a standard consent form.

Sample Tacking and Retention

The project will take place in a highly stable region of Uganda, where geographical moves are rare. In addition to recommendations garnered by focus group discussion participants in aim 1, we will use several practices to increase retention. During our interviews, youths will be asked to provide details of contacts, including telephone number, and names, addresses, and contact information for 3 people who will always know how to reach them. Participants will be reminded that if the research team were to contact the people listed, the team would never discuss any details about the participant's involvement in the study. A phone call reminder will be made prior to each assessment. Our team has effectively used these

methods in all our research projects, resulting in very low attrition [66-69]. We will keep careful records for those who drop out of the study and test for attrition bias based on data collected prior to study dropout. To the extent that such bias is present, we will limit generalizations accordingly, or, where possible, introduce statistical adjustments to address bias. Retention efforts will be periodically reassessed, reviewing best practices to reduce attrition.

Ethics Approval

We obtained approval for all study procedures from the Uganda Virus Research Institute Research Ethics Committee (Ref: GC/127/919) on August 29, 2022, Washington University in St. Louis Institutional Review Board (IRB; 202209115) on October 06, 2022, and from the Uganda National Council for Science and Technology (Ref: SS1442ES) on November 15, 2022. The study is registered in the Clinical trials.gov database (Identifier: NCT05965245).

Description of the Study Conditions

In phase 2 of the study, participants will be randomized to 2 conditions (100 youths per condition): a waitlist control condition or the Suubi-Mhealth condition, as detailed below.

Waitlist Control Condition

A waitlist control condition method will be used [70]. Participants will be randomly assigned to a waitlist and will receive the Suubi-Mhealth intervention after the active treatment group. In addition, participants will receive a smartphone without the Suubi-Mhealth app at the same time as the intervention group.

Suubi-Mhealth Treatment Condition

Overview

Participants in this condition will receive the Suubi-Mhealth intervention, with the specific components described below. All modules will be available in text, video, and audio format. All app content will be available in Luganda local language.

Evidence-Based Multimedia Psychoeducational Content to Reinforce Treatment Plans

Educational content will be provided within Suubi-Mhealth and broken into 20 modules. Users will be provided access for 2 months and will be instructed to review ≥2 modules per week. The research team has aligned Suubi-Mhealth content with state-of-the-science recommendations for CBT for ART adherence and depression as applied to HIV medication adherence [33]. In addition, the research team has implemented a group- CBT intervention to address depression and HIV-related stigma among adolescents [59,71]. This manualized intervention, developed with close consultations with mental health experts in the region, will be adapted into Suubi-Mhealth content. Core instruction will include psychoeducation on the interplay between HIV and depression; minimizing cognitive distortions related to ART adherence, stigma, and depression; challenging negative automatic thoughts; analysis and development of behavioral skills; reducing environmental stressors; creating support and helping communicate concerns adaptively and clearly; and problem-solving [37,38].

Safety Plan

To ensure safety while using the app, participants will be informed that the social networking center is informational only and not equipped for managing crises. Messages from users will be reviewed by a trained member of the research team within 24 hours. If signs of an imminent crisis are detected, a supervisor will send a crisis referral, make a report, and notify the parent so that no user waits longer than 24 hours to receive support. Emergency contact information will be shown in the corner of the survey page for all assessments.

Goal Setting and Self-Monitoring Features to Enable Self-Management

Our previous mHealth participants have indicated their desire for a goal-setting feature within an app, and studies of mobile apps have demonstrated that goal-setting, self-tracking, and monitoring features are essential to facilitate self-management skills and sustain user engagement [72,73]. With this in mind, there will be an ability to set goals and monitor symptoms of depression over time within Suubi-Mhealth. Rewards within an app have been shown to motivate and sustain healthy behaviors [74]. Our rewards feature will be used to inspire completing psychoeducation content and attaining goals by awarding digital “trophies” for participants who successfully meet a goal or reach a milestone (eg, complete a module on how to challenge negative automatic thoughts).

Clinical Dashboard to Monitor Participants’ Use of Suubi-Mhealth

A clinical management dashboard will make it efficient for the research team to input participant data and monitor participant use of the app and assessment responses.

Data Collection

Data will be obtained through an eligibility screening checklist, computer-assisted, interviewer-administered structured questionnaires, focus group discussions, and semistructured in-depth interviews. All assessments will take place at the clinic, participant’s home, or ICHAD’s field offices in Masaka. Assessments will be conducted by trained Ugandan Research Assistants.

Qualitative Assessments

Focus group discussions and semistructured interviews will be conducted. In phase 1, we will conduct 4 separate 60-minute in-person focus group discussions (6-8 youths each) and 2 focus group discussions for health care providers. Participants will be asked about impressions of expert-suggested content and design and their own suggested components for Suubi-Mhealth that could be of greatest utility for unique needs. They will also be asked for input regarding methods to increase participation and retention for follow-up assessments. All focus groups will be conducted in Luganda, will last approximately 1-hour and will be held in a private location at each clinic. In addition, we will conduct a 30-minute semistructured qualitative interview with each participant to further explore their experiences with Suubi-Mhealth, including perceived benefits and challenges of participation, and suggested modifications to improve specific components of the intervention. Complications or technical glitches with the app, and how it fared in regard to its ease of

understanding, helpfulness, intuitive flow, presentation, and pacing will also be assessed. We will also conduct in-depth interviews with research staff who will be moderating the app.

In phase 2, we will conduct semistructured in-depth interviews with 30 participants upon completion of the intervention to explore their experiences with the intervention as well as barriers and facilitators to implementation and participation. Participants will be purposefully sampled [75], using a combination of high- and low-app users, that is, those in the upper and lower quartiles of engagement with the app (15 participants per group), to take part in a 30-minute semistructured qualitative interview. Interviews will focus on participants' experience with Suubi-Mhealth and how it fared in regard to its ease of understanding, helpfulness for supporting ART adherence and depression, intuitive flow, presentation, pacing, and the likelihood that they would recommend this intervention to a peer. Reactions to specific content and suggestions for improvement will also be assessed. We will additionally perform in vivo observations in which participants actively use the tool during the interviews to more directly observe challenges to use and implementation.

Quantitative Assessments

Quantitative assessments will be administered as follows. In phase 1, interviewer-administered quantitative assessments will be collected at 2 months post intervention to examine the usability characteristics and engagement with Suubi-Mhealth. To assess usability characteristics, we will administer a modified version of the 19-item USE (Usefulness, Satisfaction, and Ease of Use) questionnaire to measure usability characteristics of Suubi-Mhealth [76,77]. The USE will ask participants to rate the ease of use and learning (ie, efficiency), usefulness (ie, technical effectiveness), and likability (ie, satisfaction) of Suubi-Mhealth on a 7-point Likert scale (with 1= strongly disagree and 7= strongly agree).

To assess engagement with Suubi-Mhealth, automatically captured data within the app platform will be used to measure app engagement for each participant, including (1) the number of modules completed, (2) the number of messages sent, (3) the number of times self-monitoring and goal-setting features used, (4) the number of times logged into the app, (5) the time spent in the app once logged in, and (6) the time difference between app log-ins.

In phase 2, assessments will be completed at baseline and at 1, 2, and 6 months post intervention to evaluate whether participants' ART adherence and self-reports on symptoms of depression, mental health functioning and physical health, and quality of life and stigma improve with access to Suubi-Mhealth and whether improvements remain consistent over time. The measures to be used are provided in Table 1 below.

Table 1. Phase 2 assessment measures.

Variable	Measures
Demographics	Sociodemographic questionnaire
Depressive symptoms	Patient Health Questionnaire-9 (PHQ-9) [61] and Brief Symptom Index (BSI) [78]
Physical health	The Medical Outcomes Study HIV Health Survey (MOS-HIV) [79]
Quality of life	Pediatric Quality of Life Inventory (PedsQL 4.0) [80,81]
HIV shame	Shame questionnaire [82,83]
HIV stigma	Berger HIV Stigma Scale [84]
Social support	The Multidimensional Scale of Perceived Social Support [85] and Social Support Behavior Scale (SS-B) [86]
ART[a] adherence	Viral load; self-reports [87]
Intervention feedback	In-depth interviews

[a]ART: antiretroviral therapy.

Data Analysis Procedures and Milestones

Phase 1, Aim 1: to Develop and Iteratively Refine an Intervention Protocol for Suubi-Mhealth Based on Formative Work

Overview

We will conduct 4 focus group discussions, each with 6-8 youths (N=32), and 2 groups with health providers (n=16) for feedback on proposed intervention content and methods to increase participation and retention. Focus groups will be audio-recorded and transcribed verbatim. Transcripts will be translated into English and imported into Dedoose to assist with qualitative data management and coding. Inductive thematic analysis of focus group transcripts will be conducted by 2 research team members using the 6 steps described by Braun and Clarke [88] (getting familiar with the data, creating initial codes, looking for themes, reviewing and refining themes, defining and naming themes, and producing the report).

Milestone for Aim 1

We will have garnered input from youths and health care providers about the proposed Suubi-Mhealth content, features, and design. Participants will provide feedback on additional suggested components for Suubi-Mhealth that could be of the greatest utility for their unique needs. Suubi-Mhealth will be refined accordingly including its technical aspects, features to add or edit, and content updates or revisions. Participants will also be asked for input regarding methods to increase participation and retention for follow-up assessments. The study design and methods will incorporate feedback received from

participants. Specifically, the research team will incorporate relevant suggested content and features into the Suubi-Mhealth intervention protocol before testing.

Phase 1, Aim 2: to Explore the Usability, Feasibility, and Acceptability of Suubi-Mhealth in a Small Sample to Inform Subsequent Refinement for the Larger Phase

Overview

Following the integration of input and feedback from focus groups to update and refine Suubi-Mhealth (phase 1, aim 1), we will β test Suubi-Mhealth among 30 youths. This is within the range of sample sizes for other pilot tests of digital therapeutics [77,89], and the suggested number of participants for pilot studies [90]. This sample size should be sufficient to explore the usability of and engagement with Suubi-Mhealth and for data saturation for qualitative interviews [91]. Participants will be instructed to use all features of Suubi-Mhealth for 2 months for the purpose of this β test. Two months for β testing is similar in length to other pilot tests for mental health apps [92,93], and will allow sufficient time for participants to engage with as many of the modules and features as they would like. Upon completion, we will garner feedback from each participant via mixed methods exploratory design in order to inform further enhancements of Suubi-Mhealth prior to the RCT (phase 2). We will conduct both quantitative assessments to examine the utility and usability of the Suubi-Mhealth and qualitative interviews to explore participants' experiences with the app.

Analysis Procedures

Quantitative assessments will be recorded using Qualtrics, an electronic data capture system. The data will be exported into the Statistical Analysis System for analysis. App usability will be examined using descriptive measures (mean, SD, median, and range) on the efficiency, technical effectiveness, and satisfaction components of the USE questionnaire. Descriptive statistics will also be used to describe engagement with the app (eg, the median number of logins and time spent in the app). Qualitative data will be analyzed in Dedoose following the same procedures provided in aim 1 above.

Adaptation and Feedback Integration Process

We will use procedures similar to those in our other studies for adapting mental health interventions based on target user feedback [94]. Specifically, participants' feedback gathered from content and usability testing, as well as from experiences obtained during in-depth interviews, will be incorporated into the app based on the level of importance and feasibility including cost. The research team, including the research staff overseeing the app and selected youth, will go over each module to make sure that relevant revisions have been incorporated. Together, the research team will review and approve the adapted content and design before launching phase 2.

Milestone for Aim 2

Participants will have, on average, engaged with 75% or more of the mobile app modules and will express enthusiasm over its potential to be a supportive tool. Participants will score Suubi-Mhealth as having high ease of use and learning (ie, efficiency), usefulness (ie, technical effectiveness), and likability (ie, satisfaction). Participants' provided feedback will be integrated into the app design.

Phase 2, Aim 1: to Pilot-Test the Preliminary Impact of Suubi-Mhealth

Overview

During phase 2, participants will be randomized to the intervention condition to engage with the Suubi-Mhealth app or the control condition (waitlist control group) to receive the app after the active intervention period. Assessments will be completed at baseline and at 1 month, 2 months, and 6 months post intervention to evaluate whether participants' self-reports on symptoms of depression, ART adherence, mental health functioning, quality of life, and stigma improve with access to Suubi-Mhealth and whether improvements remain consistent over time.

Participants will also complete the USE measure to assess acceptability and usability, as well as in-depth interviews to explore their experiences with the intervention.

Analysis Procedures

Following guidelines for clinical trial analysis, all primary analyses will be intention-to-treat analyses and missing data will be handled using multiple imputations.

Mixed-Effect Models

The principal strategy to examine primary and secondary outcomes over time between the Suubi-Mhealth group and the control group will be the use of linear mixed models and generalized linear mixed models, including a random intercept to allow for the correlation of within-participant measurements over time. Models will include the fixed effects of the intervention group (Suubi-Mhealth vs control), time, and group-by-time interaction. Effect sizes and 95% CIs will be reported.

Moderation Analysis

First, we will provide descriptive statistics on engagement (session duration, number of modules viewed) and usability scores. We will then use moderation analysis to examine whether Suubi-Mhealth engagement and usability scores moderate the effect of the interventions on our primary and secondary outcomes of interest (ie, depression, ART adherence, psychological distress, overall quality of life, shame, and HIV stigma).

Structural Equation Models

We will use mediation analysis to examine whether depression symptoms mediate ART adherence. We will test for mediation using structural equation models with CIs derived from bootstrapping of indirect and total effects. By applying mediation analyses, we will be simultaneously testing whether the intervention engages the targets and whether intervention-induced changes in targets are associated with clinical benefit. Models will account for baseline scores. For sensitivity analyses, we will use a per-protocol approach to address noncompliance by only including participants who completed the study according to the protocol.

App Engagement and Usability

Basic descriptive statistics will be reported for Suubi-Mhealth engagement (session duration and number of modules viewed), as well as app usability scores (USE scores and subscales of efficiency, technical effectiveness, and likability). To determine the relationships between app usability and engagement, we will use linear regression models with an index of engagement (derived from principal components analysis using the above raw metrics of engagement) as the dependent variable and overall usability score as the primary predictor of interest. Demographics associated with both the usability scores and the index of engagement will be included as covariates in the model. In a separate model, we will include each usability subscale (efficiency, technical effectiveness, and satisfaction) rather than the overall usability score in order to explore which subscale might be most predictive of engagement with the mobile app-based tool. In addition, linear mixed models will be used to investigate the association between the intervention engagement index with the primary outcomes over time. Covariance structures for the models will be selected as described above. Effect sizes and 95% CIs will be reported.

Sample Size and Power

The primary outcome in aim 1 is whether depression decreases between baseline and postintervention initiation. This is calculated from the depression score change between these 2 time points and categorized as yes versus no. The intracluster correlation for clinics is assumed to be 0.093 and the rate of depression decrease in the control group is 5% [95]. Given our total sample (N=200, 100 youths per condition, 5 clinics per condition), we expect to achieve at least 80% power to detect a rate difference of depression decrease when the rate of depression decrease in the intervention group is 40% and the 2-sided significance level of the test is .05.

Milestone for Phase 2, Aim 1

Successful completion of a parallel-group RCT to test the feasibility, acceptability, and preliminary efficacy of Suubi-Mhealth. Participants will not experience any adverse events. Participants will have engaged with Suubi-Mhealth daily for 2 months and engaged with at least 75% or more of the modules.

Phase 2, Aim 2: to Examine the Barriers and Facilitators for Integrating Suubi-Mhealth Into Real-World Contexts

Overview

Upon completion of the intervention, we will conduct semistructured in-depth interviews with 30 participants upon completion of the intervention to explore their experiences with the intervention as well as barriers and facilitators to implementation and participation. Based on prior research [79], we anticipate that barrier themes may include (1) lack of knowledge and self-efficacy in using mHealth tools; (2) participants' inability to receive mobile service due to lack of service coverage and connectivity issues; (3) participants' inability to understand, maintain, or properly use the mHealth tool due to technology literacy issues; and (4) financial sustainability concerns related to the inability to charge a fee for service, bill, or otherwise be reimbursed for services provided via technology. We anticipate that facilitators may include working collaboratively with the app development team to address technical barriers and adapt the app to meet participants' needs and consistently reviewing app use data to inform progress [80]. The perceived relative advantage of the app over usual care, the ease of use and ability to adapt the app to improve participants' use, and awareness of participants' needs and resources will also likely serve as facilitators.

Milestone for Phase 2, Aim 2

Completion of an implementation evaluation in which barriers and facilitators are successfully identified as actionable inputs to inform the integration of Suubi-Mhealth into real-world contexts for youths with depression living with HIV. To ensure that this assessment is constructive in facilitating future implementation, we will map each key barrier and facilitator to a relevant implementation strategy identified in the literature to address a similar barrier or leverage a similar facilitator for maximal benefit [96,97]. For example, if the barriers related to service coverage and connectivity issues are mentioned, then the actionable solution will include working with a different service or network provider. This process will yield a concise yet informative implementation toolkit to support future implementation efforts that may face similar patient, provider, and organization-level challenges.

Data Integration and Triangulation

Findings from qualitative and quantitative data analyses will be integrated during the interpretation and discussion stages [98]. Conclusions and inferences will be synthesized for a more contextualized and thorough understanding of the preliminary impact of the intervention. The mixed methods design will serve two purposes: (1) complementarity and (2) expansion [99,100]. Qualitative findings will be connected to quantitative findings where the former will provide explanations and context for findings produced by the latter. Moreover, qualitative findings will complement our understanding of attendance and participant satisfaction with the intervention.

Results

The team completed the recruitment of phase 1 study participants (phase 1, aim 1) in January 2023. A total of 32 youths and 16 health care providers from 2 health clinics were recruited. Youths and health care providers participated in focus group discussions (4 groups for youths and 2 groups for health care providers). During the discussions, participants shared their feedback on the proposed Suubi-Mhealth intervention content, methods, design, and format, to inform the development of the app. All focus group discussions were audio-recorded to ensure accuracy of participants' responses. Transcription and translation of focus group discussions have been completed. The team is currently conducting data analysis of participants' responses, to inform the development of the Suubi-Mhealth app content. Concurrently, the development of Suubi-Mhealth content is ongoing. Specifically, the team is developing short videos to be incorporated into the app, including those related to depression and its symptoms, strategies to reduce negative thoughts, skill building, daily activities, and goal monitoring, to be incorporated into the app. Upon completion, the app will

be tested among 30 youths to garner feedback on usability (phase 1, aim 2).

Discussion

Overview

People living with HIV, including adolescents, often struggle with mental health comorbidities that lower their adherence to ART treatment [7,9]. There is growing evidence that depression treatment may improve ART adherence and result in improved HIV outcomes [19,20]. This Suubi-Mhealth study will develop a mHealth intervention for use among Ugandan youths with comorbid HIV and depression, taking into account their unique contextual, cultural, and developmental needs. We expect Suubi-Mhealth to be an acceptable and feasible mHealth tool to reduce depression and improve ART adherence and overall mental health functioning among youths.

The study innovates in the following ways. First, while mHealth interventions have been tested and implemented to improve adherence to ART among youths [50,51,53], digital intervention strategies addressing depression plus ART adherence among youths living with HIV in SSA are very limited [101]. This study will generate data-driven knowledge to address depression and ART adherence and will ultimately improve HIV-related health outcomes for youths, including adherence to medication. Second, delivering CBT—a theoretically driven intervention, delivered via a mobile app—has the potential to facilitate timely linkage and access to mental health services for youths, one of the major challenges to addressing mental health in impoverished communities. Previous studies have documented the potential of CBT to improve ART treatment outcomes [102]. Third, the study makes use of existing local institutions—both research and community-based institutions and locally recruited and trained research staff—to deliver its intervention, building research capacity and ensuring eventual scale-up and sustainability. Fourth, partnering with local institutions, including health clinics and community organizations, as well as the youths, grounds the project with a practical understanding of the needs of youths in the greater Masaka region—an area of Uganda hardest hit by HIV or AIDS [4]. Finally, the study takes advantage of the increasing penetration of cellphones and mobile phone ownership in Uganda [46], to test and deliver an innovative, culturally-tailored intervention with significant public health outcomes. Taken together, this study will lay important groundwork for several initiatives at the intersection of digital therapeutics, HIV treatment, and mental illness, especially among SSA youths, as they transition through adolescence and into adult HIV care settings.

Dissemination

The research team will facilitate learning across stakeholders and maximize the use of the evidence generated through dissemination meetings. Uganda's HIV prevention and treatment guidelines and policies recognize the burden and impact of mental health and HIV stigma on HIV treatment outcomes among youths, their families, and communities. If findings warrant, we will leverage these policy guidelines to maximize dissemination of study findings.

Data Sharing

The research team is committed to open, timely, and widespread sharing and dissemination of study findings. The team adheres to the National Institutes of Health's Public Access Policy that requires final, peer-reviewed papers to be submitted to the National Library of Medicine's PubMed Central upon acceptance for publication. We will also make study results available via papers written for professional and layperson publications, presentations at scientific and professional conferences, special lectures or talks in academic and professional settings, websites, and newsletters. Once all data have been deidentified, cleaned, and validated, and the main findings have been published, the investigators expect to share data with the scientific community. The research team will make data sets available to any individual who makes a direct request to the principal investigators and indicates the data will be used for the purposes of research. In sharing participant data, the team will follow Office of Sponsored Projects' data sharing agreements at Washington University in St. Louis, which are similar in their specification of the following conditions to be met before data are shared: (1) a formal research question is specified a priori; (2) names, affiliations, and roles of any other individuals who will access the shared data; (3) the deliverables—for example, paper, conference presentation—are specified a priori; (4) proper credit and attribution—for example, authorship, coauthorship, and order—for each deliverable are specified a priori; (5) a statement indicating an understanding that the data cannot be further shared with any additional individuals or parties without the Principal Investigators' permission; and (6) IRB approval for use of the data (or documentation that IRB has determined the research is exempt).

The research team will strip data of identifiers that would permit linkages to individual research participants and variables that could lead to deductive disclosure of the identity of individual participants. We will share data in electronic format native to the software used by the research team; requestors are expected to handle converting electronic formats. Upon completion of the deliverables, the MPIs will instruct the requestor to destroy all copies of the data. If deliverables have not been produced yet, the agreement to share data will be revisited annually by the MPIs and the research team to decide whether to continue sharing or terminate the sharing agreement.

Acknowledgments

The authors would like to thank our staff and volunteers at the International Center for Child Health and Development (ICHAD) Field Office in Masaka, Uganda, and our implementing partner, Reach the Youth, for their respective contributions to study preparation and implementation. The authors are very grateful to the youth and their caregiving families, participating health

clinics, and expert clients, for agreeing to participate in the study. The study outlined in this protocol is supported by the National Institute of Mental Health (NIMH; Grant R21MH131044; MPIs: PN; PC-R, and JM). NIMH has no role in the study design, data collection, analysis, interpretation of findings, and manuscript preparation. The content is solely the responsibility of the authors and does not necessarily represent the official views of NIMH.

Conflicts of Interest

PC-R is a consultant for Rissana, LLC, PredictView, and Woebot. The other authors declare no conflicts of interest.

Multimedia Appendix 1
Peer-review reports from the National Institute of Mental Health (NIMH) | National Institutes of Health (NIH).
[PDF File (Adobe PDF File), 149 KB - resprot_v13i1e54635_app1.pdf]

References

1. UNAIDS data 2023. UNAIDS. 2023. URL: https://www.unaids.org/en/resources/documents/2023/2023_unaids_data [accessed 2024-02-01]
2. Chibanda D, Benjamin L, Weiss HA, Abas M. Mental, neurological, and substance use disorders in people living with HIV/AIDS in low- and middle-income countries. J Acquir Immune Defic Syndr 2014;67(Suppl 1):S54-S67 [FREE Full text] [doi: 10.1097/QAI.0000000000000258] [Medline: 25117961]
3. Jörns-Presentati A, Napp AK, Dessauvagie AS, Stein DJ, Jonker D, Breet E, et al. The prevalence of mental health problems in sub-Saharan adolescents: a systematic review. PLoS One 2021;16(5):e0251689 [FREE Full text] [doi: 10.1371/journal.pone.0251689] [Medline: 33989357]
4. Facts on HIV and AIDS in Uganda 2022. Uganda AIDS Commission. 2022. URL: https://uac.go.ug/index.php?option=com_sppagebuilder&view=page&id=24&Itemid=140 [accessed 2024-02-01]
5. Nalwanga D, Musiime V. Children living with HIV: a narrative review of recent advances in pediatric HIV research and their implications for clinical practice. Ther Adv Infect Dis 2022;9:20499361221077544 [FREE Full text] [doi: 10.1177/20499361221077544] [Medline: 35186289]
6. Brandt R. The mental health of people living with HIV/AIDS in Africa: a systematic review. Afr J AIDS Res 2009;8(2):123-133 [FREE Full text] [doi: 10.2989/AJAR.2009.8.2.1.853] [Medline: 25875564]
7. Vreeman RC, McCoy BM, Lee S. Mental health challenges among adolescents living with HIV. J Int AIDS Soc 2017;20(Suppl 3):21497 [FREE Full text] [doi: 10.7448/IAS.20.4.21497] [Medline: 28530045]
8. Bernard C, Dabis F, de Rekeneire N. Prevalence and factors associated with depression in people living with HIV in Sub-Saharan Africa: a systematic review and meta-analysis. PLoS One 2017;12(8):e0181960 [FREE Full text] [doi: 10.1371/journal.pone.0181960] [Medline: 28783739]
9. Too EK, Abubakar A, Nasambu C, Koot HM, Cuijpers P, Newton CR, et al. Prevalence and factors associated with common mental disorders in young people living with HIV in Sub-Saharan Africa: a systematic review. J Int AIDS Soc 2021;24(Suppl 2):e25705 [FREE Full text] [doi: 10.1002/jia2.25705] [Medline: 34164931]
10. Tao J, Vermund SH, Qian HZ. Association between depression and antiretroviral therapy use among people living with HIV: a meta-analysis. AIDS Behav 2018;22(5):1542-1550 [FREE Full text] [doi: 10.1007/s10461-017-1776-8] [Medline: 28439754]
11. Uthman OA, Magidson JF, Safren SA, Nachega JB. Depression and adherence to antiretroviral therapy in low-, middle- and high-income countries: a systematic review and meta-analysis. Curr HIV/AIDS Rep 2014;11(3):291-307 [FREE Full text] [doi: 10.1007/s11904-014-0220-1] [Medline: 25038748]
12. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. Arch Intern Med 2000;160(14):2101-2107 [FREE Full text] [doi: 10.1001/archinte.160.14.2101] [Medline: 10904452]
13. Nakimuli-Mpungu E, Bass JK, Alexandre P, Mills EJ, Musisi S, Ram M, et al. Depression, alcohol use and adherence to antiretroviral therapy in Sub-Saharan Africa: a systematic review. AIDS Behav 2012;16(8):2101-2118 [FREE Full text] [doi: 10.1007/s10461-011-0087-8] [Medline: 22116638]
14. Meffert SM, Neylan TC, McCulloch CE, Maganga L, Adamu Y, Kiweewa F, et al. East African HIV care: depression and HIV outcomes. Glob Ment Health (Camb) 2019;6:e9 [FREE Full text] [doi: 10.1017/gmh.2019.6] [Medline: 31258923]
15. Tucker JS, Burnam MA, Sherbourne CD, Kung FY, Gifford AL. Substance use and mental health correlates of nonadherence to antiretroviral medications in a sample of patients with human immunodeficiency virus infection. Am J Med 2003;114(7):573-580 [FREE Full text] [doi: 10.1016/s0002-9343(03)00093-7] [Medline: 12753881]
16. Ironson G, O'Cleirigh C, Fletcher MA, Laurenceau JP, Balbin Z, Klimas N, et al. Psychosocial factors predict CD4 and viral load change in men and women with human immunodeficiency virus in the era of highly active antiretroviral treatment. Psychosom Med 2005;67(6):1013-1021 [FREE Full text] [doi: 10.1097/01.psy.0000188569.58998.c8] [Medline: 16314608]
17. Abas M, Ali GC, Nakimuli-Mpungu E, Chibanda D. Depression in people living with HIV in Sub-Saharan Africa: time to act. Trop Med Int Health 2014;19(12):1392-1396 [FREE Full text] [doi: 10.1111/tmi.12382] [Medline: 25319189]

18. Leserman J. Role of depression, stress, and trauma in HIV disease progression. Psychosom Med 2008;70(5):539-545 [FREE Full text] [doi: 10.1097/PSY.0b013e3181777a5f] [Medline: 18519880]
19. Sin NL, DiMatteo MR. Depression treatment enhances adherence to antiretroviral therapy: a meta-analysis. Ann Behav Med 2014;47(3):259-269 [FREE Full text] [doi: 10.1007/s12160-013-9559-6] [Medline: 24234601]
20. Mendez NA, Mayo D, Safren SA. Interventions addressing depression and HIV-related outcomes in people with HIV. Curr HIV/AIDS Rep 2021;18(4):377-390 [FREE Full text] [doi: 10.1007/s11904-021-00559-w] [Medline: 34014446]
21. Sherr L, Clucas C, Harding R, Sibley E, Catalan J. HIV and depression—a systematic review of interventions. Psychol Health Med 2011;16(5):493-527 [FREE Full text] [doi: 10.1080/13548506.2011.579990] [Medline: 21809936]
22. Johnson MO, Dilworth SE, Taylor JM, Neilands TB. Improving coping skills for self-management of treatment side effects can reduce antiretroviral medication nonadherence among people living with HIV. Ann Behav Med 2011;41(1):83-91 [FREE Full text] [doi: 10.1007/s12160-010-9230-4] [Medline: 20922510]
23. Wagner GJ, Ghosh-Dastidar B, Robinson E, Ngo VK, Glick P, Mukasa B, et al. Effects of depression alleviation on ART adherence and HIV clinic attendance in Uganda, and the mediating roles of self-efficacy and motivation. AIDS Behav 2017;21(6):1655-1664 [FREE Full text] [doi: 10.1007/s10461-016-1500-0] [Medline: 27438460]
24. Brown LK, Kennard BD, Emslie GJ, Mayes TL, Whiteley LB, Bethel J, et al. Effective treatment of depressive disorders in medical clinics for adolescents and young adults living with HIV: a controlled trial. J Acquir Immune Defic Syndr 2016;71(1):38-46 [FREE Full text] [doi: 10.1097/QAI.0000000000000803] [Medline: 26761270]
25. Lofgren SM, Nakasujja N, Boulware DR. Systematic review of interventions for depression for people living with HIV in Africa. AIDS Behav 2018;22(1):1-8 [FREE Full text] [doi: 10.1007/s10461-017-1906-3] [Medline: 28900756]
26. Nachega JB, Hislop M, Nguyen H, Dowdy DW, Chaisson RE, Regensberg L, et al. Antiretroviral therapy adherence, virologic and immunologic outcomes in adolescents compared with adults in Southern Africa. J Acquir Immune Defic Syndr 2009;51(1):65-71 [FREE Full text] [doi: 10.1097/QAI.0b013e318199072e] [Medline: 19282780]
27. Zanoni BC, Archary M, Subramony T, Sibaya T, Psaros C, Haberer JE. "It was not okay because you leave your friends behind": a prospective analysis of transition to adult care for adolescents living with perinatally-acquired HIV in South Africa. Vulnerable Child Youth Stud 2021;16(3):206-220 [FREE Full text] [doi: 10.1080/17450128.2021.1876965] [Medline: 34484412]
28. Meloni ST, Agaba P, Chang CA, Yiltok E, Oguche S, Ejeliogu E, et al. Longitudinal evaluation of adherence, retention, and transition patterns of adolescents living with HIV in Nigeria. PLoS One 2020;15(7):e0236801 [FREE Full text] [doi: 10.1371/journal.pone.0236801] [Medline: 32735566]
29. Murray KR, Dulli LS, Ridgeway K, Dal Santo L, de Mora DD, Olsen P, et al. Improving retention in HIV care among adolescents and adults in low- and middle-income countries: a systematic review of the literature. PLoS One 2017;12(9):e0184879 [FREE Full text] [doi: 10.1371/journal.pone.0184879] [Medline: 28961253]
30. Zanoni BC, Sibaya T, Cairns C, Haberer JE. Barriers to retention in care are overcome by adolescent-friendly services for adolescents living with HIV in South Africa: a qualitative analysis. AIDS Behav 2019;23(4):957-965 [FREE Full text] [doi: 10.1007/s10461-018-2352-6] [Medline: 30535836]
31. Woollett N, Pahad S, Black V. "We need our own clinics": adolescents' living with HIV recommendations for a responsive health system. PLoS One 2021;16(7):e0253984 [FREE Full text] [doi: 10.1371/journal.pone.0253984] [Medline: 34197529]
32. Judd A, Davies MA. Adolescent transition among young people with perinatal HIV in high-income and low-income settings. Curr Opin HIV AIDS 2018;13(3):236-248 [FREE Full text] [doi: 10.1097/COH.0000000000000448] [Medline: 29528851]
33. Safren SA, Bedoya CA, O'Cleirigh C, Biello KB, Pinkston MM, Stein MD, et al. Cognitive behavioural therapy for adherence and depression in patients with HIV: a three-arm randomised controlled trial. Lancet HIV 2016;3(11):e529-e538 [FREE Full text] [doi: 10.1016/S2352-3018(16)30053-4] [Medline: 27658881]
34. Easthall C, Song F, Bhattacharya D. A meta-analysis of cognitive-based behaviour change techniques as interventions to improve medication adherence. BMJ Open 2013;3(8):e002749 [FREE Full text] [doi: 10.1136/bmjopen-2013-002749] [Medline: 23935093]
35. Nieuwlaat R, Wilczynski N, Navarro T, Hobson N, Jeffery R, Keepanasseril A, et al. Interventions for enhancing medication adherence. Cochrane Database Syst Rev 2014;2014(11):CD000011 [FREE Full text] [doi: 10.1002/14651858.CD000011.pub4] [Medline: 25412402]
36. Beck AT. Cognitive therapy: past, present, and future. J Consult Clin Psychol 1993;61(2):194-198. [doi: 10.1037//0022-006x.61.2.194] [Medline: 8473571]
37. Safren SA, O'Cleirigh C, Tan JY, Raminani SR, Reilly LC, Otto MW, et al. A randomized controlled trial of Cognitive Behavioral Therapy for Adherence and Depression (CBT-AD) in HIV-infected individuals. Health Psychol 2009;28(1):1-10 [FREE Full text] [doi: 10.1037/a0012715] [Medline: 19210012]
38. Simoni JM, Wiebe JS, Sauceda JA, Huh D, Sanchez G, Longoria V, et al. A preliminary RCT of CBT-AD for adherence and depression among HIV-positive Latinos on the U.S.-Mexico border: the nuevo día study. AIDS Behav 2013;17(8):2816-2829 [FREE Full text] [doi: 10.1007/s10461-013-0538-5] [Medline: 23812892]
39. Everitt-Penhale B, Kagee A, Magidson JF, Joska J, Safren SA, O'Cleirigh C, et al. 'I went back to being myself': acceptability of a culturally adapted task-shifted cognitive-behavioural therapy (CBT) treatment for depression (Ziphamandla) for South

African HIV care settings. Psychol Health Med 2019;24(6):680-690 [FREE Full text] [doi: 10.1080/13548506.2019.1566624] [Medline: 30652921]
40. Young DKW. Cognitive behavioral therapy group for reducing self-stigma for people with mental illness. Res Soc Work Pract 2016;28(7):827-837 [FREE Full text] [doi: 10.1177/1049731516681849]
41. Büchter RB, Messer M. Interventions for reducing self-stigma in people with mental illnesses: a systematic review of randomized controlled trials. Ger Med Sci 2017;15:Doc07 [FREE Full text] [doi: 10.3205/000248] [Medline: 28496396]
42. Riley KE, Lee JS, Safren SA. The relationship between automatic thoughts and depression in a cognitive-behavioral treatment for people living with HIV/AIDS: exploring temporality and causality. Cognit Ther Res 2017;41(5):712-719 [FREE Full text] [doi: 10.1007/s10608-017-9839-8] [Medline: 28989210]
43. Andersen LS, Magidson JF, O'Cleirigh C, Remmert JE, Kagee A, Leaver M, et al. A pilot study of a nurse-delivered cognitive behavioral therapy intervention (Ziphamandla) for adherence and depression in HIV in South Africa. J Health Psychol 2018;23(6):776-787 [FREE Full text] [doi: 10.1177/1359105316643375] [Medline: 27121977]
44. Molodynski A, Cusack C, Nixon J. Mental healthcare in Uganda: desperate challenges but real opportunities. BJPsych Int 2017;14(4):98-100 [FREE Full text] [doi: 10.1192/s2056474000002129] [Medline: 29093962]
45. Bella-Awusah T, Ani C, Ajuwon A, Omigbodun O. Effectiveness of brief school-based, group cognitive behavioural therapy for depressed adolescents in South West Nigeria. Child Adolesc Ment Health 2016;21(1):44-50 [FREE Full text] [doi: 10.1111/camh.12104] [Medline: 32680363]
46. Digital technologies can deliver better healthcare to Sub-Saharan Africa. Here's how. World Economic Forum. 2017. URL: https://www.weforum.org/agenda/2017/10/digital-paths-for-better-healthcare-in-sub-saharan-africa/ [accessed 2024-02-01]
47. Market perfomance report 1Q21. Uganda Communications Commission. 2021. URL: https://consumer.ucc.co.ug/wp-content/uploads/2022/03/UCC_1Q21-MARKET-PERFOMANCE-REPORT_-compressed.pdf [accessed 2024-02-01]
48. Chib A, Wilkin H, Ling LX, Hoefman B, Van Biejma H. You have an important message! evaluating the effectiveness of a text message HIV/AIDS campaign in Northwest Uganda. J Health Commun 2012;17(Suppl 1):146-157 [FREE Full text] [doi: 10.1080/10810730.2011.649104] [Medline: 22548607]
49. Siedner MJ, Haberer JE, Bwana MB, Ware NC, Bangsberg DR. High acceptability for cell phone text messages to improve communication of laboratory results with HIV-infected patients in rural Uganda: a cross-sectional survey study. BMC Med Inform Decis Mak 2012;12:56 [FREE Full text] [doi: 10.1186/1472-6947-12-56] [Medline: 22720901]
50. Kunutsor S, Walley J, Katabira E, Muchuro S, Balidawa H, Namagala E, et al. Using mobile phones to improve clinic attendance amongst an antiretroviral treatment cohort in rural Uganda: a cross-sectional and prospective study. AIDS Behav 2010;14(6):1347-1352 [FREE Full text] [doi: 10.1007/s10461-010-9780-2] [Medline: 20700644]
51. Siedner MJ, Santorino D, Lankowski AJ, Kanyesigye M, Bwana MB, Haberer JE, et al. A combination SMS and transportation reimbursement intervention to improve HIV care following abnormal CD4 test results in rural Uganda: a prospective observational cohort study. BMC Med 2015;13:160 [FREE Full text] [doi: 10.1186/s12916-015-0397-1] [Medline: 26149722]
52. Ssewamala FM, Bermudez LG, Meyer S, Ddamulira C. Suubi+adherence: family-based economic empowerment for HIV positive youth in Southern Uganda baseline study report. International Center for Child Health and Asset Development. 2018. URL: https://ichad.wustl.edu/wp-content/uploads/2018/02/Baseline-Adherence_FINAL_05June.pdf [accessed 2024-02-01]
53. Chory A, Callen G, Nyandiko W, Njoroge T, Ashimosi C, Aluoch J, et al. A pilot study of a mobile intervention to support mental health and adherence among adolescents living with HIV in Western Kenya. AIDS Behav 2022;26(1):232-242 [FREE Full text] [doi: 10.1007/s10461-021-03376-9] [Medline: 34292429]
54. Wakida EK, Okello ES, Rukundo GZ, Akena D, Alele PE, Talib ZM, et al. Health system constraints in integrating mental health services into primary healthcare in rural Uganda: perspectives of primary care providers. Int J Ment Health Syst 2019;13:16 [FREE Full text] [doi: 10.1186/s13033-019-0272-0] [Medline: 30949234]
55. Wakida EK, Obua C, Rukundo GZ, Maling S, Talib ZM, Okello ES. Barriers and facilitators to the integration of mental health services into primary healthcare: a qualitative study among Ugandan primary care providers using the COM-B framework. BMC Health Serv Res 2018;18(1):890 [FREE Full text] [doi: 10.1186/s12913-018-3684-7] [Medline: 30477492]
56. Cavazos-Rehg PA, Krauss MJ, Costello SS, Ramsey AT, Petkas D, Gunderson S, et al. Delivering information about medication assisted treatment to individuals who misuse opioids through a mobile app: a pilot study. J Public Health (Oxf) 2020;42(1):149-154 [FREE Full text] [doi: 10.1093/pubmed/fdy207] [Medline: 30445639]
57. Whittaker R, Merry S, Dorey E, Maddison R. A development and evaluation process for mHealth interventions: examples from New Zealand. J Health Commun 2012;17(Suppl 1):11-21 [FREE Full text] [doi: 10.1080/10810730.2011.649103] [Medline: 22548594]
58. Feldstein AC, Glasgow RE. A Practical, Robust Implementation and Sustainability Model (PRISM) for integrating research findings into practice. Jt Comm J Qual Patient Saf 2008;34(4):228-243 [FREE Full text] [doi: 10.1016/s1553-7250(08)34030-6] [Medline: 18468362]
59. Nabunya P, Ssewamala FM, Bahar OS, Michalopoulos LTM, Mugisha J, Neilands TB, et al. Suubi4Stigma study protocol: a pilot cluster randomized controlled trial to address HIV-associated stigma among adolescents living with HIV in Uganda. Pilot Feasibility Stud 2022;8(1):95 [FREE Full text] [doi: 10.1186/s40814-022-01055-7] [Medline: 35488323]

60. Ssewamala FM, Sauceda JA, Brathwaite R, Neilands TB, Nabunya P, Brown D, et al. Suubi + Adherence4Youth: a study protocol to optimize the Suubi intervention for adherence to HIV treatment for youth living with HIV in Uganda. BMC Public Health 2023;23(1):717 [FREE Full text] [doi: 10.1186/s12889-023-15564-4] [Medline: 37081534]
61. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001;16(9):606-613 [FREE Full text] [doi: 10.1046/j.1525-1497.2001.016009606.x] [Medline: 11556941]
62. Nakku JEM, Rathod SD, Kizza D, Breuer E, Mutyaba K, Baron EC, et al. Validity and diagnostic accuracy of the Luganda version of the 9-item and 2-item patient health questionnaire for detecting major depressive disorder in rural Uganda. Glob Ment Health (Camb) 2016;3:e20 [FREE Full text] [doi: 10.1017/gmh.2016.14] [Medline: 28596888]
63. Ssebunnya J, Medhin G, Kangere S, Kigozi F, Nakku J, Lund C. Prevalence, correlates and help-seeking behaviour for depressive symptoms in rural Uganda: a population-based survey. Glob Ment Health (Camb) 2019;6:e27 [FREE Full text] [doi: 10.1017/gmh.2019.25] [Medline: 31807311]
64. Ssewamala FM, Byansi W, Bahar OS, Nabunya P, Neilands TB, Mellins C, et al. Suubi+Adherence study protocol: a family economic empowerment intervention addressing HIV treatment adherence for perinatally infected adolescents. Contemp Clin Trials Commun 2019;16:100463 [FREE Full text] [doi: 10.1016/j.conctc.2019.100463] [Medline: 31872152]
65. Ssewamala FM, Bahar OS, Nabunya P, Thames AD, Neilands TB, Damulira C, et al. Suubi+Adherence-Round 2: a study protocol to examine the longitudinal HIV treatment adherence among youth living with HIV transitioning into young adulthood in Southern Uganda. BMC Public Health 2021;21(1):179 [FREE Full text] [doi: 10.1186/s12889-021-10202-3] [Medline: 33478469]
66. Ssewamala FM, Dvalishvili D, Mellins CA, Geng EH, Makumbi F, Neilands TB, et al. The long-term effects of a family based economic empowerment intervention (Suubi+Adherence) on suppression of HIV viral loads among adolescents living with HIV in southern Uganda: findings from 5-year cluster randomized trial. PLoS One 2020;15(2):e0228370 [FREE Full text] [doi: 10.1371/journal.pone.0228370] [Medline: 32040523]
67. Ssewamala FM, Wang JSH, Brathwaite R, Sun S, Mayo-Wilson LJ, Neilands TB, et al. Impact of a family economic intervention (bridges) on health functioning of adolescents orphaned by HIV/AIDS: a 5-year (2012-2017) cluster randomized controlled trial in Uganda. Am J Public Health 2021;111(3):504-513 [FREE Full text] [doi: 10.2105/AJPH.2020.306044] [Medline: 33476237]
68. Brathwaite R, Ssewamala FM, Mutumba M, Neilands TB, Byansi W, Namuwonge F, et al. The long-term (5-year) impact of a family economic empowerment intervention on adolescents living with HIV in Uganda: analysis of longitudinal data from a cluster randomized controlled trial from the Suubi+Adherence study (2012-2018). AIDS Behav 2022;26(10):3337-3344 [FREE Full text] [doi: 10.1007/s10461-022-03637-1] [Medline: 35429307]
69. Ssewamala FM, Brathwaite R, Bahar OS, Namatovu P, Neilands TB, Kiyingi J, et al. The post-intervention impact of Amaka Amasanyufu on behavioral and mental health functioning of children and adolescents in low-resource communities in Uganda: analysis of a cluster-randomized trial from the SMART Africa-Uganda study (2016-2022). J Adolesc Health 2023;72(5S):S3-S10 [FREE Full text] [doi: 10.1016/j.jadohealth.2022.09.035] [Medline: 37062581]
70. Sima AP, Stromberg KA, Kreutzer JS. An adaptive method for assigning clinical trials wait-times for controls. Contemp Clin Trials Commun 2021;21:100727 [FREE Full text] [doi: 10.1016/j.conctc.2021.100727] [Medline: 33604487]
71. Kizito S, Nabunya P, Ssewamala FM. Enhancing adherence to antiretroviral therapy among adolescents living with HIV through group-based therapeutic approaches in Uganda: findings from a pilot cluster-randomized controlled trial. J Pediatr Psychol 2023;48(11):907-913. [doi: 10.1093/jpepsy/jsad081] [Medline: 37935531]
72. Peng W, Kanthawala S, Yuan S, Hussain SA. A qualitative study of user perceptions of mobile health apps. BMC Public Health 2016;16(1):1158 [FREE Full text] [doi: 10.1186/s12889-016-3808-0] [Medline: 27842533]
73. Dute DJ, Bemelmans WJE, Breda J. Using mobile apps to promote a healthy lifestyle among adolescents and students: a review of the theoretical basis and lessons learned. JMIR Mhealth Uhealth 2016;4(2):e39 [FREE Full text] [doi: 10.2196/mhealth.3559] [Medline: 27150850]
74. Payne HE, Lister C, West JH, Bernhardt JM. Behavioral functionality of mobile apps in health interventions: a systematic review of the literature. JMIR Mhealth Uhealth 2015;3(1):e20 [FREE Full text] [doi: 10.2196/mhealth.3335] [Medline: 25803705]
75. Palinkas LA, Horwitz SM, Green CA, Wisdom JP, Duan N, Hoagwood K. Purposeful sampling for qualitative data collection and analysis in mixed method implementation research. Adm Policy Ment Health 2015;42(5):533-544 [FREE Full text] [doi: 10.1007/s10488-013-0528-y] [Medline: 24193818]
76. Lund AM. Measuring usability with the USE questionnaire. Usability Interface 2001;8(2):3-6 [FREE Full text]
77. Knight-Agarwal C, Davis DL, Williams L, Davey R, Cox R, Clarke A. Development and pilot testing of the Eating4two mobile phone app to monitor gestational weight gain. JMIR Mhealth Uhealth 2015;3(2):e44 [FREE Full text] [doi: 10.2196/mhealth.4071] [Medline: 26048313]
78. Boulet J, Boss MW. Reliability and validity of the brief symptom inventory. Psychol Assess 1991;3(3):433-437. [doi: 10.1037/1040-3590.3.3.433]
79. Wu AW, Rubin HR, Mathews WC, Ware JE, Brysk LT, Hardy WD, et al. A health status questionnaire using 30 items from the medical outcomes study. Preliminary validation in persons with early HIV infection. Med Care 1991;29(8):786-798. [doi: 10.1097/00005650-199108000-00011] [Medline: 1875745]

80. Varni JW, Seid M, Rode CA. The PedsQL™: measurement model for the pediatric quality of life inventory. Med Care 1999;37(2):126-139. [doi: 10.1097/00005650-199902000-00003] [Medline: 10024117]
81. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the pediatric quality of life inventory version 4.0 generic core scales in healthy and patient populations. Med Care 2001;39(8):800-812. [doi: 10.1097/00005650-200108000-00006] [Medline: 11468499]
82. Nabunya P, Namuwonge F. HIV-related shame, stigma and the mental health functioning of adolescents living with HIV: findings from a pilot study in Uganda. Child Psychiatry Hum Dev 2023;54(6):1771-1778 [FREE Full text] [doi: 10.1007/s10578-022-01374-z] [Medline: 35668284]
83. Michalopoulos LM, Meinhart M, Barton SM, Kuhn J, Mukasa MN, Namuwonge F, et al. Adaptation and validation of the shame questionnaire among Ugandan youth living with HIV. Child Indic Res 2019;12(3):1023-1042 [FREE Full text] [doi: 10.1007/s12187-018-9570-3] [Medline: 34721728]
84. Berger BE, Ferrans CE, Lashley FR. Measuring stigma in people with HIV: psychometric assessment of the HIV stigma scale. Res Nurs Health 2001;24(6):518-529. [doi: 10.1002/nur.10011] [Medline: 11746080]
85. Zimet GD, Powell SS, Farley GK, Werkman S, Berkoff KA. Psychometric characteristics of the multidimensional scale of perceived social support. J Pers Assess 1990;55(3-4):610-617. [doi: 10.1080/00223891.1990.9674095] [Medline: 2280326]
86. Vaux A, Riedel S, Stewart D. Modes of social support: the Social Support Behaviors (SS-B) scale. Am J Community Psychol 1987;15(2):209-232. [doi: 10.1007/bf00919279]
87. Wilson IB, Lee Y, Michaud J, Fowler FJ, Rogers WH. Validation of a new three-item self-report measure for medication adherence. AIDS Behav 2016;20(11):2700-2708 [FREE Full text] [doi: 10.1007/s10461-016-1406-x] [Medline: 27098408]
88. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol 2006 Jan;3(2):77-101. [doi: 10.1191/1478088706qp063oa]
89. Carey TA, Haviland J, Tai SJ, Vanags T, Mansell W. MindSurf: a pilot study to assess the usability and acceptability of a smartphone app designed to promote contentment, wellbeing, and goal achievement. BMC Psychiatry 2016;16(1):442 [FREE Full text] [doi: 10.1186/s12888-016-1168-z] [Medline: 27955643]
90. Isaac S, Michael WB. Handbook in Research and Evaluation: A Collection of Principles, Methods, and Strategies Useful in the Planning, Design, and Evaluation of Studies in Education and the Behavioral Sciences, 3rd Edition. San Diego, CA, US: EdITS Publishers; 1995.
91. Morse JM. Determining sample size. Qual Health Res 2016;10(1):3-5 [FREE Full text] [doi: 10.1177/104973200129118183]
92. Dulin PL, Gonzalez VM, Campbell K. Results of a pilot test of a self-administered smartphone-based treatment system for alcohol use disorders: usability and early outcomes. Subst Abus 2014;35(2):168-175 [FREE Full text] [doi: 10.1080/08897077.2013.821437] [Medline: 24821354]
93. Bricker JB, Mull KE, Kientz JA, Vilardaga R, Mercer LD, Akioka KJ, et al. Randomized, controlled pilot trial of a smartphone app for smoking cessation using acceptance and commitment therapy. Drug Alcohol Depend 2014;143:87-94 [FREE Full text] [doi: 10.1016/j.drugalcdep.2014.07.006] [Medline: 25085225]
94. Bahar OS, Byansi W, Kivumbi A, Namatovu P, Kiyingi J, Ssewamala FM, et al. From "4Rs and 2Ss" to "Amaka Amasanyufu" (happy families): adapting a U.S.-based evidence-based intervention to the Uganda context. Fam Process 2020;59(4):1928-1945 [FREE Full text] [doi: 10.1111/famp.12525] [Medline: 32027763]
95. Cavazos-Rehg P, Byansi W, Xu C, Nabunya P, Bahar OS, Borodovsky J, et al. The impact of a family-based economic intervention on the mental health of HIV-infected adolescents in Uganda: results from Suubi + Adherence. J Adolesc Health 2021;68(4):742-749 [FREE Full text] [doi: 10.1016/j.jadohealth.2020.07.022] [Medline: 32980245]
96. Lord S, Moore SK, Ramsey A, Dinauer S, Johnson K. Implementation of a substance use recovery support mobile phone app in community settings: qualitative study of clinician and staff perspectives of facilitators and barriers. JMIR Ment Health 2016;3(2):e24 [FREE Full text] [doi: 10.2196/mental.4927] [Medline: 27352884]
97. Powell BJ, Waltz TJ, Chinman MJ, Damschroder LJ, Smith JL, Matthieu MM, et al. A refined compilation of implementation strategies: results from the Expert Recommendations for Implementing Change (ERIC) project. Implement Sci 2015;10:21 [FREE Full text] [doi: 10.1186/s13012-015-0209-1] [Medline: 25889199]
98. Creswell JW, Clark VLP. Designing and Conducting Mixed Methods Research, 3rd Edition. Los Angeles: Sage Publications; 2018.
99. Greene JC, Caracelli VJ, Graham WF. Toward a conceptual framework for mixed-method evaluation designs. Educ Eval Policy Anal 1989;11(3):255-274. [doi: 10.3102/01623737011003255]
100. Greene JC, Caracelli VJ. Advances in Mixed-Method Evaluation: The Challenges and Benefits of Integrating Diverse Paradigms: New Directions for Evaluation, Number 74. San Francisco: Jossey-Bass Publishers; 1997.
101. Das JK, Salam RA, Lassi ZS, Khan MN, Mahmood W, Patel V, et al. Interventions for adolescent mental health: an overview of systematic reviews. J Adolesc Health 2016;59(4S):S49-S60 [FREE Full text] [doi: 10.1016/j.jadohealth.2016.06.020] [Medline: 27664596]
102. Qin K, Zeng J, Liu L, Cai Y. Effects of cognitive behavioral therapy on improving depressive symptoms and increasing adherence to antiretroviral medication in people with HIV. Front Psychiatry 2022;13:990994 [FREE Full text] [doi: 10.3389/fpsyt.2022.990994] [Medline: 36440403]

Abbreviations

ART: antiretroviral therapy
CBT: cognitive behavioral therapy
ICHAD: International Center for Child Health and Development
IRB: institutional review board
mHealth: mobile health
PHQ-9: Patient Health Questionnaire-9
PRISM: Practical, Robust Implementation, and Sustainability Model
SSA: Sub-Saharan Africa
USE: Usefulness, Satisfaction, and Ease of Use

Edited by A Mavragani; submitted 16.11.23; this is a non–peer-reviewed article;accepted 30.01.24; published 08.03.24.

Please cite as:
Nabunya P, Cavazos-Rehg P, Mugisha J, Kasson E, Namuyaba OI, Najjuuko C, Nsubuga E, Filiatreau LM, Mwebembezi A, Ssewamala FM
An mHealth Intervention to Address Depression and Improve Antiretroviral Therapy Adherence Among Youths Living With HIV in Uganda: Protocol for a Pilot Randomized Controlled Trial
JMIR Res Protoc 2024;13:e54635
URL: https://www.researchprotocols.org/2024/1/e54635
doi:10.2196/54635
PMID:38457202

Protocol

Improving Quality of ICD-10 (International Statistical Classification of Diseases, Tenth Revision) Coding Using AI: Protocol for a Crossover Randomized Controlled Trial

Taridzo Chomutare[1,2], PhD; Anastasios Lamproudis[1], MSc; Andrius Budrionis[1,3], PhD; Therese Olsen Svenning[1], MSc; Lill Irene Hind[4], BSc; Phuong Dinh Ngo[1,3], PhD; Karl Øyvind Mikalsen[3,5], PhD; Hercules Dalianis[1,6], PhD

[1]Health Data Analytics, Norwegian Centre for E-health Research, Tromsø, Norway

[2]Department of Computer Science, UiT The Arctic University of Norway, Tromsø, Norway

[3]Department of Physics and Technology, UiT The Arctic University of Norway, Tromsø, Norway

[4]Clinic for Surgery, Oncology and Women Health, University Hospital of North Norway, Tromsø, Norway

[5]The Norwegian Centre for Clinical Artificial Intelligence, University Hospital of North Norway, Tromsø, Norway

[6]Department of Computer and Systems Sciences, Stockholm University, Kista, Sweden

Corresponding Author:
Taridzo Chomutare, PhD
Department of Computer Science
UiT The Arctic University of Norway
Realfagbygget
Hansine Hansens vei 54
Tromsø, 9019
Norway
Phone: 47 47680032
Email: taridzo.chomutare@uit.no

Abstract

Background: Computer-assisted clinical coding (CAC) tools are designed to help clinical coders assign standardized codes, such as the *ICD-10* (*International Statistical Classification of Diseases, Tenth Revision*), to clinical texts, such as discharge summaries. Maintaining the integrity of these standardized codes is important both for the functioning of health systems and for ensuring data used for secondary purposes are of high quality. Clinical coding is an error-prone cumbersome task, and the complexity of modern classification systems such as the *ICD-11* (*International Classification of Diseases, Eleventh Revision*) presents significant barriers to implementation. To date, there have only been a few user studies; therefore, our understanding is still limited regarding the role CAC systems can play in reducing the burden of coding and improving the overall quality of coding.

Objective: The objective of the user study is to generate both qualitative and quantitative data for measuring the usefulness of a CAC system, Easy-ICD, that was developed for recommending *ICD-10* codes. Specifically, our goal is to assess whether our tool can reduce the burden on clinical coders and also improve coding quality.

Methods: The user study is based on a crossover randomized controlled trial study design, where we measure the performance of clinical coders when they use our CAC tool versus when they do not. Performance is measured by the time it takes them to assign codes to both simple and complex clinical texts as well as the coding quality, that is, the accuracy of code assignment.

Results: We expect the study to provide us with a measurement of the effectiveness of the CAC system compared to manual coding processes, both in terms of time use and coding quality. Positive outcomes from this study will imply that CAC tools hold the potential to reduce the burden on health care staff and will have major implications for the adoption of artificial intelligence–based CAC innovations to improve coding practice. Expected results to be published summer 2024.

Conclusions: The planned user study promises a greater understanding of the impact CAC systems might have on clinical coding in real-life settings, especially with regard to coding time and quality. Further, the study may add new insights on how to meaningfully exploit current clinical text mining capabilities, with a view to reducing the burden on clinical coders, thus lowering the barriers and paving a more sustainable path to the adoption of modern coding systems, such as the new *ICD-11*.

Trial Registration: clinicaltrials.gov NCT06286865; https://clinicaltrials.gov/study/NCT06286865

International Registered Report Identifier (IRRID): DERR1-10.2196/54593

(JMIR Res Protoc 2024;13:e54593) doi:10.2196/54593

KEYWORDS

International Classification of Diseases, Tenth Revision; ICD-10; International Classification of Diseases, Eleventh Revision; ICD-11; Easy-ICD; clinical coding; artificial intelligence; machine learning; deep learning

Introduction

Background

Artificial intelligence shows a lot of promise for many health care applications, but its implementation in clinical settings is still limited [1]. One promising implementation area is clinical coding, which involves clinical staff or trained personnel going through large amounts of clinical text, such as discharge summaries, and assigning clinical codes to the texts. Clinical staff can thus summarize the patient's stay at the hospital using a system of codes such as the International Statistical Classification of Diseases and Related Health Problems (version 10; *ICD-10*[*International Statistical Classification of Diseases, Tenth Revision*]) [2].

A systematic way of summarizing patient care at hospitals is important for multiple reasons. The primary use of such data is to judge both the quality and volume of care. The data also serve as a consideration point for resource allocation. In addition, good coding practice is important for improving the quality of data available for secondary purposes such as research and knowledge generation.

An analysis of the literature reveals at least 2 major uses for computer-assisted clinical coding (CAC) systems [3]. The first type of use is to assist clinical coders in their work in real time, while the other type of use is in auditing the quality of existing coding. Audits are a principal element of quality control, especially since there have been reports of significant coding errors in electronic health record (EHR) systems. For instance, in a Swedish study, Jacobsson and Serdén [4] reported that 20% of the main diagnosis codes were wrong. For this user study, we focus on the former type of use, that is, assisting clinical coders in real time.

Available Knowledge

In terms of the informatics methods that CAC systems use, there is wide variation. Depending on specific use cases, rule-based methods have been successfully used to extract clinical concepts from texts [5-7] or to classify clinical texts into standard terminology such as Systematized Nomenclature of Medicine—Clinical Terms or International Classification of Diseases [8,9]. Rule-based methods appear to work well, but generally, texts have to be tokenized into short phrases or n-grams. Words within each sentence are usually treated independently of each other. Unless considered separately, clinical language peculiarities such as negation [10], uncertainty and speculations, and acronyms and abbreviations [11] can obscure the meaning of words in sentences.

With the advances in deep learning, in particular, transformer architectures, longer text sequences can be processed using contextual embeddings, where the representation of each word is based on its context. This contextual understanding of words makes deep learning an appropriate tool for CAC systems that process long and complex clinical texts. Santos et al's [12] systematic review on the topic shows a clear timeline transition toward deep learning methods, and this finding is echoed in a recent review by Kaur et al [13]. However, occasioned by multiple limiting factors related to the nature of clinical coding, current state-of-the-art (SOTA) performance is still unsatisfactory and lags other application areas of deep learning.

One of the major limiting factors is that assigning clinical codes to large sequences of text is a hard problem, compounded by a very large number of codes that represent the label space (eg, more than 20,000 *ICD-10* codes for Norwegian). In addition to the large number of codes, the level of class imbalance is rather extreme in this use case. Another limiting factor is that many close codes have semantically similar descriptions. An example of 2 semantically similar codes is "Other diseases of tongue (K14.8)" and "Disease of tongue, unspecified (K14.9)." It is challenging for a model to discriminate the two, since they both appear to describe some unnamed condition of the tongue [14]. Combined with other limiting factors such as poor data quality and availability, these factors make the design of automatic *ICD-10* coding systems nearly unattainable, especially for minor languages such as Norwegian and Swedish.

To get around this automatic coding problem, 2 popular approaches have emerged. In the first approach, researchers experiment with just a small portion of the codes, for instance, top-10 [15] or top-50 codes [16]. In many instances, these few top-N codes represent the majority of the data, but such systems perform poorly on rare codes. In the second approach, rather than automatically assigning *ICD-10* codes, multiple possible codes are provided as suggestions, much like recommender systems, with top-N suggestions. It is conceivable that this second work-around approach is useful to clinical coders because it provides potentially meaningful cues and pointers to the correct codes. This is the approach taken by the current user study.

It is important to note that a number of inconsistent findings have emerged from the little that has been published. In a recent study, Chen et al [17] concluded that, while their system improved the accuracy of *ICD-10* assignment, the system did not reduce the time required to assign the codes. In complete contrast to these findings, an earlier study by Wang et al [18] found significant time efficiencies when the CAC system was used, as did Fung et al [19]. We hypothesize that text complexity partially explains the conflict. Since text complexity is a factor that has not been fully explored in existing studies, we base our analysis of accuracy and time on the complexity of the clinical text.

Specific Aims

The aim of the project is to investigate artificial intelligence tools, natural language processing specifically, to improve the

quality of *ICD-10* coding. The goal of the user study is to test whether our Easy-ICD system can reduce the burden of coding and also improve the quality of *ICD-10* coding. The main end points to measure are (1) the individual's coding accuracy averaged across all instances and F_1-score (harmonic mean of recall and precision, each of which is averaged over all instances), (2) time use for assigning codes, and (3) usability based on the system usability scale [20].

Methods

Study Population and Location

The user study will recruit clinical coders (physicians, health care staff, professional coders, etc) from Norway and Sweden on a rolling basis. Even though clinical notes are in Swedish, most of the target population understands both the Scandinavian languages.

Inclusion and Exclusion Criteria

In terms of participants, the main inclusion criterion is that the participant has coded clinical texts before, preferably *ICD-10* coding. Participants could be clinicians, nurses, professional coders, or other health care staff who understand Swedish with any amount of coding experience. We shall exclude participants outside Sweden or Norway.

Study Time Frame

Recruitment of participants commenced toward the end of 2023, and we will continue recruitment on a rolling basis until the target number of participants is reached.

Ethical Considerations

The data curated for this study is available through Permission Dnr 2022-02386-02 from the Swedish Ethical Review Authority. This user study is part of the ClinCode Project approved by The Regional Committee for Medical and Health Research Ethics, Norway (260972). Participation is based on informed consent. A web page with information based on the template from the Norwegian Centre for Research Data is used to provide information about (1) purpose of the project; (2) institution responsible for the project; (3) why the user is being asked to participate; (4) what the user is expected to do as a participant; (5) participation as voluntary; (6) user personal privacy, when and what happens with their data; (7) information about user rights (under the General Data Protection Regulation); (8) who to contact for more information or concerns; and (9) the final section where the user clicks on "Consent" or "Decline." If the user consents to participate, the consent is logged, and the user can proceed to the study. Thus, we have a written record of consent. If the user declines, they are redirected away from the study. It is important to note that no personal or identifying information is collected, and browser cookies are only used to track progress. Thus, all the data we store will be completely anonymous.

Intervention

The CAC system, Easy-ICD, is based on deep learning transformer models, also called language models. The system uses a language model trained in 3 main cycles, based on a typical natural language processing pipeline involving unsupervised or semisupervised training (pretraining) and supervised training (fine-tuning). First, the base model, Kungliga Biblioteket—Bidirectional Encoder Representations From Transformers (KB-BERT), was obtained from the transformers library [21]. KB-BERT is a Swedish general language model that was pretrained by the National Library of Sweden [22] and is publicly available. This pretraining represents the first training cycle. In the second cycle, KB-BERT was further pretrained on 17.8 GB of pseudonymized Swedish clinical text from the Health Bank infrastructure at Stockholm University [11], resulting in the current clinical language model named SweDeClinBERT [23]. In the final training cycle, also called fine-tuning, the model was fine-tuned on a pseudonymized data set, the Stockholm EPR GastroICD-10 Pseudo Corpus II, encompassing 120,000 patients. Using pseudonymized data for training improves security by decreasing the likelihood of private information leakage.

This model achieves SOTA results on this clinical coding task, comparable to results reported for English health data sets like the Medical Information Mart for Intensive Care [24]. This clinical coding task is framed as a multilabel problem, where participants can select and assign more than one *ICD-10* code to the clinical text. Actual performance results of the model are reported in a paper under consideration, and these results will be released in the final reporting of the user study.

Considering the Easy-ICD user interface, instead of displaying only the top label or labels as predicted by the model, we display the top-N predictions, where N is between 5 and 10. Through experimentation, we determined that an ensemble output from the deep learning model and fuzzy logic had the best results. Fuzzy logic is based on word-level and sentence-level minimum edit distance, using Levenshtein distance [25], comparing between *ICD-10* descriptions and the clinical text.

Easy-ICD is implemented as a web application for this user study, but in the future, the functionality will be incorporated into an EHR system. We used the classical model-view-controller pattern involving the deep learning model module, HTML 5 web interface, and a Python back-end controller, respectively. The web interface has the following sections: (1) the clinical note, (2) color-coded visualization to explain the suggestions, (3) the top-N suggestions from where the participant selects relevant *ICD-10* codes to assign, (4) qualitative feedback with star-rating and text feedback, and (5) a lookup feature for *ICD-10* codes.

Disease and Data

We use Swedish clinical notes in the gastrointestinal (gastro) domain in our study. The data used are from the gastrointestinal department of the Health Bank infrastructure at Stockholm University [11]. The data contain both in- and outpatient records of patients receiving treatment at the department, both surgery and other medical interventions. The data originate from a hospital, and no effort was made to include only similar cases; therefore, the cases vary.

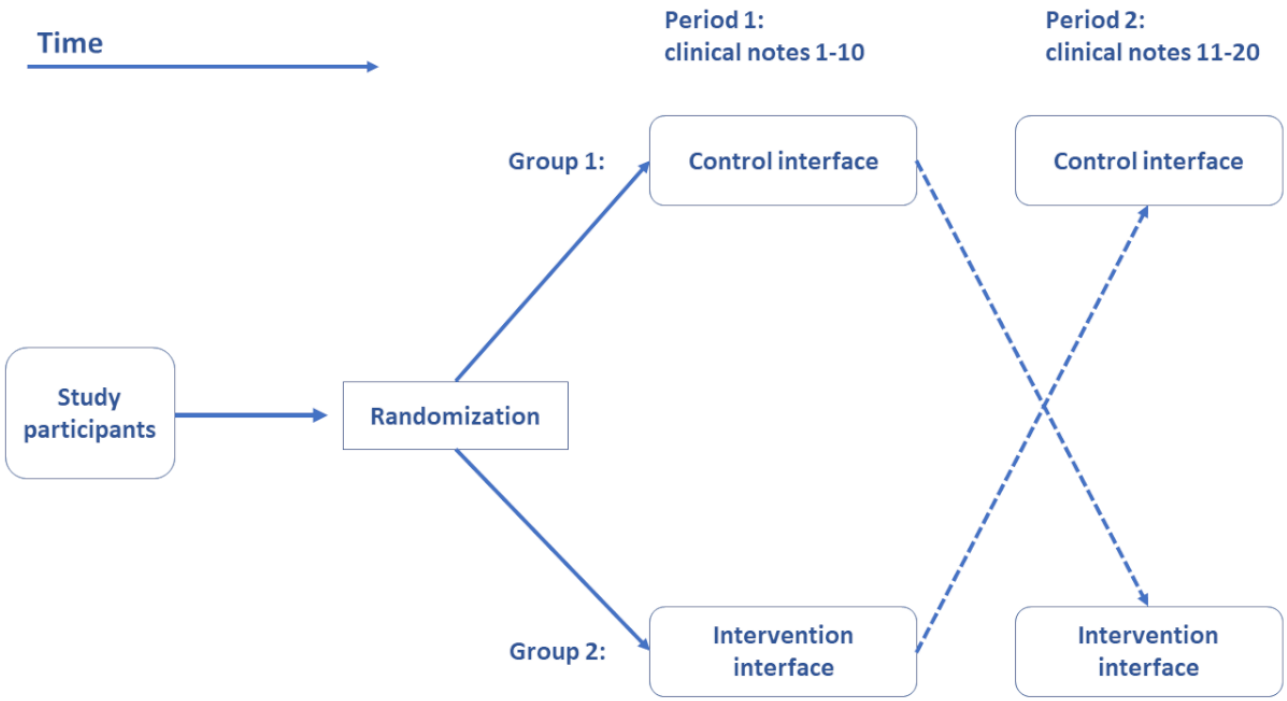
The data are pseudonymized and have been curated by 2 professional clinical coders, so as to double-check the coding

and create a gold standard. The 2 coders reviewed the data independently and reconciled their differences through discussion. This curation process also ensures that it will be possible to assign a code based on the clinical text alone, without the need for further information about the patient. This is important since the user study will not have access to further EHR data such as laboratory results or drug lists.

Study Design

This study is designed as a 2×2 crossover study as illustrated in Figure 1. This design, AB|BA (2 different sequences and 2 periods), is chosen for its uniform and balanced properties, aiming to control the carryover effect between periods. The design is suitable not only for comparing treatments but also for assessing pre-post effect of an intervention [26]. In addition, the crossover design requires a comparatively smaller number of participants than what a randomized controlled trial would ordinarily require.

Figure 1. Crossover randomized controlled trial where study participants are randomized into 2 groups. The first group first uses a control interface and then switches to our Easy-ICD tool, while the second group starts with our tool and switches to a control interface.



We will not incorporate a washout period partly because the learning element in the tasks measured is limited and partly because we do not want to risk losing participants in a long break between periods. The data sets in the 2 periods are different, and this limits any carryover effect in the sense that coders cannot memorize the text or the correct codes.

Once participants are recruited, they are randomly allocated to the 2 groups without allocation concealment. Allocation concealment will not be relevant for coders since it is known whether a participant is assisted or not, and we will not develop a placebo coding assistant. We will, however, conceal the allocation of subjects for the analyses.

In total, participants will code 20 clinical notes, where each note belongs to a single patient. The participants are asked to complete the experiment in 1 sitting without interruptions, and they cannot revisit or go back to previous notes. In the event that participants are interrupted, they are asked to exit the experiment, and any incomplete experiments are discarded as invalid.

In terms of the coding process, both the control and intervention user interfaces have a search utility for looking up *ICD-10* codes. Participants will be free to access any other additional search tools they wish to use without restriction. Since we measure time using a before and after design, the effect of additional tools is not expected to be a significant factor. The time is logged based on the browser button presses such as “Start,” “Next,” and “Complete.”

The user study process can be summarized in the following steps:

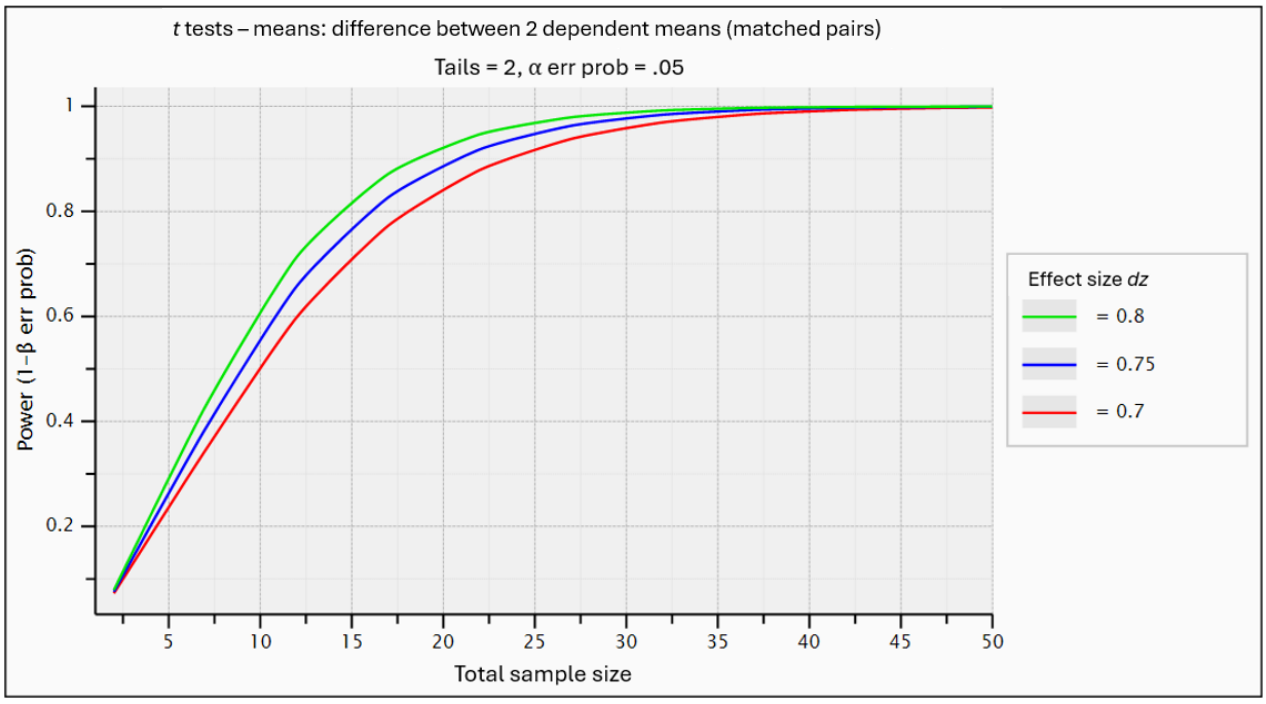
1. Study participants are randomly allocated to group 1 and group 2.
2. To prepare participants for the experiment, a short video tutorial is played after the consent form is signed and right before the clinical coding task commences.
3. In period 1 with 10 clinical notes, group 1 uses the control interface, while group 2 uses the intervention interface.
4. Data are logged in the background using button presses—time, assigned codes, and comments.
5. Then, there is an immediate crossover to period 2 for the last 10 clinical notes.
6. Data continue to be logged in the background using button presses.

7. At the end, participants in both groups will complete the system usability scale.

Sample Size Calculation

This experiment is novel, and we have not succeeded in finding many similar studies from which to estimate test parameters. Therefore, our experiment is important in that it provides baselines that may be useful for similar experiments in the future. We do expect a correlation between periods; the same coders are measured twice on mean performance in time, making a matched 2-tailed *t* test suitable for the task [26]. This matched 2-tailed *t* test (period) is done in 2 sequences, and the sample size calculation must therefore be doubled [27]. Further, each sequence will consist of approximately 10 coding instances, giving extra power to the estimation of the sequence mean. Due to the unknown nature of the expected effect size, the sample calculation in Figure 2 is made with 3 different effect estimates ranging in the upper level of medium to high effect. A pilot study is necessary to establish a probable effect size and adjust sample size estimation if needed.

Figure 2. Statistical power of a 2-tailed t test at the level of 5% depending on sample size per sequence (2-tailed t test with equal SD in both study sequences to compare means).



Based on the plot in Figure 2 derived from power analysis in G*Power [28], we aim to recruit up to 30 participants in total. Multiple methods are used to recruit participants, including contacting hospitals and health authorities directly, announcing at coding seminars and conferences, publishing news in popular science media, and advertising on social media groups and other electronic media.

Measurements and Analyses

The focus of our measurements is on how clinical coders perform with and without our system:

1. Compared with the performance of the unaided user, statistical tests of significance are used to check whether there are significant differences in the quality of coding when Easy-ICD is used, as measured by accuracy and F_1-score.
2. Time spent is the time it takes for a clinical coder to assign a code.
3. System usability survey will be given to all participants to measure usability of the web interfaces, both with and without our Easy-ICD system.

Main analyses are based on hypothesis testing using the paired *t* test and Wilcoxon test to compare the before and after means at a significance level of .05. Table 1 summarizes these hypotheses based on a test of equivalence.

Table 1. Time use and coding quality hypotheses testing to compare the before and after means.

Time use	Coding quality (accuracy and F_1-score)
Null hypothesis: (H_0: $\mu_1=\mu_2$)	
There is no time difference between using CAC[a] and not using CAC for coding Swedish clinical notes	CAC does not affect a clinical coder's coding quality
Alternative hypothesis: (H_1: $\mu_1\neq\mu_2$)	
There is a significant time difference between using CAC and not using CAC for coding Swedish clinical notes	CAC affects a clinical coder's coding quality by a significant margin

[a]CAC: computer-assisted clinical coding.

In additional exploratory analyses, we will examine the effect wrong suggestions have on the coder's performance, and how often coders adopt these wrong suggestions. In addition, the distribution of the different professions between the groups as well as the coding experience will be explored.

To enable us to analyze the main outcomes in relation to text complexity, we distinguish between two categories of clinical texts: (1) short and simple texts (<512 tokens) and (2) long and complex texts (>512 tokens). However, we only consider the length of the text as the complexity dimension, as opposed to the complexity of the case or provided care, for example.

Results

Overview

Our results will be based on the statistical significance of the 2 tests related to time use and coding quality, which will allow us to conclude whether or not our CAC tool, the Easy-ICD, has the potential to impact clinical coding practice in a meaningful way. The expected results to be published summer 2024.

Evaluation Outcomes

The evaluation outcomes are as follows: (1) clinical coders aided by our Easy-ICD system are expected to yield better performance, that is, the accuracy and F_1-score. (2) We expect that the Easy-ICD system will result in time savings during coding tasks. Looking at the 2 categories of clinical notes, it can be expected that the most time savings could be gained with large and complex texts. Such cases take more resources than shorter and simpler texts. (3) We expect the usability of the system to have a system usability score over the generally accepted normal score of 68 [29]. Further, we do not expect any significant differences between the usability of the user interfaces with and without our CAC system.

Discussion

Principal Findings

There are 2 primary areas of interpretation with which our study is concerned. The first relates to the quality or accuracy of clinical coding. If it shows that coders aided by our system perform better than unaided coders, we can conclude that our system is a useful tool to improve the quality of clinical coding. If, on the other hand, no significant improvement in accuracy is noted, we have to look to the other measurement point for complete interpretation. Time efficiency is the other interpretation point, where we would like to see significant time improvement between the intervention and control.

If the accuracy is not better, then the time savings must be significant. If there are no time savings, then the improvement in accuracy must be significant. It can also be argued that the CAC system is still useful even if the timing is slightly worse, while the performance is better by a significant margin.

If neither time nor accuracy improves, then we have to think about improving the system for future studies. Regardless, we plan to publish our findings in an international (or Nordic) peer-reviewed journal or conference and note all the facilitating factors and barriers.

In terms of usability, if there are no significant differences in usability scores, then usability issues can be ruled out. If the CAC system has significantly better usability scores, we expect the usability scores of the standard interface to be no worse than what is considered normal.

Limitations

Perhaps one limitation of this study is that we curate the clinical texts used in the study so that the participants should be able to assign a code simply by assessing the text. In practice, some clinical texts need supporting information from other information sources such as pathology or radiology systems [9]. This supporting information would normally be available in patient record systems.

Another limitation is that we only considered data from the gastrointestinal department (K-codes), and this *ICD-10* chapter has a comparatively smaller number of codes. There were 415 unique codes in the training data, and just over 480 K-codes exist in the Norwegian version of *ICD-10*. In contrast, the whole *ICD-10* system has a total of over 20,000 codes in Norwegian. Therefore, the generalizability of our system is an important factor to consider for future studies when expanding to other clinical domains.

Comparison to Prior Work

Even though there are many papers on experimental work dealing with assigning *ICD-10* codes to clinical text, only a few studies with health care staff exist. The planned user study holds the potential to yield new insights about the usefulness of CAC systems in terms of reducing coding time and improving coding quality, both of which are important impact indicators for reducing the burden on clinical coders.

Conclusions

In terms of impact, positive outcomes from this study contribute to the evidence that supports the adoption of CAC tools to reduce barriers to the implementation of modern coding systems such as the *ICD-11* (*International Classification of Diseases, Eleventh Revision*).

Acknowledgments

The authors thank professional coders at Karolinska University Hospital for their advice during the development of the Easy-ICD system and surgeons at the Gastrointestinal Department at the University Hospital of North Norway for their advice in the project. The publication charges for this paper have been funded by a grant from the publication fund of UiT The Arctic University of Norway. This research is funded by the ClinCode project through the Research Council of Norway (grant 318098 awarded to HD). The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the paper. No generative artificial intelligence was used in this study or the preparation of this paper.

Data Availability

Data sharing is not applicable to this paper as no data sets were generated or analyzed during this study.

Authors' Contributions

TC conceptualized the study. TC, AL, AB, TOS, PDN, KØM, and HD participated in methodology deliberations. TC, AL, and AB developed the software. TC prepared the original draft, and AL, AB, TOS, PDN, KØM, and HD contributed to the review and writing process. TOS and LIH worked on data curation, and LIH provided advice as a domain expert in clinical coding. TOS led the statistical analysis. HD acquired the funding and supervised the study. All authors reviewed the final paper.

Conflicts of Interest

None declared.

References

1. Chomutare T, Tejedor M, Svenning TO, Marco-Ruiz L, Tayefi M, Lind K, et al. Artificial intelligence implementation in healthcare: a theory-based scoping review of barriers and facilitators. Int J Environ Res Public Health 2022;19(23):16359 [FREE Full text] [doi: 10.3390/ijerph192316359] [Medline: 36498432]
2. International Classification of Diseases (ICD). World Health Organization. 2022. URL: https://tinyurl.com/2p9h3fzm [accessed 2024-01-25]
3. Campbell S, Giadresco K. Computer-assisted clinical coding: a narrative review of the literature on its benefits, limitations, implementation and impact on clinical coding professionals. Health Inf Manag 2020;49(1):5-18 [FREE Full text] [doi: 10.1177/1833358319851305] [Medline: 31159578]
4. Jacobsson A, Serdén L. Kodningskvalitet i patientregistret [Coding quality in the patient register]. Socialstyrelsen. 2013. URL: https://tinyurl.com/yj6h5nma [accessed 2024-01-25]
5. Uzoigwe C, Hamersky CM, Arbit DI, Weng W, Radin MS. Assessing prevalence of hypoglycemia in a medical transcription database. Diabetes Metab Syndr Obes 2020;13:2209-2216 [FREE Full text] [doi: 10.2147/DMSO.S235298] [Medline: 32612376]
6. Wulff A, Mast M, Hassler M, Montag S, Marschollek M, Jack T. Designing an openEHR-based pipeline for extracting and standardizing unstructured clinical data using natural language processing. Methods Inf Med 2020;59(S 02):e64-e78 [FREE Full text] [doi: 10.1055/s-0040-1716403] [Medline: 33058101]
7. Weegar R, Nygård JF, Dalianis H. Efficient encoding of pathology reports using natural language processing. 2017 Presented at: Proceedings of Recent Advances in Natural Language Processing; September 4-6, 2017; Varna, Bulgaria p. 778-783 URL: https://www.acl-bg.org/proceedings/2017/RANLP%202017/pdf/RANLP100.pdf [doi: 10.26615/978-954-452-049-6_100]
8. Hammami L, Paglialonga A, Pruneri G, Torresani M, Sant M, Bono C, et al. Automated classification of cancer morphology from Italian pathology reports using Natural Language Processing techniques: a rule-based approach. J Biomed Inform 2021;116:103712 [FREE Full text] [doi: 10.1016/j.jbi.2021.103712] [Medline: 33609761]
9. Nguyen AN, Truran D, Kemp M, Koopman B, Conlan D, O'Dwyer J, et al. Computer-assisted diagnostic coding: effectiveness of an NLP-based approach using SNOMED CT to ICD-10 mappings. AMIA Annu Symp Proc 2018;2018:807-816 [FREE Full text] [Medline: 30815123]
10. Budrionis A, Chomutare T, Svenning T, Dalianis H. The influence of NegEx on ICD-10 code prediction in Swedish: how is the performance of BERT and SVM models affected by negations? 2022 Presented at: The 18th Scandinavian Conference on Health Informatics; August 22-24, 2022; Tromsø, Norway URL: https://ecp.ep.liu.se/index.php/shi/article/view/457 [doi: 10.3384/ecp187029]
11. Dalianis H. Clinical Text Mining: Secondary Use of Electronic Patient Records. Cham: Springer Nature; 2018.

12. Santos T, Tariq A, Gichoya JW, Trivedi H, Banerjee I. Automatic classification of cancer pathology reports: a systematic review. J Pathol Inform 2022;13:100003 [FREE Full text] [doi: 10.1016/j.jpi.2022.100003] [Medline: 35242443]
13. Kaur R, Ginige JA, Obst O. AI-based ICD coding and classification approaches using discharge summaries: a systematic literature review. Expert Syst Appl 2023;213:118997 [FREE Full text] [doi: 10.1016/j.eswa.2022.118997]
14. Chomutare T, Budrionis A, Dalianis H. Combining deep learning and fuzzy logic to predict rare ICD-10 codes from clinical notes. : IEEE; 2022 Presented at: 2022 IEEE International Conference on Digital Health (ICDH); July 10-16, 2022; Barcelona, Spain p. 10-16. [doi: 10.1109/icdh55609.2022.00033]
15. Huang J, Osorio C, Sy LW. An empirical evaluation of deep learning for ICD-9 code assignment using MIMIC-III clinical notes. Comput Methods Programs Biomed 2019;177:141-153 [FREE Full text] [doi: 10.1016/j.cmpb.2019.05.024] [Medline: 31319942]
16. Li F, Yu H. ICD coding from clinical text using multi-filter residual convolutional neural network. Proc AAAI Conf Artif Intell 2020;34(5):8180-8187 [FREE Full text] [doi: 10.1609/aaai.v34i05.6331] [Medline: 34322282]
17. Chen PF, Wang SS, Liao WC, Kuo LC, Chen KC, Lin YC, et al. Automatic ICD-10 coding and training system: deep neural network based on supervised learning. JMIR Med Inform 2021;9(8):e23230 [FREE Full text] [doi: 10.2196/23230] [Medline: 34463639]
18. Wang SM, Chang YH, Kuo LC, Lai F, Chen YN, Yu FY, et al. Using deep learning for automatic ICD-10 classification from free-text data. Eur J Biomed Inform 2020;16(1):1-10 [FREE Full text]
19. Fung KW, Xu J, Rosenbloom ST, Campbell JR. Using SNOMED CT-encoded problems to improve ICD-10-CM coding—a randomized controlled experiment. Int J Med Inform 2019;126:19-25 [FREE Full text] [doi: 10.1016/j.ijmedinf.2019.03.002] [Medline: 31029260]
20. Brooke J. SUS: a 'quick and dirty' usability scale. In: Jordan PW, McClelland IL, Thomas B, Weerdmeester BA, editors. Usability Evaluation in Industry. Boca Raton, FL: CRC Press; 1996:189-194.
21. Wolf T, Debut L, Sanh V, Chaumond J, Delangue C, Moi A, et al. Transformers: state-of-the-art natural language processing. 2020 Presented at: Proceedings of the 2020 Conference on Empirical Methods in Natural Language Processing: System Demonstrations; November 16-20, 2020; Online p. 38-45 URL: https://aclanthology.org/2020.emnlp-demos.6/ [doi: 10.18653/v1/2020.emnlp-demos.6]
22. Malmsten M, Börjeson L, Haffenden C. Playing with words at the National Library of Sweden—making a Swedish BERT. ArXiv. Preprint posted online on July 3, 2020 [FREE Full text]
23. Vakili T, Lamproudis A, Henriksson A, Dalianis H. Downstream task performance of BERT models pre-trained using automatically de-identified clinical data. 2022 Presented at: Proceedings of the Thirteenth Language Resources and Evaluation Conference; June 20-25, 2022; Marseille, France p. 4245-4252 URL: https://aclanthology.org/2022.lrec-1.451/
24. Johnson AEW, Pollard TJ, Shen L, Lehman LWH, Feng M, Ghassemi M, et al. MIMIC-III, a freely accessible critical care database. Sci Data 2016;3:160035 [FREE Full text] [doi: 10.1038/sdata.2016.35] [Medline: 27219127]
25. Levenshtein VI. Binary codes capable of correcting deletions, insertions, and reversals. Sov Phys Dokl 1966;10(8):707-710 [FREE Full text]
26. Mills EJ, Chan AW, Wu P, Vail A, Guyatt GH, Altman DG. Design, analysis, and presentation of crossover trials. Trials 2009;10:27 [FREE Full text] [doi: 10.1186/1745-6215-10-27] [Medline: 19405975]
27. Röhrig B, du Prel JB, Wachtlin D, Kwiecien R, Blettner M. Sample size calculation in clinical trials: part 13 of a series on evaluation of scientific publications. Dtsch Arztebl Int 2010;107(31-32):552-556 [FREE Full text] [doi: 10.3238/arztebl.2010.0552] [Medline: 20827353]
28. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 2007;39(2):175-191. [doi: 10.3758/bf03193146] [Medline: 17695343]
29. Lewis JR, Sauro J. Item benchmarks for the system usability scale. J Usability Stud 2018;13(3):158-167 [FREE Full text]

Abbreviations

CAC: computer-assisted clinical coding
EHR: electronic health record
ICD-10: International Classification of Diseases, Tenth Revision
ICD-11: International Classification of Diseases, Eleventh Revision
KB-BERT: Kungliga Biblioteket—Bidirectional Encoder Representations From Transformers
SOTA: state-of-the-art

Edited by A Mavragani; submitted 15.11.23; this is a non–peer-reviewed article;accepted 16.01.24; published 12.03.24.

Please cite as:
Chomutare T, Lamproudis A, Budrionis A, Svenning TO, Hind LI, Ngo PD, Mikalsen KØ, Dalianis H
Improving Quality of ICD-10 (International Statistical Classification of Diseases, Tenth Revision) Coding Using AI: Protocol for a Crossover Randomized Controlled Trial
JMIR Res Protoc 2024;13:e54593
URL: https://www.researchprotocols.org/2024/1/e54593
doi:10.2196/54593
PMID:38470476

Protocol

Integration of an Electronic Screening, Brief Intervention, and Referral to Treatment Program Into an HIV Testing Program to Reduce Substance Use and HIV Risk Behavior Among Men Who Have Sex With Men: Protocol for Intervention Development and a Pilot Randomized Controlled Trial

Iván C Balán[1], PhD; Ruben O Marone[2], Lic; Victoria Barreda[2], Lic; Sylvie Naar[1], PhD; Yuxia Wang[1], MPH

[1]Center for Translational Behavioral Science, Department of Behavioral Science and Social Medicine, Florida State University College of Medicine, Tallahassee, FL, United States

[2]Nexo Asociacion Civil, Buenos Aires, Argentina

Corresponding Author:
Iván C Balán, PhD
Center for Translational Behavioral Science
Department of Behavioral Science and Social Medicine
Florida State University College of Medicine
2010 Levy Ave., Bldg. B, Suite 0266
Tallahassee, FL, 32310
United States
Phone: 1 2017250565
Email: ibalan@fsu.edu

Abstract

Background: Men who have sex with men (MSM) are disproportionally affected by HIV and drug and alcohol use; however, few effective HIV prevention interventions for MSM who use substances exist. Screening, Brief Intervention, and Referral to Treatment is an early intervention for non–treatment-seeking individuals with problematic substance use and for timely referral to treatment for those with substance use disorders. Electronic screening and brief interventions (e-SBIs) reduce implementation challenges. An e-SBI tailored for MSM at the time of HIV testing might be particularly opportune to strengthen their motivation to reduce substance use and HIV risk behavior.

Objective: This study aims to develop a tailored e-SBI program to reduce substance use and HIV risk behavior among MSM seeking HIV testing at Nexo Asociación Civil, our community partners in Argentina (primary); assess the feasibility and acceptability of integrating the e-SBI into the Nexo HIV testing program (primary); assess the feasibility and acceptability of implementing an adapted Men's Health Project (MHP) at Nexo (secondary); and finally, explore preliminary findings on substance use and sexual risk reduction outcomes (exploratory).

Methods: This mixed methods study has 2 stages. During stage 1 (development), we will use the User Centered Rapid App Design process consisting of focus groups (n=16), individual interviews (n=24), and a pilot deployment of the e-SBI (n=50) to iteratively develop the e-SBI. Quantitative and qualitative assessments at each step will inform the revision of the e-SBI. Furthermore, we will use the assessment, decision, administration, production, topic experts, integration, training, testing framework to adapt MHP. During stage 2 (pilot randomized controlled trial [RCT]), we will randomize 200 MSM coming to Nexo for HIV testing. They will complete a baseline assessment and then their assigned intervention (e-SBI vs screening only) and will be followed-up for 6 months. We will also conduct in-depth interviews with up to 45 participants: 15 participants from either study condition who entered or completed MHP or other substance abuse treatment and 15 from each arm who met the criteria for MHP but did not request it.

Results: The study began recruitment in October 2022, and the stage-1 pilot study is near completion. Preliminary findings from stage 1 show high e-SBI acceptability. Data analysis of the stage-1 pilot is now beginning. The stage-2 pilot RCT will be launched in March 2024, with all data collection completed by May 2025.

Conclusions: This study will allow us to assess the acceptability and feasibility of e-SBI implementation during HIV testing encounters. We will also build the necessary research infrastructure for a subsequent RCT to assess the efficacy of e-SBIs in reducing substance use and HIV sexual risk behavior among MSM in this setting.

Trial Registration: ClinicalTrials.gov NCT05542914; https://tinyurl.com/yyjj64dm.

International Registered Report Identifier (IRRID): DERR1-10.2196/56683

(JMIR Res Protoc 2024;13:e56683) doi:10.2196/56683

KEYWORDS

HIV; substance use; community health; implementation science; eHealth

Introduction

Background

Men who have sex with men (MSM) are disproportionally affected by HIV and drug and alcohol use [1-11]. Given the association between substance use and HIV risk behavior among MSM [12-25], the dearth of effective HIV prevention interventions for MSM who use substances is striking. However, as in the general population, identifying and engaging MSM with problematic substance use (PSU) in treatment is a significant challenge [26-28] that results in most MSM with PSU never receiving treatment [29].

The Substance Abuse and Mental Health Services Administration recommends Screening, Brief Intervention, and Referral to Treatment (SBIRT) as an early intervention for nontreatment-seeking individuals with risky alcohol and drug use and for timely referral to more intensive treatment for those with substance use disorders [30]. However, implementing SBIRT is a challenge; brief intervention (BI) is often missed and not evidence based, which can diminish its effectiveness. For example, when SBIRT was implemented in sexually transmitted disease clinics in New York City, out of 66,989 positive screens, only 17,474 received BI [31]. In medical settings, factors such as limited staff time, commitment to implementation, training requirements, difficulty in learning evidence-based BIs, skepticism about the effectiveness of SBIRT, and poor fidelity to recommended BI guidelines are all obstacles to the successful implementation of SBIRT [32-39]. These factors limit the BI in a particular setting. BIs can range from providing normative feedback to the individual on their level of severity (at times just a written report), brief advice (10-15 min), or a single 30- to 45-minute session. However, studies have shown that interventions that go beyond normative feedback and provide an empathic [33] or motivational component [34], or consist of multisession interventions for high-risk users, have better outcomes but can be difficult to implement. As a result, sizeable percentages of patients in a setting go unscreened, those who meet the criteria for a BI may not receive it, the BI may be delivered inconsistently, and the BI may not be of sufficient intensity to reduce substance use among those with low or moderate risk use or to improve entry into substance abuse treatment among those with high-risk use or dependence [35].

Electronic screening and brief interventions (e-SBIs) reduce implementation challenges such as extensive training, demands on staff time, and inconsistency in the delivery of BI [32,36-42], while remaining as effective as in-person SBIs [43-46]. Because an e-SBI demands only that a staff member provide an individual with a tablet or computer space to complete both the screening and BI, more individuals can be screened and receive the BI. For example, in an implementation pilot study that used e-SBI in rural clinics, approximately 92% of patients were screened, with over 95% of screen-positive women receiving the tablet-based BI, which far exceeds the rates in trials of person-delivered SBIRT (SJ Ondersma, personal communication). Furthermore, e-SBIs are consistently rated highly for acceptability among users and may facilitate greater disclosure of PSU than in-person SBIs because of concerns of being judged by providers. As such, an e-SBI tailored for PSU and sexual risk behavior among MSM at the time of HIV testing, when a contemplative client is already concerned about his risk behavior and cares enough about his health to seek an HIV test, might be particularly opportune to strengthen his motivation to reduce substance use and HIV risk behavior.

The need for such interventions is particularly acute in Argentina and Latin America, where there is little implementation of evidence-based interventions for MSM with PSU. In *Proyecto LINKS*, our study of 500 MSM in Buenos Aires [47], 61% of the men reported drug use and over 40% reported polydrug use during the previous 2 months. Marijuana, tranquilizers, cocaine, and *pasta base* (cocaine sulfate) were particularly prevalent. Furthermore, over 20% of users of these substances used them daily [9]. Most participants in the study consumed alcohol during the past 2 months: 32% of them reported drinking at least weekly and drinking enough to “feel it a lot,” “get drunk,” or “feel like you might pass out.” Substance use was higher among participants who were younger, unemployed, had greater mood variability, and did not identify as gay [9]. HIV prevalence, at 17% (31% among gay-identified men), and incidence, at 4.53 per 100 person-years (5.60 per 100 person-years in gay-identified men), were also alarming [48]. These findings highlight the critical need for effective, evidence-based HIV prevention interventions for substances using MSM in Argentina.

The proposed study seeks to address this glaring gap by using a user-centered process to develop and pilot a tablet-based e-SBI program tailored to MSM awaiting their HIV test at Nexo Asociación Civil, our community partners in Buenos Aires, who conduct over 1500 HIV tests per year with MSM. The e-SBI will integrate substance use and sexual risk behavior screeners and individually tailored motivational interviewing (MI) as the BI. Furthermore, we will adapt and pilot the implementation of the Young Men’s Health Project (YMHP)

[49], a 4-session MI-based intervention that effectively reduced substance use and condomless anal intercourse among MSM who use substances, as a brief treatment provided at Nexo for participants with moderate-risk substance use or to build motivation to enter specialized substance abuse treatment among those with high risk or dependence.

Study Objectives

As a National Institutes of Health R34 (Clinical Trial Planning Grant) study, the main goal of the study is to develop and pilot all the study components and build the necessary research infrastructure for a subsequent randomized controlled trial (RCT) to assess the efficacy of the e-SBI to reduce substance use and sexual risk behavior. The specific aims of this R34 study are as follows:

1. Develop a tailored e-SBI program to reduce substance use and HIV risk behavior among MSM seeking HIV testing
2. Conduct a pilot RCT of e-SBI versus screening only (3:1 ratio) to assess the acceptability and feasibility of integrating e-SBI into the Nexo HIV testing program and the feasibility of a future large-scale efficacy trial of e-SBI, as measured by the following:
   - Percent of MSM testing clients at Nexo who accept entry into the study (recruitment rate)
   - Percent of participants who complete the e-SBI (retention rate)
   - Retrospective acceptability ratings of the 2 RCT conditions (primary)
3. Assess the feasibility and acceptability of implementing the Men's Health Project (MHP) at Nexo, as measured by the following:
   - The percentage of MSM with moderate or high-risk substance use who enter MHP from either RCT condition (recruitment rate)
   - The percentage of MHP participants who complete all 4 sessions
   - Prospective acceptability of MHP among participants in either RCT condition
   - Retrospective acceptability of MHP among those who received it
   - Percentage of sessions conducted by each MHP counselor that meet the criteria for MI proficiency on the Motivational Interviewing Treatment Integrity (MITI.4) ratings

Methods

Study Design

This 3-year study began on August 1, 2022, and comprises 2 stages. The first stage, *Development*, will consist of developing the e-SBI, adapting the YMHP into MHP, training counselors to deliver MHP, and piloting the e-SBI with 50 MSM coming to Nexo for HIV testing. During the second stage, *the Pilot RCT*, we will randomize 200 MSM coming to Nexo for HIV testing at a 3:1 ratio (e-SBI to screening assessments only) to assess the feasibility and acceptability of the e-SBI among MSM coming to Nexo for HIV testing and establish and pilot the RCT process for a future trial. As a secondary aim, we will assess the uptake, acceptability, and feasibility of delivering MHP to participants with moderate-risk substance use and subsequent referrals to substance abuse treatment among participants with high-risk substance use or dependence. Finally, we will explore the preliminary findings on substance use and sexual risk reduction outcomes.

At the outset of the study, we will convene a Community Advisory Board (CAB) composed of 6 members, including representatives from a local community-based organization focused on policy, training, and social marketing regarding substance abuse; a representative from the Department of Sexual Health, AIDS, and STIs at the Ministry of Health of the City of Buenos Aires; and 4 MSM who report using drugs and alcohol recreationally (these criteria will not be known to others). The CAB will meet study investigators (in person or via videoconferencing) quarterly throughout the study. The CAB will be responsible for reviewing and providing feedback on the e-SBI, MHP, and assessment instruments that will be used in the study before they are used with the study participants.

This study was registered at ClinicalTrials.gov on September 16, 2022. The identifier number was NCT05542914.

Ethical Considerations

Ethics Committee Approvals

The study was reviewed and approved by the Florida State University Institutional Review Board (IRB ID: STUDY00002530) and the Ethics Committee of Nexo Asociación Civil (protocol 26082022).

All participants were provided with a written informed consent form to read before participating in the study. The consent form included an overview of the study, study procedures, risks of participation, procedures implanted to minimize risks of participation, a statement of voluntary participation, and contact information for the principal investigators in Argentina and the United States, along with contact information for the respective institutional review boards. Consent was documented with the signature of the participants and research staff.

The results of the study may be published or presented, but no information that can identify individual participants will ever be provided or released in publications or presentations. To protect the privacy and confidentiality of participants, the study staff will keep any records containing identifying information in a locked cabinet accessible only to the research staff. The computer programs used in tablet-based interventions are compliant with US regulations on personal health information, as are the servers on which the data are stored. All data captured on the tablet, although it does not include identifying information, are encrypted in transit to maintain confidentiality. Any other study data will be stored on a secure computer that is protected by passwords. All records will be kept confidential. This is consistent with the guidelines of the US National Institutes of Health. After removing all identifying information, the remaining deidentified information collected during the study could be used for future research studies or distributed to another investigator for future research studies without additional consent.

All participant incentives will be paid in cash in Argentine pesos. In stage 1, focus group (FG) participants will receive US $25; individual interview participants will receive US $20; and e-SBI pilot participants will receive US $10 and an additional US $10 for those who complete a qualitative interview. In stage 2, RCT participants will receive US $15 for completing the baseline assessment and e-SBI screeners, US $15 for the month 3 follow-up assessment, and US $20 for the month 6 follow-up assessment. Participants who complete the 6-month in-depth interview (IDI) will receive an additional US $20.

Components of the Intervention

MI Intervention

MI is the basis for both the e-SBI and MHP. MI is "a collaborative, goal-oriented method of communication aimed at strengthening an individual's motivation for and movement toward a specific goal by eliciting and exploring the person's own arguments for change." [50] In an MI session, a clinician guides rather than pushes a client toward change, sidestepping resistance, and actively works with the patient's strengths to build self-efficacy toward the desired outcome. MI uses standard tools of counseling and psychotherapy (ie, open-ended questions, affirmations, reflections, and summaries) strategically to elicit and reinforce change talk (patient statements that argue against the status quo, such as "I have been doing crazy things when I use drugs," or for behavior change, such as "I want to have sex sober so I don't want to worry the next day about whether I got HIV") and to inhibit sustain talk (patient statements that argue against change, such as "Sex a little high is fun"). Process research on the mechanisms of action in MI shows that more change talk [51,52] and less sustained talk during a session are related to better outcomes [51,53]. In addition, counselor behaviors such as advising, confronting, directing, and warning clients are associated with greater sustained talk [54,55], whereas affirming a client's strengths or effort, emphasizing client control, and supporting clients are associated with increased change talk [55,56]. Thus, to facilitate behavior change, the goal of an MI counselor is to interact with the client in a way that fosters change talk and inhibits sustain talk [51]. These key aspects of MI will inform the programming of the narrator in the e-SBI (described below), the revision of MHP, and the training of MHP counselors. The e-SBI will be created using the Computerized Intervention Authoring System (CIAS) V.3, which is an authoring tool that allows the creation and editing of electronic screening and intervention packages without the need for a programmer. Interventions built using CIAS feature a synthetic text-to-speech engine that reads all questions and speaks aloud to the participant (via headphones); synchronous interactivity; natural language reflections; branching logic; a clean user interface; and the ability to easily incorporate images, text graphs, figures, or videos. CIAS is consistent with human-computer interaction literature, suggesting that interactive, lifelike software can engage users and promote behavior change [57-61]. Thus, CIAS uses an optional interactive cartoon character capable of over 50 specific animated actions (smile, wave, read a message, express concern, etc) that talk for the entire program. The character acts as a narrator and guide throughout the process and provides occasional comic relief. Everything the character does is specifically programmed during the development phase, including interacting with participants in an MI-consistent manner and reflecting participants' change talk derived from their responses to the assessments. For example, using the participants' responses, the narrator might be programmed to say "You don't drink very often, but when you do, you drink a lot (from Alcohol Use Disorders Identification Test [AUDIT] responses) and you are noticing that it is impacting your physical health and your relationship with others (from responses to the Short Inventory of Problems)." CIAS has been used with thousands of participants (primarily those with low socioeconomic status) and has consistently received high satisfaction ratings [62-66].

YMHP Intervention

YMHP is a 4-session MI-based intervention that was the first intervention to demonstrate reductions in substance use and sexual risk behavior among non–treatment-seeking MSM who use substances [49]. Compared with the time- and content-matched control group, YMHP recipients were 18% less likely to use drugs and 24% less likely to engage in unprotected anal intercourse. On days when drug use and sex co-occurred, drug use reductions led to a decrease in unprotected anal intercourse. Secondary analyses showed that drug use among partnered participants was stable but declined significantly at all follow-up time points among single men [67]. We will adapt and implement YMHP as an in-house brief treatment for participants with PSU, either as a stand-alone treatment (for those with moderate-risk use) or as an intervention to link those with high-risk use or dependence on substance abuse treatment.

Stage 1: Development

Overview

The development of the e-SBI app will be guided by the User Centered Rapid Application Development (UCRAD) process [68-72]. UCRAD merges the streamlined and iterative Rapid Application Development approach with a user-centered design approach, which engages intended users throughout the app development process. This integrated approach aims to develop successful apps with good functionality, simple features, and usable interfaces [69]. As such, the intended users are given access to prototypes of the app, allowing them to provide feedback before the next iteration of the app. The process is relatively brief, approximately 6 to 9 months. UCRAD uses a 3-phase process as follows:

1. Predesign and interface prototyping: Data are gathered from key stakeholders to understand the requirements of the app in terms of content and interface. While continuing to assess user needs, developers offer potential solutions for the design. At the end of this stage, an initial prototype is developed based on the initial requirements.
2. System architecture and coding: The prototype is shared with the intended end users to obtain feedback. The developers update the prototype according to the feedback provided and begin system coding to develop a more complete version of the app. This version is returned to users for another round of feedback and development. The

result of this stage is an advanced but often incomplete product with basic system architecture and system specifications.

3. Deployment: The app is implemented in the field to obtain further feedback from potential end users, and further development of the application is conducted to reach a final product.

Predesign and Interface Prototyping

To accomplish this phase, we will obtain feedback from the CAB regarding the study screening instruments and preliminary plans for the e-SBI content. After incorporating their feedback, we will conduct 2 FGs with MSM (n=16) recruited from Nexo testing clients who were 18+ years of age and self-identified as male. They will complete a substance use screener consisting of an illicit drug use question on the National Institute on Drug Abuse–modified Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) brief screen and the AUDIT-C (a 3-item alcohol use screen). Those who indicate using illicit drugs at least monthly or receive a score of ≥4 on the AUDIT-C will be eligible to participate. After obtaining informed consent, they will complete paper and pencil versions of the screening instruments planned for inclusion in the e-SBI, including:

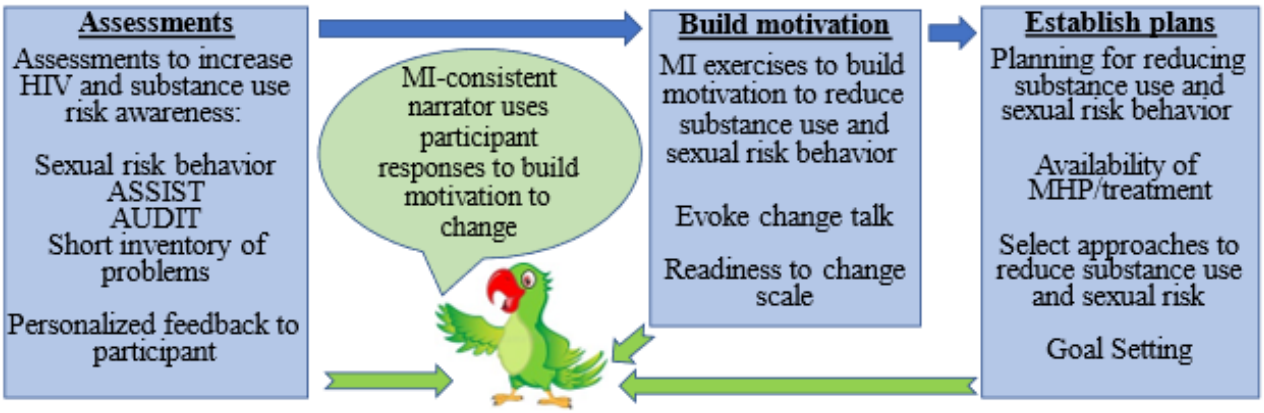
- The *National Institute on Drug Abuse–modified ASSIST* [73,74] substance use assessment, which has high consistency in detecting moderate and high substance use, and high concordance (90%-98%) and correlation (intraclass correlation coefficient 0.90-0.97) for tobacco, alcohol, and drug risk scores [75]. A self-administered computer ASSIST was found to have a 0.93 interclass correlation with the interviewer-administered version [76].
- *AUDIT* [77,78] is a widely used tool developed by the World Health Organization to identify individuals whose alcohol consumption has become hazardous or harmful to their health. AUDIT is a 10-item screening questionnaire with 3 questions on the amount and frequency of drinking, 3 questions on alcohol dependence, and 4 on problems caused by alcohol.
- *Short Inventory of Problems-Alcohol and Drug Use (SIP-AD) for MSM* [79] is a 10-item version of the SIP-AD [80] (α=.95) derived through Item Response Theory, which was found to be highly valid and reliable among non–treatment-seeking MSM. The SIP-AD assesses the frequency (0=never; 3=daily or almost daily) of commonly experienced consequences of alcohol or drug use across the physical, intrapersonal, interpersonal, social responsibility, and impulse dimensions.
- *Sexual Practices Assessment Schedule* [81] asks about the number of partners and occasions of oral, anal, and vaginal sex with male, female, and transgender sexual partners in the past 2 months; use of condoms during sexual intercourse; and assumed HIV status of the partner.
- *Readiness to Change Rulers* for alcohol use, risky sexual behavior, and drug use: although they vary in their specific wording, single-item readiness to change rulers that ask respondents to place themselves on a scale of change from 1-7 or 1-10 have shown concurrent and predictive validity for alcohol use [82-85], drug use [82,86-88], and sexual risk behavior [84,89]. These scales are also often used in MI interventions to strategically evoke change talk and increase motivation to change problem behaviors.

The 90-minute audio-recorded FGs will (1) explore participants' reactions to the screeners and their impact on risk perception and motivation to reduce PSU and risk behavior and (2) evoke content for the BI component to develop options for reasons to change and potential approaches to reduce PSU and sexual risk behavior from which e-SBI users can choose. Within 48 hours of completing the FG, we will initiate a rapid analysis of these data [90,91] using a qualitative matrix [92,93] onto which participants' responses and recommendations will be entered to quickly organize and summarize FG findings. These findings will be used to build a prototype of the e-SBI.

System Architecture and Coding

This iterative app development process will be conducted with waves of 6 MSM recruited from Nexo testing clients, with the same inclusion criteria as in the FGs. They will be recruited during 2-week intervals to maintain a steady pace of feedback and revisions. The participants completed the intervention on the tablet. They then complete a 7-item self-report instrument used by CIAS developers [64] that assesses how much participants (1) liked the e-SBI and fount it to be (2) interesting, (3) easy to use, (4) made up of understandable questions, (5) respectful, (6) annoying, and (7) humorous; each item is rated from 1=not at all to 5=very much. Afterward, participants will be debriefed during an audio-recorded interview to explore (1) their responses to the acceptability assessment; (2) overall reactions to e-SBI; (3) emotional reactions as e-SBI progressed, including heightened risk awareness, concern, or motivation to reduce substance use and sexual risk behavior; and (4) recommendations for improving the ability of the e-SBI to engage MSM with high-risk drug and alcohol use in treatment. The interview data will undergo the same matrix-based, rapid analysis process used for the FG to quickly inform the next revision of the e-SBI. This process will be repeated with waves of 6 participants until mean scores on each acceptability question are ≥4.0 (≤2.0 on annoying), which we expect within 3 to 4 cycles. Figure 1 depicts our current conceptualization of the e-SBI, with specific content informed by the stage-1 findings. The development of the e-SBI will be guided by Choice Theory [94], which has been used extensively to inform goal choice interventions [95-100], including MI interventions to reduce substance use among MSM [97,98]. Rather than preset outcome expectations (ie, abstinence), goal choice interventions highlight personal choice and goal setting to engage individuals in reducing drug and alcohol use. Goal choice interventions are equally effective as abstinence-based interventions, allowing individuals to set their own treatment goals, which appears to increase success rates [99,100].

Figure 1. Conceptualization of the electronic screening and brief intervention (e-SBI) intervention to reduce substance use and HIV sexual risk behavior among men who have sex with men in Argentina; ASSIST: Alcohol, Smoking and Substance Involvement Screening Test; AUDIT: Alcohol Use Disorders Identification Test; MI: motivational interviewing; MHP: Men's Health Project.



Deployment

The initial version of the e-SBI will be deployed with 50 MSM coming to Nexo for HIV testing to be used while awaiting their HIV test. On the basis of the findings from LINKS and Nexo screening data, we estimated that at least 50% will report using drugs and 80% will report using alcohol, and that 20% to 25% will report PSU. As such, a sample of 50 will allow us to explore reactions to the e-SBI from MSM with no, low-risk, and moderate to high-risk substance use. After obtaining informed consent, these individuals will complete the e-SBI and a brief quantitative acceptability assessment and then proceed to undergo their HIV test (to minimize participant distress). Subsequently, up to 25 of these participants will be randomly selected (5 with low-risk substance use and 20 with moderate or high-risk substance use) to undergo an audio-recorded IDI that will be guided by the theoretical framework of acceptability (TFA; see components in Textbox 1) [101], which has been used to guide qualitative and mixed methods research on the acceptability of health care interventions [102-105]. Data from these interviews will also undergo a rapid qualitative analysis as previously described for the FGs.

Textbox 1. Components of the theoretical framework of acceptability.

- *Affective Attitude:* how the individual feels about the intervention
- *Burden:* perceived amount of effort that is required to participate in the intervention
- *Ethicality:* extent to which the intervention has a good fit with an individual's value system
- *Intervention Coherence:* extent to which the participant understands the intervention and how it works
- *Opportunity Costs:* extent to which benefits, profits, or values are given up to engage in the intervention
- *Perceived Effectiveness:* extent to which the intervention is perceived as likely to achieve its purpose
- *Self-efficacy:* the participant's confidence that they can perform the behaviors required to participate in the intervention

Adaptation of YMHP to MHP

In consultation with our CAB, the research team will adapt YMPH while guided by the modified ADAPT-ITT (assessment, decision, administration, production, topic experts, integration, training, testing) framework (Textbox 2) [106]. The adaptation will focus on three main areas: (1) tailoring YMHP to Argentine MSM (including translation and cultural relevance for MSM aged over 29 y); (2) adapting YMPH from a stand-alone intervention to an intervention within an SBIRT program by minimizing duplication with e-SBI content and incorporating content to improve linkage to specialized substance abuse treatment for participants with high-risk substance use or dependence; and (3) adding content to address its poorer efficacy among partnered MSM.

Textbox 2. Overview of the ADAPT-ITT (assessment, decision, administration, production, topic experts, integration, training, testing) framework.

- Assessment phase: completed as part of our earlier studies and discussions with stakeholders
- Decision phase: completed as part of our earlier studies and discussions with stakeholders
- Administration phase: perform theater test to obtain feedback
- Production phase: produce revised intervention, maintain fidelity to core elements and underlying theory. Develop quality assurance and process measures
- Topic experts phase: involve topic experts in adapting the intervention
- Integration phase: integrate content from topical experts; integrate new assessments based on revised content
- Training phase: train staff to deliver the intervention
- Testing phase: test revised intervention in pilot study

Administration

To obtain feedback from members of the target population and key stakeholders, we video recorded a mock YMHP session (conducted in Spanish) that will be shown to the CAB, Nexo counselors (most of whom identify as gay men), and study coinvestigators. As they watch the videos, audience members will be asked to complete a feedback form, divided by portions in the session, so that they can provide feedback on issues they felt needed to adapt from the original. Next, we will discuss recommendations for addressing the issues raised.

Production

Feedback obtained during the administration phase will inform draft 1 of MHP. The revised intervention will be translated into Spanish and manualized to standardize counseling sessions and provide support and guidance for counselors.

Topic Experts and Integration

Draft 1 of MHP will be reviewed by substance abuse experts on the CAB, Nexo counselors, and coinvestigators to identify any other components of the intervention that need revision. Feedback from this review will be integrated into the intervention to create draft 2, which will be pilot-tested during the stage-2 RCT.

Training of MHP Counselors

The training of MHP counselors will be consistent with research on learning MI, which recommends a 2-day workshop with follow-up feedback and coaching [107,108]. As such, we will conduct a 4-day training with MHP providers; the first 2 days will focus on general MI principals and skills and the last 2 days will focus on specifics of MHP. Counselors will then conduct at least 2 mock cycles of MHP, which will be audio recorded and uploaded to a secure internet site for the MI trainer to rate using the MITI.4 scale [109], which captures the counselor's level of fidelity to MI and establishes specific criteria for *Proficiency* in MI. These ratings will be used to assess MI skills that require further development, which will guide videoconference coaching sessions.

Testing

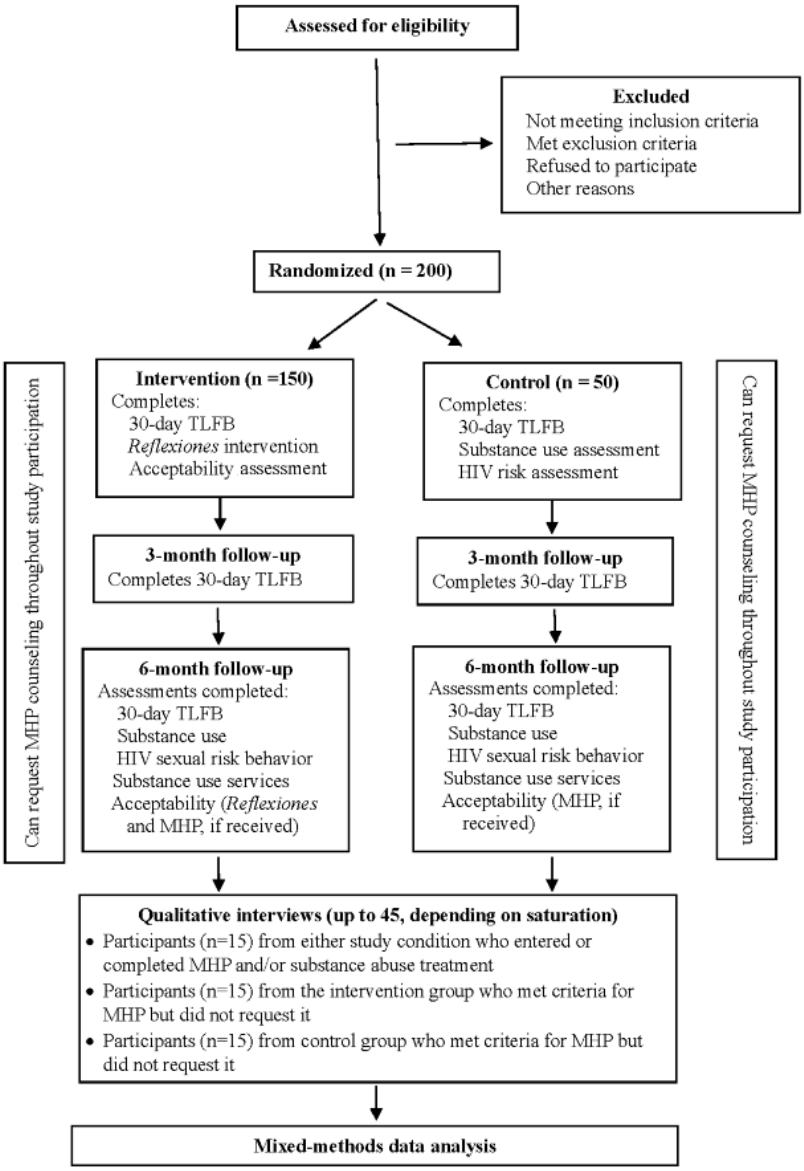
Although the primary aim of this study was to focus on the e-SBI component, as a secondary aim, we will assess the potential uptake and acceptability of MHP during the stage-2 pilot RCT.

Stage 2: Pilot RCT

Overview

With the e-SBI finalized, MHP adapted, and MHP counselors trained, the study will proceed to the stage-2 RCT comparing e-SBI to screening assessment only (see the CONSORT [Consolidated Standards of Reporting Trials] diagram for an overview; Figure 2). We will assess the feasibility and acceptability of e-SBIs and conduct a preliminary exploration of substance use and sexual risk reduction outcomes. On the basis of the findings from LINKS and Nexo data, we estimated that 50% of participants will report using drugs and 80% will report using alcohol, and that 20% to 25% will report moderate- or high-risk use based on the ASSIST and AUDIT criteria, respectively. As a secondary aim, we will assess the uptake, acceptability, and feasibility of delivering MHP at Nexo and the subsequent linkage to substance abuse treatment among those with high-risk substance use or dependence. The RCT process is described below.

Figure 2. CONSORT (Consolidated Standards of Reporting Trials) diagram for the proposed phase-2 pilot randomized controlled trial of electronic screening and brief intervention (Reflexiones). MHP: Men's Health Project; TLFB: Timeline Followback.



Recruitment

To ensure that the flow of participants is manageable during the study in the context of an HIV testing program, we will recruit up to 4 participants per day, 3 days per week, adjusting as necessary based on recruitment patterns to ensure the recruitment of all 200 participants. MSM who come to Nexo for HIV testing and are 18 years of age or older will be offered participation in the study. These clients will be given a flyer that, consistent with goal-choice interventions, will create a low threshold for study participation by stressing personal choice, goal selection, and an intervention tailored specifically for MSM to determine how to best reduce behavior that puts them at risk of HIV infection. Clients who wish to participate will complete informed consent, be randomized immediately, and be given a tablet logged on to their respective study arm (and disposable headphones) to complete their study procedures. Clients who declined participation will undergo the standard HIV testing process at Nexo. The research staff will record the number of clients who refused to participate.

Baseline Assessment

Participants in both conditions will complete a demographics questionnaire and then a self-administered, tablet-based 30-day *Timeline Followback (TLFB)* [110] to track days of drug use; number of alcoholic drinks; and HIV risk behavior, defined as anal sex with (1) an HIV-positive partner who they were not sure had an undetectable viral load or (2) a partner who had not tested HIV negative within the past 3 months. The TLFB has demonstrated good test-retest reliability, convergent validity, and agreement with collateral reports for daily drinking [111] and sexual behavior [112]. The TLFB will be used to assess primary substance use and sexual risk behavioral outcomes (which are exploratory outcomes in this study). After completing the e-SBI, participants in the intervention condition also completed a brief quantitative assessment of acceptability (8 items) based on the TFA [113].

RCT Study Conditions

Participants will be randomly assigned into 1 of 2 study arms.

Intervention Group Participants

After completing the baseline assessment, the tablet will immediately lead these participants to the e-SBI, as finalized in stage 1. The CIAS branching logic allows the e-SBI to tailor the BI based on factors such as participants' substance use risk level (based on ASSIST and AUDIT scores), risk perception, and readiness to change. Thus, BI may range from affirming and sustaining motivation among those with low-risk substance use to actively motivating and encouraging (in an MI-consistent manner) those with moderate or high-risk use to speak with a research assistant to obtain an appointment for MHP. The e-SBI will also target the participant's sexual risk behavior and help them develop a risk-reduction plan, regardless of their substance use. Then, they proceed to the usual HIV testing process at Nexo.

Control Group Participants

After completing the baseline assessment, the tablet will lead these participants to the same screening instruments as in the e-SBI, but with no MI-based BI. Due to ethical considerations, control group participants with moderate- or high-risk substance use based on the ASSIST or AUDIT scores will receive brief feedback on the tablet stating their level of risk, availability of MHP at Nexo, and instructions to see the receptionist for an appointment, if desired. Then, they proceed to the usual HIV testing process at Nexo.

Referral for MHP

All individuals with moderate- or high-risk substance use will be recommended for MHP (either *actively motivated* to enter MHP through the MI component of the e-SBI for those in the intervention condition or recommended to enter treatment and made aware of the availability of treatment at Nexo for those in the control condition). MHP sessions will be conducted in-person at Nexo (later sessions can occur remotely, based on the participant's preference) and will follow the intervention manual as finalized at the end of stage 1, with sessions expected to be 60 minutes in duration. As in the YMHP efficacy study, the 4 MHP sessions can be conducted over a period of up to 2 months. To maximize retention, participants will be offered reminder calls or text before each scheduled visit. For participants with moderate-risk substance use, MHP focuses on reducing substance use and sexual risk behavior. For participants with high-risk use or dependence, MHP sessions focus on building motivation to enter substance abuse treatment. After accepting the referral, the participant and Nexo staff contact the treatment provider to obtain an appointment at the clinic of the participant's choice (ie, closer to home). Nexo staff will offer to accompany the participant to the appointment to provide a *warm handoff* to facilitate linkage to care. To ensure intervention fidelity, all MHP sessions will be audio recorded, uploaded to a secure website, and rated using the MITI.4. MITI.4 ratings will be conducted throughout the study and used to inform weekly videoconferencing coaching sessions for MHP counselors to improve and sustain MI skills.

Follow-Up Assessments

All participants, including those who enter MHP or substance abuse treatment, will repeat the self-administered 30-day TLFB at 3 and 6 months after enrollment to assess drug use, alcohol use, and sexual risk behavior. At 6 months, they will also complete the screener instruments in the e-SBI and TFA-based quantitative retrospective acceptability assessments of e-SBI and MHP (if they enter MHP), all of which will be self-administered. We will also conduct IDIs with up to 45 participants (or less if saturation is reached): 15 participants from either study condition who entered or completed MHP and substance abuse treatment and 15 from each arm who met the criteria for MHP but did not request it. Also guided by the TFA, we expect these IDIs to be similar to those conducted in the stage-1 e-SBI pilot; however, revisions will be made to the IDI guide based on how well the questions elicited the desired material from the stage-1 participants. The use of one framework to guide all of these IDIs and the qualitative data analysis will allow us to more rigorously compare participants with PSU who entered MHP and substance abuse treatment with those who did not to identify factors that might impact their decision to enter MHP. IDIs will be conducted at Nexo, audio recorded, and transcribed.

Data Analysis

Qualitative Data Analysis for Stage-2 IDIs

For the stage-2 pilot RCT, transcripts from the audio recordings will be reviewed for accuracy and uploaded onto Dedoose for management and analysis. Codebook development will begin when 10 transcripts are available. First-level codes will be guided by TFA components, whereas second- and third-level codes emerge from themes identified in the narratives. An initial set of codes will be generated independently by 2 research staff members, compared, and then synthesized to compile shared coding categories and subcategories, all with definitions, inclusion and exclusion criteria, and examples. As transcripts become available, coding will continue, refining codebook definitions that will be used to process the remainder of the manuscript. The coders discussed discrepancies until they achieved 80% intercoder convergence. As per Patton [114], we will identify indigenous (ie, participant-generated) and analyst-constructed typologies. Once data are coded, analysis of coding reports will include categorization, abstraction, comparison (especially between groups in stage-2 RCT), integration, iteration, and refutation of themes.

Integration of Quantitative and Qualitative Data

We seek to exploit the richness of our mixed methods approach, with quantitative and qualitative findings enriching each other. Quantitative assessments allowed us to systematically explore variables of interest across all participants. Qualitative data will add nuances and new insights to quantitative findings. During data analysis, the interpretation of quantitative results will be enriched by the summary of codes for specific components of the e-SBI. In Dedoose, participants will be categorized based on their responses in the quantitative assessment (eg, severity of drug or alcohol use; ratings on readiness to change rulers) and use these categories to compare themes and concepts that emerge from the qualitative data.

Quantitative Data Analysis

Primary Aims

The primary aim of this study is to assess the feasibility and acceptability of integrating e-SBI into the HIV testing process at Nexo by estimating and comparing (1) the percentage of MSM testing clients at Nexo who accept entry into the study among those who are asked (recruitment rate); (2) the percentage of participants who complete e-SBI (retention rate); and (3) the mean score of 7-item e-SBI acceptability ratings between MSM participating in the e-SBI and those in the screening-only group. The secondary aim is to assess the feasibility and acceptability of implementing MHP at Nexo by estimating and examining the group difference with respect to (1) the percentage of MSM with moderate or high-risk substance use who enter or complete MHP; (2) percentage of high-risk enrollees in MHP who proceeded to substance abuse treatment; (3) mean acceptability of MHP and substance abuse treatment among those who received it (based on quantitative assessment to be developed); and (4) percentage of sessions conducted by each MHP counselor that meet the criteria for MI proficiency MITI.4 ratings. The estimation is accomplished by generating a point estimate with its corresponding 95% CI. We will use a 2-tailed *t* test for continuous outcomes and Fisher exact test for binary outcomes for the above comparisons. Adjustment for covariates, if necessary, with control baseline values, will be accomplished using multiple linear (continuous outcomes) or logistic (dichotomous outcomes) regression.

Exploratory Aims

Although this study did not recruit a sufficiently large sample to provide adequate power for assessing the efficacy of e-SBI, we will use data from the 30-day TLFB to explore changes in days of drug use, days of alcohol use, days of heavy alcohol use (5 or more drinks), and occasions of anal intercourse with a risky partner. To examine the efficacy of the above outcomes, a generalized linear model with a log link function was constructed, and generalized estimating equation methods were used to estimate model parameters and their SEs to account for correlation introduced by accessing the participants at multiple time points. Accompanying each of these tests will be point and interval estimates for the parameters of interest (ie, the ratio of the 2 group rate ratios). Although the hypotheses consider several simultaneous measures of effect, for the routine reporting of these results, there will be no adjustment for multiple comparisons.

Power Considerations

The primary goal of this pilot study was to collect preliminary data on the feasibility, acceptability, and target outcomes of the proposed intervention. We will use these pilot data to rule out unusually large or small true effects using standard 95% CI procedures. We confirm that the extrinsic effect sizes are contained within our CIs from the pilot. We examine the distribution of each variable and calculate the summary statistics by intervention condition. We will estimate key intervention parameters with sample means and proportions together with 2-sided 95% CIs and test the primary null hypotheses at the traditional 2-sided level α=.05 (simulation of the subsequent RCT). To plan the RCT, we will also consider 1-sided 90% confidence limits for mission-critical design parameters such as SDs and reference group end-point rates and proportions in the conservative direction. This is because we intend to plan sample size for the RCT so that power will be *excellent* (at least 80% power) for the clinically relevant effect size to be specified. This strategy will make proper allowance for the limited sample size of the pilot study with its consequent uncertainties and still yields appropriate sample sizes for the RCT. *Mission-critical* parameters include proportions for dichotomous variables (eg, recruitment rate and retention rate) and means and SDs for continuous outcomes (eg, days of drug use, days of alcohol use, acceptability of MHP and Substance abuse treatment). Large sample sizes are not required to locate these parameters approximately, but adequately, to plan the subsequent trial, whereas testing the study hypothesis in the pilot will generally not have sufficient statistical power. The estimation of mission-critical design parameters with point and CI estimates will be considered highly important; continuous outcome measures make it feasible to detect promising effect effects even in small samples. Means and SDs were estimated for continuous measures. For approximately normally distributed variables, an upper 1-sided 90% confidence limit for the SD, *sU*, was constructed from $sU = s \times c2n,.10 \times 1/2$, where *s* is the sample SD and *c2n,.10* is the upper 10th percentile of the chi-square distribution with *n* degrees of freedom. For approximately log-normally distributed variables, logarithmic transformation was applied to achieve approximate symmetry and normality. For dichotomous variables (such as the primary and secondary outcomes or the PDR performance criteria), exact binomial methods will be used for the CIs for proportions. As an example, the width of the 95% CI around a point estimate of 50% (eg, MSM with moderate- or high-risk substance use who complete e-SBI and then enter MHP) would be 43% to 57% with 200 participants.

Results

The study began with recruitment for stage 1 in October 2022. Currently, we are nearing the completion of stage 1. As part of the stage-1 development process, we conducted 2 FGs (n=16) and 2 waves of individual interviews (n=12). Consistent with the protocol, we ended the individual interviews after 2 of the 4 possible waves because acceptability scores were consistently high (mean score was >4 out of 5 for all participants). At present, we have almost completed the stage-1 pilot. At the conclusion of stage 1, we will conduct a rapid qualitative data analysis [90,91] to assess any additional changes that need to be made to the e-SBI before the stage-2 RCT, which we expect to launch in March 2024. At that time, we will also begin a deeper analysis of the stage-1 data from FGs, individual interviews, and the stage-1 pilot and include that in a future mixed methods manuscript to describe the intervention and its acceptability among the intended audience. We expect all data collection to be completed by February 2025 and the study results to be available by June 2025.

Discussion

Overview

This study addresses the critical need for interventions that reduce both PSU and HIV risk behavior among MSM in Latin America by adapting 2 evidence-based interventions, e-SBI and YMHP, for MSM in Argentina seeking HIV testing. Given that many MSM seek HIV testing in lesbian, gay, bisexual, and transgender (LGBT) community agencies, these interventions have the potential to reach large numbers of MSM, help them reflect on their use of drugs and alcohol, and help link those with PSU to evidence-based intervention (MHP). The provision of substance abuse treatment within an LGBT community agency can help facilitate entry and retention in treatment, as sexual minority men will not be concerned about the discrimination and microaggressions they might face at agencies serving the public. If proven efficacious in a future RCT, the implementation of these interventions in such agencies will help address a key contributor to HIV risk behavior and infection as well as reduce drug and alcohol use among MSM, who are disproportionately affected by HIV and substance use.

Strengths

A key strength of this study is the iterative development of the intervention based on end user feedback to ensure its high acceptability among intended users. Feedback from end users is essential to create an intervention that achieves its aim of heightening risk awareness of PSU to motivate reductions in use in a respectful, nonjudgmental manner without creating resentment or defensiveness.

An additional strength is that the study and the intervention were developed in close collaboration with a community HIV testing center, where the intervention was designed to be delivered. Development within a community HIV testing program provides an early assessment of the implementation challenges that need to be overcome to maximize access to the intervention and minimize the burden on organizational processes and resources.

Finally, the e-SBI was developed using CIAS. As this system was designed for use by nonprogrammers, the CIAS minimizes costs for developing, revising, and maintaining electronic interventions. In addition, it was designed for long-term sustainability. For example, contrary to a custom-designed platform for a specific task, CIAS is a broad platform for use by many people; supporting only this single platform will automatically support the availability of everyone is work. Its ongoing development is still funded by the US National Institutes of Health for 2 years, and additional funding will be obtained to continue support. In addition, a yearly fee for funded projects provides income to support CIAS in the long term, especially given the high interest in its use. Finally, the source code will soon be made publicly available at no cost; therefore, it can be installed on a local server. This sustainability plan addresses a key challenge to other e-interventions that support falters once study funding has concluded, impeding the use of interventions in community settings.

Limitations

This study and the intervention were designed in close collaboration with our community partners in Argentina. As such, there may be specific characteristics of our community partners and their client populations that may limit the generalizability of the findings to other community HIV testing programs. As a voluntary research study, HIV-testing clients with PSU may decide not to participate in the study, limiting the potential utility of this approach to identifying and engaging MSM with PSU to reduce their substance use. Finally, acceptability data (both quantitative and qualitative) are subject to social desirability. To minimize this risk, we will highlight for participants the importance of openly sharing their experiences and opinions, whether positive or negative.

Conclusions

Completion of this Clinical Trial Planning Grant (NIH R34) will allow us to develop and pilot all the study components and build the necessary research infrastructure for a subsequent RCT to assess the efficacy of e-SBI in reducing substance use and HIV sexual risk behavior among MSM coming to a community agency for HIV testing.

Acknowledgments

This research was supported by a grant from the US National Institute on Drug Abuse (R34 DA055503; Principal Investigator ICB). The authors are solely responsible for the content, which does not necessarily represent the official views of the National Institutes of Health (NIH). We also acknowledge the invaluable contributions of the study participants and the research staff.

Data Availability

Once the study is completed, the data sets generated and analyzed during the study will be available from the corresponding author upon reasonable request. We will compile structured deidentified data sets and make them available for additional and secondary data analyses. For data sharing, the research team will follow the “standards for privacy of individually identifiable health information.” The principal investigator and research team will develop a process to review and approve data release based on concept sheets submitted by interested investigators and whether the data request is for new lines of analysis. Formal data-sharing agreements will be developed to guide and encourage further data mining of the proposed datasets for various purposes.

Authors' Contributions

ICB was the principal investigator of the study, led the design of the study and the development of the interventions, and led the writing of this manuscript. ROM is a coinvestigator of the study and the site principal investigator in Argentina. He significantly contributed to the study design and led the implementation of the study. He critically reviewed the manuscript, provided feedback, and approved the final version. VB collaborated with the implementation of the study and led the qualitative component of the research assessing the acceptability of the interventions. She critically reviewed the manuscript, provided feedback, and approved the final version. SN is a coinvestigator who collaborated on the study design, as it pertains to the adaptation and implementation of the Young Men's Health Project (YMPH). She critically reviewed the manuscript, provided feedback, and approved the final version. YW was the data manager of this study. She collaborated in the design of the various data capture components of the study and will provide data management and statistical support for the study. She critically reviewed the manuscript, provided feedback, and approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review reports.
[PDF File (Adobe PDF File), 147 KB - resprot_v13i1e56683_app1.pdf]

References

1. Baral S, Sifakis F, Cleghorn F, Beyrer C. Elevated risk for HIV infection among men who have sex with men in low- and middle-income countries 2000-2006: a systematic review. PLoS Med 2007 Dec 1;4(12):e339 [FREE Full text] [doi: 10.1371/journal.pmed.0040339] [Medline: 18052602]
2. Bastos FI, Cáceres C, Galvão J, Veras MA, Castilho EA. AIDS in Latin America: assessing the current status of the epidemic and the ongoing response. Int J Epidemiol 2008 Aug 23;37(4):729-737. [doi: 10.1093/ije/dyn127] [Medline: 18653508]
3. Estimated HIV incidence among adults and adolescents in the United States, 2007-2010. Centers for Disease Control and Prevention. 2012. URL: https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-supplemental-report-vol-17-4.pdf [accessed 2024-01-29]
4. McCabe SE, Hughes TL, Bostwick WB, West BT, Boyd CJ. Sexual orientation, substance use behaviors and substance dependence in the United States. Addiction 2009 Aug 13;104(8):1333-1345 [FREE Full text] [doi: 10.1111/j.1360-0443.2009.02596.x] [Medline: 19438839]
5. Cochran SD, Keenan C, Schober C, Mays VM. Estimates of alcohol use and clinical treatment needs among homosexually active men and women in the U.S. population. J Consult Clin Psychol 2000 Dec;68(6):1062-1071 [FREE Full text] [doi: 10.1037//0022-006x.68.6.1062] [Medline: 11142540]
6. Drabble L, Midanik LT, Trocki K. Reports of alcohol consumption and alcohol-related problems among homosexual, bisexual and heterosexual respondents: results from the 2000 National Alcohol Survey. J Stud Alcohol 2005 Jan;66(1):111-120. [doi: 10.15288/jsa.2005.66.111] [Medline: 15830911]
7. King M, Semlyen J, Tai SS, Killaspy H, Osborn D, Popelyuk D, et al. A systematic review of mental disorder, suicide, and deliberate self harm in lesbian, gay and bisexual people. BMC Psychiatry 2008 Aug 18;8:70 [FREE Full text] [doi: 10.1186/1471-244X-8-70] [Medline: 18706118]
8. Sandfort TG, de Graaf R, Bijl RV, Schnabel P. Same-sex sexual behavior and psychiatric disorders: findings from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). Arch Gen Psychiatry 2001 Jan 01;58(1):85-91. [doi: 10.1001/archpsyc.58.1.85] [Medline: 11146762]
9. Balán IC, Carballo-Diéguez A, Dolezal C, Marone R, Pando MA, Barreda V, et al. High prevalence of substance use among men who have sex with men in Buenos Aires, Argentina: implications for HIV risk behavior. AIDS Behav 2013 May 30;17(4):1296-1304 [FREE Full text] [doi: 10.1007/s10461-012-0377-9] [Medline: 23196860]
10. Balán IC, Barreda V, Marone R, Ávila MM, Carballo-Diéguez A. Venues, patrons, and alcohol use dynamics: the creation of a high risk sexual environment. AIDS Behav 2014 Nov 2;18(11):2097-2109 [FREE Full text] [doi: 10.1007/s10461-014-0759-2] [Medline: 24691922]
11. Balán IC, Frasca T, Pando MA, Marone RO, Barreda V, Dolezal C, et al. High substance use and HIV risk behavior among young Argentine men who have sex with men. AIDS Behav 2018 Apr 18;22(4):1373-1382 [FREE Full text] [doi: 10.1007/s10461-017-1987-z] [Medline: 29151198]
12. Lisboa Donoso CL, Stuardo Ávila VS. Aspects associated with sexualised drug use among gay men and other men who have sex with men: a cross-sectional study from the Latin America MSM Internet Survey 2018 – Chile. Sex Health 2020;17(6):493. [doi: 10.1071/sh20089]
13. Salomón H, de los Ángeles Pando M. HIV epidemiology in Latin America. In: Ludert JE, Pujol FH, Arbiza J, editors. Human Virology in Latin America: From Biology to Control. Cham, Switzerland: Springer; 2017.

14. Coelho LE, Torres TS, Veloso VG, Grinsztejn B, Jalil EM, Wilson EC, et al. The prevalence of HIV among men who have sex with men (MSM) and young MSM in Latin America and the Caribbean: a systematic review. AIDS Behav 2021 Oct 15;25(10):3223-3237. [doi: 10.1007/s10461-021-03180-5] [Medline: 33587242]
15. Guerras JM, Hoyos Miller J, Agustí C, Chanos S, Pichon F, Kuske M, Euro HIV EDAT Working Group. Association of sexualized drug use patterns with HIV/STI transmission risk in an internet sample of men who have sex with men from seven European countries. Arch Sex Behav 2021 Feb 02;50(2):461-477. [doi: 10.1007/s10508-020-01801-z] [Medline: 32875382]
16. Lloyd MR, Dentato MP, Perkins NH. Examining HIV/AIDS complacency, substance use and sexual risk among MSM in a bathhouse setting. J Hum Behav Soc Environ 2020 Aug 06;30(8):1045-1059. [doi: 10.1080/10911359.2020.1791779]
17. Colfax G, Vittinghoff E, Husnik MJ, McKirnan D, Buchbinder S, Koblin B, et al. Substance use and sexual risk: a participant- and episode-level analysis among a cohort of men who have sex with men. Am J Epidemiol 2004 May 15;159(10):1002-1012. [doi: 10.1093/aje/kwh135] [Medline: 15128613]
18. Stall R, Purcell DW. Intertwining epidemics: a review of research on substance use among men who have sex with men and its connection to the AIDS epidemic. AIDS Behav 2000;4(2):191 [FREE Full text]
19. Woolf SE, Maisto SA. Alcohol use and risk of HIV infection among men who have sex with men. AIDS Behav 2009 Aug 31;13(4):757-782. [doi: 10.1007/s10461-007-9354-0] [Medline: 18236149]
20. Koblin BA, Chesney MA, Husnik MJ, Bozeman S, Celum CL, Buchbinder S, EXPLORE Study Team. High-risk behaviors among men who have sex with men in 6 US cities: baseline data from the EXPLORE Study. Am J Public Health 2003 Jun;93(6):926-932. [doi: 10.2105/ajph.93.6.926] [Medline: 12773357]
21. Celentano DD, Valleroy LA, Sifakis F, MacKellar DA, Hylton J, Thiede H, Young Men's Survey Study Group. Associations between substance use and sexual risk among very young men who have sex with men. Sex Transm Dis 2006 Apr;33(4):265-271. [doi: 10.1097/01.olq.0000187207.10992.4e] [Medline: 16434886]
22. Stueve A, O'Donnell L, Duran R, San Doval A, Geier J, Community Intervention Trial for Youth Study Team. Being high and taking sexual risks: findings from a multisite survey of urban young men who have sex with men. AIDS Educ Prev 2002 Dec;14(6):482-495. [doi: 10.1521/aeap.14.8.482.24108] [Medline: 12512849]
23. Parsons JT, Kutnick AH, Halkitis PN, Punzalan JC, Carbonari JP. Sexual risk behaviors and substance use among alcohol abusing HIV-positive men who have sex with men. J Psychoactive Drugs 2005 Mar 09;37(1):27-36 [FREE Full text] [doi: 10.1080/02791072.2005.10399746] [Medline: 15916249]
24. Purcell DW, Moss S, Remien RH, Woods WJ, Parsons JT. Illicit substance use, sexual risk, and HIV-positive gay and bisexual men: differences by serostatus of casual partners. AIDS 2005 Apr;19 Suppl 1:S37-S47. [doi: 10.1097/01.aids.0000167350.00503.db] [Medline: 15838193]
25. Irwin TW, Morgenstern J, Parsons JT, Wainberg M, Labouvie E. Alcohol and sexual HIV risk behavior among problem drinking men who have sex with men: an event level analysis of timeline followback data. AIDS Behav 2006 May 16;10(3):299-307. [doi: 10.1007/s10461-005-9045-7] [Medline: 16482407]
26. Jenkins RA. Recruiting substance-using men who have sex with men into HIV prevention research: current status and future directions. AIDS Behav 2012 Aug 21;16(6):1411-1419. [doi: 10.1007/s10461-011-0037-5] [Medline: 22016329]
27. Kanouse DE, Bluthenthal RN, Bogart L, Iguchi MY, Perry S, Sand K, et al. Recruiting drug-using men who have sex with men into behavioral interventions: a two-stage approach. J Urban Health 2005 Mar 28;82(1 Suppl 1):i109-i119 [FREE Full text] [doi: 10.1093/jurban/jti030] [Medline: 15738314]
28. Grov C, Bux D, Parsons JT, Morgenstern J. Recruiting hard-to-reach drug-using men who have sex with men into an intervention study: lessons learned and implications for applied research. Subst Use Misuse 2009 Dec 09;44(13):1855-1871 [FREE Full text] [doi: 10.3109/10826080802501570] [Medline: 20001284]
29. McCabe SE, West BT, Hughes TL, Boyd CJ. Sexual orientation and substance abuse treatment utilization in the United States: results from a national survey. J Subst Abuse Treat 2013 Jan;44(1):4-12 [FREE Full text] [doi: 10.1016/j.jsat.2012.01.007] [Medline: 22444421]
30. Screening, brief intervention, and referral to treatment in behavioral healthcare. Substance Abuse and Mental Health Association (SAMHSA). 2012. URL: https://www.samhsa.gov/sites/default/files/sbirtwhitepaper_0.pdf [accessed 2021-04-10]
31. Harris BR, Yu J, Wolff M, Rogers M, Blank S. Optimizing the impact of alcohol and drug screening and early intervention in a high-risk population receiving services in New York City sexual health clinics: a process and outcome evaluation of Project Renew. Prev Med 2018 Jul;112:160-167. [doi: 10.1016/j.ypmed.2018.04.018] [Medline: 29673885]
32. Aalto M, Pekuri P, Seppä K. Implementation of brief alcohol intervention in primary health care: do nurses' and general practitioners' attitudes, skills and knowledge change? Drug Alcohol Rev 2005 Nov 29;24(6):555-558. [doi: 10.1080/09595230500292904] [Medline: 16361214]
33. Ellis JD, Grekin ER, Beatty JR, McGoron L, LaLiberte BV, Pop DE, et al. Effects of narrator empathy in a computer delivered brief intervention for alcohol use. Contemp Clin Trials 2017 Oct;61:29-32. [doi: 10.1016/j.cct.2017.07.014] [Medline: 28732758]
34. Walters ST, Vader AM, Harris TR. A controlled trial of web-based feedback for heavy drinking college students. Prev Sci 2007 Mar 29;8(1):83-88. [doi: 10.1007/s11121-006-0059-9] [Medline: 17136461]

35. Kim TW, Bernstein J, Cheng DM, Lloyd-Travaglini C, Samet JH, Palfai TP, et al. Receipt of addiction treatment as a consequence of a brief intervention for drug use in primary care: a randomized trial. Addiction 2017 May 07;112(5):818-827 [FREE Full text] [doi: 10.1111/add.13701] [Medline: 27886657]
36. Rosário F, Santos MI, Angus K, Pas L, Ribeiro C, Fitzgerald N. Factors influencing the implementation of screening and brief interventions for alcohol use in primary care practices: a systematic review using the COM-B system and Theoretical Domains Framework. Implement Sci 2021 Jan 07;16(1):6 [FREE Full text] [doi: 10.1186/s13012-020-01073-0] [Medline: 33413487]
37. Vendetti J, Gmyrek A, Damon D, Singh M, McRee B, Del Boca F. Screening, brief intervention and referral to treatment (SBIRT): implementation barriers, facilitators and model migration. Addiction 2017 Feb 10;112 Suppl 2(S2):23-33. [doi: 10.1111/add.13652] [Medline: 28074571]
38. Wamsley M, Satterfield JM, Curtis A, Lundgren L, Satre DD. Alcohol and drug screening, brief intervention, and referral to treatment (SBIRT) training and implementation: perspectives from 4 health professions. J Addict Med 2018;12(4):262-272. [doi: 10.1097/ADM.0000000000000410] [Medline: 30063221]
39. Yarnall KS, Pollak KI, Østbye T, Krause KM, Michener JL. Primary care: is there enough time for prevention? Am J Public Health 2003 Apr;93(4):635-641. [doi: 10.2105/ajph.93.4.635] [Medline: 12660210]
40. Beich A, Gannik D, Malterud K. Screening and brief intervention for excessive alcohol use: qualitative interview study of the experiences of general practitioners. BMJ 2002 Oct 19;325(7369):870 [FREE Full text] [doi: 10.1136/bmj.325.7369.870] [Medline: 12386040]
41. Nilsen P. Brief alcohol intervention--where to from here? challenges remain for research and practice. Addiction 2010 Jun 06;105(6):954-959. [doi: 10.1111/j.1360-0443.2009.02779.x] [Medline: 20121717]
42. Wilson GB, Lock CA, Heather N, Cassidy P, Christie MM, Kaner EF. Intervention against excessive alcohol consumption in primary health care: a survey of GPs' attitudes and practices in England 10 years on. Alcohol Alcohol 2011;46(5):570-577 [FREE Full text] [doi: 10.1093/alcalc/agr067] [Medline: 21690169]
43. Schwartz RP, Gryczynski J, Mitchell SG, Gonzales A, Moseley A, Peterson TR, et al. Computerized versus in-person brief intervention for drug misuse: a randomized clinical trial. Addiction 2014 Jul 10;109(7):1091-1098 [FREE Full text] [doi: 10.1111/add.12502] [Medline: 24520906]
44. Gryczynski J, Mitchell SG, Gonzales A, Moseley A, Peterson TR, Ondersma SJ, et al. A randomized trial of computerized vs. in-person brief intervention for illicit drug use in primary care: outcomes through 12 months. J Subst Abuse Treat 2015 Mar;50:3-10 [FREE Full text] [doi: 10.1016/j.jsat.2014.09.002] [Medline: 25282578]
45. Forray A, Martino S, Gilstad-Hayden K, Kershaw T, Ondersma S, Olmstead T, et al. Assessment of an electronic and clinician-delivered brief intervention on cigarette, alcohol and illicit drug use among women in a reproductive healthcare clinic. Addict Behav 2019 Sep;96:156-163 [FREE Full text] [doi: 10.1016/j.addbeh.2019.05.007] [Medline: 31100713]
46. Gryczynski J, Mitchell SG, Schwartz RP, Dusek K, O'Grady KE, Cowell AJ, et al. Computer- vs. nurse practitioner-delivered brief intervention for adolescent marijuana, alcohol, and sex risk behaviors in school-based health centers. Drug Alcohol Depend 2021 Jan 01;218:108423 [FREE Full text] [doi: 10.1016/j.drugalcdep.2020.108423] [Medline: 33307377]
47. Carballo-Diéguez A, Balan IC, Marone R, Pando MA, Dolezal C, Barreda V, et al. Use of respondent driven sampling (RDS) generates a very diverse sample of men who have sex with men (MSM) in Buenos Aires, Argentina. PLoS One 2011 Nov 10;6(11):e27447 [FREE Full text] [doi: 10.1371/journal.pone.0027447] [Medline: 22102896]
48. Pando MA, Balán IC, Marone R, Dolezal C, Leu C, Squiquera L, et al. HIV and other sexually transmitted infections among men who have sex with men recruited by RDS in Buenos Aires, Argentina: high HIV and HPV infection. PLoS One 2012 Jun 29;7(6):e39834 [FREE Full text] [doi: 10.1371/journal.pone.0039834] [Medline: 22768137]
49. Parsons JT, Lelutiu-Weinberger C, Botsko M, Golub SA. A randomized controlled trial utilizing motivational interviewing to reduce HIV risk and drug use in young gay and bisexual men. J Consult Clin Psychol 2014 Feb;82(1):9-18 [FREE Full text] [doi: 10.1037/a0035311] [Medline: 24364800]
50. Miller WR, Rollnick S. Motivational Interviewing: Helping People Change. 3rd edition. New York, NY: The Guilford Press; 2013.
51. Moyers TB, Martin T, Houck JM, Christopher PJ, Tonigan JS. From in-session behaviors to drinking outcomes: a causal chain for motivational interviewing. J Consult Clin Psychol 2009 Dec;77(6):1113-1124 [FREE Full text] [doi: 10.1037/a0017189] [Medline: 19968387]
52. Vader AM, Walters ST, Prabhu GC, Houck JM, Field CA. The language of motivational interviewing and feedback: counselor language, client language, and client drinking outcomes. Psychol Addict Behav 2010 Jun;24(2):190-197 [FREE Full text] [doi: 10.1037/a0018749] [Medline: 20565145]
53. Apodaca TR, Longabaugh R. Mechanisms of change in motivational interviewing: a review and preliminary evaluation of the evidence. Addiction 2009 May 07;104(5):705-715 [FREE Full text] [doi: 10.1111/j.1360-0443.2009.02527.x] [Medline: 19413785]
54. Magill M, Gaume J, Apodaca TR, Walthers J, Mastroleo NR, Borsari B, et al. The technical hypothesis of motivational interviewing: a meta-analysis of MI's key causal model. J Consult Clin Psychol 2014 Dec;82(6):973-983 [FREE Full text] [doi: 10.1037/a0036833] [Medline: 24841862]

55. Moyers TB, Martin T. Therapist influence on client language during motivational interviewing sessions. J Subst Abuse Treat 2006 Apr;30(3):245-251. [doi: 10.1016/j.jsat.2005.12.003] [Medline: 16616169]
56. Magill M, Apodaca TR, Barnett NP, Monti PM. The route to change: within-session predictors of change plan completion in a motivational interview. J Subst Abuse Treat 2010 Apr;38(3):299-305 [FREE Full text] [doi: 10.1016/j.jsat.2009.12.001] [Medline: 20149571]
57. Wampold BE. The research evidence for the common factors models: a historically situated perspective. In: Duncan BL, Miller SD, Wampold BE, Hubble MA, editors. The Heart and Soul of Change: Delivering What Works in Therapy. Washington, DC: American Psychological Association; 2010:49-81.
58. Reeves B, Nass C. Media Equation Theory: How People Treat Computers, Television, and New Media Like Real People and Places. Stanford, CA: Center for the Study of Language and Information; 2009.
59. Petty RE, Cacioppo JT. The elaboration likelihood model of persuasion. In: Petty RE, Cacioppo JT, editors. Communication and Persuasion: Central and Peripheral Routes to Attitude Change. Cham, Switzerland: Springer; 1986.
60. Paivio A. Mental Representations: A Dual Coding Approach. Oxford, UK: Oxford University Press; 1986.
61. Sweller J. Cognitive load theory, learning difficulty, and instructional design. Learn Instr 1994 Jan;4(4):295-312 [FREE Full text] [doi: 10.1016/0959-4752(94)90003-5]
62. Gray J, Beatty JR, Svikis DS, Puder KS, Resnicow K, Konkel J, et al. Electronic brief intervention and text messaging for marijuana use during pregnancy: initial acceptability of patients and providers. JMIR Mhealth Uhealth 2017 Nov 08;5(11):e172 [FREE Full text] [doi: 10.2196/mhealth.7927] [Medline: 29117931]
63. Ondersma SJ, Beatty JR, Puder KS, Janisse J, Svikis DS. Feasibility and acceptability of e-screening and brief intervention and tailored text messaging for marijuana use in pregnancy. J Womens Health (Larchmt) 2019 Sep 01;28(9):1295-1301 [FREE Full text] [doi: 10.1089/jwh.2018.7169] [Medline: 30657434]
64. Ondersma SJ, Chase SK, Svikis DS, Schuster CR. Computer-based brief motivational intervention for perinatal drug use. J Subst Abuse Treat 2005 Jun;28(4):305-312 [FREE Full text] [doi: 10.1016/j.jsat.2005.02.004] [Medline: 15925264]
65. Pollick SA, Beatty JR, Sokol RJ, Strickler RC, Chang G, Svikis DS, et al. Acceptability of a computerized brief intervention for alcohol among abstinent but at-risk pregnant women. Subst Abus 2015 May 10;36(1):13-20 [FREE Full text] [doi: 10.1080/08897077.2013.857631] [Medline: 24266770]
66. Naar-King S, Outlaw AY, Sarr M, Parsons JT, Belzer M, Macdonell K, Adolescent Medicine Network for HIV/AIDS Interventions. Motivational enhancement system for adherence (MESA): pilot randomized trial of a brief computer-delivered prevention intervention for youth initiating antiretroviral treatment. J Pediatr Psychol 2013 Jul 28;38(6):638-648 [FREE Full text] [doi: 10.1093/jpepsy/jss132] [Medline: 23359664]
67. Starks TJ, Parsons JT. Drug use and HIV prevention with young gay and bisexual men: partnered status predicts intervention response. AIDS Behav 2018 Sep 19;22(9):2788-2796 [FREE Full text] [doi: 10.1007/s10461-018-2091-8] [Medline: 29556833]
68. Lank E, Withee K, Schile L, Parker T. User centred rapid application development. In: Proceedings of the 2nd International Workshop on Rapid Integration of Software Engineering Techniques. 2006 Presented at: RISE '05; September 8-9, 2005; Heraklion, Greece p. 34-49 URL: https://link.springer.com/chapter/10.1007/11751113_4 [doi: 10.1007/11751113_4]
69. Kumar S, Sharma T. User centric rapid application development. Int J Res 2014;1(10):959 [FREE Full text]
70. Martin J. Rapid Application Development. Upper Saddle River, NJ: Prentice-Hall; 1992.
71. Årsand E, Demiris G. User-centered methods for designing patient-centric self-help tools. Inform Health Soc Care 2008 Sep 12;33(3):158-169. [doi: 10.1080/17538150802457562] [Medline: 18850399]
72. De Vito Dabbs A, Myers BA, Mc Curry KR, Dunbar-Jacob J, Hawkins RP, Begey A, et al. User-centered design and interactive health technologies for patients. Comput Inform Nurs 2009;27(3):175-183 [FREE Full text] [doi: 10.1097/NCN.0b013e31819f7c7c] [Medline: 19411947]
73. NIDA-modified alcohol, smoking, and substance involvement screening test (ASSIST). National Institute of Drug Abuse. URL: https://www.drugabuse.gov/sites/default/files/pdf/nmassist.pdf [accessed 2024-01-29]
74. Alcohol, smoking and substance involvement screening test (ASSIST), version 3.0. World Health Organization. URL: http://www.who.int/substance_abuse/ [accessed 2024-01-29]
75. McNeely J, Strauss SM, Wright S, Rotrosen J, Khan R, Lee JD, et al. Test-retest reliability of a self-administered alcohol, smoking and substance involvement screening test (ASSIST) in primary care patients. J Subst Abuse Treat 2014 Jul;47(1):93-101 [FREE Full text] [doi: 10.1016/j.jsat.2014.01.007] [Medline: 24629887]
76. McNeely J, Strauss SM, Rotrosen J, Ramautar A, Gourevitch MN. Validation of an audio computer-assisted self-interview (ACASI) version of the alcohol, smoking and substance involvement screening test (ASSIST) in primary care patients. Addiction 2016 Feb 26;111(2):233-244 [FREE Full text] [doi: 10.1111/add.13165] [Medline: 26360315]
77. Babor TF. AUDIT : the alcohol use disorders identification test : guidelines for use in primary health care. World Health Organization. 1992. URL: https://www.who.int/publications/i/item/WHO-MSD-MSB-01.6a [accessed 2024-01-29]
78. Saunders JB, Aasland OG, Babor TF, de la Fuente JR, Grant M. Development of the alcohol use disorders identification test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption--II. Addiction 1993 Jun 24;88(6):791-804. [doi: 10.1111/j.1360-0443.1993.tb02093.x] [Medline: 8329970]

79. Hagman BT, Kuerbis AN, Morgenstern J, Bux DA, Parsons JT, Heidinger BE. An item response theory (IRT) analysis of the short inventory of problems-alcohol and drugs (SIP-AD) among non-treatment seeking men-who-have-sex-with-men: evidence for a shortened 10-item SIP-AD. Addict Behav 2009 Nov;34(11):948-954 [FREE Full text] [doi: 10.1016/j.addbeh.2009.06.004] [Medline: 19564078]
80. Blanchard KA, Morgenstern J, Morgan TJ, Lobouvie EW, Bux DA. Assessing consequences of substance use: psychometric properties of the inventory of drug use consequences. Psychol Addict Behav 2003 Dec;17(4):328-331. [doi: 10.1037/0893-164x.17.4.328]
81. Carballo‐Diéguez A, Remien RH, Dolezal C, Wagner G. Reliability of sexual behavior self‐reports in male couples of discordant HIV status. Journal of Sex Research 1999 May;36(2):152-158. [doi: 10.1080/00224499909551980]
82. Hogue A, Dauber S, Morgenstern J. Validation of a contemplation ladder in an adult substance use disorder sample. Psychol Addict Behav 2010 Mar;24(1):137-144 [FREE Full text] [doi: 10.1037/a0017895] [Medline: 20307121]
83. Heather N, Smailes D, Cassidy P. Development of a readiness ruler for use with alcohol brief interventions. Drug Alcohol Depend 2008 Dec 01;98(3):235-240. [doi: 10.1016/j.drugalcdep.2008.06.005] [Medline: 18639393]
84. LaBrie JW, Quinlan T, Schiffman JE, Earleywine ME. Performance of alcohol and safer sex change rulers compared with readiness to change questionnaires. Psychol Addict Behav 2005 Mar;19(1):112-115. [doi: 10.1037/0893-164x.19.1.112]
85. Maisto SA, Krenek M, Chung T, Martin CS, Clark D, Cornelius J. A comparison of the concurrent and predictive validity of three measures of readiness to change alcohol use in a clinical sample of adolescents. Psychol Assess 2011 Dec;23(4):983-994 [FREE Full text] [doi: 10.1037/a0024136] [Medline: 21767028]
86. Slavet JD, Stein LA, Colby SM, Barnett NP, Monti PM, Golembeske Jr C, et al. The Marijuana Ladder: measuring motivation to change marijuana use in incarcerated adolescents. Drug Alcohol Depend 2006 Jun 09;83(1):42-48 [FREE Full text] [doi: 10.1016/j.drugalcdep.2005.10.007] [Medline: 16289930]
87. Boudreaux ED, Sullivan A, Abar B, Bernstein SL, Ginde AA, Camargo CA. Motivation rulers for smoking cessation: a prospective observational examination of construct and predictive validity. Addict Sci Clin Pract 2012 Jun 08;7(1):8 [FREE Full text] [doi: 10.1186/1940-0640-7-8] [Medline: 23186265]
88. Smith DC, Davis JP, Mendoza N, Zhang S. Predictive validity of single-item motivational measures for emerging adults in substance-use disorder treatment. J Soc Social Work Res 2017 Jun 01;8(2):259-277. [doi: 10.1086/692018]
89. Sheinfil AZ, Giguere R, Dolezal C, Lopez-Rios J, Iribarren S, Brown W, et al. Information and motivation predict HIV-serostatus among a population of high-risk men and transgender women who have sex with men. AIDS Behav 2020 Oct 21;24(10):2863-2871 [FREE Full text] [doi: 10.1007/s10461-020-02835-z] [Medline: 32200447]
90. Taylor B, Henshall C, Kenyon S, Litchfield I, Greenfield S. Can rapid approaches to qualitative analysis deliver timely, valid findings to clinical leaders? A mixed methods study comparing rapid and thematic analysis. BMJ Open 2018 Oct 08;8(10):e019993 [FREE Full text] [doi: 10.1136/bmjopen-2017-019993] [Medline: 30297341]
91. Gale RC, Wu J, Erhardt T, Bounthavong M, Reardon CM, Damschroder LJ, et al. Comparison of rapid vs in-depth qualitative analytic methods from a process evaluation of academic detailing in the Veterans Health Administration. Implement Sci 2019 Feb 01;14(1):11 [FREE Full text] [doi: 10.1186/s13012-019-0853-y] [Medline: 30709368]
92. Al-Khanbashi M. Using the matrix as a qualitative data display for landscape research and a reflection based on the social constructivist perspective. In: Edler D, Jenal C, Kühne O, editors. Modern Approaches to the Visualization of Landscapes. Cham, Switzerland: Springer; 2020:103-118.
93. Miles MB, Huberman AM, Saldana J. Qualitative Data Analysis: A Methods Sourcebook. Thousand Oaks, CA: Sage Publications; 2018.
94. Glasser W. Choice Theory: A New Psychology of Personal Freedom. New York, NY: Harper Perennial; 1999.
95. Henssler J, Müller M, Carreira H, Bschor T, Heinz A, Baethge C. Controlled drinking-non-abstinent versus abstinent treatment goals in alcohol use disorder: a systematic review, meta-analysis and meta-regression. Addiction 2021 Aug 14;116(8):1973-1987 [FREE Full text] [doi: 10.1111/add.15329] [Medline: 33188563]
96. Moyer A, Finney JW, Swearingen CE, Vergun P. Brief interventions for alcohol problems: a meta-analytic review of controlled investigations in treatment-seeking and non-treatment-seeking populations. Addiction 2002 Mar 05;97(3):279-292. [doi: 10.1046/j.1360-0443.2002.00018.x] [Medline: 11964101]
97. Morgenstern J, Irwin TW, Wainberg ML, Parsons JT, Muench F, Bux DA, et al. A randomized controlled trial of goal choice interventions for alcohol use disorders among men who have sex with men. J Consult Clin Psychol 2007 Feb;75(1):72-84. [doi: 10.1037/0022-006x.75.1.72]
98. Morgenstern J, Bux DA, Parsons J, Hagman BT, Wainberg M, Irwin T. Randomized trial to reduce club drug use and HIV risk behaviors among men who have sex with men. J Consult Clin Psychol 2009 Aug;77(4):645-656 [FREE Full text] [doi: 10.1037/a0015588] [Medline: 19634958]
99. Enggasser JL, Hermos JA, Rubin A, Lachowicz M, Rybin D, Brief DJ, et al. Drinking goal choice and outcomes in a web-based alcohol intervention: results from VetChange. Addict Behav 2015 Mar;42:63-68 [FREE Full text] [doi: 10.1016/j.addbeh.2014.10.036] [Medline: 25671224]
100. van Amsterdam J, van den Brink W. Reduced-risk drinking as a viable treatment goal in problematic alcohol use and alcohol dependence. J Psychopharmacol 2013 Nov 02;27(11):987-997. [doi: 10.1177/0269881113495320] [Medline: 23824247]

101. Sekhon M, Cartwright M, Francis JJ. Acceptability of healthcare interventions: an overview of reviews and development of a theoretical framework. BMC Health Serv Res 2017 Jan 26;17(1):88 [FREE Full text] [doi: 10.1186/s12913-017-2031-8] [Medline: 28126032]
102. Murphy A, Gardner DM. Pharmacists' acceptability of a men's mental health promotion program using the Theoretical Framework of Acceptability. AIMS Public Health 2019;6(2):195-208 [FREE Full text] [doi: 10.3934/publichealth.2019.2.195] [Medline: 31297404]
103. Brook J, Aitken LM, MacLaren JA, Salmon D. An intervention to decrease burnout and increase retention of early career nurses: a mixed methods study of acceptability and feasibility. BMC Nurs 2021 Jan 13;20(1):19 [FREE Full text] [doi: 10.1186/s12912-020-00524-9] [Medline: 33435972]
104. Chakrapani V, Shunmugam M, Rawat S, Baruah D, Nelson R, Newman PA. Acceptability of HIV pre-exposure prophylaxis among transgender women in India: a qualitative investigation. AIDS Patient Care STDS 2020 Feb 01;34(2):92-98 [FREE Full text] [doi: 10.1089/apc.2019.0237] [Medline: 31951490]
105. Ngowi K, Pima F, Mmbaga BT, Aarnoutse RE, Reiss P, Nieuwkerk PT, et al. "I wish to continue receiving the reminder short messaging service": a mixed methods study on the acceptability of digital adherence tools among adults living with HIV on antiretroviral treatment in Tanzania. Patient Prefer Adherence 2021;15:559-568 [FREE Full text] [doi: 10.2147/PPA.S290079] [Medline: 33727801]
106. Wingood GM, DiClemente RJ. The ADAPT-ITT model: a novel method of adapting evidence-based HIV Interventions. J Acquir Immune Defic Syndr 2008 Mar 01;47 Suppl 1:S40-S46. [doi: 10.1097/QAI.0b013e3181605df1] [Medline: 18301133]
107. Miller WR, Yahne CE, Moyers TB, Martinez J, Pirritano M. A randomized trial of methods to help clinicians learn motivational interviewing. J Consult Clin Psychol 2004 Dec;72(6):1050-1062. [doi: 10.1037/0022-006x.72.6.1050]
108. Moyers TB, Manuel JK, Wilson PG, Hendrickson SM, Talcott W, Durand P. A randomized trial investigating training in motivational interviewing for behavioral health providers. Behav Cogn Psychother 2007 Nov 22;36(2):149-162. [doi: 10.1017/s1352465807004055]
109. Moyers TB, Manuel JK, Ernst D. Motivational interviewing treatment integrity coding manual 4.2.1. University of New Mexico. 2014. URL: https://motivationalinterviewing.org/sites/default/files/miti4_2.pdf [accessed 2024-01-29]
110. Sobell LC, Sobell MB. Timeline follow-back. In: Litten RZ, Allen JP, editors. Measuring Alcohol Consumption: Psychosocial and Biochemical Methods. Cham, Switzerland: Springer; 1992:41-69.
111. Sobell LC, Brown J, Leo GI, Sobell MB. The reliability of the Alcohol Timeline Followback when administered by telephone and by computer. Drug Alcohol Depend 1996 Sep;42(1):49-54. [doi: 10.1016/0376-8716(96)01263-x] [Medline: 8889403]
112. Weinhardt LS, Carey MP, Maisto SA, Carey KB, Cohen MM, Wickramasinghe SM. Reliability of the Timeline Follow-Back sexual behavior interview. Ann Behav Med 1998 Mar;20(1):25-30. [doi: 10.1007/bf02893805]
113. Sekhon M, Cartwright M, Francis JJ. Development of a theory-informed questionnaire to assess the acceptability of healthcare interventions. BMC Health Serv Res 2022 Mar 01;22(1):279 [FREE Full text] [doi: 10.1186/s12913-022-07577-3] [Medline: 35232455]
114. Patton MQ. Qualitative Research & Evaluation Methods: Integrating Theory and Practice. 4th edition. Thousand Oaks, CA: Sage Publications; 2014.

Abbreviations

ADAPT-ITT: assessment, decision, administration, production, topic experts, integration, training, testing
ASSIST: Alcohol, Smoking and Substance Involvement Screening Test
AUDIT: Alcohol Use Disorders Identification Test
BI: brief intervention
CAB: community advisory board
CIAS: Computerized Intervention Authoring System
CONSORT: Consolidated Standards of Reporting Trials
e-SBI: electronic screening and brief intervention
FG: focus group
IDI: in-depth interview
LGBT: lesbian, gay, bisexual, and transgender
MHP: Men’s Health Project
MI: motivational interviewing
MITI.4: Motivational Interviewing Treatment Integrity
MSM: men who have sex with men
PSU: problematic substance use
RCT: randomized controlled trial
SBIRT: Screening, Brief Intervention, and Referral to Treatment
SIP-AD: Short Inventory of Problems-Alcohol and Drug Use

TFA: theoretical framework of acceptability
TLFB: Timeline Followback
UCRAD: User Centered Rapid Application Development
YMHP: Young Men's Health Project

Edited by A Mavragani; submitted 23.01.24; this is a non–peer-reviewed article;accepted 05.02.24; published 14.03.24.

Please cite as:
Balán IC, Marone RO, Barreda V, Naar S, Wang Y
Integration of an Electronic Screening, Brief Intervention, and Referral to Treatment Program Into an HIV Testing Program to Reduce Substance Use and HIV Risk Behavior Among Men Who Have Sex With Men: Protocol for Intervention Development and a Pilot Randomized Controlled Trial
JMIR Res Protoc 2024;13:e56683
URL: https://www.researchprotocols.org/2024/1/e56683
doi:10.2196/56683
PMID:38483463

Protocol

Providing Lesbian, Gay, Bisexual, Transgender, Nonbinary, and Queer Adolescents With Nurturance, Trustworthiness, and Safety: Protocol for Pilot Cluster Randomized Controlled Trial Design

Robert WS Coulter[1,2,3], MPH, PhD; Isabella Kaur Mahal[1], BA; Clarisse A Lin[1]; Shari Kessel Schneider[4], MSPH; Aaryn S Mathias[1]; Karuna Baral[1]; Elizabeth Miller[1,2,3], MD, PhD; Kaleab Z Abebe[5], PhD

[1]Department of Behavioral and Community Health Sciences, School of Public Health, University of Pittsburgh, Pittsburgh, PA, United States

[2]Department of Pediatrics, School of Medicine, University of Pittsburgh, Pittsburgh, PA, United States

[3]Division of Adolescent and Young Adult Medicine, UPMC Children's Hospital of Pittsburgh, Pittsburgh, PA, United States

[4]Educational Development Center, Inc, Waltham, MA, United States

[5]Division of General Internal Medicine, School of Medicine, University of Pittsburgh, Pittsburgh, PA, United States

Corresponding Author:
Robert WS Coulter, MPH, PhD
Department of Behavioral and Community Health Sciences
School of Public Health
University of Pittsburgh
130 De Soto Street
Pittsburgh, PA, 15261
United States
Phone: 1 412 624 3001
Email: robert.ws.coulter@pitt.edu

Abstract

Background: Sexual and gender minority youths (lesbian, gay, bisexual, transgender, nonbinary, and queer individuals) face elevated risks of substance use (eg, alcohol and tobacco) and mental health issues (eg, depressive symptoms and suicidality) compared to their cisgender heterosexual peers. These inequities are hypothesized to be reduced by building supportive high school environments via the training of school staff. An intervention that trains school staff to better understand and support sexual and gender minority youths and engage in positive bystander behaviors that protect them from bullying exposure may reduce disparities in drug and alcohol use among them. Experts, school staff, and sexual and gender minority youths developed Providing LGBTQ+ Adolescents with Nurturance, Trustworthiness, and Safety (PLANTS), a web-based intervention to train school staff on how to support, affirm, and protect sexual and gender minority youths.

Objective: This paper describes the design of the PLANTS pilot trial primarily aimed at assessing its acceptability, usability, appropriateness, and feasibility. We hypothesize PLANTS will have high acceptability, usability, appropriateness, and feasibility as rated by the school staff. Secondary objectives focus on implementation, safety, and pre-post changes in high school staff outcomes, including self-efficacy and skills (eg, active-empathic listening and bullying intervention). Exploratory objectives focus on the impact of PLANTS on student health outcomes.

Methods: In a 2-arm cluster randomized controlled trial, high schools in Massachusetts are allocated to PLANTS or an active comparator group (publicly available sexual and gender minority youths resources or training). High school staff complete pretest and posttest surveys containing validated scales. Primary outcomes are validated measures of acceptability, usability, appropriateness, and feasibility of the intervention completed by staff during posttest surveys. To test our primary hypotheses for each outcome, we will calculate means and 95% CIs and *P* values using 1-sample 2-sided *t* tests against a priori thresholds or benchmarks of success. Secondary outcomes include staff's active-empathetic listening skills, self-efficacy for working with sexual and gender minority youths, bystander intervention behaviors for bullying and cyberbullying, and self-efficacy for PLANTS' change objectives completed during pretest and posttest staff surveys. Staff can also complete a posttest interview guided by the Information-Motivation-Behavior model and Consolidated Framework for Implementation Research. Exploratory outcomes include student-level data collected via the 2021 and 2023 MetroWest Adolescent Health Surveys, a health behavior surveillance system in 30 Massachusetts schools.

Results: School enrollment began in May 2023 and participant enrollment began in June 2023. Data collection is expected to be completed by February 2024.

Conclusions: This pilot trial will yield important information about the PLANTS intervention and provide necessary information to conduct a fully powered trial of the efficacy of PLANTS for reducing the deleterious health inequities experienced by sexual and gender minority youths.

Trial Registration: ClinicalTrials.gov NCT05897827; https://clinicaltrials.gov/study/NCT05897827

International Registered Report Identifier (IRRID): DERR1-10.2196/55210

(JMIR Res Protoc 2024;13:e55210) doi:10.2196/55210

KEYWORDS

sexual minority youths; gender minority youths; cluster randomized controlled trial; web-based behavior change intervention; high school staff

Introduction

Background

Sexual and gender minority youths (ie, adolescents who are lesbian, gay, bisexual, transgender, nonbinary, or queer [LGBTQ+]) are at significantly higher risk than their heterosexual peers for mental health problems and substance use [1-22]. For example, alcohol use is 123%-155% higher among sexual minority youths than among heterosexual youths and up to 250% higher among gender minority youths than among cisgender youths [2,5-7,22]. These substantial persistent health inequities make sexual and gender minority youths a priority population for interventions and were deemed so by national health agencies [3,23,24]. However, there are few efficacious substance use and mental health interventions for sexual and gender minority youths [3].

One way to reduce substance use and improve mental health for sexual and gender minority youths is to foster more supportive and inclusive high school environments by training school staff (eg, teachers, principals, nurses, and counselors) to effectively support and protect them. Sexual and gender minority youths who have support from adults at school, greater school connectedness, and lower bullying exposure also have reduced depressive symptoms, suicidality, and drug and alcohol use [5,25-30].

Unfortunately, sexual and gender minority youths are more likely than their heterosexual peers to lack supportive adults at school, have lower school connectedness, and be exposed to bullying [5,6,25,26,31-39]. An intervention that trains school staff to better understand and support sexual and gender minority youths and engage in positive bystander behaviors that protect them from bullying exposure may reduce health disparities among them. Despite many school staff having a strong desire to support sexual and gender minority youths [40], their primary barrier to supporting this population is a lack of training [40,41]. In 2014, 13% of teachers across the United States and 29% in Massachusetts received training on issues related to sexual and gender minority youths [41], highlighting the need for professional development training related to this population in schools. An intervention for training school staff is further warranted because the presence of gender-sexuality alliances and sexual and gender minority youth–inclusive school policies fail to eliminate health disparities among them [4,42-44].

Providing LGBTQ+ Adolescents with Nurturance, Trustworthiness, and Safety (PLANTS) is a new web-based training program for high school staff. This intervention was informed by the Information-Motivation-Behavior theory to target the skills, self-efficacy, knowledge, and outcome expectations of the high school staff. School staff and other collaborators invested in the well-being of sexual and gender minority youths assisted in developing PLANTS. PLANTS aims to train school staff to support, affirm, and protect sexual and gender minority youths, which is hypothesized to reduce bullying exposure, increase school support and connectedness, and mitigate health disparities among them [45].

Prior to testing efficacy, it is critical to ensure that PLANTS is acceptable to high school staff. This paper describes the design of the PLANTS pilot trial, which primarily tests the PLANTS intervention acceptability (perceptions that PLANTS is tolerable), usability (perceived extent to which PLANTS can be used effectively, efficiently, and satisfactorily), appropriateness (perceived fit and relevance of PLANTS), and feasibility (the extent to which the PLANTS intervention is successfully used and executed) as reported by high school staff. Using a cluster randomized design, this study will secondarily examine the implementation, safety, and pre-post changes in high school staff outcomes within the PLANTS arm and then compare them to an active comparator condition composed of publicly available resources. This study will also explore intervention effects on student-level behavioral health outcomes. The results from the PLANTS pilot trial will inform the development of a fully powered trial of the efficacy of PLANTS for improving health outcomes among sexual and gender minority youths.

Objectives and Hypotheses

The primary objective of the PLANTS pilot trial is to assess the acceptability, usability, appropriateness, and feasibility of the intervention. Investigators expect that high school staff will rate the PLANTS intervention as having high acceptability, usability, appropriateness, and feasibility. Investigators' benchmarks of success are averages of >3.75 out of 5 for acceptability, appropriateness, and feasibility and scores >75 out of 100 for usability.

The secondary objectives are to examine trial implementation, intervention demand, intervention safety, and pre-post changes in school staff outcomes within the PLANTS arm and then

compare them to an active comparator condition. Investigators hypothesize the following results: school staff will have high participation rates in the study (≥50% consent); school staff will have a high retention rate for the follow-up survey (≥75%); high school staff in the PLANTS arm will have high intervention demand (≥75% adhere to PLANTS); high school staff in the PLANTS arm will have low adverse event prevalence (≤20% of PLANTS participants will report adverse events); high school staff participants in the PLANTS arm will report pre-post improvements in active-empathic listening, self-efficacy for supporting, affirming, and protecting sexual and gender minority youths; positive bystander intervention behaviors for bullying; and pre-post differences will be greater in the PLANTS arm than in the active comparator arm.

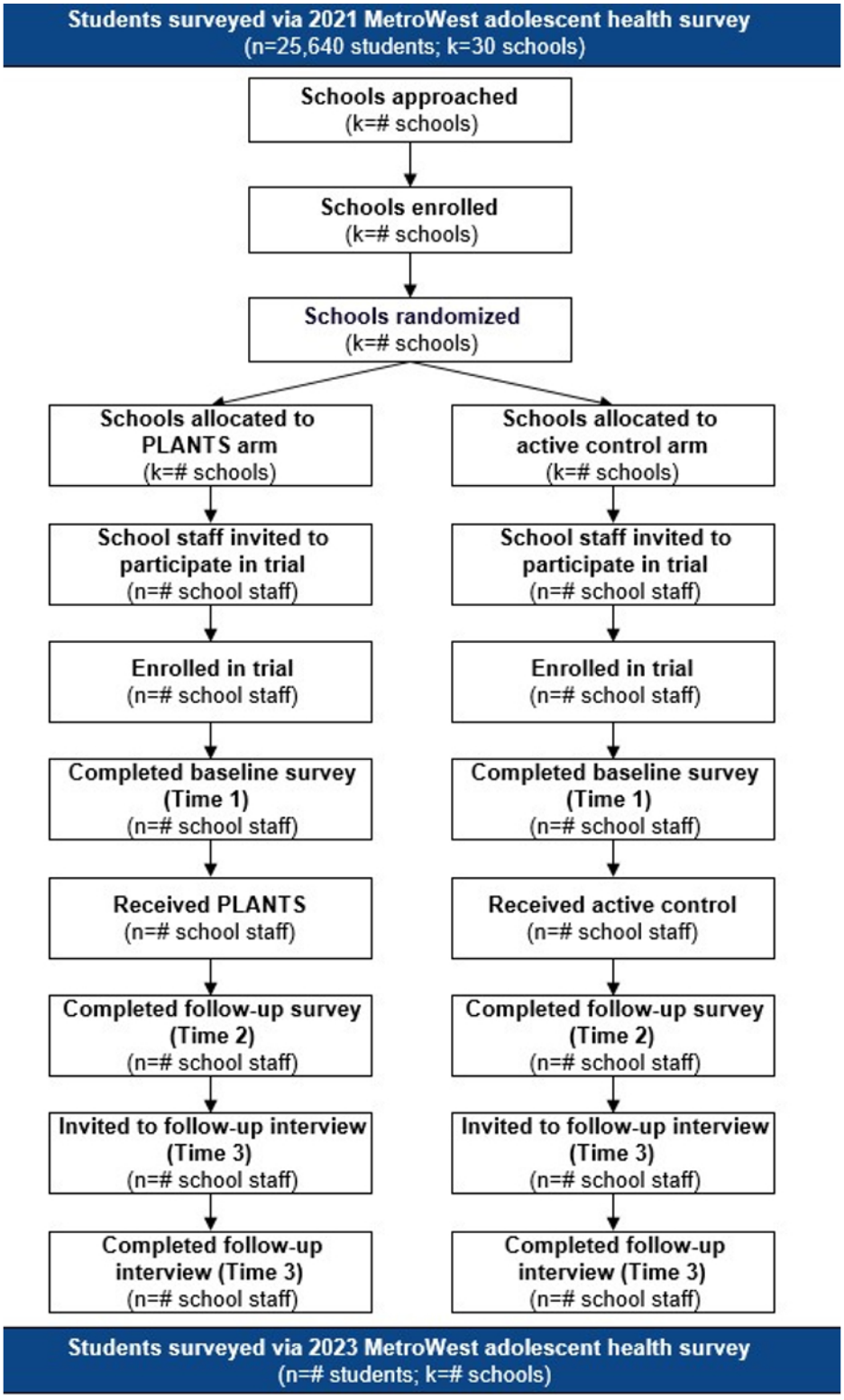
The exploratory objectives concern student-level health outcomes, including substance use, mental health, violence, and school experiences. Investigators hypothesize that sexual and gender minority youths will have greater increases in adult support at school and school connectedness and greater reductions in bullying exposure, depressive symptoms, suicidality, drug use, and alcohol use in PLANTS intervention schools versus active comparator schools, and the differences between sexual and gender minority youths and cisgender heterosexual youths in alcohol use, drug use, depressive symptoms, and suicidality will be more reduced in PLANTS intervention schools versus the active comparator schools.

Methods

Design

The PLANTS pilot trial is a cluster randomized controlled trial with 2 parallel groups and primary end points of PLANTS acceptability, usability, appropriateness, and feasibility among school staff. Such outcomes are aligned with pilot study best practices [46-49]. This unblinded study will randomly assign 4 schools in a 1:1 ratio to the intervention or comparator conditions. Importantly, investigators will analyze both student- and staff-level outcomes before and after the intervention. Figure 1 shows the study flow.

Figure 1. Study flow of the PLANTS pilot trial. PLANTS: Providing LGBTQ+ Adolescents with Nurturance, Trustworthiness, and Safety.



Setting

This study will enroll high schools (grades 9-12) from the 30 schools participating in the MetroWest Adolescent Health Survey (MWAHS) located in and near the MetroWest Region outside Boston, Massachusetts. The PLANTS pilot trial leverages the strengths of the MWAHS research infrastructure, which has biennially collected health surveillance data from a census of students since 2006. To be eligible for the PLANTS pilot trial, a school must have participated in the 2021 MWAHS, plan to participate in the 2023 MWAHS, grant investigators permission to access their MWAHS data, be willing and able to provide email addresses of all school staff, and provide a site permission letter.

Randomization

School-level randomization occurs after schools enroll in the study but before staff are enrolled. The investigators will use

block randomization in a 1:1 ratio, stratified by larger schools (≥1000 students) versus smaller schools (<1000 students). The primary investigator will create the randomization files using the "ralloc" package in Stata (StataCorp). Trained study staff will allocate schools using the REDCap (Research Electronic Data Capture; Vanderbilt University) randomization module. Allocation will be concealed from school personnel.

Study Populations, Sampling, Recruitment, and Data Collection

Students

To be eligible to participate in the MWAHS, students must be enrolled in grades 9-12 at a study school and be literate in English, Spanish, or Portuguese. Students are excluded if they provide an implausible pattern of responses via an evidence-informed algorithm that removes students with extreme responses.

Biennially, MWAHS collects student-level health surveillance data, similar to the Youth Risk Behavior Survey [50] except MWAHS data are collected from a census of students in each high school. The census-like sampling is a major strength of this study, providing a substantial sample of sexual and gender minority youths. Administered via the internet, the MWAHS is voluntary, anonymous, and data are linked at the school level across years (but cannot be linked at the student level). The baseline for intervention efficacy for students will be the fall 2021 MWAHS data, when 30 high schools participated, and 25,640 students completed surveys (83% of all students). The follow-up occurred in fall 2023.

Staff

To be eligible to participate in the PLANTS pilot trial, staff must be currently employed by an enrolled school, be 18 years or older, and consent to participate. Staff are excluded from participation if they do not interact directly with high school students at work.

At enrolled schools, all school staff will be invited to participate via email and advertisements sent by research staff and school administrators. Using REDCap, a personalized link to the screening survey will be provided to staff. If eligible, individuals will be given a digital informed consent form followed by a 30- to 45-minute baseline survey. Intervention and comparator conditions will be delivered to participants over 6 weeks. At the program's conclusion, participants will be sent a follow-up survey. A subset of participants (n=20-30 in PLANTS and n=10-20 in e-Learning to Maximize Academic Inclusion of LGBTQ+ Students [EMAILS] arms) will then be invited for a follow-up interview to explore the implementation outcomes more deeply.

Ethical Considerations

Staff

The Human Research Protection Office at the University of Pittsburgh approved the trial (STUDY23040142). Informed consent is obtained from staff participants. Consent forms describe in detail the study intervention, study procedures, foreseeable risks and discomforts, benefits to the participant, and contact information for the principal investigator. We requested and received a waiver for written consent for all staff participants because consent procedures are happening digitally, the study presents no more than minimal risk to participants, and written consent is not usually obtained for participation in a web-based program or interview outside of a research context.

Privacy and confidentiality protections are in place. For all identifiable data collected, we will remove identifiers and assign a unique study ID to protect the identity of the participant. Coded deidentified data and identifiable data will be stored in separate REDCap surveys and separate folders within a secure password-protected database and will be only accessible to select members of the research team.

To incentivize school staff to complete the baseline survey, we will provide US $20 to each participant and will conduct a drawing of an extra US $30 to 1 in 5 participants who take the survey within each school. To incentivize school staff to complete the follow-up survey, we will provide US $30 to each participant who completes the survey, and we will conduct a drawing of an extra US $40 to 1 in 5 participants who take the survey within each school. For staff who complete the follow-up interview, we will provide a US $50 incentive as a thank you for their time.

Students

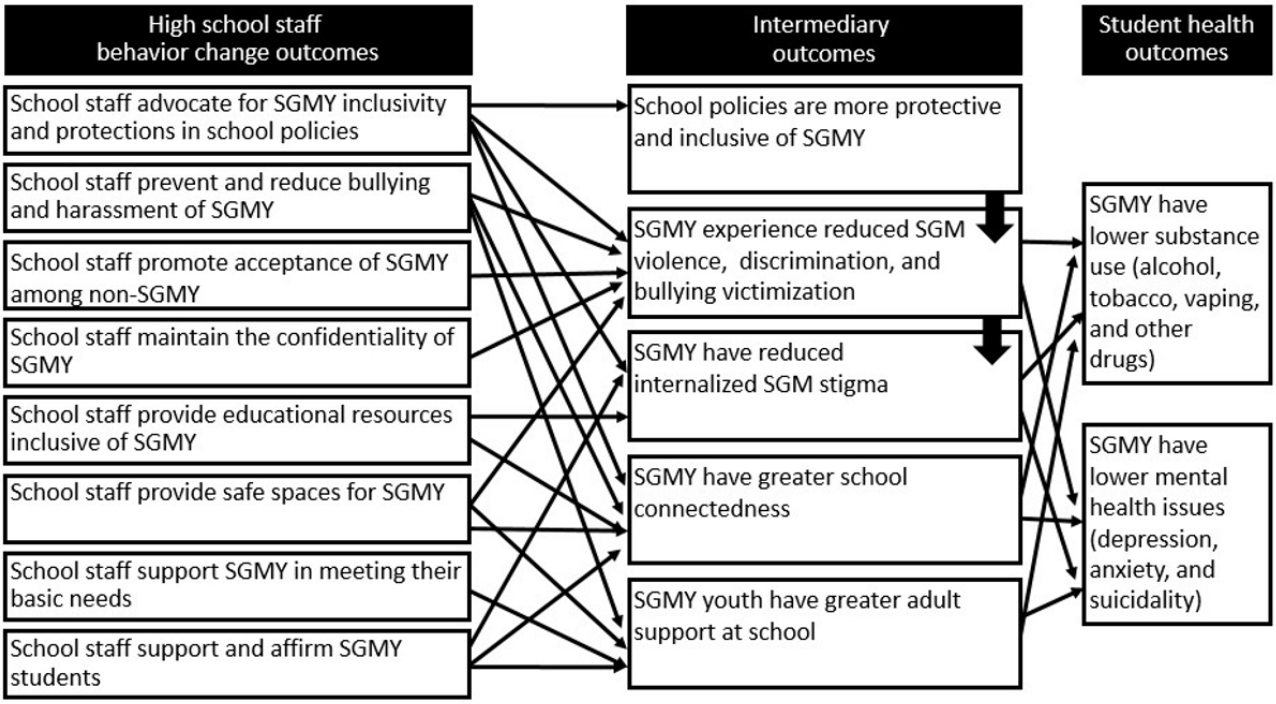
The Education Development Center's institutional review board–approved the MWAHS. Parents or guardians are provided the opportunity to opt their child out of the survey (ie, passive consent), and students provide assent to participate. Assent forms describe in detail the study procedures, foreseeable risks and discomforts, benefits to the participant, and contact information for the principal investigator. Data are collected anonymously, preserving student privacy and confidentiality. No incentives are provided to students for participation.

PLANTS Intervention

The PLANTS intervention is a web-based training program for high school staff. Figure 2 illustrates the PLANTS Behavior Change Model. Staff behavior change outcomes target evidence-based intermediary outcomes rooted in theories of minority health and general adolescent psychosocial health models. In turn, these intermediary outcomes are associated with reduced substance use and mental health issues. The behavior change outcomes are that PLANTS uses asynchronous and synchronous web-based activities to achieve the behavioral change outcomes via targeting the skills, self-efficacy, knowledge, and outcome expectations of the school staff based on Information-Motivation-Behavior theory. PLANTS has 3 primary modules: trustworthiness, safety, and nurturance. Asynchronous activities include voiceover presentations, podcasts with student and staff stories based on research [51], activities, and downloadable resources for future reference. Synchronous activities include three 1.5-hour live Zoom events; each moderated by a trained interventionist and tailored to the needs of participants. The modules were developed by the research team, including undergraduate and graduate students with a variety of academic backgrounds, in partnership with high school staff and other professionals who specialize in

LGBTQ+ youth or education. PLANTS is delivered using Canvas Learning management software (Instructure).

Figure 2. Behavior change model with high school staff behavior outcomes and student health outcomes. SGM: sexual and gender minority; SGMY: sexual and gender minority youths.



Active Comparator: EMAILS

Given the urgent need to support sexual and gender minority youths coupled with the dearth of evidence-based interventions for reducing alcohol and drug use in this population [3], choosing a comparator was difficult. Pragmatically, staff may search the internet to identify training opportunities. Thus, the active comparator, EMAILS, is an email-based intervention comprised of free existing web-based resources for supporting, affirming, and protecting sexual and gender minority youths. Informed by the Information-Motivation-Behavior theory, EMAILS has materials from Adagio Health, the Gay, Lesbian, & Straight Education Network, the American Psychological Association, and the Human Rights Campaign, which include self-paced training modules, YouTube videos, and PowerPoints. There is no direct human interaction in this intervention other than email. EMAILS is 3 hours long and is delivered in 3 modules as in PLANTS. Investigators will monitor active comparator compliance and fidelity by disseminating materials in Qualtrics, which allows for personalized link tracking and short end-of-module questionnaires about uptake or completion.

Outcomes

Primary Outcomes

The primary outcomes are intervention acceptability, usability, appropriateness, and feasibility as reported by school staff. At the follow-up survey, these are measured via scales with strong psychometric properties such as the acceptability of intervention measure (AIM), System Usability Scale (SUS), intervention appropriateness measure (IAM), and feasibility of intervention measure (FIM) [52,53]. AIM, IAM, and FIM each have 4 items with 5-point Likert scale response options. This instrument can be found in Table S1 in Multimedia Appendix 1. Investigators will calculate mean scores (range: 1-5). The SUS has 10 items with 5-point Likert scale response options. Investigators will calculate scores as recommended for the total scale (range: 0-100) [54]. The same outcomes are assessed about EMAILS among comparator participants, but these are not primary outcomes.

Secondary Outcomes

Trial Implementation

To assess the success of the pilot trial in reaching an adequate number of school staff, investigators assess the overall trial participation rate (number of people enrolled divided by the number of people invited to participate) and the follow-up survey retention rate (the number of people who take the follow-up survey divided by the number of people enrolled).

PLANTS Intervention Demand

To assess the school staff's demand for PLANTS, investigators assess PLANTS adherence, which is a composite variable ranging from 0% to 100%, comprised of 55% for module completion (based on the number of completed items divided by the total number of items offered) and 45% for Live Zoom Event attendance (where each event is 15%). These proportions are based on approximate time allocations.

Safety

Investigators assess a myriad of safety outcomes in follow-up surveys, including contact from parents or guardians because there was too much LGBTQ+ inclusivity in the school, contact from people who were upset, the school being attacked, the

school board getting upset or concerned, and LGBTQ+ censorship at the school. Response options include the frequency of each event occurrence. Investigators also assess participants' emotional discomfort with the courses using a 4-point Likert scale. For affirmative responses, open-ended textboxes are provided to describe the safety-related events. Investigators also track the presence or severity of adverse events and unanticipated problems.

Self-Efficacy for Working With Sexual and Gender Minority Youths

Investigators assess participants' perceived abilities for working with LGBTQ high school students using 9 items adapted from the Gay Affirmative Practice Scale [55]. Originally for social work practitioners, investigators replaced therapy-oriented words with school-oriented words (eg, "students" instead of "clients").

Example items include "I am able to help LGBTQ+ students develop positive identities as LGBTQ+ individuals" and "I am able to challenge misinformation about LGBTQ+ individuals in the classroom." Response options include a 5-point Likert scale. Investigators will calculate the mean score. In a prior study, the Cronbach α is 0.90 [56].

Active-Empathic Listening

Investigators measure the valid and reliable Active-Empathic Listening Scale containing 11 items [57]. This scale has 3 domains: sensing (4 items), processing (3 items), and responding (4 items). Response options include a 7-point Likert scale. Investigators will calculate the mean score for the total scale. Prior research showed a Cronbach score of α=0.88-0.90 [56].

Bystander Intervention Behaviors for Bullying and Cyberbullying

Two multidimensional scales (Teacher Bystander Intervention Model in Traditional Bullying and Teacher Bystander Intervention Model in Cyberbullying [58,59]) measure 5 subscales of bystander behaviors for bullying and cyberbullying: noticing the event (3 items), interpreting the event as an emergency (3 items), accepting responsibility to help (3 items), knowing how to help (3 items), and implementing intervention decision (4 items). The psychometric properties of these subscales are acceptable (Cronbach α=0.57-0.88). Investigators will calculate average subscale scores.

Self-Efficacy of PLANTS' Change Objectives

Given the limited research on validated scales of behavior change pertaining to LGBTQ+ inclusive practices in schools, investigators developed items pertaining directly to the self-efficacy change objectives in PLANTS. There are 50 total items across the following domains: provide interpersonal support and affirmation to sexual and gender minority youths; provide educational resources that are inclusive of this population; provide safe spaces for them; promote the acceptance of this population among cisgender heterosexual youths; prevent and reduce bullying, cyberbullying, and harassment of this population; evaluate and advocate for their inclusivity and protections in school policies; and maintain the confidentiality of sexual and gender minority youths.

Exploratory Outcomes

Student-level outcomes will be explored using the MWAHS data. Measures are described in Table S2 in Multimedia Appendix 1, and most have strong test-retest reliability and internal consistency.

Follow-Up Interview Questions

The purpose of the follow-up interview is to better understand trial and intervention implementation. Interviews are guided by the CFIR (Consolidated Framework for Intervention Research) [60]. Question domains include intervention characteristics (relative advantage, adaptability, and design quality), outer setting (external policies and incentives), inner setting (structural characteristics, networks, communication, culture, implementation climate, compatibility, relative priority, and leadership engagement), characteristics of individuals (beliefs about the intervention and self-efficacy), and process (opinion leaders). Interview questions are based on the publicly provided CFIR interview questions [60].

Demographics and Potential Confounders

Staff and student surveys assess many potential confounders. Table S3 in Multimedia Appendix 1 contains measurement details. School-level data will be collected from the Massachusetts Department of Elementary and Secondary Education public website.

Analyses

General Approach

Investigators will calculate baseline descriptive statistics for each study arm and test for differences in potential confounders between intervention and comparator arms using baseline student-, staff-, and school-level data with Rao-Scott chi-square tests and linear mixed models accounting for school clustering. Secondary analyses will adjust for imbalances between arms.

For validated scales, investigators will report internal consistency via Cronbach α. For newly created items, investigators will conduct exploratory factor analyses to examine the dimensions of outcomes using baseline surveys. Investigators will use the most recent version of Stata, 2-tailed tests, and α=.05.

Investigators will also conduct bias assessments. Selection bias assessment will compare participants' demographics to publicly available school-level data. The attrition bias assessment will compare staff respondents who completed follow-up surveys versus those who did not by baseline demographics and outcomes. Investigators will report significant differences as potential validity threats.

Primary Outcome Analyses

To answer the primary research questions, investigators will use best practices for pilot or feasibility studies [46-49]. Investigators will analyze the primary outcomes using descriptive statistics [46-49] and will not correct for multiple tests [46-49]. Among people in the PLANTS arm, investigators will calculate means and 95% CIs for participants' responses to the FIM, AIM, IAM, and SUS [53] and *P* values using 1 sample two-sided *t* tests against a priori thresholds.

Secondary Outcome Analyses

For trial implementation outcomes, investigators will calculate the participation and retention rates with a percentage and 95% CIs in the overall study sample. For PLANTS intervention demand, investigators will calculate average adherence with a percentage and a 95% CI among participants in the PLANTS study arm.

For safety outcomes, investigators will estimate the prevalence of adverse events reported by school staff at any time after intervention or comparator deployment. Investigators will report by study arm: the overall frequency of adverse events; the frequency of each type; and the frequency and percentage of school staff reporting adverse events.

To examine the pre-post changes in high school staff outcomes, investigators will first use descriptive statistics, such as means and percentages at each timepoint within arms. To test for within-arm statistical significance, investigators will use linear mixed models for continuous outcomes and generalized linear mixed models for binary outcomes, which account for within-school and within-person clustering using random effects. Investigators will estimate the intraclass correlations for within-school and within-person effects. These models will adjust for school size (a priori design variable).

Subsequently, investigators will compare pre-post changes between arms using regression models that include a fixed term for school size (a priori design variable), intervention group (intervention or comparator), time (baseline or follow-up), and the interaction of the intervention group×time (variable of interest for between-arm differences in pre-post changes). The intervention effects on secondary outcomes will be primarily based on intent-to-treat (ITT) estimates. Investigators will estimate as-treated and per-protocol effects in secondary models. If there are differences in potential confounders by intervention group, investigators will adjust for them in secondary multivariable analyses.

Exploratory Outcome Analyses

To explore the intervention effects among sexual and gender minority youths (within-group analyses), investigators will conduct ITT analyses using linear mixed models or generalized linear models accounting for within-school clustering effects using random effects. Investigators will restrict the sample to participants who reported a sexual minority identity or gender minority identity. Regression models will include a fixed term for school size (a priori design variable), intervention group (intervention or comparator), time (baseline or follow-up), and the interaction of intervention group×time (variable of interest). First, investigators will estimate ITT effects. Second, because subsetting a randomized sample may lead to naturally imbalanced arms, investigators will adjust for any imbalanced confounders.

To explore the intervention effects on inequities among sexual and gender minority youths (between-group analyses), investigators will use mixed models like previously described, except investigators who will include all student data in these analyses, including cisgender heterosexual youths, to assess reductions in inequities. Regression models will include fixed terms for the intervention group (PLANTS or EMAILS), time (baseline or follow-up), all 2-way interactions between the intervention group, time, and sexual and gender minority youths, and the 3-way interaction of the intervention group×time×sexual and gender minority youths (exploratory variable of interest for this hypothesis). Investigators will primarily explore the ITT effects.

Qualitative Analyses

Investigators will transcribe, deidentify, and check the quality of all data [61-64]. Investigators will perform use CFIR as a guiding framework. Two trained qualitative coders from our research team will independently read interviews and compare coding until they agree. Once the coders agree all major codes have been identified, they will create a final codebook with definitions, rules, and examples for each code [63,64]. Two coders will then recode all data using the final codes. Investigators will calculate inter-rater reliability (Kappa statistic) to examine code application between coders [65]. Coders will discuss any discrepancies until they reach an agreement; the principal investigator (RWSC) will resolve disagreements [63,64]. Investigators will use either a qualitative descriptive coding approach [66] (describing and counting code applications) or axial coding [67] (combining inductive codes into broader categories to define emerging patterns or themes). Investigators will identify and interpret patterns using thematic analysis [68].

Sample Size

Investigators calculated statistical power based on the primary outcomes, a 5% error rate, and best practices for feasibility studies. The median number of teachers at each MetroWest region high school is 86. With 4 schools, investigators anticipate inviting a total of ≥344 school staff (including teachers and other school staff with direct contact with students) to participate in the pilot study. Assuming 50% agree to participate, 50% of participants are in the PLANTS study arm, and 75% of PLANTS participants complete the follow-up survey (reduced n=65), investigators can estimate 95% CI widths ≤0.33 for AIM and IAM, and ≤10.1 for SUS. Such precision levels are sufficient. For qualitative interviews, investigators aim to interview people with a diversity of intervention fidelity, acceptability, usability, feasibility, and appropriateness. This is an exploratory interview study in nature, so idea generation and exploration are the goal, not thematic saturation. Investigators aim to interview PLANTS (n=20-30) and EMAILS (n=10-20) participants, and these sample sizes will provide ample information about the CFIR domains.

Results

School enrollment began in May 2023 and participant enrollment began in June 2023. Data collection is expected to be completed by January 2024. As of December 4, 2023, a total of 99 school staff enrolled in the study. Data collection is expected to be completed in January 2024.

Discussion

Principal Findings

This pilot trial rigorously evaluates the acceptability, usability, appropriateness, and feasibility of PLANTS, a web-delivered intervention aimed at improving school staff's skills, self-efficacy, knowledge, and outcome expectations for working with sexual and gender minority youths. Schools provide an ideal setting for interventions specific to sexual and gender minority youths for health disparities. High school students spend ~1195 hours per year in school [69], and sexual and gender minority youths regularly interact with adults who are professionally bound by certifying bodies to support the needs of students, including this population [70-73]. Implementing interventions in schools is challenging because of schools' limited resources, increasing demands placed on teachers, and difficulty in acquiring school buy-in. By using an economical and easily implementable web-based intervention, and by developing interventions and implementation strategies in collaboration with school personnel, these barriers may be overcome. PLANTS meets each of these criteria. A strength of this study is how it is embedded within the existing surveillance infrastructure. MWAHS conducts a census of students and has high student participation rates, minimizing biases common in convenience samples of sexual and gender minority youths.

Limitations

The primary limitation is generalizability because the study is solely in Massachusetts, a predominantly liberal US state. Selection bias could be present, for example, if school staff with the greatest stigmatizing attitudes toward sexual and gender minority youths do not participate. Investigators will examine if attitudes toward sexual and gender minority youths are associated with retention or attrition. Despite using numerous validated measures, the reliance on self-reported measures for both staff and students can be seen as a limitation. Because there is concern that school staff may be dishonest, investigators include a measure of social desirability bias [74]. Investigators will control for social desirability in analyses if it is high or if it is unevenly distributed among intervention versus comparator schools. For the exploratory student-level outcomes, another limitation is the lack of assessing individual-level change in student outcomes, since MWAHS data are collected biennially and anonymously. Investigators minimize historical and maturation biases by comparing youths in intervention schools to their same-aged peers in comparator schools across the same time periods while also assessing school-level policy and programmatic changes via surveys.

Conclusions

This study will rigorously test the hypothesis that PLANTS will be rated highly acceptable, usable, appropriate, and feasible by high school staff. PLANTS is hypothesized to be more efficacious for improving staff's support of sexual and gender minority youths and therefore reducing health inequities in this population than the active comparator. The results from this pilot trial will inform a fully powered trial of the efficacy of PLANTS for fostering health equity in sexual and gender minority youths.

Acknowledgments

The research reported in this publication was supported by the National Institute on Alcohol Abuse and Alcoholism of the National Institutes of Health under award number (K01AA027564 to Coulter). MetroWest Adolescent Health Survey is funded by the MetroWest Health Foundation in 26 school districts, with 3 additional school districts providing direct funding to Education Development Center, Inc. Funders had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the MetroWest Health Foundation.

Data Availability

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

Authors' Contributions

RWSC conceived of the PLANTS pilot trial. RWSC and SKS secured funding. RWSC, SKS, EM, and KZA designed the study. IKM, CAL, SKS, ASM, and KB helped with the study implementation and acquisition of data. KZA provided statistical expertise in clinical trial design. RWSC and IKM are conducting statistical analyses. All authors contributed to the refinement of the study protocol and approved the final manuscript.

Conflicts of Interest

EM receives royalties for writing content for UpToDate, Wolters Kluwer. The other authors received no external funding.

Multimedia Appendix 1
Survey items for primary outcomes, secondary outcomes, exploratory outcomes, demographics, and confounders.
[PDF File (Adobe PDF File), 156 KB - resprot_v13i1e55210_app1.pdf]

Multimedia Appendix 2

Peer-reviewer report from the National Institute on Alcohol Abuse and Alcoholism.
[PDF File (Adobe PDF File), 162 KB - resprot_v13i1e55210_app2.pdf]

References

1. Kann L, McManus T, Harris WA, Shanklin SL, Flint KH, Queen B, et al. Youth risk behavior surveillance—United States, 2017. MMWR Surveill Summ 2018;67(8):1-114 [FREE Full text] [doi: 10.15585/mmwr.ss6708a1] [Medline: 29902162]
2. Marshal MP, Friedman MS, Stall R, King KM, Miles J, Gold MA, et al. Sexual orientation and adolescent substance use: a meta-analysis and methodological review. Addiction 2008;103(4):546-556 [FREE Full text] [doi: 10.1111/j.1360-0443.2008.02149.x] [Medline: 18339100]
3. Committee on Lesbian, Gay, Bisexual, and Transgender Health Issues and Research Gaps and Opportunities, Institute of Medicine (US). The Health of Lesbian, Gay, Bisexual, and Transgender People: Building a Foundation for Better Understanding. Washington, D.C: National Academies Press; 2011.
4. Coulter RWS, Birkett M, Corliss HL, Hatzenbuehler ML, Mustanski B, Stall RD. Associations between LGBTQ-affirmative school climate and adolescent drinking behaviors. Drug Alcohol Depend 2016;161:340-347 [FREE Full text] [doi: 10.1016/j.drugalcdep.2016.02.022] [Medline: 26946989]
5. Coulter RWS, Bersamin M, Russell ST, Mair C. The effects of gender- and sexuality-based harassment on lesbian, gay, bisexual, and transgender substance use disparities. J Adolesc Health 2018;62(6):688-700 [FREE Full text] [doi: 10.1016/j.jadohealth.2017.10.004] [Medline: 29241986]
6. Reisner SL, Greytak EA, Parsons JT, Ybarra ML. Gender minority social stress in adolescence: disparities in adolescent bullying and substance use by gender identity. J Sex Res 2015;52(3):243-256 [FREE Full text] [doi: 10.1080/00224499.2014.886321] [Medline: 24742006]
7. Day JK, Fish JN, Perez-Brumer A, Hatzenbuehler ML, Russell ST. Transgender youth substance use disparities: results from a population-based sample. J Adolesc Health 2017;61(6):729-735 [FREE Full text] [doi: 10.1016/j.jadohealth.2017.06.024] [Medline: 28942238]
8. Fish JN, Schulenberg JE, Russell ST. Sexual minority youth report high-intensity binge drinking: the critical role of school victimization. J Adolesc Health 2019;64(2):186-193 [FREE Full text] [doi: 10.1016/j.jadohealth.2018.07.005] [Medline: 30660247]
9. Phillips G, Turner B, Salamanca P, Birkett M, Hatzenbuehler ML, Newcomb ME, et al. Victimization as a mediator of alcohol use disparities between sexual minority subgroups and sexual majority youth using the 2015 National Youth Risk Behavior Survey. Drug Alcohol Depend 2017;178:355-362 [FREE Full text] [doi: 10.1016/j.drugalcdep.2017.05.040] [Medline: 28692946]
10. Corliss HL, Rosario M, Wypij D, Fisher LB, Austin SB. Sexual orientation disparities in longitudinal alcohol use patterns among adolescents: findings from the Growing Up Today Study. Arch Pediatr Adolesc Med 2008;162(11):1071-1078 [FREE Full text] [doi: 10.1001/archpedi.162.11.1071] [Medline: 18981356]
11. Garofalo R, Wolf RC, Kessel S, Palfrey SJ, DuRant RH. The association between health risk behaviors and sexual orientation among a school-based sample of adolescents. Pediatrics 1998;101(5):895-902. [doi: 10.1542/peds.101.5.895] [Medline: 9565422]
12. Russell ST, Driscoll AK, Truong N. Adolescent same-sex romantic attractions and relationships: implications for substance use and abuse. Am J Public Health 2002;92(2):198-202 [FREE Full text] [doi: 10.2105/ajph.92.2.198] [Medline: 11818291]
13. Talley AE, Hughes TL, Aranda F, Birkett M, Marshal MP. Exploring alcohol-use behaviors among heterosexual and sexual minority adolescents: intersections with sex, age, and race/ethnicity. Am J Public Health 2014;104(2):295-303 [FREE Full text] [doi: 10.2105/AJPH.2013.301627] [Medline: 24328614]
14. Marshal MP, Friedman MS, Stall R, Thompson AL. Individual trajectories of substance use in lesbian, gay and bisexual youth and heterosexual youth. Addiction 2009;104(6):974-981 [FREE Full text] [doi: 10.1111/j.1360-0443.2009.02531.x] [Medline: 19344440]
15. Marshal MP, King KM, Stepp SD, Hipwell A, Smith H, Chung T, et al. Trajectories of alcohol and cigarette use among sexual minority and heterosexual girls. J Adolesc Health 2012;50(1):97-99 [FREE Full text] [doi: 10.1016/j.jadohealth.2011.05.008] [Medline: 22188841]
16. Dermody SS. Risk of polysubstance use among sexual minority and heterosexual youth. Drug Alcohol Depend 2018;192:38-44. [doi: 10.1016/j.drugalcdep.2018.07.030] [Medline: 30205306]
17. Fish JN, Baams L. Trends in alcohol-related disparities between heterosexual and sexual minority youth from 2007 to 2015: findings from the Youth Risk Behavior Survey. LGBT Health 2018;5(6):359-367 [FREE Full text] [doi: 10.1089/lgbt.2017.0212] [Medline: 30010480]
18. Marshal MP, Sucato G, Stepp SD, Hipwell A, Smith HA, Friedman MS, et al. Substance use and mental health disparities among sexual minority girls: results from the Pittsburgh girls study. J Pediatr Adolesc Gynecol 2012;25(1):15-18 [FREE Full text] [doi: 10.1016/j.jpag.2011.06.011] [Medline: 22051788]
19. Dermody SS, Marshal MP, Cheong J, Chung T, Stepp SD, Hipwell A. Adolescent sexual minority girls are at elevated risk for use of multiple substances. Subst Use Misuse 2016;51(5):574-585 [FREE Full text] [doi: 10.3109/10826084.2015.1126743] [Medline: 27008283]

20. Dermody SS, Friedman M, Chisolm DJ, Burton CM, Marshal MP. Elevated risky sexual behaviors among sexual minority girls: indirect risk pathways through peer victimization and heavy drinking. J Interpers Violence 2020;35(11-12):2236-2253. [doi: 10.1177/0886260517701450] [Medline: 29294701]
21. Marshal MP, Dermody SS, Shultz ML, Sucato GS, Stepp SD, Chung T, et al. Mental health and substance use disparities among urban adolescent lesbian and bisexual girls. J Am Psychiatr Nurses Assoc 2013;19(5):271-279 [FREE Full text] [doi: 10.1177/1078390313503552] [Medline: 24055956]
22. 1991-2019 high school youth risk behavior survey data. Centers for Disease Control and Prevention. URL: http://yrbs-explorer.services.cdc.gov/ [accessed 2021-05-23]
23. Pérez-Stable EJ. Sexual and gender minorities formally designated as a health disparity population for research purposes. National Institute on Minority Health and Health Disparities. 2016. URL: https://www.nimhd.nih.gov/about/directors-corner/message.html [accessed 2017-11-08]
24. U.S. Department of Health and Human Services. Healthy people 2020. National Center for Health Statistics. Washington, D.C: Government Printing Office; 2010. URL: https://www.cdc.gov/nchs/healthy_people/hp2020.htm [accessed 2024-02-07]
25. Bontempo DE, D'Augelli AR. Effects of at-school victimization and sexual orientation on lesbian, gay, or bisexual youths' health risk behavior. J Adolesc Health 2002;30(5):364-374. [doi: 10.1016/s1054-139x(01)00415-3] [Medline: 11996785]
26. Rosario M, Corliss HL, Everett BG, Russell ST, Buchting FO, Birkett MA. Mediation by peer violence victimization of sexual orientation disparities in cancer-related tobacco, alcohol, and sexual risk behaviors: pooled youth risk behavior surveys. Am J Public Health 2014;104(6):1113-1123. [doi: 10.2105/AJPH.2013.301764] [Medline: 24825215]
27. Darwich L, Hymel S, Waterhouse T. School avoidance and substance use among lesbian, gay, bisexual, and questioning youths: the impact of peer victimization and adult support. J Educ Psychol 2012;104(2):381-392. [doi: 10.1037/a0026684]
28. De Pedro KT, Esqueda MC, Gilreath TD. School protective factors and substance use among lesbian, gay, and bisexual adolescents in California Public Schools. LGBT Health 2017;4(3):210-216. [doi: 10.1089/lgbt.2016.0132] [Medline: 28498005]
29. Seil KS, Desai MM, Smith MV. Sexual orientation, adult connectedness, substance use, and mental health outcomes among adolescents: findings from the 2009 New York City Youth Risk Behavior Survey. Am J Public Health 2014;104(10):1950-1956 [FREE Full text] [doi: 10.2105/AJPH.2014.302050] [Medline: 25121812]
30. Whitaker K, Shapiro VB, Shields JP. School-based protective factors related to suicide for lesbian, gay, and bisexual adolescents. J Adolesc Health 2016;58(1):63-68. [doi: 10.1016/j.jadohealth.2015.09.008] [Medline: 26707230]
31. Coulter RWS, Schneider SK, Beadnell B, O'Donnell L. Associations of outside- and within-school adult support on suicidality: moderating effects of sexual orientation. Am J Orthopsychiatry 2017;87(6):671-679 [FREE Full text] [doi: 10.1037/ort0000209] [Medline: 27598866]
32. Stone DM, Luo F, Lippy C, McIntosh WL. The role of social connectedness and sexual orientation in the prevention of youth suicide ideation and attempts among sexually active adolescents. Suicide Life Threat Behav 2015;45(4):415-430 [FREE Full text] [doi: 10.1111/sltb.12139] [Medline: 25388375]
33. Coulter RWS, Herrick AL, Friedman MR, Stall RD. Sexual-orientation differences in positive youth development: the mediational role of bullying victimization. Am J Public Health 2016;106(4):691-697. [doi: 10.2105/AJPH.2015.303005] [Medline: 26794177]
34. Russell ST, Everett BG, Rosario M, Birkett M. Indicators of victimization and sexual orientation among adolescents: analyses from youth risk behavior surveys. Am J Public Health 2014;104(2):255-261 [FREE Full text] [doi: 10.2105/ajph.2013.301493]
35. Friedman MS, Marshal MP, Guadamuz TE, Wei C, Wong CF, Saewyc EM, et al. A meta-analysis of disparities in childhood sexual abuse, parental physical abuse, and peer victimization among sexual minority and sexual nonminority individuals. Am J Public Health 2011;101(8):1481-1494 [FREE Full text] [doi: 10.2105/AJPH.2009.190009] [Medline: 21680921]
36. Coulter RWS, Bersamin M, Russell S, Mair C. Sexuality- and gender-biased bullying victimization partially explains substance use disparities for LGBT adolescents. Society for Research on Adolescence Biennial Meeting. Baltimore, Maryland; 2015. URL: https://www.s-r-a.org/ [accessed 2024-02-07]
37. Schneider SK, O'Donnell L, Stueve A, Coulter RWS. Cyberbullying, school bullying, and psychological distress: a regional census of high school students. Am J Public Health 2012;102(1):171-177 [FREE Full text] [doi: 10.2105/AJPH.2011.300308] [Medline: 22095343]
38. Goodenow C, Watson RJ, Adjei J, Homma Y, Saewyc E. Sexual orientation trends and disparities in school bullying and violence-related experiences, 1999-2013. Psychol Sex Orientat Gend Divers 2016;3(4):386-396 [FREE Full text] [doi: 10.1037/sgd0000188] [Medline: 29322064]
39. Coulter RWS, Paglisotti T, Montano G, Bodnar K, Bersamin M, Russell ST, et al. Intersectional differences in protective school assets by sexuality, gender, race/ethnicity, and socioeconomic status. J Sch Health 2021;91(4):318-330 [FREE Full text] [doi: 10.1111/josh.13005] [Medline: 33740272]
40. Swanson K, Gettinger M. Teachers' knowledge, attitudes, and supportive behaviors toward LGBT students: relationship to gay-straight alliances, antibullying policy, and teacher training. J LGBT Youth 2016;13(4):326-351. [doi: 10.1080/19361653.2016.1185765]

41. Demissie Z, Rasberry CN, Steiner RJ, Brener N, McManus T. Trends in secondary schools' practices to support lesbian, gay, bisexual, transgender, and questioning students, 2008-2014. Am J Public Health 2018;108(4):557-564. [doi: 10.2105/AJPH.2017.304296] [Medline: 29470123]
42. Konishi C, Saewyc E, Homma Y, Poon C. Population-level evaluation of school-based interventions to prevent problem substance use among gay, lesbian and bisexual adolescents in Canada. Prev Med 2013;57(6):929-933 [FREE Full text] [doi: 10.1016/j.ypmed.2013.06.031] [Medline: 23850517]
43. Hatzenbuehler ML, Birkett M, Van Wagenen A, Meyer IH. Protective school climates and reduced risk for suicide ideation in sexual minority youths. Am J Public Health 2014;104(2):279-286 [FREE Full text] [doi: 10.2105/AJPH.2013.301508] [Medline: 24328634]
44. Hatzenbuehler ML, Jun H, Corliss HL, Austin SB. Structural stigma and cigarette smoking in a prospective cohort study of sexual minority and heterosexual youth. Ann Behav Med 2014;47(1):48-56 [FREE Full text] [doi: 10.1007/s12160-013-9548-9] [Medline: 24136092]
45. Coulter RWS, Miller E. Professional development and research to improve school practices and LGBTQ health in US schools. Am J Public Health 2018;108(4):443-444. [doi: 10.2105/AJPH.2018.304331] [Medline: 29513599]
46. Bowen DJ, Kreuter M, Spring B, Cofta-Woerpel L, Linnan L, Weiner D, et al. How we design feasibility studies. Am J Prev Med 2009;36(5):452-457 [FREE Full text] [doi: 10.1016/j.amepre.2009.02.002] [Medline: 19362699]
47. Moore CG, Carter RE, Nietert PJ, Stewart PW. Recommendations for planning pilot studies in clinical and translational research. Clin Transl Sci 2011;4(5):332-327 [FREE Full text] [doi: 10.1111/j.1752-8062.2011.00347.x] [Medline: 22029804]
48. Kistin C, Silverstein M. Pilot studies: a critical but potentially misused component of interventional research. JAMA 2015;314(15):1561-1562 [FREE Full text] [doi: 10.1001/jama.2015.10962] [Medline: 26501530]
49. Kraemer HC, Mintz J, Noda A, Tinklenberg J, Yesavage JA. Caution regarding the use of pilot studies to guide power calculations for study proposals. Arch Gen Psychiatry 2006;63(5):484-489. [doi: 10.1001/archpsyc.63.5.484] [Medline: 16651505]
50. 2017 State and Local Youth Risk Behavior Survey. Centers for Disease Control and Prevention. 2017. URL: https://www.cdc.gov/healthyyouth/data/yrbs/pdf/2017/2017_yrbs_standard_hs_questionnaire.pdf [accessed 2018-02-04]
51. Coulter RWS, Henderson ER, Corey SL, Gagnon K, Chugani CD, Egan JE, et al. Exploring how U.S. high school staff support, protect, and affirm sexual and gender minority youth: methods and lessons learned from a qualitative interview study. Int J Qual Methods 2022;21:1-18 [FREE Full text] [doi: 10.1177/16094069221093132]
52. Bangor A, Kortum PT, Miller JT. An empirical evaluation of the system usability scale. Int J Hum-Comput Int 2008;24(6):574-594. [doi: 10.1080/10447310802205776]
53. Weiner BJ, Lewis CC, Stanick C, Powell BJ, Dorsey CN, Clary AS, et al. Psychometric assessment of three newly developed implementation outcome measures. Implement Sci 2017;12(1):108 [FREE Full text] [doi: 10.1186/s13012-017-0635-3] [Medline: 28851459]
54. Brooke J. SUS: a 'quick and dirty' usability scale. In: Jordan PW, McClelland IL, Thomas B, Weerdmeester BA, editors. Usability Evaluation in Industry. Boca Raton, FL: CRC Press; 1996:189-194.
55. Crisp C. The Gay Affirmative Practice Scale (GAP): a new measure for assessing cultural competence with gay and lesbian clients. Soc Work 2006;51(2):115-126. [doi: 10.1093/sw/51.2.115] [Medline: 16858917]
56. Coulter RWS, Colvin S, Onufer LR, Arnold G, Akiva T, D'Ambrogi E, et al. Training pre-service teachers to better serve LGBTQ high school students. J Educ Teach 2021;47(2):234-254 [FREE Full text] [doi: 10.1080/02607476.2020.1851137] [Medline: 33986557]
57. Bodie GD. The Active-Empathic Listening Scale (AELS): conceptualization and evidence of validity within the interpersonal domain. Commun Q 2011;59(3):277-295. [doi: 10.1080/01463373.2011.583495]
58. Nickerson AB, Aloe AM, Livingston JA, Feeley TH. Measurement of the bystander intervention model for bullying and sexual harassment. J Adolesc 2014;37(4):391-400. [doi: 10.1016/j.adolescence.2014.03.003] [Medline: 24793386]
59. Eldridge MA. Teacher characteristics and influence with the Bystander Intervention Model. Masters Theses.: Eastern Illinois University; 2017. URL: https://thekeep.eiu.edu/theses/2669/ [accessed 2024-02-07]
60. CFIR Research Team-Center for Clinical Management Research. Interview guide tool. CFIR guide. 2023. URL: https://cfirguide.org/guide/app/#/ [accessed 2023-12-27]
61. Saldaña J. The Coding Manual for Qualitative Researchers, Third Edition. Los Angeles: SAGE Publications; 2016.
62. Miles MB, Huberman AM, Saldaña J. Qualitative Data Analysis: A Methods Sourcebook, Third Edition. Thousand Oaks, CA: SAGE Publications; 2014.
63. MacQueen KM, McLellan E, Kay K, Milstein B. Codebook development for team-based qualitative analysis. Cult Anthropol Methods 2016;10(2):31-36. [doi: 10.1177/1525822X980100020301]
64. Fernald DH, Duclos CW. Enhance your team-based qualitative research. Ann Fam Med 2005;3(4):360-364 [FREE Full text] [doi: 10.1370/afm.290] [Medline: 16046570]
65. Cohen J. A coefficient of agreement for nominal scales. Educ Psychol Meas 2016;20(1):37-46. [doi: 10.1177/001316446002000104]
66. Sandelowski M. Whatever happened to qualitative description? Res Nurs Health 2000;23(4):334-340 [FREE Full text] [doi: 10.1002/1098-240x(200008)23:4<334::aid-nur9>3.0.co;2-g]

67. Thomas DR. A general inductive approach for analyzing qualitative evaluation data. Am J Eval 2016;27(2):237-246. [doi: 10.1177/1098214005283748]
68. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol 2006;3(2):77-101. [doi: 10.1191/1478088706qp063oa]
69. Schools and Staffing Survey (SASS). U.S. Department of Education, National Center for Education Statistics. 2008. URL: https://nces.ed.gov/surveys/sass/tables/sass0708_035_s1s.asp [accessed 2018-06-07]
70. The Code of Ethics of the Education. National Education Association of the United States, Committee on Professional Ethics. 1963. URL: https://www.nea.org/resource-library/code-ethics-educators [accessed 2024-02-07]
71. Code of ethics. The School Superintendents Association (AASA). URL: http://aasa.org/content.aspx?id=1390 [accessed 2018-06-07]
72. Code of ethics of the National Association of Social Workers. National Association of Social Workers, Inc.: NASW Distribution Center; 1999. URL: https://books.google.co.in/books?hl=en&lr=&id=drBlAgAAQBAJ&oi=fnd&pg=PA395&dq=related:7MOMANIfRxYJ:scholar.google.com/&ots=_hU7K0Btpr&sig=smMLnew0seOdYq0wXmbKfLBXQgk#v=onepage&q&f=false [accessed 2024-02-07]
73. Code of ethics. National Association of School Nurses. URL: https://www.nasn.org/nasn-resources/professional-topics/codeofethics [accessed 2018-06-07]
74. Reynolds WM. Development of reliable and valid short forms of the marlowe-crowne social desirability scale. J Clin Psychol 1982;38(1):119-125. [doi: 10.1002/1097-4679(198201)38:1<119::aid-jclp2270380118>3.0.co;2-i]

Abbreviations

AIM: Acceptability of Intervention Measure
CFIR: Consolidated Framework for Intervention Research
EMAILS: e-Learning to Maximize Academic Inclusion of LGBTQ+ Students
FIM: feasibility of intervention measure
IAM: intervention appropriateness measure
ITT: intent-to-treat
LGBTQ: Lesbian, Gay, Bisexual, Transgender, Nonbinary, and Queer
MWAHS: MetroWest Adolescent Health Survey
REDCap: Research Electronic Data Capture
PLANTS: Providing LGBTQ+ Adolescents with Nurturance, Trustworthiness, and Safety
SUS: System Usability Scale

Edited by A Mavragani; submitted 07.12.23; this is a non–peer-reviewed article;accepted 01.02.24; published 19.03.24.

Please cite as:
Coulter RWS, Mahal IK, Lin CA, Schneider SK, Mathias AS, Baral K, Miller E, Abebe KZ
Providing Lesbian, Gay, Bisexual, Transgender, Nonbinary, and Queer Adolescents With Nurturance, Trustworthiness, and Safety: Protocol for Pilot Cluster Randomized Controlled Trial Design
JMIR Res Protoc 2024;13:e55210
URL: https://www.researchprotocols.org/2024/1/e55210
doi:10.2196/55210
PMID:38502156

Protocol

A Social Media–Delivered Melanoma Prevention Program for Young Women Engaged in Frequent UV Tanning: Protocol for a Randomized Controlled Trial

Jerod L Stapleton[1], PhD; Sharon L Manne[2], PhD; Sherry L Pagoto[3], PhD; Allison Leip[4], BS; Kathryn Greene[5], PhD; Joel J Hillhouse[6], PhD; Allison S Merritt[1], MPH; Brent J Shelton[7], PhD

[1]Markey Cancer Center, College of Public Health, University of Kentucky, Lexington, KY, United States

[2]Rutgers Cancer Institute of New Jersey, Rutgers Robert Wood Johnson Medical School, Rutgers, The State University of New Jersey, New Brunswick, NJ, United States

[3]Institute for Collaboration on Health, Intervention and Policy, University of Connecticut, Storrs, CT, United States

[4]Department of Family Sciences, University of Kentucky, Lexington, KY, United States

[5]Department of Communication, Rutgers, The State University of New Jersey, New Brunswick, NJ, United States

[6]Department of Community and Behavioral Health, East Tennessee State University, Johnson City, TN, United States

[7]Markey Cancer Center, College of Medicine, University of Kentucky, Lexington, KY, United States

Corresponding Author:
Jerod L Stapleton, PhD
Markey Cancer Center
College of Public Health
University of Kentucky
342 Bowman Hall
Lexington, KY, 40508
United States
Phone: 1 8593237224
Email: jerod.stapleton@uky.edu

Abstract

Background: Rates of melanoma have increased dramatically in the United States over the past 25 years, and it has become among the most prevalent cancers for young adult women. Intentional skin tanning leads to a pattern of intense and intermittent UV radiation exposure that is associated with increased risk of melanoma. Frequent tanning is most common among young women and is linked to a variety of sociocultural pressures that negatively impact body image and drive appearance control behaviors. Unfortunately, there are no established interventions designed for frequent tanners. This intervention addresses this gap with unique content informed by body image and acceptance-based interventions. The intervention is delivered using Facebook secret groups, an approach designed to support behavior change and ensure scalability.

Objective: This study aims to describe the rationale and methodology of a randomized controlled trial of a melanoma prevention program targeting young women engaged in frequent indoor or outdoor UV tanning.

Methods: Participants are women aged 18-25 years who report high-risk tanning (ie, at least 10 indoor tanning sessions in the past 12 months or 10 outdoor sessions in the previous summer). After recruitment and screening, participants completed a baseline survey and were randomly assigned to receive the intervention or an attention-matched control condition. Both conditions were 8-week-long Facebook groups (approximately 25 members each) with daily posting of content. Follow-up surveys are administered at 3, 8, and 18 months after baseline. The primary trial outcome is the combined number of indoor and outdoor tanning sessions reported at the 8-month follow-up. Hypothesized intervention mediators are assessed at the 3-month follow-up.

Results: This project was funded by a National Cancer Institute award (R01 CA218068), and the trial procedures were approved by the University of Kentucky Institutional Review Board in February 2020. Trial recruitment and enrollment occurred in 6 waves of data collection, which started in February 2022 and closed in May 2023. The study is closed to enrollment but remains open for follow-ups, and this protocol report was prepared before data analyses. As of February 2024, all participants have completed the 8-month follow-up assessment, and data collection is scheduled to close by the end of 2024 after the collection of the 18-month follow-up.

Conclusions: This trial will contribute unique knowledge to the field of skin cancer prevention, as no fully powered trials have examined the efficacy of an intervention designed for frequent indoor or outdoor tanning. The trial may also contribute evidence of the value in translating principles of body image and acceptance-based interventions into the field of skin cancer prevention and beyond. If successful, the use of the Facebook platform is intended to aid in dissemination as it provides a way to embed the intervention into individuals' everyday routines.

Trial Registration: ClinicalTrials.gov NCT03441321; https://clinicaltrials.gov/study/NCT03441321

International Registered Report Identifier (IRRID): DERR1-10.2196/56562

(JMIR Res Protoc 2024;13:e56562) doi:10.2196/56562

KEYWORDS

acceptance and commitment therapy; body image; dissonance-based intervention; eHealth; Facebook; indoor tanning bed; melanoma; randomized controlled trial; skin cancer; social media; sunbathing

Introduction

Tanning and Skin Cancer Risk

Prolonged exposure to UV radiation induces a skin tanning process in response to cellular skin DNA damage that can lead to skin cancer [1]. Excessive UV exposure through the use of artificial UV-emitting tanning beds or intense, intermittent sun exposures, like outdoor tanning (eg, sunbathing), has been linked to increased risk for all skin cancer types, including melanoma [2-6]. Excessive UV exposure is most common among young adult women and is likely driving concerning melanoma trends in the United States, including a decades-long climb in overall and site-specific melanoma incidence (eg, melanoma of the trunk) [7]. Melanoma has become among the most common cancers among women aged between 20 and 29 years [8].

Public health and policy efforts have produced an increasing number of federal regulations and state-level restrictions on access to tanning beds among minors in the past 2 decades. These efforts have helped to produce a continuing decline in the overall prevalence of tanning bed use in the United States from a peak in 2009 [9-11]. However, recent studies suggest nearly 7% of adolescents and 13% of adults still use indoor tanning in the United States each year [12], and rates of frequent, higher-risk indoor tanning remain concerning, with 24% of recent tanners reporting tanning 25 or more times in the past year in 2018 compared to 13% in 2007 [13]. Internet search results have revealed that public interest in outdoor tanning may have increased during the widespread shutdowns of tanning salons during the height of COVID-19–related restrictions [14]. National prevalence estimates of outdoor tanning are lacking because the behavior is not routinely assessed in surveillance surveys, but recent studies of young adults have found between 32% and 64% report outdoor tanning [15,16]. A recent analysis of protanning videos on the popular social media platform TikTok showed that outdoor tanning was nearly twice as likely to be portrayed as indoor tanning [17]. Overall, while indoor tanning rates have declined, intentional outdoor UV exposure or sunbathing may have increased in popularity.

Public health efforts and existing behavioral interventions have primarily focused on preventing the uptake of indoor tanning and lack attention to frequent tanning behaviors that increase the risk for melanoma development [18]. Indeed, the *Surgeon General's Call to Action to Prevent Skin Cancer* identified a critical research gap related to an absence of interventions that target high-risk tanners and address underlying motives for tanning, including "the desire to look attractive and healthy and to conform to societal beauty standards" [19]. Further, recent trends support the need for interventions targeting frequent indoor and outdoor tanners. The proposed study addresses a gap in the melanoma prevention field by testing a skin cancer risk reduction intervention targeted to frequent indoor or outdoor tanners.

Behavioral Determinants of Tanning Behaviors

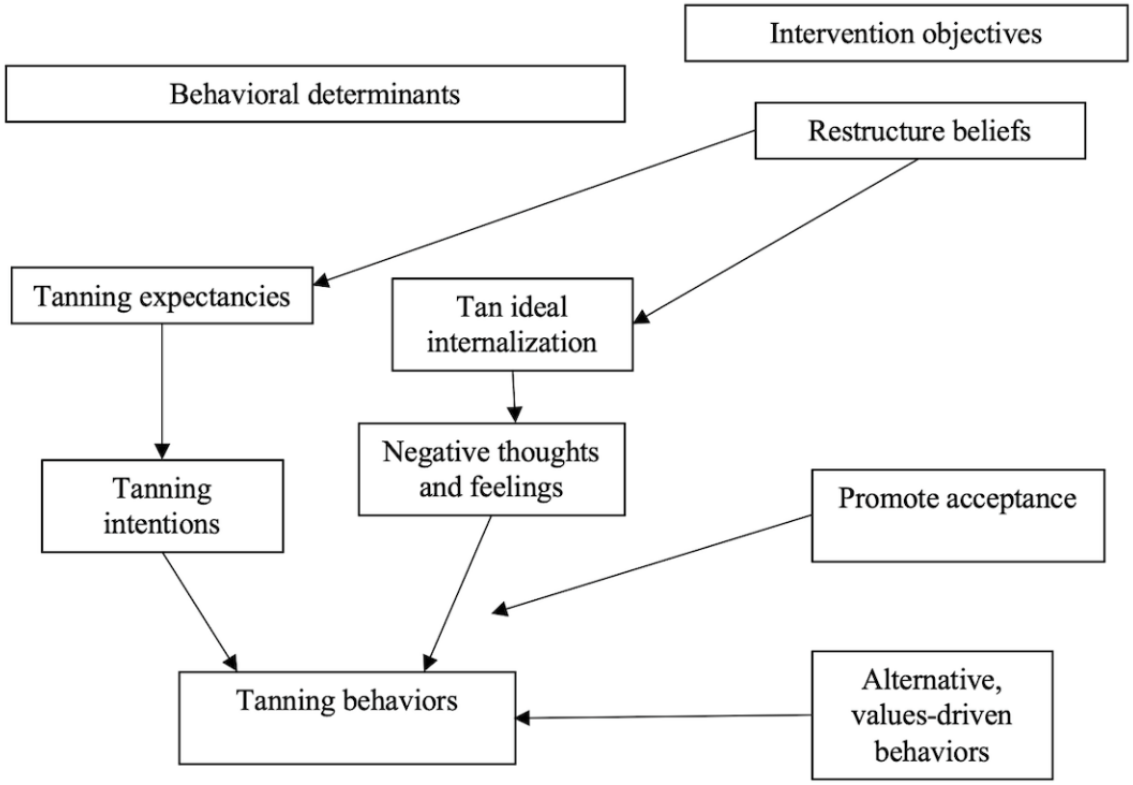
Our intervention is designed to address key factors from our conceptual dual-process model of tanning, which is supported by a body of behavioral research that demonstrates tanning is both an intentional, planned behavior to maintain appearance and a reactionary behavior used to avoid negative thoughts and feelings (Figure 1).

The intentional pathway is supported by studies demonstrating the role of tanning expectancies (ie, the anticipated positive and negative aspects of tanning) on tanning intentions and behavior. Tanners endorse positive aspects of tanning, including perceiving a tanned appearance as attractive, rating others with tans as more attractive than their pale counterparts, viewing indoor tanning as a convenient way to enhance appearance, and believing their peers approve of and engage in tanning [20-24]. Many young women experiment with indoor tanning in preparation for a special event, such as getting a tan before a high school prom or a wedding [25-27]. Those experimenting with tanning may begin viewing it as a regular part of their beauty routine and transition to frequent use [27]. Relaxation expectancies are also a primary motive for tanning [28], which have been reinforced by a marketing approach emphasizing a spa-like experience or fitness or health amenities for tanning [29]. This marketing may contribute to tanners' beliefs that tanning has positive health benefits by contributing to mental wellness or self-care [28,30].

Sociocultural body image theories posit that societal influences and perceived expectations regarding appearance negatively influence body image, including how women think and feel about their bodies, and, as a result, drive them to engage in reactive behaviors they know are physically harmful for the sake of appearance enhancement and relief of body image concerns [31,32]. Research from our team and others has demonstrated that constructs from body image theories relate

to indoor tanning and thus form important skin cancer risk factors among female tanners [33-38]. Tanners are likely to experience perceived pressure to look tan, which is produced in Western cultures that associate being tan as a central aspect of feminine beauty ideals and is reinforced through interactions with peers and family members. Through her buy-in and internalization to the tan ideal, a tanner views being tan as central to feeling attractive and begins actively monitoring her tan. Perceived discrepancies between her current and ideal tan will lead to dissatisfaction and negative appearance-related thoughts or feelings. In this reactive pathway, tanning represents a behavior driven by a desire to avoid such unwanted thoughts and feelings driven by routine thinking that is often flawed, negatively biased, or self-critical.

Figure 1. The dual process model of tanning behavioral determinants is a summary of key tanning motives identified in behavioral studies. The corresponding intervention objectives show how the intervention content is designed to target these key determinants to produce behavior change.



Intervention Content

This intervention incorporates behavior change techniques and content that have been tested in our pilot tanning interventions [39-41] (see Methods section) and are designed to address both intentional and reactionary aspects of tanning (Figure 1). First, our intervention is designed to restructure key psychosocial drivers of tanning, specifically tanning-related expectancies, and body image–related beliefs underlying the internalization of a tan ideal. Participants engaged in risky behaviors may not be highly motivated to change their behavior but are likely to hold views about why they should and should not continue their risky behavior, called behavioral ambivalence [42]. Indeed, most tanners hold positive expectancies about the appearance and relaxation benefits of tanning while also reporting concerns about the appearance-damaging effects of UV exposure and perceiving advantages to reducing their tanning [43-46]. Our intervention is designed to restructure tanning expectancies by encouraging participants to reflect on underlying reasons for tanning and undesirable aspects. Such reflection has been shown to shift the balance of perceived benefits and costs of behaviors, promoting openness to behavioral change [41,42,47,48]. Drawn from body image theory–informed interventions, we also seek to restructure tanners' body image beliefs that underlie tan internalization with content that encourages participants to critique image ideals (in this intervention, through comments in response to intervention content prompts) [49-54]. Body image interventions, including those for tanning [39,40,55], have consistently found that asking participants to consider perspectives that are critical of body image ideals and advocate for counterperspectives can change these underlying beliefs (eg, reduce perceived pressure to tan), which can ultimately reduce buy-in to these beliefs (ie, reduce internalization) and associated body image dissatisfaction. These approaches can be particularly powerful when this process occurs in a group-based setting [53,56]. Accordingly, we use Facebook groups to deliver intervention content to frequent tanners.

Although body image beliefs can be changed in brief interventions, it can be challenging because of the pervasiveness of societal messages focused on women's appearance. Thus, the intervention is also designed to raise awareness of the impact of self-critical thoughts and negative feelings on behaviors such as tanning. The intervention messaging is consistent with the acceptance and commitment therapy (ACT) perspective that uncomfortable thoughts and feelings that accompany some deeply held beliefs cannot be controlled and attempts to do so often perpetuate self-critical thinking and maladaptive coping behaviors [57-59]. Our acceptance-based content encourages

participants to embrace an acceptance mindset, defined as an increased tolerance for experiencing negative thoughts and feelings that can drive unhealthy behaviors, rather than attempting to control them through such behaviors. The intervention also includes mindfulness skill–building exercises, which are critical for enacting acceptance through increasing the ability to identify and sit with negative thoughts and feelings as they occur [57,59].

Finally, our final intervention encourages participants to focus on healthier self-care behaviors as a substitute for tanning. Consistent with ACT principles, the intervention encourages participants to consider the importance of making daily choices guided by higher-order values to ensure they spend time on the things that are truly important to them (eg, healthy lifestyle, helpful self-care, self-compassion, acceptance, and personal growth) [57,60,61]. Participants identify their core values and contrast them with the values underlying societal messages about appearance that often drive critical self-talk. Participants are then asked to consider whether their ongoing behaviors, including tanning, are consistent with their core values (eg, healthy lifestyle) and, if not, consider approaches for enacting alternative behaviors better aligned with these core values.

Trial Objectives and Design

This randomized controlled trial (RCT) aims to examine the intervention's efficacy versus an attention-matched control group on reducing tanning behaviors among high-risk tanners. Both interventions are delivered through the secret groups feature of Facebook, with a target group size of 25 members each. Participants were frequent tanners (indoor or outdoor) recruited from across the United States. After completing an eligibility screening and a baseline survey, participants were randomized with a 1:1 allocation ratio to each condition after finishing the baseline survey. The 8-week intervention and control groups began 1-3 weeks after baseline completion. Self-reported surveys captured tanning-related beliefs and behaviors at baseline, with follow-ups at 3, 8, and 18 months after baseline. Our primary outcome analysis will compare the tanning rates of intervention and control participants at the 8-month follow-up study. Our study is also designed to explore the impact of hypothesized mediators of intervention efficacy collected on the 3-month postbaseline survey. We hypothesize that intervention participants will report lower tanning rates at the 8-month follow-up, and these effects will be mediated by psychosocial constructs, including increasing tanning expectancies, tanning-related body image factors, and openness to changing indoor tanning. Exploratory outcomes include tanning intentions and an 18-month long-term follow-up assessment to test whether any observed intervention effects extend to the following year.

Intervention Delivery

Intervention content is delivered within secret groups on the social media site Facebook. Participants are invited to join a Facebook group and receive twice-daily intervention content posts from a study moderator. Participants are asked to read and react to posts through the "like" feature or by commenting on them. Facebook groups provide a remotely delivered opportunity to facilitate group-based interactions within the intervention, which can facilitate stronger attitude and behavior change in disordered eating dissonance–based interventions (typically delivered within small groups) [54,56,62,63]. Further, participants in group-based social media interventions often share information and receive and provide motivation to others [64,65], which may facilitate intervention goals related to boosting positive body image and adopting healthy behaviors. Facebook remains the most popular social media site among all adults and is used by 70% of individuals on the internet who are aged between 18 and 29 years [66]. Our preliminary research found that 72% of high-risk tanners used Facebook at least once a day [67] and that Facebook-delivered tanning interventions are feasible and acceptable to our target audience.

Choice of Control

The control condition is administered using the same procedures as the intervention, including delivery through secret Facebook groups. However, the post content differs, with posts related to nontanning health topics of interest identified in our pilot research (eg, physical activity, healthy eating, alcohol misuse prevention, stress reduction, and sleep). An attention-matched control ensures that the conditions are matched on total social media exposure, amount and type of content delivered, and intervention engagement. The design also avoids threats from demoralization among control users who expect but do not receive health content in a no-treatment control.

Methods

Participants

Study Setting

Study participants were young adult women recruited with web-based methods with reach throughout the United States. Recruitment and screening procedures were conducted primarily in partnership with Qualtrics and using Facebook advertisements. A few participants were recruited through additional methods, including posting on social media pages and recruitment flyers posted on a US college campus. Participants completed all study procedures electronically (ie, surveys and participating in Facebook groups) from their chosen location. All study enrollment, tracking, and participant engagement were conducted at the University of Kentucky. Moderating and monitoring of the Facebook groups was performed by research personnel at both the University of Kentucky and the University of Connecticut.

Eligibility

Eligible participants were women aged between 18 and 25 years who reported high-risk tanning (defined as using an indoor tanning bed or intentionally tanning outdoors at least 10 times in the previous 12 months) [68-70]. The study population was limited to young women due to the intervention's emphasis on body image theory and the use of content targeted to this group. We also required that participants report regular use of Facebook (defined as self-reported use of Facebook at least 4-6 times per week in the past 4 weeks). Social media use requirements are standard in trials to ensure that participants have incorporated the chosen platform into their daily media activities and are likely to engage in the intervention [71-74].

Procedures

Recruitment and Screening

Participants were primarily recruited by the internet research recruitment company Qualtrics Sample Providers using their participant panels that comply with or exceed all applicable industry standards [75]. Qualtrics emailed a randomly selected sample frame of panel participants with a study invitation, which contained a brief description of the study procedures and a brief screening eligibility assessment. Qualtrics also supplemented recruitment with web advertisements posted on various websites and platforms of their partner organizations. Additional recruitment approaches included Facebook advertisement posts with study information and links to access the screening assessment and printed flyers with QR codes to access the screener on a US college campus.

Study announcements and advertisements included a link to a 7-item brief screening assessment. Screener items assessed the eligibility criteria of gender, age, Facebook use, and past 12 months of indoor and outdoor tanning. The 2 additional health behavior questions related to the frequency of physical activity and fruit and vegetable intake were included to mask the purpose of the study. The screening survey was programmed with skip logic to identify eligible participants based on their responses. Eligible participants were provided a brief description of the study procedures immediately following the screening assessment and asked if they were interested in getting additional detailed information about the study. If they clicked yes, participants provided their contact information, which was recorded with their screening results. Screening data were reviewed for quality control to identify potentially fraudulent responses or bots. Specifically, we reviewed the pattern of responses, the total completion time, and IP addresses to identify responses that were likely from duplicate or fake respondents (including bots). Suspicious responses were removed from consideration for the study at the time of screening.

Study Procedures

Following screening, eligible participants who indicated their interest were emailed by study staff a link to a web-based baseline survey that also included the implied consent form. The baseline survey (and all follow-up surveys) were programmed using Research Electronic Data Capture (REDCap) survey software (Vanderbilt University) with encrypted responses collected on the University of Kentucky's secure servers.

After completing the baseline survey, participants were randomized with a 1:1 allocation ratio to either condition. We used a permuted block randomization design to create 2 randomly shuffled assignment lists (ie, intervention or control) in each of 2 strata (ie, indoor tanning: n=500 and outdoor tanning: n=500). These lists were used to assign participants sequentially based on tanning status (within the 2 strata) following their completion of the web-based baseline survey. Following randomization, participants were invited to their assigned group using the group email feature on Facebook. As secondary options, we emailed participants to remind them to join the Facebook groups and asked participants to "friend" the moderator's Facebook account to add them to the appropriate group manually [72].

At 3 months after baseline, each participant was invited by email to complete the first web-based follow-up survey (follow-up 1). Additional follow-ups occur at 8 months (follow-up 2) and 18 months after baseline (follow-up 3). All surveys were designed to be completed in 30 minutes. Incentives were US $30 gift cards for completing each baseline and 3- and 8-month follow-ups and US $40 for the 18-month follow-up based on similar incentive structures that have produced high retention rates in our previous indoor tanning intervention studies [76,77]. High-risk tanners often use indoor tanning throughout the year, with a peak in use in spring (ie, March-May) and outdoor tanning peaks during the summer [25,77,78]. Accordingly, our intervention was designed to be delivered during peak indoor tanning season, with the 8-month follow-up distributed near the end of the year to capture indoor tanning and cover outdoor tanning during the North American summer season. The 18-month follow-up survey will determine if intervention effects extend to tanning behaviors in the subsequent year.

Intervention

Preliminary Data

Our first pilot intervention trial was designed to test the feasibility, acceptability, and preliminary efficacy of the content and messaging strategy that form the foundation of the current intervention [39]. The text-based intervention was delivered through a self-paced, single-session website. Participants were provided psychoeducation content, encouraged to reflect on their tanning behavior, and prompted to type responses to counterattitudinal perspectives to the tan ideal. We conducted an RCT in 2014 with 186 young women who reported indoor tanning at least once in the previous year assigned to receive the website or a waitlist-control condition. We found preliminary evidence of efficacy as intervention participants reported 2.29 times higher odds of abstaining from indoor tanning over a 6-week follow-up period than participants in the waitlist control ($P<.05$). Intervention participants also reported significantly lower intentions to tan. Participants also provided positive overall acceptability and favorability ratings of the website and content focused on body image and behavioral reflection.

Our subsequent pilot trial was to adapt this website intervention content for delivery across 8 weeks through posts to a secret Facebook group [40]. Website content was divided and delivered using 2 daily posts in the group, and participants responded to the reflection posts using the comments feature. We conducted a small, single-arm feasibility trial of the adapted intervention in a study of 17 young women who used indoor tanning beds. On average, participants viewed 92% (26/28) of all posts, reacted to (eg, "liked") 32% (9/28), and commented on 27% (2/28) during the 8-week intervention group period. Further, 82% (14/17) of participants indicated they would recommend the intervention to a friend, and all agreed that they would continue to check the group if it were to continue. Responses to evaluation questions indicated that participants felt connected to and identified with the group, both of which are important for sustaining interest in Facebook groups [79]. Importantly, participants reported a lower number of average past-month

indoor tanning sessions at the postintervention assessment (mean 0.69, SD 2.3) compared to the baseline (mean 2.31, SD 4.4; Cohen *d*=0.47).

Intervention Refinement

Together, our pilot work demonstrated that our intervention content and delivery platform were feasible and acceptable and had the potential to reduce tanning intentions and behavior. Before this RCT, we conducted 2 formative studies with tanners to refine our content and messaging approach further. The first was a 2018 focus group study of indoor tanners (4 focus groups [total n=20]) designed to (1) refine our planned advertising, recruitment, and enrollment strategies; (2) receive feedback on our general Facebook strategy as well as our examples of planned intervention posts; and (3) receive recommendations for how to best integrate indoor tanning as a discussion topic within the intervention. Although most participants shared that Facebook was not their most frequently used social media platform, most were active users, and they felt the Facebook group feature was uniquely valuable in connecting them with larger groups of friends or others with shared interests. Participants in all 4 groups suggested broadening the intervention purpose and post topics beyond a tanning-specific focus to promoting physical and mental wellness as part of a healthy lifestyle. Messaging related to body acceptance and female empowerment was also suggested as key desirable topics associated with a healthy lifestyle. Participants also expressed interest in content design to help them establish healthy routines and habits (eg, eating, going to the gym, and sleeping). Most participants viewed tanning as a bad habit but not necessarily as inconsistent with a healthy lifestyle. For example, tanners did not often equate tanning with other behaviors considered to be "unhealthy," such as smoking or poor diet. However, when asked to reflect on the harms of tanning, members acknowledged that it is indeed a risky behavior and consistent with other unhealthy lifestyle choices. Finally, most participants felt they commonly encountered body image messaging and recommended we expand the discussion of body image to more broadly reflect pressures that young women experience beyond physical appearance, such as the pressure to live a "perfect" life that may cause mental stress and be inconsistent with their personal preferences.

We made several changes to the planned intervention based on this feedback. First, we refined the intervention framing, messaging, and post content to focus on promoting healthy self-care and empowerment to embrace a physical and mental wellness lifestyle. We named the intervention "empowerfulme" to reflect this focus. We also incorporated the concept of helpful self-care behaviors (ie, those with health benefits) as a contrast to unhelpful self-care behaviors, which were defined as "things we do that feel like self-care but often cause problems." We crafted new intervention content that encouraged participants to reflect on the short- and long-term consequences of unhelpful self-care, using tanning as an example of how unhelpful self-care may be perpetuated by idealistic thinking and societal messaging. Our incorporation of messaging and exercises based on ACT approaches was also in response to the described interest in learning more about self-acceptance and living by internal values over externally imposed values.

After content refinement, we conducted a usability trial in a sample of 29 frequent tanners using the same procedures as the fully powered RCT (except for multiple follow-up assessments). We experienced a slower-than-expected rate of recruitment and enrollment that delayed enrolling a sufficient number of tanners into Facebook groups to start groups with a targeted size of 25 participants. This led to an expansion of our recruitment strategy and study description. We also examined participants' interactions with our posts in this version and modified those that received low levels of engagement.

Intervention Engagement and Posting Strategy

Our intervention is administered within a study-specific "secret" Facebook group with membership and content limited to invited group members. Facebook groups ran for 8 weeks and contained 25 members each. Given that ideal intervention length and group size have not been empirically established and differ based on intervention content and objectives [74], we modeled our intervention on our pilot Facebook study. Our intervention included strategies found to boost participant involvement and group engagement in Facebook group–delivered health interventions for young adults [40,71,72,80,81]. We provided clear expectations, including checking the group study account at least once a day and "icebreaker" activities to increase comfort with commenting. We also used a young woman as the intervention moderator; all posts came from this account. Under the research team's guidance, the moderator commented or reacted to various posts (ie, liking them) to reinforce participant activity and encourage engagement.

Intervention content was delivered through posts made by the group moderator twice daily for 8 weeks, for a total of 112 posts. Each week addressed a thematic topic introduced in the first weekly post (Monday morning), with corresponding goal-setting and monitoring activities throughout the week (Table 1). Other posts were designed with activities and prompts to address change objectives, reinforce intervention messaging, or promote group engagement [40]. We also structured the content and timing of our posts to maximize engagement. Posts were written in a conversational tone and designed to take less than 3 minutes to read and comment on. A graphic designer enhanced the visual appeal of our posts and included relevant photos and videos [82]. We included polls and prompts in our posts for participants to share tips and successes with others [74,83].

Table 1. A description of the types, frequency, purpose, and content of the posts used for intervention and control group content.

Post type	Weekly frequency	Purpose and content
Goals	3	Participants set a goal related to the weekly topic (Monday evening), completed monitoring or check-in related to progress (Thursday morning), and reported back about goal progress (Sunday).
Reflection and discussions	5	To restructure key expectancies and beliefs with content that is discussion-based and designed to encourage reflection on one's ongoing behavior or speaking out against idealistic perspectives.
Reinforcement messages	2-3	Posts drawn from popular sources and designed to reinforce intervention messaging. Unlike other "active ingredient" posts, content may change between waves to accommodate ongoing events or provide recent and relevant articles.
Sharing content	2-3	Memes, inspirational quotes, and humorous posts intended to promote engagement and provide positive messaging.

Intervention Content

Our intervention strategy and content were developed through a mapping process [84] that included (1) identifying specific behavioral determinants (ie, factors that lead to tanning behavior) to target for change (described previously); (2) developing specific performance objectives (POs) to specify the changes in these targets that must occur to produce the overall behavioral outcome of reducing tanning; and (3) applying behavior change theory and techniques to produce intervention content to meet the POs.

POs 1-3 (Table 2) are designed to restructure tanning expectancies and body image beliefs that drive tanning intentions and idealistic thinking. Initial intervention content is framed within the context of considering that "self-care" behaviors can be either helpful (eg, exercise) or unhelpful (ie, they may provide some immediate benefit but have costs in the short- or long-run). Participants are asked to reflect on their self-care and reflect on their view of whether tanning is helpful or unhelpful self-care (POs 1 and 2). Participants are asked to consider the balance of benefits and problems with various forms of self-care and consider plans to increase helpful and reduce unhelpful self-care. Tanning-specific content encourages participants to reflect on underlying reasons and undesirable aspects of tanning to restructure beliefs by shifting the balance of pros and cons and thus promoting openness to behavioral change [41,42,47,48].

PO 3 also seeks to restructure beliefs by incorporating counterattitudinal advocacy techniques that effectively alter risky body image beliefs [49-54]. This approach has the person speak out against and question commonly held idealistic thoughts. If done effectively, the alternative perspectives considered during these exercises will conflict with idealistic thinking, producing psychological discomfort (ie, cognitive dissonance) [63]. The person is then motivated to seek psychological relief by altering their original unhealthy beliefs to be more consistent with the healthier perspective being advocated. Creating dissonance is optimized when participants share counter perspectives in group-based settings, which leads to more robust attitude and behavior change [53,56]. Accordingly, the intervention approach is to solicit counterattitudinal comments as responses to our Facebook group posts.

POs 4 and 5 are guided by the ACT concept of promoting acceptance. It can be difficult to completely change and mitigate the impact of strongly ingrained beliefs, such as those underlying idealistic thinking. ACT defines fused beliefs as routine thinking that can be self-critical and may lead to unwanted thoughts and feelings that drive habitual behaviors that are often unhealthy in an attempt to control these difficult experiences [57-59]. The intervention provides psychoeducational content and messaging that thoughts and feelings cannot be controlled and attempts to control them can create additional problems and perpetuate self-critical thinking. The intervention messages emphasize the value of willingness to experience negative thoughts and feelings by using mindfulness skills [57-59].

Finally, PO 6 encourages participants to consider the importance of making daily choices guided by higher-order values [57,60,61]. The intervention content encourages participants to consider the importance of broad values (eg, healthy lifestyle, helpful self-care, self-compassion, acceptance, and personal growth) and consider their alignment with societal messages and expectations promoting tanning. Participants identify their core values and contrast them with the values underlying societal messages about "perfection" in appearance and other aspects that often drive self-critical thinking. They are also asked to consider whether their ongoing behaviors are consistent with their core values and engage in goal-setting for enacting behaviors aligned with them [57,60,61].

Table 2. The intervention performance objectives (POs) that guided the content of corresponding intervention posts.

POs	Intervention content
PO 1: engage in helpful self-care behaviors	1a. Describe helpful self-care behaviors
	1b. Identify benefits of helpful self-care behaviors
	1c. Identify and enact plans for increasing helpful self-care behaviors
PO 2: reduce unhelpful self-care behaviors (with tanning as an example)	2a. Identify unhealthy forms of self-care, including tanning
	2b. Describe how tanning is not aligned with helpful self-care. Describe problems with tanning.
	2c. Identify and enact plans to reduce unhelpful self-care
PO 3: reduce buy-in to appearance messages about ideal women	3a. Critique societal expectations for women that lead to negative affect and unhealthy behaviors like tanning
	3b. Describe the messages underlying these expectations and their sources
	3c. Speak out against the problems caused by self-critical appearance values
PO 4: increase acceptance and willingness to experience uncomfortable feelings	4a. Identify problems with trying to control thoughts and feelings through behaviors like tanning
	4b. Understand the concept of acceptance
	4c. Express a commitment to adopting an acceptance mindset
PO 5: practice mindful acceptance	5a. Enact general skills for self-observation (ie, mindfulness skills)
	5b. Practice identifying self-critical beliefs and related feelings and sitting with them
PO 6: engage in behaviors that are consistent with personal growth values	6a. Describe the most important personal growth values
	6b. Evaluate alignment of current behaviors with growth values
	6c. Identify and enact plans to ensure values-consistent behavior

Measures

Self-Report Survey Items

Our primary outcomes are self-reports of indoor and outdoor tanning at the 8-month follow-up (Table 3). We chose items that are expert-recommended [85] and commonly used in tanning intervention trials [39,41,77]. Outcomes have open-ended response options to increase reporting accuracy and have been shown to be reliable compared to daily diary reports of behavior assessed over the same period [77,86]. Mediators and other measures are also listed in Table 3 and include measures adapted for tanning and validated in our previous research [38].

Table 3. The trial measures captured with self-report surveys.

Construct	Description of measures
Primary outcomes (measured at 8-month follow-up)	
Indoor tanning	• Open-ended reporting of the number of times participants used a tanning bed or booth in the past 8 months [85]
Outdoor tanning	• Open-ended reporting of the number of times spent outdoor tanning in the most recent summer (eg, between June 1, 2023, and August 31, 2023) [86]
Secondary outcomes	
Tanning intentions	• Intentions to use indoor tanning or spend time outdoor tanning (2 separate questions) in the next 12 months [39,41,77]
Long-term tanning	• Indoor and outdoor tanning outcomes assessed at the 18-month follow-up
Primary mediators (measured at 3-month follow-up)	
Tanning expectancies	• Beliefs related to tanning benefits (eg, tanning is attractive and relaxing) and risks (eg, appearance damage and skin cancer risk), tanning attitudes, and temptations to tan [87,88]
Tanning-specific body-image factors	• Items adapted from the Objectified Body Consciousness Scale to assess actively monitoring and comparing one's tans with others [38,89] • Internalization of the thin and tan ideal [21,35,38,88] • Appearance conversations with friends [90] • Items adapted from the Multidimensional Body Self-Relations Questionnaire to reflect tan dissatisfaction [38,91]
Openness to changing tanning	• Perceived difficulty in stopping indoor or outdoor tanning (2 separate questions) [92] • The Readiness to Change Questionnaire adapted to tanning behavior [93]
Exploratory mediators	
Values and values-consistent living	• Valued Living Questionnaire [94] • Valuing Questionnaire [95]
General body image acceptance	• The Acceptance and Action Questionnaire II [96] • Beliefs About Appearance Scale [97]
Perceptions and use of tanning alternatives	• For both sunless tanning products and spray-tanning, past 12 use, intention, attitudes, and self-efficacy [77,85]
Mindfulness	• Mindful Attention Awareness Scale [98]
Covariates	
Demographics	• Age, education, race, ethnicity, urban, rural, and SESa
Sun protection habits	• Typical use of sun protection (eg, shade and sunscreen) [99]
Use of social media	• Frequency of use of popular social media sites and integration of Facebook within social behaviors and daily routines [67,100]
Melanoma risk factors	• Natural hair color, eye color, skin type, skin reactivity to the sun, and history of sunburns [101]
Depression, anxiety, and stress	• The Depression Anxiety Stress Scale-10 [102]
Other health behaviors	• Alcohol use [103] • Cigarette use [104] • Physical activity [105] • Sedentary behavior [106] • Sleep [107] • Diet [108]

[a]SES: socio-economic status.

Facebook Engagement

The 3-month follow-up survey contained several Facebook-specific evaluation items, including perceived connectedness with a group, identification with posts and other group members, enjoyment, and ease of participation [79,109,110]. Items from the Audience Engagement Scale were used to measure key aspects of engagement with intervention content, including personal involvement (ie, was information judged to be personally relevant) and personal reflection (ie, was the knowledge acquired used to reevaluate personal conduct) [111]. Software (GRYTICS [112]) was also used to capture objective measures of participants' engagement, including comments and reactions to our posts or comments from others within our posts.

Statistical Analysis

Power

The primary outcome will be a sum of the 8-month indoor tanning outcome and the number of outdoor tanning sessions in the summer. One of the only intervention trials to focus on high-risk tanners was an in-person counseling intervention that produced significantly lower tanning rates among intervention participants at a 3-month follow-up [113]. This analysis suggested means for indoor tanning sessions of 4.40 (SD 7.74) for the intervention group and 11.78 (SD 13.03) for controls for a between-group difference of 7.38, which corresponded to a moderate to large size effect (0.69). Because our intervention is less intensive than a counseling intervention, we powered our study based on the scenario that the treatment effect will be at least 60% of the counseling study (corresponding to an effect size of 0.41). In our usability trial baseline data, the mean number of previous 3-month measures of indoor tanning and past summer outdoor tanning was 22.5 (SD 22.9; our means will likely be higher in the trial since the past 8-month indoor tanning will be used). Assuming similar means in our trial control group, an intervention effect of 0.41 would produce a mean of 13.1 (SD 22.9) tanning sessions in the intervention group, a difference of 9.4 total tanning sessions. Assuming these estimates from our follow-up means (ie, tanning control: mean 22.5, SD 22.9; tanning intervention, mean 9.4, SD 22.9), we will achieve 80% power with at least 186 participants (93 in each group). We anticipated a 70% follow-up rate at the primary 8-month outcome, which led us to target the enrollment of 266 participants to test the effects adequately.

Primary Outcome Analyses

Using intention-to-treat analyses, 2-sided tests for the effect of treatment will be conducted at the 0.05 level. If less than 10% (26/266) of outcomes are missing, we will consider data to be missing at random and apply multiple imputations. If missing data are more than 10% (27/266), we will examine patterns of missing data, including comparing demographics for those with and without missing outcomes. If missing data are not random, we will consider alternative missing data approaches. We will also conduct sensitivity analyses by first comparing baseline characteristics by condition and modifying the analyses to adjust for differences.

Multilevel models (eg, random coefficient) will test the primary study hypothesis that participants who received the intervention will report less total tanning behavior at 8-month follow-up compared to those who received the control. The level 1 model represents individuals nested within Facebook groups (the level 2 model). In particular, the effect of the intervention will be considered a random effect that may vary by block (ie, Facebook group). Thus, the model for analysis will use the following form as a starting point: $Y_{ij} = \beta_{0j} + \beta_{1j}T + \varepsilon_{ij}$, where Y_{ij} represents the number of tanning sessions used for the *i*th individual within the *j*th block, T is an indicator for whether the individual was randomized to the treatment or control. As such, the analysis accounts for (by including the random intercept β_{0j}) random differences between blocks (eg, previous tanning behavior) and allows the effect of the intervention to vary by block (with β_{1j}). If necessary, sensitivity analyses may control for individual-level covariates and appropriate transformations (ie, square root), or additional analysis methods will be considered if the normality assumption is strongly violated.

Mediation Analyses

Mediator analysis will be used to assess whether participant attitudinal factors (level 1 variables), including tanning expectancies, tanning-related body image factors and change perceptions, mediate the effect of the intervention. In particular, for each potential mediator, the 4 component steps [114] will be examined through regression models similar to those described above. The contribution of the mediated effect will be assessed directly using the approach recommended by Kenny and colleagues [115]. For multilevel models, we will calculate the product of the 2 pieces of the mediating path (from intervention group assignment to the mediating variable and from the mediating variable to the outcome). Bootstrap procedures will be used to formally test for the significance of the mediating pathway.

Ethical Considerations

The University of Kentucky Institutional Review Board reviewed and approved all study procedures before data collection (review number 56153 2019). A web-based informed consent form was included as the first page of the baseline survey, and it described the study procedures, privacy, confidentiality, risks, benefits, and data protection. Participants provided implied consent by agreeing to the consent form and starting the survey. All survey data were collected with a deidentified approach, using a unique participant identifier in place of a name or other personal information. The engagement data downloaded from Facebook were deidentified before storage or analysis by replacing participant names with their unique identifier. Our consent form also provided a description of the certificate of confidentiality provided by the National Institutes of Health as part of their funding support. Participants were emailed Amazon gift card incentives in the amount of US $30 for completing each of the baseline, 3-month, and 8-month surveys and US $40 for the 18-month follow-up.

Results

This trial was funded by the National Cancer Institute (R01 CA218068) in July 2017 and approved by the University of Kentucky Institutional Review Board in February 2020. Trial recruitment and enrollment occurred in 6 waves of data collection, starting in February 2022 and closing in May 2023. The study is closed to enrollment but remains open for follow-up. This protocol report was prepared before data analyses. As of February 2024, all participants have completed the 8-month follow-up assessment, and data collection is scheduled to close by the end of 2024 after the collection of the 18-month follow-up.

Discussion

Frequent tanning has been linked to an exponential increase in melanoma risk, but there are no established interventions targeting this group. This is the first study to test an intervention for frequent tanners in a fully powered trial. The prevailing approach to tanning interventions has been to raise awareness about the health risks as well as the appearance-damaging effects of tanning (eg, premature skin aging and wrinkling) [77,116-120]. These interventions have been delivered as educational-based interventions in various formats, with some incorporating UV facial photographs showing existing skin damage in combination with health risk information. Several trials have demonstrated the efficacy of these appearance-focused interventions when tested among typical tanners (eg, participants who have tanned at least once). However, the efficacy of this approach is likely to be limited among more frequent tanners [121] who generally report knowledge of and perceived susceptibility to the appearance risks of tanning but believe the immediate benefits outweigh the longer-term risks [20,122,123].

Beyond their primary focus on occasional tanners, appearance-focused interventions do not address key motives that are likely driving frequent tanning, including sociocultural influences, body image, and tanning dissatisfaction. This intervention approach represents an extension of the previous intervention literature by attempting to change core motives and influences that make tanning "worth the risks" among frequent tanners as well as incorporating key elements of an acceptance-based intervention. A small number of studies have demonstrated the potential value of using dissonance-based, body image–focused intervention strategies in melanoma prevention efforts [39,40,55,124]. This trial extends this work by (1) testing a fully powered skin cancer prevention program delivered entirely through social media; (2) delivering the intervention to both frequent indoor tanners and sunbathers; (3) broadening the intervention content focus beyond body image ideals to also challenging general expectations of how young women should look, think, and act; and (4) translating concepts from ACT principles to create acceptance-based content that encourage participants to accept that negative thoughts and feelings will happen and consider the importance of making daily choices that are guided by higher-order values.

Existing indoor tanning interventions have not been widely disseminated. The use of social media to deliver intervention content embeds the intervention into a platform that has become ingrained in the lives of our target young adult population and is a preferred method for exchanging information and communicating with peers [125]. A Facebook-delivered intervention can be integrated into individuals' existing, routine social media habits and avoids the burden of requiring users to find and use a stand-alone, unfamiliar website. The impact of this work lies in the potential for dissemination in a variety of contexts, given the use of a familiar and freely available intervention platform. This study will produce an intervention guide and content library of posts that could be implemented with minimal costs and staffing. Further, the intervention allows for social connection and self-expression among participants, which are key reasons people use social media [109]. These intervention features, along with the focus on positive body image, may increase the interest of potential intervention participants and thus lead to a more impactful intervention.

Limitations

Potential limitations to using Facebook include the fact that the nascent social media literature lacks firmly established, empirically based guidelines for effective practice. Thus, several of our choices (eg, content, length, and group size) are based on our experiences in pilot studies and available best practice guidelines. An alternative to the proposed Facebook approach would be retaining the previously tested website intervention. Websites have advantages, including increased control over content, easier user tracking, and the ability to deliver more in-depth content. However, website interventions have restrictive barriers for the target population, including the need to direct them to an unfamiliar website and a possible lack of interest in engaging on the website for any substantive period of time (as noted in our focus group research). The group discussions critical to the success of dissonance-based intervention are more easily implemented on the freely available Facebook setting but are more difficult to achieve with a website. There are also limitations in using Facebook to deliver content across several weeks. Developers of Facebook group support interventions for smoking cessation have raised concerns about the "empty room phenomenon," which describes the hesitancy of some social media users to engage with strangers [64]. We have engaged in several formative user-centered studies to inform the messaging and content of our intervention, but low engagement can occur in social media–delivered interventions. It is possible that users could alter the topic of discussion in ways not conducive to indoor tanning prevention or make unfavorable comments. We attempt to prevent this behavior by providing general guidelines for posting, daily monitoring, and following an established intervention manual for moderators.

Conclusions

This trial will contribute unique knowledge to the field of skin cancer prevention, as no fully powered trials have examined the efficacy of an intervention designed for frequent indoor or outdoor tanning. Our intervention builds from and meaningfully extends existing skin cancer interventions and incorporates innovative elements from body image and acceptance-based

interventions in its content and delivery. If efficacious, findings can inform best practices in skin cancer prevention and provide evidence of the value of translating principles from body image and acceptance-based interventions to target other behavioral contexts. The use of Facebook groups allows group-based interactions among participants, which can facilitate stronger changes in attitudes and behaviors and provide a platform to embed the intervention into individuals' everyday routines.

Acknowledgments

This work was supported by the National Cancer Institute (award R01CA218068; principal investigator JS), the Patient-Oriented and Population Sciences and Biostatistics and Bioinformatics Shared Resources of the University of Kentucky Markey Cancer Center (P30CA177558), and the National Institutes of Health (NIH)–funded National Center for Advancing Translational Sciences (UL1TR001998). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Data Availability

The data sets generated during this study are not publicly available due to the data sharing plan that was approved as part of our funded application and the certificate of confidentiality provided by the National Institutes of Health. Deidentified data sets are available from the corresponding author on reasonable request following the issuance of our final project funding report.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report by the National Cancer Institute (National Institutes of Health).
[PDF File (Adobe PDF File), 134 KB - resprot_v13i1e56562_app1.pdf]

References

1. Gilchrest BA. Molecular aspects of tanning. J Invest Dermatol 2011;131(E1):E14-E17 [FREE Full text] [doi: 10.1038/skinbio.2011.6] [Medline: 22094400]
2. Boniol M, Autier P, Boyle P, Gandini S. Cutaneous melanoma attributable to sunbed use: systematic review and meta-analysis. BMJ 2012;345:e4757 [FREE Full text] [doi: 10.1136/bmj.e4757] [Medline: 22833605]
3. Lazovich D, Vogel RI, Weinstock MA, Nelson HH, Ahmed RL, Berwick M. Association between indoor tanning and melanoma in younger men and women. JAMA Dermatol 2016;152(3):268-275 [FREE Full text] [doi: 10.1001/jamadermatol.2015.2938] [Medline: 26818409]
4. Wehner MR, Chren MM, Nameth D, Choudhry A, Gaskins M, Nead KT, et al. International prevalence of indoor tanning: a systematic review and meta-analysis. JAMA Dermatol 2014;150(4):390-400 [FREE Full text] [doi: 10.1001/jamadermatol.2013.6896] [Medline: 24477278]
5. Wehner MR, Shive ML, Chren MM, Han J, Qureshi AA, Linos E. Indoor tanning and non-melanoma skin cancer: systematic review and meta-analysis. BMJ 2012;345:e5909 [FREE Full text] [doi: 10.1136/bmj.e5909] [Medline: 23033409]
6. Chang C, Murzaku EC, Penn L, Abbasi NR, Davis PD, Berwick M, et al. More skin, more sun, more tan, more melanoma. Am J Public Health 2014;104(11):e92-e99 [FREE Full text] [doi: 10.2105/AJPH.2014.302185] [Medline: 25211764]
7. Chen ST, Geller AC, Tsao H. Update on the epidemiology of melanoma. Curr Dermatol Rep 2013;2(1):24-34 [FREE Full text] [doi: 10.1007/s13671-012-0035-5] [Medline: 23580930]
8. Miller KD, Fidler-Benaoudia M, Keegan TH, Hipp HS, Jemal A, Siegel RL. Cancer statistics for adolescents and young adults, 2020. CA Cancer J Clin 2020;70(6):443-459 [FREE Full text] [doi: 10.3322/caac.21637] [Medline: 32940362]
9. Geller AC. The story behind the sharp decline in US tanning bed rates. Am J Public Health 2018;108(8):971-973. [doi: 10.2105/AJPH.2018.304521] [Medline: 29995485]
10. Qin J, Holman DM, Jones SE, Berkowitz Z, Guy GP. State indoor tanning laws and prevalence of indoor tanning among US high school students, 2009-2015. Am J Public Health 2018;108(7):951-956 [FREE Full text] [doi: 10.2105/AJPH.2018.304414] [Medline: 29771612]
11. Stapleton JL, Hrywna M, Coups EJ, Delnevo C, Heckman CJ, Xu B. Prevalence and location of indoor tanning among high school students in New Jersey 5 years after the enactment of youth access restrictions. JAMA Dermatol 2020;156(11):1223-1227 [FREE Full text] [doi: 10.1001/jamadermatol.2020.2935] [Medline: 32876658]
12. Rodriguez-Acevedo AJ, Green AC, Sinclair C, van Deventer E, Gordon LG. Indoor tanning prevalence after the International Agency for Research on Cancer statement on carcinogenicity of artificial tanning devices: systematic review and meta-analysis. Br J Dermatol 2020;182(4):849-859. [doi: 10.1111/bjd.18412] [Medline: 31381131]
13. Bowers JM, Geller AC, Schofield E, Li Y, Hay JL. Indoor tanning trends among US adults, 2007-2018. Am J Public Health 2020;110(6):823-828. [doi: 10.2105/AJPH.2020.305605] [Medline: 32298165]

14. Drozdowski R, Gronbeck C, Feng H. Evaluating the impact of the COVID-19 pandemic and state restrictions on public interest in tanning: a Google Trends analysis. Clin Exp Dermatol 2021;46(8):1579-1582 [FREE Full text] [doi: 10.1111/ced.14774] [Medline: 34053109]
15. Bowers JM, Hamilton JG, Lobel M, Kanetsky PA, Hay JL. Sun exposure, tanning behaviors, and sunburn: examining activities associated with harmful ultraviolet radiation exposures in college students. J Prim Prev 2021;42(5):425-440 [FREE Full text] [doi: 10.1007/s10935-021-00638-z] [Medline: 34155576]
16. Daniel CL, Gassman NR, Fernandez AM, Bae S, Tan MCB. Intentional tanning behaviors among undergraduates on the United States' Gulf Coast. BMC Public Health 2018;18(1):441 [FREE Full text] [doi: 10.1186/s12889-018-5345-5] [Medline: 29615031]
17. Kream EJ, Watchmaker JD, Dover JS. TikTok sheds light on tanning: tanning is still popular and emerging trends pose new risks. Dermatol Surg 2022;48(9):1018-1021. [doi: 10.1097/DSS.0000000000003549] [Medline: 35862647]
18. Stapleton JL, Hillhouse J, Levonyan-Radloff K, Manne SL. Review of interventions to reduce ultraviolet tanning: need for treatments targeting excessive tanning, an emerging addictive behavior. Psychol Addict Behav 2017;31(8):962-978 [FREE Full text] [doi: 10.1037/adb0000289] [Medline: 28639816]
19. The Surgeon General's Call to Action to Prevent Skin Cancer. US Department of Health and Human Services. 2014. URL: https://www.ncbi.nlm.nih.gov/books/NBK247172/ [accessed 2024-01-20]
20. Hillhouse GCJ, Thompson JK, Jacobsen PB, Hillhouse J. Investigating the role of appearance-based factors in predicting sunbathing and tanning salon use. J Behav Med 2009;32(6):532-544. [doi: 10.1007/s10865-009-9224-5] [Medline: 19653089]
21. Cafri G, Thompson JK, Roehrig M, Rojas A, Sperry S, Jacobsen PB, et al. Appearance motives to tan and not tan: evidence for validity and reliability of a new scale. Ann Behav Med 2008;35(2):209-220 [FREE Full text] [doi: 10.1007/s12160-008-9022-2] [Medline: 18365298]
22. Hillhouse JJ, Turrisi R, Heckman C, Manne S. Motivations for tanning: a review of theoretical models of indoor tanning use. In: Shedding Light on Artificial Tanning. New York, NY: Springer; 2011.
23. Lake JR, Thomson CS, Twelves CJ, Davies EA. A qualitative investigation of the motivations, experiences and views of female sunbed users under the age of 18 in England. J Public Health (Oxf) 2014;36(1):56-64 [FREE Full text] [doi: 10.1093/pubmed/fds107] [Medline: 23365261]
24. Noar SM, Myrick JG, Zeitany A, Kelley D, Morales-Pico B, Thomas NE. Testing a social cognitive theory-based model of indoor tanning: implications for skin cancer prevention messages. Health Commun 2015;30(2):164-174. [doi: 10.1080/10410236.2014.974125] [Medline: 25470441]
25. Hillhouse J, Turrisi R, Shields AL. Patterns of indoor tanning use: implications for clinical interventions. Arch Dermatol 2007;143(12):1530-1535 [FREE Full text] [doi: 10.1001/archderm.143.12.1530] [Medline: 18087003]
26. Kelley DE, Noar SM, Myrick JG, Morales-Pico B, Zeitany A, Thomas NE. An empirical analysis of indoor tanners: implications for audience segmentation in campaigns. J Health Commun 2016;21(5):564-574. [doi: 10.1080/10810730.2015.1114051] [Medline: 27115046]
27. Stapleton JL, Crabtree BF. "These people, you just guide them until they become these people": learning to become a frequent indoor tanner. BMC Psychol 2017;5(1):11 [FREE Full text] [doi: 10.1186/s40359-017-0181-4] [Medline: 28376928]
28. Eden M, Lyons S, Lorigan P, Payne K, Green AC, Epton T. Reasons for using indoor tanning devices: a systematic review of qualitative evidence. Br J Health Psychol 2023;28(1):22-46 [FREE Full text] [doi: 10.1111/bjhp.12610] [Medline: 35808920]
29. Diehl K, Breitbart EW, de Buhr Y, Schneider S, Görig T. Shift in place of tanning bed use from tanning salons to spa, fitness, and beauty facilities: a trend perspective. Photodermatol Photoimmunol Photomed 2022;38(1):83-85 [FREE Full text] [doi: 10.1111/phpp.12711] [Medline: 34157183]
30. Stapleton JL, Darabos K, Hudson SV, Greene K, Manne SL. "OMG I'm so pale. Is everyone going to think I look weird?": a focus group study of social influences and body image on indoor tanning. 2015 Presented at: Annual Society of Behavioral Medicine Meeting; April 2015; San Antonio, TX.
31. Fredrickson BL, Roberts TA. Objectification theory: toward understanding women's lived experiences and mental health risks. Psychol Women Q 2016;21(2):173-206. [doi: 10.1111/j.1471-6402.1997.tb00108.x]
32. Thompson JK, Stice E. Thin-ideal internalization: mounting evidence for a new risk factor for body-image disturbance and eating pathology. Curr Dir Psychol Sci 2016;10(5):181-183. [doi: 10.1111/1467-8721.00144]
33. Cho H, Lee S, Wilson K. Magazine exposure, tanned women stereotypes, and tanning attitudes. Body Image 2010;7(4):364-367 [FREE Full text] [doi: 10.1016/j.bodyim.2010.04.002] [Medline: 20573553]
34. Darlow SD, Heckman CJ, Munshi T. Tan and thin? Associations between attitudes toward thinness, motives to tan and tanning behaviors in adolescent girls. Psychol Health Med 2016;21(5):618-624. [doi: 10.1080/13548506.2015.1093643] [Medline: 26448364]
35. Gillen MM, Markey CN. The role of body image and depression in tanning behaviors and attitudes. Behav Med 2012;38(3):74-82. [doi: 10.1080/08964289.2012.685499] [Medline: 22873732]
36. Prichard I, Kneebone A, Hutchinson AD, Wilson C. The relationship between skin tone dissatisfaction and sun tanning behaviour. Aust J Psychol 2020;66(3):168-174 [FREE Full text] [doi: 10.1111/ajpy.12039]

37. Prior SM, Fenwick KD, Peterson JC. Adolescents' reasons for tanning and appearance motives: a preliminary study. Body Image 2014;11(1):93-96. [doi: 10.1016/j.bodyim.2013.09.004] [Medline: 24129215]
38. Stapleton JL, Manne SL, Greene K, Darabos K, Carpenter A, Hudson SV, et al. Sociocultural experiences, body image, and indoor tanning among young adult women. J Health Psychol 2017;22(12):1582-1590 [FREE Full text] [doi: 10.1177/1359105316631198] [Medline: 26929174]
39. Stapleton JL, Manne SL, Darabos K, Greene K, Ray AE, Turner AL, et al. Randomized controlled trial of a web-based indoor tanning intervention: acceptability and preliminary outcomes. Health Psychol 2015;34(S):1278-1285 [FREE Full text] [doi: 10.1037/hea0000254] [Medline: 26651469]
40. Stapleton JL, Manne SL, Day AK, Levonyan-Radloff K, Pagoto SL. Healthy body image intervention delivered to young women via Facebook groups: formative study of engagement and acceptability. JMIR Res Protoc 2018;7(2):e54 [FREE Full text] [doi: 10.2196/resprot.9429] [Medline: 29463495]
41. Stapleton JL, Ray AE, Glenn SD, McLouth LE, Parmar V, Manne SL. A randomized controlled trial of a web-based personalized feedback intervention targeting frequent indoor tanning bed users: engagement, acceptability, and preliminary behavioral outcomes. J Health Psychol 2022;27(4):923-935. [doi: 10.1177/1359105320982038] [Medline: 33353412]
42. Hardcastle SJ, Hancox J, Hattar A, Maxwell-Smith C, Thøgersen-Ntoumani C, Hagger MS. Motivating the unmotivated: how can health behavior be changed in those unwilling to change? Front Psychol 2015;6:835 [FREE Full text] [doi: 10.3389/fpsyg.2015.00835] [Medline: 26136716]
43. Glanz K, Jordan A, Lazovich D, Bleakley A. Frequent indoor tanners' beliefs about indoor tanning and cessation. Am J Health Promot 2019;33(2):293-299. [doi: 10.1177/0890117118784235] [Medline: 29973065]
44. Harrington CR, Beswick TC, Leitenberger J, Minhajuddin A, Jacobe HT, Adinoff B. Addictive-like behaviours to ultraviolet light among frequent indoor tanners. Clin Exp Dermatol 2011;36(1):33-38. [doi: 10.1111/j.1365-2230.2010.03882.x] [Medline: 20545951]
45. Mosher CE, Danoff-Burg S. Addiction to indoor tanning: relation to anxiety, depression, and substance use. Arch Dermatol 2010;146(4):412-417 [FREE Full text] [doi: 10.1001/archdermatol.2009.385] [Medline: 20404230]
46. Poorsattar SP, Hornung RL. UV light abuse and high-risk tanning behavior among undergraduate college students. J Am Acad Dermatol 2007;56(3):375-379. [doi: 10.1016/j.jaad.2006.08.064] [Medline: 17257709]
47. Hardcastle S, Blake N, Hagger MS. The effectiveness of a motivational interviewing primary-care based intervention on physical activity and predictors of change in a disadvantaged community. J Behav Med 2012;35(3):318-333 [FREE Full text] [doi: 10.1007/s10865-012-9417-1] [Medline: 22476812]
48. Neal DJ, Carey KB. Developing discrepancy within self-regulation theory: use of personalized normative feedback and personal strivings with heavy-drinking college students. Addict Behav 2004;29(2):281-297. [doi: 10.1016/j.addbeh.2003.08.004] [Medline: 14732417]
49. Becker CB, Smith LM, Ciao AC. Reducing eating disorder risk factors in sorority members: a randomized trial. Behav Therapy 2005;36(3):245-253. [doi: 10.1016/s0005-7894(05)80073-5]
50. Heinicke BE, Paxton SJ, McLean SA, Wertheim EH. Internet-delivered targeted group intervention for body dissatisfaction and disordered eating in adolescent girls: a randomized controlled trial. J Abnorm Child Psychol 2007;35(3):379-391. [doi: 10.1007/s10802-006-9097-9] [Medline: 17243014]
51. Roehrig M, Thompson JK, Brannick M, van den Berg P. Dissonance-based eating disorder prevention program: a preliminary dismantling investigation. Int J Eat Disord 2006;39(1):1-10. [doi: 10.1002/eat.20217] [Medline: 16254869]
52. Stewart DA, Carter JC, Drinkwater J, Hainsworth J, Fairburn CG. Modification of eating attitudes and behavior in adolescent girls: a controlled study. Int J Eat Disord 2001;29(2):107-118. [doi: 10.1002/1098-108x(200103)29:2<107::aid-eat1000>3.0.co;2-1] [Medline: 11429973]
53. Stice E, Rohde P, Butryn M, Menke KS, Marti CN. Randomized controlled pilot trial of a novel dissonance-based group treatment for eating disorders. Behav Res Ther 2015;65:67-75 [FREE Full text] [doi: 10.1016/j.brat.2014.12.012] [Medline: 25577189]
54. Stice E, Rohde P, Durant S, Shaw H. A preliminary trial of a prototype internet dissonance-based eating disorder prevention program for young women with body image concerns. J Consult Clin Psychol 2012;80(5):907-916 [FREE Full text] [doi: 10.1037/a0028016] [Medline: 22506791]
55. Chait SR, Thompson JK, Jacobsen PB. Preliminary development and evaluation of an appearance-based dissonance induction intervention for reducing UV exposure. Body Image 2015;12:68-72. [doi: 10.1016/j.bodyim.2014.09.004] [Medline: 25462883]
56. Cruwys T, Haslam SA, Fox NE, McMahon H. "That's not what we do": evidence that normative change is a mechanism of action in group interventions. Behav Res Ther 2015;65:11-17. [doi: 10.1016/j.brat.2014.12.003] [Medline: 25544661]
57. Harris R. ACT Made Simple: An Easy-To-Read Primer on Acceptance and Commitment Therapy. Oakland, CA: New Harbinger Publications; 2019.
58. LeJeune C. The Worry Trap: How to Free Yourself from Worry & Anxiety Using Acceptance and Commitment Therapy. Oakland, CA: New Harbinger Publications; 2007.
59. Thompson BL, Luoma JB, LeJeune JT. Using acceptance and commitment therapy to guide exposure-based interventions for posttraumatic stress disorder. J Contemp Psychother 2013;43(3):133-140. [doi: 10.1007/s10879-013-9233-0]

60. LeJeune J, Luoma J. 12 Values in acceptance and commitment therapy. In: Twohig MP, Levin ME, Petersen JM, editors. The Oxford Handbook of Acceptance and Commitment Therapy. New York, NY: Oxford University Press; 2023:271-294.
61. LeJeune J, Luoma JB. Values in Therapy: A Clinician's Guide to Helping Clients Explore Values, Increase Psychological Flexibility, and Live a More Meaningful Life. Oakland, CA: New Harbinger Publications; 2019.
62. Green M, Scott N, Diyankova I, Gasser C. Eating disorder prevention: an experimental comparison of high level dissonance, low level dissonance, and no-treatment control. Eat Disord 2005;13(2):157-169. [doi: 10.1080/10640260590918955] [Medline: 16864339]
63. Stice E, Shaw H, Becker CB, Rohde P. Dissonance-based interventions for the prevention of eating disorders: using persuasion principles to promote health. Prev Sci 2008;9(2):114-128 [FREE Full text] [doi: 10.1007/s11121-008-0093-x] [Medline: 18506621]
64. Cobb NK, Graham AL, Byron MJ, Niaura RS, Abrams DB, Workshop Participants. Online social networks and smoking cessation: a scientific research agenda. J Med Internet Res 2011;13(4):e119 [FREE Full text] [doi: 10.2196/jmir.1911] [Medline: 22182518]
65. Dahl AA, Hales SB, Turner-McGrievy GM. Integrating social media into weight loss interventions. Curr Opin Psychol 2016;9:11-15. [doi: 10.1016/j.copsyc.2015.09.018]
66. Auxier B, Anderson M. Social media use in 2021. Pew Research Center. 2021. URL: https://www.pewresearch.org/internet/2021/04/07/social-media-use-in-2021/ [accessed 2023-12-15]
67. Stapleton JL, Hillhouse J, Coups EJ, Pagoto S. Social media use and indoor tanning among a national sample of young adult nonHispanic white women: a cross-sectional study. J Am Acad Dermatol 2016;75(1):218-220 [FREE Full text] [doi: 10.1016/j.jaad.2016.01.043] [Medline: 27317521]
68. Blashill AJ. Psychosocial correlates of frequent indoor tanning among adolescent boys. Body Image 2013;10(2):259-262 [FREE Full text] [doi: 10.1016/j.bodyim.2012.11.005] [Medline: 23276832]
69. Guy GP, Berkowitz Z, Watson M, Holman DM, Richardson LC. Indoor tanning among young non-Hispanic white females. JAMA Intern Med 2013;173(20):1920-1922 [FREE Full text] [doi: 10.1001/jamainternmed.2013.10013] [Medline: 23959651]
70. O'Riordan DL, Field AE, Geller AC, Brooks DR, Aweh G, Colditz GA, et al. Frequent tanning bed use, weight concerns, and other health risk behaviors in adolescent females (United States). Cancer Causes Control 2006;17(5):679-686. [doi: 10.1007/s10552-005-0453-9] [Medline: 16633915]
71. Cavallo DN, Tate DF, Ries AV, Brown JD, DeVellis RF, Ammerman AS. A social media-based physical activity intervention: a randomized controlled trial. Am J Prev Med 2012;43(5):527-532 [FREE Full text] [doi: 10.1016/j.amepre.2012.07.019] [Medline: 23079176]
72. Napolitano MA, Hayes S, Bennett GG, Ives AK, Foster GD. Using facebook and text messaging to deliver a weight loss program to college students. Obesity (Silver Spring) 2013;21(1):25-31 [FREE Full text] [doi: 10.1002/oby.20232] [Medline: 23505165]
73. Pechmann C, Pan L, Delucchi K, Lakon CM, Prochaska JJ. Development of a Twitter-based intervention for smoking cessation that encourages high-quality social media interactions via automessages. J Med Internet Res 2015;17(2):e50 [FREE Full text] [doi: 10.2196/jmir.3772] [Medline: 25707037]
74. Pagoto S, Waring ME, May CN, Ding EY, Kunz WH, Hayes R, et al. Adapting behavioral interventions for social media delivery. J Med Internet Res 2016;18(1):e24 [FREE Full text] [doi: 10.2196/jmir.5086] [Medline: 26825969]
75. Online research panels and samples. Qualtrics. URL: https://www.qualtrics.com/uk/research-services/online-sample/?rid=ip&prevsite=en&newsite=uk&geo=GB&geomatch=uk [accessed 2024-01-10]
76. Hillhouse J, Turrisi R, Scaglione NM, Cleveland MJ, Baker K, Florence LC. A web-based intervention to reduce indoor tanning motivations in adolescents: a randomized controlled trial. Prev Sci 2017;18(2):131-140 [FREE Full text] [doi: 10.1007/s11121-016-0698-4] [Medline: 27549602]
77. Hillhouse J, Turrisi R, Stapleton J, Robinson J. A randomized controlled trial of an appearance-focused intervention to prevent skin cancer. Cancer 2008;113(11):3257-3266 [FREE Full text] [doi: 10.1002/cncr.23922] [Medline: 18937268]
78. Reed DD. Google search trends for tanning salons: temporal patterns indicate peak interest in mid spring. J Am Acad Dermatol 2015;73(6):1055-1056. [doi: 10.1016/j.jaad.2015.09.012] [Medline: 26470890]
79. Lin KY, Lu HP. Intention to continue using Facebook fan pages from the perspective of social capital theory. Cyberpsychol Behav Soc Netw 2011;14(10):565-570. [doi: 10.1089/cyber.2010.0472] [Medline: 21381968]
80. Ramo DE, Thrul J, Chavez K, Delucchi KL, Prochaska JJ. Feasibility and quit rates of the tobacco status project: a Facebook smoking cessation intervention for young adults. J Med Internet Res 2015;17(12):e291 [FREE Full text] [doi: 10.2196/jmir.5209] [Medline: 26721211]
81. Valle CG, Tate DF, Mayer DK, Allicock M, Cai J. A randomized trial of a Facebook-based physical activity intervention for young adult cancer survivors. J Cancer Surviv 2013;7(3):355-368 [FREE Full text] [doi: 10.1007/s11764-013-0279-5] [Medline: 23532799]
82. Maher C, Ryan J, Kernot J, Podsiadly J, Keenihan S. Social media and applications to health behavior. Curr Opin Psychol 2016;9:50-55. [doi: 10.1016/j.copsyc.2015.10.021]

83. Hales SB, Davidson C, Turner-McGrievy GM. Varying social media post types differentially impacts engagement in a behavioral weight loss intervention. Transl Behav Med 2014;4(4):355-362 [FREE Full text] [doi: 10.1007/s13142-014-0274-z] [Medline: 25584084]
84. Bartholomew LK, Parcel GS, Kok G. Intervention mapping: a process for developing theory- and evidence-based health education programs. Health Educ Behav 1998;25(5):545-563. [doi: 10.1177/109019819802500502] [Medline: 9768376]
85. Lazovich D, Stryker JE, Mayer JA, Hillhouse J, Dennis LK, Pichon L, et al. Measuring nonsolar tanning behavior: indoor and sunless tanning. Arch Dermatol 2008;144(2):225-230 [FREE Full text] [doi: 10.1001/archdermatol.2007.45] [Medline: 18283180]
86. Hillhouse J, Turrisi R, Jaccard J, Robinson J. Accuracy of self-reported sun exposure and sun protection behavior. Prev Sci 2012;13(5):519-531 [FREE Full text] [doi: 10.1007/s11121-012-0278-1] [Medline: 22855253]
87. Hillhouse JJ, Turrisi R, Kastner M. Modeling tanning salon behavioral tendencies using appearance motivation, self-monitoring and the theory of planned behavior. Health Educ Res 2000;15(4):405-414 [FREE Full text] [doi: 10.1093/her/15.4.405] [Medline: 11066458]
88. Noar SM, Myrick JG, Morales-Pico B, Thomas NE. Development and validation of the Comprehensive Indoor Tanning Expectations Scale. JAMA Dermatol 2014;150(5):512-521 [FREE Full text] [doi: 10.1001/jamadermatol.2013.9086] [Medline: 24500373]
89. McKinley NM, Hyde JS. The objectified body consciousness scale: development and validation. Psychol Women Q 2016;20(2):181-215. [doi: 10.1111/j.1471-6402.1996.tb00467.x]
90. Jones DC, Vigfusdottir TH, Lee Y. Body image and the appearance culture among adolescent girls and boys: an examination of friend conversations, peer criticism, appearance magazines, and the internalization of appearance ideals. J Adolesc Res 2016;19(3):323-339. [doi: 10.1177/0743558403258847]
91. Cash TF. User's Manual for the Multidimensional Body-Self Relations Questionnaire. Norfolk, VA: Old Dominion University; 2000.
92. Zeller S, Lazovich D, Forster J, Widome R. Do adolescent indoor tanners exhibit dependency? J Am Acad Dermatol 2006;54(4):589-596. [doi: 10.1016/j.jaad.2005.12.038] [Medline: 16546579]
93. Heather N, Rollnick S, Bell A. Predictive validity of the readiness to change questionnaire. Addiction 1993;88(12):1667-1677. [doi: 10.1111/j.1360-0443.1993.tb02042.x] [Medline: 8130706]
94. Wilson KG, Sandoz EK, Kitchens J, Roberts M. The valued living questionnaire: defining and measuring valued action within a behavioral framework. Psychol Rec 2017;60(2):249-272. [doi: 10.1007/bf03395706]
95. Smout M, Davies M, Burns N, Christie A. Development of the Valuing Questionnaire (VQ). J Contextual Behav Sci 2014;3(3):164-172. [doi: 10.1016/j.jcbs.2014.06.001]
96. Bond FW, Hayes SC, Baer RA, Carpenter KM, Guenole N, Orcutt HK, et al. Preliminary psychometric properties of the Acceptance and Action Questionnaire-II: a revised measure of psychological inflexibility and experiential avoidance. Behav Ther 2011;42(4):676-688. [doi: 10.1016/j.beth.2011.03.007] [Medline: 22035996]
97. Spangler DL, Stice E. Validation of the beliefs about appearance scale. Cognitive Ther Res 2001;25:813-827. [doi: 10.1023/A:1012931709434]
98. Brown KW, Ryan RM. The benefits of being present: mindfulness and its role in psychological well-being. J Pers Soc Psychol 2003;84(4):822-848. [doi: 10.1037/0022-3514.84.4.822] [Medline: 12703651]
99. Glanz K, Yaroch AL, Dancel M, Saraiya M, Crane LA, Buller DB, et al. Measures of sun exposure and sun protection practices for behavioral and epidemiologic research. Arch Dermatol 2008;144(2):217-222 [FREE Full text] [doi: 10.1001/archdermatol.2007.46] [Medline: 18283179]
100. Jenkins-Guarnieri MA, Wright SL, Johnson B. Development and validation of a social media use integration scale. Psychol Pop Media Cult 2013;2(1):38-50. [doi: 10.1037/a0030277]
101. Glanz K, Schoenfeld E, Weinstock MA, Layi G, Kidd J, Shigaki DM. Development and reliability of a brief skin cancer risk assessment tool. Cancer Detect Prev 2003;27(4):311-315. [doi: 10.1016/s0361-090x(03)00094-1] [Medline: 12893080]
102. Halford WK, Frost ADJ. Depression anxiety stress scale-10: a brief measure for routine psychotherapy outcome and progress assessment. Behav Change 2021;38(4):221-234. [doi: 10.1017/bec.2021.12]
103. Nelson DE, Naimi TS, Brewer RD, Roeber J. US state alcohol sales compared to survey data, 1993-2006. Addiction 2010;105(9):1589-1596. [doi: 10.1111/j.1360-0443.2010.03007.x] [Medline: 20626370]
104. Marshall LT, Schooley M, Ryan H, Cox P, Easton A. Youth Tobacco Surveillance; United States, 2001-2002. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention (CDC); 2006.
105. Gu JK, Charles LE, Ma CC, Andrew ME, Fekedulegn D, Hartley TA, et al. Prevalence and trends of leisure-time physical activity by occupation and industry in U.S. workers: the National Health Interview Survey 2004-2014. Ann Epidemiol 2016;26(10):685-692 [FREE Full text] [doi: 10.1016/j.annepidem.2016.08.004] [Medline: 27659584]
106. Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 2003;35(8):1381-1395 [FREE Full text] [doi: 10.1249/01.MSS.0000078924.61453.FB] [Medline: 12900694]
107. Buysse DJ, Reynolds CF, Monk TH, Hoch CC, Yeager AL, Kupfer DJ. Quantification of subjective sleep quality in healthy elderly men and women using the Pittsburgh Sleep Quality Index (PSQI). Sleep 1991;14(4):331-338. [Medline: 1947597]

108. Merlo CL, Jones SE, Michael SL, Chen TJ, Sliwa SA, Lee SH, et al. Dietary and physical activity behaviors among high school students—youth risk behavior survey, United States, 2019. MMWR Suppl 2020;69(1):64-76 [FREE Full text] [doi: 10.15585/mmwr.su6901a8] [Medline: 32817612]
109. Moreno MA, Kota R, Schoohs S, Whitehill JM. The Facebook influence model: a concept mapping approach. Cyberpsychol Behav Soc Netw 2013;16(7):504-511 [FREE Full text] [doi: 10.1089/cyber.2013.0025] [Medline: 23621717]
110. Smock AD, Ellison NB, Lampe C, Wohn DY. Facebook as a toolkit: a uses and gratification approach to unbundling feature use. Comput Hum Behav 2011;27(6):2322-2329. [doi: 10.1016/j.chb.2011.07.011]
111. Greene K, Yanovitzky I, Carpenter A, Banerjee SC, Magsamen-Conrad K, Hecht ML, et al. A theory-grounded measure of adolescents' response to a media literacy intervention. J Media Lit Educ 2015;7(2):35-49. [Medline: 28042522]
112. GRYTICS. URL: https://grytics.com/ [accessed 2024-02-21]
113. Turrisi R, Mastroleo NR, Stapleton J, Mallett K. A comparison of 2 brief intervention approaches to reduce indoor tanning behavior in young women who indoor tan very frequently. Arch Dermatol 2008;144(11):1521-1524 [FREE Full text] [doi: 10.1001/archderm.144.11.1521] [Medline: 19015434]
114. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. J Pers Soc Psychol 1986;51(6):1173-1182. [doi: 10.1037//0022-3514.51.6.1173] [Medline: 3806354]
115. Kenny DA, Korchmaros JD, Bolger N. Lower level mediation in multilevel models. Psychol Methods 2003;8(2):115-128. [doi: 10.1037/1082-989x.8.2.115] [Medline: 12924810]
116. Gibbons FX, Gerrard M, Lane DJ, Mahler HIM, Kulik JA. Using UV photography to reduce use of tanning booths: a test of cognitive mediation. Health Psychol 2005;24(4):358-363. [doi: 10.1037/0278-6133.24.4.358] [Medline: 16045371]
117. Greene K, Brinn LS. Messages influencing college women's tanning bed use: statistical versus narrative evidence format and a self-assessment to increase perceived susceptibility. J Health Commun 2003;8(5):443-461. [doi: 10.1080/713852118] [Medline: 14530147]
118. Greene K, Campo S, Banerjee SC. Comparing normative, anecdotal, and statistical risk evidence to discourage tanning bed use. Commun Q 2010;58(2):111-132 [FREE Full text] [doi: 10.1080/01463371003773366]
119. Hillhouse JJ, Turrisi R. Examination of the efficacy of an appearance-focused intervention to reduce UV exposure. J Behav Med 2002;25(4):395-409. [doi: 10.1023/a:1015870516460] [Medline: 12136499]
120. Lazovich D, Choi K, Rolnick C, Jackson JM, Forster J, Southwell B. An intervention to decrease adolescent indoor tanning: a multi-method pilot study. J Adolesc Health 2013;52(5 Suppl):S76-S82 [FREE Full text] [doi: 10.1016/j.jadohealth.2012.08.009] [Medline: 23601614]
121. Stapleton J, Turrisi R, Hillhouse J, Robinson JK, Abar B. A comparison of the efficacy of an appearance-focused skin cancer intervention within indoor tanner subgroups identified by latent profile analysis. J Behav Med 2010;33(3):181-190. [doi: 10.1007/s10865-009-9246-z] [Medline: 20058183]
122. Banerjee SC, Hay JL, Greene K. College students' cognitive rationalizations for tanning bed use: an exploratory study. Arch Dermatol 2012;148(6):761-762 [FREE Full text] [doi: 10.1001/archdermatol.2012.398] [Medline: 22710466]
123. Knight JM, Kirincich AN, Farmer ER, Hood AF. Awareness of the risks of tanning lamps does not influence behavior among college students. Arch Dermatol 2002;138(10):1311-1315 [FREE Full text] [doi: 10.1001/archderm.138.10.1311] [Medline: 12374536]
124. Cho H, Yu B, Cannon J, Zhu YM. Efficacy of a media literacy intervention for indoor tanning prevention. J Health Commun 2018;23(7):643-651 [FREE Full text] [doi: 10.1080/10810730.2018.1500659] [Medline: 30058942]
125. Sundar SS, Limperos AM. Uses and Grats 2.0: new gratifications for new media. J Broadcast Electron Media 2013;57(4):504-525. [doi: 10.1080/08838151.2013.845827]

Abbreviations

ACT: acceptance and commitment therapy
PO: performance objective
RCT: randomized controlled trial

Edited by A Mavragani; submitted 07.02.24; this is a non–peer-reviewed article;accepted 09.02.24; published 19.03.24.

Please cite as:
Stapleton JL, Manne SL, Pagoto SL, Leip A, Greene K, Hillhouse JJ, Merritt AS, Shelton BJ
A Social Media–Delivered Melanoma Prevention Program for Young Women Engaged in Frequent UV Tanning: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2024;13:e56562
URL: https://www.researchprotocols.org/2024/1/e56562
doi:10.2196/56562
PMID:38502173

Protocol

Efficacy of Integrating the Management of Pain and Addiction via Collaborative Treatment (IMPACT) in Individuals With Chronic Pain and Opioid Use Disorder: Protocol for a Randomized Clinical Trial of a Digital Cognitive Behavioral Treatment

R Ross MacLean[1,2], PhD; Brett Ankawi[2,3], PhD; Mary A Driscoll[2,3], PhD; Melissa A Gordon[2], MFA; Tami L Frankforter[2], BA; Charla Nich[2], MS; Sara K Szollosy[1], MPH; Jennifer M Loya[2], PhD; Larissa Brito[2], BS; Margaridha I P Ribeiro[2], BA; Sara N Edmond[2,3], PhD; William C Becker[2,3], MD; Steve Martino[1,2], PhD; Mehmet Sofuoglu[1,2], MD, PhD; Alicia A Heapy[2,3], PhD

[1]VA Connecticut Healthcare System, West Haven, CT, United States

[2]School of Medicine, Yale University, New Haven, CT, United States

[3]Pain Research, Informatics, Multimorbidities, and Education (PRIME) Health Services Research and Development Center of Innovation, VA Connecticut Healthcare System, West Haven, CT, United States

Corresponding Author:
R Ross MacLean, PhD
VA Connecticut Healthcare System
950 Campbell Ave
West Haven, CT, 06516
United States
Phone: 1 2039325711
Email: ross.maclean@yale.edu

Abstract

Background: Chronic pain is common among individuals with opioid use disorder (OUD) who are maintained on medications for OUD (MOUD; eg, buprenorphine or methadone). Chronic pain is associated with worse retention and higher levels of substance use. Treatment of individuals with chronic pain receiving MOUD can be challenging due to their increased clinical complexity. Given the acute and growing nature of the opioid crisis, MOUD is increasingly offered in a wide range of settings, where high-quality, clinician-delivered, empirically validated behavioral treatment for chronic pain may not be available. Therefore, digital treatments that support patient self-management of chronic pain and OUD have the potential for wider implementation to fill this gap.

Objective: This study aims to evaluate the efficacy of Integrating the Management of Pain and Addiction via Collaborative Treatment (IMPACT), an interactive digital treatment program with asynchronous coach feedback, compared to treatment as usual (TAU) in individuals with chronic pain and OUD receiving MOUD.

Methods: Adult participants (n=160) receiving MOUD and reporting bothersome or high-impact chronic pain will be recruited from outpatient opioid treatment programs in Connecticut (United States) and randomized 1:1 to either IMPACT+TAU or TAU only. Participants randomized to IMPACT+TAU will complete an interactive digital treatment that includes 9 modules promoting training in pain and addiction coping skills and a progressive walking program. The program is augmented with a weekly personalized voice message from a trained coach based on daily participant-reported pain intensity and interference, craving to use opioids, sleep quality, daily steps, pain self-efficacy, MOUD adherence, and engagement with IMPACT collected through digital surveys. Outcomes will be assessed at 3, 6, and 9 months post randomization. The primary outcome is MOUD retention at 3 months post randomization (ie, post treatment). Secondary outcomes include pain interference, physical functioning, MOUD adherence, substance use, craving, pain intensity, sleep disturbance, pain catastrophizing, and pain self-efficacy. Semistructured qualitative interviews with study participants (n=34) randomized to IMPACT (completers and noncompleters) will be conducted to evaluate the usability and quality of the program and its outcomes.

Results: The study has received institutional review board approval and began recruitment at 1 site in July 2022. Recruitment at a second site started in January 2023, with a third and final site anticipated to begin recruitment in January 2024. Data collection is expected to continue through June 2025.

Conclusions: Establishing efficacy for a digital treatment for addiction and chronic pain that can be integrated into MOUD clinics will provide options for individuals with OUD, which reduce barriers to behavioral treatment. Participant feedback on the intervention will inform updates or modifications to improve engagement and efficacy.

Trial Registration: ClinicalTrials.gov NCT05204576; https://clinicaltrials.gov/ct2/show/NCT05204576

International Registered Report Identifier (IRRID): DERR1-10.2196/54342

(JMIR Res Protoc 2024;13:e54342) doi:10.2196/54342

KEYWORDS

chronic pain; digital treatment; medications for opioid use disorder; methadone; opioid use disorder

Introduction

Background

Despite increased attention from the media, policy makers, researchers, and clinicians, the opioid epidemic in the United States remains a significant public health crisis. Approximately 107,000 US adults died by drug overdose in 2021, with increases in every age group and an overall age-adjusted 14% increase from the previous year [1]. An estimated two-thirds of overdose deaths involved synthetic opioids other than methadone (eg, illicitly manufactured fentanyl) [2]. Medications for opioid use disorder (MOUD), including buprenorphine and methadone, are protective against mortality in individuals with opioid use disorder (OUD) [3,4], reducing overdose death and all-cause death by 8 and 2.5 times, respectively [5]. Furthermore, longer retention in MOUD is associated with a continued reduction in mortality [5]. Retention of at least 6 months, and often longer, is needed to obtain full benefits, including a return to work and improvements in fulfilling family and social responsibilities [6,7]. Despite these benefits, only 36% of individuals who initiate are retained in MOUD for 6 months, with retention rates falling to 22% at 1 year [8]. Therefore, developing interventions that support MOUD retention and address co-occurring conditions that interfere with retention is essential to enabling people with OUD to obtain the full benefits of MOUD treatment.

Role of Pain in the Development of OUD

One condition that commonly co-occurs with OUD is chronic pain, frequently defined as pain that persists for 3 months or more. Chronic pain is a widespread affliction in the United States, affecting approximately 1 in 5 adults [9], and is more common among people with OUD. A large study of electronic health records revealed that 64.4% of individuals with OUD also had a chronic pain condition [10]. Chronic pain can be a pathway to OUD, with 4 out of 5 individuals who use heroin reporting their initial exposure to opioids was through a prescription for pain treatment [11,12]. It is a common misconception, even among addiction providers, that methadone and buprenorphine provide adequate pain treatment for individuals with OUD [13]. Unsurprisingly, chronic pain typically persists when MOUD is the sole treatment modality. Among individuals enrolled in methadone or buprenorphine treatment, estimates of chronic pain range from 40% to 80% [14-17].

Chronic Pain Negatively Affects MOUD Outcomes

The presence of chronic pain may undermine the effectiveness of MOUD. A large randomized, controlled multisite trial of buprenorphine in individuals with OUD found greater pain severity significantly increased the odds of opioid use in the following week [18]. Follow-up analyses revealed that variability or volatility in pain intensity was associated with craving, relapse to opioid use, and poorer outcomes [18,19]. Furthermore, the experience of pain has been cited as the most common reason for returning to use while engaged in MOUD [20]. Finally, few people receiving MOUD receive adequate evidence-based pain care; this has been recognized as an important gap in the treatment of comorbid OUD and chronic pain [15,21-24].

Individuals with chronic pain receiving MOUD, compared to those without chronic pain, have higher rates of psychiatric and medical comorbidities, including sleep disturbances, and higher rates of health service use and levels of functional impairment [21,25-27]. Comprehensive treatment for individuals with concurrent chronic pain and OUD may require interventions that address mood, anxiety, sleep, and functional difficulties to maximize OUD treatment outcomes, such as MOUD retention. That is, chronic pain with OUD does not necessarily indicate more severe OUD; rather, it represents a concurrent disorder that may have a different clinical course and treatment response than OUD alone [22,28]. Accordingly, treatments should consider the relationship between chronic pain and opioid use while addressing barriers to engagement in resource-limited MOUD clinics.

Cognitive Behavioral Therapy Is an Evidence-Based Treatment for Both Chronic Pain and Substance Use, but it has Limited Accessibility

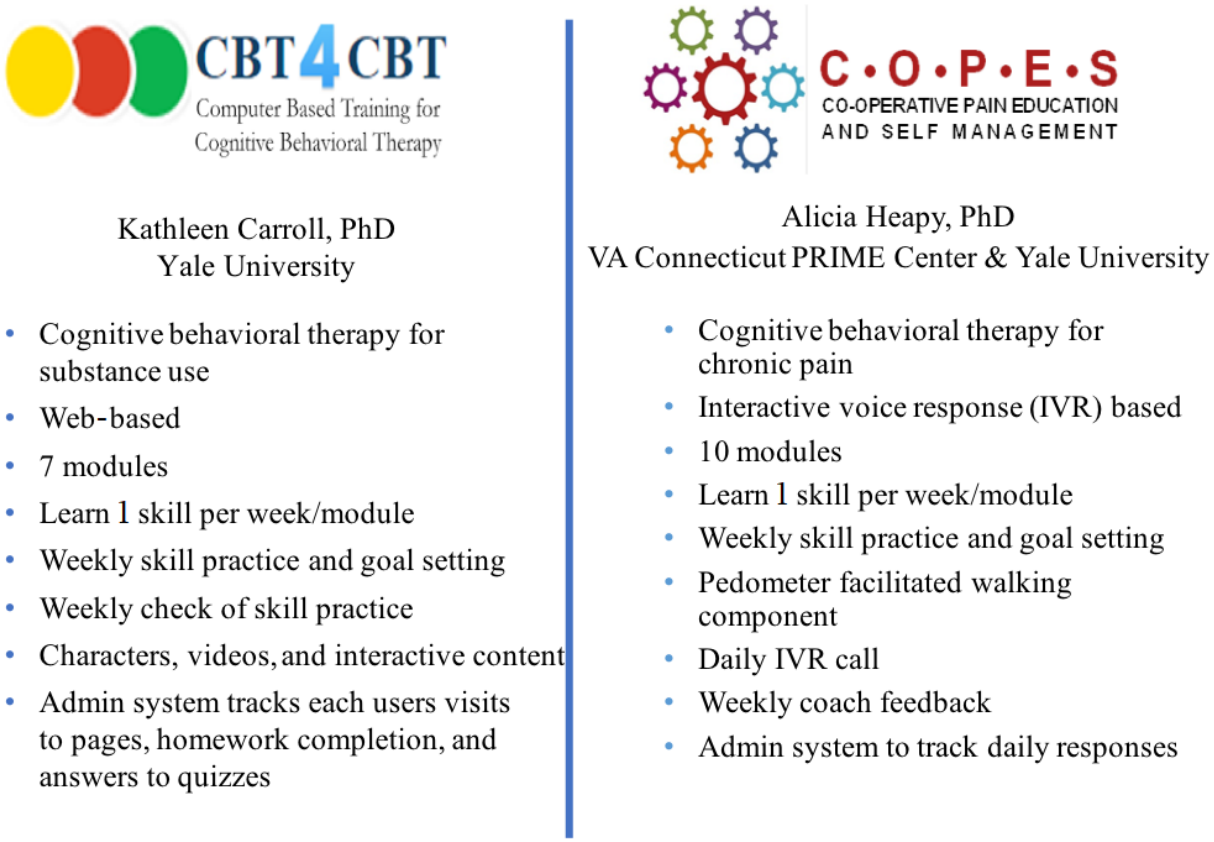
Cognitive behavioral therapy (CBT) has a strong evidence base for the treatment of chronic pain [29] and substance use disorders [30-33]. CBT for chronic pain has been recommended by the Centers for Disease Control and Prevention and the National Institutes of Health (NIH) as a first-line treatment to reduce pain and improve function [34,35]. Although MOUD clinicians report interest in nonpharmacologic pain treatment, very few report confidence in their own ability to address chronic pain [36]. Similar to chronic pain, CBT for substance use disorders has been shown to have moderate effects on reducing substance use, promoting abstinence from substances, increasing the use of coping skills, and promoting other positive psychosocial outcomes in individuals with addiction [37]. Engagement in CBT for substance use disorder is a mainstay

in outpatient and inpatient treatment, but, akin to CBT for chronic pain, implementing CBT with high fidelity is challenging due to the lack of trained clinicians in the setting [38,39]. For these reasons, offering adjunctive CBT in MOUD clinics has resulted in mixed findings [40-42]. Taken together, there is a critical gap in treatment where individuals with OUD receiving MOUD have few options for addiction or pain treatment. Accordingly, there has been a recent call to develop rigorous, evidence-based digital treatments for individuals with OUD, which can be integrated into MOUD clinical settings [43].

Development of Integrating the Management of Pain and Addiction via Collaborative Treatment

Integrating the Management of Pain and Addiction via Collaborative Treatment (IMPACT) combines 2 evidence-based digital CBT treatments: Computer-Based Treatment for Cognitive Behavioral Therapy (CBT4CBT) and Cooperative Pain Education and Self-Management (COPES) treatment programs (Figure 1). CBT4CBT is a web-based program designed to improve behavioral and cognitive coping skills that have been evaluated in a range of substance use disorders [44-47], including 2 trials indicating its effectiveness and durability for individuals with OUD on methadone maintenance [48,49] and office-based buprenorphine maintenance [50]. COPES is an interactive voice response–based treatment for chronic pain that is delivered asynchronously through telephone [51] and has been shown to be similarly effective in reducing pain intensity and improving physical functioning, sleep quality, and quality of life as real-time CBT with a therapist [52]. IMPACT was designed to provide an easily accessible, standardized evidence-based intervention for those with OUD and chronic pain that could ultimately be easily integrated into MOUD clinic settings.

Figure 1. Core program features of the Computer-Based Treatment for Cognitive Behavioral Therapy (CBT4CBT) and Cooperative Pain Education and Self-Management (COPES) programs.



This study was funded by the National Center for Complementary and Integrative Health's Behavioral Research to Improve Medication-Based Treatment (BRIM) program. The goal of BRIM, funded by NIH's Helping to End Addiction Long-Term (HEAL) initiative, is to examine the role of behavioral interventions in improving the outcomes of MOUD, particularly MOUD access and retention. The R61/R33 award described here consists of 2 phases: a preparatory R61 phase used to develop the intervention and identify recruiting sites and the R33 clinical trial that is the focus of this protocol.

Study Objectives

The study is designed to evaluate the efficacy of IMPACT along with treatment as usual (IMPACT+TAU) versus TAU only at 3 months post randomization (primary end point). The primary OUD outcome is verified retention in MOUD treatment, defined as enrollment in MOUD (ie, yes or no), with evidence of MOUD use in the week before the 3-month time point. Secondary treatment outcomes will include pain interference, physical functioning, MOUD adherence, substance use, craving, pain intensity, sleep disturbance, pain catastrophizing, and pain self-efficacy at 3 months post randomization. The secondary aim is to evaluate the durability of effects for MOUD retention

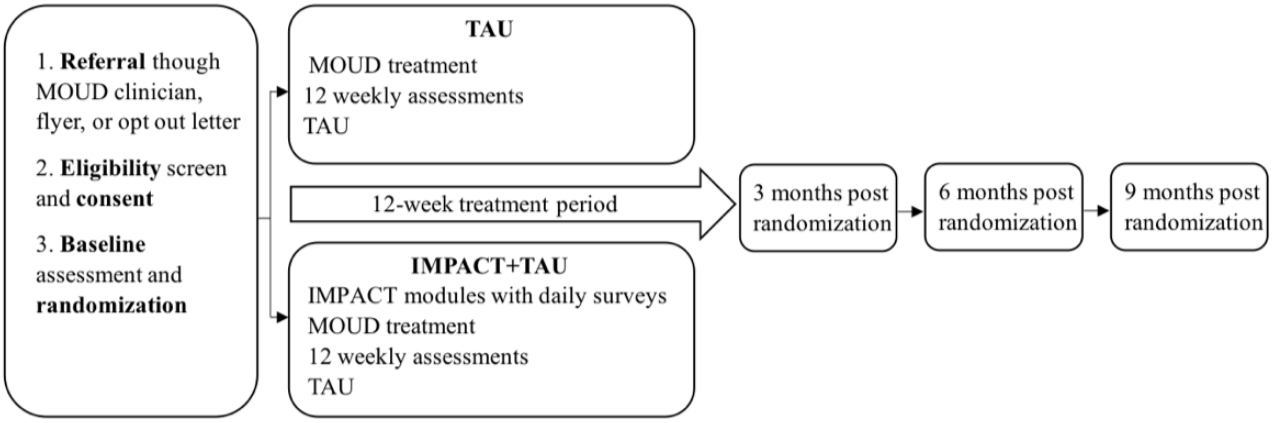
at 6 and 9 months post randomization. The tertiary aim is to examine treatment usability and quality through qualitative interviews with individuals randomized to IMPACT.

Methods

Study Design

This is a randomized clinical trial comparing the efficacy of IMPACT+TAU relative to TAU among individuals enrolled in MOUD treatment who have chronic pain. Outcomes will be assessed at baseline, 3, 6, and 9 months post randomization (Figure 2).

Figure 2. Study protocol for Integrating the Management of Pain and Addiction via Collaborative Treatment (IMPACT). MOUD: medications for opioid use disorder; TAU: treatment as usual.



Study Population and Setting

Participants will be 160 individuals with chronic pain receiving MOUD (methadone or buprenorphine) at participating outpatient opioid treatment program (OTP) sites located in Bridgeport, Danbury, and Waterbury (Connecticut).

Ethical Considerations

The study was approved by the Yale University Institutional Review Board on September 4, 2019 (2000026276). Subsequent modifications were implemented to add posttreatment qualitative interviews to assess treatment satisfaction and usability, as well as to refine recruitment materials and add recruitment sites. The study was subsequently approved by the Veterans Affairs Connecticut Human Subjects Subcommittee because, although not enrolling Veteran Affairs patients, several study staff are employees of the Department of Veterans Affairs.

Study Population

Textbox 1 contains inclusion and exclusion criteria for patients.

Textbox 1. Eligibility criteria for patients.

Inclusion criteria

- Be 18 years of age or older
- Meet the

  Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition) criteria for opioid use disorder and be enrolled in methadone or buprenorphine treatment at the participating medications for opioid use disorder (MOUD) clinic
- Receiving a stable (ie, unchanged in 2 weeks) dose of MOUD as judged by the prescribing clinician
- Report bothersome or high-impact chronic pain defined by the Graded Chronic Pain Scale–Revised
- Have a self-reported ability to walk at least 1 block

Exclusion criteria

- Inability to read, write, and speak English at a third-grade level
- Untreated or inadequately treated bipolar or psychotic disorder or current suicide risk for the previous 2 weeks before screening (identified using baseline measures)
- Life-threatening health conditions that would impede participation (eg, end-stage renal failure, malignant cancer requiring chemotherapy)
- Planned surgical treatment related to pain
- Pending legal action or planned relocation that would interfere with participation

Justification for Criteria

Participants will be adults receiving a stable dose of MOUD because, until the dose is stable, pain ratings may fluctuate and obscure the intervention's effect. We require bothersome or high-impact chronic pain (ie, moderate to severe pain that limits life and work activities on most days or every day in the past 3 months) because, compared to individuals with mild chronic pain, it is more commonly associated with negative health indicators addressed in cognitive behavioral treatment for chronic pain (eg, negative pain coping beliefs, pain interference, and psychological distress) [53]. IMPACT contains a progressive walking program; therefore, to ensure participant safety, participants must be able to walk at least 1 block. Individuals with low literacy (ie, <third grade) or medical or psychiatric diagnoses that would interfere with their ability to meaningfully participate in the IMPACT treatment, such as severe mental health conditions (eg, unmedicated or untreated bipolar or psychotic disorder, current suicide risk, or diagnoses requiring palliative or end-of-life care), are excluded. Individuals with circumstances that may predictably interfere with participation (eg, legal actions with imminent incarceration) or produce large changes in pain (pain-related surgeries) will be excluded. Women of childbearing age will be included, as there is no contraindication for CBT for pain or substance use disorder for pregnant women. Participants who do not have a digital device (eg, smartphone or tablet) for participating in IMPACT will be supplied with one for the duration of the study.

Recruitment, Screening, and Consent Procedures

Study recruitment occurs through clinician referral of interested patients and patient self-referral in response to informational study materials posted in patient care areas at the recruiting sites. Site clinicians receive information about the study and eligibility criteria through research staff presentations and study informational material provided at clinical staff meetings. Self- and clinician-referred individuals are screened by a study research assistant and, if eligible, invited to consent and complete a baseline assessment. Procedures are conducted in a quiet and private office space provided by the OTP clinic to the research team. The research assistant and the participant discuss the consent document, and potential participants are provided an opportunity to ask questions and time to consider their decision to participate. A comprehension quiz is given to ensure the participant has an adequate understanding of the study, and a copy of the consent form is given to the participant. After consent, the research assistant assigns a unique study ID code and administers baseline measures on a study laptop using the REDCap (Research Electronic Data Capture) software platform.

Randomization and Masking

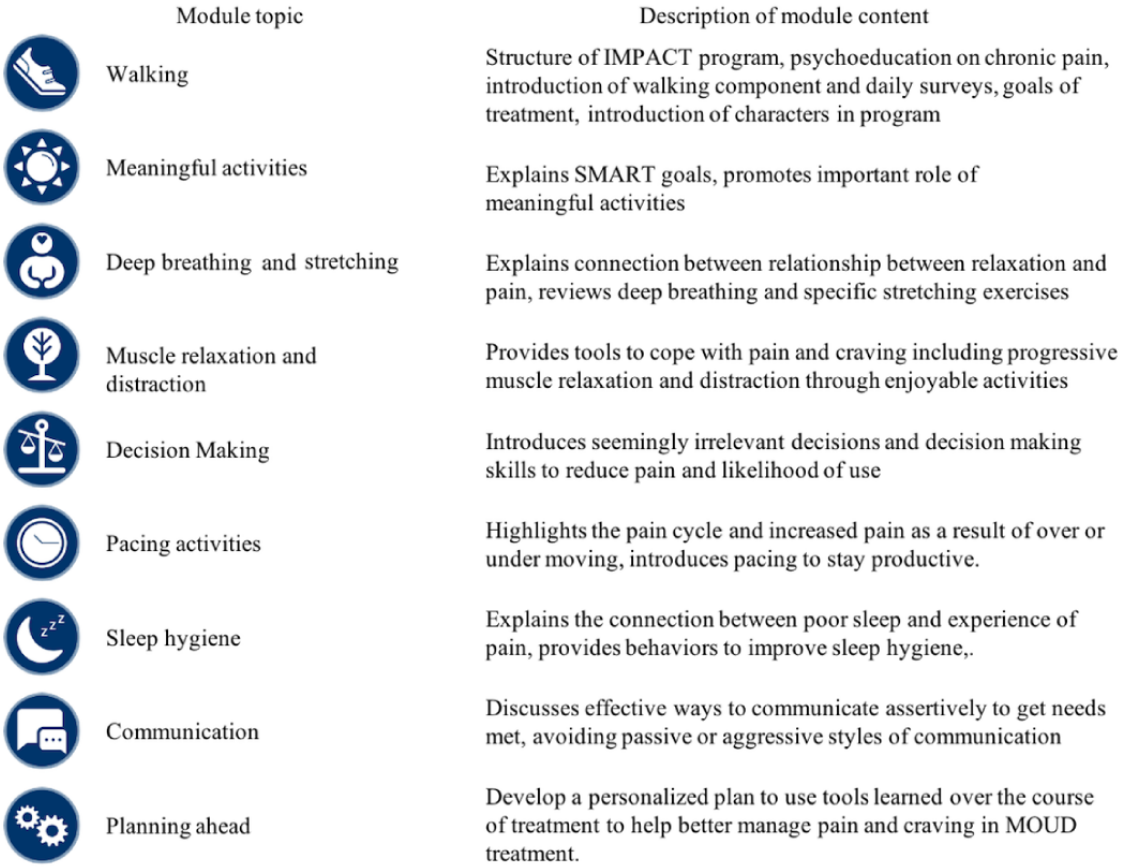
Following the baseline assessment, participants are randomized 1:1 to IMPACT+TAU or TAU (control) using urn randomization [54] balanced by demographic variables (self-reported gender identification and race or ethnicity [combination of ethnicity and racial identity]), as well as likely prognostic variables (severity of OUD as mild, moderate, or severe based on the DSM-5 [*Diagnostic and Statistical Manual of Mental Disorders* {Fifth Edition} OUD symptom count), buprenorphine versus methadone treatment, and length of MOUD treatment (<6 months, 6-12 months, and >12 months). Allocation is masked using a Microsoft Access (Microsoft Corp) program that our group has developed and implemented successfully in multiple previous trials [55-58]. Participants randomized to IMPACT+TAU are provided with a unique username and password to access the IMPACT website. To facilitate their participation in the walking portion of the treatment, participants are given a pedometer and a brief demonstration of its use. Study staff measure each participant's stride length and calibrate the pedometer accordingly. The research assistant then guides the participants through the first IMPACT module to ensure they are comfortable using the program and answer any questions they might have.

Interventions

IMPACT

Participants allocated to IMPACT+TAU receive standard MOUD treatment (ie, TAU) along with access to IMPACT for 12 weeks. IMPACT is a self-directed, 9-module digital treatment program with weekly personalized feedback messages from a trained masters- or doctoral-level coach under the supervision of a clinical psychologist. Participants are asked to complete 1 module per week using a study laptop that is available in the MOUD clinic or outside of the clinic using their own web-enabled device (eg, at home). We hope to maximize treatment adherence and engagement by providing multiple ways of accessing the IMPACT program [50]. The IMPACT program passively tracks individual behaviors to capture engagement (ie, number of logins, access to each module and component, time spent using the program, and digital survey completion). Module topics are shown in Figure 3. For each module, participants are asked to practice a specific skill that corresponds with the topic for that week. After indicating a baseline average number of steps during their first week of completing the daily survey, participants are provided with a daily step goal by their coach during the weekly feedback message. The goal is to increase their daily steps by 10% of the average daily step count reported in the previous week. All modules include a narrated introduction of the skill, video vignettes of characters in challenging situations and using skills, interactive practice exercises and weekly skill practice goals, and a quiz to evaluate the understanding of the module content. The IMPACT dashboard landing page displays personalized information for each participant, including a badge for each completed module, stars for completion of practice exercises, weekly averages of daily steps and step goals in graphical form, and a link to weekly coach messages.

Figure 3. Integrating the Management of Pain and Addiction via Collaborative Treatment (IMPACT) module topics and descriptions. MOUD: medications for opioid use disorder; SMART: specific, measurable, achievable, relevant, and time-bound.



Participants receive links to daily digital surveys through MMS text messages on their mobile phone at a participant-selected time for the duration of treatment. Surveys assess pain intensity, pain interference, pedometer-measured step counts, sleep quality, sleep duration, craving to use opioids, self-efficacy, MOUD adherence, and questions regarding the practice of the treatment skills. Based on our previous work, digital surveys are estimated to take no longer than 2 minutes to complete. Coaches review summaries of the daily survey data through a web portal that displays survey responses from the past week (as weekly averages or individual days). The coach records an audio message based on the participant-provided responses to the current week's surveys, as well as previous weeks, that is uploaded to the participant's IMPACT dashboard. The coach's message provides reinforcement of skill practice and goal attainment and highlights associations between participants' daily responses and trends in weekly averages over the course of treatment. Coaches receive training in message preparation and attend weekly supervision with a clinical psychologist. Participants are not able to directly respond to the coach's feedback through the program but are able to indirectly communicate with the coach by leaving a message with the research assistant during their weekly clinic visit, who can relay the message to the coaches.

TAU (Control)

Participants in both conditions receive TAU for the buprenorphine and methadone programs at participating MOUD clinics, which includes regular medication management by the clinic physician and regular individual and group counseling sessions delivered on-site by counselors employed at participating MOUD clinics. Participants randomized to IMPACT+TAU and TAU will receive MOUD dosing as indicated by their OTP clinician in conjunction with regular meetings as dictated by their treatment plan. Both groups are free to access any OTP clinic resources, including prescriptive services for mental health issues, group treatment, and individual counseling as offered at each recruitment site.

Assessment Visits

The study includes a baseline visit followed by brief weekly visits during treatment (up to 12 weeks) and a 3-, 6-, and 9-month postrandomization assessment visit. Neither participants nor research assistants are blinded to group assignments. However, outcome measures are obtained through self-report using REDCap digital assessments, and MOUD retention will be verified with MOUD clinic records, limiting the potential for bias. Participants complete the baseline, weekly visit, posttreatment, and follow-up measures at their outpatient MOUD clinic to facilitate the collection of a urine sample for urine toxicology analysis (Table 1). After baseline, if in-person attendance is not possible, study measures may be completed remotely. Remote participation is facilitated by the use of digital data collection, videoconferencing, or the telephone.

Table 1. Study measures.

Measure	Items	Baseline	Weekly	3 months	6 and 9 months
Baseline measures					
Demographic information, MOUD[a] information, and clinical characteristics of chronic pain		✓			
MINI[b] International Neuropsychological Interview [59]	Interview	✓			
Graded Chronic Pain Scale–Revised (frequency, severity, and impact of pain) [53]	6	✓			
Addiction Severity Index [60]	Interview	✓		✓	✓
Primary outcome (in 3 months)					
Buprenorphine retention	none	✓		✓	✓
Secondary outcome measures					
PROMIS[c] Pain Interference 6a [61]	6	✓		✓	✓
MOUD Adherence[d]	None	✓	✓	✓	✓
The Craving Scale [62]	3	✓		✓	✓
Timeline Follow-Back Substance Use Calendar [63]	Interview	✓	✓	✓	✓
Urine toxicology	None	✓	✓	✓	✓
NRS[e] Pain Intensity Rating [64]	1	✓		✓	✓
PROMIS Physical Function 6b [65]	7	✓		✓	✓
Pain Catastrophizing Scale [66]	14	✓		✓	✓
Pain Self-Efficacy Questionnaire [67]	11	✓		✓	✓
PROMIS Sleep Disturbance 6a and Duration [68]	9	✓		✓	✓
Other measures					
Brief Symptom Inventory [69]	18	✓		✓	✓
Cold pressor task	None	✓		✓	✓
PHQ-4[f] (brief screen for anxiety and depression) [70]	4	✓		✓	✓
Program and Client Cost-Substance Abuse Treatment (treatment use) [71]	Interview	✓		✓	✓
IMPACT[g] engagement data (IMPACT+TAU[h] only)	None		✓		

[a]MOUD: medications for opioid use disorder.

[b]MINI: Mini-International Neuropsychiatric Interview.

[c]PROMIS: Patient Reported Outcomes Measurement Information System.

[d]Adherence will be assessed with the Timeline Followback for daily MOUD use for the previous week, clinic dispensing records, and urine toxicology screen for buprenorphine or methadone collected at each weekly assessment visit.

[e]NRS: Numerical Rating Scale.

[f]PHQ-4: Patient Health Questionnaire-4.

[g]IMPACT: Integrating the Management of Pain and Addiction via Collaborative Treatment.

[h]TAU: treatment as usual.

Primary Outcome Measure (Retention in MOUD)

Retention is defined as dichotomous enrollment in MOUD (ie, yes or no), with evidence of MOUD uptake in the week before the 3- (primary), 6-, and 9-month time points. Using data from the 7 days before the 3-month time point, dichotomous enrollment in MOUD services will be verified by clinic records and evidence of MOUD compliance will be assessed using clinic records and self-report. When these sources disagree, clinic records will be used to determine compliance. Retention will be a binary outcome, with 1=retained (conditions met) and 0=not retained.

Secondary Treatment Outcome Measures

We will also collect OUD (ie, MOUD adherence, craving, and substance use) and pain (ie, pain interference, physical functioning, pain intensity, sleep disturbance, pain catastrophizing, and pain self-efficacy) secondary outcome measures. These outcomes evaluate other important treatment effects that have an evidence base in OUD and chronic pain

treatment studies and will provide a more detailed assessment of possible treatment outcomes. Outcome measures are detailed in Table 1.

Other Measures

To better characterize other treatment effects, we will also evaluate general psychological symptoms, depression symptoms, anxiety symptoms, OTP treatment use and cost, cold pressor task (pain threshold), and digital treatment engagement (only participants randomized to IMPACT+TAU).

Data Sharing

Data collected during baseline, post treatment, and follow-up visits will be made available in compliance with the HEAL Public Access and Data Sharing policy. The study is registered in ClinicalTrials.gov and is in the process of being registered in the HEAL Data Platform. Once data collection is complete, 1 master data file will be created that includes all variables necessary to address the primary study aims and hypotheses. All analyses will be performed using the master data file. The final master data set will then be submitted to the appropriate HEAL-approved repository. All data will be deidentified before submission using procedures that are in compliance with the HIPAA (Health Insurance Portability and Accountability Act), the Yale Human Investigation Committee, and NIH standards.

Qualitative Interviews

Among those randomized to IMPACT+TAU, individual interviews (N=34) will be conducted at 3-month follow-up with a sample of completers (n=17) and noncompleters (n=17). This sample size should be sufficient to achieve saturation on interview themes; however, if saturation is not reached, additional participants will be interviewed until saturation is attained [72]. Completers will be defined as any participant that engages in 7-9 IMPACT modules. Noncompleters will be defined as any participant who completed between 1 and 4 IMPACT modules. Interviews will take place on the internet or in person, be digitally recorded, and be transcribed. All respondents will be asked a series of open-ended questions to probe participant experiences with IMPACT, including barriers or facilitators to engagement and how IMPACT influenced their ability to manage pain and OUD. Semistructured questions will elicit feedback on various features of the intervention, including the various module topics (Figure 3), the walking component, impressions of the weekly personalized feedback, the IMPACT platform, study outcomes, daily surveys, and combined emphasis on pain or OUD.

Data Analyses

Quantitative Data Analysis

Data will be reported for each treatment arm and overall at all time points in the study. Summary descriptions of recruitment rates, attrition, daily survey completion, and treatment outcomes will be calculated. The baseline demographic characteristics of both groups will be summarized.

We will perform a true intent-to-treat analysis of the primary MOUD retention outcome that will include all randomized participants and use logistic regression models to assess differences in MOUD retention by treatment condition at the 3-month time point. MOUD type (ie, buprenorphine or methadone) will be specified as a covariate. Similarly, the logistic regression model will be used to assess differences in MOUD retention by treatment condition at each follow-up time point (ie, 6 and 9 months post randomization).

In addition to retention, we will run secondary analyses to evaluate differences in several OUD (ie, MOUD adherence, craving, and substance use) and pain (ie, pain interference, physical functioning, pain intensity, sleep disturbance, pain catastrophizing, and pain self-efficacy) measures by treatment condition and by time using multilevel longitudinal models with MOUD type (ie, buprenorphine or methadone) specified as a between-person covariate.

Qualitative Data Analysis

Analysis of qualitative data will be conducted using Atlas.ti, a qualitative software program allowing fluid interaction of data across types or sources [73]. A qualitative-descriptive approach is suitable when information is needed to develop, summarize, or refine an intervention [74]. A constant comparative approach with sequential analysis will be used to reach a thematic consensus. Memos, field notes, and debriefing notes after each interview will also be incorporated into the analysis [75]. Each transcript will first be read in its entirety and then coded, proceeding from line-by-line in vivo codes to more broad codes and themes, comparing data across participants [75]. Coding will be completed independently by 2 researchers and compared, and final themes will be arrived at through consensus. Findings will be summarized and presented in tables. It is expected that the collected data will reflect mechanisms underlying engagement and participant perspectives of IMPACT.

Results

The funding for the clinical trial component of the study (phase 2) was obtained in June 2022, and the trial study protocol that included changes from phase 1 was approved by the institutional review board in January 2022. Enrollment began on July 15, 2022, at a single outpatient clinic; a second outpatient clinic was added on March 6, 2023; and a third site is expected in January 2024. Enrollment is expected to continue until June 2024. Final data are expected to be collected in March to May 2025, and the primary results of the study are expected to be published in March to May 2026.

Discussion

Summary of Study Significance

Given the prevalence of OUD and the increased mortality by overdose, the provision of MOUD and support for retention in MOUD are critical. Only a third of individuals receiving MOUD are retained in treatment after 6 months. Clearly, many people receiving MOUD require additional support to remain in treatment and attain its full benefit. Chronic pain, a common co-occurring condition among those receiving MOUD, interferes with MOUD retention and diminishes functioning and quality of life. An asynchronous digital integrated treatment for addiction and chronic pain, such as IMPACT, holds promise to increase access to evidence-based behavioral treatment in

MOUD clinical care. IMPACT is designed to be accessible, low-burden, and easily integrated into MOUD clinics despite their limited resources.

Benefits of Daily Surveys

Importantly, IMPACT collects individual responses through daily surveys that are used to generate weekly personalized feedback for participants. These data are the foundation of personalized coach feedback that may enhance engagement with treatment, which has been suggested in previous reviews [76] and yield relatively fine-grained data on patient reports of pain and pain interference, craving to use opioids, sleep problems, and physical activity for a comparatively large sample of individuals enrolled in MOUD. Daily ratings of pain and pain fluctuations in this population are unique, and the data generated will be critical in addressing key gaps in the literature, including understanding fluctuations in relationships between pain and pain interference, drug craving, treatment retention, sleep, and functioning in this population. These data may provide actionable information for further treatment refinement.

Benefit of Digital Interventions in the MOUD Setting

An integrated, digital intervention offers 2 particularly attractive benefits in the MOUD setting: a means to both (1) obtain treatment in a less stigmatizing manner and (2) provide treatment with high fidelity to evidence-based protocols without adding staff. Individuals receiving MOUD report high levels of stigma that can significantly impact the course of treatment [77-79]. Increased stigma is a primary barrier to engaging in MOUD treatment and is present even among addiction providers. In a recent qualitative study of MOUD providers, the perception of psychosocial interventions is mixed, with some providers suggesting that MOUD undermines the effectiveness of behavioral treatment while others argue that any provision of behavioral treatment is not a necessary component of MOUD treatment [80]. Furthermore, integrating evidence-based psychotherapies, such as CBT, into MOUD clinical care has been met with mixed results [81-83]. Some researchers have posited that the inconsistent findings are likely related to methodological flaws in previous research, including low fidelity and an inadequate control group [42]. IMPACT treatment materials can be delivered with a high degree of fidelity and consistency, effectively removing a lack of fidelity as a potential driver of outcomes in this study. The patient demands of MOUD clinical care often preclude trained providers from delivering behavioral treatment [84]. Technology-based and digital interventions, such as IMPACT, can address these barriers by offering treatment with high fidelity that can be completed outside the clinic, further reducing the possible stigma of discussing problems related to addiction and pain in MOUD settings.

Limitations

There are several limitations to the current protocol. First, as is common in behavioral intervention trials, participants will be unblinded to the condition once randomized. However, all participants and researchers will be blind to the condition when completing baseline structured interview measures. The primary outcome is based on objective measures and clinic attendance and, therefore, is less vulnerable to biases associated with being unblinded. Other treatment outcomes are collected through self-reported responses in REDCap, which also limits the potential for bias. There is also no attention control for IMPACT. We chose to use TAU as the control condition to maximize our ability to determine the efficacy of adding a digital treatment to the existing gold standard treatment (ie, MOUD). Next, participants randomized to IMPACT may not complete all daily surveys, resulting in missing data. While we expect that participants will miss surveys, completing the surveys benefits participants because they provide personalized feedback; and even 1-2 surveys per week can provide insight for weekly coach feedback. Additionally, previous research on COPES has shown high survey completion [85], which is consistent with findings from other asynchronous chronic pain interventions using daily surveys [86]. Finally, participants in both groups may receive other pain and addiction treatments both within and outside their MOUD clinic. We will inquire about additional treatment at weekly visits during treatment to account for any effects that could be attributed to other interventions.

Conclusions

Access to behavioral treatment for individuals with OUD and chronic pain is a critical gap in MOUD care. Offering access to a combined pain and addiction treatment may help retain individuals in MOUD while improving clinical outcomes for people who otherwise may not receive treatment. Digital treatments are especially well-suited to MOUD treatment settings because they reduce stigma and provide access to high fidelity, evidence-based behavioral treatment.

Acknowledgments

We would like to respectfully acknowledge the late Kathy M Carroll, PhD, for her contributions to the design of this study before her untimely passing in late 2020. Dr Carroll's brilliance was only surpassed by her unwavering commitment to increasing the accessibility of evidence-based treatment to improve the lives of individuals with substance use disorders. With this project, we continue her legacy with the same compassion and empathy that defined her professional and personal life. This research is supported by R61/33AT010619 (Heapy). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health, the National Center for Complementary and Integrative Health, or the Department of Veterans Affairs.

Data Availability

Deidentified data sets generated during the course of this study will be made available on the Helping to End Addiction Long-Term (HEAL) Data Platform through a HEAL-approved repository.

Authors' Contributions

AAH, MAG, TLF, CN, WCB, SM, and MS contributed to the conceptualization of the study. AAH, RRM, BA, MAG, TLF, CN, SNE, WCB, SM, and MS contributed to the study design, development of the Integrating the Management of Pain and Addiction via Collaborative Treatment (IMPACT) program during the R61 phase, and clinical trial during the R33 phase. RRM wrote the initial draft, and AAH, SKS, JML, LB, MIPR, MAG, and MAD provided critical edits. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-viewer report from the National Centre for National Center for Complementary and Integrative Health (NCCIH).
[PDF File (Adobe PDF File), 200 KB - resprot_v13i1e54342_app1.pdf]

References

1. Spencer MR, Miniño AM, Warner M. Drug overdose deaths in the United States, 2001-2021. NCHS Data Brief 2022(457):1-8 [FREE Full text] [Medline: 36598401]
2. O'Donnell J, Tanz LJ, Gladden RM, Davis NL, Bitting J. Trends in and characteristics of drug overdose deaths involving illicitly manufactured fentanyls—United States, 2019-2020. MMWR Morb Mortal Wkly Rep 2021;70(50):1740-1746 [FREE Full text] [doi: 10.15585/mmwr.mm7050e3] [Medline: 34914673]
3. Degenhardt L, Bucello C, Mathers B, Briegleb C, Ali H, Hickman M, et al. Mortality among regular or dependent users of heroin and other opioids: a systematic review and meta-analysis of cohort studies. Addiction 2011;106(1):32-51. [doi: 10.1111/j.1360-0443.2010.03140.x] [Medline: 21054613]
4. Larochelle MR, Bernson D, Land T, Stopka TJ, Wang N, Xuan Z, et al. Medication for opioid use disorder after nonfatal opioid overdose and association with mortality: a cohort study. Ann Intern Med 2018;169(3):137-145 [FREE Full text] [doi: 10.7326/M17-3107] [Medline: 29913516]
5. Ma J, Bao YP, Wang RJ, Su MF, Liu MX, Li JQ, et al. Effects of medication-assisted treatment on mortality among opioids users: a systematic review and meta-analysis. Mol Psychiatry 2019;24(12):1868-1883. [doi: 10.1038/s41380-018-0094-5] [Medline: 29934549]
6. Ling W, Nadipelli VR, Aldridge AP, Ronquest NA, Solem CT, Chilcoat H, et al. Recovery from Opioid Use Disorder (OUD) after monthly long-acting buprenorphine treatment: 12-month longitudinal outcomes from RECOVER, an observational study. J Addict Med 2020;14(5):e233-e240 [FREE Full text] [doi: 10.1097/ADM.0000000000000647] [Medline: 32187112]
7. Gossop M, Marsden J, Stewart D, Kidd T. The National Treatment Outcome Research Study (NTORS): 4-5 year follow-up results. Addiction 2003;98(3):291-303. [doi: 10.1046/j.1360-0443.2003.00296.x] [Medline: 12603229]
8. Krawczyk N, Williams AR, Saloner B, Cerdá M. Who stays in medication treatment for opioid use disorder? A national study of outpatient specialty treatment settings. J Subst Abuse Treat 2021;126:108329 [FREE Full text] [doi: 10.1016/j.jsat.2021.108329] [Medline: 34116820]
9. Zelaya CE, Dahlhamer JM, Lucas JW, Connor EM. Chronic pain and high-impact chronic pain among U.S. adults, 2019. NCHS Data Brief 2020(390):1-8. [Medline: 33151145]
10. Hser YI, Mooney LJ, Saxon AJ, Miotto K, Bell DS, Huang D. Chronic pain among patients with opioid use disorder: results from electronic health records data. J Subst Abuse Treat 2017;77:26-30 [FREE Full text] [doi: 10.1016/j.jsat.2017.03.006] [Medline: 28476267]
11. Muhuri PK, Gfroerer JC, Davies C. Associations of nonmedical pain reliever use and initiation of heroin use in the United States. CBHSQ Data Review. 2013. URL: https://www.samhsa.gov/data/sites/default/files/DR006/DR006/nonmedical-pain-reliever-use-2013.htm [accessed 2024-02-13]
12. Shah A, Hayes CJ, Martin BC. Characteristics of initial prescription episodes and likelihood of long-term opioid use—United States, 2006-2015. MMWR Morb Mortal Wkly Rep 2017;66(10):265-269 [FREE Full text] [doi: 10.15585/mmwr.mm6610a1] [Medline: 28301454]
13. Alford DP, Compton P, Samet JH. Acute pain management for patients receiving maintenance methadone or buprenorphine therapy. Ann Intern Med 2006;144(2):127-134 [FREE Full text] [doi: 10.7326/0003-4819-144-2-200601170-00010] [Medline: 16418412]

14. Dhingra L, Perlman DC, Masson C, Chen J, McKnight C, Jordan AE, et al. Longitudinal analysis of pain and illicit drug use behaviors in outpatients on methadone maintenance. Drug Alcohol Depend 2015;149:285-289 [FREE Full text] [doi: 10.1016/j.drugalcdep.2015.02.007] [Medline: 25735466]
15. Rosenblum A, Joseph H, Fong C, Kipnis S, Cleland C, Portenoy RK. Prevalence and characteristics of chronic pain among chemically dependent patients in methadone maintenance and residential treatment facilities. JAMA 2003;289(18):2370-2378 [FREE Full text] [doi: 10.1001/jama.289.18.2370] [Medline: 12746360]
16. Jamison RN, Kauffman J, Katz NP. Characteristics of methadone maintenance patients with chronic pain. J Pain Symptom Manage 2000;19(1):53-62 [FREE Full text] [doi: 10.1016/s0885-3924(99)00144-x] [Medline: 10687327]
17. Barry DT, Savant JD, Beitel M, Cutter CJ, Moore BA, Schottenfeld RS, et al. Pain and associated substance use among opioid dependent individuals seeking office-based treatment with buprenorphine-naloxone: a needs assessment study. Am J Addict 2013;22(3):212-217 [FREE Full text] [doi: 10.1111/j.1521-0391.2012.00327.x] [Medline: 23617861]
18. Griffin ML, McDermott KA, McHugh RK, Fitzmaurice GM, Jamison RN, Weiss RD. Longitudinal association between pain severity and subsequent opioid use in prescription opioid dependent patients with chronic pain. Drug Alcohol Depend 2016;163:216-221 [FREE Full text] [doi: 10.1016/j.drugalcdep.2016.04.023] [Medline: 27161860]
19. Worley MJ, Heinzerling KG, Shoptaw S, Ling W. Volatility and change in chronic pain severity predict outcomes of treatment for prescription opioid addiction. Addiction 2017;112(7):1202-1209 [FREE Full text] [doi: 10.1111/add.13782] [Medline: 28164407]
20. Ellis MS, Kasper Z, Cicero T. Assessment of chronic pain management in the treatment of opioid use disorder: gaps in care and implications for treatment outcomes. J Pain 2021;22(4):432-439 [FREE Full text] [doi: 10.1016/j.jpain.2020.10.005] [Medline: 33197581]
21. Dunn KE, Finan PH, Tompkins DA, Fingerhood M, Strain EC. Characterizing pain and associated coping strategies in methadone and buprenorphine-maintained patients. Drug Alcohol Depend 2015;157:143-149 [FREE Full text] [doi: 10.1016/j.drugalcdep.2015.10.018] [Medline: 26518253]
22. Manhapra A, Becker WC. Pain and addiction: an integrative therapeutic approach. Med Clin North Am 2018;102(4):745-763. [doi: 10.1016/j.mcna.2018.02.013] [Medline: 29933827]
23. Ilgen MA, Trafton JA, Humphreys K. Response to methadone maintenance treatment of opiate dependent patients with and without significant pain. Drug Alcohol Depend 2006;82(3):187-193. [doi: 10.1016/j.drugalcdep.2005.09.005] [Medline: 16219429]
24. Dunn KE, Brooner RK, Clark MR. Severity and interference of chronic pain in methadone-maintained outpatients. Pain Med 2014;15(9):1540-1548 [FREE Full text] [doi: 10.1111/pme.12430] [Medline: 24703517]
25. Barry DT, Beitel M, Garnet B, Joshi D, Rosenblum A, Schottenfeld RS. Relations among psychopathology, substance use, and physical pain experiences in methadone-maintained patients. J Clin Psychiatry 2009;70(9):1213-1218 [FREE Full text] [doi: 10.4088/JCP.08m04367] [Medline: 19607760]
26. Barry DT, Cutter CJ, Beitel M, Kerns RD, Liong C, Schottenfeld RS. Psychiatric disorders among patients seeking treatment for co-occurring chronic pain and opioid use disorder. J Clin Psychiatry 2016;77(10):1413-1419 [FREE Full text] [doi: 10.4088/JCP.15m09963] [Medline: 27574837]
27. Peles E, Schreiber S, Adelson M. Variables associated with perceived sleep disorders in methadone maintenance treatment (MMT) patients. Drug Alcohol Depend 2006;82(2):103-110. [doi: 10.1016/j.drugalcdep.2005.08.011] [Medline: 16154297]
28. MacLean RR, Sofuoglu M, Stefanovics E, Rosenheck R. Opioid use disorder with chronic pain increases disease burden and service use. Psychol Serv 2023;20(1):157-165 [FREE Full text] [doi: 10.1037/ser0000607] [Medline: 34968125]
29. Ehde DM, Dillworth TM, Turner JA. Cognitive-behavioral therapy for individuals with chronic pain: efficacy, innovations, and directions for research. Am Psychol 2014;69(2):153-166. [doi: 10.1037/a0035747] [Medline: 24547801]
30. Dutra L, Stathopoulou G, Basden SL, Leyro TM, Powers MB, Otto MW. A meta-analytic review of psychosocial interventions for substance use disorders. Am J Psychiatry 2008;165(2):179-187 [FREE Full text] [doi: 10.1176/appi.ajp.2007.06111851] [Medline: 18198270]
31. Magill M, Ray LA. Cognitive-behavioral treatment with adult alcohol and illicit drug users: a meta-analysis of randomized controlled trials. J Stud Alcohol Drugs 2009;70(4):516-527 [FREE Full text] [doi: 10.15288/jsad.2009.70.516] [Medline: 19515291]
32. Magill M, Ray L, Kiluk B, Hoadley A, Bernstein M, Tonigan JS, et al. A meta-analysis of cognitive-behavioral therapy for alcohol or other drug use disorders: treatment efficacy by contrast condition. J Consult Clin Psychol 2019;87(12):1093-1105 [FREE Full text] [doi: 10.1037/ccp0000447] [Medline: 31599606]
33. Carroll KM, Kiluk BD. Cognitive behavioral interventions for alcohol and drug use disorders: through the stage model and back again. Psychol Addict Behav 2017;31(8):847-861 [FREE Full text] [doi: 10.1037/adb0000311] [Medline: 28857574]
34. Thomas D, Frascella J, Hall T, Smith W, Compton W, Koroshetz W, et al. Reflections on the role of opioids in the treatment of chronic pain: a shared solution for prescription opioid abuse and pain. J Intern Med 2015;278(1):92-94 [FREE Full text] [doi: 10.1111/joim.12345] [Medline: 25556772]
35. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. MMWR Recomm Rep 2016;65(1):1-49 [FREE Full text] [doi: 10.15585/mmwr.rr6501e1] [Medline: 26987082]

36. Oberleitner LM, Beitel M, Schottenfeld RS, Kerns RD, Doucette C, Napoleone R, et al. Drug counselors' attitudes toward nonpharmacologic treatments for chronic pain. J Addict Med 2016;10(1):34-39 [FREE Full text] [doi: 10.1097/ADM.0000000000000177] [Medline: 26690289]
37. McHugh RK, Hearon BA, Otto MW. Cognitive behavioral therapy for substance use disorders. Psychiatr Clin North Am 2010;33(3):511-525 [FREE Full text] [doi: 10.1016/j.psc.2010.04.012] [Medline: 20599130]
38. Carroll KM, Onken LS. Behavioral therapies for drug abuse. Am J Psychiatry 2005;162(8):1452-1460 [FREE Full text] [doi: 10.1176/appi.ajp.162.8.1452] [Medline: 16055766]
39. Carroll KM, Rounsaville BJ. A vision of the next generation of behavioral therapies research in the addictions. Addiction 2007;102(6):850-862; discussion 863-869 [FREE Full text] [doi: 10.1111/j.1360-0443.2007.01798.x] [Medline: 17523974]
40. Wen H, Xiang X, Jiang Y, Zhang H, Zhang P, Chen R, et al. Comparative efficacy of psychosocial interventions for opioid-dependent people receiving methadone maintenance treatment: a network meta-analysis. Addiction 2023;118(6):1029-1039. [doi: 10.1111/add.16167] [Medline: 36787637]
41. Rice D, Corace K, Wolfe D, Esmaeilisaraji L, Michaud A, Grima A, et al. Evaluating comparative effectiveness of psychosocial interventions adjunctive to opioid agonist therapy for opioid use disorder: a systematic review with network meta-analyses. PLoS One 2020;15(12):e0244401 [FREE Full text] [doi: 10.1371/journal.pone.0244401] [Medline: 33370393]
42. Carroll KM, Weiss RD. The role of behavioral interventions in buprenorphine maintenance treatment: a review. Am J Psychiatry 2017;174(8):738-747 [FREE Full text] [doi: 10.1176/appi.ajp.2016.16070792] [Medline: 27978771]
43. Sugarman A, Vittitow A, Cheng A, Malone M, McDonald R, Pace N, et al. Opioid use disorder treatments: an evidence map. Drug Alcohol Depend 2022;241:109657. [doi: 10.1016/j.drugalcdep.2022.109657] [Medline: 36332588]
44. Kiluk BD, Nich C, Buck MB, Devore KA, Frankforter TL, LaPaglia DM, et al. Randomized clinical trial of computerized and clinician-delivered CBT in comparison with standard outpatient treatment for substance use disorders: primary within-treatment and follow-up outcomes. Am J Psychiatry 2018;175(9):853-863 [FREE Full text] [doi: 10.1176/appi.ajp.2018.17090978] [Medline: 29792052]
45. Carroll KM, Ball SA, Martino S, Nich C, Babuscio TA, Nuro KF, et al. Computer-assisted delivery of cognitive-behavioral therapy for addiction: a randomized trial of CBT4CBT. Am J Psychiatry 2008;165(7):881-888 [FREE Full text] [doi: 10.1176/appi.ajp.2008.07111835] [Medline: 18450927]
46. Carroll KM, Ball SA, Martino S, Nich C, Babuscio TA, Rounsaville BJ. Enduring effects of a computer-assisted training program for cognitive behavioral therapy: a 6-month follow-up of CBT4CBT. Drug Alcohol Depend 2009;100(1-2):178-181 [FREE Full text] [doi: 10.1016/j.drugalcdep.2008.09.015] [Medline: 19041197]
47. Kiluk BD, Devore KA, Buck MB, Nich C, Frankforter TL, LaPaglia DM, et al. Randomized trial of computerized cognitive behavioral therapy for alcohol use disorders: efficacy as a virtual stand-alone and treatment add-on compared with standard outpatient treatment. Alcohol Clin Exp Res 2016;40(9):1991-2000 [FREE Full text] [doi: 10.1111/acer.13162] [Medline: 27488212]
48. Carroll KM, Kiluk BD, Nich C, Gordon MA, Portnoy GA, Marino DR, et al. Computer-assisted delivery of cognitive-behavioral therapy: efficacy and durability of CBT4CBT among cocaine-dependent individuals maintained on methadone. Am J Psychiatry 2014;171(4):436-444 [FREE Full text] [doi: 10.1176/appi.ajp.2013.13070987] [Medline: 24577287]
49. Carroll KM, Nich C, DeVito EE, Shi JM, Sofuoglu M. Galantamine and computerized cognitive behavioral therapy for cocaine dependence: a randomized clinical trial. J Clin Psychiatry 2018;79(1):17m11669 [FREE Full text] [doi: 10.4088/JCP.17m11669] [Medline: 29286595]
50. Shi JM, Henry SP, Dwy SL, Orazietti SA, Carroll KM. Randomized pilot trial of Web-based cognitive-behavioral therapy adapted for use in office-based buprenorphine maintenance. Subst Abus 2019;40(2):132-135 [FREE Full text] [doi: 10.1080/08897077.2019.1569192] [Medline: 30714880]
51. Heapy AA, Higgins DM, LaChappelle KM, Kirlin J, Goulet JL, Czlapinski RA, et al. Cooperative Pain Education and Self-Management (COPES): study design and protocol of a randomized non-inferiority trial of an interactive voice response-based self-management intervention for chronic low back pain. BMC Musculoskelet Disord 2016;17:85 [FREE Full text] [doi: 10.1186/s12891-016-0924-z] [Medline: 26879051]
52. Heapy AA, Higgins DM, Goulet JL, LaChappelle KM, Driscoll MA, Czlapinski RA, et al. Interactive voice response-based self-management for chronic back pain: the COPES noninferiority randomized trial. JAMA Intern Med 2017;177(6):765-773 [FREE Full text] [doi: 10.1001/jamainternmed.2017.0223] [Medline: 28384682]
53. Von Korff M, DeBar LL, Krebs EE, Kerns RD, Deyo RA, Keefe FJ. Graded chronic pain scale revised: mild, bothersome, and high-impact chronic pain. Pain 2020;161(3):651-661 [FREE Full text] [doi: 10.1097/j.pain.0000000000001758] [Medline: 31764390]
54. Stout RL, Wirtz PW, Carbonari JP, Del Boca FK. Ensuring balanced distribution of prognostic factors in treatment outcome research. J Stud Alcohol Suppl 1994;12:70-75. [doi: 10.15288/jsas.1994.s12.70] [Medline: 7723001]
55. Ball SA, Martino S, Nich C, Frankforter TL, Van Horn D, Crits-Christoph P, et al. Site matters: multisite randomized trial of motivational enhancement therapy in community drug abuse clinics. J Consult Clin Psychol 2007;75(4):556-567 [FREE Full text] [doi: 10.1037/0022-006X.75.4.556] [Medline: 17663610]

56. Carroll KM, Fenton LR, Ball SA, Nich C, Frankforter TL, Shi J, et al. Efficacy of disulfiram and cognitive behavior therapy in cocaine-dependent outpatients: a randomized placebo-controlled trial. Arch Gen Psychiatry 2004;61(3):264-272 [FREE Full text] [doi: 10.1001/archpsyc.61.3.264] [Medline: 14993114]
57. Carroll KM, Ball SA, Nich C, O'Connor PG, Eagan DA, Frankforter TL, et al. Targeting behavioral therapies to enhance naltrexone treatment of opioid dependence: efficacy of contingency management and significant other involvement. Arch Gen Psychiatry 2001;58(8):755-761 [FREE Full text] [doi: 10.1001/archpsyc.58.8.755] [Medline: 11483141]
58. Marijuana Treatment Project Research Group. Brief treatments for cannabis dependence: findings from a randomized multisite trial. J Consult Clin Psychol 2004;72(3):455-466. [doi: 10.1037/0022-006X.72.3.455] [Medline: 15279529]
59. Sheehan D, Janavs J, Baker R, Sheehan KH, Knapp E, Sheehan M. The MINI international neuropsychiatric interview (Version 7.0. 2) for DSM-5. Harm Research Institute. URL: https://harmresearch.org/product/mini-international-neuropsychiatric-interview-mini-7-0-2-14/ [accessed 2024-02-13]
60. Bovasso GB, Alterman AI, Cacciola JS, Cook TG. Predictive validity of the Addiction Severity Index's composite scores in the assessment of 2-year outcomes in a methadone maintenance population. Psychol Addict Behav 2001;15(3):171-176. [Medline: 11563793]
61. Amtmann D, Cook KF, Jensen MP, Chen WH, Choi S, Revicki D, et al. Development of a PROMIS item bank to measure pain interference. Pain 2010;150(1):173-182 [FREE Full text] [doi: 10.1016/j.pain.2010.04.025] [Medline: 20554116]
62. McHugh RK, Trinh CD, Griffin ML, Weiss RD. Validation of the craving scale in a large sample of adults with substance use disorders. Addict Behav 2021;113:106651 [FREE Full text] [doi: 10.1016/j.addbeh.2020.106651] [Medline: 33086155]
63. Sobell LC, Sobell MB. Timeline follow-back. In: Litten RZ, Allen JP, editors. Measuring Alcohol Consumption. Totowa, NJ: Humana Press; 1992.
64. Turk DC, Rudy TE. Neglected factors in chronic pain treatment outcome studies—referral patterns, failure to enter treatment, and attrition. Pain 1990;43(1):7-25. [doi: 10.1016/0304-3959(90)90046-G] [Medline: 2277718]
65. Rose M, Bjorner JB, Becker J, Fries JF, Ware JE. Evaluation of a preliminary physical function item bank supported the expected advantages of the Patient-Reported Outcomes Measurement Information System (PROMIS). J Clin Epidemiol 2008;61(1):17-33. [doi: 10.1016/j.jclinepi.2006.06.025] [Medline: 18083459]
66. Sullivan MJL, Bishop SR, Pivik J. The pain catastrophizing scale: development and validation. Psychol Assess 1995;7(4):524-532. [doi: 10.1037//1040-3590.7.4.524]
67. Nicholas MK. The pain self-efficacy questionnaire: taking pain into account. Eur J Pain 2007;11(2):153-163. [doi: 10.1016/j.ejpain.2005.12.008] [Medline: 16446108]
68. Yu L, Buysse DJ, Germain A, Moul DE, Stover A, Dodds NE, et al. Development of short forms from the PROMIS™ sleep disturbance and sleep-related impairment item banks. Behav Sleep Med 2011;10(1):6-24 [FREE Full text] [doi: 10.1080/15402002.2012.636266] [Medline: 22250775]
69. Derogatis LR. BSI 18, Brief Symptom Inventory 18: Administration, Scoring and Procedure Manual. Minneapolis, MN: NCS Pearson, Incorporated; 2001.
70. Amtmann D, Bamer AM, Liljenquist KS, Cowan P, Salem R, Turk DC, et al. The Concerns About Pain (CAP) Scale: a patient-reported outcome measure of pain catastrophizing. J Pain 2020;21(11-12):1198-1211 [FREE Full text] [doi: 10.1016/j.jpain.2020.03.004] [Medline: 32544603]
71. Olmstead TA, Ostrow CD, Carroll KM. Cost-effectiveness of computer-assisted training in cognitive-behavioral therapy as an adjunct to standard care for addiction. Drug Alcohol Depend 2010;110(3):200-207 [FREE Full text] [doi: 10.1016/j.drugalcdep.2010.02.022] [Medline: 20392575]
72. Hennink M, Kaiser BN. Sample sizes for saturation in qualitative research: a systematic review of empirical tests. Soc Sci Med 2022;292:114523 [FREE Full text] [doi: 10.1016/j.socscimed.2021.114523] [Medline: 34785096]
73. Friese S. ATLAS. ti 6: User Guide and Reference. Berlin, Germany: ATLAS ti Scientific Software Development GmbH; 2011.
74. Sullivan-Bolyai S, Bova C, Harper D. Developing and refining interventions in persons with health disparities: the use of qualitative description. Nurs Outlook 2005;53(3):127-133. [doi: 10.1016/j.outlook.2005.03.005] [Medline: 15988449]
75. Krueger RA, Casey MA. Focus Groups: A Practical Guide for Applied Research, 5th Edition. Thousand Oaks, CA: SAGE Publications; 2015.
76. Borghouts J, Eikey E, Mark G, De Leon C, Schueller SM, Schneider M, et al. Barriers to and facilitators of user engagement with digital mental health interventions: systematic review. J Med Internet Res 2021;23(3):e24387 [FREE Full text] [doi: 10.2196/24387] [Medline: 33759801]
77. Madden EF. Intervention stigma: how medication-assisted treatment marginalizes patients and providers. Soc Sci Med 2019;232:324-331. [doi: 10.1016/j.socscimed.2019.05.027] [Medline: 31125801]
78. Woo J, Bhalerao A, Bawor M, Bhatt M, Dennis B, Mouravska N, et al. "Don't judge a book its cover": a qualitative study of methadone patients' experiences of stigma. Subst Abuse 2017;11:1178221816685087 [FREE Full text] [doi: 10.1177/1178221816685087] [Medline: 28469424]
79. Anvari MS, Kleinman MB, Massey EC, Bradley VD, Felton JW, Belcher AM, et al. "In their mind, they always felt less than": the role of peers in shifting stigma as a barrier to opioid use disorder treatment retention. J Subst Abuse Treat 2022;138:108721 [FREE Full text] [doi: 10.1016/j.jsat.2022.108721] [Medline: 35067397]

80. Madden EF, Barker KK, Guerra J, Villanueva C, Sulzer SH. Variation in intervention stigma among medications for opioid use disorder. SSM—Qual Health Res 2022;2:100161 [FREE Full text] [doi: 10.1016/j.ssmqr.2022.100161]
81. Samples H, Williams AR, Crystal S, Olfson M. Psychosocial and behavioral therapy in conjunction with medication for opioid use disorder: patterns, predictors, and association with buprenorphine treatment outcomes. J Subst Abuse Treat 2022;139:108774 [FREE Full text] [doi: 10.1016/j.jsat.2022.108774] [Medline: 35337716]
82. Wyse JJ, Morasco BJ, Dougherty J, Edwards B, Kansagara D, Gordon AJ, et al. Adjunct interventions to standard medical management of buprenorphine in outpatient settings: a systematic review of the evidence. Drug Alcohol Depend 2021;228:108923 [FREE Full text] [doi: 10.1016/j.drugalcdep.2021.108923] [Medline: 34508958]
83. Dugosh K, Abraham A, Seymour B, McLoyd K, Chalk M, Festinger D. A systematic review on the use of psychosocial interventions in conjunction with medications for the treatment of opioid addiction. J Addict Med 2016;10(2):93-103 [FREE Full text] [doi: 10.1097/ADM.0000000000000193] [Medline: 26808307]
84. Madden A, Lea T, Bath N, Winstock AR. Satisfaction guaranteed? What clients on methadone and buprenorphine think about their treatment. Drug Alcohol Rev 2008;27(6):671-678. [doi: 10.1080/09595230801935706] [Medline: 19378450]
85. Ankawi B, Piette JD, Buta E, Edmond SN, MacLean RR, Higgins DM, et al. Adherence to daily interactive voice response calls for a chronic pain intervention. J Technol Behav Sci 2022;7(3):343-350. [doi: 10.1007/s41347-022-00254-6]
86. Piette JD, Rosland AM, Marinec NS, Striplin D, Bernstein SJ, Silveira MJ. Engagement with automated patient monitoring and self-management support calls: experience with a thousand chronically ill patients. Med Care 2013;51(3):216-223 [FREE Full text] [doi: 10.1097/MLR.0b013e318277ebf8] [Medline: 23222527]

Abbreviations

BRIM: Behavioral Research to Improve Medication-Based Treatment
CBT: cognitive behavioral therapy
CBT4CBT: Computer-Based Treatment for Cognitive Behavioral Therapy
COPES: Cooperative Pain Education and Self-Management
DSM-5: Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)
HEAL: Helping to End Addiction Long-Term
HIPAA: Health Insurance Portability and Accountability Act
IMPACT: Integrating the Management of Pain and Addiction via Collaborative Treatment
MOUD: medications for opioid use disorder
NIH: National Institutes of Health
OTP: opioid treatment program
OUD: opioid use disorder
REDCap: Research Electronic Data Capture
TAU: treatment as usual

Edited by A Mavragani; submitted 08.11.23; this is a non–peer-reviewed article;accepted 25.01.24; published 20.03.24.

Please cite as:
MacLean RR, Ankawi B, Driscoll MA, Gordon MA, Frankforter TL, Nich C, Szollosy SK, Loya JM, Brito L, Ribeiro MIP, Edmond SN, Becker WC, Martino S, Sofuoglu M, Heapy AA
Efficacy of Integrating the Management of Pain and Addiction via Collaborative Treatment (IMPACT) in Individuals With Chronic Pain and Opioid Use Disorder: Protocol for a Randomized Clinical Trial of a Digital Cognitive Behavioral Treatment
JMIR Res Protoc 2024;13:e54342
URL: https://www.researchprotocols.org/2024/1/e54342
doi:10.2196/54342
PMID:38506917

Proposal

Personalized AI-Driven Real-Time Models to Predict Stress-Induced Blood Pressure Spikes Using Wearable Devices: Proposal for a Prospective Cohort Study

Ali Kargarandehkordi[1], MSc; Christopher Slade[1], MSc; Peter Washington[1], PhD

Department of Information and Computer Sciences, University of Hawaii at Manoa, Honolulu, HI, United States

Corresponding Author:
Peter Washington, PhD
Department of Information and Computer Sciences
University of Hawaii at Manoa
1680 East-West Road
Honolulu, HI, 96822
United States
Phone: 1 5126800926
Email: pyw@hawaii.edu

Abstract

Background: Referred to as the "silent killer," elevated blood pressure (BP) often goes unnoticed due to the absence of apparent symptoms, resulting in cumulative harm over time. Chronic stress has been consistently linked to increased BP. Prior studies have found that elevated BP often arises due to a stressful lifestyle, although the effect of exact stressors varies drastically between individuals. The heterogeneous nature of both the stress and BP response to a multitude of lifestyle decisions can make it difficult if not impossible to pinpoint the most deleterious behaviors using the traditional mechanism of clinical interviews.

Objective: The aim of this study is to leverage machine learning (ML) algorithms for real-time predictions of stress-induced BP spikes using consumer wearable devices such as Fitbit, providing actionable insights to both patients and clinicians to improve diagnostics and enable proactive health monitoring. This study also seeks to address the significant challenges in identifying specific deleterious behaviors associated with stress-induced hypertension through the development of personalized artificial intelligence models for individual patients, departing from the conventional approach of using generalized models.

Methods: The study proposes the development of ML algorithms to analyze biosignals obtained from these wearable devices, aiming to make real-time predictions about BP spikes. Given the longitudinal nature of the data set comprising time-series data from wearables (eg, Fitbit) and corresponding time-stamped labels representing stress levels from Ecological Momentary Assessment reports, the adoption of self-supervised learning for pretraining the network and using transformer models for fine-tuning the model on a personalized prediction task is proposed. Transformer models, with their self-attention mechanisms, dynamically weigh the importance of different time steps, enabling the model to focus on relevant temporal features and dependencies, facilitating accurate prediction.

Results: Supported as a pilot project from the Robert C Perry Fund of the Hawaii Community Foundation, the study team has developed the core study app, CardioMate. CardioMate not only reminds participants to initiate BP readings using an Omron HeartGuide wearable monitor but also prompts them multiple times a day to report stress levels. Additionally, it collects other useful information including medications, environmental conditions, and daily interactions. Through the app's messaging system, efficient contact and interaction between users and study admins ensure smooth progress.

Conclusions: Personalized ML when applied to biosignals offers the potential for real-time digital health interventions for chronic stress and its symptoms. The project's clinical use for Hawaiians with stress-induced high BP combined with its methodological innovation of personalized artificial intelligence models highlights its significance in advancing health care interventions. Through iterative refinement and optimization, the aim is to develop a personalized deep-learning framework capable of accurately predicting stress-induced BP spikes, thereby promoting individual well-being and health outcomes.

International Registered Report Identifier (IRRID): DERR1-10.2196/55615

(JMIR Res Protoc 2024;13:e55615) doi:10.2196/55615

KEYWORDS

stress; hypertension; precision health; personalized artificial intelligence; wearables; ecological momentary assessments; passive sensing; mobile phone

Introduction

How This Research Benefits the People of Hawaii

According to the Department of Health Chronic Disease Prevention and Health Promotion Division, 1 in every 3 adults in Hawaii has been diagnosed with hypertension [1]. Mortality rates associated with heart disease are particularly high for Native Hawaiian and Other Pacific Islander populations, leading to 628 deaths per 100,000 residents as opposed to 154 deaths per 100,000 residents among Asian residents and 167 deaths per 100,000 among White residents in Hawaii [1].

A recent study conducted by researchers at the John A Burns School of Medicine found that Native Hawaiian and Other Pacific Islander individuals under a physician's care for hypertension experienced an 18.3 point drop in systolic blood pressure (BP) on average when participating in a 12-week hula program [2,3]. This study provides strong evidence that stress-reducing interventions can reduce hypertension in Native Hawaiian individuals. We hope to build upon this foundational research by leveraging consumer devices (ie, Fitbit) to detect moments of high stress and to provide just-in-time interventions that are culturally grounded. The first step of this long-term research plan is to develop the artificial intelligence (AI) that will power the digital intervention, and that first step is the focus of this grant proposal.

Clinical and Unmet Needs

Hypertension is an indirect cause of hundreds of thousands of annual deaths in the United States alone [4]. Known as the "silent killer"[5], elevated BP often remains unnoticed by affected individuals due to a lack of perceptible symptoms, resulting in accumulated harm over the years. While several causes of hypertension are related to an underlying health condition such as kidney disease, diabetes, sleep apnea, or hormone problems [6]; health condition; and medications combined only account for roughly 1 in 20 cases [7]. Chronic stress has been repeatedly documented to increase BP [8-10].

Prior studies have found that elevated BP often arises due to a stressful lifestyle, although the effect of exact stressors varies drastically between individuals. Due to the heterogeneous nature of both the stress and BP response to a multitude of lifestyle decisions, it can be difficult if not impossible to pinpoint the most deleterious behaviors in a personalized manner using the traditional mechanism of clinical interviews. Passive sensing technologies deployed on consumer devices have the potential to disrupt this status quo in a positive manner. By continuously monitoring a patient's lifestyle in naturalistic settings, digital technologies can provide clinicians and patients alike with actionable insights into their health trends with fine-grained precision.

We are interested in the use of wearable technologies to sense cardiovascular signals, as they are noninvasive and are already widely adopted. We will develop machine learning (ML) algorithms that analyze these biosignals to make real-time predictions about BP spikes. The resulting predictions could be used to alert, in real time, patients about unintentionally adverse behaviors as well as clinicians about the frequency of such behaviors. There is a critical opportunity and need to improve diagnostics for repeat health events to enable clinicians to monitor their patients and forecast future issues.

Innovation

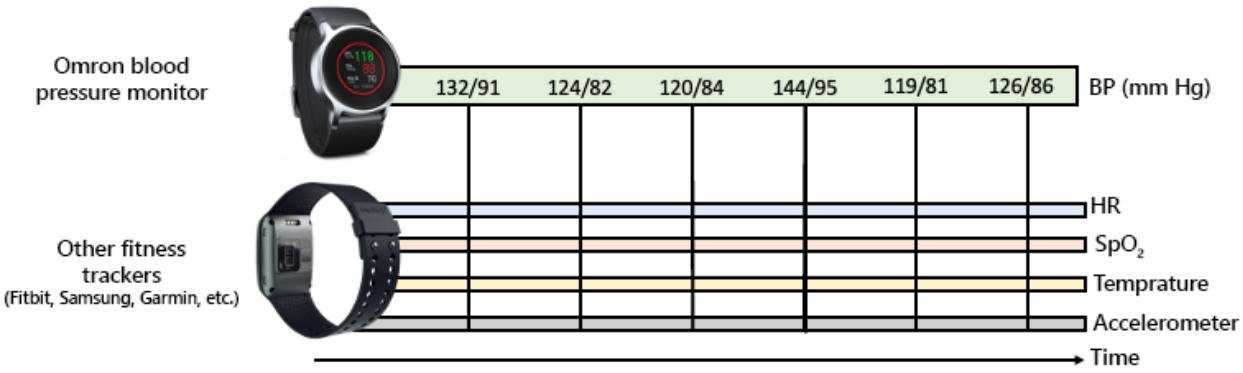
There are countless situations in health care and biomedicine where vast amounts of unlabeled data are collected from a single patient [11]. Annotations for the event of interest are frequently sparsely dispersed. The development of predictive supervised ML models is infeasible in such circumstances, as classical approaches cannot handle the complexity of the data and modern deep learning approaches require vast amounts of data [12]. For example, continuous readings from continuously worn glucose monitors can provide enough input data to train a model to make a prediction about patient energy based on glucose, but it is impracticable to require users to log their perceived energy at the same sampling frequency as a wearable device. Similar situations arise from data collected by consumer wearable health devices (eg, smart watches), smartphones, and other devices that measure biological signals.

To support AI development in these situations where vast longitudinal data are collected with minimal human-provided annotations, we propose the development of personalized ML models that are trained solely on an individual's unlabeled data to learn feature representations that are specific to their baseline temporal dynamics. We will train these models with a novel data set of Fitbit biosignals and corresponding BP readings (Figure 1). We are creating a novel method and framework, which has never been explored in health care, consisting of pretraining neural networks to learn the temporal dynamics of a patient's biosignals. This method will enable powerful, deep networks to be trained using relatively small data sets, which would not be possible without the self-supervised approach proposed here. From a usability standpoint, patients will only be required to provide tens of annotations tens of times to get a personalized predictive model.

While we propose to apply this new technological innovation toward the prediction of cardiac signals, multimodal time-series personalization can be applied to a variety of other biology and health problems where (1) multiple signals are emitted, (2) the baseline signal patterns are specific to each individual or organism, and (3) it is infeasible to acquire the vast amounts of labels required to train a supervised deep learning model from scratch. Examples of future apps of the proposed methodology include predictions stemming from nanopore signal data or multielectrode neuronal recordings. This method has the potential to dramatically advance the field of precision health care by enabling reliable ML predictions from massive but mostly unlabeled data sets which are trained in a self-supervised manner on data from a single user.

While this novel methodology could be applied to myriad domains within health and biology, a natural application is the prediction of cardiac events from wearable biosignals data. We will focus on high BP.

Figure 1. We will collect wearable biosignals from a Fitbit and use them to predict BP as measured by an Omron HeartGuide wearable BP monitor. We will use personalized self-supervised learning to enable the prediction of BP using minimal samples from the end user. BP: blood pressure; HR: heart rate.



Dissemination Plan

We plan to disseminate our research findings through a combination of (1) research publications in journals, (2) presentations at conferences, (3) as preliminary data for an National Institutes of Health (NIH) R01 application, and (4) as the basis of community-based participatory design sessions where we iteratively develop a culturally informed digital intervention using the AI created in this project. Target journals for submission include Nature Digital Medicine, Science Translational Medicine, Institute of Electrical and Electronics Engineers (IEEE) Transactions on Affective Computing, PLoS Digital Medicine, and Cell patterns. Target conferences include the American Medical Informatics Association (AMIA) Annual Symposium, the Pacific Symposium on Biocomputing (PSB), and the Conference for Computer-Human Interaction (CHI). There are several notices of special interest posted by the NIH that would support a large R01 grant application using the preliminary data from this work.

Specific Aims

We propose the following specific aims: (1) aim 1: create a novel data set of wearable sensor data and corresponding BP measurements, (2) aim 2: develop a personalized self-supervised pretraining procedure for time-series data using both contrastive learning and masked predictions, and (3) aim 3: develop a novel personalized pretraining procedure which exploits the multimodal nature of wearable time series-data.

Methods

Recruitment

We will recruit 40 carefully selected participants with diagnosed hypertension and self-reported stressful lifestyles to each participate in a 4-week remote data collection period. Each participant will wear an Omron HeartGuide BP wearable device and a Fitbit Sense 2 wearable watch during all waking hours for at least 15 hours each day. Apart from wearing the devices and periodically syncing the data to the cloud, participants will be asked to follow their normal routine for the duration of the study.

We will recruit adults aged 30 to 70 years in the state of Hawaii who have been diagnosed with hypertension and self-identify as living a high-stress lifestyle. Given the diversity of the population of Hawaii [13], we aim for the following demographic composition of our participants: 23% White, 37% Asian, 11% Native Hawaiian or Pacific Islander, 7% Black or African American, and 22% of 2 or more races. Approximately 9.5% of the recruited population will have Hispanic or Latino ethnicity.

PW has a network of clinical collaborators at the John A Burns School of Medicine at the University of Hawaii at Mānoa who also practice at local medical centers such as Queen's Medical Center and Kaiser Permanente's branch in Hawaii. We will recruit using the following sources: (1) direct recruitment from the Hawaii Pacific Health Center, which the collaborators at the Department of Psychiatry at the University of Hawaii are affiliated with and where they practice clinically; (2) via flyers and emails at the clinics which the Department of Psychiatry at the University of Hawaii regularly provides inpatient and outpatient psychiatric services and consultation at, including The Queen's Medical Center, Kapi olani Medical Center for Women and Children, and Hawaii State Hospital Community mental health centers on Hawaii Island, Moloka i, Maui, Kaua i, and Lāna i; (3) advertisements posted on the University of Hawaii campus and in public settings in Honolulu; and (4) targeted advertisements posted to social media websites. We will work with Anthony Guerrero, the chair of the Department of Psychiatry at the University of Hawaii, to ensure that the recruitment strategies and advertisement of the research program translate across cultures and to ensure effective recruitment as well as diverse and representative data.

We will exclude participants younger than 30 years and older than 70 years. We will require all potential participants to remotely complete the Perceived Stress Scale (PSS), a 10-item scale that is the most widely used psychological instrument for measuring the perception of stress [14]. We will exclude participants whose PSS score does not exceed 1 SD above the mean for at least one of their demographic brackets (age, gender, or race) as reported by Cohen et al [14]. We will also ask participants to self-report their BP. We will also exclude

participants who do not own a smartphone with continuous network connectivity. During the in-person study intake, we will measure the BP of potential study participants 3 times. We will exclude participants whose BP does not exceed 130/80 mm Hg for at least one of the measurements, as 130/80 mm Hg is the minimum cutoff for stage 1 hypertension.

Data Collection and Storage

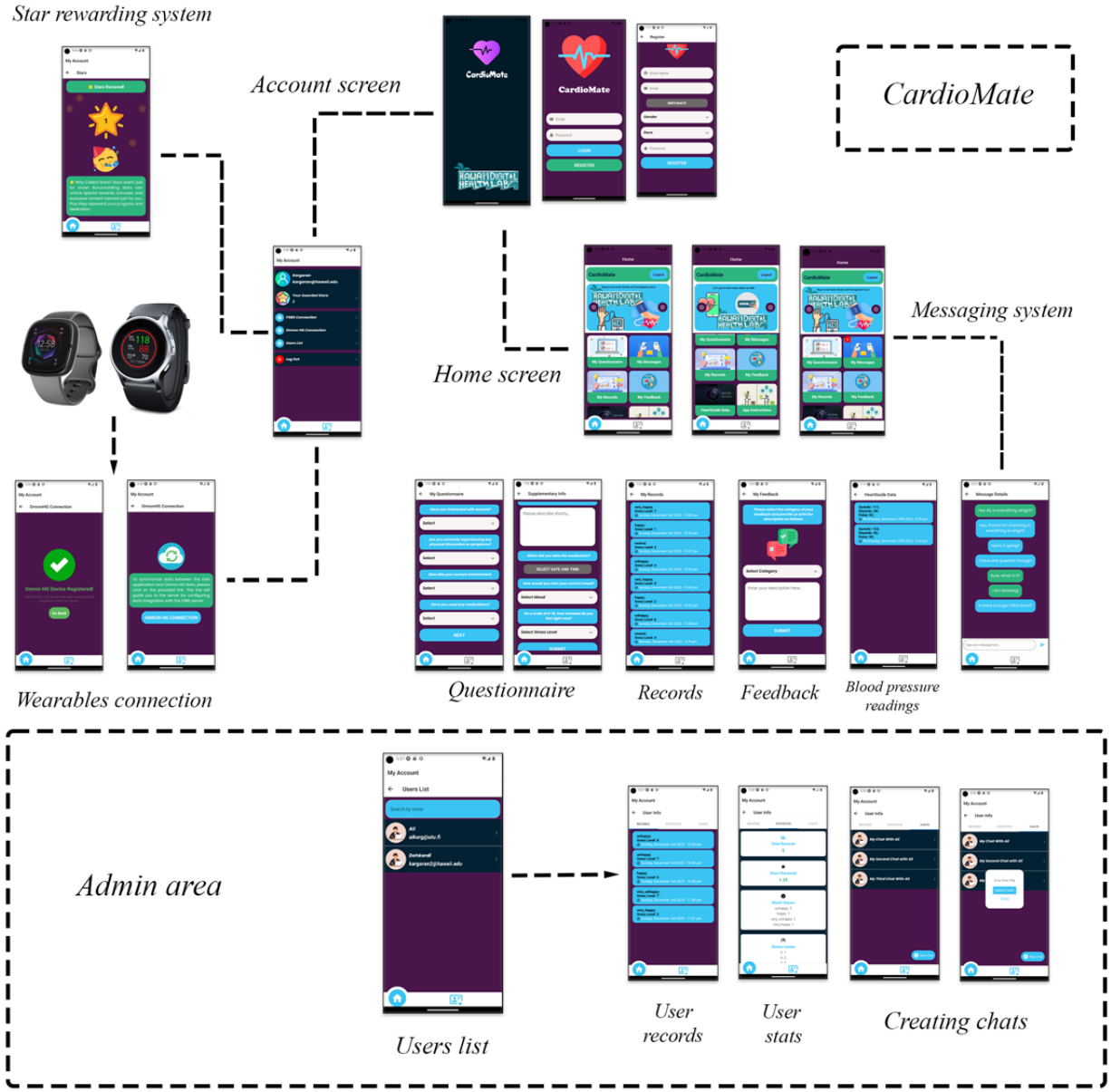
We will leverage the existing application programming interface (API) provided by both Omron and Fitbit to record the user's wearable sensor readings and upload the data to the cloud. Omron's health care API offers access to time-stamped BP readings as well as activity and sleep approximations. The Fitbit API provides access to sensor readings of heart rate (HR), gyroscope, accelerometer, breathing rate, blood oxygen levels (SpO_2), and skin temperature sensor readings. The data will be managed on each participant's smartphone devices through a mobile app, implemented for both iOS (Apple Inc) and Android, that we will develop. The study team will install the app on the user's smartphone and configure the Omron and Fitbit devices during study onboarding. The smartphone app will periodically trigger a notification reminding the participant to (1) measure their BP with the Omron wearable, (2) sync the Omron and Fitbit data to the app, and (3) connect to a network while the study app is open to allow the data to be uploaded to a centralized server.

We will store the curated data from each participant on a centralized server hosted on Amazon Web Services (AWS). Because Fitbit is owned by Google, participants' Fitbit data will be uploaded directly to Google's cloud servers, which use the same level of security as other Google products such as Gmail. Access to each participant's Fitbit data on Google's cloud servers is implemented through OAuth, which provides clients with secure delegated access to server resources on behalf of a resource owner (ie, the participants of this study). This mechanism is used by companies such as Amazon (Amazon.com, Inc), Google (Alphabet Inc), Facebook (Meta Platforms, Inc), Microsoft Corporation, and X (X Corp) to permit users to share information about their accounts with third-party applications or websites. In this case, the "third party" is the study team. The Fitbit data and BP readings will be preprocessed on an Elastic Cloud Compute instance on AWS, which is HIPAA (Health Insurance Portability and Accountability Act)-compliant. The Elastic Cloud Compute instance will store the data onto respective database tables using DynamoDB (Amazon.com). Each table will have columns for the child ID and the time-stamp. We will encrypt all server-side data and require secret access keys for data access. DynamoDB tables are automatically encrypted on the server side. To add an additional layer of security, we will implement client-side encryption on the mobile app, ensuring encrypted data transmission over HTTPS connection to move BP data between the devices and AWS. Data access will require a secret access key provided by the AWS administrators to any data analysis team. The data will not be accessible without this key. For further security, we will anonymize all user data on the server side by removing all protected health information from the DynamoDB tables.

We intend to release the curated data (Figure 2) as a publicly available data set for use in the evaluation of multimodal time-series ML models. Such data sets exist for activity and emotion recognition from wearable data, but the prediction of BP from these measurements will be a challenging task that other researchers can attempt with the release of our data set. This will be the first publicly available data set that includes at-home BP measurements alongside wearable sensors such as HR, SpO_2, and accelerometer readings. This fully anonymized data set will only be released to researchers who sign a Data Use Agreement, which will be approved by the University of Hawaii Data Governance Office.

The app comprises 2 primary screens, account and home. The account screen features user details, a star reward system for active participation in the study, and options to link 2 wearable devices (Fitbit and Omron Heartguide) for data synchronization with our secure and encrypted database. The home screen is divided into 6 sections, including questionnaires, messages, feedback, records, BP readings, and app instructions. Additionally, the CardioMate app includes an administrative area for study managers to view participant statistics and initiate personalized chats, complete with alarm and notification functions.

Figure 2. Workflow of the CardioMate app, comprising account and home screens with user details, study rewards, wearable device integration, and an administrative section for study managers.



Feasibility

The most difficult aspect of this aim will be maintaining participant engagement throughout the 4-week study period. The graduate research assistant funded by this project will dedicate some time each day toward running the study and interfacing with participants. We expect participants to open the smartphone app to sync and upload their data on a daily basis, which is a 1-minute time commitment per day.

While we expect no trouble recruiting 40 subjects for participants, we expect some participants to drop off during the study. Since we will have enough devices for 5 concurrent subjects, it will take 8 months to collect all data if no participants drop off. Our study timeline allocates 6 additional months of make-up time to collect data from new participants, accounting for >50% drop-off rate. Given the remote nature of the data collection procedures, we expect some participants to drop off from the study prematurely or to not comply with the study processes. We will therefore remotely monitor the upload progress and send an automated text and email notification to the participant if the data are not uploaded in a timely manner. If 3 consecutive days of participant noncompliance are detected, we will contact the participant for a device return.

Ethical Considerations

Under an expedited review procedure, this research project was approved on April 26, 2023, by the University of Hawaii Institutional Review Board (UHMUIF_2023-00130). The application qualified for expedited review under CFR 46.110 and 21 CFR 56.110, categories 1b, 4a, 4d, and 6. The informed consent process for this human subject research study involves participants completing an interview session where they receive comprehensive information about the research, including its purpose, procedures, and potential risks and benefits. Participants are assured of the voluntary nature of their participation and their right to refuse or withdraw at any time without penalty. For secondary analyses of research data, it is

clarified that the original informed consent allows for such analyses without additional consent, as approved by the institutional review board. Privacy and confidentiality protections are emphasized, with participant data anonymized and stored securely on HIPAA-compliant servers. Compensation for participation includes US $135 upon completion along with an additional US $15 for certain eligibility interview tasks, reflecting the time and effort required from participants while respecting the ethical standards. The consent form ensures that no identification of individual participants or users is possible in any images or supplementary materials without explicit consent, with researchers providing relevant consent forms or written communications to uphold participant privacy and consent.

AI Model Training

Self-supervised learning (SSL) is usually used to pretrain an entire data set with no explicit labeling by humans to guide the supervision task. We propose to redesign the SSL paradigm toward the task of model personalization. By pretraining a model only on the vast amounts of data curated from a single individual, the weights of the neural network will learn to make predictions using the inherent structure of each participant's biosignals. This is essential because the baseline HR, SpO_2, skin temperature, and movement patterns, regardless of stress, will vary drastically across individuals, limiting the performance of general-purpose ML models.

To train ML models that predict BP based on a user's wearable biometrics, we will develop and evaluate a series of both long short-term memory and transformer neural networks. The inputs to the models will consist of a separate 1D convolutional backbone for each biometric modality. The convolutional features will be fused upstream into a shared joint dense representation space and finally a dense prediction layer with linear activation for regression prediction. We will implement all models using Tensorflow (Google Brain) [15].

We will perform a series of self-supervised pretraining tasks to allow the networks to learn the baseline temporal dynamics of each individual's biosignals. As a pretraining task, we will develop contrastive learning methods to automatically learn embeddings that encode the structure of the signal. For each wearable sensor modality, we will run a sliding window to isolate short-time segments. We will apply signal-based data augmentation techniques to derive a new signal. We will perform contrastive learning to learn neural network embeddings that maximize the similarity between each original segment and its modified version while minimizing the similarity across segments.

We will develop a modified version of the SimCLR (simple framework for contrastive learning of visual representations) algorithm, which will be tuned for the task of personalization to a user's wearable signal readings. It is often the case that biosignals look highly similar, either due to temporal locality or relative homogeneity of the individual's activity. To account for this possibility of recurring signal patterns, we will weigh the attract and repel strength of SimCLR based on the temporal distance between two segments of a particular signal. We will run a grid search to tune this repel strength.

The data augmentation techniques that we apply to the signals will be domain-specific, keeping in mind the inherent nature of each sensor. For example, for accelerometer data, rotations simulate different sensor placements and cropping is used to diminish the dependency of event locations [16]. Across several modalities, sensor noise can be simulated through scaling, magnitude-warping, and jittering [16]. We will be careful to not apply augmentation strategies that might change the meaning of the underlying signal.

As another pretraining task, we will perform generative pretraining by masking the input signal and predicting the missing portion of the signal using a deep autoencoder architecture. Pretraining in this manner will teach the model to understand the dynamics of each time series signal independent of BP or any other labels.

We will train the model on the first 60% of data (by time), tune hyperparameters on the next 20% of data, and calculate the mean absolute error and mean squared error on the final 20%. This evaluation pattern mimics real-world use, where a model will be calibrated by a user prior to real-world deployment. It is important to emphasize that we will train and test a separate personalized ML model for each individual.

We will evaluate the models by comparing the performance with respect to the number of labeled examples used for supervised fine-tuning. A plot of this comparison will elucidate the number of BP measurements required for model calibration to a single individual. We will plot the mean squared error at 10, 20, 30, 40, 50, 75, 100, 125, and 150 BP annotations, as these are feasible amounts of labels that might be provided by a user in real-world use. To ensure a robust evaluation, we will bootstrap at least 20 random samples of BP annotation subsets for each point on the x-axis and will report the mean and 90% CI. Just as in the plain supervised learning condition, we will create a separate plot for each study participant, as the ML portion of this proposal is testing the personalization of ML models rather than a general-purpose one-size-fits-all ML model which is more typical in ML evaluations.

We will perform a similar style of analysis for other clinical outcomes using publicly available data sets such as the Wearable Stress and Affect Detection (WESAD) [17] data set, a multimodal sensor data set for stress detection of nurses in a hospital [18], and K-EmoCon, a multimodal sensor data set for continuous emotion recognition in naturalistic conversations [19]. Each of these data sets, as well as several other publicly available data sets, contains several hours of multimodal biosignal data that overlap with the signals that we propose to collect, such as skin temperature, accelerometer streams, and HR. These data sets also include time-stamped annotations of end points that are likely to be correlated with BP, including self-perceived stress.

In prior work by other researchers, SSL pretraining approaches have repeatedly demonstrated improved performance over pure supervised learning in a variety of contexts [20-23]. Our preliminary data (see Results section) support that self-supervised pretraining on data solely from each individual results in improved models over purely supervised learning. While unlikely given our preliminary data and prior SSL

publications, it is possible that minimal performance gains will be observed when applying the SSL strategies in a personalized manner. In such cases, the negative result would be a noteworthy finding due to prior successes of SSL.

Results

We have developed a smartphone app, CardioMate, that will prompt participants to measure their BP and log their stress (Figure 2). The app comprises 2 primary screens, account and home. The account screen features user details, a star reward system for active participation in the study, and options to link 2 wearable devices (Fitbit and Omron Heartguide) for data synchronization with our secure, encrypted database. The home screen is divided into 6 sections, including questionnaires, messages, feedback, records, BP readings, and app instructions. Additionally, the CardioMate app includes an administrative area for study managers to view participant statistics and initiate personalized chats, complete with alarm and notification functions.

Data collection commenced on February 15, 2024. As of the manuscript submission date of February 24, 2024, a total of 2 participants have been recruited. The data collection period for each participant spans 28 days. Upon completion of the data collection period for each participant, we will proceed with the personalized machine learning model development to predict stress-induced BP spikes in real time. We aim to recruit a total of at least 45 participants and complete the relevant data collection, data analysis, and personalized ML development for each participant by the end of December 2024.

Our initial sets of published experiments have demonstrated promise for personalized SSL of stress but with some caveats. Our experiments on the WESAD data set demonstrated that deep learning model performance improves drastically when using self-supervised personalization when compared to personalization without SSL when there are a small number of labeled data points for supervision [24]. This effect diminishes with increasing amounts of labeled data [25,26], aligning with prior work that demonstrates that SSL is only beneficial under low-label settings. We have also tried these methods on a particularly challenging data set, a multimodal sensor data set for stress detection of nurses in a hospital [18]. This data set consists of wearable biosignals measured from nurses who wore Empatica E4 wristbands while conducting their normal shifts. This data set is difficult because (1) the data were collected in the wild rather than in controlled laboratory settings and (2) individual nurses were not consistent about their labeling practices, leading to sparse, irregular, noisy, and otherwise messy labels. Consequently, we found that the difference in area under curve and the receiver operating characteristic curve scores for self-supervised models was only about 2.5% higher on average compared against an equivalent baseline model [27], and this increase is within the margin of error due to the limited sample size. This lack of improvement in noisy annotation settings highlights the need for HCI innovations to improve data labeling quality for personalized AI within naturalistic settings.

We have also observed improved performance when personalizing affect-related prediction tasks without personalization both using classical ML [28] and deep learning [29], as well as when only applying SSL without personalization [30]. When disentangling and comparing the effects of SSL and personalization separately, we find that SSL yields more benefit than individualization on nonaffective medical data with large time intervals between data points, suggesting that the sampling frequency and other data considerations must be considered [30]. Collectively, these preliminary results demonstrate promise for the core ML approach that we propose.

Discussion

The primary objective of this study is to leverage ML algorithms for real-time predictions of stress-induced BP spikes using consumer wearable devices such as Fitbit, providing actionable insights to both patients and clinicians to improve diagnostics and enable proactive health monitoring. Our study is motivated by recent research conducted at the John A Burns School of Medicine, which found that Native Hawaiian and other Pacific Islander individuals under a physician's care for hypertension experienced an average drop of 18.3 points in systolic BP after participating in a 12-week hula program [2,3]. This study provides strong evidence that stress-reducing interventions can reduce hypertension in Native Hawaiian individuals. We hope to build upon this foundational research by leveraging consumer devices, such as Fitbit, to detect moments of high stress and provide just-in-time interventions that are culturally grounded. The first phase of this long-term research plan involves developing the AI necessary to power the digital intervention, which is the primary focus of this proposal.

The successful development of ML algorithms tailored to individual participants signifies a significant advancement in personalized health care interventions. By using longitudinal data from Fitbit devices and corresponding stress level labels from Ecological Momentary Assessment reports, the study will be able to capture individual-specific patterns effectively, enabling accurate predictions of stress-induced BP spikes. This approach not only enhances the understanding of stress-related hypertension but also provides opportunities for targeted interventions and improved patient outcomes.

Furthermore, the findings of this study contribute to the growing body of literature on the use of wearable devices and ML in health care. The adoption of transformer models for personalized prediction tasks, coupled with SSL techniques for pretraining, represents a novel approach to leveraging advanced computational techniques for real-time health monitoring. By dynamically weighing the importance of different time steps and focusing on relevant temporal features and dependencies, transformer models offer a powerful tool for predicting complex physiological responses such as stress-induced BP spikes. These findings will add to the existing literature by highlighting the potential of ML in improving the accuracy and efficiency of health monitoring systems, particularly in the context of personalized interventions for stress-related hypertension.

It is essential to acknowledge the limitations of this study design. One limitation is the relatively small sample size, which may

limit the generalizability of the findings. Additionally, the study focuses primarily on predicting stress-induced BP spikes using wearable device data streams and may not capture other factors contributing to hypertension. Future research should aim to address these limitations by including larger and more diverse samples and exploring additional predictors of hypertension.

The findings of this study will demonstrate the feasibility and potential benefits of leveraging ML algorithms for real-time predictions of stress-induced BP spikes using consumer wearable devices. By developing personalized AI models based on individual biosignals, the study will provide valuable insights into the monitoring and management of stress-related hypertension. These findings will have broader implications for personalized health care interventions and underscore the importance of integrating advanced computational techniques into health care systems to improve patient outcomes. Through iterative refinement and optimization, we aim to develop a personalized deep-learning framework capable of accurately predicting stress-induced BP spikes, thereby promoting individual well-being and health outcomes.

Acknowledgments

This project received a grant (#MedRes_2023_00002689) from the Robert C Perry Fund of the Hawaii Community Foundation.

Data Availability

Upon the completion of the data collection phase, the data sets generated and analyzed during this study will be available in a public repository. The data citation should include a persistent identifier (eg, web URL or DOI) cited per journal style in the reference list. The amassed data will be fully anonymized and made accessible to the academic community. Subsequently, comprehensive guidelines, together with a designated link facilitating data retrieval and use, will be provided.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review reports from the Medical Research Advisory Committee of the Hawaii Community Foundation (HCF).
[PDF File (Adobe PDF File), 949 KB - resprot_v13i1e55615_app1.pdf]

References

1. Ige DY, Virginia P. Hawaii Department of Health urges everyone to “check your pressure” during American Heart Month. Department of Health, State of Hawaii. 2018. URL: https://health.hawaii.gov/news/files/2018/01/18-012-American-Heart-Month-Revised.pdf [accessed 2023-02-05]
2. Kaholokula JK, Look M, Mabellos T, Zhang G, de Silva M, Yoshimura S, et al. Cultural dance program improves hypertension management for Native Hawaiians and Pacific Islanders: a pilot randomized trial. J Racial Ethn Health Disparities 2017;4(1):35-46 [FREE Full text] [doi: 10.1007/s40615-015-0198-4] [Medline: 27294768]
3. Maskarinec GG, Look M, Tolentino K, Trask-Batti M, Seto T, de Silva M, et al. Patient perspectives on the Hula Empowering Lifestyle Adaptation Study: benefits of dancing hula for cardiac rehabilitation. Health Promot Pract 2015;16(1):109-114 [FREE Full text] [doi: 10.1177/1524839914527451] [Medline: 24677383]
4. About multiple cause of death, 1999-2020. Centers for Disease Control and Prevention, National Center for Health Statistics. Atlanta, GA; 1999. URL: https://wonder.cdc.gov/mcd-icd10.html [accessed 2022-02-21]
5. A global brief on hypertension: silent killer, global public health crisis: World Health Day 2013. World Health Organization. 2013. URL: https://www.who.int/publications/i/item/a-global-brief-on-hypertension-silent-killer-global-public-health-crisis-world-health-day-2013 [accessed 2024-02-08]
6. Charles L, Triscott J, Dobbs B. Secondary hypertension: discovering the underlying cause. Am Fam Physician 2017;96(7):453-461 [FREE Full text] [Medline: 29094913]
7. Causes: high blood pressure (hypertension). United Kingdom National Health Service. 2022. URL: https://www.nhs.uk/conditions/high-blood-pressure-hypertension/causes/ [accessed 2024-02-08]
8. Brady SS, Matthews KA. Chronic stress influences ambulatory blood pressure in adolescents. Ann Behav Med 2006;31(1):80-88 [FREE Full text] [doi: 10.1207/s15324796abm3101_12] [Medline: 16472042]
9. Brand N, Hanson E, Godaert G. Chronic stress affects blood pressure and speed of short-term memory. Percept Mot Skills 2000;91(1):291-298. [doi: 10.2466/pms.2000.91.1.291] [Medline: 11011900]
10. Hassoun L, Herrmann-Lingen C, Hapke U, Neuhauser H, Scheidt-Nave C, Meyer T. Association between chronic stress and blood pressure: findings from the German Health Interview and Examination Survey for Adults 2008-2011. Psychosom Med 2015;77(5):575-582. [doi: 10.1097/PSY.0000000000000183] [Medline: 25967356]
11. Krishnan R, Rajpurkar P, Topol EJ. Self-supervised learning in medicine and healthcare. Nat Biomed Eng 2022;6(12):1346-1352. [doi: 10.1038/s41551-022-00914-1] [Medline: 35953649]

12. Najafabadi MM, Villanustre F, Khoshgoftaar TM, Seliya N, Wald R, Muharemagic E. Deep learning applications and challenges in big data analytics. J Big Data 2015;2(1):1 [FREE Full text] [doi: 10.1186/s40537-014-0007-7]
13. America Counts Staff. Hawaii added more than 94,000 people since 2010. US Census Bureau. 2021. URL: https://www.census.gov/library/stories/state-by-state/hawaii-population-change-between-census-decade.html [accessed 2022-08-31]
14. Cohen S, Kamarck T, Mermelstein R. Perceived stress scale. Measuring Stress 1994;10(2):1-2.
15. Abadi M. TensorFlow: learning functions at scale. 2016 Presented at: ICFP 2016: Proceedings of the 21st ACM SIGPLAN International Conference on Functional Programming; September 18-24, 2016; Nara, Japan p. 1-1. [doi: 10.1145/2951913.2976746]
16. Um TT, Pfister FMJ, Pichler D, Endo S, Lang M, Hirche S, et al. Data augmentation of wearable sensor data for Parkinson's disease monitoring using convolutional neural networks. 2017 Presented at: ICMI '17: Proceedings of the 19th ACM International Conference on Multimodal Interaction; November 13-17, 2017; Glasgow, UK p. 216-220. [doi: 10.1145/3136755.3136817]
17. Schmidt P, Attila R, Robert D, Claus M, Van Laerhoven K. Introducing WESAD, a multimodal dataset for wearable stress and affect detection. 2018 Presented at: ICMI '18: Proceedings of the 20th ACM International Conference on Multimodal Interaction; October 16-20, 2018; Boulder, CO, USA p. 400-408. [doi: 10.1145/3242969.3242985]
18. Hosseini S, Gottumukkala R, Katragadda S, Bhupatiraju RT, Ashkar Z, Borst CW, et al. A multimodal sensor dataset for continuous stress detection of nurses in a hospital. Sci Data 2022;9(1):255 [FREE Full text] [doi: 10.1038/s41597-022-01361-y] [Medline: 35650267]
19. Park CY, Cha N, Kang S, Kim A, Khandoker AH, Hadjileontiadis L, et al. K-EmoCon, a multimodal sensor dataset for continuous emotion recognition in naturalistic conversations. Sci Data 2020;7(1):293 [FREE Full text] [doi: 10.1038/s41597-020-00630-y] [Medline: 32901038]
20. Chowdhury A, Rosenthal J, Waring J, Umeton R. Applying self-supervised learning to medicine: review of the state of the art and medical implementations. Informatics 2021;8(3):59 [FREE Full text] [doi: 10.3390/informatics8030059]
21. Lan X, Ng D, Hong S, Feng M. Intra-inter subject self-supervised learning for multivariate cardiac signals. Proc AAAI Conf Artif Intell 2022;36(4):4532-4540 [FREE Full text] [doi: 10.1609/aaai.v36i4.20376]
22. Li Y, Wei D, Chen J, Cao S, Zhou H, Zhu Y, et al. Efficient and effective training of COVID-19 classification networks with self-supervised dual-track learning to rank. IEEE J Biomed Health Inform 2020;24(10):2787-2797 [FREE Full text] [doi: 10.1109/JBHI.2020.3018181] [Medline: 32816680]
23. Tiu E, Talius E, Patel P, Langlotz CP, Ng AY, Rajpurkar P. Expert-level detection of pathologies from unannotated chest X-ray images via self-supervised learning. Nat Biomed Eng 2022;6(12):1399-1406 [FREE Full text] [doi: 10.1038/s41551-022-00936-9] [Medline: 36109605]
24. Islam T, Washington P. Individualized stress mobile sensing using self-supervised pre-training. Appl Sci 2023;13(21):12035 [FREE Full text] [doi: 10.3390/app132112035]
25. Islam T, Washington P. Personalization of stress mobile sensing using self-supervised learning. ArXiv 2023 [FREE Full text] [doi: 10.48550/arXiv.2308.02731]
26. Islam T, Washington P. Personalized prediction of recurrent stress events using self-supervised learning on multimodal time-series data. ArXiv 2023:9 [FREE Full text] [doi: 10.48550/arXiv.2307.03337]
27. Eom S, Eom S, Washington P. SIM-CNN: self-supervised individualized multimodal learning for stress prediction on nurses using biosignals. In: Machine Learning for Multimodal Healthcare Data: First International Workshop, ML4MHD 2023, Honolulu, Hawaii, USA, July 29, 2023, Proceedings. Cham: Springer Nature Switzerland; 2023:155-171.
28. Kargarandehkordi A, Kaisti M, Washington P. Personalization of affective models using classical machine learning: a feasibility study. Appl Sci 2024 Feb 06;14(4):1337 [FREE Full text] [doi: 10.3390/app14041337]
29. Li J, Washington P. A comparison of personalized and generalized approaches to emotion recognition using consumer wearable devices: machine learning study. arXiv Preprint published online August 28, 2023. [FREE Full text] [doi: 10.2196/preprints.52171]
30. Nimitsurachat P, Washington P. Self-supervised learning for audio-based emotion recognition. ArXiv 2023 [FREE Full text] [doi: 10.48550/arXiv.2307.12343]

Abbreviations

AI: artificial intelligence
AMIA: American Medical Informatics Association
API: application programming interface
AWS: Amazon Web Services
BP: blood pressure
CHI: Computer-Human Interaction
HIPAA: Health Insurance Portability and Accountability Act
HR: heart rate
IEEE: Institute of Electrical and Electronics Engineers

ML: machine learning
NIH: National Institutes of Health
PSB: Pacific Symposium on Biocomputing
PSS: Perceived Stress Scale
SimCLR: simple framework for contrastive learning of visual representations
SpO_2: blood oxygen level
SSL: self-supervised learning
WESAD: Wearable Stress and Affect Detection

Edited by A Mavragani; submitted 18.12.23; this is a non–peer-reviewed article;accepted 05.02.24; published 25.03.24.

Please cite as:
Kargarandehkordi A, Slade C, Washington P
Personalized AI-Driven Real-Time Models to Predict Stress-Induced Blood Pressure Spikes Using Wearable Devices: Proposal for a Prospective Cohort Study
JMIR Res Protoc 2024;13:e55615
URL: https://www.researchprotocols.org/2024/1/e55615
doi:10.2196/55615
PMID:38526539

Protocol

Computer-Facilitated Screening and Brief Intervention for Alcohol Use Risk in Adolescent Patients of Pediatric Primary Care Offices: Protocol for a Cluster Randomized Controlled Trial

Lydia A Shrier[1,2], MPH, MD; Madison M O'Connell[1], MPH; Alessandra Torres[3], MPH; Laura P Shone[3], MSW, DrPH; Alexander G Fiks[4], MD, MSCE; Julia A Plumb[1], BS; Jessica L Maturo[1], BA; Nicholas H McCaskill[1], BA; Donna Harris[3], MA; Pamela J Burke[1,5], RN, PhD, PPCNP-BC; Thatcher Felt[6], DO; Marie Lynd Murphy[7], MD; Lon Sherritt[8], MPH; Sion Kim Harris[1,2], RN, PhD, CPH

[1]Division of Adolescent/Young Adult Medicine, Boston Children's Hospital, Boston, MA, United States

[2]Department of Pediatrics, Harvard Medical School, Boston, MA, United States

[3]Primary Care Research, American Academy of Pediatrics, Itasca, IL, United States

[4]Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA, United States

[5]School of Nursing, Bouvé College of Health Sciences, Northeastern University, Boston, MA, United States

[6]Yakima Valley Farm Workers Clinic, Grandview, WA, United States

[7]Elmwood Pediatric Group, Rochester, NY, United States

[8]Cornerstone Systems Northwest, Lynden, WA, United States

Corresponding Author:
Lydia A Shrier, MPH, MD
Division of Adolescent/Young Adult Medicine
Boston Children's Hospital
300 Longwood Ave
Mailstop 3189
Boston, MA, 02115
United States
Phone: 1 617 355 8306
Email: lydia.shrier@childrens.harvard.edu

Abstract

Background: Alcohol and other substance use disorders usually begin with substance use in adolescence. Pediatric primary care offices, where most adolescents receive health care, are a promising venue for early identification of substance use and for brief intervention to prevent associated problems and the development of substance use disorder.

Objective: This study tests the effects of a computer-facilitated screening and brief intervention (cSBI) system (the *CRAFFT [Car, Relax, Alone, Forget, Family/Friends, Trouble] Interactive System* [CRAFFT-IS]) on heavy episodic drinking, riding with a driver who is substance impaired, or driving while substance impaired among adolescents aged 14 to 17 years presenting for a well visit at pediatric primary care practices.

Methods: We are conducting a cluster randomized controlled trial of the CRAFFT-IS versus usual care and recruiting up to 40 primary care clinicians at up to 20 pediatric primary care practices within the American Academy of Pediatrics (AAP) Pediatric Research in Office Settings network. Clinicians are randomized 1:1 within each practice to implement the CRAFFT-IS or usual care with a target sample size of 1300 adolescent patients aged 14 to 17 years. At study start, intervention clinicians complete web-based modules, trainer-led live sessions, and mock sessions to establish baseline competency with intervention counseling. Adolescents receive mailed recruitment materials that invite adolescents to complete an eligibility survey. Eligible and interested adolescents provide informed assent (parental permission requirement has been waived). Before their visit, enrolled adolescents seeing intervention clinicians complete a self-administered web-based CRAFFT screening questionnaire and view brief psychoeducational content illustrating substance use–associated health risks. During the visit, intervention clinicians access a computerized summary of the patient's screening results and a tailored counseling script to deliver a motivational interviewing–based brief intervention. All participants complete previsit, postvisit, and 12-month follow-up study assessments. Primary outcomes include past 90-day heavy episodic drinking and riding with a driver who is substance impaired at 3-, 6-, 9-, and 12-month follow-ups. Multiple logistic regression modeling with generalized estimating equations and mixed effects modeling will be used

in outcomes analyses. Exploratory aims include examining other substance use outcomes (eg, cannabis and nicotine vaping), potential mediators of intervention effect (eg, self-efficacy not to drink), and effect moderation by baseline risk level and sociodemographic characteristics.

Results: The AAP Institutional Review Board approved this study. The first practice and clinicians were enrolled in August 2022; as of July 2023, a total of 6 practices (23 clinicians) had enrolled. Recruitment is expected to continue until late 2024 or early 2025. Data collection will be completed in 2025 or 2026.

Conclusions: Findings from this study will inform the promotion of high-quality screening and brief intervention efforts in pediatric primary care with the aim of reducing alcohol-related morbidity and mortality during adolescence and beyond.

Trial Registration: ClinicalTrials.gov NCT04450966; https://www.clinicaltrials.gov/study/NCT04450966

International Registered Report Identifier (IRRID): DERR1-10.2196/55039

(JMIR Res Protoc 2024;13:e55039) doi:10.2196/55039

KEYWORDS

alcohol; substance use; adolescent; primary care; prevention; intervention; screening; brief intervention; computer-facilitated screening and brief intervention; cSBI; mobile phone

Introduction

Background and Rationale

Alcohol and other drugs are a major contributor to morbidity and mortality each year [1]. Most substance use disorders (SUDs) have a pediatric origin, and substance use remains among the most prevalent of adolescent risk behaviors [2-4]. In addition, motor vehicle crashes remain a leading cause of death among adolescents, and alcohol- or drug-impaired driving and riding with a driver who is substance impaired play a major role [5].

Pediatric primary care offices, where the majority of adolescents receive health care [6], are a promising venue for early identification of problematic substance use among adolescents and for brief intervention to prevent further problems. A substantial and increasing proportion of adolescents see a primary care clinician yearly [7] and have trusting, longitudinal relationships with their clinicians [8]. Primary care visits are opportunities for private conversations that support adolescents' autonomy and confidentiality while placing topics such as substance use in a nonpejorative health risk context.

The American Academy of Pediatrics (AAP) recommends alcohol, tobacco, and other drug use annual screening as part of routine care starting at age 11 years [9,10]. However, a national survey found that only approximately half of adolescents who had a past-year visit with a physician reported being asked about alcohol use [11,12]. Even when substance use screenings are performed, they can be of low quality if clinicians do not use a structured, validated screening tool or if they ask questions while caregivers are present [13,14]. Screenings also seldom include questions about substance-impaired driving or riding with a driver who is substance impaired [15]. Pediatric primary care clinicians also face barriers to brief intervention based on screen responses, including insufficient time during the appointment, a lack of familiarity with validated screening tools, and a lack of experience with managing care for patients who screen positive [16-18].

To overcome these barriers, digital technology can be applied to support consistent, effective screening and tailored intervention for adolescent substance use using evidence-based tools and approaches [19,20]. Clinicians may prefer to use technological tools such as tablet computers for previsit screening and electronic medical record–embedded decision support to enable brief intervention delivery [21]. Accordingly, we designed the CRAFFT (Car, Relax, Alone, Forget, Family/Friends, Trouble) Interactive System (CRAFFT-IS) to increase the frequency and quality of screenings in pediatric primary care, support a personalized response to results, and efficiently address alcohol and drug use and associated riding risks [22]. The CRAFFT-IS comprises a computer self-administered screening for patients (using the well-validated and widely used CRAFFT screening tool [23-25]), followed by psychoeducational content on the health risks of substance use, which adolescents complete before the clinician encounter. Clinicians access a computerized dashboard to view their patient's screening results and prompts for brief motivational interviewing (MI)–based counseling tailored to their patient's screening responses (clinician report).

CRAFFT-IS development was informed by the information-motivation-behavioral skills model [26], the health belief model [27,28], and social cognitive theory [29,30]. These models posit that individuals' health risk behaviors are predicted by their *attention* to the behavior, *knowledge* about its health impacts, perceived *severity* of the harms that could result, perceived *benefits* of avoiding the behavior, and perceived *self-efficacy* to avoid the behavior. The CRAFFT-IS uses an MI-based approach to alert patients' attention to the topic of alcohol use within a health context, enhance their awareness and perceived severity of the potential health harms of alcohol use, and boost their motivation and self-efficacy to avoid use.

We tested an initial version of the CRAFFT-IS among adolescent primary care patients at 9 practices in 3 New England states (Connecticut, Massachusetts, and Vermont) using a quasi-experimental design in which each office served as its own historical control (usual care [UC] phase followed by intervention phase; details reported elsewhere) [31-34]. Compared to UC patients, intervention patients reported double

the rate of receiving clinician advice about alcohol and, among those with prior drinking at baseline, had one-third lower drinking risk in the 3-month follow-up [31]. We also found a 22% lower risk for heavy episodic drinking (HED) among those with prior HED at baseline and a 30% lower risk for riding with a driver who is substance impaired [33].

We then enhanced the clinician advice to include brief MI strategies (eg, eliciting a patient's own reasons for avoiding use) while keeping the counseling brief enough for delivery by busy primary care clinicians. We pilot-tested this enhanced system compared to UC among adolescent patients seen for well visits at 5 Boston-area pediatric practices in a patient-randomized controlled trial. Intervention patients reported a 21% higher rate of receiving counseling about alcohol. Those reporting prior drinking at baseline (n=192) had a 34% lower risk for reporting HED during the 12-month follow-up [22]. Furthermore, those with riding risk at baseline (n=99) had a 42% lower risk of reporting riding with a driver who is substance impaired at the 12-month follow-up [35]. The CRAFFT-IS was also highly acceptable to the clinicians in the study, with 90% of the 49 clinicians agreeing that the system was useful, and 82% reporting that it increased their confidence in providing brief counseling [36].

To evaluate the replicability of these findings in a larger, more geographically diverse sample, we are now conducting a multisite effectiveness trial of the CRAFFT-IS among adolescent patients aged 14 to 17 years presenting for a well visit at practices within the national AAP Pediatric Research in Office Settings (PROS) network. This trial uses a clinician-randomized design, plans an adequately powered sample, and tests the intervention more broadly beyond New England. The CRAFFT-IS being tested in this study includes an updated version of the CRAFFT screen that includes nicotine vaping, now a leading form of substance use among adolescents [37]. It also includes updated psychoeducation material to reflect more current scientific knowledge and a revised brief counseling protocol to enhance alignment with MI-based counseling approaches.

Objectives

The primary objective of the Adolescent Substance Use Prevention and Intervention Research (ASPIRE) study is to test the effect of the CRAFFT-IS on past 90-day HED over 12 months' follow-up among adolescents who report past 12-month drinking at baseline. Our secondary objective is to test the effect of the CRAFFT-IS on riding with a driver who is substance impaired or driving while substance impaired (*riding or driving risk*) over 12 months' follow-up. Additional exploratory study objectives include evaluating (1) hypothesized effect mediators (eg, perceived risk of harm and refusal self-efficacy) and moderators (eg, baseline risk level and gender), (2) efficacy for reducing the use of other commonly used substances among adolescents (ie, nicotine and cannabis), and (3) efficacy for reducing the negative consequences of substance use.

Methods

Study Team

This study is being performed in the national AAP PROS network of pediatric primary care practices. The AAP PROS network consists of 67,000 pediatrician members whose guiding mission is to foster and conduct national collaborative practice-based research for improving child health. Boston Children's Hospital (BCH) investigators are conducting the study in collaboration with the AAP PROS team. BCH conducts patient recruitment; participant retention; and data collection, management, and analysis activities. BCH also provides training and fidelity monitoring for clinicians delivering the intervention and convenes the data safety and monitoring board (DSMB). The AAP PROS team leads practice and clinician recruitment and data collection activities and hosts 2 PROS-member pediatrician advisors who provide input on study decisions from the perspective of community-based pediatric primary care clinicians.

Ethical Considerations

The AAP Institutional Review Board (IRB) is the single IRB for the study. The AAP IRB initially approved this study on May 27, 2022, after full board review (#22 HA 01). Approval included a waiver of parental permission and a partial waiver of Health Insurance Portability and Accountability Act (HIPAA) authorization. We sought a partial waiver of HIPAA authorization because patient recruitment activities involve the exchange of patient health information from practices to the BCH study team. Furthermore, we sought a waiver of parental permission due to the minimal risk nature of the study, the developmental maturity of the target sample (adolescents aged 14-17 years), and the sensitivity of the substance-related topic. Our previous study on consent in adolescent substance use research showed that requiring parental permission resulted in a substantially higher study refusal rate (60% vs 20%) and a sample biased toward lower levels of substance use and substance-related problems [38]. Importantly, recruitment and assent materials state the voluntary nature of the study, emphasize that eligible adolescents *do not* have to have used alcohol or other substances to join the study, and encourage—but do not require—adolescents to discuss the study with their caregivers. The combination of these conditions supports parental involvement, preserves the privacy and confidentiality of adolescents who *do* use alcohol or other substances, and acknowledges adolescent autonomy to make an informed decision about participating.

The protocol version described in this paper was approved on June 21, 2023. Should there be modifications to the approved protocol or study materials, we will submit an amendment to the AAP IRB, and if applicable, the relying IRB at BCH. In addition, we will report scientific changes to the National Institute on Alcohol Abuse and Alcoholism (NIAAA) as needed or in the yearly progress report, at which point we will also update the trial registry on ClinicalTrials.gov.

In this trial, patient privacy and confidentiality protection is supported by executing a data transfer agreement between participating practices and BCH, assigning patients a numeric

study identifier and by storing identifiable data in secure and restricted-access network locations separate from survey data. This study operates under a National Institutes of Health certificate of confidentiality. Assent materials state that only deidentified data will be shared outside of the study team (refer to the Data Access and Dissemination subsection).

Participating clinicians and practice staff members are required to provide informed consent. AAP PROS staff will send study recruitment materials to the designated contact clinician at each potentially eligible practice. Practices that are interested in participating will have a designated lead clinician submit a practice intake survey to confirm study eligibility of the practice and its clinicians. If practices are eligible, the AAP PROS staff will obtain written informed consent from all participating clinicians (Multimedia Appendix 1) as well as designated practice staff members who will handle and exchange patient data, answer patient or family questions, and otherwise support study activities at their site. Each participating practice will be offered a US $1000 honorarium after concluding patient recruitment at their practice and be able to keep all intervention-related materials, including the tablet computers provided for CRAFFT-IS implementation. Clinicians will be offered lunch accommodations (up to US $25 per person) for attending study orientation training and debriefing focus groups. In addition, clinicians in both trial arms can receive up to 12 continuing medical education credits for completing study training activities (UC clinicians will be offered CRAFFT-IS training at study completion at their practice). Board-certified pediatricians in the intervention arm may also receive optional maintenance of Certification Part 4 (up to 25 points) for a quality improvement activity spanning at least 3 quarterly feedback cycles. To complete this certification, intervention clinicians receive their participating patients' aggregated postvisit data reporting receipt of counseling and compare their performance with a standardized benchmark. Intervention clinicians receive a US $5 electronic merchandise gift card for attending an optional *office hour* with the trainers by videoconference every 1 to 2 months and US $10 for completing a debriefing survey about their experience of, and views about, the CRAFFT-IS at study completion.

Adolescents must provide verbal informed assent to participate (Multimedia Appendix 2). On a regular schedule (eg, every 2 weeks), each practice will send a BCH research assistant (RA) a list of age-eligible adolescent patients with upcoming well visits in the next 2 to 6 weeks. The BCH RA will then mail a study invitation coaddressed to adolescents and their caregivers, which includes an informational letter on the practice's letterhead and a study flyer with a QR code that leads to the brief study eligibility survey. Recruitment materials emphasize that adolescents do not need to have used substances to join the study, just as those with riding risk do not need to have used a substance themselves. Within 2 weeks of an adolescent's scheduled visit, the RA will attempt to contact the adolescent by telephone to invite them to complete the eligibility survey, which the RA, based on the adolescent's preference, can administer verbally or send for self-completion using an electronic link by SMS text message or email. At any point, a caregiver or adolescent can opt out of being contacted further.

Eligible patients will be directed to an electronic information sheet and a 5-minute video brochure developed in collaboration with youth advisors. During a telephone call before the adolescent patients' visit, a BCH RA will summarize key information using a standard assent script. If willing to join the study and able to answer 6 questions assessing study understanding correctly, adolescents will have the option to discuss the study with a parent or guardian and may then provide their verbal assent to participate. Adolescents who turn 18 during the study period will be asked to consent as an adult on or near their 18th birthday.

In addition to obtaining study assent, we will ask adolescents whether they assent or decline to have their deidentified study data shared with the NIAAA Data Archive ($NIAAA_{DA}$), a national data repository to which NIAAA-funded investigators conducting human subjects research are expected to submit deidentified individual-level data [39]. This data sharing is not a condition of study participation and does not require parental permission. Adolescents can receive up to US $100 in small-value merchandise electronic gift cards for completion of study surveys (US $5, US $10, or US $15 for a survey, depending on its length).

Study Design and Randomization

The study is a cluster randomized controlled trial involving 2 arms, intervention (CRAFFT-IS) and control (UC), with prospective follow-up for 12 months. Clinician randomization occurs within practice and on a rolling basis as practices enroll into the study. Participating pediatric primary care clinicians (doctor of medicine [MD], doctor of osteopathic medicine [DO], nurse practitioner [NP], and physician assistant [PA]) are randomly assigned to 1 of the study arms in a 1:1 ratio. Randomization is performed using a computerized, adaptive biased coin minimization scheme, which minimizes imbalance on the following factors, ranked by priority: clinician type (MD or DO vs NP or PA) and years in practice (≥10 vs <10) [40,41]. Compared to permuted blocks, adaptive biased coin minimization randomization has superior efficiency for achieving balance across multiple factors in studies with small units of randomization.

Clinicians are assigned a unique numeric code for temporary blinding while being randomized. After randomization, clinician study arm assignments are unblinded and shared with the study team. Study arm assignments cannot be blinded because the study team needs to train clinicians according to group assignment.

Study Population, Sample Size, and Statistical Power

Practices and Clinicians

We will recruit up to 20 practices within the AAP PROS network, with up to 40 clinicians enrolled across these practices. To be eligible to participate, practices must (1) have at least 2 interested and eligible clinicians (clinician eligibility criteria are presented later in this subsection), (2) have a high-speed wireless internet connection available to ensure connectivity of study tablet computers, and (3) have an adolescent patient population that is primarily English speaking (the CRAFFT-IS has, to date, been tested only in English). Practices must not (1)

be a practice or continuity clinic where residents or medical students routinely provide adolescent care (because trainees may not be available for training, implementation, and data collection for the duration of the practice's participation in the study) or (2) have recently participated or be participating in other initiatives to improve adolescent substance use screening and brief intervention in their practice. Eligible clinicians (1) must be a clinician (MD, DO, NP, or PA) who sees patients for well visits and (2) must see ≥6 adolescents aged 14 to 17 years per week, on average, or approximately 300 adolescents per year, for well visits.

Adolescents

We aim to enroll a minimum of 1300 adolescent participants. Eligible adolescents must (1) present for an annual well visit with a participating clinician in either study arm, (2) be aged 14 to 17 years at the time of their well visit, (3) report past 12-month alcohol use or past 12-month riding risk, and (4) have a smartphone and be willing to share their mobile phone number with the study team. We chose the minimum age of 14 years because there is low prevalence of prior alcohol use among younger adolescents (<5% of adolescents aged 12-13 years in our prior studies reported past 12-month drinking [Harris SK, unpublished data, 2019]). In addition, to be considered fully enrolled, all adolescents must complete the previsit survey before seeing their clinician, as well as the CRAFFT screen for those scheduled to see a clinician in the intervention arm. Adolescents must be willing and able to complete monthly surveys for 12 months after their well visit.

Adolescent patients must not be (1) in foster care, (2) in college or trade school at the time of their well visit, (3) currently receiving counseling or treatment for a substance use concern from a specialty clinician, or (4) perceived by their clinician to be inappropriate for the study (eg, due to neurodevelopmental delays or another medical priority at the time of visit).

We calculated the adolescent patient sample size by applying recruitment and retention rates, alcohol use and riding risk prevalence rates, intervention effect sizes, a within-clinician clustering design effect (0.90), and the clinician intraclass correlation coefficient for HED (0.008) seen in our pilot study [22]. We estimated a 37% past 12-month drinking prevalence rate, 28% riding risk prevalence rate among adolescents with past 12-month drinking, and a 5.8% riding risk rate among those with no past 12-month drinking. The 37% past 12-month drinking prevalence rate is similar to the 36.1% prevalence rate found on the 2018 Monitoring the Future Survey [42]. We applied slightly more conservative rates of participation (80% vs 82%) and retention (70% vs 75%) than those found in our pilot study to ensure that we achieve a sample size with sufficient power. With α set at ≤.05 and β at ≥.80, our power calculation indicated that a minimum analysis sample size of 888 participants with 12-month follow-up data would provide 86% power to detect an effect size of ≥20% in our primary outcome measure of HED. Applying the conservative estimate of 70% retention at 12 months, we need to recruit a minimum of 1268 participants. Thus, we estimate needing approximately 4200 adolescents to complete the eligibility survey, with 1600 (40% of those screened) meeting eligibility criteria, and 1300 (80% of those eligible) enrolling. To enroll this sample, we anticipate enrolling an average of 40 patients per clinician among up to 40 clinicians completing the study.

Intervention

Overview

The CRAFFT-IS was developed to leverage the power of digital technology to provide a time-efficient and feasible way for busy pediatric practices to improve both the frequency and quality of adolescent substance use screening and counseling in primary care. To this end, the CRAFFT-IS consists of the following components: (1) previsit self-administered screen (CRAFFT version with extra questions that are related to nicotine vaping and tobacco use [CRAFFT 2.1+N]), immediately followed by (2) brief interactive psychoeducational content on substance use–related health risks, and (3) clinician delivery of brief MI-based counseling during the confidential portion of the well visit, guided by a computerized point-of-care decision support tool called the clinician report. In addition, as an intervention to reduce riding and driving risk, intervention clinicians provide all participating patients and their caregivers with the *Contract for Life* document [34,43]. These components are described in greater detail in the following subsections.

Previsit Screening

To complete the previsit self-administered substance use screening, adolescents will log in to a secure website via their smartphone (before or at visit) or a tablet computer (at visit only) and complete the CRAFFT 2.1+N, which assesses past 12-month substance use frequency, substance-related riding and driving, and signs of problematic use (eg, uses when alone) [44]. At a cut point of ≥2 *yes* answers, the CRAFFT is highly sensitive (91%) and specific (90%) for detecting SUD in adolescents [23]. The CRAFFT 2.1+N includes an item on past 12-month days of nicotine vaping and tobacco use and, if yes, an item on past 30-day use. Endorsement of past 30-day nicotine vaping or tobacco use is followed by the Hooked on Nicotine Checklist (HONC), a well-validated 10-item screen for detecting loss of autonomy over nicotine use in adolescents [45]. This study will use a modified HONC that incorporates nicotine vaping.

After completing the substance use screen, adolescents will be asked to choose up to 3 personal values from a prespecified list of 14 values (eg, creativity, family, honesty, and wealth), with the option to write in their own. The selected values are presented in the clinician report to support clinician-patient rapport building and patient-centered MI-based counseling.

Previsit Psychoeducation

Next, adolescents view brief interactive psychoeducational web pages on the health risks of substance use. These web pages illustrate the unique vulnerability of adolescents to the health harms of substance use through the presentation of scientific evidence and true-life stories of adolescents. We developed this content based on input from focus groups of youth who reported that this type of information was compelling [31]. For this study, the content was updated to include information about the health risks of nocotine vaping.

Clinician Report and Brief Counseling Protocol

The clinician report is a web-based dashboard designed to help clinicians efficiently view their adolescent patients' responses to the substance use screening and values items and deliver brief counseling tailored to the responses. On the basis of the screening responses, counseling guidance is tailored to 1 of three substance use profiles: (1) *recent use* (use of alcohol, cannabis, or another drug in the past 3 months or use of tobacco or nicotine in the past 30 days), (2) *distant use* (use of any substance in the past 12 months but not in the past 3 months or past 30 days for nicotine vaping and tobacco), and (3) *riding risk* (no past 12-month substance use but past 12-month riding in a vehicle with a driver who was substance impaired).

The brief counseling protocol is a modified form of the brief negotiated interview, a structured MI-based counseling intervention originally developed for use in emergency departments and found to be efficacious in reducing substance use in adolescents [46]. The counseling protocol is designed for delivery in 5 to 10 minutes, depending on the severity of risk. Counseling steps are summarized in Table 1.

Table 1. Overview of the Adolescent Substance Use Prevention Intervention Research (ASPIRE) multisite cluster randomized controlled trial's brief counseling protocol, which is delivered by intervention clinicians to participating adolescent patients who present for a well visit and report past 12-month alcohol use, past 12-month riding risk, or both.

Counseling protocol steps	Recent use[a]	Distant use[b]	Riding risk[c]
1. Engage and build rapport	✓	✓	✓
2. Review screening results and assess further	✓	✓	✓
3. Consider pros and cons of substance use (decisional balance)	✓		
4. Discuss health risks of substance use and riding risk	✓	✓	✓
5. Evaluate readiness to change substance use (readiness ruler [47]) and reasons for change	✓		
6. Elicit next steps toward behavior change and anticipate challenges	✓	✓	✓[d]
7. Wrap up by summarizing discussion and affirming autonomy and self-efficacy	✓[d]	✓[d]	✓

[a]Patient reports past 3-month substance use. Patient may or may not report past 12-month riding with a driver who was substance impaired.

[b]Patient reports past 12-month substance use but no past 3-month use. Patient may or may not report past 12-month riding with a driver who was substance impaired.

[c]Patient reports past 12-month riding with a driver who was substance impaired and no past 12-month substance use.

[d]Clinician provides patient with the *Contract for Life* [43].

Recent use counseling uses the MI style of communication to elicit the adolescent's reasons for and problems with substance use. The clinician discusses the adolescent's values, shares health information, explores the adolescent's reasons for and readiness to change their substance use behavior using a readiness ruler [47], and guides the adolescent through planning behavior change. The counseling concludes by summarizing the discussion and affirming the adolescent's autonomy and self-efficacy. *Distant use* counseling involves affirming and supporting the adolescent's continued nonuse, discussing health risks associated with past substance use, and anticipating and planning for challenges with maintaining abstinence. *Riding risk* counseling also includes affirmation and support of the adolescent's continued nonuse, discussion of health risks associated with riding with a driver who is substance impaired, and counseling to identify and plan safe transportation at all times. Both the *distant use* and *riding risk* counseling protocols are guided in a structured step-by-step manner similar to *recent use* counseling.

Near the end of the brief tailored counseling, intervention clinicians provide *all* participating patients with a paper or electronic version of the *Contract for Life*. Developed by Students Against Destructive Decisions, the *Contract for Life* asks youth and their caregivers to develop and commit to a plan to ensure that adolescents always have a safe ride home with a sober driver [43].

Intervention Training and Fidelity Monitoring

Two clinicians with expertise in MI train intervention clinicians to deliver the intervention counseling. Training was initially structured as 5 self-study modules on a web-based learning platform and 5 live sessions with expert trainers (approximately 7 total training hours). As scheduling the 5 live sessions was found to be challenging with the first practice, the study team restructured the training to include longer self-paced asynchronous modules to reduce scheduling challenges without changing the total number of training hours. The updated training schedule consists of 5 self-study modules with recorded lectures, 2 live counseling practice sessions, and 1 live technical training session to orient clinicians to the clinician report and tablet computers.

The self-study modules include video-recorded presentations on MI-based counseling principles, the counseling steps for each of the 3 risk categories, video-recorded mock counseling demonstrations with accompanying annotated transcripts, and self-assessment questions. In the 2 live sessions, the expert trainers guide clinicians through case-based practice of the counseling steps and provide feedback.

To establish baseline competency, each clinician completes the counseling steps with a standardized patient for each of the 3 risk categories in a single recorded videoconference session. The trainers and 2 research staff members review these recordings using a standardized rating form. The trainers then

meet with each clinician for individualized feedback and coaching. For fidelity monitoring, clinicians complete mock counseling sessions and receive feedback quarterly. In addition, the intervention trainers host optional live videoconference sessions (*office hours*) every 1 to 2 months for extra coaching.

Intervention Modification or Discontinuation

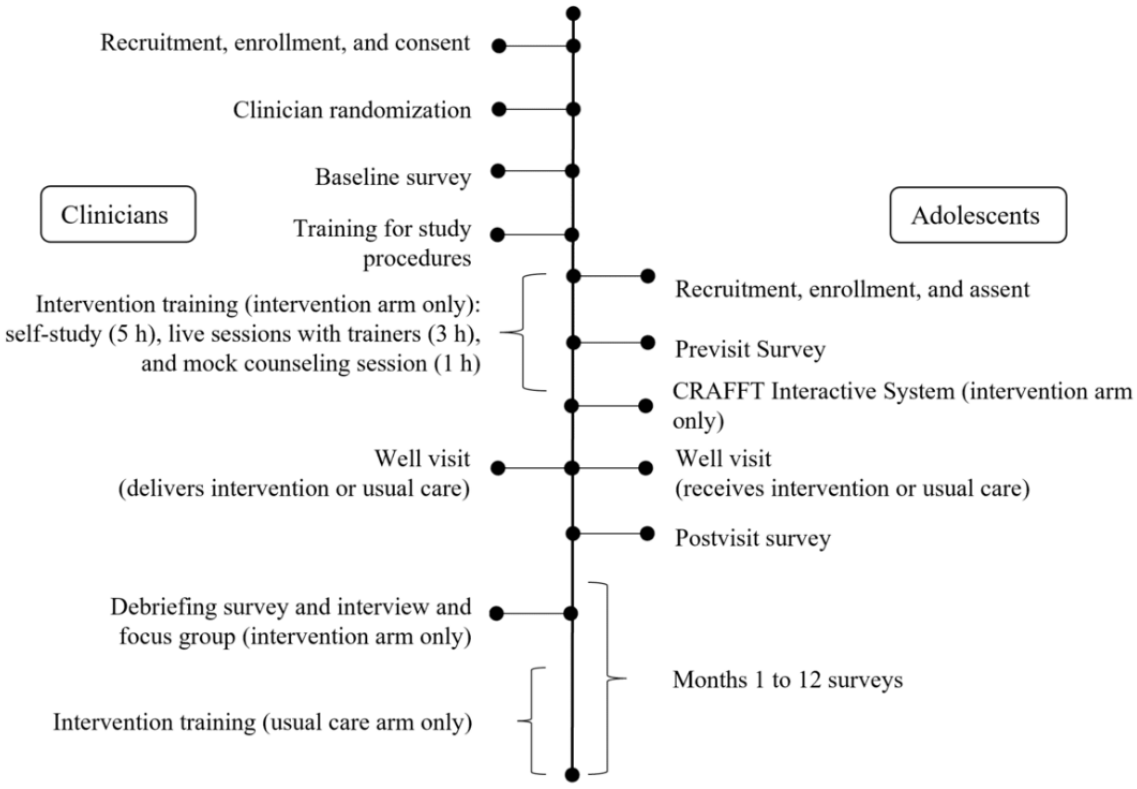
No concomitant care and interventions are prohibited during the trial beyond those defined in the practice inclusion criteria. We will withdraw a participant from the study if there is evidence to suggest that continuing in the study may be inappropriate (ie, there are intervening medical, mental health, or social circumstances that preclude or disrupt participation). Data collected from withdrawn participants will still be used in the analysis.

Outcomes and Measures

Study Activities and Assessment Timeline

Figure 1 illustrates the chronology of participating clinician and adolescent study activities.

Figure 1. Chronological overview of clinician and adolescent milestones during the Adolescent Substance Use Prevention Intervention Research (ASPIRE) multisite cluster randomized trial. CRAFFT: Car, Relax, Alone, Forget, Family/Friends, Trouble.



Outcome Measures

A detailed listing of study outcome measures, their reference sources where applicable, and time points of data collection is presented in Table 2, and thus they are only briefly described here. These measures are also reported in the ClinicalTrials.gov registry.

Our primary outcome measure is past 90-day HED, as reported by adolescents during the 12-month follow-up period, among adolescents who report past 12-month drinking at baseline. HED is defined using the age- and sex-specific cut points recommended by the NIAAA: ≥3 drinks on a single occasion for youth assigned female at birth who are aged 14 to 17 years, ≥4 drinks for youth assigned male at birth who are aged 14 to 15 years, and ≥5 drinks for youth assigned male at birth who are aged 16 to 17 years [68]. Our secondary outcome measure is any past 90-day riding with a driver who was substance impaired (who used alcohol, cannabis, or another drug) or driving while substance impaired. The exploratory outcomes of interest include past 90-day days of use of other commonly used substances among adolescents (ie, nicotine and cannabis) and experience of negative consequences associated with alcohol use (eg, missing school or work and getting into trouble at school, home, or work). In addition, we will explore the following intermediate outcome measures as hypothesized effect mediators: (1) report of readiness to reduce or stop alcohol use using a readiness ruler [47], (2) perceived risk of harm from use, and (3) self-efficacy to refuse alcohol.

Table 2. Adolescent participant study assessment measures by data collection time point across 12 months in the Adolescent Substance Use Prevention Intervention Research (ASPIRE) multisite cluster randomized controlled trial.

Measure	Data collection time point								
	Eligibility survey	Previsit survey	CRAFFT-IS[a]	Postvisit survey	Monthly[b]	3 mo	6 mo	9 mo	12 mo
Primary outcomes									
Heavy episodic drinking[c]									
TLFB[d,e] [48,49]		✓			✓	✓	✓	✓	✓
AUDIT-C[f,e] [50]		✓			✓	✓	✓	✓	✓
Substance use[g] (CRAFFT[h] [24,44] on eligibility and TLFB all other times)	✓	✓			✓	✓	✓	✓	✓
Negative consequences									
Negative consequences of alcohol and cannabis use scales[e] [51]		✓				✓	✓	✓	✓
PEI[i] Personal Consequences Scale[e] [52,53]		✓				✓	✓	✓	✓
NCANDA[j] study[e] [54]		✓				✓	✓	✓	✓
Secondary outcome									
Riding and driving risk frequency									
National College Alcohol Study[e] [55]		✓				✓	✓	✓	✓
Young Adult Driving Questionnaire[e] [56]		✓				✓	✓	✓	✓
Adapted from previous cSBI[k] studies [22,54]		✓				✓	✓	✓	✓
Other measures									
Hypothesized mediators									
Readiness to reduce or stop use (readiness ruler [47] used in previous cSBI study [22])		✓		✓					
Perceived risk of harm (National Monitoring the Future Survey[e] [37])		✓		✓		✓	✓	✓	✓
Refusal self-efficacy (DRSEQ-SRA[l,e] [57])		✓		✓		✓	✓	✓	✓
Receipt of health services for substance use (adapted from previous cSBI study [22])						✓	✓	✓	✓
Control variables									
Substance use severity profile									
CRAFFT	✓		✓						
TLFB		✓			✓	✓	✓	✓	✓
ASSIST[m,e] [58]		✓				✓	✓	✓	✓
Peer substance use (PEI)		✓				✓	✓	✓	✓
Family substance use (PEI)		✓					✓		✓
Patient-clinician relationship									
Number of previous visits with clinician				✓					

Measure	Data collection time point								
	Eligibility survey	Previsit survey	CRAFFT-IS[a]	Postvisit survey	Monthly[b]	3 mo	6 mo	9 mo	12 mo
Youth Connectedness to Provider Scale [8,31]				✓					
Process measures									
Intervention duration (new)			✓						
Visit format (new)				✓					
Protocol adherence and visit quality (adapted from previous cSBI studies [8,31])				✓					
Contract for Life [43] discussion with caregivers (adapted from previous cSBI study [35])						✓			
Validation of modified HONC[n]									
Nicotine use disorder risk									
HONC[e] [45,59]			✓						
PROMIS-E[o,e] [60]		✓							
Other exploratory variables									
Quality of life and overall health									
CHU9D[p] [61]		✓				✓	✓	✓	✓
PATH[q] Study [62]		✓				✓	✓	✓	✓
YRBS[r,e] [63]		✓				✓	✓	✓	✓
Sexual and gender minority status (YRBS and others [64-66])	✓					✓	✓	✓	✓
Social determinants of health									
MSPSS[s] [67]		✓				✓	✓	✓	✓
YRBS		✓				✓	✓	✓	✓

[a]CRAFFT-IS: CRAFFT (Car, Relax, Alone, Forget, Family/Friends, Trouble) Interactive System (collected before the well visit among intervention arm patients only).

[b]Monthly surveys 1, 2, 4, 5, 7, 8, 10, and 11 are brief in length; monthly surveys 3, 6, 9, and 12 are extended in length.

[c]Defined by the National Institute on Alcohol Abuse and Alcoholism Alcohol Screening and Brief Intervention for Youth Guide [68].

[d]TLFB: timeline followback.

[e]Modified or adapted for purposes of this study.

[f]AUDIT-C: Alcohol Use Disorders Identification Test–Concise.

[g]Includes alcohol, nicotine, tobacco, marijuana, inhalants, misused prescription medication, and other drugs (synthetic marijuana, stimulants, opioids, and hallucinogens).

[h]CRAFFT: Car, Relax, Alone, Forget, Family/Friends, Trouble.

[i]PEI: Personal Experience Inventory.

[j]NCANDA: National Consortium on Alcohol and Neurodevelopment in Adolescence.

[k]cSBI: computer-facilitated screening and brief intervention.

[l]DRSEQ-SRA: Drinking Refusal Self-Efficacy Questionnaire–Shortened Revised Adolescent version.

[m]ASSIST: Alcohol, Smoking and Substance Involvement Screening Test.

[n]HONC: Hooked on Nicotine Checklist.

[o]PROMIS-E: Patient-Reported Outcomes Measurement Information System Nicotine Dependence Item Bank for Electronic Cigarettes.

[p]CHU9D: Child Health Utility–9 Dimensions.

[q]PATH: Population Assessment of Tobacco and Health.

[r]YRBS: Youth Risk Behavior Survey.

[s]MSPSS: Multidimensional Scale of Perceived Social Support.

Other Measures

We will explore potential intervention effect moderation by age group, sexual and gender identity and social determinants of health that enhance substance use risk for sexual and gender minority youth, baseline severity of substance use involvement, peer and family substance use, and patient-clinician relationship (number of prior visits the patient had with this clinician and perceived connectedness to their clinician).

We will also examine intervention implementation measures, including the time required to deliver the various CRAFFT-IS components and patient-reported receipt and quality of substance use counseling during their visit. Time information will be collected through computerized capture of patient clickstream times and clinician counseling start and stop times, as well as clinician report of average substance use–related counseling time and overall visit length on the clinician debriefing questionnaire completed at the end of patient recruitment at a practice. Adolescents complete an immediate postvisit questionnaire that includes items on the health topics discussed during the visit, ratings of counseling quality and the degree to which it reflected an MI-based counseling style, and whether they received the *Contract for Life*.

To assess the validity of the modified HONC for identifying risk for nicotine use disorder in adolescents, we will compare it to the 4-item Patient-Reported Outcomes Measurement Information System Nicotine Dependence Item Bank for Electronic Cigarettes (PROMIS-E) [60] administered in the previsit assessment. While the CRAFFT screening items are well validated [24], the modified HONC, which now includes nicotine vaping and is included in the CRAFFT-IS previsit screening for adolescents seeing intervention clinicians, needs validation.

Data Collection

Clinicians

Enrolled clinicians are assigned a unique numeric identifier for use in data collection throughout the study. A baseline survey assesses previous experience and training and UC practices around screening, brief intervention, and referral to treatment (10 min), as well as training on study procedures and human subjects protections (up to 90 min; all clinicians). Clinicians assigned to the intervention arm additionally complete brief (5 min each) postsession evaluation surveys after each live training session and a final summative evaluation after all training components have concluded. Clinician surveys and evaluations are completed on paper or by email or SMS text message link to an online survey per clinician preference. After adolescent recruitment and intervention delivery have concluded at a practice, intervention clinicians complete a 10-minute debriefing survey assessing experience using the CRAFFT-IS and seeking suggestions for improving the system, as well as participate in a 30- to 60-minute interview or focus group (along with participating staff) to offer feedback on their study experience.

Adolescents

All adolescent participants are assigned a unique numeric identifier at the time of recruitment for use in data collection, storage, and linkage throughout their study participation. Once assented, participants indicate their contact preferences. Adolescents who agree to have their data shared with the $NIAAA_{DA}$ are assigned a Global Unique Identifier using their first, middle, and last names; sex assigned at birth; and date and city of birth. Global Unique Identifiers are numeric codes that allow participant data to be submitted to the $NIAAA_{DA}$ without any personally identifiable information. All participants self-administer the confidential electronic previsit survey (approximately 20 min; refer to Table 2 for details on all surveys), and participants seeing an intervention clinician complete the screening and psychoeducational components of the CRAFFT-IS (5 min) before seeing their clinician. After their visit, all participants complete the immediate postvisit survey (approximately 10 min), and then, through the 12-month follow-up period, brief monthly surveys about their past 30-day substance use and longer surveys at 3, 6, 9, and 12 months (approximately 15 min each). Participants may choose to skip questions or entire surveys and still remain in the study.

All surveys can be completed electronically on smartphones and desktop or tablet computers through a link sent by SMS text message or email to participants' personal mobile phone numbers or email addresses, as preferred. Electronic surveys are protected by a password set by the adolescent. Adolescents can also complete a survey by mobile phone with a study RA. If the adolescent does not complete a survey after electronic reminders, a study RA will call the adolescent to encourage survey completion.

Data Management

Study data, including survey responses and internal study tracking data, will be collected and stored in Research Electronic Data Capture (REDCap), a HIPAA-compliant web-based data management and survey distribution tool hosted at BCH [69,70]. Data transmission among BCH, AAP PROS staff, and practices will occur securely via password-protected email or fax. Paper-based data (eg, faxes and verbally administered surveys) will be stored securely for 7 years and identifiable electronic data for 3 years. Deidentified data will be kept indefinitely.

Data Analysis Plan

Analysts will be blinded to treatment arm. We will evaluate randomization success and level of attrition bias by comparing baseline characteristics of adolescents by treatment arm and by those retained versus those lost to follow-up (ie, adolescent participants who stop completing study surveys during the 12 months after their well visit). Baseline variables meeting a P value of <.20 in randomized group comparisons will be entered as control variables in multivariable modeling of the intervention effect to yield adjusted estimates of effect. We will compare rates of counseling receipt and patient ratings of their visit between groups. We will also generate variables related to intervention *dose* (eg, receipt of clinician counseling and receipt of *Contract for Life*) for use in sensitivity analyses.

To assess intervention effects on our primary and secondary outcome measures (past 90-day HED and any past 90-day riding or driving risk) at each of the 3-, 6-, 9-, and 12-month follow-up time points, we will use multiple logistic regression modeling with generalized estimating equations to compute adjusted

relative risk ratios (CRAFFT-IS vs UC). Generalized estimating equations account for clustering of participants within practice and clinician. Furthermore, we will explore intervention effects on the number of days of drinking and of HED and on the number of times participants experienced alcohol-related negative consequences from baseline to each follow-up time point. As these variables are likely to have distributions that are highly skewed and overdispersed, we will specify a negative binomial distribution and log link in these regression models. We will also conduct longitudinal data analysis using mixed effects modeling to compare group outcomes trajectories through the entire 12-month follow-up period. We plan to explore intervention effect mediation by applying the product of coefficients test for mediation [71,72] and potential effect moderation by future-determined variables by testing the significance of interaction terms in regression models.

All intervention effect analyses will use intent-to-treat groups. We will transform continuous variables with skewed data and collapse categories as needed to preserve adequate cell sizes. To handle missing data, we will use multiple imputation based on regression modeling and compare the results of analyses using the imputed data set versus the original data set [73].

Safety and Monitoring

We define the following as nonemergency safety risks: drinking twice the NIAAA-defined HED amount for the adolescent's age and sex [68], daily use of alcohol or cannabis, use of other drugs on >6 days during the past 3 months, driving after use of substances >1 time in the past 3 months, and riding with a driver who is substance impaired >1 time in the past 3 months. When an adolescent's survey responses indicate any of these nonemergency risks, a BCH RA will notify the patient's clinician within 1 business day. If an adolescent spontaneously discloses an emergency safety risk (eg, abuse, suicide risk, or intentions to harm others), a BCH RA will immediately notify their clinician or appropriate contact person according to site-specific preferences.

This study has an independent DSMB that consists of 3 members: a child psychiatrist with expertise in adolescent SUD screening and treatment research (chair), a biostatistician with experience in clinical trial research, and an adolescent medicine primary care clinician. The DSMB will (1) review study procedures and progress, including recruitment, retention, and dropout; and (2) assess adverse events and unanticipated problems, if any, and their relationship to study participation. The full DSMB will meet annually to review overall study progress and will also convene as needed to review and address any adverse events or other study-related problems, should they arise. The DSMB is responsible for recommending whether to stop the study; no interim analyses are planned.

Given that this is a minimal risk study, we do not anticipate that participants will experience harm from study participation. However, we have planned for situations in which participants spontaneously report harms. Harms may consist of nonserious adverse events (eg, participant complaints or upset related to study activities and inadvertent disclosure of confidential information) or serious adverse events (eg, motor vehicle crashes and hospital visits). If we learn of an adverse event, we will consult with the DSMB chair and notify the AAP IRB and the patient's practice. The DSMB will determine whether a serious adverse event is related to study participation and recommend the appropriate response, including possible study withdrawal. Study data are protected by a certificate of confidentiality from the National Institutes of Health.

Results

Recruitment and Enrollment

The first practice enrolled in August 2022. As of July 2023, a total of 6 practices (23 clinicians) had enrolled in the study.

Adolescent recruitment began in December 2022 and is expected to continue until late 2024 or early 2025. Data collection is expected to conclude in 2025 or 2026, and data analysis will follow.

Data Access and Dissemination

The final trial deidentified data set will be provided to the study's biostatistician, the AAP PROS team, and any other interested investigators upon request. We will report results on ClinicalTrials.gov, and select deidentified data will be available to researchers worldwide via the $NIAAA_{DA}$.

In addition to this paper, we aim to publish at least 2 papers that disseminate study findings: 1 focused on our primary alcohol use–related outcomes and 1 focused on other substance use outcomes. We also anticipate submitting at least 2 abstracts to present at national conferences. Members of the study team will develop and write all publications resulting from this study. Authorship will be designated according to those who offer intellectual contribution to the design or preparation of a given publication and claim responsibility for its contents.

Discussion

The ASPIRE study aims to test the effectiveness of the CRAFFT-IS, compared to UC, in reducing alcohol use and substance use–related riding risk among adolescents aged 14 to 17 years presenting for well visits. Despite the AAP's recommendation for universal substance use screening in primary care beginning at age 11 years, the US Preventive Services Task Force gave primary care–based adolescent alcohol screening and brief behavioral counseling an "I" rating in its most recent review, indicating insufficient evidence for or against its recommendation [74]. The ASPIRE study builds on prior research supporting the promise of CRAFFT-IS as a feasible, acceptable, and efficacious approach to increasing high-quality screening and counseling.

Our study protocol has limitations. Although our virtual recruitment and enrollment approach allows the study team to contact a larger volume of individuals over an expanded time frame (eg, in comparison to in-person recruitment restricted to clinic operating hours), practices may not have up-to-date contact information for adolescent patients. Likewise, it is not guaranteed that adolescents will see or read the mailed recruitment invitation before their visit. Our approach also reduces burden on practice staff to conduct recruitment activities, but it may underuse pre-established connections

between practice staff and adolescent patients. Furthermore, the addition of the CRAFFT-IS to well visits may delay clinic flow. Further limitations to our study may emerge during the trial and will be reported in future outcomes manuscripts.

If the CRAFFT-IS is shown to be effective, we intend to scale, promote, and widely disseminate the instrument for use in pediatric practice, either as a tablet application or as a confidential add-on to existing electronic health record systems. We also envision this study informing future investigators interested in studying computer-facilitated screening and brief intervention for youth substance use, whether in primary care settings or elsewhere, with the aim of reducing alcohol-related morbidity and mortality during adolescence and beyond.

Acknowledgments

This research was supported by a grant from the National Institute on Alcohol Abuse and Alcoholism (NIAAA; R01AA027253; principal investigators: SKH and LAS; peer-review reports: Multimedia Appendix 3) and supplemental grants (3R01AA027253-03S1 and 3R01AA027253-03S2). In addition, infrastructure support was provided by the American Academy of Pediatrics and the Health Resources and Services Administration of the US Department of Health and Human Services (National Research Network to Improve Children's Health: UA6MC15585 and Pediatric Research Network Program: U5DMC39344). The contents are those of the authors and do not necessarily represent the official position or policy of, nor an endorsement by, the Health Resources and Services Administration, the US Department of Health and Human Services, or the US government. The NIAAA was not involved in any aspect of study design or implementation, nor in the preparation, review, or approval of this manuscript for publication. The authors would like to acknowledge the valuable contributions of youth advisors and interns who supported study activities and provided feedback on procedures and materials. The authors would like to thank Dr Jeremy Bray and Anna Goodall at the University of North Carolina Greensboro for their leadership in designing the cost-effectiveness analysis component of the study, which was not discussed in this manuscript. Finally, this research would not have been possible without the support of providers, practice staff, and patients in the American Academy of Pediatrics Pediatric Research in Office Settings network, to whom we owe the greatest thanks.

Data Availability

Data sharing is not applicable to this paper as no data sets were generated or analyzed.

Authors' Contributions

LAS and SKH conceptualized, designed, and obtained funding for the study. MMO and AT obtained ethics approval for the study, with oversight from LPS and AGF and assistance from JAP, JLM, NHM, and DH. LAS and PJB developed the intervention counseling. TF and MLM served as pediatrician advisors to the study. LS codeveloped and programmed the computer-facilitated screening and brief intervention. All authors contributed to the development of the protocol and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Clinician consent form.
[PDF File (Adobe PDF File), 318 KB - resprot_v13i1e55039_app1.pdf]

Multimedia Appendix 2
Verbal assent script delivered to eligible adolescents.
[PDF File (Adobe PDF File), 349 KB - resprot_v13i1e55039_app2.pdf]

Multimedia Appendix 3
Peer-review reports from the Clinical, Treatment and Health Services Research Review Subcommittee, National Institute on Alcohol Abuse and Alcoholism Initial Review Group (National Institutes of Health).
[PDF File (Adobe PDF File), 190 KB - resprot_v13i1e55039_app3.pdf]

References

1. National Center for Health Statistics. Health, United States, annual perspective, 2020-2021. Centers for Disease Control and Prevention. URL: https://stacks.cdc.gov/view/cdc/122044 [accessed 2024-02-25]
2. Lundahl LH, Cannoy C. COVID-19 and substance use in adolescents. Pediatr Clin North Am 2021 Oct;68(5):977-990 [FREE Full text] [doi: 10.1016/j.pcl.2021.05.005] [Medline: 34538307]

3. Hoots BE, Li J, Hertz MF, Esser MB, Rico A, Zavala EY, et al. Alcohol and other substance use before and during the COVID-19 pandemic among high school students - youth risk behavior survey, United States, 2021. MMWR Suppl 2023 Apr 28;72(1):84-92 [FREE Full text] [doi: 10.15585/mmwr.su7201a10] [Medline: 37104552]
4. Youth risk behavior survey data summary & trends report: 2011-2021. Centers for Disease Control and Prevention. 2023 Feb 13. URL: https://www.cdc.gov/healthyyouth/data/yrbs/pdf/yrbs_data-summary-trends_report2023_508.pdf [accessed 2023-08-16]
5. Web-based injury statistics query and reporting system (WISQARS). Centers for Disease Control and Prevention. 2023. URL: https://www.cdc.gov/injury/wisqars/index.html [accessed 2023-07-17]
6. Uddin S, O'Connor K, Ashman J. Physician office visits by children for well and problem-focused care: United States, 2012. National Center for Health Statistics. 2012. URL: https://www.cdc.gov/nchs/data/databriefs/db248.pdf [accessed 2023-11-17]
7. Adams SH, Park MJ, Twietmeyer L, Brindis CD, Irwin CE. Association between adolescent preventive care and the role of the affordable care act. JAMA Pediatr 2018 Jan 01;172(1):43-48 [FREE Full text] [doi: 10.1001/jamapediatrics.2017.3140] [Medline: 29114725]
8. Harris SK, Woods ER, Sherritt L, Van Hook S, Boulter S, Brooks T, et al. A youth-provider connectedness measure for use in clinical intervention studies. Journal of Adolescent Health 2009 Feb;44(2):S35-S36 [FREE Full text] [doi: 10.1016/j.jadohealth.2008.10.099]
9. Levy SJ, Williams JF, Committee on Substance Use and Prevention. Substance use screening, brief intervention, and referral to treatment. Pediatrics 2016 Jul;138(1):e20161211. [doi: 10.1542/peds.2016-1211] [Medline: 27325634]
10. Bright futures guidelines: recommendations for preventive pediatric health care. Bright Futures/American Academy of Pediatrics. 2023. URL: https://downloads.aap.org/AAP/PDF/periodicity_schedule.pdf [accessed 2023-09-11]
11. Hingson RW, Zha W, Iannotti RJ, Simons-Morton B. Physician advice to adolescents about drinking and other health behaviors. Pediatrics 2013 Feb;131(2):249-257 [FREE Full text] [doi: 10.1542/peds.2012-1496] [Medline: 23359580]
12. Voltarelli L, Bagley S, Hadland S, LaRochelle M. Healthcare providers' role in adolescents' perceived risk of alcohol use. In: Proceedings of the 41st annual meeting of the Association for Medical Education and Research in Substance Abuse. 2017 Presented at: AMERSA 2017; November 2-4, 2017; Washington, DC.
13. Wilson CR, Sherritt L, Gates E, Knight JR. Are clinical impressions of adolescent substance use accurate? Pediatrics 2004 Nov;114(5):e536-e540. [doi: 10.1542/peds.2004-0098] [Medline: 15520086]
14. Grilo SA, Catallozzi M, Santelli JS, Yan H, Song X, Heitel J, et al. Confidentiality discussions and private time with a health-care provider for youth, United States, 2016. J Adolesc Health 2019 Mar;64(3):311-318. [doi: 10.1016/j.jadohealth.2018.10.301] [Medline: 30638752]
15. Hingson RW, Heeren T, Edwards EM, Saitz R. Young adults at risk for excess alcohol consumption are often not asked or counseled about drinking alcohol. J Gen Intern Med 2012 Feb;27(2):179-184 [FREE Full text] [doi: 10.1007/s11606-011-1851-1] [Medline: 21935753]
16. Rahm AK, Boggs JM, Martin C, Price DW, Beck A, Backer TE, et al. Facilitators and barriers to implementing screening, brief intervention, and referral to treatment (SBIRT) in primary care in integrated health care settings. Subst Abus 2015;36(3):281-288. [doi: 10.1080/08897077.2014.951140] [Medline: 25127073]
17. Harris SK, Herr-Zaya K, Weinstein Z, Whelton K, Perfas FJ, Castro-Donlan C, et al. Results of a statewide survey of adolescent substance use screening rates and practices in primary care. Subst Abus 2012;33(4):321-326. [doi: 10.1080/08897077.2011.645950] [Medline: 22989275]
18. Van Hook S, Harris SK, Brooks T, Carey P, Kossack R, Kulig J, New England Partnership for Substance Abuse Research. The "Six T's": barriers to screening teens for substance abuse in primary care. J Adolesc Health 2007 May;40(5):456-461. [doi: 10.1016/j.jadohealth.2006.12.007] [Medline: 17448404]
19. Marsch LA, Borodovsky JT. Technology-based interventions for preventing and treating substance use among youth. Child Adolesc Psychiatr Clin N Am 2016 Oct;25(4):755-768 [FREE Full text] [doi: 10.1016/j.chc.2016.06.005] [Medline: 27613350]
20. Wong CA, Madanay F, Ozer EM, Harris SK, Moore M, Master SO, et al. Digital health technology to enhance adolescent and young adult clinical preventive services: affordances and challenges. J Adolesc Health 2020 Aug;67(2S):S24-S33 [FREE Full text] [doi: 10.1016/j.jadohealth.2019.10.018] [Medline: 32718511]
21. Yonek JC, Velez S, Satre DD, Margolis K, Whittle A, Jain S, et al. Addressing adolescent substance use in an urban pediatric federally qualified health center. J Subst Abuse Treat 2022 Apr;135:108653 [FREE Full text] [doi: 10.1016/j.jsat.2021.108653] [Medline: 34840042]
22. Knight JR, Sherritt L, Gibson EB, Levinson JA, Grubb LK, Samuels RC, et al. Effect of computer-based substance use screening and brief behavioral counseling vs usual care for youths in pediatric primary care: a pilot randomized clinical trial. JAMA Netw Open 2019 Jun 05;2(6):e196258 [FREE Full text] [doi: 10.1001/jamanetworkopen.2019.6258] [Medline: 31225897]
23. Mitchell SG, Kelly SM, Gryczynski J, Myers CP, O'Grady KE, Kirk AS, et al. The CRAFFT cut-points and DSM-5 criteria for alcohol and other drugs: a reevaluation and reexamination. Subst Abus 2014;35(4):376-380 [FREE Full text] [doi: 10.1080/08897077.2014.936992] [Medline: 25036144]

24. Knight JR, Sherritt L, Shrier LA, Harris SK, Chang G. Validity of the CRAFFT substance abuse screening test among adolescent clinic patients. Arch Pediatr Adolesc Med 2002 Jun;156(6):607-614. [doi: 10.1001/archpedi.156.6.607] [Medline: 12038895]
25. Harris SK, Knight JR, Van Hook S, Sherritt L, Brooks TL, Kulig JW, et al. Adolescent substance use screening in primary care: validity of computer self-administered versus clinician-administered screening. Subst Abus 2016;37(1):197-203 [FREE Full text] [doi: 10.1080/08897077.2015.1014615] [Medline: 25774878]
26. Fisher JD, Fisher WA. Changing AIDS-risk behavior. Psychol Bull 1992;111(3):455-474. [doi: 10.1037//0033-2909.111.3.455]
27. Janz NK, Becker MH. The health belief model: a decade later. Health Educ Q 1984;11(1):1-47. [doi: 10.1177/109019818401100101] [Medline: 6392204]
28. Harrison JA, Mullen PD, Green LW. A meta-analysis of studies of the health belief model with adults. Health Educ Res 1992 Mar;7(1):107-116. [doi: 10.1093/her/7.1.107] [Medline: 10148735]
29. Bandura A. Self-efficacy: toward a unifying theory of behavioral change. Psychol Rev 1977 Mar;84(2):191-215. [doi: 10.1037//0033-295x.84.2.191] [Medline: 847061]
30. Rosenstock IM, Strecher VJ, Becker MH. Social learning theory and the Health Belief Model. Health Educ Q 1988;15(2):175-183. [doi: 10.1177/109019818801500203] [Medline: 3378902]
31. Harris SK, Csémy L, Sherritt L, Starostova O, Van Hook S, Johnson J, et al. Computer-facilitated substance use screening and brief advice for teens in primary care: an international trial. Pediatrics 2012 Jun;129(6):1072-1082 [FREE Full text] [doi: 10.1542/peds.2011-1624] [Medline: 22566420]
32. Louis-Jacques J, Knight JR, Sherritt L, Van Hook S, Harris SK. Do risky friends change the efficacy of a primary care brief intervention for adolescent alcohol use? J Adolesc Health 2014 Apr;54(4):449-453 [FREE Full text] [doi: 10.1016/j.jadohealth.2013.09.012] [Medline: 24216313]
33. Knight JR, Kuzubova K, Csemy L, Sherritt L, Copelas S, Harris SK. Computer-facilitated screening and brief advice to reduce adolescents' heavy episodic drinking: a study in two countries. J Adolesc Health 2018 Jan;62(1):118-120 [FREE Full text] [doi: 10.1016/j.jadohealth.2017.08.013] [Medline: 29054734]
34. Knight JR, Csemy L, Sherritt L, Starostova O, Van Hook S, Bacic J, et al. Screening and brief advice to reduce adolescents' risk of riding with substance-using drivers. J Stud Alcohol Drugs 2018 Jul;79(4):611-616 [FREE Full text] [doi: 10.15288/jsad.2018.79.611] [Medline: 30079877]
35. Harris SK, Sherritt L, Grubb L, Samuels R, Silva TJ, Vernacchio L, et al. A randomized controlled trial of primary care screening and brief clinician intervention to reduce adolescents' riding with an intoxicated driver. J Adolesc Health 2019 Feb;64(2):S7. [doi: 10.1016/j.jadohealth.2018.10.027]
36. Gibson EB, Knight JR, Levinson JA, Sherritt L, Harris SK. Pediatric primary care provider perspectives on a computer-facilitated screening and brief intervention system for adolescent substance use. J Adolesc Health 2021 Jul;69(1):157-161 [FREE Full text] [doi: 10.1016/j.jadohealth.2020.09.037] [Medline: 33143987]
37. Miech RA, Johnston LD, Pat ME, O'Malley PM, Bachman JG, Schulenberg JE. Monitoring the future: national survey results on drug use, 1975-2022: Secondary school students. The National Institute on Drug Abuse. 2023. URL: https://monitoringthefuture.org/wp-content/uploads/2022/12/mtf2022.pdf [accessed 2024-02-25]
38. Rojas NL, Sherrit L, Harris S, Knight JR. The role of parental consent in adolescent substance use research. J Adolesc Health 2008 Feb;42(2):192-197. [doi: 10.1016/j.jadohealth.2007.07.011] [Medline: 18207098]
39. NIAAA data archive. National Institute on Alcohol Abuse and Alcoholism (NIAAA). URL: https://www.niaaa.nih.gov/research/niaaa-data-archive [accessed 2023-07-17]
40. Zhao W. A better alternative to stratified permuted block design for subject randomization in clinical trials. Stat Med 2014 Dec 30;33(30):5239-5248 [FREE Full text] [doi: 10.1002/sim.6266] [Medline: 25043719]
41. Han B, Enas NH, McEntegart D. Randomization by minimization for unbalanced treatment allocation. Stat Med 2009 Nov 30;28(27):3329-3346. [doi: 10.1002/sim.3710] [Medline: 19739238]
42. Miech RA, Schulenberg JE, Johnston LD, Bachman JG, O'Malley PM, Patrick ME. National adolescent drug trends in 2018. Monitoring the Future. 2018 Dec 17. URL: https://isr.umich.edu/news-events/news-releases/national-adolescent-drug-trends-in-2018/ [accessed 2019-07-01]
43. Students Against Destructive Decisions. Resources. SADD Nation. URL: https://www.sadd.org/resources [accessed 2023-06-21]
44. Get the CRAFFT. Center for Adolescent Behavioral Health Research (CABHRe). 2021. URL: https://crafft.org/get-the-crafft/ [accessed 2024-02-25]
45. Wheeler KC, Fletcher KE, Wellman RJ, Difranza JR. Screening adolescents for nicotine dependence: the Hooked on Nicotine Checklist. J Adolesc Health 2004 Sep;35(3):225-230. [doi: 10.1016/s1054-139x(03)00531-7]
46. Academic ED SBIRT Research Collaborative. The impact of screening, brief intervention and referral for treatment in emergency department patients' alcohol use: a 3-, 6- and 12-month follow-up. Alcohol Alcohol 2010;45(6):514-519 [FREE Full text] [doi: 10.1093/alcalc/agq058] [Medline: 20876217]
47. Heather N, Smailes D, Cassidy P. Development of a Readiness Ruler for use with alcohol brief interventions. Drug Alcohol Depend 2008 Dec 01;98(3):235-240. [doi: 10.1016/j.drugalcdep.2008.06.005] [Medline: 18639393]

48. Sobell LC, Sobell MB. Timeline follow-back: a technique for assessing self-reported alcohol consumption. In: Litten RZ, Allen JP, editors. Measuring Alcohol Consumption: Psychosocial and Biochemical Methods. Humana Totowa, NJ: Humana Press; 1992:41-72.
49. Robinson SM, Sobell LC, Sobell MB, Leo GI. Reliability of the Timeline Followback for cocaine, cannabis, and cigarette use. Psychol Addict Behav 2014 Mar;28(1):154-162. [doi: 10.1037/a0030992] [Medline: 23276315]
50. McCambridge J, Thomas BA. Short forms of the AUDIT in a web-based study of young drinkers. Drug Alcohol Rev 2009 Jan;28(1):18-24. [doi: 10.1111/j.1465-3362.2008.00010.x] [Medline: 19320671]
51. D'Amico EJ, Parast L, Shadel WG, Meredith LS, Seelam R, Stein BD. Brief motivational interviewing intervention to reduce alcohol and marijuana use for at-risk adolescents in primary care. J Consult Clin Psychol 2018 Sep;86(9):775-786 [FREE Full text] [doi: 10.1037/ccp0000332] [Medline: 30138016]
52. Winters K, Stinchfield R, Henly G. The Personal Experience Inventory Test and Manual. Los Angeles, CA: Western Psychological Services; 1988.
53. Winters KC, Stinchfield RD, Henly GA, Schwartz RH. Validity of adolescent self-report of alcohol and other drug involvement. Int J Addict 1990;25(11A):1379-1395. [doi: 10.3109/10826089009068469] [Medline: 2132719]
54. Cummins KM, Brumback T, Chung T, Moore RC, Henthorn T, Eberson S, et al. Acceptability, validity, and engagement with a mobile app for frequent, continuous multiyear assessment of youth health behaviors (mNCANDA): mixed methods study. JMIR Mhealth Uhealth 2021 Feb 10;9(2):e24472 [FREE Full text] [doi: 10.2196/24472] [Medline: 33565988]
55. Nelson TF, Xuan Z, Lee H, Weitzman ER, Wechsler H. Persistence of heavy drinking and ensuing consequences at heavy drinking colleges. J Stud Alcohol Drugs 2009 Sep;70(5):726-734. [doi: 10.15288/jsad.2009.70.726] [Medline: 19737497]
56. Jessor R, Donovan JE, Costa FM. Questionnaire guide: health behavior questionnaire, Spring 1992. Institute of Behavioral Science, University of Colorado. 1992. URL: https://ibs.colorado.edu/jessor/questionnaires/questionnaire_guide_hbq92.pdf [accessed 2023-11-30]
57. Patton K, Connor JP, Rundle-Thiele S, Dietrich T, Young RM, Gullo MJ. Measuring adolescent drinking-refusal self-efficacy: development and validation of the Drinking Refusal Self-Efficacy Questionnaire-Shortened Adolescent version (DRSEQ-SRA). Addict Behav 2018 Jun;81:70-77. [doi: 10.1016/j.addbeh.2018.02.007] [Medline: 29432915]
58. Gryczynski J, Kelly SM, Mitchell SG, Kirk A, O'Grady KE, Schwartz RP. Validation and performance of the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) among adolescent primary care patients. Addiction 2015 Feb;110(2):240-247 [FREE Full text] [doi: 10.1111/add.12767] [Medline: 25311148]
59. McKelvey K, Baiocchi M, Halpern-Felsher B. Adolescents' and young adults' use and perceptions of pod-based electronic cigarettes. JAMA Netw Open 2018 Oct 05;1(6):e183535 [FREE Full text] [doi: 10.1001/jamanetworkopen.2018.3535] [Medline: 30646249]
60. Morean ME, Krishnan-Sarin S, S O'Malley SS. Assessing nicotine dependence in adolescent e-cigarette users: the 4-item Patient-Reported Outcomes Measurement Information System (PROMIS) nicotine dependence item bank for electronic cigarettes. Drug Alcohol Depend 2018 Jul 01;188:60-63 [FREE Full text] [doi: 10.1016/j.drugalcdep.2018.03.029] [Medline: 29753155]
61. Ratcliffe J, Flynn T, Terlich F, Stevens K, Brazier J, Sawyer M. Developing adolescent-specific health state values for economic evaluation: an application of profile case best-worst scaling to the Child Health Utility 9D. Pharmacoeconomics 2012 Aug 01;30(8):713-727. [doi: 10.2165/11597900-000000000-00000] [Medline: 22788261]
62. Population assessment of tobacco and health (PATH) study. National Institute on Drug Abuse (NIDA). 2022. URL: https://nida.nih.gov/research/nida-research-programs-activities/population-assessment-tobacco-health-path-study [accessed 2023-02-01]
63. Youth risk behavior surveillance system. Centers for Disease Control and Prevention. 2021. URL: https://www.cdc.gov/healthyyouth/data/yrbs/index.htm [accessed 2022-08-22]
64. Bauer GR, Braimoh J, Scheim AI, Dharma C. Transgender-inclusive measures of sex/gender for population surveys: mixed-methods evaluation and recommendations. PLoS One 2017;12(5):e0178043 [FREE Full text] [doi: 10.1371/journal.pone.0178043] [Medline: 28542498]
65. Badgett MV, Baker KE, Conron KJ, Gates GJ, Gill A, Greytak E, et al. Best practices for asking questions to identify transgender and other gender minority respondents on population-based surveys (GenIUSS). The Williams Institute. 2014. URL: https://williamsinstitute.law.ucla.edu/publications/geniuss-trans-pop-based-survey/ [accessed 2023-09-11]
66. Cheloff AZ, Jarvie E, Tabaac AR, Katz-Wise SL, Fygetakis LM, Keuroghlian A. Sexual orientation, gender identity, and sex development: recommendations for data collection and use in clinical, research, and administrative setting. Harvard Medical School, Dean's LGBT Advisory Committee. URL: https://dicp.hms.harvard.edu/sites/default/files/2022-10/SOGI%20Data%20Collection.pdf [accessed 2022-07-26]
67. Zimet GD, Powell SS, Farley GK, Werkman S, Berkoff KA. Psychometric characteristics of the multidimensional scale of perceived social support. J Pers Assess 1990;55(3-4):610-617. [doi: 10.1080/00223891.1990.9674095] [Medline: 2280326]
68. Alcohol screening and brief intervention for youth: a practitioner's guide. National Institute on Alcohol Abuse and Alcoholism. 2021. URL: https://www.niaaa.nih.gov/alcohols-effects-health/professional-education-materials/alcohol-screening-and-brief-intervention-youth-practitioners-guide [accessed 2023-01-19]

69. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, REDCap Consortium. The REDCap consortium: building an international community of software platform partners. J Biomed Inform 2019 Jul;95:103208 [FREE Full text] [doi: 10.1016/j.jbi.2019.103208] [Medline: 31078660]
70. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009 Apr;42(2):377-381 [FREE Full text] [doi: 10.1016/j.jbi.2008.08.010] [Medline: 18929686]
71. MacKinnon DP, Lockwood CM, Hoffman JM, West SG, Sheets V. A comparison of methods to test mediation and other intervening variable effects. Psychol Methods 2002 Mar;7(1):83-104 [FREE Full text] [doi: 10.1037/1082-989x.7.1.83] [Medline: 11928892]
72. Hayes AF. Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-Based Approach. New York, NY: The Guilford Press; 2013.
73. McCleary L. Using multiple imputation for analysis of incomplete data in clinical research. Nurs Res 2002;51(5):339-343. [doi: 10.1097/00006199-200209000-00012] [Medline: 12352784]
74. O'Connor EA, Perdue LA, Senger CA, Rushkin M, Patnode CD, Bean SI, et al. Screening and behavioral counseling interventions to reduce unhealthy alcohol use in adolescents and adults: an updated systematic review for the U.S. Preventive Services Task Force. Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. 2018. URL: https://www.ncbi.nlm.nih.gov/books/NBK534916/pdf/Bookshelf_NBK534916.pdf [accessed 2024-03-03]

Abbreviations

AAP: American Academy of Pediatrics
ASPIRE: Adolescent Substance Use Prevention Intervention Research
BCH: Boston Children's Hospital
CRAFFT 2.1+N: CRAFFT version with extra questions that are related to nicotine vaping and tobacco use
CRAFFT: Car, Relax, Alone, Forget, Family/Friends, Trouble
CRAFFT-IS: CRAFFT Interactive System
cSBI: computer-facilitated screening and brief intervention
DO: Doctor of Osteopathic Medicine
DSMB: data safety and monitoring board
HED: heavy episodic drinking
HIPAA: Health Insurance Portability and Accountability Act
HONC: Hooked on Nicotine Checklist
IRB: institutional review board
MD: Doctor of Medicine
MI: motivational interviewing
NIAAA: National Institute on Alcohol Abuse and Alcoholism
NIAAADA: National Institute on Alcohol Abuse and Alcoholism Data Archive
NP: nurse practitioner
PA: physician assistant
PROMIS-E: Patient-Reported Outcomes Measurement Information System Nicotine Dependence Item Bank for Electronic Cigarettes
PROS: Pediatric Research in Office Settings
RA: research assistant
REDCap: Research Electronic Data Capture
SUD: substance use disorder
UC: usual care

Edited by A Mavragani; submitted 30.11.23; this is a non–peer-reviewed article;accepted 05.02.24; published 26.03.24.

Please cite as:
Shrier LA, O'Connell MM, Torres A, Shone LP, Fiks AG, Plumb JA, Maturo JL, McCaskill NH, Harris D, Burke PJ, Felt T, Murphy ML, Sherritt L, Harris SK
Computer-Facilitated Screening and Brief Intervention for Alcohol Use Risk in Adolescent Patients of Pediatric Primary Care Offices: Protocol for a Cluster Randomized Controlled Trial
JMIR Res Protoc 2024;13:e55039
URL: https://www.researchprotocols.org/2024/1/e55039
doi:10.2196/55039
PMID:38530346

Protocol

eHealth-Enhanced Peer Navigation for Substance Use Treatment and HIV Prevention Service Linkage for Young Adults Surveilled by the Criminal Legal System: Protocol for a Pilot Randomized Trial Study

Stephanie L Creasy[1], MPH; Sheridan Sweet[1,2], BA, BS; Janet J Myers[3], MPH, PhD; Martha Shumway[4], PhD; Marina Tolou-Shams[5], PhD; Nicole McCaffrey[1], BM; Emily F Dauria[1], MPH, PhD

[1]Department of Behavioral and Community Health Sciences, School of Public Health, University of Pittsburgh, Pittsburgh, PA, United States

[2]Department of Infectious Diseases and Microbiology, School of Public Health, University of Pittsburgh, Pittsburgh, PA, United States

[3]Division of Prevention Science, Department of Medicine, University of California, San Francisco, CA, United States

[4]Department of Psychiatry and Behavioral Sciences, School of Medicine, University of California, San Francisco, CA, United States

[5]Department of Psychiatry, Zuckerberg San Francisco General Hospital and Trauma Center, University of California, San Francisco, CA, United States

Corresponding Author:
Stephanie L Creasy, MPH
Department of Behavioral and Community Health Sciences
School of Public Health
University of Pittsburgh
130 De Soto St
6th Floor
Pittsburgh, PA, 15261
United States
Phone: 1 4126243136
Email: STC69@pitt.edu

Abstract

Background: In the United States, the proportion of criminal legal–involved (CLI) adults with a substance use disorder reaches 72%, and ~150,000 persons with HIV pass through a carceral setting annually, which represents 16% of the HIV-infected population nationally. Despite the high need for substance use treatment and HIV prevention services, few carceral settings successfully link CLI individuals to treatment upon release. Young adults represent 41.9% of the adults incarcerated in the United States and have the highest HIV incidence rates nationally. Peer patient navigation has successfully increased community-based care linkage for people living with HIV leaving jail; yet, peer-led navigation for HIV prevention among HIV-negative CLI populations is undeveloped and untested. eHealth approaches to substance use and HIV prevention services hold promise because they improve access to effective intervention services, particularly for younger people.

Objective: This paper describes a protocol for a pilot randomized controlled trial that aims to improve linkage to substance use treatment and HIV prevention services using peer navigation and a codeveloped eHealth technology adjunct.

Methods: The three aims of this study are to (1) adapt an existing evidence-based navigator model and incorporate codeveloped eHealth technology to refer and link young adults (18 to 29 years) surveilled by the criminal legal system to substance use and pre-exposure prophylaxis (PrEP) services; (2) refine and test the intervention with criminal legal–involved young adults (CLI-YAs); and (3) assess the feasibility, acceptability, and impact of the intervention. Data to inform the intervention will be collected via system partner interviews (n=4) and focus groups with CLI-YAs (n=24). Next, an open trial (n=10) will be conducted. The intervention will be refined via interviews with participants and facilitators, and a randomized pilot trial (n=75) will be conducted to assess the feasibility, acceptability, and preliminary impact of the eHealth-enhanced navigation on substance use and PrEP services linkage. Exit interviews conducted with a subsample of intervention participants (n=10), the navigator (n=1), and system partners (n=4) will assess intervention acceptability and suggestions for improvement. A community of practice, a group of system partners with an interest in working toward solutions to common problems, will inform each phase of the study.

Results: The project is currently ongoing. The project was funded in September 2022. Internal review board approval was received on March 21, 2022. The first results from early study aims are expected to be published in 2025.

Conclusions: This study provides an opportunity to reduce HIV acquisition and improve access to substance use treatment in a systemically marginalized group: young CLI-YAs. The results will contribute to the development and testing of a future multilevel randomized controlled trial.

International Registered Report Identifier (IRRID): DERR1-10.2196/54815

(JMIR Res Protoc 2024;13:e54815) doi:10.2196/54815

KEYWORDS

substance use; HIV prevention; carceral system; intervention development; young adult

Introduction

In the United States, annually, individuals involved in the criminal legal (CL) system are at an increased risk of substance use disorders (SUDs) and HIV acquisition [1-4]. HIV rates among CL-involved (CLI) adults range from 3 to 15 times the rate among individuals not involved in the CL system [2]. Individuals involved in the CL system have high rates of lifetime and recent substance use: between 81% and 84% report lifetime substance use and between 63% and 83% test positive for substance use at the time of their arrest [3]. The proportion of CLI individuals with an SUD reaches 72% [3]. Despite the high need for treatment services, few correctional settings link CLI individuals to community-based substance use treatment upon release.

Young adults (YAs; ages 18-34 years) represent 41.9% of the adults impacted by the carceral system [5] and have the highest HIV incidence rates nationally; YAs aged 20 to 24 years and 25 to 29 years have the highest rates of HIV infections (27.9 and 32.6 per 100,000, respectively) [6]. YAs also disproportionately experience SUD, with 25.6% of those aged 18 to 25 years estimated to meet the Diagnostic and Statistical Manual of Mental Disorders criteria for SUD in the last year (as of 2021) compared to 16.1% of those over the age of 26 years [6]. Factors that increase the likelihood of substance misuse and SUD among YAs include an imbalance of brain maturity through the second decade of life as well as psychosocial factors like increased peer influence and substance use as part of identity exploration [7]. Notably, the criminalization of substance use can also shape vulnerability to HIV as periods of detention can disrupt health care access, employment, caregiving, and social networks [8].

Significant racial disparities exist among new HIV acquisitions for YAs; African American populations accounted for 45.7% of all new HIV infections among YAs, and Hispanic populations accounted for 28.8% [9]. Given the disproportionate number of racial and ethnic minoritized CLI-YAs [10], prioritizing interventions that reduce racial and ethnic disparities in HIV and SUD treatment engagement for CLI-YAs is essential [11,12]. Multiple negative outcomes are known to be associated with involvement with the carceral system itself, including increased prevalence of SUD and infectious diseases like hepatitis C and HIV, increased indicators of poor mental health, and high prevalence of traumatic experiences (physical, sexual, and emotional) that linked directly to carceral policies (eg, solitary confinement) [13,14]. In light of the fact that ~5 million adults pass through CL settings annually and one-third are YAs [10], it is critical to link CLI-YAs who misuse substances and are at risk for HIV with innovative prevention strategies (ie, pre-exposure prophylaxis [PrEP]) and substance use treatment.

PrEP, in the form of a fixed-dose combination of 2 antiretroviral drugs, has emerged as a powerful HIV prevention tool [15]. In addition to 2 oral PrEP medications available (ie, Truvada and Descovy), the US Food and Drug Administration recently approved long-acting injectable PrEP (ie, Apretude) as another PrEP administration tool [15]. Significant disparities exist both between PrEP eligibility and uptake. For example, there are significant racial disparities with low PrEP uptake for Black individuals compared to people with other racial identities [16]. Hispanic and Latinx populations face similar disparities in PrEP use; people assigned female at birth, transgender populations, and bisexual and heterosexual populations also experience lower odds of PrEP use compared to their counterparts despite their not insignificant HIV incidence rates [16]. A variety of factors impede efforts to increase PrEP and substance use treatment access among CLI populations including discrimination based on one's racial or ethnic identity, misinformation about HIV transmission and treatment, stigma related to an individual's intersecting identities (eg, CLI status, substance use, race, and ethnicity), distrust of the CL and medical systems, psychiatric symptoms, inability to pay for transportation, lack of familial and social support, and inconsistent access to health care [17-20]. Although PrEP has been found to be efficacious, its maximal impact depends on uptake among those at high risk, including CLI-YAs.

Peer navigation holds strong potential to address multifactorial and complex barriers to PrEP and substance use treatment linkage and uptake for CLI-YAs. Navigation uses a one-on-one relationship to promote the timely movement of an individual through a health care continuum by eliminating barriers [18]. One such intervention, The Navigator Project (NAV), found that navigation-enhanced case management supported linkage to care (<30 days) and consistent retention in care (<1 year) for persons with HIV leaving jail as compared to persons with HIV living in the community and not exposed to jail detention. Using a harm reduction framework, peer navigators use motivational interviewing and prevention care management to navigate reentry back into the community, including referrals for mental health treatment, substance use treatment and harm reduction support, housing, employment, legal aid, and social services [20]. While peer navigation has been successful in increasing connections to care for persons with HIV leaving jail settings [20,21], peer-led navigation for HIV prevention among HIV-negative CLI populations is nascent [22].

In tandem with patient navigation, eHealth has the potential to improve health care engagement for CLI-YAs [23,24]. eHealth-enhanced peer navigation for HIV-infected individuals released from jail has been shown to be effective in maintaining virologic suppression [21]. The private nature of eHealth makes it an appealing modality to deliver components of a navigation intervention and link individuals with stigmatized services (eg, HIV prevention and SUD treatment) [25-27]. Of YAs aged 18-29 years, nearly 100% own a mobile phone and 92% possess a smartphone, making eHealth health intervention approaches feasible [23]. eHealth interventions can improve attendance at health care appointments [28,29], medication adherence [30,31], and behavior changes [32], and can provide support in real time [33]. To our knowledge, however, eHealth-enhanced navigation is untested for integrated substance use treatment and HIV prevention service linkage for CLI-YAs who have returned to the community after incarceration or who are subject to community surveillance. This study aims to address this gap in the literature by examining the feasibility, acceptability, and impact of an eHealth-enhanced peer navigator-led SUD and HIV prevention referral and linkage intervention for CLI-YAs supervised in the community. This paper is intended to provide a thorough summary of this study protocol.

The objectives of this study are to (1) adapt an existing evidence-based navigator mode (NAV) and incorporate codeveloped eHealth technology to refer and link CLI-YAs (ages 18-29 years) to substance use treatment and HIV prevention (PrEP) services; (2) refine the adapted eHealth-enhanced navigator-led substance use treatment and HIV prevention (PrEP) linkage intervention for CLI-YAs and test for fidelity, appropriateness, and satisfaction; and (3) assess the feasibility, acceptability, and impact of the adapted eHealth-enhanced navigator program to refer and link CLI-YAs to substance use treatment and HIV prevention (PrEP) services.

Methods

Study Setting

Surveillance data from Allegheny County, Pennsylvania, the study location, indicate that YAs (aged 20-29 years) account for 43% of all new HIV infections [34]. Notably, most adults newly diagnosed with HIV in Allegheny County are from racial and ethnic minority groups (65.8% in 2020) [34], making research in this geographic area generalizable to other high HIV incidence US locales. As of 2020, 30% of individuals who died from drug overdoses in Allegheny County were involved with adult probation and 19% had been booked in a county jail in the prior year. Additionally, Black residents in Allegheny County were disproportionately represented in overdose deaths, with a rate more than 2 times that of White residents [35].

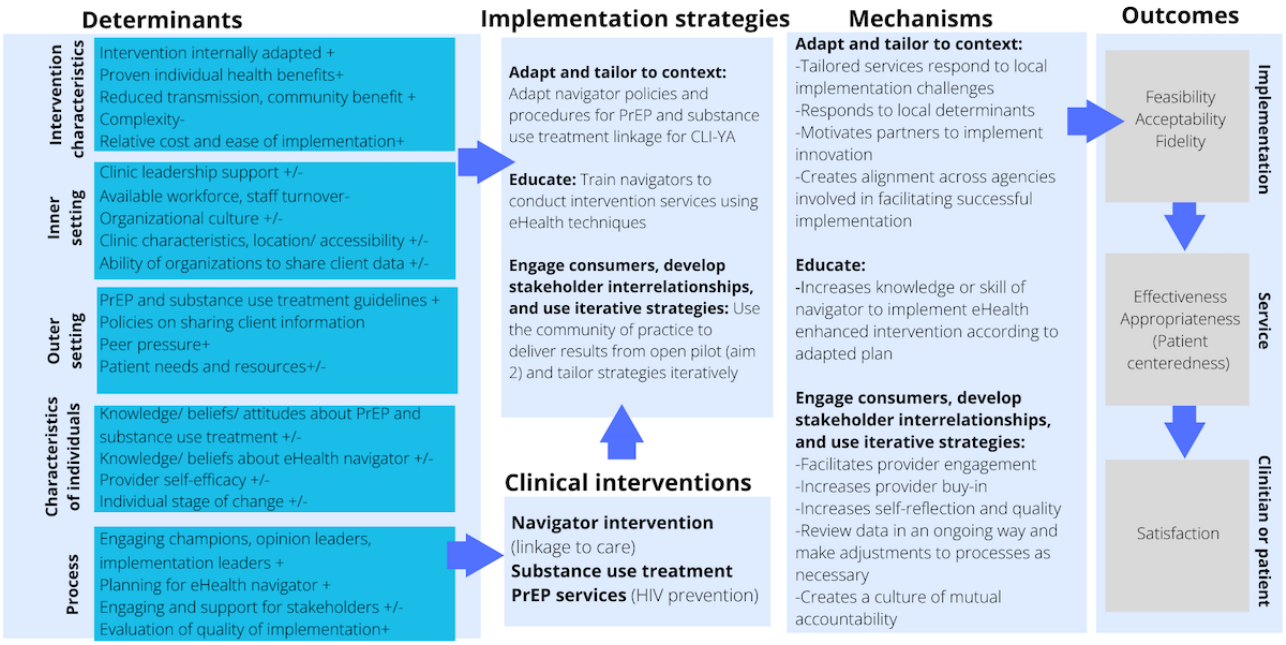
eHealth Enhancement

The proposed technology is a non-native web-based app that will facilitate resource linkage and communication between the navigator and participants. Expected functions of the eHealth technology include appointment scheduling and reminders, the provision of tailored resources (eg, substance use treatment information), motivational messages, and linkage to support persons. The partner for developing this technology is Chorus Innovations, Inc, which uses a participatory informatics approach that combines best practices from community-based participatory research (eg, equity and power sharing) [36] and user-centered design (eg, active user participation in design) to build technology products [37]. These practices ensure that the user participates in the design process [38], and there is a collaborative and equitable partnership in the research and design process, the process is iterative, and knowledge and action are mutually beneficial to all partners.

Implementation Research Logic Model

This study uses the CFIR (Consolidated Framework for Implementation Research) to identify key determinants [39], the “Expert Recommendations for Implementing Change” [40,41] to describe implementation strategies, and the Proctor Framework [42] to define implementation, service, and participant outcomes (Figure 1). The CFIR is organized into 5 domains based on context (intervention, outer setting, inner setting, individual, and process). We will use three implementation strategies from Expert Recommendations for Implementing Change [41] to (1) adapt and tailor to context for the eHealth enhancement protocol; (2) education to train navigators; and (3) engage consumers, develop stakeholder interrelationships, and use evaluative and iterative strategies achieved via the community of practice (CoP). This study focuses on feasibility, acceptability, fidelity (implementation outcomes), effectiveness, appropriateness (service outcomes), and satisfaction (clinical outcomes).

Figure 1. Intervention logic model for a 90-day randomized controlled trial designed to link young adults impacted by the criminal legal system to substance use and HIV prevention services in Allegheny County, PA, based on the CFIR (Consolidated Framework for Implementation Research), Expert Recommendations for Implementing Change (ERIC), and the Proctor Framework. +/- in the determinants column indicates directionality of impact. CLI-YA: criminal legal–involved young adult; PrEP: pre-exposure prophylaxis.



CoP

A CoP, originally conceptualized by anthropologists Lave and Wenger [43], is a community with a shared domain of interest or knowledge that provides support, resources, strategies, and best practices related to the shared domain. Our CoP will meet regularly throughout the intervention and be comprised of individuals from the public health and social service sectors with knowledge of substance use treatment and HIV prevention in CL settings, navigators with previous experience working with CLI-YAs, and YAs with a history of CLI. The CoP will be community experts who will participate in and support all 3 aims of the study including reviewing data collection tools and sampling frames, examining results from each aim, providing guidance on navigation structure and content, codeveloping the adaptation of the Chorus-supported navigation intervention in real time, and guiding research dissemination.

Aim 1: Development Phase

Participants

We present eligibility criteria by separate participant population. CLI-YAs (ages 18-29 years; n=24) will be eligible if they self-report recent CLI (past year); self-identify as HIV negative; endorse behaviors in the past 6 months indicating consideration of PrEP per the Center for Disease Control and Prevention's risk indices [44]; meet the Tobacco, Alcohol, Prescription medication, and other Substance use Tools' criteria for identifying the Diagnostic and Statistical Manual of Mental Disorders SUD (ie, ≥2 for tobacco, alcohol, and marijuana, and ≥1 for other substances) [45]; and are conversant in English. Exclusion criteria include being on PrEP, cognitive delays that would interfere with consent or participation, or inability to provide contact information for ≥2 locator individuals. CL system partners (n=2) will be in probation administration or frontline staff (eg, probation officers). Medical or public health system partners (n=2) will be involved in substance use treatment delivery and PrEP participant care in a setting where CLI participants are referred and will include individuals who have had experience navigating CLI to health services.

Recruitment

CLI-YAs will be recruited for participation in focus groups. To recruit focus groups, study staff are partnering with community-based carceral settings and community-based organizations serving CLI-YAs. Study staff will approach YAs for participation when they (1) come to meetings with their probation officers or (2) access services at community-based agencies serving CLI-YAs.

System partners will be recruited for individual interviews. Recruitment will be conducted using purposive sampling of community partners via email and phone outreach. We will identify initial contacts who work in CL and public health or health care spaces relevant to the study and use snowball sampling to include additional unknown system partners.

Data Collection

Overview

Focus groups and interviews will be held at times and locations convenient for participants (eg, for CLI-YAs, around probation visits, work schedules, or on weekends; for system partners, during lunch, or after work). Focus groups will be held via Zoom (Zoom Technologies Inc) or in a private room depending on participant preference and availability, while individual

interviews will be conducted by phone; both will be audio-recorded. A semistructured focus group and individual interview format will allow participants to respond freely and in an open-ended way [46].

Focus Groups

The research team will conduct 3 separate (75-90 minutes) focus groups with CLI-YAs (n=24). Focus groups will be informed by 2 domains of the CFIR relevant to CLI-YAs: characteristics of the intervention and individuals involved in the intervention. Sample content areas will assess the (1) knowledge about navigation as an effective approach to substance use treatment and HIV prevention service linkage, (2) perceptions of relevance of *NAV* content and gap areas, (3) strategies to support the likelihood of engaging with a navigator throughout the intervention period, and (4) attitudes toward and capabilities of using eHealth intervention enhancements of the CLI-YAs.

Interviews

As with the focus groups, individual interviews will be guided by several domains from the CFIR (eg, inner setting, intervention characteristics, and implementation process). Sample interview topics include (1) how a navigation intervention could be adopted, delivered, and sustained within the probation system; (2) perceptions of what YAs do or do not like to hear from them and what they might or might not like to have the navigator do on the topics of substance use, HIV risk, PrEP eligibility, and linkage; (3) identify intervention practices that might facilitate information sharing within and across probation and medical system while respecting participant privacy and confidentiality; and (4) areas of training relevant for navigators. At the end of the focus groups and individual interviews, study staff will administer a brief questionnaire to assess the sociodemographic characteristics of the sample.

Data Management and Analysis

We will conduct a content analysis, guided by CFIR domains, of notes collected as part of the CoP meetings occurring during this aim, focus groups, and individual interviews. Executive summaries, which provide data quickly, and evidence of whether theme redundancy is achieved, will be written within 48 hours of data collection. Digital recordings of all qualitative data will be transcribed verbatim. Following transcription and the completion of the executive summaries, data will be analyzed according to Inductive Thematic Analysis [47]. Inductive Thematic Analysis is often used to find solutions to real-world problems and provide program recommendations [48]. An initial codebook will be developed based on the focus group and individual interview guides and transcripts. To improve reliability and ensure adequate intercoder agreement, members of the research team will compare coding patterns, and the codebook will be refined until consensus is reached. Study team staff will generate memos to highlight connections between codes and subcodes. The team will meet weekly to discuss data as they are being collected and to come to a consensus on themes. To identify unique developmental, gender, and cultural perspectives, we will also examine data by race, ethnicity, sexual orientation, gender identity, and age or development (18-25 vs 26-29 years). NVivo (QSR International) will be used to facilitate analyses.

Outcomes

The primary outcome of aim 1's formative work is the adaptation of the existing navigator model (NAV) and the codevelopment of the proposed technology for eHealth enhancement. Both will be informed by the CoP and findings from focus groups with CLI-YAs and individual interviews with system partners. Both adaptation of the existing model and navigator training will be completed prior to the open pilot in aim 2.

Aim 2: Open Pilot Phase

Participants

To refine and test the adapted eHealth-enhanced intervention for CLI-YA, we will pilot the intervention with CLI-YAs (n=10). Final eligibility criteria for aims 2 and 3 will be determined from insights gained through the implementation and data collection of aim 1.

Recruitment

To recruit participants, study staff will be stationed in probation offices and community-based organizations working with individuals involved in the carceral system and will approach individuals to ask if they are interested in participating in the study screening. After consent, the study staff will refer participants to the navigator who will make contact within 24 hours.

Pilot Intervention Navigation Protocol

The navigation process will be informed by evidence-based practices from NAV, including harm reduction, peer navigation, motivational interviewing, and prevention care management to navigate reentry back into the community (eg, referrals for mental health treatment, substance use treatment, and social services) [20]. Navigation processes will be informed by 2 cascade frameworks: the *PrEP Continuum of Care* model [49] and the *JuvenileJusticeBehavioralHealth ServicesCascade* [50]. The PrEP continuum emphasizes identifying individuals at risk for HIV acquisition, increasing awareness of and willingness to take PrEP, ensuring linkage and access to PrEP, and adherence to PrEP medications. The *Juvenile Justice Behavioral Health Services Cascade* [50] was developed to move CLI youth from substance use screening and identification in CL settings to community-based treatment initiation and engagement; this cascade will be adapted to reflect processes specific to YAs.

Navigators will act as role models who can steer participants through the upstream steps of these cascades from screening to linkage with an exploratory look at engagement or initiation, adherence (PrEP specific), and continuing care (substance use treatment) or persistence (PrEP specific). We will test a 30-day intervention period (Textbox 1 for sample navigator visits, adapted from *NAV*). The first session (~75 minutes) will occur within 5 days of referral. In line with the *NAV* protocol, the navigator will initiate contact with the participant ≥3 times per week after the first session (the number of contacts may be higher, depending on the participant's needs and desires) [20]. Additional contacts could be made throughout the 30-day period in-person or with support via Chorus (eg, SMS text messages). Visits can occur via Zoom, telephonically, or in person based

on the participant's preferences. To maximize program retention, each navigation session will begin by updating the participant's contact information. If detention interrupts intervention delivery, we will "reset," where the participant left off to complete 30 days of exposure. Intervention "graduation" will be acknowledged and included in each participant's action plan (eg, certificate of completion).

Textbox 1. Sample navigator session content for a 90-day randomized controlled trial designed to link young adults impacted by the criminal legal system to substance use and HIV prevention services in Allegheny County, PA.

Session 1: Program orientation, relationship building, and needs assessment (~75 minutes)

- The navigator will build rapport by introducing themselves, their role, and the program. The navigator will identify significant contacts, and complete study documentation (eg, release of information forms). Finally, the navigator will conduct a comprehensive needs assessment of sexual health and substance use to develop an individual risk reduction plan. Relevant community resources will be presented to the participant.
- eHealth approaches identified in aim 1 (eg, SMS text messages, appointment reminders, motivational messages, and telehealth sessions) will be incorporated into session content.

Session 2: Substance use education and treatment cascade (~60 minutes)

- Provide psychosocial education on substance use (tailored to the client's behaviors and needs identified in session 1), provide participants with information on how patterns of substance use can affect their health, social, and legal outcomes and the Juvenile Justice Behavioral Health Services Cascade. The navigator will revisit the risk reduction plan (session l) and tailor it to any changes in the participant's life. Participants will be referred to local substance use treatment.
- eHealth approaches identified in aim 1 (eg, SMS text messages, appointment reminders, motivational messages, and telehealth sessions) will be incorporated into session content.

Session 3: HIV and Pre-exposure Prophylaxis knowledge and care cascade (~60 minutes)

- Provide psychosocial education on sexual health (tailored to the client's behaviors and needs identified in session 1) and can shape an individual's risk of sexually transmitted infections and HIV. Provide basic HIV (eg, transmission) and pre-exposure prophylaxis information, and outline the pre-exposure prophylaxis Care Continuum. The navigator will revisit the risk reduction plan (session 1) and tailor to any changes in the participant's life. Participants will be referred to local pre-exposure prophylaxis–related services.
- eHealth approaches identified in aim 1 (eg, SMS text messages, appointment reminders, motivational messages, and telehealth sessions) will be incorporated into session content.

Session 4. Substance use and Pre-exposure Prophylaxis care appointment scheduling and goal setting (~60 minutes)

- Provide follow-up information on where and how to access substance use and pre-exposure prophylaxis–related services. Develop a plan for substance use and pre-exposure prophylaxis linkage and maintenance to include planning for transportation to health care services, keeping appointment dates, obtaining medication (pre-exposure prophylaxis), formulating a medication schedule, and identifying motivation for appointment attendance and pre-exposure prophylaxis adherence.
- eHealth approaches identified in aim 1 (eg, SMS text messages, appointment reminders, motivational messages, and telehealth sessions) will be incorporated into session content.

Follow-up contacts (~30 minutes)

- Maintain regular contact between the navigator and the participant, provide guidance and support for goal setting, and ongoing emotional and psychosocial support.
- eHealth approaches identified in aim 1 (eg, SMS text messages and telehealth) will be incorporated to support follow-up contacts.

Navigator Training

The Navigator will receive a minimum of 7 days of training focused on relational service provisions (ie, emotional and psychosocial support), logistical service provisions (ie, assistance to overcome task-oriented barriers like scheduling and finding transportation to appointments), technology training, and population-specific training (eg, carceral system processes and harms perpetuated by the carceral system) [51]. Aim 1 system partner interviews will inform additional areas of training relevant to implementing a peer-led model, as well as preferred navigator characteristics (ie, peer navigators will share an age range and at least 1 intersecting identity or experience such as CLI, PrEP use, or substance use treatment with participants).

Intervention Fidelity

During the open pilot, navigators will audio record and complete a checklist documenting the delivery of session material [52]. Navigators will engage in weekly supervision with the principal investigator, and the principal investigator will periodically audit records and conduct field visits to observe sessions (required activities will be rated for completeness using a 4-point scale ranging from 0 "not at all" to 3 "completely").

Exit Interviews

The research team will collect qualitative feedback on the open pilot regarding intervention content, structure, and delivery (type of contact, ie, in-person or over the phone, eHealth [Chorus] enhancement acceptability, and a number of contacts) via individual interviews with CLI-YAs. We will also obtain

feedback from system partners regarding intervention recruitment, referral, delivery, and implementation. The navigator will be actively involved in the intervention pilot testing as well as in making further intervention manual revisions according to their lived experience of navigation delivery. Exit interview data will be analyzed using rapid qualitative analysis methods to reduce the time completing analysis to ensure timely results for use in aim 3; rapid analysis has been shown to have considerable overlapping findings with traditional qualitative analytic approaches [53,54].

Open Pilot Outcomes

In addition to completing a 7-day minimum navigator training, the open pilot's primary outcome is qualitative feedback to assess appropriateness and satisfaction. The results will be used to refine the intervention for pilot testing in aim 3.

Aim 3: Pilot Randomized Controlled Trial Phase

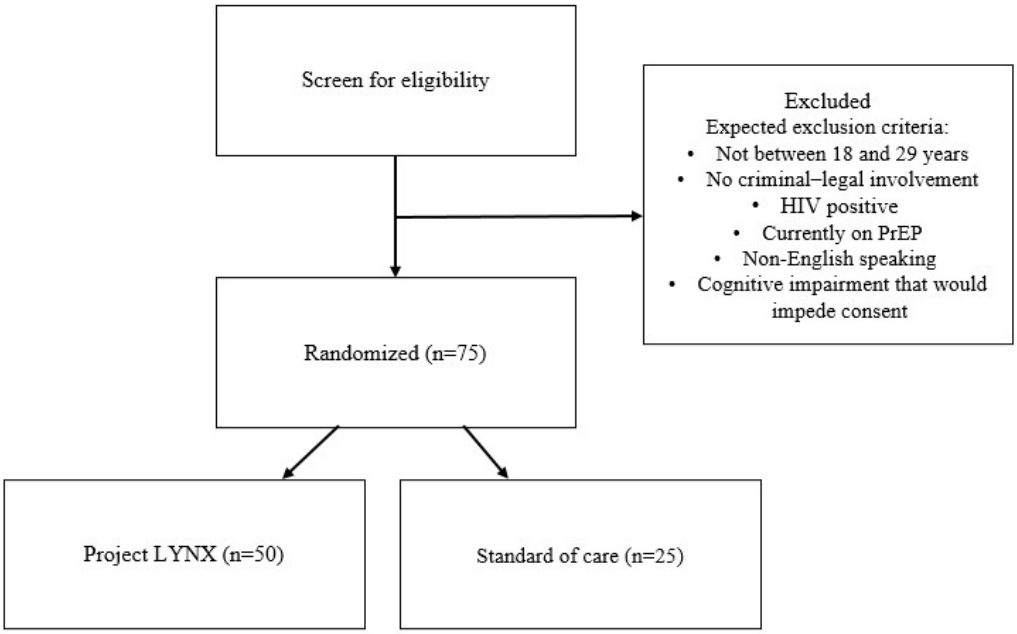
Participants

To assess the feasibility, acceptability, and impact of the adapted eHealth-enhanced intervention for CLI-YAs, we will test the intervention in a randomized pilot trial with CLI-YAs (n=75).

Recruitment and Randomization

Recruitment procedures will be informed by aim 2 results. Participants will be randomized either to the intervention group (n=50) or the standard of care (n=25) using a 2:1 randomization allocation scheme (Figure 2). Figure 3 provides a schematic of our study processes. Each participant will complete a baseline assessment immediately following the consent process. At the end of the baseline assessment, participants will be randomized to the intervention or control condition using a computerized algorithm programmed into REDCap (Research Electronic Data Capture; Vanderbilt University). Randomization will be blocked to avoid "runs" of assignment to the same.

Figure 2. Randomization protocol for aim 3, a 90-day randomized controlled trial designed to link young adults impacted by the criminal legal system to substance use and HIV prevention services in Allegheny County, PA. PrEP: pre-exposure prophylaxis.



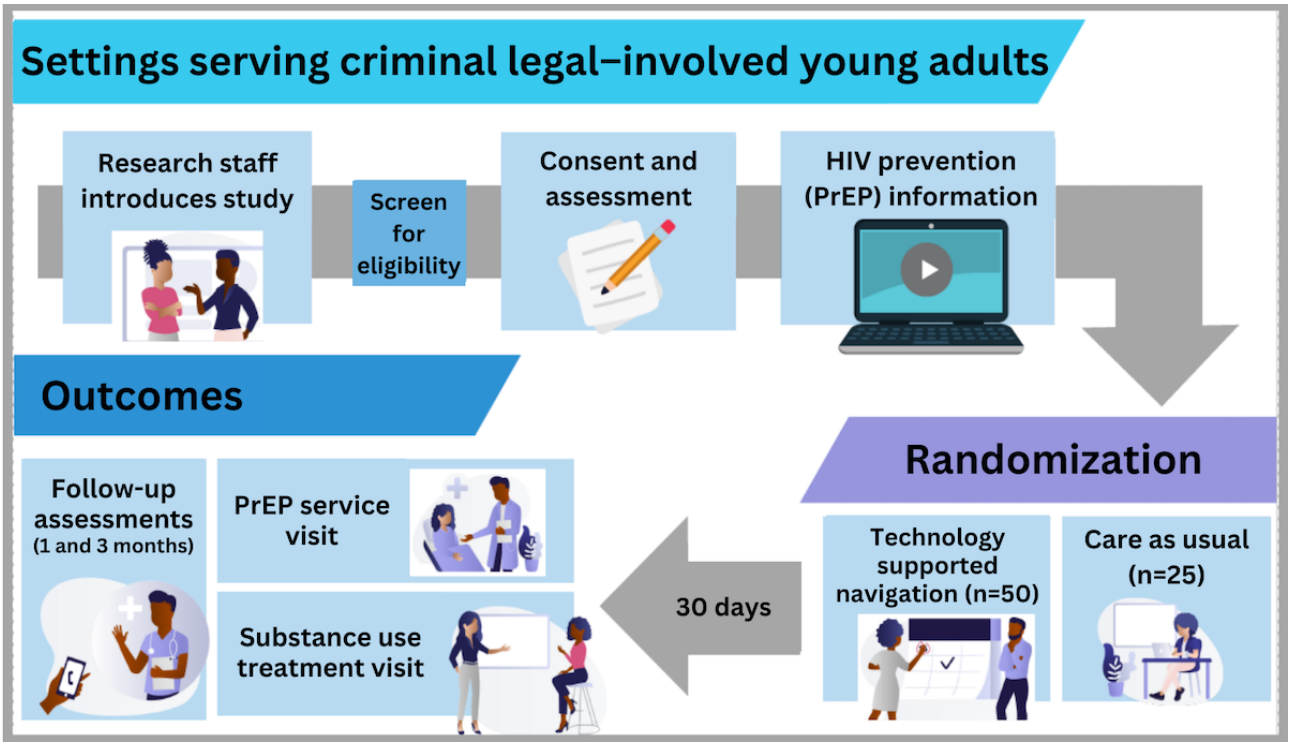
Standard of Care

The standard of care is a referral to substance use treatment and HIV prevention services from an individual's case worker.

Data Collection

The baseline assessment will occur immediately following participant consent, prior to randomization, and follow-up assessments will occur at 1 month and 3 months (Figure 3). Data will be collected via face-to-face one-on-one interviews in private locations to ensure confidentiality. If face-to-face interviews are not possible, a participant will be given the option of completing the assessment via a secure web-based survey link. Regardless of the method of interview administration, REDCap will be used to collect data (ie, in person on tablets or via a secure REDCap survey sent via email). If completing the assessment via a secure link, specific instructions will be provided to the participant to inform them about how to keep their data private.

Figure 3. Recruitment, randomization, and intervention practices for aim 3, a 90-day randomized controlled trial designed to link young adults impacted by the criminal legal system to substance use and HIV prevention services in Allegheny County, PA. PrEP: pre-exposure prophylaxis.



Pilot Trial Outcomes

Primary outcomes are linkage to substance use treatment and PrEP services. Because PrEP and substance use treatment health service linkage are a process and not a 1-time event, we will also explore prelinkage (eg, navigator satisfaction) and downstream outcomes (eg, PrEP initiation, adherence, and substance use treatment continuing of care) in an exploratory fashion [55]. The navigator will track these outcomes, but the primary outcomes of (1) PrEP linkage will be attendance at a PrEP services appointment, verified by medical records and (2) substance use treatment linkage will be attendance at a substance use treatment appointment, verified by the navigator and medical provider collateral (if the participant agrees). Other exploratory outcomes include time to health service linkage (substance use and PrEP) and data on HIV testing at the PrEP linkage appointment (uptake, result). Participants will be asked whether and for how long they have experienced hospitalization, residential treatment, and detention since the intervention to account for any system barriers to linkage. We will also assess preferred methods for communicating with the navigator as well as participant satisfaction with the intervention and navigator services. Table 1 provides additional detail on outcomes and correlates.

Table 1. Description and schedule of outcomes from a 90-day randomized controlled trial designed to link young adults impacted by the criminal legal system to substance use and HIV prevention services in Allegheny County, PA.

Primary outcomes	Baseline	30 days	90 days
PrEP[a] linkage: medical record		✓	✓
Substance use treatment linkage: self-report, medical provider collateral if the participant agrees		✓	✓
Secondary outcomes			
Navigator satisfaction: NAVSAT Pt 1		✓	
Client intervention satisfaction: Study Participant Feedback Questionnaire	✓	✓	✓
PrEP care continuum (accepted, initiated, and adhered): navigator report, medical record, and self-report		✓	✓
Substance use treatment continuum (accepted, initiated, and adhered): navigator report, medical record, and self-report		✓	✓
Linkage to other services: self-report and Navigator report		✓	✓
Sociodemographic, psychosocial, and behavioral correlates			
Demographic information (age in years, race or ethnicity, legal history, etc)	✓		✓
Health care use	✓		✓
Medical mistrust: Health Care System Distrust Scale	✓		✓
HIV knowledge or attitudes or risk: HIV-related knowledge scale, HIV-related attitudes scale, HIV stigma scale	✓		✓
PrEP knowledge or attitudes: willingness, intentions to use, barriers, stigma or conspiracy beliefs	✓		✓
Substance use: Alcohol use Disorders Identification Test, Texas Christian University Drug Screen V, Internalized Stigma of Substance Abuse	✓		✓
Psychiatric symptoms: Global Appraisal of Individual Needs-Short Screener	✓		✓

[a]PrEP: pre-exposure prophylaxis.

Data Management and Analysis

REDCap will facilitate routine data checking and exportation of data for analysis. Analyses will be conducted using SAS (version 9.4; SAS Institute). Preliminary analyses will include the examination of descriptive statistics, distributions, and internal consistency reliability of scaled measures. Logistic regression will be used to examine the relationship between the condition and the primary outcomes (services linkage, ie, PrEP, substance use treatment), and all other dichotomous outcomes (eg, acceptance of PrEP and substance use treatment referral). Dependent variables in initial analyses will be summary dichotomous indicators based on both month 1 and 3 assessments, reflecting whether the outcome ever occurred. Subsequent analyses will separately examine whether outcomes occurred by month 1 and by month 3. Generalized linear models will be used to examine variously distributed continuous outcomes (navigator contacts, time-to-service linkage, and satisfaction). Exploratory analyses will build on these models to preliminarily examine the impact of potential moderating variables including sociodemographic characteristics, HIV risk behaviors and perceptions, PrEP-related knowledge and attitudes, substance use treatment behaviors, psychiatric symptoms, social support, and substance use on primary and secondary outcomes.

Exit Interviews

We will conduct exit interviews with a subsample of intervention arm participants (n=10), the navigator (n=1), and partners from participating systems (n=4). Interviews will assess intervention acceptability and suggestions for improvement. To recruit for qualitative exit interviews, a member of the study team will contact intervention participants to invite them to a phone interview (~30 minutes). To ensure a range of responses, we will sample for (1) participants who connect or did not connect to the navigator and who linked or did not link to PrEP and substance use treatment services and (2) variation in characteristics that may impact the intervention (eg, psychiatric symptoms). We will seek to understand reasons why the intervention was or was not successful for a particular participant (via participant and navigator report). To analyze exit interview data, we will mirror aim 2's rapid qualitative analysis processes.

Ethical Considerations

Overview

This study was approved by the University of Pittsburgh internal review board (reference 22020053). As the intervention is refined, changes to the protocol will be submitted to the internal review board for further approval. Additional protections for participants are provided via a Certificate of Confidentiality through the National Institute of Health. This certificate allows the researchers to legally refuse to disclose information that may identify participants, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. To ensure confidentiality, all data will be deidentified and participants will be assigned a unique participant ID. Participant contact information will be stored

separately from any data that have been collected (eg, screening surveys, transcripts, and assessments).

Aim 1: Development Phase

CLI-YA

To determine eligibility, participants will undergo a confidential screening survey with study personnel. Following screening, participants will be compensated US $10 regardless of eligibility status. Eligible participants will undergo a verbal consent process with study personnel prior to participating in focus groups. The consent process will include (1) a review of the information sheet in detail, (2) an explanation of all study procedures in full detail, and (3) an opportunity for the participant to ask questions and have them answered. Potential participants will be asked to paraphrase the information sheet and will be asked basic questions to determine their understanding of key elements of the informed consent. Participants will be compensated US $40 following focus group participation.

System Partners

Prior to participating in interviews, system partners will undergo a verbal consent process that follows the same protocol as the focus group consent process outlined above. Participants will be compensated US $50 following completion of an individual interview.

Aim 2: Pilot Trial Phase

Prior to participation in the pilot trial, CLI-YAs will undergo a 2-step consent process. Potential participants will be given an information sheet and provide verbal informed consent for screening. Next, should individuals be interested in participating and eligible based on their HIV risk assessment and SUD screening, they will provide written informed consent to allow participation in the open pilot navigation intervention and exit interview. Participants will be compensated US $40 for participating in exit interviews.

Aim 3: Assessment Phase

The consent process for aim 3 follows the same 2-step process as outlined above for aim 2. Participants will be compensated US $40 for the baseline assessment, US $20 for the 1-month assessment, US $40 for the 3-month assessment, and US $30 for participating in exit interviews.

Results

The project was funded in September 2022. Internal review board approval was received on March 21, 2022. Data collection for aim 1 began on April 19, 2023, and is ongoing. At the time of publication, 5 system stakeholders and 16 CLI-YAs have been enrolled in aim 1 data collection activities. The first results from early study aims are expected to be published in 2025.

Discussion

Principal Findings

This study provides an opportunity to reduce HIV acquisition and improve access to substance use treatment in a systemically marginalized group of YAs. This emerging area of research has been rapidly amplified in the context of the ongoing coronavirus pandemic, for which empirical study of effective adjunctive technology tools to promote increased substance use and HIV prevention services access is greatly needed. The results will contribute to the development and testing of a future multilevel randomized controlled trial targeting CLI-YAs, CL system partners, and treatment providers.

Gaps in Literature and Comparisons With Prior Work

Previous studies leveraging peer navigation as a mechanism to link CLI individuals to HIV care have proved efficacious [19,20]. Patient navigation interventions led by individuals who share key personal characteristics, circumstances, or qualities with their participants (eg, ethnic background, culture, and membership in a subpopulation [formerly engaged in transactional sex or IDU]) or “peers” are ideal because they have demonstrated efficacy in building trust and reducing stigma and discrimination-related barriers to health care engagement, particularly among vulnerable populations [24,56]. The inclusion of eHealth technology in patient navigation is appealing because it provides a discrete platform for individuals to engage with potentially stigmatizing services (eg, substance use treatment and HIV prevention services). It also has the potential to facilitate frequent, meaningful communication between individuals and their peer navigators. Previous studies have found eHealth-enhanced peer navigation effective in maintaining viral suppression among people living with HIV [21]. However, there has been little research using this framework to link CLI-YAs to HIV prevention and substance use treatment services. This study will fill an important gap in the literature and provide insights that will inform future efforts to improve service linkage for CLI-YAs, a vulnerable and structurally precarious population [57].

Strengths and Limitations

A core tenet of this study is the codevelopment of the eHealth technology and navigation protocol. Including the perspectives of individuals who are a part of the population of focus, in addition to system partners, ensures the intervention will be reflective of the wants and needs of the community it will be serving. The inclusion of system partners and people with lived experience in the CoP is important but comes with challenges due to encounter challenges related to power dynamics between these groups. For example, individuals with lived experience may be hesitant to share their thoughts and opinions when they are in a room of service providers and system partners with whom they might already be familiar. The study team will begin each meeting with an overview of agreements and expectations and moderate the discussion to mitigate issues as they arise; however, we acknowledge the challenge that navigating these relationships might pose.

Additionally, the technology being developed will not be a native app. The benefit of this is that it will be accessible from a mobile device or a computer, which ensures that participants will be able to access the technology whether they have regular access to a mobile device. However, data will not be stored directly on a participant’s personal device, so it will not be accessible without an internet connection. This could be a

limiting factor for participants who have a phone but do not have regular internet access.

The inclusion of the eHealth portion of the study has the potential to expand access to linkage services for CLI-YAs. This is especially important because CLI-YAs experience structural and institutional obstacles that can hinder their ability to regularly engage in services [57]. However, there is no funding to distribute phones to participants if they do not have them. This may limit the eHealth functionalities available to participants who do not have phones (eg, SMS text messaging) and may make it difficult for them to engage in the intervention in the same way as participants with their personal devices. We will measure where and how participants are engaging with the technology to better examine the impact of technology access.

Conclusions

This study provides an opportunity to reduce HIV acquisition and improve access to substance use treatment in a vulnerable, underserved group of young adults (CLI-YAs) by adapting an evidence-based navigation intervention and incorporating eHealth technology. The need to further this line of research has been rapidly amplified in the context of the COVID-19 pandemic, for which empirical study of effective adjunctive technology tools that can promote access to substance use and HIV prevention services is greatly needed. The results will contribute to the development and testing of a future multilevel randomized controlled trial targeting CLI-YAs, CL system partners, and substance use treatment and PrEP providers.

Acknowledgments

With gratitude, the authors acknowledge the participants in previous studies whose pilot data contributed to this grant being funded. The funding for this study was provided by the National Institute on Drug Abuse (grant R34DA054853; EFD principal investigator).

Data Availability

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

Authors' Contributions

SLC wrote the original draft and contributed to manuscript review and editing, and is assisting with project administration. SS and NM supported the writing of the original draft and contributed to manuscript review and editing, and is assisting with project administration including conducting data collection activities and supporting data analysis, and contributing to intervention refinement JJM, MS, and MTS contributed to project conceptualization and manuscript review and editing. EFD led the conceptualization of the project and the development of the proposed methodology, acquired project funding, supported the writing of the original draft and contributed to manuscript review and editing, and is leading the overall project administration.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review grant documentation from the National Institute on Drug Abuse.
[PDF File (Adobe PDF File), 99 KB - resprot_v13i1e54815_app1.pdf]

References

1. Maruschak LM. HIV in prisons and jails, 2007-2008. U.S. Department of Justice. Washington, DC; 2009. URL: https://bjs.ojp.gov/content/pub/pdf/hivp08.pdf [accessed 2024-02-24]
2. Spaulding AC, Seals RM, Page MJ, Brzozowski AK, Rhodes W, Hammett TM. HIV/AIDS among inmates of and releasees from US correctional facilities, 2006: declining share of epidemic but persistent public health opportunity. PLoS One 2009 Nov 11;4(11):e7558 [FREE Full text] [doi: 10.1371/journal.pone.0007558] [Medline: 19907649]
3. Bronson J, Stroop J, Zimmer S, Berzofsky M. Drug use, dependence, and abuse among state prisoners and jail inmates, 2007-2009: special report. U.S. Department of Justice. 2017. URL: https://bjs.ojp.gov/content/pub/pdf/dudaspji0709.pdf [accessed 2024-02-24]
4. Moore KE, Oberleitner L, Pittman BP, Roberts W, Verplaetse TL, Hacker RL, et al. The prevalence of substance use disorders among community-based adults with legal problems in the U.S. Addict Res Theory 2020;28(2):165-172 [FREE Full text] [doi: 10.1080/16066359.2019.1613524] [Medline: 32952490]
5. Carson EA. Prisoners in 2021—statistical tables. U.S. Department of Justice. 2022. URL: https://bjs.ojp.gov/library/publications/prisoners-2021-statistical-tables [accessed 2024-02-24]
6. Substance Abuse and Mental Health Services Administration. Key substance use and mental health indicators in the United States: results from the 2021 national survey on drug use and health. Center for Behavioral Health Statistics and Quality. 2022. URL: https://www.samhsa.gov/data/sites/default/files/reports/rpt39443/2021NSDUHNNR122322/

2021NSDUHNNR122322.htm#:~:text=Among%20people%20aged%2012%20or%20older%20in%202021%2C%2057.8%20percent,and%2014.3%20percent%20(or%2040.0 [accessed 2024-02-24]
7. Substance misuse prevention for young adults. Substance Abuse and Mental Health Services Administration. Rockville, MD; 2019. URL: https://store.samhsa.gov/product/substance-misuse-prevention-young-adults/pep19-pl-guide-1 [accessed 2024-02-24]
8. Wildeman C, Wang EA. Mass incarceration, public health, and widening inequality in the USA. Lancet 2017;389(10077):1464-1474. [doi: 10.1016/S0140-6736(17)30259-3] [Medline: 28402828]
9. HIV surveillance report, 2021. Centers for Disease Control and Prevention. 2020. URL: https://www.cdc.gov/hiv/library/reports/hiv-surveillance.html [accessed 2024-02-24]
10. Kaeble D. Probation and parole in the United States, 2016. U.S. Department of Justice. 2018. URL: https://bjs.ojp.gov/content/pub/pdf/ppus16.pdf [accessed 2024-02-24]
11. Binswanger IA, Redmond N, Steiner JF, Hicks LS. Health disparities and the criminal justice system: an agenda for further research and action. J Urban Health 2012;89(1):98-107 [FREE Full text] [doi: 10.1007/s11524-011-9614-1] [Medline: 21915745]
12. Beckwith CG, Zaller ND, Fu JJ, Montague BT, Rich JD. Opportunities to diagnose, treat, and prevent HIV in the criminal justice system. J Acquir Immune Defic Syndr 2010 Dec;55 Suppl 1(Suppl 1):S49-S55 [FREE Full text] [doi: 10.1097/QAI.0b013e3181f9c0f7] [Medline: 21045600]
13. Piper A, Berle D. The association between trauma experienced during incarceration and PTSD outcomes: a systematic review and meta-analysis. J Forensic Psychiatry Psychol 2019;30(5):854-875. [doi: 10.1080/14789949.2019.1639788]
14. Creasy SL, Hawk M, Friedman MR, Mair C, McNaboe J, Egan JE. Previously incarcerated transgender women in Southwestern Pennsylvania: a mixed methods study on experiences, needs, and resiliencies. Ann LGBTQ Public Population Health 2023;4(3):281-296. [doi: 10.1891/lgbtq-2021-0045]
15. Dean LT, Predmore Z, Skinner A, Napoleon S, Chan PA, Raifman J. Optimizing uptake of long-acting injectable pre-exposure prophylaxis for HIV prevention for men who have sex with men. AIDS Behav 2023 Aug;27(8):2606-2616 [FREE Full text] [doi: 10.1007/s10461-023-03986-5] [Medline: 36670210]
16. Hamilton K, Hasney L, Cohn T, Posnak JP. PrEP demographics and disparity: the race, ethnicity, gender identity, sex assigned at birth, sexual orientation and age of current PrEP use. J Community Health Nurs 2022;39(4):213-226. [doi: 10.1080/07370016.2022.2073791] [Medline: 36189944]
17. Dauria EF, Levine A, Hill SV, Tolou-Shams M, Christopoulos K. Multilevel factors shaping awareness of and attitudes toward pre-exposure prophylaxis for HIV prevention among criminal justice-involved women. Arch Sex Behav 2021;50(4):1743-1754 [FREE Full text] [doi: 10.1007/s10508-020-01834-4] [Medline: 33236275]
18. Freeman HP, Rodriguez RL. History and principles of patient navigation. Cancer 2011 Aug;117(15 Suppl):3539-3542 [FREE Full text] [doi: 10.1002/cncr.26262] [Medline: 21780088]
19. Koester KA, Morewitz M, Pearson C, Weeks J, Packard R, Estes M, et al. Patient navigation facilitates medical and social services engagement among HIV-infected individuals leaving jail and returning to the community. AIDS Patient Care STDS 2014;28(2):82-90 [FREE Full text] [doi: 10.1089/apc.2013.0279] [Medline: 24517539]
20. Myers JJ, Dufour MSK, Koester KA, Morewitz M, Packard R, Klein KM, et al. The effect of patient navigation on the likelihood of engagement in clinical care for HIV-infected individuals leaving jail. Am J Public Health 2018;108(3):385-392. [doi: 10.2105/AJPH.2017.304250] [Medline: 29345992]
21. Cunningham WE, Weiss RE, Nakazono T, Malek MA, Shoptaw SJ, Ettner SL, et al. Effectiveness of a peer navigation intervention to sustain viral suppression among HIV-positive men and transgender women released from jail: the LINK LA randomized clinical trial. JAMA Intern Med 2018 Apr 01;178(4):542-553 [FREE Full text] [doi: 10.1001/jamainternmed.2018.0150] [Medline: 29532059]
22. Dauria EF, Kulkarni P, Clemenzi-Allen A, Brinkley-Rubinstein L, Beckwith CG. Interventions designed to improve HIV continuum of care outcomes for persons with HIV in contact with the carceral system in the USA. Curr HIV/AIDS Rep 2022 Aug;19(4):281-291 [FREE Full text] [doi: 10.1007/s11904-022-00609-x] [Medline: 35674879]
23. Muessig KE, Nekkanti M, Bauermeister J, Bull S, Hightow-Weidman LB. A systematic review of recent smartphone, internet and web 2.0 interventions to address the HIV continuum of care. Curr HIV/AIDS Rep 2015;12(1):173-190 [FREE Full text] [doi: 10.1007/s11904-014-0239-3] [Medline: 25626718]
24. Hightow-Weidman LB, Muessig KE, Bauermeister J, Zhang C, LeGrand S. Youth, technology, and HIV: recent advances and future directions. Curr HIV/AIDS Rep 2015;12(4):500-515 [FREE Full text] [doi: 10.1007/s11904-015-0280-x] [Medline: 26385582]
25. Mason M, Ola B, Zaharakis N, Zhang J. Text messaging interventions for adolescent and young adult substance use: a meta-analysis. Prev Sci 2015;16(2):181-188. [doi: 10.1007/s11121-014-0498-7] [Medline: 24930386]
26. Heron KE, Smyth JM. Ecological momentary interventions: incorporating mobile technology into psychosocial and health behaviour treatments. Br J Health Psychol 2010;15(Pt 1):1-39 [FREE Full text] [doi: 10.1348/135910709X466063] [Medline: 19646331]
27. Savic M, Best D, Rodda S, Lubman DI. Exploring the focus and experiences of smartphone applications for addiction recovery. J Addict Dis 2013;32(3):310-319. [doi: 10.1080/10550887.2013.824331] [Medline: 24074196]

28. Donker T, Petrie K, Proudfoot J, Clarke J, Birch MR, Christensen H. Smartphones for smarter delivery of mental health programs: a systematic review. J Med Internet Res 2013;15(11):e247 [FREE Full text] [doi: 10.2196/jmir.2791] [Medline: 24240579]
29. Harrison V, Proudfoot J, Wee PP, Parker G, Pavlovic DH, Manicavasagar V. Mobile mental health: review of the emerging field and proof of concept study. J Ment Health 2011;20(6):509-524. [doi: 10.3109/09638237.2011.608746] [Medline: 21988230]
30. Warmerdam L, Riper H, Klein M, van den Ven P, Rocha A, Henriques MR, et al. Innovative ICT solutions to improve treatment outcomes for depression: the ICT4Depression project. Stud Health Technol Inform 2012;181:339-343. [Medline: 22954884]
31. Moullin JC, Dickson KS, Stadnick NA, Rabin B, Aarons GA. Systematic review of the Exploration, Preparation, Implementation, Sustainment (EPIS) framework. Implement Sci 2019;14(1):1 [FREE Full text] [doi: 10.1186/s13012-018-0842-6] [Medline: 30611302]
32. LeBlanc A, Kenny DA, O'Connor AM, Légaré F. Decisional conflict in patients and their physicians: a dyadic approach to shared decision making. Med Decis Making 2009;29(1):61-68. [doi: 10.1177/0272989X08327067] [Medline: 19196706]
33. Bass SB, Gordon TF, Ruzek SB, Hausman AJ. Mapping perceptions related to acceptance of smallpox vaccination by hospital emergency room personnel. Biosecur Bioterror 2008;6(2):179-190. [doi: 10.1089/bsp.2007.0054] [Medline: 18563995]
34. Portela G, Mertz K, Wiesenfeld K. Allegeny county STD/HIV annual report, 2020. Allegheny County Health Department. 2020. URL: https://www.alleghenycounty.us/files/assets/county/v/1/government/health/documents/std-report_2020_final.pdf [accessed 2024-02-24]
35. Accidental overdose deaths in Allegheny County, January 2016—June 2020. Allegheny County Department of Human Services and the Allegheny County Health Department. 2021. URL: https://www.alleghenycountyanalytics.us/wp-content/uploads/2021/05/21-ACDHS-05-AccidentalOverdoses-04-09-2021_final-1.pdf [accessed 2024-02-24]
36. Israel BA, Schulz AJ, Parker EA, Becker AB. Review of community-based research: assessing partnership approaches to improve public health. Annu Rev Public Health 1998;19:173-202 [FREE Full text] [doi: 10.1146/annurev.publhealth.19.1.173] [Medline: 9611617]
37. Chorus Innovations Inc. 2020. URL: https://www.joinchorus.com/ [accessed 2024-02-24]
38. User-centered design basics. U.S. General Services Administration. 2023. URL: https://www.usability.gov/what-and-why/user-centered-design.html [accessed 2023-09-02]
39. Keith RE, Crosson JC, O'Malley AS, Cromp D, Taylor EF. Using the Consolidated Framework for Implementation Research (CFIR) to produce actionable findings: a rapid-cycle evaluation approach to improving implementation. Implement Sci 2017;12(1):15 [FREE Full text] [doi: 10.1186/s13012-017-0550-7] [Medline: 28187747]
40. Waltz TJ, Powell BJ, Chinman MJ, Smith JL, Matthieu MM, Proctor EK, et al. Expert Recommendations for Implementing Change (ERIC): protocol for a mixed methods study. Implement Sci 2014;9:39 [FREE Full text] [doi: 10.1186/1748-5908-9-39] [Medline: 24669765]
41. Powell BJ, Waltz TJ, Chinman MJ, Damschroder LJ, Smith JL, Matthieu MM, et al. A refined compilation of implementation strategies: results from the Expert Recommendations for Implementing Change (ERIC) project. Implement Sci 2015;10:21 [FREE Full text] [doi: 10.1186/s13012-015-0209-1] [Medline: 25889199]
42. Proctor EK, Landsverk J, Aarons G, Chambers D, Glisson C, Mittman B. Implementation research in mental health services: an emerging science with conceptual, methodological, and training challenges. Adm Policy Ment Health 2009;36(1):24-34 [FREE Full text] [doi: 10.1007/s10488-008-0197-4] [Medline: 19104929]
43. Lave J, Wenger E. Situated Learning: Legitimate Peripheral Participation. Cambridge: Cambridge University Press; 1991.
44. Pre-Exposure Prophylaxis (PrEP). Centers for Disease Control and Prevention. 2023. URL: https://www.cdc.gov/hiv/risk/prep/index.html [accessed 2023-09-22]
45. McNeely J, Wu LT, Subramaniam G, Sharma G, Cathers LA, Svikis D, et al. Performance of the Tobacco, Alcohol, Prescription Medication, and Other Substance Use (TAPS) tool for substance use screening in primary care patients. Ann Intern Med 2016;165(10):690-699 [FREE Full text] [doi: 10.7326/M16-0317] [Medline: 27595276]
46. Crosby R, DiClemente RJ, Salazar LF. Research Methods in Health Promotion. Hoboken, New Jersey: Wiley; 2011.
47. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol 2006;3(2):77-101. [doi: 10.1191/1478088706qp063oa]
48. Denzin NK, Lincoln YS. The SAGE Handbook of Qualitative Research. Thousand Oaks, California: Sage Publications; 2005.
49. Nunn AS, Brinkley-Rubinstein L, Oldenburg CE, Mayer KH, Mimiaga M, Patel R, et al. Defining the HIV pre-exposure prophylaxis care continuum. AIDS 2017;31(5):731-734 [FREE Full text] [doi: 10.1097/QAD.0000000000001385] [Medline: 28060019]
50. Belenko S, Knight D, Wasserman GA, Dennis ML, Wiley T, Taxman FS, et al. The juvenile justice behavioral health services cascade: a new framework for measuring unmet substance use treatment services needs among adolescent offenders. J Subst Abuse Treat 2017;74:80-91 [FREE Full text] [doi: 10.1016/j.jsat.2016.12.012] [Medline: 28132705]

51. Paskett ED, Harrop JP, Wells KJ. Patient navigation: an update on the state of the science. CA Cancer J Clin 2011;61(4):237-249 [FREE Full text] [doi: 10.3322/caac.20111] [Medline: 21659419]
52. Metsch LR, Feaster DJ, Gooden L, Matheson T, Stitzer M, Das M, et al. Effect of patient navigation with or without financial incentives on viral suppression among hospitalized patients with HIV infection and substance use: a randomized clinical trial. JAMA 2016 Jul 12;316(2):156-170 [FREE Full text] [doi: 10.1001/jama.2016.8914] [Medline: 27404184]
53. Taylor B, Henshall C, Kenyon S, Litchfield I, Greenfield S. Can rapid approaches to qualitative analysis deliver timely, valid findings to clinical leaders? A mixed methods study comparing rapid and thematic analysis. BMJ Open 2018;8(10):e019993 [FREE Full text] [doi: 10.1136/bmjopen-2017-019993] [Medline: 30297341]
54. Gale RC, Wu J, Erhardt T, Bounthavong M, Reardon CM, Damschroder LJ, et al. Comparison of rapid vs in-depth qualitative analytic methods from a process evaluation of academic detailing in the veterans health administration. Implement Sci 2019;14(1):11 [FREE Full text] [doi: 10.1186/s13012-019-0853-y] [Medline: 30709368]
55. Das M, Christopoulos KA, Geckeler D, Huriaux E, Cohen SE, Philip S, et al. Linkage to HIV care in San Francisco: implications of measure selection. J Acquir Immune Defic Syndr 2013;64(Suppl 1(0 1)):S27-S32 [FREE Full text] [doi: 10.1097/QAI.0b013e3182a99c73] [Medline: 24126446]
56. Sullivan PS, Driggers R, Stekler JD, Siegler A, Goldenberg T, McDougal SJ, et al. Usability and acceptability of a mobile comprehensive HIV prevention app for men who have sex with men: a pilot study. JMIR Mhealth Uhealth 2017;5(3):e26 [FREE Full text] [doi: 10.2196/mhealth.7199] [Medline: 28279949]
57. Ellis R. What do we mean by a "hard-to-reach" population? Legitimacy versus precarity as barriers to access. Sociol Methods Res 2021;52(3):1556-1586. [doi: 10.1177/0049124121995536]

Abbreviations

CFIR: Consolidated Framework for Implementation Research
CL: criminal legal
CLI: criminal legal involved
CLI-YA: criminal legal–involved young adult
CoP: community of practice
NAV: The Navigator Project
PrEP: pre-exposure prophylaxis
SUD: substance use disorder
YA: young adult

Edited by A Mavragani; submitted 22.11.23; this is a non–peer-reviewed article;accepted 22.02.24; published 26.03.24.

Please cite as:
Creasy SL, Sweet S, Myers JJ, Shumway M, Tolou-Shams M, McCaffrey N, Dauria EF
eHealth-Enhanced Peer Navigation for Substance Use Treatment and HIV Prevention Service Linkage for Young Adults Surveilled by the Criminal Legal System: Protocol for a Pilot Randomized Trial Study
JMIR Res Protoc 2024;13:e54815
URL: https://www.researchprotocols.org/2024/1/e54815
doi:10.2196/54815
PMID:38530335

Protocol

The Feasibility of Using the National PulsePoint Cardiopulmonary Resuscitation Responder Network to Facilitate Overdose Education and Naloxone Distribution: Protocol for a Randomized Controlled Trial

Jon Agley[1], MPH, PhD; Cris Henderson[1], MA, MPH; Dong-Chul Seo[2], PhD; Maria Parker[3], MPH, MS, PhD; Lilian Golzarri-Arroyo[4], MS; Stephanie Dickinson[4], MS; David Tidd[1], MS

[1]Prevention Insights, Department of Applied Health Science, School of Public Health Bloomington, Indiana University Bloomington, Bloomington, IN, United States

[2]Department of Applied Health Science, School of Public Health Bloomington, Indiana University Bloomington, Bloomington, IN, United States

[3]Department of Epidemiology and Biostatistics, School of Public Health Bloomington, Indiana University Bloomington, Bloomington, IN, United States

[4]Biostatistics Consulting Center, School of Public Health Bloomington, Indiana University Bloomington, Bloomington, IN, United States

Corresponding Author:
Jon Agley, MPH, PhD
Prevention Insights
Department of Applied Health Science, School of Public Health Bloomington
Indiana University Bloomington
809 E. 9th St.
Bloomington, IN, 47405
United States
Phone: 1 812 855 3123
Email: jagley@indiana.edu

Abstract

Background: The use of naloxone, an opioid antagonist, is a critical component of the US response to fatal opioid-involved overdoses. The importance and utility of naloxone in preventing fatal overdoses have been widely declaimed by medical associations and government officials and are supported by strong research evidence. Still, there are gaps in the current US national strategy because many opioid-involved overdose fatalities have no evidence of naloxone administration. Improving the likelihood that naloxone will be used to prevent fatal overdoses is predicated on facilitating an environment wherein naloxone is available near each overdose and can be accessed by someone who is willing and able to use it. How to accomplish this on a national scale has been unclear. However, there exists a national network of >1 million cardiopulmonary resuscitation (CPR) layperson responders and 4800 emergency responder agencies linked through a mobile phone app called *PulsePoint Respond*. *PulsePoint* responders certify that they are trained to administer CPR and are willing to respond to possible cardiac events in public. When such an event occurs near their mobile phone's location, they receive an alert to respond. These motivated citizens are ideally positioned to carry naloxone and reverse overdoses that occur in public.

Objective: This randomized controlled trial will examine the feasibility of recruiting first responder agencies and layperson CPR responders who already use *PulsePoint* to obtain overdose education and carry naloxone.

Methods: This will be a 3-arm parallel-group randomized controlled trial. We will randomly select 180 first responder agencies from the population of agencies contracting with the PulsePoint Foundation. The 3 study arms will include a standard recruitment arm, a misperception-correction recruitment arm, and a control arm (1:1:1 allocation, with random allocation stratified by zip code designation [rural or nonrural]). We will study agency recruitment and, among the agencies we successfully recruit, responder certification of receiving overdose and naloxone education, carrying naloxone, or both. Hypothesis 1 contrasts agency recruitment success between arms 1 and 2, and hypothesis 2 contrasts the ratios of layperson certification across all 3 arms. The primary analyses will be a logistic regression comparing the recruitment rates among the arms, adjusting for rural or nonrural zip code designation.

Results: This study was reviewed by the Indiana University Institutional Review Board (20218 and 20219). This project was funded beginning September 14, 2023, by the National Institute on Drug Abuse.

Conclusions: The hypotheses in this study will test whether a specific type of messaging is particularly effective in recruiting agencies and layperson responders. Although we hypothesize that arm 2 will outperform the other arms, our intention is to use the best-performing approach in the next phase of this study if any of our approaches demonstrates feasibility.

Trial Registration: OSF Registries osf.io/egn3z; https://osf.io/egn3z

International Registered Report Identifier (IRRID): PRR1-10.2196/57280

(JMIR Res Protoc 2024;13:e57280) doi:10.2196/57280

KEYWORDS

naloxone; PulsePoint; randomized controlled trial; RCT; first responder; overdose; community engagement; citizen mobilization; opioids; Narcan; mobile phone

Introduction

Background

In 2017, the US Acting Secretary of Health and Human Services formally declared that the opioid overdose crisis in the United States is a public health emergency [1]. Since that time, the prevalence of morbidity and mortality related to opioid overdoses has gotten substantively worse [2]. Beyond the prima facie impact of tens of thousands of overdose-involved deaths annually, the secondary impacts of the crisis strain the health care system across numerous axes; for example, even in 2013, when annual fatal prescription overdose incidence was "only" 16,235 persons, scientists at the Centers for Disease Control and Prevention found that these fatal cases accrued US $21.5 billion in costs [3]. The magnitude of the emergency is such that even in the midst of major global news on multiple fronts, news stories about fatal opioid overdoses are ubiquitous, often with calls from family members to build awareness and seek solutions [4]. Overdose and harm reduction strategies (including naloxone administration) have also received direct attention from the federal government, including as part of the 2023 State of the Union address [5].

Naloxone Is a Critical Part of the US Overdose Emergency Response

Naloxone (including Narcan, Kloxxado, Evzio, Zimhi, and other formulations) is an opioid antagonist that can be used to reverse an opioid overdose and restore breathing, converting a potentially fatal overdose into a nonfatal overdose [6,7]. Even before the formal declaration of a public health emergency around opioids, the Department of Health and Human Services included expanded use and distribution of naloxone in its 3 priority areas to address the overdose epidemic [8]. The importance and utility of naloxone have been widely declaimed, including by the American Medical Association ("should be available almost everywhere") [9], the American Society of Addiction Medicine ("remarkably effective, inexpensive and safe") [10], and the US Surgeon General ("Be Prepared. Get Naloxone. Save a Life.") [11]. Such statements are predicated on strong evidence of, and arguments for, naloxone's effectiveness and utility in reducing fatal opioid-involved overdoses [12-16].

Barriers Exist That Inhibit Proliferation of Expedient and Effective Overdose Responses

Data from 2019 indicate that in the majority of fatal opioid-involved overdoses, there is no evidence of naloxone administration [17]. Given the current evidence for the effectiveness of overdose education and naloxone distribution (OEND) programs [12-16], the national expansion of such programs [18,19], and simultaneous high rates of fatal opioid-involved overdoses without naloxone administration [17], we might reasonably conclude that there are one or more gaps in the current US national approach to opioid-involved overdose reversal.

For many years, the lack of availability of naloxone has been seen as a primary barrier. Most states have passed legislation intended to increase layperson access to naloxone and provide limited legal immunity to those who administer naloxone to persons experiencing an opioid-related overdose [10]. By 2021, a total of 47 states and Washington, District of Columbia, had enacted both Good Samaritan and naloxone access laws [20], and programs to facilitate distribution of naloxone to laypersons have steadily become more common [18], especially since 2010 [19]. Unfortunately, a 2018 study in Indiana and Arizona found that such policies did not always sufficiently facilitate layperson access [21]. The availability of naloxone *at cost* will likely increase in the United States in the next several years given a recent 19-0 US Food and Drug Administration advisory committee vote in favor of granting some naloxone products over-the-counter (OTC) status [22]. However, national data from a similar OTC change in Australia suggest that people may not automatically begin purchasing naloxone in response [23] (eg, other factors such as willingness may be salient).

More ubiquity in carrying and being willing to use naloxone is critical because, as described by Kim et al [24], the efficacy of naloxone is fundamentally time dependent. Brain injury from hypoxia is more likely the longer oxygen deprivation occurs [25]. In some cases, overdose death from heroin can be extremely rapid [26], and death typically occurs within 1 to 3 hours [27]. Overdoses from fentanyl and fentanyl analogs often present differently than other opioid overdoses and may be even more likely to rapidly result in fatality [28]. Thus, it is important that naloxone is *present at or near the scene* and *used as quickly as possible.* Unfortunately, despite a surge in OEND programs in the United States, relatively few people carry and are willing to use naloxone [29].

Misperceptions About Naloxone and Overdose May Inhibit OEND Programs

Evidence suggests that misperceptions about overdose and naloxone, as well as stigmatizing beliefs about people who use drugs, may affect both layperson and first responder willingness and interest in carrying and using naloxone [29-33]; for example, first responders may be ambivalent about "providing naloxone to those they deem undeserving" [34], and a review found that stigmatizing attitudes among first responders may reduce the likelihood of bystander response [35]. Some first responders have noted that laypersons in their communities may fear "real and perceived cultural opposition" to harm reduction strategies [36]. Such reticence and stigma may even persist after OEND training [29,37] and have been described as fundamentally hindering the US response to the opioid overdose crisis [38].

To the best of our knowledge, the prevalence of specific belief statements about naloxone and overdose that do not align with current scientific evidence had not been explored in depth until 2022 [39]. We conducted a study (using the Prolific platform) consisting of 702 respondents who were representative of the US adult population across race, ethnicity, gender, and age. Several misperceptions around naloxone and overdose were fairly common in our sample, and there was a surprisingly large minority of participants (approximately one-seventh of the sample) who believed that users could "get high on naloxone" [39]. We also observed potential evidence of cognitive dissonance about OEND; specifically, large latent profiles simultaneously believed, in the framed context of naloxone reversing an opioid overdose, that "if trained and provided with naloxone, bystanders can effectively prevent overdoses in the community" and "opioid users will use more opioids if they know they have access to naloxone" [39].

Our Proposed Study to Mitigate Barriers to Effective Overdose Response

Improving the likelihood that naloxone will be used to prevent fatal overdose is logically predicated on facilitating an environment wherein naloxone is available near each overdose and can be accessed by someone who is willing and able to use it. Conceptually, in a given community, the likelihood of an opioid overdose in the given community being reversed with naloxone is proportional to the likelihood that a trained person with access to naloxone is nearby, willing to administer it, and aware of the need. As noted, current approaches to OEND have not succeeded in reaching the threshold of sufficient coverage. With too few trained persons and sparse coverage, overdose survivability can be subject to the whims of chance, something implicitly recognized even in how lay news sometimes covers overdose reversals ("finds herself in the right place at the right time" [40]).

Recent, innovative pilot work demonstrated that a smartphone app (*UnityPhilly*) could support overdose reversal in a small group of volunteers [41]. Other innovative projects include multifaceted technology-based efforts by Brave Technology Co-Op [42]. In these cases, building to scale will take substantial time and investment. However, it may also be possible to integrate OEND within widespread but existing systems that perform other but similar services. Our particular interest is in a large, highly engaged system for cardiopulmonary resuscitation (CPR) that already exists nationally (*PulsePoint*), with >1,085,000 active monthly layperson users across approximately 4800 communities overseen by >755 agencies [43]. These individuals respond to unconscious and unresponsive persons within a prespecified radius of their smartphone based on alerts generated by local first responder agencies. While *PulsePoint* does not specifically generate alerts for an opioid overdose, the designation *unconscious and unresponsive* can refer to individuals possibly in need of CPR or those who may need overdose reversal; therefore, these laypersons are likely already responding to possible overdoses. However, they are neither systematically being encouraged to receive training around overdose and naloxone nor being reminded to carry naloxone.

We believe that the *PulsePoint* network may be an effective means of achieving widespread OEND coverage in the United States. With this preliminary study, our goal is to better understand whether and how it is feasible to recruit first responder organizations and *PulsePoint*-connected laypersons to broaden the scope of their voluntary service to include opioid overdose reversal.

Objectives

Overview

We will conduct a feasibility trial to assess whether, in a random sample of 180 agencies where *PulsePoint* is already active, revised procedures (hereinafter *PulsePoint-OD*) to facilitate OEND can successfully recruit first responder agencies and layperson responders. For this study, *agency* refers to a single implementation site where *PulsePoint* is active and that is bound by the service area or jurisdiction of the first responder agency collaborating with *PulsePoint* (we provide more detailed information about agencies in the *Methods* section).

Using a parallel-group randomized controlled trial design, we will randomize 180 agencies using a 1:1:1 allocation ratio within strata to 1 of 3 arms: arm 1 (*PulsePoint-OD*, which will include the recruitment of coordinating community first responder agencies; targeted recruitment, eg, push messages, aimed toward 100% of the active *PulsePoint* users in these communities; ongoing solicitation for training of these users; and naloxone facilitation), arm 2 (same as arm 1 but with stigma-focused misinformation-debunking messages embedded), or arm 3 (a control condition).

Hypotheses

We will test the following hypotheses:

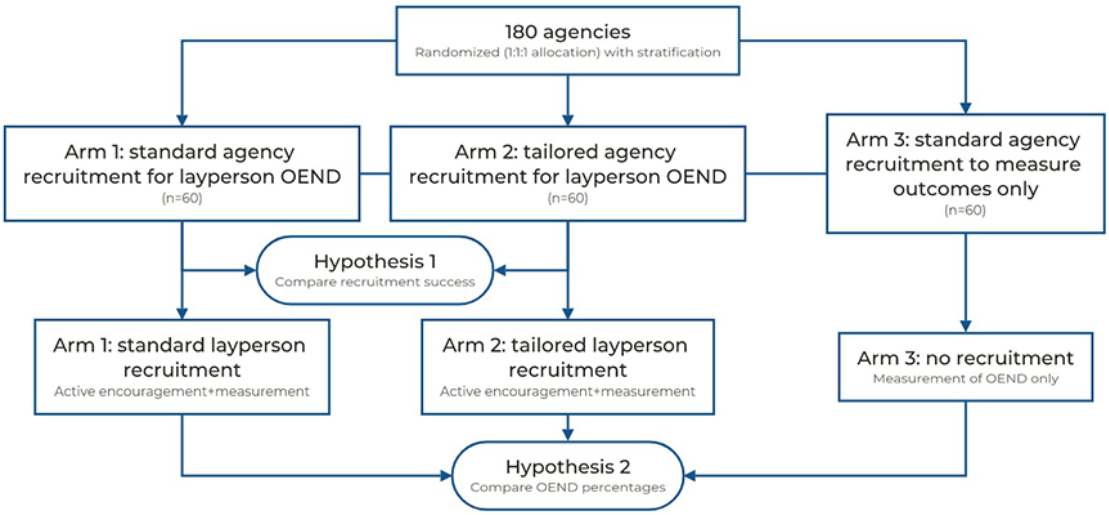
- H1: more first responder agencies will be successfully recruited by arm 2 than by arm 1.
- H2: more layperson responders will report engaging with OEND programming in arm 2 than in arms 1 or 3 and in arm 1 than in arm 3.

As an exploratory follow-up, we will conduct incentivized qualitative follow-up interviews with agencies to better understand barriers to participation and how to improve uptake feasibility.

Methods

As the participant types for H1 and H2 are different, we provide separate methodologies for each hypothesis. A conceptual diagram of the study and hypotheses is provided in Figure 1.

Figure 1. Conceptual diagram of the study and hypotheses. OEND: overdose education and naloxone distribution.



H1: First Responder Agencies

Parameters

The following parameters describe the interrelationships between communities and agencies for this study:

- The PulsePoint Foundation reports that approximately 4800 communities currently use the *PulsePoint* app.
- Community participation and the use of the *PulsePoint* app are supported by agency contract holders; there are >755 such contracts in place.
- A contract-holding agency can serve multiple communities (eg, a county 911 office can offer *PulsePoint* to 9 different communities in the county, such as townships). An agency can also serve a single community (eg, a city fire department can offer *PulsePoint* to that city only).
- Any number of *additional* first responder agencies (eg, fire or police departments, emergency medical services, 911 call centers, or related entities) can contribute to a community or cluster of communities covered by a single *PulsePoint* contract, but these agencies are not contract holders.

When *PulsePoint* is introduced to a community for layperson use, the PulsePoint Foundation neither directly recruits nor interfaces with individual lay responders. Instead, the contracted first responder agencies conduct local recruitment and have the ability to send *push messages* (app-driven notices and messages) to users. Therefore, to integrate OEND into the *PulsePoint* network (eg, *PulsePoint-OD*) and for our study team to directly contact the subset of active users within each study community, it is necessary that the contract-holding first responder agencies in each community agree to participate. This first phase of the overall study (and the first hypothesis) pertains to agency-level recruitment.

Participants, Eligibility, and Assignment

We will use the complete list of *PulsePoint* contracting agencies as constituted approximately 3 months before the study start date (to ensure sufficient experience with the *PulsePoint* program) as the population from which to draw a random sample. At present, this list includes >755 agencies, but the actual number will vary depending on the final start date and changes in *PulsePoint* membership.

All active agencies on the final list will be eligible for sampling and randomization, with 2 exceptions. First, an agency will be excluded (and a replacement resampled and assigned to the same study arm) if further communication identifies that it is not actually a *PulsePoint* subscriber. Second, we will exclude agencies a priori or a posteriori if we learn of a similar project being conducted, or having been conducted, with *PulsePoint* with the agency. Random sampling of communities will be accomplished by having a study statistician generate a random sequence of numbers, including all values between *1* and *X*, where *X* is the total number of eligible agencies. These numbers will be directly overlaid on the list of agencies, and agencies with the lowest 180 numbers will be selected. These numbers will also be carried forward to indicate the random arm assignment.

Agencies will be randomly assigned to a study arm using stratified allocation, with a 1:1:1 allocation ratio. Specifically, one-third of the rural agencies will be randomly assigned to each study arm, and separately, one-third of the nonrural agencies will be randomly assigned to each study arm. We will determine rural status using the definition from the US Office of Management and Budget (zip codes within metropolitan areas with an urban core of ≥50,000 people are not rural, and all other areas are rural [44]). In cases where agencies hold *PulsePoint* contracts that cover both rural and nonrural areas, we will assign a status based on the location of the numeric

majority of the population in the area. Arm assignment will be according to sequential numbers (from the simple random sample; therefore, this allocation approach is also by definition random) within each stratum (eg, if there are 60 rural agencies, the 20 rural agencies with the lowest random numbers will be assigned to arm 1). This procedure will ensure allocation concealment from the rest of the investigative team until the moment of assignment. Agencies will not be informed that they have been assigned to a specific trial arm; they will simply be contacted using the procedures developed for that arm. Thus, this can be considered a blinded trial.

Establishing Correspondence With Local PulsePoint Decision Makers

Although the PulsePoint Foundation will provide us with a list of participating agencies, its database does not include raw contact details (eg, telephone number and email address), and even these details may not link our study team with the people within the agency who manage the *PulsePoint* system. On the basis of discussions with the PulsePoint Foundation, the following examples describe cases that have occurred in the past:

- The point of contact on the agency list may be the accounting or billing representative for the agency, not the person who manages the program, especially among long-term subscribers.
- The decision makers for the agency may be different now than when the subscription to *PulsePoint* was purchased.

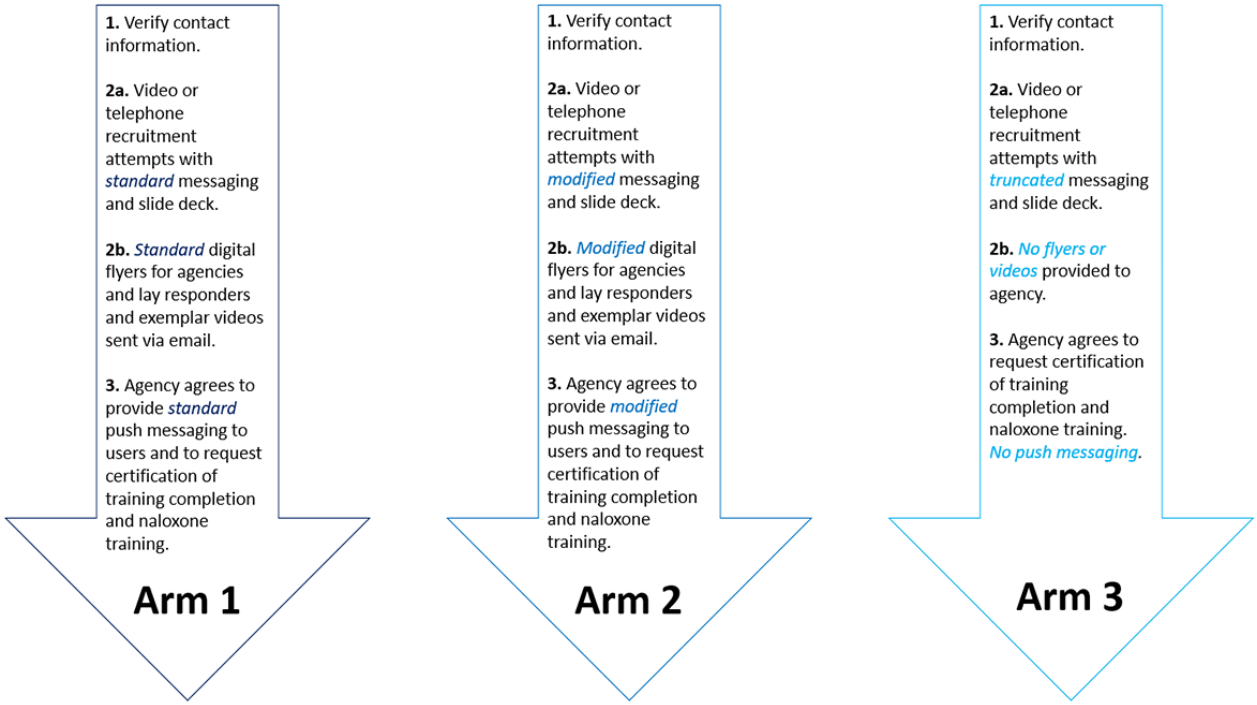
We will need to locate contact information for agencies and verify that the contact details link us with the person who manages the *PulsePoint* subscription, and if not, identify who in the agency does so and how to contact them. In other words, while our trial is intended to study recruitment strategies, we must first ensure that we can access the appropriate individuals at an agency. Once we have identified these points of contact, we can begin recruitment at the agency.

Intervention (Recruitment) Arm 1

Overview

The minimum goal of agency recruitment is to reach a memorandum of understanding (MOU) with agencies in which they agree to encourage their layperson *PulsePoint* responders to attend OEND programming and to carry naloxone (arms 1 and 2) and to indicate whether they have done so (arms 1, 2, and 3; Figure 2). The agencies will be asked to accomplish this using push messages prepared by our team and sent out by the agencies; the specific nature of these agency activities is outlined in the *H2: Layperson Responders* section.

Figure 2. Differing agency recruitment procedures for the PulsePoint-OD study by study arm.



Development

Our agency recruitment materials will be developed during the first phase of the study and provided in full when the study results are published. Oversight and review of marketing development will be provided by members of the study team and marketing consultants external to the study team. Review of all marketing materials will be granted to the PulsePoint Foundation (a not-for-profit 501[c][3] organization) to ensure consistency with the organization's branding. As a result of the development timeline, the exact phrases and examples used to illustrate components of the recruitment processes may change between the submission of this paper and the launch of the study.

Approaches

To be replicable at scale, recruitment will be conducted using a combination of video or telephone correspondence (preferably Zoom [Zoom Video Communications, Inc], but telephone where necessary), web links, and emails containing tangible materials. A full recruitment attempt with fidelity to our model will consist

of providing emailed materials and web links and attempting between 6 and 10 telephone contacts over approximately 6 months, based on best practice telephone recommendations from the American Association for Public Opinion Research [45]. Recruitment efforts will stop in the event that (1) an agency agrees to participate in the project, (2) an agency asks not to be contacted about the project again, (3) the aforementioned recruitment approaches clearly seem unlikely to yield a change in disposition, or (4) the recruitment timeline ends without the agency making a decision.

Materials

Members of our project staff will develop a short visual presentation to be used as a guideline for videoconference recruitment, along with a parallel set of core written or verbal statements reflecting the content of the presentation in cases where only telephone calls are possible. Drawing lessons from our previous successful agency and organization recruitment experiences [46-49], both the presentation and written statements will cover a limited list of important concepts that need to be imparted (eg, "Participating in this project will require very little time from your agency – we are only asking you to send out one push message each month."). While moving through these concepts, we will allow conversation to flow freely (eg, semistructured messaging) and also use live documentation of key concepts to ensure message fidelity.

The tangible documentation will consist of digital flyers based on the open-source marketing tools developed by the PulsePoint Foundation for general community agency recruitment, including the use of similar graphical assets and fonts. However, flyers will be differentiated sufficiently from the default *PulsePoint* flyers to make it clear that the organization itself is not conducting this project (eg, we will not use the *PulsePoint* logo). For reference, *PulsePoint*-branded recruitment flyers can be viewed by clicking on the hyperlink provided in the associated reference [50]. As community agencies have already committed to offering standard *PulsePoint* services, we expect that distributing these modified documents to agencies will be a high-leverage recruitment approach. Key messaging will be drawn from local demonstration projects by the study team (eg, "Be a Lifesaver" and "Citizen Opioid Responders") [51] as well as general marketing and recruitment principles.

As supplemental recruitment content, exemplar videos will be drawn from work produced by the Dearborn County Health Department in Lawrenceburg, Indiana, in collaboration with the study authors to create awareness of this type of initiative and will be included as web links to YouTube versions of the videos [51].

After Recruitment

When communities agree to participate, they will be asked to sign an MOU regarding their participation and to respond to a small set of readiness and implementation items, such as whether the organization is already involved in naloxone distribution and whether there are local laws pertaining to opioid overdose reversal. This information will be used to locally tailor piped text into messages used for H2 (layperson recruitment).

Intervention (Recruitment) Arm 2

The recruitment procedures for arm 2 will be similar to those outlined for arm 1. The primary difference will be that the messaging in arm 2 will proactively address several misperceptions or stigmatizing ideas about overdose and naloxone that our recent research has suggested may be prevalent [39]. In particular, content in the fact sheets and scripts for recruitment used in arm 2 will address and preempt the following scientifically unsupported ideas (potentially among others):

- "Naloxone causes risk compensation or presents a moral hazard": it is fairly well established that OEND is not associated with increased opioid use [52-55], nor is it associated with reduced risk perceptions for heroin use [56].
- "Repeated overdoses are inevitable and people who experience nonfatal overdoses will die of an overdose in the near future": while individuals who nonfatally overdose are at meaningfully increased risk, especially if they do not matriculate into a cascade of care, the substantive majority will not overdose again in the near future, and even fewer will die of a fatal overdose in the near future [57-60].
- "Individuals can get high from naloxone": while this is not possible [6], our study found that 14.2% of our nationally-representative sample still believed this claim [39] to some extent.

Though brief, our debunking content will follow specific procedures that recent research (particularly around COVID-19 misinformation and vaccine hesitancy) has found to improve the efficacy of debunking messaging. These include ensuring the credibility of the source of the factual correction [61] and including a sufficient level of detail and explanation for *why* the facts are correct and the misperceptions are not [62]. This level of detail will vary in extensiveness depending on the format of a given piece of communication. The use of such short-format corrections does not seem to result in a backfire effect [63]; for example, a statement made in the arm 1 recruitment flyer (standard) might be, "Overdoses involving opioids are a public health emergency in the United States (US). The US Surgeon General recommends: 'Be Prepared. Get Naloxone. Save a Life.'" The permutation for the arm 2 recruitment fact sheet (modified), in parallel, would be, "Rapid use of naloxone (Narcan) nasal spray is often an overdose victim's best chance for survival. Studies show that opioid use in a community does not increase when naloxone is widely available."

Inert Arm for H1 (Arm 3)

Arm 3 recruitment will mirror recruitment for arm 1, except that the stated goal for the agencies will be only to ask layperson respondents to indicate at 3 different time points whether they have attended OEND programming or carry naloxone (eg, no encouragement or messaging campaign will occur in this arm). This arm will not be actively analyzed when we test H1.

Outcome Variables and Measurement

In H1, we hypothesize that more community first responder agencies will agree to participate in the *PulsePoint-OD* program when contacted using procedures in arm 2 (tailored messaging)

compared to procedures in arm 1 (standard messaging) within 6 and 12 months of initial contact. Our primary outcome to test this hypothesis will be the number of agencies that agree to participate in the project as a percentage of the number of agencies with which we have been able to identify appropriate points of contact for recruitment. This metric *M* will be computed as follows:

- Each agency from the initial PulsePoint Foundation list that is randomized to participate in the study will be given a value *A* that is set at *0*, which indicates that we have not yet identified the appropriate point of contact at the agency.
- When we have identified a point of contact who can discuss *PulsePoint*, we will set the value for *A* at *1*.
- To define when a community first responder agency has agreed to participate, each agency will be assigned an ordinal value *R* ranging from *0* to *2*, where *0* will indicate nonparticipation or refusal, *1* will indicate that there is an agreement in principle to participate but that no formal MOU has been established, and *2* will indicate that a formal MOU has been put into place between the agency and the study team. For the purposes of hypothesis testing, we will aggregate values of *1* and *2*, but the data will be documented in ordinal form so that we can identify whether there is a concern with agencies failing to enter the MOU stage after agreeing in principle to participate.
- Next, the agency recruitment metric *M* for each arm will be the ratio of recruited agencies to total agencies with which active communication has been established: $M=(R_{R>0}/A_{A>0})$.

In addition to computation of the primary outcome metric, recruitment activities will be documented in a shared internal database, which will track, at a minimum, the nature, date, and outcome of each instance of correspondence with each community to inform our understanding of the uptake of *PulsePoint-OD* among *PulsePoint* communities and support ongoing mitigation of any issues with recruitment. Using this documentation, we will be able to estimate several secondary descriptive outcomes:

- An estimate of the dose-response uptake of the intervention (eg, mean number and types of correspondence associated with agreement to participate and completion of an MOU)
- An estimate of the average length of time between initial contact and agreement to participate

H1: Sample Size, Power, and Analysis

Although we plan for 180 agencies to compose the total sample size, only 120 (66.7%) will be allocated to arms 1 (n=60) and 2 (n=60), meaning that the sample size for this hypothesis is 120. With 60 agencies in each arm, we will have 80% power to detect significant differences (2-tailed α=.05) between arms 1 and 2 in the proportions of agencies that are successfully recruited if the difference in proportions is at least 0.25 (eg, 18/60, 30% recruited in arm 1 vs 33/60, 55% recruited in arm 2). The primary analysis will be conducted using logistic regression, comparing the recruitment rate between the arms. We will report exact P values and commit to a cautious interpretation of the findings, avoiding overreliance on P values as the single arbiter of meaning [64]. We do not expect any missing data in the outcome variable because the nature of its computation is such that missing data mean that either *A=0* or *R=0* and are therefore built into outcome variable *M*.

The primary study outcome (*M*) will be tested separately for the periods 6 and 12 months after initial recruitment correspondence. Analysis covariates are planned to include, but may not be limited to, community rurality and the community's percentage vote share for the Republican candidate in the 2020 presidential election (available for 2523 US counties and separable by zip code [65]), given that political orientation was 1 of 2 strongly predictive variables in our regression model examining misperceptions of OEND [39].

H2: Layperson Responders

Overview

Layperson responders who are part of the *PulsePoint* system register with a local first responder agency using their smartphone. Most layperson responders (eg, those who are not also off-duty first responders themselves) are only alerted to incidents in public spaces. No identifying information is collected from these users except the unique ID of the device.

The first responder agency in each community that manages the *PulsePoint* subscription can only determine the number of active users and, broadly, the type of smartphone being used (eg, Android smartphone or iPhone). Each time a first responder agency sends out a push notification, it is provided with an exact count of the number of unique devices, separated by type, that were active in the system and reached by the message.

It is important to note that we will have a count of unique active devices but not necessarily a count of unique active users (eg, it is unlikely but possible that someone will install the app on 2 different mobile phones at the same time). In correspondence with the PulsePoint Foundation, it is likely that the count of unique active devices serves as a very close approximation of unique active users. Furthermore, by virtue of randomization, the distribution of any unmeasured anomalies related to user-device mismatches should be evenly distributed across the arms.

Conceptualizing Recruitment for Layperson Responders

Currently, for a *PulsePoint* user to be officially recruited as a CPR responder and to be sent notifications regarding unconscious and unresponsive persons in public places, they need to affirmatively indicate that they are trained in CPR *and* are "willing to assist in case of an emergency." Individuals who so verify are sent push alerts and auditory alert tones, regardless of whether the app is open, whenever there is an unresponsive and unconscious person within a specific radius of their mobile phone (the radius is specified by the first responder agency for that community) [66].

For the purposes of this study, a layperson responder will be considered to have been recruited for *PulsePoint-OD* if they certify that they have received training on overdose and naloxone and that they currently carry naloxone on their person (both outcomes are of interest, which we describe later in the *Outcome Variables and Measurement* section). Once an MOU is in place with a first responder agency, it will send out a

customized baseline push message to all active users containing a link to a landing page. This page will contain brief introductory text explaining the importance of recognizing an overdose when responding to unconscious persons and the efficacy of naloxone, as well as 2 questions asking them to indicate, by pressing radio buttons, whether they have received training on recognizing an overdose and administering naloxone and whether they currently carry naloxone on their person. Additional push messages encouraging users to respond to the certification questions will be sent twice within the month to maximize the number of participants providing baseline data. A user's responses to these questions will not change their status within the app or the behavior of the app because all users are already alerted to unresponsive or unconscious persons who may have experienced an overdose. This certification procedure will be repeated twice (6 months and 12 months after the baseline certification requests are sent). These messages will emphasize that even users who have previously provided such information should do so again.

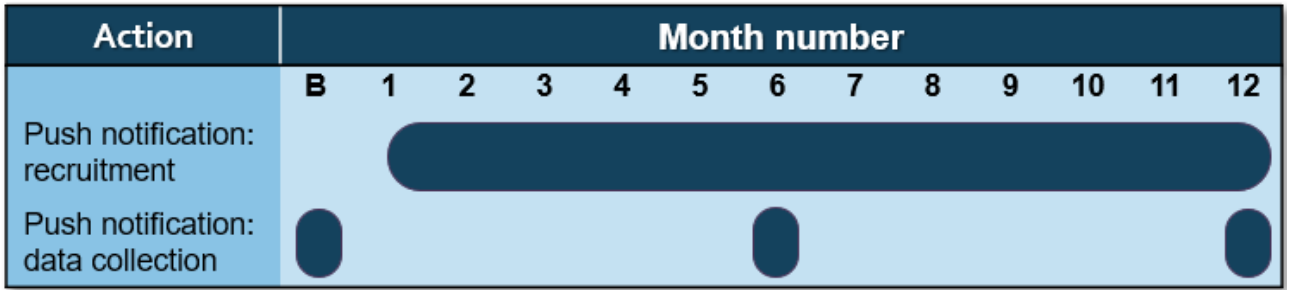
The *PulsePoint* app is structured in such a way that push notification hyperlinks can open an external web page in a web browser window inside the app. Using the style guides and templates from the PulsePoint Foundation, the certification web pages will be designed to be similar to the appearance of the app to avoid disrupting the user experience while avoiding cross-contamination of messaging between the study arms. Each web page will be accessible only via the hyperlink in its associated push notification, and users will not be able to navigate among web pages or access the web pages for other study arms.

As multiple data collection reminders will be sent each time (baseline, 6 months, and 12 months), we want to minimize the likelihood of an individual repeatedly certifying their involvement. This risk exists because of the completely anonymous way that individual *PulsePoint* users are managed by the system. Thus, the landing page will be configured to store a cookie [67] on the mobile device. Although cookies are typically perceived as tracking devices, this cookie will not *record anything except whether the user has previously responded to either question on the landing page* during the data collection cycle, and it will be programmed to delete itself after each data collection period (eg, 3 weeks). When users who have already completed the questions return to the landing page, the cookie will prevent the questions from being displayed, although we anticipate that some of the users may clear their smartphone browser cache or actively prevent the use of cookies.

Layperson Intervention (Recruitment) Arm 1

Users randomized to arm 1 will receive standard monthly recruitment push messages. These push messages will differ from the certification messages because they will contain language intended to foster engagement with OEND services (eg, to get trained and carry naloxone) alongside the link to a landing page (eg, "Are you trained to recognize an overdose? Be a community hero! Click here for more information!"). The messages will be developed based on best practice recruitment principles in cooperation with an external marketing team and then reviewed and finalized by the study team. Messages will be different each month. The monthly time frame was selected based on our need to balance contact with responders and research or expert opinions on push messaging saturation. In a hypothesis-driven objective measure study, increased push messaging frequency was associated with additional app uninstalls *and* lower push message opening rates [68]. This information is generally consistent with the much larger volume of layperson marketing gray literature on push notification optimization (eg, *how-to* blogs [69]). Figure 3 displays the planned timing of the recruitment and data collection messages.

Figure 3. Push notification types and timing relative to agency recruitment. B: baseline.



The landing page for recruitment will be updated to include a link to the Community Overdose Responder naloxone training [70], which has been designed specifically for laypersons and integrates elements of OEND programming and *PulsePoint*. Where provided by community first responder agencies, we will also include a list of ways to obtain free or reduced-cost naloxone locally as well as information about upcoming local OEND events. Separately, we note that accessing at-cost naloxone (ie, not free or subsidized) will be relatively easy, in principle, given its transition to OTC status [22].

Layperson Intervention (Recruitment) Arm 2

As in the case of the differentiation between agency recruitment in arm 1 and arm 2, the recruitment of layperson responders for arm 2 will follow the same procedures that are described for arm 1 but will use separate messaging. Specifically, the push messages and landing page will contain additional, brief messages that specifically provide factual information that counteracts misperceptions about overdose and naloxone [39]; for example, whereas an example message for arm 1 might be "Are you trained to recognize an overdose? Be a community hero! Click here for more information!" the permutation for arm 2 might be "Are you trained to recognize an overdose? Studies show that most people revived with naloxone will not overdose again within the next year! Click here for more information!"

Layperson Intervention (Control) Arm 3

Arm 3 functions as the control arm and will not receive any monthly recruitment messaging or encouragement, but laypersons will still be asked, using push notifications, to provide information at baseline and 6 and 12 months later to document whether they have been trained to recognize an overdose and administer naloxone and whether they currently carry naloxone on their person (eg, "Please let us know whether you have ever been trained to recognize an overdose or if you carry naloxone by clicking here."). The landing page will likewise contain the questions with radio button responses but will not link to training opportunities or contain additional information.

Outcome Variables and Measurement

In H2, we hypothesize that more layperson responders will indicate that they have received OEND programming and carry naloxone on their person within 6 and 12 months of initial contact using procedures in arm 2 (tailored messaging) compared to procedures in arm 1 (standard messaging) and using procedures in either arms 1 or 2 versus arm 3 (control). We will use several different data points to assess our hypothesis.

All push notifications sent out by first responder agencies already return information through the *PulsePoint* app indicating the total number of active devices, by type, that were messaged. As we explained previously, this is a strong proxy measure for the total number of active users messaged because most people use a single smartphone.

For purposes of computation, this total number of recipients of any push notification will be designated as *T*. Next, the total number of individuals who click on the pushed link will be represented by *O*, which will be a number between *0* and *T*. Importantly, the link will also be coded using HTML and CSS so that it sends additional data when clicked, indicating the originating community (cluster identity) and the data collection point (*D*, a value ranging from *0*, which is the initial push message cluster, to *2*, which is the final data collection message set at 12 months after baseline). Subsequently, the number of instances of an individual (ie, unique device) indicating that they have been trained on recognizing an overdose and administering naloxone (represented by *N*, a binary value of *0* or *1*) and whether they currently carry naloxone (represented by *C*, also a binary value of *0* or *1*) will be captured from the landing page itself.

This information will allow us to determine the following, separately by community:

- At baseline, we will calculate the ratio of persons certifying that they are trained (numeric count of *N*) compared to the total number of push message recipients (*T*), the ratio of persons certifying that they carry naloxone (numeric count of *C*) compared to the total number of push message recipients (*T*), and the ratio of individuals who clicked on the link (*O*) compared to the total number of push message recipients (*T*).
- Separately at 6- and 12-month follow-ups, the numbers of certifications of training and carrying naloxone (*N* and *C*, respectively) that were submitted compared to the numbers of push recipients (*T*) in each period (tracked by *D*) and the ratio of individuals who clicked on the link (*O*) each month compared to the number of total push message recipients (*T*).
- Our outcome variables are ratios: $X = (N / T)$ for each value of *D* (0, 1, or 2) and $Y = (C / T)$ for each value of *D*. The ratio $Z = (O / T)$ is a covariate representing engagement with push messages at each value of *D*.

Sample Size, Power, and Analysis

Our power analysis for H2 depends on the number of communities that agree to participate during the agency recruitment conducted as part of testing H1. To compare the average proportions of users who certify that they have received overdose education and personally carry naloxone, we sought 80% power to detect significant differences (2-tailed α=.05) among the 3 arms across 3 time points. Assuming a correlation of 0.5 in responses over time, we expect that we will be able to detect a medium effect size ranging from f=0.21 (if 50, 83% of the 60 communities participate in each arm on average) to f=0.34 (if 20, 33% of the 60 communities participate in each arm on average).

Our primary analyses will be metrics *X* and *Y* (as described previously), which will be analyzed separately. The primary analyses will be conducted using generalized linear mixed models, adjusting the *df* for the number of agencies. As with H1, we will report exact P values and commit to a cautious interpretation of the findings, avoiding overreliance on P values as the single arbiter of meaning [64]. In addition, as in the case of H1, we do not expect any missing data in the outcome variable because the nature of its computation is such that missing data mean that either *N=0* or *C=0* and are therefore built into outcome variables *X* and *Y*. Study covariates will include but may not be limited to variable *Z* to control for the conversion of push messages to clicks.

Exploratory Agency Follow-Up

We will conduct a set of intensive follow-up agency interviews with community first responder organizations with whom we have established active communication. We will prioritize qualitative recruitment of organizations and agencies that did not agree to be recruited after establishing correspondence because the elicitation of barriers to participation in the *PulsePoint-OD* program may be most informative when carried out with those who did not participate. This procedure will be similar in principle to, but more extensive than, our brief study of clinical providers who dropped out from a continuing medical education program [71]. However, we will not exclude participating agencies from the qualitative component of the project; instead, we will continue data collection until we have reached a point of theoretical inductive saturation, when new conversations and data no longer seem to add to our understanding of the topic [72]. Interviews will be guided by a semistructured interview guide to be developed during the agency recruitment process and will be coded using the general inductive approach to qualitative analysis [73], which does not make a priori assumptions about the data and allows themes to emerge organically based on repeated readings of the data.

Ethical Considerations

Ethics approval for the proposed work was determined to fall into 2 separate categories. Agency-level recruitment and interaction were determined not to constitute human participant research (Indiana University Institutional Review Board: 20218). The collection of information from layperson responders was approved under an expedited procedure (Indiana University Institutional Review Board: 20219). Data from layperson responders will be anonymous (no identifiers will be collected). Participation in the intensive follow-up agency interviews will be incentivized with an honorarium (US $500) to the organization to encourage participation.

Results

At the time of protocol submission, we had not engaged in any data collection or participant recruitment. This research was funded beginning September 14, 2023, by the National Institute on Drug Abuse of the National Institutes of Health (R34DA058162).

Discussion

Summary

The primary goal of this study is to understand the feasibility of recruiting current *PulsePoint* communities and layperson responders to complete overdose and naloxone training and to carry naloxone. Our hypotheses are intended to determine whether a specific type of correspondence targeting anticipated misunderstandings around opioid overdose and naloxone performs better when recruiting agencies and laypersons than standard messaging and whether active recruitment of laypersons using either message type performs better than the control.

At the same time, a separate consideration—regardless of the results of null hypothesis significance testing—is an overall sense of recruitment feasibility (eg, data on agency and responder uptake). Successful completion of this study is anticipated to improve the level of naloxone coverage in the United States, which remains insufficient [29]. We are also interested in examining elements that did and did not work and how we would ideally structure a similar recruitment process for a larger, outcomes-focused study (eg, comparing fatal overdose ratios in communities). Our exploratory discussions with agencies will be important to facilitate a better understanding of the mechanisms through which the proposed recruitment procedures did (or did not) work as intended.

Where possible, we have tried to control for anticipated limitations at the stage of study design. Owing to the nature of this real-world study, we still anticipate some limitations in the interpretation of the results. In particular, the degree to which agencies will agree to participate in arm 3 is uncertain because participation does not directly benefit those communities (unlike arms 1 and 2). This would not affect H1 (which only includes arms 1 and 2) but might affect the statistical power of H2. We expect that additional limitations may be uncovered in the process of conducting the study, and we plan to transparently note, and where possible mitigate, all such limitations, providing a comprehensive description of this information in subsequent documentation of the study.

Conclusions

If we successfully recruit agencies and laypersons and thereby facilitate training around overdose and naloxone and increase the numbers of layperson responders carrying naloxone, the next step will be to conduct a larger study examining opioid-involved overdose reversals using these procedures. This is predicated on current evidence for OEND, which allows us to hypothesize that our successful mobilization of layperson responders might reduce the prevalence of opioid-involved overdose [12-16], a theory that we will then prospectively test.

Acknowledgments

The authors would like to thank the PulsePoint Foundation for their encouragement of this project, with particular appreciation due to Kraig Erickson, vice president of community engagement.

Portions of this paper, including some verbatim text, will be presented as a 5-minute “lightning talk” and abstract at the 2024 American Academy of Health Behavior conference in Savannah, Georgia.

The research reported in this publication was supported by the National Institute on Drug Abuse of the National Institutes of Health (R34DA058162; JA). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or of the PulsePoint Foundation. Portions of this paper, including some verbatim text, were drawn from the grant narrative prepared and submitted to the National Institute on Drug Abuse.

Data Availability

Data sharing is not applicable to this paper because no data have been obtained or analyzed at this stage of the study.

Authors' Contributions

JA, CH, and DCS contributed to conceptualization. DT contributed to software development. JA contributed to visualization, supervision, and project administration. All authors contributed to methodology, resources, funding acquisition, and writing the original draft as well as reviewing and editing it.

Conflicts of Interest

JA, CH, MP, and DCS have received funding through their employer (Indiana University) to conduct various research projects pertaining to opioids, harm reduction, and naloxone from federal, state, and local government entities and nonprofit foundations. CH was co–principal investigator of a National Institute on Drug Abuse Small Business Innovation Research grant that facilitated the development of a web-based naloxone training (Community Overdose Responders) being provided as an option for layperson responders in this study, but their participation was as an Indiana University employee; therefore, they do not have any mechanisms in place (eg, trademarks, patents, and access agreements) that would result in any personal profit or financial benefits accruing from the use of the training. All other authors declare no other conflicts of interest.

Multimedia Appendix 1
Peer-review report by the National Institute on Drug Abuse of the National Institutes of Health.
[PDF File (Adobe PDF File), 81 KB - resprot_v13i1e57280_app1.pdf]

References

1. HHS acting secretary declares public health emergency to address national opioid crisis. U.S. Department of Health & Human Services. 2017 Oct 26. URL: https://public3.pagefreezer.com/browse/HHS.gov/31-12-2020T08:51/https://www.hhs.gov/about/news/2017/10/26/hhs-acting-secretary-declares-public-health-emergency-address-national-opioid-crisis.html [accessed 2022-05-02]
2. Provisional drug overdose death counts. Centers for Disease Control and Prevention. 2023 Feb 15. URL: https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm [accessed 2023-05-23]
3. Florence CS, Zhou C, Luo F, Xu L. The economic burden of prescription opioid overdose, abuse, and dependence in the United States, 2013. Med Care 2016 Oct;54(10):901-906 [FREE Full text] [doi: 10.1097/MLR.0000000000000625] [Medline: 27623005]
4. Peetz C. After Whitman student's fentanyl overdose, family hopes awareness will prevent similar tragedy. MoCo360. 2022 Apr 23. URL: https://moco360.media/2022/04/23/after-whitman-students-fentanyl-overdose-family-hopes-awareness-will-prevent-similar-tragedy/ [accessed 2024-03-13]
5. FACT SHEET: in State of the Union, president Biden to outline vision to advance progress on unity agenda in year ahead. The White House. 2023 Feb 07. URL: https://www.whitehouse.gov/briefing-room/statements-releases/2023/02/07/fact-sheet-in-state-of-the-union-president-biden-to-outline-vision-to-advance-progress-on-unity-agenda-in-year-ahead/ [accessed 2023-03-03]
6. Naloxone for opioid overdose: life-saving science. National Institute on Drug Abuse. URL: https://www.drugabuse.gov/publications/naloxone-opioid-overdose-life-saving-science [accessed 2021-12-15]
7. Naloxone DrugFacts. National Institute on Drug Abuse. URL: https://nida.nih.gov/publications/drugfacts/naloxone [accessed 2022-05-03]
8. Lim JK, Bratberg JP, Davis CS, Green TC, Walley AY. Prescribe to prevent: overdose prevention and naloxone rescue kits for prescribers and pharmacists. J Addict Med 2016;10(5):300-308 [FREE Full text] [doi: 10.1097/ADM.0000000000000223] [Medline: 27261669]
9. Berg S. Lifesaving naloxone should be available almost everywhere. American Medical Association. 2019 Jun 11. URL: https://www.ama-assn.org/delivering-care/opioids/lifesaving-naloxone-should-be-available-almost-everywhere [accessed 2022-05-03]
10. Public policy statement on the use of naloxone for the prevention of opioid overdose deaths. American Society of Addiction Medicine. URL: https://www.asam.org/docs/default-source/public-policy-statements/use-of-naloxone-for-the-prevention-of-opioid-overdose-deaths-final.pdf [accessed 2022-05-03]
11. U.S. surgeon general's advisory on naloxone and opioid overdose. U.S. Department of Health and Human Services. URL: https://www.hhs.gov/surgeongeneral/priorities/opioids-and-addiction/naloxone-advisory/index.html [accessed 2021-07-03]
12. Ballreich J, Mansour O, Hu E, Chingcuanco F, Pollack HA, Dowdy DW, et al. Modeling mitigation strategies to reduce opioid-related morbidity and mortality in the US. JAMA Netw Open 2020 Nov 02;3(11):e2023677 [FREE Full text] [doi: 10.1001/jamanetworkopen.2020.23677] [Medline: 33146732]
13. Beletsky L, Rich JD, Walley AY. Prevention of fatal opioid overdose. JAMA 2012 Nov 14;308(18):1863-1864 [FREE Full text] [doi: 10.1001/jama.2012.14205] [Medline: 23150005]
14. Chimbar L, Moleta Y. Naloxone effectiveness: a systematic review. J Addict Nurs 2018;29(3):167-171. [doi: 10.1097/jan.0000000000000230]
15. Razaghizad A, Windle SB, Filion KB, Gore G, Kudrina I, Paraskevopoulos E, et al. The effect of overdose education and naloxone distribution: an umbrella review of systematic reviews. Am J Public Health 2021 Aug;111(8):e1-12. [doi: 10.2105/AJPH.2021.306306] [Medline: 34214412]
16. Smart R, Davis CS. Reducing opioid overdose deaths by expanding naloxone distribution and addressing structural barriers to care. Am J Public Health 2021 Aug;111(8):1382-1384. [doi: 10.2105/ajph.2021.306376]

17. Quinn K, Kumar S, Hunter CT, O'Donnell J, Davis NL. Naloxone administration among opioid-involved overdose deaths in 38 United States jurisdictions in the State Unintentional Drug Overdose Reporting System, 2019. Drug Alcohol Depend 2022 Jun 01;235:109467 [FREE Full text] [doi: 10.1016/j.drugalcdep.2022.109467] [Medline: 35461083]
18. Doyon S, Aks SE, Schaeffer S. Expanding access to naloxone in the United States. Clin Toxicol (Phila) 2014 Dec 06;52(10):989-992. [doi: 10.3109/15563650.2014.968657] [Medline: 25283253]
19. Wheeler E, Jones TS, Gilbert MK, Davidson PJ. Opioid overdose prevention programs providing naloxone to laypersons - United States, 2014. MMWR Morb Mortal Wkly Rep 2015 Jun 19;64(23):631-635 [FREE Full text] [Medline: 26086633]
20. Drug misuse: most states have good samaritan laws and research indicates they may have positive effects. United States Government Accountability Office. 2021 Mar. URL: https://www.gao.gov/assets/gao-21-248.pdf [accessed 2022-06-03]
21. Meyerson BE, Moehling TJ, Agley JD, Coles HB, Phillips J. Insufficient access: naloxone availability to laypeople in Arizona and Indiana, 2018. J Health Care Poor Underserved 2021;32(2):819-829. [doi: 10.1353/hpu.2021.0107] [Medline: 34120979]
22. Facher L. FDA advisers recommend approval of over-the-counter naloxone to fight opioid overdose. StatNews. 2023 Feb 15. URL: https://www.statnews.com/2023/02/15/naloxone-otc-opioisa-fda-panel-recommends/ [accessed 2023-02-21]
23. Tse WC, Sanfilippo P, Lam T, Dietze P, Nielsen S. Community pharmacy naloxone supply, before and after rescheduling as an over-the-counter drug: sales and prescriptions data, 2014-2018. Med J Aust 2020 Apr 03;212(7):314-320. [doi: 10.5694/mja2.50524] [Medline: 32124984]
24. Kim D, Irwin KS, Khoshnood K. Expanded access to naloxone: options for critical response to the epidemic of opioid overdose mortality. Am J Public Health 2009 Mar;99(3):402-407. [doi: 10.2105/ajph.2008.136937]
25. Michiels C. Physiological and pathological responses to hypoxia. Am J Pathol 2004 Jun;164(6):1875-1882. [doi: 10.1016/s0002-9440(10)63747-9]
26. Baca CT, Grant KJ. Take-home naloxone to reduce heroin death. Addiction 2005 Dec 23;100(12):1823-1831. [doi: 10.1111/j.1360-0443.2005.01259.x] [Medline: 16367983]
27. Opioid poisoning, overdose and prevention: 2015 report to the Governor and NYS Legislature. New York State Department of Health. 2015. URL: https://www.health.ny.gov/diseases/aids/general/opioid_overdose_prevention/docs/annual_report2015.pdf [accessed 2024-03-11]
28. Pergolizzi JV, Webster LR, Vortsman E, Ann LeQuang J, Raffa RB. Wooden chest syndrome: the atypical pharmacology of fentanyl overdose. J Clin Pharm Ther 2021 Dec 08;46(6):1505-1508. [doi: 10.1111/jcpt.13484] [Medline: 34240442]
29. Tobin K, Clyde C, Davey-Rothwell M, Latkin C. Awareness and access to naloxone necessary but not sufficient: examining gaps in the naloxone cascade. Int J Drug Policy 2018 Sep;59:94-97 [FREE Full text] [doi: 10.1016/j.drugpo.2018.07.003] [Medline: 30075401]
30. Koester S, Mueller SR, Raville L, Langegger S, Binswanger IA. Why are some people who have received overdose education and naloxone reticent to call emergency medical services in the event of overdose? Int J Drug Policy 2017 Oct;48:115-124 [FREE Full text] [doi: 10.1016/j.drugpo.2017.06.008] [Medline: 28734745]
31. Murphy J, Russell B. Police officers' views of naloxone and drug treatment: does greater overdose response lead to more negativity? J Drug Issues 2020 Jun 01;50(4):455-471. [doi: 10.1177/0022042620921363]
32. Marcu G, Aizen R, Roth A, Lankenau S, Schwartz DG. Acceptability of smartphone applications for facilitating layperson naloxone administration during opioid overdoses. JAMIA Open 2020 Apr;3(1):44-52 [FREE Full text] [doi: 10.1093/jamiaopen/ooz068] [Medline: 32607487]
33. Earnshaw VA. Stigma and substance use disorders: a clinical, research, and advocacy agenda. Am Psychol 2020 Dec;75(9):1300-1311 [FREE Full text] [doi: 10.1037/amp0000744] [Medline: 33382299]
34. Baumgart-McFarland M, Chiarello E, Slay T. Reluctant saviors: professional ambivalence, cultural imaginaries, and deservingness construction in naloxone provision. Soc Sci Med 2022 Sep;309:115230. [doi: 10.1016/j.socscimed.2022.115230] [Medline: 35995012]
35. Miller NM, Waterhouse-Bradley B, Campbell C, Shorter GW. How do naloxone-based interventions work to reduce overdose deaths: a realist review. Harm Reduct J 2022 Feb 23;19(1):18 [FREE Full text] [doi: 10.1186/s12954-022-00599-4] [Medline: 35197057]
36. Filteau MR, Green B, Kim F, McBride KA. 'It's the same thing as giving them CPR training': rural first responders' perspectives on naloxone. Harm Reduct J 2022 Oct 03;19(1):111 [FREE Full text] [doi: 10.1186/s12954-022-00688-4] [Medline: 36192736]
37. Dahlem CH, Granner J, Boyd CJ. Law enforcement perceptions about naloxone training and its effects post-overdose reversal. J Addict Nurs 2022;33(2):80-85. [doi: 10.1097/JAN.0000000000000456] [Medline: 35640211]
38. Tsai AC, Kiang MV, Barnett ML, Beletsky L, Keyes KM, McGinty EE, et al. Stigma as a fundamental hindrance to the United States opioid overdose crisis response. PLoS Med 2019 Nov 26;16(11):e1002969 [FREE Full text] [doi: 10.1371/journal.pmed.1002969] [Medline: 31770387]
39. Agley J, Xiao Y, Eldridge L, Meyerson B, Golzarri-Arroyo L. Beliefs and misperceptions about naloxone and overdose among U.S. laypersons: a cross-sectional study. BMC Public Health 2022 May 10;22(1):924 [FREE Full text] [doi: 10.1186/s12889-022-13298-3] [Medline: 35538566]

40. Medical student finds herself in the right place at the right time. MetroHealth. 2017 Sep 6. URL: https://news.metrohealth.org/medical-student-finds-herself-in-the-right-place-at-the-right-time/ [accessed 2022-06-05]
41. Schwartz DG, Ataiants J, Roth A, Marcu G, Yahav I, Cocchiaro B, et al. Layperson reversal of opioid overdose supported by smartphone alert: a prospective observational cohort study. EClinicalMedicine 2020 Aug 03;25:100474 [FREE Full text] [doi: 10.1016/j.eclinm.2020.100474] [Medline: 32954238]
42. Overdose detection for people who use drugs. Brave App. URL: https://www.brave.coop/overdose-detection-app [accessed 2023-10-09]
43. Stats. PulsePoint. URL: https://www.pulsepoint.org/stats [accessed 2023-10-09]
44. Defining rural population. Health Resources & Services Administration. URL: https://www.hrsa.gov/rural-health/about-us/definition/index.html [accessed 2022-05-05]
45. Operational issues in RDD cell phone surveys. American Association for Public Opinion Research. URL: https://www.aapor.org/Education-Resources/Reports/Cell-Phone-Task-Force-Report/Operational-Issues.aspx [accessed 2022-05-22]
46. Agley J, Barnes P, Tidd D, Todd A, Friedman K, Gordon S, et al. Integrating telepsychiatry into rural primary care for upstream prevention: feasibility case study of the faith net program. Inquiry 2022;59:469580221097428 [FREE Full text] [doi: 10.1177/00469580221097428] [Medline: 35475403]
47. Agley J, Jun M, Eldridge L, Agley DL, Xiao Y, Sussman S, et al. Effects of ACT out! Social issue theater on social-emotional competence and bullying in youth and adolescents: cluster randomized controlled trial. JMIR Ment Health 2021 Jan 06;8(1):e25860 [FREE Full text] [doi: 10.2196/25860] [Medline: 33338986]
48. Agley J, Xiao Y, Jayawardene W, Gay A, King R, Horne K, et al. HIV/AIDS and substance use prevention for African American young adults: field evaluation of “Color it Real”. SAGE Open 2021;11(2):1-7. [doi: 10.1177/21582440211019734]
49. Eldridge LA, Meyerson BE, Agley J. Pilot implementation of the PharmNet naloxone program in an independent pharmacy. J Am Pharm Assoc (2003) 2023;63(1):374-82.e12 [FREE Full text] [doi: 10.1016/j.japh.2022.09.004] [Medline: 36209035]
50. PulsePoint respond. PulsePoint. URL: https://d34h86nwtgo5zp.cloudfront.net/default/PulsePoint_Fact_Sheet_07-01-2020.pdf [accessed 2022-05-06]
51. Share the training. Prevention Insights. URL: https://prevention.iu.edu/projects/naloxone/share.php [accessed 2023-03-03]
52. Coffin PO, Behar E, Rowe C, Santos GM, Coffa D, Bald M, et al. Nonrandomized intervention study of naloxone coprescription for primary care patients receiving long-term opioid therapy for pain. Ann Intern Med 2016 Aug 16;165(4):245-252 [FREE Full text] [doi: 10.7326/M15-2771] [Medline: 27366987]
53. Doe-Simkins M, Quinn E, Xuan Z, Sorensen-Alawad A, Hackman H, Ozonoff A, et al. Overdose rescues by trained and untrained participants and change in opioid use among substance-using participants in overdose education and naloxone distribution programs: a retrospective cohort study. BMC Public Health 2014 Apr 01;14:297 [FREE Full text] [doi: 10.1186/1471-2458-14-297] [Medline: 24684801]
54. Jones JD, Campbell A, Metz VE, Comer SD. No evidence of compensatory drug use risk behavior among heroin users after receiving take-home naloxone. Addict Behav 2017 Aug;71:104-106 [FREE Full text] [doi: 10.1016/j.addbeh.2017.03.008] [Medline: 28325710]
55. Tse WC, Djordjevic F, Borja V, Picco L, Lam T, Olsen A, et al. Does naloxone provision lead to increased substance use? a systematic review to assess if there is evidence of a 'moral hazard' associated with naloxone supply. Int J Drug Policy 2022 Feb;100:103513. [doi: 10.1016/j.drugpo.2021.103513] [Medline: 34798434]
56. Kelly BC, Vuolo M. Do naloxone access laws affect perceived risk of heroin use? evidence from national US data. Addiction 2022 Mar;117(3):666-676 [FREE Full text] [doi: 10.1111/add.15682] [Medline: 34617356]
57. Larochelle MR, Liebschutz JM, Zhang F, Ross-Degnan D, Wharam JF. Opioid prescribing after nonfatal overdose and association with repeated overdose: a cohort study. Ann Intern Med 2016 Jan 05;164(1):1-9. [doi: 10.7326/M15-0038] [Medline: 26720742]
58. Lowder EM, Amlung J, Ray BR. Individual and county-level variation in outcomes following non-fatal opioid-involved overdose. J Epidemiol Community Health 2020 Apr;74(4):369-376 [FREE Full text] [doi: 10.1136/jech-2019-212915] [Medline: 31919146]
59. Olfson M, Crystal S, Wall M, Wang S, Liu SM, Blanco C. Causes of death after nonfatal opioid overdose. JAMA Psychiatry 2018 Aug 01;75(8):820-827 [FREE Full text] [doi: 10.1001/jamapsychiatry.2018.1471] [Medline: 29926090]
60. Peterson C, Liu Y, Xu L, Nataraj N, Zhang K, Mikosz CA. U.S. national 90-day readmissions after opioid overdose discharge. Am J Prev Med 2019 Jun;56(6):875-881 [FREE Full text] [doi: 10.1016/j.amepre.2018.12.003] [Medline: 31003811]
61. Ecker UK, Antonio LM. Can you believe it? An investigation into the impact of retraction source credibility on the continued influence effect. Mem Cognit 2021 May;49(4):631-644 [FREE Full text] [doi: 10.3758/s13421-020-01129-y] [Medline: 33452666]
62. Swire B, Ecker UK, Lewandowsky S. The role of familiarity in correcting inaccurate information. J Exp Psychol Learn Mem Cogn 2017 Dec;43(12):1948-1961 [FREE Full text] [doi: 10.1037/xlm0000422] [Medline: 28504531]
63. Ecker UK, O'Reilly Z, Reid JS, Chang EP. The effectiveness of short-format refutational fact-checks. Br J Psychol 2020 Feb;111(1):36-54 [FREE Full text] [doi: 10.1111/bjop.12383] [Medline: 30825195]

64. Wasserstein RL, Lazar NA. The ASA statement on P-values: context, process, and purpose. Am Stat 2016 Jun 09;70(2):129-133. [doi: 10.1080/00031305.2016.1154108]
65. Park A, Smart C, Taylor R, Watkins M. An extremely detailed map of the 2020 election. The New York Times. URL: https://www.nytimes.com/interactive/2021/upshot/2020-election-map.html [accessed 2022-05-19]
66. Inform and engage your community. PulsePoint. URL: https://www.pulsepoint.org/pulsepoint-respond [accessed 2022-05-20]
67. Delete and manage cookies. Microsoft. URL: https://support.microsoft.com/en-us/windows/delete-and-manage-cookies-168dab11-0753-043d-7c16-ede5947fc64d [accessed 2022-05-26]
68. Wohllebe A, Hübner DS, Radtke U, Podruzsik S. Mobile apps in retail: effect of push notification frequency on app user behavior. Innov Market 2021 May 28;17(2):102-111. [doi: 10.21511/im.17(2).2021.10]
69. Gilmour A. How to develop a successful push notification marketing strategy. Adjust. 2024 Jan 26. URL: https://www.adjust.com/blog/how-to-develop-a-successfull-push-notification-strategy/ [accessed 2024-03-13]
70. Get trained. Save a life. Prevention Insights. URL: https://prevention.iu.edu/projects/naloxone/index.php [accessed 2023-02-26]
71. Agley J, Henderson C, Adams Z, Hulvershorn L. Provider engagement in Indiana's opioid use disorder ECHO programme: there is a will but not always a way. BMJ Open Qual 2021 Apr 13;10(2):e001170 [FREE Full text] [doi: 10.1136/bmjoq-2020-001170] [Medline: 33849905]
72. Saunders B, Sim J, Kingstone T, Baker S, Waterfield J, Bartlam B, et al. Saturation in qualitative research: exploring its conceptualization and operationalization. Qual Quant 2018 Sep 14;52(4):1893-1907 [FREE Full text] [doi: 10.1007/s11135-017-0574-8] [Medline: 29937585]
73. Thomas DR. A general inductive approach for analyzing qualitative evaluation data. Am J Eval 2016 Jun 30;27(2):237-246. [doi: 10.1177/1098214005283748]

Abbreviations

CPR: cardiopulmonary resuscitation
MOU: memorandum of understanding
OEND: overdose education and naloxone distribution
OTC: over-the-counter

Edited by A Mavragani; submitted 10.02.24; this is a non–peer-reviewed article;accepted 04.03.24; published 29.03.24.

Please cite as:
Agley J, Henderson C, Seo DC, Parker M, Golzarri-Arroyo L, Dickinson S, Tidd D
The Feasibility of Using the National PulsePoint Cardiopulmonary Resuscitation Responder Network to Facilitate Overdose Education and Naloxone Distribution: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2024;13:e57280
URL: https://www.researchprotocols.org/2024/1/e57280
doi:10.2196/57280
PMID:38551636

Protocol

The Effects of an Educational Intervention About Front-of-Package Labeling on Food and Beverage Selection Among Children and Their Caregivers: Protocol for a Randomized Controlled Trial

Diana Avila-Montiel[1*], MSc; Jenny Vilchis-Gil[1*], PhD; América Liliana Miranda-Lora[1*], PhD; Lubia Velázquez-López[2*], PhD; Miguel Klünder-Klünder[1*], PhD

[1]Epidemiological Research Unit in Endocrinology and Nutrition, Hospital Infantil de México Federico Gómez, CDMX, Mexico

[2]Clinical Epidemiology Research Unit Dr. Carlos Mac Gregor Sánchez Navarro, Mexican Social Security Institute, CDMX, Mexico

[*]all authors contributed equally

Corresponding Author:
Miguel Klünder-Klünder, PhD
Epidemiological Research Unit in Endocrinology and Nutrition
Hospital Infantil de México Federico Gómez
Dr. Marquez 162
CDMX, 06720
Mexico
Phone: 52 5552289917 ext 4319
Email: klunderk@gmail.com

Abstract

Background: Overweight and obesity pose a global public health challenge and have a multifactorial origin. One of these factors includes obesogenic environments, which promote ultraprocessed foods characterized by being high in calories, saturated fats, added sugars, and sodium. In Mexico, it has been estimated that 30% of the total energy consumed comes from processed foods. The Modification to the Official Mexican Standards introduces nutritional information through black octagonal seals that alert consumers about products with excessive amounts of some components for a better food selection in the population. However, the effects of warning labels on processed food selection and purchases among children remain unknown.

Objective: We aimed to evaluate the impact of a digital educational intervention focusing on front-of-package warning labels on the food selection and purchasing behavior of elementary schoolchildren and their caregivers.

Methods: Children from 4 elementary schools in Mexico City, 2 public and 2 private schools, will participate in a randomized controlled trial. The schools will be chosen by simple random sampling. Schools will be randomized into 2 groups: intervention and control. In the control group, the dyads (caregiver-schoolchildren) will receive general nutritional education, and in the intervention group, they will receive guidance on reading labels and raising awareness about the impact of consuming ultraprocessed products on health. The educational intervention will be conducted via a website. Baseline measurements will be taken for both groups at 3 and 6 months. All participants will have access to an online store through the website, allowing them to engage in exercises for selecting and purchasing food and beverages. In addition, other measures will include a brief 5-question exam to evaluate theoretical understanding, a 24-hour reminder, a survey on food habits and consumption, application of a food preference scale, anthropometric measurements, and recording of school lunch choices.

Results: Registration and funding were authorized in 2022, and we will begin data collection in September 2024. Recruitment has not yet taken place, but the status of data analysis and expected results will be published in April 2025.

Conclusions: The study is expected to contribute to evaluating whether reinforcing front-of-package warning labels with education enhances its effects and makes them more sustainable. Conducting this study will allow us to propose whether or not it is necessary to develop new intervention strategies related to front-of-package labeling for a better understanding of the population, improved food choices, and better health outcomes.

Trial Registration: ClinicalTrials.gov NCT06102473; https://clinicaltrials.gov/study/NCT06102473

International Registered Report Identifier (IRRID): PRR1-10.2196/54783

(JMIR Res Protoc 2024;13:e54783) doi:10.2196/54783

KEYWORDS

e-Health nutrition education; ultraprocessed foods; malnutrition; children; Mexico; intervention; obesity; food; food selection; labeling; package labeling

Introduction

Overweight and obesity pose a global public health challenge. In Mexico, data from the National Health and Nutrition Surveys from 2012, 2018, and 2020 show that the combined prevalence of overweight and obesity in children between the ages of 5 and 10 years has remained high (33.2%, 35.6%, and 38.2%, respectively) [1].

Obesity has a multifactorial etiology, involving genetic, environmental, and behavioral aspects. Obesogenic environments promote ultraprocessed foods, which are high in calories, saturated fats, added sugars, and sodium [2,3].

Therefore, public policies aimed at reducing the incidence and prevalence of childhood obesity must consider actions that modify the environment to improve nutrition. Labeling of ultraprocessed products has been a common strategy that governments worldwide use to improve people's diets [4].

In Mexico, it has been estimated that more than 30% of the total energy consumed comes from ultraprocessed foods, favoring the prevalence of overweight and obesity. The daily dietary guidelines by the Ministry of Economy and the Ministry of Health in Mexico were an effort for people to improve their food selection and purchasing; however, they did not show good results due to the complexity of interpreting them [5].

The Modification to the Official Mexican Standard (NOM-051-SCFI/SSA1-2010 [NOM 051]) was approved in 2020. This proposed a front labeling system for foods and beverages that consisted of nutritional information through black octagonal seals, with legends like "excess calories," "excess sodium," "excess saturated fat," "excess trans fat," "excess sugars," and other explanations, such as "contains caffeine, avoid for children" and "contains sweeteners, not recommended for children," to provide information to the consumers to help them make food selections [5,6].

Ultraprocessed products targeted at children are offered in all supermarkets and represent an important commercial income for the food industry [7,8]. At home, parents are primarily responsible for purchasing food and have a significant influence on their children's eating behaviors [7-10].

On the other hand, children also influence parents' purchasing decisions, especially when they want to choose unhealthy foods, which is why the influence of front labeling must be studied from both perspectives (ie, children's and parents') [11]. To reduce the purchase and consumption of ultraprocessed foods, various marketing strategies have been implemented, especially for products aimed at school children; however, the results have been varied and limited [12,13].

It is known that food packaging has an impact on how children perceive these products. For instance, the use of drawings and bright colors can make them associate the product with something suitable to eat, which is why changes have been made to packaging designs to discourage consumption, mainly by removing cartoon slogans or legends that promote their consumption [14].

Some types of front-of-package labeling guide the daily intake by indicating the proportion (%) of nutrients found in a serving according to the recommended daily intake for adults. This includes the traffic light system, which uses colors (green, yellow, and red) to indicate the amount of nutrients in a product, as well as warning labels, which are black octagonal symbols, which indicate the excess of nutrients, energy, and substances present in the product and are intended to discourage purchase and consumption [15].

Having identified the relationship between packaging and food consumption, it is expected that front-of-package nutritional labels will reduce the consumption of unhealthy foods [16].

Furthermore, it has been documented that another effective strategy to improve food selection is to enhance nutritional education to develop skills to distinguish healthy products from those that are not considered healthy [17].

Mobile nutritional interventions have been observed to reach a broader range of social and demographic groups and can facilitate the selection of healthy foods at the point of purchase, optimizing decision-making times [18].

In Mexico, it is estimated that 78.6% of the Mexican population aged 6 years and older has access to the internet, with 97% connecting through mobile devices. This is why various health institutions have implemented web portals, social networks, and the use of cell phone messages, telephone, and mobile apps for managing, preventing, and treating health-related activities [19-21].

The objective of this clinical trial is to evaluate the impact of a digital educational intervention focusing on front-of-package warning labels on the food selection and purchasing behavior of elementary school children and their caregivers [22].

Methods

Recruitment and Study Design

Third-, fourth-, and fifth-grade elementary school students and their caregivers from 4 primary schools—2 public and 2 private schools—in Mexico City will participate in the study. The schools will be chosen by simple random sampling. Schools will be randomized into 2 groups: intervention and control.

After approval from the directors of the primary schools, meetings will be held with parents to invite them to participate; they will be explained the intervention's objectives, activities, and duration. Parents and schoolchildren will be invited to sign a consent and informed assent, respectively, clarifying that their participation is voluntary, and they may choose to discontinue at any time without affecting their activities at school.

The main question this study aims to answer is the following: What is the effect of a digital educational intervention about front-of-package warning labels on food selection among children attending primary schools in Mexico City, compared to a control group?

Schools will be randomized into 2 groups. In the control group, the dyads (caregiver-schoolchildren), will receive general nutritional education, and in the intervention group, they will also receive guidance on reading labels, which raises awareness about the impact of consuming processed or ultraprocessed foods on health.

The intervention will be carried out via a website [23] (Figure 1) with audiovisual material, and all participants will also be asked to complete a multiple-choice evaluation (5 questions) to ensure a theoretical understanding of the topics. Other measures will include a lunch register, 24-hour dietary recall, a survey of food habits and consumption, a validated food preference questionnaire, anthropometric measurements (eg, weight, height, and waist circumference), a socioeconomic survey, as well as participation in a simulated web-based food and beverage selection and shopping activity. These measures will help assess if the digital educational intervention on front-of-package warning labeling for children and caregivers improves the selection and purchase of foods.

Figure 1. Website “Applicate por tu salud” (www.viviendo-saludable.org).

Inclusion Criteria

Inclusion criteria for children are as follows: students in third, fourth, and fifth grades (aged 8 to 12 years), of both sexes, enrolled in the selected primary schools, with normal weight, overweight, and obesity, who sign the written informed consent.

Inclusion criteria for caregivers are as follows: primary caregivers of any sex of children in the third, fourth, and fifth grades with normal weight, overweight and obesity, who sign the written informed consent.

Exclusion Criteria

Caregivers and children without internet access, computers, or mobile devices, as well as those participating in a weight reduction program with pharmacological treatment, will be excluded.

Nutritional Education Interventions

The control group and the intervention group in dyads (caregiver-schoolchildren) will receive general nutritional education, and only the intervention group will receive guidance on reading warning labels, which raises awareness about the impact of consuming processed and ultraprocessed foods on health.

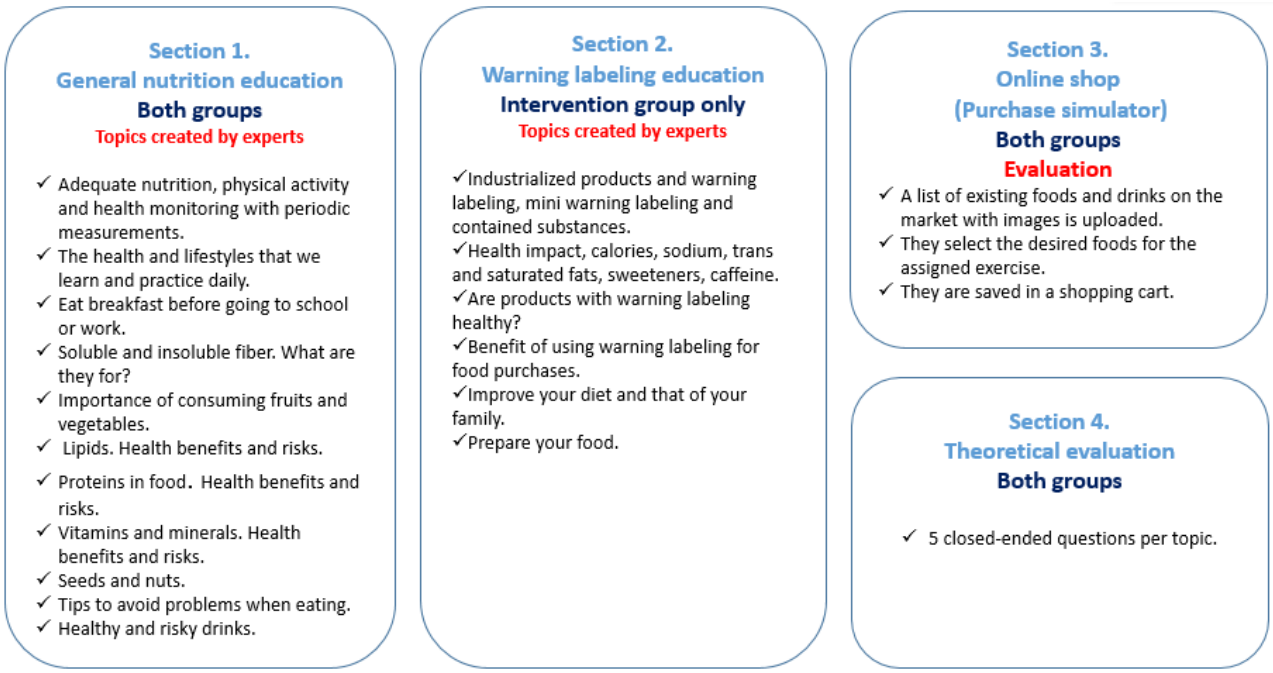
On the website, there will be 4 sections. Participants will receive an account and password to access the educational content corresponding to the group they belong, intervention or control group.

The intervention and control groups will have access to the first section, which contains general nutritional education topics. The second section will contain nutritional education topics related to warning labeling, and only the intervention group will have access to it.

Each topic will be presented through videos, released every 15 days, as well as weekly infographics and tips to the caregivers and children via the website. This material will also be sent to the participants’ mobile devices.

The third section will have the “Online shop,” which will be used as part of the food selection evaluation. The fourth section will evaluate theoretical understanding with 5 multiple-choice questions per topic (Figure 2).

Figure 2. Nutritional intervention topics by groups.



Primary Outcomes

Time Frame

The measurements will be carried out in 2 scenarios (in schools and through the website) at baseline (1 week before starting the educational interventions), at 3 months, and at 6 months after the intervention ends.

A socioeconomic survey will be used in the baseline measurement.

The following assessments will be conducted at 3 frame times (baseline, 3 months, and 6 months): a food preference questionnaire, a 24-hour dietary recall, lunch register, and a survey of food habits and consumption. Anthropometric measurements (eg, weight, height, and waist circumference) will only be performed at baseline and the end of the 6-month intervention.

Through the website, dyads will engage in food and beverage purchasing exercises in the online shop simulator at the 3 measurement points (baseline, 3 months, and 6 months), along with multiple-choice evaluation (5 questions).

Food and Drink Selection

The percentage of products purchased by each participant in the online store, whose content indicates “high in calories, sugar, fat, and sodium” and the average content of these nutrients in 100 g of each product will be measured.

Energy and Macronutrient Intake

The amount of kilocalories consumed as well as saturated fat, trans fat, sodium, and added sugar will be measured.

Statistical Analysis

Descriptive statistics will be used to characterize variables, and tables will be made with summary measures. Independent *t* tests and chi-square tests for categorical data will be used to compare baseline characteristics between the intervention and control groups. The Mann-Whitney *U* test will be used to evaluate differences between groups in case of nonnormal distribution.

Repeated measures ANOVA will be used to evaluate the change in the number of warning labels in nutrient consumption between groups and throughout the intervention. We will use a mixed-effects model to evaluate the effect of the intervention on changes in food and beverage selection, adjusting for confounding variables. Intention-to-treat analysis will be performed.

Ethical Considerations

The protocol has obtained ethics approval by the bioethics committees of the Hospital Infantil de México Federico Gómez (HIM/2022/054). This protocol has also been registered with ClinicalTrials.gov (NCT06102473).

The objectives and activities of the study will be explained to the caregivers and children. To participate, they must sign the informed consent and informed assent forms to give their authorization to participate, with confidentiality guaranteed.

The website will contain health education material and an online shop to simulate the selection and shopping of food and beverages. No personal or medical information will be uploaded to the website. The results will only be used for the study and will be stored by the research team on password-protected computers. In case of any changes to the protocol, the ethics committee will be informed.

Results

The protocol was registered in 2022 and was approved by the committees of the Federico Gómez Children's Hospital of Mexico, and they also obtained federal resources for the project. We expect to begin the study in schools in September 2024.

We are not recruiting yet. The results will be analyzed and published in April and May 2025.

Discussion

Expected Outcomes

This protocol aims to study a public health policy in Mexico, which seeks to contribute to improving the health of the Mexican population by facilitating the understanding of nutritional information about ultraprocessed foods and beverages using front-of-package warning labeling. Studying the effects of this intervention on the population is essential for continuing with the initiative, improving it, or considering other measures to achieve the expected health outcomes.

Some studies have been conducted around the world on different types of front labeling, exploring their effectiveness in selecting and purchasing healthier foods.

A study on adults [24] explored the effectiveness of different types of frontal labeling. Participants were given a brief educational session through a smartphone app before being exposed to 2 experimental shopping tasks. The study found that all types of front labeling, after the educational intervention, resulted in better food selection. In Mexico, a study [25] provided guidance on front labeling via video before participants engaged in online food selection, showing positive effects on food selection.

Another study [26] demonstrated that nutritional warning labels with stamps significantly reduced the percentage of participants who selected products with excessive content of at least one nutrient, compared to the control group (62% vs 85%), and a statistically significant difference was observed for participants who selected products with an excess of certain nutrients, such as sugar (P<.001), saturated fats (P<.001), and sodium (P=.01).

A study in the United States [27] targeting parents concluded that warning labels on sugary beverages reduced the purchase of these products for their children. Although the evidence indicates that front-of-package warning labels can improve the selection of foods and beverages, the effects of these labels on the pediatric population and how children influence the selection and purchase of foods in their homes are still unknown.

On the other hand, the guidance received by participants in the aforementioned studies is limited to ensuring understanding of reading the label.

One limitation of the study is that the exercise of food and beverage selection will be made in a simulated shopping scenario, which may differ from real-life situations of food and beverage purchasing and consumption; however, this study is important to determine whether a structured educational intervention on key nutrients and raising awareness about their implication in health enhances the effects of front-of-package warning labeling to reduce overweight and obesity as well as other chronic diseases, such as diabetes and hypertension.

Conclusions

It is expected that the study will contribute to evaluating whether reinforcing front-of-package warning labeling with education enhances its effects and makes them more sustainable. Carrying out this study will allow us to propose whether or not it is necessary to develop new intervention strategies related to front-of-package labeling for a better understanding of the population, improved food choices, and better health outcomes.

Acknowledgments

The authors would like to acknowledge the academic and administrative support provided by the Research Directorate of the Health Institute Hospital Infantil de México Federico Gómez and the Master's and Doctorate programs in Medical, Dental, and Health Sciences of the Universidad Autónoma de México for their interest in the subject and for providing the conditions required to conduct this study.

Data Availability

The data sets generated and analyzed during this study are not publicly available to comply with the ethical requirements and participants' confidentiality protection but are available from the corresponding author upon reasonable request.

Authors' Contributions

DAM, JVG, and MKK conceptualized the study and drafted the manuscript. ALML and LVL conceptualized the study and reviewed the manuscript.

Conflicts of Interest

None declared.

References

1. Romero-Martínez M, Shamah-Levy T, Vielma-Orozco E, Heredia-Hernández O, Mojica-Cuevas J, Cuevas-Nasu L, et al. [National Health and Nutrition Survey 2018-19: methodology and perspectives]. Salud Publica Mex 2019 Dec 05;61(6):917-923. [doi: 10.21149/11095] [Medline: 31869555]

2. Walley AJ, Asher JE, Froguel P. The genetic contribution to non-syndromic human obesity. Nat Rev Genet 2009 Jul;10(7):431-442. [doi: 10.1038/nrg2594] [Medline: 19506576]
3. Monasta L, Batty GD, Cattaneo A, Lutje V, Ronfani L, Van Lenthe FJ, et al. Early - life determinants of overweight and obesity: a review of systematic reviews. Obesity Reviews 2010 Mar 16;11(10):695-708. [doi: 10.1111/j.1467-789x.2010.00735.x]
4. Hawkes C, Smith TG, Jewell J, Wardle J, Hammond RA, Friel S, et al. Smart food policies for obesity prevention. The Lancet 2015 Jun;385(9985):2410-2421. [doi: 10.1016/s0140-6736(14)61745-1]
5. Kaufer-Horwitz M, Tolentino-Mayo L, Jáuregui A, Sánchez-Bazán K, Bourges H, Martínez S, et al. [A front-of-pack labelling system for food and beverages for Mexico: a strategy of healthy decision-making.]. Salud Publica Mex 2018 Jun 28;60(4):479-486. [doi: 10.21149/9615] [Medline: 30137950]
6. Chavez Reynoso IJ, Ochoa Estrada R, Valenzuela Paredes L, Gayosso García Sancho LE, Tolano Villaverde IDJ. Actualización de la norma oficial Mexicana NOM-051-SCFI/SSA1 en la industria de alimentos y bebidas [Article in Spanish]. Jour Bol Cien 2021 Apr 23;17(Especial):6-18. [doi: 10.52428/20758944.v17iespecial.1]
7. Chacon V, Letona P, Barnoya J. Child-oriented marketing techniques in snack food packages in Guatemala. BMC Public Health 2013 Oct 18;13(1):967. [doi: 10.1186/1471-2458-13-967] [Medline: 24139325]
8. Palfreyman Z, Haycraft E, Meyer C. Parental modelling of eating behaviours: observational validation of the Parental Modelling of Eating Behaviours scale (PARM). Appetite 2015 Mar;86:31-37 [FREE Full text] [doi: 10.1016/j.appet.2014.08.008] [Medline: 25111293]
9. Ventura A, Worobey J. Early influences on the development of food preferences. Curr Biol 2013 May 06;23(9):R401-R408. [doi: 10.1016/j.cub.2013.02.037] [Medline: 23660363]
10. Watts AW, Loth K, Berge JM, Larson N, Neumark-Sztainer D. No time for family meals? parenting practices associated with adolescent fruit and vegetable intake when family meals are not an option. J Acad Nutr Diet 2017 May;117(5):707-714 [FREE Full text] [doi: 10.1016/j.jand.2016.10.026] [Medline: 27989447]
11. O'Dougherty M, Story M, Stang J. Observations of parent-child co-shoppers in supermarkets: children's involvement in food selections, parental yielding, and refusal strategies. J Nutr Educ Behav 2006 May;38(3):183-188. [doi: 10.1016/j.jneb.2005.11.034] [Medline: 16731454]
12. Cairns G, Angus K, Hastings G, Caraher M. Systematic reviews of the evidence on the nature, extent and effects of food marketing to children. A retrospective summary. Appetite 2013 Mar;62:209-215. [doi: 10.1016/j.appet.2012.04.017] [Medline: 22561190]
13. Estudio exploratorio sobre la promoción y publicidad de alimentos y bebidas no saludables dirigida a niños en América Latina y el Caribe. UNICEF. 2013. URL: https://www.unicef.org/lac/sites/unicef.org.lac/files/2018-05/20150612_UNICEF_LACRO_Estudio_promocion_alimentos_no_saludables_LAC_Resumen.pdf [accessed 2024-01-01]
14. Population-based approaches to childhood obesity prevention. World Health Organization. 2012. URL: https://iris.who.int/handle/10665/80149 [accessed 2024-03-07]
15. Lima M, Ares G, Deliza R. How do front of pack nutrition labels affect healthfulness perception of foods targeted at children? Insights from Brazilian children and parents. Food Qual Prefer 2018 Mar;64:111-119. [doi: 10.1016/j.foodqual.2017.10.003]
16. Hawley KL, Roberto CA, Bragg MA, Liu PJ, Schwartz MB, Brownell KD. The science on front-of-package food labels. Public Health Nutr 2012 Mar 22;16(3):430-439. [doi: 10.1017/s1368980012000754]
17. Tarabashkina L, Quester P, Crouch R. Exploring the moderating effect of children's nutritional knowledge on the relationship between product evaluations and food choice. Soc Sci Med 2016 Jan;149:145-152. [doi: 10.1016/j.socscimed.2015.11.046] [Medline: 26717561]
18. West JH, Belvedere LM, Andreasen R, Frandsen C, Hall PC, Crookston BT. Controlling your "app"etite: how diet and nutrition-related mobile apps lead to behavior change. JMIR Mhealth Uhealth 2017 Jul 10;5(7):e95. [doi: 10.2196/mhealth.7410] [Medline: 28694241]
19. Turner-McGrievy GM, Beets MW, Moore JB, Kaczynski AT, Barr-Anderson DJ, Tate DF. Comparison of traditional versus mobile app self-monitoring of physical activity and dietary intake among overweight adults participating in an mHealth weight loss program. J Am Med Inform Assoc 2013 May 01;20(3):513-518. [doi: 10.1136/amiajnl-2012-001510] [Medline: 23429637]
20. Encuesta Nacional Sobre Disponibilidad Y Uso De Tecnologías De La Información En Los Hogares (ENDUTIH) [Article in Spanish]. Instituto Nacional de Estadística y Geografía. 2022. URL: https://www.inegi.org.mx/programas/dutih/2022/ [accessed 2023-12-30]
21. García-Cuéllar M, Ochoa-Tello L, Atrián-Salazar M, Palacio-Mejía L, Hernández-Ávila J, González-González E. Web Tools 2.0 for health promotion in Mexico. JART 2013 Oct;11(5):708-713. [doi: 10.1016/s1665-6423(13)71579-7]
22. Jáuregui A, Pacheco-Miranda S, Ayvar-Gama Y, Alejandro-Torres NZ, Cuno A, Espinosa-de Candido AF, et al. Diseño de una estrategia de comunicación para la promoción del uso del etiquetado de advertencia en niños, niñas y adolescentes mexicanos. Salud Publica Mex 2023 Jan 02;65(1, ene-feb):70-81 [FREE Full text] [doi: 10.21149/14120] [Medline: 36750070]
23. Applicate por tu Salud. URL: https://www.viviendo-saludable.org/ [accessed 2024-03-13]

24. Vanderlee L, Franco-Arellano B, Ahmed M, Oh A, Lou W, L'Abbé MR. The efficacy of 'high in' warning labels, health star and traffic light front-of-package labelling: an online randomised control trial. Public Health Nutr 2020 Oct 06;24(1):62-74. [doi: 10.1017/s1368980020003213]
25. Jáuregui A, Vargas-Meza J, Nieto C, Contreras-Manzano A, Alejandro NZ, Tolentino-Mayo L, et al. Impact of front-of-pack nutrition labels on consumer purchasing intentions: a randomized experiment in low- and middle-income Mexican adults. BMC Public Health 2020 Apr 06;20(1):463 [FREE Full text] [doi: 10.1186/s12889-020-08549-0] [Medline: 32252716]
26. Machín L, Curutchet MR, Giménez A, Aschemann-Witzel J, Ares G. Do nutritional warnings do their work? Results from a choice experiment involving snack products. Food Qual Prefer 2019 Oct;77:159-165. [doi: 10.1016/j.foodqual.2019.05.012]
27. Musicus AA, Roberto CA, Moran AJ, Sorscher S, Greenthal E, Rimm EB. Effect of front-of-package information, fruit imagery, and high-added sugar warning labels on parent beverage choices for children: a randomized clinical trial. JAMA Netw Open 2022 Oct 03;5(10):e2236384 [FREE Full text] [doi: 10.1001/jamanetworkopen.2022.36384] [Medline: 36227595]

Edited by A Mavragani; submitted 21.11.23; this is a non–peer-reviewed article;accepted 23.02.24; published 01.04.24.

Please cite as:
Avila-Montiel D, Vilchis-Gil J, Miranda-Lora AL, Velázquez-López L, Klünder-Klünder M
The Effects of an Educational Intervention About Front-of-Package Labeling on Food and Beverage Selection Among Children and Their Caregivers: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2024;13:e54783
URL: https://www.researchprotocols.org/2024/1/e54783
doi:10.2196/54783
PMID:38557591

Protocol

Investigating the Impact of AI on Shared Decision-Making in Post-Kidney Transplant Care (PRIMA-AI): Protocol for a Randomized Controlled Trial

Bilgin Osmanodja[1], Dr med; Zeineb Sassi[2], MA; Sascha Eickmann[2], MSc; Carla Maria Hansen[1], Dr med; Roland Roller[3], PhD; Aljoscha Burchardt[3], PhD; David Samhammer[4], PhD; Peter Dabrock[4], PhD; Sebastian Möller[3,5], PhD; Klemens Budde[1], Dr med; Anne Herrmann[2,6], PhD

[1]Department of Nephrology and Medical Intensive Care, Charité – Universitätsmedizin Berlin, Berlin, Germany

[2]Department of Epidemiology and Preventive Medicine, Medical Sociology, University Regensburg, Regensburg, Germany

[3]German Research Center for Artificial Intelligence, Berlin, Germany

[4]Institute for Systematic Theology II (Ethics), Friedrich-Alexander University Erlangen Nürnberg, Erlangen, Germany

[5]Quality and Usability Lab, Technical University of Berlin, Berlin, Germany

[6]School of Medicine and Public Health, University of Newcastle, Callaghan, Australia

Corresponding Author:
Bilgin Osmanodja, Dr med
Department of Nephrology and Medical Intensive Care
Charité – Universitätsmedizin Berlin
Charitéplatz 1
Berlin, 10117
Germany
Phone: 49 30450614368
Email: bilgin.osmanodja@charite.de

Abstract

Background: Patients after kidney transplantation eventually face the risk of graft loss with the concomitant need for dialysis or retransplantation. Choosing the right kidney replacement therapy after graft loss is an important preference-sensitive decision for kidney transplant recipients. However, the rate of conversations about treatment options after kidney graft loss has been shown to be as low as 13% in previous studies. It is unknown whether the implementation of artificial intelligence (AI)–based risk prediction models can increase the number of conversations about treatment options after graft loss and how this might influence the associated shared decision-making (SDM).

Objective: This study aims to explore the impact of AI-based risk prediction for the risk of graft loss on the frequency of conversations about the treatment options after graft loss, as well as the associated SDM process.

Methods: This is a 2-year, prospective, randomized, 2-armed, parallel-group, single-center trial in a German kidney transplant center. All patients will receive the same routine post–kidney transplant care that usually includes follow-up visits every 3 months at the kidney transplant center. For patients in the intervention arm, physicians will be assisted by a validated and previously published AI-based risk prediction system that estimates the risk for graft loss in the next year, starting from 3 months after randomization until 24 months after randomization. The study population will consist of 122 kidney transplant recipients >12 months after transplantation, who are at least 18 years of age, are able to communicate in German, and have an estimated glomerular filtration rate <30 mL/min/1.73 m^2. Patients with multi-organ transplantation, or who are not able to communicate in German, as well as underage patients, cannot participate. For the primary end point, the proportion of patients who have had a conversation about their treatment options after graft loss is compared at 12 months after randomization. Additionally, 2 different assessment tools for SDM, the CollaboRATE mean score and the Control Preference Scale, are compared between the 2 groups at 12 months and 24 months after randomization. Furthermore, recordings of patient-physician conversations, as well as semistructured interviews with patients, support persons, and physicians, are performed to support the quantitative results.

Results: The enrollment for the study is ongoing. The first results are expected to be submitted for publication in 2025.

Conclusions: This is the first study to examine the influence of AI-based risk prediction on physician-patient interaction in the context of kidney transplantation. We use a mixed methods approach by combining a randomized design with a simple quantitative end point (frequency of conversations), different quantitative measurements for SDM, and several qualitative research methods

(eg, records of physician-patient conversations and semistructured interviews) to examine the implementation of AI-based risk prediction in the clinic.

Trial Registration: ClinicalTrials.gov NCT06056518; https://clinicaltrials.gov/study/NCT06056518

International Registered Report Identifier (IRRID): PRR1-10.2196/54857

(JMIR Res Protoc 2024;13:e54857) doi:10.2196/54857

KEYWORDS

shared decision-making; SDM; kidney transplantation; artificial intelligence; AI; decision-support system; DSS; qualitative research

Introduction

Shared decision-making (SDM) is increasingly important in health policy and clinical practice. Over the past decades, researchers, patient advocates, and policymakers all over the world have increased efforts to shift health care from a paternalistic to a patient-centered approach, focusing on the patient as a person [1,2]. Kidney transplantation is the most frequently performed solid organ transplantation and although the application of SDM prior to kidney transplantation has been discussed, little is known about how to improve SDM after transplantation [3]. This is surprising as there are numerous potentially preference-sensitive decisions that patients, support persons, and physicians have to make in this setting, for instance relating to the management of comorbidities, effects of treatment on fertility, use of immunosuppressant drugs, and resulting second cancers [4,5].

In patients with chronic kidney disease, choosing the right kidney replacement therapy and the optimal timing for kidney replacement therapy is an important preference-sensitive decision. Implementing SDM has been shown to leave more patients satisfied with their choice of dialysis modality [6]. Not only the modality itself but also details like the vascular access and the specific dialysis regimen are preference-sensitive and should be part of an SDM process that also considers age-dependent needs [7-9].

Since most patients after kidney transplantation eventually face the risk of graft loss with the concomitant need for dialysis or retransplantation, comparable considerations should be applied to kidney transplant recipients at risk for graft loss. However, the rate of conversations about treatment options after kidney graft loss is as low as 13% in conventional physician-centered care settings [10]. This leaves room for optimization with respect to the frequency of conversations as well as the associated SDM process. While care-based interventions have shown to be effective in increasing the frequency of conversations about treatment options after graft loss, it is unknown whether the implementation of artificial intelligence (AI)–based risk prediction models can have such influence on physician-patient interactions [10].

Different risk prediction models for graft loss using methods of statistics or AI have been introduced and show good predictive performance [11,12]. More importantly, they are more accurate than experienced physicians in predicting risks for graft loss [11,13]. Implementing such models into routine care could indicate patients at risk for graft loss and thereby increase the frequency of conversations about treatment options after graft loss. However, little is known about the impact of AI-based interventions on the interaction between patients, support persons, and physicians [14].

While there are several studies discussing the potential of AI to support SDM in the bioethical literature [15], there is a lack of empirical studies to systematically investigate the impact of AI on SDM [16].

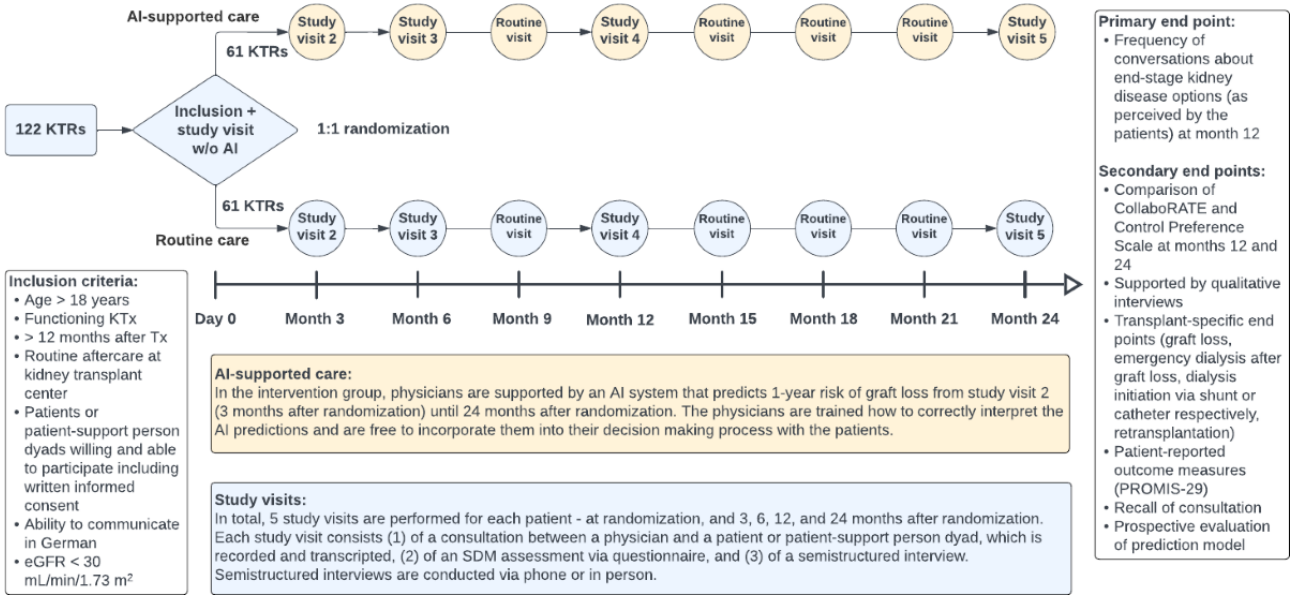
In this study, we aim to evaluate the influence of an AI-based risk prediction model for 1-year risk of graft loss on the frequency of conversations about treatment options after graft loss, as well as the associated SDM process, in patients who had kidney transplants with low estimated glomerular filtration rate (eGFR).

Methods

Study Design and Setting

The Prospectively investigating the Impact of AI on Shared Decision-Making in Post-Kidney Transplant Care (PRIMA-AI) trial is a 2-year, prospective, randomized, 2-armed, parallel-group, single-center trial in a German kidney transplant center (KTC). Patients more than 12 months after kidney transplantation with eGFR <30 mL/min/1.73 m^2 and support persons will be randomized to routine care or to AI-supported care in a 1:1 ratio. During the study, 5 study visits are planned at the KTC—at randomization, and 3, 6, 12, and 24 months after randomization (Figure 1). In both groups, routine care visits will be scheduled as needed, depending on the patient's medical condition and time posttransplant, which is usually every 3 months.

Figure 1. Study flowchart summarizing inclusion criteria, interventions, and end points. An estimated number of 122 KTRs will be recruited in the outpatient clinic of a tertiary care center and randomized 1:1 into routine care or AI-supported care and followed up over 24 months. AI: artificial intelligence; eGFR: estimated glomerular filtration rate; KTR: kidney transplant recipient; KTx: kidney transplantation; PROMIS-29: Patient Reported Outcomes Measurement Information System 29; SDM: shared decision-making; Tx: transplantation.



Recruitment Process

Patients after kidney transplantation regularly undergo routine follow-up at the KTC in an outpatient clinic. Patient data are available in a proprietary electronic health record that allows data extraction for research purposes [17]. Patients who are potentially eligible for the study based on their previous medical data will be contacted via telephone 1 week before their next scheduled appointment and will be asked if they are interested in study participation. If patients are potentially interested, they are provided detailed information about the study by trained study physicians and provide written informed consent after checking inclusion and exclusion criteria at the time of their next outpatient visit at the KTC. Recruitment will occur in the regular outpatient treatment at the KTC by designated study physicians who are not the treating physicians. After recruitment and randomization, the first study visit is performed. No study investigations are performed before written informed consent is obtained from the patients. The KTC is a tertiary care center specializing in kidney transplantation, where approximately 200 kidney transplantations per year are performed.

Participants

Participants may enter the trial if all the following apply: (1) they provide written informed consent, (2) they are patients with a functioning kidney allograft, (3) it has been at least 12 months after kidney transplantation, (4) they have an eGFR <30 mL/min/1.73 m^2 according to Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2021 formula, (5) they are aged at least 18 years, (6) they can communicate in German, and (7) they attend regular follow-ups at KTC. Participants may not enter the trial if any of the following apply: (1) they have undergone multi-organ transplantation, (2) it has been less than 12 months after kidney transplantation, (3) they have an eGFR >30 mL/min/1.73 m^2 according to CKD-EPI 2021 formula, (4) they are aged less than 18 years, (5) they cannot communicate in German, (6) they do not attend regular follow-ups at KTC, and (7) they enrolled in another interventional study less than 1 month before participation in this study. Additionally, support persons will be eligible if they are nominated by the patient as someone helping them cope with the consequences of their kidney transplant through support, encouragement, and communication. Support persons will be aged 18 years or older, German-speaking, and able to provide informed consent. Treating physicians who work at the participating clinics and use the AI-based decision-support system (DSS) will be eligible to participate in the study. Clinic staff will record the age and gender of nonconsenters who provided permission, which allows for the examination of consent bias.

Sample Size

The primary analysis will be performed based on the frequency of conversations about treatment options after graft loss as perceived by the patient, which is assessed in a questionnaire after the respective consultation. Based on the data from Bissonnette et al [10], we estimate that in the control group, 10%-15% of patients will have a conversation about therapy options at the end of graft function. Regarding the intervention studied herein, we estimate that this frequency can be increased to 40%-45%, which is half of the effect size achieved by Bissonnette et al [10]. Using a 2-sided χ^2 test, an α error of .05, and a power of 80%, 25-49 patients per group are needed. Estimating a dropout rate of 10% per year, this increases to 31-61 patients per group. Therefore, 61 patients per group were regarded as sufficient. In order to identify 122 participating patients, local study personnel will have to screen approximately 150 potentially eligible kidney transplant recipients over a period of 6 months.

Randomization

Randomization will be performed using a predefined variable block randomization scheme using a web-based randomization

service [18]. After screening for eligibility and assignment of the individual patient identifier, each patient-support person dyad can only be assigned once to 1 of the treatment arms. The sites will record the time of randomization.

Blinding

Blinding of participants and study staff is not possible given the nature of the intervention.

Intervention

Control Group: Routine Care

Routine care will be scheduled according to the current standard of care [19], which depends on the time after transplantation, medical condition, and other individual factors. Standard immunosuppression will be applied according to the international recommendations [20]. The prophylaxis and treatment of infections will follow the current standard of care as outlined in recent guidelines [21-26], for example, *Pneumocystis jirovecii* pneumonia prophylaxis for 4 to 6 months, cytomegalovirus prophylaxis according to the guidelines, and regular posttransplant BK virus monitoring according to guidelines [19]. Screenings for the antibodies against human leukocyte antigen once within the first 3 months, after 1 year, and every year thereafter, as well as in case of suspected rejection [27]. The overall medical treatment of kidney transplant recipients will be performed according to the Kidney Disease Improving Global Outcomes guidelines [19] and in patients with suspected rejection, a kidney biopsy should be performed and classified according to the most recent Banff criteria [28]. An integral part of the current routine aftercare is regular visits to the home nephrologist and KTC, where data are captured in an electronic health record [17]. Table 1 highlights the proposed schedule for posttransplant aftercare. The proposed schedule is adapted to the individual patient's needs.

Table 1. Frequency of routine visits in the outpatient clinic of the kidney transplant center (KTC) depending on time after transplantation.

Time after transplantation	Frequency of routine visits
Month 1	Once per week after discharge at the KTC
Month 2	Once per week
Month 3	Once per 2 weeks
Months 4 to 6	Once per 3 weeks
Months 6 to 12	Once per month
After 12 months	Once every 3 months

Intervention Group: AI-Supported Care

The kidney transplant recipients, who are randomized to the interventional arm, will receive identical routine posttransplant care as patients in the control group (see Table 1). In addition, the physicians in the KTC will be provided an AI-based decision support system making predictions for the risk of graft loss based on the patient's most recent clinical, laboratory, and histopathology data, beginning from the second visit. A previous version of the AI-based decision support system has been studied in silico and in a reader study [11]. The physicians are provided a recommendation on how to proceed in case of a high-risk score. Briefly, physicians are recommended to inform the patients about this risk and discuss the potential necessity of return to dialysis or retransplantation, as well as planning, which mode of renal replacement therapy is preferred by the patient (hemodialysis, peritoneal dialysis, or listing for retransplantation by living donation). Depending on the patient's preference, preparation for a smooth transition to dialysis or retransplantation should be performed.

Outcomes

Primary End Points

For the primary end point, the frequency of conversations about treatment options after graft loss as perceived by the patient will be compared between the 2 groups at 12 months after randomization.

Secondary End Points

As the main secondary end points, the 2 different assessment tools for SDM, the CollaboRATE mean score and the Control Preference Scale (CPS; adapted version as used in previous studies [29]), are compared between the 2 groups at 12 months after randomization. The CPS is widely used as a validated tool to assess involvement in SDM [29,30]. However, it has been suggested that CPS may be misleading in some contexts of medical decision-making since it does refer explicitly to a "decision," whereas, CollaboRATE is a brief process-orientated measure that recognizes that study participants may not always realize that a decision has been made or have difficulties focusing on 1 decision in the context of a complex care experience [31,32]. CollaboRATE has shown discriminative validity and interrater reliability. To supplement the quantitative outcome measures, qualitative data collection in the form of interviews will be performed and analyzed. All questionnaires and interview guides will be developed with the help of a multidisciplinary research group and pilot tested with patients and support persons to optimize acceptability and feasibility. Other secondary end points are summarized in Textbox 1.

Textbox 1. Secondary end points and time frame after which they are assessed

End points

- CollaboRATE mean score of all study visits from study inclusion until month 12 (values 0-9, higher values indicating better outcome)
- CollaboRATE mean score of all study visits from study inclusion until month 24 (values 0-9, higher values indicating better outcome)
- Mean Control Preferences Scale of all study visits from study inclusion until month 12 (values 1-5, higher values indicating better outcome)
- Mean Control Preferences Scale of all study visits from study inclusion until month 24 (values 1-5, higher values indicating better outcome)
- Frequency of kidney replacement therapy after graft loss at 12 months
- Frequency of kidney replacement therapy after graft loss at 24 months
- Frequency of emergency dialysis after graft loss at 12 months
- Frequency of emergency dialysis after graft loss at 24 months
- Frequency of dialysis initiation via arteriovenous-shunt after graft loss at 12 months
- Frequency of dialysis initiation via arteriovenous-shunt after graft loss at 24 months
- Frequency of dialysis initiation via permanent catheter after graft loss at 12 months
- Frequency of dialysis initiation via permanent catheter after graft loss at 24 months
- Frequency of retransplantation after graft loss at 12 months
- Frequency of retransplantation after graft loss at 24 months
- Qualitative analysis of semistructured interviews after at 24 months
- Qualitative analysis of physician-patient conversations after at 24 months
- Frequency of conversations about treatment options after graft loss as perceived by the patient will be compared between the 2 groups at 24 months

Procedures

Overview

The study plan is summarized in Table 2.

Table 2. Study plan including the data and time points at which these are assessed.

Data	Day 0 (visit 1)	Month 3 (visit 2)	Month 6 (visit 3)	Month 12 (visit 4)	Month 24 (visit 5)
Consent	✓				
Inclusion or exclusion criteria	✓				
Randomization	✓				
AI[a] system (intervention group)		✓	✓	✓	✓
Demography, transplant data, medical history, and height	✓	✓	✓	✓	✓
CollaboRATE score	✓	✓	✓	✓	✓
Control preferences scale	✓	✓	✓	✓	✓
Qualitative interviews	✓	✓	✓	✓	✓
Recall	✓	✓	✓	✓	✓
Vital signs (BP[b], HR[c], and weight)	✓	✓	✓	✓	✓
Safety lab	✓			✓	✓
Serum creatinine and eGFR[d]	✓	✓	✓	✓	✓
Proteinuria or albuminuria	✓	✓	✓	✓	✓
HLA[e] antibodies	✓			✓	
Tacrolimus trough level	✓	✓	✓	✓	✓
Quality of life (PROMIS-29[f])	✓	✓	✓	✓	✓
Clinical assessment	✓	✓	✓	✓	✓
AEs[g] or SAEs[h], AEs of interest, graft loss, and death	✓	✓	✓	✓	✓
Hospitalizations (reason, length, and type)	✓	✓	✓	✓	✓
Physician visits and contacts	✓	✓	✓	✓	✓
Immunosuppression	✓	✓	✓	✓	✓
Prior or concomitant medications	✓	✓	✓	✓	✓

[a]AI: artificial intelligence.

[b]BP: blood pressure.

[c]HR: heart rate.

[d]eGFR: estimated glomerular filtration rate.

[e]HLA: human leukocyte antigen.

[f]PROMIS-29: Patient Reported Outcomes Measurement Information System 29.

[g]AE: adverse event.

[h]SAE: serious adverse event.

Details of the AI-Based DSS and Recommended Procedures

An AI-based prediction model will be implemented to provide real-time predictions of the 1-year risk for graft loss based on the patient's clinical, laboratory, immunological, and histopathological data. A previous version of the prediction model has been described in detail before, and all substantial changes will be made publically available. The predictions are provided as regression scores from 0 to 100 with higher scores indicating higher risk. For ease of interpretability, each score is classified into low-, medium-, or high-risk categories, which are color-coded as green, yellow, and red. Along with the risk score and risk category over time, relevant risk factors are provided to increase interpretability for the latest risk assessment.

Physicians will undergo training, in which technical details of the underlying model (training cohort, inclusion and exclusion criteria, end point definition, and performance), and results of preclinical studies are presented [11]. Hereby, the physicians can gain familiarity with the AI-DSS and also discuss potential limitations with the developers and study physicians. These training sessions will be recorded and analyzed as part of the qualitative subproject.

During the study, the physicians are advised to use the AI-DSS as an additional source of information and be especially cautious in case of high risks detected by the AI-DSS. In any case, it will

be left to the physician's choice on how to include the system's information in the conversation with patients and support persons.

However, if the AI-DSS shows a high risk for graft loss, the physicians are free to discuss this with the patient and offer 1 procedure depending on their own assessment. First, physician—high risk for graft loss: if the physician agrees that there is a high risk of graft loss in a patient during the next year, the physician is advised to discuss this risk with the patient, when the situation is appropriate (enough time, no other major problems to be discussed, etc) or to discuss it during the next appointment. The physician should assess, whether the preferred renal replacement modality (hemodialysis, peritoneal dialysis, and retransplantation) of the patient is known and take measures to ensure a smooth transition without the need for emergency hospitalization (shunt planning, peritoneal dialysis catheter implantation, appointment for living donation, etc). Second, physician—low risk for graft loss: if the physician disagrees with the AI system and estimates a low risk for graft loss in a particular patient, the physician is advised to reconsider potential risk factors. The physician is free to incorporate or ignore the AI-DSS assessment into the SDM with patients and support persons.

Details on Qualitative Research Methodology

Overview

The physician-patient conversation will be recorded if physicians, patients, and support persons do not withdraw consent at randomization, as well as 3, 6, 12, and 24 months after randomization. Additionally, patients will be interviewed at randomization, as well as 3, 6, 12, and 24 months after randomization. Data collection at randomization, as well as 12 and 24 months after randomization will be conducted face-to-face, if possible and preferred by study participants. Data collection at 3 and 6 months after randomization will be conducted via telephone. This is to reduce the research-related burden on the participants. It has been suggested that telephone interviews produce similar quality data as face-to-face interviews [33-35]. Also, patients may appreciate being interviewed via telephone as they may feel more relaxed when being interviewed on the telephone and may find it easier to rearrange a telephone interview, rather than having to rearrange a face-to-face interview [36-39]. Participants will be encouraged to tell their views on how the AI-based DSS impacted physician-patient-support person communication and how treatment decisions were made, in the way they prefer, with as little interruption as possible from the interviewer. This narrative approach will help elicit the variety and interplay of potential factors related to treatment discussions [40]. The initial narrative will be followed by semistructured questions which will be developed based on a literature review and discussions among the research team which involves experts in the areas of medicine, communication and behavioral science, health services research, ethics, and medical informatics.

Influence of AI-Based Decision Support on the Normative Foundations of the Use of AI in SDM

Participants will be asked questions on their perceptions of concepts such as trust, agency, or transparency, for instance about how they evaluate the outputs of the tool and how these outputs relate to their physicians' judgments. Participants may also be asked to report on their views on the system's validity, effectiveness, and the perceived likelihood of errors, as well as on who is morally and legally liable for single treatment decisions.

Use of AI-Based Decision Support and Barriers and Enablers to its Implementation

Participants will be asked about their perceptions of acceptability, ease of use, agreement with specific components of the system's outputs, and self-efficacy (ie, the belief that one can understand and use the system's output). Participants will also be asked about further potential barriers to the use of AI in routine care, such as environmental factors like time pressure. These questions will be informed by the literature and discussions among the research team [41,42].

Sociodemographic and Disease Variables

Sociodemographic and disease variables obtained from patients and support persons will include gender, marital status, country of birth, postcode, highest level of education completed, income, and perceived health status. The support persons will also be asked to self-report their relationship to the patient and whether they are living with the patient. All sociodemographic and disease variables will be assessed at baseline and follow-ups to account for changes in participants' circumstances which may affect their views and experiences [43]. With patients' permission, information regarding diagnosis, disease stage, and treatments received will be obtained from patients' medical records to decrease the research-related burden on patients. At the end of the interview, participants will be given the option to provide additional comments.

Statistical Analysis

Preliminary analysis will involve computing descriptive statistics for all quantitative variables. For continuous variables, means, SDs, and quartiles will be estimated, while categorical variables will be summarized with counts and percentages in each category. Summaries will be performed by group and by assessment, as well as for the entire study group. Primary data analysis of the primary end point will involve comparing the frequencies of conversations about treatment options after graft loss between both groups using a 2-sided χ^2 test. Secondary data analysis will include a comparison in secondary outcomes between both groups using a χ^2 test. In general, test results will be described as significant if their P values are less than .05 without adjustments for multiple inferences. Multiple imputations will be used to deal with missing data.

Qualitative Research Analysis

Interviews will be transcribed verbatim. The interviews will be recorded for the purpose of transcription on provided devices and will be deleted after the end of the research process. Transcripts will be checked for accuracy by 1 researcher and

analyzed using framework analysis. This approach belongs to a broad family of qualitative data analysis methods often related to as "thematic analysis" or "qualitative content analysis" [44]. As suggested by these approaches, both manifest and latent content will be analyzed and descriptive and explanatory conclusions will be drawn from the data [45]. Each interview will serve as a unit of analysis. A journal of reasoning and additional ideas regarding data analysis will help ensure transparency in the coding process. This strategy has been extensively used to facilitate the reconstruction of the analysis and provide justification for the analytical steps undertaken [46,47]. Codes will frequently be compared with each other and parts of the material will be recoded, if necessary, as an intercoder agreement test and additional measure for reliability [48]. This method of qualitative data analysis will provide a systematic model for mapping and interpreting the data and is thus considered appropriate to develop a profound in-depth understanding of participants' communication experiences and preferences [46,49].

Data Management

Designated investigator staff must enter the information required by the protocol into the assigned database. Individual interviews, telephone interviews, and patient-physician conversations will be audio recorded, transcribed verbatim by a professional transcriptionist or a research team member, deidentified, and filed for data management and analysis. All qualitative data will be collected by a research team member with extensive experience in qualitative research.

Safety

Safety assessments will consist of monitoring and recording all adverse events (AEs) and serious AEs, the regular monitoring of blood chemistry and urine, and regular monitoring of vital signs, physical condition, and body weight. Appropriate sponsor personnel and investigators will monitor the safety of the participants throughout the conduct of the study. AEs mean "any untoward occurrence in a trial subject administered an investigational medicinal product and which does not necessarily have a causal relationship with this treatment" [50]. In the PRIMA-AI trial, subjects will not receive any investigational medicinal product, but physicians will be assisted by an AI-based decision support system. Thus, in this study, an AE can be any unfavorable and unintended sign, symptom, or disease (including concomitant illness), deterioration of a preexisting illness, accident, any suspected drug reaction, or a clinically relevant change of laboratory values whether or not considered to be related to the AI-based intervention. Adverse reactions (ARs) mean "all untoward and unintended responses to an investigational medicinal product unrelated to the dose administered" [50]. In PRIMA-AI, subjects will not receive any investigational medicinal product. Therefore, the definition of AR implies in this trial a reasonable possibility of a causal relationship between the event and the investigational AI-based intervention.

The period of observation for AEs extends from the baseline visit (month 0, visit 1) after informed consent was given until and including month 24 (visit 5). AEs have to be followed up until resolution or stabilization or until the subject's end-of-study visit (month 24, visit 5), whichever comes first. Preexisting conditions that do not worsen during the course of the study are not reportable as AE. To determine whether a condition has worsened, it is compared to the condition of the subject at baseline visit (month 0, visit 1). All AEs, whether volunteered by the patient, discovered by investigator questioning, or detected through physical examination, laboratory test, or other means will be assessed and recorded in detail in the subject's file and on the case report form, the AE report form. All AEs will be coded appropriately at the end of the clinical study using MeDRA or, in addition, on request by the study coordinator.

The following information must be recorded: (1) AE diagnosis (if possible) or main symptom; (2) date (and time, if relevant) of onset; (3) severity (maximum observed); (4) causal relationship (reasonable possibility or no reasonable possibility); (5) seriousness (yes or no); (6) outcome; (7) action taken with the study intervention; (8) AE leading to discontinuation of the study subject (yes or no); (9) treatment of AE; and (10) stop date (and time, if relevant). For the assessment of severity, the investigator should use grades from 1 to 5 as outlined in Textbox 2.

Textbox 2. Grades of assessments of severity for adverse events.

Grade 1

Mild or asymptomatic symptoms, clinical or diagnostic observations only, and intervention not indicated.

Grade 2

Moderate, minimal, local, or noninvasive intervention indicated, and limiting age-appropriate instrumental activities of daily living. Instrumental activities of daily living are activities such as preparing meals, shopping for groceries or clothes, using the telephone, managing money.

Grade 3

Severe or medically significant but not immediately life-threatening, hospitalization or prolongation of hospitalization indicated, disabling, and limiting self-care activities of daily living. Self-care activities of daily living are activities such as bathing, dressing and undressing, feeding oneself, using the toilet, taking medications, and not being bedridden.

Grade 4

Life-threatening consequences and urgent intervention indicated.

Grade 5

Death related to adverse event.

Ethical Considerations

Written informed consent will be collected from all study participants before performing any research activity by a research team member. To ensure the eligibility of a participate in the trial, the researcher will review the inclusion and exclusion criteria with potential participants prior to beginning the informed consent process. Prospective participants will be asked to personally sign and date the latest approved version of the informed consent forms before any trial procedure is performed. During the informed consent process, study participants will be informed of their right to withdraw from the study at any time without any impact on their treatment at the KTC. This study will be conducted in accordance with the tenets of the Declaration of Helsinki (1996). The ethics committee of Charité—Universitätsmedizin Berlin approved this study (EA1/177/23; August 08, 2023).

The trial results will be disseminated through a variety of strategies, including academic publications, research reports, infographics, media releases, and community events. Trial participants' anonymity and confidentiality will be protected during these activities by removing all identifiable information from the knowledge dissemination products.

Results

As of March 10, 2024, we enrolled 19 participants. The first results are expected to be submitted for publication in 2025.

Discussion

Principal Findings

This study is designed to investigate the influence of AI-based risk prediction on the frequency of conversations about treatment options after graft loss and the associated SDM process with a randomized design using a mixed methods approach. It is the first study in the context of kidney transplantation to analyze the potential effects of AI-based interventions on physician-patient interaction.

Despite tremendous enthusiasm surrounding the potential for AI to improve medical prognosis, diagnosis, and decision-making, only limited empirical data are available to help understand patients' and physicians' perspectives on how AI impacts their interactions, specifically SDM [16]. In the context of kidney transplantation, AI research has mostly focused on technical and medical challenges relating to robustness and implementation, excluding the sociotechnical environment into which such systems are embedded [12-14]. In the treatment of patients with cancer, an intervention that delivered machine learning mortality predictions with behavioral nudges to oncology clinicians significantly increased the rate of serious illness conversations [51,52]. While serious illness conversations are only in part comparable to conversations about graft loss, returning to dialysis after transplantation is also a life-changing event with serious effects on quality of life. We argue that increasing the frequency of conversation about treatment options after graft loss and improving SDM may improve patient satisfaction comparable to patients with chronic kidney disease without transplantation [6].

Strengths and Limitations

The main strength of this study is the mixed methods approach that will support the analysis of the primary end point with validated assessment tools for SDM and qualitative data from semistructured interviews. It is the first study in the context of kidney transplantation that investigates the impact of AI-based risk prediction on physician-patient interaction. While performed in a tertiary care setting, transplant nephrologists often serve as primary caregivers to kidney transplant recipients. Therefore, the results may generalize to a broader range of care settings as well. The randomized design enables to detect potential effects of the AI-based risk prediction on the conversation frequency about graft loss, which can improve patient information and patient care. It also provides us with a control group, in which SDM about treatment options after graft loss in kidney transplantation can be studied without any intervention, which has not been done so far. Another strength is the long observation time of 24 months, which enables to detect potential adaptations of physicians, patients, and support persons to the novel AI system and the emergence of a sociotechnical system in the recordings of patient-physician interactions as well as the semistructured interviews.

The main limitation is that potential effects of the AI intervention on SDM are indirect since no specific SDM intervention has been implemented and the AI system is not designed to improve SDM in particular, for example, by providing different scenarios or enabling input of patient preferences. Another potential limitation is that participation in the trial may influence physicians to talk about treatment options after graft loss, which may reduce the potential effect size of the AI intervention. Furthermore, the open-label design, which is unavoidable, introduces the possibility of bias, especially since the primary end point is not a medical end point.

Conclusions

In conclusion, this study will generate novel and important data about the impact of AI on physician-patient interaction and SDM in the context of kidney transplantation, which may be applicable to other disease contexts as well.

Acknowledgments

This work is supported by German Federal Ministry of Education and Research grants (01GP2202A, 01GP2202B, 01GP2202C, and 01GP2202D). No generative artificial intelligence was used to write this paper.

Data Availability

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

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the German Federal Ministry of Education and Research.
[PDF File (Adobe PDF File), 367 KB - resprot_v13i1e54857_app1.pdf]

References

1. Gerteis M, Edgman-Levitan S, Daley J, Delbanco TL. Through the Patient's Eyes: Understanding and Promoting Patient-Centered Care. San Francisco, CA: Jossey-Bass; 1993.
2. Härter M, van der Weijden T, Elwyn G. Policy and practice developments in the implementation of shared decision making: an international perspective. Z Evid Fortbild Qual Gesundhwes 2011;105(4):229-233. [doi: 10.1016/j.zefq.2011.04.018] [Medline: 21620313]
3. Gordon EJ, Butt Z, Jensen SE, Lehr ALM, Franklin J, Becker Y, et al. Opportunities for shared decision making in kidney transplantation. Am J Transplant 2013;13(5):1149-1158 [FREE Full text] [doi: 10.1111/ajt.12195] [Medline: 23489435]
4. Cassidy BP, Getchell LE, Harwood L, Hemmett J, Moist LM. Barriers to education and shared decision making in the chronic kidney disease population: a narrative review. Can J Kidney Health Dis 2018;5:2054358118803322 [FREE Full text] [doi: 10.1177/2054358118803322] [Medline: 30542621]
5. Tuso P. Choosing wisely and beyond: shared decision making and chronic kidney disease. Perm J 2013;17(4):75-78 [FREE Full text] [doi: 10.7812/tpp/13-006] [Medline: 24361024]
6. Yu X, Nakayama M, Wu MS, Kim YL, Mushahar L, Szeto CC, et al. Shared decision-making for a dialysis modality. Kidney Int Rep 2022;7(1):15-27 [FREE Full text] [doi: 10.1016/j.ekir.2021.10.019] [Medline: 35005310]
7. Auguste BL, Bargman JM. Peritoneal dialysis prescription and adequacy in clinical practice: core curriculum 2023. Am J Kidney Dis 2023;81(1):100-109 [FREE Full text] [doi: 10.1053/j.ajkd.2022.07.004] [Medline: 36208963]
8. Kanbay M, Basile C, Battaglia Y, Mantovani A, Yavuz F, Pizzarelli F, et al. Shared decision making in patients with kidney failure. Nephrol Dial Transplant 2023:gfad211 [FREE Full text] [doi: 10.1093/ndt/gfad211] [Medline: 37742209]
9. Murea M, Grey CR, Lok CE. Shared decision-making in hemodialysis vascular access practice. Kidney Int 2021;100(4):799-808 [FREE Full text] [doi: 10.1016/j.kint.2021.05.041] [Medline: 34246655]
10. Bissonnette J, Woodend K, Davies B, Stacey D, Knoll GA. Evaluation of a collaborative chronic care approach to improve outcomes in kidney transplant recipients. Clin Transplant 2013;27(2):232-238. [doi: 10.1111/ctr.12068] [Medline: 23330974]
11. Roller R, Mayrdorfer M, Duettmann W, Naik MG, Schmidt D, Halleck F, et al. Evaluation of a clinical decision support system for detection of patients at risk after kidney transplantation. Front Public Health 2022;10:979448 [FREE Full text] [doi: 10.3389/fpubh.2022.979448] [Medline: 36388342]
12. Loupy A, Aubert O, Orandi BJ, Naesens M, Bouatou Y, Raynaud M, et al. Prediction system for risk of allograft loss in patients receiving kidney transplants: international derivation and validation study. BMJ 2019;366:l4923 [FREE Full text] [doi: 10.1136/bmj.l4923] [Medline: 31530561]
13. Divard G, Raynaud M, Tatapudi VS, Abdalla B, Bailly E, Assayag M, et al. Comparison of artificial intelligence and human-based prediction and stratification of the risk of long-term kidney allograft failure. Commun Med 2022;2(1):150 [FREE Full text] [doi: 10.1038/s43856-022-00201-9] [Medline: 36418380]
14. Ho CWL, Caals K. A call for an ethics and governance action plan to harness the power of artificial intelligence and digitalization in nephrology. Semin Nephrol 2021;41(3):282-293 [FREE Full text] [doi: 10.1016/j.semnephrol.2021.05.009] [Medline: 34330368]
15. Lorenzini G, Arbelaez Ossa L, Shaw DM, Elger BS. Artificial intelligence and the doctor-patient relationship expanding the paradigm of shared decision making. Bioethics 2023 Jun;37(5):424-429 [FREE Full text] [doi: 10.1111/bioe.13158] [Medline: 36964989]
16. Rahimi SA, Cwintal M, Huang Y, Ghadiri P, Grad R, Poenaru D, et al. Application of artificial intelligence in shared decision making: scoping review. JMIR Med Inform 2022;10(8):e36199 [FREE Full text] [doi: 10.2196/36199] [Medline: 35943793]
17. Schmidt D, Osmanodja B, Pfefferkorn M, Graf V, Raschke D, Duettmann W, et al. TBase—an integrated electronic health record and research database for kidney transplant recipients. J Vis Exp 2021(170):e61971. [doi: 10.3791/61971] [Medline: 33938875]
18. Simple randomisation service. Sealed Envelope Ltd. 2022. URL: https://www.sealedenvelope.com/simple-randomiser/v1/ [accessed 2024-03-07]

19. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant 2009;9(Suppl 3):S1-S155 [FREE Full text] [doi: 10.1111/j.1600-6143.2009.02834.x] [Medline: 19845597]
20. Kälble T, Lucan M, Nicita G, Sells R, Revilla FJB, Wiesel M. EAU guidelines on renal transplantation. Eur Urol 2005;47(2):156-166. [doi: 10.1016/j.eururo.2004.02.009] [Medline: 15661409]
21. Kotton CN. Updates on antiviral drugs for cytomegalovirus prevention and treatment. Curr Opin Organ Transplant 2019;24(4):469-475. [doi: 10.1097/MOT.0000000000000666] [Medline: 31157669]
22. Kotton CN, Kumar D, Caliendo AM, Huprikar S, Chou S, Danziger-Isakov L, et al. The third international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. Transplantation 2018;102(6):900-931 [FREE Full text] [doi: 10.1097/TP.0000000000002191] [Medline: 29596116]
23. Allen UD, Preiksaitis JK, AST Infectious Diseases Community of Practice. Post-transplant lymphoproliferative disorders, Epstein-Barr virus infection, and disease in solid organ transplantation: guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant 2019;33(9):e13652. [doi: 10.1111/ctr.13652] [Medline: 31230381]
24. Pergam SA, Limaye AP, AST Infectious Diseases Community of Practice. Varicella zoster virus in solid organ transplantation: guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant 2019;33(9):e13622. [doi: 10.1111/ctr.13622] [Medline: 31162727]
25. Fishman JA, Gans H, AST Infectious Diseases Community of Practice. Pneumocystis jiroveci in solid organ transplantation: guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant 2019;33(9):e13587. [doi: 10.1111/ctr.13587] [Medline: 31077616]
26. Hirsch HH, Randhawa PS, AST Infectious Diseases Community of Practice. BK polyomavirus in solid organ transplantation-guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant 2019;33(9):e13528. [doi: 10.1111/ctr.13528] [Medline: 30859620]
27. Unterrainer C, Döhler B, Niemann M, Lachmann N, Süsal C. Can PIRCHE-II matching outmatch traditional HLA matching? Front Immunol 2021;12:631246 [FREE Full text] [doi: 10.3389/fimmu.2021.631246] [Medline: 33717167]
28. Loupy A, Haas M, Roufosse C, Naesens M, Adam B, Afrouzian M, et al. The Banff 2019 Kidney Meeting Report (I): updates on and clarification of criteria for T cell- and antibody-mediated rejection. Am J Transplant 2020;20(9):2318-2331 [FREE Full text] [doi: 10.1111/ajt.15898] [Medline: 32463180]
29. Tariman JD, Berry DL, Cochrane B, Doorenbos A, Schepp K. Preferred and actual participation roles during health care decision making in persons with cancer: a systematic review. Ann Oncol 2010;21(6):1145-1151 [FREE Full text] [doi: 10.1093/annonc/mdp534] [Medline: 19940010]
30. Singh JA, Sloan JA, Atherton PJ, Smith T, Hack TF, Huschka MM, et al. Preferred roles in treatment decision making among patients with cancer: a pooled analysis of studies using the control preferences scale. Am J Manag Care 2010;16(9):688-696 [FREE Full text] [Medline: 20873956]
31. Barr PJ, Thompson R, Walsh T, Grande SW, Ozanne EM, Elwyn G. The psychometric properties of CollaboRATE: a fast and frugal patient-reported measure of the shared decision-making process. J Med Internet Res 2014;16(1):e2 [FREE Full text] [doi: 10.2196/jmir.3085] [Medline: 24389354]
32. Elwyn G, Barr PJ, Grande SW, Thompson R, Walsh T, Ozanne EM. Developing CollaboRATE: a fast and frugal patient-reported measure of shared decision making in clinical encounters. Patient Educ Couns 2013;93(1):102-107 [FREE Full text] [doi: 10.1016/j.pec.2013.05.009] [Medline: 23768763]
33. Holt A. Using the telephone for narrative interviewing: a research note. Qual Res 2010;10(1):113-121. [doi: 10.1177/1468794109348686]
34. Irvine A. Duration, dominance and depth in telephone and face-to-face interviews: a comparative exploration. Int J Qual Methods 2011;10(3):202-220 [FREE Full text] [doi: 10.1177/160940691101000302]
35. Novick G. Is there a bias against telephone interviews in qualitative research? Res Nurs Health 2008;31(4):391-398 [FREE Full text] [doi: 10.1002/nur.20259] [Medline: 18203128]
36. Herrmann A, Boyle F, Butow P, Hall AE, Zdenkowski N. Exploring women's experiences with a decision aid for neoadjuvant systemic therapy for operable breast cancer. Health Sci Rep 2018;1(1):e13 [FREE Full text] [doi: 10.1002/hsr2.13] [Medline: 30623032]
37. Herrmann A, Hall A, Proietto A. Using the health belief model to explore why women decide for or against the removal of their ovaries to reduce their risk of developing cancer. BMC Womens Health 2018;18(1):184 [FREE Full text] [doi: 10.1186/s12905-018-0673-2] [Medline: 30428865]
38. Herrmann A, Hall A, Zdenkowski N. Women's experiences with deciding on neoadjuvant systemic therapy for operable breast cancer: a qualitative study. Asia Pac J Oncol Nurs 2018;5(1):68-76 [FREE Full text] [doi: 10.4103/apjon.apjon_60_17] [Medline: 29379837]
39. Herrmann A, Mansfield E, Tzelepis F, Lynagh M, Hall A. Use of the supportive care framework to explore haematological cancer survivors' unmet needs: a qualitative study. BMC Health Serv Res 2020;20(1):1062 [FREE Full text] [doi: 10.1186/s12913-020-05927-7] [Medline: 33228652]

40. Przyborski A, Wohlrab-Sahr M. Qualitative Sozialforschung: Ein Arbeitsbuch. Munich, Germany: Oldenbourg Wissenschaftsverlag; 2014.
41. Légaré F, Ratté S, Gravel K, Graham ID. Barriers and facilitators to implementing shared decision-making in clinical practice: update of a systematic review of health professionals' perceptions. Patient Educ Couns 2008;73(3):526-535. [doi: 10.1016/j.pec.2008.07.018] [Medline: 18752915]
42. Holmes-Rovner M, Nelson WL, Pignone M, Elwyn G, Rovner DR, O'Connor AM, et al. Are patient decision aids the best way to improve clinical decision making? Report of the IPDAS symposium. Med Decis Making 2007;27(5):599-608. [doi: 10.1177/0272989X07307272] [Medline: 17873257]
43. Butow PN, Maclean M, Dunn SM, Tattersall MH, Boyer MJ. The dynamics of change: cancer patients' preferences for information, involvement and support. Ann Oncol 1997;8(9):857-863 [FREE Full text] [doi: 10.1023/a:1008284006045] [Medline: 9358935]
44. Draucker CB, Martsolf DS, Ross R, Rusk TB. Theoretical sampling and category development in grounded theory. Qual Health Res 2007;17(8):1137-1148. [doi: 10.1177/1049732307308450] [Medline: 17928484]
45. Graneheim UH, Lundman B. Qualitative content analysis in nursing research: concepts, procedures and measures to achieve trustworthiness. Nurse Educ Today 2004;24(2):105-112. [doi: 10.1016/j.nedt.2003.10.001] [Medline: 14769454]
46. Gale NK, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. BMC Med Res Methodol 2013;13:117 [FREE Full text] [doi: 10.1186/1471-2288-13-117] [Medline: 24047204]
47. Denzin NK, Lincoln YS. Strategies of Qualitative Inquiry. Thousand Oaks, CA: Sage Publications; 1998.
48. Willig C, Rogers WS. The SAGE Handbook of Qualitative Research in Psychology. Thousand Oaks, CA: Sage Publications; 2017.
49. Hsieh HF, Shannon SE. Three approaches to qualitative content analysis. Qual Health Res 2005;15(9):1277-1288. [doi: 10.1177/1049732305276687] [Medline: 16204405]
50. Verordnung über die Anwendung der Guten Klinischen Praxis bei der Durchführung von klinischen Prüfungen mit Arzneimitteln zur Anwendung am Menschen (GCP-Verordnung). GCP-Verordnung. 2004 Aug 9. URL: https://beck-online.beck.de/Dokument?vpath=bibdata%2Fges%2Fgcpv%2Fcont%2Fgcpv.htm&anchor=Y-100-G-GCPV [accessed 2024-03-12]
51. Manz CR, Parikh RB, Small DS, Evans CN, Chivers C, Regli SH, et al. Effect of integrating machine learning mortality estimates with behavioral nudges to clinicians on serious illness conversations among patients with cancer: a stepped-wedge cluster randomized clinical trial. JAMA Oncol 2020;6(12):e204759 [FREE Full text] [doi: 10.1001/jamaoncol.2020.4759] [Medline: 33057696]
52. Manz CR, Zhang Y, Chen K, Long Q, Small DS, Evans CN, et al. Long-term effect of machine learning-triggered behavioral nudges on serious illness conversations and end-of-life outcomes among patients with cancer: a randomized clinical trial. JAMA Oncol 2023;9(3):414-418 [FREE Full text] [doi: 10.1001/jamaoncol.2022.6303] [Medline: 36633868]

Abbreviations

AE: adverse event
AI: artificial intelligence
AR: adverse reaction
CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration
CPS: Control Preference Scale
DSS: decision-support system
eGFR: estimated glomerular filtration rate
KTC: kidney transplant center
PRIMA-AI: Prospectively investigating the Impact of AI on Shared Decision-Making in Post-Kidney Transplant Care
SDM: shared decision-making

Edited by A Mavragani; submitted 24.11.23; this is a non–peer-reviewed article;accepted 05.02.24; published 01.04.24.

Please cite as:
Osmanodja B, Sassi Z, Eickmann S, Hansen CM, Roller R, Burchardt A, Samhammer D, Dabrock P, Möller S, Budde K, Herrmann A
Investigating the Impact of AI on Shared Decision-Making in Post-Kidney Transplant Care (PRIMA-AI): Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2024;13:e54857
URL: https://www.researchprotocols.org/2024/1/e54857
doi:10.2196/54857
PMID:38557315

Protocol

Combined Motivational Interviewing and Ecological Momentary Intervention to Reduce Hazardous Alcohol Use Among Sexual Minority Cisgender Men and Transgender Individuals: Protocol for a Randomized Controlled Trial

Carolyn Lauckner[1*], PhD; Bryce Puesta Takenaka[2], MPH; Fidelis Sesenu[1], MPhil; Jaime S Brown[1], BA; Sally J Kirklewski[2], MEd; Erin Nicholson[2], MPH; Kimberly Haney[1], MLS; Reuben Adatorwovor[3], PhD; Donte T Boyd[4,5], MSW, PhD; Keisa Fallin-Bennett[6], MPH, MD; Arjee Javellana Restar[2,7], MPH, PhD; Trace Kershaw[2*], PhD

[1]Center for Health Equity Transformation, University of Kentucky, Lexington, KY, United States

[2]Department of Social and Behavioral Sciences, Yale School of Public Health, New Haven, CT, United States

[3]Department of Biostatistics, University of Kentucky, Lexington, KY, United States

[4]College of Social Work, The Ohio State University, Columbus, OH, United States

[5]Center for Interdisciplinary Research on AIDS, Yale University, New Haven, CT, United States

[6]Department of Family and Community Medicine, University of Kentucky, Lexington, KY, United States

[7]Department of Epidemiology, Department of Health Systems and Population Health, University of Washington, Seattle, WA, United States

[*]these authors contributed equally

Corresponding Author:
Carolyn Lauckner, PhD
Center for Health Equity Transformation
University of Kentucky
465 Healthy Kentucky Bldg
760 Press Ave
Lexington, KY, 40536
United States
Phone: 1 859 562 3335
Email: carolyn.lauckner@uky.edu

Abstract

Background: Sexual minority cisgender men and transgender (SMMT) individuals, particularly emerging adults (aged 18-34 years), often report hazardous drinking. Given that alcohol use increases the likelihood of HIV risk behaviors, and HIV disproportionately affects SMMT individuals, there is a need to test interventions that reduce hazardous alcohol use and subsequent HIV risk behaviors among this population. Ecological momentary interventions (EMIs), which use mobile phones to deliver risk reduction messages based on current location and behaviors, can help to address triggers that lead to drinking in real time.

Objective: This study will test an EMI that uses motivational interviewing (MI), smartphone surveys, mobile breathalyzers, and location tracking to provide real-time messaging that addresses triggers for drinking when SMMT individuals visit locations associated with hazardous alcohol use. In addition, the intervention will deliver harm reduction messaging if individuals report engaging in alcohol use.

Methods: We will conduct a 3-arm randomized controlled trial (N=405 HIV-negative SMMT individuals; n=135, 33% per arm) comparing the following conditions: (1) Tracking and Reducing Alcohol Consumption (a smartphone-delivered 4-session MI intervention), (2) Tracking and Reducing Alcohol Consumption and Environmental Risk (an EMI combining MI with real-time messaging based on geographic locations that are triggers to drinking), and (3) a smartphone-based alcohol monitoring–only control group. Breathalyzer results and daily self-reports will be used to assess the primary and secondary outcomes of drinking days, drinks per drinking day, binge drinking episodes, and HIV risk behaviors. Additional assessments at baseline, 3 months, 6 months, and 9 months will evaluate exploratory long-term outcomes.

Results: The study is part of a 5-year research project funded in August 2022 by the National Institute on Alcohol Abuse and Alcoholism. The first 1.5 years of the study will be dedicated to planning and development activities, including formative research, app design and testing, and message design and testing. The subsequent 3.5 years will see the study complete participant recruitment,

data collection, analyses, report writing, and dissemination. We expect to complete all study data collection in or before January 2027.

Conclusions: This study will provide novel evidence about the relative efficacy of using a smartphone-delivered MI intervention and real-time messaging to address triggers for hazardous alcohol use and sexual risk behaviors. The EMI approach, which incorporates location-based preventive messaging and behavior surveys, may help to better understand the complexity of daily stressors among SMMT individuals and their impact on hazardous alcohol use and HIV risk behaviors. The tailoring of this intervention toward SMMT individuals helps to address their underrepresentation in existing alcohol use research and will be promising for informing where structural alcohol use prevention and treatment interventions are needed to support SMMT individuals.

Trial Registration: ClinicalTrials.gov NCT05576350; https://www.clinicaltrials.gov/study/NCT05576350

International Registered Report Identifier (IRRID): PRR1-10.2196/55166

(JMIR Res Protoc 2024;13:e55166) doi:10.2196/55166

KEYWORDS

alcohol use; sexual minority; transgender; young adults; mobile health; mHealth; HIV risk behaviors; sexual risk behaviors; motivational interviewing; ecological momentary interventions; mobile phone

Introduction

Background

Those who identify as sexual and gender minority individuals (eg, gay, bisexual, transgender, or queer individuals) are more likely to report hazardous drinking, defined as "drinking behavior (such as per episode, daily, or weekly) that reflects meaningful increases in risk of negative alcohol-related outcomes" [1] and to have alcohol use disorders (AUDs) than their cisgender and heterosexual peers [2-5]. Similarly, emerging adult (aged 18-34 years) sexual and gender minority individuals are at increased odds of being diagnosed with AUDs compared to older adults, with up to 44% meeting AUD criteria [3,6]. An extensive body of research suggests that the increased use of alcohol among young sexual and gender minority populations is attributable to interlocking structural underpinnings of stigma, homophobia, transphobia, and other manifestations of violence against queer people [5,7-9]. These trends are concerning because multiple studies have found that alcohol use increases the likelihood of acquiring HIV through various behaviors [10-13] and that HIV disproportionately affects emerging adult sexual minority cisgender men and transgender (SMMT) individuals [14]. Consequently, individuals who have reported unhealthy levels of alcohol use also were likely to experience interference with their decision-making with regard to adhering to pre-exposure prophylaxis (PrEP) [15], which can prevent HIV. Thus, it is essential to test interventions for reducing alcohol use among SMMT individuals as a means of preventing HIV among these populations considered to be at high risk.

A recent systematic review found that motivational interviewing (MI) is a frequently used method for reducing alcohol use [16]. MI is a goal-oriented and patient-centered approach to motivating behavior change and increasing self-efficacy. While it has been effective for reducing alcohol use among gay and bisexual men [17-19], this review found only 1 alcohol-related MI intervention for transgender people [20], suggesting the need for more research with this population. Prior studies also suggest the effectiveness of MI being delivered through technology to support the reduction of alcohol use behaviors [21]. The Tracking and Reducing Alcohol Consumption (TRAC) intervention, recently tested among people with HIV and currently being tested (since July 2023) among young adult survivors of cancer, uses smartphones to deliver 4 to 8 weekly sessions of MI for reducing risky drinking. The sessions focus on identifying triggers for drinking and strategies for addressing these triggers. TRAC also incorporates daily smartphone-based alcohol monitoring (SAM) using mobile breathalyzers and surveys. While preliminary results are promising in terms of TRAC's effectiveness and acceptability [22], there is potential for enhancing it by reinforcing content in real-time situations where people are more likely to experience triggers to use alcohol.

Ecological momentary interventions (EMIs), which use smartphones to deliver messages to reduce alcohol use and related risk behaviors during or before drinking events, can help to address triggers in real time. GPS tracking can determine when individuals visit places where they have previously reported drinking or triggers to drink, and then EMI messages can be delivered upon arrival to *prevent* hazardous alcohol use. However, this GPS-based approach has rarely been studied to date and has generally targeted individuals with AUDs (as opposed to those who engage in hazardous drinking but do not have an AUD) [23,24]. We have developed a mobile app for a previous observational study that uses GPS tracking to determine when emerging adult SMMT individuals visit *riskylocations* and then delivers a survey asking about aspects of the location's social and geographic context that may relate to drinking and other risk behavior.

Objectives

The goal of the proposed study is to use this app to enhance TRAC by delivering messages that encourage participants to use strategies discussed during TRAC sessions when arriving at risky locations. When they leave these locations, they will complete a survey and a breathalyzer reading to collect event-level self-report and biological data on alcohol use and HIV risk. If their breathalyzer result indicates alcohol use, they will receive harm reduction messaging. It is expected that combining TRAC with EMI (Tracking and Reducing Alcohol

Consumption and Environmental Risk [TRAC-ER]) will increase effectiveness by reinforcing topics discussed during sessions, providing in-the-moment messaging to address triggers, and collecting real-time alcohol use data.

We will conduct a randomized controlled trial (RCT) of the TRAC and TRAC-ER interventions, examining their effects on alcohol use and HIV risk behaviors among SMMT individuals compared with a SAM-only control group. We will examine 2 aims.

- Aim 1: assess the effects of intervention conditions on drinking days (primary end point), drinks per drinking day, and binge drinking episodes (secondary end points).
  Hypothesis:
  TRAC and TRAC-ER will lead to significantly fewer drinking days compared with a SAM-only control group, with TRAC-ER having the strongest effects.
- Aim 2: assess the effects of intervention conditions on HIV risk behaviors (unprotected sex, number of partners, concurrent sex and substance use, and PrEP nonadherence).
  Hypothesis:
  TRAC and TRAC-ER will lead to significantly fewer HIV risk behaviors compared with a SAM-only control group, with TRAC-ER having the strongest effects.

Methods

Study Design

We will conduct a 3-arm RCT of TRAC and TRAC-ER (n=405 HIV-negative SMMT individuals; n=135, 33% per arm), with the following conditions: (1) SAM-only comparison group, (2) SAM+TRAC (no EMI messaging), and (3) SAM+TRAC-ER (participants receive EMI messaging when visiting risky locations).

Breathalyzer results and daily self-reports will be used to assess the primary and secondary outcomes of drinking days, drinks per drinking day, binge drinking episodes, and HIV risk behaviors. Additional assessments at baseline (T1), 3 months (T2), 6 months (T3), and 9 months (T4) will evaluate exploratory long-term outcomes, including diagnoses of HIV or other sexually transmitted infections (STIs).

Participants and Recruitment

Overview

Participants will be recruited using web-based and community-based recruitment, as well as through health clinics that serve SMMT individuals. A combination of venue-based and purposive sampling approaches appropriate for accessing populations considered to be hard to reach and at risk will be used to recruit participants [25-27]. Previous intervention studies with young adult SMMT populations have found 6-month dropout rates of 15% to 25% [28-30]. To reach our target final sample (n=324; refer to the Sample Size Justification subsection), we will recruit 405 individuals, accounting for an estimated 20% dropout rate based on prior literature.

Health Clinics

All patients presenting for appointments at participating clinics will be screened using a preprogrammed tablet computer to determine eligibility. The principal investigators will provide instruction to clinic staff regarding screening patients and distribute quick-reference study information sheets to keep in offices. The study coordinator will be available during business hours to help clinic staff as needed.

Web-Based and Community-Based Recruitment

Our previous studies have successfully used a variety of recruitment methods to reach SMMT individuals, which we will also leverage in the proposed study: flyer outreach (in locations frequented by SMMT individuals), social media recruitment (including paid and free posts on Instagram, Facebook, Reddit, and dating apps), a study website, and institutional collaborations. All advertisements will direct participants to the web-based screener. We will use a community advisory board, comprising members representing different subsets of the SMMT population, to obtain further guidance regarding ideal participant recruitment methods.

Inclusion and Exclusion Criteria

Participants will be eligible to participate if they meet the following inclusion criteria: (1) self-identify as a gender minority individual (eg, transgender man, transgender woman, nonbinary individual, agender individual, or gender fluid individual) or a sexual minority cisgender man (ie, assigned male sex at birth and identifies as a man with a sexual orientation other than heterosexual), (2) is aged between 18 and 35 years at the start of the study, (3) owns a smartphone, (4) is HIV-negative (confirmed through a test at baseline), (5) meets Centers for Disease Control and Prevention PrEP eligibility criteria (individuals will be eligible if they have had anal or vaginal sex in the past 6 months and have at least one of the following characteristics: a sexual partner with HIV, inconsistent condom and PrEP use, or a sexually transmitted disease diagnosis in the past 6 months; or if they inject drugs and have an injection partner with HIV or share needles, syringes, or other equipment to inject drugs) [31], and (6) screens positively for hazardous alcohol use. As most alcohol screening instruments rely on biological sex, we will use a combination of the Alcohol Use Disorders Identification Test–Concise (AUDIT-C), a validated 3-item screener for hazardous alcohol use [32], and a 1-item yes or no screening question to determine whether they engage in hazardous alcohol use (“Have you had 5 or more drinks on one occasion in the past year?”). This question was found to be a valid measure of hazardous alcohol use among gender-diverse individuals; despite it being a single item, this screening method performed better than the AUDIT-C for lower drink thresholds (eg, ≥4 drinks) in predicting hazardous alcohol use [33]. However, because this is still a new approach to assessing hazardous drinking and because we will also be enrolling cisgender individuals, we will consider AUDIT-C scores too; participants must also score ≥4 on the AUDIT-C to qualify [32].

Exclusion criteria include (1) not speaking English; (2) active psychosis or severe mental illness; (3) actively detoxifying from

substances and needing medical supervision; or (4) a score of ≥20 on the Alcohol Use Disorders Identification Test [32], which indicates that participants exhibit increased or higher risk drinking behaviors.

Regardless of the recruitment method used, all participants will complete a web-based screener. If participants are determined to be eligible according to the screener, they will be informed of their eligibility and invited to provide their contact information if they wish to learn more about the study.

Sample Size Justification

Sample size determination was based on the primary outcome variable: number of drinking days in the past month across the repeated visits corresponding to T1, T2, T3, and T4 for the 3 groups (SAM only, SAM+TRAC, and SAM+TRAC-ER). Data on effect sizes from previous alcohol use interventions [34,35] and our preliminary data (within-participant correlation of 0.69) were used to derive the mean number of days of alcohol use and their SDs. With a final sample size of n=324 (after accounting for a 20% dropout rate with a total n=405), 108 (33%) participants in each group will give us at least 90% power at 5% type I error rate to detect a significant difference among the groups for an effect size of 0.071 when comparing the groups over the study period. This effect size is smaller than a *small* effect as defined by Cohen et al [36].

We expect our sample to have the following characteristics: 48.1% (195/405) cisgender men, 24.9% (101/405) transgender men, 20% (81/405) transgender women, and 6.9% (28/405) nonbinary individuals. Our sample will likely have a higher proportion of transgender participants compared to the general population due to recruitment within health clinics that provide care for transgender patients; we view this as a strength of our study, given the underrepresentation of gender minority individuals in previous alcohol intervention and HIV prevention research.

Enrollment

If participants are determined to be eligible according to their responses to the web-based screener, they will be informed of their eligibility and invited to provide their contact information if they wish to learn more about the study. If participants are ineligible, they will be informed of this upon completion of the screener. A member of the study team will contact eligible participants via their preferred contact method to complete an interview confirming eligibility. This interview is conducted via Zoom (Zoom Video Communications, Inc) and is included as protection against spam or false screener responses.

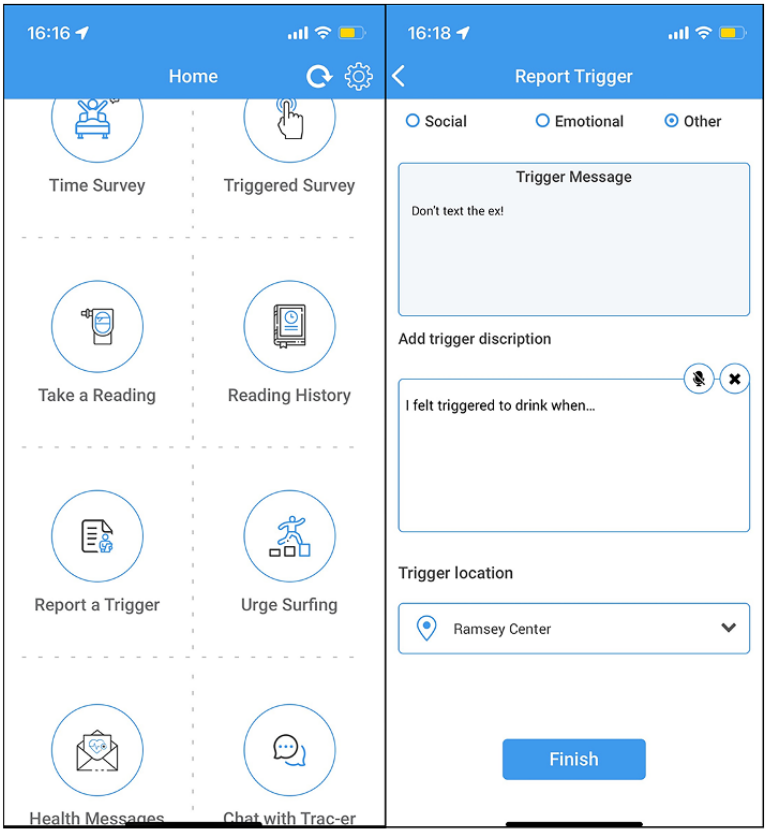
Study Interventions and Procedures

Description of TRAC-ER Study App

The app developed for this study has been designed to track participants' physical location through continuous GPS monitoring and to deliver assessments and messages at specific times of the day and in response to participants' physical location. At baseline, all participants will be asked to list the locations where they most frequently engage, or are triggered to engage, in alcohol use, unprotected sex, or other HIV risk behaviors as part of an activity space assessment. For each listed location, they will provide information regarding the types of alcohol triggers they experience (eg, social, situational, or emotional). These locations will then be programmed into the app and given a geofence (a distance around the location such that when participants break the geofence, intervention-specific actions such as surveys or messages are delivered). Before each follow-up monitoring period, participants will complete a short questionnaire that lists the locations they identified in the activity space assessment, as well as locations where they reported drinking via the random breathalyzer reading requests during prior monitoring periods. They will have the opportunity to revise the list of locations, which will ensure that the triggered surveys are being delivered for locations most relevant to the participants.

Every morning during the SAM periods, participants will receive a push notification asking them to report the number of drinks consumed in the previous day (if applicable), time spent drinking, alcohol withdrawal symptoms, and sexual risk behaviors. The app will also send requests for breathalyzer readings at least 2 times per day in response to visits to risky locations and through random requests. At the time of providing the breathalyzer reading, participants will also complete a brief mobile survey using the study app that includes questions related to their alcohol use. Participants can view a log of their breathalyzer readings in the app. Participants will have the option to report a trigger in the app and provide details about the trigger, including the location where the trigger was generated. Participants who are randomized to the TRAC-ER intervention will receive a harm reduction message based on the type of trigger (social, emotional, or other) they report. A guided breathing exercise and urge surfing exercise are included in the app for those in the TRAC and TRAC-ER conditions. Figure 1 presents a screenshot of the app. If, at any point during the monitoring periods, the app stops collecting GPS data, the study team will reach out to determine whether the participant accidentally turned off location tracking, lost their mobile phone, or is experiencing other technical difficulties.

Figure 1. Tracking and Reducing Alcohol Consumption and Environmental Risk (TRAC-ER) app screenshots (app developed by Vista IT Solutions, LLC).



Description of Study Arms

Overview

Participants will be enrolled in the study for 9 months, including the 2-month intervention period and multiple follow-up monitoring periods to assess long-term effects. All participants will begin with a 30-day monitoring period, which will establish baseline alcohol use through daily breathalyzer reading requests and surveys. After this 30-day period, they will complete additional baseline measures (T1) and then begin their assigned intervention, if applicable. After the interventions are delivered, participants will complete an additional self-report (T2). Subsequently, there will be 2 additional monitoring periods and assessments spread across the 9-month study period to assess long-term intervention effects, with some months involving no study activities. A depiction of the participation timeline is included in Figure 2, and details of study activities completed across the study timeline and RCT arms are provided in Table 1.

Figure 2. Participation timeline. STI: sexually transmitted infection; TRAC: Tracking and Reducing Alcohol Consumption; TRAC-ER: Tracking and Reducing Alcohol Consumption and Environmental Risk.

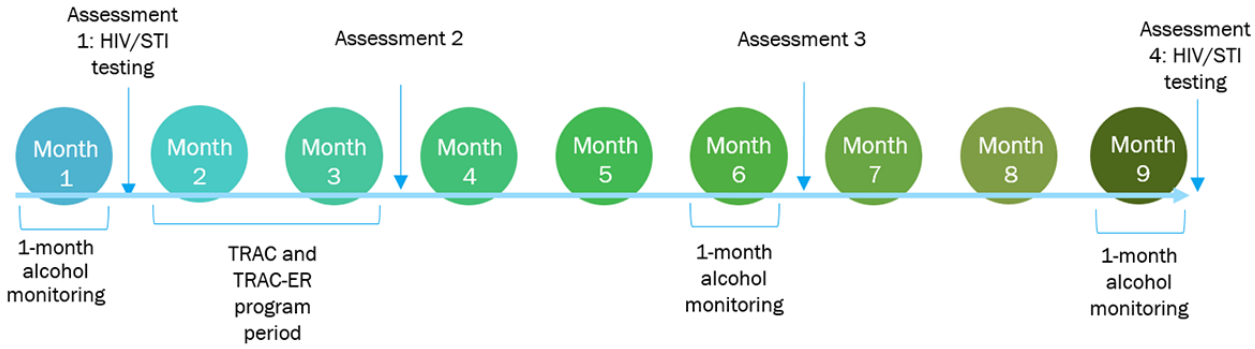


Table 1. Summary of research activities across the randomized controlled trial conditions.

Days and research activities	Control	TRAC[a]	TRAC-ER[b]
1-30			
Morning survey: sent between 7 AM and 10 AM (based on participant preference)	✓	✓	✓
Random breathalyzer reading and breathalyzer request survey: request at a random time between 11 AM and 5 PM and at a random time between 5 PM and 11 PM	✓	✓	✓
Location survey and breathalyzer reading: request breathalyzer survey and breathalyzer reading when participant leaves a risky location	✓	✓	✓
31-90			
Morning survey: sent between 7 AM and 10 AM (based on participant preference)	✓	✓	✓
Random breathalyzer reading and breathalyzer request survey: request at a random time between 11 AM and 5 PM and at a random time between 5 PM and 11 PM	✓	✓	✓
Location survey and breathalyzer reading: request breathalyzer request survey and breathalyzer reading when participant leaves a risky location	✓	✓	✓
TRAC intervention			
Participant completes 4 TRAC sessions via video or telephone call on a weekly basis		✓	✓
TRAC-ER in-app messages			
Deliver prevention message upon arrival at risky location			✓
Deliver harm reduction message if, upon leaving a risky location, participants have a positive			✓
Deliver a self-help message if participant taps *report a trigger* in the app			✓
91-150			
No research activities			
151-180			
Morning survey: sent between 7 AM and 10 AM (based on participant preference)	✓	✓	✓
Random breathalyzer reading and breathalyzer request survey: request at a random time between 11 AM and 5 PM and at a random time between 5 PM and 11 PM	✓	✓	✓
Location survey and breathalyzer reading: request breathalyzer request survey and breathalyzer reading when participant leaves a risky location	✓	✓	✓
181-240			
No research activities			
241-270			
Morning survey: sent between 7 AM and 10 AM (based on participant preference)	✓	✓	✓
Two random breathalyzer readings and breathalyzer request survey: request at a random time between 11 AM and 5 PM and at a random time between 5 PM and 11 PM	✓	✓	✓
Location survey and breathalyzer reading: request breathalyzer request survey and breathalyzer reading when participant leaves a risky location	✓	✓	✓

[a]TRAC: Tracking and Reducing Alcohol Consumption.

[b]TRAC-ER: Tracking and Reducing Alcohol Consumption and Environmental Risk.

SAM-Only Participants

Participants will complete alcohol self-monitoring tasks using the study app (daily surveys and breathalyzer readings) during months 1 to 3, month 6, and month 9. During these designated months, participants will receive prompts to complete morning surveys, random breathalyzer requests, and location surveys, as described in Table 1.

SAM-only participants will also complete the T1 to T4 assessments on the schedule illustrated in Figure 1.

TRAC Participants

TRAC participants will complete alcohol self-monitoring tasks and assessments following the schedule described for SAM-only participants. In addition, participants will receive the 4-session TRAC intervention. Individuals will meet for 30 minutes with an interventionist on a weekly basis via telephone or video chat, although the 6-week intervention period allows for some cancellations or rescheduling. Textbox 1 presents an overview of the 4-session TRAC intervention. Participants will be mailed a paper workbook to complete during the sessions. The SAM app will provide supplementary materials, including a triggers

diary, a guided breathing exercise, and a record of the participants' goals for reducing their drinking. After participants complete all intervention sessions, they will continue daily monitoring for the remainder of the 2-month intervention period. Participants will complete the T1 to T4 assessments following the schedule described for SAM-only participants.

Textbox 1. Session overview of the Tracking and Reducing Alcohol Consumption (TRAC) intervention.

Session 1

- Introduction (5-8 minutes)
- Alcohol and health factsheet (10 minutes)
- Review current alcohol use (15 minutes)
- Complete change plan (10 minutes)
- Diaphragmatic breathing (8 minutes)
- Wrap up and schedule next session (5 minutes)

Session 2

- Recap of past session, check-in, and agenda setting (5 minutes)
- Review weekly drinking data and change goals from last week (10 minutes)
- Review strategies for managing triggers (20 minutes)
- Urge surfing skill (10 minutes)
- Wrap up and schedule next session (5 minutes)

Session 3

- Recap of past session, check-in, and agenda setting (5 minutes)
- Review weekly drinking data and change goals from last week (10 minutes)
- Strategies for reducing alcohol-related harm (20 minutes)
  - Before known drinking occasions
  - While drinking alcohol
  - After drinking alcohol
- Wrap up and schedule next session (5 minutes)

Session 4

- Recap of past session, check-in, and agenda setting (5 minutes)
- Review weekly drinking data and change goals from last week (5-8 minutes)
- Review overall progress (5-8 minutes)
- Set goals and plan for going forward (10-15 minutes)
- Wrap up and give reminder of remaining study tasks (5 minutes)

TRAC-ER Participants

Overview

Participants will complete all aspects of the TRAC intervention condition. In addition to receiving triggered surveys when they leave a risky location, participants will also receive prevention messaging when they first arrive at a risky location. This messaging will be tailored based on the data collected regarding participants' risky locations and the strategies to address triggers discussed during the MI intervention sessions. In addition, if participants return a breathalyzer reading >0.00%, they will receive harm reduction messaging encouraging them to engage in protective behaviors. These messages will continue throughout the 2-month intervention period, including after the 4 TRAC sessions have been completed. Participants will complete the T1 to T4 assessments following the schedule described for SAM-only participants.

MI Interventionist Training and Fidelity Assessment

The full-time study interventionist, an individual with a master's degree in counseling, will receive refresher training from a supervisor who is a licensed clinical social worker regarding the principles of MI as they relate to substance use and the key components of the TRAC intervention through 12 hours of instruction and mock interviews. This supervisor will review the interventionist's first TRAC case (or additional cases, if needed). Fidelity ratings will be conducted using a combination of the Motivational Interviewing Treatment Integrity (MITI)

4.2.1 coding system and adherence checklists to be developed by the study team to code for the presence of specific skills and exercises included in the TRAC protocol. MITI is an established structured behavioral coding system that serves as a treatment fidelity measure for clinical trials of MI [37,38]. It provides a global impression of empathy and MI spirit, a reflection-to-question ratio, and summary scores for MI components based on behavior count ratios of complex reflections, open questions, and MI-adherent utterances. The interventionist will be *certified* as able to deliver the protocol with fidelity. Certification will involve meeting adherence of at least 80% of TRAC-specific skills and exercises and the recommended MI competency threshold on at least 80% of sessions for a given case. Until the interventionist is certified, the supervisor will review entire session recordings weekly to code TRAC adherence, and a randomly selected 20-minute segment will be coded with MITI. Individual feedback and training will be provided weekly. Overall trial fidelity ratings (adherence to TRAC skills and exercises and MI competency) will be determined via review of an additional randomly selected 20% of interviews (10% from each site), in line with recommendations for RCTs of MI [39], including double coding by the supervisor and a research assistant, both of whom will be certified in MITI coding.

Data Collection Procedures

Overview

As this study is examining both short- and long-term effects and comparing them among the groups, the primary end point of the number of past-month drinking days will be assessed based on SAM results collected before T1, throughout the intervention, and before T3 and T4. Secondary end points include drinks per drinking day and binge drinking episodes. All other variables measured, including those related to HIV risk behaviors, will be used to conduct exploratory analyses. The sources of data for this RCT include SAM data (including surveys and breathalyzer results, discussed in detail previously), baseline and follow-up self-report measures (T1-T4), HIV and STI testing, app-based process measures, and qualitative interviews.

Baseline and Follow-Up Measures

An assessment battery will be administered to all participants at T1, T2, T3, and T4. This will include several measures of alcohol use as well as more exploratory variables, including alcohol cravings, alcohol consequences, the use of alcohol treatment services, HIV risk behaviors, and experiences of discrimination related to participants' identity as sexual and gender minority individuals. Table 2 presents a description of the key study measures.

Table 2. Description of key study measures.

Construct and time	Measure	End point	Description
Drinking days, 2× daily	Breath alcohol content	Primary	BACtrack Mobile breathalyzer result sent via mobile app; measured 2× daily for 8 weeks during the intervention and for 1 month before T1[a], T3[b], and T4[c]; 2 negative readings per day=nondrinking day
Drinks per drinking day, daily	Self-reported alcohol use through app	Secondary	3 items: alcohol consumed (yes or no), number of drinks, and time spent drinking; measured daily during the intervention and for 1 month before T1, T3, and T4
Binge drinking episodes, daily	Self-reported alcohol use through app	Secondary	Occasions when participants had ≥5 drinks based on self-reported number of drinks; measured daily during the intervention and for 1 month before T1, T3, and T4
Alcohol withdrawal symptoms, daily	Single-item AWSC[d] [40]	Exploratory	1 item: alcohol withdrawal symptom severity on a scale of 0 to 9; those scoring ≥2 are asked to complete the 17-item AWSC, which assesses the severity of symptoms; measured daily during intervention and for 1 month before T1, T3, and T4
Sexual activity, daily	Self-reported through app	Exploratory	6 items: past-day sexual activity, number of partners, partner type, partner HIV status, type of sexual activity, condomless sex, and PrEP[e] use
Location characteristics, up to 2× daily	Self-reported through app	Exploratory	12 items assessing alcohol and substance use, sexual behaviors, peer use of alcohol or substances, and harassment or discrimination experienced
Alcohol use, T1, T2[f], T3, and T4	PROMIS[g] Short Form–Alcohol Use 7a [41]	Exploratory	7 items that assess general alcohol use and problem drinking in the past 30 days (eg, drank too much and drank heavily)
Alcohol consequences			
T1, T2, T3, and T4	PROMIS Short Form–Alcohol Use–Negative Consequences 7a [41]	Exploratory	7 items that assess the negative consequences of using alcohol in the previous 30 days (eg, unreliability, social problems, and judgment)
T1, T2, T3, and T4	PROMIS Short Form–Alcohol Use–Positive Consequences 7a [41]	Exploratory	7 items that assess the positive consequences of using alcohol in the previous 30 days (eg, self-esteem, confidence, and enjoyment)
Alcohol expectancies			
T1, T2, T3, and T4	PROMIS Short Form–Alcohol Use–Negative Expectancies 7a [41]	Exploratory	7 items that assess the negative expectancies of alcohol use (eg, making bad decisions and behaving rudely)
T1, T2, T3, and T4	PROMIS Short Form–Alcohol Use–Positive Expectancies 7a [41]	Exploratory	7 items that assess the positive expectancies of alcohol use (eg, improves mood and sociability)
Readiness to change drinking, T1, T2, T3, and T4	Readiness to Change Questionnaire [42]	Exploratory	12 items that assess the stage of change toward reducing alcohol use (precontemplation, contemplation, and action)
Drinking refusal self-efficacy, T1, T2, T3, and T4	Drinking Refusal Self-Efficacy Questionnaire–Revised [43]	Exploratory	19 items that assess individuals' belief in their ability to resist alcohol, with 3 subscales: social pressure drinking, emotional relief drinking, and opportunistic drinking
Sexual risk behaviors, T1, T2, T3, and T4	National HIV Behavioral Surveillance System [44]	Exploratory	≥6 items: number of partners in previous 12 (T1) or 3 (T2-T4) months; partner type (main vs casual); partner HIV status; frequency of condomless sex (anal, vaginal, or oral), transactional sex, and concurrent sex and drug or alcohol use; and PrEP use
Condom attitudes, T1, T2, T3, and T4	Multidimensional Condom Attitudes Scale [45]	Exploratory	16 items that measure attitudes toward condoms across 7 factors: reliability, effectiveness, pleasure, identity stigma, embarrassment about purchase, negotiation, and action maintenance
Perceived HIV risk, T1, T2, T3, and T4	Perceived Risk of HIV Scale [46]	Exploratory	8 items that assess likelihood estimates, intuitive judgments, and salience of HIV risk based on previous behaviors
Discrimination due to sexual or gender identity, T1, T2, T3, and T4	Heterosexist Harassment, Rejection, and Discrimination Scale [47]	Exploratory	12 items that assess harassment, rejection, and family discrimination related to LGBTQ[h] identities
Alcohol cravings, T1, T2, T3, and T4	Penn Alcohol Craving Scale [48]	Exploratory	5 items that assess alcohol-related cravings; higher scores indicate higher rates of alcohol cravings

Construct and time	Measure	End point	Description
Alcohol Use, T1, T2, T3, and T4	Alcohol Quantity Measures	Exploratory	7 items that assess alcohol use over the past 30 days

[a]T1: baseline assessment.

[b]T3: 6-month assessment.

[c]T4: 9-month assessment.

[d]AWSC: alcohol withdrawal symptom checklist.

[e]PrEP: pre-exposure prophylaxis.

[f]T2: 3-month assessment.

[g]PROMIS: Patient-Reported Outcomes Measurement Information System.

[h]LGBTQ: lesbian, gay, bisexual, transgender, and queer.

HIV and STI Testing

At T1 and T4, participants will receive HIV and 3-site gonorrhea and chlamydia testing. We will use myLAB Box, with whom we have worked successfully in prior research, to deliver home testing kits to participants. myLAB Box is a fully laboratory-certified company using College of American Pathologists– and Clinical Laboratory Improvement Amendments–certified testing organizations and a HIPAA (Health Insurance Portability and Accountability Act)–compliant web interface [49]. The home testing kits include written instructions for how to collect the samples; participants will complete a finger prick blood sample for the HIV test and collect swab and urine samples for the gonorrhea and chlamydia testing. The test kits will be mailed by the participants to myLAB Box using prepaid shipping boxes. Before completing testing, participants will complete a HIPAA release form giving permission for their results to be shared with the study team. In the case of a positive test, the participant will have the opportunity to complete a telehealth visit (free of charge) with one of myLAB Box's providers to discuss medications and linkage to care. The research team will also follow up with the participant to ensure that they have been connected to care and, in the case of a positive HIV test at T1, to communicate that they are no longer eligible to participate in the study.

Process Measures

We will assess several process measures related to the study app, including the number of opened and completed daily surveys, the number of messages opened, the length of time messages stayed open, the number of completed breathalyzer readings and location-based surveys, the frequency of missing GPS data, and the number of reported app issues. For each participant completing monitoring, we will generate a weekly report of these metrics to address any ongoing technical issues in a timely manner and to encourage the completion of surveys and breathalyzer readings if they are nonadherent. For the TRAC intervention, the interventionist will complete fidelity checklists after each session. We will also assess session attendance, dropout rates, and time spent in sessions. At the end of the intervention, we will conduct an overall fidelity assessment to aid in the interpretation of the intervention results. Overall, these process measures will inform future dissemination and implementation efforts.

Qualitative Intervention Assessment

At the T2 assessment, we will conduct a semistructured qualitative interview to obtain feedback on the SAM-only, and SAM+ TRAC, and SAM + TRAC-ER conditions. As applicable according to their intervention group, the interview will address the effects of the monitoring of alcohol use, attitudes toward MI intervention content, the impact of the EMI messages on drinking and HIV risk behavior, the impressions of intervention relevance and effects, challenges encountered during the intervention, and suggestions for improvement.

Participant Training

Participants in each condition will be trained to navigate the app and complete tasks, including completing location-based and daily assessments, reading messages, and providing breathalyzer readings. They will also be instructed on data safety and confidentiality procedures and how to remotely wipe their mobile phone data if it is lost or stolen. Wallet-size cards with information from the training and text reminders to carry the mobile phone and breathalyzers will be provided. A lack of response will be followed up with texts and telephone calls to ascertain the reason for noncompliance. If participants report problems, we will complete video calls to troubleshoot and further train participants, if needed.

Methods to Decrease Attrition and Missing Data

During the first 3 months of the study, participants will receive daily reminders to complete SAM, which will include information about potential incentives. Individuals in the SAM+TRAC and SAM+TRAC-ER arms will have weekly contact with research staff during the TRAC sessions and will receive reminders about upcoming appointments. We will contact participants 1 month before their follow-up monitoring periods to remind them about upcoming tasks and to ensure that contact information is up to date. The use of a novel smartphone app and a mobile breathalyzer, which has been highly rated by participants in past studies, will also help to ensure continued engagement with, and enthusiasm for, the study.

Ethical Considerations

All procedures were approved by the University of Kentucky Institutional Review Board (79109), with Yale University relying on the University of Kentucky for human participant oversight. All responses of participants will be held in confidence and kept secure. Only the researchers involved in this study and those responsible for the research oversight will have access to the information that may identify the participants.

All participants will complete informed consent before beginning research activities. All consenting procedures will be completed remotely and electronically using the REDCap (Research Electronic Data Capture; Vanderbilt University) *eConsent* framework. First, participants will be given basic information about the study. If they indicate interest in learning more and meet eligibility criteria after completing a brief screening survey, a member of the research team will contact them via their preferred contact method to confirm eligibility, provide more details about the research procedures, and obtain informed consent.

The research team will review all aspects of the study, including specific research procedures, the length of time participants will be enrolled in the study, and the associated risks and benefits of participation (eg, benefiting from free alcohol reduction counseling, which may impact overall health, and the risks of emotional distress from completing sessions and assessments and of a loss of confidentiality). Contact information for study staff, the principal investigators, the University of Kentucky's Office of Research Integrity, and Yale University's Human Research Protection Program will be provided, and the participant will be encouraged to contact any of the relevant individuals if they have questions or concerns regarding this research or to discuss their rights as a research participant.

If a participant chooses to sign up for the study after this conversation with the research team, they will complete consent by providing an electronic signature in REDCap. A copy of the consent form will be provided to the participant electronically and retained in REDCap's file repository for study records. By signing this form, participants agree to allow for future use, and sharing of, their deidentified study data with other researchers, without additional informed consent. No participant will begin research procedures without first providing signed informed consent.

To protect confidentiality, participants will be assigned a unique study ID number. Any identifying information will not be stored alongside survey responses and will be permanently deleted after the completion of data collection in accordance with the University of Kentucky Institutional Review Board policies.

The research team will take all precautions to prevent a loss of confidentiality, one of the primary risks of this study. Data collected and stored on mobile phones are inherently less secure than other storage methods; however, participants will be advised on how to protect data stored on mobile phones, and study staff will be trained on best practices for securing information on mobile phones.

Electronic data will be stored and managed in REDCap and will be accessible only to authorized study personnel. All data collected through the mobile app will be hosted on a secure private server at Yale University. myLAB Box uses a HIPAA-compliant web portal that encrypts all medical information, and all communications sent by the company will minimize personal details. Due to the sensitive nature of HIV and STI results, we will give the test results a unique ID in addition to the study ID and maintain them in a separate REDCap database without other identifying information. Access to these, and all other study data, will be permitted only to authorized personnel, who will be trained in the areas of ethics, clinical trials, confidentiality protection, and human participant protection.

Participants can earn up to US $825 (US $685 for monitoring tasks and US $140 for assessments). All participants will receive a US $1 compliance payment for each breathalyzer sample submitted within a 90-minute period. They will also receive a US $1 payment for submitting their daily morning surveys. Thus, those who complete all monitoring tasks (all breathalyzer readings and daily self-reports) during the whole study (4 weeks before T1, 8 weeks during the intervention, and 4 weeks before T3 and T4) will receive US $685. Participants will also receive US $35 for completing the T1 assessment (US $20 for the questionnaire and US $15 for HIV and STI testing), US $25 for T2, US $30 for T3, and US $50 for T4. Escalating payments will be used to discourage study attrition.

While the compensation amount is relatively high, it is for activities completed across a full 9 months of participation. Total time spent on study activities ranges from 45 hours (SAM-only participants) to 50 hours (SAM+TRAC and SAM+TRAC-ER participants) when considering daily monitoring, assessments, time spent on screening and enrollment, and time spent in MI sessions. This results in an average compensation of US $16-$18 per hour in exchange for participation in study activities.

We will pay participants with reloadable debit cards, administered using OnCore clinical trial software (Advarra). Funds will be added to these cards as payments are earned, which then become immediately available. This system will allow for frequent payments without the burden of office visits or the delays from mailing checks.

Data Analysis Plan

Analysis of Alcohol Use Outcomes

Descriptive statistics for breathalyzer reading data will be summarized overall, by group (SAM only, SAM+TRAC, and SAM+TRAC-ER) and across time periods (T1-T4). The primary outcome is the number of drinking days in the past month, which is defined as the days on which individuals did not report 2 negative breathalyzer results. The rate of drinking (incidence of drinking) is the number of drinking days observed within the past month. The secondary outcomes include the number of drinks per drinking day, the number of days with binge drinking episodes, and the number of days for which HIV risk behaviors occur. All these outcomes are count data. The goal of this analysis is 2-fold: first, short-term analysis at the end of the 2-month intervention period, and, second, long-term analysis at the end of 9 months. We will fit a generalized linear model [50], with a general formulation for count data as follows:

$$g(E(y_i)) = g(\mu_i) = x'_i\beta \quad (1)$$

where y_i is the outcome variable for (i=1,2,3,...,n), n is the total number of observations, μ_i=$E(y_i)$ is the expected count, g is the link function (a mathematical function connecting the counts with the explanatory variables), β is a vector of regression parameters to be estimated, and x_i is a vector of independent covariates to be included in the model. These covariates include

group, time, age (or age group), gender identity, sexual orientation, and site.

Short-Term Outcome Analyses

After 3 months, we will fit the aforementioned model to the data and compare the groups at T1 and T2 while adjusting for the covariates. The PROC GENMOD procedure in SAS (SAS Institute Inc) will be implemented to estimate the parameters of the model, where we specify a log-link function, Poisson distribution for the count data, an offset (which is a function of the total exposure), and the covariates. We will address overdispersion using negative binomial distribution. Overdispersion occurs when the expected count for the outcome variable is not the same as its variance. The generalized estimating equation procedure will be used to account for correlation induced by the repeated observations at T2.

Long-Term Outcome Analyses

At 9 months, the time variable will include observations at T1 to T4, and the procedure implemented for the short-term analysis will be repeated with the inclusion of additional covariates in the form of interaction terms among the groups and follow-up times (T1-T4). The interaction effect is central to the comparison of the groups over the study period. Generalized estimating equation fit criteria and quasi-likelihood under the independence model criterion value will be used to determine the adequacy of model fit. This modeling framework facilitates the easy computation of hypothesis tests and CIs for effects, which will form the basis of our inferential strategy in this project. Specifically, contrast statements will be used to test specific subgroup comparisons. Multiple imputation procedure will be implemented whenever necessary for missing data points. SAS (version 9.4 or higher) will be used for all analyses, and a standard 5% significance level will be used for all statistical tests.

Addressing Biological Variables

As this project is focused on SMMT individuals, rather than assessing the effects of biological sex, we will screen for the effects of gender identity and sexual orientation in the aforementioned modeling framework. This is accomplished by introducing indicator variables for these subgroups into the analyses and assessing statistical and practical significance. The stratified randomization procedure should prevent systematic differences at baseline among the groups. We will check for statistically significant differences after randomization and adjust for such differences in the analysis in the rare event that they manifest.

Qualitative Data Analysis

Audio files of postintervention interviews will be transcribed and imported into NVivo software (Lumivero). Each transcript will be examined and coded using a grounded thematic approach [51], drawing on observed themes regarding intervention attitudes, experiences, and effects. The research team will develop the coding scheme based on an initial review of the transcripts; next, 2 coders will independently code a random sample of 10% of the transcripts. Interrater reliability will be assessed, and the coding scheme will be refined if reliability is not acceptable (acceptable interrater agreement: >90%). Once interrater agreement is achieved, the coders will code the remaining transcripts and collect representative quotations.

Gender-Inclusive and Gender-Specific Approach to Analysis

As an analytic framing to examine inequities in alcohol behaviors within SMMT populations, we will use gender-inclusive and gender-specific approaches throughout the study's quantitative and qualitative analyses, following guidelines from Restar et al [52]. Given that there is epidemiological evidence that transgender and cisgender populations' health outcomes and behaviors, such as alcohol use, are dissimilar to each other and that the drivers of these inequities are contextually uniquely different [6,53-55], applying this approach to our analysis is appropriate. This approach allows our analytical modeling to examine and discern any potential shared versus differential intervention experiences and outcomes across gender groups (ie, between cisgender and transgender participants and within gender subgroups of transgender participants). On the basis of the findings, it will also allow us to provide future intervention recommendations for either the entire sample (ie, gender inclusive) or specific to each gender group (ie, gender specific).

Scientific Rigor

The proposed study uses a rigorous randomized comparative effectiveness trial design to assess intervention effects on alcohol use outcomes. The following characteristics add to the rigor of the study: (1) the use of a SAM-only control group so that all groups can be compared using daily-level alcohol use data, (2) the incorporation of breathalyzers to enhance the validity of self-reported alcohol use, (3) the inclusion of follow-up self-report and SAM data to assess long-term outcomes, (4) recruitment strategies that use in-person and web-based methods to enhance the diversity of the sample, (5) the inclusion of a dedicated biostatistician to provide rigorous outcome analyses, (6) support from app programmers to customize the app and address technical issues, and (7) the inclusion of a licensed social worker to ensure high-quality MI training and fidelity.

Results

The study is part of a 5-year National Institutes of Health research project that was funded in August 2022 by the National Institute on Alcohol Abuse and Alcoholism. The first 1.5 years of the study will be dedicated to planning and development activities, including formative research, app design and testing, and message design and testing. The subsequent 3.5 years will see the study complete participant recruitment, data collection, analyses, report writing, and dissemination. We expect to complete all study data collection in or before January 2027.

As of February 2024, we have published 1 manuscript, a systematic review exploring interventions for addressing alcohol use and sexual HIV risk–related behaviors [16]. We have also completed 2 rounds of focus groups to refine the intervention content and harm reduction messages delivered in TRAC-ER. Overall, 34 participants were enrolled in the first round of focus groups; however, 5 were excluded after further review showed they did not meet the eligibility criteria. This resulted in a final sample of 29 individuals for the first round of focus groups. We

enrolled 22 participants for the second round of focus groups. First, we conducted separate focus groups with participants of different gender identities (sexual minority cisgender men, nonbinary and gender nonconforming participants, transgender men, and transgender women) to obtain feedback on harm reduction content added to the intervention manual and to help us generate initial harm reduction messaging. Next, we conducted an additional blended focus group to help us further refine the messages and develop our final *library* of messages that will be programmed into the app. A manuscript describing this process and the results is forthcoming.

Discussion

Summary

This manuscript describes the protocol for a 3-arm RCT evaluating the efficacy of a mobile-based EMI for reducing alcohol use and HIV risk behaviors among emerging adult SMMT individuals (N=405). We will compare a monitoring-only control to TRAC, a mobile-based MI intervention, and to TRAC-ER, an intervention combining TRAC with in-the-moment messaging to prevent hazardous alcohol use and reduce harm when participants visit risky locations. Mobile breathalyzers and surveys will be used to collect frequent data on alcohol and HIV risk behaviors. We will assess outcomes immediately before and after the intervention, as well as at 6-month and 9-month follow-ups. The primary outcome is the number of drinking days. Formative development work for this RCT has been completed, with the trial to begin recruiting soon (as of February 2024).

This study will make significant contributions to the literature on alcohol use interventions for SMMT populations. It uses an innovative precision health approach that draws upon the frequent use of smartphone technologies by emerging adult populations and the high acceptability of mobile breathalyzers. Despite the proliferation of mobile devices in society, the field of EMIs remains understudied, with very few RCTs being conducted related to alcohol use. In addition, EMIs have shown initial promise in being paired with MI approaches [56-58]; therefore, the proposed study would help to add to the fledgling evidence base regarding the effectiveness of this approach. The use of mobile technology and remote delivery of the tested interventions means that once the ideal approach is identified in terms of efficacy, the intervention will be easily scalable to individuals across wide geographic areas.

Our study has promising strengths, but it must be considered in light of several limitations. While the use of ecological momentary assessment (EMA) provides advantageous opportunities for real-time trigger location data and convenience reporting through smartphones, prior EMA studies highlight the potential exhaustion that participants may experience, which may reduce the level of participation. This study may further explore convenient assessment windows to diminish the intensity of EMA sampling. In addition, as previously mentioned, SMMT communities experience unique sociostructural challenges, such as unemployment, homelessness, forced displacement, and community violence [59]. These systems of power may operate dynamically and render difficulties in participating fully and equitably in hazardous alcohol use prevention programs [60]. Finally, the real-time tracking of alcohol use behaviors of participants may give rise to reporting bias. In the context of alcohol-related stigma, social desirability biases may subject participants to aligning their responses to the expectations of societal norms around alcohol consumption; however, the use of breathalyzers will help to protect against self-report bias.

Prior studies have also reported concerns for temporal bias, where participants were reluctant to complete location- and time-based–triggered EMA surveys due to the inconvenient times at which the surveys were sent. Similarly, EMA studies related to substance use have mentioned challenges with the time frame for EMA sampling [61]. In this study, EMA assessments will occur between 11 AM and 11 PM to avoid disturbing participants. However, participants in prior studies have discussed that these hours may not be representative of the time frames when drinking occurs because alcohol use may occur later at night, along with variations in mood and social activities. Thus, we may explore the potential options for personalized hours of EMA sampling for participants. Breathalyzer device loss may also pose a challenge. However, unlike prior EMA studies that distributed mobile phones and experienced challenges with device loss [62], our study enables participants to use their existing smartphones to use the app, which will reduce instances of device loss or misplacement.

We plan to follow this study with dissemination and implementation research that takes the most effective approach identified here and distributes it to a wider population of SMMT individuals. Overall, by reducing hazardous alcohol use among emerging adult SMMT individuals, we hope to reduce the rates of alcohol-associated HIV transmission among this population considered to be at high risk.

Conclusions

This protocol describes an RCT of an innovative intervention for reducing alcohol use and HIV risk among SMMT individuals. This study will provide evidence about the relative efficacy of using a smartphone-delivered MI intervention and real-time messaging to address triggers for hazardous alcohol use and sexual risk behaviors. The study has potential implications for advancing science and improving public health for a subpopulation that is disproportionately stigmatized and disconnected from prevention research and services.

Acknowledgments

The research reported in this publication was supported by the National Institute on Alcohol Abuse and Alcoholism (R01AA030487) and the National Center for Advancing Translational Sciences (UL1TR001998). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The authors thank Vista IT

Solutions, LLC, as well as IntelliTransit Solutions, Inc, who developed the Tracking and Reducing Alcohol Consumption and Environmental Risk (TRAC-ER) app.

Data Availability

The data sets generated and analyzed during this study are available in the National Institute of Mental Health Data Archive repository (ID C4476) [63].

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the National Institutes of Health.
[PDF File (Adobe PDF File), 257 KB - resprot_v13i1e55166_app1.pdf]

References

1. MacKillop J, Agabio R, Feldstein Ewing SW, Heilig M, Kelly JF, Leggio L, et al. Hazardous drinking and alcohol use disorders. Nat Rev Dis Primers 2022 Dec 22;8(1):80 [FREE Full text] [doi: 10.1038/s41572-022-00406-1] [Medline: 36550121]
2. Coulter RW, Blosnich JR, Bukowski LA, Herrick AL, Siconolfi DE, Stall RD. Differences in alcohol use and alcohol-related problems between transgender- and nontransgender-identified young adults. Drug Alcohol Depend 2015 Sep 01;154:251-259 [FREE Full text] [doi: 10.1016/j.drugalcdep.2015.07.006] [Medline: 26210734]
3. Fish JN, Exten C. Sexual orientation differences in alcohol use disorder across the adult life course. Am J Prev Med 2020 Sep;59(3):428-436 [FREE Full text] [doi: 10.1016/j.amepre.2020.04.012] [Medline: 32713615]
4. Kelly J, Davis C, Schlesinger C. Substance use by same sex attracted young people: prevalence, perceptions and homophobia. Drug Alcohol Rev 2015 Jul;34(4):358-365. [doi: 10.1111/dar.12158] [Medline: 24890312]
5. Slater ME, Godette D, Huang B, Ruan WJ, Kerridge BT. Sexual orientation-based discrimination, excessive alcohol use, and substance use disorders among sexual minority adults. LGBT Health 2017 Oct;4(5):337-344 [FREE Full text] [doi: 10.1089/lgbt.2016.0117] [Medline: 28876167]
6. Hughto JM, Quinn EK, Dunbar MS, Rose AJ, Shireman TI, Jasuja GK. Prevalence and co-occurrence of alcohol, nicotine, and other substance use disorder diagnoses among US transgender and cisgender adults. JAMA Netw Open 2021 Feb 01;4(2):e2036512 [FREE Full text] [doi: 10.1001/jamanetworkopen.2020.36512] [Medline: 33538824]
7. Connolly D, Gilchrist G. Prevalence and correlates of substance use among transgender adults: a systematic review. Addict Behav 2020 Dec;111:106544. [doi: 10.1016/j.addbeh.2020.106544] [Medline: 32717497]
8. Gonzalez CA, Gallego JD, Bockting WO. Demographic characteristics, components of sexuality and gender, and minority stress and their associations to excessive alcohol, cannabis, and illicit (noncannabis) drug use among a large sample of transgender people in the United States. J Prim Prev 2017 Aug;38(4):419-445 [FREE Full text] [doi: 10.1007/s10935-017-0469-4] [Medline: 28405831]
9. Hughes TL, Wilsnack SC, Kantor LW. The influence of gender and sexual orientation on alcohol use and alcohol-related problems: toward a global perspective. Alcohol Res 2016;38(1):121-132 [FREE Full text] [Medline: 27159819]
10. Delgado JR, Segura ER, Lake JE, Sanchez J, Lama JR, Clark JL. Event-level analysis of alcohol consumption and condom use in partnership contexts among men who have sex with men and transgender women in Lima, Peru. Drug Alcohol Depend 2017 Jan 01;170:17-24 [FREE Full text] [doi: 10.1016/j.drugalcdep.2016.10.033] [Medline: 27865150]
11. Newcomb ME. Moderating effect of age on the association between alcohol use and sexual risk in MSM: evidence for elevated risk among younger MSM. AIDS Behav 2013 Jun;17(5):1746-1754 [FREE Full text] [doi: 10.1007/s10461-013-0470-8] [Medline: 23553348]
12. Operario D, Nemoto T, Iwamoto M, Moore T. Unprotected sexual behavior and HIV risk in the context of primary partnerships for transgender women. AIDS Behav 2011 Apr;15(3):674-682 [FREE Full text] [doi: 10.1007/s10461-010-9795-8] [Medline: 20740376]
13. Vosburgh HW, Mansergh G, Sullivan PS, Purcell DW. A review of the literature on event-level substance use and sexual risk behavior among men who have sex with men. AIDS Behav 2012 Aug;16(6):1394-1410. [doi: 10.1007/s10461-011-0131-8] [Medline: 22323004]
14. HIV by group. Centers for Disease Control and Prevention. URL: https://www.cdc.gov/hiv/group/index.html [accessed 2023-10-27]
15. Shuper PA, Joharchi N, Bogoch II, Loutfy M, Crouzat F, El-Helou P, et al. Alcohol consumption, substance use, and depression in relation to HIV Pre-Exposure Prophylaxis (PrEP) nonadherence among gay, bisexual, and other men-who-have-sex-with-men. BMC Public Health 2020 Nov 25;20(1):1782 [FREE Full text] [doi: 10.1186/s12889-020-09883-z] [Medline: 33256651]

16. Lauckner C, Haney K, Sesenu F, Kershaw T. Interventions to reduce alcohol use and HIV risk among sexual and gender minority populations: a systematic review. Curr HIV/AIDS Rep 2023 Aug;20(4):231-250 [FREE Full text] [doi: 10.1007/s11904-023-00660-2] [Medline: 37225923]
17. Kahler CW, Pantalone DW, Mastroleo NR, Liu T, Bove G, Ramratnam B, et al. Motivational interviewing with personalized feedback to reduce alcohol use in HIV-infected men who have sex with men: a randomized controlled trial. J Consult Clin Psychol 2018 Aug;86(8):645-656 [FREE Full text] [doi: 10.1037/ccp0000322] [Medline: 30035581]
18. Lelu iu-Weinberger C, Manu M, Ionescu F, Dogaru B, Kovacs T, Dorobăn escu C, et al. An mHealth intervention to improve young gay and bisexual men's sexual, behavioral, and mental health in a structurally stigmatizing national context. JMIR Mhealth Uhealth 2018 Nov 14;6(11):e183 [FREE Full text] [doi: 10.2196/mhealth.9283] [Medline: 30429117]
19. Parsons JT, Lelutiu-Weinberger C, Botsko M, Golub SA. A randomized controlled trial utilizing motivational interviewing to reduce HIV risk and drug use in young gay and bisexual men. J Consult Clin Psychol 2014 Feb;82(1):9-18 [FREE Full text] [doi: 10.1037/a0035311] [Medline: 24364800]
20. Glynn TR, van den Berg JJ. A systematic review of interventions to reduce problematic substance use among transgender individuals: a call to action. Transgend Health 2017 Mar 1;2(1):45-59 [FREE Full text] [doi: 10.1089/trgh.2016.0037] [Medline: 28861547]
21. Shingleton RM, Palfai TP. Technology-delivered adaptations of motivational interviewing for health-related behaviors: a systematic review of the current research. Patient Educ Couns 2016 Jan;99(1):17-35 [FREE Full text] [doi: 10.1016/j.pec.2015.08.005] [Medline: 26298219]
22. Taylor E, Patel D, Marconi V, Whitmire A, Hansen N, Kershaw T, et al. Pilot trial of a smartphone-based intervention to reduce alcohol consumption among veterans with HIV. Mil Behav Health 2023;11(1-2):66-77 [FREE Full text] [doi: 10.1080/21635781.2023.2221465] [Medline: 38405355]
23. Dulin PL, Gonzalez VM, Campbell K. Results of a pilot test of a self-administered smartphone-based treatment system for alcohol use disorders: usability and early outcomes. Subst Abus 2014;35(2):168-175 [FREE Full text] [doi: 10.1080/08897077.2013.821437] [Medline: 24821354]
24. Gustafson DH, McTavish FM, Chih MY, Atwood AK, Johnson RA, Boyle MG, et al. A smartphone application to support recovery from alcoholism: a randomized clinical trial. JAMA Psychiatry 2014 May;71(5):566-572 [FREE Full text] [doi: 10.1001/jamapsychiatry.2013.4642] [Medline: 24671165]
25. Biernacki P, Waldorf D. Snowball sampling: problems and techniques of chain referral sampling. Sociol Methods Res 1981;10(2):141-163 [FREE Full text] [doi: 10.1177/004912418101000205]
26. Etikan I. Comparison of convenience sampling and purposive sampling. Am J Theor Appl Stat 2016 Jan;5(1):1. [doi: 10.11648/j.ajtas.20160501.11]
27. Muhib FB, Lin LS, Stueve A, Miller RL, Ford WL, Johnson WD, et al. A venue-based method for sampling hard-to-reach populations. Public Health Rep 2001;116 Suppl 1(Suppl 1):216-222 [FREE Full text] [doi: 10.1093/phr/116.S1.216] [Medline: 11889287]
28. Gower AL, Rider GN, Brown C, McMorris BJ, Coleman E, Taliaferro LA, et al. Supporting transgender and gender diverse youth: protection against emotional distress and substance use. Am J Prev Med 2018 Dec;55(6):787-794 [FREE Full text] [doi: 10.1016/j.amepre.2018.06.030] [Medline: 30344037]
29. Ramos SR, Lardier DTJ, Opara I, Turpin RE, Boyd DT, Gutierrez JI, et al. Intersectional effects of sexual orientation concealment, internalized homophobia, and gender expression on sexual identity and HIV risk among sexual minority men of color: a path analysis. J Assoc Nurses AIDS Care 2021;32(4):495-511 [FREE Full text] [doi: 10.1097/JNC.0000000000000274] [Medline: 34101701]
30. Ramos SR, Lardier DTJ, Boyd DT, Gutierrez JIJ, Carasso E, Houng D, et al. Profiles of HIV risk, sexual power, and decision-making among sexual minority men of color who engage in transactional sex: a latent profile analysis. Int J Environ Res Public Health 2021 May 07;18(9):4961 [FREE Full text] [doi: 10.3390/ijerph18094961] [Medline: 34066948]
31. Pre-exposure prophylaxis (PrEP). HIVInfo, National Institutes of Health. URL: https://tinyurl.com/5a2tsk4c [accessed 2023-12-02]
32. Bush K, Kivlahan DR, McDonell MB, Fihn SD, Bradley KA. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test. Arch Intern Med 1998 Sep 14;158(16):1789-1795. [doi: 10.1001/archinte.158.16.1789] [Medline: 9738608]
33. Flentje A, Barger BT, Capriotti MR, Lubensky ME, Tierney M, Obedin-Maliver J, et al. Screening gender minority people for harmful alcohol use. PLoS One 2020 Sep 14;15(4):e0231022-e0231095 [FREE Full text] [doi: 10.1371/journal.pone.0231022] [Medline: 32255781]
34. Lundahl B, Kunz C, Brownell C, Tollefson D, Burke B. A Meta-Analysis of Motivational Interviewing: Twenty-Five Years of Empirical Studies. Research on Social Work Practice 2010 Jan 11;20(2):137-160. [doi: 10.1177/1049731509347850]
35. Wang L, Miller LC. Just-in-the-Moment Adaptive Interventions (JITAI): A Meta-Analytical Review. Health Commun 2020 Nov 11;35(12):1531-1544. [doi: 10.1080/10410236.2019.1652388] [Medline: 31488002]
36. Cohen J. A power primer. Psychol Bull 1992 Jul;112(1):155-159. [doi: 10.1037//0033-2909.112.1.155] [Medline: 19565683]

37. Moyers T, Manuel J, Ernst D. Motivational interviewing treatment integrity coding manual 4.1 (MITI 4.1). Unpublished manual 2014.
38. Moyers TB, Rowell LN, Manuel JK, Ernst D, Houck JM. The Motivational Interviewing Treatment Integrity Code (MITI 4): Rationale, Preliminary Reliability and Validity. J Subst Abuse Treat 2016 Jun;65(12):36-42 [FREE Full text] [doi: 10.1016/j.jsat.2016.01.001] [Medline: 26874558]
39. Jelsma JG, Mertens VC, Forsberg L, Forsberg L. How to Measure Motivational Interviewing Fidelity in Randomized Controlled Trials: Practical Recommendations. Contemp Clin Trials 2015 Jul;43:93-99. [doi: 10.1016/j.cct.2015.05.001] [Medline: 25962891]
40. Pittman B, Gueorguieva R, Krupitsky E, Rudenko AA, Flannery BA, Krystal JH. Multidimensionality of the Alcohol Withdrawal Symptom Checklist: a factor analysis of the Alcohol Withdrawal Symptom Checklist and CIWA-Ar. Alcohol Clin Exp Res 2007 Apr;31(4):612-618. [doi: 10.1111/j.1530-0277.2007.00345.x] [Medline: 17374040]
41. Pilkonis PA, Yu L, Colditz J, Dodds N, Johnston KL, Maihoefer C, et al. Item banks for alcohol use from the Patient-Reported Outcomes Measurement Information System (PROMIS): use, consequences, and expectancies. Drug Alcohol Depend 2013 Jun 01;130(1-3):167-177 [FREE Full text] [doi: 10.1016/j.drugalcdep.2012.11.002] [Medline: 23206377]
42. Rollnick S, Heather N, Gold R, Hall W. Development of a short 'readiness to change' questionnaire for use in brief, opportunistic interventions among excessive drinkers. Br J Addict 1992 May;87(5):743-754. [doi: 10.1111/j.1360-0443.1992.tb02720.x] [Medline: 1591525]
43. Oei TP, Hasking PA, Young RM. Drinking refusal self-efficacy questionnaire-revised (DRSEQ-R): a new factor structure with confirmatory factor analysis. Drug Alcohol Depend 2005 Jun 01;78(3):297-307. [doi: 10.1016/j.drugalcdep.2004.11.010] [Medline: 15893161]
44. National HIV Behavioral Surveillance (NHBS): Methods and Questionnaires. Centeres for Disease Control and Prevention. URL: https://www.cdc.gov/hiv/statistics/systems/nhbs/methods-questionnaires.html [accessed 2024-03-07]
45. Conley TD, Collins BE. Differences between condom users and condom nonusers in their multidimensional condom attitudes. J Appl Soc Pyschol 2005 Mar;35(3):603-620. [doi: 10.1111/j.1559-1816.2005.tb02137.x]
46. Napper LE, Fisher DG, Reynolds GL. Development of the perceived risk of HIV scale. AIDS Behav 2012 May;16(4):1075-1083 [FREE Full text] [doi: 10.1007/s10461-011-0003-2] [Medline: 21785873]
47. Smith ER, Perrin PB, Sutter ME. Factor analysis of the heterosexist harassment, rejection, and discrimination scale in lesbian, gay, bisexual, transgender, and queer people of colour. Int J Psychol 2020 Jun;55(3):405-412 [FREE Full text] [doi: 10.1002/ijop.12585] [Medline: 31161655]
48. Flannery BA, Volpicelli JR, Pettinati HM. Psychometric Properties of the Penn Alcohol Craving Scale. Alcohol Clin & Exp Res 2006 May 30;23(8):1289-1295. [doi: 10.1111/j.1530-0277.1999.tb04349.x] [Medline: 10470970]
49. myLAB Box home page. myLAB Box. URL: https://www.mylabbox.com/ [accessed 2023-11-30]
50. Nelder J, Wedderburn R. Generalized Linear Models. Journal of the Royal Statistical Society. Series A (General) 1972 Jun;135(3):370-342. [doi: 10.2307/2344614] [Medline: 26874558]
51. Glaser B, Strauss A. Discovery of Grounded Theory: Strategies for Qualitative Research. New York: Routledge; 1999.
52. Restar A, Jin H, Operario D. Gender-inclusive and gender-specific approaches in trans health research. Transgend Health 2021 Oct 4;6(5):235-239 [FREE Full text] [doi: 10.1089/trgh.2020.0054] [Medline: 34993295]
53. Dermody SS, Lamb KM, Kerr DC. Heavy drinking and drinking harms for cisgender and transgender college students. Psychol Addict Behav 2022 Aug;36(5):466-476. [doi: 10.1037/adb0000778] [Medline: 34498889]
54. Connolly DJ, Davies E, Lynskey M, Maier LJ, Ferris JA, Barratt MJ, et al. Differences in alcohol and other drug use and dependence between transgender and cisgender participants from the 2018 global drug survey. LGBT Health 2022 Nov;9(8):534-542. [doi: 10.1089/lgbt.2021.0242] [Medline: 35878065]
55. Connolly D, Davies E, Lynskey M, Barratt MJ, Maier L, Ferris J, et al. Comparing intentions to reduce substance use and willingness to seek help among transgender and cisgender participants from the Global Drug Survey. J Subst Abuse Treat 2020 May;112:86-91. [doi: 10.1016/j.jsat.2020.03.001] [Medline: 32199550]
56. Kazemi DM, Borsari B, Levine MJ, Li S, Shehab M, Fang F, et al. Effectiveness of a Theory-Based mHealth Intervention for High-Risk Drinking in College Students. Subst Use Misuse 2020;55(10):1667-1676. [doi: 10.1080/10826084.2020.1756851] [Medline: 32394772]
57. Shrier LA, Burke PJ, Kells M, Scherer EA, Sarda V, Jonestrask C, et al. Pilot randomized trial of MOMENT, a motivational counseling-plus-ecological momentary intervention to reduce marijuana use in youth. Mhealth 2018;4(10):29-1676 [FREE Full text] [doi: 10.21037/mhealth.2018.07.04] [Medline: 30148142]
58. Shrier LA, Burke PJ, Parker S, Edwards R, Jonestrask C, Pluhar E, et al. Development and pilot testing of a counseling-plus-mHealth intervention to reduce risk for pregnancy and sexually transmitted infection in young women with depression. Mhealth 2020;6(10):17-1676 [FREE Full text] [doi: 10.21037/mhealth.2019.11.05] [Medline: 32270009]
59. Henderson ER, Goldbach JT, Blosnich JR. Social determinants of sexual and gender minority mental health. Curr Treat Options Psych 2022 Jun 25;9:229-245. [doi: 10.1007/s40501-022-00269-z]
60. Stryker S. Transgender History: The Roots of Today's Revolution, Second Edition. New York, NY: Basic Books; 2017.
61. Shiffman S. Ecological momentary assessment (EMA) in studies of substance use. Psychol Assess 2009 Dec;21(4):486-497 [FREE Full text] [doi: 10.1037/a0017074] [Medline: 19947783]

62. Kirk GD, Linas BS, Westergaard RP, Piggott D, Bollinger RC, Chang LW, et al. The exposure assessment in current time study: implementation, feasibility, and acceptability of real-time data collection in a community cohort of illicit drug users. AIDS Res Treat 2013;2013:594671 [FREE Full text] [doi: 10.1155/2013/594671] [Medline: 24307943]
63. Lauckner C. Evaluation of a combined motivational interviewing and ecological momentary intervention to reduce risky alcohol use among sexual minority males and transgender individuals. National Institutes of Health. URL: https://nda.nih.gov/edit_collection.html?id=4476 [accessed 2024-02-13]

Abbreviations

AUD: alcohol use disorder
AUDIT-C: Alcohol Use Disorders Identification Test–Concise
EMA: ecological momentary assessment
EMI: ecological momentary intervention
HIPAA: Health Insurance Portability and Accountability Act
MI: motivational interviewing
MITI: Motivational Interviewing Treatment Integrity
PrEP: pre-exposure prophylaxis
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SAM: smartphone-based alcohol monitoring
SMMT: sexual minority cisgender men and transgender
STI: sexually transmitted infection
TRAC: Tracking and Reducing Alcohol Consumption
TRAC-ER: Tracking and Reducing Alcohol Consumption and Environmental Risk

Edited by A Mavragani; submitted 05.12.23; this is a non–peer-reviewed article;accepted 20.02.24; published 05.04.24.

Please cite as:
Lauckner C, Takenaka BP, Sesenu F, Brown JS, Kirklewski SJ, Nicholson E, Haney K, Adatorwovor R, Boyd DT, Fallin-Bennett K, Restar AJ, Kershaw T
Combined Motivational Interviewing and Ecological Momentary Intervention to Reduce Hazardous Alcohol Use Among Sexual Minority Cisgender Men and Transgender Individuals: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2024;13:e55166
URL: https://www.researchprotocols.org/2024/1/e55166
doi:10.2196/55166
PMID:38578673

Protocol

Smartphone App–Delivered Mindfulness-Based Intervention for Mild Traumatic Brain Injury in Adolescents: Protocol for a Feasibility Randomized Controlled Trial

Andrée-Anne Ledoux[1,2,3,4], PhD; Roger Zemek[1,4,5], MD; Molly Cairncross[6,7], PhD; Noah Silverberg[7,8,9], PhD; Veronik Sicard[1], PhD; Nicholas Barrowman[1], PhD; Gary Goldfield[1,3,4,5], PhD; Clare Gray[10,11], MD; Ashley D Harris[12], PhD; Natalia Jaworska[2,4,13], PhD; Nick Reed[14], PhD; Bechara J Saab[15], PhD; Andra Smith[3,4], PhD; Lisa Walker[3,4,16], PhD

[1]Children's Hospital of Eastern Ontario Research Institute, Ottawa, ON, Canada
[2]Department of Cellular Molecular Medicine, Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada
[3]School of Psychology, Faculty of Social Sciences, University of Ottawa, Ottawa, ON, Canada
[4]University of Ottawa Brain and Mind Research Institute, University of Ottawa, Ottawa, ON, Canada
[5]Department of Pediatrics, Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada
[6]Department of Psychology, Simon Fraser University, Burnaby, BC, Canada
[7]BC Children's Hospital Research Institute, Vancouver, BC, Canada
[8]Department of Psychology, University of British Columbia, Vancouver, BC, Canada
[9]Rehabilitation Research Program, Centre for Aging SMART, Vancouver Coastal Health Research Institute, Vancouver, BC, Canada
[10]Children's Hospital of Eastern Ontario, Ottawa, ON, Canada
[11]Department of Psychiatry, Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada
[12]Department of Radiology, Hotchkiss Brain Institute, Alberta Children's Hospital Research Institute, University of Calgary, Calgary, AB, Canada
[13]Royal Ottawa Mental Health Centre, Ottawa, ON, Canada
[14]Department of Occupational Science & Occupational Therapy, University of Toronto, Toronto, ON, Canada
[15]Mobio Interactive, Singapore, Singapore
[16]The Ottawa Hospital, Ottawa, ON, Canada

Corresponding Author:
Andrée-Anne Ledoux, PhD
Children's Hospital of Eastern Ontario Research Institute
401 Smyth Road
Ottawa, ON, K1H 8L1
Canada
Phone: 1 6137377600 ext 4104
Email: aledoux@cheo.on.ca

Abstract

Background: Concussion in children and adolescents is a significant public health concern, with 30% to 35% of patients at risk for prolonged emotional, cognitive, sleep, or physical symptoms. These symptoms negatively impact a child's quality of life while interfering with their participation in important neurodevelopmental activities such as schoolwork, socializing, and sports. Early psychological intervention following a concussion may improve the ability to regulate emotions and adapt to postinjury symptoms, resulting in the greater acceptance of change; reduced stress; and recovery of somatic, emotional, and cognitive symptoms.

Objective: The primary objective of this study is to assess the feasibility of conducting a parallel-group (1:1) randomized controlled trial (RCT) to evaluate a digital therapeutics (DTx) mindfulness-based intervention (MBI) in adolescents aged 12 to <18 years. The attention-matched comparator intervention (a math game also used in previous RCTs) will be delivered on the same DTx platform. Both groups will be provided with the standard of care guidelines. The secondary objective is to examine intervention trends for quality of life; resilience; self-efficacy; cognition such as attention, working memory, and executive functioning; symptom burden; and anxiety and depression scores at 4 weeks after concussion, which will inform a more definitive RCT. A subsample will be used to examine whether those randomized to the experimental intervention group have different brain-based imaging patterns compared with those randomized to the control group.

Methods: This study is a double-blind Health Canada–regulated trial. A total of 70 participants will be enrolled within 7 days of concussion and randomly assigned to receive the 4-week DTx MBI (experimental group) or comparator intervention. Feasibility will be assessed based on the recruitment rate, treatment adherence to both interventions, and retention. All outcome measures will be evaluated before the intervention (within 7 days after injury) and at 1, 2, and 4 weeks after the injury. A subset of 60 participants will undergo magnetic resonance imaging within 72 hours and at 4 weeks after recruitment to identify the neurophysiological mechanisms underlying the potential benefits from MBI training in adolescents following a concussion.

Results: The recruitment began in October 2022, and the data collection is expected to be completed by September 2024. Data collection and management is still in progress; therefore, data analysis is yet to be conducted.

Conclusions: This trial will confirm the feasibility and resolve uncertainties to inform a future definitive multicenter efficacy RCT. If proven effective, a smartphone-based MBI has the potential to be an accessible and low-risk preventive treatment for youth at risk of experiencing prolonged postconcussion symptoms and complications.

Trial Registration: ClinicalTrials.gov NCT05105802; https://classic.clinicaltrials.gov/ct2/show/NCT05105802

International Registered Report Identifier (IRRID): DERR1-10.2196/57226

(JMIR Res Protoc 2024;13:e57226) doi:10.2196/57226

KEYWORDS

pediatric; concussion; persisting symptoms after concussion; mindfulness; randomized controlled trial; feasibility RCT; psychological intervention; youth; digital therapeutics; eHealth; mobile health; mHealth; mobile phone

Introduction

Background and Rationale

Approximately 30% to 35% of the children and adolescents who experience a concussion are considered to have persisting symptoms after concussion (PSAC) [1,2], defined as the persistence of somatic (eg, headache, dizziness, and fatigue); cognitive (eg, memory, concentration, and confusion); and other physical, psychological, and behavioral changes lasting beyond 1 month [3]. PSAC may impair daily activities including schoolwork, socializing, and sports and thereby reduce the quality of life (QoL) [4]. Studies have demonstrated that both noninjury and injury factors predict PSAC following a concussion [2,5,6], with the contribution of injury factors to PSAC decreasing over time. However, premorbid conditions such as preinjury somatic symptoms [7], migraine [2], preinjury cognitive ability [8], preexisting attention and mood concerns [9], anxiety [10], and coping strategies [11] remain important predictors of symptom persistence over time [8,12]. Preventive, early rehabilitation programs such as interventions focusing on building psychological resiliency, emotional regulation, and self-efficacy might be key to managing concussions, reducing PSAC risk, and promoting neural recovery.

Mindfulness-based interventions (MBIs) are *present-centered* interventions that encourage acceptance of thoughts and emotions as they occur in the moment without judgment. MBIs have been demonstrated to improve attentional focus, cognitive flexibility, depression and anxiety symptoms, self-concept, resiliency, and academic achievements as well as reduce affective reactivity and fear in clinical youth samples [13]. In addition, in-person MBIs seem effective at treating preinjury predictors of PSAC, such as mood disorders [14-17], somatization-related illness [14,18,19], headache disorders [20], and chronic pain [21]. However, in-person interventions may not be suitable for adolescents with acute concussion owing to high cost and low accessibility [22,23] and require commitment from parents and children for in-person weekly meetings for periods varying from 8 to 16 weeks. Brief (as short as 3 days to 4 weeks) web-based MBIs with guided meditation have been shown to have positive effects on anxiety, negative mood, perceived stress, and attention in different clinical populations [24-27]. MBIs may foster adaptive coping, increase resiliency, and reduce the risk of PSAC following pediatric concussion. Smartphone, or mobile, apps may present a versatile and personalized platform for the delivery of a dedicated MBI for populations experiencing a concussion [28].

Health care digital therapeutics (DTx; smartphone app) have gained popularity in the past decade as a means of screening patients, monitoring symptoms, and delivering psychoeducation and interventions [28,29]. The efficacy of mobile apps in delivering psychological interventions has been demonstrated in mental health samples, particularly in the treatment of depression and anxiety. Randomized controlled trials (RCTs) have shown that app-based interventions can effectively improve depressive and anxiety symptoms compared with waiting list, alternative care, or control conditions [29-34]. Similarly, a recent meta-analysis of RCTs on app-based MBIs has demonstrated significant small-to-medium effects in improving perceived stress, symptoms of depression and anxiety, QoL, psychological well-being, and positive affects, compared with control conditions, waitlist, and alternative interventions [35]. However, the application of an app-based MBI in pediatric concussion has not yet been studied.

We partnered with Mobio Interactive Inc (Toronto, Ontario, Canada), the creator of a clinically validated platform called *AmDTx*, to create an app-based dedicated DTx MBI for pediatric concussion. We assessed the acceptability and usability of the DTx with a small open-label single-arm study (N=10) [36]. The participants reported high satisfaction and found the app easy to use and the treatment to be credible. They also developed a strong alliance with their MBI guides (ie, those who are leading the meditation and psychoeducation sessions) [37]. The primary aim of this study is to assess the feasibility of the 4-week planned RCT methods to determine whether we can advance

to an efficacy trial and, thereby, elevate our understanding of the optimal time points for collecting outcome measures. At 4 weeks, those randomized to the DTx MBI will have the opportunity to continue for another 4 weeks, that is, completing a total of 8 weeks of MBI. The goal of this additional 4-week intervention is to explore feasibility outcomes in an 8-week intervention. Finally, those who are part of the DTx control group (attention-matched comparator intervention) will have the opportunity to cross over to the DTx MBI group.

Primary Research Objective

The primary research objectives are to assess the feasibility of conducting a larger RCT by evaluating recruitment efficiency, adherence to treatment, credibility, and retention.

Secondary Research Objectives

The secondary research objectives were as follows:

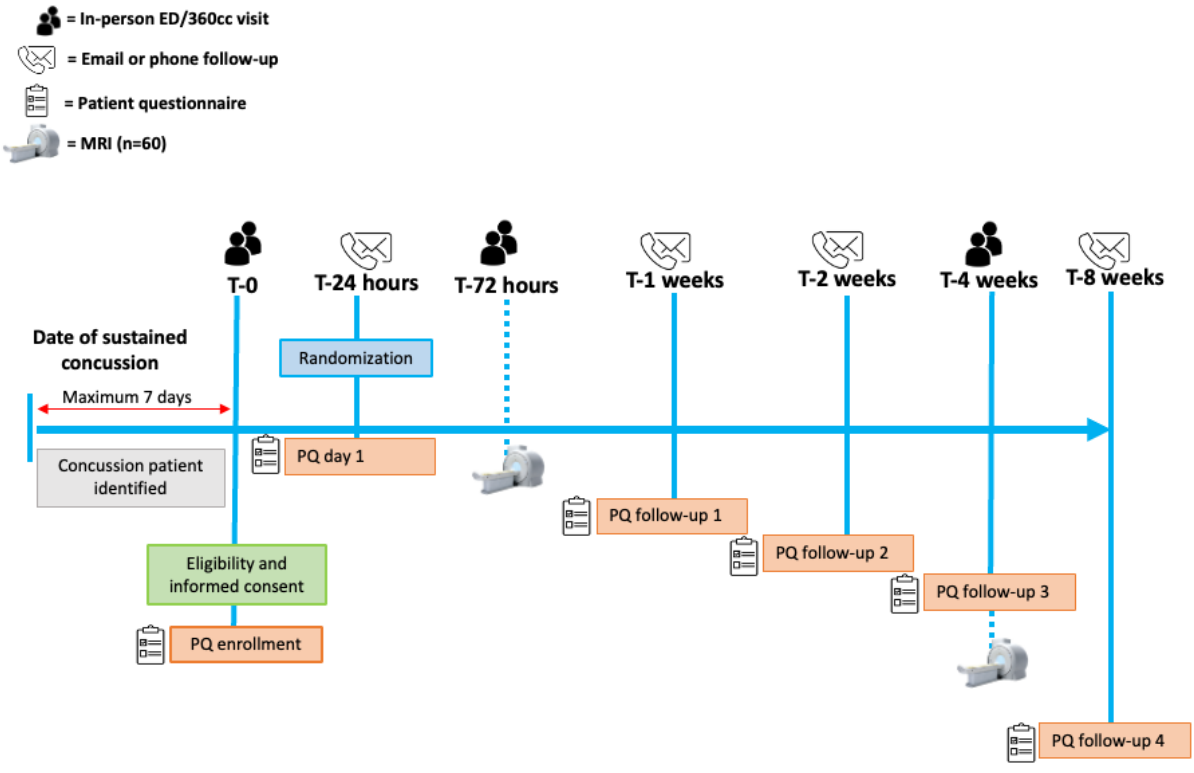
1. Establish the participants' expectancy toward both interventions.
2. Examine the participants' satisfaction with the interventions.
3. Generate estimates to inform sample size calculations for a future multicenter RCT.
4. Assess whether there is preliminary evidence of an efficacy signal for QoL, fatigue, symptoms, resiliency, self-efficacy, cognition, anxiety, depression, and mindfulness.
5. Examine the experimental group's baseline characteristics, adherence, and attrition rates in those who chose to continue for an additional 4 weeks compared with those who chose to complete the study at 4 weeks compared with those who were lost to follow-up.
6. Examine the control group's baseline characteristics, adherence, and attrition rates in those who chose to cross over to the experimental interventions at 4 weeks versus those who chose to complete the study at 4 week versus those who were lost to follow-up.
7. Examine whether the experimental intervention is associated with differential brain-based imaging patterns of functional connectivity, cerebral blood flow, and spectroscopy.
8. Examine safety by examining whether the experimental intervention has increased adverse events (ie, total number) relative to the control intervention.

Methods

Trial Design

The proposed study is a Health Canada–regulated parallel-group (1:1) RCT, where patients within 7 days of a concussion will be randomly assigned to one of the two groups: (1) experimental group (n=35), early introduction of the DTx MBI program and (2) control group (n=35), sham DTx attention-matched comparator intervention. The participants will start the intervention the next day after being enrolled in the study. After 4 weeks, those in the experimental group will be offered the MBI program with 4-week additional education modules. Those who are part of the control group will be offered to cross over to start the DTx MBI. Of the 70 participants enrolled, 60 (86%) consenting participants (n=30, 50% from the experimental group and n=30, 50% from the control group) will be enrolled in neuroimaging, which requires participation in a brain scanning session within 72 hours of enrollment and during week 4 of the study. For a schematic diagram of the trial design, procedures, and stages, refer to the study flow diagram in Figure 1.

Figure 1. Flowchart of the study procedures. 360cc: 360 Concussion Care; ED: emergency department; MRI: magnetic resonance imaging; PQ: patient questionnaire.



Study Setting

The study will be conducted at the Children's Hospital of Eastern Ontario (CHEO) and the 360 Concussion Care (360cc) clinic, a tertiary health care concussion clinic. The neuroimaging component of the study will be completed at the Royal Ottawa Mental Health Centre's Brain Imaging Centre on a 3-Tesla Siemens magnetic resonance-positron emission tomography system with a 32-channel head coil (Siemens Biograph mMR, Siemens).

Eligibility Criteria

Inclusion Criteria

Adolescents presenting to either CHEO's emergency department (ED) or 360cc after sustaining a direct or indirect mild traumatic brain injury (TBI) will be eligible to participate in this study if they (1) are aged 12 to <18 years; (2) have a diagnosed concussion (by a physician), (3) presented to the ED or 360cc within 7 days of TBI; (4) have a score >4 on the Predicting and Preventing Post-Concussive Problems in Pediatrics (5P) clinical risk score, a prediction rule to identify those at risk of poorer outcomes at 4 weeks postinjury [2]; and (5) are proficient in English [38]. To increase the probability of including adolescents with a true concussion, the adapted version of the American Congress of Rehabilitation Medicine [39] framework will be used [40]. Those with either 1 *highest level of certainty* symptom (dazed, confused, or trouble thinking within minutes after injury, difficulty remembering what happened just before or minutes after injury, and loss of consciousness) or 2 *higher level of certainty* symptoms (nausea or vomiting, headache, dizziness, clumsy or balance problems, blurred or double or change in vision, difficulty concentrating, and sensitivity to light or noise) immediately or within 1 hour of injury will be included.

Exclusion Criteria

Patients will be excluded if they present with TBIs with any of the following: (1) a Glasgow Coma Scale score of ≤13; (2) abnormality on standard neuroimaging studies [41], including positive head computed tomography findings (neuroimaging is not required, but may be performed if clinically indicated); (3) neurosurgical operative intervention, intubation, or intensive care required; (4) multisystem injuries with the treatment requiring hospital admission, operating room, or procedural sedation in ED (hospital admission for observation or management of ongoing concussion symptoms is not an exclusion criteria); (5) severe chronic neurological developmental delay resulting in communication difficulties; (6) intoxication to alcohol or drugs at the time of ED presentation as per clinician judgment; (7) no clear history of trauma as primary event to the concussion (eg, seizure, syncope, and migraine); (8) prior psychiatric hospitalization; (9) inability to obtain written informed consent or assent (eg, language barrier); (10) legal guardian not present (certain forms need to be completed by parents or legal guardians); (11) no internet and mobile or tablet access; and (12) currently in therapy.

In addition, patients will not be included in the magnetic resonance imaging (MRI) component if they present with the following: (1) previous neurological or neurodevelopmental disorder such as epilepsy, intellectual disability, or autism (history of attention-deficit or hyperactivity disorder or learning disability is not exclusionary); (2) previous stroke or transient ischemic attacks; (3) sedation medication (eg, propofol, ketamine, nitrous oxide, midazolam, benzodiazepines, and fentanyl) administered before or during ED visit; (4) inability to be present at the 72-hour (+48 or –48 hours) and 4-week (+5 or –5 days) MRI follow-up visits; and (5) medical contraindications to MRI (eg, claustrophobia, pregnancy, or presence of braces or spacers or other metal implants).

Randomization, Blinding, and Allocation

Sequence Generation

The CHEO Clinical Research Unit will provide data management services for this study and retain randomization codes. The randomization sequence will be created using R software (version 3.1.1; R Foundation for Statistical Computing) [42] and will be stratified by sex, with a 1:1 allocation using random blocks.

Allocation Concealment

A statistician at the CHEO CRU (not involved in the study) will maintain the master list.

Implementation

The day after enrollment and once all questionnaire data are complete, research assistants (RAs) will call participants over the phone, and RAs will log into REDCap (Research Electronic Data Capture; Vanderbilt University) to obtain the patient's group allocation. Only the RAs who randomized participants will be unblinded. The research team will be blinded to data acquisition. In case of a serious adverse event, the principal investigator and appropriate research staff will be unblinded to the participant's group.

Methods for Protecting Against Bias

The investigators, coaches, other research staff, data management staff, and biostatisticians will be blinded to the group assignment. Patients and families will be blinded to the purpose and expected results of the interventions and to the other treatment arm.

Intervention Description

Experimental Group Description: MBI Training

To be delivered via the *AmDTx* platform (Figure 2), the targeted DTx MBI training consists of a 4- to 8-week custom-made program (containing 8-modules) for adolescents with concussion, including setting intentions and check-ins on mood and stress, audio-recorded lectures, guided meditations such as focused attention exercises, and journaling events (Table 1). Each standardized psychoeducation or meditation practice will be unlocked as the participant progresses through the MBI program. Participants will be encouraged to participate in the DTx MBI activities for approximately 10 minutes every day, for a minimum of 4 days a week, over the 4- to-8-week period. Those who choose to end their therapy on the fourth week will be immediately directed to module 8 *Reviewing the program and how to maintain practice*. Those who choose to continue for an additional 4 weeks will move on to modules 5 through

8. The curriculum is based on previously validated *AmDTx* MBI app protocols [27,43] and team expertise in youth MBI (Sonia Roth, Craig Mackie, MC, and AAL) and was peer reviewed by experts in the field and parent engagement leaders (Ana Maria Vranceanu, Jonathan Greenberg, and Erin McCarthy). The intervention was piloted on 10 pediatric participants with concussion, and their feedback was integrated into the MBI and protocol [36]. We will track *meaningful* in-app use time, defined as the time spent engaging in meditation, psychoeducation, self-monitoring, and self-reflection, with a minimum threshold of 3 minutes per day. Any use time <3 minutes will not be counted toward the total weekly minutes spent using the *DTx*.

Figure 2. Adolescent concussion dedicated experimental and control interventions delivered through the AmDTx platform. (A) Initial loading screen of AmDTx; (B) main menu or home screen of AmDTx as seen by the participants randomized to the experimental intervention; (C) journey selection screen. Concussion Journey is shown; (D) main or menu page of the concussion MBI. Slices of the badge are awarded upon the completion of each module; (E) main or menu page of module 1; (F) stage 1 of module 1 play screen; (G) to complete the stage, the participant taps on the arrows at the top right; (H) main or menu page of module 3, with participant progression up to stage 5. (I, J and L) Before and after each the participant is prompted to complete the wellbeing measurements “Snapshot”; (K) stage 4 of module 2, “Body Scan” preplay screen with 2 meditation guide options; (L) snapshot ecological momentary assessment for stress and the open field box features; (M) journaling feature menu; (N) journaling feature input page relating to goal setting; (O) main menu or home screen of AmDTx as seen by the participants randomized to the control intervention. The feature “Concussion Recovery” is where the control math game is found; (P) main screen of the control task; (Q) to ensure as much similarity in the experience as possible and to collect valuable insights into the well-being of participants, the control is also book-ended with snapshots. Shown here is the mood circumplex feature; (R) control task midway through completion; (S) timer message prompting the participant to end their cognitive training for the day; (T) snapshot selfie scan feature after video has been captured; (U) the My Insights page where the participants randomized to either group can view how individual intervention stages or the control task impacted their well-being.

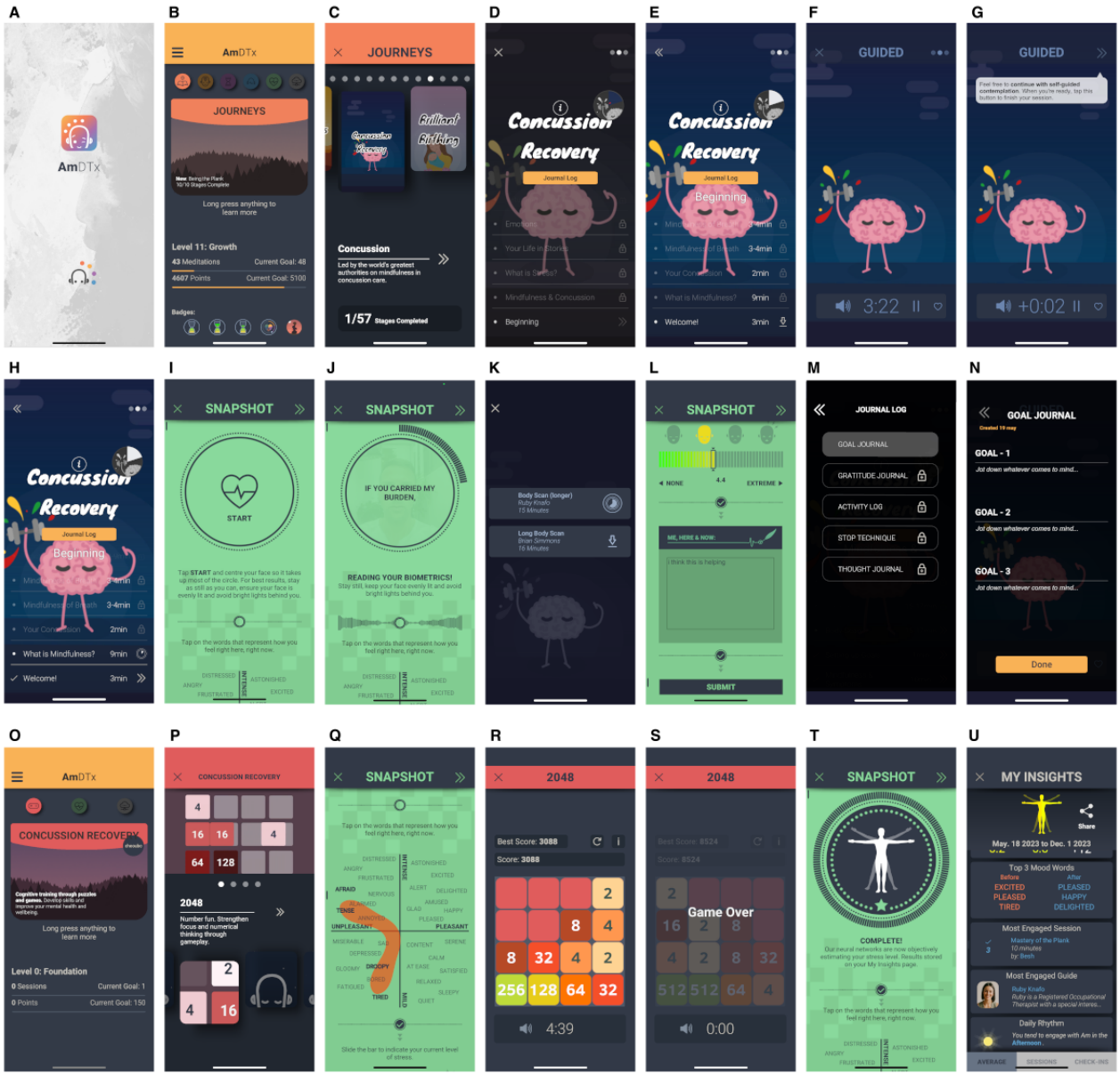


Table 1. Four- or 8-week experimental intervention consisting of a targeted digital therapeutics mindfulness-based intervention for adolescents with concussion that includes setting intentions and check-ins on mood and stress, audio-recorded lectures, guided meditations such as focused attention exercises, and journaling events.

Module	Course or focus	Meditation practices	Exercise
1	• What is mindfulness • Setting intentions • Belly breathing exercise • Introduction to body scan	• Body scan (short): 7 minutes × 2 • Belly breathing: 3 minutes × 2	• N/A[a]
2	• Mindful attitudes (nonjudgment and acceptance) • How to skillfully meet concussion symptoms	• Mindfulness of breath: 5 minutes × 2 • Body scan: 15 minutes × 2	• Setting goals • Positive event journal • Doing 1 daily routine mindfully
3	• Stress response • The biology of stress • Inner narrative and chronic stress • STOP technique	• Mindful of breath: 10 minutes × 2 • STOP technique • Mindful movement: 7 minutes × 2	• Symptoms of stress checklist and mapping stress on the body • Journal when you used the STOP technique
4	• Thoughts: the stories we tell ourselves • Reframing symptoms with thoughts and attitudes • Moving mindfully through your life	• Mindfulness of sound transitioning to thoughts: 10 minutes × 2 • Mindfulness movement: 10 minutes × 2	• Thought journal
5	• Pain and emotions • How to mindfully manage pain • Being mindful of your emotion • The Breathe-Calm-Okay-Observe-Love technique	• Body scan: 12 minutes × 2 • Practice sitting meditation with emphasis on emotion: 10 minutes × 2	• N/A
6	• How to return to activities • Gratitude—who or what has helped you in your recovery	• Mindful movement practice: 10 minutes × 2 • Loving-kindness and gratitude practice: 10 minutes × 2	• Thought journal
7	• Integrating mindfulness more fully into daily life • Barriers to practice	• Open awareness practice: 10 minutes × 2 • Users choice practice: 5-15 minutes × 2	• Thought journal
4 or 8	• Review of program, strategies for maintaining practice, and reflection on how mindfulness has helped cope with your concussion or otherwise	• Users choice practice: 5-15 minutes × 4	• Review treatment goals • Goal setting for the future

[a]N/A: not applicable.

Control Group Description: Sham App

To control for daily access to the *AmDTx* platform, expectation, and clinical attention bias, we created a sham DTx for the control group. The sham DTx will be delivered on the same main interface, within *AmDTx*; however, these participants will not have access to any of the MBI training or psychoeducational content. Their sham DTx will consist of playing an open-source math game called 2048 developed by Gabriele Cirulli [44]; this will be communicated to the control participants as *cognitive training*. The game requires participants to slide number tiles on a grid and combine them to create a tile with the number 2048. In a previous study, *AmDTx* was compared with 2048, revealing that 2048 did not reduce stress or improve psychological well-being in university students with anxiety [27]. Furthermore, 2048 was previously tested in a pediatric population with concussion, and the study found no evidence of harm or symptom improvement at 4 weeks [45]. It is expected that the control intervention will not bother individuals with sensitivity to light or high velocity motion because it lacks fast visuals or movement. The game is programmed to only be accessible for 10 minutes per day.

Coaching

All participants will be followed weekly by a coach through SMS text messaging. The coaches' role will be to ensure that the participants adhere to the intervention. All the participants will receive weekly text messages from a coach. These messages will be sent on the same day and time every week and will be limited to 160 characters. The coaches will use a standardized question and answer protocol developed by the team. Coaches will also remind the participants to complete their follow-up surveys.

Furthermore, both interventions are equipped with automated reminders (triggered by inactivity).

Standard of Care

All the participants will receive standard of care [46] instructions pamphlet provided by RAs in the ED or at 360cc. The standard of care indicates that the patient refrains from physical and cognitive activities for 24 to 48 hours after injury. After the rest period, it is recommended that low-to-moderate levels of physical and cognitive activity be gradually started, including screen time. The activities should be performed at a level that does not result in the recurrence or exacerbation of symptoms. Adolescents must refrain from any activities that increase the risk of reinjury (eg, contact sports or anything with risk of falls) until fully asymptomatic and cleared by their primary care or other medical providers.

Measures and Outcomes

Primary Outcomes

The prespecified thresholds (criteria for success), as outlined in Table 2 for the feasibility, are based on established benchmarks of previous feasibility trials [47,48] and our previous experience in recruiting pediatric patients with concussion from an ED [49]. We will use the *traffic light* system to determine whether proceeding to a full-scale trial is appropriate [50]. Progression can take place without any changes (green zone), with correctable adjustments (amber zone), or not occur because of issues that cannot be readily addressed (red zone). The decision to progress to a full-scale trial will be contingent on the criterion with the least favorable performance [50].

Table 3 provides an overview of all outcome measures collected and their specific end points.

Table 2. The criteria for success for progression to a full-scale efficacy trial.

Feasibility outcomes	Green zone (go)	Amber zone (amend)	Red zone (stop)
Eligibility	>40% of participants screened are eligible	20%-40% of participants screened are eligible	<20% of participants screened are eligible
Recruitment	>50% of eligible participants will be randomized [49]	30%-50% of eligible participants will be randomized	<30% of eligible participants will be randomized
Adherence	>70% of participants complete the minimum requirements, that is, approximately 10 minutes of activity 4 times a week	>50% of participants complete the minimum requirements, that is, approximately 10 minutes of activity 4 times a week	<50% of participants complete the minimum requirements, that is, approximately 10 minutes of activity 4 times a week
Credibility[a]	>70% of participants have score above the scale midpoint	>50% of participant have a score above the scale midpoint	<50% of participants have a score above the scale midpoint
Retention	>75% participants complete the follow-up assessment [49]	50%-75% participants complete the follow-up assessment	<50% participants complete the follow-up assessment

[a]Treatment credibility and expectancy will be assessed using the Credibility and Expectancy Questionnaire [51]. It is a 6-item questionnaire, scored using a Likert scale ranging from 1 to 9. The treatment will be considered credible (questions 1-3) if the participants scored above the midpoint. Furthermore, credibility and expectancy will be assessed to rule out the possibility of differential credibility as an explanation for the differences in therapy outcomes between the experimental and control groups. The credibility and expectancy of the intervention will be assessed at 1 week after enrollment.

Table 3. Measures organized by domain, source of data, and assessment occasion.

Measures	Source or reporter	Time to complete (minutes)	CHEO ED[a]	360cc[b]	Daily[c]	Day 1 (CHEO)	Day 1 (360cc)	72-hours	Day 7	Day 14	Week 3	Week 4	Week 8
ED visit													
Screening form	RA[d]	N/A[e]	✓	✓									
Case report (acute signs and symptoms)	RA and MD[f]	5 RA and 5 MD	✓	✓									
Balance (balance error scoring system)	CP[g]	5-10	✓	✓									
Outcomes													
Psychological													
Self-Efficacy Questionnaire for Children	C	2-5				✓	✓					✓	✓
Connor-Davidson Resilience Scale	C	2-5				✓	✓					✓	✓
Generalized Anxiety Disorder 7-item scale	C	2-5	✓				✓					✓	✓
Center for Epidemiologic Studies Depression Scale for Children	C	2-5	✓				✓					✓	✓
Child and Adolescent Mindfulness Scale	C	2-5	✓				✓					✓	✓
Credibility Expectancy Questionnaire	C	5							✓				
Client Satisfaction Questionnaire	CP	5										✓	
Postconcussive symptoms (secondary)													
Health and Behavior Inventory	C	5-10	✓	✓						✓		✓	✓
Post-Concussion Symptom Inventory	C	5	✓	✓						✓		✓	✓
Functional impairments (secondary)													
Quality of Life (PedsQL[h,i]) scale	C	5-10	✓				✓					✓	✓
PedsQL Fatigue scale	N/A	N/A										✓	✓
Neurophysiological measures (subset of 60 participants)		45											
Arterial spin labeling	C							✓				✓	

Measures	Source or reporter	Time to complete (minutes)	CHEO ED[a]	360cc[b]	Daily[c]	Day 1 (CHEO)	Day 1 (360cc)	72-hours	Day 7	Day 14	Week 3	Week 4	Week 8
Resting-state fMRI[j]	C							✓				✓	
MRS[k]	C							✓				✓	
Cognitive measures													
NIH[l] Toolbox	C	25										✓	
App Measurements	N/A	N/A			✓								
Godin-Shephard Leisure-Time Physical Activity Questionnaires	C	5				✓	✓			✓		✓	✓
Puberty Questionnaire	C	5	✓				✓						

[a]CHEO ED: Children's Hospital of Eastern Ontario emergency department.

[b]360cc: 360 Concussion Care.

[c]When accessing the app.

[d]RA: research assistant.

[e]N/A: not applicable.

[f]MD: treated ED physician.

[g]CP: concussed child and parent or guardian.

[h]PedsQL: Pediatric Quality of Life Inventory.

[i]Outcome measure.

[j]fMRI: functional magnetic resonance imaging.

[k]MRS: magnetic resonance spectroscopy.

[l]NIH: National Institutes of Health.

Secondary Outcomes

Treatment Expectancy

Treatment expectancy will be assessed with the Credibility and Expectancy Questionnaire (questions 4 to 6) [51]. Expectancy will be considered good if the participants score above the midpoint on questions 4 to 6. Expectancy will be assessed at 1 week after the enrollment.

Intervention Satisfaction

Intervention satisfaction will be assessed with the modified version of the Client Satisfaction Questionnaire [52]. This is a validated, reliable, 8-item questionnaire used to measure client satisfaction with a particular program or service. In this case, the questionnaire has been modified to assess participant satisfaction with the digital intervention. The intervention will be deemed satisfactory if >70% of the participants score above the midpoint on the questionnaire [52]. Intervention satisfaction will be assessed at 4 weeks after the enrollment (end of the intervention).

Quality of Life

QoL will be measured using the Pediatric Quality of Life Inventory (PedsQL; version 4.0) [53,54]. The PedsQL is a reliable and valid measure of QoL in healthy children and adolescents and in those with acute or chronic health conditions [55]. It is a 23-item, 5-point Likert scale questionnaire yielding a total score (0-92) and 4 domain scores: physical, emotional, social, and school. QoL will be collected in the ED (for CHEO participants) or on day 1 (for 360cc participants) and at the 4- and 8-week follow-ups.

Fatigue

Fatigue will be measured using the Multidimensional Fatigue Scale PedsQL. This 18-item, 5-point Likert scale assessment comprises 3 scales: the General Fatigue Scale (6 items), Sleep-Rest Fatigue Scale (6 items), and Cognitive Fatigue Scale (6 items). The PedsQL Multidimensional Fatigue Scale has demonstrated excellent internal consistency, reliability, and validity [56-58]. The assessment will be collected in the ED (for CHEO participants) or on day 1 (for 360cc participants) and at the 4- and 8-week follow-ups.

Symptom Burden

Symptom burden will be measured in the ED or at 360cc (both retrospective and postinjury acute symptoms) and at 1, 2, 4, and 8 weeks after enrollment using the Health and Behavior Inventory (HBI) [3]. The HBI is a 20-item self-report questionnaire that uses a 4-point Likert scale, with a total range

0-60. It provides scores for cognitive and somatic symptom scales. Emotional symptoms and sleep disturbances will be assessed using the Post-Concussion Symptom Inventory (PCSI) [59-61]. The PCSI [59,60] is a validated, reliable, comprehensive, and self-administered instrument [59-61]. For the purpose of this study, the emotional and sleep domains of the PCSI adolescent scale version (20-item, 7-point Likert scale) will be used. The domains will be assessed in the ED or at 360cc and at 2, 4, and 8 weeks after enrollment.

Self-Efficacy

Self-efficacy will be measured using the Self-Efficacy Questionnaire for Children (SEQ-C). Self-efficacy is the individual's perceived and personal competence in their abilities to handle a situation. Self-efficacy reflects one's confidence in the ability to exert control over one's motivation, behavior, and social environment. Previous studies have demonstrated that at 12 weeks after the injury, children with a concussion lack confidence during physical activities at 12 weeks after a concussion as compared with that before the injury [62]. The SEQ-C is a valid and reliable assessment tool. It is a 24-item, 5-point Likert scale yielding a sum score (0-120) and emotional, social, and academic self-efficacy subscores [63]. The SEQ-C will be administered on day 1 and at 4 and 8 weeks after enrollment.

Attention, Working Memory, and Executive Function

Attention, working memory, and executive function will be assessed using the National Institutes of Health (NIH) Toolbox Cognitive Battery [64]. The NIH Toolbox is a validated and reliable computerized battery designed to measure executive function, attention, episodic memory, language, processing speed, working memory, and fluid cognition. Previous studies have demonstrated lower working memory, attention, and executive functioning scores after injury in pediatric samples with concussion [65-68]. Moreover, mindfulness has been shown to improve attention, working memory, and executive functioning [26,69,70]. The NIH Toolbox will be administered at the 4-week follow-up.

Resiliency

Resiliency will be measured using the Connor-Davidson Resilience Scale-10 (CD-RISC-10) [71]. The CD-RISC-10 is a 10-item questionnaire, scored on a 5-point Likert scale, that assesses an individual's perception of hardiness or perceived stress. Resiliency is defined as the ability to harbor interpersonal qualities, such as positive acceptance, to adapt or thrive in the face of adversity [71]. Previous research has shown that MBI increases resiliency in youth [13]. The CD-RISC-10 has been validated in an adolescent population with a concussion [72] and will be administered on day 1 and at 4 and 8 weeks after enrollment.

Anxiety and Depression

Anxiety and *depression* (mood) are frequently reported symptoms in pediatric concussion [73-75]. *Anxiety* will be measured using the Generalized Anxiety Disorder 7-item scale [73]. The Generalized Anxiety Disorder-7 is a validated, reliable, and sensitive to treatment-related changes tool that assesses anxiety symptoms in youth [76]. It is a 7-item, 3-point Likert scale that provides a sum score (0 to 21) of general anxiety symptoms. It will be administered in the ED (for CHEO participants) or on day 1 (for 360cc participants), capturing preinjury anxiety, and at 4- and 8-week intervals after enrollment to assess postenrollment anxiety.

Depression symptoms will be measured using the validated and reliable Center for Epidemiologic Studies Depression Scale for Children [74,75]. It is a 10-item, 4-point Likert scale that provides a total score (0-30). The Center for Epidemiologic Studies Depression Scale for Children will be administered in the ED (for CHEO participants) or on day 1 (for 360cc participants), capturing preinjury mood, and at 4- and 8-week intervals after enrollment to assess postenrollment mood.

Mindfulness

Mindfulness will be assessed using the validated Child and Adolescent Mindfulness Measure [77,78]. It is a 10-item, 5-point Likert scale. It will be administered in the ED (for CHEO participants) or on day 1 (for 360cc participants), capturing preintervention mindfulness, and at 4- and 8-week intervals after enrollment to assess postenrollment mindfulness.

Safety

Safety of the MBI will be determined by capturing and monitoring the worsening of symptoms and adverse events. Adverse events will be defined as an unscheduled visit to the ED or primary medical provider because of exacerbation of symptoms during or within 30 minutes after using the app. The participant will be asked about any possible adverse events at the 1-, 2-, 4-, and 8-week follow-ups.

Longitudinal Mental Well-Being

AmDTx contains 4 easy-to-use measurement features that together provide a longitudinal readout of patient well-being. First, psychological stress is objectively quantified via a 30-second *selfie* video that uses photoplethysmography to extract heart rate and 2 power bands of heart rate variability from biosignals inherent to the human face [79]. The amount of psychological stress is determined via a deep neural network trained on tens of thousands of selfie scans captured in parallel with a validated ecological momentary assessment of stress. The artificial intelligence output has reported 86% accuracy for determining an individual's stress as *very low*, *medium low*, *medium high*, or *very high* [80]. Second, emotional affect and arousal levels are obtained via a digital 4-quadrant emotion mapping board (circumplex) that lists feelings such as *afraid*, *droopy*, and at ease ranging on one axis from unpleasant to pleasant (valence axis) and along another axis from mild to intense (arousal axis). Each emotion listed is associated with a score that is not disclosed to the user and is used to calculate an implicit measure of mood. Third, subjective stress is obtained via a slider ranging from *none* to *extreme*. Fourth, personal notes are imputed using an open field text box. The outputs of the mood and stress slider ecological momentary assessments have been benchmarked to standard psychological surveys [27]. If a participant chooses to use the selfie camera to observe their biological stress levels, there will be no recording or storage of the generated video in the app or elsewhere. The AmDTx uses secure web authentication, data logging, and encryption that

ensure security and confidentiality of any personal identifiable information and in-app data. Personally identifiable information remains with the customer (ie, it is not downloaded by Mobio).

Imaging Measurements

Imaging measurements will be acquired within 72 hours of injury and during week 4 of the study on a subset of 60 participants. Each brain scanning session lasts 45 to 60 minutes and includes the following sequences: 3D T1-weighted anatomical scan to measure regional volumes and cortical thickness, resting-state functional MRI (rs-fMRI) to assess functional connectivity features or neural networks, arterial spin labeling to assess perfusion or cerebral blood flow, and magnetic proton spectroscopy in a single voxel in the anterior cingulate cortex to assess metabolite concentrations (ie, glutamate and gamma-aminobutyric acid). Table 3 lists the key imaging parameters.

Covariate Measurements

Information about injuries will be collected from medical records and medical personnel using a standardized case report form. Details regarding the injury and acute signs and symptoms of concussion (ie, loss of consciousness, Glasgow Coma Scale scores, mechanism of injury, neurological status, and other clinical features) will be collected by RAs, with clarification by physicians when necessary. The data will be verified by the site investigator. To calculate the 5P clinical risk score [2], balance will be evaluated by the RA using the balance error scoring system [81], a widely used instrument in the field of sports concussion [82] for objective assessment of postural stability. Pubertal status will be measured using a puberty questionnaire [83]. The questionnaire is a 5-item, self-administered rating scale for pubertal development without pictorial representations or interviews. Demographic data (ie, household annual income and parental education level) will be used as a proxy of socioeconomic status (SES). SES will be collected to assess whether randomization is equally distributed in both groups. If SES is not equally represented in the sample, it will be controlled for in our analysis.

Studies have shown that physical activity can reduce anxiety, improve mood, and help alleviate postconcussive symptoms [84]. We will evaluate physical activity to ensure balance between groups; physical activity levels will be assessed using the Godin-Shepard Leisure-Time Physical Activity Questionnaire [85] on day 1 and then at 2, 4, and 8 weeks after injury.

Procedures

Data Collection Methods

Recruitment will be conducted similar to the successful Pediatric Concussion Assessment of Rest and Exertion multicenter concussion study [86]. When an adolescent with a mechanism of injury and symptoms consistent with concussion presents to the ED, the nurse will triage the child as per the existing protocols. Once in the ED, a member of the ED clinical team (ie, an ED volunteer) will introduce the study to families of potentially eligible children to inquire whether they are interested in learning more about the study. If so, the electronic charts of potentially eligible participants will be flagged, and the research team will be notified. At 360cc, a health information custodian who is a part of the circle of care will mention to the family that there is a study on children who have head injuries and ask if they are interested in learning more about the study. In both the ED and 360cc, the RA will then approach the family to discuss the research study, and if they are interested, the RA will complete the screening form on an iPad.

During the screening procedure, we will evaluate the likelihood that the patients had a *definitive* or *probable* concussion based on the aforementioned inclusion criteria. Their 5P clinical risk score [2] will also be calculated with the following variables: age, sex, prior concussion and length of recovery, history of migraine, slow answers to questions, balance, headache, sensitivity to noise, and feeling fatigued. Only patients with a 5P score >4 will be eligible for the study. Patients who are ineligible based on the initial screening will be thanked for their time. Eligible and willing parents along with adolescents capable of consenting on their own behalf will be asked for written informed consent, and the adolescents who are unable to provide consent on their own behalf will be asked for assent.

Once enrolled in the study, the families will complete a series of questionnaires in an electronic survey format using a portable tablet computer on REDCap [87]. The survey includes questions regarding patient demographics, preinjury and injury characteristics, a symptoms checklist, and diagnostic history.

The day following the ED or 360cc visit, participants will receive a phone call from an RA to randomize the participants to either the experimental or the control group and give instructions to register an account on a study-dedicated landing page using a unique link for each participant. Following registration, participants will install *AmDTx* on the mobile device of their choice. After creating an account and logging in to *AmDTx*, each participant will be automatically directed to their assigned intervention (MBI or control).

During this phone call, an MRI appointment will be scheduled for the participants who have agreed to participate in that component of the study. Participants will complete the surveys or questionnaires for day 1 and MRI screener. They will have the option of completing the survey via phone or REDCap.

Follow-Up Procedures

The proposed duration of the app-based MBI is 4 to 8 weeks. After 4 weeks, all participants in the experimental group will be given the opportunity to pursue the MBI for an additional 4 weeks. At that time, participants in the control group will be offered to cross over and start the MBI intervention.

Participants will complete electronic follow-up questionnaires on REDCap at 1, 2, 4, and 8 weeks after enrollment and will have an in-person follow-up at 4 weeks for the cognitive assessment (and the MRI scan for a subset of participants). Cognitive testing will be conducted before brain scanning.

Neuroimaging Procedures

A subset of 60 participants (30 from each group) will undergo a 45-minute MRI scan at <72 hours and 4 weeks after injury. During the day 1 phone call, participants who have consented

to the MRI component of the study will complete the MRI screener and schedule their MRI appointment.

Each scanning session will be approximately 1 hour and will include a high-resolution structural scan, arterial spin labeling, rs-fMRI, and magnetic proton spectroscopy (Table 4).

Table 4. Magnetic resonance imaging acquisition.

Image type	Sequence name	Total time (minutes:seconds)	Resolution (mm×mm×mm)	Slices, n	FOV[a] (mm)	TR[b] (milliseconds)	TE[c] (milliseconds)	Other
High-resolution anatomical	MEMPRAGE	5:48	1.0×1.0×1.0	192	256	2500	1.69, 3.55, 5.41, and 7.27	Flip angle=7; inversion time=1050 milliseconds; phase FOV=100%
rs-fMRI[d]	—[e]	12:08	3.0×3.0×3.0	40	204	2160	25	Flip angle=70; acceleration factor=2; 334 volumes
ASL[f]	3D ASL (GRACE)	5:37	1.8×1.8×5.0	34	230	4600	15.56	Perfusion mode=Flow-sensitive Alternating Inversion Recovery-QII; bolus duration=700 milliseconds; inversion time=860 milliseconds, 1060 milliseconds, 1260 milliseconds, 1460 milliseconds, 1660 milliseconds, 1860 milliseconds, 2060 milliseconds, 2260 milliseconds, 2460 milliseconds, 2660 milliseconds, 2860 milliseconds, 3060 milliseconds; average=1
ASL	Calibration image (M0)	0:54	1.8×1.8×5.0	34	230	7500	15.92	Perfusion mode=Flow-sensitive Alternating Inversion Recovery-QII; bolus duration=700; inversion time=7000 milliseconds; average=1
MRS[g]	PRESS	4:38	40×20×15	—	—	2000	30	Average=128
MRS	MEGAPRESS	4:36 (×2)	40×20×15	—	—	2000	68	Average=64

[a]FOV: field of view.

[b]TR: repetition time.

[c]TE: echo time.

[d]rs-fMRI: resting-state functional magnetic resonance imaging.

[e]Not available.

[f]ASL: arterial spin labeling.

[g]MRS: magnetic resonance spectroscopy.

Data Management

The CHEO Clinical Research Unit Data Coordinating Centre will be used as a central location for data processing and management. Data will be kept private and secured to industry standards for both clinical and patient-sensitive data in Canada. Data for the study will be collected and managed using REDCap [88] tools hosted and supported by the CHEO Research Institute. REDCap is a secure, web-based application designed to support data capture for research studies. Only members of the research team will be granted access to the database. Users will be assigned to *Data Access Groups* that will restrict their rights to viewing and entering data. For monitoring purposes, the study coordinator will be able to view the data. Within the Data Access

Group, user privileges will be designated by the study coordinator to ensure that the research team members have only the minimum required rights to perform their duties. All identifying information that is collected will be flagged in the database and removed from data export unless the identifying information is required for statistical analysis (eg, date of birth).

Statistical Analysis

Primary Outcomes

Descriptive statistics will be used to summarize patient baseline characteristics and clinical information. The primary objective of this study is to assess the feasibility outcomes of the trial. This will be done by computing the observed points estimates for each criterion (eligibility, recruitment, adherence, credibility, and retention) and comparing them with our predefined red zone upper limits and green zone lower limits. The 3-tiered progression criteria will be used for each criterion (Textbox 1).

Textbox 1. Three-tiered progression criteria where E denotes the observed point estimate (ranging from 0 to 1 for proportions or percentages 0%-100%) [50].

Progression criteria

- Red (unacceptable): E≤red zone upper limit (*P* value nonsignificant, *P* value≥α)
- Amber (amend): red zone upper limit<E<green lower limit
- Green (acceptable): E≥G lower limit (*P* value significant, *P* value<α)

Secondary Outcomes

Mean and SDs will be computed for each collected measure. Pre-post correlations will be generated to assess preliminary evidence of *efficacy signal* for QoL, fatigue, symptoms, resiliency, self-efficacy, cognition, anxiety, depression, and mindfulness.

Neuroimaging Component: Nested Study

To acquire preliminary data on the association between the interventions and MRI metrics, per-protocol analyses will be conducted. A multivariable linear regression will be performed for each neuroimaging outcome, with age, sex, and handedness (for rs-fMRI) as covariates. If the groups differ at baseline on potentially confounding variables, such as attention-deficit or hyperactivity disorder, anxiety, medication, prior concussion, physical activity, and puberty, these variables will also be entered as covariates in the models. Per-protocol analyses will include only those participants who have adhered to the intervention.

Statistical Power

Feasibility Objective

The sample size calculations were informed on recommendations for feasibility trials using the *traffic light* system [50,89]. The significance cutoff points for each criterion, with green lower and red upper limits, were determined. Using Table 1 from the study by Lewis et al [50], to meet the individual >90% power requirements for each of the five criteria we would need the following: (1) for eligibility, the number of participants to be screened is 46; (2) for recruitment, the number of participants to be randomized is 54; (3) for adherence, the required number of participants to evaluate adherence is 55; (4) for credibility, the required number of participants is 55; and (5) for retention, the required number of participants is 34. To determine the overall sample size for the whole study, we based our decision on the criterion that requires the largest numbers (ie, adherence, n=55). Considering an approximately 20% rate of loss to follow-up and withdrawals, the required sample size for the adherence criteria is 70. We expect that 40% of the participants screened will be eligible and there will be a 50% recruitment uptake. Given these numbers, 350 children are expected to be screened: 350=[(1/0.4)×(1/0.5×70)]. Assuming that 70 of the 350 screened participants are randomized, criteria 1, 2, 3, 4, and 5 will have statistical powers of 100%, 99.9%, 95.8%, 95.8%, and 98.7%, respectively. This means that the null hypotheses can be rejected with a collective power of 90.5% if the alternative hypotheses (for acceptable feasibility outcomes) are true in each case.

Sample Size for the Nested Neuroimaging Component

As per Desmond and Glover [90], a liberal threshold of α=.05 requires 24 participants (12 per group) to achieve an 80% power for the single-voxel level for typical activations. To control the error rate when conducting multiple comparisons, it is suggested that the number of participants should be doubled to maintain this level of power. On the basis of our Pediatric Concussion Assessment of Rest and Exertion and MRI study, of the 89 participants with concussion who provided consent, 13 were lost to follow-up, 3 had incidental findings, and 5 had excessive motion [91]. Considering a 20% attrition, a total sample size of 60 participants (30 per group) will be recruited.

Data Safety and Monitoring

Data Safety Monitoring Board

The independent data safety monitoring board (DSMB) will consist of 1 independent pediatric ED physician, 1 neuropsychologist who specializes in pediatric concussion, and 1 statistician who is not involved in the research study. In keeping with the StaRChild Health guidelines [92], the DSMB will, in collaboration with the trial steering committee, establish safety outcomes and termination rules before the start of the study. The DSMB will be immediately advised of severe adverse events, and they will meet in case a serious adverse event occurs. The DSMB will meet annually to review enrollment, study procedures, form completion, data quality, loss to follow-up, and interim safety results. Given the low-risk intervention and

no intention to stop the trial for benefit or futility, only an annual meeting will be required. On the basis of negative data trends (increased symptoms) and adverse events, the DSMB may decide to meet earlier than planned and may request unblinding if deemed necessary.

Potential Harms

The safety outcomes include (1) severe worsening of symptoms identified on HBI reliable changes or (2) any symptoms requiring an unscheduled visit to the ED or primary care provider. If concussion symptoms worsen during the treatment to the degree that the participant requires an unscheduled visit to the ED or primary care provider, then symptoms will be considered as a possible adverse event. Symptoms could develop into an adverse event if they become unbearable and the patient needs immediate medical attention. Patients will report possible adverse events through REDCap reports, and their responses will be monitored by RAs. In the case of a possible adverse event, defined as the *worsening of symptoms requiring an unscheduled visit to the ED or primary care provider*, site investigators will be notified to determine if the event is linked to the treatment. If linked, the event will be monitored and the CHEO Research Ethics Board and DSMB will be notified.

Ethical Considerations

This study was approved by the Research Ethics Board (protocol number 20/72X) of the CHEO Research Institute in August 2020. Authorization from Health Canada was granted in July 2022. The study will be carried out according to the principles outlined in the Declaration of Helsinki [93] and Good Clinical Practices, within the laws and regulations of the Tri-Council Policy Statement, and the institutional policies of the CHEO REB.

Before consent is sought, the study will be introduced, and its purpose will be explained verbally. The consent form will also present the purpose of the research, the procedures, potential risks and benefits, and the use and security of the data. Informed written consent will be obtained from the parents and participants deemed capable of consenting. Informed assent will be obtained from the participants deemed by the RA to be cognitively unable to provide informed consent.

The participants will be remunerated with a CAD $20 (US $15) gift certificate (eg, Tango) for completing surveys. Participants will receive an additional CAD $20 (US $15) gift certificate for completing the MRIs. The gift certificate will be sent electronically to their email address. They will also receive a parking voucher or vouchers for in-person meeting or meetings and a letter attesting that they have completed 20 hours of volunteer work (5 hours per week completing the intervention).

Participant information will be coded using study identification numbers. Research personnel will take all appropriate and customary steps to ensure that data remain secure and that patient privacy and confidentiality are maintained.

Results

Project Initiation

This trial is funded by the Children's Hospital Academic Medical Organization Innovation Fund and the multidisciplinary team grant from the University of Ottawa Brain and Mind Research Institute. Recruitment began in October 2022, and data collection is expected to be completed by September 2024. Data collection and management is still in progress; therefore, data analysis is yet to be conducted.

Dissemination

The results will be disseminated at international conferences and in scientific manuscripts to peer-reviewed journals. The main manuscript presenting the results of the primary objective will be published in a high-impact peer-reviewed journal. Furthermore, separate manuscripts will be written on the secondary objectives of the protocol, and these will also be submitted for publication in peer-reviewed journals. We plan to engage key stakeholder groups (eg, families, Parachute, Canadian Concussion Network, and Mobio Interactive) to ensure mobilization and uptake of the findings to end users to progress to the next step, that is, the efficacy trial.

Discussion

First, we will use this study to examine the feasibility of our RCT methods, including delivering a DTx-containing MBI to participants who are acutely or subacutely concussed, and whether we can move to the efficacy trial. Second, to better inform our larger RCT, this study will allow us to estimate the effect sizes of QoL and the symptoms at 4 and 8 weeks after enrollment compared with those randomized to the control group (sham intervention). Third, we will use this study to assess whether MBI induces measurable brain-based effects, that is, examine whether the intervention modulates neuroimaging indicators such as functional connectivity. This trial will offer insight into a cost-effective way to manage pediatric concussion in the acute and subacute phases of injury. This study will help support the development of a future full-efficacy trial to assess the effectiveness of the intervention in increasing QoL and decreasing the concussion symptom burden.

The development of an intervention to increase adaptive interpersonal qualities in acute settings is important for reducing the risk of PSAC. Formal in-person MBIs such as mindfulness-based stress reduction have been shown to increase perceived self-efficacy and teach positive acceptance of change [13]. However, these interventions may not be suitable for a youth population with acute concussion as they are costly and not easily accessible. A brief web-based MBI with guided meditation had positive effects on anxiety, negative mood, perceived stress, and attention in different clinical populations [24-27]. Furthermore, a 3-week RCT using the DTx MBI within *AmDTx* increased stress resilience and attentional control in university students self-described as experiencing mild anxiety [27]. The customization of a novel MBI, designed in collaboration with MBI therapists, patients, and Mobio Interactive, will bring a required concussion treatment into the

homes of all patients, with the goal of increasing adaptive skills and cognitive performance, promoting neural recovery, and reducing the risk of PSAC. If found to be effective, DTx MBI holds promise as an accessible and low-risk preventative treatment for youth at risk for prolonged postconcussion symptoms and sequelae.

Acknowledgments

This study is funded by CHAMO Innovation grant, University of Ottawa Brain and Mind Research Institute, Martin Osmond Research Grant Award CHEORI and the Ontario Brain Institute NERD program.

Data Availability

Data sharing is not applicable to this paper as no data sets were generated or analyzed during this study.

Conflicts of Interest

AAL is one of the authors of the Mindfulness-Based Intervention for Concussion protocol used in this study, but she did not receive any financial benefit. AAL received funding from the Ontario Brain Institute Neurotech Early Research & Development Program for a separate component of the study. AAL has no other conflict of interest to disclose. RZ received financial support through competitively funded research grants from the Canadian Institutes of Health Research, Ontario Neurotrauma Foundation, Physician Services Incorporated Foundation, Children's Hospital of Eastern Ontario Foundation, University of Ottawa Brain and Mind Research Institute, Ontario Brain Institute, National Football League, Ontario Ministry of Health, Public Health Agency of Canada, Health Canada, Parachute Canada, and Ontario SPOR Support Unit. RZ was supported by a Tier 1 Clinical Research Chair in Pediatric Concussion from the University of Ottawa. All grant funding goes directly to the institution. RZ sits on the board of directors for the North American Brain Injury Society, which is a volunteer (unpaid) role. RZ is a founding partner and a minority shareholder of 360 Concussion Care (a learning health system and network of interdisciplinary concussion clinics in Ontario); no proceeds have been transferred to RZ. MC is one of the authors of the Mindfulness-Based Intervention for Concussion protocol used in this study, but she did not receive any financial benefit. ADH holds a Canada Research Chair in Magnetic Resonance Spectroscopy in Brain Injury and received funding from the Canadian Institutes of Health Research; Natural Sciences and Engineering Research Council of Canada; the New Frontiers in Research Fund; the Alberta Workers Compensation Board; The Arthritis Society; and both the Hotchkiss Brain Institute and the Alberta Children's Hospital Research Institute, University of Calgary. LW received an honorarium for a speaking engagement. BJS is a cofounder of Mobio Interactive Ptd Ltd, and at the time of submitting the manuscript, owned approximately 23% of the company's shares. NR holds a Canada Research Chair (Tier 2) in Pediatric Concussion and has received research funding from the Canadian Institutes of Health Research (CIHR), Social Sciences and Humanities Research Council (SSHRC), Ontario Neurotrauma Foundation (ONF), Public Health Agency of Canada (PHAC), Parachute Canada, Special Olympics Canada, Greater Toronto Hockey League, Dr. Tom Pashby Sport Safety Fund, Holland Bloorview Kids Rehabilitation Hospital and Scotiabank. NR is an Executive Board Member for the International Pediatric Brain Injury Society (IPIBS) which is an unpaid and volunteer role. All other authors declare no other conflicts of interest.

Multimedia Appendix 1
Peer review comments from the Children's Hospital Academic Medical Organization (CHAMO), Innovation Fund.
[PDF File (Adobe PDF File), 67 KB - resprot_v13i1e57226_app1.pdf]

Multimedia Appendix 2
Peer review comments from the University of Ottawa Brain and Mind Research Institute Team Grant.
[PDF File (Adobe PDF File), 1067 KB - resprot_v13i1e57226_app2.pdf]

Multimedia Appendix 3
Peer review comments from the Children's Hospital of Eastern Ontario Research Insitute Research Growth Award.
[PDF File (Adobe PDF File), 329 KB - resprot_v13i1e57226_app3.pdf]

References

1. Chadwick L, Sharma MJ, Madigan S, Callahan BL, Owen Yeates K. Classification criteria and rates of persistent postconcussive symptoms in children: a systematic review and meta-analysis. J Pediatr 2022 Jul;246:131-7.e2. [doi: 10.1016/j.jpeds.2022.03.039] [Medline: 35358589]
2. Zemek R, Barrowman N, Freedman SB, Gravel J, Gagnon I, McGahern C, et al. Clinical risk score for persistent postconcussion symptoms among children with acute concussion in the ED. JAMA 2016 Mar 08;315(10):1014-1025. [doi: 10.1001/jama.2016.1203] [Medline: 26954410]

3. Ayr LK, Yeates KO, Taylor HG, Browne M. Dimensions of postconcussive symptoms in children with mild traumatic brain injuries. J Int Neuropsychol Soc 2009 Jan;15(1):19-30 [FREE Full text] [doi: 10.1017/S1355617708090188] [Medline: 19128525]
4. Novak Z, Aglipay M, Barrowman N, Yeates KO, Beauchamp MH, Gravel J, et al. Association of persistent postconcussion symptoms with pediatric quality of life. JAMA Pediatr 2016 Dec 05;170(12):e162900. [doi: 10.1001/jamapediatrics.2016.2900] [Medline: 27775762]
5. Iverson GL, Gardner AJ, Terry DP, Ponsford JL, Sills AK, Broshek DK, et al. Predictors of clinical recovery from concussion: a systematic review. Br J Sports Med 2017 Jun;51(12):941-948 [FREE Full text] [doi: 10.1136/bjsports-2017-097729] [Medline: 28566342]
6. Ledoux AA, Tang K, Yeates KO, Pusic MV, Boutis K, Craig WR, et al. Natural progression of symptom change and recovery from concussion in a pediatric population. JAMA Pediatr 2019 Jan 01;173(1):e183820 [FREE Full text] [doi: 10.1001/jamapediatrics.2018.3820] [Medline: 30398522]
7. Nelson LD, Tarima S, LaRoche AA, Hammeke TA, Barr WB, Guskiewicz K, et al. Preinjury somatization symptoms contribute to clinical recovery after sport-related concussion. Neurology 2016 May 17;86(20):1856-1863 [FREE Full text] [doi: 10.1212/WNL.0000000000002679] [Medline: 27164666]
8. McNally KA, Bangert B, Dietrich A, Nuss K, Rusin J, Wright M, et al. Injury versus noninjury factors as predictors of postconcussive symptoms following mild traumatic brain injury in children. Neuropsychology 2013 Jan;27(1):1-12 [FREE Full text] [doi: 10.1037/a0031370] [Medline: 23356592]
9. Plourde V, Yeates KO, Brooks BL. Predictors of long-term psychosocial functioning and health-related quality of life in children and adolescents with prior concussions. J Int Neuropsychol Soc 2018 Mar 21;24(6):540-548. [doi: 10.1017/s1355617718000061]
10. Brooks BL, Plourde V, Beauchamp MH, Tang K, Yeates KO, Keightley M, et al. Predicting psychological distress after pediatric concussion. J Neurotrauma 2019 Mar 01;36(5):679-685. [doi: 10.1089/neu.2018.5792] [Medline: 30032719]
11. Woodrome SE, Yeates KO, Taylor HG, Rusin J, Bangert B, Dietrich A, et al. Coping strategies as a predictor of post-concussive symptoms in children with mild traumatic brain injury versus mild orthopedic injury. J Int Neuropsychol Soc 2011 Jan 18;17(2):317-326. [doi: 10.1017/s1355617710001700]
12. Barlow KM. Postconcussion syndrome: a review. J Child Neurol 2016 Jan;31(1):57-67. [doi: 10.1177/0883073814543305] [Medline: 25330797]
13. Dunning DL, Griffiths K, Kuyken W, Crane C, Foulkes L, Parker J, et al. Research review: the effects of mindfulness-based interventions on cognition and mental health in children and adolescents - a meta-analysis of randomized controlled trials. J Child Psychol Psychiatry 2019 Mar;60(3):244-258 [FREE Full text] [doi: 10.1111/jcpp.12980] [Medline: 30345511]
14. Spijkerman MP, Pots WT, Bohlmeijer ET. Effectiveness of online mindfulness-based interventions in improving mental health: a review and meta-analysis of randomised controlled trials. Clin Psychol Rev 2016 Apr;45:102-114 [FREE Full text] [doi: 10.1016/j.cpr.2016.03.009] [Medline: 27111302]
15. Boettcher J, Aström V, Påhlsson D, Schenström O, Andersson G, Carlbring P. Internet-based mindfulness treatment for anxiety disorders: a randomized controlled trial. Behav Ther 2014 Mar;45(2):241-253 [FREE Full text] [doi: 10.1016/j.beth.2013.11.003] [Medline: 24491199]
16. Hofmann SG, Sawyer AT, Witt AA, Oh D. The effect of mindfulness-based therapy on anxiety and depression: a meta-analytic review. J Consult Clin Psychol 2010 Apr;78(2):169-183 [FREE Full text] [doi: 10.1037/a0018555] [Medline: 20350028]
17. Ly KH, Trüschel A, Jarl L, Magnusson S, Windahl T, Johansson R, et al. Behavioural activation versus mindfulness-based guided self-help treatment administered through a smartphone application: a randomised controlled trial. BMJ Open 2014 Jan 09;4(1):e003440 [FREE Full text] [doi: 10.1136/bmjopen-2013-003440] [Medline: 24413342]
18. Fjorback LO, Arendt M, Ornbøl E, Walach H, Rehfeld E, Schröder A, et al. Mindfulness therapy for somatization disorder and functional somatic syndromes: randomized trial with one-year follow-up. J Psychosom Res 2013 Jan;74(1):31-40. [doi: 10.1016/j.jpsychores.2012.09.006] [Medline: 23272986]
19. Lakhan SE, Schofield KL. Mindfulness-based therapies in the treatment of somatization disorders: a systematic review and meta-analysis. PLoS One 2013 Aug 26;8(8):e71834 [FREE Full text] [doi: 10.1371/journal.pone.0071834] [Medline: 23990997]
20. Gu Q, Hou JC, Fang XM. Mindfulness meditation for primary headache pain: a meta-analysis. Chin Med J (Engl) 2018 Apr 05;131(7):829-838 [FREE Full text] [doi: 10.4103/0366-6999.228242] [Medline: 29578127]
21. Hilton L, Hempel S, Ewing BA, Apaydin E, Xenakis L, Newberry S, et al. Mindfulness meditation for chronic pain: systematic review and meta-analysis. Ann Behav Med 2017 Apr;51(2):199-213 [FREE Full text] [doi: 10.1007/s12160-016-9844-2] [Medline: 27658913]
22. van Emmerik AA, Berings F, Lancee J. Efficacy of a mindfulness-based mobile application: a randomized waiting-list controlled trial. Mindfulness (N Y) 2018;9(1):187-198 [FREE Full text] [doi: 10.1007/s12671-017-0761-7] [Medline: 29387266]
23. Fish J, Brimson J, Lynch S. Mindfulness interventions delivered by technology without facilitator involvement: what research exists and what are the clinical outcomes? Mindfulness (N Y) 2016;7(5):1011-1023 [FREE Full text] [doi: 10.1007/s12671-016-0548-2] [Medline: 27642370]

24. Manotas M, Segura C, Eraso M, Oggins J, McGovern K. Association of brief mindfulness training with reductions in perceived stress and distress in Colombian health care professionals. Int J Stress Manag 2014;21(2):207-225. [doi: 10.1037/a0035150]
25. Zeidan F, Johnson SK, Gordon NS, Goolkasian P. Effects of brief and sham mindfulness meditation on mood and cardiovascular variables. J Altern Complement Med 2010 Aug;16(8):867-873. [doi: 10.1089/acm.2009.0321] [Medline: 20666590]
26. Zeidan F, Johnson SK, Diamond BJ, David Z, Goolkasian P. Mindfulness meditation improves cognition: evidence of brief mental training. Conscious Cogn 2010 Jun;19(2):597-605. [doi: 10.1016/j.concog.2010.03.014] [Medline: 20363650]
27. Walsh KM, Saab BJ, Farb NA. Effects of a mindfulness meditation app on subjective well-being: active randomized controlled trial and experience sampling study. JMIR Ment Health 2019 Jan 08;6(1):e10844 [FREE Full text] [doi: 10.2196/10844] [Medline: 30622094]
28. Luxton DD, McCann RA, Bush NE, Mishkind MC, Reger GM. mHealth for mental health: integrating smartphone technology in behavioral healthcare. Prof Psychol Res Pr 2011;42(6):505-512. [doi: 10.1037/a0024485]
29. Miralles I, Granell C, Díaz-Sanahuja L, Van Woensel W, Bretón-López J, Mira A, et al. Smartphone apps for the treatment of mental disorders: systematic review. JMIR Mhealth Uhealth 2020 Apr 02;8(4):e14897 [FREE Full text] [doi: 10.2196/14897] [Medline: 32238332]
30. Lüdtke T, Pult LK, Schröder J, Moritz S, Bücker L. A randomized controlled trial on a smartphone self-help application (Be Good to Yourself) to reduce depressive symptoms. Psychiatry Res 2018 Nov;269:753-762. [doi: 10.1016/j.psychres.2018.08.113] [Medline: 30273901]
31. Roepke AM, Jaffee SR, Riffle OM, McGonigal J, Broome R, Maxwell B. Randomized controlled trial of SuperBetter, a smartphone-based/internet-based self-help tool to reduce depressive symptoms. Games Health J 2015 Jun;4(3):235-246. [doi: 10.1089/g4h.2014.0046] [Medline: 26182069]
32. Birney AJ, Gunn R, Russell JK, Ary DV. MoodHacker mobile web app with email for adults to self-manage mild-to-moderate depression: randomized controlled trial. JMIR Mhealth Uhealth 2016 Jan 26;4(1):e8 [FREE Full text] [doi: 10.2196/mhealth.4231] [Medline: 26813737]
33. Hur JW, Kim B, Park D, Choi SW. A scenario-based cognitive behavioral therapy mobile app to reduce dysfunctional beliefs in individuals with depression: a randomized controlled trial. Telemed J E Health 2018 Sep;24(9):710-716. [doi: 10.1089/tmj.2017.0214] [Medline: 29323626]
34. Mantani A, Kato T, Furukawa TA, Horikoshi M, Imai H, Hiroe T, et al. Smartphone cognitive behavioral therapy as an adjunct to pharmacotherapy for refractory depression: randomized controlled trial. J Med Internet Res 2017 Nov 03;19(11):e373 [FREE Full text] [doi: 10.2196/jmir.8602] [Medline: 29101095]
35. Gál É, tefan S, Cristea IA. The efficacy of mindfulness meditation apps in enhancing users' well-being and mental health related outcomes: a meta-analysis of randomized controlled trials. J Affect Disord 2021 Jan 15;279:131-142. [doi: 10.1016/j.jad.2020.09.134] [Medline: 33049431]
36. Sicard V, O'Kane K, Brown O, Butterfield L, Kardish R, Choi E, et al. Acceptability, usability, and credibility of a mindfulness-based digital therapeutic for pediatric concussion: a mixed-method study. JMIR Preprints Preprint posted online December 5, 2022 [FREE Full text] [doi: 10.2196/preprints.44757]
37. O'Kane KM, Otamendi T, Silverberg ND, Choi E, Sicard V, Zemek R, et al. Development of therapeutic alliance and social presence in a digital intervention for pediatric concussion: a qualitative exploratory study. JMIR Preprints. Preprint posted online June 27, 2023 2024 [FREE Full text] [doi: 10.2196/49133]
38. Zemek R, Osmond MH, Barrowman N, Pediatric Emergency Research Canada (PERC) Concussion Team. Predicting and preventing postconcussive problems in paediatrics (5P) study: protocol for a prospective multicentre clinical prediction rule derivation study in children with concussion. BMJ Open 2013 Aug 01;3(8):e003550 [FREE Full text] [doi: 10.1136/bmjopen-2013-003550] [Medline: 23906960]
39. Silverberg ND, Iverson GL, ACRM Brain Injury Special Interest Group Mild TBI Task Force members:, Cogan A, Dams-O-Connor K, Delmonico R, ACRM Mild TBI Diagnostic Criteria Expert Consensus Group:, et al. The American congress of rehabilitation medicine diagnostic criteria for mild traumatic brain injury. Arch Phys Med Rehabil 2023 Aug;104(8):1343-1355. [doi: 10.1016/j.apmr.2023.03.036] [Medline: 37211140]
40. McCrory P, Meeuwisse W, Dvořák J, Aubry M, Bailes J, Broglio S, et al. Consensus statement on concussion in sport-the 5 international conference on concussion in sport held in Berlin, October 2016. Br J Sports Med 2017 Jun;51(11):838-847. [doi: 10.1136/bjsports-2017-097699] [Medline: 28446457]
41. McCrory P, Meeuwisse W, Aubry M, Cantu B, Dvořák J, Echemendia R, et al. Consensus statement on concussion in sport - the 4th international conference on concussion in sport held in Zurich, November 2012. Phys Ther Sport 2013 May;14(2):e1-13. [doi: 10.1016/j.ptsp.2013.03.002] [Medline: 23664041]
42. R Core Team. R: a language and environment for statistical computing. R Foundation for Statistical Computing. 2019. URL: https://www.R-project.org/ [accessed 2024-03-21]
43. Subnis UB, Farb NA, Piedalue KA, Speca M, Lupichuk S, Tang PA, et al. A smartphone app-based mindfulness intervention for cancer survivors: protocol for a randomized controlled trial. JMIR Res Protoc 2020 May 11;9(5):e15178 [FREE Full text] [doi: 10.2196/15178] [Medline: 32390591]

44. 2048. Play 2048. URL: https://play2048.co/ [accessed 2024-03-27]
45. Teel E, Brossard-Racine M, Corbin-Berrigan LA, Gagnon I. Perceptual cognitive training does not improve clinical outcomes at 4 and 12 weeks following concussion in children and adolescents: a randomized controlled trial. J Head Trauma Rehabil 2021;36(2):E97-107. [doi: 10.1097/HTR.0000000000000633] [Medline: 33201041]
46. Reed N, Zemek R, Dawson J, Ledoux AA. Living guideline for diagnosing and managing pediatric concussion. Ontario Neurotrauma Foundation. 2019. URL: https://islandscholar.ca/islandora/object/ir%3A23211/datastream/PDF/view [accessed 2024-03-21]
47. Silverberg ND, Cairncross M, Brasher PM, Vranceanu AM, Snell DL, Yeates KO, et al. Feasibility of concussion rehabilitation approaches tailored to psychological coping styles: a randomized controlled trial. Arch Phys Med Rehabil 2022 Aug;103(8):1565-73.e2. [doi: 10.1016/j.apmr.2021.12.005] [Medline: 34971596]
48. Mace RA, Greenberg J, Lemaster N, Duarte B, Penn T, Kanaya M, et al. Live video mind-body program for patients with knee osteoarthritis, comorbid depression, and obesity: development and feasibility pilot study. JMIR Form Res 2022 Apr 27;6(4):e34654 [FREE Full text] [doi: 10.2196/34654] [Medline: 35475787]
49. Ledoux AA, Barrowman N, Bijelić V, Borghese MM, Davis A, Reid S, et al. Is early activity resumption after paediatric concussion safe and does it reduce symptom burden at 2 weeks post injury? The pediatric concussion assessment of rest and exertion (PedCARE) multicentre randomised clinical trial. Br J Sports Med 2022 Mar;56(5):271-278. [doi: 10.1136/bjsports-2021-105030] [Medline: 34836880]
50. Lewis M, Bromley K, Sutton CJ, McCray G, Myers HL, Lancaster GA. Determining sample size for progression criteria for pragmatic pilot RCTs: the hypothesis test strikes back!. Pilot Feasibility Stud 2021 Feb 03;7(1):40 [FREE Full text] [doi: 10.1186/s40814-021-00770-x] [Medline: 33536076]
51. Devilly GJ, Borkovec TD. Psychometric properties of the credibility/expectancy questionnaire. J Behav Ther Exp Psychiatry 2000 Jun;31(2):73-86. [doi: 10.1016/s0005-7916(00)00012-4] [Medline: 11132119]
52. Boß L, Lehr D, Reis D, Vis C, Riper H, Berking M, et al. Reliability and validity of assessing user satisfaction with web-based health interventions. J Med Internet Res 2016 Aug 31;18(8):e234 [FREE Full text] [doi: 10.2196/jmir.5952] [Medline: 27582341]
53. Desai AD, Zhou C, Stanford S, Haaland W, Varni JW, Mangione-Smith RM. Validity and responsiveness of the pediatric quality of life inventory (PedsQL) 4.0 generic core scales in the pediatric inpatient setting. JAMA Pediatr 2014 Dec;168(12):1114-1121. [doi: 10.1001/jamapediatrics.2014.1600] [Medline: 25347549]
54. Varni JW, Burwinkle TM, Seid M, Skarr D. The PedsQL 4.0 as a pediatric population health measure: feasibility, reliability, and validity. Ambul Pediatr 2003;3(6):329-341. [doi: 10.1367/1539-4409(2003)003<0329:tpaapp>2.0.co;2] [Medline: 14616041]
55. Adelson PD, Pineda J, Bell MJ, Abend NS, Berger RP, Giza CC, et al. Common data elements for pediatric traumatic brain injury: recommendations from the working group on demographics and clinical assessment. J Neurotrauma 2012 Mar 01;29(4):639-653 [FREE Full text] [doi: 10.1089/neu.2011.1952] [Medline: 21939389]
56. Varni JW, Burwinkle TM, Szer IS. The PedsQL multidimensional fatigue scale in pediatric rheumatology: reliability and validity. J Rheumatol 2004 Dec;31(12):2494-2500. [Medline: 15570657]
57. Varni JW, Beaujean AA, Limbers CA. Factorial invariance of pediatric patient self-reported fatigue across age and gender: a multigroup confirmatory factor analysis approach utilizing the PedsQL™ Multidimensional Fatigue Scale. Qual Life Res 2013 Nov;22(9):2581-2594. [doi: 10.1007/s11136-013-0370-4] [Medline: 23423759]
58. Gordijn MS, Cremers EM, Kaspers GJ, Gemke RJ. Fatigue in children: reliability and validity of the Dutch PedsQL™ Multidimensional Fatigue Scale. Qual Life Res 2011 Sep;20(7):1103-1108 [FREE Full text] [doi: 10.1007/s11136-010-9836-9] [Medline: 21246290]
59. Sady MD, Vaughan CG, Gioia GA. Psychometric characteristics of the postconcussion symptom inventory in children and adolescents. Arch Clin Neuropsychol 2014 Jun;29(4):348-363 [FREE Full text] [doi: 10.1093/arclin/acu014] [Medline: 24739735]
60. Gioia GA, Isquith PK, Schneider JC, Vaughan CG. New approaches to assessment and monitoring of concussion in children. Top Lang Disord 2009 Jul;29(3):266-281. [doi: 10.1097/TLD.0b013e3181b5322b]
61. Gioia GA, Schneider JC, Vaughan CG, Isquith PK. Which symptom assessments and approaches are uniquely appropriate for paediatric concussion? Br J Sports Med 2009 May;43 Suppl 1:i13-i22. [doi: 10.1136/bjsm.2009.058255] [Medline: 19433419]
62. Gagnon I, Swaine B, Friedman D, Forget R. Exploring children's self-efficacy related to physical activity performance after a mild traumatic brain injury. J Head Trauma Rehabil 2005;20(5):436-449. [doi: 10.1097/00001199-200509000-00005] [Medline: 16170252]
63. Muris P. A brief questionnaire for measuring self-efficacy in youths. J Psychopathol Behav Assess 2001;23:145-149. [doi: 10.1023/A:1010961119608]
64. Gershon RC, Wagster MV, Hendrie HC, Fox NA, Cook KF, Nowinski CJ. NIH toolbox for assessment of neurological and behavioral function. Neurology 2013 Mar 12;80(11 Suppl 3):S2-S6 [FREE Full text] [doi: 10.1212/WNL.0b013e3182872e5f] [Medline: 23479538]

65. Chadwick L, Roth E, Minich NM, Taylor HG, Bigler ED, Cohen DM, et al. Cognitive outcomes in children with mild traumatic brain injury: an examination using the national institutes of health toolbox cognition battery. J Neurotrauma 2021 Sep 15;38(18):2590-2599 [FREE Full text] [doi: 10.1089/neu.2020.7513] [Medline: 33906429]
66. Sicard V, Stephenson DD, Hergert DC, Dodd AB, Robertson-Benta CR, Pabbathi Reddy S, et al. Investigating the diagnostic accuracy of a paper-and-pencil and a computerized cognitive test battery for pediatric mild traumatic brain injury. Neuropsychology 2022 Sep;36(6):565-577 [FREE Full text] [doi: 10.1037/neu0000803] [Medline: 35377682]
67. Robertson-Benta CR, Pabbathi Reddy S, Stephenson DD, Sicard V, Hergert DC, Dodd AB, et al. Cognition and post-concussive symptom status after pediatric mild traumatic brain injury. Child Neuropsychol 2024 Feb;30(2):203-220. [doi: 10.1080/09297049.2023.2181946] [Medline: 36825526]
68. Moore DR, Pindus DM, Raine LB, Drollette ES, Scudder MR, Ellemberg D, et al. The persistent influence of concussion on attention, executive control and neuroelectric function in preadolescent children. Int J Psychophysiol 2016 Jan;99:85-95. [doi: 10.1016/j.ijpsycho.2015.11.010] [Medline: 26608697]
69. Basso JC, McHale A, Ende V, Oberlin DJ, Suzuki WA. Brief, daily meditation enhances attention, memory, mood, and emotional regulation in non-experienced meditators. Behav Brain Res 2019 Jan 01;356:208-220. [doi: 10.1016/j.bbr.2018.08.023] [Medline: 30153464]
70. Zoogman S, Goldberg SB, Hoyt WT, Miller L. Mindfulness interventions with youth: a meta-analysis. Mindfulness 2014 Jan 15;6(2):290-302. [doi: 10.1007/s12671-013-0260-4]
71. Connor KM, Davidson JR. Development of a new resilience scale: the Connor-Davidson Resilience Scale (CD-RISC). Depress Anxiety 2003;18(2):76-82. [doi: 10.1002/da.10113] [Medline: 12964174]
72. Laliberté Durish C, Yeates KO, Brooks BL. Convergent and divergent validity of the Connor-Davidson Resilience Scale in children with concussion and orthopaedic injury. Brain Inj 2018;32(12):1525-1533. [doi: 10.1080/02699052.2018.1502471] [Medline: 30047782]
73. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006 May 22;166(10):1092-1097. [doi: 10.1001/archinte.166.10.1092] [Medline: 16717171]
74. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. Appl Psychol Meas 2016 Jul 26;1(3):385-401. [doi: 10.1177/014662167700100306]
75. Björgvinsson T, Kertz SJ, Bigda-Peyton JS, McCoy KL, Aderka IM. Psychometric properties of the CES-D-10 in a psychiatric sample. Assessment 2013 Aug;20(4):429-436. [doi: 10.1177/1073191113481998] [Medline: 23513010]
76. Mossman SA, Luft MJ, Schroeder HK, Varney ST, Fleck DE, Barzman DH, et al. The Generalized Anxiety Disorder 7-item scale in adolescents with generalized anxiety disorder: signal detection and validation. Ann Clin Psychiatry 2017 Nov;29(4):227-34A [FREE Full text] [Medline: 29069107]
77. Greco LA, Baer RA, Smith GT. Assessing mindfulness in children and adolescents: development and validation of the Child and Adolescent Mindfulness Measure (CAMM). Psychol Assess 2011 Sep;23(3):606-614. [doi: 10.1037/a0022819] [Medline: 21480722]
78. Kuby AK, McLean N, Allen K. Validation of the Child and Adolescent Mindfulness Measure (CAMM) with non-clinical adolescents. Mindfulness 2015 May 22;6(6):1448-1455. [doi: 10.1007/s12671-015-0418-3]
79. Chwyl B, Chung AG, Amelard R, Deglint J, Clausi DA, Wong A. SAPPHIRE: stochastically acquired photoplethysmogram for heart rate inference in realistic environments. In: Proceedings of the IEEE International Conference on Image Processing (ICIP). 2016 Presented at: ICIP 2016; September 25-28, 2016; Phoenix, AZ URL: https://ieeexplore.ieee.org/document/7532554 [doi: 10.1109/icip.2016.7532554]
80. Al-Jebrni AH, Chwyl B, Wang XY, Wong A, Saab BJ. AI-enabled remote and objective quantification of stress at scale. Biomed Signal Process Control 2020 May;59:101929. [doi: 10.1016/j.bspc.2020.101929]
81. Guskiewicz KM. Postural stability assessment following concussion: one piece of the puzzle. Clin J Sport Med 2001 Jul;11(3):182-189. [doi: 10.1097/00042752-200107000-00009] [Medline: 11495323]
82. Guskiewicz KM, Ross SE, Marshall SW. Postural stability and neuropsychological deficits after concussion in collegiate athletes. J Athl Train 2001 Sep;36(3):263-273 [FREE Full text] [Medline: 12937495]
83. Carskadon MA, Acebo C. A self-administered rating scale for pubertal development. J Adolesc Health 1993 May;14(3):190-195. [doi: 10.1016/1054-139x(93)90004-9] [Medline: 8323929]
84. Grool AM, Aglipay M, Momoli F, Meehan WP3, Freedman SB, Yeates KO, et al. Association between early participation in physical activity following acute concussion and persistent postconcussive symptoms in children and adolescents. JAMA 2016 Dec 20;316(23):2504-2514. [doi: 10.1001/jama.2016.17396] [Medline: 27997652]
85. Godin G. The Godin-Shephard leisure-time physical activity questionnaire. Health Fitness J Canada 2011;4(1):18-22. [doi: 10.14288/hfjc.v4i1.82]
86. Ledoux AA, Barrowman NJ, Boutis K, Davis A, Reid S, Sangha G, et al. Multicentre, randomised clinical trial of paediatric concussion assessment of rest and exertion (PedCARE): a study to determine when to resume physical activities following concussion in children. Br J Sports Med 2019 Feb 12;53(3):195. [doi: 10.1136/bjsports-2017-097981] [Medline: 28701360]
87. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009 Apr;42(2):377-381 [FREE Full text] [doi: 10.1016/j.jbi.2008.08.010] [Medline: 18929686]

88. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009 Apr;42(2):377-381 [FREE Full text] [doi: 10.1016/j.jbi.2008.08.010] [Medline: 18929686]
89. Sim J, Lewis M. The size of a pilot study for a clinical trial should be calculated in relation to considerations of precision and efficiency. J Clin Epidemiol 2012 Mar;65(3):301-308. [doi: 10.1016/j.jclinepi.2011.07.011] [Medline: 22169081]
90. Desmond JE, Glover GH. Estimating sample size in functional MRI (fMRI) neuroimaging studies: statistical power analyses. J Neurosci Methods 2002 Aug 30;118(2):115-128 [FREE Full text] [doi: 10.1016/s0165-0270(02)00121-8] [Medline: 12204303]
91. Healey K, Fang Z, Smith A, Zemek R, Ledoux AA. Adolescents with a concussion have altered brain network functional connectivity one month following injury when compared to adolescents with orthopedic injuries. Neuroimage Clin 2022;36:103211 [FREE Full text] [doi: 10.1016/j.nicl.2022.103211] [Medline: 36182818]
92. Sampson MR, Benjamin DK, Cohen-Wolkowiez M. Evidence-based guidelines for pediatric clinical trials: focus on StaR Child Health. Expert Rev Clin Pharmacol 2012 Sep;5(5):525-531 [FREE Full text] [doi: 10.1586/ecp.12.52] [Medline: 23121275]
93. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013 Nov 27;310(20):2191-2194. [doi: 10.1001/jama.2013.281053] [Medline: 24141714]

Abbreviations

360cc: 360 Concussion Care
5P: Predicting and Preventing Post-Concussive Problems in Pediatrics
CD-RISC-10: Connor-Davidson Resilience Scale-10
CHEO: Children's Hospital of Eastern Ontario
DSMB: data safety monitoring board
DTx: digital therapeutics
ED: emergency department
HBI: Health and Behavior Inventory
MBI: mindfulness-based intervention
MRI: magnetic resonance imaging
NIH: National Institutes of Health
PCSI: Post-Concussion Symptom Inventory
PedsQL: Pediatric Quality of Life Inventory
PSAC: persisting symptoms after concussion
QoL: quality of life
RA: research assistant
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
rs-fMRI: resting-state functional magnetic resonance imaging
SEQ-C: Self-Efficacy Questionnaire for Children
SES: socioeconomic status
TBI: traumatic brain injury

Edited by A Mavragani; submitted 08.02.24; this is a non–peer-reviewed article;accepted 04.03.24; published 11.04.24.

Please cite as:
Ledoux AA, Zemek R, Cairncross M, Silverberg N, Sicard V, Barrowman N, Goldfield G, Gray C, Harris AD, Jaworska N, Reed N, Saab BJ, Smith A, Walker L
Smartphone App–Delivered Mindfulness-Based Intervention for Mild Traumatic Brain Injury in Adolescents: Protocol for a Feasibility Randomized Controlled Trial
JMIR Res Protoc 2024;13:e57226
URL: https://www.researchprotocols.org/2024/1/e57226
doi:10.2196/57226
PMID:38602770

Protocol

Exploring Medical Career Choice to Better Inform Swiss Physician Workforce Planning: Protocol for a National Cohort Study

Milena Abbiati[1], PhD; Mathieu R Nendaz[1,2], MD, MHPE; Bernard Cerutti[1], MPH, PhD; Monika Brodmann Mäder[3,4], MD, MME; Giatgen A Spinas[3], MD; David Vicente Alvarez[5], MS; Douglas Teodoro[5], PhD; Georges L Savoldelli[1,6], MD, MEd; Nadia M Bajwa[1,7], MD, MHPE, PhD

[1]Unit of Development and Research in Medical Education, Faculty of Medicine, University of Geneva, Geneva, Switzerland

[2]Division of Internal Medicine, Department of Medicine, Geneva University Hospitals, Geneva, Switzerland

[3]Swiss Institute for Medical Education, Bern, Switzerland

[4]Department of Emergency Medicine, University Hospital Bern, Bern University, Bern, Switzerland

[5]Department of Radiology and Medical Informatics, Faculty of Medicine, University of Geneva, Geneva, Switzerland

[6]Division of Anesthesia, Department of Anesthesiology, Clinical Pharmacology, Intensive Care and Emergency Medicine, Geneva University Hospitals, Geneva, Switzerland

[7]Division of General Pediatrics, Department of Women, Children, and Adolescents, Geneva University Hospitals, Geneva, Switzerland

Corresponding Author:
Milena Abbiati, PhD
Unit of Development and Research in Medical Education
Faculty of Medicine
University of Geneva
Centre Médical Universitaire
1 Rue Michel-Servet
Geneva, 1206
Switzerland
Phone: 41 22 379 59 63
Fax: 41 22 379 51 22
Email: Milena.Abbiati@unige.ch

Abstract

Background: A medical student's career choice directly influences the physician workforce shortage and the misdistribution of resources. First, individual and contextual factors related to career choice have been evaluated separately, but their interaction over time is unclear. Second, actual career choice, reasons for this choice, and the influence of national political strategies are currently unknown in Switzerland.

Objective: The overall objective of this study is to better understand the process of Swiss medical students' career choice and to predict this choice. Our specific aims will be to examine the predominately static (ie, sociodemographic and personality traits) and predominately dynamic (ie, learning context perceptions, anxiety state, motivation, and motives for career choice) variables that predict the career choice of Swiss medical school students, as well as their interaction, and to examine the evolution of Swiss medical students' career choice and their ultimate career path, including an international comparison with French medical students.

Methods: The Swiss Medical Career Choice study is a national, multi-institution, and longitudinal study in which all medical students at all medical schools in Switzerland are eligible to participate. Data will be collected over 4 years for 4 cohorts of medical students using questionnaires in years 4 and 6. We will perform a follow-up during postgraduate training year 2 for medical graduates between 2018 and 2022. We will compare the different Swiss medical schools and a French medical school (the University of Strasbourg Faculty of Medicine). We will also examine the effect of new medical master's programs in terms of career choice and location of practice. For aim 2, in collaboration with the Swiss Institute for Medical Education, we will implement a national career choice tracking system and identify the final career choice of 2 cohorts of medical students who graduated from 4 Swiss medical schools from 2010 to 2012. We will also develop a model to predict their final career choice. Data analysis will be conducted using inferential statistics, and machine learning approaches will be used to refine the predictive model.

Results: This study was funded by the Swiss National Science Foundation in January 2023. Recruitment began in May 2023. Data analysis will begin after the completion of the first cohort data collection.

Conclusions: Our research will inform national stakeholders and medical schools on the prediction of students' future career choice and on key aspects of physician workforce planning. We will identify targeted actions that may be implemented during medical school and may ultimately influence career choice and encourage the correct number of physicians in the right specialties to fulfill the needs of currently underserved regions.

International Registered Report Identifier (IRRID): DERR1-10.2196/53138

(JMIR Res Protoc 2024;13:e53138) doi:10.2196/53138

KEYWORDS

career choice; medical specialty; medically underserved area; motivation; professional practice; medical students; residents; prediction model; machine learning; physician workforce

Introduction

Background

The unbalanced distribution of medical staff is identified by the Global Health Workforce Alliance as the major public health challenge of the 21st century [1]. The equitable distribution of physicians in the appropriate specialties and in the appropriate regions challenges high-income countries that are currently dependent on foreign-trained physicians. The increasing pressure to supplement the physician workforce is because of the growing medical needs of an aging population coupled with an aging physician workforce [2,3]. A misdistribution of the physician workforce has been clearly predicted in recent statistics owing to increasing rates of part-time employment, difficulties in recruiting physicians to certain specialties, and growing gender gaps in certain specialties and places of practice [4,5].

This is particularly true in Switzerland, where life expectancy is high and 1 of 4 physicians is currently aged >60 years [2,3]. To increase the number of physicians, the federal and cantonal states have financed the creation of 4 new medical schools. However, there is little link, if any, between the physician and general population ratio and the distribution of the medical workforce; therefore, this strategy may be largely insufficient to meet the needs of the population [6,7].

Medical schools and postgraduate medical education policymaking bodies play a key role in this dynamic. They are responsible for the supply of an adequate medical workforce to meet demands for quality, quantity, and appropriate distribution of physicians among specialties and geographic areas [8-10]. The regulation of the Swiss medical postgraduate training system offers great flexibility to physician graduates regarding specialty selection, postgraduate program duration, and location. It is unique and differs from other systems in neighboring countries, where the specialty choice and training site are based on numerus clausus [2-4]. Beyond the regulation system, there is often an imbalance between students' wishes, the need for specialists, and the positions available, leading to shortages in some specialties and high levels of competition in others [11]. Furthermore, once specialization is achieved, concentrations in certain types of practice (private outpatient rather than hospital based) and in certain geographic areas (advantaged urban rather than rural or disadvantaged urban areas) are unbalanced [12]. Consequently, there is a growing effort to better understand what factors contribute to the physician workforce shortage and misdistribution.

These factors are impacted by the societal, political, and regulatory aspects of postgraduate medical training. The Bland-Meurer theoretical framework for medical career decision-making indicates that both specialty characteristics (eg, type of practice and person oriented) and students' career needs (eg, prestige and work-life balance) are shaped by students' individual static (eg, demographic) and dynamic (eg, motivation) features, by life experiences, and by the values and culture of the training institution [13,14]. Studies on predominately dynamic characteristics, such as motivational factors, show that students' specialty choice can be driven by internal motives ("intrinsic motivation"), such as personal abilities, interest in helping patients, intellectual challenge, and by external motives ("extrinsic motivation"), such as salary, status, and workload [15]. Their importance differs by specialty [16,17] and gender [18-21].

Various methods of artificial intelligence and machine learning have also been investigated to provide decision support for and predict individual career choice [22-28]. These career choice prediction and decision support studies have achieved some success at being able to predict career choice, with performance varying from 68% to 85% area under the receiver operating characteristic curve. To the best of our knowledge, only 1 study has used modern machine learning methods to predict a medical student's career choice [29]. To date, it remains unknown how these models perform in career choice analyses in which individual and contextual data are available. Moreover, how machine learning models perform in predictive scenarios for multiple medical career choices is yet to be explored.

Current State of Our Own Research

In our previous research, we explored the areas of intention to practice (urban and rural) of graduating students at 4 Swiss medical schools [30]. We found that 13.7% expressed an intention to practice in underserved areas (62.1% of whom intended to practice in rural areas) and 41.1% were undecided. These intentions varied from one school to another and were related to different motivational factors. Work variety and work conditions appear to be factors that might attract interested and undecided students to work in underserved areas. Among those who wished to practice in underserved areas, general practice (21.6%) was the most preferred specialty. Motivational factors influencing specialty choice were intellectual challenges, work variety, work conditions, and enthusiasm. In addition, using the same cohort at 4 Swiss medical schools, we analyzed the motivating factors that influence the choice of obstetrics and gynecology as career intentions. The results highlighted the

importance of "experiential factors" and gender in this specialty choice. These findings provide useful information for targeted interventions to promote obstetrics and gynecology during undergraduate and postgraduate training by providing more hands-on experiences and improving the integration of male students and residents [31]. We also explored the degree of motivation for general practice, surgery, radiology, and psychiatry throughout the preclinical years. We specifically focused on personal and motivational individual characteristics correlated with general practice and surgical career intention [32-35].

The Swiss Medical Career Choice study is the continuation of 2 preliminary studies [12,36]. We will explore the role of students' individual static and dynamic features as well as that of the educational organizational context and training institution culture on career choice, that is, specialty, type, and place of practice, from medical school to postgraduate training. Thus, the present proposal seeks to understand the process of Swiss medical student career choice and attempts to predict this choice. First, we will examine the static and dynamic variables that predict the career choice of Swiss medical school graduates and their interaction. Second, we will examine the evolution of Swiss medical students' career choice and their ultimate career path.

Study Objectives

Primary Objectives

The primary objectives are to determine the current career intentions of Swiss medical students (choice of specialty and type of practice) and to assess the personal and contextual factors that determine their choice.

Secondary Objectives

The secondary objectives are as follows:

- To assess the influence of static factors such as gender and socioeconomic status
- To assess the influence of dynamic factors such as student perceptions of medical specialties and motivation
- To examine the interactions between both types of factors
- To attempt to predict career choice based on static, dynamic, and motivational factors and to design and test data-driven methods (artificial intelligence) to predict medical students' career choice
- To determine how career choice intentions vary during medical school within and across different medical school sites and during postgraduate training
- To determine how career choice intentions of Swiss medical school graduates have evolved over the last decade, considering the political strategies that have been put into place
- To compare how career choice intentions differ from the final choice in the Swiss nonregulated system and the French regulated system

Methods

Study Design

The Swiss Medical Career Choice is a 24-month longitudinal prospective national investigation implemented over 4 years (2 data collection time points) for 4 cohorts of medical students across all Swiss medical schools as well as a follow-up during postgraduate training.

For comparison purposes, this study also includes (1) a follow-up of 2 previous cohorts of medical students from Western Switzerland during postgraduate training, (2) a follow-up of the final career choice of 2 previous cohorts of medical students from 4 Swiss medical schools, and (3) a follow-up of the final career choice of 2 cohorts of medical students from Strasbourg, France.

Participants

In Switzerland, medical school consists of a 6-year curriculum divided into 3 years of bachelor's (basic science training) and 3 years of master's (clinical training). For the national prospective study, eligible participants will be medical students entering year 4 (master's 1) between 2022 and 2024 and finishing year 6 (graduates) between 2023 and 2026. The total number of eligible participants is approximately 1440 per cohort. Participants who have completed the questionnaire either in year 4 or 6 and have a response rate of >90% on the structured scale will be eligible for the follow-up study in postgraduate training year 2.

Data Collection

Data will be collected through 4 different sources: (1) a questionnaire administered during undergraduate year 4 (master's 1) and year 6 (master's 2), (2) a short survey during postgraduate training year 2, (3) data extracted from the residents' logbook of the Swiss Institute for Medical Education (SIME), and (4) exogenous contextual data extracted from the Federal Offices of Public Health and Statistics and the Swiss Medical Association (FMH).

Undergraduate participants will be invited to complete the questionnaire (approximately 30 min) during a compulsory class at the beginning of year 4 and at the end of year 6. Data will be anonymized for confidentiality reasons and for data protection issues. Participants will provide their student ID for matching purposes for the duration of the study. During the postgraduate years, participants (residents) will be invited to complete the short questionnaire (approximately 10 min) by invitation from the SIME, and relevant data will be extracted from their logbook. Data matching between the 2 data sources (undergraduate survey and data collected during residency) will be performed for each participant based on their ID number.

Ethical Considerations

The Chair of the Cantonal Commission for Ethical Research designated this study as exempt from formal review (protocol BASEC 2020-00813) as the aim of the study aim is outside the scope of the Swiss law as defined in Article 2 of the Human Research Act (HRA).

To obtain informed consent for undergraduate data collection, eligible participants will receive an email 10 days before the survey to inform them about the research project's main goals, the content, and the testing conditions (confidential and voluntary participation). Students who agree to participate will confirm their informed consent by marking a box on the first page of the questionnaire. Comparison cohorts of medical students consented previously to this study.

Data matching will be performed by a technical administrator who is not involved in the data analysis and interpretation. Researchers will only have access to deidentified data. Anonymous responses will be collected and stored on the secure web-based server Evasys. Survey data will be extracted from Evasys and stored in a password-protected Excel (version 21; Microsoft Corporation) file that is accessible only to the central study team. The University of Geneva standards for data handling will be followed for all data management and record keeping.

Participants will not receive compensation for completing the questionnaire.

Measures

Main Outcomes

The intention of practice of the undergraduates will be assessed through a single-choice question among 6 possible options grouped into four categories: (1) hospital-based medicine (senior physician in a nonuniversity public hospital and academic and clinical career in a university hospital), (2) office-based medicine (private clinical practice in a solo practice and private clinical practice in a group practice), (3) research and teaching, and (4) undecided. The students' specialty intentions will be gathered through a single-choice question among the 46 federal specialist titles issued by the SIME plus geriatrics, emergency medicine, and an undecided option. Specialties will be further regrouped into seven categories of intentions: (1) surgical, (2) acute care, (3) diagnostic medicine, (4) preventive medicine, (5) medical subspecialties, (6) general practice, and (7) undecided. Categories 1, 2, and 3 will be grouped together in the supracategory of "technically oriented specialties." Categories 4, 5, and 6 will be grouped in the supracategory "person-centered specialties." Data collected during the postgraduate training and extracted from the SIME residents' logbook include the specialty in which the residents are currently registered, specialist title for which the resident is aiming, number of months completed in the desired specialty, and the number of months completed in different specialties. The index of change during medical school or residency will be calculated as follow: if the student does not change=0, if the student changes their intention in the same specialty category=0.5, and if the student changes for another supracategory=1. The frequency of changes will also be calculated.

Demographic Data

The demographic will include age, gender, nationality (Swiss, European, or other), medical school, high school diploma (scientific vs other), place of origin, marital status, mother tongue, and 2 indirect measures of students' socioeconomic level, that is, parents' highest educational achievement (primary, secondary, or tertiary), and parents' profession (elementary, employee, executive, or professional) [37,38].

Motivational Factors

A total of 5 global motivational factors identified in the scientific literature as influencing the choice of specialty, validated by Beaulieu et al [36], will be ranked by their importance. The degree of motivation to become a surgeon as well as a general practitioner will be measured on a 6-point Likert scale: 1=very unmotivated to 6=very motivated. The global motivational factors mentioned earlier will be broken down into 12 specific motivational factors [34] influencing the choice to become a surgeon and a general practitioner (measured on a 6-point Likert scale: 1=very dissuasive to 6=very attractive). In total, 2 single-choice questions will assess (1) students' intention to practice in medically underserved areas (yes, undecided, or no) and (2) if yes, they will be asked to specify the desired location of practice (rural, mountain, or urban areas). The desired percentage of employment will be measured as the percentage of full-time employment on a 10-point Likert scale (0=0% to 10=100%).

Individual Characteristics

The previous academic background will be identified through 2 items asking students to report the type of high school degree and the grade obtained. Personality traits will be measured through the NEO Five Factor Inventory, which is widely used to assess the major personality traits as described in the Big Five Model [39]. It consists of 60 items, 12 per trait, scored on 5-point Likert scales (0=strongly disagree to 4=strongly agree). Motivation will be measured through the Academic Motivation Scale, which is widely used to assess self-determinate motivation in educational settings [40]. It consists of 28 items scored on a 7-point Likert scale (1=strongly disagree to 7=strongly agree) assessing intrinsic motivation (12 items), extrinsic motivation (12 items), and amotivation (4 items). Students' anxiety will be measured through the State-Trait Anxiety Inventory Form Y-State. Notably, we will assess state anxiety using the state anxiety subscale [41]. It consists of 20 items scored on a 4-point Likert scale (1=yes to 4=no). The total score ranges from 20 to 80. Scores are categorized into a 3-point cutoff: below 55 (average anxiety), 56 to 65 (high anxiety), and above 65 (severe anxiety). Students' gender representation will be measured through 6 items assessing gender bias [42]. Single-item scores will be standardized into *t* scores, and a total score will be calculated.

Context Characteristics

Students' perception of learning context will be measured using a brief revised version of the students' perception of teachers in the Dundee Ready Educational Environment Measure 11-item subscale [43]. This revised version consists of 6 items scored from 0 (strongly disagree) to 4 (strongly agree) as in the original version (max score of 24). The selected questions will assess if students have identified a person they view as a role model (yes, during my medical school training; yes, but not during my medical school training; and no). If yes, 2 open-ended questions will assess (1) the function of this person and (2) in what context they met them. A total of 2 single-choice questions will assess

(1) if the actual program location is the desired one and (2), if not, which location is the desired one. In total, 2 6-point Likert scale questions will assess (3) the degree of importance of the language of instruction and (4) the degree of importance of the cultural context.

Exogenous data collected from the Federal Medical and Population Statistics and the FMH include population density and medical density (of area of origin and of medical schools), number of professionals per specialty, specialist density per region, average specialist salary, and average number of working hours.

Table 1 summarizes domains, constructs, and measures by time points of data collection.

Table 1. Overview of domains, constructs, and measures by collection time points.

Domain and construct	Measure	Collection time point[a]		
		Master 1[b]	Master 3[c]	PGY[d]
Main outcomes				
Type or category of practice	Single-choice question	✓[e]		
Type or category of specialty	Single-choice question	✓	✓	✓
Rate of specialty or practice change	Homemade scale		✓	✓
Demographics				
Age, gender, and other demographics	Single-choice questions	✓	✓	
Marital status	Single-choice question			✓
Motivational factors				
Global motives for career choice	6-point Likert scale	✓	✓	✓
Motivation for general practice and surgery	6-point Likert scale	✓	✓	✓
Motives to choose general practice or surgery	6-point Likert scale	✓	✓	✓
Intention to practice in underserved areas	Single-choice question	✓	✓	✓
Desired percentage of employment	9-point Likert scale	✓	✓	✓
Individual factors				
Previous academic background	Single-choice question	✓	✓	
Personality	NEO-FFI[f] [39]		✓	
Motivation	AMS[g] [40]	✓	✓	✓
Anxiety	STAI-A[h] [41]	✓	✓	✓
Gender bias	Homemade scale	✓	✓	✓
Context				
Learning context	DREEM-R[i] [43]	✓	✓	✓
Role modeling	Single-choice questions	✓	✓	✓
Master's or training program location	Single-choice questions	✓	✓	✓
Exogenous data	Official records	✓	✓	✓

[a]The questionnaires will be collected annually from 2023 to 2026 from all fourth-year and sixth-year medical students and residents of Switzerland.

[b]Master 1: fourth year of medical school.

[c]Master 3: sixth year of medical school.

[d]PGY: postgraduate year.

[e]Data collection for the associated variable at the time point.

[f]NEO-FFI: NEO Five Factor Inventory.

[g]AMS: Academic Motivation Scale.

[h]STAI-A: State-Trait Anxiety Inventory Form A.

[i]DREEM-R: Dundee Ready Educational Environment Measure.

In the postgraduate survey, the selected items of individual characteristic measures will be used, except for the State-Trait Anxiety Inventory Form A. Data collection for the Western Switzerland and French comparison cohorts is similar to that

for the prospective national cohort. For the Western Switzerland cohorts, we will conduct 2 cross-sectional data collections at 2 different time points. For all comparison cohorts, we will retrieve the career choice through the residents' logbook of the SIME and through the National Examination (Epreuves Nationales) and the National Classifying Examinations (Epreuves Classantes Nationales) official site in France.

Data Analysis

This study adheres to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for cohort studies [44].

Descriptive statistics will be applied to demographics, career intention, motivational factors, and individual and contextual characteristics. A chi-square test will be used to compare intentions by medical school as well as to compare previous cohorts with the national prospective cohorts. The type I error rate will be set at .05.

To examine specific motivational factors, a principal component analysis with varimax rotation will be run to aggregate the motives out of the 12, demonstrating a frequency of >10%. Data suitability will be confirmed using the Kaiser-Meyer-Olkin index of sampling adequacy. Combined criteria (ie, scree plot, eigenvalue >1.0, and interpretability) will be used to determine the number of factors [45]. The critical value for significant factor loading will be >0.40 [46]. Each factor obtained from the principal component analysis procedure will be labeled according to its content.

Appropriate statistical tests will be applied to measure changes in motivational factors, the Academic Motivation Scale, anxiety, and contextual characteristics between different time points, such as rank-order stability (Spearman correlation *r* coefficient), the Cohen *d* effect size magnitude ratios [47], and the Reliable Change Index [48].

To examine whether the demographic, motivational factors, and individual and contextual characteristics will correlate with our main outcomes, logistic regression (odds ratio and 95% CIs) and linear regression will be used. These statistical analyses will be performed using R (version 4 or above; R Foundation for Statistical Computing) and SPSS (version 27; IBM Corp).

Following a machine learning approach, the questionnaire data and exogenous contextual data from the Federal Medical and Population Statistics and the FMH will be combined in an attempt to obtain a comprehensive view of the different medical careers within the working environment. This combined data set will then be preprocessed according to the input format of the machine learning models and will link medical students and exogenous contextual data to their career intentions. To avoid issues of data bias being injected into the algorithms, data augmentation via downsampling and oversampling strategies will be assessed to reflect equal gender distribution in the training set. For the model design and experiments, different machine learning algorithms will be investigated, in particular extreme gradient boosting [49] and CatBoost [50], which provide state-of-the-art performance for categorical data, to learn career choice patterns from the collected data set. In our experiments, the data set will be randomly divided into training (60%), development (20%), and test (20%) sets to train the model parameters and hyperparameters and to evaluate the models' performance, respectively. Hyperparameter tuning and evaluation metrics will be computed using cross-fold validation to increase the robustness of the results. Standard classification evaluation metrics such as area under the receiver operating characteristic curve, F_1-score, precision, and recall will be reported. The comparison of models' predictive results will be measured using the McNemar statistical test. The type I error rate will be set at .05. The Shapley additive explanation method [51], a consistent, fast, and deterministic method for extracting feature contributions at the individual prediction level, will be used to identify factors impacting career choices.

Statistical Power

Regarding the planned analyses, all the main outcomes deal with the estimation of proportions (eg, specialty choice and practice in underserved areas). Considering the smallest subgroup population of the study (2 cohorts of residents, ie, approximately n=2880) and the proportion associated with the highest variability of the estimates (P=.50), a sample size of 864 (ie, 2×432; refer to Table 1) would allow to estimate any proportion with a precision of +2.790% to −2.790% (95% CIs derived from the hypergeometric distribution).

Results

The project has been peer reviewed and funded by the Swiss National Science Foundation in November 2022 with a start date of January 1, 2023, and an end date of December 31, 2026 (Multimedia Appendix 1). Data collection is currently underway, with the longitudinal cohort study having launched nationally on March 31, 2023. Because of organizational constraints, the postgraduate follow-up of historical cohorts will be launched from autumn 2023 to winter 2024. We expect to obtain preliminary results by mid-2024.

Discussion

Overview

This paper describes a longitudinal, prospective national investigation that will survey 4 cohorts of medical students across all Swiss medical schools as well as residents during their initial postgraduate training. The main objectives are to better understand the career choice process of Swiss medical students and to try to predict this choice.

This project will allow us to better understand the individual and contextual factors influencing Swiss medical students' career path, from students' intention at the end of medical school to postgraduate medical training and final specialization. This study will deepen preliminary findings on the relative influence and interaction of static and dynamic variables such as gender, work-life balance, and students' medical specialty perceptions [12,32-36]. The fact that the study is conducted in all Swiss medical schools will also pinpoint the differences between the various Swiss medical schools and, in particular, the effects of new medical master's programs regarding career choice and location of practice. This study will allow us to inform national stakeholders and medical schools both through prediction of

students' future choices and key aspects of physician workforce planning. Finally, by drawing comparisons with a regulated postgraduate training system such as France's, this study will also have potential benefits at the international level.

Strengths

To the best of our knowledge, this study is the first to investigate the personal characteristics and the evolution of students' career choices during their medical studies and postgraduate training at a national level. Similarly, there is a lack of data regarding the follow-up from the initial intention to the definitive choice. This information is essential because better monitoring and understanding of career choice paths could help promote the management of physician resources and direct undergraduate and postgraduate interventions aimed at a better distribution of these resources [8-10].

We will provide information and prediction tools to meet demands for quality, quantity, and appropriate distribution of physicians among specialties and among geographic areas.

Using both individual and contextual data from medical students, we should be able to improve the predictive performance of the machine learning models as compared with questionnaire-only data [29]. By enabling better estimates than standard past averages, we expect that the predictive models will provide more effective support to decision makers for capacity planning. Moreover, by identifying the factors impacting career choice, decision makers will have data-driven information to support mitigation actions against specialty shortage. Finally, the predictive models may also help medical students in their career choice.

Limitations

Difficulties in recruiting collaborators within each medical school and coordination for survey administration may hinder response rates from students and therefore impact the realization of the study's objectives. Finally, most of the variables are self-reported and therefore subject to personal bias. However, this study will use questionnaires with established evidence to support their validity. In addition, the project has received official support from the Joint Commission of Swiss Medical Schools. This allows us to include students from all medical schools and from multiple years of study. The partnership with the Swiss postgraduate governing body, SIME, is key to enabling data collection and follow-up of subjects during the postgraduate training years. The interdisciplinary research team brings together a psychologist, a statistician, a computer engineer, and 5 medical doctors, all involved in medical education at the undergraduate and postgraduate level and holding different specialty titles.

Conclusions

Exploring the individual and contextual factors associated with the career path of all medical students in Switzerland and the establishment of a follow-up system will provide important information for improving the quality of medical workforce planning.

We will identify targeted actions that may be implemented during medical school and may ultimately influence career choice and encourage the correct number of physicians in the right specialties to fulfill the needs of currently underserved regions. Potentially, these results could contribute to better management of the medical workforce by balancing future physician distribution and, in turn, increasing the efficiency of the health care system and meeting the needs of Swiss society.

Acknowledgments

This work is supported by the Swiss National Science Foundation (grant 100019_213172/1). The Swiss National Science Foundation played no role in the creation, review, or approval of this manuscript for publication. The authors would like to thank Zoya Horcik, Dr Philippe Conus, Dr David Gachoud, Dr Régis Marion-Veyron, Dr Julie Palix, and Dr Romano Regazzi of the University of Lausanne, Dr Michele Ghielmini, and Dr Marilu Guigli-Poretti of the University of Italian-speaking Switzerland, Dr Jean Sibilia and Dr Thierry Pelaccia of the University of Strasbourg, and Dr Raphael Bonvin and Dr Elke Bayha of the University of Fribourg for their support in the initial implementation of the study at their respective universities. The authors would like to thank Eva Hennel and Lukas Wyss for their help with the postgraduate aspect of their current collaboration with the Swiss Institute for Medical Education.

Data Availability

The data sets generated and/or analyzed in preparation for / prior to this study that underpin a publication are available from the corresponding author on reasonable request. The data sets generated and/or analyzed as part of this study that underpin a publication will be available in due course at the Yareta, University of Geneva data repository.

Authors' Contributions

MA, MRN, DVA, DT, GLS, and NMB contributed to the initial draft of the manuscript, whereas BC, MBM, and GAS reviewed, revised, and approved the final submission. GLS and NMB contributed equally to this manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the Swiss National Science Foundation.
[PDF File (Adobe PDF File), 293 KB - resprot_v13i1e53138_app1.pdf]

References

1. Global strategy on human resources for health: workforce 2030. World Health Organization. 2016. URL: https://www.who.int/publications/i/item/9789241511131 [accessed 2023-12-10]
2. Bernheim L, Balavoine JF. Pénurie de médecins en Suisse: mythe ou réalité? Rev Med Suisse 2016 Feb 03;12(504):280-281. [Medline: 27000000]
3. Schweizer C, Hostettler S, Kraft E. La qualité des soins dépend d'une relève suffisante et qualifiée. Bull Med Suisses 2022 Mar 22;103(12):379-381 [FREE Full text] [doi: 10.4414/bms.2022.20632]
4. Hostettler S, Kraft E. Statistique médicale 2018 de la FMH: peu de femmes aux postes de cadre. Bull Med Suisses 2019 Mar 20;100(12):411-416 [FREE Full text] [doi: 10.4414/bms.2019.17687]
5. Hostettler S, Kraft E. Statistique médicale 2019 de la FMH: fort dépendance de l'étranger. Bull Med Suisses 2020 Mar 24;de la FMH:450-455 [FREE Full text] [doi: 10.4414/bms.2020.18725]
6. Statistics A-Z. Eurostat. 2017. URL: http://ec.europa.eu/eurostat/data/statistics-a-z/abc [accessed 2023-12-10]
7. Gorman D. Matching the production of doctors with national needs. Med Educ 2018 Jan 19;52(1):103-113. [doi: 10.1111/medu.13369] [Medline: 28722157]
8. Boelen C. Coordinating medical education and health care systems: the power of the social accountability approach. Med Educ 2018 Jan 07;52(1):96-102. [doi: 10.1111/medu.13394] [Medline: 28884465]
9. World Federation for Medical Education. The Edinburgh declaration. Med Educ 1988;22(5):481 [FREE Full text] [doi: 10.1111/j.1365-2923.1988.tb00788.x]
10. Doctors for health: a WHO global strategy for changing medical education and medical practice for health for all. World Health Organization. 1996. URL: https://iris.who.int/handle/10665/62997 [accessed 2023-12-10]
11. Durning SJ, Elnicki DM, Cruess DF, Reddy S, Kernan WN, Harrell HE, et al. Almost internists: analysis of students who considered internal medicine but chose other fields. Acad Med 2011 Feb;86(2):194-200. [doi: 10.1097/ACM.0b013e3182045ee5] [Medline: 21169784]
12. Abbiati M, Savoldelli GL, Baroffio A, Bajwa NM. Motivational factors influencing student intentions to practise in underserved areas: authors' reply. Med Educ 2020 Oct 12;54(10):965-966. [doi: 10.1111/medu.14263] [Medline: 32519372]
13. Bland CJ, Meurer LN, Maldonado G. Determinants of primary care specialty choice: a non-statistical meta-analysis of the literature. Acad Med 1995 Jul;70(7):620-641. [doi: 10.1097/00001888-199507000-00013] [Medline: 7612128]
14. Querido SJ, Vergouw D, Wigersma L, Batenburg RS, De Rond ME, Ten Cate OT. Dynamics of career choice among students in undergraduate medical courses. A BEME systematic review: BEME guide no. 33. Med Teach 2016;38(1):18-29. [doi: 10.3109/0142159X.2015.1074990] [Medline: 26372112]
15. Harris MG, Gavel PH, Young JR. Factors influencing the choice of specialty of Australian medical graduates. Med J Aust 2005 Sep 19;183(6):295-300. [doi: 10.5694/j.1326-5377.2005.tb07058.x] [Medline: 16167868]
16. Aubrion A, Goncalves P, Kowalski V, Reichling A, Mansour V. Facteurs influençant le choix de la spécialité de médecine générale par les étudiants en médecine. Pédagogie Médicale 2017 Mar 27;17(3):173-187 [FREE Full text] [doi: 10.1051/pmed/2017002]
17. Takeda Y, Morio K, Snell L, Otaki J, Takahashi M, Kai I. Characteristic profiles among students and junior doctors with specific career preferences. BMC Med Educ 2013 Sep 12;13(1):125 [FREE Full text] [doi: 10.1186/1472-6920-13-125] [Medline: 24028298]
18. Alers M, Verdonk P, Bor H, Hamberg K, Lagro-Janssen A. Gendered career considerations consolidate from the start of medical education. Int J Med Educ 2014 Sep 13;5:178-184 [FREE Full text] [doi: 10.5116/ijme.5403.2b71] [Medline: 25341228]
19. Buddeberg-Fischer B, Klaghofer R, Abel T, Buddeberg C. Swiss residents' speciality choices--impact of gender, personality traits, career motivation and life goals. BMC Health Serv Res 2006 Oct 23;6(1):137 [FREE Full text] [doi: 10.1186/1472-6963-6-137] [Medline: 17054803]
20. Dorsey ER, Jarjoura D, Rutecki GW. The influence of controllable lifestyle and sex on the specialty choices of graduating U.S. medical students, 1996-2003. Acad Med 2005 Sep;80(9):791-796. [doi: 10.1097/00001888-200509000-00002] [Medline: 16123455]
21. van der Horst K, Siegrist M, Orlow P, Giger M. Residents' reasons for specialty choice: influence of gender, time, patient and career. Med Educ 2010 Jun;44(6):595-602. [doi: 10.1111/j.1365-2923.2010.03631.x] [Medline: 20604856]
22. Damayanti AS, Wibawa AP, Pujianto U, Nafalski A. The use of adaptive Neuro Fuzzy Inference system in determining students' suitable high school major. In: Proceedings of the 4th International Conference on Education and Technology. 2018 Presented at: ICET '18; May 23-24, 2018; Malang, Indonesia p. 1-4 URL: https://ieeexplore.ieee.org/document/8693933 [doi: 10.1109/iceat.2018.8693933]
23. Gupta MV, Patil P, Deshpande S, Arisetty S, Asthana S. FESCCO: fuzzy expert system for career counselling. Int J Recent Innov Trends Comput Commun 2017;5(12):239-243 [FREE Full text] [doi: 10.17762/ijritcc.v5i12.1363]

24. Jamal K, Kurniawan R, Husti I, Nazri MZ, Arifin J. Predicting career decisions among graduates of tafseer and hadith. In: Proceedings of the 2nd International Conference on Computer and Information Sciences. 2020 Presented at: ICCIS '20; April 7-9, 2020; Sakaka, Saudi Arabia p. 1-4 URL: https://ieeexplore.ieee.org/document/9257663 [doi: 10.1109/iccis49240.2020.9257663]
25. Kiselev P, Kiselev B, Matsuta V, Feshchenko A, Bogdanovskaya I, Kosheleva A. Career guidance based on machine learning: social networks in professional identity construction. Procedia Comput Sci 2020;169:158-163. [doi: 10.1016/j.procs.2020.02.128]
26. Nie M, Xiong Z, Zhong R, Deng W, Yang G. Career choice prediction based on campus big data—mining the potential behavior of college students. Appl Sci 2020 Apr 20;10(8):2841 [FREE Full text] [doi: 10.3390/app10082841]
27. Razak TR, Hashim MA, Noor NM, Abd HI, Shamsul NF. Career path recommendation system for UiTM Perlis students using fuzzy logic. In: Proceedings of the 5th International Conference on Intelligent and Advanced Systems. 2014 Presented at: ICIAS '14; June 3-5, 2014; Kuala Lumpur, Malaysia p. 1-5 URL: https://ieeexplore.ieee.org/document/6869553 [doi: 10.1109/icias.2014.6869553]
28. Sahu R, Dash SR, Das S. Career selection of students using hybridized distance measure based on picture fuzzy set and rough set theory. Decis Mak Appl Manag Eng 2021 Mar 15;4(1):104-126 [FREE Full text] [doi: 10.31181/dmame2104104s]
29. Petek Šter M, Švab I, Šter B. Prediction of intended career choice in family medicine using artificial neural networks. Eur J Gen Pract 2015 Mar 16;21(1):63-69. [doi: 10.3109/13814788.2014.933314] [Medline: 25223737]
30. Abbiati M, Savoldelli GL, Baroffio A, Bajwa NM. Motivational factors influencing student intentions to practise in underserved areas. Med Educ 2020 Apr 02;54(4):356-363. [doi: 10.1111/medu.14063] [Medline: 31953862]
31. Fehlmann A, Abbiati M, Dällenbach P, Savoldelli LG. Motives influencing students' preferences for obstetrics and gynaecology speciality: a cross-sectional multi-site Swiss study. Eur J Obstet Gynecol Reprod Biol 2019 Jun;237:157-163. [doi: 10.1016/j.ejogrb.2019.04.036] [Medline: 31051419]
32. Abbiati M, Baroffio A, Gerbase M, Horcik Z. Personal and motivational factors influencing undergraduate medical students? preferences for general practice career: results of a longitudinal study. In: Proceedings of the 2016 International Association for Medical Education Conference; Barcellona 2016. amee.assetbank-server.com. 2016 Presented at: AMEE '16; August 28-31, 2019; Barcelona, Spain URL: https://amee.assetbank-server.com/assetbank-amee/action/viewAsset?id=3650&index=19&total=31&view=viewSearchItem
33. Abbiati M, Horcik Z, Gerbase M, Baroffio A. The role of personality and motivational factors on students? Career intentions for primary care and surgery during their clinical training. In: Proceedings of the 2017 International Association for Medical Education Conference. 2017 Presented at: AMEE '17; August 26-30, 2017; Helsinki, Finland URL: https://amee.assetbank-server.com/assetbank-amee/action/viewAsset?id=3651&index=20&total=31&view=viewSearchItem
34. Pelaccia T, Roy PM, Douillet D, Bilbault P, Abbiati M. Qu'est-ce qui motive [ou non] les étudiants en médecine à choisir comme spécialité la médecine d'urgence ? Ann Fr Med Urgence 2019 Jun 30;9(4):221-228 [FREE Full text] [doi: 10.3166/afmu-2019-0166]
35. Pfarrwaller E, Abbiati M, Baroffio A, Haller DM. Geneva medical students increasingly identify primary care physicians as role models after introduction of a compulsory clerkship. Eur J Gen Pract 2021 Dec 10;27(1):326-330 [FREE Full text] [doi: 10.1080/13814788.2021.1999925] [Medline: 34755578]
36. Abbiati M, Baroffio A, Gerbase MW. Personal profile of medical students selected through a knowledge-based exam only: are we missing suitable students? Med Educ Online 2016 Apr 12;21(1):29705 [FREE Full text] [doi: 10.3402/meo.v21.29705] [Medline: 27079886]
37. International Labor Office. International Standard Classification of Occupations 2008 (ISCO-08). Geneva, Switzerland: International Labour Office Publications; 2012.
38. International Standard Classification of Education. Montréal, QC: UNESCO Institute for Statistics; 2013.
39. McCrae RR, Costa PT. Personality trait structure as a human universal. Am Psychol 1997 May;52(5):509-516. [doi: 10.1037/0003-066x.52.5.509]
40. Vallerand RJ, Pelletier LG, Blais MR, Briere NM, Senecal C, Vallieres EF. The academic motivation scale: a measure of intrinsic, extrinsic, and amotivation in education. Educ Psychol Meas 1992;52(4):1003-1017 [FREE Full text] [doi: 10.1177/0013164492052004025]
41. Spielberger CD, Bruchon-Schweitzer M, Paulhan I. Inventaire d'anxie´te´ E´tat-Trait : Forme Y. Paris, France: Éditions du centre de psychologie appliquée; 1993.
42. Yoon H, Scopelliti I, Morewedge CK. Decision making can be improved through observational learning. Organ Behav Hum Decis Process 2021 Jan;162:155-188. [doi: 10.1016/j.obhdp.2020.10.011]
43. Roff S. The Dundee Ready Educational Environment Measure (DREEM)--a generic instrument for measuring students' perceptions of undergraduate health professions curricula. Med Teach 2005 Jun 03;27(4):322-325. [doi: 10.1080/01421590500151054] [Medline: 16024414]
44. Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Epidemiology 2007 Nov;18(6):805-835 [FREE Full text] [doi: 10.1097/EDE.0b013e3181577511] [Medline: 18049195]

45. Schönrock-Adema J, Heijne-Penninga M, Van Hell EA, Cohen-Schotanus J. Necessary steps in factor analysis: enhancing validation studies of educational instruments. The PHEEM applied to clerks as an example. Med Teach 2009 Jun 27;31(6):e226-e232. [doi: 10.1080/01421590802516756] [Medline: 19089728]
46. O' Rourke N, Hatcher L. A Step-by-Step Approach to Using SAS ® for Factor Analysis and Structural Equation Modeling. Bloomington, MN: SAS Publishing; Jul 28, 2015.
47. Cohen J. Statistical Power Analysis for the Behavioral Sciences. New York, NY: Routledge; 1988.
48. Christensen L, Mendoza JL. A method of assessing change in a single subject: an alteration of the RC index. Behav Ther 1986 Jun;17(3):305-308. [doi: 10.1016/s0005-7894(86)80060-0]
49. Chung C, He T, Benesty M, Khotilovich V, Tang Y, Cho H, et al. XGBoost: extreme gradient boosting, R package version 04-2. Cran R Project. URL: https://cran.r-project.org/web/packages/xgboost/index.html [accessed 2023-12-10]
50. Dorogush AV, Ershov V, Gulin A. CatBoost: gradient boosting with categorical features support. arXiv. Preprint posted online October 24, 2018 2018 [FREE Full text] [doi: 10.48550/arXiv.1810.11363]
51. Lundberg SM, Lee SI. A unified approach to interpreting model predictions. arXiv. Preprint posted online May 22, 2017. 2017. URL: https://arxiv.org/abs/1705.07874 [accessed 2022-05-20]

Abbreviations

FMH: Swiss Medical Association
SIME: Swiss Institute for Medical Education
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

Edited by A Mavragani; submitted 06.10.23; this is a non–peer-reviewed article;accepted 23.11.23; published 17.01.24.

Please cite as:
Abbiati M, Nendaz MR, Cerutti B, Brodmann Mäder M, Spinas GA, Vicente Alvarez D, Teodoro D, Savoldelli GL, Bajwa NM
Exploring Medical Career Choice to Better Inform Swiss Physician Workforce Planning: Protocol for a National Cohort Study
JMIR Res Protoc 2024;13:e53138
URL: https://www.researchprotocols.org/2024/1/e53138
doi:10.2196/53138
PMID:38231561

Protocol

Participatory Development and Assessment of Audio-Delivered Interventions and Written Material and Their Impact on the Perception, Knowledge, and Attitudes Toward Leprosy in Nigeria: Protocol for a Cluster Randomized Controlled Trial

Ngozi Murphy-Okpala[1], MBBS, FMCPH; Tahir Dahiru[2], MBBS, MPH; Anna T van 't Noordende[3], MSc, PhD; Carolin Gunesch[4], MA; Joseph Chukwu[1], MBBS, MPH; Charles Nwafor[1], MBBS, MPH; Suleiman Hudu Abdullahi[2], MBBS; Chukwuma Anyaike[5], MBBS, DTM&H, MCommH, FWACP; Ugochinyere Angelic Okereke[6], NCE, BAEd, ME; Anthony Meka[1], MBBS, MPH; Chinwe Eze[1], BSc, MPH; Okechukwu Ezeakile[1], MBBS, MPH; Ngozi Ekeke[1], MBBS, MPH, FWACP

[1]RedAid Nigeria, Enugu, Nigeria

[2]Leprosy and Tuberculosis Relief Initiative, Jos, Nigeria

[3]NLR International, The Netherlands, Amsterdam, Netherlands

[4]DAHW-German Leprosy and TB Relief Association, Wurzburg, Germany

[5]National Tuberculosis and Leprosy Control Programme, Federal Ministry of Health, Abuja, Nigeria

[6]Department of Art Education, University of Nigeria, Nsukka, Nigeria

Corresponding Author:
Ngozi Murphy-Okpala, MBBS, FMCPH
RedAid Nigeria
56 Nza Street, Independence Layout
Enugu, 23401
Nigeria
Phone: 234 706 749 0052
Email: ngozi.murphyokpala@redaid-nigeria.org

Abstract

Background: In Nigeria, similar to many leprosy-endemic countries, leprosy is highly stigmatized. High levels of stigma among community members as well as internalized stigma among persons affected by leprosy often result in negative psychosocial consequences for those affected. To break this vicious cycle, it is important to conduct context-specific behavioral change activities. Although written material has been successful in improving knowledge and perception, it is not suitable for populations with low educational levels. Audio-delivered interventions are likely to be more suitable for people who are illiterate. This study proposes to assess the impact of an audio-delivered intervention on the perception (knowledge, attitudes, and beliefs) of community members with regard to leprosy in Nigeria.

Objective: This study aims to assess the impact of audio-delivered and written health education on the perception of leprosy. Specific objectives are to (1) investigate the perception (local beliefs, knowledge, and attitudes) of community members toward leprosy and persons affected by leprosy; (2) investigate whether there is a difference in impact on perception between participants who have received audio-delivered health education and those who have received written health education, with specific reference to gender differences and differences between rural and urban areas; and (3) assess the impact of the participatory development of the audio-delivered and written interventions on empowerment and internalized stigma of persons affected by leprosy who developed the interventions. Additionally, we will translate and cross-culturally validate 4 study instruments measuring outcomes in 2 major Nigerian languages.

Methods: We will use a mixed methods, cross-sectional study design for the intervention development and a 3-arm cluster randomized controlled trial for its implementation and evaluation, comprising (1) baseline assessments of knowledge, attitudes, perceptions, and fears of community members, to develop the audio-delivered content and written material, and the self-esteem and internalized stigma of persons affected by leprosy; and (2) participatory development of the audio-delivered content and written material by persons affected by leprosy and the pilot and implementation of the interventions. This will be done among

different groups (selected using cluster randomization) that will be compared (control group, audio-intervention group, and written material group) to evaluate the intervention and the impact of developing the intervention on the persons affected.

Results: This study was funded in June 2022, and community member participant recruitment started in January 2023. Baseline data collection was completed by May 2023 (n=811). Participatory cocreation of the audio and written health education content began in July 2023, and the materials are currently under development. Study results are expected in September 2024.

Conclusions: Study findings will contribute to developing evidence-based, context-specific behavioral change interventions, which are critical to addressing stigma in many leprosy-endemic communities where leprosy is highly stigmatized, and contribute toward global triple zero leprosy efforts.

Trial Registration: Pan African Clinical Trial Registry PACTR202205543939385; https://pactr.samrc.ac.za/TrialDisplay.aspx?TrialID=23667

International Registered Report Identifier (IRRID): DERR1-10.2196/53130

(JMIR Res Protoc 2024;13:e53130) doi:10.2196/53130

KEYWORDS

audio health education; community perception of leprosy; health education; leprosy; Nigeria; persons affected by leprosy

Introduction

Overview

Leprosy is an infectious disease caused by *Mycobacterium leprae* [1]. Leprosy has been stigmatized since ancient times [2]. Stigma refers to a negative social response from one group toward a low-power, stigmatized group [3]. Stigma is "a social process, experienced or anticipated, characterized by exclusion, rejection, blame, or devaluation that results from experience, perception, or reasonable anticipation of an adverse social judgment about a person or group" [4]. Stigma can occur at different levels, for example, at the intrapersonal, interpersonal, community, institutional, and structural levels [5]. Many people affected by leprosy experience the negative consequences of their condition [6,7]. Stigma can have a very negative effect on employment and education opportunities, social interaction, housing, and access to health care [8]. Stigma can also indirectly cause stress and negatively impact mental well-being, quality of life, and physical health [8]. Stigma can delay seeking treatment [9] and can also impede adherence to treatment [10]. Family members and friends may experience courtesy stigma (stigma by association) [11,12].

Perception, which refers to how individuals or groups "see" an object, person, event, or institution [13-15], is an important driver of stigma [4]. The origin of stigma lies in public perceptions about people who are stigmatized. Perception comprises knowledge, beliefs, and attitudes, which are in turn influenced by personal factors (eg, personality and experience) and environmental factors (eg, culture and religion) [13,14]. Leprosy-related stigma is mainly caused by fears of contagion, external manifestations, and disabilities; religious and cultural beliefs; misconceptions; and a lack of knowledge [2,16]. Personal characteristics such as age, gender, occupation, education, and living area have also been associated with leprosy-related community stigma [17-20]. Stigma reduction (which often consists of positively influencing the perception of leprosy and increasing knowledge of leprosy) is crucial to improving the lives of people affected by leprosy and to improving leprosy services. Several interventions have successfully reduced leprosy-related stigma [21-24]. Interventions that are culture-specific and contextualized tend to be more effective [25,26].

Nigeria is among 23 global priority countries identified by the World Health Organization (WHO). In 2019, a total of 2424 new patients with leprosy were detected in Nigeria, 15% of whom had Grade 2 disabilities (G2Ds) [27]. Nigeria is among the few countries that reported more cases of G2Ds in 2019 than in previous years [27]. G2D among new patients is used as an indicator of late detection of leprosy. In addition, G2Ds (visible impairments) often exacerbate stigma and discrimination [28,29]. Leprosy is a stigmatized disease in Nigeria [30,31]. In a study among persons affected by leprosy and community members in Western Nigeria, the stigmatization of leprosy was mainly linked to perceived infectivity and perceived immoral behavior [31].

Despite progress in the control of leprosy in the last decades, the disease remains highly stigmatized [7], especially in Nigeria [30,31]. High levels of community stigma as well as internalized stigma among persons affected by leprosy may result in delayed diagnosis and disabilities [32]. To break this vicious cycle, it is important that context-specific attitude and behavior change activities are carried out. From other studies, we know that changing perceptions and improving knowledge can lead to behavior change [18,33,34]. For example, between March and June 2020, several printed materials that aimed to improve the perception of leprosy and increase knowledge about leprosy were evaluated in Uttar Pradesh, India. These context-specific materials were developed as part of NLR International's Post-Exposure Prophylaxis project. Analysis revealed an association between the number of posters seen and a positive change in knowledge and stigma scores [35].

Access to appropriate health information is an essential step in the fight against stigma and discrimination. However, written materials are not suitable for populations with low educational levels [36]. To make health information accessible to people who are illiterate in many leprosy-endemic communities of the global south (especially women and girls), it is important to provide information through modalities other than printed materials. It is believed that audio-delivered interventions would be more suitable for people who are illiterate and low-literate.

Audio-delivered interventions, for example, radio, have been shown to be successful for different stigmatized conditions such as HIV, leprosy, and albinism [37-39].

This study aims to assess the impact of an audio-delivered intervention on the perception (knowledge, beliefs, and attitudes) of community members regarding leprosy by comparing an audio-delivered intervention with written health education. The study will be conducted in Nigeria.

Primary and Secondary Objectives

Our primary objective is to assess the impact of audio-delivered and written health education on the perception of leprosy in Nigeria. Additionally this study has the following secondary objectives: (1) to investigate the perception (local beliefs, knowledge, and attitudes) of community members toward leprosy and persons affected by leprosy; (2) to investigate whether there is a difference in impact on perception between participants who have received audio-delivered health education and those who have received written health education, with specific reference to gender differences and differences between rural and urban areas; and (3) to assess the impact of the participatory development of the audio and written interventions on empowerment and internalized stigma of persons affected by leprosy who developed the interventions.

Methods

Study Design

We will conduct a cross-sectional study (intervention development) and a 3-arm cluster randomized controlled trial (RCT; intervention implementation and evaluation). The three arms consist of (1) an intervention group who will receive the audio-delivered intervention, (2) an intervention group who will receive the written intervention (poster or flyer), and (3) a control group who will not receive any intervention.

Study Location and Setting

The study will be carried out in 6 local government areas (LGAs), 3 each in Cross River State (Boki, Calabar-South, and Obubra) and Taraba State (Jalingo, Yorro, and Zing). The 3 LGAs per area will be selected based on similarity in terms of literacy rate and prevalence of leprosy. Cross River is located in southern Nigeria, while Taraba is in the north. The total population of the study area is 940,540, estimated from the 2006 census, with 542,494 in Cross River and 398,046 in Taraba states. Both states have been selected because of the high prevalence of leprosy and G2D.

Cross River State notified a total of 106 new cases (17% with G2D) in 2019. The most common language spoken in Cross River State is Nigerian Pidgin. Over 90% of the people living in the selected LGAs in southern Nigeria speak Nigerian Pidgin. Other languages spoken in Cross River State include Efik, Ekoi, and Yala. The illiteracy rate (those with no schooling or primary or secondary education who cannot read at all) is 12.2% and 26.4% for male and female individuals, respectively. Occupations include farming, trading, and civil service employment. About 58% of women own mobile phones, compared with 71% among men [40]. Cross River State's poverty index is 0.146, and the poverty headcount rate is 36.3%. The case notification rate for leprosy is 2.76 per 100,000 people based on 2020 data.

Taraba is among the 15 high-burden states for leprosy in Nigeria; an average of 100 new cases were detected between 2013 and 2017, with an average of 6% and 5% of children and G2D cases, respectively. This figure is likely to be underreported, considering the significant presence of isolated populations such as nomadic pastoralists and internally displaced people in the state.

The most common language spoken in the selected LGAs in Taraba State is Hausa; 80% to 90% of the people living in the selected LGAs in Northern Nigeria speak Hausa. Other languages spoken in Taraba State include Mummuye and Fulfulde. The illiteracy rate is 30.1% and 64.9% in Taraba State for male and female individuals, respectively. Occupations in Taraba include farming, mainly crop production and cattle rearing, petty trading, and civil service employment. The majority of men (71%) own a mobile phone, while only 44.6% of women do. Taraba State's poverty index is 0.448, and the poverty headcount rate is 87.7%. The case notification rate for leprosy is 2.30 per 100,000 people.

Study Population

The following 2 groups of participants will be included in the study: persons affected by leprosy (for the participatory development of the interventions) and community members (the target group of the interventions).

Inclusion and Exclusion Criteria

Individuals aged 18 years or older will be included in this study. Individuals who do not speak Nigerian Pidgin or Hausa and who are unable or unwilling to give informed consent will be excluded from the study.

Study Duration and Sample Size Calculation

This study's duration will be 2 years. The sample size for the various components of the study is as follows. (1) A total of 200 community members (100 for each language per study area) will be included in the cross-cultural validation of the Explanatory Model Interview Catalogue Community Stigma Scale (EMIC-CSS) and Social Distance Scale (SDS), while 100 persons affected by leprosy (50 for each language per study area) will be included in the cross-cultural validation of the Internalized Stigma of Mental Illness (ISMI) scale and Rosenberg Self-Esteem Scale (RSES; see below). (2) A total of 770 community members will be included in the baseline and follow-up questionnaire interviews. This means a random sample of at least 385 persons in Taraba State (northern Nigeria) and at least 385 persons in Cross River State (southern Nigeria), which will consist of 114 in the audio intervention group, 114 in the written material intervention group, and 157 in the control group in each region.

This RCT will have three arms: (1) an audio-delivered intervention group, (2) a written material intervention group, and (3) a control group. The sample size calculation is based on 2 calculations. The intervention group calculation is based on an estimate of the difference in knowledge improvement

between the audio-delivered intervention and the written material intervention groups. We used data from a perception study in India. In this study, postintervention scores improved by 12.5% after a poster intervention and community meetings. We estimate that the effect of posters alone would be an increase of 10%. We want to be able to detect an improvement of at least 15% between the audio-delivered and the written material intervention groups. The sample size of the intervention group is therefore based on a proportion 1 of 10 (estimated percentage of improvement in knowledge of leprosy in the written intervention group) and a proportion 2 of 25 (ie, an improvement of 15% or more). With a power of 80%, a significance level of .05, and a 15% loss to follow-up, 114 participants are needed in each intervention group.

We expect an increase of 2% in the knowledge score in the control group. The control group calculation is therefore as follows: proportion 1:10, proportion 2:2, power 80%, significance .05, and 15% loss to follow-up, resulting in 157 participants.

A total of 25 people will be included in the participatory development of the material [41]. In each state, these will consist of 10 persons affected by leprosy and 2-3 community members. Semistructured interviews will be conducted until data saturation is reached.

Description of the Intervention

The interventions consist of (1) an audio-delivered intervention and (2) a written or printed intervention (such as posters or flyers) for education on leprosy, awareness-raising, and stigma reduction.

We will compare the effect of the interventions with a control group. The audio-delivered and written content will be developed based on local beliefs, misconceptions, and fears about leprosy identified in the baseline study. This will be done using participatory approaches. A group of persons affected by leprosy and a few members of the community will be formed, who will be guided by a researcher to develop the messages and materials (participatory development). The key messages of the audio-delivered and written interventions will be the same. The materials will be developed in the main languages spoken in the study areas: Nigerian Pidgin (Cross River State) and Hausa (Taraba State). The majority (>80%) of our target group speaks either Nigerian Pidgin or Hausa, which will hence be the language used for this study. The audio-delivered intervention will be incorporated into Audiopedia [42]. Audiopedia's website was designed to provide access to open knowledge foremost on health, livelihood, and well-being to both community-based organizations and nongovernmental organizations and individuals. Community-based organizations and nongovernmental organizations can benefit from using Audiopedia as part of their social and behavior change communication strategy, as it enables them to search, download, embed, and share audio files. Approximately 5000 audio clips, with a total runtime of 150 hours, are available in 11 languages. Audiopedia was optimized for search engines, thus making contents easy to find. Audiopedia also provides several technological solutions to make audio-based contents accessible to both literate and illiterate audiences, such as solar-powered audio players, mobile web applications for smart (feature) phones, and Wi-Fi hotspots that can stream audio-based contents without the need for internet connectivity, etc.

Participant Recruitment and Follow-Up

Persons affected by leprosy and community members will be selected based on purposive sampling. They will develop the content of the interventions. This is therefore, ideally, a diverse group of people who represent multiple perspectives. We will select participants based on purposive sampling to ensure adequate representation of age, gender, and villages.

The intervention will be implemented in North and South Nigeria, 2 areas that are very different. Therefore, we will cluster-randomize the interventions to ensure comparable groups are included in both areas. There are three different "groups" in each site (North and South): (1) the audio-delivered intervention, (2) the written materials intervention, and (3) no intervention (control group).

We will select 3 LGAs in North and South Nigeria (6 in total); each LGA will have either the audio-delivered or the written intervention or be a control group. The three LGAs per area will be selected based on their similarity in terms of literacy rate and endemicity of leprosy.

The interventions will be randomly allocated to clusters (LGAs) based on a random numbers list. This is a 2-stage random sampling. We will select a random sample of LGAs and a random sample of participants within each LGA. The participants in each LGA will be selected using the "spin the bottle" approach: a bottle will be spun in front of the most central place in the village (rural area) or neighborhood (urban area); the direction the bottle points at is the direction we start walking and counting. The first house to be included is selected by casting a die. Participant selection will be done by proportional sampling among the clusters. We will include the same participants at baseline and follow-up (a paired sample). This study protocol is reported in accordance with the SPIRIT statement (see checklist in Multimedia Appendix 1). The timeline schedule for participants during the study period is represented in Table 1, and a schematic description of the study flow chart is depicted in Figure 1.

Table 1. Study schedule for enrollment, intervention, and assessment.

Schedule	Study period and time point					
	Enrollment	Allocation	Postallocation			Close out
	t_{-1}	t_0 (month 0)	t_1 (baseline)	t_2 (intervention)	t_3 (6 months follow-up)	t_4
Enrollment						
Eligibility screening	✓					
Informed consent	✓					
Randomization and allocation		✓				
Intervention group						
Audio-delivered intervention				✓		
Written				✓		
Control (no intervention)						
Assessments						
Baseline variables						
KAP[a], EMIC-CSS[b], and SDS[c]			✓			
RSES[d] and L-ISMI[e] scale			✓			
CNA[f]			✓			
Outcome variables						
KAP, EMIC-CSS, and SDS					✓	
RSES and L-ISMI scale					✓	
Analysis						
Data analysis						✓

[a]KAP: knowledge, attitudes, and practices.

[b]EMIC-CSS: Explanatory Model Interview Catalogue Community Stigma Scale.

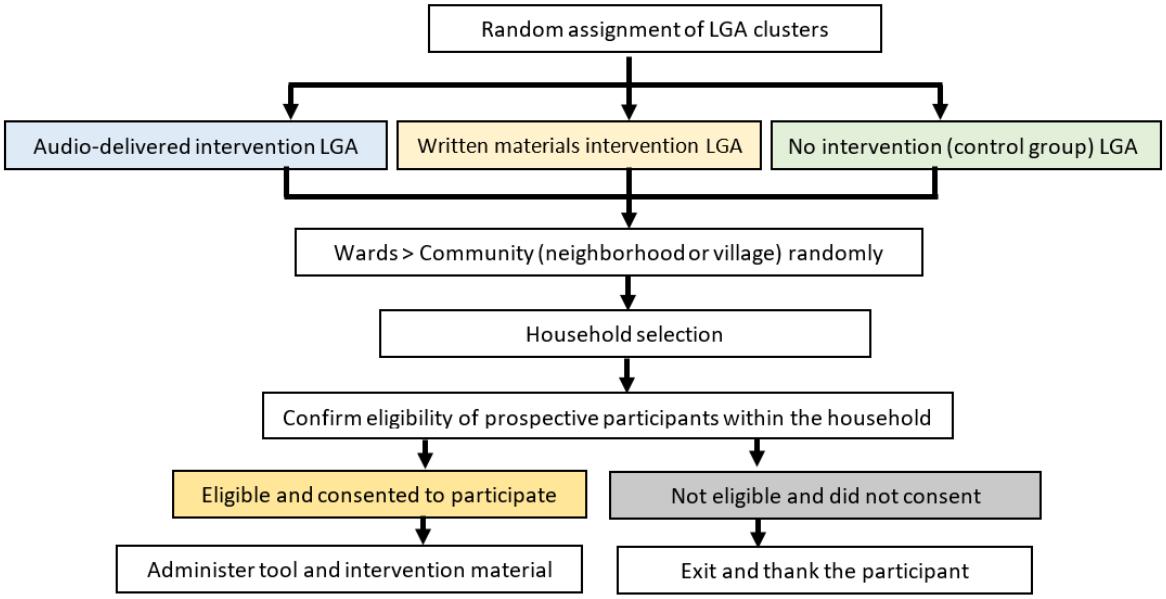
[c]SDS: Social Distance Scale.

[d]RSES: Rosenberg Self-Esteem Scale.

[e]L-ISMI: Leprosy-adapted Internalized Stigma of Mental Illness.

[F]CNA: Communication Needs Assessment.

Figure 1. Study flow chart. LGA: local government area.



Primary and Secondary End Points

The outputs of this study will be an audio-delivered intervention and written or printed health education material for education on leprosy, awareness-raising, and stigma reduction.

In addition, all 4 scales will be translated and cross-culturally validated in Nigerian Pidgin and Hausa languages as part of this study. The qualitative outcomes are knowledge and attitudes toward (persons affected by) leprosy (eg, local beliefs, fears, and misconceptions).

Outcome measures used to be assessed at baseline and follow-up are as follows:

- Demographic information: to disaggregate data by gender, the "knowledge, attitudes, and practices" (KAP) measure includes a form to collect demographic information.
- The KAP measure, as used in a study in India [16], covers 8 main topics: early symptoms, cause, mode of transmission, treatment, prevention, curability, contagiousness when on treatment, and prevention of disabilities. The KAP is a questionnaire and has not been formally validated as a scale (nor will it be used as a scale). We will translate and pilot test the KAP measure.
- Community stigma, using the EMIC-CSS (used in Nigeria but not validated in Nigerian Pidgin and Hausa yet [17]).
- Desired social distance toward persons affected by leprosy as a proxy for attitudes and fear, using the SDS (used among persons affected by leprosy in Nigeria but not validated in Nigerian Pidgin and Hausa yet [17]).
- Self-esteem and internalized stigma of persons affected by leprosy, using the RSES (used in Nigeria but not validated in Nigerian Pidgin and Hausa yet) and the leprosy-adapted ISMI (used among persons affected by leprosy and used in Nigeria but not formally validated yet [17]).

Data Collection

Overview

We will use a mixed methods approach and collect qualitative data (in-depth interviews and focus group discussions [FGDs]) and quantitative data (the KAP measure, EMIC-CSS, SDS, communication needs assessment, RSES, and ISMI). We will also collect demographic information (including literacy levels) from each participant.

This study consists of the steps and phases outlined in the following subsections.

Step 1

None of the tools listed in step 2 have been validated in Nigerian Pidgin and Hausa yet; therefore, they will be cross-culturally validated before use. We will assess conceptual, item, semantic, operational, and measurement equivalence using a framework for cross-cultural equivalence testing based on the work of Herdman et al [43], Terwee et al [44], and Stevelink and van Brakel [45]. In addition, the interview and group discussion guides (outlined in step 2) will be pilot tested among a small sample of participants before use. The KAP measure will be translated and pilot-tested.

Step 2

A baseline study to assess the perceptions of community members using mixed methods will be conducted, consisting of both in-depth interviews and FGD sessions and questionnaires (KAP, EMIC-CSS, and SDS). A communication needs assessment will be conducted as part of the baseline study to determine the most appropriate mode of delivery of the audio intervention and the most appropriate duration and frequency of the audio intervention. We will also conduct a baseline study among the persons affected by leprosy group who will be involved in the development of the interventions. Self-esteem and internalized stigma will be assessed using in-depth interviews, RSES, and ISMI.

Step 3

The participatory development of the audio-delivered and written content of the interventions is based on the knowledge gaps, beliefs, misconceptions, fears, and community attitudes identified in the baseline study. We will use the "6 steps in quality intervention development (6SQuID) framework [46], consisting of (1) defining and understanding the problem and its causes, (2) identifying which causal or contextual factors are modifiable: which have the greatest scope for change and who would benefit most, (3) deciding on the mechanisms of change, (4) clarifying how these will be delivered, (5) testing and adapting the intervention, and (6) collecting sufficient evidence of effectiveness to proceed to a rigorous evaluation. The final step of 6SQuID (step 6) is part of step 5 of this study—evaluation. The group of persons affected by leprosy who play a leading role in the development of the messages and materials (participatory development) will codetermine both the content of the materials (based on the knowledge gaps, beliefs, misconceptions, fears, and community attitudes identified in the baseline study) and the mode of delivery (based on the most appropriate means of communication determined by the communication needs assessment conducted as part of the baseline study).

Step 4

Implementation of the interventions in the study areas will be done in 2 groups: one intervention group will receive the audio-delivered intervention, and the other intervention group will receive the written intervention (poster or flyer). A control group will not receive any intervention. The groups will be cluster-randomized.

Step 5

Step 5 involves evaluating the impact of (1) the intervention on the community and (2) developing the intervention on persons affected, using the same mixed methods as the baseline studies (described in step 2). It should be noted that the in-depth interviews at baseline are mainly conducted to get insight into specific fears, local beliefs, and misconceptions about leprosy among community members, as well as insight into the self-esteem and internalized stigma of persons affected by leprosy. At follow-up, the communication needs questionnaire will not be administered anymore. In addition, FGDs will be held with community members at baseline and follow-up in the 6 LGAs and with the persons affected by leprosy group. In addition to further exploring themes that arose during the in-depth interviews, additional questions will be asked (at follow-up) to get insight into, among other things, awareness of, experiences with, and exposure or access to the audio and written interventions; thoughts about content; mode of delivery and frequency; and strengths and points of improvement.

Data Management and Data Analysis

Quantitative data collection will be done using electronic forms developed in the Open Data Kit, and all data will be securely stored in the cloud with access only to the research team. The recordings of the in-depth interviews and FGDs will be transcribed to the local languages, translated to English, and analyzed by 2 independent researchers using open, inductive coding and content analysis. Similar phrases with recurring themes will be coded in NVivo (QSR International). Quantitative data will be collected in the KoboCollect (Kobo Inc) mobile phone app. Data analysis will be done in the software package SPSS Statistics (SPSS Inc). Simple descriptive methods will be used to generate a demographic profile of the study sample. Differences between participants in the groups (audio, written materials, and control groups) will be evaluated using the Mann-Whitney *U* test or 1-tailed *t* test for continuous variables and the chi-square statistic for categorical variables. The mean (SD) or median (IQR), depending on the distribution of the data, of the total scores of the scales used will be calculated per intervention area. Stepwise multivariate regression with backward elimination will be done to examine what factors will have an independent effect on the outcomes. We will calculate the percentage change and corresponding 95% CI before and after the interventions are implemented and the statistical significance of this difference using a z test for differences between proportions. Effect sizes will also be calculated. If necessary, we will correct for differences in demographic information between study arms using quantile regression. We will compare the differences in follow-up assessment between the audio-delivered and written interventions. The knowledge gaps, beliefs, misconceptions, fears, etc identified in the baseline study will be summarized into a narrative review and will be used by the persons affected by leprosy group as input for the development of the content of the interventions. The most appropriate modes of delivery will be determined based on the communication needs assessment that will be conducted as part of the baseline study. The interventions will be developed using participatory methods.

Confidentiality and anonymity of data will be ensured in data collection, storage, analysis, and publication. Research assistants who will collect the data will be trained in data management, the maintenance of confidentiality, and ensuring privacy during data collection. Data will only be analyzed and shared with the Dutch and German researchers (outside of Nigeria) when they have been fully anonymized. The lead applicant will take full responsibility for ensuring the appropriate storage and security of data. Data will be kept for 5 years and destroyed after this time frame when no longer required.

Ethical Considerations

Ethical approval has been obtained from the Health Research and Ethics Committee of the University of Nigeria Teaching Hospital, Ituku-Ozalla, Enugu (NHREC/05/01/2008B-FWA00002458-1RB00002323). In addition, appropriate clearance was sought and obtained from the respective ethics committees of both the Taraba and Cross Rivers State Ministries of Health. The confidentiality of the study participants and the data collected from them will be ensured.

Written informed consent (Multimedia Appendix 2) will be obtained from the study participants. The questionnaire will be translated into the local languages included in this study and back-translated to ensure the soundness of the translation process. The consent form explicitly states the right of the participant to refuse giving consent or withdraw from the study

at any point. Also, he or she can decline to answer any question. Informed consent will be obtained from each participant before participation. Each participant will be given a copy of the participant information sheet and consent form to keep.

This RCT study was prospectively registered with and listed on the Pan African Clinical Trials Registry (PACTR202205543939385).

Results

This study was funded in June 2022, and community member participant recruitment started in January 2023. Baseline data collection was completed by May 2023, with a total of 811 respondents. Participatory cocreation of the audio and written health education content began in July 2023, and the materials are currently under development. Intervention will be administered after pilot-testing, and the follow-up period will last for 6 months. Neither the implementation of the study intervention nor the data analysis have commenced as of the time of submission. Study results are expected in September 2024.

Discussion

Principal Considerations

In this study, we will apply mixed methods to compare the impact of audio-delivered versus written health education intervention materials and a control group without any intervention on the perception (knowledge, beliefs, and attitudes) of community members regarding leprosy. Through a participatory cocreation process, we will develop the content of the intervention materials alongside persons affected by leprosy and implement a 3-arm cluster RCT to evaluate the effect of the intervention. The effect of the cocreation process on internalized stigma among the affected persons will also be evaluated.

Developing context-specific behavioral change intervention activities is critical to addressing stigma in many leprosy-endemic communities where leprosy is highly stigmatized. The outcome of this intervention is expected to influence knowledge and, hopefully, improve the attitudes of community members toward leprosy, as well as improve self-esteem among persons affected by leprosy. In the long run, early leprosy case finding will be boosted following stigma reduction. To the best of our knowledge, this is the first study of this kind in Nigeria. The generated educational materials (both the audio and written content) are reusable products that may be adopted or used by the national program. The audio-delivered educational content will be freely available on the Audiopedia platform, licensed under Creative Commons (CC BY).

Limitations

There are inherent limitations associated with cluster-randomized studies, such as cluster size variability. With the challenge of achieving uniform cluster sizes, variability in cluster size could impact the generalizability of the results. Additionally, there is a risk of contamination between clusters; however, this is minimal given the geographic distance between the study cluster locations.

The study sites were purposefully selected due to their similarity in having a high prevalence of leprosy and G2Ds; thus, the findings from this study may not be generalizable to the entire Nigerian populace.

Conclusion

Outputs from the research will offer policy makers, national and regional program managers, and partners reliable evidence for a new approach toward stigma reduction activities, thereby contributing toward global triple zero leprosy efforts. Content generated provides pragmatic and contextual evidence-based tools for effective health education campaigns and awareness creation, especially among populations with low literacy levels, both in Nigeria and other low- and middle-income countries.

Acknowledgments

This work is supported by the Leprosy Research Initiative Foundation (grant FP_22\15). The funding source had no role in the study design, collection, analysis, and interpretation of data; the writing of the report; or the decision to submit the article for publication.

The authors deeply appreciate the contributions of persons affected by leprosy and the kind support of the central unit of the National Tuberculosis, Leprosy, and Buruli Ulcer Control Programme, Federal Ministry of Health, Abuja, Nigeria, as well as the respective team members of both Cross River State and Taraba State Tuberculosis, Leprosy, and Buruli Ulcer Control Programme.

Data Availability

This is a study protocol manuscript. Deidentified research data that support the findings from this study will be made publicly available when the study is completed and published.

Authors' Contributions

AVTN and CG conceived the original research idea. AVTN, NMO, and JC contributed to fully conceptualizing the research proposal. AVTN, NMO, JC, CN, TD, SA, CG, UAO, AM, CE, OE, and NE all contributed to the design and planning of the study. NMO wrote the draft of the study protocol manuscript and the SPIRIT (Standard Protocol Items: Recommendations for

Interventional Trials) checklist. SA illustrated the study flow chart. All authors discussed the study protocol and contributed to the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents.
[DOCX File , 45 KB - resprot_v13i1e53130_app1.docx]

Multimedia Appendix 2
Participant information sheet and informed consent form.
[DOCX File , 29 KB - resprot_v13i1e53130_app2.docx]

Multimedia Appendix 3
Peer review report by Leprosy Research Initiative (LRI), Amsterdam, The Netherlands.
[PDF File (Adobe PDF File), 117 KB - resprot_v13i1e53130_app3.pdf]

References

1. Suzuki K, Akama T, Kawashima A, Yoshihara A, Yotsu RR, Ishii N. Current status of leprosy: epidemiology, basic science and clinical perspectives. J Dermatol 2012;39(2):121-129 [FREE Full text] [doi: 10.1111/j.1346-8138.2011.01370.x] [Medline: 21973237]
2. Sermrittirong S, van Brakel WH. Stigma in leprosy: concepts, causes and determinants. Lepr Rev 2014;85(1):36-47. [Medline: 24974441]
3. Link BG, Phelan JC. Conceptualizing Stigma. Annu Rev Sociol 2001;27(1):363-385. [doi: 10.1146/annurev.soc.27.1.363]
4. Weiss MG, Ramakrishna J, Somma D. Health-related stigma: rethinking concepts and interventions. Psychol Health Med 2006;11(3):277-287. [doi: 10.1080/13548500600595053] [Medline: 17130065]
5. Heijnders M, van der Meij S. The fight against stigma: an overview of stigma-reduction strategies and interventions. Psychol Health Med 2006;11(3):353-363. [doi: 10.1080/13548500600595327] [Medline: 17130071]
6. Heijnders ML. The dynamics of stigma in leprosy. Int J Lepr Other Mycobact Dis 2004;72(4):437-447. [doi: 10.1489/1544-581X(2004)72<437:TDOSIL>2.0.CO;2] [Medline: 15755198]
7. Rafferty J. Curing the stigma of leprosy. Lepr Rev 2005;76(2):119-126 [FREE Full text] [doi: 10.47276/lr.76.2.119]
8. Link BG, Phelan JC. Stigma and its public health implications. Lancet 2006;367(9509):528-529. [doi: 10.1016/S0140-6736(06)68184-1] [Medline: 16473129]
9. Henry M, GalAn N, Teasdale K, Prado R, Amar H, Rays MS, et al. Factors contributing to the delay in diagnosis and continued transmission of leprosy in Brazil—an explorative, quantitative, questionnaire based study. PLoS Negl Trop Dis 2016;10(3):e0004542 [FREE Full text] [doi: 10.1371/journal.pntd.0004542] [Medline: 26977811]
10. Barrett R. Self-mortification and the stigma of leprosy in Northern India. Med Anthropol Q 2005;19(2):216-230. [doi: 10.1525/maq.2005.19.2.216] [Medline: 15974328]
11. Somar P, Waltz MM, van Brakel WH. The impact of leprosy on the mental wellbeing of leprosy-affected persons and their family members—a systematic review. Glob Ment Health (Camb) 2020;7:e15 [FREE Full text] [doi: 10.1017/gmh.2020.3] [Medline: 32742673]
12. Goffman E. Stigma and social identity. In: Stigma: Notes on the Management of Spoiled Identity. USA: Prentice-Hall Inc; 1963.
13. Pickens J. Attitudes and perceptions. In: Borkowski N, editor. Organizational Behavior in Health Care. Sudbury, MA: Jones and Bartlett Publishers; 2005:43-76.
14. Hiebert PG. Transforming Worldviews: An Anthropological Understanding of How People Change. Grand Rapids, MI: Baker Publishing Group; 2008.
15. Broadbent E, Wilkes C, Koschwanez H, Weinman J, Norton S, Petrie KJ. A systematic review and meta-analysis of the brief illness perception questionnaire. Psychol Health 2015;30(11):1361-1385. [doi: 10.1080/08870446.2015.1070851] [Medline: 26181764]
16. van 't Noordende AT, Korfage IJ, Lisam S, Arif MA, Kumar A, van Brakel WH. The role of perceptions and knowledge of leprosy in the elimination of leprosy: a baseline study in Fatehpur district, Northern India. PLoS Negl Trop Dis 2019;13(4):e0007302 [FREE Full text] [doi: 10.1371/journal.pntd.0007302] [Medline: 30951526]
17. Ibikunle PO, Nwokeji SC. Assessment of stigma among people living with Hansens disease in south-east Nigeria. Lepr Rev 2017;88(1):43-57 [FREE Full text] [doi: 10.47276/lr.88.1.43]

18. van den Broek J, O'Donoghue J, Ishengoma A, Masao H, Mbega M. Evaluation of a sustained 7-year health education campaign on leprosy in Rufiji District, Tanzania. Lepr Rev 1998;69(1):57-74 [FREE Full text] [doi: 10.5935/0305-7518.19980007] [Medline: 9628096]
19. Raju MS, Reddy JV. Community attitude to divorce in leprosy. Indian J Lepr 1995;67(4):389-403. [Medline: 8849916]
20. Singh R, Singh B, Mahato S. Community knowledge, attitude, and perceived stigma of leprosy amongst community members living in Dhanusha and Parsa districts of Southern Central Nepal. PLoS Negl Trop Dis 2019;13(1):e0007075 [FREE Full text] [doi: 10.1371/journal.pntd.0007075] [Medline: 30633780]
21. Dadun D, van Brakel WH, Peters RMH, Lusli M, Zweekhorst MBM, Bunders JGF, Irwanto. Impact of socio-economic development, contact and peer counselling on stigma against persons affected by leprosy in Cirebon, Indonesia—a randomised controlled trial. Lepr Rev 2017;88(1):2-22 [FREE Full text] [doi: 10.47276/lr.88.1.2]
22. Wong ML. Guest editorial: designing programmes to address stigma in leprosy: issues and challenges. Asia Pacific Disabil Rehabil J 2004;15:3-12.
23. Sermrittirong S, van Brakel WH, Bunbers-Aelen JFG. How to reduce stigma in leprosy—a systematic literature review. Lepr Rev 2014;85(3):149-157. [Medline: 25509715]
24. Ebenso B, Fashona A, Ayuba M, Idah M, Adeyemi G, S-Fada S. Impact of socio-economic rehabilitation on leprosy stigma in Northern Nigeria: findings of a retrospective study. Asia Pac Disabil Rehabil J 2007;18(2):98-119 [FREE Full text]
25. Opala J, Boillot F. Leprosy among the Limba: illness and healing in the context of world view. Soc Sci Med 1996;42(1):3-19. [doi: 10.1016/0277-9536(95)00026-7] [Medline: 8745104]
26. Chen PC, Sim HC. The development of culture-specific health education packages to increase case-finding of leprosy in Sarawak. Southeast Asian J Trop Med Public Health 1986;17(3):427-432. [Medline: 3563610]
27. World Health Organization. Global leprosy (Hansen disease) update, 2019: time to step-up prevention initiatives. Weekly Epidemiological Record, 4 September 2020 2020;95(36):417-440 [FREE Full text]
28. Navon L. Beggars, metaphors, and stigma: a missing link in the social history of leprosy. Soc Hist Med 1998;11(1):89-105. [doi: 10.1093/shm/11.1.89] [Medline: 11620156]
29. Adhikari B, Kaehler N, Raut S, Marahatta SB, Ggyanwali K, Chapman RS. Risk factors of stigma related to leprosy—a systematic review. J Manmohan Meml Inst Heal Sci 2013;1(2):3-11 [FREE Full text] [doi: 10.3126/jmmihs.v1i2.9902]
30. Arulanantham S. Addressing inequality and exclusion—the opinion of people affected by leprosy in Africa and Asia, as to what should be included in any post Millennium Development Goal framework. Lepr Rev 2014;85(3):133-140 [FREE Full text] [doi: 10.47276/lr.85.3.133]
31. Ebenso B, Newell J, Emmel N, Adeyemi G, Ola B. Changing stigmatisation of leprosy: an exploratory, qualitative life course study in Western Nigeria. BMJ Glob Health 2019;4(2):e001250 [FREE Full text] [doi: 10.1136/bmjgh-2018-001250] [Medline: 30997168]
32. Engelbrektsson UB, Subedi M. Stigma and leprosy presentations, Nepal. Lepr Rev 2018;89(4):362-369. [doi: 10.47276/lr.89.4.362]
33. Arole S, Premkumar R, Arole M, Maury M, Saunderson P. Social stigma: a comparative qualitative study of integrated and vertical care approaches to leprosy. Lepr Rev 2002;73(2):186-196. [doi: 10.47276/lr.73.2.186]
34. Lusli M, Peters R, van Brakel W, Zweekhorst M, Iancu S, Bunders J, Irwanto, et al. The impact of a rights-based counselling intervention to reduce stigma in people affected by leprosy in Indonesia. PLoS Negl Trop Dis 2016;10(12):e0005088 [FREE Full text] [doi: 10.1371/journal.pntd.0005088] [Medline: 27959932]
35. van 't Noordende AT, Lisam S, Singh V, Sadiq A, Agarwal A, Hinders DC, et al. Changing perception and improving knowledge of leprosy: an intervention study in Uttar Pradesh, India. PLoS Negl Trop Dis 2021;15(8):e0009654 [FREE Full text] [doi: 10.1371/journal.pntd.0009654] [Medline: 34424909]
36. Gilder ME, Moo P, Hashmi A, Praisaengdet N, Wai K, Pimanpanarak M, et al. "I can't read and don't understand": health literacy and health messaging about folic acid for neural tube defect prevention in a migrant population on the Myanmar-Thailand border. PLoS One 2019;14(6):e0218138 [FREE Full text] [doi: 10.1371/journal.pone.0218138] [Medline: 31194796]
37. Creel AH, Rimal RN, Mkandawire G, Böse K, Brown JW. Effects of a mass media intervention on HIV-related stigma: 'Radio Diaries' program in Malawi. Health Educ Res 2011;26(3):456-465. [doi: 10.1093/her/cyr012] [Medline: 21393376]
38. Brown W. Can social marketing approaches change community attitudes towards leprosy? Lepr Rev 2006;77(2):89-98. [Medline: 16895065]
39. Breaking the Stigma of Albinism: An assessment of two radio-based interventions to improve knowledge and reduce stigmatizing attitudes related to albinism in Tanzania. 2019. URL: https://theses.ubn.ru.nl/server/api/core/bitstreams/34a57c1f-6153-45f9-b549-fe4a96c7f758/content [accessed 2023-12-28]
40. National Population Commission Nigeria, ICF. Nigeria Demographic Health Survey 2018. The DHS Program ICF. Rockville, Maryland, USA; 2019. URL: https://dhsprogram.com/publications/publication-fr359-dhs-final-reports.cfm [accessed 2023-12-14]
41. Hertzog MA. Considerations in determining sample size for pilot studies. Res Nurs Health 2008;31(2):180-191. [doi: 10.1002/nur.20247] [Medline: 18183564]
42. Audiopedia. URL: https://www.audiopedia.io [accessed 2021-01-21]

43. Herdman M, Fox-Rushby J, Badia X. A model of equivalence in the cultural adaptation of HRQoL instruments: the universalist approach. Qual Life Res 1998;7(4):323-335. [doi: 10.1023/a:1024985930536] [Medline: 9610216]
44. Terwee CB, Bot SDM, de Boer MR, van der Windt DAWM, Knol DL, Dekker J, et al. Quality criteria were proposed for measurement properties of health status questionnaires. J Clin Epidemiol 2007;60(1):34-42. [doi: 10.1016/j.jclinepi.2006.03.012] [Medline: 17161752]
45. Stevelink SAM, van Brakel WH. The cross-cultural equivalence of participation instruments: a systematic review. Disabil Rehabil 2013;35(15):1256-1268. [doi: 10.3109/09638288.2012.731132] [Medline: 23789790]
46. Wight D, Wimbush E, Jepson R, Doi L. Six steps in quality intervention development (6SQuID). J Epidemiol Community Health 2016;70(5):520-525 [FREE Full text] [doi: 10.1136/jech-2015-205952] [Medline: 26573236]

Abbreviations

6SQuID: 6 steps in quality intervention development
EMIC-CSS: Explanatory Model Interview Catalogue Community Stigma Scale
FGD: focus group discussion
G2D: grade 2 disability
ISMI: Internalized Stigma of Mental Illness scale
KAP: knowledge, attitudes, and practices
LGA: local government area
RCT: randomized controlled trial
RSES: Rosenberg Self-Esteem Scale
SDS: Social Distance Scale
WHO: World Health Organization

Edited by A Mavragani; submitted 28.09.23; this is a non–peer-reviewed article;accepted 04.12.23; published 24.01.24.

Please cite as:
Murphy-Okpala N, Dahiru T, van 't Noordende AT, Gunesch C, Chukwu J, Nwafor C, Abdullahi SH, Anyaike C, Okereke UA, Meka A, Eze C, Ezeakile O, Ekeke N
Participatory Development and Assessment of Audio-Delivered Interventions and Written Material and Their Impact on the Perception, Knowledge, and Attitudes Toward Leprosy in Nigeria: Protocol for a Cluster Randomized Controlled Trial
JMIR Res Protoc 2024;13:e53130
URL: https://www.researchprotocols.org/2024/1/e53130
doi:10.2196/53130
PMID:38265859

Protocol

Effectiveness of a Nursing Educational Intervention in Adults to Promote Control Behaviors Against Dengue: Protocol for a Randomized Controlled Trial

Yolima Judith Llorente Pérez[1,2], RN, MSc; Alba Luz Rodríguez-Acelas[1], RN, MSc, PhD; Rita Mattiello[3], MSc, PhD; Wilson Cañon-Montañez[1], RN, MSc, PhD

[1]Faculty of Nursing, Universidad de Antioquia, Medellín, Colombia

[2]Nursing Program, Universidad de Córdoba, Montería, Colombia

[3]Postgraduate Program in Epidemiology, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

Corresponding Author:
Yolima Judith Llorente Pérez, RN, MSc
Nursing Program
Universidad de Córdoba
Calle 31 b # 3w - 27 Campo alegre
Montería, 230001
Colombia
Phone: 57 3116882792
Email: yolima.llorente@udea.edu.co

Abstract

Background: The increase in dengue cases can be attributed to social, demographic, environmental changes, or community-driven factors. In this regard, different strategies have been established in health education, using educational interventions as necessary tools for the reduction of the disease with the aim of reinforcing and stimulating the prevention and control of dengue.

Objective: This study aims to evaluate the effectiveness of a nursing educational intervention for dengue control.

Methods: A randomized controlled trial will be conducted with adults living in rural areas and participating in health promotion and disease prevention programs. We will enroll 116 adults. Adults will be randomized 1:1, with 58 adults assigned to the educational intervention group and 58 to the usual care group. Participants will receive 4 sessions over the course of a month, 1 week apart, and will be followed up for 1 month after the end of the educational intervention. Nursing Outcome Classification labels will be used to measure the outcomes: risk control (1902) and participation in health care decisions (1606).

Results: The participants in the intervention group are expected to achieve better dengue control behaviors than those in the usual care group.

Conclusions: Risk factors are fostered by the community, largely caused by artificial reservoirs or unprotected tanks in homes; also, the lack of information hinders the identification of symptomatology and the poor implementation of effective measures, and the development of standardized educational strategies can contribute to efficient and cost-effective control of the disease.

Trial Registration: ClinicalTrials.gov NCT05321264; https://clinicaltrials.gov/study/NCT05321264

International Registered Report Identifier (IRRID): PRR1-10.2196/54286

(JMIR Res Protoc 2024;13:e54286) doi:10.2196/54286

KEYWORDS

dengue; health education; health promotion; nursing care; prevention & control

Introduction

The World Health Organization, in a report for 2023, reported that between 100 and 400 million cases of dengue occur annually [1]. It also indicates that in the Americas for the year 2021, there was an incidence of 123 cases per 100,000 inhabitants, with a case fatality rate of 0.034% [2].

Dengue in general has a global annual cost of US $8.9 billion, with an average annual cost per case of US $151 in 2013 [3] and a global burden of 1.14 million disability-adjusted life years [4]. The main burden on affected countries is the enormous

number of hospitalizations and sick days, with older people being the most affected population [3,5]. For the economy, the negative effects are due to the high costs of controlling epidemics and absenteeism from work and school [6,7].

In addition, dengue generates indirect costs that are usually enormous. These costs are given by the consultations or medicines taken by the members of the family nucleus [8], or by the loss of income of the patients and their families due to hospitalizations and disabilities, which at the same time reflect a reduction in the supply of work from home [9,10], not to mention the distress that the patient and his family are exposed to, generated by the doubt, uncertainty, or disability that the disease can bring. Living in low socioeconomic strata in rural areas, urbanization, global warming, and increased human mobility may be factors contributing to the increased burden of the disease [11,12].

Studies in endemic countries, specifically in Latin America, reveal a low level of knowledge about dengue among the population [13]. In Peru, Gutiérrez and Montenegro-Idrogo [14] indicated that the population has a poor level of knowledge about dengue control and prevention. In Colombia, de Maria Cáceres-Manrique et al [15] reported that the knowledge of the participants about dengue is scarce, with favorable attitudes toward control but insufficient practices, and they also consider the disease to be something normal. Likewise, other studies reflect scarce knowledge about dengue, the adoption of risky practices that favor the development of the disease, and a lack of knowledge about ways to prevent dengue [16,17].

The increase of cases in these regions, apart from having behavioral and cognitive root components, such as the behavior and cultural patterns manifested by the population, essentially related to beliefs, customs, and traditions, which sometimes determine the circumstances in which the dengue virus vector lives, also presents factors that may favor the dynamics of the disease, such as socioeconomic (level of schooling, strata, overcrowding, and lack of public services), climatic, and political factors, where there is little participation of health institutions [18,19].

Research conducted in the study setting (Montería, Colombia) has related a lack of knowledge or inadequate knowledge, unfavorable attitudes, and inadequate behaviors in relation to dengue; in addition to this, people live in homes with characteristics that favor the development and multiplication of the vector, leading to recommendations for other interventions aimed at reducing contact with the vector, taking into account the conditions in which families live [20].

The presence or multiplication of dengue cases may be mostly preceded by the inadequate application of health behaviors in the management and control of the vector, having as a background the scarcity of knowledge for the appropriation and incorporation of sanitary measures in the different environments.

In view of the lack of knowledge and control measures for dengue, the literature points to several determining factors, such as sex [13], level of schooling, and socioeconomic level, since diseases such as dengue have a greater impact on low-income populations, where the conditions for the presence of vector breeding sites are more likely to occur. A low level of education generally coincides with a lack of knowledge of the disease. Other factors include residence in rural areas, occupation, overcrowding, and a lack of public services [19].

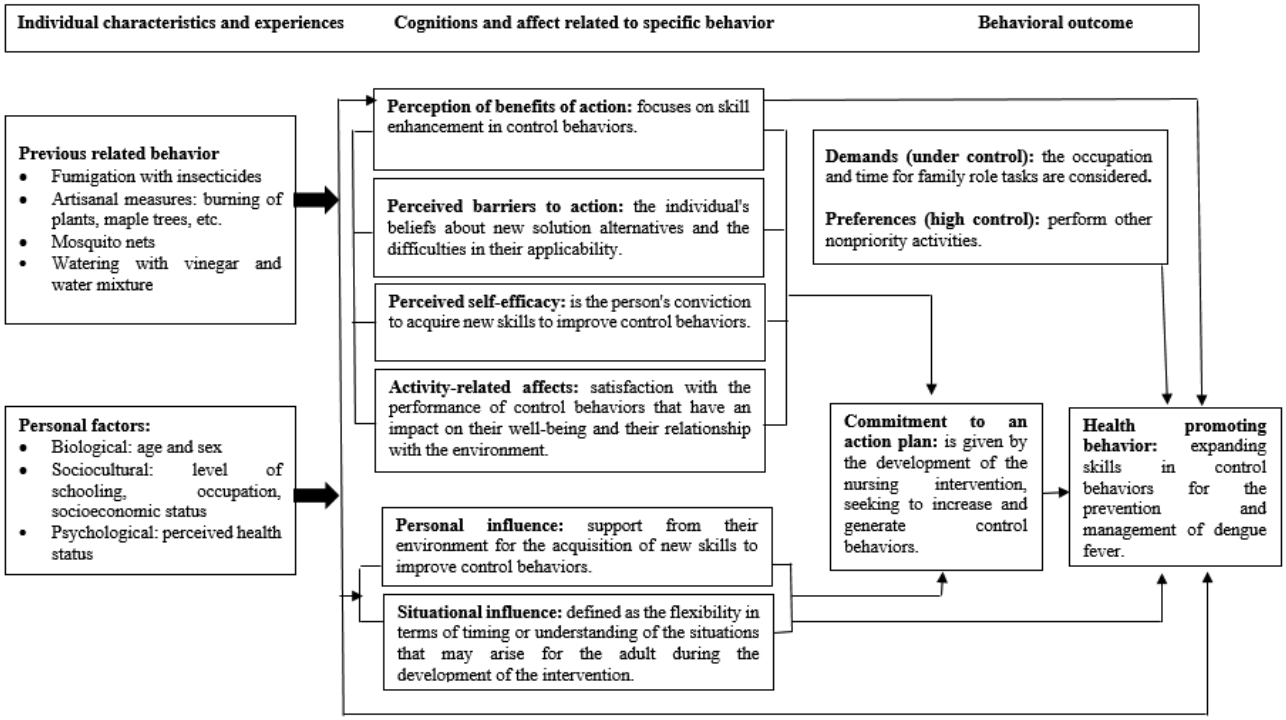
Other factors are lack of motivation and willingness, negative attitudes (low sense of belonging), inadequate habits or inappropriate cultural practices, lack of knowledge, difficult access to health services, lack of time, perception of risk, low involvement of health institutions, and limited economic and human resources allocated to public health infrastructures [21].

Thus, the evidence points to the increase in cases of dengue fever and cognitive and behavioral factors, which will be addressed in light of Nola Pender's Health Promotion Model (HPM). This model proposes that people interact with the environment, trying to achieve an adequate state of health, schematizing the nexus between personal characteristics and experiences, knowledge, beliefs, and situational aspects linked to the health behaviors or behaviors that are intended to be achieved [22], it raises dimensions and relationships that participate to generate or modify the health-promoting behavior [22], being the positive response that is expected to the actions carried out.

From the HPM perspective, the core concepts and subconcepts are used to achieve health-promoting behavior. Once the individual characteristics and experiences, cognitions, and affects related to the specific behavior are identified, the commitment to an action plan is expected, mediated in the research through the development of the nursing intervention that will generate a behavioral outcome, which is considered the expansion of skills in control behaviors in the prevention and management of dengue (Figure 1).

The objective of this study is to evaluate the effect of a nursing educational intervention to promote dengue control behaviors. We hypothesize that the participants in the intervention group will achieve better dengue control behaviors than participants in the usual care group.

Figure 1. Description of the conceptual elements for the study of health promoting behavior.



Methods

Study Design

A randomized controlled trial that follows the guidelines of SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) is used [23]. The study protocol was registered in ClinicalTrials.gov (NCT05321264).

Randomization and Blinding

Simple randomization into groups of equal size will be performed using the EPIDAT 4.2 program (Department of Health, Council of Galicia, Spain). Study participants will be randomized 1:1 to receive either the educational intervention or usual care. The randomization and allocation concealment will be carried out by the principal investigator. A centralized telephone randomization system will be used for masking [24]. With respect to blinding, the nurse who will perform the intervention will be blinded and will not know the outcome indicators of the study; the outcome assessors will be blinded and will not know to which group (intervention or control) the participants belong.

Participants, Setting, and Sample

The study participants are rural residents attending health promotion and disease prevention programs in a health care institution located in the municipality of Montería. It is a city in Colombia and capital of the department of Córdoba. It has 490,935 inhabitants and is considered a cattle-raising town.

Participants will be recruited during the opening hours established by the health institution. A sample size of 116 (58 participants for each group) was calculated according to the following parameters: effect size: an expected difference of 0.5 in the score of the nursing outcome labels between both groups [24], a statistical power of 90%, an α type error of 5%, a SD of the outcome scores of 1.0, an average correlation between the first and second evaluations of 0.3, an intervention/control ratio of 1:1, and a loss adjustment of 20%. Stata (version 16.0; StataCorp) software was used for this purpose.

Procedures

Eligibility Criteria

Persons older than 18 years of age, residing in a rural area of the municipality of Monteria in an endemic area with dengue or with exposure to dengue, attending health promotion and disease prevention programs of a health institution with an initial score ≤a 3.5 in the Nursing Outcome Labels (NOC) risk control (1902) and participation in health care decisions (1606), will be included in the study [25].

The Study Intervention

The educational nursing intervention in adults to promote dengue control behaviors, in terms of its structure, will follow the guidelines established by Sidani and Braden [26]. In addition, it will have as a theoretical reference Nola Pender's HPM, which is articulated for the phenomenon under study, to allow reaching a health-promoting behavior, which lies specifically in the expansion of skills in control behaviors in the face of dengue. The intervention contemplates 3 active ingredients that influence dengue control behavior: an educational component, behavioral support, and attitudinal support (Textbox 1).

Textbox 1. Content of the intervention.

Active ingredients and components

- Session 1: educational component

General information on dengue: definition of the disease, etiological agent, mosquito life cycle, modes of transmission, period of transmissibility, and personal and environmental risk factors (tanks, flower vases, pet drinkers, and plastic containers).

- Session 2: educational component

Dengue overview: health threats, clinical manifestations, diagnostic aids, treatment, prevention and control strategies, and barriers that may prevent the implementation of effective measures.

- Session 3: behavioral support

Commitment to the implementation of preventive strategies (personal, home, and environmental care), achievements obtained with the implementation of dengue strategies, self-control in dengue decision-making, and lifestyle changes.

- Session 4: attitudinal support

Main support networks that people can find in their environment: family, friends, health, and community resources. How to take advantage of available resources?

The intervention will consist of 4 face-to-face meetings with an interval of 1 week for 1 month, each lasting 45 minutes (Textbox 2). The first session will include an educational component and address issues related to dengue, etiological agents, transmission mechanisms, and personal and environmental risk factors. The second session will cover topics such as health threats, clinical manifestations, diagnostic aids, treatment, prevention and control strategies, and barriers that may prevent the application of effective measures against dengue, also belonging to the educational component. The third session will cover personal care practices, home and environment care, and lifestyle modification, which correspond to behavioral support. Final, the fourth session covers attitudinal support, which will review support networks and the use of resources.

Textbox 2. General characteristics of the intervention.

- Objective: increase knowledge and application of dengue control behaviors.
- Duration of the intervention: 1 month
- Number of sessions: 4 sessions
- Frequency: once a week for a period of 1 month.
- Environment: institution providing health services in rural areas (promotion and prevention program).
- Delivery strategies: individual, face-to-face, standardized educational material, and use of digital tools.
- Receiver: adult who meets inclusion criteria.
- Provider: qualified and trained nurse, with previous performance verification (does not work in health institution).
- Outcome measures: risk control and participation in health care decisions.

The intervention will be delivered in a personalized, face-to-face manner [27], and standardized educational material (booklet) will be used [28-30]. It also indicates that feedback, reviews of key points, and commitments will be made in each session that is held.

Intervention Fidelity

The intervention will be delivered to adults as it is designed, seeking to generate the desired changes in the results [26]. For this, it is necessary to develop methodological strategies to ensure the application of the active ingredients (delivery mode, doses, and activities) of the intervention, called fidelity. The fidelity of the intervention contemplates 2 fundamental levels: the theoretical level and the operational level, which are described in Table 1.

Table 1. Operationalization of intervention fidelity.

Levels and criteria	Objective	Strategies to ensure fidelity
Theoretical		
Study design control	Ensure that the intervention is consistent with the theoretical propositions of the Health Promoting Behavior.	The content of the study will be validated by experts to determine consistency between the active ingredients and the proposed theoretical component.
Operational		
Interventionist training	Ensure that the intervention is delivered in accordance with the protocol.	A course on dengue will be held and nurse training will be provided.
Delivery of the intervention	To reduce variability in the application of the intervention.	The intervention will be delivered by a trained nurse and performance will be verified. Development of the intervention protocol manual, with standardized educational material.
Treatment exposure	Ensure that all adults receive the intervention on equal terms.	Provide the intervention to all participants as defined in the intervention protocol manual: frequency, dosage, duration, delivery method, and sequence.
Treatment reception	Verify the appropriation and use of the active components of the intervention: educational, behavioral, and attitudinal support.	At the end of each session, there will be a space for feedback, review of key points, and commitments.
Follow-up of treatment compliance	Verify the implementation of health promoting behavior.	Face-to-face and telephone sessions will be held to provide feedback on the proposed objectives to achieve health-promoting behavior.

Data Collection and Measures

An intervention will be developed in 4 sessions with baseline, end line, and 2-month postintervention measures. The NOC labels chosen to evaluate the effect of the intervention are risk control (1902) and participation in health care decisions (1606).

To characterize the participants in both the intervention and control groups, a form containing variables such as age, sex, education level, marital status, actual occupation, health system affiliation, socioeconomic stratum, and dengue diagnosis will be filled out.

To evaluate the cognitive aspects or mental state of the adult, the mini mental test will be used, which is composed of 30 dichotomous items that evaluate 6 cognitive processes: temporal orientation, spatial orientation, fixation memory, evocation memory, attention and calculation, and language [31,32].

Outcomes

The outcomes of risk control and participation in health care decisions, which belong to the NOC classification, which is useful for analyzing and measuring the impact and quality of nursing interventions, will be evaluated.

Risk Control

Corresponding to code 1902, it consists of 21 indicators on a Likert-type scale with a score from 1 to 5 (1=never demonstrated, 2=rarely demonstrated, 3=sometimes demonstrated, 4=frequently demonstrated, and 5=always demonstrated) and is defined as personal actions to understand, avoid, eliminate, or reduce health threats that are modifiable [33]. It includes items that seek the implementation of behaviors by the adult.

Participation in Health Care Decisions

Defined as personal involvement in the selection and evaluation of health care options to achieve a desired outcome, it corresponds to code 1606 and consists of 15 indicators. It uses measurement scale 13, which is defined as the frequency of clarifying by report or behavior and has a score from 1 to 5 (1=never demonstrated, 2=rarely demonstrated, 3=sometimes demonstrated, 4=frequently demonstrated, and 5=always demonstrated) [33]. It contains several indicators that respond to some subconcepts of the theory, such as perceptions of benefits to action, perceptions of barriers to action, and preferences, which are the ones intended to be measured.

Follow-Up

Participants will be followed up 1 month after the end of the study intervention [34-36]. Individual and face-to-face follow-up is planned to assess the effect of the intervention over time.

Data Analysis

The information will be tabulated using the EpiData program, and the Stata software will be used for statistical analysis, following the principle of intention-to-treat analysis, which allows the patients to be analyzed as they were originally assigned or randomized [37]. Statistical hypothesis tests will be performed with an α level of 5%. A descriptive analysis of the baseline variables will be made to observe the behavior in each of the groups, using the student 2-tailed *t* test and the Fisher exact test. Categorical variables will be presented with absolute and relative frequencies. Quantitative variables with normal distribution will be presented with mean and SD, and for variables that do not comply with the principle of normal distribution, they will be presented with median and IQR (IQR=Q3–Q1). Normality will be assessed using the Kolmogorov-Smirnov test.

Baseline variables will be compared between the control group and the intervention group. The chi-square test will be used for categorical variables. The student *t* test will be used to compare the means in the 2 groups when the normality assumption is met, and otherwise, the nonparametric Mann-Whitney *U* test will be used.

To control for possible confounding variables, a statistical adjustment will be made through an analysis of covariance with their respective 95% CIs.

The effect of the intervention will be measured through analysis of covariance by means of the delta value or difference of the NOC label score between the 2 comparison groups.

Paired *t* tests will be performed to observe separately how each group fared before and after the intervention and at follow-up.

Ethical Considerations

The trial will be conducted taking into account the ethical guidelines established in the Declaration of Helsinki, the Belmont Report (1979), the Council for International Organizations of Medical Sciences (2002), and Resolution 8430 of 1993 (Ministry of Health, Colombia, 1993). Ethical approval was granted by the Research Ethics Committee of the Faculty of Nursing of the University of Antioquia (#2021-29). Adults willing to participate voluntarily in the study will be selected, applying the principle of fairness, and the information provided by them will be maintained under strict confidentiality. Alphanumeric codes will be used to record the information, and no names or any other personal identification data will be used. The participants in the control group at the end of the research will receive the same educational intervention as the intervention group.

Results

It is expected that participants in the nursing education intervention group will have better dengue control behaviors than those in the usual care group (effect size increase of at least 0.5 of the δ score in each of the NOC outcomes). The results are expected to be published in 2025.

Discussion

Principal Result

Dengue is linked to household sanitation. The existence of breeding sites is due to specific human behaviors that favor them, whether individual, community, or institutional [15]. Insufficient knowledge about the disease is one of the factors that precipitates the application of inadequate measures [38,39]. Research indicates that risk factors are fostered by the community, largely caused by artificial reservoirs or unprotected tanks in homes [40,41]; it also indicates that the lack of information hinders the identification of symptoms [38] and the poor application of effective measures.

In the study scenario, there is evidence of inadequate knowledge and practices regarding dengue [20], aspects that this study seeks to improve in order to generate favorable changes in the behavior of the population and, therefore, of the disease.

The results of the research may serve as a basis for the identification of lines of action that should be strengthened in the prevention and control of dengue, including the induction and reinduction of the human talent necessary for health care.

Likewise, the research is a window for theoretical-practical integration in health promotion scenarios, and at the same time, it is configured as an opportunity for the visibility of care and its standardization in the rural population. It is hoped that the results will serve to strengthen the role of nursing as an active member of health risk management.

Limitations

Length of follow-up, cointerventions, and attrition during the study are anticipated limitations. To reduce these limitations, the selection of participants will be controlled by random assignment to the intervention, specific eligibility criteria for entry into the study, and intention-to-treat analysis. Both the intervention and outcome assessors will receive appropriate training. Masking and adjustments to the statistical analysis will be performed as needed. Health care professionals will be sensitized to avoid cointervention in the study. The principal investigator will be the study supervisor and will not be involved in intervention delivery or outcome assessment.

Conclusion

The scarcity of studies with a high level of evidence, such as randomized clinical trials, provides an opportunity for the development of the present research, which has a quantitative approach and aims to generate new knowledge based on the best scientific evidence for the care of vector-borne diseases in rural populations.

With the evaluation of results through the NOC, the possibility of having measurement indicators for the discipline is opened, which allow making contributions based on evidence, given that the studies carried out show scarce application of the same, so they become important work elements for the development of care processes in favor of the less favored collectivities.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the Universidad de Antioquia, Colombia.
[PDF File (Adobe PDF File), 685 KB - resprot_v13i1e54286_app1.pdf]

References

1. Organización Mundial de la Salud y Organización Panamericana de la Salud. URL: https://www.who.int/es/news-room/fact-sheets/detail/dengue-and-severe-dengue [accessed 2023-04-10]
2. PLISA plataforma de información en salud para las Américas. Dengue: análisis de las Américas y subregiones. Organización Mundial de la Salud y Organización Panamericana de la Salud. 2021. URL: https://www3.paho.org/data/index.php/es/temas/indicadores-dengue.html [accessed 2023-04-10]
3. Shepard DS, Undurraga EA, Halasa YA, Stanaway JD. The global economic burden of dengue: a systematic analysis. Lancet Infect Dis 2016;16(8):935-941. [doi: 10.1016/S1473-3099(16)00146-8] [Medline: 27091092]
4. Stanaway JD, Shepard DS, Undurraga EA, Halasa YA, Coffeng LE, Brady OJ, et al. The global burden of dengue: an analysis from the global burden of disease study 2013. Lancet Infect Dis 2016;16(6):712-723 [FREE Full text] [doi: 10.1016/S1473-3099(16)00026-8] [Medline: 26874619]
5. Du M, Jing W, Liu M, Liu J. The global trends and regional differences in incidence of dengue infection from 1990 to 2019: an analysis from the global burden of disease study 2019. Infect Dis Ther 2021;10(3):1625-1643 [FREE Full text] [doi: 10.1007/s40121-021-00470-2] [Medline: 34173959]
6. Reyes JA, Guzmán TG, Ramírez BR, Hernández CM, García GM, Maria DT, et al. Impacto económico del dengue en pacientes y familiares. Rev Cubana Med Trop 2019;71(3):e419 [FREE Full text]
7. da Silva Oliveira LN, Itria A, Lima EC. Cost of illness and program of dengue: a systematic review. PLoS One 2019;14(2):e0211401 [FREE Full text] [doi: 10.1371/journal.pone.0211401] [Medline: 30785894]
8. Hernández SJM, Martínez SLM, Doria REM, Roldán TMD, Bustamante B, Morales QN. Gastos de bolsillo de pacientes con diagnóstico de dengue en Medellín y Montería. Enf Infec Microbiol 2019;39(1):7-11.
9. Taborda A, Chamorro C, Quintero J, Carrasquilla G, Londoño D. Cost-effectiveness of a dengue vector control intervention in Colombia. Am J Trop Med Hyg 2022;107(1):180-185 [FREE Full text] [doi: 10.4269/ajtmh.20-0669] [Medline: 35436764]
10. Wilastonegoro NN, Kharisma DD, Laksono IS, Halasa-Rappel YA, Brady OJ, Shepard DS. Cost of dengue illness in Indonesia across hospital, ambulatory, and not medically attended settings. Am J Trop Med Hyg 2020;103(5):2029-2039 [FREE Full text] [doi: 10.4269/ajtmh.19-0855] [Medline: 32901596]
11. Lai YJ, Lai HH, Chen YY, Ko MC, Chen CC, Chuang PH, et al. Low socio-economic status associated with increased risk of dengue haemorrhagic fever in Taiwanese patients with dengue fever: a population-based cohort study. Trans R Soc Trop Med Hyg 2020;114(2):115-120. [doi: 10.1093/trstmh/trz103] [Medline: 31688926]
12. Yang X, Quam MBM, Zhang T, Sang S. Global burden for dengue and the evolving pattern in the past 30 years. J Travel Med 2021;28(8):taab146 [FREE Full text] [doi: 10.1093/jtm/taab146] [Medline: 34510205]
13. Rivera AH, Rodríguez AP, Meléndrez HE. Factores de riesgos asociados a la infección por dengue en San Mateo, Anzoátegui, Venezuela. Rev cub salud pública 2009;27(3):388-395 [FREE Full text] [doi: 10.1590/s0864-34662009000400015]
14. Gutiérrez C, Montenegro-Idrogo JJ. Conocimiento sobre dengue en una región endémica de Perú: estudio de base poblacional. Acta Med Peru 2018;34(4):283-288 [FREE Full text] [doi: 10.35663/amp.2017.344.458]
15. de María Cáceres-Manrique F, Angulo-Silva ML, Vesga-Gómez C. Efficacy of the social mobilization and the social participation in dengue control measures. Biomedica 2010;30(4):539-550. [Medline: 21713357]
16. Hernández-Escolar J, Consuegra-Mayor C, Herazo-Beltrán Y. Knowledge, attitudes and practice regarding dengue in a neighborhood forming part of the city of Cartagena. Rev Salud Publica (Bogota) 2014;16(2):281-292 [FREE Full text] [Medline: 25383501]
17. Castrillón CA, Santa GV, Loaiza GD, Ortiz DJ, Aragon MV. Relación entre conocimientos, hábitos y participación comunitaria frente a la transmisión del dengue y chikungunya. CES Salud Pública 2017;8(1):70-81. [doi: 10.21615/4422]
18. Álvarez EMDC, Torres Á, Torres Á, Semper AI, Romeo AD. Dengue, chikungunya, virus de zika. Determinantes sociales. Rev Medica Electron 2018;40(1):120-128 [FREE Full text]
19. Castrillón JC, Castaño JC, Urcuqui S. Dengue in Colombia: ten years of database records. Rev Chilena Infectol 2015;32(2):142-149 [FREE Full text] [doi: 10.4067/S0716-10182015000300002] [Medline: 26065446]
20. Benítez CL, Romero GI. Conocimientos, actitudes y prácticas sobre manejo integrado de vectores. Córdoba. Colombia. Cultura del Cuidado Enfermería 2019;16(2):7-18 [FREE Full text]
21. Criollo FIZ, Bernal BAY, Castañeda PO. Conocimientos, actitudes y prácticas sobre dengue, tras aplicación de estrategias de movilización social. Yopal-casanare, Colombia, 2012. rev. investig. Andin 2014;16(29):1001-1015 [FREE Full text]
22. Hoyos GPA, Borjas DMB, Ramos AS, Meléndez RMO. El modelo de promoción de la salud de Nola Pender: una reflexión en torno a su comprensión. Enferm univ 2018;8(4):16-23. [doi: 10.22201/eneo.23958421e.2011.4.248]
23. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med 2013;158(3):200-207 [FREE Full text] [doi: 10.7326/0003-4819-158-3-201302050-00583] [Medline: 23295957]
24. Lazcano-Ponce E, Salazar-Martínez E, Gutiérrez-Castrellón P, Angeles-Llerenas A, Hernández-Garduño A, Viramontes JL. Randomized clinical trials: variants, randomization methods, analysis, ethical issues and regulations. Salud Publica Mex 2004;46(6):559-584 [FREE Full text] [doi: 10.1590/s0036-36342004000600012] [Medline: 15624861]

25. Gencbas D, Bebis H, Cicek H. Evaluation of the efficiency of the nursing care plan applied using NANDA, NOC, and NIC linkages to elderly women with incontinence living in a nursing home: a randomized controlled study. Int J Nurs Knowl 2018;29(4):217-226. [doi: 10.1111/2047-3095.12180] [Medline: 28560756]
26. Sidani S, Braden CJ. Desing, evaluation, and translation of nursing interventions. Wiley-Blackwell 2011:11-17. [doi: 10.1111/2047-3095.12180]
27. Arosteguí J, Coloma J, Hernández-Alvarez C, Suazo-Laguna H, Balmaseda A, Harris E, et al. Beyond efficacy in water containers: temephos and household entomological indices in six studies between 2005 and 2013 in Managua, Nicaragua. BMC Public Health 2017;17(Suppl 1):434 [FREE Full text] [doi: 10.1186/s12889-017-4296-6] [Medline: 28699558]
28. Arneliwati N, Agrina A, Dewi AP. The effectiveness of health education using audiovisual media on increasing family behavior in preventing dengue Hemorrhagic Fever (DHF). Enfermería Clínica 2019;29(1):30-33. [doi: 10.1016/j.enfcli.2018.11.013]
29. Bhattarai AH, Sanjaya GY, Khadka A, Kumar R, Ahmad RA. The addition of mobile SMS effectively improves dengue prevention practices in community: an implementation study in Nepal. BMC Health Serv Res 2019;19(1):699 [FREE Full text] [doi: 10.1186/s12913-019-4541-z] [Medline: 31615484]
30. Rodríguez AS, Soidán JLG, Gómez MJA, Del Álamo Alonso A, Rodríguez RL, Fernández MRP. Educational intervention on cardiovascular parameters in perimenopausal women with a cardiovascular risk factor. Randomised clinical trial. Med Clin (Barc) 2018;150(5):178-184. [doi: 10.1016/j.medcli.2017.06.020] [Medline: 28743399]
31. Pedraza OL, Sánchez E, Plata SJ, Montalvo C, Galvis P, Chiquillo A, et al. Puntuaciones del MoCA y el MMSE en pacientes con deterioro cognitivo leve y demencia en una clínica de memoria en Bogotá. Acta Neurol Colomb 2014;30(1):22-31. [doi: 10.22379/2422402282]
32. Rojas-Gualdrón DF, Segura CA, Cardona AD, Segura C, Garzón DMO. Análisis rasch del Mini Mental State Examination (MMSE) en adultos mayores de Antioquia, Colombia. CES Psicología 2017;10(2):17-27.
33. Moorhead S, Johnson M, Mass M, Swanson E. Clasificación de Resultados de Enfermería (NOC): Medición de Resultados en Salud, 6th Edition. Amsterdam, The Netherlands: Elsevier; 2019.
34. Overgaard HJ, Alexander N, Matiz MI, Jaramillo JF, Olano VA, Vargas S, et al. A cluster-randomized controlled trial to reduce diarrheal disease and dengue entomological risk factors in rural primary schools in Colombia. PLoS Negl Trop Dis 2016;10(11):e0005106 [FREE Full text] [doi: 10.1371/journal.pntd.0005106] [Medline: 27820821]
35. Toledo YM, Marroquin L. Ambiente limpio, comunidad feliz: análisis de resultados de una campaña de comunicación para la prevención de la fiebre del dengue en las comunidades Luis XV, en guápiles, costa rica. RCyS 2017;7:103-117. [doi: 10.35669/revistadecomunicacionysalud.2017.7(1).103-117]
36. Caprara A, De Oliveira Lima JW, Peixoto ACR, Motta CMV, Nobre JMS, Sommerfeld J, et al. Entomological impact and social participation in dengue control: a cluster randomized trial in Fortaleza, Brazil. Trans R Soc Trop Med Hyg 2015;109(2):99-105 [FREE Full text] [doi: 10.1093/trstmh/tru187] [Medline: 25604760]
37. Dettori JR, Norvell DC. Intention-to-treat: is that fair? Global Spine J 2020;10(3):361-363 [FREE Full text] [doi: 10.1177/2192568220903001] [Medline: 32313802]
38. Martínez M, Espino C, Moreno N, Rojas E, Mazzarri M, Mijares V, et al. Conocimientos, actitudes y prácticas sobre dengue y su relación con hábitats del vector en Aragua-Venezuela. Bol Mal Salud Amb 2015;55(1):86-93.
39. Morales MMDJ, Betancourt BJA, Acao FL, León RC. Actitudes, conocimientos y prácticas sobre el dengue y su vector en el municipio Camagüey. AMC 2016;20(3):253-261.
40. Terazón MO, Muñiz SZ, Terazón MM. Seroprevalencia del virus del dengue en el distrito de puntares, para estimar la población de riesgo. Medisan 2014;18(4):528-536.
41. Llorente-Pérez YJ, Rodríguez-Acelas AL, Cañon-Montañez W. Intervenciones educativas para la prevención y control del dengue en adultos: una revisión integrativa. Enfermería Clínica 2023;33(2):157-166. [doi: 10.1016/j.enfcli.2022.10.004]

Abbreviations

HPM: Health Promotion Model
NOC: Nursing Outcome Classification
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

Edited by A Mavragani; submitted 03.11.23; this is a non–peer-reviewed article;accepted 25.01.24; published 23.02.24.

Please cite as:
Llorente Pérez YJ, Rodríguez-Acelas AL, Mattiello R, Cañon-Montañez W
Effectiveness of a Nursing Educational Intervention in Adults to Promote Control Behaviors Against Dengue: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2024;13:e54286
URL: https://www.researchprotocols.org/2024/1/e54286
doi:10.2196/54286
PMID:38393755

Protocol

Effectiveness of the Pasifika Women's Diabetes Wellness Program (PWDWP): Protocol for a Pilot Intervention and Feasibility Randomized Controlled Trial

Heena Akbar[1,2], MPH, PhD; Madison Contor[3], BSc; Winnie Niumata[4], RN; Debra Anderson[5], PhD; Danielle Gallegos[2], PhD

[1]School of Public Health, Faculty of Medicine, The University of Queensland, Brisbane, Australia

[2]Centre for Childhood Research, School of Exercise and Nutrition Sciences, Faculty of Health, Queensland University of Technology, Brisbane, Australia

[3]Faculty of Medicine, The University of Queensland, Brisbane, Queensland, Australia

[4]Logan Central Community Health Centre, Metro South Health, Logan Central, Queensland Health, Brisbane, Australia

[5]Faculty of Health, University of Technology Sydney, NSW, Australia

Corresponding Author:
Heena Akbar, MPH, PhD
School of Public Health
Faculty of Medicine
The University of Queensland
288 Herston Rd
Herston
Brisbane, 4006
Australia
Phone: 61 423460211
Email: h.akbar@uq.edu.au

Abstract

Background: Type 2 diabetes poses public health challenges for Māori and Pasifika communities in Australia. The women of these communities face a greater burden from type 2 diabetes–related mortality and comorbidities. Lifestyle modification behaviors through previous women's wellness programs have been shown to reduce the risk of developing complications in established type 2 diabetes. The Pasifika Women's Diabetes Wellness Program (PWDWP) pilot study, co-designed with Māori and Pasifika communities, was aimed at addressing late hospital presentations from diabetes-related complications.

Objective: This study (1) examines the efficacy of women with type 2 diabetes in the intervention group for improved glycated hemoglobin (HbA_{1c}) clinical levels and diabetes self-management compared with the control group from baseline (T_0) to week 12 (T_1) and week 24 (T_2; postintervention) and (2) assesses the cultural adaptability, acceptability, and feasibility of the pilot intervention for future studies.

Methods: This study uses a quasiexperimental design that involves a 24-week intervention. We recruited 50 Māori and Pasifika women with type 2 diabetes (25 in the intervention group from the south side of Brisbane and 25 in the control group from the north side of Brisbane) using participatory talanoa methodologies. The intervention group participated in face-to-face and virtual whānau education workshops (5 weeks) and had access to individual coaching and virtual support delivered by trained Māori and Pasifika health professionals and community health workers. The control group received usual care with their identified health provider. Both groups received copies of the PWDWP journal, fact sheets, and a health check passbook with tailored motivational text messages. An advisory committee was set up to oversee the program implementation, including protocols of engagement, health checks, and data collection in community settings. The quantitative data were collected at T_0, T_1, and T_2 with HbA_{1c} as the primary outcome measure. Secondary outcomes measured changes in diabetes self-care and body composition (eg, BMI, waist circumference). Qualitative data will ascertain the program's feasibility and cultural adaptability using talanoa focus groups.

Results: This pilot study was approved by the Queensland University of Technology Human Ethic Research Committee (5609) and began in January 2023 after participant recruitment between July 2022 and December 2022. The final data collection including the health check, focus group, and survey data was completed in November 2023, and data analysis and reporting are expected to conclude in 2024.

Conclusions: This study provides a blueprint for PWDWP. Collaborative partnerships with community organizations and stakeholders are crucial for program success and suggest a potential model for targeting diabetes management for Māori and Pasifika communities, emphasizing the need for culturally relevant interventions. The findings will have significant implications for policymakers and practitioners when developing and implementing public health initiatives, particularly for communities with unique cultural nuances.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12622001100785p; https://anzctr.org.au/Trial/Registration/TrialReview.aspx?id=384470&isReview=true

International Registered Report Identifier (IRRID): DERR1-10.2196/55435

(JMIR Res Protoc 2024;13:e55435) doi:10.2196/55435

KEYWORDS

type 2 diabetes; Māori and Pasifika women; diabetes self-management; culturally co-design intervention; Pasifika diaspora; talanoa

Introduction

Background

The global prevalence of diabetes and its threat to public health continue to increase each year. Almost 90% of the estimated 537 million people currently living with diabetes worldwide have type 2 diabetes, despite it being largely preventable [1]. The Western Pacific region accounts for over one-third of the worldwide burden of diabetes, with 6 Pacific Island Countries and Territories (PICTs) among the top 10 globally with the highest prevalence of type 2 diabetes [1,2]. Additionally, PICTs face a higher prevalence of complications from debilitating diabetes as well as a higher prevalence of undiagnosed diabetes compared with other regions [2-5]. There are disparities in diabetes and diabetes-related conditions between people from PICTs and people from high-income countries, with similar disparities in Australia between Indigenous and non-Indigenous Australians [6]. As the prevalence of diabetes is positively associated with social and economic costs to individuals, families, and society, the severity and burden of type 2 diabetes are clearly highlighted [7-10].

Type 2 diabetes remains a major public health challenge for Māori and Pasifika peoples living in Queensland, which has the largest Pasifika diaspora after New Zealand [11]. Pasifika is a collective term used for Pacific peoples in Australia. Significant disparities in diabetes prevalence exist in these populations, who are 2 to 4 times more likely to be hospitalized and die from diabetes-related complications than non-Māori and Pasifika populations [12]. Evidence indicates that culturally and linguistically diverse women, in particular, face a greater burden of type 2 diabetes–related mortality and comorbidities including cardiovascular disease, kidney disease, vision impairment, and depression [12-15]. Diabetes care and support programs are less likely to be used by Māori and Pasifika women with diabetes due to low levels of health literacy, language barriers, and a strong cultural reluctance to seek help. Lack of culturally appropriate health and social services have resulted in an avoidance of engagement by Māori and Pasifika women [15]. Māori and Pasifika women carry significant cultural responsibility including expectations of acting as carers, leaders, and nurturers within their communities, often at the expense of their own chronic disease management [15]. This has significant implications for providing accessible, low-cost, and culturally appropriate diabetes care for Māori and Pasifika women with type 2 diabetes [15].

Encouraging healthier behaviors in Māori and Pasifika women with type 2 diabetes could potentially improve the health and well-being of women [15,16]. Modification of personal behaviors through women's wellness programs aimed at early intervention have been shown to reduce the risk of developing complications in established type 2 diabetes and may reduce hospitalization rates due to preventable complications [14]. A qualitative study of a multimodal behavioral intervention, the Women's Wellness with Type 2 Diabetes, found it to be effective at supporting women with developing strategies to improve their well-being and avoid complications associated with diabetes [16]. Another study with Māori and Pasifika women with type 2 diabetes in Queensland reported effective strategies to improve self-management through culturally appropriate interventions and educational resources [15,17]. Thus, the first culturally framed intervention, the Pasifika Women's Diabetes Wellness Program (PWDWP) emerged from these studies that informed the study's principles and processes, including recruitment strategies and co-design of the delivery format into a whaˉnau (family)-centered approach that harnesses digital technology [15,17]. The intervention was co-designed with Māori and Pasifika women living with type 2 diabetes in Queensland, underpinned by social cognitive theory and the Fonofale Pasifika Health Model that focuses on family, culture, community, and spirituality using talanoa, a Pacific form of dialogue, to promote sustainable self-management of type 2 diabetes [17-20]. This 24-week program is whānau-centered with 5 diabetes self-care behavior and wellness components (Figure 1) and delivered by trained Māori and Pasifika health professionals. The program takes into consideration the cultural shame associated with acknowledging the disease and tailors the interventions using talanoa as the key strategy to reach a shared meaning for behavioral changes [20].

Figure 1. The Pasifika Women's Diabetes Wellness Program and the "wellness" components.

The program team has previously ensured successful translation of interventions into practice through meaningful engagement with consumers, policymakers, health service managers, and clinicians [15,17,18,20-22]. This program will further consolidate collaborative partnerships between clinicians, health service providers, Māori and Pasifika communities and organizations, and consumer advocates. The study will evaluate the clinical benefits of the intervention and will target improvements in glycated hemoglobin (HbA_{1c}; measured using a point-of-care device [18]) and diabetes self-care including diet, physical activity, stress and medication management, and routine health checks of Māori and Pasifika women with type 2 diabetes from data collected via validated questionnaires using Qualtrics [24]. The study builds on a robust and systematic program of work, beginning with scoping studies, needs assessments, and early wellness trials with women [15-17].

Research Aim

The pilot study will evaluate the feasibility, acceptability, delivery, and effectiveness of PWDWP using mixed methods, in partnership with Māori and Pasifika community organizations and key stakeholders in southeast Queensland.

Objectives

The primary objective is to examine efficacy, defined as the women with type 2 diabetes in the intervention group having improved clinical HbA_{1c} levels from baseline (T_0) to week 12 (T_1) and week 24 (T_2) postintervention compared with the control group.

The secondary objective is to determine whether, compared with control participants, the intervention group achieves changes to bring body composition measurements closer to the recommended healthy range for specific cultural groups (eg, BMI ≤30 kg/m^2 and waist circumference <80 cm based on World Health Organization criteria) and improved diabetes self-care scores on diet, physical activity, routine health checks, and medication adherence assessed using the validated Summary of Diabetes Self-Care Activities scale [23,25-31].

In addition, we will assess the potential for success of the proposed intervention by examining accessibility, acceptability, uptake, and cultural adaptability of the intervention; sustainability of and adherence to the intervention over time; participants' perceptions of measurement burden; the effectiveness of the planned recruitment strategy and retention of participants; and documentation of women's experience with PWDWP through digital stories.

Hypotheses

H1 is that, compared with control participants, intervention participants who receive intensive wha¯nau face-to-face and virtual support for type 2 diabetes management will have improved HbA_{1c} levels at 12 weeks and 24 weeks (postintervention sustainability).

H2 is that, compared with control participants, intervention participants who receive intensive wha¯nau face-to-face and virtual support for type 2 diabetes management will have reduced waist circumference and BMI at 12 weeks and 24 weeks.

H3 is that, compared with control participants, intervention participants who receive intensive wha¯nau face-to-face and virtual support for type 2 diabetes management will have improved diabetes self-care at 12 weeks and 24 weeks.

Data collection occurred at 3 time points: T_0 (before the commencement of the pilot program, week 1), T_1 (postintervention, week 12), and T_2 (postintervention, week 24). Data on the feasibility, accessibility, and affordability of the PWDWP were collected via satisfaction surveys for the intervention group at the end of the workshop (week 5), week 12, and week 24. For the control group, satisfaction surveys were completed in week 12 and week 24.

Qualitative data obtained through talanoa focus groups with participants will determine measurement burden, acceptability, potential translation, and ease of intervention access. Feasibility covers how the participants were referred to the program, time taken to complete questionnaires, any strengths or weaknesses of the intervention, its cultural relevance, experience with accessing the intervention, perceptions of the digitally delivered coaching sessions and online virtual support sessions as well as the face-to-face intervention, and any suggested improvements to the study design or intervention.

Methods

Advisory Committee

An advisory committee (AC) was established to oversee the pilot study, including its setup, ongoing management, promotion, implementation, and evaluation with outcome deliverables including appropriate dissemination. The AC includes members of the Māori and Pasifika communities including the Pasifika Women's Alliance and Pacific Island Council of Queensland and key organizations such as the Good Start Program for Māori and Pacific Islander Peoples (Children's Health Queensland) and academia (eg, Queensland University of Technology [QUT] and University of Technology Sydney through the Women's Wellness Research Program). A series of group talanoa undertaken with AC community members ensures that the pilot study is implemented and evaluated within the talanoa cultural framework. The AC meets regularly every 4 months to review the study protocols including recruitment strategies, health checks, and data collection methods and approaches and how these are disseminated. The AC provides input on the trial progress, adherence to the protocol, participant safety, and consideration of new information as well as advice on the location and place of delivery (intervention and data collection) considered to be culturally acceptable to the participants.

Participatory Talanoa Methodologies

The research uses participatory action research using co-design and talanoa methods as the theoretical and cultural framework in the collection and analysis of data.

Talanoa is a way of communicating in a Pacific context. It has been described as the co-construction of knowledge through respectful, reciprocal conversation. It is a process enabling critical discussions and knowledge construction allowing for rich contextual and inter-related information to surface as co-constructed stories [19]. Vaioleti [19] uses the following metaphor of kakala:

- "Toli" is deciding on, selecting, and picking the flowers, equating to recognizing a problem, how participants are chosen, and which data are collected and analyzed [19].
- "Tui" is the process of making and weaving the kakala, in which the stories and emotions of deep talanoa encounters are integrated and synthesized. This involves deciding on the type and amount of data to use, how the data are arranged in relation to each other, and how they are presented.
- "Luva" is the giving away of the kakala, when the research is given for the benefit of the community, where solutions can be found.

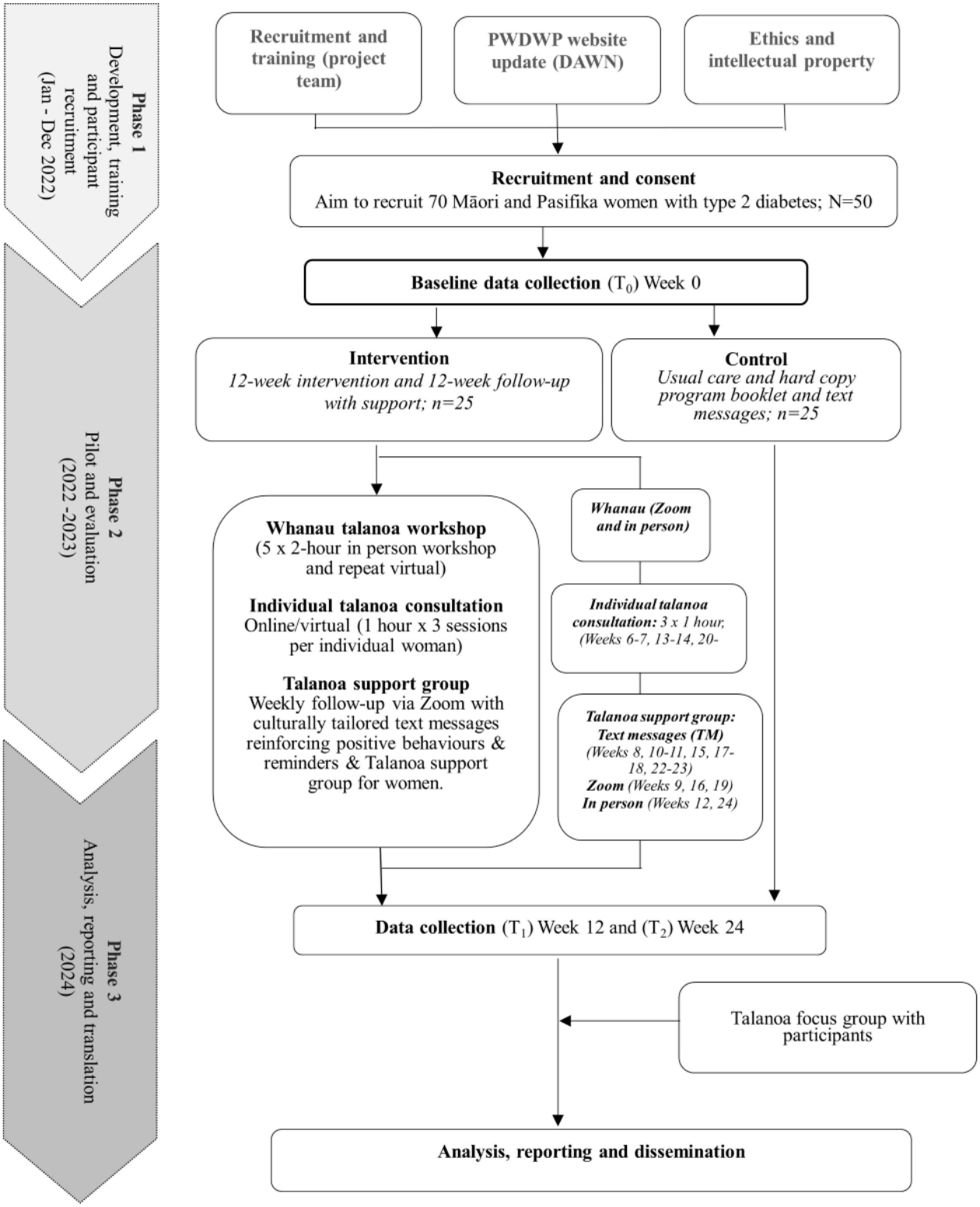
In this context, community engagement, including recruitment, data collection, and analysis processes, is a form of talanoa. All data are analyzed through talanoa with the AC and community researchers. In this context, talanoa is a method embedded within a participatory methodology [19] that informs the protocol of this study.

Study Design

This pilot study is a quasiexperimental design with 2 arms: an intervention (delivered in person and online for those who preferred virtual delivery) and an attention control arm (receiving written information and text messages). The study is being conducted to trial a 12-week intervention followed by a 12-week follow-up period (over 24 weeks) delivered by trained Māori and Pasifika health professionals (diabetes educator, clinicians, community health workers [CHWs], and community researchers). The study is conducted in southeast Queensland, Australia, with Māori and Pasifika women living with type 2 diabetes who were recruited through participatory community engagement with the Māori and Pasifika community leaders and organizations.

The study uses participatory talanoa methodologies using in-depth interviews and surveys and involves an in-person talanoa education workshop (5 weeks) as well as virtual workshops (5 weeks for those participants not in Brisbane and unable to attend in person), 3 online individual talanoa consultations (coaching) via Zoom, and an online virtual talanoa support group with motivational SMS text messages. The control participants received the usual care with their identified health professionals, a hard copy of the program materials (which includes a program journal, recipe book, fact sheets, and passbook), as well as general motivational SMS text messages. The process evaluation includes satisfaction surveys after the workshop sessions at week 5, week 12, and week 24 as well as a talanoa focus group with the participants after the intervention. Figure 2 is an overview of the PWDWP pilot study in southeast Queensland, Australia (2022-2024). The detailed intervention is described in the following sections.

Figure 2. Overview of the Pasifika Women's Diabetes Wellness Program (PWDWP) pilot study in southeast Queensland, Australia (2022-2024).



Intervention

The PWDWP intervention includes a whānau talanoa workshop, individual talanoa consultations, and a talanoa support group and text messages.

Whānau Talanoa Workshop

Five 2-hour sessions covered the wellness components. Whānau talanoa workshops provided interactive knowledge-based education on targeted health knowledge and behaviors with culturally specific tools to manage type 2 diabetes within family, community, and spiritual contexts (see Table 1).

Table 1. Whānau talanoa education workshops on diabetes wellness components delivered by a trained Pasifika diabetes educator and community health workers.

Education component	Content delivery	Weeks delivered
Becoming Healthy	This workshop provides practical information on type 2 diabetes and its symptoms, risk factors, diagnosis, treatment and management, medication, and self-care. This session also covers practical and cultural ways to deal with issues related to the shame and stigma of developing type 2 diabetes and the impact of denial.	1
Healthy Thinking & Feeling	This workshop provides information and tools to deal and cope with stress and barriers and ways to improve wellness that incorporate elements of Pasifika values, spirituality, and faith.	2
Healthy Eating	This workshop provides information and tools for healthy eating with a self-care healthy eating plan and strategies for managing cultural hospitality requirements without losing face.	3
Staying Active	This workshop covers ways to get moving, types of exercises to do with your family, and practical tips to remain motivated to stay active while managing family and community obligations.	4
Healthy Living	This workshop encourages, motivates, and maintains healthy living including looking after your bones, eyes, kidney, and heart; sleep; and menopause with spirituality, family, and community well-being.	5

Individual Talanoa Consultations

Three 1-hour, 1-on-1 sessions were conducted. The first session consisted of a routine check-up, appropriate screenings, and a discussion to facilitate tailored education, goal setting, and specialist advice to support individualized plans and goals for a healthy weight, diet, physical activity, stress management, sleep, and medications. The second session revisited goals set during session 1 and, if necessary, discusses prevention strategies and identification of barriers. The third session reviewed participant progress including barriers to self-management, reinforcement of positive behaviors, and setting future goals for maintenance.

Talanoa Support Group and Text Messages

A virtual peer support group facilitated by CHWs encouraged and supported women with targeted topics including stress management, barriers, understanding family situations, mindfulness, nutrition and diet, importance of health checks, regular visits to general practitioners and specialists, monitoring blood glucose levels, medication adherence, and maintenance. Motivational SMS text messages were sent regularly to reinforce key messages.

Cross-Intervention and Control Conditions

The intervention group received the complete intervention over the 24 weeks and had access to an interactive program journal (hard copy and electronic), a recipe book, a passbook for health check, and fact sheets as well as text messages with reinforcing positive motivational behaviors (Table 2). The participants also had access to a website that includes culturally developed resources (such as podcasts, digital stories, and information materials).

Table 2. The intervention component for the Māori and Pasifika women with type 2 diabetes from the south side of Brisbane, Queensland, Australia.

Intervention components	Weeks (1-24)
Whānau talanoa workshops (in person and virtual)	1-5[a]
Individual talanoa consultation (coaching via Zoom)	6-7, 13-14, 20-21
Motivational SMS text messaging	8, 10-11, 15, 17-18, 22-23
Talanoa support group (via Zoom)	9, 16, 19
Data collection (T_0, T_1, T_2; in person)	0 (baseline), 12, 24
Talanoa focus group (in person)	24

[a]Offered either (1) in person (face to face) with women or (2) online (virtual) for those who cannot attend in person.

The program provided all necessary health promotion content and supported participants with logging relevant health information in the journal (either hard copy or an electronic version). A weekly diet, physical activity, and diabetes self-care checklist encouraged participants to plan ahead. The interactive website aims to reinforce educational content, enabling home monitoring of measurable health indicators, and allowed participants to fill out questionnaires and other data. The website will also be adapted for all computing platforms, including mobile phones for future studies. Figure 3 illustrates the intervention participant journey of Māori and Pasifika women with type 2 diabetes from the south side of Brisbane over 24 weeks (January 2023 to November 2023).

Figure 3. Intervention participant journey of Māori and Pasifika women with type 2 diabetes from the south side of Brisbane, Queensland, over 24 weeks (January 2023 to November 2023), including five 2-hour education workshops (WS; either face to face or virtual), 3 individual talanoa (IT) consultations, and 3 virtual talanoa support group (VTSG) sessions with text messages (TM). DC: data collection.

The control group received their usual care with the hard copy of the program materials (ie, program journal, recipe book, fact sheets, and passbook) and SMS text messages (Table 3). At the completion of the intervention, control participants received a modified 1-day workshop covering talanoa education workshops. Figure 4 illustrates the control participant journey of the Māori and Pasifika women with type 2 diabetes from the north side of Brisbane over 24 weeks (January 2023 to November 2023).

Table 3. The control component for the Māori and Pasifika women with type 2 diabetes from the north side of Brisbane, Queensland, Australia.

Control components	Weeks (1-24)
Usual care with a hard copy program booklet (participants will be asked to document in the study journal [encouraged daily or weekly] but will be at their own discretion)	1-24
Motivational SMS text messaging	4, 8, 10-11, 15, 17-18, 22-23
Data collection (T_0, T_1, T_2; in person)	0 (baseline), 12, 24
Talanoa focus group (in person)	24

Figure 4. Control participant journey of Māori and Pasifika women with type 2 diabetes from the north side of Brisbane over 24 weeks (January 2023 to November 2023), including usual care with their preferred health provider and motivation text messages (TM). DC: data collection.

Inclusion and Exclusion Criteria

Inclusion criteria included Māori and Pasifika women with type 2 diabetes, aged ≥18 years, diagnosed with type 2 diabetes, and with access to the internet. Participants were excluded if they were pregnant and diagnosed with gestational diabetes, had a high-risk pregnancy, or were not diagnosed with type 2 diabetes.

Locations and Online Forums

Whānau Talanoa Intervention (Onsite)

The onsite face-to-face whānau talanoa sessions occurred in the community setting as recommended by the AC to ensure they were culturally acceptable to the participants in a whānau setting that is inclusive of the community.

Online Virtual Talanoa Intervention

The online sessions occurred via the Zoom platform over 5 weeks and covered the same content delivered in the face-to-face session. The Zoom setup was organized and managed through the secure QUT system, which enabled the project coordinator to host and manage each session and recordings. All the recordings and transcripts are stored with password protection and security in the QUT shared drive project folder, which can be accessed by the project team only (principal investigator and coordinator).

Individual Talanoa Consultation

The individual talanoa consultations (either via Zoom or telephone) were delivered by a trained CHW educator and managed through case notes that were uploaded (including

Zoom recordings) to a secure project folder within the QUT shared drive.

Study Population and Setting

Study Type

This is a participatory community-based study. Māori and Pasifika women living with type 2 diabetes were recruited from the Pasifika communities in southeast Queensland through a range of organizations, representing various sectors of the Māori and Pasifika communities in Queensland. The intervention and control groups were geographically distinct to minimize cross-communication, as members within the same community socialize, and this is the design the AC recommended as culturally appropriate.

Intervention Group

The intervention participants were recruited from the south side of Brisbane, including Logan, Ipswich, and Gold Coast, and geographically separated from the control group. Inclusion criteria for intervention participants were women aged ≥18 years from the south side of Brisbane, diagnosed with type 2 diabetes, and with access to the internet.

Control Group

The control participants were recruited from the north side of Brisbane, including the Sunshine Coast. Inclusion criteria for control participants were women aged ≥18 years from the north side of Brisbane who have been diagnosed with type 2 diabetes.

The exclusion criteria for intervention and control groups were pregnant women diagnosed with gestational diabetes or with a high risk of pregnancy. Women from each arm were also excluded depending on the location (eg, South side women were excluded from the control group and vice versa).

Sample Size

The sample size was calculated based on previous studies for detecting a difference of 1% reduction in HbA_{1c} (primary outcome) with a standard deviation of 1.4% in the intervention group. A significance level (α) of .05 was considered with a study power of 80% [32]. Based on this, a sample of 64 participants was needed (32 for the control group and 32 for the intervention group), with a target sample of 90 participants to compensate for a 40% attrition rate. Although the program received approximately 90 expression-of-interest responses, challenges with community engagement, complexities arising from COVID-19, and participant dropout resulted in a total of 50 participants, with 25 in the control group and 25 in the intervention group who enrolled and completed the pilot program.

Community Settings

The program for the intervention group was provided in community settings: Pasifika Te Haus in Runcorn and Adam Gould Community Centre in Logan on the south side of Brisbane. There is a large Māori and Pasifika population in southeast Queensland. For the control group, the first health checks and data collection occurred at a Pasifika Community Church, but for the follow-up visits, home visits were undertaken as requested by the participants. The community locations were recommended by the AC.

Recruitment Strategies

Recruitment for both intervention and control groups was multimodal and through distribution of study flyers, email invitations, and advertisements via social media (Facebook, websites); local ethnic radio stations; newsletters; and community networks including church groups, organizations, and Māori and Pasifika health workers. Recruitment also occurred through presentations and dialogue with community partners and organizations, including the Pasifika Women's Alliance Inc, Oceania Pacific Health Association, and Multicultural Communities Council Gold Coast, who have representatives on the AC, and they promoted the study through their networks and social media.

Ethical Considerations

The PWDWP was approved by the QUT Human Ethic Research Committee (5609). All data will be aggregated, with no individuals able to be identified. Collected data will be coded for analysis. The anonymity and privacy of all participants will be maintained through the use of fictional names, unique participant identification numbers, and secure data storage. All data will be stored securely on a password-protected research drive as per QUT's management of research data policy and the National Health and Medical Research Council guidelines for trials, with access restricted to only the principal investigator and co-investigator.

Potential participants were contacted to discuss the study and consent processes. Those who agreed received a "participant information pack" with an introduction letter detailing the program information, timelines, demographic questionnaires, and participant consent information. The project officer conducted 2 follow-up phone calls with each participant before the intervention to finalize details regarding the program; confirm the mode of preference for participating in part 1 (in person or online) of the intervention; and discuss issues or concerns with participation, access to their own GP, and dropout as well as any other issues that the women would like to discuss. Participants who consented to participate were asked to get a medical checkup prior to the start of the program and raise any concerns with the project officer. All participants (intervention and control) who consented were allocated a unique ID number and registered in a trial database. Any reasons for nonparticipation were recorded. The original informed consent for the primary data collection allows secondary analysis without additional consent.

Any cultural, spiritual, and personal concerns about disclosure in relation to cultural and religious beliefs especially around stigma associated with a diabetes diagnosis were discussed and clarified with participants before obtaining consent to disclose or use any sensitive information. Cultural sensitivity and respect form the underpinning guiding value in this research process especially when working with Māori or Pasifika families from various ethnic and religious backgrounds. This also included talanoa style of conversations to clearly explain the reason for choosing the 2 different locations (sites) for recruitment of

control and intervention participants and the benefits and risks with each group allocation.

Although we acknowledge that the Pasifika communities are well connected and share familial relationships, there was a possibility for the lack of confidentiality. One way this is addressed is by discussing with participants the importance of anonymity while at the same time acknowledging that this can be difficult in close-connected collective communities. This is a limitation to the study.

All participants, including control and intervention participants, were remunerated ("Koha") with gift vouchers (A$20 [US$13.05] for the health check and A$30 [US$19.57] for the talanoa focus group) to compensate for for their out-of-pocket expenses, travel time, and costs for participating at each data collection.

Data Collection and Analysis

Training of Community Health Workers, Community Researchers, and Research Team

Before the study commenced (July 2022 to December 2022), the Pasifika CHWs, health professionals, facilitators, and project team (including community researchers) received training on cultural protocols for engagement, community values, working with families across different Māori and Pasifika communities including the use of talanoa methods and approaches to coaching and delivering interventions within cultural Pasifika health model frameworks, and the protocols to be followed.

Training was undertaken by the principal investigator and diabetes educator in the form of role play, storytelling, and interactive activities using scenarios. The AC was invited to participate in the training as well as to contribute and share cultural experiences and advice in relation to working with Māori and Pasifika communities in a culturally safe and sensitive manner. All training was recorded, minutes were taken, and registration attendance was noted. The community researchers were also provided a step-by-step instruction manual on data collection.

Quantitative Outcomes

Quantitative data were collected through face-to-face or in-person sessions using online questionnaires at 3 time intervals (T_0, T_1, T_2) between January 2023 and December 2023 in a community-based location for both intervention and control participants. Data collected included anthropometric (height, weight, waist circumference, BMI), sociodemographic (age, marital status, employment status, income, post code, ethnicity), diabetes (self-care, self-efficacy), physical activity and dietary changes, and clinical (HbA_{1c} using the DVA Vantage point-of-care HbA_{1c} kit, Siemens) data [23,25-31]. The diabetes educator and CHWs collected anthropometric and clinical data, and the community researchers completed an online Qualtrics survey [24] using a tablet. Each participant was given a unique identifier.

Quantitative Data Analysis

Quantitative data analysis will be conducted in 2 steps. Raw data will be examined for missing entries, inconsistencies, and data entry errors. Any identified problems will be corrected by checking the data against the hard copy questionnaire. To further ensure reliability and accuracy of the data entry, the researcher will randomly re-enter 10% of the collected data and compare the 2 files [32].

Data are analyzed using SPSS 24 (IBM Corp), and missing data, outliers, normality, and multicollinearity will be examined using procedures outlined by Pallant [32,33]. Methods of data analysis will include descriptive, bivariate, and logistic regression analyses. The levels of statistical significance will be set at P=.49 to reduce the risk of type 1 errors [32]. The analyses will identify changes in the primary and secondary outcomes from baseline to week 12 and week 24 for Māori and Pasifika women with type 2 diabetes who completed the intervention. Descriptive statistics will examine participants' baseline measures and characteristics and will also explore trends in the data over time. Means (SDs) will be reported for continuous variables, and percentages and frequencies will be reported for categorical variables. Independent *t* tests will be used for continuous variables, and chi - square tests for categorical variables will be used to compare mean groups. Normality of the included variables will be evaluated using the Shapiro - Wilks normality test, and a nonparametric test (Mann - Whitney *U* test) will be used if data are not normally distributed to detect differences between groups. A 2 - sided P=.49 will be considered significant for all analyses [32,33].

The study will also provide initial parameter estimates for the primary endpoint, from which sample size calculations can be performed to determine sufficient power for the main trial. The primary endpoint between group differences at 12 and 24 weeks will be estimated using a linear mixed model with a treatment-time interaction. Although aiming for an intention-to-treat analysis, we recognize there were withdrawal from the study. A prespecified multiple imputation model will be used to obtain intention-to-treat estimates. Sensitivity analyses will explore the impact of nonignorable missing data. Analysis of secondary endpoints will follow the same approach in which changes will be compared between intervention and control groups using linear mixed models.

Process Evaluation

The process evaluation includes satisfaction surveys and a talanoa focus group involving the intervention and control participants to evaluate the feasibility of the program. This includes evaluating the training of Pasifika CHWs, community researchers, and the project team; types of delivery (in person and online or virtual for education sessions); whether core messages through text messaging reinforces a positive mindset and behaviors; the talanoa approach via online and in-person delivery of the intervention; shared understanding and core messages across the project team including CHWs, community researchers, and the workshop facilitator; and satisfaction with the program assessed at T_1 and T_2. In addition, we will capture where the participants heard about the program, if accessibility to the program was easy, some of the challenges with the program, and what the participants would change about the program.

Qualitative Outcomes

Qualitative data were collected using a talanoa focus group to gather information about the participants' experiences with the program and its acceptability, usefulness, barriers and enablers to participation, feasibility of time commitment, burden, and cultural relevance. Data gathered will explore time taken to complete data surveys, strengths and weaknesses of the intervention, perceptions of the digitally delivered sessions, and any suggested improvements to the study design or intervention as well as whether control participants had heard about the program, spoken to the intervention participants, and the influence of this on their participation.

Qualitative Data Analysis

Talanoa focus groups were conducted in a community setting, facilitated by community researchers and the principal researcher using a guide co-developed with the AC. The talanoa discussions, which lasted 90 minutes, were audio-recorded using a digital recorder and transcribed verbatim for analysis [20]. The trained community researcher took detailed notes using the guide. Immediately after the talanoa focus group session, the notetaker and community researcher summarized and prepared debrief notes that highlighted key points from the group. These were presented back to the focus group. The participants were also given the opportunity to read a copy of what they said and make any changes [20].

NVivo software will be used for data management and manual coding or identifying recurring keywords and phrases to ascertain measurement burden, acceptability, potential translation, and ease of intervention access. Co-analysis using inductive and deductive approaches will involve participatory talanoa processes with the Pasifika community researcher and participants iteratively [19,20]. The key themes from the co-analysis will be collated and presented to the AC for discussion. Patterns of meanings and interpretations during the analysis processes will be further deliberated by the AC to ensure community and cultural contexts are considered. Participants will be given progress feedback of the results and study outcomes. Giving feedback will be an integral part of the participatory research cycle in which the participants will have the opportunity to construct, reconstruct or retell, and reflect on the stories of their experience in the pilot program including both positive and negative feedback. A copy of the result findings and action outcomes will be disseminated to the participants, health providers, community organizations, and research team.

Results

Pilot Program

The pilot program began in February 2023 with 50 participants who were enrolled between January 2022 and January 2023. For the intervention group, 35 women were recruited, and there were 10 dropouts, resulting in 25 women in the intervention group. For the control group, 27 women were recruited, and there were 2 dropouts, resulting in 25 women in the control group.

Data were collected from January 2023 to December 2023. Methods of quantitative data analysis will include descriptive, bivariate, and logistic regression analyses. The focus group was conducted in November 2023, and the results are being analyzed using an inductive-deductive approach. Film and digital story production are underway and expected to be complete in April 2024. Data analysis is planned to occur from March 2024 to July 2024.

Importance of the Results

The study participants in the intervention and control groups are from diverse Pacific cultural backgrounds and include Fijians, Fiji Indians, Samoans, Māori, Tongans, Cook Islanders, and those who identify with more than one cultural group. The anticipated results from the quantitative and qualitative analyses would highlight the relevance that culturally co-designed programs could lead to improved diabetes self-care outcomes including clinical HbA_{1c} levels, positive changes in body composition measurements such as BMI and waist circumference, and enhanced diabetes self-care scores within the intervention group.

Dissemination Plan

Results are expected to be published as early as December 2024 and extend through July 2025. The study findings will be disseminated through presentations at state and national meetings (eg, Queensland Women's Health Forum, Australian Public Health), international meetings and conferences (eg, the International Diabetes Congress), and publication in peer-reviewed journals. In addition, we will work closely with Māori and Pasifika community partners to identify strategies to disseminate study findings in the community through community talanoa forums and meetings. Other social media network platforms and local community radio will be used to disseminate the study findings.

Discussion

Type 2 diabetes is a costly, rapidly growing, and largely preventable disease. Encouraging healthier lifestyles in Māori and Pasifika women with type 2 diabetes could potentially improve the health and well-being of women, prevent complications, and reduce health expenditure.

This paper describes the protocol of a quasiexperimental pilot study based on a culturally co-designed whānau-centered intervention for Māori and Pasifika women living with type 2 diabetes in Queensland, Australia [15]. The study consists of 2 arms (intervention and control) to trial a 12-week intervention followed by a 12-week follow up-period delivered by trained Māori and Pasifika health professionals and CHWs.

This study will report the clinical benefits of the intervention and will target improvements in HbA_{1c} and diabetes self-care including diet, physical activity, medication management, and routine health checks for Māori and Pasifika women with type 2 diabetes. Community-based interventions among Australian Samoans in Sydney, Australia, showed a reduction in HbA_{1c} [34], which would be promising for our study. Studies with Māori and Pasifika have shown that using community-based approaches and culturally tailored interventions are likely to

improve health behaviors [35,36]. The qualitative data from the focus groups will inform measurement burden, acceptability, potential translation, and ease of intervention access, which has not been evaluated in other community-based studies with Māori and Pasifika communities in Australia. The potential for success of the proposed intervention will be examined using accessibility, acceptability, uptake, sustainability, adherence, participants' perceptions of measurement burden, effectiveness of the recruitment strategy and retention, and the participants' overall experience, based on women's wellness resulting from type 2 diabetes programs [16]. This will inform the program's cultural adaptability, acceptability, and feasibility for future studies.

This study recruited 50 Māori and Pasifika women with type 2 diabetes through community-led participatory approaches and with the input from the AC to ensure that the protocols of engagement with the community, recruitment of participants, and implementation and evaluation of the program were community-driven and culturally appropriate [20-22] Interventions that are specifically co-designed with communities ensure cultural relevance, effectiveness, and sustainability for addressing chronic conditions such as type 2 diabetes [22,37]. Equally important is the community-led participatory approach that embeds Māori and Pasifika cultural values within program design and implementation, which is pivotal to engaging and empowering communities to successfully improve health behaviors, particularly when tackling type 2 diabetes [21,22,37]. Developing health and lifestyle programs within communities and partnering with stakeholders including health services, governmental and nongovernmental organizations, and academic institutions have been shown to be essential to empowering underserved populations, particularly as the programs aim to understand and support behavioral changes leading to better health and well-being outcomes [21,22,36,38]. This program supports the participants in developing knowledge and practical skills for preventing and managing type 2 diabetes as well as overcoming challenges that participants and their families may face in living a healthy life [21]. As a result, this has enabled the production of 5 digital stories of women from diverse Pasifika backgrounds in the intervention, documenting their experiences and journeys, which will be used as a health promotion resource for the program in future studies.

Despite these strengths, this pilot study has limitations. One inherent limitation is the potential for cross-communication. Due to the close nature of the included communities, it is likely that they will speak to each other regarding the program. For this reason, the intervention and control groups were allocated based on geographic location to attempt to minimize this. The sample size is too small to assess the extent to which the metabolic improvements are due to self-management (eg, lifestyle change) or clinical management and may also result in nonsignificant ($P<.05$) results for some of the measurement outcomes. In addition, community-based studies are difficult to conduct in a rigorous randomized controlled trial (RCT) design without significant funding, for which pilot data are important to inform study design, including power calculations [34]. However, this study was undertaken as a pilot study to provide a proof of concept prior to undertaking a stepped-wedge RCT or multicenter RCT. Regardless of this, the outcomes of this pilot study will provide valuable information regarding culturally appropriate implementation and evaluation. The lessons learned in this pilot trial will help us to plan the larger trial with regard to recruitment strategies, intervention implementation, and data collection. The evidence-based synthesis of findings with community participants and researchers, including dissemination of the pilot study outcomes, will have future applications aimed at leading to larger studies implementing a state or nation-wide program and undertaking translation research with the potential to develop innovative digital or virtual delivery of the program with a health data collection interphase, website platform for virtual delivery, and use of a mobile app.

In conclusion, this study provides a blueprint for PWDWP and proposes a model for evaluating intervention efficacy and effectiveness in partnership with Māori and Pasifika community organizations and key stakeholders in southeast Queensland, Australia. The study findings will have significant implications for policy makers and practitioners when implementing a diabetes management program for Māori and Pasifika communities, emphasizing the need for culturally relevant interventions. Collaboration with communities and stakeholders is crucial when developing diabetes management and lifestyle programs, particularly for communities with unique cultural nuances. The findings of this study may suggest a potential model for addressing health disparities in other culturally and linguistically diverse populations.

Acknowledgments

We would like to thank the Māori and Pasifika women with type 2 diabetes; the advisory committee members, many of whom are elders and leaders within their communities; and the Pasifika health workers for their dedication, time, and commitment to the design of this study protocol.

The research program was successful in securing funding through Diabetes Australia Research Program Grant (grant number Y22G-AKBH) and Australian Health Research Alliance (AHRA) Women's Health Research Translation Network (WHRTN) Early and Mid-Career Researcher Funded Award 2021. A progress interim report and final report with study findings and outcomes will be provided to the funders.

Data Availability

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

Authors' Contributions

The authors fulfil the criteria for authorship by contributing to the planning, development, and writing of the protocol for this study. HA is the principal investigator, and DG is the co-investigator. HA and DG drafted the preliminary protocol, ethics application, and trial registry. HA, WN, and DG contributed to the design of the study protocol. HA and WN provided Pasifika cultural oversight. MC drafted the initial paper for publication with input and advice from HA. All authors contributed to the writing of the paper, and all have read and approved the final manuscript.

Conflicts of Interest

The authors declared the following potential conflicts of interest with respect to the research, authorship, and publication of this paper: DG is currently funded by the Queensland Children's Hospital Foundation via a philanthropic grant from Woolworths. All other authors have no conflicts of interest to declare.

Multimedia Appendix 1
Peer Reviewed RR1 Registered Report.
[PDF File (Adobe PDF File), 111 KB - resprot_v13i1e55435_app1.pdf]

Multimedia Appendix 2
SPIRIT PROTOCOL Checklist.
[DOCX File , 21 KB - resprot_v13i1e55435_app2.docx]

References

1. International Diabetes Federation. IDF Diabetes Atlas 2021. International Diabetes Federation. 2021. URL: https://diabetesatlas.org/atlas/tenth-edition/ [accessed 2023-07-03]
2. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract 2022 Jan;183:109119. [doi: 10.1016/j.diabres.2021.109119] [Medline: 34879977]
3. Bitton A, Zaslavsky AM, Ayanian JZ. Health risks, chronic diseases, and access to care among US Pacific Islanders. J Gen Intern Med 2010 May 9;25(5):435-440 [FREE Full text] [doi: 10.1007/s11606-009-1241-0] [Medline: 20143177]
4. Win Tin ST, Laesango N, Gadabu E, Colagiuri R. Comparing metabolic control and complications in type 2 diabetes in two Pacific Islands at baseline and following diabetes care intervention. J Clin Transl Endocrinol 2016 Jun;4:32-37 [FREE Full text] [doi: 10.1016/j.jcte.2016.03.001] [Medline: 29159128]
5. Ogurtsova K, da Rocha Fernandes J, Huang Y, Linnenkamp U, Guariguata L, Cho N, et al. IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. Diabetes Res Clin Pract 2017 Jun;128:40-50. [doi: 10.1016/j.diabres.2017.03.024] [Medline: 28437734]
6. Hill K, Ward P, Grace BS, Gleadle J. Social disparities in the prevalence of diabetes in Australia and in the development of end stage renal disease due to diabetes for Aboriginal and Torres Strait Islanders in Australia and Maori and Pacific Islanders in New Zealand. BMC Public Health 2017 Oct 11;17(1):802 [FREE Full text] [doi: 10.1186/s12889-017-4807-5] [Medline: 29020957]
7. Volaco A, Cavalcanti AM, Filho RP, Précoma DB. Socioeconomic status: the missing link between obesity and diabetes mellitus? Curr Diabetes Rev 2018 Jun 28;14(4):321-326. [doi: 10.2174/1573399813666170621123227] [Medline: 28637406]
8. Hill-Briggs F, Adler NE, Berkowitz SA, Chin MH, Gary-Webb TL, Navas-Acien A, et al. Social determinants of health and diabetes: a scientific review. Diabetes Care 2020 Nov 02;44(1):258-279 [FREE Full text] [doi: 10.2337/dci20-0053] [Medline: 33139407]
9. Kivimäki M, Vahtera J, Tabák AG, Halonen JI, Vineis P, Pentti J, et al. Neighbourhood socioeconomic disadvantage, risk factors, and diabetes from childhood to middle age in the Young Finns Study: a cohort study. The Lancet Public Health 2018 Aug;3(8):e365-e373. [doi: 10.1016/s2468-2667(18)30111-7]
10. Australia's Health 2020 Data Insights. Australian Institute of Health and Welfare. 2020. URL: https://www.aihw.gov.au/getmedia/be95235d-fd4d-4824-9ade-34b7491dd66f/aihw-aus-231.pdf [accessed 2023-07-03]
11. Colagiuri S. Diabetes in Indigenous Australians and Other Underserved Communities in Australia. In: Dagogo-Jack S, editor. Diabetes Mellitus in Developing Countries and Underserved Communities. Cham, Switzerland: Springer; 2017:151-163.
12. Diabetes-related complications. Australian Institute of Health and Welfare. 2015. URL: https://www.aihw.gov.au/reports/diabetes/diabetes/contents/impact-of-diabetes/diabetes-related-complications [accessed 2023-04-15]

13. Eades A, Hackett ML, Liu H, Brown A, Coffin J, Cass A. Qualitative study of psychosocial factors impacting on Aboriginal women's management of chronic disease. Int J Equity Health 2020 Jan 13;19(1):8 [FREE Full text] [doi: 10.1186/s12939-019-1110-3] [Medline: 31931810]
14. Seib C, Parkinson J, McDonald N, Fujihira H, Zietek S, Anderson D. Lifestyle interventions for improving health and health behaviours in women with type 2 diabetes: A systematic review of the literature 2011-2017. Maturitas 2018 May;111:1-14 [FREE Full text] [doi: 10.1016/j.maturitas.2018.02.008] [Medline: 29673826]
15. Akbar H. Socio-cultural context of managing type 2 diabetes in Australian Pacific Islander women living in Queensland. Brisbane: Queensland University of Technology; 2021 Jul 01. URL: https://eprints.qut.edu.au/119162/ [accessed 2023-02-03]
16. Anderson D, Sturt J, McDonald N, Sapkota D, Porter-Steele J, Rogers R, et al. Women's Wellness with Type 2 Diabetes Program (WWDP): Qualitative findings from the UK and Australian feasibility study. Diabetes Res Clin Pract 2021 Feb;172:108654. [doi: 10.1016/j.diabres.2021.108654] [Medline: 33422587]
17. Akbar H. Using 'talanoa' to explore diabetes self-management of Australian Pacific Islander (API) women. 2019 Presented at: PHAA Public Health Prevention Conference; June 12-14, 2019; Melbourne, Australia. [doi: 10.13140/RG.2.2.18798.05440?]
18. Lingervelder D, Koffijberg H, Kusters R, IJzerman MJ. Point-of-care testing in primary care: A systematic review on implementation aspects addressed in test evaluations. Int J Clin Pract 2019 Oct 19;73(10):e13392 [FREE Full text] [doi: 10.1111/ijcp.13392] [Medline: 31313873]
19. Vaioleti TM. Talanoa research methodology: a developing position on Pacific research. Waikato Journal of Education 2016;12(1):1 [FREE Full text] [doi: 10.15663/wje.v12i1.296]
20. Akbar H, Windsor C, Gallegos D, Manu-Sione I, Anderson D. Using talanoa in community-based research with Australian Pacific Islander women with type 2 diabetes. Progress in Community Health Partnerships 2022 Mar;16(1):119-128. [doi: 10.1353/CPR.2022.0011]
21. Akbar H, Gallegos D, Anderson D, Windsor C. Deconstructing type 2 diabetes self-management of Australian Pacific Islander women: Using a community participatory research and talanoa approach. Health Soc Care Community 2022 Sep;30(5):1988-1999 [FREE Full text] [doi: 10.1111/hsc.13580] [Medline: 34580935]
22. Akbar HG, Gallegos D, Te Kani AW, Anderson D, Windsor C. Towards collective community education: Pasifika diabetes health forums in Southeast Queensland, Australia. AlterNative: An International Journal of Indigenous Peoples 2023 Oct 30;19(4):933-944. [doi: 10.1177/11771801231196777]
23. Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus. World Health Organization. 2011 Jan 13. URL: https://www.who.int/publications/i/item/use-of-glycated-haemoglobin-(-hba1c)-in-diagnosis-of-diabetes-mellitus [accessed 2024-02-03]
24. Qualtrics. URL: https://www.qualtrics.com [accessed 2024-02-03]
25. Gallegos D, Do H, To QG, Vo B, Goris J, Alraman H. The effectiveness of living well multicultural-lifestyle management program among ethnic populations in Queensland, Australia. Health Promot J Austr 2021 Jan 27;32(1):84-95. [doi: 10.1002/hpja.329] [Medline: 32053254]
26. Toobert D, Hampson S, Glasgow R. The summary of diabetes self-care activities measure: results from 7 studies and a revised scale. Diabetes Care 2000 Jul;23(7):943-950. [doi: 10.2337/diacare.23.7.943] [Medline: 10895844]
27. Lorig K, Ritter PL, Villa FJ, Armas J. Community-based peer-led diabetes self-management: a randomized trial. Diabetes Educ 2009 Apr 30;35(4):641-651. [doi: 10.1177/0145721709335006] [Medline: 19407333]
28. Moon SJ, Lee W, Hwang JS, Hong YP, Morisky DE. Accuracy of a screening tool for medication adherence: A systematic review and meta-analysis of the Morisky Medication Adherence Scale-8. PLoS One 2017 Nov 2;12(11):e0187139 [FREE Full text] [doi: 10.1371/journal.pone.0187139] [Medline: 29095870]
29. Fitzgerald JT, Funnell MM, Anderson RM, Nwankwo R, Stansfield RB, Piatt GA. Validation of the revised brief Diabetes Knowledge Test (DKT2). Diabetes Educ 2016 Apr 14;42(2):178-187. [doi: 10.1177/0145721715624968] [Medline: 26769757]
30. Physical status: the use of and interpretation of anthropometry, report of a WHO expert committee. World Health Organization. 1995. URL: https://www.who.int/publications/i/item/9241208546 [accessed 2024-02-03]
31. Waist circumference and waist-hip ratio: report of a WHO expert consultation. World Health Organization. 2008 Dec. URL: https://www.who.int/publications/i/item/9789241501491 [accessed 2024-02-03]
32. Pallant J. SPSS Survival Manual: A Step by Step Guide to Data Analysis Using IBM SPSS, 5th edition. Maidenhead, Berkshire, United Kingdom: Open University Press; 2013.
33. IBM SPSS Statistics. IBM. URL: https://www.ibm.com/products/spss-statistics [accessed 2024-02-03]
34. Ndwiga DW, MacMillan F, McBride KA, Thompson R, Reath J, Alofivae-Doorbinia O, et al. Outcomes of a church-based lifestyle intervention among Australian Samoans in Sydney - Le Taeao Afua diabetes prevention program. Diabetes Res Clin Pract 2020 Feb;160:108000. [doi: 10.1016/j.diabres.2020.108000] [Medline: 31904445]
35. Yu D, Zhao Z, Osuagwu UL, Pickering K, Baker J, Cutfield R, et al. Ethnic differences in mortality and hospital admission rates between Māori, Pacific, and European New Zealanders with type 2 diabetes between 1994 and 2018: a retrospective, population-based, longitudinal cohort study. The Lancet Global Health 2021 Feb;9(2):e209-e217. [doi: 10.1016/s2214-109x(20)30412-5]

36. Firestone R, Faeamani G, Okiakama E, Funaki T, Henry A, Prapaveissis D, et al. Pasifika prediabetes youth empowerment programme: evaluating a co-designed community-based intervention from a participants' perspective. Kōtuitui: New Zealand Journal of Social Sciences Online 2021 Feb 04;16(1):210-224. [doi: 10.1080/1177083x.2021.1876743]
37. Queensland Health response to Pacific Islander and Māori health needs assessment. Queensland Health. 2011. URL: https://www.health.qld.gov.au/multicultural/health_workers/pac-island-needs [accessed 2023-02-03]
38. Hardt J, Canfell OJ, Walker JL, Webb K, Brignano S, Peu T, et al. Healthier Together: Co-design of a culturally tailored childhood obesity community prevention program for Māori and Pacific Islander children and families. Health Promot J Austr 2021 Feb;32 Suppl 1:143-154. [doi: 10.1002/hpja.438] [Medline: 33141972]

Abbreviations

AC: advisory committee
CHW: community researchers
HbA1c: glycated hemoglobin
PICTs: Pacific Island Countries and Territories
PWDWP: The Pasifika Women's Diabetes Wellness Program
QUT: Queensland University of Technology
RCT: randomized controlled trial
T0: baseline
T2: week 24

Edited by A Mavragani; submitted 12.12.23; this is a non–peer-reviewed article;accepted 28.01.24; published 11.03.24.

Please cite as:
Akbar H, Contor M, Niumata W, Anderson D, Gallegos D
Effectiveness of the Pasifika Women's Diabetes Wellness Program (PWDWP): Protocol for a Pilot Intervention and Feasibility Randomized Controlled Trial
JMIR Res Protoc 2024;13:e55435
URL: https://www.researchprotocols.org/2024/1/e55435
doi:10.2196/55435
PMID:38286130

Protocol

Inhibitory Control Training for Anxiety and Math Achievement in Primary School Children: Protocol for a Proof-of-Concept Study

Elizabeth Edwards[1*], BEd, BSocSci(Psych), PhD; Khanh Linh Chu[1*], E-BBA, MEdSt; Annemaree Carroll[1*], BEd, BSci(Psych), MEd, PhD

The University of Queensland, St Lucia, Australia
[*]all authors contributed equally

Corresponding Author:
Elizabeth Edwards, BEd, BSocSci(Psych), PhD
The University of Queensland
School of Education
St Lucia, Q 4072
Australia
Phone: 61 0481906968
Fax: 61 733652866
Email: elizabeth.edwards@uq.edu.au

Abstract

Background: Cognitive control training (CCT) has shown potential to reduce emotional vulnerability in adults and adolescents. However, there is scant literature testing the efficacy of CCT for the reduction of anxiety and transferring the effects to educational outcomes in children. Building on the evidence that a greater ability to suppress a prepotent response (inhibitory control) is associated with higher math achievement in children, it is plausible that training inhibitory processes using a CCT paradigm may be beneficial for reducing anxiety, improving inhibitory control, and in turn increasing math achievement.

Objective: This proof-of-concept study aims to investigate the efficacy of 15 sessions of inhibitory control training for reduction in anxiety and improvement in math achievement in primary school children.

Methods: We will use a 2 (group: CCT, adaptive Go/No-Go vs active control, low-load task) multiplied by 4 (time: pre- vs posttraining vs 1-month vs 3-month follow-up) randomized design in a nonselected sample of 100 children aged 8-10 years. Both groups will complete 10 minutes of daily training for 3 weeks at school. The dependent variables will be anxiety and correlates (Spence Children's Anxiety Scale, Penn State Worry Questionnaire for Children, Revised Children's Anxiety and Depression Scale, Child Response Style Questionnaire, and Modified Abbreviated Math Anxiety Scale), inhibitory control (Go/No-Go task), shifting (color-shape shifting task), updating (*n*-back task), and math achievement (Applied Problems, Calculation, and Math Facts Fluency subtests from the Woodcock-Johnson IV Tests of Achievement).

Results: We opened enrollment in September 2023. The initial results are expected to be published in late 2024. We predict that children in the CCT group will show a reduction in emotional symptoms; improvements in inhibition, shifting, and updating performance; and advances in math achievement from pre- to posttraining, and that these effects will be maintained at 1- and 3-month follow-ups, compared to children in the active control group.

Conclusions: The CCT paradigm used in our study will provide a greater understanding of the emotional and cognitive transfer effects on children and inform future work. Specifically, the findings will advance the knowledge of deploying inhibitory control training with children and provide valuable insights into its use for reducing anxiety and advancing math achievement.

Trial Registration: Open Science Framework ofs.io/de2qa; https://doi.org/10.17605/OSF.IO/DE2QA

International Registered Report Identifier (IRRID): PRR1-10.2196/52929

(JMIR Res Protoc 2024;13:e52929) doi:10.2196/52929

KEYWORDS

cognitive control training; anxiety; inhibitory control; math achievement

Introduction

Overview

Anxiety is the most reported mental health problem in young people across and beyond the pandemic [1,2]. Childhood anxiety is associated with excessive worry, avoidance, physical symptoms, and severe social and academic problems [3]. Interventions for anxiety in children are typically expensive to administer (eg, 1:1 psychological therapy) with long waitlists to see providers in the public health system. Hence, there is a need for novel approaches to closing the treatment gap, that is, reducing the discrepancy between the percentage of children with mental health problems and the percentage who receive treatment [4]. The focus of this proof-of-concept study is treating childhood anxiety by targeting the modifiable cognitive processes that underpin emotional symptoms. We will deliver an intervention at school as part of regular classroom routines and examine its efficacy in reducing anxiety and improving cognitive and academic outcomes (more specifically, math achievement).

Research has shown that the ability to control the focus of one's attention (attentional control or cognitive control) is vital to learning and requires top-down cognitive processes to coordinate thoughts and behaviors to achieve a goal [5]. Attentional control theory [6] proposes that anxiety upsets the balance between the top-down (goal-driven) and bottom-up (stimulus-driven) attentional processes such that it is associated with increased activation of the stimulus-driven system (ie, attention to internal and external stimuli) and decreased influence of the goal-directed system (ie, attention to task demands). Furthermore, attentional control theory posits that highly anxious individuals direct their attention toward potentially threatening information (eg, worrisome thoughts) which in turn reduces the ability to perform ongoing tasks. The theory suggests that the cognitive processes or executive functions most affected by anxiety are inhibitory control, which requires inhibiting distractors and withholding a dominant response, shifting, which entails switching between tasks or demands of a task, and updating, which requires monitoring and updating information in working memory; see Miyake et al [7]. For example, an anxious child might direct their attention to emotional thoughts and be unable to inhibit distracting worries such as "this work is too hard" or "I might fail" and have difficulty shifting their focus back to the task at hand, and when new information is presented requiring them to update their working memory, the demands of controlling attention are borne out in poorer task performance.

There is growing empirical support for targeting or training the cognitive processes most vulnerable to anxiety (ie, inhibitory control, shifting, and updating) and reducing emotional symptoms in adults [8-12] and adolescents [13]. These paradigms are known by the umbrella term, cognitive control training (CCT) or if directly targeting the inhibitory control function, inhibitory control training. A small number of CCT studies have been conducted with children. Results from a systematic review [14] highlighted that of the 8 studies that showed promise for CCT to reduce anxiety only 2 were conducted with primary school-aged children (younger than 12 years of age). Bigorra et al [15] used commercial working memory training with children of 7-12 years with attention-deficit or hyperactivity disorder (ADHD) and behavioral difficulties and Shanok et al [16] used inhibitory control training with typically developing children aged 8-12 years. Both studies reported reduced anxiety in combination with improved cognitive performance (working memory and inhibitory control, respectively); however, neither study examined the transfer of these effects to educational outcomes.

Research in math achievement in school students supports the importance of cognitive control on executive functioning. For instance, Bull and Lee [17] suggest that during math problem-solving, inhibitory control is needed to suppress unwanted information or inappropriate strategies or prepotent number representations, shifting is required to switch math operations within and between more complex problems, and updating is vital for holding and monitoring information in working memory. However, age-related variances in the development of executive function need consideration, particularly as math skill requirements change across the school years [17]. Updating is associated with math achievement in preschoolers [18] and inhibitory control and shifting have also been implicated in early math skill variability [19]. In primary school children, nonetheless, inhibitory control has been shown to be vital for math achievement [20]. Given that the development of executive functioning increases rapidly in the early years of schooling [19,21] and attenuates in adolescence [22], it is plausible that targeting inhibitory control in children aged 8-10 years may serve to boost math performance at a critical time point. The focus of this study is to use a CCT paradigm to reduce anxiety, improve inhibitory control and in turn, math achievement.

This Study

This proof-of-concept study will examine the effect of inhibitory control training in typically developing children aged 8-10 years. We will compare emotional symptoms (indexed using self-reported scales of anxiety and correlates), inhibitory control, shifting and updating skills (assessed using computerized tasks), and math achievement (measured using standardized math tests) of children completing 15 sessions of daily inhibitory control training versus an active control task from pre- to posttraining and at 1- and 3-month follow-ups. The study will be conducted in year 4 and 5 classrooms. This study aims to determine whether 10 minutes of daily inhibitory control training for 3 weeks can reduce anxiety (and correlates) and improve math achievement and whether any changes are maintained 1 and 3 months after training.

Methods

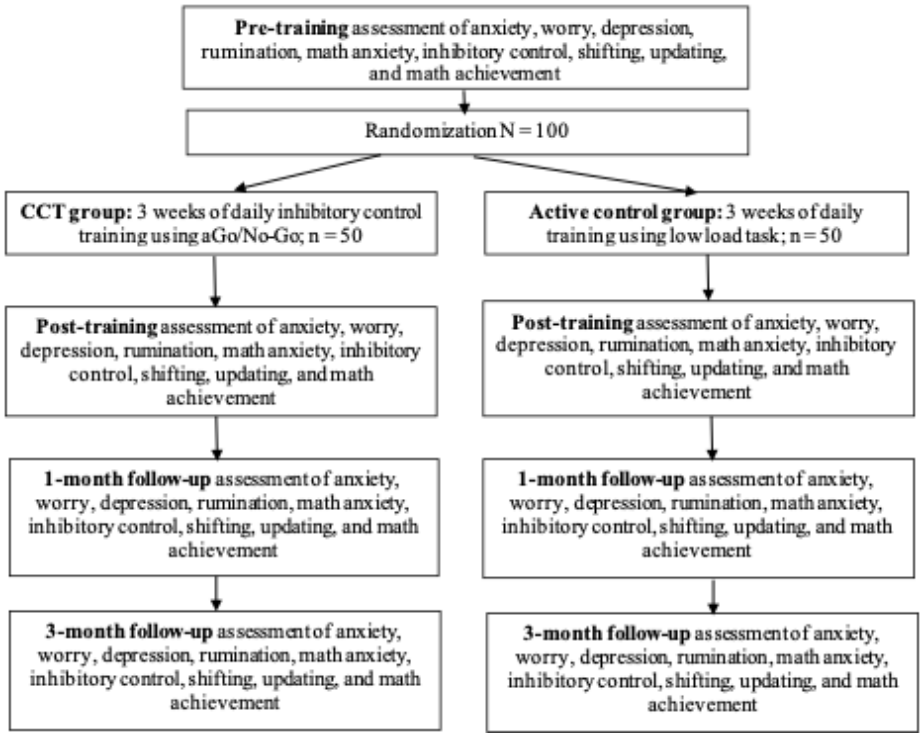
Ethical Considerations

The University of Queensland Human Research Ethics Committee provided approval to conduct this research (2023/HE000462). Gatekeeper approval was also received from participating education departments and schools. Parent consent and child assent will be gained prior to participation. The trial was registered on the Open Science Framework (ofs.io/de2qa).

Study Design

We will use a 2 (group: CCT, adaptive Go/No-Go vs active control, low-load task) multiplied by 4 (time: pre- vs posttraining vs 1-month vs 6-month follow-up) randomized design (see Figure 1). Children in both the CCT and active control groups will train for 10 minutes each day for 3 weeks (15 sessions) as part of their daily classroom routine. Changes in the dependent variables (anxiety, worry, depression, rumination, inhibitory control, shifting, updating, and math achievement) will be examined pre- to posttraining, and compared to 1- and 3-month follow-up.

Figure 1. Study flowchart.



Participants

A nonselect sample of children aged 8-10 years will be recruited from primary schools. An a priori power analysis revealed that 66 participants are required to detect small effects (d=0.20) approaching those reported by previous studies with 80% or greater power on primary outcome measures relative to controls [9,23,24]. To allow for approximately 30% attrition we will recruit 100 children proportionately balanced for sex and age across 8, 9, and 10 years. To incentivize enrollment and study completion, participating children will be compensated using monetary tokens redeemed at the end of the study; Aus $ 2.00 (US $1.31) for the completed questionnaires at each of 4 time points and Aus $ 2.00 (US $1.31) for each training session (~Aus $ 40.00; US $26.14 per participant). Given that teachers are required to supervise and monitor the daily training, they will be incentivized for their class's participation (minimum 20 students) at the rate of 1 teacher relief day for each data collection time point (pre- and posttraining and 1- and 3-month follow-ups).

Primary and P-12 schools, as well as private, independent, and Catholic schools, will be approached regarding participation in the study. A recruitment package of materials (including a university ethics approval letter, gatekeeper permission request, pamphlet, study protocol, participant information sheets for parents, teachers and children, consent forms, and an information sheet about children's anxiety and depression) will be sent to the school principal to determine interest in participation. Information sessions will be held face-to-face or using a video communications platform (eg, Zoom) for principals, teachers, and parents, as required.

Measures and Tasks

Anxiety

Anxiety will be measured using the Spence Children's Anxiety Scale [25], a self-report assessment of specific anxiety symptoms in children aged 8-11 years, categorized as social phobia (6 items), panic or agoraphobia (9 items), generalized anxiety (6 items), obsessive-compulsive (6 items), separation anxiety (6 items), and physical injury fears (5 items). Children respond using a 4-point Likert scale from 0=never to 3=always. Anxiety symptoms will be examined separately (eg, social phobia, and separation anxiety) in addition to the inspection of change in an overall anxiety score calculated by summing the 38 items. Higher scores represent higher symptoms of anxiety.

Worry

Worry will be assessed using the Penn State Worry Questionnaire for Children [26], a 14-item questionnaire that measures the tendency to engage in excessive, generalized, and uncontrollable worry in children aged 7-17 years. Items are rated on a 4-point Likert scale from 0=never to 3=always. Total worry scores are calculated (after reversing 3 items) by summing the scores on all items and range from 0 to 42; higher scores represent a greater tendency to worry.

Depression

Depression will be indexed by the Low Mood subscale from the Revised Children's Anxiety and Depression Scale [27], a self-report assessment of symptoms of major depressive disorder in children aged 8-18 years. The low mood subscale includes 10 items and children respond using a 4-point Likert scale from 0=never to 3=always. Total scores range from 0 to 30 with higher scores indicative of lower mood.

Rumination

The rumination subscale from the Child Response Style Questionnaire [28] will be used to capture repetitive negative thinking or rumination. Children respond to 13 items on a 4-point Likert scale from 0=almost never to 3=almost always. Total scores range from 0 to 39 with higher scores representing greater rumination.

Math Anxiety

The Modified Abbreviated Math Anxiety Scale [29] will be used to assess math anxiety. The 9-item self-report measure comprises 2 subscales, math evaluation anxiety (4 items), for example, thinking about a math test the day before you take it, and math learning anxiety (5 items), for example, starting a new topic in math. Children respond to statements asking how anxious they would feel during certain situations involving math using a 5-point Likert scale from 1=low anxiety to 5=high anxiety.

Inhibitory Control

A standard (ie, nonadaptive) Go/No-Go Task [30] will be used to measure inhibitory control. The Go/No-Go Task requires children to view visually presented stimuli and inhibit a dominant response based on instructions, for example, press the spacebar when they see a particular target (go) but do not press the spacebar when they see a different target (no-go). The task captures accuracy and reaction time (RT).

Shifting

The Color Shape-Shifting Task [31] will be used to assess shifting performance. In this task, children are presented with some colored shapes and are required to sort the stimuli by shape or color, as fast as they can. Children are given letter cues; for example, *S* for shape and *C* for color before each stimulus appears to indicate the characteristic to focus on. The task captures accuracy and RT.

Updating

The *n*-back Task [32] will be used to index updating performance. The task requires children to monitor letters presented in blocks of increasing difficulty (ie, *n*) and indicate when presented with a letter seen on the previous trial (1-back), after 1 intervening trial (2-back), or after 2 intervening trials (3-back). Difficulty increases with the number of intervening trials. Children indicate the same or different with a keyboard button press based on the letter 1-, 2-, or 3-back from this letter. The task captures accuracy and RT.

Math Achievement

A total of 3 subscales from the Woodcock-Johnson IV Tests of Achievement [33] will be used to assess math achievement, namely, Applied Problems, Calculation, and Math Fact Fluency. Administration and scoring will be consistent with the authors' manual. To avoid measurement error due to the practice effects, different test forms will be used at each data collection point.

Training Groups

We will randomly assign participants to 1 of the 2 training groups. Groups comprise an experimental CCT group that will train using an adaptive Go/No-Go Task (aGo/No-Go) targeting inhibitory control, and an active control group that will train using a low-load task. The active control task does not require the same cognitive load as the aGO/No-Go task; thus, we do not expect it to produce emotional or cognitive changes. Children in both groups will undertake 10 minutes of training per day for 3 weeks, allowing 15 sessions to be completed.

Inhibitory Control Training

The aGo/No-Go task requires participants to focus on desired cues related to a continuous stream of blended stimuli and press the spacebar when the desired cue appears and withhold a response when it does not appear (as per Go/No-Go). The adaptive nature of the task adjusts to the child's performance such that if the child is doing well, the task reduces the time for responding, whereas if the child is having difficulty the task allows more time for responding, thus positively reinforcing success.

Active Control Training

The low-load task presents children with a continuous stream of blended stimuli and requires them to identify target items.

Equipment and Procedure

All assessments and training will be completed on iPads (9th generation, iOS 16, 64GB; Apple Inc) specific to this project. Self-report symptom scales will be hosted on a computer-based survey platform (Qualtrics) such that the participating children can complete them under the supervision of their classroom teacher, during class time. Inquisit cognitive tasks will be deployed (retrieved from Millisecond Test Library). Math achievement tests will be administered 1:1 in a quiet room by the research team. Daily training of the aGo/No-Go and 1-back will be conducted using a computer-based experiment builder (Gorilla Experiment Builder) and include some minor gamification features to improve motivation and engagement. Training will be completed under the supervision of the classroom teacher.

Data Analytic Plan

Mixed between-within ANOVA will be used with Group (CCT, aGo/No-Go vs active control; low-load task) as the between-subjects factor and time (pre- vs posttraining vs 1- vs 3-month follow-up) as the within-subjects factor. Separate tests will be conducted with the emotional symptom scores, cognitive measures (ie, accuracy and RT), and math achievement scores as dependent variables. Intention-to-treat analyses will be used to account for missing data, as appropriate. Descriptive and inferential statistics will be performed using SPSS (IBM Corp). We will apply Bonferroni corrections to follow-up tests to control for type 1 error.

Results

Recruitment and testing opened in September 2023 and will continue for 12 months. We will begin analyzing our data on the completion of the data collection, and the publication of results is expected by the end of 2024.

Discussion

This study will examine the effect of inhibitory control training on anxiety and math achievement in children aged 8-10 years, relative to an active control condition. We predict children in the CCT group will report reduced emotional symptoms (anxiety, worry, depression, and rumination) and demonstrate improved inhibitory control, shifting, updating, and math achievement when comparing pre- to posttraining, 1-, and 3-month follow-up, relative to controls. Results will inform whether inhibitory control training affords promise as an intervention for anxiety in this age group and advance knowledge of factors affecting math achievement. These findings would provide a foundation for the development of a training app that has the capacity to reach those not well-served, be delivered on large scale for low cost, and afford the possibility of administration across a wide range of settings [4].

This research has several limitations worth noting. We realize using a small sample of children aged 8-10 years means we may not be able to generalize our findings to a larger population or a broader age group. However, pending our results, we aim to replicate our work using a larger cohort and a randomized control design. There are constructs outside the scope of this project. For example, our design will be unable to determine whether inhibitory control training affects other educational outcomes, especially language and reading, which are linked to math achievement. With these potential shortcomings in mind, we hope this work becomes the catalyst for other research using CCT paradigms with children.

Acknowledgments

We thank all participants for their valuable contribution. This study is funded by a Spencer Foundation Research Grants on Education: Small (2023-2024).

Data Availability

Data generated during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

EE and KLC conceptualized the project with the involvement of AC. KLC prepared the first draft and EE read and edited further versions. All authors participated in writing and reading drafts and approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer reviews.
[PDF File (Adobe PDF File), 55 KB - resprot_v13i1e52929_app1.pdf]

References

1. Racine N, McArthur BA, Cooke JE, Eirich R, Zhu J, Madigan S. Global prevalence of depressive and anxiety symptoms in children and adolescents during COVID-19: a meta-analysis. JAMA Pediatr 2021;175(11):1142-1150 [FREE Full text] [doi: 10.1001/jamapediatrics.2021.2482] [Medline: 34369987]
2. Knopf A. During and after COVID‐19, anxiety and depression will increase: study. Child Adolesc Behav 2020;36(9):6-7. [doi: 10.1002/cbl.30488]
3. Campbell MA. Anxiety in early childhood. Educ Young Child 2006;12(2):31-33 [FREE Full text]
4. Kazdin AE. Addressing the treatment gap: a key challenge for extending evidence-based psychosocial interventions. Behav Res Ther 2017;88:7-18. [doi: 10.1016/j.brat.2016.06.004] [Medline: 28110678]
5. Cohen JD. Cognitive control: core constructs and current considerations. In: Egner T, editor. The Wiley Handbook of Cognitive Control. Chichester, UK: Wiley Blackwell; 2017:18-28.
6. Eysenck MW, Derakshan N, Santos R, Calvo MG. Anxiety and cognitive performance: attentional control theory. Emotion 2007;7(2):336-353. [doi: 10.1037/1528-3542.7.2.336] [Medline: 17516812]
7. Miyake A, Friedman NP, Emerson MJ, Witzki AH, Howerter A, Wager TD. The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: a latent variable analysis. Cogn Psychol 2000;41(1):49-100. [doi: 10.1006/cogp.1999.0734] [Medline: 10945922]

8. Van den Bergh N, Vermeersch S, Hoorelbeke K, Vervaeke J, De Raedt R, Koster EHW. Cognitive control training as an augmentation strategy to CBT in the treatment of fear of failure in undergraduates. Cogn Ther Res 2020;44(6):1199-1212. [doi: 10.1007/s10608-020-10129-w]
9. Koster EHW, Hoorelbeke K, Onraedt T, Owens M, Derakshan N. Cognitive control interventions for depression: a systematic review of findings from training studies. Clin Psychol Rev 2017;53:79-92. [doi: 10.1016/j.cpr.2017.02.002] [Medline: 28273486]
10. Cohen N, Mor N, Henik A. Linking executive control and emotional response: a training procedure to reduce rumination. Clin Psychol Sci 2014;3(1):15-25. [doi: 10.1177/2167702614530114]
11. Schroder E, Dubuson M, Dousset C, Mortier E, Kornreich C, Campanella S. Training inhibitory control induced robust neural changes when behavior is affected: a follow-up study using cognitive event-related potentials. Clin EEG Neurosci 2020;51(5):303-316. [doi: 10.1177/1550059419895146] [Medline: 31858835]
12. Course-Choi J, Saville H, Derakshan N. The effects of adaptive working memory training and mindfulness meditation training on processing efficiency and worry in high worriers. Behav Res Ther 2017;89:1-13 [FREE Full text] [doi: 10.1016/j.brat.2016.11.002] [Medline: 27838273]
13. Schweizer S, Samimi Z, Hasani J, Moradi A, Mirdoraghi F, Khaleghi M. Improving cognitive control in adolescents with post-traumatic stress disorder (PTSD). Behav Res Ther 2017;93:88-94 [FREE Full text] [doi: 10.1016/j.brat.2017.03.017] [Medline: 28391116]
14. Edwards EJ, Zec D, Campbell M, Hoorelbeke K, Koster EHW, Derakshan N, et al. Cognitive control training for children with anxiety and depression: a systematic review. J Affect Disord 2022;300:158-171. [doi: 10.1016/j.jad.2021.12.108] [Medline: 34983006]
15. Bigorra A, Garolera M, Guijarro S, Hervás A. Long-term far-transfer effects of working memory training in children with ADHD: a randomized controlled trial. Eur Child Adolesc Psychiatry 2016;25(8):853-867. [doi: 10.1007/s00787-015-0804-3] [Medline: 26669692]
16. Shanok NA, Meltzer K, Frank C, Lugo V, Jones NA. Computerized inhibitory control training reduces anxiety in preadolescent students. Appl Neuropsychol Child 2022;11(3):455-470. [doi: 10.1080/21622965.2021.1884984] [Medline: 33605177]
17. Bull R, Lee K. Executive functioning and mathematics achievement. Child Dev Perspectives 2014;8(1):36-41. [doi: 10.1111/cdep.12059]
18. Kolkman ME, Hoijtink HJ, Kroesbergen EH, Leseman PP. The role of executive functions in numerical magnitude skills. Learn Individ Differ 2013;24:145-151. [doi: 10.1016/j.lindif.2013.01.004]
19. Clark CAC, Pritchard VE, Woodward LJ. Preschool executive functioning abilities predict early mathematics achievement. Dev Psychol 2010;46(5):1176-1191. [doi: 10.1037/a0019672] [Medline: 20822231]
20. Gilmore C, Attridge N, Clayton S, Cragg L, Johnson S, Marlow N, et al. Individual differences in inhibitory control, not non-verbal number acuity, correlate with mathematics achievement. PLoS One 2013;8(6):e67374 [FREE Full text] [doi: 10.1371/journal.pone.0067374] [Medline: 23785521]
21. McClelland MM, Cameron CE, Duncan R, Bowles RP, Acock AC, Miao A, et al. Predictors of early growth in academic achievement: the head-toes-knees-shoulders task. Front Psychol 2014;5:599 [FREE Full text] [doi: 10.3389/fpsyg.2014.00599] [Medline: 25071619]
22. Boschloo A, Krabbendam L, Aben A, de Groot R, Jolles J. Sorting test, tower test, and BRIEF-SR do not predict school performance of healthy adolescents in preuniversity education. Front Psychol 2014;5:287 [FREE Full text] [doi: 10.3389/fpsyg.2014.00287] [Medline: 24782794]
23. Beloe P, Derakshan N. Adaptive working memory training can reduce anxiety and depression vulnerability in adolescents. Dev Sci 2020;23(4):e12831. [doi: 10.1111/desc.12831] [Medline: 30927316]
24. Faul F, Erdfelder E, Buchner A, Lang AG. Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. Behav Res Methods 2009 Nov;41(4):1149-1160. [doi: 10.3758/BRM.41.4.1149] [Medline: 19897823]
25. Spence SH. A measure of anxiety symptoms among children. Behav Res Ther 1998;36(5):545-566. [doi: 10.1016/s0005-7967(98)00034-5] [Medline: 9648330]
26. Chorpita BF, Tracey SA, Brown TA, Collica TJ, Barlow DH. Assessment of worry in children and adolescents: an adaptation of the Penn State Worry Questionnaire. Behav Res Ther 1997;35(6):569-581 [FREE Full text] [doi: 10.1016/s0005-7967(96)00116-7] [Medline: 9159982]
27. Chorpita BF, Yim L, Moffitt C, Umemoto LA, Francis SE. Assessment of symptoms of DSM-IV anxiety and depression in children: a revised child anxiety and depression scale. Behav Res Ther 2000;38(8):835-855. [doi: 10.1016/s0005-7967(99)00130-8] [Medline: 10937431]
28. Abela JRZ, Aydin CM, Auerbach RP. Responses to depression in children: reconceptualizing the relation among response styles. J Abnorm Child Psychol 2007;35(6):913-927. [doi: 10.1007/s10802-007-9143-2] [Medline: 17549619]
29. Carey E, Hill F, Devine A, Szűcs D. The modified abbreviated math anxiety scale: a valid and reliable instrument for use with children. Front Psychol 2017;8:11 [FREE Full text] [doi: 10.3389/fpsyg.2017.00011] [Medline: 28154542]

30. Casey BJ, Trainor RJ, Orendi JL, Schubert AB, Nystrom LE, Giedd JN, et al. A developmental functional MRI study of prefrontal activation during performance of a Go-No-Go task. J Cogn Neurosci 1997;9(6):835-847. [doi: 10.1162/jocn.1997.9.6.835] [Medline: 23964603]
31. Miyake A, Emerson MJ, Padilla F, Ahn JC. Inner speech as a retrieval aid for task goals: the effects of cue type and articulatory suppression in the random task cuing paradigm. Acta Psychol (Amst) 2004;115(2-3):123-142. [doi: 10.1016/j.actpsy.2003.12.004] [Medline: 14962397]
32. Jaeggi SM, Buschkuehl M, Perrig WJ, Meier B. The concurrent validity of the N-back task as a working memory measure. Memory 2010;18(4):394-412. [doi: 10.1080/09658211003702171] [Medline: 20408039]
33. Schrank FA, McGrew KS, Mather N, Wendling BJ, LaForte EM. Woodcock-Johnson IV Tests of Achievement. Rolling Meadows, IL: Riverside Publishing Company; 2014.

Abbreviations

ADHD: attention-deficit/hyperactivity disorder
aGo/No-Go: adaptive Go/No-Go
CCT: cognitive control training
RT: reaction time

Edited by A Mavragani; submitted 19.09.23; this is a non–peer-reviewed article;accepted 25.01.24; published 13.03.24.

Please cite as:
Edwards E, Chu KL, Carroll A
Inhibitory Control Training for Anxiety and Math Achievement in Primary School Children: Protocol for a Proof-of-Concept Study
JMIR Res Protoc 2024;13:e52929
URL: https://www.researchprotocols.org/2024/1/e52929
doi:10.2196/52929
PMID:38477976

Protocol

The Effectiveness of Brain Injury Family Intervention in Improving the Psychological Well-Being of Caregivers of Patients With Traumatic Brain Injury: Protocol for a Randomized Controlled Trial

Siti Aminah Omar[1,2*], MClinPsych; Nor Sheereen Zulkefly[2*], PhD; Firdaus Mukhtar[2*], PhD

[1]Department of Psychiatry, Faculty of Medicine, Universiti Teknologi MARA, Sungai Buloh, Malaysia

[2]Department of Psychiatry, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang, Malaysia

[*]all authors contributed equally

Corresponding Author:
Firdaus Mukhtar, PhD
Department of Psychiatry
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
Jalan Universiti 1
Serdang, 43400
Malaysia
Phone: 60 397692541
Email: drfirdaus@upm.edu.my

Abstract

Background: Globally, traumatic brain injury (TBI) is recognized as one of the most significant contributors to mortality and disability. Most of the patients who have experienced TBI will be discharged home and reunited with their families or primary caregivers. The degree of severity of their reliance on caregivers varies. Therefore, the task of delivering essential care to the patients becomes demanding for the caregivers. A significant proportion of caregivers expressed considerable burden, distress, and discontentment with their lives. Therefore, it is critical to comprehend the dynamic of TBI and caregivers to optimize patient care, rehabilitation, and administration. The effectiveness of the Brain Injury Family Intervention (BIFI) program tailored for caregivers of patients with TBI has been widely proven in Western countries. However, the impact is less clear among caregivers of patients with TBI in Malaysia.

Objective: This study aims to assess the effectiveness of BIFI in reducing emotional distress and burden of care, fulfilling the needs, and increasing the life satisfaction of caregivers of patients with TBI at government hospitals in Malaysia.

Methods: This is a 2-arm, single-blinded, randomized controlled trial. It will be conducted at Hospital Rehabilitasi Cheras and Hospital Sungai Buloh. In total, 100 caregivers of patients with TBI attending the neurorehabilitation unit will be randomized equally to the intervention and control groups. The intervention group will undergo the BIFI program, whereas the control group will receive standard treatment. Caregivers aged ≥18 years, caring for patients who have completed >3 months after the injury, are eligible to participate. The BIFI program will be scheduled for 5 sessions as recommended by the developer of the module. Each session will take approximately 90 to 120 minutes. The participants are required to attend all 5 sessions. A total of 5 weeks is needed for each group to complete the program. Self-reported questionnaires (ie, Beck Depression Inventory, Positive and Negative Affect Schedule, Caregiver Strain Index, Satisfaction With Life Scale, and Family Needs Questionnaire) will be collected at baseline, immediately after the intervention program, at 3-month follow-up, and at 6-month follow-up. The primary end point is the caregivers' emotional distress.

Results: The participant recruitment process began in January 2019 and was completed in December 2020. In total, 100 participants were enrolled in this study, of whom 70 (70%) caregivers are women and 30 (30%) are men. We are currently at the final stage of data analysis. The results of this study are expected to be published in 2024. Ethics approval has been obtained.

Conclusions: It is expected that the psychological well-being of the intervention group will be better compared with that of the control group after the intervention at 3-month follow-up and at 6-month follow-up.

Trial Registration: Iranian Registry of Clinical Trials IRCT20180809040746N1; https://irct.behdasht.gov.ir/trial/33286

International Registered Report Identifier (IRRID): RR1-10.2196/53692

(JMIR Res Protoc 2024;13:e53692) doi:10.2196/53692

KEYWORDS

traumatic brain injury; TBI; caregiver; randomized controlled trial; psychological well-being; Malaysia

Introduction

Background and Rationale

Traumatic brain injury (TBI) is defined as any injury sustained by the head as a result of blunt or penetrating trauma, acceleration or deceleration forces [1]. It remains as a leading cause of mortality and morbidity worldwide [2]. In Malaysia, despite investment in various preventive efforts, the incidence of TBI continues to increase yearly [3]. In 2009, as many as 166,768 trauma cases were recorded in 8 hospitals in Malaysia, most cases (76.8%) being road traffic accidents [4]. A recent study reported an extremely high cost of treatment for patients with TBI in Malaysia. The estimated annual cost of treatment for 49 patients with TBI was as high as MYR 1.5 million (US $313840) [5]. In the long term, this would lead to an adverse impact on the social and economic development of the country.

The effects of TBI depend largely on the severity and location of the injury and the age and personality of the patient [1]. TBI will affect their self-care ability, employment capacity, and social functioning. Upon discharge from hospitals, most patients with moderate to severe levels of TBI would need to move back in with their families to receive the care they need [6,7]. Patients with severe TBI are unlikely to return to their previous employment as they require a significant amount of care [8]. As most of the patients with TBI are highly dependent, their caregivers are tasked with providing the necessary physical care for them. The caregivers are also constantly involved in any ongoing rehabilitation of the patients, for example, encouraging them to perform physiotherapy exercises and reminding them to take medication. Moreover, the caregivers need to deal with difficult behaviors and challenging emotional states of patients with TBI [9-12]. These extra demands can be unfavorable to the health and well-being of the caregivers.

Many studies have highlighted the importance of understanding the dynamics of TBI on caregivers. There is an extensive body of research on the effect of TBI on caregivers globally [13-22]. However, local data are scarce, as only a few studies have been conducted to assess the effects of TBI on Malaysian caregivers [23-25]. The available studies have found that most TBI caregivers in Malaysia reported high burden and poor life satisfaction as a result of caregiving activities [25]. Similarly, there is also a lack of information regarding the needs of caregivers of patients with TBI in developing countries. It was suggested that caregivers of patients with TBI should be provided a postdischarge rehabilitation program to reduce their burden as caregivers [25]. A systematic review has suggested that caregivers of patients with TBI should be prioritized in TBI rehabilitation [26], as evidence abounds on the benefits of intervention programs tailored for caregivers toward patients with TBI [27-30].

In Malaysia, there is a lack of specific or structured intervention programs focusing on the psychological well-being of caregivers of patients with TBI. Identifying caregivers at an increased risk of burden is important for preventing emotional distress and caregiver burden to improve care for both patients and caregivers. Therefore, it is important to design a proper intervention plan to improve the quality of life of caregivers of patients with TBI. Ultimately, this will result in better care and management of patients with TBI.

Conceptual Framework

This study is based on 2 major theories, namely, the Family System Theory (FST) and Cognitive Behavior Therapy (CBT) [31].

The first theory, FST, assumes that the whole family is interconnected to one another [32]. For instance, if a family member is affected by TBI, the whole family system will also be affected [31]. Patients with TBI would most likely depend on their family members for activities of daily living, routine follow-up, rehabilitation, and financial support. This would increase the burden on the caregivers. Family members would also need to look for coping resources to overcome their problems [13,33,34]. As a result of the sudden changes in the family's functioning, family members often reported a lack of coping skills, in addition to high levels of burden, anxiety, and emotional distress [17,33,35-40], thus resulting in a decrease in psychological well-being [19,41-43]. Therefore, Brain Injury Family Intervention (BIFI) incorporates family therapy techniques such as normalization and validation to assist patients with TBI and their families.

The second theory, CBT, is widely known for its use in treating various types of psychological disorders [44]. Several studies have applied CBT to provide psychological interventions to patients with TBI and their caregivers [28,45-50]. A systematic review revealed that CBT has a significant impact on improving the psychological well-being of TBI caregivers [32,45]. CBT would equip caregivers of patients with TBI with strategies to deal with psychological problems such as depression and anxiety [44]. A specific component of CBT would also be implemented in BIFI that covers important aspects such as psychoeducation, problem-solving skills, management of emotions, setting of realistic goals and expectations, and stress management.

Aims of This Study

This study aims to assess the effectiveness of BIFI in reducing emotional distress and burden of care, besides fulfilling the needs and increasing the life satisfaction of caregivers of patients with TBI in selected hospitals.

The hypotheses of this study are as follows:

1. There is a significant association between the sociodemographic and clinical characteristics of patients with TBI and the emotional distress, burden of care, needs, and life satisfaction of caregivers of patients with TBI.

2. There is a significant difference in the mean scores of caregivers' emotional distress, burden of care, needs, and life satisfaction between the intervention and control groups before the intervention, after the intervention, at 3-month follow-up, and at 6-month follow-up.
3. The sociodemographic and clinical characteristics of the patients are predictors of the intervention outcomes.

Methods

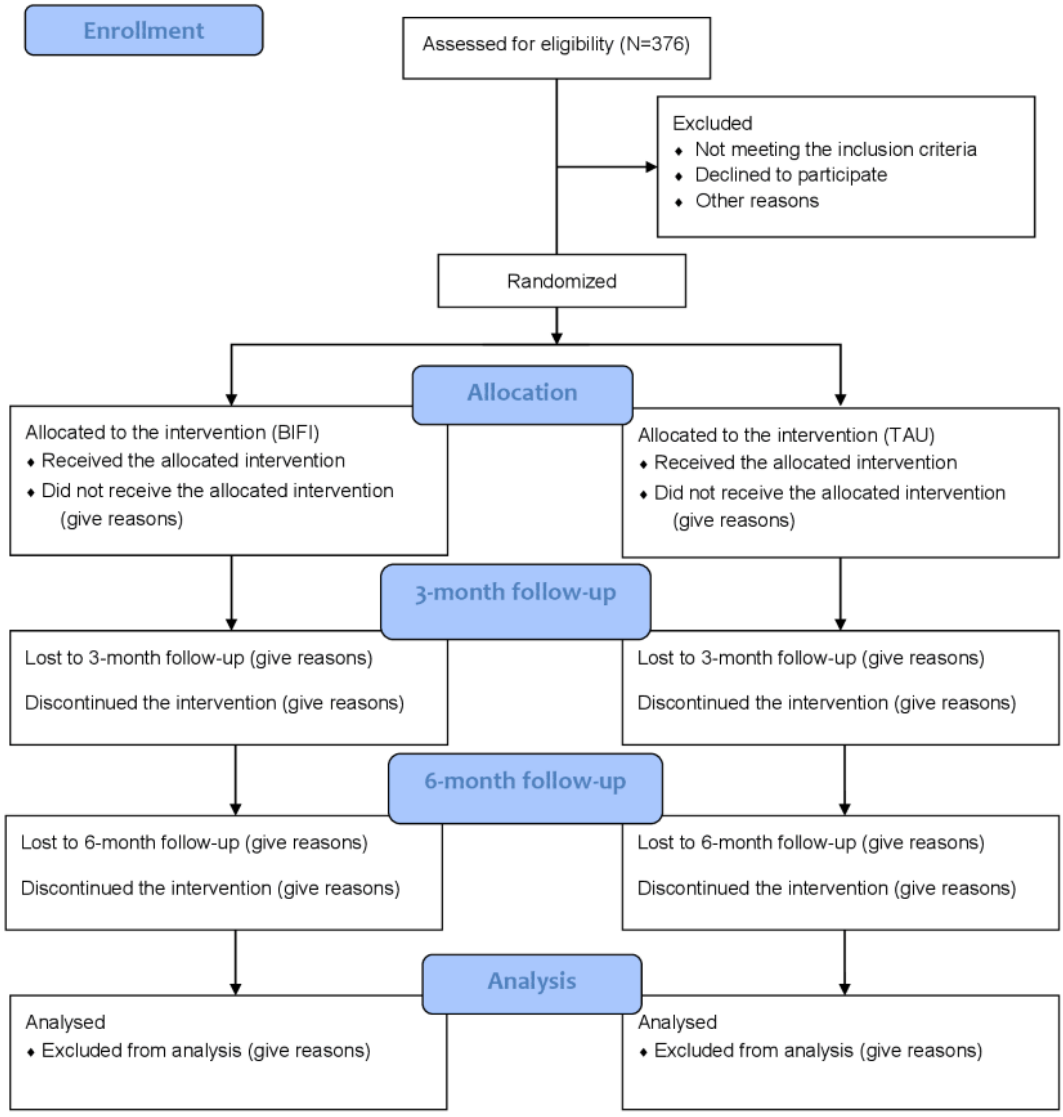
Study Design

This is a 2-arm, single-blinded, randomized controlled trial (RCT). All participants will be randomly assigned to the intervention group or control group. Only the investigators will be aware of the treatment allocation.

Study Setting

This study will be conducted at Hospital Rehabilitasi Cheras (HRC) and Hospital Sungai Buloh (HSB). These hospitals are the main referral hospitals for patients with TBI. A specific room in each site will be used for data collection. Figure 1 outlines the study flow according to CONSORT (Consolidated Standards of Reporting Trials) 2010.

Figure 1. Research flowchart. BIFI: Brain Injury Family Intervention; TAU: treatment as usual.



Participants

A total of 100 participants were recruited for this study. Of the 100 participants, 50 (50%) were randomly assigned to the intervention and control groups, respectively. All caregivers of patients with TBI who attend follow-up with patients with TBI at the Neuro Rehabilitation outpatient clinic of HRC and HSB were screened for eligibility to participate in this study.

Inclusion and Exclusion Criteria

To be eligible, caregivers of patients with TBI must be citizens or permanent residents of Malaysia and be aged ≥18 years, regardless of their race, ethnicity, and sex. The participants must be able to read or write in Bahasa Malaysia or English. The caregivers can be the parents, spouses, siblings, sons or daughters, or relatives of the patients with TBI. Only 1 caregiver per patient with TBI can be recruited for the program. Time

since injury for the patient with TBI must be >3 months and time spent on caring for the patients must be at least 2 hours per day. All types of injury severity were included. However, paid caregivers were excluded.

Withdrawal Criteria

The participants may choose to withdraw at any point of time without any penalty. The participants may be withdrawn if the investigator believes that it is harmful or risky for the participants to continue.

Sample Size Estimation

Sample size estimation is based on the formula for clinical superiority trial [51]:

$$N=2x\ (Z_{1-\alpha} + Z_{1-\beta})^2 \times S^2 / (\delta-\delta_0).$$

The sample size is calculated with 80% power ($Z_{1-\beta}$=0.845) at a significance level (α) of .05, with 95% CI ($Z_{1-\alpha}$=1.96), 25% dropout rate, and medium size effect of 0.60. The parameters used in the formula will be based on a previous study [45], including δ^2=9.355 (pooled SD) and depression (Beck Depression Inventory [BDI] score) $\delta-\delta_0$=5.86 (mean difference). According to the calculation, a total of 50 participants per arm will be needed for this study.

The parameter used to compute the prevalence of caregivers of patients with TBI was taken from the paper titled "Life satisfaction and strain among informal caregivers of patients with traumatic brain injury in Malaysia" [25].

Sample Size Calculation for Prevalence Studies

In this formula, n=sample size, z=z statistic for the level of confidence, P=expected prevalence, and d^2=allowable error. This formula assumes that P and d^2 are decimal values but would also hold true if they are percentages, except that the term, 1–P, in the numerator would become 100–P [52]:

$$N=Z^2P\ (1–P) / d^2$$

Percentage of caregiver's burden=57.4%, level of significance=5%, power=80%, and d=0.05:

$$N=(1.96)^2\ 0.574\ (1 – 0.574) / 0.05^2$$

$$N=376$$

This study aimed to assess eligibility for at least 376 caregivers of patients with TBI.

Allocation

Allocation Sequence Generation

Methods of random allocation are used to ensure that all study participants have the same chance of allocation to the treatment or control group. Caregivers of patients with TBI who are eligible and consent to participate will be number coded before randomization. A simple random sampling method using computer-generated random sampling will be used to assign participants to the intervention group or control group. The procedure would be performed by following the 1:1 allocation format. Randomization will be performed by the principal investigator. All participants will have equal chance of being assigned to the intervention or control group.

Contamination Bias

To minimize contamination bias, the intervention program will be conducted outside their follow-up clinic time. The intervention program will be conducted at the seminar room of the designated hospitals. Participants are strongly encouraged not to disclose the program materials or discuss them with other caregivers of patients with TBI outside the program.

Blinding

The method of blinding in RCT is used to ensure that there are no differences in the way in which each group is assessed or managed and therefore minimize bias. In this study, only the principal investigator is aware of the treatment allocated to the participants.

Statistical Analysis

Data analysis will be performed using SPSS software (version 24.0; IBM Corp). Descriptive statistics will be used to describe the characteristics of participants. Continuous data will be reported as means and SDs or as medians and IQRs. Categorical data will be reported as percentages and frequencies. The comparison of the means between the 2 groups will be performed using a paired samples 2-tailed *t* test. In addition, 1-way ANOVA and repeated measure ANOVA will be conducted to identify any significant differences in mean scores of emotional distress (BDI), caregiver's needs (Family Needs Questionnaire [FNQ]), burden of care (Caregiver Strain Index [CSI]), and life satisfaction (Satisfaction With Life Scale [SWLS]) before the intervention, after the intervention, at 3-month follow-up, and at 6-month follow-up between the intervention and control groups. Multivariate regression analysis will be used to determine the predictors of intervention outcomes.

The intention-to-treat analysis will be performed accordingly. Assumptions of normality and homogeneity of variance will be conducted and adjusted where necessary.

Program Assessment and Translation

The BIFI manual has undergone several stages of thorough forward and backward translation, content review, and revision by a panel of local experts. The expert panel included 2 clinical psychologists, 1 certified translator (psychology content translator), and 2 rehabilitation physicians. All the panels had experience with working in the related fields for >5 years.

On the basis of the experts' feedback and comments, a few changes were made to the module. The first change was the use of a more simple Malay language. The second change was related to the pictures used in the material. The experts suggested changing to universal pictures, so that they can be adapted locally.

The final product of the manual was revised to match the local population and to ensure the intervention's fidelity.

Pilot Study

A pilot study was conducted to assess the feasibility of the BIFI program among caregivers of patients with TBI in Malaysia. In total, 10 caregivers of patients with TBI participated, and only 8 (80%) managed to complete all 5 sessions. A caregiver withdrew owing to work commitments and another withdrew owing to personal issues. Challenges included (1) punctuality of the participants, (2) duration of the sessions, and (3) homework material.

Overall, participants were satisfied with the content and delivery of the program. Some suggested to increase the duration of the sessions and to reduce the amount of homework given. All feedback was taken into consideration, and slight alterations were performed to accommodate the participants and the program.

Intervention

BIFI will be the main intervention tool. It is a structured intervention module specifically for patients with TBI and their caregivers, developed by Professor Dr Jeffry Kreutzer and colleagues from Virginia Commonwealth University, United States. This module is based on CBT [44] and FST [53].

This module consists of several objectives: (1) providing patients and caregivers with fundamental information about brain injury, (2) helping caregivers to better understand the effects of brain injury, (3) teaching patients and caregivers about problem-solving skills, (4) teaching coping strategies, (5) recognizing progress and personal strengths and helping them to access community and professional resources, and (6) teaching effective communication skills.

BIFI was designed to be implemented in 5 sessions, with 90 to 120 minutes for each session. In total, 2 or 3 topics will be covered in each session. Using a standardized and family-focused intervention, BIFI was found to be beneficial for caregivers of patients with TBI both immediately and at 3 months after the intervention [31,54,55]. Furthermore, another study also showed that patients with TBI and caregivers reported high ratings of helpfulness, goal attainment, and satisfaction regarding the BIFI program [55].

Several measures will be taken to ensure that all participants comply with the intervention program. The program would also be conducted during weekends to accommodate the schedule of caregivers of patients with TBI. They are also allowed to choose any day during weekends at their convenience. However, they are required to complete all 5 sessions within the stipulated time frame.

Control Group

The control group or treatment-as-usual group will not receive any additional treatment during the study period. Participants in the control group will receive the usual treatment at their respective hospitals. According to the Malaysian Clinical Practice Guidelines for early management of head injury, all patients who have been discharged are recommended to attend follow-up sessions at the hospital [56]. It is recommended that patients with moderate and severe head injuries are scheduled for routine clinic follow-up. However, patients with a mild head injury can be followed up via clinic visits or telephone calls. Apart from the routine follow-up, other programs tailored for patients with TBI and their caregivers are also considered as treatment as usual in this RCT. For example, the Acquired Brain Injury Rehabilitation Unit in HRC would offer a program known as “Return to Work” for suitable patients and caregivers. A similar program is also available in HSB.

Outcomes

Overview

The outcomes of this study will be assessed using self-report questionnaires at four periods: (1) baseline, (2) 5 weeks (after the treatment), (3) 3-month follow-up, and (4) 6-month follow-up. The schedule of enrollment, interventions, and assessments are presented in Table 1.

Table 1. Schedule of enrollment, interventions, and assessments.

	Study period					
	Enrollment	Allocation	After allocation		Follow-up	
Time point	$-t_1$	0	Baseline t_1	5-week intervention t_2	3 months t_3	6 months t_4
Enrollment						
Eligibility screen	✓					
Informed consent	✓					
Randomization	✓					
Allocation		✓				
Interventions						
BIFI[a] and TAU[b]						
TAU only						
Assessments						
Sociodemographic data		✓				
BDI[c]			✓	✓	✓	✓
PANAS[d]			✓	✓	✓	✓
CSI[e]			✓	✓	✓	✓
FNQ[f]			✓	✓	✓	✓

[a]BIFI: Brain Injury Family Intervention.

[b]TAU: treatment as usual.

[c]BDI: Beck Depression Inventory.

[d]PANAS: Positive and Negative Affect Schedule.

[e]CSI: Caregiver Strain Index.

[f]FNQ: Family Needs Questionnaire.

Primary Outcomes

The primary outcome for this study is the TBI caregiver's emotional distress, which will be measured using two scales: (1) BDI and (2) Positive and Negative Affect Schedule (PANAS). The measures are described in the Methods section.

Secondary Outcomes

The secondary outcomes will include (1) burden (CSI), (2) life satisfaction (SWLS), and (3) caregiver's needs (FNQ). The measures are described in the Methods section.

Data Collection and Time Frame

Recruitment for potential participants was conducted by the rehabilitation physicians at both hospitals, who are also the coinvestigators of the study. They screened for potential participants among the caregivers of patients with TBI who attend regular rehabilitation therapy and follow-up at their clinics. These caregivers were then invited to participate in this study. If the caregiver was interested in learning more about the study, they were led to another room, where the investigator explained the study in great detail and answered any questions that the caregivers had. At this stage, a patient information sheet about the nature of the study was provided to the potential participants.

The investigator then left the room for 10 to 15 minutes to allow the caregiver to read the information and to think about whether they would like to participate in the study. If they expressed interest in participating, they were asked to sign the consent form before completing the questionnaire. The same questionnaire used at baseline will be distributed immediately after the intervention, at 3-month follow-up, and at 6-month follow-up. The questionnaire will take approximately 30 to 40 minutes to complete. Data collection was performed between December 2018 and December 2020.

Measures

BDI Questionnaire

The original version of BDI is a self-reporting questionnaire consisting of 21 items on a 4-point scale. It is assessed using a Likert scale ranging from 0 (symptom not present) to 3 (symptom very intense). The total score can range from 0 to 63. BDI is used to measure the main symptoms of depression such as mood, pessimism, sense of failure, self-dissatisfaction, guilt, punishment, self-dislike, self-accusation, suicidal ideas, crying, irritability, social withdrawal, indecisiveness, body image change, work difficulty, insomnia, fatigability, loss of appetite, weight loss, somatic preoccupation, and loss of libido [57]. Respondents who scored between 0 and 9 are considered negative for depression. In contrast, those who score >9 are screened positive for depression, whereby a score between 10

and 18 indicates mild to moderate depression, score between 19 and 29 indicates moderate to severe depression, and score between 30 and 63 indicates severe depression (60). The BDI test is widely used globally, and its content, concurrent, and construct validity have been tested. High concurrent validity ratings are detected between BDI and other depression instruments such as the Minnesota Multiphasic Personality Inventory and the Hamilton Depression Scale. Correlation rating of 0.77 was obtained between the inventory and psychiatric ratings. BDI also showed high construct validity with the medical symptoms it measures. The study by Beck and Steer [58] reported a coefficient α rating of 0.92 for patients at outpatient clinics and 0.93 for college students. BDI has been translated into the Malay language and validated for use among the Malaysian population. Internal consistency (Cronbach α) ranged from 0.71 to 0.91, and the validity of BDI-Malay was deemed as satisfactory [59].

PANAS Questionnaire

PANAS comprises 2 mood scales that measure the positive affect (PA) and negative affect (NA), respectively. PANAS is used to assess the relationship between positive and negative effects on personality traits. Each of the PA and NA scales consists of 10 items that define their meanings. Respondents need to answer 20 items on a 5-point scale that ranges from 1 (very slightly or not at all) to 5 (extremely). The total score generated will range between 10 and 50, with low scores indicating low (positive or negative) affect and high scores indicating high (positive or negative) affect. The reliability and validity of PANAS were moderately good [60]. For the PA scale, the Cronbach α coefficient was between 0.86 and 0.90, and for the NA scale, it was between 0.84 and 0.87. Over 8 weeks, the test-retest correlations were between 0.47 and 0.68 for PA and between 0.39 and 0.71 for NA. PANAS also had strong validity with other measures of general distress and dysfunction, depression, and anxiety [61]. The Malay-translated version of PANAS had Cronbach α coefficient of 0.73 [62].

CSI Questionnaire

CSI is a self-rated, 13-item questionnaire that measures strain related to care provision. It consists of 5 major domains related to employment, financial, social, time, and physical aspects. The items can be answered as yes (score=1) or no (score=0). The maximum score for the questionnaire is 13. A score >7 is categorized as “having strain,” whereas a score <7 is defined as “no strain.” There is no age limit for the individuals who could be assessed with the tool**.** CSI has been translated into the Malay language, and the Cronbach α coefficient for the 13-item CSI-Malay was 0.79, indicating good internal consistency reliability of the scale [63].

SWLS Questionnaire

SWLS evaluates the respondents’ agreement with 5 statements on overall satisfaction with life (eg, in most ways, my life is close to my ideal). It uses a 7-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree), giving rise to a range of scores between 5 and 35. A score of 20 is considered the neutral point of the scale. Scores between 5 and 9 indicate that the respondent is extremely dissatisfied with life. In contrast, scores between 31 and 35 show that the respondent is extremely satisfied. SWLS is reported as having excellent internal consistency (Cronbach α=0.88) and good test-retest reliability (r=0.68). SWLS has been translated into the Malay language and validated among the Malaysian population [64,65]. The Malay SWLS has been found to have good internal consistency (Cronbach α=0.83).

FNQ Questionnaire

FNQ is a self-administered questionnaire consisting of 37 items. It was designed to determine the family needs of patients with TBI. The family members will rate the importance of each need on a scale ranging from 1 (not important) to 4 (very important). FNQ is divided into 6 areas, namely, health information, emotional support, instrumental support, professional support, community support network, and involvement with care. It has been proven to have good content and construct validity and good internal consistency Spearman-Brown split-half reliability at 0.75 [66].

Study Procedure

All the screening procedures to identify the participants based on inclusion and exclusion criteria were performed before the intervention program by rehabilitation physicians in the respective hospitals. The recruitment started in November 2018 and was continued until the required sample size was achieved. The BIFI program will be conducted in the Malay or English language depending on the needs of the caregivers. The participants in the intervention group will be divided into smaller groups of 10 people each. Each group will receive a scheduled time and date to attend the program at the hospital. The program will be conducted by the principal investigator, who is also a clinical psychologist. The clinical psychologist must at least have 5 years of experience.

At the baseline of the program (T1), all participants are required to complete the questionnaires (BDI, CSI, PANAS, FNQ, and SWLS). The same questionnaire will be distributed immediately after the intervention program (T2), at 3-month follow-up (T3), and at 6-month follow-up (T4). The average time needed to complete the questionnaire is 30 to 40 minutes. The follow-up sessions (T3 and T4) will be scheduled by the coinvestigators. The session will be conducted at the respective hospitals by the coinvestigators to prevent any bias during follow-up. The participants were also encouraged not to share the intervention materials with other caregivers until data collection is completed.

The intervention group will undergo the BIFI program. The BIFI program will be scheduled for 5 sessions as recommended by the developer of the module. Each session will take approximately 90 to 120 minutes. The participants are required to attend all 5 sessions. A total of 5 weeks is needed for each group to complete the program, and 2 groups will be scheduled every week. All the sessions will start with an overview of the topic and end with the summary and homework assignments. Participants will be required to complete the homework given according to the module. This homework will then be reviewed by the principal investigator in the subsequent session.

For the control group that receives the usual standard treatment, the caregivers will need to complete the questionnaires at similar time points as the intervention group.

Patient Involvement

Patients were involved during the early stage of cultural adaptation of the intervention program. The patients were invited to give their comments and feedback and review all the materials. Their valuable feedback was taken into account to ensure this program is suitable to the current culture and population.

Ethical Considerations

Approval

This study has been reviewed by the Medical Research and Ethics Committee Malaysia, Ministry of Health Malaysia (NMRR 18-2253-42951). Ethics approval has been obtained from the National Medical Research Register (NMRR-18-2253-42951-IIR) for the study to be conducted at the Ministry of Health settings. Please refer to Multimedia Appendices 1 and 2 for further details of Research Ethics comments and review. The approval letter was received on December 19, 2018. The recruitment period started in December 2018 and was completed on December 18, 2020.

Compensation

All the participants in the intervention group will be given incentives for attending the intervention program and completing the questionnaires. All participants are compensated with a travel token at the baseline (MYR 25), immediately after the program (MYR 25), at 3-month follow-up (MYR 25), and at 6-month follow-up (MYR 25).

Consent

The investigator will explain the potential risks and benefits of involvement to the participants using an information leaflet before they determine whether to participate in the study. They might ask the researcher any questions they may have regarding the study before deciding whether to participate. Once the investigator is confident that they have understood the potential risks and benefits of participating, the participant will be asked to sign a consent form. The consent forms are obtained in the written format during primary data collection and secondary data analysis is allowed to proceed without additional informed consent.

Data Management

Consent forms and paper copies of the questionnaire will be stored separately in a locked filing cabinet at University Teknologi MARA. After data collection is complete, they will be transferred to a locked filing cabinet. They will be maintained by the principal investigator for 10 years according to university regulations. Data will be accessible to the researchers and anyone authorized by Universiti Teknologi MARA to conduct a research audit.

Electronic copies of the data will be maintained by the principal investigator. These electronic files will not contain any personal identifying information and will not contain the identifying code that links the paper copies of the questionnaires with the consent forms. They will be stored only on password-protected electronic devices. Once the thesis submission and other publications are completed, these files will be destroyed. The files will be accessible to the principal investigator, the research team, and anyone authorized by Universiti Teknologi MARA to conduct a research audit.

No personal identifying details, such as names and contact details, will be recorded on the questionnaire; they will appear only on the consent form. The questionnaires will be linked to the consent forms by a unique code appearing on both documents. No digital record of the personal identifying details will be maintained, and these details will not be included in the data file. The report of the findings will also not include any such details.

Dissemination Plan

The findings of this study will be published in an academic or medical journal, and they will be presented at academic conferences. Only the research team has access to the data. As with any anonymously obtained data, the participants will not be named in any of the study's reports or publications. Permission from the Medical Research and Ethics Commission will be sought before publication.

Results

The participant recruitment process began in January 2019 and was completed in December 2020. A total of 100 participants were enrolled in this study, of whom 70 (70%) caregivers are women and 30 (30%) are men. We are currently at the final stage of data analysis. The result of this study is expected to be published in 2024.

Discussion

Anticipated Findings

In this study, we will be evaluating the effectiveness of BIFI in reducing the emotional distress and burden of care, fulfilling the needs, and increasing the life satisfaction of caregivers of patients with TBI. A total of 100 caregivers were recruited in this study. Most of the caregivers are women (70/100, 70%) and the remaining are men (30/100, 30%). The age range of the caregivers was between 22 and 55 years, with a mean age of 39.85 (SD 8.184) years. Most caregivers were Malay (65/100, 65%), followed by Chinese (21/100, 21%), Indians (12/100, 12%), and other races (2/100, 2%). Initial analysis showed promising result where there was significant reduction in emotional distress among caregivers (intervention group) immediately after the program and at the 3-month follow-up as compared with the control group.

Limitations

This study also has limitations. It was observed that during the implementation of the program, most participants (90/100, 90%) requested the program to be conducted during the weekends, whereas others wanted it to be conducted during the weekdays. This was because some of them needed to arrange for the patient's care if they were to attend the program. Hence, the program was conducted during weekends and weekdays to

accommodate their request. The participants were allowed to choose when they wanted to attend the program. Owing to this issue, the intervention program took a long period to complete.

It is also important to address that data collection was conducted during the COVID-19 pandemic. The intervention program was halted for several months owing to Movement Control Order by the Malaysian Government. Therefore, participants were hesitant to visit the research site owing to fear of contracting COVID-19; the social distancing policy exacerbated this difficulty. It is hoped that future studies might to consider implementing intervention programs over the web to ease the participants. Web-based intervention program is another emerging approach and is more suited to current trends. However, web-based intervention versus physical intervention is still debated, and more studies are needed to answer this question.

Conclusions

To the best of our knowledge, this study would be among the first to use RCT methods to assess the effectiveness of BIFI in improving the psychological functioning of caregivers of patients with TBI in Malaysia. Perhaps, this module could be incorporated into the *Return to Work* program as standard clinical care and be made available to all. It is hoped that the results will provide more knowledge and scientific evidence to improve the rehabilitation services for patients with TBI and their caregivers.

Acknowledgments

This study was supported partially by Universiti Teknologi MARA (grant number 600-IRMI/MyRA 5/3/ LESTARI [036/2017]). The authors acknowledge the contribution of the Ministry of Health Malaysia and Universiti Teknologi MARA for aiding and support throughout the study. The authors also thank Professor Dr Jeffrey S Kreutzer and Dr Emilie Godwin, developers of Brain Injury Family Intervention therapy, Virginia Commonwealth University, Richmond, Virginia, United States, for their assistance.

Data Availability

The data of this study are available upon request from the corresponding author, and it is subject to approval from the Ministry of Health Malaysia and Universiti Teknologi MARA.

Authors' Contributions

SAO is the principal investigator of this study and drafted the manuscript. FM and NSZ contributed to review of the paper and content development. All authors provided written review and feedback and revised and approved the final paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Research ethics comments.
[PDF File (Adobe PDF File), 172 KB - resprot_v13i1e53692_app1.pdf]

Multimedia Appendix 2
Peer-review report by the Medical Research and Ethics Committee Malaysia.
[DOCX File , 51 KB - resprot_v13i1e53692_app2.docx]

References

1. Lezak MD, Howieson DB, Loring DW, Hannay HJ, Fischer JS. Neuropsychological Assessment 4th Edition. Oxford, UK: Oxford University Press; 2004.
2. Arango-Lasprilla JC, Kreutzer J. International perspectives on caregiving. NeuroRehabilitation 2010 Jul 06;27(1):1-3. [doi: 10.3233/nre-2010-0576]
3. Sarani R, Rahim SA, Wong SV, Wong S. Predicting Malaysian road fatalities for year 2020. In: Proceedings of the Road Safety and Simulation International Conference. 2013 Presented at: RSS2013; October 22-25, 2013; Rome, Italy URL: https://www.researchgate.net/publication/283299518_Predicting_Malaysian_Road_Fatalities_for_Year_2020
4. Jamaluddin SF, Wahab MA, Wahab MY, Ming MY, Saiboon IM. National trauma database January 2009 to December 2009– fourth report. National Trauma Database and Clinical Research Centre, Ministry of Health. 2011 Jul. URL: https://www.acrm.org.my/ntrd/report/ntrdReport_2009.pdf [accessed 2024-02-19]
5. You X, Liew BS, Rosman AK, DCSN, Musa KI, Idris Z. The estimated cost of surgically managed isolated traumatic head injury secondary to road traffic accidents. Neurosurg Focus 2018 May;44(5):E7. [doi: 10.3171/2018.1.FOCUS17796] [Medline: 29712526]
6. Kowlakowsky-Hayner KA. Removing barriers to rehabilitation: theory-based family intervention in community settings after brain injury. NeuroRehabilitation 2012 Apr 18;31(1):75-83. [doi: 10.3233/nre-2012-0776]

7. Pierini D, Hoerold D. Back home after an acquired brain injury: building a “low-cost” team to provide theory-driven cognitive rehabilitation after routine interventions. NeuroRehabilitation 2014 Feb 18;34(1):65-80. [doi: 10.3233/nre-131023]
8. Qadeer A, Khalid U, Amin M, Murtaza S, Khaliq MF, Shoaib M. Caregiver's burden of the patients with traumatic brain injury. Cureus 2017 Aug 21;9(8):e1590 [FREE Full text] [doi: 10.7759/cureus.1590] [Medline: 29062622]
9. Lovasik D, Kerr ME, Alexander S. Traumatic brain injury research: a review of clinical studies. Crit Care Nurs Q 2001 Feb;23(4):24-41. [doi: 10.1097/00002727-200102000-00003] [Medline: 11852948]
10. Doser K, Norup A. Family needs in the chronic phase after severe brain injury in Denmark. Brain Inj 2014 Jun 02;28(10):1230-1237. [doi: 10.3109/02699052.2014.915985] [Medline: 24884472]
11. Kreutzer JS, Marwitz JH, Godwin EE, Arango-Lasprilla JC. Practical approaches to effective family intervention after brain injury. J Head Trauma Rehabil 2010;25(2):113-120. [doi: 10.1097/HTR.0b013e3181cf0712] [Medline: 20134331]
12. Arango-Lasprilla JC, Quijano MC, Aponte M, Cuervo MT, Nicholls E, Rogers HL, et al. Family needs in caregivers of individuals with traumatic brain injury from Colombia, South America. Brain Inj 2010;24(7-8):1017-1026 [FREE Full text] [doi: 10.3109/02699052.2010.490516] [Medline: 20545455]
13. Adams D, Dahdah M. Coping and adaptive strategies of traumatic brain injury survivors and primary caregivers. NeuroRehabilitation 2016 Aug 04;39(2):223-237. [doi: 10.3233/nre-161353]
14. Berry JW, Elliott TR, Grant JS, Edwards G, Fine PR. Does problem-solving training for family caregivers benefit their care recipients with severe disabilities? A latent growth model of the Project CLUES randomized clinical trial. Rehabil Psychol 2012 May;57(2):98-112 [FREE Full text] [doi: 10.1037/a0028229] [Medline: 22686549]
15. Elliott CS, Kajankova M, Murray N, Lu W, Kaplan E, Dijkers MP. Empirically-supported programs for caregivers of adults with traumatic brain injury: a systematic review. Arch Phys Med Rehab 2015 Oct;96(10):e117 [FREE Full text] [doi: 10.1016/j.apmr.2015.08.394]
16. Moriarty H, Winter L, Robinson K, Piersol CV, Vause-Earland T, Iacovone DB, et al. A randomized controlled trial to evaluate the veterans' in-home program for military veterans with traumatic brain injury and their families: report on impact for family members. PM R 2016 Jun 26;8(6):495-509. [doi: 10.1016/j.pmrj.2015.10.008] [Medline: 26514790]
17. Calvete E, de Arroyabe EL. Depression and grief in Spanish family caregivers of people with traumatic brain injury: the roles of social support and coping. Brain Inj 2012 May 14;26(6):834-843. [doi: 10.3109/02699052.2012.655363] [Medline: 22583174]
18. Rietdijk R, Togher L, Power E. Supporting family members of people with traumatic brain injury using telehealth: a systematic review. J Rehabil Med 2012 Nov;44(11):913-921 [FREE Full text] [doi: 10.2340/16501977-1058] [Medline: 23027316]
19. Petranovich CL, Wade SL, Taylor HG, Cassedy A, Stancin T, Kirkwood MW, et al. Long-term caregiver mental health outcomes following a predominately online intervention for adolescents with complicated mild to severe traumatic brain injury. J Pediatr Psychol 2015 Aug 13;40(7):680-688 [FREE Full text] [doi: 10.1093/jpepsy/jsv001] [Medline: 25682211]
20. Coy AE, Perrin PB, Stevens LF, Hubbard R, Díaz Sosa DM, Espinosa Jove IG, et al. Moderated mediation path analysis of Mexican traumatic brain injury patient social functioning, family functioning, and caregiver mental health. Arch Phys Med Rehabil 2013 Feb;94(2):362-368 [FREE Full text] [doi: 10.1016/j.apmr.2012.08.210] [Medline: 22940090]
21. Wade SL, Narad ME, Kingery KM, Taylor HG, Stancin T, Kirkwood MW, et al. Teen online problem solving for teens with traumatic brain injury: rationale, methods, and preliminary feasibility of a teen only intervention. Rehabil Psychol 2017 Aug;62(3):290-299 [FREE Full text] [doi: 10.1037/rep0000160] [Medline: 28836809]
22. Samartkit N, Kasemkitvattana S, Thosingha O, Vorapongsathorn T. Caregiver role strain and rewards: caring for Thais with a traumatic brain injury. Pacific Rim Int J Nurs Res 2010;14(4):297-314 [FREE Full text]
23. Syed Hassan ST, Khaw WF, Rosna AR, Husna J. Traumatic brain injury: Caregiversâ€™ problems and needs. J Nepal Med Assoc 2011 Mar 31;51(181). [doi: 10.31729/jnma.50]
24. Syed Hassan ST, Jamaludin H, Abd Raman R, Mohd Riji H, Wan Fei K. Mental trauma experienced by caregivers of patients with diffuse axonal injury or severe traumatic brain injury. Trauma Mon 2013 Sep 11;18(2):56-61 [FREE Full text] [doi: 10.5812/traumamon.11522] [Medline: 24350153]
25. Mazlan M, Ghani SZ, Tan KF, Subramanian P. Life satisfaction and strain among informal caregivers of patients with traumatic brain injury in Malaysia. Disabil Rehabil 2016;38(22):2198-2205 [FREE Full text] [doi: 10.3109/09638288.2015.1123307] [Medline: 26731553]
26. Baker A, Barker S, Sampson A, Martin C. Caregiver outcomes and interventions: a systematic scoping review of the traumatic brain injury and spinal cord injury literature. Clin Rehabil 2017 Jan 10;31(1):45-60. [doi: 10.1177/0269215516639357] [Medline: 27009058]
27. Backhaus S, Neumann D, Parrot D, Hammond FM, Brownson C, Malec J. Examination of an intervention to enhance relationship satisfaction after brain injury: a feasibility study. Brain Inj 2016 May 16;30(8):975-985. [doi: 10.3109/02699052.2016.1147601] [Medline: 27185387]
28. Backhaus SL, Ibarra SL, Klyce D, Trexler LE, Malec JF. Brain injury coping skills group: a preventative intervention for patients with brain injury and their caregivers. Arch Phys Med Rehabil 2010 Jun;91(6):840-848. [doi: 10.1016/j.apmr.2010.03.015] [Medline: 20510972]

29. Carnevale GJ, Anselmi V, Johnston MV, Busichio K, Walsh V. A natural setting behavior management program for persons with acquired brain injury: a randomized controlled trial. Arch Phys Med Rehabil 2006 Oct;87(10):1289-1297. [doi: 10.1016/j.apmr.2006.06.010] [Medline: 17023236]
30. Grill E, Ewert T, Lipp B, Mansmann U, Stucki G. Effectiveness of a community-based 3-year advisory program after acquired brain injury. Eur J Neurol 2007 Nov 19;14(11):1256-1265. [doi: 10.1111/j.1468-1331.2007.01963.x] [Medline: 17956446]
31. Kreutzer JS, Marwitz JH, Sima AP, Godwin EE. Efficacy of the brain injury family intervention: impact on family members. J Head Trauma Rehabil 2015;30(4):249-260. [doi: 10.1097/HTR.0000000000000144] [Medline: 26147315]
32. Kreutzer JS, Stejskal TM, Ketchum JM, Marwitz JH, Taylor LA, Menzel JC. A preliminary investigation of the brain injury family intervention: impact on family members. Brain Inj 2009 Jun 21;23(6):535-547. [doi: 10.1080/02699050902926291] [Medline: 19484627]
33. Klum MA. Coping in caregivers of family members with traumatic brain injury and the effects on the caregivers' quality of life. Massey University. 2012. URL: https://mro.massey.ac.nz/items/08fc9279-fc35-4289-8bdc-e0ffb2695d75 [accessed 2024-02-14]
34. Gan C, Gargaro J, Brandys C, Gerber G, Boschen K. Family caregivers' support needs after brain injury: a synthesis of perspectives from caregivers, programs, and researchers. NeuroRehabilitation 2010 Jul 06;27(1):5-18. [doi: 10.3233/nre-2010-0577]
35. Saban KL, Griffin JM, Urban A, Janusek MA, Pape TL, Collins E. Perceived health, caregiver burden, and quality of life in women partners providing care to veterans with traumatic brain injury. J Rehabil Res Dev 2016;53(6):681-692. [doi: 10.1682/jrrd.2015.07.0143]
36. Ponsford J, Schönberger M. Family functioning and emotional state two and five years after traumatic brain injury. J Int Neuropsychol Soc 2010 Feb 04;16(2):306-317. [doi: 10.1017/s1355617709991342]
37. Tam S, McKay A, Sloan S, Ponsford J. The experience of challenging behaviours following severe TBI: a family perspective. Brain Inj 2015;29(7-8):813-821 [FREE Full text] [doi: 10.3109/02699052.2015.1005134] [Medline: 25914927]
38. Doyle ST, Perrin PB, Díaz Sosa DM, Espinosa Jove IG, Lee GK, Arango-Lasprilla JC. Connecting family needs and TBI caregiver mental health in Mexico City, Mexico. Brain Inj 2013 Aug 19;27(12):1441-1449. [doi: 10.3109/02699052.2013.826505] [Medline: 23957747]
39. Mbakile-Mahlanza L, Manderson L, Downing M, Ponsford J. Family caregiving of individuals with traumatic brain injury in Botswana. Disabil Rehabil 2017 Mar 13;39(6):559-567. [doi: 10.3109/09638288.2016.1152605] [Medline: 26972548]
40. Foster AM, Armstrong J, Buckley A, Sherry J, Young T, Foliaki S, et al. Encouraging family engagement in the rehabilitation process: a rehabilitation provider's development of support strategies for family members of people with traumatic brain injury. Disabil Rehabil 2012 Apr 10;34(22):1855-1862. [doi: 10.3109/09638288.2012.670028] [Medline: 22489631]
41. Godwin E, Chappell B, Kreutzer J. Relationships after TBI: a grounded research study. Brain Inj 2014 Jan 29;28(4):398-413. [doi: 10.3109/02699052.2014.880514] [Medline: 24475746]
42. Saban KL, Hogan NS, Hogan TP, Pape TL. He looks normal but … challenges of family caregivers of veterans diagnosed with a traumatic brain injury. Rehabil Nurs 2015;40(5):277-285. [doi: 10.1002/rnj.182] [Medline: 25424609]
43. Nonterah CW, Jensen BJ, Perrin PB, Stevens LF, Cabrera TV, Jiménez-Maldonado M, et al. The influence of TBI impairments on family caregiver mental health in Mexico. Brain Inj 2013;27(11):1287-1293 [FREE Full text] [doi: 10.3109/02699052.2013.812243] [Medline: 24020441]
44. Beck JS. Cognitive Behavior Therapy: Basics and Beyond Second Edition. New York, NY: Guilford Publications; 2011.
45. Backhaus S, Ibarra S, Parrott D, Malec J. Comparison of a cognitive-behavioral coping skills group to a peer support group in a brain injury population. Arch Phys Med Rehabil 2016 Feb;97(2):281-291. [doi: 10.1016/j.apmr.2015.10.097] [Medline: 26551230]
46. Kreutzer JS, Kolakowsky-Hayner SA, Demm SR, Meade MA. A structured approach to family intervention after brain injury. J Head Trauma Rehabil 2002 Aug;17(4):349-367 [FREE Full text] [doi: 10.1097/00001199-200208000-00008] [Medline: 12106003]
47. Ponsford J, Lee NK, Wong D, McKay A, Haines K, Alway Y, et al. Efficacy of motivational interviewing and cognitive behavioral therapy for anxiety and depression symptoms following traumatic brain injury. Psychol Med 2015 Dec 28;46(5):1079-1090. [doi: 10.1017/s0033291715002640]
48. Malec JF, Van Houtven CH, Tanielian T, Atizado A, Dorn MC. Impact of TBI on caregivers of veterans with TBI: burden and interventions. Brain Inj 2017 Oct 05;31(9):1235-1245 [FREE Full text] [doi: 10.1080/02699052.2016.1274778] [Medline: 28981343]
49. Chun HY, Newman R, Whiteley WN, Dennis M, Mead GE, Carson AJ. A systematic review of anxiety interventions in stroke and acquired brain injury: efficacy and trial design. J Psychosom Res 2018 Jan;104:65-75 [FREE Full text] [doi: 10.1016/j.jpsychores.2017.11.010] [Medline: 29275788]
50. Meixner C, O'Donoghue CR, Hart V. Impact of the Brain Injury Family Intervention (BIFI) training on rehabilitation providers: a mixed methods study. NeuroRehabilitation 2017 Jun 09;40(4):545-552. [doi: 10.3233/nre-171441]
51. Zhong B. How to calculate sample size in randomized controlled trial? J Thorac Dis 2009 Dec;1(1):51-54 [FREE Full text] [Medline: 22263004]

52. Arya R, Antonisamy B, Kumar S. Sample size estimation in prevalence studies. Indian J Pediatr 2012 Nov 6;79(11):1482-1488. [doi: 10.1007/s12098-012-0763-3] [Medline: 22562262]
53. Peters MF, Massey G. Mundane extreme environmental stress in family stress theories: the case of Black families in White America. Marriage Fam Rev 2008 Oct 26;6(1-2):193-218. [doi: 10.1300/j002v06n01_10]
54. Kreutzer JS, Stejskal TM, Godwin EE, Powell VD, Arango-Lasprilla JC. A mixed methods evaluation of the Brain Injury Family Intervention. NeuroRehabilitation 2010 Jul 06;27(1):19-29. [doi: 10.3233/nre-2010-0578]
55. Gan C, Ballantyne M. Brain injury family intervention for adolescents: a solution-focused approach. NeuroRehabilitation 2016 May 04;38(3):231-241. [doi: 10.3233/nre-1601315]
56. Early management of head injury in adults. Malaysia Health Technology Assessment Section (MaHTAS). URL: https://tinyurl.com/27r3ca2c [accessed 2024-02-14]
57. Beck AT, Steer RA, Carbin MG. Psychometric properties of the Beck Depression Inventory: twenty-five years of evaluation. Clin Psychol Rev 1988 Jan;8(1):77-100. [doi: 10.1016/0272-7358(88)90050-5]
58. Beck AT, Steer R. Manual for the Beck Depression Inventory. San Antonio, TX: Psychological Corporation; 1987.
59. Oei TP, Mukhtar F. Exploratory and confirmatory factor validation and psychometric properties of the Automatic Thoughts Questionnaire for Malays (ATQ-Malay) in Malaysia. Hong Kong J Psychiatry 2011 Jan;18(3) [FREE Full text]
60. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. J Pers Soc Psychol 1988 Jun;54(6):1063-1070 [FREE Full text] [doi: 10.1037//0022-3514.54.6.1063] [Medline: 3397865]
61. Juengst SB, Arenth PM, Whyte EM, Skidmore ER. Brief report of affective state and depression status after traumatic brain injury. Rehabil Psychol 2014 May;59(2):242-246 [FREE Full text] [doi: 10.1037/a0036294] [Medline: 24708234]
62. Masdin MB, Rathakrishnan B, Cosmas G. Pengaruh optimistik, kecekapan kendiri umum dan sokongan sosial terhadap kebahagian remaja miskin di Sabah. e BANGI 2016;11(1):45-58 [FREE Full text]
63. Othman Z, Wong TS. Validation of Malay caregiver strain index. East J Med 2014 Sep 01;19(2):102-104. [doi: 10.5281/zenodo.2596359]
64. Swami V, Chamorro-Premuzic T. Psychometric evaluation of the Malay satisfaction with life scale. Soc Indic Res 2008 Jul 16;92(1):25-33. [doi: 10.1007/s11205-008-9295-7]
65. Mustapha M. Subjective well-being among Malaysian students. University of Plymouth. 2016. URL: https://pearl.plymouth.ac.uk/handle/10026.1/5279 [accessed 2024-02-19]
66. Serio CD, Kreutzer JS, Witol AD. Family needs after traumatic brain injury: a factor analytic study of the Family Needs Questionnaire. Brain Inj 1997 Jan 03;11(1):1-9. [doi: 10.1080/026990597123764] [Medline: 9012547]

Abbreviations

BDI: Beck Depression Inventory
BIFI: Brain Injury Family Intervention
CBT: Cognitive Behavior Therapy
CSI: Caregiver Strain Index
CONSORT: Consolidated Standards of Reporting Trials
FNQ: Family Needs Questionnaire
FST: Family System Theory
HRC: Hospital Rehabilitasi Cheras
HSB: Hospital Sungai Buloh
NA: negative affect
PA: positive affect
PANAS: Positive and Negative Affect Schedule
RCT: randomized controlled trial
SWLS: Satisfaction With Life Scale
TBI: traumatic brain injury

Edited by A Mavragani; submitted 16.10.23; this is a non–peer-reviewed article;accepted 07.02.24; published 14.03.24.

Please cite as:
Omar SA, Zulkefly NS, Mukhtar F
The Effectiveness of Brain Injury Family Intervention in Improving the Psychological Well-Being of Caregivers of Patients With Traumatic Brain Injury: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2024;13:e53692
URL: https://www.researchprotocols.org/2024/1/e53692
doi:10.2196/53692
PMID:38483466

Protocol

Testing Biological and Psychological Pathways of Emotion Regulation as a Primary Mechanism of Action in Yoga Interventions for Chronic Low Back Pain: Protocol for a Randomized Controlled Trial

Angela R Starkweather[1], PhD; Wanli Xu[2], PhD; Katherine E Gnall[3], MS; Mariel Emrich[3], BS; Camille L Garnsey[3], BA; Zachary E Magin[3], MS; Weizi Wu[2], BS; Joseph Fetta[1], PhD; Erik J Groessl[4,5], PhD; Crystal Park[3], PhD

[1]Department of Biobehavioral Nursing Science, College of Nursing, University of Florida, Gainesville, FL, United States

[2]School of Nursing, University of Connecticut, Storrs, CT, United States

[3]Department of Psychological Sciences, University of Connecticut, Storrs, CT, United States

[4]Herbert Wertheim School of Public Health & Human Longevity Science, University of California San Diego, San Diego, CA, United States

[5]Veteran's Affairs San Diego Health System, San Diego, CA, United States

Corresponding Author:
Angela R Starkweather, PhD
Department of Biobehavioral Nursing Science
College of Nursing
University of Florida
1225 Center Drive
Gainesville, FL, 32610
United States
Phone: 1 352 263 6321
Fax: 1 352 263 9000
Email: a.starkweather@ufl.edu

Abstract

Background: Interventions that promote adaptive emotion regulation (ER) skills reduce pain in patients with chronic pain; however, whether the effects of yoga practice on chronic low back pain (CLBP) are due to improvements in ER remains to be examined.

Objective: This study will test whether the effects of yoga on CLBP (improved pain severity and interference) are mediated by improved ER, the extent to which effects are related to specific aspects of ER, and the role of pain sensitization as a mediator or moderator of effects. In this study, pain sensitization will be assessed by quantitative sensory testing and gene expression profiles to examine whether pain sensitization moderates yoga's effects on pain or whether yoga and ER abilities reduce pain sensitization, leading to decreased pain severity and interference.

Methods: For this 2-arm parallel group blinded randomized controlled trial, we will enroll 204 adults with CLBP who will be randomized to receive the yoga (n=102) or a control stretching and strengthening (n=102) intervention, which are delivered via web-based synchronous biweekly 75-minute sessions over 12 weeks. Participants are encouraged to practice postures or exercises for 25 minutes on other days using accessible prerecorded practice videos that are sent to participants digitally. Participants will be assessed at 5 time points: baseline, midintervention (6 weeks), postintervention (12 weeks), and 3- and 6-month follow-ups. Assessments of ER, pain severity and interference, pain sensitivity including somatosensory and gene expression profiles, and physical strength and flexibility will be conducted at each visit. The fidelity of the interventions is assessed using a manualized checklist to evaluate recorded group sessions to ensure consistent instructor delivery.

Results: The primary outcome will be the mean change in pain severity as measured by the Brief Pain Inventory-Short Form at 12 weeks. The primary mechanism of action is ER measured by change in the Difficulties in Emotion Regulation Scale total score. Secondary outcomes include pain sensitivity, physical strength and flexibility, pain interference, and quality of life. A mediation path analysis and series of moderated mediation path analyses will be conducted to test the study hypotheses. As of January 2024, we have enrolled 138 participants. We expect the study to be completed by May 2025.

Conclusions: The study will provide important data for evaluating whether improvements in ER are responsible for reduced pain perception and pain sensitivity as well as increased quality of life in the context of chronic pain. The study findings have important implications for determining the mechanism of action for yoga and possibly other mind-body interventions as nonpharmacological therapies for pain management. The results of the study will inform the content, delivery, and measures for intervention trials involving yoga as a modality for relieving pain and improving function.

Trial Registration: ClinicalTrials.gov NCT04678297; https://clinicaltrials.gov/study/NCT04678297

International Registered Report Identifier (IRRID): DERR1-10.2196/56016

(JMIR Res Protoc 2024;13:e56016) doi:10.2196/56016

KEYWORDS

chronic low back pain; clinical trial; emotion regulation; mind-body interventions; pain sensitivity; yoga

Introduction

Background

Yoga has been shown to reduce pain and improve function in populations with chronic low back pain (CLBP) in multiple randomized controlled trials (RCTs) [1,2]. However, results vary, and effects are generally modest [3]. This variation is perhaps due to differences in the specific neurobiological mechanisms through which yoga exerts clinical improvements on pain that are affected by different yoga interventions. These mechanisms, which have been only minimally identified, could potentially be harnessed to achieve more consistent and optimal outcomes from yoga interventions. A study that examined mediators of yoga's effects on pain lacked strong theoretical bases for assessment of the mechanisms involved [4]. Using a comprehensive theoretical emotion regulation (ER) model of yoga [5], we will conduct the first test of ER as a primary mechanism of yoga's effects on CLBP. We will also test the role of pain sensitization using somatosensory and gene expression profiles in this model [6] and examine the specific aspects of ER.

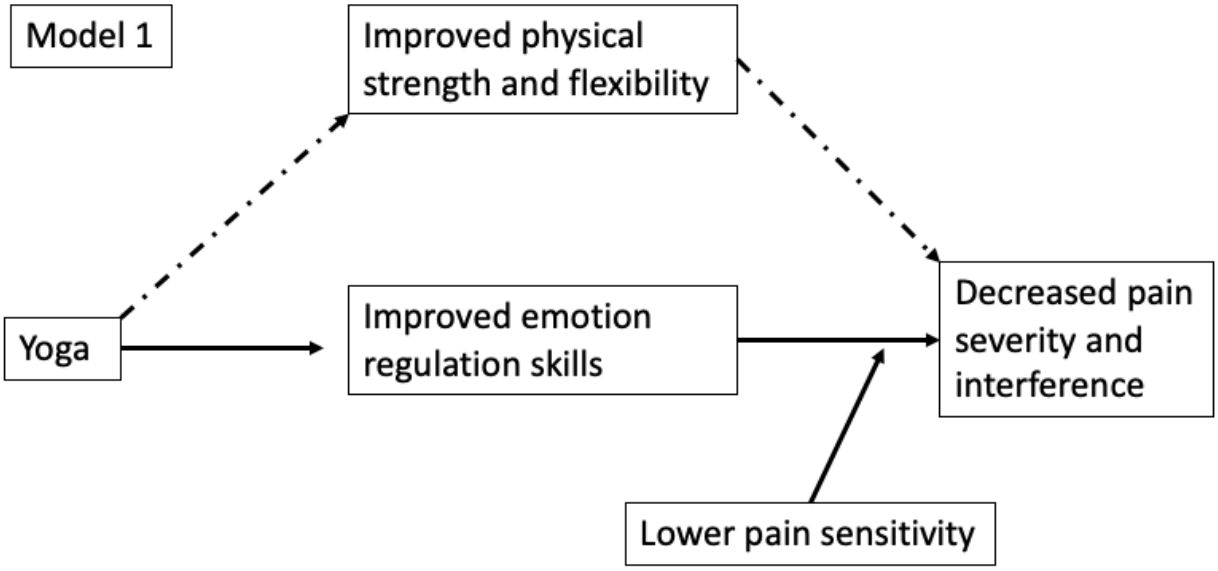
ER refers to "extrinsic and intrinsic processes responsible for monitoring, evaluating, and modifying emotional reactions, especially their intensive and temporal features, to accomplish one's goals" [7]. Emotions strongly influence perceptions of pain intensity and predict disability [8], particularly among individuals with CLBP [9,10]. Interventions that promote adaptive ER skills reduce pain in patients with chronic pain [11]. Increasing evidence demonstrates that consistent yoga practice can promote improved ER [12,13], but research has not yet tested whether the effects of yoga practice on CLBP are due to improvements in ER.

Integrative Model of Yoga's Effects on ER

Given the importance of ER in managing chronic pain and yoga's demonstrated promotion of improved ER, we developed an integrative model of yoga's effects on CLBP that highlights the key role of ER. Previous work by our team [14,15] and others [16] demonstrated that yoga simultaneously comprises multiple components and that physical activity (poses and transitions between poses), breathwork, and meditation are all important therapeutic elements. Thus, although physical activity interventions alone have demonstrated salutary effects on negative emotion [17] and ER [18,19], yoga's inclusion of breathwork and meditation along with physical activity may more potently improve ER [5].

Yoga provides myriad opportunities to develop ER skills helpful to people managing chronic pain. Practitioners can learn how to experience sensation without negative evaluative judgments, cultivating nonreactivity. Due to cognitive priming and reinforcement during movement, yoga provides simultaneous input to cognitive, motor, and sensory pathways, which may allow practitioners to consciously influence their interpretation of sensation or pain and manage its affective dimensions. Given the myriad components of yoga that can facilitate developing ER skills, we posit that ER is a key mechanism by which yoga exerts effects on individuals with CLBP. The few studies examining links among yoga, ER, and pain support our model (Figure 1). For example, yoga practitioners were better able to tolerate experimentally induced pain compared to nonpractitioners, with corresponding greater left intrainsular white matter connectivity [20]. Further, the yoga practitioners reported coping with the pain stimulus using (adaptive) ER strategies such as relaxation, nonjudgmental focusing, and reappraisal. Thus, the ability to minimize the affective dimensions of pain may dampen physiological responses to negative emotions such as anxiety, which have been associated with the perception of pain [21,22].

Figure 1. Model of primary and alternative mechanisms of action. Model 1 proposes that pain sensitization moderates yoga's effects on pain, in that chronic low back pain patients with higher sensitization may benefit less given that their pain is more centralized.



Pain Sensitivity May Influence the Effects of Yoga and ER on CLBP via Moderation or Mediation

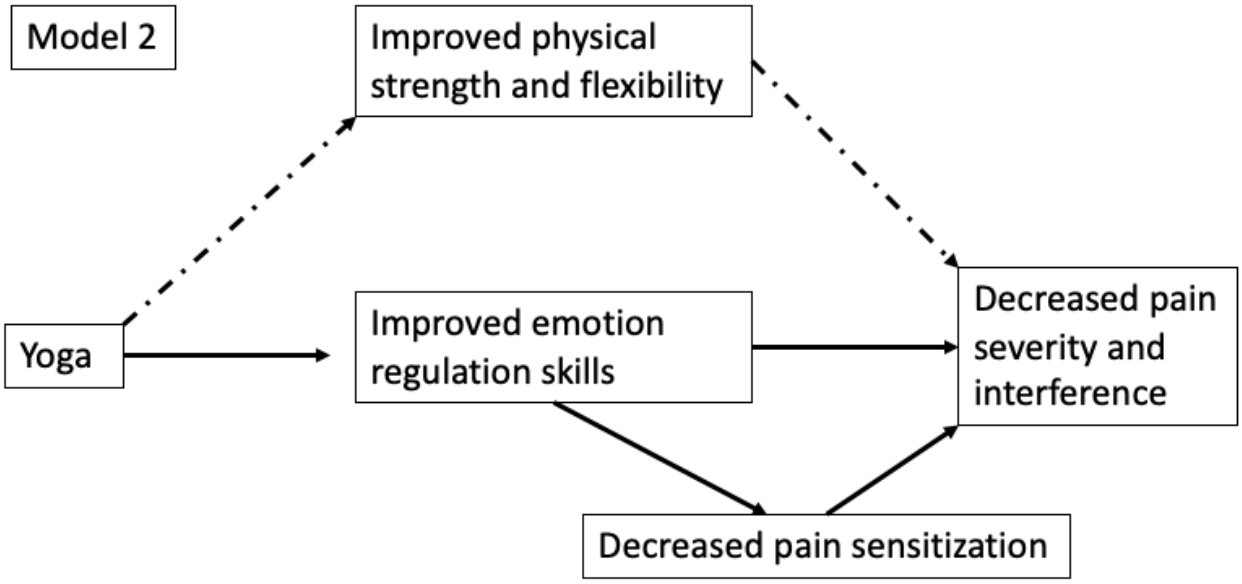
Recent studies document that patients with CLBP demonstrate sensory and functional alterations reflecting peripheral and central nervous system sensitization associated with enhanced pain sensitivity [23-25]. Enhanced pain sensitivity as a mechanism of CLBP includes sensitization of nociceptors and neuronal circuits [26] and increased pain signaling through membrane excitability and synaptic efficacy [27], which are conferred through altered expression of pain sensitivity (and immune-related) genes [6,28]. The somatosensory changes associated with enhanced pain sensitivity in CLBP involve decreased thermal and mechanical pain thresholds at the site of pain and remote areas [25,26].

Preliminary research suggests that negative emotion is an important determinant of pain sensitivity [29,30], predicting up to 23% of the variance in CLBP-related disability [31,32]. For instance, greater pain catastrophizing and anxiety are associated with lower standardized values of heat pain threshold and tolerance in patients with chronic pain [33]. In turn, negative emotions and inability to tolerate stress have been shown to activate inflammatory pathways through the release of proinflammatory cytokines and substance P [34,35]. To date, only 2 small studies have examined whether yoga specifically influences pain sensitivity. However, in a systematic review of 15 RCTs, yoga was associated with decreases in interleukin-1β, interleukin-6, and tumor necrosis factor-α [36]. In addition, specific components of yoga (meditation, relaxation, and breathing) have been shown to alter gene expression profiles and levels of inflammatory mediators [37-39].

As shown in Figure 1, we propose that pain sensitization moderates yoga's effects on pain, where patients with CLBP with higher sensitization may benefit less [40,41], given that their pain is more centralized [42,43]. This is a fairly novel hypothesis with some supportive evidence [44,45]. We will also explore the possibility that yoga and improved ER abilities might actually *improve* sensitization and thus decrease pain (Figure 2).

Little research has demonstrated that treatments for pain, including behavioral interventions, modify sensitization once it has occurred [46,47], although a reversal of central sensitization was observed in patients with structural pain–related pathology who underwent corrective surgery [48] as well as patients with migraine and chronic pancreatitis [49,50]. We considered alternative strategies to test these linkages. For example, a systematic review of 1037 individuals with CLBP provided moderate evidence that structural brain differences in specific cortical and subcortical areas of the brain and altered functional connectivity in pain-related areas following painful stimulation differentiate chronic pain from pain-free individuals [51]. While brain imaging provides 1 way to examine changes in pain sensitivity, we assert that identifying specific cellular mechanisms through which ER affects pain sensitivity will generate greater translational capacity for the clinical care of individuals with CLBP.

Figure 2. Moderated mediation model of emotion regulation. Model 2 will explore the possibility that yoga and improved emotion regulation abilities might actually improve sensitization and thus decrease pain.



Controlling for Improvements in Physical Strength and Flexibility

To be comprehensive, our model includes improved strength and flexibility, given that improvements in these domains are common in yoga intervention trials. In fact, yoga typically shows the effects on strength, flexibility, and other physical outcomes that are as substantial as those of physical therapy or stretching-strengthening exercise groups [52,53]. Sherman et al [4] demonstrated that strength and flexibility may mediate some of yoga's effects on pain. Overall, accumulating evidence demonstrates moderate but varied effects of yoga for reducing CLBP pain and disability; much remains to be learned about *how* yoga exerts these effects and why its effects vary. Understanding the proposed mechanism of actions (MOAs) of yoga will provide not only a more solid scientific basis to assure clinicians of the value of yoga to patients with CLBP and other conditions but also important targets for intervention modification and optimization.

Objectives

To address this gap, we will test the impact of a yoga intervention on ER and pain severity and functioning compared to a general stretching or strengthening intervention. This design allows us to isolate the additional effects of yoga above and beyond more general movement practices, thereby testing ER as a key MOA underlying the clinical effects of yoga on CLBP. Specifically, we will test whether yoga's effects on CLBP (improved pain severity and interference) are mediated by improved ER, the extent to which effects are related to specific aspects of ER, and the role of pain sensitization as a mediator or moderator of effects.

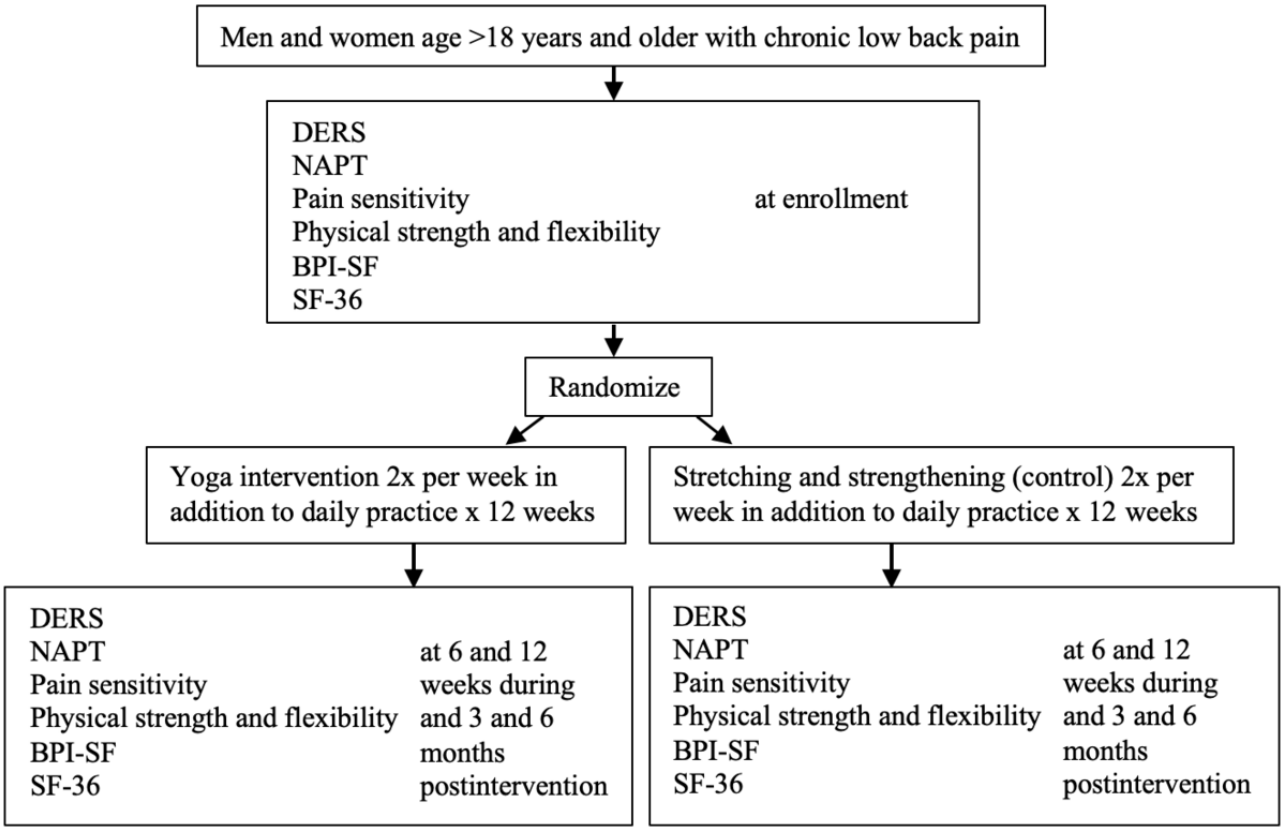
For the active comparison intervention, we chose to use stretching and strengthening exercises, given that we are interested in determining not only whether yoga influences ER but also the extent to which these effects are due to aspects of yoga above and beyond nonspecific factors (eg, expectancies, time, attention, and effort) [13] as well as improvements in strength and flexibility [4]. The 2 intervention groups will be similar in many aspects, but only yoga will incorporate aspects that we hypothesize will facilitate ER (eg, breathwork, mindfulness, and relaxation). We selected the hypothesized MOA based on our extensive work regarding the therapeutic characteristics of yoga and mechanisms of CLBP [5,14]. Our 3-month and 6-month follow-ups will allow us to examine whether the effects of yoga emerge later or persist. The study is highly innovative in its approach to testing the MOA of yoga for alleviating CLBP. By identifying the specific mechanisms through which yoga may influence pain, these results will facilitate optimizing interventions to improve therapeutic accuracy for prescribing and using yoga for CLBP, a highly prevalent and costly health condition in the United States and worldwide.

Methods

Design

This study is a 2-arm parallel group blinded RCT to examine ER as a MOA of yoga in individuals with CLBP (Figure 3). In total, 204 people with CLBP will be randomized to receive yoga or the stretching and strengthening intervention with assessments of pain severity and interference; ER; pain sensitivity; physical strength and flexibility; and quality of life at baseline, 6 weeks (midway through the intervention), 12 weeks (after completion of the intervention), and 3 and 6 months after the completion of the intervention. Both groups will be instructed to continue the use of any other strategies or treatments that they have been using to manage their CLBP throughout the study.

Figure 3. Study overview. BPI-SF: Brief Pain Inventory Short-form; DERS: Difficulties with Emotion Regulation Scale; NAPT: Negative Affective Priming Task; Pain sensitivity measured by quantitative sensory testing and blood drawn for gene expression profile; SF-36: 36-item Short Form Health Survey.



Participants

We will enroll 204 men and women aged 18 years and older with nonspecific CLBP who meet eligibility (Textbox 1). Nonspecific CLBP is defined as pain without a specific cause or need for surgical intervention that is anywhere in the region of the low back bound superiorly by the thoracolumbar junction and inferiorly by the lumbosacral junction, which has been present for more than 3 months out of the prior 6 months and is currently rated at a level of ≥2 on the numeric rating scale. Eligibility will be determined by asking the following screening questions [54]: (1) How long has back pain been an ongoing problem for you? (2) How often has low-back pain been an ongoing problem for you over the past 6 months? Responses of greater than 3 months to question 1 and "at least half the days in the past 6 months" to question 2 will define CLBP.

Textbox 1. Inclusion and exclusion criteria to determine eligibility for study participation.

Inclusion criteria

- Aged 18 years and older
- Report low back pain for more than 3 months out of 6 months
- Willing to attend 12 weeks of yoga or stretching (twice per week)
- Willing to complete 5 assessments
- English literacy
- No changes in pain treatments in the past month
- Willing to not change pain treatments during the study unless medically necessary
- Have not practiced yoga more than 2 times in the last 3 months

Exclusion criteria

- Back surgery within the last 1 year
- Back pain due to specific systemic problem (eg, lupus)
- Lower extremity weakness (motor strength four-fifths of the quads, glutes, hamstrings, and extensor hallucis longus)
- Sciatica or (+) straight leg raise
- Coexisting chronic pain problem (migraine headaches and fibromyalgia)
- Serious or unstable psychiatric illness (eg, psychosis, mania, and history of suicide attempt) and current suicidal ideation
- Major coexisting medical illness (eg, cancer, chronic obstructive pulmonary disease, and morbid obesity)
- Positive Romberg test (with or without sensory neuropathy)

Recruitment and Retention Strategies

Active and passive recruitment strategies will be used to recruit individuals with CLBP include (1) contacting CLBP participants enrolled in an institutional review board (IRB)–approved pain registry, (2) advertisements on social media (Instagram, Facebook, Twitter, Reddit, and Craigslist), (3) placing printed advertisements in public transportation vehicles and local newspapers, and (4) distributing flyers at local outpatient clinical sites and local universities. We will recruit continuously and start a new cohort every 6 months, so that there will be cohorts in both interventions and follow-up phases throughout the study. This approach will help control for seasonal effects and other potential confounds. All participants will receive a yoga or exercise mat, block, and strap prior to their first session, and US $70 following the baseline, 6- and 12-week postintervention, and 3- and 6-month follow-up assessments with an additional US $50 for those who complete all data collection sessions.

Interested volunteers are asked to complete a web-based screening questionnaire via REDCap (Research Electronic Data Capture; Vanderbilt University), which includes questions to ensure they meet inclusion and exclusion criteria and can participate safely. Volunteers who are deemed eligible to participate are contacted by study staff to schedule their baseline appointment.

Ethical Considerations

The study was approved by the University of Connecticut IRB (#H19-191). Prior to completing any study procedures, all participants provide written informed consent on a form that was approved by the IRB at the University of Connecticut (IRB#H19-191). All study procedures are in accordance with the ethical standards described by the Helsinki Declaration. Study participants are assigned an identification number, allowing all stored records to be deidentified. Deidentified data are kept in locked file room or stored in a password-protected database on a password-protected computer. All participants are monetarily compensated for their participation up to US $400 for completing all study visits. Participants can withdraw from the study at any time.

Procedures

Randomization and Blinding

Eligible volunteers are scheduled to meet with a study staff member who will follow all informed consent procedures. After written consent is obtained, participants are randomized to the yoga or stretching and strengthening group using a stratified randomization scheme based on biological sex to ensure balance between groups, and the assigned group is known only by the study staff managing the participant and instructor schedules.

We will use blinding whenever possible. Assessments, evaluations, and data analysis will be conducted without the knowledge of participants' assigned group. We will blind the study personnel to the assigned condition of subjects when conducting data collection by using unique study identification numbers, by following a strict script to refrain from discussing participant activities, and by using different members of the study team to coordinate assigned condition activities and collect data. Deidentified data with codes for assigned condition will facilitate blinded data analysis.

Data Collection Visits

At each study visit, venous blood samples (15 mL) will be collected in one 10-mL PAXgene vacutainer and one 6-mL K2 ethylenediaminetetraacetic acid vacutainer by a research team member experienced in venipuncture. The samples will be immediately placed in a biohazard container and transported to the laboratory where they will be processed and stored in a –80 °C freezer for bulk processing of genetic and protein measures. Physiological and quantitative sensory measurements will be conducted by a trained research assistant. Participants will be asked to complete all study questionnaires via REDCap after completion of the laboratory data collection.

Interventions

All yoga and stretching and strengthening sessions will take place on a secure web-based platform. This delivery modality will provide more inclusive participation and reduce barriers such as participant transportation and parking. For both study arms, 75-minute classes will be offered 3 times per week for 12 weeks. Participants will be asked to attend at least 2 out of 3 of the offered classes per week. The importance of attending 2 sessions per week is emphasized during the first session and throughout all subsequent sessions. Participants who repeatedly miss sessions without notifying the study personnel will be contacted to check on the reason for nonattendance and to encourage resuming participation as soon as possible. Participants are encouraged to consult with the instructor individually before or after class about problems or difficulties they are encountering at home or in the formal sessions.

Participants are asked to practice exercises at home on days they do not attend formal synchronous sessions to maximize the benefit of the intervention. Participants will be emailed daily links to prerecorded practice videos that are approximately 25 minutes in length and asked to record the amount of time they spent on the practice videos.

Yoga Intervention

Overview

The yoga intervention will be led by certified 500-hour registered yoga teachers trained in working with patients with back pain. The yoga for CLBP protocol [55] consists of classical hatha yoga with influences from vinyasa and Iyengar yoga. These yoga styles are those most commonly offered in clinical and community settings and emphasize the importance of modifications and adaptations including the use of props such as straps and blocks to minimize the risk of injury and make the poses accessible to people with health problems and limitations [56]. The manual developed to standardize the yoga classes offered in the intervention contains pictures and a description of how to perform each pose. The manual also includes suggested instructor dialogue, which may be paraphrased or varied slightly yet promotes consistent delivery, which enhances the replicability and generalization of results. The intervention includes some poses that could aggravate back conditions in some people if they are not modified; therefore, multiple modifications are suggested, and many poses are only worked up to after weeks of practice and individual attention from the instructor. The more challenging poses are never included in the home practice videos.

For each yoga class in the protocol, the instructor leads participants through a series of 23 yoga poses (32 total variations) at a slow-moderate pace. During the formal sessions, participants are instructed to take slow deep breaths, timing their inhales and their exhales with specific phases of poses. Participants are encouraged to emulate optimal alignment as demonstrated by the instructor and to focus on a goal or positive direction for their yoga practice. Yoga classes are constructed to allow optimal flow from one pose to another. Each session begins with a few minutes of deep breathing and mindfulness or meditation followed by 15 minutes of basic postures (poses 1-8) to warm up muscles by increasing circulation to provide increased flexibility as the class progresses. Most poses are conducted once per side. After the warm up, the instructor leads participants through a series of standing poses (poses 9-14) for 15 minutes. After the standing poses, the class moves into floor poses (poses 15-23) for 20 minutes. Sessions end with 5-7 minutes of complete relaxation in the standard ending pose “savasana,” during which additional positive affirmations are provided.

Stretching and Strengthening Control Intervention

This intervention is designed to require a similar amount of physical exertion (stretching and strengthening exercises only, with no extreme movement). Classes will be led by physical therapists or other skilled therapeutic exercise instructors and involve conventional exercises appropriate for patients with CLBP, including a comprehensive set of exercises that stretch all the major muscle groups, with an emphasis on the trunk and legs. The intervention will include 12 stretching exercises used in the exercise arm of previous studies that have successfully compared exercise to yoga [57,58] (ie, gastrocnemius, soleus, quadriceps, posterior and inferior shoulder, upper trapezius, hip flexor, back extension, back rotation, hamstrings, hip external rotators, and back flexion). It will also include 3 additional stretches (hip internal rotators, hip adductors, and hip flexion). Each stretch will be held for approximately 60 seconds and repeated once. In addition to a complete set of full-body stretches, the class will begin with a 5-minute warm up period consisting of basic aerobics steps (ie, 1 minute each of walking in place, marching, lateral shuffling, turning and reaching, and box step) and will also include 4 exercises that strengthen the back, abdomen, and hips (ie, squats, crunches, oblique crunches, and back extensions). Over the 12 weeks, the repetitions of each strength exercise are increased from 8 to 30. Specific strength exercises are practiced in separate sets of 5 to 10 repetitions.

Treatment Fidelity

All sessions will be recorded, and instructor fidelity to the yoga intervention or stretching intervention manuals will be evaluated using video-recordings of sessions. Instructors and participants will be aware of and consent to the recordings. We will select 1 session per week from each condition for rating by trained research assistants, who will review sessions using a manual checklist for instructor adherence to the manuals, using a 0-10 rating scale for each procedure or instruction. If the rating is

less than 100% adherent, we will meet with the instructor to discuss the places in the session that were not adherent.

Measures

The assessments of pain intensity, pain interference, ER, and other parameters will be taken at baseline, 6 and 12 weeks, and 3 and 6 months post intervention.

Primary Outcome: Primary MOA

Pain severity will be measured with the Brief Pain Inventory-Short Form (BPI-SF) [59] at 12 weeks. The BPI-SF has been validated with CLBP and has shown good reliability [60].

ER as the primary MOA will be measured using the Difficulties in Emotion Regulation Scale (DERS) score at 12 weeks. The DERS is the gold standard self-report measure of individuals' abilities to respond to emotional experiences in a goal-oriented manner [60]. The 36-item DERS taps aspects of difficulties with ER, which we anticipate will lessen with yoga practice [61]. Participants rate the extent to which each of 36 statements currently applies to them, and the measure yields a total score comprising summed subscales. The DERS is sensitive to change over time in ER, and internal consistency reliability is high [60].

The Negative Affective Priming Task [62] will also be used to capture individual differences in emotional attention, reactivity and appraisal, and ability to inhibit negative emotion and purposefully shift attention to more positive aspects of daily life. Participants are exposed to neutral and affective words with a strong positive and negative valence in consecutive paired trials, one word serving as the "target" and the other as a "distractor." Participants are instructed to ignore the distractor and to attend to the target in both control and negative priming conditions, with "inhibition ability" operationalized as a difference score between response latencies in control and negative priming conditions. The stronger one's inhibition abilities, the longer the latency in the negative priming condition compared to the control condition (scored in milliseconds). Individuals with chronic depression and greater tendency to engage in maladaptive rumination demonstrate reduced ability to inhibit negative, as opposed to neutral, words with no difference in the ability to inhibit positive words [63,64].

Secondary Outcomes

Overview

There are 4 secondary outcomes for this study: pain sensitivity, physical strength and flexibility, pain interference, and quality of life.

Pain Sensitivity: Peripheral and Central Sensitivity

We will use a comprehensive quantitative sensory testing (QST) battery of mechanical and thermal stimuli [65]: (1) cutaneous mechanical pain sensitivity, involving measures of tolerance, threshold, temporal summation, and after sensations; (2) heat and cold pain sensitivity, involving threshold, tolerance, and ratings of suprathreshold stimuli; and (3) pressure pain thresholds. Interrater reliability of the QST protocol has been reported in several clinical trials, with each individual test achieving a CI of 0.87-0.94 [66,67].

In addition to the QST battery, we will isolate total RNA from whole blood for sequencing at each time point. We will prepare libraries per Illumina standard protocols and sequence RNA on the Illumina HiSeq2500 System (Illumina Inc) to obtain 150 base pair paired-end reads. We will examine how changes in the expression of pain sensitivity genes, as well as the entire transcriptome, differ between the experimental and control group (those with complete data from yoga vs stretching) × sex using statistical modeling and construct a database of gene expression profiles to generate a profile of change in ER, as well as identify novel therapeutic targets for better pain management. We will use a candidate approach to examine genes identified from our preliminary studies, and a hypothesis-generating approach to identify differentially expressed genes.

Physical Strength and Flexibility

Physical measures include grip strength and core stabilization and strength. Grip strength will be measured using 2 trials for each hand with a hydraulic dynamometer. The best performance is selected for each side, and the average of the left and right hand is used for analysis. Painful or injured hands or wrists are not tested, and the result of the good hand is used. Good reliability and predictive validity have been shown [68]. Core stabilization and strength will be assessed using prone and supine bridge positions [69]. Participants begin on their elbows in the prone position with shoulders, hips, and ankles aligned. The supine position is tested next, with knees flexed 90° and pelvis raised from the floor with shoulders, hips, and knees aligned. Assessors record the length of time (120 seconds maximum) that each position is held in proper form.

Pain Interference

Interference of function due to pain will be measured with the Brief Pain Inventory [60]. The pain interference score is the mean of the 7 interference items.

Quality of Life

The 36-item Short Form Health Survey [70] will be administered at each time point to gain a deeper understanding of the psychological, physical, and social limitations that participants experience as a result of pain. Subscales characterize participants' physical functioning, role functioning as impacted by physical and emotional health, energy or fatigue, emotional well-being, social functioning, pain, and general health. The 36-item Short Form Health Survey demonstrates excellent strong psychometric properties and predictive validity in a variety of diverse samples, including those experiencing chronic pain [71].

Exploratory Variables

Demographics, class attendance or home practice, expectancies, and substance use will be measured to examine the impact on the primary and secondary outcomes. A brief questionnaire (minimum data set as recommended by the National Institutes of Health Taskforce on Research Standards for CLBP) [54] will assess demographics (age, gender, race or ethnicity, education, and employment status) and medical or psychiatric history (comorbidities, medication usage, and ongoing treatments). Attendance at yoga or stretching sessions will be assessed using attendance data from the session recordings. The Essential

Properties of Yoga Questionnaire [72] will be used to rate both interventions (yoga and stretching or strengthening) and measures the extent to which 14 different dimensions are emphasized in a mind-body intervention (eg, physical challenge, breathwork, restorative postures, and mindfulness). The Credibility Expectancy Questionnaire [73], a 6-item self-report instrument, will be used to assess treatment credibility and patient expectancy for improvement [74]. In order to assess participants' use of tobacco, alcohol, prescription medicines, cannabis, and other nonprescribed substances, the Alcohol, Smoking, and Substance Involvement Screening Test [75] will be administered by study staff at each time point.

Statistical Analysis

The primary aim of this study will test the null hypothesis that the 2 population means are equal between the yoga and stretching and strengthening groups on the primary outcome, pain severity as measured by the BPI-SF, as well as the primary MOA, ER as assessed by the DERS. Power calculations incorporated prior effect sizes from works by others. A proposed sample size of 102 per group, which adjusted for attrition, was calculated to detect statistically significant results with 80% power (estimated d=0.50). In consideration of our secondary aims, we also powered the detection of paths a and b within pain interference mediation models. This was done using simulation in R (R Foundation for Statistical Computing; N=5000). Following simulation methods (N=5000) presented in Fritz and MacKinnon [76], sample size was determined by increasing simulation sample size until 90% of simulations significantly detected both paths a and b with estimated effect size magnitudes of d=0.39 (path a) and d=0.26 (path b) at α=.05. A proposed sample size of 116 was calculated, which was already reached when powering our primary aim.

Data Analysis

All analyses will be performed in SPSS (version 29; IBM Corp). A P value of .05 or less will be considered statistically significant. The primary outcome is pain severity (BPI-SF) and the primary MOA is ER (DERS). We will examine baseline demographics and study variables descriptively and test for differences between yoga and stretching and strengthening groups. If assumptions are met, a series of 2-sided t tests, mixed effects models, and path analyses will test our hypotheses. A mediation path analysis will be conducted examining the indirect path of group and change in ER from baseline to 6 weeks (path a), and change in ER from baseline to 6 weeks and pain severity (BPI-SF) at 12 weeks (path b) controlling for baseline pain severity. The magnitude of indirect path b will be assessed controlling for path a and the direct path between group and change in pain severity at 12 weeks (path c) to test if changes in ER predict subsequent changes in pain severity. Identical models will be created with change in ER from baseline to 12 weeks and pain severity at 3- and 6-month follow-ups. The magnitude of indirect path b will be compared between groups to test if the path between ER and pain severity is greater in the yoga group than in the stretching and strengthening group. If 95% CIs of path estimates do not contain 0, they will be considered meaningful. Finally, a series of moderated mediation path analyses will be conducted, examining the measures of baseline pain sensitivity (QST scores and normalized gene expression values), strength and flexibility, pain interference, and quality of life as moderators of the identical mediation model. All analyses will also be adjusted for important covariates including, but not limited to demographics (eg, biological sex, race, and sex), cohort, instructor, and intervention components (Essential Properties of Yoga Questionnaire) and credibility or perception of success (Credibility Expectancy Questionnaire). Sensitivity analyses will examine whether treatment responders and nonresponders differ significantly in baseline ER abilities. Baseline DERS scores will also be examined as a continuous moderator in main study analyses to establish whether some individuals may enjoy greater benefit from this intervention more than others.

Results

This project is funded by the National Center for Complementary and Integrative Health and reviewed by the University of Connecticut's IRB. Recruitment began in September 2020. As of January 2024, we have enrolled 138 participants. We expect the study to be completed by May 2025. No interim analyses are planned for evaluation of the primary and secondary outcomes. Analyses will be conducted following final data collection using a mediation path analysis and series of moderated mediation path analyses to examine the mechanisms through which yoga reduces pain.

Discussion

Yoga has been shown to decrease pain severity in individuals with CLBP. This study aims to determine whether ER is a mechanism of yoga through which a significant reduction in pain can be achieved. We will also determine whether yoga can lead to improvements in pain sensitivity, physical strength and flexibility, pain interference, and quality of life.

This will be the first study to assess ER as an MOA of yoga and interrogate plausible biological and psychological pathways that impact the contribution of ER on pain relief. The study results will provide empirical data on the role of ER as a MOA for yoga interventions and inform future studies on whether ER could be bolstered as a component of yoga or other mind-body interventions to improve pain outcomes.

Limitations of the study include that it will be performed at 1 site within the United States, and the interventions are only delivered in English. As a first step to determine whether ER is a MOA of yoga, the study may support evaluating or targeting ER in yoga interventions among more diverse populations, with delivery in other languages, and with other chronic pain conditions.

This 2-arm parallel group blinded RCT will examine ER as the MOA of yoga in individuals with CLBP. The study will provide important data for evaluating whether improvements in ER are responsible for reduced pain, whether pain sensitization moderates yoga's effects on pain, or if yoga and improved ER abilities reduce pain sensitivity and thereby relieves pain. The study findings have important implications for future yoga

research studies, as well as other mind-body modalities designed to improve pain management.

Acknowledgments

This work was supported by the National Institutes of Health (grants R01AT010555, MPI: Park/Starkweather; and F31AT012315, Gnall).

Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Authors' Contributions

ARS and CP wrote the initial manuscript, designed the tables and figures, and acquired funding. EJG designed and helped to modify the yoga intervention. All authors contributed to revisions and reviewed the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report by the National Center for Complementary and Integrative Health (National Institutes of Health).
[PDF File (Adobe PDF File), 167 KB - resprot_v13i1e56016_app1.pdf]

References

1. Cramer H, Lauche R, Haller H, Dobos G. A systematic review and meta-analysis of yoga for low back pain. Clin J Pain 2013 May;29(5):450-460. [doi: 10.1097/AJP.0b013e31825e1492] [Medline: 23246998]
2. Groessl EJ, Liu L, Chang DG, Wetherell JL, Bormann JE, Atkinson JH, et al. Yoga for military veterans with chronic low back pain: a randomized clinical trial. Am J Prev Med 2017 Nov;53(5):599-608 [FREE Full text] [doi: 10.1016/j.amepre.2017.05.019] [Medline: 28735778]
3. Wieland LS, Skoetz N, Pilkington K, Vempati R, D'Adamo CR, Berman BM. Yoga treatment for chronic non-specific low back pain. Cochrane Database Syst Rev 2017 Jan 12;1(1):CD010671 [FREE Full text] [doi: 10.1002/14651858.CD010671.pub2] [Medline: 28076926]
4. Sherman KJ, Wellman RD, Cook AJ, Cherkin DC, Ceballos RM. Mediators of yoga and stretching for chronic low back pain. Evid Based Complement Alternat Med 2013;2013:130818 [FREE Full text] [doi: 10.1155/2013/130818] [Medline: 23690832]
5. Gard T, Noggle JJ, Park CL, Vago DR, Wilson A. Potential self-regulatory mechanisms of yoga for psychological health. Front Hum Neurosci 2014;8:770 [FREE Full text] [doi: 10.3389/fnhum.2014.00770] [Medline: 25368562]
6. Dorsey SG, Renn CL, Griffioen M, Lassiter CB, Zhu S, Huot-Creasy H, et al. Whole blood transcriptomic profiles can differentiate vulnerability to chronic low back pain. PLoS One 2019;14(5):e0216539 [FREE Full text] [doi: 10.1371/journal.pone.0216539] [Medline: 31095601]
7. Thompson RA. Emotion regulation: a theme in search of definition. Monogr Soc Res Child Dev 1994;59(2-3):25-52. [Medline: 7984164]
8. Peters ML. Emotional and Cognitive Influences on Pain Experience. In: Finn DP, Leonard BE, editors. Mod Trends Pharmacopsychiatry. Basel, Switzerland: Karger Publishers; 2015:138-152.
9. Chou R, Shekelle P. Will this patient develop persistent disabling low back pain? JAMA 2010 Apr 07;303(13):1295-1302. [doi: 10.1001/jama.2010.344] [Medline: 20371789]
10. Hill JC, Fritz JM. Psychosocial influences on low back pain, disability, and response to treatment. Phys Ther 2011 May;91(5):712-721. [doi: 10.2522/ptj.20100280] [Medline: 21451093]
11. Davis MC, Zautra AJ, Wolf LD, Tennen H, Yeung EW. Mindfulness and cognitive-behavioral interventions for chronic pain: differential effects on daily pain reactivity and stress reactivity. J Consult Clin Psychol 2015 Feb;83(1):24-35 [FREE Full text] [doi: 10.1037/a0038200] [Medline: 25365778]
12. Daly LA, Haden SC, Hagins M, Papouchis N, Ramirez PM. Yoga and emotion regulation in high school students: a randomized controlled trial. Evid Based Complement Alternat Med 2015;2015:794928 [FREE Full text] [doi: 10.1155/2015/794928] [Medline: 26356561]
13. Park CL, Groessl E, Maiya M, Sarkin A, Eisen SV, Riley K, et al. Comparison groups in yoga research: a systematic review and critical evaluation of the literature. Complement Ther Med 2014 Oct;22(5):920-929 [FREE Full text] [doi: 10.1016/j.ctim.2014.08.008] [Medline: 25440384]

14. Park CL, Lee SY, Finkelstein-Fox L, Sanderson K. Yoga to promote physical, mental and spiritual well-being: self-regulation on and off the mat. In: Plante TG, editor. Healing with Spiritual Practices: Proven Techniques for Disorders from Addictions and Anxiety to Cancer and Chronic Pain. New York City: Praeger/ABC-CLIO; 2018:72-85.
15. Elwy AR, Groessl EJ, Eisen SV, Riley KE, Maiya M, Lee JP, et al. A systematic scoping review of yoga intervention components and study quality. Am J Prev Med 2014 Aug;47(2):220-232 [FREE Full text] [doi: 10.1016/j.amepre.2014.03.012] [Medline: 24996759]
16. de Manincor M, Bensoussan A, Smith C, Fahey P, Bourchier S. Establishing key components of yoga interventions for reducing depression and anxiety, and improving well-being: a Delphi method study. BMC Complement Altern Med 2015 Mar 26;15:85 [FREE Full text] [doi: 10.1186/s12906-015-0614-7] [Medline: 25888411]
17. Josefsson T, Lindwall M, Archer T. Physical exercise intervention in depressive disorders: meta-analysis and systematic review. Scand J Med Sci Sports 2014;24(2):259-272 [FREE Full text] [doi: 10.1111/sms.12050] [Medline: 23362828]
18. Hallgren M, Herring MP, Owen N, Dunstan D, Ekblom Ö, Helgadottir B, et al. Exercise, physical activity, and sedentary behavior in the treatment of depression: broadening the scientific perspectives and clinical opportunities. Front Psychiatry 2016;7:36 [FREE Full text] [doi: 10.3389/fpsyt.2016.00036] [Medline: 27014101]
19. Park CL, Iacocca MO. A stress and coping perspective on health behaviors: theoretical and methodological considerations. Anxiety Stress Coping 2014;27(2):123-137. [doi: 10.1080/10615806.2013.860969] [Medline: 24192138]
20. Villemure C, Ceko M, Cotton VA, Bushnell MC. Insular cortex mediates increased pain tolerance in yoga practitioners. Cereb Cortex 2014;24(10):2732-2740 [FREE Full text] [doi: 10.1093/cercor/bht124] [Medline: 23696275]
21. Lerman SF, Rudich Z, Brill S, Shalev H, Shahar G. Longitudinal associations between depression, anxiety, pain, and pain-related disability in chronic pain patients. Psychosom Med 2015;77(3):333-341. [doi: 10.1097/PSY.0000000000000158] [Medline: 25849129]
22. Mehta S, Rice D, Janzen S, Teasell R. Trait anxiety mediates the effect of catastrophizing on pain disability. Arch Phys Med Rehab 2017;98(10):e122 [FREE Full text] [doi: 10.1016/j.apmr.2017.08.396]
23. Clauw DJ. Diagnosing and treating chronic musculoskeletal pain based on the underlying mechanism(s). Best Pract Res Clin Rheumatol 2015;29(1):6-19. [doi: 10.1016/j.berh.2015.04.024] [Medline: 26266995]
24. Curatolo M, Arendt-Nielsen L. Central hypersensitivity in chronic musculoskeletal pain. Phys Med Rehabil Clin N Am 2015;26(2):175-184. [doi: 10.1016/j.pmr.2014.12.002] [Medline: 25952059]
25. Starkweather AR, Ramesh D, Lyon DE, Siangphoe U, Deng X, Sturgill J, et al. Acute low back pain: differential somatosensory function and gene expression compared with healthy no-pain controls. Clin J Pain 2016;32(11):933-939 [FREE Full text] [doi: 10.1097/AJP.0000000000000347] [Medline: 26736025]
26. Giesecke T, Gracely RH, Grant MAB, Nachemson A, Petzke F, Williams DA, et al. Evidence of augmented central pain processing in idiopathic chronic low back pain. Arthritis Rheum 2004;50(2):613-623 [FREE Full text] [doi: 10.1002/art.20063] [Medline: 14872506]
27. Gold MS, Gebhart GF. Nociceptor sensitization in pain pathogenesis. Nat Med 2010;16(11):1248-1257 [FREE Full text] [doi: 10.1038/nm.2235] [Medline: 20948530]
28. Jankowski MP, Koerber HR. Neurotrophic factors and nociceptor sensitization. In: Kruger L, Light AR, editors. Translational Pain Research: From Mouse to Man. Boca Raton (FL): CRC Press/Taylor & Francis; 2010.
29. van Laarhoven AIM, Walker AL, Wilder-Smith OH, Kroeze S, van Riel PLCM, van de Kerkhof PCM, et al. Role of induced negative and positive emotions in sensitivity to itch and pain in women. Br J Dermatol 2012;167(2):262-269. [doi: 10.1111/j.1365-2133.2012.10933.x] [Medline: 22404598]
30. Vidor LP, Torres ILS, Medeiros LF, Dussán-Sarria JA, Dall'agnol L, Deitos A, et al. Association of anxiety with intracortical inhibition and descending pain modulation in chronic myofascial pain syndrome. BMC Neurosci 2014;15:42 [FREE Full text] [doi: 10.1186/1471-2202-15-42] [Medline: 24645677]
31. Hübscher M, Moloney N, Rebbeck T, Traeger A, Refshauge KM. Contributions of mood, pain catastrophizing, and cold hyperalgesia in acute and chronic low back pain: a comparison with pain-free controls. Clin J Pain 2014;30(10):886-893. [doi: 10.1097/AJP.0000000000000045] [Medline: 24145929]
32. Wertli MM, Eugster R, Held U, Steurer J, Kofmehl R, Weiser S. Catastrophizing-a prognostic factor for outcome in patients with low back pain: a systematic review. Spine J 2014;14(11):2639-2657. [doi: 10.1016/j.spinee.2014.03.003] [Medline: 24607845]
33. Terry MJ, Moeschler SM, Hoelzer BC, Hooten WM. Pain catastrophizing and anxiety are associated with heat pain perception in a community sample of adults with chronic pain. Clin J Pain 2016;32(10):875-881. [doi: 10.1097/AJP.0000000000000333] [Medline: 26626297]
34. Rosenkranz MA. Substance P at the nexus of mind and body in chronic inflammation and affective disorders. Psychol Bull 2007;133(6):1007-1037. [doi: 10.1037/0033-2909.133.6.1007] [Medline: 17967092]
35. Stellar JE, John-Henderson N, Anderson CL, Gordon AM, McNeil GD, Keltner D. Positive affect and markers of inflammation: discrete positive emotions predict lower levels of inflammatory cytokines. Emotion 2015;15(2):129-133. [doi: 10.1037/emo0000033] [Medline: 25603133]
36. Falkenberg RI, Eising C, Peters ML. Yoga and immune system functioning: a systematic review of randomized controlled trials. J Behav Med 2018;41(4):467-482. [doi: 10.1007/s10865-018-9914-y] [Medline: 29429046]

37. Black DS, Cole SW, Irwin MR, Breen E, Cyr NMS, Nazarian N, et al. Yogic meditation reverses NF-κB and IRF-related transcriptome dynamics in leukocytes of family dementia caregivers in a randomized controlled trial. Psychoneuroendocrinology 2013;38(3):348-355 [FREE Full text] [doi: 10.1016/j.psyneuen.2012.06.011] [Medline: 22795617]
38. Bhasin MK, Dusek JA, Chang BH, Joseph MG, Denninger JW, Fricchione GL, et al. Relaxation response induces temporal transcriptome changes in energy metabolism, insulin secretion and inflammatory pathways. PLoS One 2013;8(5):e62817 [FREE Full text] [doi: 10.1371/journal.pone.0062817] [Medline: 23650531]
39. Twal WO, Wahlquist AE, Balasubramanian S. Yogic breathing when compared to attention control reduces the levels of pro-inflammatory biomarkers in saliva: a pilot randomized controlled trial. BMC Complement Altern Med 2016;16:294 [FREE Full text] [doi: 10.1186/s12906-016-1286-7] [Medline: 27538513]
40. Ferrándiz MEA, Nijs J, Gidron Y, Roussel N, Vanderstraeten R, Van Dyck D, et al. Auto-targeted neurostimulation is not superior to placebo in chronic low back pain: a fourfold blind randomized clinical trial. Pain Physician 2016;19(5):E707-E719 [FREE Full text] [Medline: 27389114]
41. Kim SH, Yoon KB, Yoon DM, Yoo JH, Ahn KR. Influence of centrally mediated symptoms on postoperative pain in osteoarthritis patients undergoing total knee arthroplasty: a prospective observational evaluation. Pain Pract 2015;15(6):E46-E53. [doi: 10.1111/papr.12311] [Medline: 25980527]
42. Hodges PW, Barbe MF, Loggia ML, Nijs J, Stone LS. Diverse role of biological plasticity in low back pain and its impact on sensorimotor control of the spine. J Orthop Sports Phys Ther 2019;49(6):389-401 [FREE Full text] [doi: 10.2519/jospt.2019.8716] [Medline: 31151376]
43. Nijs J, Apeldoorn A, Hallegraeff H, Clark J, Smeets R, Malfliet A, et al. Low back pain: guidelines for the clinical classification of predominant neuropathic, nociceptive, or central sensitization pain. Pain Physician 2015;18(3):E333-E346 [FREE Full text] [Medline: 26000680]
44. Arendt-Nielsen L, Morlion B, Perrot S, Dahan A, Dickenson A, Kress HG, et al. Assessment and manifestation of central sensitisation across different chronic pain conditions. Eur J Pain 2018;22(2):216-241 [FREE Full text] [doi: 10.1002/ejp.1140] [Medline: 29105941]
45. Georgopoulos V, Akin-Akinyosoye K, Zhang W, McWilliams DF, Hendrick P, Walsh DA. Quantitative sensory testing and predicting outcomes for musculoskeletal pain, disability, and negative affect: a systematic review and meta-analysis. Pain 2019;160(9):1920-1932 [FREE Full text] [doi: 10.1097/j.pain.0000000000001590] [Medline: 31045746]
46. Jensen KB, Kosek E, Wicksell R, Kemani M, Olsson G, Merle JV, et al. Cognitive behavioral therapy increases pain-evoked activation of the prefrontal cortex in patients with fibromyalgia. Pain 2012;153(7):1495-1503. [doi: 10.1016/j.pain.2012.04.010] [Medline: 22617632]
47. Malfliet A, Kregel J, Coppieters I, De Pauw R, Meeus M, Roussel N, et al. Effect of pain neuroscience education combined with cognition-targeted motor control training on chronic spinal pain: a randomized clinical trial. JAMA Neurol 2018;75(7):808-817 [FREE Full text] [doi: 10.1001/jamaneurol.2018.0492] [Medline: 29710099]
48. Čeko M, Shir Y, Ouellet JA, Ware MA, Stone LS, Seminowicz DA. Partial recovery of abnormal insula and dorsolateral prefrontal connectivity to cognitive networks in chronic low back pain after treatment. Hum Brain Mapp 2015;36(6):2075-2092 [FREE Full text] [doi: 10.1002/hbm.22757] [Medline: 25648842]
49. Zhang N, Chen CF, Yu FY. Effects of pregabalin on central sensitization in patients with migraine. Int J Clin Pharmacol Ther 2015;53(4):277-283. [doi: 10.5414/CP202205] [Medline: 25669613]
50. Bouwense SAW, Olesen SS, Drewes AM, Poley JW, van Goor H, Wilder-Smith OHG. Effects of pregabalin on central sensitization in patients with chronic pancreatitis in a randomized, controlled trial. PLoS One 2012;7(8):e42096 [FREE Full text] [doi: 10.1371/journal.pone.0042096] [Medline: 22879908]
51. Kregel J, Meeus M, Malfliet A, Dolphens M, Danneels L, Nijs J, et al. Structural and functional brain abnormalities in chronic low back pain: a systematic review. Semin Arthritis Rheum 2015;45(2):229-237. [doi: 10.1016/j.semarthrit.2015.05.002] [Medline: 26092329]
52. Saper RB, Lemaster C, Delitto A, Sherman KJ, Herman PM, Sadikova E, et al. Yoga, physical therapy, or education for chronic low back pain: a randomized noninferiority trial. Ann Intern Med 2017;167(2):85-94 [FREE Full text] [doi: 10.7326/M16-2579] [Medline: 28631003]
53. Gothe NP, McAuley E. Yoga is as good as stretching-strengthening exercises in improving functional fitness outcomes: results from a randomized controlled trial. J Gerontol A Biol Sci Med Sci 2016;71(3):406-411 [FREE Full text] [doi: 10.1093/gerona/glv127] [Medline: 26297940]
54. Deyo RA, Dworkin SF, Amtmann D, Andersson G, Borenstein D, Carragee E, et al. Report of the NIH Task Force on research standards for chronic low back pain. Int J Ther Massage Bodywork 2015;8(3):16-33 [FREE Full text] [doi: 10.3822/ijtmb.v8i3.295] [Medline: 26388962]
55. Groessl EJ, Schmalzl L, Maiya M, Liu L, Goodman D, Chang DG, et al. Yoga for veterans with chronic low back pain: design and methods of a randomized clinical trial. Contemp Clin Trials 2016;48:110-118. [doi: 10.1016/j.cct.2016.04.006] [Medline: 27103548]
56. Ruiz-Aranda D, Salguero JM, Fernández-Berrocal P. Emotional regulation and acute pain perception in women. J Pain 2010;11(6):564-569 [FREE Full text] [doi: 10.1016/j.jpain.2009.09.011] [Medline: 20015703]

57. Sherman KJ, Cherkin DC, Erro J, Miglioretti DL, Deyo RA. Comparing yoga, exercise, and a self-care book for chronic low back pain: a randomized, controlled trial. Ann Intern Med 2005;143(12):849-856 [FREE Full text] [doi: 10.7326/0003-4819-143-12-200512200-00003] [Medline: 16365466]
58. Sherman KJ, Cherkin DC, Wellman RD, Cook AJ, Hawkes RJ, Delaney K, et al. A randomized trial comparing yoga, stretching, and a self-care book for chronic low back pain. Arch Intern Med 2011;171(22):2019-2026 [FREE Full text] [doi: 10.1001/archinternmed.2011.524] [Medline: 22025101]
59. Cleeland CS. Pain assessment in cancer. In: Osoba D, editor. Effect of Cancer on Quality of Life. Boca Raton, Florida: CRC Press, Inc; 1991:293-305.
60. Keller S, Bann CM, Dodd SL, Schein J, Mendoza TR, Cleeland CS. Validity of the brief pain inventory for use in documenting the outcomes of patients with noncancer pain. Clin J Pain 2004;20(5):309-318. [doi: 10.1097/00002508-200409000-00005] [Medline: 15322437]
61. Gratz KL, Roemer L. Multidimensional assessment of emotion regulation and dysregulation: development, factor structure, and initial validation of the difficulties in emotion regulation scale. J Psychopathol Behav Assess 2004;26:41-54 [FREE Full text] [doi: 10.1007/s10862-008-9102-4]
62. Gallant SN. Mindfulness meditation practice and executive functioning: breaking down the benefit. Conscious Cogn 2016;40:116-130. [doi: 10.1016/j.concog.2016.01.005] [Medline: 26784917]
63. Joormann J, Dkane M, Gotlib IH. Adaptive and maladaptive components of rumination? Diagnostic specificity and relation to depressive biases. Behav Ther 2006;37(3):269-280. [doi: 10.1016/j.beth.2006.01.002] [Medline: 16942978]
64. Joormann J, Gotlib IH. Emotion regulation in depression: relation to cognitive inhibition. Cogn Emot 2010;24(2):281-298 [FREE Full text] [doi: 10.1080/02699930903407948] [Medline: 20300538]
65. Rolke R, Magerl W, Campbell KA, Schalber C, Caspari S, Birklein F, et al. Quantitative sensory testing: a comprehensive protocol for clinical trials. Eur J Pain 2006;10(1):77-88. [doi: 10.1016/j.ejpain.2005.02.003] [Medline: 16291301]
66. Law LAF, Sluka KA, McMullen T, Lee J, Arendt-Nielsen L, Graven-Nielsen T. Acidic buffer induced muscle pain evokes referred pain and mechanical hyperalgesia in humans. Pain 2008;140(2):254-264 [FREE Full text] [doi: 10.1016/j.pain.2008.08.014] [Medline: 18835099]
67. Siegenthaler A, Eichenberger U, Schmidlin K, Arendt-Nielsen L, Curatolo M. What does local tenderness say about the origin of pain? An investigation of cervical zygapophysial joint pain. Anesth Analg 2010;110(3):923-927 [FREE Full text] [doi: 10.1213/ANE.0b013e3181cbd8f4] [Medline: 20185669]
68. Hogrel JY. Grip strength measured by high precision dynamometry in healthy subjects from 5 to 80 years. BMC Musculoskelet Disord 2015;16:139 [FREE Full text] [doi: 10.1186/s12891-015-0612-4] [Medline: 26055647]
69. Liemohn WP, Baumgartner TA, Gagnon LH. Measuring core stability. J Strength Cond Res 2005 Aug;19(3):583-586. [doi: 10.1519/1533-4287(2005)19[583:MCS]2.0.CO;2] [Medline: 16095406]
70. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30(6):473-483. [Medline: 1593914]
71. Elliott TE, Renier CM, Palcher JA. Chronic pain, depression, and quality of life: correlations and predictive value of the SF-36. Pain Med 2003;4(4):331-339 [FREE Full text] [doi: 10.1111/j.1526-4637.2003.03040.x] [Medline: 14750909]
72. Park CL, Elwy AR, Maiya M, Sarkin AJ, Riley KE, Eisen SV, et al. The Essential Properties of Yoga Questionnaire (EPYQ): psychometric properties. Int J Yoga Therap 2018;28(1):23-38 [FREE Full text] [doi: 10.17761/2018-00016R2] [Medline: 29498893]
73. Devilly GJ, Borkovec TD. Psychometric properties of the credibility/expectancy questionnaire. J Behav Ther Exp Psychiatry 2000;31(2):73-86. [doi: 10.1016/s0005-7916(00)00012-4] [Medline: 11132119]
74. Cohen M, Beard C, Björgvinsson T. Examining patient characteristics as predictors of patient beliefs about treatment credibility and expectancies for treatment outcome. J Psychother Integrat 2015;25(2):90-99 [FREE Full text] [doi: 10.1037/a0038878]
75. WHO ASSIST Working Group. The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST): development, reliability and feasibility. Addiction 2002;97(9):1183-1194 [FREE Full text] [doi: 10.1046/j.1360-0443.2002.00185.x] [Medline: 12199834]
76. Fritz MS, MacKinnon DP. Required sample size to detect the mediated effect. Psychol Sci 2007;18(3):233-239 [FREE Full text] [doi: 10.1111/j.1467-9280.2007.01882.x] [Medline: 17444920]

Abbreviations

BPI-SF: Brief Pain Inventory-Short Form
CLBP: chronic low back pain
DERS: Difficulties in Emotion Regulation Scale
ER: emotion regulation
IRB: institutional review board
MOA: mechanism of action
QST: quantitative sensory testing

RCT: randomized controlled trial
REDCap: Research Electronic Data Capture

Edited by A Mavragani; submitted 11.01.24; this is a non–peer-reviewed article;accepted 05.02.24; published 14.03.24.

Please cite as:
Starkweather AR, Xu W, Gnall KE, Emrich M, Garnsey CL, Magin ZE, Wu W, Fetta J, Groessl EJ, Park C
Testing Biological and Psychological Pathways of Emotion Regulation as a Primary Mechanism of Action in Yoga Interventions for Chronic Low Back Pain: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2024;13:e56016
URL: https://www.researchprotocols.org/2024/1/e56016
doi:10.2196/56016
PMID:38483469

Protocol

A Web-Based Physical Activity Promotion Intervention for Inactive Parent-Child Dyads: Protocol for a Randomized Controlled Trial

Daniel Phipps[1,2], PhD; Weldon Thomas Green[1], MSc; Reetta Aho[1]; Eeva Kettunen[1], PhD; Stuart Biddle[1,3], PhD; Kyra Hamilton[2,4], PhD; Arto Laukkanen[1], PhD; Kaisa Aunola[5], PhD; Derwin King Chan[6], PhD; Nelli Hankonen[7], PhD; Mary Hassandra[8], PhD; Tommi Kärkkäinen[5], PhD; Virpi-Liisa Kykyri[5], PhD; Juho Polet[1,5,9], PhD; Ryan Rhodes[10], PhD; Montse C Ruiz[1], PhD; Arja Sääkslahti[1], PhD; Jekaterina Schneider[11], PhD; Hanna-Mari Toivonen[1], MSc; Taru Lintunen[1], PhD; Martin Hagger[1,4,12], PhD; Keegan Knittle[1], PhD

[1]Faculty of Sport and Health Sciences, University of Jyväskylä, Jyväskylä, Finland

[2]School of Applied Psychology, Griffith University, Brisbane, Australia

[3]Centre for Health Research, University of Southern Queensland, Brisbane, Australia

[4]Health Sciences Research Institute, University of California - Merced, Merced, CA, United States

[5]Department of Psychology, University of Jyväskylä, Jyväskylä, Finland

[6]Department of Early Childhood Education, Education University of Hong Kong, Hong Kong, China (Hong Kong)

[7]Faculty of Social Sciences, Tampere University, Tampere, Finland

[8]Department of Physical Education and Sport Science, University of Thessaly, Thessaly, Greece

[9]Centre of Excellence in Learning Dynamics and Intervention Research (InterLearn), University of Jyväskylä and University of Turku, Jyväskylä, Finland

[10]School of Exercise Science, Physical and Health Education, University of Victoria, Victoria, BC, Canada

[11]Centre for Appearance Research, School of Social Sciences, University of the West of England, Bristol, United Kingdom

[12]Department of Psychological Science, University of California - Merced, Merced, CA, United States

Corresponding Author:
Martin Hagger, PhD
Health Sciences Research Institute
University of California - Merced
5200 North Lake Rd
Merced, CA, 95343
United States
Phone: 1 (209) 228 4400
Email: mhagger@ucmerced.edu

Abstract

Background: Low levels of physical activity are associated with numerous adverse health outcomes, yet sedentary lifestyles are common among both children and adults. Physical activity levels tend to decline steeply among children aged between 8 and 12 years, even though children's behavioral patterns are largely governed by familial structures. Similarly, parents' activity levels have been generally reported as lower than those of nonparents of comparable age. For this reason, family-based physical activity promotion interventions are a potentially valuable and relatively underresearched method for mitigating physical activity declines as children develop into adolescents and for increasing physical activity in parents.

Objective: This study aims to assess the efficacy, feasibility, and acceptability of a novel theory-based web-based physical activity promotion intervention among parent-child dyads in Finland who do not meet physical activity recommendations at baseline.

Methods: Participants (target N=254) will be recruited from the general population using a panel company and advertisements on social media and randomly assigned to either an immediate intervention group or a waitlist control group. The intervention consists of 4 web-based group workshops over the course of 10 weeks, web-based tasks and resources, and a social support chat group. Data on physical activity behavior and constructs from the integrated behavior change model will be collected through self-report surveys assessing physical activity, autonomy support, autonomous motivation, attitude, subjective norm, perceived behavioral control, intention, self-monitoring, habit, and accelerometer measurements at baseline, post intervention, and 3 months post intervention. Exit interviews with participants will assess the feasibility and acceptability of the intervention procedures.

Results: This study will reveal whether the intervention changes leisure-time physical activity among intervention participants relative to the control group and will examine the intervention's effects on important theoretical predictors of physical activity. It will also yield data that can be used to refine intervention materials and inform further implementation. Trial recruitment commenced in September 2023, and data collection should be completed by December 2024.

Conclusions: The planned intervention has potential implications for both theory and practice. Practically, the use of an entirely web-based intervention may have scalable future uses for improving physical activity in 2 key populations, while also potentially informing on the value of dyadic, family-based strategies for encouraging an active lifestyle as an alternative to strategies that target either parents or children independently. Further, by assessing change in psychological constructs alongside potential change in behavior, the intervention also allows for important tests of theory regarding which constructs are most linked to favorable behavior change outcomes.

Trial Registration: ClinicalTrials.gov NCT06070038; https://clinicaltrials.gov/study/NCT06070038

International Registered Report Identifier (IRRID): DERR1-10.2196/55960

(JMIR Res Protoc 2024;13:e55960) doi:10.2196/55960

KEYWORDS

dyadic behavior change; family behavior change; intervention; physical activity; theory of planned behavior

Introduction

Overview

Low levels of physical activity in adult and youth populations are associated with an increased risk of physical and mental health conditions and a reduced quality of life. Conversely, regular physical activity participation is associated with reduced chronic disease risk and better psychological health and well-being [1]. Accordingly, the World Health Organization has published evidence-based guideline levels of physical activity required to realize these health benefits. The guidelines recommend that adults aged between 18 and 64 years participate in at least 75 minutes of vigorous physical activity, 150 minutes of moderate physical activity, or an equivalent combination of both per week, while children aged between 7 and 17 years are recommended to participate in at least 60 minutes of physical activity per day. Studies indicate that most people do not achieve these guideline levels of physical activity [2]. Further, studies have observed a sharp drop in physical activity participation in child and adolescent populations, followed by generally low participation levels into and throughout adulthood [3].

Given the steep decline in activity levels, as children transition into adolescence, the development and implementation of behavioral interventions to encourage an active lifestyle is a key target area for health promotion research. One strategy proposed to enhance the efficacy of behavior change strategies for children's activity levels is to target the family unit rather than children themselves. Specifically, parents of preteen children retain a strong influence on their child's behavior, both through their own activity levels [4,5] and through the opportunity to provide support for and foster motivation toward leisure-time physical activity behaviors [6,7]. Further, evidence indicates that children likely influence physical activity behaviors and beliefs in their parents, as parents tend to be less active than nonparents [8], often citing their children's lack of motivation or support as a barrier to being physically active [9]. This evidence of within-family effects indicates the potential utility of dyadic interventions for both parents and children [10], using theory-driven, group-based behavior change strategies to bolster social support, foster motivation, and reduce the perceived barriers to behavior in both the parent and child. Yet, despite evidence for the potential utility of these strategies, few physical activity interventions have been applied for parent-child dyads, and those that have tend not to have a strong basis in behavioral theory and are seldom evaluated systematically [11], inhibiting meaningful conclusions on their efficacy. In response to the relative scarcity of theory-driven, family-based physical activity intervention programs, we aim to develop and test an intervention to promote physical activity in low-active parents and their children based on the integrated behavior change model, an approach that outlines the multiple determinants and potential targets for intervention derived from multiple theoretical perspectives [12].

The Integrated Behavior Change Model

The integrated behavior change model draws from several well-established behavioral theories: self-determination theory [13], the theory of planned behavior [14], the health action process approach [15], and the reflective impulsive model [16]. Central to the model is that individuals' quality of motivation, which reflects whether their behavior is consistent with the self-endorsed reasons, is highly influential in individuals' intentions to perform physical activity and physical activity participation. This premise is derived from self-determination theory, which makes the distinction between autonomous and controlled forms of motivation. Autonomous motivation reflects an individual's performing physical activity consistent with their own interests, choices, needs, and sense of personal involvement [13,17]. By contrast, controlled motivation reflects performing activities for externally referenced reasons, such as for rewards or out of obligation to others. Of critical importance when it comes to performing physical activity, individuals who perform physical activities for autonomous motives are more likely to form intentions to perform physical activity in the future and are more likely to develop routines and habits, which can translate to long-term physical activity persistence [18]. This is because those citing autonomous reasons for performing physical activity are likely to persist because their motivation emanates from themselves, while those whose motives are controlled will only persist as long as the external contingencies

(eg, rewards and demands from others) persist. A key tenant of self-determination theory [17,19], is that autonomous motivation for physical activity can be fostered through the support of salient others, such as parents or teachers. For example, parents who display behaviors that indicate support for children's autonomy and competence toward physical activity and demonstrate a sense of unconditional relatedness with their children for physical activities, are more likely to foster autonomous motives in their children toward performing physical activity in the future [6,7,20]. As such, enabling parents to display autonomy-supportive behaviors with respect to presenting, discussing, and performing physical activity with their children is likely an important strategy to promote physical activity participation in children and may be particularly valuable in family-based interventions aimed at promoting physical activity. It is also likely to be useful in parent-child dyads, where both parent and child can be encouraged to display behaviors that support each other's autonomous motivation. This is supported in empirical data, where autonomy-supportive parenting has been associated with autonomous motivation in children as well as positive behavioral outcomes [21], including enhanced physical activity [6].

The integrated behavior change model also specifies the processes by which autonomous motivation leads to intention toward, and actual participation in, physical activity in the future. Specifically, individuals who are autonomously motivated toward a behavior are proposed to be more likely to form adaptive beliefs in favor of performing that behavior in the future [12,22-24] and, as a consequence, form an intention to perform physical activity in the future. Such beliefs are represented in the model by the belief-based attitude, subjective norm, and perceived behavioral control constructs from the theory of planned behavior [14], a prototypical theory that identifies the antecedents of intentional behaviors such as physical activity. The theory stipulates intention is the salient predictor of subsequent behavior, and intentions themselves are a function of attitudes (beliefs about the perceived likely affective or instrumental outcomes of engaging in a behavior), subjective norms (beliefs about where important others in one's life would want them to engage in a behavior or not), and perceived behavioral control (beliefs about whether engaging in a behavior is under one's own control or within their abilities). Research has demonstrated that these beliefs tend to be reliably related to physical activity intentions and participation, signaling their potential as modifiable constructs that could be targeted in intervention strategies aimed at promoting positive intentions toward, and actual participation in, physical activity. Accordingly, interventions based on the theory and targeting the belief-based constructs have shown efficacy in changing intentions and behavior [25]. For example, interventions presenting persuasive messages that highlight the advantages of behavior and downplay the disadvantages, targeting attitude change, or prompting practice that assists individuals in successfully mastering the target behavior and overcoming obstacles, targeting perceived behavior control change, have been shown to be effective in promoting intention and behavior change in physical activity contexts [26].

While there is evidence for the utility of interventions based on the recommendations of self-determination theory (eg, use of strategies like fostering autonomy support in influential others) or the theory of planned behavior (eg, providing persuasive communications targeting belief change), the integrated behavior change model also acknowledges that these strategies are often more efficacious in changing motivation or intention than changing behavior [27]. Recognizing the shortfall in the association between motivation and behavior, such as relatively modest intention-behavior relations observed in physical activity [28-32], other strategies that bolster intentions may be useful. For example, researchers adopting action control frameworks have suggested that leveraging [28,33] intervention strategies such as planning and self-monitoring may strengthen the intention-behavior relationship and increase the likelihood that individuals act on their good intentions when performing physical activity [15,34].

Study Overview Objectives

Given the need for interventions to help children maintain physical activity levels as they transition into adolescence and to help parents become more physically active, our group used the integrated model as a starting point to develop a novel, remotely delivered dyadic physical activity promotion intervention. By applying the integrated behavior change model to a parent-child intervention, we aim to use and strengthen within-family dynamics to foster autonomous motivation and encourage physical activity in both parents and preteen children. In this protocol, we describe a planned randomized controlled trial for testing the effects of this intervention in a sample of insufficiently active Finnish-speaking parents and children.

Methods

Trial Design

The trial will adopt a randomized waitlist control design in which parent-child dyads are the unit of randomization. Families will be randomized on sign-up to either an intervention group that receives the intervention immediately after baseline data collection or to a waitlist control group that will receive the intervention after all outcome data have been collected.

Participant Recruitment and Eligibility

Parent-child dyads will be recruited from the general Finnish population through direct contact with a panel company, through social media advertisements, and through posts on parenting discussion boards and forums. Individuals who responded to the advertisements were directed to a screening survey hosted on the Webropol platform. To be eligible for inclusion, dyads must consist of a parent or guardian aged >18 years and a child aged 8-12 years, and both dyad members need to be considered sedentary. Parents are considered sedentary if they were not active for at least 30 minutes a day on 5 or more days in the past week, and children are considered sedentary if they were not active for at least 60 minutes per day in the past week. Dyads will be excluded if either the parent or child reported having a medical condition or injury likely to prevent them from safely engaging in physical activity. People meeting the inclusion criteria can continue in the Webropol survey to read information

about the trial and are then offered the opportunity to provide their contact details to opt-in to the trial.

Power Analysis

The projected sample size was estimated from a statistical power analysis conducted using G*Power (version 3.1; Heinrich-Heine-Universität Düsseldorf). The analysis assumed a small to medium effect size (Cohen *f*=0.235) for the intervention on our primary outcome variable, leisure time physical activity, calculated from an average of effect sizes from meta-analyses of self-determination theory–based interventions (Hedges *g*=0.45 [35]) and interventions targeting self-efficacy (Cohen *d*=0.48 [36]), with α set at .05 and statistical power set at .80 reveal a projected total sample size of 178 participants. We also assumed a projected 30% attrition rate in participants through the study based on similar trials [37], resulting in a sample of 254 participants (ie, 127 dyads) to be recruited at baseline.

Study Procedures

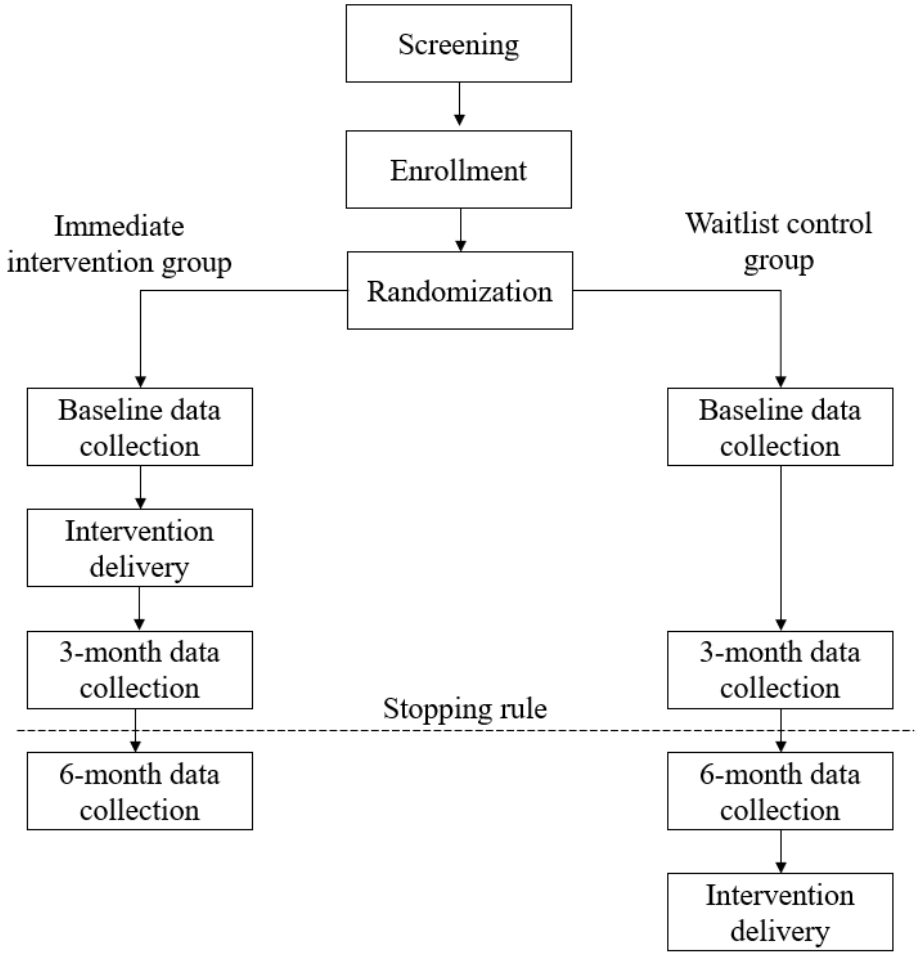
All recruitment materials will be delivered in a web-based format with a URL forwarding participants to a screening and informed consent survey hosted on the Webropol platform. First, parents will be presented with an eligibility questionnaire to assess whether they and their children making reference to themselves and their least active child aged between 8 and 12 years, meet the inclusion criteria. Eligible parents will then be presented with information about the study and an informed consent form. Parents who provide informed consent to participate in the study will be prompted to provide their name, contact details, and the name of their least active child, aged between 8 and 12 years, and will be enrolled in the study.

After enrolling in the trial, dyads will be assigned by computerized random-digit generation to 1 of 2 groups: an immediate intervention group that receives the intervention immediately after baseline data collection, or a waitlist control group that will receive the intervention after all outcome data have been collected.

Participants in both groups will be asked to provide outcome data immediately after randomization, 3 months later, and 6 months later. Outcome data will be collected through web-based surveys hosted on the Webropol platform and through physical activity measurement devices mailed to participants' homes. For web-based surveys, parents will be emailed 2 separate URLs: 1 for themselves and 1 for their child. Parents will be instructed that they may help their child understand the survey items but should avoid influencing their child's answers to the questionnaire.

Participants in the immediate intervention group will receive the intervention between the baseline and 3-month data collection points, while participants in the waitlist control group will receive the intervention after all data collection has been completed. While data are planned to be collected at baseline, 3 months, and 6 months, the trial includes a stopping rule, such that 6-month follow-up data will not be collected if there is no effect of the intervention on the primary outcome (ie, leisure time physical activity) at the 3-month follow-up. The trial design flow diagram is presented in Figure 1.

Figure 1. A flowchart of enrollment and data collection for the ProAct trial.



Intervention

Immediate Intervention Group

The intervention consists of 4 web-based sessions hosted through a videoconferencing platform (Zoom Inc) and facilitated by 1 or 2 members of the research team. The 4 sessions will be delivered in weeks 1, 3, 5, and 8 of the program. Summaries of each session, including the target constructs and behavior change techniques used in each session, are presented in Table 1. The first session will involve only parents and will last 90 minutes. It focuses on instructing parents in the use of autonomy-supporting parenting behaviors. The remaining 3 sessions will involve both parents and children and will last 45 minutes. Session 2 prompts a discussion of the benefits of an active lifestyle, including enjoyment and importance, and gets participants to set individual and joint physical activity-related goals. Session 3 teaches participants how to make action plans and coping plans (ie, problem-solving) when pursuing physical activity goals. Session 4 covers social norms related to physical activity, has participants specify their identity related to physical activity, and prompts social support strategies within each dyad.

Table 1. Content and targets for each intervention session in the ProAct trial. Behavior change techniques preceded by an "M" are drawn from the Motivation and Behavior Change Techniques [38]. Behavior change techniques preceded by a "T" are drawn from the Behavior Change Taxonomy version 1 [39].

Session	Target constructs	Behavior change techniques
Session 1: 90 minutes and parents only	Autonomy supportive parenting	• M3. Use non-controlling, informational language • M5. Provide a meaningful rationale • M6. Provide choice • M7. Encourage the person to experiment and self-initiate the behavior • M10. Show unconditional regard • M12. Use empathic listening • M16. Clarify expectations • T1.1 Goal setting yeah • T1.4 Action planning • T4.1 Instruction on how to perform the behavior • T4.2 Information about antecedents • T5.3 Information about social and environmental consequences • T5.6 Information about emotional consequences • T8.1 Behavioral practice/rehearsal • T16.3 Vicarious consequences
Session 2: 45 minutes, parents, and children	Attitude	• M4. Explore life aspirations and values • M6. Provide choice • M7. Encourage the person to experiment and self-initiate the behavior • M16. Clarify expectations • M17. Assist in setting optimal challenge • M19 Help develop a clear and concrete plan of action • M20 Promote self-monitoring • T1.1 Goal Setting (behavior) • T1.3. Goal Setting (outcome) • T1.5 Review behavior goal(s) • T1.6 Discrepancy between current behavior and goal • T2.3 Prompt self-monitoring of behavior • T4.1 Instruction on how to perform the behavior • T5.6 Information about emotional consequences • T15.3 Focus on past success
Session 3: 45 minutes, parents, and children	Perceived behavioral control and self-regulation	• M15. Address obstacles for change • M19. Help develop a clear and concrete plan of action • M20. Promote self-monitoring • M21. Explore ways of dealing with pressure • T1.2 Problem-solving • T1.5 Review behavioral goals • T1.6. Discrepancy between current behavior and goal • T2.2 Feedback on behavior • T8.7 Graded Tasks • T15.1 Verbal persuasion about capability • T15.3 Focus on past success.
Session 4: 45 minutes, parents, and children	Subjective Norm and perceived autonomy support	• M2 Prompt identification of sources of pressure for behavior change • M8. Acknowledge and respect perspectives and feelings • M9. Encourage asking of questions • M14. Prompt identification and seek available social support • T1.1 Goal Setting (behavior) • T1.3 Goal Setting (outcome) • T1.4 Action planning • T1.5 Review behavioral goals • T1.7 Review Outcome Goals • T3.2 Social Support (Practical) • T3.3 Social Support (Emotional) • T6.2 Social comparison • T6.3 Information on others' approval. • T13.1 Identification of self as role model • T13.5 Identity associated with changed behavior

In addition to the web-based sessions, participants will have access to a website that includes materials that support the content of each session. This includes worksheets, slide decks and recorded versions of the sessions, a menu of physical

activities suitable for parents and children, and further practice materials.

Between sessions, participants will receive SMS text messages that ask them to provide written feedback on their progress; offer advice, suggestions, or reminders; or prompt reflection on their motives for physical activity. Parent participants will also be granted access to a moderated web-based chat forum (WhatsApp group [Meta Facebook, Inc]) in which parents can share their experiences with the sessions and provide and receive social support from other participating parents. Intervention materials are available on the internet [40].

Waitlist Control Group

Participants assigned to the waitlist control group will complete the same data collection procedures as the immediate intervention group but will not be required to undertake any alternative intervention tasks during the data collection period. After the data collection period, participants in the waitlist control group will be invited to receive the intervention and accompanying materials.

Outcomes

Overview

Measures of psychological constructs will be assessed using multi-item scaled survey measures, while leisure-time physical activity is to be assessed using self-reported surveys and observationally through accelerometer measurements. All items were translated into Finnish by native speakers and piloted on a sample of 8- to 12-year-old Finnish children and their parents. Full measures are available on the internet [40].

Primary Outcomes (Physical Activity and Sedentary Time)

Self-reported physical activity and time spent in sedentary activities for both parents and children will be assessed using the Godin-Shepard leisure time exercise questionnaire [41], where participants will be required to report the number of occasions they engaged in light, moderate, and vigorous physical activity for 15 minutes or longer. Sedentary time will be measured using 2 items per participant, targeting weekdays and weekend days separately (eg, “In the past 7 days, how much time did you spend sitting during a typical weekday after school or weekend day?”) [42]. Items are scored on a sliding scale from “no time” upwards in increments of half an hour.

Secondary Outcomes

Device-Measured Physical Activity

Physical activity will also be assessed using a hip-worn triaxial accelerometer (Hookie AM20; Traxmeet Ltd). Each dyad will be mailed 2 accelerometers, detailed instructions on wearing the device, and a diary for recording when they wore the accelerometer, how they commuted to school or work, and any events that may have inhibited accurate data (eg, missed days and exercise done without the device). Raw data from accelerometers will be processed using the *GGIR* package in R software (R Foundation for Statistical Computing) [43], with outcome scores provided as the amount of time spent engaged in sedentary behavior, light physical activity, moderate physical activity, and vigorous physical activity.

Autonomy-Supportive Parenting

Autonomy-supportive parenting practices will be assessed using a 4-item questionnaire based on measures used in a previous study [44], with responses provided on 5-point scales (1=strongly disagree to 5=strongly agree).

Perceived Autonomy Support

Perceived autonomy support will be assessed using the perceived autonomy support scale for exercise settings [45]. For children, the scale refers to autonomy support from parents, while for parents, the scale makes reference to autonomy support received from family. All items are scored on a 5-point Likert scale (1=strongly disagree to 5=strongly agree).

Autonomous and Controlled Motivation

Autonomous and controlled motivation for both parents and children is assessed using 4 items each [46], with responses provided on 5-point scales (1=strongly disagree to 5=strongly agree).

Attitude

Attitude toward engaging in physical activity is assessed using 3 items with a common stem [44,47], with responses provided on a 5-point semantic differential scale (eg, unenjoyable [1] to enjoyable [5]).

Subjective Norms

Subjective norms in parents are assessed using 3 items referring to important others [44,47]. Children answered similar items, but in specific reference to family and friends separately. All items are scored on a 5-point Likert scale (1=strongly disagree to 5=strongly agree).

Perceived Behavioral Control

Perceived behavioral control is assessed in both parents and children using 2 items [44,47], with responses provided on 5-point scales (1=strongly disagree to 5=strongly agree).

Intention

Intention to engage in leisure time physical activity is assessed in both parents and children through 3 items [44,47], with responses provided on 5-point scales (1=strongly disagree to 5=strongly agree).

Self-Monitoring

Self-monitoring toward physical activity is assessed using 2 items [44,48], each scored on a 5-point Likert scale (1=strongly disagree to 5=strongly agree).

Habit

Habits are assessed using the 4-item automaticity subscale of the self-reported habit index [49,50], with responses provided on 5-point scales (1=strongly disagree to 5=strongly agree).

Acceptability

For participants in the immediate intervention group, the postintervention (3 months) web-based questionnaire will include survey items assessing the accessibility and feasibility of intervention procedures. Participants will also be invited to

attend a 45-minute web-based exit interview to explore participant perceptions of the intervention content and possible improvements for future implementation.

Data Analysis

Hypotheses will be tested using R software. All analyses will initially be performed as intention-to-treat, and per-protocol analyses will also be undertaken for comparison. Patterns of missing data will be explored using the Little missing completely at random test. Missing data in the final analysis will be inferred using full-information maximum likelihood analysis. We will test the efficacy of the intervention on our primary outcome, self-reported leisure-time physical activity, using an iterative series of generalized linear models. Independent variables will include time, intervention condition, demographic covariates (eg, start date, gender, and age), delivery group clustering, within-dyad clustering, and person-intervention theory fit $P\Delta$ [51]. Each variable group will be added in a subsequent iteration of the model, and model fit statistics will be examined at each iteration. This process will be repeated for each secondary outcome variable (perceived autonomy support, autonomous motivation, attitude, subjective norm, perceived behavioral control, action planning, coping planning, self-monitoring, and behavioral automaticity).

We also intend to assess the effect of theory-based mediators on change in physical activity using a path model. Specifically, we aim to assess whether the effects of intervention conditions on change scores in physical activity outcomes (both primary and secondary) are mediated by change scores in each of the psychological constructs targeted by the intervention (ie, perceived autonomy support, autonomous motivation, attitude, subjective norm, perceived behavioral control, action planning, coping planning, self-monitoring, and behavioral automaticity).

Ethical Considerations

All study procedures have been approved by the University of Jyväskylä Human Sciences Ethics Committee (statement number 806/13.00.04.00/2023). All parents interested in participating in the study will be presented with detailed information about the intervention, potential risks to participants, the right to withdraw, and data security arrangements. Parents will have the chance to read this information and ask questions of the research team before providing their informed consent to participate. Data will be stored on secure cloud-based servers hosted by the University of Jyväskylä consistent with our data archiving and storage management plan, compliant with university guidelines. At the conclusion of data collection, participants' physical activity and data on psychological measures at each measurement point will be matched using pseudonymized codes and deidentified to the greatest extent possible. Participants will not be offered any financial or other compensation for their participation.

Results

The project team received final notification of research funding approval for the current project from the Finnish Ministry of Education and Culture, Sport Science Funds, in March 2022 (PROJECT 350904), and the trial has been preregistered on ClinicalTrials.gov (ID 806/13.00.04.00/2023). Enrollment into the trial commenced on September 20, 2023. Enrollment is scheduled to continue until March 2024, with the final collection of follow-up data scheduled for December 2024.

We expect that the research will provide valuable formative evidence for the efficacy of a theory-driven family-based physical activity intervention strategy. Further, as the proposed trial includes open materials and tests of the theory-driven mechanistic effects that may encourage behavior change, this research may also serve as a valuable stepping stone to the development of more large-scale, low-cost interventions for family behavior change.

Discussion

Overview

This protocol presents a randomized controlled trial aiming to increase physical activity levels in inactive parent-child dyads within Finland, based on the integrated behavior change model. We hypothesize in this protocol that both parents and children will show increased levels of physical activity, our primary outcome variable, both at the immediate and 3-month postintervention stage, relative to a waitlist control group. Further, we hypothesize we will observe similar changes in the trial's secondary outcomes, the psychological constructs of the integrated behavior change model (ie, autonomy support, autonomous motivation, attitude, subjective norm, perceived behavioral control, self-monitoring, intentions, and habit), in the intervention group relative to the waitlist control group.

Potential Findings and Implications

Children transitioning into adolescence have shown a sharp decline in activity levels [3], while parents are generally less active than similar adults without children [8]. Thus, both populations individually represent valuable targets for intervention. Recognizing this, governments and health departments have recommended behavioral interventions to promote physical activity participation in both groups. However, beyond strategies to influence physical activity in either children or parents separately, research indicates that parents and children likely have a noteworthy influence on each other's physical activity behaviors and beliefs [6,7,9]. Thus, the delivery of interventions in family contexts, such as parent-child dyads, represents a potentially highly valuable strategy to promote physical activity participation in both populations. This is supported to a degree in meta-analysis, as dyadic interventions encouraging an active lifestyle demonstrated slightly larger effects than those targeting individuals [10]. Yet, such interventions remain relatively rare compared to more traditional, individual-targeted programs, particularly those that are based on behavioral theory which may contribute to their efficacy and relevance to health sciences overall [10].

This study tests a theory-based family behavioral intervention aimed at promoting change in physical activity participation in parent-child dyads. The intervention aims to foster autonomous motivation, enhance social support, and reduce perceived barriers to exercise in an atmosphere that is accepting and open. The intervention will make a unique contribution to practice

and theory. Given the low levels of physical activity participation in adult and child populations, demonstrating the efficacy of web-based behavioral intervention in increasing physical activity that is both replicable and potentially scalable will make a valuable contribution to practice in health care contexts. In this research, we aim to enhance the potential usefulness of this intervention in the context of informing refined, scalable interventions based on results with the use of open materials and data, including intervention content and delivery guides. Further, from a scientific perspective, the application of a theory-based intervention developed in line with current practice intervention guidelines presents a potentially valuable test of mechanistic effects presented in the integrated behavior change theory and its component models [12-15], identifying the "active ingredients" of the intervention that are associated with desired outcomes. That is, while the integrated behavior change theory has been supported in several correlational studies [22,23,52], such research only provides an indication of the likely variables most important in determining behavior and can by their correlational nature not be used for any assertions of direction or causality. Thus, a key contribution of this intervention is assessing not only whether the program is successful in changing behavior, but also in assessing which target constructs mediate the effects of the intervention on behavior change and may therefore be most valuable when refining current strategies or developing new programs.

Limitations

Beyond the expected value presented by the research, it is also important to note that the trial faces some expected and inherent challenges and limitations. For example, as the intervention does not include any reward or payment to participants beyond the benefits of the intervention itself, it is likely that parents who consent to enroll themselves and their child in the program will already be at least somewhat motivated to change their physical activity behavior. Such an issue has been noted in the previous parent-for-child interventions [53]. If this is the case, it is likely that the intervention effects will not be as strong as expected, as already motivated participants possess a lesser degree of potential for change than might be expected in families with unmotivated parents. While this nonetheless poses a challenge to the intervention, it is important to note that motivation or knowledge of the need for physical activity is commonplace [9,54], even as actual activity levels remain low. As the strategies used in this intervention include training parents in autonomy support rather than controlling strategies that may inhibit their child's autonomy and thus harm the development of active lifestyles [20,55], as well as strategies to bridge the intention-behavior gap, this trial still has bona fide value in targeting this key population. However, the problem of accessing and enrolling unmotivated families into intervention programs remains a concern for behavior change research.

Conclusions

Given the generally low levels of physical activity in Finnish parents and children, there is a notable need for intervention strategies aiming to encourage an active lifestyle in these populations. This protocol presents an upcoming randomized control trial based upon the integrated behavior change model, which aims to use a series of web-based, theory-based behavior-change strategies delivered to both parents and children as a dyadic program. In doing so, the proposed trial aims to extend upon current literature in several key aspects. First, by targeting parents and children as a dyad, the proposed study aims to add to the available literature on whether physical activity behavior change programs may be more efficacious when targeting the family unit, rather than parents or children individually. Second, as this study uses a theory-based design, testing change in both physical activity and related psychological constructs, the trial also offers an opportunity to test which beliefs and psychological factors are most associated with concomitant change in physical activity. These data, combined with the trial's open materials, may thus serve as a valuable stepping stone to the development of more large-scale, low-cost interventions for family behavior change.

Acknowledgments

This intervention has received funding from the Finnish Ministry of Education, Science, and Culture, Sports Science Funds (grant 350904, principal investigator MH).

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the Finnish Ministry of Education and Culture.
[PDF File (Adobe PDF File), 44 KB - resprot_v13i1e55960_app1.pdf]

References

1. Haskell WL, Blair SN, Hill JO. Physical activity: health outcomes and importance for public health policy. Prev Med 2009;49(4):280-282. [doi: 10.1016/j.ypmed.2009.05.002] [Medline: 19463850]
2. Wennman H, Borodulin K. Associations between physical activity types and reaching the physical activity guidelines: the FinHealth 2017 study. Scand J Med Sci Sports 2021;31(2):418-426. [doi: 10.1111/sms.13840] [Medline: 32996175]

3. Lounassalo I, Salin K, Kankaanpää A, Hirvensalo M, Palomäki S, Tolvanen A, et al. Distinct trajectories of physical activity and related factors during the life course in the general population: a systematic review. BMC Public Health 2019;19(1):271 [FREE Full text] [doi: 10.1186/s12889-019-6513-y] [Medline: 30841921]
4. Christofaro DGD, Andersen LB, de Andrade SM, de Barros MVG, Saraiva BTC, Fernandes RA, et al. Adolescents' physical activity is associated with previous and current physical activity practice by their parents. J Pediatr (Rio J) 2018;94(1):48-55 [FREE Full text] [doi: 10.1016/j.jped.2017.01.007] [Medline: 28754602]
5. Fuemmeler BF, Anderson CB, Mâsse LC. Parent-child relationship of directly measured physical activity. Int J Behav Nutr Phys Act 2011;8:17 [FREE Full text] [doi: 10.1186/1479-5868-8-17] [Medline: 21385455]
6. Tilga H, Kalajas-Tilga H, Hein V, Raudsepp L, Koka A. Perceived autonomy support from peers, parents, and physical education teachers as predictors of physical activity and health-related quality of life among adolescents—a one-year longitudinal study. Educ Sci 2021;11(9):457 [FREE Full text] [doi: 10.3390/educsci11090457]
7. Hagger M, Chatzisarantis NLD, Hein V, Soós I, Karsai I, Lintunen T, et al. Teacher, peer and parent autonomy support in physical education and leisure-time physical activity: a trans-contextual model of motivation in four nations. Psychol Health 2009;24(6):689-711. [doi: 10.1080/08870440801956192] [Medline: 20205021]
8. Berge JM, Larson N, Bauer KW, Neumark-Sztainer D. Are parents of young children practicing healthy nutrition and physical activity behaviors? Pediatrics 2011;127(5):881-887 [FREE Full text] [doi: 10.1542/peds.2010-3218] [Medline: 21482603]
9. Hamilton K, White KM. Identifying parents' perceptions about physical activity: a qualitative exploration of salient behavioural, normative and control beliefs among mothers and fathers of young children. J Health Psychol 2010;15(8):1157-1169. [doi: 10.1177/1359105310364176] [Medline: 20472605]
10. Carr RM, Prestwich A, Kwasnicka D, Thøgersen-Ntoumani C, Gucciardi DF, Quested E, et al. Dyadic interventions to promote physical activity and reduce sedentary behaviour: systematic review and meta-analysis. Health Psychol Rev 2019;13(1):91-109 [FREE Full text] [doi: 10.1080/17437199.2018.1532312] [Medline: 30284501]
11. O'Connor TM, Jago R, Baranowski T. Engaging parents to increase youth physical activity a systematic review. Am J Prev Med 2009;37(2):141-149. [doi: 10.1016/j.amepre.2009.04.020] [Medline: 19589450]
12. Hagger MS, Chatzisarantis NLD. Integrating the theory of planned behaviour and self-determination theory in health behaviour: a meta-analysis. Br J Health Psychol 2009;14(Pt 2):275-302. [doi: 10.1348/135910708X373959] [Medline: 18926008]
13. Deci EL, Ryan RM. Intrinsic Motivation and Self-Determination in Human Behavior. New York: Plenum Press; 1985.
14. Ajzen I. The theory of planned behavior. Organ Behav Hum Decis Process 1991;50(2):179-211. [doi: 10.1016/0749-5978(91)90020-T]
15. Schwarzer R, Luszczynska A. How to overcome health-compromising behaviors. Eur Psychol 2008;13(2):141-151. [doi: 10.1027/1016-9040.13.2.141]
16. Strack F, Deutsch R. Reflective and impulsive determinants of social behavior. Pers Soc Psychol Rev 2004;8(3):220-247 [FREE Full text] [doi: 10.1207/s15327957pspr0803_1] [Medline: 15454347]
17. Deci EL, Ryan RM. The "what" and "why" of goal pursuits: human needs and the self-determination of behavior. Psychol Inq 2000;11(4):227-268. [doi: 10.1207/s15327965pli1104_01]
18. Teixeira PJ, Carraça EV, Markland D, Silva MN, Ryan RM. Exercise, physical activity, and self-determination theory: a systematic review. Int J Behav Nutr Phys Act 2012;9:78 [FREE Full text] [doi: 10.1186/1479-5868-9-78] [Medline: 22726453]
19. Ryan RM, Deci EL. Self-determination theory and the facilitation of intrinsic motivation, social development, and well-being. Am Psychol 2000;55(1):68-78. [doi: 10.1037//0003-066x.55.1.68] [Medline: 11392867]
20. Cheung CS, Pomerantz EM, Wang M, Qu Y. Controlling and autonomy-supportive parenting in the United States and China: beyond children's reports. Child Dev 2016;87(6):1992-2007. [doi: 10.1111/cdev.12567] [Medline: 27317628]
21. Vasquez AC, Patall EA, Fong CJ, Corrigan AS, Pine L. Parent autonomy support, academic achievement, and psychosocial functioning: a meta-analysis of research. Educ Psychol Rev 2015;28(3):605-644. [doi: 10.1007/s10648-015-9329-z]
22. Hagger MS, Trost N, Keech JJ, Chan DKC, Hamilton K. Predicting sugar consumption: application of an integrated dual-process, dual-phase model. Appetite 2017;116:147-156. [doi: 10.1016/j.appet.2017.04.032] [Medline: 28461198]
23. Phipps DJ, Hagger MS, Hamilton K. Predicting limiting 'free sugar' consumption using an integrated model of health behavior. Appetite 2020;150:104668. [doi: 10.1016/j.appet.2020.104668] [Medline: 32184092]
24. Phipps DJ, Hannan T, Hamilton K. A cross-lagged model of habits, implicit attitudes, autonomous motivation, and physical activity during COVID-19. Psychol Health Med 2023;28(10):2813-2824. [doi: 10.1080/13548506.2022.2151634] [Medline: 36469542]
25. Steinmetz H, Knappstein M, Ajzen I, Schmidt P, Kabst R. How effective are behavior change interventions based on the theory of planned behavior? Z Psychol 2016;224(3):216-233. [doi: 10.1027/2151-2604/a000255]
26. Tsorbatzoudis H. Evaluation of a school-based intervention programme to promote physical activity: an application of the theory of planned behavior. Percept Mot Skills 2005;101(3):787-802. [doi: 10.2466/pms.101.3.787-802] [Medline: 16491680]
27. Webb TL, Sheeran P. Does changing behavioral intentions engender behavior change? A meta-analysis of the experimental evidence. Psychol Bull 2006;132(2):249-268. [doi: 10.1037/0033-2909.132.2.249] [Medline: 16536643]

28. Rhodes RE, de Bruijn GJ. How big is the physical activity intention-behaviour gap? A meta-analysis using the action control framework. Br J Health Psychol 2013;18(2):296-309. [doi: 10.1111/bjhp.12032] [Medline: 23480428]
29. Orbell S, Sheeran P. 'Inclined abstainers': a problem for predicting health-related behaviour. Br J Soc Psychol 1998;37(Pt 2):151-165. [doi: 10.1111/j.2044-8309.1998.tb01162.x] [Medline: 9639861]
30. Feil K, Fritsch J, Rhodes RE. The intention-behaviour gap in physical activity: a systematic review and meta-analysis of the action control framework. Br J Sports Med 2023;57(19):1265-1271. [doi: 10.1136/bjsports-2022-106640] [Medline: 37460164]
31. Phipps DJ, Hannan TE, Rhodes RE, Hamilton K. A dual-process model of affective and instrumental attitudes in predicting physical activity. Psychol Sport Exerc 2021;54:101899. [doi: 10.1016/j.psychsport.2021.101899]
32. Phipps DJ, Rhodes RE, Jenkins K, Hannan TE, Browning NG, Hamilton K. A dual process model of affective and instrumental implicit attitude, self-monitoring, and sedentary behavior. Psychol Sport Exerc 2022;62:102222. [doi: 10.1016/j.psychsport.2022.102222]
33. Sniehotta FF, Presseau J, Araújo-Soares V. Time to retire the theory of planned behaviour. Health Psychol Rev 2014;8(1):1-7 [FREE Full text] [doi: 10.1080/17437199.2013.869710] [Medline: 25053004]
34. Hamilton K, Ng HTH, Zhang CQ, Phipps DJ, Zhang R. Social psychological predictors of sleep hygiene behaviors in Australian and Hong Kong university students. Int J Behav Med 2021;28(2):214-226. [doi: 10.1007/s12529-020-09859-8] [Medline: 32130683]
35. Ntoumanis N, Ng JYY, Prestwich A, Quested E, Hancox JE, Thøgersen-Ntoumani C, et al. A meta-analysis of self-determination theory-informed intervention studies in the health domain: effects on motivation, health behavior, physical, and psychological health. Health Psychol Rev 2021;15(2):214-244 [FREE Full text] [doi: 10.1080/17437199.2020.1718529] [Medline: 31983293]
36. Sheeran P, Maki A, Montanaro E, Avishai-Yitshak A, Bryan A, Klein WMP, et al. The impact of changing attitudes, norms, and self-efficacy on health-related intentions and behavior: a meta-analysis. Health Psychol 2016;35(11):1178-1188. [doi: 10.1037/hea0000387] [Medline: 27280365]
37. Rhodes RE, Naylor PJ, McKay HA. Pilot study of a family physical activity planning intervention among parents and their children. J Behav Med 2010;33(2):91-100. [doi: 10.1007/s10865-009-9237-0] [Medline: 19937106]
38. Teixeira PJ, Marques MM, Silva MN, Brunet J, Duda JL, Haerens L, et al. A classification of motivation and behavior change techniques used in self-determination theory-based interventions in health contexts. Motiv Sci 2020;6(4):438-455. [doi: 10.1037/mot0000172]
39. Michie S, Ashford S, Sniehotta FF, Dombrowski SU, Bishop A, French DP. A refined taxonomy of behaviour change techniques to help people change their physical activity and healthy eating behaviours: the CALO-RE taxonomy. Psychol Health 2011;26(11):1479-1498. [doi: 10.1080/08870446.2010.540664] [Medline: 21678185]
40. OSF. URL: https://osf.io/bs5ng/ [accessed 2024-02-08]
41. Godin G. The Godin-Shephard leisure-time physical activity questionnaire. Health Fit J Can 2011;4(1):18-22 [FREE Full text] [doi: 10.14288/hfjc.v4i1.82]
42. Hagströmer M, Oja P, Sjöström M. The International Physical Activity Questionnaire (IPAQ): a study of concurrent and construct validity. Public Health Nutr 2006;9(6):755-762 [FREE Full text] [doi: 10.1079/phn2005898] [Medline: 16925881]
43. van Hees VT, Migueles JH, Sabia S, Patterson MR, Fang Z, Heywood J, et al. GGIR: raw accelerometer data analysis. CRAN. 2023. URL: https://cran.r-project.org/web/packages/GGIR/index.html [accessed 2024-02-06]
44. Polet J, Hassandra M, Lintunen T, Laukkanen A, Hankonen N, Hirvensalo M, et al. Using physical education to promote out-of school physical activity in lower secondary school students—a randomized controlled trial protocol. BMC Public Health 2019;19(1):157 [FREE Full text] [doi: 10.1186/s12889-019-6478-x] [Medline: 30727989]
45. Hagger MS, Chatzisarantis NL, Hein V, Pihu M, Soós I, Karsai I. The Perceived Autonomy Support Scale for Exercise Settings (PASSES): development, validity, and cross-cultural invariance in young people. Psychol Sport Exerc 2007;8(5):632-653. [doi: 10.1016/j.psychsport.2006.09.001]
46. Ryan RM, Connell JP. Perceived locus of causality and internalization: examining reasons for acting in two domains. J Pers Soc Psychol 1989;57(5):749-761. [doi: 10.1037//0022-3514.57.5.749] [Medline: 2810024]
47. Ajzen I. Constructing a theory of planned behavior questionnaire. University of Massachusetts Amherst. Amherst, MA; 2006. URL: https://www.researchgate.net/publication/235913732_Constructing_a_Theory_of_Planned_Behavior_Questionnaire [accessed 2024-02-06]
48. Gholami M, Schwarzer R. Brief scales for the multilingual assessment of HAPA variables. Freie Universität Berlin. 2014. URL: https://www.psyc.de/hapascales.pdf [accessed 2024-02-06]
49. Gardner B, Abraham C, Lally P, de Bruijn GJ. Towards parsimony in habit measurement: testing the convergent and predictive validity of an automaticity subscale of the Self-Report Habit Index. Int J Behav Nutr Phys Act 2012;9:102 [FREE Full text] [doi: 10.1186/1479-5868-9-102] [Medline: 22935297]
50. Verplanken B, Orbell S. Reflections on past behavior: a self-report index of habit strength. J Applied Social Pyschol 2006;33(6):1313-1330. [doi: 10.1111/j.1559-1816.2003.tb01951.x]
51. Knittle K, Peters GJ. Potential for change (PΔ): new metrics for tailoring and predicting response to behavior change interventions. OSF Preprints. Preprint posted online on February 2, 2019 [FREE Full text] [doi: 10.17605/OSF.IO/25EWR]

52. Hagger MS, Chatzisarantis NLD. An integrated behavior change model for physical activity. Exerc Sport Sci Rev 2014;42(2):62-69 [FREE Full text] [doi: 10.1249/JES.0000000000000008] [Medline: 24508739]
53. Hamilton K, Phipps D, Peden A. Supervising and restricting young children's access to water: program evaluation of 'keep watch'. Griffith University and Royal Life Saving Society—Australia. 2019. URL: https://research-repository.griffith.edu.au/handle/10072/385125 [accessed 2024-02-06]
54. Hamilton K, White KM. Understanding parental physical activity: meanings, habits, and social role influence. Psychol Sport Exerc 2010;11(4):275-285. [doi: 10.1016/j.psychsport.2010.02.006]
55. Roemmich JN, Lambiase MJ, McCarthy TF, Feda DM, Kozlowski KF. Autonomy supportive environments and mastery as basic factors to motivate physical activity in children: a controlled laboratory study. Int J Behav Nutr Phys Act 2012;9:16 [FREE Full text] [doi: 10.1186/1479-5868-9-16] [Medline: 22353207]

Edited by A Mavragani; submitted 31.12.23; this is a non–peer-reviewed article;accepted 02.02.24; published 21.03.24.

Please cite as:
Phipps D, Green WT, Aho R, Kettunen E, Biddle S, Hamilton K, Laukkanen A, Aunola K, Chan DK, Hankonen N, Hassandra M, Kärkkäinen T, Kykyri VL, Polet J, Rhodes R, Ruiz MC, Sääkslahti A, Schneider J, Toivonen HM, Lintunen T, Hagger M, Knittle K
A Web-Based Physical Activity Promotion Intervention for Inactive Parent-Child Dyads: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2024;13:e55960
URL: https://www.researchprotocols.org/2024/1/e55960
doi:10.2196/55960
PMID:38512336

Protocol

Equity-Centered Postdischarge Support for Medicaid-Insured People: Protocol for a Type 1 Hybrid Effectiveness-Implementation Stepped Wedge Cluster Randomized Controlled Trial

J Margo Brooks Carthon[1*], RN, PhD; Heather Brom[1*], RN, PhD; Marsha Grantham-Murrillo[2], RN, MSN; Kathy Sliwinski[1], BSN, RN; Aleigha Mason[1], BSN, RN; Mindi Roeser[3], MD; Donna Miles[3], CRNP, MSN; Dianne Garcia[1], BSN, RN; Jovan Bennett[4], BS; Michael O Harhay[1], PhD; Emilia Flores[5], RN, PhD; Kelvin Amenyedor[1], MPH, MD; Rebecca Clark[3], RN, PhD

[1]University of Pennsylvania, Philadelphia, PA, United States

[2]Penn Medicine at Home, Philadelphia, PA, United States

[3]Pennsylvania Hospital, Philadelphia, PA, United States

[4]Penn Center for Community Health Workers, Philadelphia, PA, United States

[5]University of Pennsylvania Health System, Philadelphia, PA, United States

[*]these authors contributed equally

Corresponding Author:
J Margo Brooks Carthon, RN, PhD
University of Pennsylvania
418 Curie Boulevard
Philadelphia, PA, 19104
United States
Phone: 1 215 498 8050
Email: jmbrooks@nursing.upenn.edu

Abstract

Background: Disparities in posthospitalization outcomes for people with chronic medical conditions and insured by Medicaid are well documented, yet interventions that mitigate them are lacking. Prevailing transitional care interventions narrowly target people aged 65 years and older, with specific disease processes, or limitedly focus on individual-level behavioral change such as self-care or symptom management, thus failing to adequately provide a holistic approach to ensure an optimal posthospital care continuum. This study evaluates the implementation of THRIVE—an evidence-based, equity-focused clinical pathway that supports Medicaid-insured individuals with multiple chronic conditions transitioning from hospital to home by focusing on the social determinants of health and systemic and structural barriers in health care delivery. THRIVE services include coordinating care, standardizing interdisciplinary communication, and addressing unmet clinical and social needs following hospital discharge.

Objective: The study's objectives are to (1) examine referral patterns, 30-day readmission, and emergency department use for participants who receive THRIVE support services compared to those receiving usual care and (2) evaluate the implementation of the THRIVE clinical pathway, including fidelity, feasibility, appropriateness, and acceptability.

Methods: We will perform a sequential randomized rollout of THRIVE to case managers at the study hospital in 3 steps (4 in the first group, 4 in the second, and 5 in the third), and data collection will occur over 18 months. Inclusion criteria for THRIVE participation include (1) being Medicaid insured, dually enrolled in Medicaid and Medicare, or Medicaid eligible; (2) residing in Philadelphia; (3) having experienced a hospitalization at the study hospital for more than 24 hours with a planned discharge to home; (4) agreeing to home care at partner home care settings; and (5) being aged 18 years or older. Qualitative data will include interviews with clinicians involved in THRIVE, and quantitative data on health service use (ie, 30-day readmission, emergency department use, and primary and specialty care) will be derived from the electronic health record.

Results: This project was funded in January 2023 and approved by the institutional review board on March 10, 2023. Data collection will occur from March 2023 to July 2024. Results are expected to be published in 2025.

Conclusions: The THRIVE clinical pathway aims to reduce disparities and improve postdischarge care transitions for Medicaid-insured patients through a system-level intervention that is acceptable for THRIVE participants, clinicians, and their teams in hospitals and home care settings. By using our equity-focused case management services and leveraging the power of the electronic medical record, THRIVE creates efficiencies by identifying high-need patients, improving communication across

acute and community-based sectors, and driving evidence-based care coordination. This study will add important findings about how the infusion of equity-focused principles in the design and evaluation of evidence-based interventions contributes to both implementation and effectiveness outcomes.

International Registered Report Identifier (IRRID): DERR1-10.2196/54211

Trial Registration: ClinicalTrials.gov NCT05714605; https://clinicaltrials.gov/ct2/show/NCT05714605

(JMIR Res Protoc 2024;13:e54211) doi:10.2196/54211

KEYWORDS

health care disparities; evidence-based practice; Medicaid; transitional care; implementation science; socioeconomic disparities in health

Introduction

Background

Complex care management provides critical support in the days and weeks following hospitalization for individuals with multiple chronic conditions. This postdischarge support can be especially beneficial for nearly 80 million individuals in the United States who are insured by Medicaid [1] and experience higher rates of chronic illness [2], more frequent hospitalizations, and worse clinical outcomes following discharge [3-5]. Readmissions among adults insured by Medicaid ages 45-64 years stand at 24% compared to 20% for older adults insured by Medicare [6]. Similarly, about 34% of individuals insured by Medicaid will experience an emergency department (ED) visit annually, far exceeding the rates of those insured commercially [7]. They experience deficits in primary care assessment and treatment and fewer preventive treatments and guideline-concordant care [8,9]. Thus, Medicaid-insured patients may present to the hospital with poorly managed chronic medical conditions compared with other patients and subsequently require more intensive transitional care coordination in the aftermath of a hospitalization. The need to improve support for Medicaid-insured people following hospitalization prompted our development of the THRIVE clinical pathway. THRIVE is a clinical pathway that supports Medicaid-insured individuals with multiple chronic conditions transitioning from hospital to home by coordinating care, standardizing communication, and addressing unmet needs following hospital discharge, including the social determinants of health.

Most existing postdischarge or transitional care programs were not developed to attend to the specific needs of people insured by Medicaid and instead support older adults or patients with specific chronic illnesses such as heart failure. Other postdischarge support programs require the addition of trained health care providers such as advanced practice nurses or patient navigators to coordinate care [10-12]. At least 1 randomized controlled trial (RCT) evaluating the use of community health workers (CHWs) has demonstrated lower rates of rehospitalization for enrolled low-income individuals with significant social needs [13]. Despite facilitating important links to community-based services, CHWs are unable to manage clinical needs [13-15]. Other postdischarge support programs such as the Camden Coalition Care Model provide transitional care support to people with significant social needs with high rates of health care use, many of whom are insured through Medicaid [16]. An RCT of the Camden Coalition Care Model demonstrated no differences in readmissions at 180 days between treatment and comparison [17]. The care transitions innovation model also provides transitional care support for economically disadvantaged adults, although an RCT found no reductions in 30-day readmissions or ED use [12]. At least 3 additional studies by Liss et al [18], Balaban et al [19], and Jackson et al [20] featured weekly health coaching, self-management education, and medical home follow-up for medically and socially complex patients, although the results of these interventions have been mixed. Inconsistent findings among existing postdischarge support programs suggest the need for alternative innovations that focus on systemic and structural barriers in health care delivery.

Similar to other inequities, posthospitalization disparities among people insured by Medicaid can be traced to a long history of institutional and economic inequities impacting care delivery and outcomes. Racial and ethnically minoritized populations are overrepresented in Medicaid compared to other forms of insurance, with approximately half of Medicaid enrollees younger than 65 years of age being members of racial and ethnically diverse backgrounds [21]. With incomes 138% below the federal poverty level [22], people insured by Medicaid experience the impact of the social determinants of health, including higher levels of financial strain and concerns over out-of-pocket costs, and experience more challenges in accessing specialists and community-based care [23-28]. People insured by Medicaid are also more likely to experience the impact of systemic and institutional racism. Systemic racism refers to the distribution of goods and services in such a way that advantages one group over another or fails to provide adequate resources in the face of need. Systemic factors such as inadequate discharge planning and poor care coordination similarly contribute to unfavorable posthospitalization outcomes [21,27-29]. Interpersonal racism is often expressed through bias and discrimination and is often expressed through microaggressions and stigmatizing language. Distinct from Medicare, Medicaid has its roots in the public welfare system, which has resulted in significant social stigma. Medicaid beneficiaries have described encounters with medical professionals where they were subjected to racial and socioeconomic prejudice [29,30]. These experiences may result in the avoidance of health care settings altogether and more difficulties accessing timely specialty care, all of which paradoxically increase ED use or lead to avoidable

hospitalizations due to delayed management of chronic illnesses [31,32].

Given the long-standing disparities experienced by people insured by Medicaid during and following hospitalization, there is a need for transitional care support focused on systemic and structural barriers to care and social determinants of health. The Centers for Disease Control and Prevention [33] defines health equity as "the state where everyone has a fair and just opportunity to attain their highest level of health." Using an equity lens draws attention to those at greatest risk to how social and economic strata shape access to material resources while also identifying the impact of marginalizing conditions such as racism and health resource constraints that intersect and result in disparate outcomes [34]. Using an equity lens also emphasizes what Peterson et al [35] refer to as the multiple, intersecting spheres of power, defined as the practices, processes, and policies that determine the distribution and access to resources and opportunities needed to be healthy. These spheres of power intersect with individual factors (eg, personal agency) to produce disparate outcomes. From this perspective, addressing postdischarge disparities requires a focus on optimizing service delivery and interdisciplinary collaborations across settings.

Codeveloping the THRIVE Clinical Pathway

Using an equity lens, our interdisciplinary team of clinicians, researchers, and community members formed to engage in meaningful action to support people insured by Medicaid and transform health care practices and processes that impeded sufficient transitional care support [36]. We began with months of participatory activities informed by an equity lens and principles of human-centered design [37], machine learning [38], and mixed methods approaches [39], which culminated in the development of THRIVE [40]. The THRIVE clinical pathway was launched in a large Level 1 Trauma Center in Philadelphia in 2019 and includes five core components: (1) the identification of individuals insured by Medicaid and coordination of home care referral during discharge planning while hospitalized; (2) provision of immediate home care services where nurses perform medication reconciliation, intensive teaching, and chronic disease management; (3) continued clinical oversight by discharging physicians; and (4) standardized communication between community and acute care providers via web-based case management that (5) prioritizes health-related social needs such as housing or food insecurity faced by Medicaid-insured patients (Figure 1). Our work as a team is anchored by our advisory board, which is comprised of community members, some of whom are Medicaid insured. The THRIVE Community Advisory Board meets quarterly to meaningfully engage past THRIVE participants, caregivers, and community members to ensure that the program goals are rooted in the vision and values of the community we serve.

In many health care settings, posthospitalization disparities among economically disadvantaged people are linked to personal deficits or behaviors. They are often referred to by their volume of health resource use, invariably referred to as "high-cost high needs," "superusers," "frequent flyers," "noncompliant," or "bounce backs," and are essentially blamed for poor outcomes. From this perspective, postdischarge disparities are often regarded as immutable social circumstances or moral failures beyond the purview of medicine's reach instead of a result of the impact of the social determinants of health, structural determinants such as failures in service delivery (eg, fragmented care coordination), and interpersonal racism [41]. In developing THRIVE, we sought to counter long-standing stigmatizing views and instead directed our focus on re-engineering service delivery and intensifying resources to those most in need while maintaining active involvement with affected community members in programmatic design and sustainability efforts.

Published results from a nonrandomized pilot of the first year of the THRIVE pathway revealed that participants experienced increased connections to postacute care services, including social support, and a 50% decrease in rates of 30-day readmissions and ED use compared to patients receiving standard care [42]. With these early findings, we are now poised to evaluate a scalable and sustainable postdischarge management process in a new setting and with a more rigorous evaluation and attention to organizational factors influencing success.

This study will deploy a type 1 hybrid effectiveness-implementation stepped wedge cluster RCT across a single hospital in Philadelphia [43]. The advantage of this trial design is that it offers an efficient and practical way to introduce THRIVE to new sites while reducing the ethical concerns of withholding an intervention that has shown benefit for economically disadvantaged populations. This study will also be guided by the Exploration, Preparation, Implementation, Sustainment framework; Proctor's outcomes framework; and the Health Equity Implementation Framework (HEIF) [44-46]. The HEIF adapts the Integrated Promoting Action on Research in Implementation in Health Services framework. The HEIF proposes determinants that are believed to predict the successful and equitable implementation of an intervention. The 3 health equity domains included in the HEIF include cultural factors, clinical encounter factors, and societal context [47]. Our use of the framework will help us to detect any factors that might lead to uneven referrals to THRIVE; disparate benefits to the intervention; and any barriers that might prevent organizations, health care providers, or administrators from engaging in the intervention. In their recently published paper, Brownson et al [48] noted that "Incorporating a strong equity focus in implementation science requires not only a deliberate emphasis on the needs, culture, and history of the populations and communities but also more critical analyses and deeper understanding of systems and policies, including care delivery and provider attitudes from which inequities might arise." They propose action steps for making health equity more prominent in implementation science. To that end, we incorporate and adapt our study design to ensure principles of equity in the approach to data collection, measures, contextual alignment, and dissemination practices (Table 1).

Figure 1. Components of the THRIVE clinical pathway. APP: advanced practice provider; EHR: electronic health record; MD: medical doctor; OT: occupational therapy; PRN: pro re nata (as needed); PT: physical therapy; RN: registered nurse; SW: social worker.

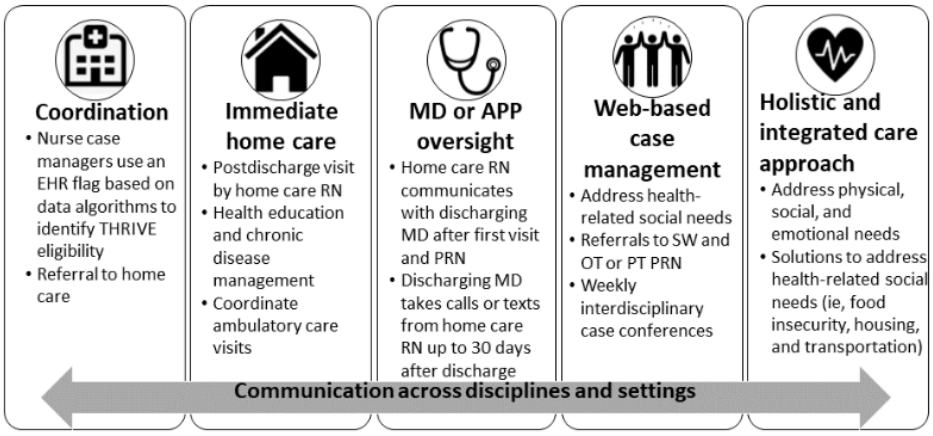


Table 1. Equity-relevant domains included in the implementation and outcome evaluation of THRIVE [48].

Domain	Recommendation	Core elements within this study
Evidence base	Link social determinants with health outcomes	Implement THRIVE for all Medicaid-insured individuals at a new study site to meet the postdischarge clinical and social needs of an economically disadvantaged population.
Methods and measures	Integrate equity into implementation models	Incorporate the 3 domains of the Health Equity Implementation Framework into the implementation evaluation.
Context	Engage organizations in internal and external equity efforts	Engage with clinical partners, administrators, and community advisory board members to implement THRIVE at a new site.
Cross-cutting issues	Focus on equity in dissemination efforts	Plan activities with THRIVE Community Advisory Board to disseminate study results.

Aims and Hypotheses

The specific aims of this research are to:

1. Examine referral patterns, 30-day readmission, and ED use patterns for participants who receive THRIVE support services compared to those receiving usual care.
   - Hypothesis 1: We anticipate that referral patterns will increase and that 30-day readmissions and ED use will decrease for THRIVE participants compared to usual care.
2. Evaluate the implementation of the THRIVE clinical pathway, including fidelity, feasibility, appropriateness, and acceptability.

Methods

Overview

Our study methods are described per the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement and the CONSORT (Consolidated Standards of Reporting Trials) extension for stepped wedge cluster RCTs [49,50]. The SPIRIT and CONSORT checklists are included as Multimedia Appendices 1 and 2.

Study Setting

The study setting includes a single site—Pennsylvania Hospital (PAH), the nation's first acute care setting in the country and 1 of 6 hospitals in the University of Pennsylvania Health System. More than 50% of PAH's patient population on the hospitalist service self-identify as racial or ethnic minority individuals, and >25% are Medicaid insured [34]. PAH provides over 40,000 ED visits and >18,000 adult admissions annually.

Design and Randomization

Overview

This is a prospective single-site type 1 hybrid effectiveness-implementation pragmatic stepped wedge cluster RCT. Our stepped wedge design will include a sequential randomized rollout of the intervention to case managers at PAH in 3 steps, and data collection will occur over 18 months. This mixed methods (quantitative and qualitative) study design involves simultaneous collection and analysis of quantitative and qualitative data, giving priority weight to the quantitative data to evaluate program referrals, outcomes, and program fidelity, while qualitative data will evaluate the process through detailed descriptions of perspectives of barriers and facilitators faced by health care providers in implementing the THRIVE intervention [51]. This study includes qualitative interviews and surveys of clinicians and administrators to assess their perspectives on appropriateness, feasibility, and acceptability of THRIVE. Nesting the qualitative interviews within an RCT of the THRIVE intervention will allow us to determine whether the intervention improved primary outcomes (referrals to home care, 30-day readmission, ED use, and connection to primary care providers) and to identify professional and organizational barriers to implementation. Combining these insights with effectiveness outcome data will allow consideration for meaningful contextual factors that are considered critical to the implementation of THRIVE and subsequent outcomes.

Randomization

Groups of case managers (4 in the first group, 4 in the second, and 5 in the third) were randomly assigned by the study methodologist to each sequence using a random number generator. A stepped wedge design—that is, a 1-time crossover design—was used for THRIVE (Table 2).

Specifically, following a baseline data collection period, 4 case managers will be randomized to receive training on the THRIVE clinical pathway. Following training, they begin referring to the THRIVE clinical pathway. At 8-week intervals, the remaining case managers will be trained in the THRIVE intervention and will be able to begin submitting referrals. Since case managers from the sequences work within the same space, the ability to conceal allocation was limited; however, all case managers were made aware of their upcoming ability to refer to the THRIVE clinical pathway.

Table 2. Study design for the type 1 hybrid effectiveness-implementation stepped wedge cluster randomized controlled trial of the THRIVE clinical pathway.

Cluster	Baseline (3 months)	Enrollment period 1 (8 weeks)	Enrollment period 2 (8 weeks)	Enrollment period 3 (8 weeks)	Follow-up (18 months)
Sequence 1 (4 case managers)		✓	✓	✓	✓
Sequence 2 (4 case managers)			✓	✓	✓
Sequence 3 (5 case managers)				✓	✓

THRIVE Eligibility Criteria

Individuals eligible for a THRIVE referral include (1) being Medicaid insured, dually enrolled in Medicaid and Medicare, or Medicaid eligible; (2) residing in Philadelphia; (3) having experienced a hospitalization at the study hospital for more than 24 hours with a planned discharge to home; (4) agreeing to home care at partner home care settings; and (5) being aged 18 years or older. If home care services are declined at any time following discharge, THRIVE services are also discontinued. If palliative or hospice services are ordered following discharge, THRIVE services will not be offered.

Clinician Eligibility and Recruitment

Nurse case managers (CMs), home care nurses, physicians, advanced practice providers, and administrators who are actively involved in supervisory roles or in referring to THRIVE will be invited to provide feedback on the appropriateness, accessibility, feasibility, and workload involved in referring to the THRIVE clinical pathway. During the consenting process, the research coordinator will obtain preferences for the best communication method to schedule the interview (eg, email or telephone call). A total of 22 interviews and surveys are planned. Participants who complete both the surveys and interviews will receive a US $90 gift card by mail.

Ethical Considerations

This study was approved by the University of Pennsylvania's Institutional Review Board (IRB #4 approved this protocol #852910 on March 10, 2023). The study will be conducted according to the Declaration of Helsinki and national regulations. Study participation is voluntary, and written consent will be obtained prior to clinician interviews. Our IRB approval includes a HIPAA (Health Insurance Portability and Accountability Act) waiver of informed consent for THRIVE participants' clinical data. All study data collected will be deidentified, pseudonyms will be used, and data will only be accessible to the research team and stored on password-protected computers. Clinicians will be compensated US $90 by gift card for interview participation. Individual participants will not be identifiable in any published material.

Data Collection and Management

THRIVE Participants and Usual Care Group

Characteristics of THRIVE participants captured in weekly case conferences (eg, home care services, social determinants of health identified and met, and community-based services) will be stored on a Research Electronic Data Capture (REDCap; developed by Vanderbilt University) database. Data will be derived from the patient electronic health record (EHR) and hospital billing system to compare the postdischarge outcomes of participants receiving THRIVE compared to those who do not. These data will be deidentified, and a HIPAA waiver of informed consent was obtained by the University of Pennsylvania's IRB. Data will be stored on a secure password-protected data server, and access will be provided to the study statisticians (MOH), who will be blinded to the assignment of the intervention. All aspects of study design, database integrity, and study conduct will be overseen by our data and evaluation core team, which includes doctorly prepared health service researchers and statisticians.

Clinicians and Administrators

Case managers at PAH will be recruited and enrolled in the study per the stepped wedge design. At 8 weeks and 18 months, we will survey clinicians via Qualtrics (Qualtrics) and convene one-on-one interviews (or focus groups depending on clinician availability). Interviews will be conducted in the setting of the clinician's choice, either in a conference room in the hospital or via Zoom (Zoom Video Communications). During interviews, clinicians and administrators will be asked for permission to audio record the interview. If the participant agrees, all conversations from that point forward will be recorded. If the clinician or administrator consents to the interview but does not agree to recording, to retain the participant, the interviewer will take detailed notes during the conversation instead of recording. Interview documents are labeled with a unique identification number stored separately for identifying information about the participant. The study timeline is outlined in a SPIRIT diagram (Figure 2).

Figure 2. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) diagram—THRIVE schedule of evaluations. ED: emergency department; PCP: primary care provider.

			Study period			
	Preallocation	Site enrollment	Post allocation (THRIVE referral period)			Follow-up
Timepoint	Retrospective data (Nov 27, 2022)	Study start (Mar 27, 2023)	Mar 27, 2023	May 22, 2023	July 17, 2023	Study end (Dec 27, 2024)
Enrollment:						
Nurse case manager		✓				
Sequence assignment		✓				
Interventions:						
Baseline data	←	→				
Sequence 1			←	—	—	→
Sequence 2				←	—	→
Sequence 3					←	→
Assessments:						
Use measures *Patient level (readmissions, ED use, PCP, and specialist appointments)			✓	✓		✓
Implementation measures *Clinician level (eg, appropriateness, acceptability, feasibility, and workload)			✓	✓		✓

Sample Size

We anticipate a sample size of 534 inclusive of THRIVE referrals and the comparison group (derived from the EHR). Based on a power analysis, a sample size of 472 (236 THRIVE participants and 236 comparisons) for the outcome of readmissions, or a sample of 534 (267 THRIVE participants and 267 comparisons) for the outcome of ED visits, will yield 80% power to detect significance at the .05 level. We will target a sample size of 534 to ensure adequate power for both outcomes. We anticipate consenting 22 clinicians and administrators to complete surveys and interviews to provide data for implementation outcomes.

The THRIVE Intervention

Current Usual Care

To provide evidence of the effectiveness and implementation of THRIVE, we will compare individuals receiving THRIVE services to patients receiving usual care. The current usual care will serve as the control condition that patients will receive during the control phases of the design. Usual care may include discharge care planning that reflects the patient's medical needs, which may or may not include referrals to home care, skilled nursing or rehabilitation facilities, and other outpatient services.

Enrollment in THRIVE

Enrollment in THRIVE begins with identification by CMs during hospitalization using a validated predictive algorithm developed by our team [31]. The algorithm is housed in the EHR and leverages principles of behavioral economics to "nudge" CMs to initiate a THRIVE referral. The THRIVE EHR flag was introduced to alleviate the need for CMs to manually identify THRIVE participants.

Once identified, THRIVE participants will receive a home care referral to Penn Medicine at home care services. The initial home care visit will be scheduled and completed by a nurse within 48 hours of discharge, at which time, medications are reconciled, discharge orders are reviewed, and person-centered goals of care are set. During the initial evaluation, home care nurses will determine the frequency of visits deemed necessary, with weekly visits ranging from 1 to 3 times depending on needs. Participants may receive additional services, such as speech or occupational therapy as required. All THRIVE participants receive a social work referral, their psychosocial needs are further assessed, and connections to community resources are provided. THRIVE participants receive a CHW referral as deemed necessary.

As a part of the THRIVE pathway, physician colleagues will extend continuity of care into the home following discharge to

all THRIVE participants. Home care nurses will provide a brief patient status update to discharging physicians following the first home visit. During calls, nurses can raise questions about medications, clarify discharge orders, and receive guidance on emerging symptoms with the provider most recently involved with care. Extended supervision by discharging physicians will be provided for up to 30 days or until THRIVE participants have seen a primary care provider or specialist.

THRIVE participants will receive further support during discussions in our weekly interdisciplinary case management conferences for 4 weeks following discharge. During case management meetings, we will support connections to postacute primary, specialty care, behavioral health, and substance use services as needed. If a source of primary care is absent, we work to link THRIVE participants to community providers. Our intensive support addresses many of the social determinants of health that are known to influence health inequities such as housing, food insecurity, and limitations in access to behavioral health (Figure 1).

Implementation Strategies

We will use a series of implementation strategies to improve the effectiveness of THRIVE and promote its use [52]. These strategies will include (1) building and sustaining a coalition of diverse stakeholders through regular meetings and providing updates on THRIVE outcomes; (2) developing educational materials and conducting ongoing training of CMs, physicians, and advanced practice providers in the hospital and nurses and managers in home care using a scripted in-person training module to teach them about the elements of THRIVE and their role in implementing it; (3) auditing and providing feedback through the use of a referral dashboard to monitor all eligible THRIVE participants to document the individuals who were eligible for the intervention and not referred and providing feedback to case managers and document reasons for why referrals did not take place; (4) emailing reminders to case managers at weeks 2, 4, and 6; (5) identifying and preparing champions to promote the use of THRIVE; and (6) engaging of our advisory board to seek feedback for improvements.

Evaluation

Aim 1

Aim 1 is to examine referral patterns, 30-day readmission, and 30-day ED use patterns for participants who receive THRIVE support services compared to those receiving usual care.

Outcomes and Measures

The primary outcome includes the referral rate to home care made by CMs compared to baseline and the nonrandomized cluster. The secondary outcomes are 30-day readmissions and ED visits. Additional covariate data at the patient (eg, demographics and comorbidities) and unit levels (eg, type of unit and discharging team or provider) will be collected from analyses. For THRIVE participants, these outcomes will be assessed from the date of hospitalization, which resulted in a referral to THRIVE. For the usual care group, we will identify all readmissions and ED visits occurring after the first index hospitalization identified in the EHR for the calendar year of the study. Outcome measures, guiding framework, data sources, collection, and timing are described in Table 3.

Table 3. Summary of outcomes, measures, data sources, collection method, and timing.

Construct and framework	Design	Method of collection	Timing
Aim 1: Examine referral patterns, 30-day readmission, and ED[a] use patterns for participants who receive THRIVE support services compared to those receiving usual care			
• THRIVE referrals[b] • 30-day readmissions[c] • 30-day ED visits[c] • Primary care visit within 30 days of discharge[c] • Specialty care visit within 30 days of discharge[c]	Stepped wedge cluster randomized controlled trial	Electronic health record	Baseline and at the study end
Aim 2: Evaluate the implementation of the THRIVE clinical pathway, including fidelity, feasibility, appropriateness, and acceptability			
Health Equity Implementation Framework (HEIF)			
• Culturally relevant factors[d] • Clinical encounter[e] • Societal context[f]	Mixed methods approach to determine if HEIF factors are associated with uneven or disparate benefits to the intervention and to assess the implementation of THRIVE at a new site	Interviews with clinicians and administrators involved with THRIVE	8-week postintervention from the start of each sequence and at the study end
Exploration, Preparation, Implementation, Sustainment			
• Adoption[g] • Active implementation[h]	Mixed methods approach to determine the adoption and implementation of THRIVE in a new site	Interviews with clinicians and administrators	8-week postintervention from the start of each sequence and at the study end
Proctor implementation outcomes			
• Acceptability[i] • Appropriateness[j] • Feasibility[k]	Mixed methods approach to determine the Proctor implementation outcomes	Survey and interviews with clinicians and administrators	8-week postintervention from the start of each sequence and at the study end
• Fidelity[l]	Retrospective chart review	Standardized THRIVE checklist	Monthly

[a]ED: emergency department.

[b]Proportion of THRIVE referrals of those who are THRIVE eligible.

[c]Proportion of THRIVE participants experiencing the outcome within 30 days of discharge compared to usual care group.

[d]Organizational commitment to addressing disparities.

[e]Relative advantage of THRIVE to patients, degree of fit with existing practice, competing demands, and bias.

[f]Structures outside of the hospital that affect patient care.

[g]Organizational values, culture embedding, and championing adaption.

[h]Organizational priorities and goals and readiness for change and culture or climate.

[i]How fair or reasonable THRIVE is deemed.

[j]To what extent THRIVE seems suitable.

[k]The practicality and ease of delivering THRIVE.

[l]Fidelity to THRIVE's core components.

Analysis

We will develop monthly reports to monitor the referral patterns to the THRIVE clinical pathway. The target estimate and effect measure is the time-adjusted difference in participant outcomes [53,54]. The analysis of use outcomes (eg, 30-day readmissions and ED use) will use a mixed effects negative binomial regression model with random effects for the medical team and fixed effects for time to account for the stepped wedge cluster randomized design. Sensitivity analyses may be performed using logistic regression for health service use based on the distribution of the data. We will also examine the stability of effect estimates using generalized estimation equations with small sample adjustment, given the study design [55].

Equity Evaluation

Our analyses will consider several equity metrics and include interaction terms to capture racial and ethnic differences and biological sex for THRIVE participants compared to patients receiving usual care. Using all payor data obtained from the EHR, we will also conduct a secondary analysis to examine health service use across all insurance payor types for THRIVE participants and the usual care group, allowing a proxy measurement for differences across socioeconomic strata.

Aim 2

Aim 2 is to evaluate the implementation of the THRIVE clinical pathway, including fidelity, feasibility, appropriateness, and acceptability.

Outcomes and Measures

Fidelity will be assessed using a standardized checklist and monthly report. Surveys and interviews of clinicians and administrators involved with THRIVE will be used to assess the secondary implementation outcomes of interest. These outcomes will be measured twice (at 8 weeks from the start of each sequence and at the end of the study). The surveys will use validated instruments that measure (1) feasibility, practicality, and ease of delivering THRIVE; (2) acceptability, how fair or reasonable THRIVE is deemed; (3) appropriateness, to what extent THRIVE seems suitable; and (4) clinician workload, an objective assessment of the demand of the THRIVE clinical pathway on clinician time. Clinician interviews will assess the determinants of THRIVE implementation using the HEIF [44,45]. Demographics of clinicians and administrators will also be collected.

Analysis

Summary statistics will be produced from the quantitative measures of feasibility, acceptability, appropriateness, and clinician workload. All interview data will be analyzed using constant comparative analysis to examine data across cases. Initially, we will use an iterative process of close readings and discussion of a random sample of interview transcripts and will analyze patterns in the recurrence and distribution of emergent concepts across participants. The principal investigator and research coordinator staff will then create a data dictionary and apply codes for themes that emerge while reading what the respondents say. The HEIF will inform the development of the codebook, including definitions and subsequent integration of the qualitative and quantitative data [47]. The integration of the qualitative data will help to extend and expand the findings of the quantitative findings. We will use NVivo (version 12; Lumivero) to manage our data.

Dissemination

Our team will lead several efforts to promote the dissemination and translation of our findings. First, results will be shared widely through publications, conference presentations, policy briefs, and well-established channels via the Penn School of Nursing Communication Office and the Center for Health Outcomes & Policy Research's national and international networks. Examples of print and public engagements will include up to 5 publications (at minimum 1-2 papers per aim), annual scientific presentations or conferences, infographics, and guest features on podcasts (eg, AmplifyNursing). We have built a customized THRIVE website with plans to share open-access modules on the components of THRIVE and the process for implementation. We will engage with our THRIVE Community Advisory Board to develop equity-focused dissemination efforts that are system and community focused. For example, we have previously participated in health fairs at local churches. We anticipate that the focus of this project will be of equal interest to other faith-based and community organizations and look forward to collaborating throughout the study period, not just at the end.

Results

This project was funded in January 2023. We received IRB approval on March 10, 2023. Data collection will occur from March 2023 to July 2024. Results are expected to be published in 2025.

Discussion

Expected Findings

We anticipate that patients who participate in the THRIVE clinical pathway will experience fewer 30-day readmissions and ED visits as well as more connections to primary and specialty care compared to usual care. We also expect that clinicians will value and appreciate the additional supports provided to patients with an increased burden of health-related social needs.

Comparisons With Prior Work

Most current transitional care programs were not developed to meet the needs of people insured by Medicaid and require additional personnel to implement them [10-12]. Several clinical trials of transitional care programs have resulted in mixed findings, with some noting decreased rehospitalization, while others have found no reductions in 30-day readmissions or ED use [12-17]. Similarly, other transitional care models have incorporated interventions including weekly health coaching and self-management education, though findings are inconsistent [18-20].

Strengths and Limitations

The main strength of this study is the use of a stepped wedge approach. In this design, after all of the case managers have "stepped in" to refer to THRIVE, all eligible patients will be able to receive THRIVE services. A limitation of this study is that it is a single-institution trial. However, we believe this study will yield important findings, given the rigor of the design and the focus on embedding equity-based principles throughout our implementation.

Conclusions

The goal of THRIVE is to reduce disparities and improve postdischarge care transitions for Medicaid-insured patients through a feasible system-level intervention that is satisfying for THRIVE participants, clinicians, and their teams in hospitals and home care settings. By using our equity-focused case management services and leveraging the power of the electronic medical record, THRIVE creates efficiencies by identifying high-need patients, improving communication across acute and community-based sectors, and driving evidence-based care coordination. This study will advance the field of equity-focused evidence-based interventions by testing both the effectiveness of patients' health improvement and the adoption of THRIVE by typical clinical practices. It will add important findings about how the infusion of equity-focused principles in the design and

evaluation contributes to both implementation and effectiveness outcomes.

Acknowledgments

Funding for this project was provided by the Rita and Alex Hillman Foundation (A-3004, to JMBC, principal investigator) and the Center for Health Outcomes & Policy Research (CHOPR) and Office of Nursing Research (ONR), University of Pennsylvania School of Nursing and the National Institutes of Nursing Research T32-NR-007104 (PI McHugh). There are no awards or grant numbers for CHOPR and ONR funding sources.

Data Availability

The data that will support the findings of this study is available from the Penn Data Store and the electronic medical record and is not publicly available.

Authors' Contributions

JMBC, HB, MG-M, JB, DM, DG, KA, and MR contributed to the conceptualization and drafting of the paper. MOH, KS, AM, EF, and RC contributed to the data curation and analytic plan. All authors contributed to the editing of this paper and read and gave the final approval.

Conflicts of Interest

MOH received statistical consulting fees from Unlearn.AI and fees for editorial services from Elsevier and the American Thoracic Society, all for work unrelated to this project. JMBC, HB, MG-M, KS, AM, MR, DM, DG, JB, EF, KA, and RC have no competing interests to declare.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) reporting checklist for protocol of a clinical trial.
[DOCX File , 29 KB - resprot_v13i1e54211_app1.docx]

Multimedia Appendix 2
CONSORT (Consolidated Standards of Reporting Trials) checklist for stepped wedge trials.
[DOCX File , 22 KB - resprot_v13i1e54211_app2.docx]

Multimedia Appendix 3
Peer Review Feedback from funder.
[PDF File (Adobe PDF File), 134 KB - resprot_v13i1e54211_app3.pdf]

References

1. Allen HL, Golberstein E, Bailey Z. Eliminating health disparities will require loking at how much and how Medicaid pays participating providers. Milbank Q Opin 2022;41(7):939-946 [FREE Full text] [doi: 10.1599/mqop.2022.0223]
2. Kronick R, Bella M, Gilmer TP. The faces of Medicaid III: refining the portrait of people with multiple chronic conditions. Center for Health Care Strategies, Inc. 2009. URL: https://www.chcs.org/media/Executive_Summary_-_Faces_III1.pdf [accessed 2024-02-07]
3. Barrett ML, Wier LM, Jiang HJ, Steiner CA. All-cause readmissions by payer and age, 2009-2013. Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project (HCUP): Statistical Briefs #199. 2015. URL: https://hcup-us.ahrq.gov/reports/statbriefs/sb199-Readmissions-Payer-Age.jsp [accessed 2024-02-14]
4. Gilmer T, Hamblin A. Hospital readmissions among Medicaid beneficiaries with disabilities: identifying targets of opportunity. Center for Health Care Strategies, Inc. 2010. URL: https://www.chcs.org/media/CHCS_readmission_101215b.pdf [accessed 2024-02-07]
5. Trudnak T, Kelley D, Zerzan J, Griffith K, Jiang HJ, Fairbrother GL. Medicaid admissions and readmissions: understanding the prevalence, payment, and most common diagnoses. Health Aff (Millwood) 2014;33(8):1337-1344. [doi: 10.1377/hlthaff.2013.0632] [Medline: 25092834]
6. Hospital guide to reducing medicaid readmissions. Agency for Health Research & Quality. 2014. URL: https://www.ahrq.gov/sites/default/files/publications/files/medreadmissions.pdf [accessed 2024-02-07]
7. Singer AJ, Thode HC, Pines JM. US emergency department visits and hospital discharges among uninsured patients before and after implementation of the Affordable Care Act. JAMA Netw Open 2019;2(4):e192662 [FREE Full text] [doi: 10.1001/jamanetworkopen.2019.2662] [Medline: 31002327]

8. Hsiang WR, Lukasiewicz A, Gentry M, Kim CY, Leslie MP, Pelker R, et al. Medicaid patients have greater difficulty scheduling health care appointments compared with private insurance patients: a meta-analysis. Inquiry 2019;56:46958019838118 [FREE Full text] [doi: 10.1177/0046958019838118] [Medline: 30947608]
9. Kaspers M, Llamocca E, Quick A, Dholakia J, Salani R, Felix AS. Black and Hispanic women are less likely than white women to receive guideline-concordant endometrial cancer treatment. Am J Obstet Gynecol 2020;223(3):398.e1-398.e18 [FREE Full text] [doi: 10.1016/j.ajog.2020.02.041] [Medline: 32142825]
10. Naylor MD, Brooten DA, Campbell RL, Maislin G, McCauley KM, Schwartz JS. Transitional care of older adults hospitalized with heart failure: a randomized, controlled trial. J Am Geriatr Soc 2004;52(5):675-684. [doi: 10.1111/j.1532-5415.2004.52202.x] [Medline: 15086645]
11. Cutts T, Gunderson G. Evaluating two mysteries: Camden Coalition findings. NAM Perspect 2020;2020:1-5 [FREE Full text] [doi: 10.31478/202007d] [Medline: 35291733]
12. Englander H, Michaels L, Chan B, Kansagara D. The Care Transitions Innovation (C-TraIn) for socioeconomically disadvantaged adults: results of a cluster randomized controlled trial. J Gen Intern Med 2014;29(11):1460-1467 [FREE Full text] [doi: 10.1007/s11606-014-2903-0] [Medline: 24913003]
13. Kangovi S, Mitra N, Grande D, Huo H, Smith RA, Long JA. Community health worker support for disadvantaged patients with multiple chronic diseases: a randomized clinical trial. Am J Public Health 2017;107(10):1660-1667. [doi: 10.2105/AJPH.2017.303985] [Medline: 28817334]
14. Kangovi S, Mitra N, Norton L, Harte R, Zhao X, Carter T, et al. Effect of community health worker support on clinical outcomes of low-income patients across primary care facilities: a randomized clinical trial. JAMA Intern Med 2018;178(12):1635-1643 [FREE Full text] [doi: 10.1001/jamainternmed.2018.4630] [Medline: 30422224]
15. Kangovi S, Mitra N, Grande D, White ML, McCollum S, Sellman J, et al. Patient-centered community health worker intervention to improve posthospital outcomes: a randomized clinical trial. JAMA Intern Med 2014;174(4):535-543 [FREE Full text] [doi: 10.1001/jamainternmed.2013.14327] [Medline: 24515422]
16. Mann C. Targeting Medicaid super-utilizers to decrease costs and improve quality. Center for Medicaid and CHIP Services. 2013. URL: https://www.hhs.gov/guidance/sites/default/files/hhs-guidance-documents/CIB-07-24-2013_207.pdf [accessed 2024-02-07]
17. Finkelstein A, Zhou A, Taubman S, Doyle J. Health care hotspotting—a randomized, controlled trial. N Engl J Med 2020;382(2):152-162 [FREE Full text] [doi: 10.1056/NEJMsa1906848] [Medline: 31914242]
18. Liss DT, Ackermann RT, Cooper A, Finch EA, Hurt C, Lancki N, et al. Effects of a transitional care practice for a vulnerable population: a pragmatic, randomized comparative effectiveness trial. J Gen Intern Med 2019;34(9):1758-1765 [FREE Full text] [doi: 10.1007/s11606-019-05078-4] [Medline: 31144279]
19. Balaban RB, Galbraith AA, Burns ME, Vialle-Valentin CE, Larochelle MR, Ross-Degnan D. A patient navigator intervention to reduce hospital readmissions among high-risk safety-net patients: a randomized controlled trial. J Gen Intern Med 2015;30(7):907-915 [FREE Full text] [doi: 10.1007/s11606-015-3185-x] [Medline: 25617166]
20. Jackson CT, Trygstad TK, DeWalt DA, DuBard CA. Transitional care cut hospital readmissions for North Carolina Medicaid patients with complex chronic conditions. Health Aff (Millwood) 2013;32(8):1407-1415. [doi: 10.1377/hlthaff.2013.0047] [Medline: 23918485]
21. Nguyen KH, Wilson IB, Wallack AR, Trivedi AN. Racial and ethnic disparities in patient experience of care among nonelderly Medicaid managed care enrollees. Health Aff (Millwood) 2022;41(2):256-264 [FREE Full text] [doi: 10.1377/hlthaff.2021.01331] [Medline: 35130065]
22. Medicaid access in brief: adults' experiences in obtaining medical care. Medicaid and CHIP Payment and Access Commission. 2016. URL: https://www.macpac.gov/wp-content/uploads/2016/11/Adults-Experiences-in-Obtaining-Medical-Care.pdf [accessed 2024-02-07]
23. Allaudeen N, Vidyarthi A, Maselli J, Auerbach A. Redefining readmission risk factors for general medicine patients. J Hosp Med 2011;6(2):54-60 [FREE Full text] [doi: 10.1002/jhm.805] [Medline: 20945293]
24. Cheung PT, Wiler JL, Lowe RA, Ginde AA. National study of barriers to timely primary care and emergency department utilization among Medicaid beneficiaries. Ann Emerg Med 2012;60(1):4-10.e2 [FREE Full text] [doi: 10.1016/j.annemergmed.2012.01.035] [Medline: 22418570]
25. Clark CR, Ommerborn MJ, Coull BA, Pham DQ, Haas JS. Income inequities and Medicaid expansion are related to racial and ethnic disparities in delayed or forgone care due to cost. Med Care 2016;54(6):555-561 [FREE Full text] [doi: 10.1097/MLR.0000000000000525] [Medline: 26974677]
26. Ladhania R, Haviland AM, Venkat A, Telang R, Pines JM. The effect of Medicaid expansion on the nature of new enrollees' emergency department use. Med Care Res Rev 2021;78(1):24-35 [FREE Full text] [doi: 10.1177/1077558719848270] [Medline: 31132912]
27. Parekh N, Jarlenski M, Kelley D. Disparities in access to primary care and emergency department utilization in a large Medicaid program. J Health Disparities Res Pract 2018;11(4):1 [FREE Full text]
28. Brom H, Anusiewicz CV, Udoeyo I, Chittams J, Carthon JMB. Access to post-acute care services reduces emergency department utilisation among individuals insured by Medicaid: an observational study. J Clin Nurs 2022;31(5-6):726-732 [FREE Full text] [doi: 10.1111/jocn.15932] [Medline: 34240494]

29. Okoro ON, Hillman LA, Cernasev A. "We get double slammed!": healthcare experiences of perceived discrimination among low-income African-American women. Womens Health (Lond) 2020;16:1-12 [FREE Full text] [doi: 10.1177/1745506520953348] [Medline: 32856564]
30. Okunrintemi V, Khera R, Spatz ES, Salami JA, Valero-Elizondo J, Warraich HJ, et al. Association of income disparities with patient-reported healthcare experience. J Gen Intern Med 2019;34(6):884-892 [FREE Full text] [doi: 10.1007/s11606-019-04848-4] [Medline: 30783877]
31. Varcoe C, Bungay V, Browne AJ, Wilson E, Wathen CN, Kolar K, et al. EQUIP emergency: study protocol for an organizational intervention to promote equity in health care. BMC Health Serv Res 2019;19(1):687 [FREE Full text] [doi: 10.1186/s12913-019-4494-2] [Medline: 31601199]
32. Weech-Maldonado R, Hall A, Bryant T, Jenkins KA, Elliott MN. The relationship between perceived discrimination and patient experiences with health care. Med Care 2012;50(9 Suppl 2):S62-S68 [FREE Full text] [doi: 10.1097/MLR.0b013e31825fb235] [Medline: 22895233]
33. What is health equity? Centers for Disease Control and Prevention. URL: https://www.cdc.gov/nchhstp/healthequity/index.html [accessed 2023-05-19]
34. Varcoe C, Browne AJ, Bungay V, Perrin N, Wilson E, Wathen CN, et al. Through an equity lens: illuminating the relationships among social inequities, stigma and discrimination, and patient experiences of emergency health care. Int J Health Serv 2022;52(2):246-260 [FREE Full text] [doi: 10.1177/00207314221075515] [Medline: 35098791]
35. Peterson A, Charles V, Yeung D, Coyle K. The health equity framework: a science- and justice-based model for public health researchers and practitioners. Health Promot Pract 2021;22(6):741-746 [FREE Full text] [doi: 10.1177/1524839920950730] [Medline: 32814445]
36. Brom H, Brooks Carthon JM. THRIVE: addressing patients' social needs ater hospitalization. University of Pennsylvania: Leonard Davis Institute of Health Economics. 2019. URL: https://ldi.upenn.edu/our-work/research-updates/thrive-addressing-patients-social-needs-after-hospitalization [accessed 2024-02-07]
37. Carthon JMB, Brom H, Kim V, Hedgeland T, Ponietowicz E, Cacchione P. How innovation and design thinking can improve care for patients with significant social needs. Am Nurse 2021;16(6):30-33 [FREE Full text]
38. Brom H, Carthon JMB, Ikeaba U, Chittams J. Leveraging electronic health records and machine learning to tailor nursing care for patients at high risk for readmissions. J Nurs Care Qual 2020;35(1):27-33 [FREE Full text] [doi: 10.1097/NCQ.0000000000000412] [Medline: 31136529]
39. Carthon JMB, Hedgeland T, Brom H, Hounshell D, Cacchione PZ. "You only have time for so much in 12 hours" unmet social needs of hospitalised patients: a qualitative study of acute care nurses. J Clin Nurs 2019;28(19-20):3529-3537 [FREE Full text] [doi: 10.1111/jocn.14944] [Medline: 31162863]
40. Reid-Ponte P. Human-centered design innovation to help all patients THRIVE: an interview with J. Margo Brooks Carthon. J Nurs Adm 2022;52(2):71-72. [doi: 10.1097/NNA.0000000000001105] [Medline: 35060948]
41. Golden TL, Wendel ML. Public health's next step in advancing equity: re-evaluating epistemological assumptions to move social determinants from theory to practice. Front Public Health 2020;8:131 [FREE Full text] [doi: 10.3389/fpubh.2020.00131] [Medline: 32457863]
42. Carthon JMB, Brom H, French R, Daus M, Grantham-Murillo M, Bennett J, et al. Transitional care innovation for Medicaid-insured individuals: early findings. BMJ Open Qual 2022;11(3):e001798 [FREE Full text] [doi: 10.1136/bmjoq-2021-001798] [Medline: 35981741]
43. Mdege ND, Man MS, Brown CATN, Torgerson DJ. Systematic review of stepped wedge cluster randomized trials shows that design is particularly used to evaluate interventions during routine implementation. J Clin Epidemiol 2011;64(9):936-948. [doi: 10.1016/j.jclinepi.2010.12.003] [Medline: 21411284]
44. Proctor E, Silmere H, Raghavan R, Hovmand P, Aarons G, Bunger A, et al. Outcomes for implementation research: conceptual distinctions, measurement challenges, and research agenda. Adm Policy Ment Health 2011;38(2):65-76 [FREE Full text] [doi: 10.1007/s10488-010-0319-7] [Medline: 20957426]
45. Woodward EN, Matthieu MM, Uchendu US, Rogal S, Kirchner JE. The health equity implementation framework: proposal and preliminary study of hepatitis C virus treatment. Implement Sci 2019;14(1):26 [FREE Full text] [doi: 10.1186/s13012-019-0861-y] [Medline: 30866982]
46. Aarons GA, Green AE, Palinkas LA, Self-Brown S, Whitaker DJ, Lutzker JR, et al. Dynamic adaptation process to implement an evidence-based child maltreatment intervention. Implement Sci 2012;7:32 [FREE Full text] [doi: 10.1186/1748-5908-7-32] [Medline: 22512914]
47. Woodward EN, Singh RS, Ndebele-Ngwenya P, Castillo AM, Dickson KS, Kirchner JE. A more practical guide to incorporating health equity domains in implementation determinant frameworks. Implement Sci Commun 2021;2(1):61 [FREE Full text] [doi: 10.1186/s43058-021-00146-5] [Medline: 34090524]
48. Brownson RC, Kumanyika SK, Kreuter MW, Haire-Joshu D. Implementation science should give higher priority to health equity. Implement Sci 2021;16(1):28 [FREE Full text] [doi: 10.1186/s13012-021-01097-0] [Medline: 33740999]
49. Hemming K, Taljaard M, McKenzie JE, Hooper R, Copas A, Thompson JA, et al. Reporting of stepped wedge cluster randomised trials: extension of the CONSORT 2010 statement with explanation and elaboration. BMJ 2018;363:k1614 [FREE Full text] [doi: 10.1136/bmj.k1614] [Medline: 30413417]

50. Chan AW, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ 2013;346:e7586 [FREE Full text] [doi: 10.1136/bmj.e7586] [Medline: 23303884]
51. Palinkas LA, Aarons GA, Horwitz S, Chamberlain P, Hurlburt M, Landsverk J. Mixed method designs in implementation research. Adm Policy Ment Health 2011;38(1):44-53 [FREE Full text] [doi: 10.1007/s10488-010-0314-z] [Medline: 20967495]
52. McMillan SS, Kendall E, Sav A, King MA, Whitty JA, Kelly F, et al. Patient-centered approaches to health care: a systematic review of randomized controlled trials. Med Care Res Rev 2013;70(6):567-596. [doi: 10.1177/1077558713496318] [Medline: 23894060]
53. Kahan BC, Li F, Copas AJ, Harhay MO. Estimands in cluster-randomized trials: choosing analyses that answer the right question. Int J Epidemiol 2023;52(1):107-118 [FREE Full text] [doi: 10.1093/ije/dyac131] [Medline: 35834775]
54. Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. ICH E9 (R1). 2020. URL: https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf [accessed 2024-02-07]
55. Zhu AY, Mitra N, Hemming K, Harhay MO, Li F. Leveraging baseline covariates to analyze small cluster-randomized trials with a rare binary outcome. Biom J 2024;66(1):e2200135 [FREE Full text] [doi: 10.1002/bimj.202200135] [Medline: 37035941]

Abbreviations

CHW: community health worker
CM: nurse case manager
CONSORT: Consolidated Standards of Reporting Trials
ED: emergency department
EHR: electronic health record
HEIF: Health Equity Implementation Framework
HIPAA: Health Insurance Portability and Accountability Act
IRB: institutional review board
PAH: Pennsylvania Hospital
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

Edited by A Mavragani; submitted 01.11.23; this is a non–peer-reviewed article;accepted 31.01.24; published 26.03.24.

Please cite as:
Brooks Carthon JM, Brom H, Grantham-Murrillo M, Sliwinski K, Mason A, Roeser M, Miles D, Garcia D, Bennett J, Harhay MO, Flores E, Amenyedor K, Clark R
Equity-Centered Postdischarge Support for Medicaid-Insured People: Protocol for a Type 1 Hybrid Effectiveness-Implementation Stepped Wedge Cluster Randomized Controlled Trial
JMIR Res Protoc 2024;13:e54211
URL: https://www.researchprotocols.org/2024/1/e54211
doi:10.2196/54211
PMID:38530349

Protocol

High-Flow Humidified Oxygen as an Early Intervention in Children With Acute Severe Asthma: Protocol for a Feasibility Randomized Controlled Trial

Hector Rojas-Anaya[1,2], BEng, PhD; Akshat Kapur[3], MBBS; Graham Roberts[4,5], DM; Damian Roland[6,7], BMedSci, BMBS, PhD; Atul Gupta[8], MD; Michaela Lazner[9], MBChB, MMedSci; Jane Bayreuther[10], BMBS; John Pappachan[5], BChir, MA, MB; Christina Jones[11], PhD, CPsychol; Stephen Bremner[2], BSc, MSc, PhD; Fleur Cantle[12], BSc, MBBS, MSc, DCH; Paul Seddon[3], MB, ChB, PGCertMedEd

[1]University Hospitals Sussex National Health Service Foundation Trust, Brighton, United Kingdom

[2]Brighton and Sussex Clinical Trials Unit, Brighton and Sussex Medical School, Brighton, United Kingdom

[3]Respiratory Care, Royal Alexandra Children's Hospital, University Hospitals Sussex National Health Service Foundation Trust, Brighton, United Kingdom

[4]Department of Paediatric Allergy and Respiratory Medicine, University of Southampton, Southampton, United Kingdom

[5]National Institute for Heath Research Southampton Biomedical Research Centre, University Hospital Southampton National Health Service Foundation Trust, Southampton, United Kingdom

[6]Paediatric Emergency Medicine Leicester Academic Group, Children’s Emergency Department, Leicester Royal Infirmary, Leicester, United Kingdom

[7]Social science APPlied Healthcare and Improvement REsearch Group, Department of Population Health Sciences, Leicester University, Leicester, United Kingdom

[8]Paediatric Respiratory Medicine, King's College Hospital, London, United Kingdom

[9]Children's Emergency Department, Royal Alexandra Children's Hospital, University Hospitals Sussex National Health Service Foundation Trust, Brighton, United Kingdom

[10]Children's Emergency Department, University Hospital Southampton National Health Service Foundation Trust, Southampton, United Kingdom

[11]School of Psychology, Faculty of Health and Medical Sciences, University of Surrey, Guildford, United Kingdom

[12]Emergency Department, King's College Hospital, London, United Kingdom

Corresponding Author:
Paul Seddon, MB, ChB, PGCertMedEd
Respiratory Care
Royal Alexandra Children's Hospital
University Hospitals Sussex National Health Service Foundation Trust
Eastern Road
Brighton, BN2 5BE
United Kingdom
Phone: 44 7714777361
Email: seddop@gmail.com

Abstract

Background: Acute severe asthma (ASA) is a leading cause of hospital attendance in children. Standard first-line therapy consists of high-dose inhaled bronchodilators plus oral corticosteroids. Treatment for children who fail to respond to first-line therapy is problematic: the use of intravenous agents is inconsistent, and side effects are frequent. High-flow humidified oxygen (HiFlo) is widely used in respiratory conditions and is increasingly being used in ASA, but with little evidence for its effectiveness. A well-designed, adequately powered randomized controlled trial (RCT) of HiFlo therapy in ASA is urgently needed, and feasibility data are required to plan such an RCT. In this study, we describe the protocol for a feasibility study designed to fill this knowledge gap.

Objective: This study aims to establish whether a full RCT of early HiFlo therapy in children with ASA can be conducted successfully and safely, to establish whether recruitment using deferred consent is practicable, and to define appropriate outcome measures and sample sizes for a definitive RCT. The underlying hypothesis is that early HiFlo therapy in ASA will reduce the need for more invasive treatments, allow faster recovery and discharge from hospital, and in both these ways reduce distress to children and their families.

Methods: We conducted a feasibility RCT with deferred consent to assess the use of early HiFlo therapy in children aged 2 to 11 years with acute severe wheeze not responding to burst therapy (ie, high-dose inhaled salbutamol with or without ipratropium). Children with a Preschool Respiratory Assessment Measure score ≥5 after burst therapy were randomized to commence HiFlo therapy or follow standard care. The candidate primary outcomes assessed were treatment failure requiring escalation and time to meet hospital discharge criteria. Patient and parent experiences were also assessed using questionnaires and telephone interviews.

Results: The trial was opened to recruitment in February 2020 but was paused for 15 months owing to the COVID-19 pandemic. The trial was reopened at the lead site in July 2021 and opened at the other 3 sites from August to December 2022. Recruitment was completed in June 2023.

Conclusions: This feasibility RCT of early HiFlo therapy in children with ASA recruited to the target despite major disturbances owing to the COVID-19 pandemic. The data are currently being analyzed and will be published separately.

Trial Registration: International Standard Randomised Controlled Trial Number Registry ISRCTN78297040; https://www.isrctn.com/ISRCTN78297040

International Registered Report Identifier (IRRID): DERR1-10.2196/54081

(JMIR Res Protoc 2024;13:e54081) doi:10.2196/54081

KEYWORDS

asthma; child; wheezing; oxygen therapy; high-flow humidified oxygen therapy

Introduction

Background

Asthma is a common chronic disorder of reversible airway obstruction characterized by bronchial smooth muscle contraction, airway inflammation, and increased airway secretion [1]. It is the most common noncommunicable disease in childhood, affecting 1 in 10 children worldwide [2] and causing >1000 deaths per day [3]. Children with asthma are prone to episodes of acute severe airway obstruction, characterized by wheezing and increased work of breathing, and often require hospital treatment. Acute severe asthma (ASA) is a leading cause of hospital attendance in children, accounting for up to 7% of all pediatric emergency visits [4] and 8.5% of pediatric admissions from emergency departments (EDs) [5], the most common single cause. Many preschool children who have not yet been diagnosed with asthma are admitted to the hospital with episodes of acute severe wheezing. They present identically and are treated in the same way as older children diagnosed with asthma, although they can be less responsive to therapy [6]. In this paper, the term ASA is used to describe children presenting with acute wheezing and breathing difficulty, whether they have an established diagnosis of asthma.

Therapy for ASA is directed at (1) relieving bronchoconstriction with bronchodilators, (2) decreasing airway inflammation with corticosteroids, and (3) clearing airway secretions so that they do not become thick and block the airways. Standard first-line emergency treatment [7] for ASA in children starts with burst therapy in the first hour (3 doses of high-dose inhaled salbutamol, sometimes with inhaled ipratropium, via a spacer device or nebulizer) and oral corticosteroids. During the next 1 to 4 hours, many children improve clinically and may be discharged. However, some children fail to respond to standard therapy and require hospital admission for more intensive, second-line treatment; without effective treatment, these children are at risk of fatigue, respiratory failure, and death [8]. Second-line treatment commonly includes intravenous bronchodilators (≥1 of aminophylline, salbutamol, and magnesium sulfate). However, evidence for the efficacy of such treatments is limited and inconsistent, with frequent side effects, including tachycardia, jitteriness, tremor, palpitations, nausea, vomiting, elevated lactate level, and hypokalemia [7], which can cause considerable distress to the child and family. Current guidelines [7,9] provide little guidance (because of the scarcity of evidence) regarding which second-line treatment clinicians should use. Therefore, there is a need to investigate other options for treating ASA to improve the effectiveness of the treatment and reduce adverse effects.

High-flow humidified oxygen (HiFlo) therapy is an innovative health care technology that supports breathing by supplying a warm, humidified mixture of air and oxygen at high-flow rates via fine nasal cannulae that has shown promising results in other acute respiratory conditions in children [10]. Traditional oxygen therapy uses cold, unhumidified oxygen directly from a cylinder or a wall outlet. Although this is helpful in improving oxygenation, it is uncomfortable for patients and causes drying and cooling of the nose and mouth, and potentially of the lower airways, which can cause worsening of airway obstruction and even airway damage. Therefore, unmodified oxygen therapy can only be delivered at very low flow rates. Using HiFlo technology, the air or oxygen percentage mix can be varied; it is warmed to body temperature and delivered at 100% humidity. As a result, much higher flows can be delivered without discomfort or adverse effects on the airways.

There is now considerable experience with the use of this technology in both adults and children [10]. Most of the clinical experience and evidence for the efficacy of HiFlo therapy in children is derived from studies performed in preterm neonates with surfactant deficiency. In this population, HiFlo therapy appears to be as effective as continuous positive airway pressure (CPAP) therapy and has become a standard therapy [11]. The physiological basis of its effectiveness is unclear [10,12]: HiFlo therapy itself may generate CPAP [13,14], but it may also reduce nasopharyngeal dead space, reduce upper airway resistance, and reduce the metabolic demand required to humidify inspired gases [15]. In recent years, there has been increased use of HiFlo

therapy in infants with acute bronchiolitis [16]. Retrospective studies have suggested that introducing HiFlo therapy for acute bronchiolitis is associated with a reduced need for intubation [17,18]. Prospective trials comparing HiFlo with standard bronchiolitis therapy (low-flow 100% oxygen) have shown improved oxygen saturation levels [19], fewer treatment failures [20,21], and a nonsignificant trend toward faster weaning from oxygen [20]. A Cochrane systematic review concluded that HiFlo therapy is feasible and well-tolerated in infants with bronchiolitis but that further evidence for its effectiveness is needed [22].

To date, there have been no substantial randomized controlled trials (RCTs) of HiFlo therapy in children with ASA, although its use in ASA has been rapidly increasing [23]. The pathophysiology of ASA is very different from that of bronchiolitis. Bronchiolitis is characterized by more mechanical distal airway obstruction [22], whereas in ASA, bronchial smooth muscle constriction plays a major role [1,6]. Retrospective observational studies of HiFlo therapy in children with ASA have suggested improvements in physiological parameters and asthma severity scores [24,25] but have also raised concerns that using HiFlo therapy may delay the initiation of other forms of respiratory support [26]. There have been 2 small single-center pilot RCTs on HiFlo therapy in children with acute asthma. Ballestero et al [27] randomized 62 children with ASA with acute respiratory failure to HiFlo therapy versus conventional oxygen therapy. The asthma score of a higher proportion of children on HiFlo therapy reduced (*pulmonary score*—unreferenced) by 2 points in the first 2 hours of treatment; however, there was no difference in the need for admission or length of hospital stay. Gauto Benítez et al [28] randomized 65 children in a single center in Paraguay to HiFlo therapy or conventional oxygen therapy: the inclusion criteria were somewhat unclear, and both groups received continuous intravenous magnesium in addition to inhaled bronchodilators as a standard practice in this institution. They found no difference in the proportion reducing their asthma score (*pulmonary index score*—again unreferenced) by 2 points or in the length of hospital stay. A recent review of HiFlo in children with ASA by Chao et al [23] concluded that "large well-designed randomized controlled trials assessing the clinical efficacy of high-flow nasal cannula oxygen for children with asthma exacerbation are urgently warranted." The evidence from published studies is encouraging but mixed and is lacking in clinical outcomes. It does not provide the feasibility information required to plan an RCT on the clinical effectiveness of early HiFlo therapy in childhood ASA.

In summary, ASA in childhood is a common emergency condition with important impacts on health care costs and quality of life and presents a risk to life. HiFlo is a novel therapy that has the potential to treat patients with ASA more effectively and reduce hospital stays and intensive care admissions. However, its use is becoming widespread in clinical practice despite a lack of good evidence. If HiFlo therapy in patients with ASA is not evaluated objectively, there is a risk that a treatment without proven benefits (but with significant costs) may drift into widespread practice. Therefore, there is an urgent need for a well-designed, adequately powered RCT of HiFlo therapy in patients with ASA. To plan such an RCT, feasibility data are required. A definitive RCT would be large and expensive to run, and it is unclear whether it would be feasible, how large it would need to be, and what are the most appropriate outcome measures. This paper presents the protocol of a feasibility study designed to fill this knowledge gap, which has been successfully executed in 4 children's hospitals in the United Kingdom. The formal results will be published separately.

Study Aim and Feasibility Objectives

This feasibility study aimed to establish whether a full RCT of early HiFlo therapy in children with ASA can be conducted successfully and safely and whether recruitment to such a trial, using deferred consent, is practicable in children aged 2 to 11 years presenting to the hospital with ASA. The underlying hypothesis is that early HiFlo therapy in children with ASA will reduce the need for more invasive treatments, allow faster recovery and discharge from hospital and, in both these ways, reduce distress to children and their families. The trial was designed to generate the data required to plan a definitive RCT that would satisfy the clinical and health economic end points and the requirements of children, parents, clinicians, and health services.

Methods

Primary Feasibility Objectives and Outcome Measures

A total of 6 feasibility objectives and associated outcome measures (Table 1) were established to help determine the feasibility of progressing to a full RCT, which would require the following 4 conditions to be met:

1. At least 50% enrollment rate among eligible children (feasibility outcome 1)
2. At least 70% deferred consent rate [29] (feasibility outcome 2)
3. At least 80% of data collection is complete per participant for candidate primary outcome measures (feasibility outcome 3)
4. Confirmation that the predicted sample size, number of centers, and recruitment rates would allow an appropriately powered RCT to be conducted in the United Kingdom for 3 years (feasibility outcome 5)

Discussions with colleagues indicated that at least 15 large UK pediatric centers would be interested in participating in a definitive RCT on this question. The study has been discussed with two relevant research networks: (1) the UK National Institute for Health and Care Research (NIHR) Children Respiratory and Cystic Fibrosis Clinical Studies Group and (2) Pediatric Emergency Research in the United Kingdom and Ireland [30], a network of research-active pediatric emergency care clinicians who have indicated that they will facilitate the process of identifying appropriate centers for the definitive study.

The 2 candidate primary outcome measures recorded and evaluated are provided in Textbox 1.

Table 1. Primary feasibility objectives and outcome measures.

Feasibility objectives	Feasibility outcome measures	Time point of evaluation
To evaluate enrollment rates	Proportion of enrolled (ie, randomized) children among eligible patients with ASA[a]	Enrollment
To evaluate deferred consent rates	Proportion of children with signed deferred consent among those enrolled into the study	Deferred consent
To assess feasibility of recording candidate primary outcome measures	Proportion of data collection completed per participant for the 2 candidate primary outcome measures	Discharge
To estimate the variability of candidate primary outcome measures	Summary statistics for the 2 candidate primary outcome measures	Discharge
To determine design characteristics for a subsequent definitive study	Proposed design, sample size, and number of centers for a definitive study	End of study
To assess the acceptability of HiFlo[b] therapy and the deferred consent model to children, parents, and staff	Satisfaction ratings on the end-of-study questionnaire	Discharge

[a]ASA: acute severe asthma.

[b]HiFlo: high-flow humidified oxygen.

Textbox 1. Candidate primary outcome measures.

- Treatment failure needing escalation of therapy as defined in the *Treatment Failure and Escalation* section.
- The time (h) between presentation to the emergency department and meeting hospital discharge criteria as defined by the following criteria:
  - The ability of the child to maintain arterial oxygen saturation (SpO_2) measured by pulse oximeter at ≥92% without supplemental oxygen or respiratory support for a 4-hour period
  - The ability of the child to remain clinically stable for a minimum of 4 hours between inhaled bronchodilator doses
  - The ability to maintain these conditions continuously until hospital discharge

Treatment Failure and Escalation

Textbox 2 lists the criteria recorded for treatment failure needing escalation in therapy.

Escalations in therapy for the primary analysis are described in Textbox 3. Pragmatically, senior clinicians on duty managing these patients had the discretion to escalate treatment if deemed clinically appropriate and justified but were asked to clearly state the reason for escalation using the abovementioned criteria. The order in which escalations are listed in Textbox 3 does not imply that they needed to be implemented in that order. The clinicians were free, for example, to implement HiFlo therapy in the standard care group before administering the second or third intravenous agent.

For the primary analysis, administering a first intravenous agent is not categorized as *treatment failure requiring escalation* in the standard care group because starting an intravenous agent would be the standard following step in a child who fails burst therapy. However, it was possible that some children randomized to the standard care group may not have received an intravenous agent directly.

Furthermore, it was useful to examine whether commencing early HiFlo therapy has an effect on the total burden of invasive treatments required. Therefore, a secondary analysis, in which escalations of therapy are defined as in Textbox 4, was carried out.

The candidate secondary outcome measures are provided in Textbox 5.

Textbox 2. Criteria for treatment failure needing escalation in therapy.

- Preschool Respiratory Assessment Measure (PRAM) score [31] rising or not falling
- Respiratory rate rising or not falling
- Heart rate rising or not falling
- Rising oxygen requirement
- Rising partial pressure of carbon dioxide (pCO_2) in capillary, venous, or arterial blood
- Other clinical concerns (specified)

Textbox 3. Escalations in therapy for primary analysis.

High-flow humidified oxygen (HiFlo) group

- Commencing intravenous bronchodilator therapy
- Commencing the second or third intravenous agent
- Re-escalating inhaled bronchodilator therapy to an hourly or more frequent dosage
- Commencing noninvasive ventilation with bilevel positive airway pressure (BiPAP) ventilation
- Intubation for invasive ventilation

Standard care group

- Commencing HiFlo therapy
- Commencing the second or third intravenous agent
- Re-escalating inhaled bronchodilator therapy to an hourly or more frequent dosage
- Commencing noninvasive ventilation with BiPAP ventilation
- Intubation for invasive ventilation

Textbox 4. Escalations in therapy for secondary analysis.

High-flow humidified oxygen (HiFlo) group

- Commencing administration of the first, second, or third intravenous agent
- Re-escalating inhaled bronchodilator therapy to an hourly or more frequent dosage
- Commencing noninvasive ventilation with bilevel positive airway pressure (BiPAP) ventilation
- Intubation for invasive ventilation

Standard care group

- Commencing administration of the first, second, or third intravenous agent
- Commencing HiFlo therapy
- Re-escalating inhaled bronchodilator therapy to an hourly or more frequent dosage
- Commencing noninvasive ventilation with BiPAP ventilation
- Intubation for invasive ventilation

Textbox 5. Candidate secondary outcome measures.

- Time (h) between presentation to the emergency department (ED) and the actual hospital discharge
- Time (h) between presentation to the ED and achieving a Preschool Respiratory Assessment Measure (PRAM) [31] score of ≤3
- Time (h) between presentation to the ED and the ability to maintain oxygen saturation (SpO_2) at ≥92% without supplemental oxygen or respiratory support
- Need for intravenous bronchodilator therapy
- Duration of intravenous bronchodilator therapy
- Requirement for noninvasive ventilation
- Requirement for invasive ventilation (intubation)
- Treatment-related adverse effects:
  - Intravenous or inhaled bronchodilator–related side effects (eg, vomiting, tachycardia, and lactic acidosis)
  - Poor compliance with HiFlo therapy
- Hospital readmission within 48 hours of discharge
- Acceptability and comfort scores for treatment during the episode (recorded using the end-of-study questionnaire and qualitative interview following the episode). These measures were codeveloped with the Lived Experience Advisory Panel before the trial commenced.

Study Design and Setting

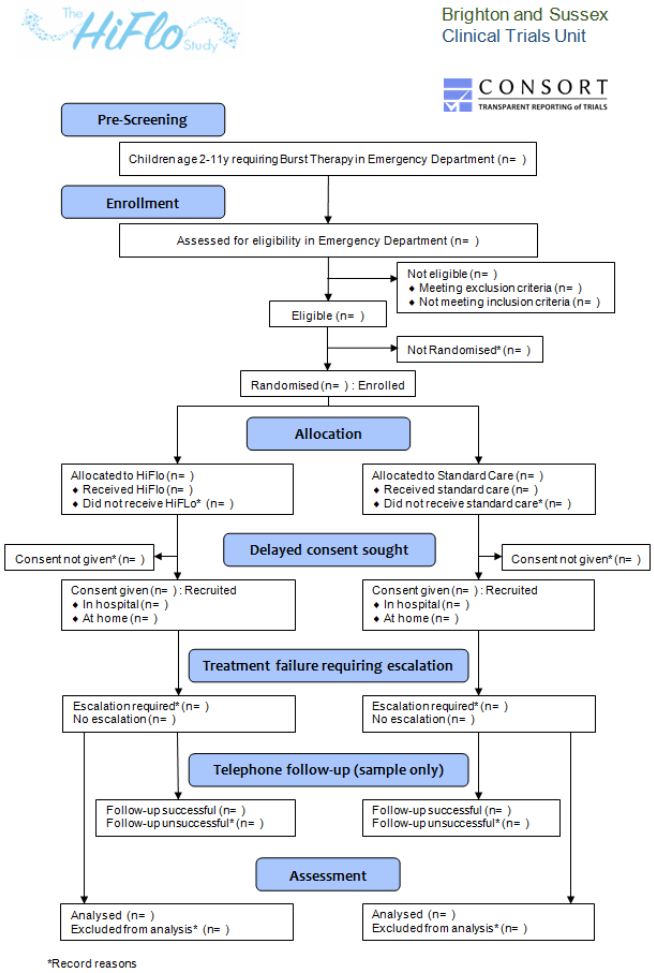
This was a multicenter feasibility RCT of 50 children in the following 4 National Health Service (NHS) Trusts in England:

- The University Hospitals Sussex (UHSx) NHS Foundation Trust, Royal Alexandra Children's Hospital, Brighton
- The King's College Hospital NHS Foundation Trust, London
- The University Hospital Southampton NHS Foundation Trust, Southampton
- The University Hospitals of Leicester NHS Trust, Leicester Royal Infirmary, Leicester

Eligible children were randomized to the intervention (HiFlo therapy) or control (standard care) arms, as shown in the CONSORT (Consolidated Standards of Reporting Trials) diagram (Figure 1). Screening, recruitment, and randomization were performed in the relevant EDs of the participating hospitals. Randomization was stratified by site, age (<5 years and ≥5 years), and severity of acute asthma (the Preschool Respiratory Assessment Measure [PRAM] score at study entry: <8 and ≥8, refer to the *PRAM Scoring* section), with an equal ratio between both arms.

The study was pragmatic, with HiFlo therapy being an add-on to the existing therapy in those randomized to the intervention arm, and was clearly not blinded as this would have been impossible. The children were not denied access to the existing standard second-line interventions (eg, intravenous bronchodilators) because they participated in the study. The treating clinical team was allowed to initiate intravenous bronchodilators as clinically indicated in either treatment arm. In children randomized to the intervention arm, HiFlo therapy was commenced as soon as possible after randomization as the subsequent treatment was initiated rather than intravenous bronchodilators. As the existing treatment guidelines [7,9] make no specific recommendations and because the choice of intravenous bronchodilators is physician dependent across the 4 institutions, the study protocol was physician led and did not specify which intravenous bronchodilator is initiated first. Similarly, if a child randomized to the standard care arm was failing to respond, as defined by the preset criteria, the clinical team could opt to initiate HiFlo as rescue therapy—the child remained in the study on an intention-to-treat basis. The reasons for discontinuing the intervention prematurely or for other protocol violations were recorded.

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram of the study. HiFlo: high-flow humidified oxygen.



Sample Size and Planned Recruitment Rate

The size of the study was determined by the number of children required to provide an accurate estimate of the variability in the candidate primary outcome measures: recommendations for this vary between 50 [32] and 70 [33]. The larger number was chosen to allow 30% attrition to deferred consent [29]. Therefore, the study originally aimed to recruit 70 children aged

<18 months. The recruitment target was subsequently lowered to 48 after an agreement with the NIHR Clinical Research Network that this number was sufficient to meet the objectives of the feasibility RCT. Initially, the recruitment was planned to be from 3 collaborating centers; the fourth site (Leicester) was subsequently added. The subsequent definitive RCT will determine whether HiFlo therapy is an effective intervention for children with ASA.

Participants and Eligibility Criteria

Children aged 2 to 11 years were eligible if they presented to the ED with ASA and failed to respond to standard first-line therapy (high-dose inhaled bronchodilators) based on the eligibility criteria listed in Textbox 6.

The PRAM was chosen because it has been validated across the age range of intended participants [31] and has been shown to be a good predictor of the need for admission and escalation of therapy [35]. A child with a PRAM score of 5 would typically have moderately increased work of breathing, audible wheeze, and oxygen saturation <92% but >90%. The threshold of PRAM score ≥5 was selected based on the advice of the team that designed PRAM (Professor Francine Ducharme, MD, personal communication, April 2019) and because this threshold had been successfully used as an entry criterion in a previous trial of administering nebulized magnesium to patients with acute asthma [36].

Textbox 6. Inclusion and exclusion criteria.

Inclusion criteria

- Participants having an acceptable individual capable of giving consent on their behalf (eg, parent or guardian of a child aged <16 years)
- Participants aged 2 to 11 years
- ASA, defined as respiratory distress combined with wheezing on auscultation (a formal preceding diagnosis of asthma was not necessary)
- Failure to respond to standard initial emergency management [7] with burst therapy (back-to-back 3 consecutive inhaled or nebulized doses of salbutamol with or without the addition of ipratropium bromide for a 1-h period) and systemic corticosteroids, with or without subsequent intravenous bronchodilator therapy as deemed appropriate by the treating physician. Failure to respond will be defined as a Preschool Respiratory Assessment Measure (PRAM) score of ≥5 between 1 hour and 4 hours after starting burst therapy.

Exclusion criteria

- Clinical or radiological evidence of bacterial pneumonia: fever >38.5°C and focal signs on auscultation or chest x-ray
- Signs of impending respiratory failure mandating immediate intubation. These were at the discretion of the treating clinical team but included elevated pCO_2, refractory hypoxemia, and exhaustion
- Contraindications to the use of HiFlo therapy are as follows:
  - Air leak (eg, pneumothorax, pneumomediastinum, or subcutaneous emphysema)
  - Decreased level of consciousness—AVPU (Alert, Voice, Pain, Unresponsive) score [34] P or worse
  - Recent (within 6 wk) bowel surgery
  - Intractable vomiting
- Other major respiratory, cardiovascular, or neurological condition
- Previous participation in the HiFlo ASA study during a prior hospital episode

Study Procedures

This section summarizes the procedures and evaluations conducted to support the feasibility objectives. The timing of the procedures in relation to the established study visits is given in Table 2. A detailed description of each procedure is provided in Section 6 of the study protocol in Multimedia Appendix 1 [1,4-8,10,11,13-15,17-24,27,29,31-33,37-49].

Table 2. Schedule of events.

Study procedures	Visit				
	Screening	Enrollment	Treatment	Hospital discharge	Follow-up
Inform parents regarding the study (eg, poster and leaflet)	✓		✓		
Eligibility assessment	✓				
Demographics and medical history	✓				
Observations, including physical examination, vital signs, PRAM[a] scoring, and oxygen requirement	✓		✓		
Eligibility check and randomization		✓			
Early HiFlo[b] or standard therapy (including treatment escalation and weaning)			✓		
Deferred informed consent			✓		
Routine blood investigations			✓		
Concomitant medications			✓		
Adverse event assessments			✓		
CRF[c] completion and data query resolution			✓	✓	✓
End-of-study questionnaire				✓	
Qualitative interviews with health care professionals and parents					✓

[a]PRAM: Preschool Respiratory Assessment Measure.

[b]HiFlo: high-flow humidified oxygen.

[c]CRF: Case Report Form.

Screening

All children arriving at the participating EDs were routinely triaged by an experienced nurse and reviewed clinically during and after completing burst therapy. Children potentially eligible for the study were identified and actively screened for inclusion by ED clinical staff or research nurses according to their local capacity. Screening information included Trust ID number, age, and reasons for not being eligible for trial participation or if they were eligible but declined participation.

Enrollment and Randomization

The children who met all inclusion criteria and had no exclusion criteria were enrolled in the study and randomized to the intervention (early HiFlo therapy) or control (conventional therapy) arms only after the confirmation of eligibility by a treating clinician delegated to conduct this task. Randomization occurred at enrollment and before consent, as explained in the *Deferred Consent and Recruitment* section; it was implemented using the *Sealed Envelope* (Sealed Envelope Ltd) web-based randomization software [50] and conducted by a member of the research team trained in the study.

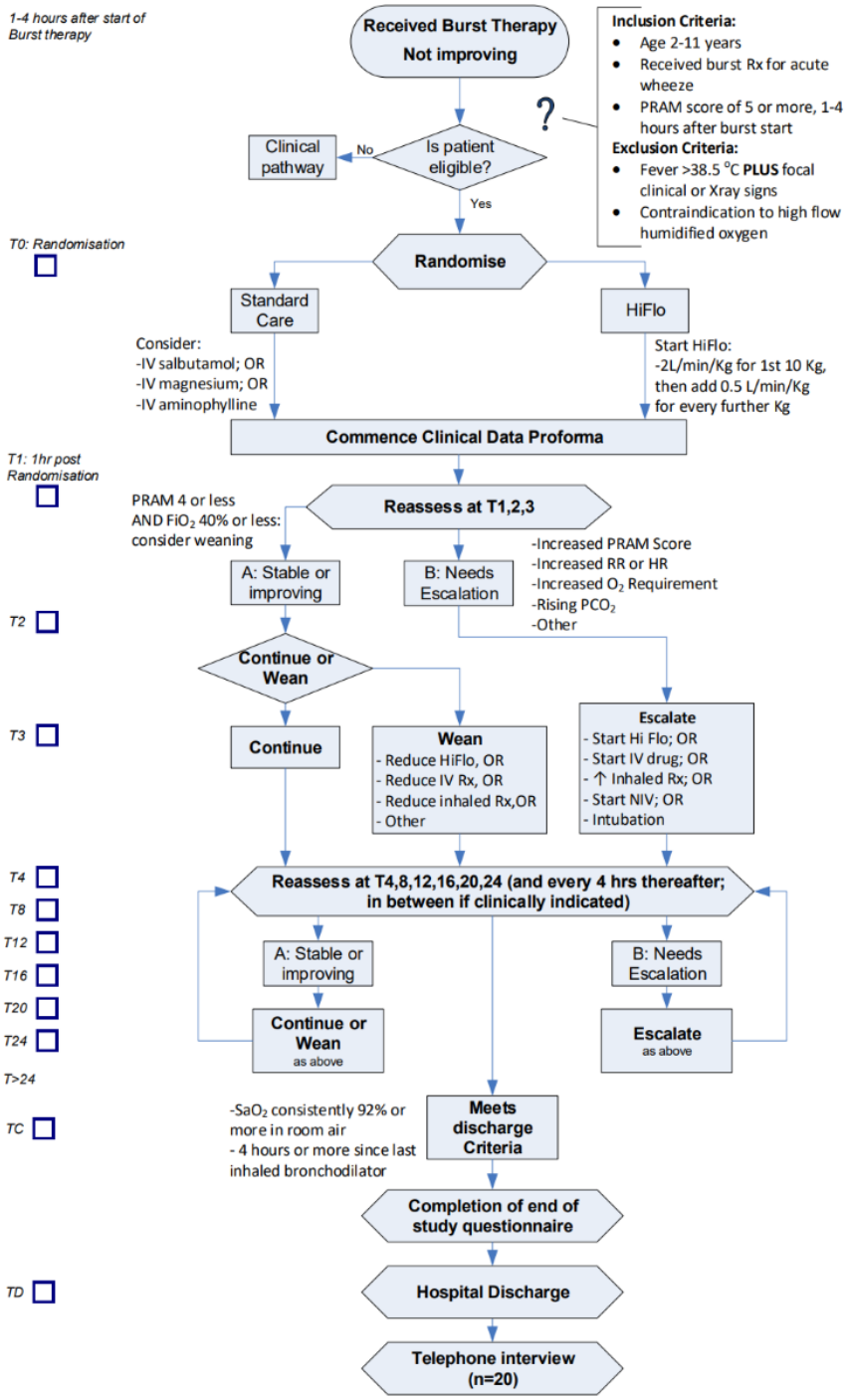
Treatment

The intervention was an add-on to standard care. The key difference between the groups in the 2 arms was the early use of HiFlo therapy, that is, starting HiFlo therapy as the next measure after the failure of burst therapy, and it is this strategy which was examined.

HiFlo Intervention

The use of HiFlo therapy in the study followed established practices and was standardized as far as possible while allowing for clinical judgment (Figure 2). The reasons for escalating and reducing treatment were recorded, and these data will help in defining treatment escalation and weaning pathways for the definitive RCT. The HiFlo therapy was commenced at a flow rate of 2 L/kg/min for the first 10 kg of body weight, with an additional flow rate of 0.5 L/kg/min for every kilogram of body weight >10 kg to a maximum absolute flow rate of 40 L/min, and fraction of inspired oxygen (FiO_2) was adjusted appropriately to maintain oxygen saturation ≥92%. At the discretion of the treating clinician, the flow could be increased to 3 L/kg/min but again with a maximum absolute flow rate of 40 L/min.

Figure 2. Flowchart of the study. FiO_2: fraction of inspired oxygen; HiFlo: high-flow humidified oxygen; HR: heart rate; IV: intravenous; NIV: noninvasive ventilation; O_2: oxygen; pCO_2: partial pressure of carbon dioxide; PRAM: Preschool Respiratory Assessment Measure; RR: respiratory rate; SaO_2: arterial oxygen saturation.



Equipment

Vapotherm, a manufacturer of portable and fixed HiFlo equipment, provided sufficient Precision Flow Plus units and consumables to make the early HiFlo intervention available free of cost in the 4 participating hospitals for the duration of the study.

Aerogen provided in-line Aerogen solo nebulizers and controller units to be used with all Vapotherm systems during the study.

HiFlo Therapy Training

HiFlo therapy was already in use in high-dependency units (HDUs, EDs) in all participating hospitals, and further staff training was undertaken in the setup period before the start of the study. HiFlo hands-on sessions were organized for staff from the EDs, HDUs, and relevant or equivalent clinical wards of participating centers by the UK Vapotherm representative Solus Medical Limited, with the aim of having at least 1 member of staff fully trained per shift. Local nursing and clinical staff members were trained as *super users* to support with

opportunistic training, retraining, and on-site competency checks.

Weaning From HiFlo

Weaning commenced once the child was clinically stable, according to the standard criteria agreed upon across the 4 centers. The weaning strategy was not rigidly protocolized but broadly followed the schema published in the protocol for the FIRST-ABC (FIRST-line support for assistance in breathing in children) study by Richards-Belle et al [51]. Essentially, the reduction in FiO_2 occurred first, and then the flow rate was reduced in a stepwise manner once FiO_2 was consistently ≤40% (Figure 2).

Deferred Consent and Recruitment

A deferred consent model was used to avoid delay in treatment and minimize distress to families who presented to the ED with acutely unwell children. The consent process is summarized in this section (complete details are provided in section 6.4 of the study protocol in Multimedia Appendix 1).

Informed consent was not sought before randomization, but the parents were approached for informed consent within a maximum of 72 hours of randomization once their child's condition was stable. The parents were approached for informed consent by trained staff from the direct care team, who explained the study and provided information sheets to the parents and children (if age appropriate). The parents were given time to read and understand the information and the opportunity to clarify any questions regarding the study and their child's participation. Written informed consent was obtained from all the parents.

If a child was discharged from hospital before parents could be approached for deferred consent, they were contacted by a trained research nurse who explained the study via phone. Written participant information and consent forms were then sent out by post. This model was successfully used, for example, in the Emergency treatment with levetiracetam or phenytoin in status epilepticus in children (EcLIPSE) study by Lyttle et al [52], and feedback from parents was positive [37]. There was a possibility for parents to provide verbal consent via phone in special circumstances. A special process for the sensitive case of having to approach bereaved parents for consent was designed.

If neither written nor verbal consent was received, the child was not recruited into the study, and the data collected were not included in the study analysis.

Hospital Discharge

Hospital Discharge Criteria

It was recognized that the timing of discharge from hospital is affected by multiple factors in addition to the child's medical condition; therefore, criteria of fitness for discharge were defined as a more robust and reproducible candidate primary outcome measure in addition to actual hospital discharge, which was used as a candidate secondary outcome measure. Hospital discharge criteria are defined in Textbox 7.

Textbox 7. Hospital discharge criteria.

- The ability of the child to maintain arterial oxygen saturation (SpO_2) measured by pulse oximeter at ≥92% without supplemental oxygen or respiratory support for a 4-hour period
- The ability of the child to remain clinically stable for a minimum of 4 hours between inhaled bronchodilator doses
- Maintaining these conditions continuously until hospital discharge

End-of-Study Questionnaire

The study included a patient satisfaction questionnaire, tailored to children with acute severe wheezing, for all parents and their children to be collected at the time of hospital discharge.

Although validated measures of satisfaction existed within the ED setting, these were not tailored to the case of children with acute severe wheezing. Therefore, questionnaire items measuring global satisfaction outcomes were adapted with the help of patient and public involvement (PPI) groups (refer to the *PPI group* section).

The items related to treatment effectiveness, treatment satisfaction, service satisfaction, information and consent, physical comfort, pain, and communication [38] were included in the questionnaire to be rated on a Likert or visual analog scale for parents and using pictographic tools, similar to the FACES pain scale [39] and the widely used childhood Asthma-Control Test [40] for children aged ≥4 years.

Follow-Up (Telephone Interviews)

A qualitative substudy was incorporated to explore the acceptability of HiFlo therapy compared with conventional therapy and the acceptability of the deferred consent process among parents and health care professionals. Parents and health care professionals across the 4 sites were invited to participate in a semistructured telephone interview with an experienced qualitative researcher to elicit their views and opinions of the therapy and the study more generally. All telephone interviews lasted for a maximum of 30 minutes and were recorded for later transcribing. Section 6.7 of the study protocol in Multimedia Appendix 1 presents a detailed account of the recruitment and interview process and the qualitative analysis followed during this substudy. A topic guide for the interviews presented in Textbox 8 was devised with the assistance of the Lived Experience Advisory Panel (LEAP) described in the *PPI group* section.

Textbox 8. Topic guide for qualitative interviews with parents and health care professionals (HCPs).

1. How acceptable did parents, children, and health professionals find the treatment approach used in this study?
2. What aspects of the treatment and the study more generally worked well?
3. What aspects of the treatment and the study more generally needed improvement?
4. If applicable, how did the treatment approach differ from those experienced in the past?
5. What would parents, children, and HCPs change about the therapy or study more generally?
6. Were there any outcomes which weren't measured which should have been?
7. What did parents, children, and HCPs think about the deferred consent process?
8. What would encourage other parents, children, and HCPs to participate in this study?

Clinical Data Recording

The standard of care was guided by a well-defined wheezing or asthma care pathway for children agreed upon by the participating centers, which included various observations to aid with treatment decision-making. Key observations and assessments conducted and recorded for this study are summarized in Textbox 9 (a detailed description is available in section 6.7 of the study protocol in Multimedia Appendix 1).

Textbox 9. Trial observations and assessments.

- Physical examination: this includes evaluation of suprasternal retraction, scalene muscle contraction, air entry, wheezing, work of breathing (respiratory distress), chest findings, and cardiovascular system findings.
- Vital signs: vital signs at initial assessment (triage) and during subsequent reassessments include respiratory rate, heart rate, oxygen saturation (SpO_2), capillary refill time, and temperature.
- Preschool Respiratory Assessment Measure scoring: assessments required involve a physical examination and pulse oximetry, which are all routine procedures in the participating centers.
- Oxygen requirement: this includes monitoring of oxygen (O_2) flow and fraction of inspired oxygen (FiO_2).
- Blood gases: a proportion of patients may have blood gas measurements performed routinely. Specifically, partial pressure of carbon dioxide (pCO_2) results (if available) will be used for treatment escalation decisions. In children, these will normally be measured using capillary or venous blood.

PRAM Scoring and Training

Progress was monitored regularly from hospital admission until discharge using PRAM scores (34), assessed hourly in the ED and 4-hourly after admission to an inpatient ward. PRAM scoring was included in the wheeze or asthma care pathway document adapted by the sites for local implementation. In this study, PRAM scoring was considered the standard of care and documented in the pathway document as source data to be used for patient selection (eligibility). If the pathway document could not be implemented at the ED, then the study screening and eligibility process was adapted for the recording and documentation of PRAM scores. After randomization, PRAM scoring was considered study-specific and documented in a clinical data pro forma as source data to be used for treatment monitoring.

In order to ensure consistency across all study sites, intensive training in recording PRAM scores was undertaken. Data quality was reviewed regularly, and training was updated throughout the study. The principal investigator (PI) and local investigators were responsible for promoting the clinical use of the agreed care pathway in advance of the study, for training ED staff on PRAM scoring in the context of the pathway, and for training staff in other departments (eg, HDU and ward) on the use of PRAM. Various training resources were made available to the sites, including locally produced training videos and a web-based PRAM teaching module from Centre Hospitalier Universitaire Sainte-Justine, University of Montréal [53].

Maintaining an adequate level of training for staff regarding the use of PRAM was challenging. Only one of the sites had staff who were familiar with PRAM scoring, and one of the items (palpable scalene muscle contraction) required specific training. Clinical staff had a range of opinions regarding the clinical value of asthma severity scores, and high staff turnover meant that training had to be revisited at frequent intervals.

Safety Reporting

Overview

Section 7 of the study protocol in Multimedia Appendix 1 provides standard definitions of safety reporting technology appropriate for trials other than Clinical Trials of Investigational Medicinal Products, including adverse event (AE), adverse reaction, serious AE (SAE), serious adverse reaction (SAR), and suspected unexpected SAR, and details of the safety reporting procedures (actions and required timelines) used in this study.

Recording of AEs

The operational definitions of the AEs collected from randomization to hospital discharge are given in Textbox 10 and include two types of events:

1. Air leaks: ASA is a well-recognized risk factor for air leak. Higher HiFlo rates (>2 L/kg) can mimic the effects of CPAP, which is a theoretical additional risk factor for air leak. This study used more conservative flow levels, previously used safely in HiFlo therapy in patients with asthma [23]; therefore, the risk of air leaks was regarded as low. Air leaks in any of the following 3 manifestations were regarded as an SAE and prompted immediate reporting: pneumothorax, pneumomediastinum, or subcutaneous emphysema.
2. Standard treatment–related AE: Vomiting, tachycardia, tremor, lactic acidosis, and others are known potential side effects of intravenous or inhaled bronchodilators that could be seen in both the HiFlo and standard care groups. Documentation of their occurrences was needed to evaluate the candidate secondary outcome measures (treatment-related side effects). If serious, they could be reported as SAEs.

Textbox 10. Definitions of adverse events.

1. Pneumothorax: single episode to be reported per patient.
2. Pneumomediastinum: single episode to be reported per patient.
3. Subcutaneous emphysema: single episode to be reported per patient.
4. Vomiting: a period of sequential vomiting is considered a single episode, but if there is a pause of ≥4 hours, then the next occurrence is the start of a new episode.
5. Tachycardia (heart rate ≥160 in children aged 2 to 4 years and ≥140 in those aged 5 to 11 years): an episode lasts for as long as the patient is in tachycardic range, but if there is a pause of ≥4 hours, then the next occurrence is the start of a new episode.
6. Tremor: an episode lasts as long as any tremor is present, but if there is a pause of ≥4 hours, then the next occurrence is the start of a new episode.
7. Lactic acidosis (venous or capillary lactate >2.2 mmol/L or arterial lactate >1.6 mmol/L): an episode starts every time an abnormal laboratory value is detected. The episode lactate value is recorded.
8. Hypokalemia (potassium <3.5 mmol/L): an episode starts every time an abnormal laboratory value is detected.
9. Sedation received to tolerate high-flow humidified oxygen (HiFlo) therapy: single episode to be reported per patient.
10. Patient unable to tolerate HiFlo therapy (HiFlo discontinued): single episode to be reported per patient.
11. Other: any other untoward medical occurrence or serious adverse event in a study participant.

Responsibilities of Safety Reporting

The PI at each site was responsible for reporting any SAE or SAR to the clinical trials unit (CTU). The trial manager (TM) was responsible for ensuring that all SAE and SAR reports were complete and accurate and for following up with the research teams to ensure this. The TM was responsible for maintaining and updating all the SAE and SAR records required for reporting to the sponsor and the Research Ethics Committee (REC). All AEs and SAEs were monitored by the TM at the CTU and reported and reviewed at the trial steering committee (TSC) meetings.

Statistics and Data Analysis

Statistical Analysis Plan

Participant flow through the trial will be represented in a CONSORT flowchart (Figure 1) according to the CONSORT extension for pilot and feasibility trials [41]. The available cases will be analyzed, following the intention-to-treat principles. Normally distributed variables will be summarized by means and SDs, skewed continuous variables by medians and IQRs, and categorical variables by frequencies and percentages. The difference in means between the trial arms for the primary and secondary outcomes will be estimated, together with bootstrapped 95% CIs. All analyses will be conducted using Stata (version 18; StataCorp LLC).

Qualitative Data Analysis

The interview transcripts will be anonymized and transcribed verbatim. Thematic content analysis will be performed on the interview transcripts based on a 14-stage structured approach [42]. The initial codes will be semantically clustered into subthemes, and finally, these subthemes will be clustered into main themes. The final thematic structure will be described and supported with illustrative interview quotes.

Subgroup Analyses and Participant Population

Subgroup analysis will be limited to 3 variables on which randomization was stratified: site, age, and severity of acute episode. The analysis will be conducted on an intention-to-treat basis; all the recruited participants with consent received will be included in the analysis. In addition, we will examine the screening logs at the sites to identify factors involved in the failure to recruit, which may be relevant to the design of the full RCT. Furthermore, per-protocol analysis will be performed, in which deviation from the trial protocol will result in exclusion from data analysis from that point of protocol deviation onward. Examples of protocol deviations include the following:

- A child is randomized to the HiFlo therapy arm, but for logistical reasons (eg, no equipment is available), this therapy never commenced.
- A child in the HiFlo arm is commenced on therapy, which is later discontinued or changed to another modality because of transfer to a ward area that is unable to provide this care.

The per-protocol analysis will be interpreted cautiously because of the small sample size.

Data Management

A research team pack was used to ensure accurate data collection and included clinical observation sheets and case report forms to record the outcome data. Pseudonymized data were electronically entered by trained research nurses at each site onto a web-based, password-protected data management system (REDCap; Research Electronic Data Capture; Vanderbilt University) designed by a data manager from the Brighton and Sussex CTU (BSCTU). The data manager oversaw data quality and ensured that the database was ready for analysis. Once the data had been cleaned and the database locked, they were transferred securely to the trial statistician for descriptive analysis by the trial arm.

It was agreed that all investigators and trial site staff must comply with the requirements of the General Data Protection Regulation 2018 guidance for researchers—Health Research Authority (HRA) [54]. A specific data management plan and a monitoring plan were developed for this study (available from BSCTU). Archiving will be authorized by the sponsor following the submission of the end-of-trial report. All essential documents will be archived for a minimum of 5 years after trial completion. Destruction of essential documents will require authorization from the sponsor.

Trial Management and Monitoring

The BSCTU oversaw the management of the study. A TM worked closely with the chief investigator (CI) and research team to ensure that the timelines were met, recruitment was tracked, and remote monitoring was undertaken for quality assurance. The TM supported the setup of the sites, ensuring that all documentation and processes were in line with the research governance and HRA processes. Monthly trial management group (TMG) meetings with the CI, DM, statistician, PIs, and research nurses from the sites were conducted to oversee the study's progress.

The TSC consisted of the TMG and 3 independent members (a lay member—parent of a child with asthma, a pediatrician with relevant expertise, and a statistician). The TSC reviewed the reports from the TMG and met to oversee the overall progress. With its independent membership, the TSC also reviewed the data and safety issues, fulfilling the role of this feasibility trial of a data and safety monitoring board. Financial management for the study was overseen by the TM with institutional supervision by the head of research at the UHSx NHS Foundation Trust.

Ethical Considerations

The study protocol and all applicable documents and amendments were approved by the West Midlands–Solihull Research Ethics Committee (REC) and the Health Research Authority (HRA) according to applicable regulations (REC reference: 19/WM/0219, IRAS: 261627). This study was registered with International Standard Randomised Controlled Trial Number registry (ISRCTN78297040) [55]. The HiFlo ASA project proposal was successful in competition 35 of the NIHR Research for Patient Benefit Program after 2 stages of independent peer review by the program's designated expert advisory panel. The study protocol for this feasibility study was further developed and discussed by researchers from the participating centers, with the involvement of the BSCTU.

Dissemination

In this feasibility trial, the important aspects of dissemination concern the use of trial data in designing a full RCT and preparing an application to fund it. Therefore, dissemination will be principally among the study team, the PPI groups involved, and the stakeholders (both professional and patient or parent groups) to be involved in the full multicenter RCT. We intend to publish a protocol for this feasibility trial.

Trial Sponsorship

The sponsor was responsible for ensuring that the trial was being conducted under appropriate governance. The sponsor is the UHSx NHS Foundation Trust.

Committees

The composition, roles, and responsibilities of the TMG, TSC, and LEAP are described in the *General Information* section (part 6) at the beginning of the study protocol in Multimedia Appendix 1.

PPI Group

PPI was sought at different stages in the development of the study, with a plan for continuing input during the research and its dissemination.

The detailed involvement of the following PPI groups is described in section 11.3 of the study protocol in Multimedia Appendix 1:

- Two local patient groups from Kent, Surrey, and Sussex (KSS), funded by the NIHR, participated in the trial design and will be informed of the findings of the study: KSS young people's advisory group and KSS parent and carer advisory group (KSS, Generation R).
- A separate NIHR research support grant enabled the creation of a LEAP—a group of 6 to 8 parents whose young children have been admitted with ASA, together with 4 children with experience of ASA—to provide disease-specific PPI into the study.

Results

The trial was opened to recruitment at the lead site in February 2020, but a month later, the COVID-19 pandemic reached the United Kingdom, and the study was put on hold in March 2020. There was a 15-month pause because of a combination of factors, including general concerns about face-to-face research, specific concerns about HiFlo therapy as an *aerosol-generating procedure*, and redeployment of research staff to clinical duties during the pandemic. The trial was reopened at the lead site in July 2021 and opened at the other 3 sites between August and December 2022. The follow-up was completed in July 2023. The results are currently being analyzed and will be reported separately.

Discussion

This paper describes the protocol for a multicenter feasibility RCT of 50 children that has been successfully executed at 4 sites in the United Kingdom. The trial aimed to establish whether a full RCT of early HiFlo therapy in ASA can be conducted successfully and safely and whether recruitment for such a trial, using deferred consent, is practicable in children aged 2 to 11 years presenting to hospital with ASA. If it is determined that a definitive RCT is feasible, the data from the study will inform the outcome measures and sample size needed for adequate power.

A total of 2 previous pilot RCTs of HiFlo therapy in acute asthma have been published [27,28], but neither provided the feasibility data required to design a definitive RCT to assess the clinical effectiveness. Both studies used an asthma severity score as the main outcome measure, but neither the *Pulmonary Score* used by Ballestero et al [27] nor the *Pulmonary Index Score* used by Gauto Benítez et al [28] were referenced, and it is unclear what any differences in these outcomes would mean for clinical management. In this protocol, we chose 2 candidate primary outcome measures that had been determined by clinicians and by parents and children to be meaningful and likely to impact practice. Both the need for escalation of therapy owing to treatment failure and the time to reach readiness for discharge are important in determining resource use and care costs.

We used an asthma scoring system and selected PRAM because it was the only asthma scoring system validated across the entire age range of 2 to 11 years. At least 17 different asthma severity scores have been published, but few EDs in the United Kingdom regularly use any of them as part of routine clinical practice [56], and only one of our sites had any prior familiarity with PRAM. The study protocol used the PRAM score in 2 ways: as one of the entry criteria (PRAM score ≥5 after first-line treatment) and as a candidate (secondary) outcome measure (time to achieve a PRAM score of ≤3). As noted above, implementing PRAM at the study sites and maintaining PRAM competency, despite high staff turnover, required considerable input of training resources. The advantage of using a validated asthma score as an entry criterion was that it standardized the severity of acute asthma in children entering the study, allowed comparison with other acute asthma trials [36], and allowed us to stratify randomization by asthma severity at entry. A potential disadvantage was that it risked reducing out-of-hours recruitment owing to PRAM-trained staff not being available.

As with many clinical trials since 2019, the conduct of this study was severely affected by the COVID-19 pandemic. It was necessary to pause recruitment for a prolonged period because of general logistic issues affecting all clinical research and specific concerns relating to the theoretical risks of aerosol generation and COVID-19 transmission from HiFlo therapy. The experience gained by the research team (both in adapting trial procedures and disseminating new research findings on aerosol generation) to allow the successful completion of the trial will be valuable in planning a definitive RCT.

Acknowledgments

This project was funded by the UK National Institute for Health and Care Research under its Research for Patient Benefit Program (grant PB-PG-1217-20024). The views expressed are those of the authors and not necessarily those of the National Institute for Health and Care Research or the Department of Health and Social Care.

The sponsor of this study is the University Hospital Sussex NHS Foundation Trust. The sponsor's representative is Mr Scott Harfield.

We would like to acknowledge the support of Vapotherm Inc who loaned the HiFlo equipment, and Aerogen Ltd who loaned the nebuliser equipment for the study.

Conflicts of Interest

In March 2023, PS chaired an advisory board for Aerogen Ltd, who loaned nebulizer equipment for the study, and received an honorarium. ML attended the same advisory board, and received an honorarium. All other authors declare no other conflicts of interest.

Multimedia Appendix 1
Full study protocol.
[PDF File (Adobe PDF File), 1201 KB - resprot_v13i1e54081_app1.pdf]

Multimedia Appendix 2
Peer-review report from the National Institute for Health Research.
[PDF File (Adobe PDF File), 606 KB - resprot_v13i1e54081_app2.pdf]

References

1. Martinez FD, Vercelli D. Asthma. Lancet 2013 Oct 19;382(9901):1360-1372. [doi: 10.1016/S0140-6736(13)61536-6] [Medline: 24041942]
2. Asher MI, Rutter CE, Bissell K, Chiang CY, El Sony A, Ellwood E, et al. Worldwide trends in the burden of asthma symptoms in school-aged children: Global Asthma Network Phase I cross-sectional study. Lancet 2021 Oct 30;398(10311):1569-1580 [FREE Full text] [doi: 10.1016/S0140-6736(21)01450-1] [Medline: 34755626]
3. Asher I, Bissell K, Chiang CY, El Sony A, Ellwood P, García-Marcos L, et al. Calling time on asthma deaths in tropical regions-how much longer must people wait for essential medicines? Lancet Respir Med 2019 Jan;7(1):13-15 [FREE Full text] [doi: 10.1016/S2213-2600(18)30513-7] [Medline: 30553847]
4. Chawla J, Seear M, Zhang T, Smith A, Carleton B. Fifty years of pediatric asthma in developed countries: how reliable are the basic data sources? Pediatr Pulmonol 2012 Mar;47(3):211-219. [doi: 10.1002/ppul.21537] [Medline: 21905263]
5. Merrill C, Owens PL. Reasons for being admitted to the hospital through the emergency department for children and adolescents, 2004. In: Healthcare Cost and Utilization Project (HCUP) Statistical Briefs. Rockville, MD: Agency for Healthcare Research and Quality (US); 2004.
6. Brand PL, Baraldi E, Bisgaard H, Boner AL, Castro-Rodriguez JA, Custovic A, et al. Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. Eur Respir J 2008 Oct;32(4):1096-1110 [FREE Full text] [doi: 10.1183/09031936.00002108] [Medline: 18827155]
7. British guideline on the management of asthma. Scottish Intercollegiate Guidelines Network & British Thoracic Society. 2003. URL: https://www.sign.ac.uk/media/1773/sign158-updated.pdf [accessed 2024-02-29]
8. Why asthma still kills. Royal College of Physicians. 2015. URL: https://www.rcplondon.ac.uk/projects/outputs/why-asthma-still-kills [accessed 2024-02-29]
9. Global strategy for asthma management and prevention. Guideline Central. 2023 May 11. URL: https://www.guidelinecentral.com/guideline/41774/ [accessed 2024-02-29]
10. Haq I, Gopalakaje S, Fenton AC, McKean MC, J O'Brien C, Brodlie M. The evidence for high flow nasal cannula devices in infants. Paediatr Respir Rev 2014 Jun;15(2):124-134. [doi: 10.1016/j.prrv.2013.12.002] [Medline: 24472697]
11. Yoder BA, Stoddard RA, Li M, King J, Dirnberger DR, Abbasi S. Heated, humidified high-flow nasal cannula versus nasal CPAP for respiratory support in neonates. Pediatrics 2013 May;131(5):e1482-e1490. [doi: 10.1542/peds.2012-2742] [Medline: 23610207]
12. Nolasco S, Manti S, Leonardi S, Vancheri C, Spicuzza L. High-flow nasal cannula oxygen therapy: physiological mechanisms and clinical applications in children. Front Med (Lausanne) 2022 Jun 03;9:920549 [FREE Full text] [doi: 10.3389/fmed.2022.920549] [Medline: 35721052]
13. Locke RG, Wolfson MR, Shaffer TH, Rubenstein SD, Greenspan JS. Inadvertent administration of positive end-distending pressure during nasal cannula flow. Pediatrics 1993 Jan;91(1):135-138. [Medline: 8416477]
14. Arora B, Mahajan P, Zidan MA, Sethuraman U. Nasopharyngeal airway pressures in bronchiolitis patients treated with high-flow nasal cannula oxygen therapy. Pediatr Emerg Care 2012 Nov;28(11):1179-1184. [doi: 10.1097/PEC.0b013e318271a671] [Medline: 23114244]
15. Dysart K, Miller TL, Wolfson MR, Shaffer TH. Research in high flow therapy: mechanisms of action. Respir Med 2009 Oct;103(10):1400-1405 [FREE Full text] [doi: 10.1016/j.rmed.2009.04.007] [Medline: 19467849]
16. Lin J, Zhang Y, Xiong L, Liu S, Gong C, Dai J. High-flow nasal cannula therapy for children with bronchiolitis: a systematic review and meta-analysis. Arch Dis Child 2019 Jun;104(6):564-576. [doi: 10.1136/archdischild-2018-315846] [Medline: 30655267]
17. McKiernan C, Chua LC, Visintainer PF, Allen H. High flow nasal cannulae therapy in infants with bronchiolitis. J Pediatr 2010 Apr;156(4):634-638. [doi: 10.1016/j.jpeds.2009.10.039] [Medline: 20036376]
18. Schibler A, Pham TM, Dunster KR, Foster K, Barlow A, Gibbons K, et al. Reduced intubation rates for infants after introduction of high-flow nasal prong oxygen delivery. Intensive Care Med 2011 May;37(5):847-852. [doi: 10.1007/s00134-011-2177-5] [Medline: 21369809]
19. Hilliard TN, Archer N, Laura H, Heraghty J, Cottis H, Mills K, et al. Pilot study of vapotherm oxygen delivery in moderately severe bronchiolitis. Arch Dis Child 2012 Feb;97(2):182-183. [doi: 10.1136/archdischild-2011-301151] [Medline: 22100741]
20. Kepreotes E, Whitehead B, Attia J, Oldmeadow C, Collison A, Searles A, et al. High-flow warm humidified oxygen versus standard low-flow nasal cannula oxygen for moderate bronchiolitis (HFWHO RCT): an open, phase 4, randomised controlled trial. Lancet 2017 Mar 04;389(10072):930-939. [doi: 10.1016/S0140-6736(17)30061-2] [Medline: 28161016]
21. Franklin D, Babl FE, Schlapbach LJ, Oakley E, Craig S, Neutze J, et al. A randomized trial of high-flow oxygen therapy in infants with bronchiolitis. N Engl J Med 2018 Mar 22;378(12):1121-1131 [FREE Full text] [doi: 10.1056/NEJMoa1714855] [Medline: 29562151]
22. Beggs S, Wong ZH, Kaul S, Ogden KJ, Walters JA. High-flow nasal cannula therapy for infants with bronchiolitis. Cochrane Database Syst Rev 2014 Jan 20;2014(1):CD009609 [FREE Full text] [doi: 10.1002/14651858.CD009609.pub2] [Medline: 24442856]
23. Chao KY, Chien YH, Mu SC. High-flow nasal cannula in children with asthma exacerbation: a review of current evidence. Paediatr Respir Rev 2021 Dec;40:52-57. [doi: 10.1016/j.prrv.2021.01.003] [Medline: 33771473]

24. Baudin F, Buisson A, Vanel B, Massenavette B, Pouyau R, Javouhey E. Nasal high flow in management of children with status asthmaticus: a retrospective observational study. Ann Intensive Care 2017 Dec;7(1):55 [FREE Full text] [doi: 10.1186/s13613-017-0278-1] [Medline: 28534235]
25. González Martínez F, González Sánchez MI, Toledo Del Castillo B, Pérez Moreno J, Medina Muñoz M, Rodríguez Jiménez C, et al. [Treatment with high-flow oxygen therapy in asthma exacerbations in a paediatric hospital ward: experience from 2012 to 2016]. An Pediatr (Engl Ed) 2019 Feb;90(2):72-78 [FREE Full text] [doi: 10.1016/j.anpedi.2018.06.015] [Medline: 30322768]
26. Pilar J, Modesto I Alapont V, Lopez-Fernandez YM, Lopez-Macias O, Garcia-Urabayen D, Amores-Hernandez I. High-flow nasal cannula therapy versus non-invasive ventilation in children with severe acute asthma exacerbation: an observational cohort study. Med Intensiva 2017 Oct;41(7):418-424 [FREE Full text] [doi: 10.1016/j.medin.2017.01.001] [Medline: 28216104]
27. Ballestero Y, De Pedro J, Portillo N, Martinez-Mugica O, Arana-Arri E, Benito J. Pilot clinical trial of high-flow oxygen therapy in children with asthma in the emergency service. J Pediatr 2018 Mar;194:204-10.e3. [doi: 10.1016/j.jpeds.2017.10.075] [Medline: 29331328]
28. Gauto Benítez R, Morilla Sanabria LP, Pavlicich V, Mesquita M. High flow nasal cannula oxygen therapy in patients with asthmatic crisis in the pediatric emergency department. Rev Chil Pediatr 2019 Dec;90(6):642-648 [FREE Full text] [doi: 10.32641/rchped.v90i6.1145] [Medline: 32186587]
29. Gilbert RE, Mok Q, Dwan K, Harron K, Moitt T, Millar M, et al. Impregnated central venous catheters for prevention of bloodstream infection in children (the CATCH trial): a randomised controlled trial. Lancet 2016 Apr 23;387(10029):1732-1742 [FREE Full text] [doi: 10.1016/S0140-6736(16)00340-8] [Medline: 26946925]
30. Prioritisation exercise. PERUKI. URL: https://www.peruki.org/ [accessed 2024-03-01]
31. Chalut DS, Ducharme FM, Davis GM. The Preschool Respiratory Assessment Measure (PRAM): a responsive index of acute asthma severity. J Pediatr 2000 Dec;137(6):762-768. [doi: 10.1067/mpd.2000.110121] [Medline: 11113831]
32. Sim J, Lewis M. The size of a pilot study for a clinical trial should be calculated in relation to considerations of precision and efficiency. J Clin Epidemiol 2012 Mar;65(3):301-308. [doi: 10.1016/j.jclinepi.2011.07.011] [Medline: 22169081]
33. Teare MD, Dimairo M, Shephard N, Hayman A, Whitehead A, Walters SJ. Sample size requirements to estimate key design parameters from external pilot randomised controlled trials: a simulation study. Trials 2014 Jul 03;15:264 [FREE Full text] [doi: 10.1186/1745-6215-15-264] [Medline: 24993581]
34. Zadravecz FJ, Tien L, Robertson-Dick BJ, Yuen TC, Twu NM, Churpek MM, et al. Comparison of mental-status scales for predicting mortality on the general wards. J Hosp Med 2015 Oct;10(10):658-663 [FREE Full text] [doi: 10.1002/jhm.2415] [Medline: 26374471]
35. Alnaji F, Zemek R, Barrowman N, Plint A. PRAM score as predictor of pediatric asthma hospitalization. Acad Emerg Med 2014 Aug;21(8):872-878 [FREE Full text] [doi: 10.1111/acem.12422] [Medline: 25176153]
36. Schuh S, Sweeney J, Rumantir M, Coates AL, Willan AR, Stephens D, et al. Effect of nebulized magnesium vs placebo added to albuterol on hospitalization among children with refractory acute asthma treated in the emergency department: a randomized clinical trial. JAMA 2020 Nov 24;324(20):2038-2047 [FREE Full text] [doi: 10.1001/jama.2020.19839] [Medline: 33231663]
37. Lyttle MD, Rainford NE, Gamble C, Messahel S, Humphreys A, Hickey H, et al. Levetiracetam versus phenytoin for second-line treatment of paediatric convulsive status epilepticus (EcLiPSE): a multicentre, open-label, randomised trial. Lancet 2019 May 25;393(10186):2125-2134 [FREE Full text] [doi: 10.1016/S0140-6736(19)30724-X] [Medline: 31005385]
38. Rydman RJ, Roberts RR, Albrecht GL, Zalenski RJ, McDermott M. Patient satisfaction with an emergency department asthma observation unit. Acad Emerg Med 1999 Mar;6(3):178-183 [FREE Full text] [doi: 10.1111/j.1553-2712.1999.tb00152.x] [Medline: 10192667]
39. Wong DL, Baker CM. Pain in children: comparison of assessment scales. Pediatr Nurs 1988;14(1):9-17. [Medline: 3344163]
40. Bime C, Gerald JK, Wei CY, Holbrook JT, Teague WG, Wise RA, et al. Measurement characteristics of the childhood asthma-control test and a shortened, child-only version. NPJ Prim Care Respir Med 2016 Oct 20;26:16075 [FREE Full text] [doi: 10.1038/npjpcrm.2016.75] [Medline: 27763622]
41. Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ 2016 Oct 24;355:i5239 [FREE Full text] [doi: 10.1136/bmj.i5239] [Medline: 27777223]
42. Burnard P. A method of analysing interview transcripts in qualitative research. Nurse Educ Today 1991 Dec;11(6):461-466. [doi: 10.1016/0260-6917(91)90009-y] [Medline: 1775125]
43. Asthma + Lung UK home page. Asthma + Lung UK. URL: https://www.asthmaandlung.org.uk/media [accessed 2024-03-01]
44. Papiris SA, Manali ED, Kolilekas L, Triantafillidou C, Tsangaris I. Acute severe asthma: new approaches to assessment and treatment. Drugs 2009;69(17):2363-2391. [doi: 10.2165/11319930-000000000-00000] [Medline: 19911854]
45. Mukherjee M, Stoddart A, Gupta RP, Nwaru BI, Farr A, Heaven M, et al. The epidemiology, healthcare and societal burden and costs of asthma in the UK and its member nations: analyses of standalone and linked national databases. BMC Med 2016 Aug 29;14(1):113 [FREE Full text] [doi: 10.1186/s12916-016-0657-8] [Medline: 27568881]

46. Bahadori K, Doyle-Waters MM, Marra C, Lynd L, Alasaly K, Swiston J, et al. Economic burden of asthma: a systematic review. BMC Pulm Med 2009 May 19;9:24 [FREE Full text] [doi: 10.1186/1471-2466-9-24] [Medline: 19454036]
47. Jones AJ, Mathew S, Wong SW, Patel M, Equi A, Sukhani S, et al. A regional audit of high-flow nasal cannula therapy use for bronchiolitis in London district general hospitals. Arch Dis Child 2017 Mar;102(3):296-297. [doi: 10.1136/archdischild-2016-312462] [Medline: 28119404]
48. Malterud K, Siersma VD, Guassora AD. Sample size in qualitative interview studies: guided by information power. Qual Health Res 2016 Nov;26(13):1753-1760. [doi: 10.1177/1049732315617444] [Medline: 26613970]
49. Hazell CM, Jones CJ, Hayward M, Bremner SA, O'Connor DB, Pinfold V, et al. Caring for Caregivers (C4C): study protocol for a pilot feasibility randomised control trial of Positive Written Disclosure for older adult caregivers of people with psychosis. Pilot Feasibility Stud 2017 Nov 21;3:63 [FREE Full text] [doi: 10.1186/s40814-017-0206-z] [Medline: 29201390]
50. Randomisation and online databases for clinical trials. Sealed Envelope. URL: https://www.sealedenvelope.com/ [accessed 2024-03-01]
51. Richards-Belle A, Davis P, Drikite L, Feltbower R, Grieve R, Harrison DA, et al. FIRST-line support for assistance in breathing in children (FIRST-ABC): a master protocol of two randomised trials to evaluate the non-inferiority of high-flow nasal cannula (HFNC) versus continuous positive airway pressure (CPAP) for non-invasive respiratory support in paediatric critical care. BMJ Open 2020 Aug 04;10(8):e038002 [FREE Full text] [doi: 10.1136/bmjopen-2020-038002] [Medline: 32753452]
52. Lyttle MD, Gamble C, Messahel S, Hickey H, Iyer A, Woolfall K, et al. Emergency treatment with levetiracetam or phenytoin in status epilepticus in children-the EcLiPSE study: study protocol for a randomised controlled trial. Trials 2017 Jun 19;18(1):283 [FREE Full text] [doi: 10.1186/s13063-017-2010-8] [Medline: 28629473]
53. Online training center. CHU Sainte-Justine. URL: https://formation.chusj.org/fr [accessed 2024-03-01]
54. Health research authority. National Health Service Health Research Authority. URL: https://www.hra.nhs.uk/ [accessed 2024-03-01]
55. The HiFlo study: a feasibility trial of using high flow humidified oxygen in acute asthma. BioMed Central Ltd. 2024 Mar 05. URL: https://www.isrctn.com/ISRCTN78297040 [accessed 2024-03-05]
56. Chacko J, King C, Harkness D, Messahel S, Grice J, Roe J, et al. Pediatric acute asthma scoring systems: a systematic review and survey of UK practice. J Am Coll Emerg Physicians Open 2020 Jun 02;1(5):1000-1008 [FREE Full text] [doi: 10.1002/emp2.12083] [Medline: 33145551]

Abbreviations

AE: adverse event
ASA: acute severe asthma
BSCTU: Brighton and Sussex clinical trials unit
CONSORT: Consolidated Standards of Reporting Trials
CPAP: continuous positive airway pressure
CTU: clinical trials unit
ED: emergency department
FiO_2: fraction of inspired oxygen
HDU: high-dependency unit
HiFlo: high-flow humidified oxygen
HRA: Health Research Authority
KSS: Kent, Surrey, and Sussex
LEAP: Lived Experience Advisory Panel
NIHR: National Institute for Health and Care Research
PI: principal investigator
PPI: patient and public Involvement
PRAM: Preschool Respiratory Assessment Measure
RCT: randomized controlled trial
REC: Research Ethics Committee
REDCap: Research Electronic Data Capture
SAE: serious adverse event
SAR: serious adverse reaction
TM: trial manager
TMG: trial management group
TSC: trial steering committee
UHSx: University Hospitals Sussex

Edited by A Mavragani; submitted 01.11.23; this is a non–peer-reviewed article;accepted 25.01.24; published 28.03.24.

Please cite as:
Rojas-Anaya H, Kapur A, Roberts G, Roland D, Gupta A, Lazner M, Bayreuther J, Pappachan J, Jones C, Bremner S, Cantle F, Seddon P
High-Flow Humidified Oxygen as an Early Intervention in Children With Acute Severe Asthma: Protocol for a Feasibility Randomized Controlled Trial
JMIR Res Protoc 2024;13:e54081
URL: https://www.researchprotocols.org/2024/1/e54081
doi:10.2196/54081
PMID:38546733

Protocol

Enhancing Psychotherapy Outcomes by Encouraging Patients to Regularly Self-Monitor, Reflect on, and Share Their Affective Responses Toward Their Therapist: Protocol for a Randomized Controlled Trial

Alberto Stefana[1,2], PsyD, PhD; Eduard Vieta[3], MD, PhD; Paolo Fusar-Poli[1,4,5], MD, PhD; Eric A Youngstrom[2,6,7,8], PhD

[1]Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy

[2]Department of Psychology and Neuroscience, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States

[3]Bipolar and Depressive Disorders Unit, Hospital Clinic, IDIBAPS, CIBERSAM, University of Barcelona,, Barcelona, Spain

[4]OASIS Service, South London and Maudsley NHS Foundation Trust, London, United Kingdom

[5]Early Psychosis: Interventions and Clinical-detection Lab, Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, United Kingdom

[6]Institute for Mental and Behavioral Health Research, Nationwide Children's Hospital, Division of Child and Family Psychiatry, The Ohio State University, Columbus, OH, United States

[7]Helping Give Away Psychological Science, Chapel Hill, NC, United States

[8]Department of Psychiatry, The Ohio State University, Columbus, OH, United States

Corresponding Author:
Alberto Stefana, PsyD, PhD
Department of Brain and Behavioral Sciences
University of Pavia
Via Agostino Bassi, 21
Pavia, 27100
Italy
Phone: 39 0 382 98725
Email: alberto.stefana@gmail.com

Abstract

Background: The quality of the therapeutic relationship is pivotal in determining psychotherapy outcomes. However, facilitating patients' self-awareness, reflection on, and sharing of their affective responses toward their therapist remains underexplored as a potential tool for enhancing this relationship and subsequent treatment outcomes.

Objective: The primary objective of this study is to examine whether and how the patients' regular self-monitoring and self-reflection (fostered by the systematic compilation of a brief postsession battery) on their affective reactions toward the psychotherapist impact the quality of the therapeutic relationship and treatment outcomes in individual psychotherapy. Secondary objectives are to (1) explore whether and how the characteristics of the patient, the therapist, and the process moderate the effect of regular self-monitoring on the therapeutic relationship and outcomes; (2) examine the relationships between the affective response of the patient, the alliance, and the result of the therapy session outcome; and (3) explore how the affective responses of the patient unfold or change throughout the course of the therapy.

Methods: We conducted a 1:1 randomized controlled trial of adults in individual psychotherapy versus individual psychotherapy plus self-monitoring. Participants will be enrolled through the web-based recruitment platforms "ResearchMatch" and "Research for Me," and data will be collected through web-based surveys. Participants in the control group will receive only their regular individual psychotherapy (treatment as usual) and will not complete postsession questionnaires. Participants in the intervention group will continue their regular individual psychotherapy sessions and complete the "in-Session Patient Affective Reactions Questionnaire" and the "Rift In-Session Questionnaire" following each therapy session in the 10 weeks of the trial. Additionally, after completion of the postsession battery, they will receive general written feedback encouraging them to discuss their feelings and reflections with their therapist. Participants in both groups will complete a comprehensive psychological assessment at baseline, midtrial (week 5), and end-of-trial (week 10). The primary outcome measure of the trial is the "Clinical Outcomes in Routine Evaluation-Outcome Measure," while the secondary outcomes are the "Real Relationship Inventory-Client-Short Form,"

the "Working Alliance Inventory-Short Revised," and the number of scheduled therapy sessions that the patient has missed or canceled.

Results: The trial was approved by the institutional review board of the University of North Carolina at Chapel Hill. Recruitment started in September 2023. A total of 475 individuals completed the baseline assessment. Data collection was completed in February 2024. The results are expected to be published in the autumn of 2024.

Conclusions: This study could reveal key information on how regular self-monitoring and introspection can influence both the therapeutic relationship and treatment outcomes. Findings have the potential to shape interventions, enhance the efficacy of psychotherapeutic sessions, and possibly offer a cost-effective strategy for improving patients' well-being.

Trial Registration: ClinicalTrials.gov NCT06038747; https://classic.clinicaltrials.gov/ct2/show/NCT06038747

International Registered Report Identifier (IRRID): DERR1-10.2196/55369

(JMIR Res Protoc 2024;13:e55369) doi:10.2196/55369

KEYWORDS

adult patients; evidence-based assessment; patient's perspective; psychotherapy; randomized controlled trial; systematic client feedback; therapeutic relationship; treatment outcome

Introduction

Background

Emotions lie at the core of human existence, emerging as products of evolutionary mechanisms designed to equip individuals to handle critical interpersonal interactions and life challenges [1,2]. Since the dawn of psychotherapy, the role of emotions, whether emanating from the patient or the therapist, has been recognized as crucial to the therapeutic journey [3-5].

Studies on emotional expression within the therapeutic realm emphasize their substantial influence on the outcomes of both single sessions and the entire treatment journey [2,6,7]. Emotions intertwine with both specific and generic therapeutic methodologies that underpin clinical success [8,9]. Facilitating patients to gain emotional awareness and use these emotions constructively stands central to therapeutic transformation [10,11]. For this transformative effect, therapists must engage collaboratively with the patient's in-session emotions, guiding them through recognition, acceptance, regulation, and management [12-14].

The therapeutic setting can illuminate suppressed emotions, allowing patients to confront neglected self-awareness and experience new emotional dimensions. Such insights present valuable data on patients' inherent needs and reactions, offering a platform to confront past fears and integrate new experiences [11,15]. Emotions directed toward the therapist during sessions hold significant implications for the therapeutic journey's success [16,17]. An environment characterized by empathy and affirmation determines if the emotional engagement will steer the therapy positively or detrimentally [18]. Furthermore, such an environment is both the catalyst for change and the foundation for effective psychotherapy [19].

The dawn of the new millennium saw the advent of routine outcome monitoring and feedback [20]. These systems, which track and report the patient's therapeutic progress, have seen widespread adoption and study in varied mental health contexts over recent years. These feedback mechanisms, unified by their use of standardized measures, monitor outcomes like well-being, symptomatology, and functional aspects, sometimes focusing on specific therapeutic processes like the working alliance [21]. Meta-analyses show that systematic feedback enhances therapy outcomes by reducing symptom intensity and attrition rates [22,23]. They also highlight reductions in treatment time frames and associated costs [24-26].

Given these insights, the American Psychological Association has been advocating for feedback and outcome monitoring since the early 2000s [27,28]. Feedback systems are now integral to mental health frameworks globally, especially in countries such as Australia, the Netherlands, and the United Kingdom, where monitoring outcomes is a statutory mandate for health service providers. With the capacity to tweak treatments based on progress or disruptions in the therapist-patient relationship, many experts regard progress monitoring as a pivotal strategy to enhance real-world therapy outcomes [29,30].

Study Objectives

In light of the above, the primary objective of this study is to examine the influence of a brief postsession battery, which is apt to foster patient self-monitoring and reflection on their emotional reactions toward their psychotherapist and on the quality of the therapeutic relationship and treatment outcomes.

Secondary objectives are to (1) explore whether and how the characteristics of the patient, the therapist, and the process moderate the effect of regular self-monitoring on the therapeutic relationship and outcomes; (2) examine the relationships between the affective response of the patient, the alliance, and the result of the therapy session outcome; and (3) explore how the affective responses of the patient unfold or change throughout the course of therapy.

Methods

Ethical Considerations

The institutional review board of the University of North Carolina (UNC) at Chapel Hill approved this study (23-1067) on July 31, 2023. This research was designed and executed in accordance with ethical standards for studies involving human participants.

Before starting the baseline survey, participants will receive a detailed web-based consent form regarding the study. This form will include the purpose, rationale, and methodology of the study, as well as the contact information for both the principal investigator and the institutional review board. It will be explained to potential participants that to protect their identities, only relevant and minimally necessary information will be collected. Furthermore, it will be assured that any published results will report on groups, not individual participants. Participants will be prompted with a consent statement and given options: "I consent to participate in this study" or "I do not consent to participate in this study." Those who choose not to consent will be immediately directed to a closing page. All participants are informed that they can opt out of the study at any time without providing a reason.

Only the central research team will have access to the data until the research results are published. Once the study concludes and the primary findings are released, external applications for access to deidentified data will be entertained. These applications must adhere to data privacy rules, and the intended research must be scientifically and ethically robust. Following the publication of the research findings, the data will be publicly shared through the Open Science Framework [31].

No financial incentives were offered for participation in this trial. However, upon completing the trial, participants from both the intervention and control groups were given the opportunity to request a free copy of the scales and general feedback used in the intervention group by emailing the principal investigator.

Study Design

This study is a randomized controlled trial (NCT06038747) of 1:1 for individual psychotherapy versus individual psychotherapy plus self-monitoring. A predetermined computer-generated randomization list will be generated to assign patients to 1 of the 2 arms. Patients will not be blind to treatment allocation. Patients will be enrolled through the web-based recruitment platforms "ResearchMatch" and "Research for Me," and data will be collected through web-based surveys facilitated by the Qualtrics software hosted by the UNC at Chapel Hill.

Intervention

Participants in the intervention group will continue their regular individual psychotherapy sessions. Additionally, after each session, they will complete a brief postsession battery consisting of 2 scales on the affective reactions of the patients toward their therapist during the session and read general feedback encouraging them to discuss their feelings and reflections with their therapist. This questionnaire aims to prompt reflection on one's own experience of the therapeutic relationship.

Treatment as Usual

Patients in the control group will receive only their regular individual psychotherapy (treatment as usual) and will not complete postsession questionnaires. Additionally, they will not receive any communication encouraging them to discuss their emotional responses with their therapist during the session.

Measures

This study uses a comprehensive set of self-report instruments to collect extensive data on the therapeutic process and various patient-related factors. The data will cover 5 main domains. The sociodemographic and clinical domains capture the patient's demographic, clinical, and treatment specifics. The mental health state domain focuses on the present symptoms of anxiety and depression that impact the daily lives of respondents. The therapeutic relationship domain evaluates the specific facets of the relationship between the patient and the therapist. The last domain evaluates session and therapy outcomes.

The primary outcome measure of the trial is the "Clinical Outcomes in Routine Evaluation-Outcome Measure" (CORE-OM) [32], while the secondary outcomes are the "Real Relationship Inventory-Client-Short Form" (RRI-C-SF) [33], the "Working Alliance Inventory-Short Revised" (WAI-SR) [34], and the number of scheduled therapy sessions that have been missed or canceled by the patient.

Sociodemographic Domain

The "sociodemographic data form" collects self-reported details such as the patient's age, gender, education level, and ethnicity.

Clinical Domain

The "clinical data form A" gathers patient-provided data on the duration and frequency of the ongoing psychotherapy, session attendance method (in-person, video call, telephone, and mixed), presence or absence of a diagnosed mental disorder, any prescribed psychotropic medications, and the therapist's gender.

The "clinical data form B" records information on sessions attended, missed, and canceled over the last 5 weeks and any change in psychiatric medications during this time frame.

Mental Health State Domain

The Patient Health Questionnaire-9 (PHQ-9) [35] is a 9-item self-report depression screening tool that captures the severity of depressive symptoms during the past week. It allows the evaluation of symptoms according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for major depression. The PHQ-9 administered in the primary care sample showed a Cronbach α of 0.89.

The Generalized Anxiety Disorder-7 (GAD-7) [36] is a 7-item self-report anxiety screening tool with a focus on symptoms of generalized anxiety disorder. It assesses the severity and frequency of anxiety symptoms during the past week. GAD-7 showed a Cronbach α of 0.92.

Therapeutic Relationship Domain

The RRI-C-SF [33] is an 8-item self-report tool measuring the "real relationship" between a therapist and patient from the patient's viewpoint. It includes 2 subscales: "genuineness" and "realism," both of which represent closely related dimensions of authenticity and perceptual accuracy within the therapeutic relationship. The RRI-C-SF has a McDonald's ω total of 0.93.

The WAI-SR [34] is a 12-item self-report measure of the quality of the working alliance between patient and therapist from the patient's perspective. WAI-SR includes three 4-item subscales

that focus on agreement on therapy tasks, goals, and the development of an emotional bond. Items are rated on a 6-point Likert scale, with higher scores indicating a more robust alliance. The Cronbach α for the total scale was 0.91, while the α coefficients for the subscales spanned a range from 0.85 to 0.90.

The "in-Session Patient Affective Reactions Questionnaire" (SPARQ) [37,38] is a patient-reported tool that comprises 8 items that explore the patterns of thought, feeling, and behavior activated and experienced by the patients toward their therapist during a session. It consists of 2 scales: "positive affect" and "negative affect." The positive affect scale exhibited a Cronbach α coefficient of 0.84 and an average interitem correlation of 0.51. On the other hand, the negative affect scale demonstrated an α of 0.76 and an average interitem correlation of 0.39.

The "Rift In-Session Questionnaire" (RISQ) [37] is a 4-item self-report questionnaire designed to measure the patient's risk of experiencing ruptures in the therapeutic relationship. The RISQ measures feelings of belittlement, rejection, disparagement, and attack, as well as any tendencies toward disobedience or "naughtiness" toward the therapist. The RISQ demonstrated good internal consistency with a Cronbach α coefficient of 0.73 and an average interitem correlation of 0.35.

Session and Therapy Outcomes Domain

The Session Evaluation Scale (SES) [39] assesses the quality of the therapy session from the perspective of the patient. The SES comprises 5 items rated on a 5-point Likert scale and showed Cronbach α coefficients ranging from 0.88 to 0.89.

The CORE-OM [32] is a 34-item self-report measure of change in psychotherapy that comprises 4 domains: subjective well-being, symptoms, function, and risk. The CORE-OM demonstrated good internal and test-retest reliability between 0.75 and 0.95, and convergent validity against a battery of validated measures.

Efforts to Minimize Potential Sources of Bias

In our research, extensive steps will be taken to minimize potential biases. First, participants will be sourced from ResearchMatch, a national web-based registry that boasts a broad and varied volunteer pool from all over the United States, reducing selection bias and enhancing the external validity of our study. Second, our methodology is closely tuned to gender perspectives, giving weight to nonbinary gender as a key factor in both data evaluation and result interpretation, fortifying the scientific rigor and clinical significance of the study. Third, our comprehensive set of measures covers a spectrum of therapeutic and individual aspects, from sociodemographic details to personality characteristics, providing a comprehensive snapshot of the therapeutic landscape and limiting measurement bias. Data will be gathered through Qualtrics, a trusted web-based tool that protects respondent privacy and minimizes potential biases in responses. Furthermore, great care was taken in calculating the required sample size, accounting for potential dropouts, to ensure that we had ample statistical power, thereby sidestepping the pitfalls of weak analyses or insufficient representation.

Sample Size Calculation

Assuming a power of 0.80, a 2-tailed α level of .05, an effect size (*d*) of 0.50, and an allocation ratio of 1:1, we calculated a minimum sample size of 128 patients, or 64 participants per group, using the *R package pwr* (version 1.3-0; The Comprehensive R Archive Network). However, to enhance statistical power and precision, we aim for a target total sample size of 520 participants, with 260 participants per group. This adjustment also accounts for the possibility that only 50% of participants in the intervention group will complete all postsession scales.

Inclusion and Exclusion Criteria

Participants are eligible for the study if they are aged 18 years or older, fluent in English, and currently undergoing individual psychotherapy with a minimum frequency of 2 sessions per month. Individuals with a legal guardian will be excluded from the study.

Recruitment

Patients will be enrolled through ResearchMatch and Research for Me. ResearchMatch [40] is a disease-neutral, institution-neutral, US national web-based registry designed to enroll volunteers for clinical studies. Established by various educational entities and supported in part by the National Institutes of Health's National Center for Advancing Translational Sciences, this platform provides access to more than 155,000 volunteers across the United States and has proven effective. Research for Me is a community of volunteers acting as the primary gateway for patients and local residents who wish to participate in research at the UNC at Chapel Hill. This initiative was established by the North Carolina Translational and Clinical Sciences Institute, which is the central component of the National Institutes of Health's Clinical and Translational Science Awards program at UNC at Chapel Hill. Data suggest that individuals enrolled through online research platforms reliably report their demographic and psychological details, especially when there is no monetary incentive involved [41].

Randomization

Participants will be assigned to either the intervention or control group using a pre-established computer-generated randomization list. This assignment will occur after the baseline assessment is completed.

Data Collection Process

Participants in both the intervention and control groups will undergo assessments at baseline, midtrial (week 5), and end-of-trial (week 10). Additionally, those in the intervention group will have postsession evaluations. These assessments will be delivered through Qualtrics, a secure web-based survey platform hosted by the UNC at Chapel Hill.

Baseline assessment: All participants will complete the demographic and clinical data forms in addition to the measures for mental health state, therapeutic relationship, and session and therapy outcome domains (Table 1).

Table 1. Instruments and time line for assessment in the trial.

Domains and measures	Baseline	Midtrial[a]	End-of-trial[b]
Demographic domain			
Sociodemographic data form	✓		
Clinical domain			
Clinical data form A	✓		
Clinical data form B		✓	✓
Mental health state domain			
Patient Health Questionnaire-9 [35]	✓	✓	✓
Generalized Anxiety Disorder-7 [36]	✓	✓	✓
Therapeutic relationship domain			
Real Relationship Inventory-Client-Short Form [33]	✓	✓	✓
Working Alliance Inventory-Short Revised [34]	✓	✓	✓
in-Session Patient Affective Reactions Questionnaire [37,38]	✓	✓	✓
Rift In-Session Questionnaire [37]	✓	✓	✓
Session and therapy outcome domain			
Session Evaluation Scale [39]	✓	✓	✓
Clinical Outcomes in Routine Evaluation-Outcome Measures [32]	✓	✓	✓

[a]5 weeks after the baseline assessment.

[b]10 weeks after the baseline assessment.

Postsession assessment (only for the intervention group): participants in the intervention group will be required to complete SPARQ and RISQ [37] after each session throughout the 10-week duration of the trial. Immediately after completion of the postsession battery, participants will be presented with a general feedback statement emphasizing the importance of discussing session-related feelings with their therapist.

Mid-trial assessment: 5 weeks postbaseline evaluation, all participants will retake the scales used in the baseline assessment (Table 1).

End-of-trial assessment: 10 weeks after the baseline, all participants will again be asked to complete the initial assessment battery (Table 1).

Dealing With Missing Values

We will examine data for degree and patterns of missingness at the patient and scale level, use propensity scoring to model the pattern of missingness, and include the propensity score as a covariate in analyses if indicated [42]. Missing items will be prorated so long as at least 75% of the items are available, and otherwise the scale score will be treated as missing [43].

Planned Analysis

A comprehensive statistical strategy will be formulated and documented before starting the data analysis. R (R Foundation for Statistical Computing) will be used for data cleaning, labeling, scale scoring, and subsequent analyses. The basic characteristics of the study participants will be clearly described for each arm while also being aggregated to a sufficient level to reduce the risk of deductive identification. Baseline categorical variables will undergo a comparative evaluation between the intervention and control groups using chi-square evaluations. Continuous variables will be compared using 2-tailed *t* tests and Mann-Whitney *U* tests. Outcome metrics will be presented for each research group at various intervals. These outcomes will be detailed based on cumulative scores and the percentage of participants that demonstrate improvement from the start point.

Statistical Analysis

Analysis of covariance will be used to evaluate the influence of treatment conditions on primary and secondary outcomes since it is the most appropriate statistical method for the analysis of continuous outcomes in RCTs [44,45]. Analysis of covariance is a linear regression in which treatment assignment and baseline scores are included as covariates. Patient clinical and demographic characteristics, as well as therapist demographic and professional characteristics, will be included as exploratory variables. A total of 2 analyses will be carried out: the intention-to-treat analysis to examine the general effect and the per protocol analysis as a sensitivity analysis. The time will be measured in weeks, and the baseline is coded with the value 0. Analyses will be performed using R statistical computing software (version 4.3.1 or higher; R Foundation for Statistical Computing).

Trial Status

At the time of submission of this protocol's manuscript, recruitment is complete.

Dissemination Policy

The results of this research project will first appear as preprints and subsequently be shared through scholarly journals and

presentations at conferences. The Open Science Framework will host a repository containing study tools and data, scoring guidelines, presentations, and preprint versions. Wikiversity pages, tailored to offer technical assets for both practitioners and researchers, will feature links directing to this repository. Furthermore, this study's conclusions could be communicated to pertinent mental health associations, contributing to future studies and potential improvements in psychotherapeutic relationships. Our goal is to adopt a comprehensive and broad-based communication approach that engages scholars, health care professionals, and the general public.

Results

Participant recruitment started in September 2023. Baseline data collection was completed in December 2023, with a total of 520 recruited participants, 475 of whom completed the baseline assessment (243 participants were assigned to the intervention group and 232 were assigned to the control group). Data was completed February 2024. Data analysis has not begun as of the time of submission. The results are expected to be published in the autumn of 2024.

Discussion

This clinical study is designed to assess the impact of introducing a concise postsession questionnaire able to trigger the self-awareness and introspection of patients about their experience of the psychotherapeutic relationship. The primary goal is to understand its influence on the effectiveness of treatment, with the CORE-OM serving as the primary outcome measure.

Should our battery prove to increase symptom reduction rates or improve overall well-being, its ease of delivery directly to patients—requiring no additional therapist involvement—suggests potential for seamless adoption across therapeutic contexts without incurring extra expenses for patients or placing added demands on therapists. This could make the system highly cost-efficient. Furthermore, the insights from this study could shed light on the nuanced interaction between specific elements of the therapeutic bond and the results of sessions or general treatment. This knowledge would empower clinicians and policy makers to recognize and prioritize those aspects of the therapeutic relationship that strengthen or hinder the efficacy of psychotherapy.

One of the main strengths of this study is its ability to gauge the benefits of regular patient self-monitoring and subsequent reflection on their emotional reactions toward their therapists in a real-world setting. The study sample accurately represents the diverse patient population within the United States, further enhancing its relevance. Other key advantages include robust statistical power, the use of an external outcome measure not related to the intervention, and a comprehensive consideration of the patient, the therapist, and treatment variables. However, there are limitations, such as the lack of information from the clinician or observer and the extended duration of data collection. Furthermore, an important potential limitation inherent in our approach concerns the adherence of the participants to the research protocol, specifically the regular completion of the battery after each therapy session, and their compliance with the recommendation to share their emotional responses toward their therapist directly and openly with the therapist.

To this day, efforts to implement and test regular self-monitoring of patient affective experiences during sessions, with systematic feedback provided directly to patients without the therapist's intervention, seem inadequate. The introduction of a newly developed systematic client feedback system for psychotherapy may offer improvements in treatment outcomes while also serving as a cost-effective tool in real-world clinical practice.

Data Availability

Data sharing is not applicable to this article, as no data sets were generated or analyzed during this study protocol. The data sets generated during the actual research study will be made available in the Open Science Framework repository [31].

Conflicts of Interest

EV has received grants and served as consultant, advisor, or CME speaker for the following entities: AB-Biotics, AbbVie, Angelini, Biogen, Biohaven, Boehringer-Ingelheim, Celon Pharma, Compass, Dainippon Sumitomo Pharma, Ethypharm, Ferrer, Gedeon Richter, GH Research, Glaxo-Smith Kline, Idorsia, Janssen, Lundbeck, Medincell, Novartis, Orion Corporation, Organon, Otsuka, Rovi, Sage, Sanofi-Aventis, Sunovion, Takeda, and Viatris, outside the submitted work. EAY is the co-founder and Executive Director of Helping Give Away Psychological Science, a 501c3; he has consulted about psychological assessment with Signant Health and received royalties from the American Psychological Association and Guilford Press, and he holds equity in Joe Startup Technologies.

References

1. Ekman P. Basic emotions. In: Dalgleish T, Power MJ, editors. Handbook of Cognition and Emotion. Chichester: John Wiley and Sons, Ltd; 2005:45-60.
2. Schore AN. Right Brain Psychotherapy, 1st Edition. New York: WW Norton and Company; 2019.
3. Stefana A. The origins of the notion of countertransference. Psychoanal Rev 2015;102(4):437-460 [FREE Full text] [doi: 10.1521/prev.2015.102.4.437] [Medline: 26290942]

4. Stefana A. History of Countertransference: From Freud to the British Object Relations School, 1st Edition. Abingdon, Oxon: Routledge; 2017.
5. Stefana A. Erotic transference. Brit J Psychotherapy 2017;33(4):505-513. [doi: 10.1111/bjp.12231]
6. Chui H, Hill CE, Kline K, Kuo P, Mohr JJ. Are you in the mood? Therapist affect and psychotherapy process. J Couns Psychol 2016;63(4):405-418. [doi: 10.1037/cou0000155] [Medline: 27177026]
7. Pascual-Leone A. How clients "change emotion with emotion": a programme of research on emotional processing. Psychother Res 2018;28(2):165-182. [doi: 10.1080/10503307.2017.1349350] [Medline: 28714778]
8. Faustino B. Minding my brain: fourteen neuroscience-based principles to enhance psychotherapy responsiveness. Clin Psychol Psychother 2022;29(4):1254-1275. [doi: 10.1002/cpp.2719] [Medline: 35112428]
9. Lane RD, Subic-Wrana C, Greenberg L, Yovel I. The role of enhanced emotional awareness in promoting change across psychotherapy modalities. J Psychother Integr 2022;32(2):131-150. [doi: 10.1037/int0000244]
10. Greenberg LS. Emotions, the great captains of our lives: their role in the process of change in psychotherapy. Am Psychol 2012;67(8):697-707. [doi: 10.1037/a0029858] [Medline: 23163464]
11. Schore AN. The Science of the Art of Psychotherapy, 1st Edition. New York: W.W. Norton & Company; 2012.
12. Greenberg LS, Goldman RN. Theory of practice of emotion-focused therapy. In: Clinical Handbook of Emotion-Focused Therapy. Washington: American Psychological Association; 2019:61-89.
13. Stefana A, Fusar-Poli P, Gnisci C, Vieta E, Youngstrom EA. Clinicians' emotional reactions toward patients with depressive symptoms in mood disorders: a narrative scoping review of empirical research. Int J Environ Res Public Health 2022;19(22):15403 [FREE Full text] [doi: 10.3390/ijerph192215403] [Medline: 36430122]
14. Stefana A, Youngstrom EA, Vieta E. Empirical support for the use and further study of the countertransference construct in the clinical care of patients with bipolar disorder. Bipolar Disord 2022;24(1):84-85 [FREE Full text] [doi: 10.1111/bdi.13153] [Medline: 34773350]
15. Greenberg LS. Theory of functioning in emotion-focused therapy. In: Greenberg LS, Goldman RN, editors. Clinical Handbook of Emotion-Focused Therapy. Washington: American Psychological Association; 2019:37-59.
16. Subic-Wrana C, Greenberg LS, Lane RD, Michal M, Wiltink J, Beutel ME. Affective change in psychodynamic psychotherapy: theoretical models and clinical approaches to changing emotions. Z Psychosom Med Psychother 2016;62(3):207-223 [FREE Full text] [doi: 10.13109/zptm.2016.62.3.207] [Medline: 27594599]
17. Ulberg R, Hummelen B, Hersoug AG, Midgley N, Høglend PA, Dahl HSJ. The First Experimental Study of Transference work-In Teenagers (FEST-IT): a multicentre, observer- and patient-blind, randomised controlled component study. BMC Psychiatry 2021;21(1):106 [FREE Full text] [doi: 10.1186/s12888-021-03055-y] [Medline: 33596856]
18. Peluso PR, Freund RR. Emotional expression. In: Norcross JC, Lambert MJ, editors. Psychotherapy Relationships that Work. Volume 1: Evidence-Based Therapist Contributions, 3rd Edition. New York, NY: Oxford University Press; 2019:421-460.
19. Hayes JA, Vinca M. Therapist presence, absence, and extraordinary presence. In: Castonguay LG, Hill CE, editors. How and why are Some Therapists Better than Others?: Understanding Therapist Effects. Washington: American Psychological Association; 2017:85-99.
20. Barkham M, Broglia E, The SCORE Consortium. Routine Outcome Monitoring (ROM) and feedback in university student counselling and mental health services: considerations for practitioners and service leads. Couns Psychother Res 2023:1-13 [FREE Full text] [doi: 10.1002/capr.12694]
21. Kendrick T, El-Gohary M, Stuart B, Gilbody S, Churchill R, Aiken L, et al. Routine use of Patient Reported Outcome Measures (PROMs) for improving treatment of common mental health disorders in adults. Cochrane Database Syst Rev 2016;7(7):CD011119 [FREE Full text] [doi: 10.1002/14651858.CD011119.pub2] [Medline: 27409972]
22. de Jong K, Conijn JM, Gallagher RAV, Reshetnikova AS, Heij M, Lutz MC. Using progress feedback to improve outcomes and reduce drop-out, treatment duration, and deterioration: a multilevel meta-analysis. Clin Psychol Rev 2021;85:102002 [FREE Full text] [doi: 10.1016/j.cpr.2021.102002] [Medline: 33721605]
23. Østergård OK, Randa H, Hougaard E. The effect of using the partners for change outcome management system as feedback tool in psychotherapy-a systematic review and meta-analysis. Psychother Res 2020;30(2):195-212. [doi: 10.1080/10503307.2018.1517949] [Medline: 30213240]
24. Delgadillo J, Overend K, Lucock M, Groom M, Kirby N, McMillan D, et al. Improving the efficiency of psychological treatment using outcome feedback technology. Behav Res Ther 2017;99:89-97 [FREE Full text] [doi: 10.1016/j.brat.2017.09.011] [Medline: 29024821]
25. Delgadillo J, McMillan D, Gilbody S, de Jong K, Lucock M, Lutz W, et al. Cost-effectiveness of feedback-informed psychological treatment: evidence from the IAPT-FIT trial. Behav Res Ther 2021;142:103873 [FREE Full text] [doi: 10.1016/j.brat.2021.103873] [Medline: 33945983]
26. Janse PD, De Jong K, Van Dijk MK, Hutschemaekers GJM, Verbraak MJPM. Improving the efficiency of cognitive-behavioural therapy by using formal client feedback. Psychother Res 2017;27(5):525-538. [doi: 10.1080/10503307.2016.1152408] [Medline: 27013204]

27. Kazdin AE. Evidence-based treatment and practice: new opportunities to bridge clinical research and practice, enhance the knowledge base, and improve patient care. Am Psychol 2008;63(3):146-159. [doi: 10.1037/0003-066X.63.3.146] [Medline: 18377105]
28. Norcross JC. Psychotherapy Relationships that Work: Evidence-Based Responsiveness, 2nd Edition. New York: Oxford University Press; 2011.
29. Langkaas TF, Wampold BE, Hoffart A. Five types of clinical difference to monitor in practice. Psychotherapy (Chic) 2018;55(3):241-254. [doi: 10.1037/pst0000194] [Medline: 30179031]
30. Wampold BE. How important are the common factors in psychotherapy? An update. World Psychiatry 2015;14(3):270-277 [FREE Full text] [doi: 10.1002/wps.20238] [Medline: 26407772]
31. Open Science Framework. URL: https://osf.io/amzqk/ [accessed 2024-02-19]
32. Evans C, Connell J, Barkham M, Margison F, McGrath G, Mellor-Clark J, et al. Towards a standardised brief outcome measure: psychometric properties and utility of the CORE-OM. Br J Psychiatry 2002;180:51-60 [FREE Full text] [doi: 10.1192/bjp.180.1.51] [Medline: 11772852]
33. Stefana A, Fusar-Poli P, Vieta E, Gelso CJ, Youngstrom EA. Development and validation of an 8-item version of the Real Relationship Inventory-Client form. Psychother Res 2024 (forthcoming) [FREE Full text] [doi: 10.1080/10503307.2024.2320331]
34. Hatcher RL, Gillaspy JA. Development and validation of a revised short version of the working alliance inventory. Psychother Res 2006;16(1):12-25. [doi: 10.1080/10503300500352500]
35. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001;16(9):606-613 [FREE Full text] [doi: 10.1046/j.1525-1497.2001.016009606.x] [Medline: 11556941]
36. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006;166(10):1092-1097 [FREE Full text] [doi: 10.1001/archinte.166.10.1092] [Medline: 16717171]
37. Stefana A, Langfus JA, Vieta E, Fusar-Poli P, Youngstrom EA. Development and initial validation of the in-Session Patient Affective Reactions Questionnaire (SPARQ) and the Rift In-Session Questionnaire (RISQ). J Clin Med 2023;12(15):5156 [FREE Full text] [doi: 10.3390/jcm12155156] [Medline: 37568559]
38. Stefana A, Fusar-Poli P, Vieta E, Youngstrom E. Assessing the patients' affective perception of their psychotherapist: Validation of the in-Session Patient Affective Reactions Questionnaire (SPARQ). Front Psychiatry (forthcoming) 2024.
39. Lent RW, Hoffman MA, Hill CE, Treistman D, Mount M, Singley D. Client-specific counselor self-efficacy in novice counselors: relation to perceptions of session quality. J Couns Psychol 2006;53(4):453-463. [doi: 10.1037/0022-0167.53.4.453]
40. Harris PA, Scott KW, Lebo L, Hassan N, Lightner C, Pulley J. ResearchMatch: a national registry to recruit volunteers for clinical research. Acad Med 2012;87(1):66-73 [FREE Full text] [doi: 10.1097/ACM.0b013e31823ab7d2] [Medline: 22104055]
41. Chandler J, Shapiro D. Conducting clinical research using crowdsourced convenience samples. Annu Rev Clin Psychol 2016;12:53-81 [FREE Full text] [doi: 10.1146/annurev-clinpsy-021815-093623] [Medline: 26772208]
42. Guo S, Fraser MW. Propensity Score Analysis: Statistical Methods and Applications. Thousand Oaks, CA, US: Sage Publications, Inc; 2010.
43. Goodman R. The extended version of the strengths and difficulties questionnaire as a guide to child psychiatric caseness and consequent burden. J Child Psychol Psychiatry 1999;40(5):791-799. [Medline: 10433412]
44. Egbewale BE, Lewis M, Sim J. Bias, precision and statistical power of analysis of covariance in the analysis of randomized trials with baseline imbalance: a simulation study. BMC Med Res Methodol 2014;14:49 [FREE Full text] [doi: 10.1186/1471-2288-14-49] [Medline: 24712304]
45. Twisk J, Proper K. Evaluation of the results of a randomized controlled trial: how to define changes between baseline and follow-up. J Clin Epidemiol 2004;57(3):223-228. [doi: 10.1016/j.jclinepi.2003.07.009] [Medline: 15066681]

Abbreviations

CORE-OM: Clinical Outcomes in Routine Evaluation-Outcome Measure
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
GAD-7: Generalized Anxiety Disorder-7
PHQ-9: Patient Health Questionnaire-9
RISQ: Rift In-Session Questionnaire
RRI-C-SF: Real Relationship Inventory-Client-Short Form
SES: Session Evaluation Scale
SPARQ: in-Session Patient Affective Reactions Questionnaire
UNC: University of North Carolina
WAI-SR: Working Alliance Inventory-Short Revised

Edited by A Mavragani; submitted 11.12.23; this is a non–peer-reviewed article;accepted 30.01.24; published 08.04.24.

Please cite as:
Stefana A, Vieta E, Fusar-Poli P, Youngstrom EA
Enhancing Psychotherapy Outcomes by Encouraging Patients to Regularly Self-Monitor, Reflect on, and Share Their Affective Responses Toward Their Therapist: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2024;13:e55369
URL: https://www.researchprotocols.org/2024/1/e55369
doi:10.2196/55369
PMID:38587881

Protocol

Psychotherapy for Ketamine's Enhanced Durability in Chronic Neuropathic Pain: Protocol for a Pilot Randomized Controlled Trial

Akash Goel[1,2*], MD, MPH; Bhavya Kapoor[1,3*]; Hillary Chan[4], BSc; Karim Ladha[1,2,5], MD, MSc; Joel Katz[2,6,7,8,9], PhD; Hance Clarke[2,7,8], MD; Janneth Pazmino-Canizares[1], MSc; Zaaria Thomas[1], BA; Kaylyssa Philip[1,4], BHSc, MPH; Gabriella Mattina[1], PhD; Paul Ritvo[6,9], PhD

[1]Department of Anesthesia and Pain Medicine, St Michael's Hospital, Toronto, ON, Canada
[2]Department of Anesthesiology and Pain Medicine, University of Toronto, Toronto, ON, Canada
[3]Department of Medicine, Royal College of Surgeons in Ireland, Dublin, Ireland
[4]Temerty Faculty of Medicine, University of Toronto, Toronto, ON, Canada
[5]Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada
[6]Department of Psychology, York University, Toronto, ON, Canada
[7]Department of Anesthesia and Pain Management, Toronto General Hospital, Toronto, ON, Canada
[8]Centre for the Study of Pain, University of Toronto, Toronto, ON, Canada
[9]School of Kinesiology and Health Sciences, York University, Toronto, ON, Canada
[*]these authors contributed equally

Corresponding Author:
Akash Goel, MD, MPH
Department of Anesthesia and Pain Medicine
St Michael's Hospital
30 Bond Street
65-501 Donnelly South
Toronto, ON, M5B1W8
Canada
Phone: 1 4168645071
Fax: 1 (416) 864 6014
Email: akash.goel@unityhealth.to

Abstract

Background: Chronic pain affects approximately 8 million Canadians (~20%), impacting their physical and mental health while burdening the health care system with costs of upwards of US $60 billion a year. Indeed, patients are often trialed on numerous medications over several years without reductions to their symptoms. Therefore, there is an urgent need to identify new therapies for chronic pain to improve patients' quality of life, increase the availability of treatment options, and reduce the burden on the health care system.

Objective: The primary objective of this study is to examine the feasibility of a parallel 3-arm pilot randomized controlled trial whereby patients are randomized to either intravenous ketamine alone, cognitive behavioral therapy (CBT) and mindfulness meditation (MM) training (CBT/MM), or the combination of intravenous ketamine and CBT/MM. The secondary outcome is to assess the durability and efficacy of combination intravenous ketamine and CBT/MM for treatment of chronic pain as compared to CBT/MM or intravenous ketamine alone (assessed at week 20 of the study).

Methods: This is a single-center, 16-week, 3-arm pilot study that will take place at the Chronic Pain Clinic at St. Michael's Hospital, Toronto, Ontario, which receives 1000 referrals per year. Patients will be enrolled in the study for a total of 20 weeks. Participants who are allocated CBT/MM therapy will receive remote weekly psychotherapy from week 1 to week 16, inclusive of health coaching administered through the NexJ Health Inc (NexJ Health) platform. Patients who are allocated ketamine-infusion therapy will receive monthly ketamine infusion treatments on weeks 2, 7, and 12. Patients who are allocated ketamine+CBT/MM will receive weekly psychotherapy from weeks 1 to 16, inclusive, as well as ketamine infusion treatments on weeks 2, 7, and 12. We will be assessing recruitment rates, consent rates, withdrawal rates, adherence, missing data, and adverse events as pilot outcome measures. Secondary clinical outcomes include changes relative to baseline in pain intensity and pain interference.

Results: As of November 1, 2023, the recruitment process has not been initiated. Given the recruitment, consent, and intervention target of 30 participants for this feasibility study, with each patient undergoing monitoring and treatments for a course of 20 weeks, we expect to complete the study by December 2025.

Conclusions: This study assesses the feasibility of conducting a 3-arm randomized controlled trial to examine the effects of ketamine administration with the concurrent use of CBT/MM in a population with chronic neuropathic pain. The results of this pilot randomized controlled trial will inform the development of a larger-scale randomized controlled trial. Future studies will be aimed at including a sufficiently powered sample that will inform decisions about optimal treatment calibration and treatment effect duration.

Trial Registration: ClinicalTrials.gov NCT05639322; https://classic.clinicaltrials.gov/ct2/show/NCT05639322

International Registered Report Identifier (IRRID): PRR1-10.2196/54406

(JMIR Res Protoc 2024;13:e54406) doi:10.2196/54406

KEYWORDS

3-arm parallel group; cognitive behavior therapy; ketamine hydrochloride; pain intensity; pain interference; psychotherapy; randomized controlled trial

Introduction

Chronic pain affects approximately 8 million Canadians (~20%) and profoundly impacts their physical and mental health. The broad ranging consequences of this disease are evidenced by estimated health care system costs upwards of US $60 billion a year [1]. In the United States, chronic pain also affects 1 in 5 people, and the annual cost is estimated as greater than US $0.5 trillion [2]. Indeed, chronic pain is associated with poor quality of life, psychiatric symptoms, and mobility restrictions. It has significant physical, functional, social, and economic impacts at the individual and system levels. Current pain therapies aim to decrease pain to manageable levels. In most cases however, chronic pain cannot be completely eliminated. Patients are often trialed on numerous medications without adequate relief, and therapies are often limited by their lack of durability and adverse effects. There is an urgent need to identify new therapies for chronic pain to improve patients' quality of life and the availability of treatment options, while reducing health care system burdens.

Ketamine is an N-methyl-D-aspartate receptor antagonist which results in pain reduction. It is also associated with reductions in opioid-induced hyperalgesia and opioid consumption [3]. At high doses, it is an agonist at the mu receptor, the D2-R, and L-Type voltage-gated calcium channel. Current evidence supports intermittent ketamine therapy for neuropathic pain. Double-blind randomized controlled trials (RCTs) investigating the use of ketamine for neuropathic pain have demonstrated clinically significant reductions (25% to 43%) in chronic pain versus control conditions [3]. However, ketamine appears to have limited durability as studies have shown short term reductions in neuropathic pain secondary to spinal cord injury and fibromyalgia but no long-term benefits [4,5]. Although timelines and follow-ups vary significantly, the lack of durability is consistent across all ketamine infusion regimens studied [6]. Indeed, a systematic review by Cohen et al [3] indicated a lack of evidence for durable benefits, affirming the need for adjunctive therapies that improve durability and improve outcomes.

Internet-delivered cognitive behavioral therapy (CBT) for chronic pain, depression, and anxiety is associated with significant reductions in pain disability, symptoms of depression, and pain catastrophizing at 1 year follow-up [7]. Nonetheless, an integrative review [8] concluded CBT research must further address longer-term efficacy (>12 months). This same review highlighted the significant variations in the duration and total dose hours of CBT interventions and delivery methods (remote, group, or individual). Despite variations, existing studies and emergent guidelines support the synergistic effects of pharmacological therapies strategically combined with CBT-based strategies [7].

The primary objective of this trial is to study the effects of concurrent ketamine and CBT for chronic neuropathic pain relief. Biological and neurocognitive factors suggest that concurrent pharmacotherapy and psychotherapy can result in more durable and effective analgesic responses than either intervention alone. Ketamine administration induces physiological changes during and after delivery that result in powerful experiential responses with important psychological and emotional impacts [9]. The physiological changes associated with ketamine therapy are likely to influence important habitual thinking and behavior patterns. Studies suggest that ketamine alters functional brain connectivity, even to the point of disrupting spatiotemporal patterns of neural activity and increasing functional communications between brain regions typically isolated [9].

Despite the biologic plausibility of ketamine-assisted psychotherapy being an effective cotreatment for chronic neuropathic pain, there is a lack of rigorous evidence supporting its use. Our group conducted a systematic review to examine existing evidence on concurrent ketamine dosing and psychotherapy [10]. This knowledge synthesis showed substantial methodologic variations across 17 studies. The most common indications studied included posttraumatic stress disorder (6 studies), major depressive disorder (6 studies), substance use disorder (6 studies), and obsessive compulsive disorder (2 studies). Only 2 publications (a case report and a case series) examined continuous multiday ketamine infusions with concurrent psychotherapy in individuals with chronic pain.

Ocker et al [11] described a 5-day continuous ketamine infusion regimen combined with CBT to successfully taper opioids in a patient with complex regional pain syndrome who was taking 330 mg of daily morphine equivalents. They attribute the sustained results to an observed synergism between ketamine and the outpatient CBT protocol. Keizer et al [12] described a case series of 11 patients who received ketamine-enhanced psychotherapy for comorbid neuropathic pain and posttraumatic stress disorder. A 96-hour ketamine infusion was delivered with daily bedside psychotherapy. Although it resulted in a moderate but clinically meaningful reduction in pain symptoms, the brief follow up of 5 days precluded in-depth examination of the potential synergism.

This systematic review also revealed no evidence that a single protocol or therapy strategy was decidedly more beneficial than any other. To date, no RCT has combined ketamine and psychotherapeutic intervention for patients with chronic pain. The results of this review highlight the poor methodological quality of existing studies and need for higher quality evidence on the potential impact of combined interventions. By means of this pilot study, our intention is to determine whether a customized CBT along with mindfulness and meditation (MM; ie, CBT/MM) psychotherapy regimen can be effectively and safely integrated with a ketamine-induced state in a chronic neuropathic pain sample.

The Psychotherapy for Ketamine's Enhanced Durability in Chronic Neuropathic Pain study has received partial funding from the Canadian Pain Society in partnership with the Pfizer Early Career Investigator Award as well as the St. Michael's Hospital Association Innovation Fund.

Methods

Aim

The primary objective of this study is to enroll 30 participants with chronic neuropathic pain and assess the feasibility of conducting a 3-arm parallel group pilot RCT. The secondary aim of the study is to examine whether the combined effects of ketamine and CBT/MM (as delivered through the NexJ Health Inc platform by trained navigator-coaches) can reduce pain intensity and pain interference by week 20 of the study (ie, limited efficacy at week 20).

Recruitment and Randomization

Recruitment will occur at the Chronic Pain Clinic at St. Michael's Hospital, Toronto, Ontario. The clinic receives approximately 1000 referrals per year. An estimated 3% of these referrals would be eligible for inclusion in this trial.

A staff member who does not belong to the study team will be provided with the instructions to use a remote random number generator, the "Sealed Envelope" website to generate an allocation sequence at random. The allocation list will be sent to the Research Pharmacy staff at St. Michael's Hospital directly, without the knowledge of the study team, to maintain the blindness. After participant enrollment, the pharmacy staff will randomize the patient and inform a delegated research team member as to the allocated intervention arm. The delegated unblinded research team member will then notify the patient which arm they have been randomized to and will coordinate with the anesthesiologists and psychologists, who will be unblinded, to schedule in-person study visits on weeks 2, 7, and 12 according to the randomized treatment arm. For patients randomized to Arm 1 or 3, the Research Pharmacy staff will prepare ketamine-hydrochloride for weeks 2, 7, and 12. The outcome assessors are the only research staff to remain blinded to patient treatment (currently, we only have 1 delegated outcome assessor).

Participants will be randomized to receive either (1) ketamine-hydrochloride infusions alone, (2) CBT/MM alone, or (3) a combination ketamine-hydrochloride infusion and CBT/MM.

Participants will be eligible for this study as per the inclusion and exclusion criteria listed (Textbox 1).

Textbox 1. Inclusion and exclusion criteria regarding participant eligibility for PYSKED-NP.

Inclusion criteria

- Aged 18 years or older.
- Diagnosis of chronic neuropathic pain as determined by a pain specialist with moderate to severe neuropathic pain as per ID pain questionnaire, with mean pain scores >3 on an 11-point (0-10) Numeric Rating Scale, in the 7 days preceding inclusion.
- For participants of childbearing potential, use of highly effective or double-barrier methods of contraception. Abstinence is acceptable if it is the preferred and usual lifestyle of the participant.
- Capacity to provide informed consent

Exclusion criteria

- Patients aged younger than 18 years.
- Current or lifetime history of schizophrenia, psychotic disorder, bipolar disorder, or borderline personality disorder.
- Known history of hypersensitivity or allergy to ketamine-hydrochloride.
- Current history of dissociative disorders.
- Current concomitant use of theophylline or aminophylline.
- Current elevated intracranial pressure.
- Pregnancy or ongoing breastfeeding in female participants.
- Concomitant active substance use in the 6 months preceding enrollment (amphetamines, alcohol, and ketamine).
- Contraindication to receiving ketamine-hydrochloride (eg, current or lifetime history of cerebrovascular accident, current significant hypertension [systolic blood pressure higher than 160 mm Hg in combination with or with an isolated diastolic blood pressure higher than 100 mm Hg], and current severe cardiac decompensation [eg, presence of dyspnea, peripheral edema, elevated jugular venous pressure, hepatomegaly, pulmonary rales, and pleural effusions]).

Withdrawal Criteria

A participant will be withdrawn if the participant presents with a severe adverse event or unknown allergic reaction during the first administration of ketamine-hydrochloride or if the participant wants to withdraw from the study for any reason. The participant will receive the necessary treatment to alleviate any untoward events and will be monitored by the study physician until judged appropriate for discharge. Participants will be followed up on the following day to ascertain more details on their condition. Data from a participant who has been withdrawn will be collected up to the day following their withdrawal to ensure that the participant has no more complications. If a participant withdraws from the study at any time, the reasons for withdrawal will be collected and documented as a feasibility study outcome.

Since this is a feasibility study without a specific sample size required to analyze any outcome, participants will not be replaced or added.

Intervention

Intervention Description

Participants will be randomly assigned to one of 3 arms. Arm 1: Ketamine-hydrochloride infusions alone, Arm 2: CBT in combination with MM (CBT/MM), or Arm 3: Ketamine-hydrochloride infusions in combination with CBT/MM.

Ketamine-hydrochloride will be delivered intravenously for patients in Arm 1 and Arm 3. For this study, 1 mg/kg of ketamine intravenous will be dosed by total body weight and administered over 2 hours up to a maximum dose of 100 mg as per our local institutional protocol.

Arm 1: Ketamine-Hydrochloride Infusion Alone

Patients in Arm 1 receiving a ketamine-hydrochloride infusion alone will receive ketamine infusions on weeks 2, 7, and 12 of the study. After the study intervention, participants will have their vital signs and adverse events monitored for one hour. The anesthesia provider will be responsible for assessing the participant before discharge. Participants will not be allowed to drive after the intervention; therefore, measures will be taken to ensure the participant has an adequate plan of transportation (ie, a companion or suitable transportation).

For safety reasons, the anesthesia provider administering the medication will not be blinded. However, the study personnel designated to collect the outcome data will be unaware of the treatment assignment. Patients will not be blinded to their therapy for the purposes of this feasibility study.

Arm 2: CBT/MM Alone

Participants in Arm 2 receiving CBT/MM alone will receive weekly CBT/MM treatment in collaboration with NexJ Health Inc and supplemented by the designated psychotherapist trained for and experienced in previous studies [13]. About 16 hours of CBT/MM therapy will be delivered over 16 weeks. Participants will be assigned to a 3-hour CBT/MM workshop remotely, to be administered by the delegated psychotherapist. The CBT-MM programming will combine exposure to smartphone- and computer-accessible workbooks with phone-based mental health counseling (16 hours in 16 weeks)

that coordinates with ongoing software interactions (eg, secure text messaging) [14,15].

The software for delivering the CBT/MM therapy is a standalone platform, called "Connected Wellness Platform," developed by NexJ Health Inc. Connected Wellness Platform is a customized, secure (2-level log-in with 128-bit encryption) interface accessible through both a smartphone and a computer.

Arm 3: Ketamine-Hydrochloride Infusion in Combination With CBT/MM

Finally, participants in Arm 3 receiving ketamine infusion+CBT/MM will receive both the standard CBT/MM and ketamine-hydrochloride infusion protocols as described above. Participants in this arm will have psychotherapy delivered concurrently with their ketamine infusions on weeks 2, 7, and 12 in person by the delegated psychotherapist. Participants in Arm 3 will also receive 16 weeks of CBT/MM remotely.

Hypothesis

In line with the primary aim of this study, this pilot study will prove to be feasible for a large-scale clinical trial. We expect that we will be able to successfully meet our recruitment target (30 participants) within the 1-year time frame of the study and expect this study withdrawal rate to be less than 10% (3/30 patients). Feasibility of this study will be determined by the following set variables and cutoff percentages; recruitment success with the specific aim to recruit all necessary patients within the first year of the trial period, adequate consent rate (30/100, >30% of eligible patients consent to participate in the study), intervention adherence as define by the percentage of patients who complete all medication and psychotherapy visits (27/30, >90%), percentage of patients who withdraw from the study (ie, due to side effects; 6/30, <20%), percentage of patients with incomplete pain intensity and pain interference data at 1 month, (eg, withdrawal due to side effects, loss to follow up, or missing data; 3/30, <10%), and rate of adverse outcomes. We do not foresee any issues arising with the protocol of the study or the delivery of each arm.

While not powered to examine these effects, we hypothesize that patients allocated to the combination ketamine and CBT/MM arm of this study will have the greatest reduction in pain intensity and pain interference.

Blinding Mechanism

The intervention delivery providers (anesthesiologists and psychologists) and other members of the research team will be aware of each participant's assigned intervention. Within the research team, blinded members will be responsible for inputting all of the data into the REDCap (Research Electronic Data Capture; Vanderbilt University) database, with the exception of any ketamine-specific data, that is, semistructured interviews after the ketamine intervention and any adverse events. Following data collection, we will request blinded staff to record their "best guess" of each patient's intervention to assess blinding efficacy. The research team currently has 1 blinded member who will serve as the outcome assessor and be responsible for data input.

Emergency Unblinding

To optimize study quality, emergency unblinding will only occur when knowledge of the intervention is essential for participant care, as determined by the principal investigator. In the case of emergency unblinding, the timing, reason for doing so, and personnel involved will be recorded in the case report form, while blinding is maintained by as many other study personnel as possible.

Outcome Measures

Primary Outcome

The primary outcome of this pilot trial is to determine the feasibility of a large-scale multicenter trial. Feasibility outcomes will include the following variables, with all thresholds listed in parentheses:

1. Recruitment success (with the specific aim of recruiting all necessary patients within the first year of the trial period).
2. Adequate consent rate (>30% of eligible patients consent to participate in the study).
3. Percentage of patients who complete all medication and psychotherapy visits (ie, intervention adherence; >90%).
4. Percentage of patients who withdraw from the study (eg, due to side effects or other reasons; <20%).
5. Percentage of patients with incomplete pain intensity and pain interference data at 1 month and stated or ascribed reason (eg, withdrawal due to side effects, loss of follow-up, or missing data; <10%).
6. Rate of adverse outcomes (ie, 0 serious adverse events).

Based on the result for each primary feasibility outcome, we will determine whether the definitive study is feasible as proposed (ie, all feasibility targets are met), feasible with protocol modifications (modifications specified), or not feasible because feasibility targets could not be met even with protocol modifications. These cutoffs, identified in the parentheses above, will help determine whether protocol changes are required before proceeding with a definitive trial.

Secondary Outcome

The secondary outcomes chosen for the definitive trial follow consensus recommendations of core domains that should be addressed in studies examining chronic pain. Information will be collected in these domains as part of the pilot trial using survey-based outcome assessments, either in person during study visits or over the telephone by trained research personnel. The following pain score questionnaires will be used:

1. Pain intensity on an 11-point (0-10) Numeric Rating Scale.
2. Pain interference on the Patient-Reported Outcomes Measurement Information System (PROMIS-PI) scale.
3. Catastrophic thinking about pain, as measured by the Pain Catastrophizing Scale (PCS).
4. Features of depression, as measured by the Patient Health Questionnaire-9 (PHQ-9).
5. Features of anxiety, as measured by the Generalized Anxiety Disorder-7 (GAD-7).
6. Patient Global Impression of Change Scale (PGIC).

Secondary clinical outcomes will include changes relative to baseline assessment in pain intensity and pain interference at week 20 (4 weeks post-completion of treatment; Figure 1). Scores for all outcomes at weeks 2, 7, 12, 16, and 20 will be compared to baseline scores to assess any progressive additive effects between the treatments. For any patients who withdraw before week 20, their last documented responses will be used as a comparison against baseline data. Patients will be allowed to adjust the dosages of other analgesic medications in conjunction with their primary physician. Analgesic medication use and doses will be tracked at the above time points to assess changes over time. Semistructured interviews will be conducted at 2 points within the study period: at weeks 1 and 20 and after the ketamine infusions (Table 1). The interviews will be audio-recorded to ensure the responses are accurately captured. In-person interviews will be recorded with an encrypted device, and phone interviews will be recorded through the Unity Health Zoom (Zoom Video Communications Inc) recording option. The audio recording files will be saved on St. Michael's Hospital secure and restricted servers, and the files will be labeled by the study number. The recordings will be transcribed by the research team, and after verifying that the transcriptions are accurate, the audio recordings will be destroyed. Questionnaires will be delivered to patients at prespecified time points, as outlined in the study timeline below.

Figure 1. Overview of study design with primary and secondary outcomes. CBT/MM: cognitive behavior therapy/mindfulness and meditation.

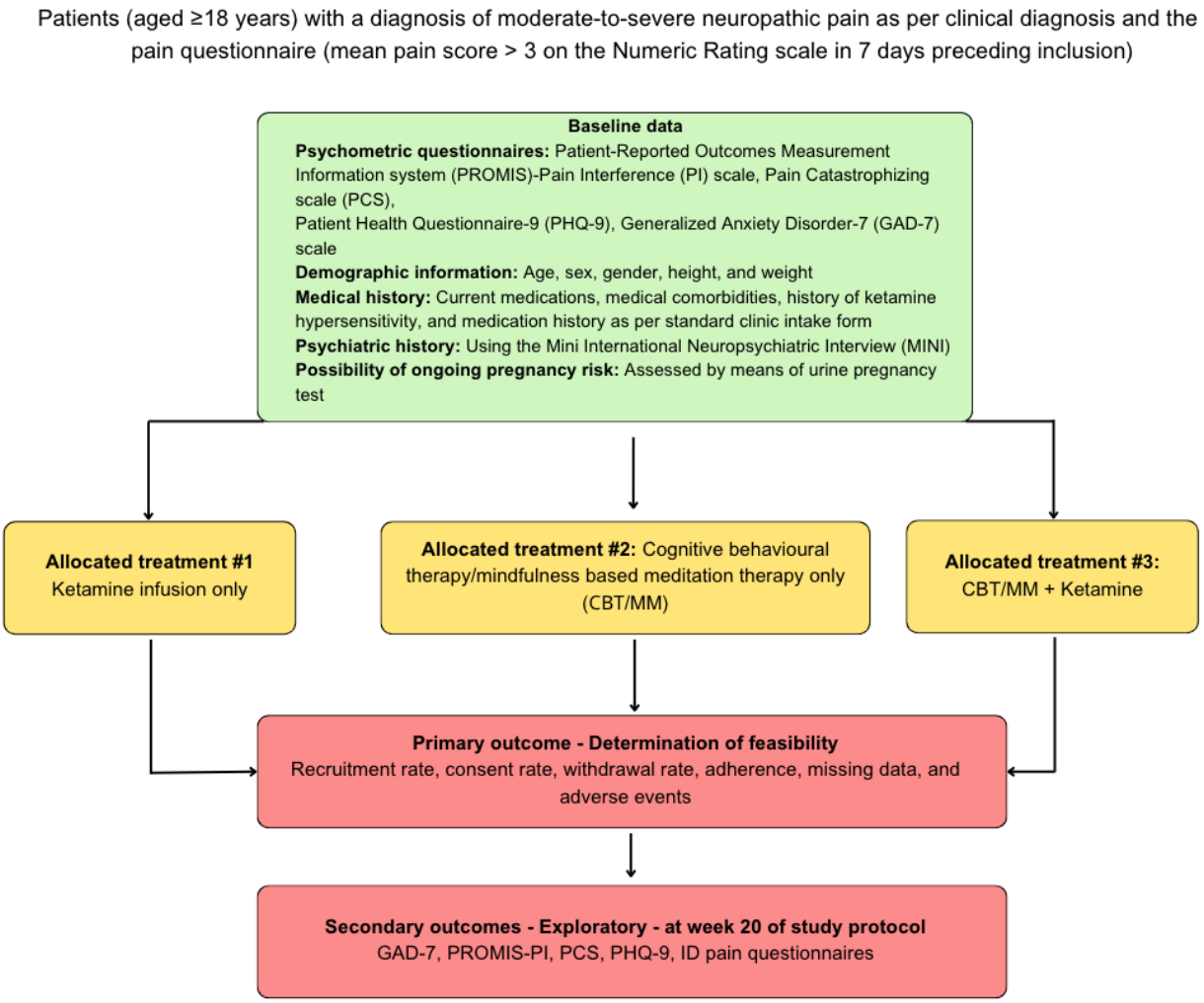


Table 1. Study timeline from weeks 1-20.

Time point	Screening	Week 1	Week 2	Week 7	Week 12	Week 16	Week 20
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Enrollment							
Eligibility screen	✓						
Informed consent	✓						
MINI[a]	✓						
Randomization		✓					
Interventions							
Ketamine-hydrochloride infusion (arm 1 and arm 3)			✓	✓	✓		
Remote CBT/MM[b] (arm 2 and arm 3)		✓	✓	✓	✓	✓	
In-person CBT/MM (arm 2 and arm 3)			✓	✓	✓		
Assessments							
Baseline data		✓					
Semistructured interviews		✓[c,d]	✓[d]	✓[d]	✓[d]		✓[c,d]
Pregnancy test (if applicable)[e]			✓	✓	✓		
Questionnaires: PROMIS-PI[f], PGIC[g], GAD-7[h], PHQ-9[i], and PCS[j]		✓	✓	✓	✓	✓	✓
Adverse events			✓	✓	✓	✓	✓

[a]MINI: Mini International Neuropsychiatric Interview.

[b]CBT/MM: cognitive behavior therapy/mindfulness and meditation.

[c]Participants randomized to receive CBT/MM alone (arm 2), will receive a semistructured interview on weeks 1 and 20.

[d]Participants randomized to receive ketamine-hydrochloride infusion + CBT/MM (arm 3) will receive a semistructured interview on weeks 1 and 20 as well as a semistructured interview during the ketamine infusion on weeks 2, 7, and 12.

[e]Only female participants randomized to receive ketamine-hydrochloride alone (arm 1) or the ketamine-hydrochloride infusion + CBT/MM (arm 3) will require a pregnancy test on the day of infusion.

[f]PROMIS-PI: Patient-Reported Outcomes Measurement Information System.

[g]PGIC: Patient Global Impression of Change Scale.

[h]GAD-7: Generalized Anxiety Disorder-7.

[i]PHQ-9: Patient Health Questionnaire-9.

[j]PCS: Pain Catastrophizing Scale.

Ethical Considerations

This study will be conducted in accordance with the ethical principles laid down in the Declaration of Helsinki, the protocol, Good Clinical Practice guidelines, and applicable regulatory requirements. This study received a “No Objection Letter” from Health Canada on October 13, 2022, indicating the study protocol was deemed acceptable.

Full written informed consent will be obtained from participants before conducting any study activities. The study was reviewed and approved by the Research Ethics Board at St. Michael’s Hospital on May 5, 2023 (22-217). This trial was designed and will be reported according to the CONSORT (Consolidated Standards of Reporting Trials) clinical trials statement checklist and the CONSORT-Outcomes 2022 extension [16].

Results

Prestudy Screening

Eligible participants will be screened at the Chronic Pain Clinic at St. Michael’s Hospital. Participants diagnosed with chronic neuropathic pain that meet the criteria from the ID pain questionnaire will be approached and asked to consider study participation.

After participants have provided informed consent, they will be asked about their medical comorbidities, psychiatric history as based on the Mini International Neuropsychiatric Interview, history of ketamine hypersensitivity, and concomitant medications to confirm eligibility. If a participant is eligible to participate in the study, the participant will be enrolled in the study, and the study coordinator will book an appointment for the participant’s study intervention.

At this current point, November 1, 2023, the study has not started enrolling and consenting patients.

Baseline Data

After initial screening and informed consent are obtained, the following data will be collected at baseline (week 1):

1. Demographic information: age, sex, gender, height, and weight.
2. Detailed data regarding current medications and medical comorbidities, as well as medication history, is collected by our standard intake form.
3. Chronic neuropathic pain severity and other relevant covariates will be assessed at baseline using:
    - PROMIS-PI
    - PCS
    - PHQ-9
    - GAD-7
    - PGIC

Follow-Up Data

In all arms, at each follow-up visit, participants will complete the PROMIS-PI scale, PCS, PHQ-9, GAD-7, and the PGIC to assess outcome measurements. Follow-ups will be conducted every 4 weeks over the phone to maintain the blindness of the research team.

For females, a urine pregnancy test will be required for those randomized to the ketamine-hydrochloride infusion alone or the ketamine-hydrochloride infusion+CBT/MM arms in order to confirm that the patient is not pregnant before each ketamine infusion treatment.

Outcome Analysis

Based on the primary end points, we will determine whether or not this pilot study is as follows:

1. Feasible: all feasibility outcomes are met; no protocol modifications are needed,
2. Feasible with modification: all feasibility outcomes are met or can be met with protocol modifications, and
3. Not feasible: Even with protocol modifications, some feasibility outcomes cannot be met.

In terms of statistical analyses for this feasibility study, preliminary analyses will consist of univariate tests to compare clinical and demographic variables of interest. Linear regression analysis will be used to quantify the strength and magnitude of the relationship between the intervention and the coprimary outcomes. Secondary outcomes will be analyzed as continuous measures using generalized linear regression models.

For any missing data where patients do not attend the allocated sessions or do not complete all components of the relevant questionnaires, this will be noted and documented to assess the overall feasibility of this study. Data will not be extrapolated or interpreted for these missing data sets.

Study Status As of Date

As of the current date, November 1, 2023, the study has not started to recruit patients.

Discussion

It is hypothesized that concurrent pharmacotherapy and psychotherapy have combined effects on the analgesic response. In addition to ketamine's anesthetic-analgesic properties, it also uniquely alters the individual's level of consciousness at variable doses. Some researchers posit that the therapeutic experience of psychotherapy may be augmented by ketamine's alteration of conscious awareness [10]. As demonstrated by this systematic review, few studies have examined ketamine-assisted psychotherapy (KAP) for chronic neuropathic pain. RCTs have not been published on this topic. In addition, there appears to be wide variability in the indication, dosage, and patient treatment setting, such that the current literature is inconclusive.

The 3-arm design allows us to compare the feasibility of KAP with ketamine alone and CBT/MM. We will track feasibility outcomes, including recruitment rate and adverse event rate, to estimate the acceptability of this intervention compared to controls. There are also limitations to this study. Due to the participatory nature of CBT/MM, we are unable to blind patients and the research team to patients' assigned interventions. To mitigate this, the outcome assessors will be blinded to minimize bias, and we will request and report their "best guess" estimate of each patient's assigned intervention at the end of the study. We also recognize that there may be different patient outcomes based on the mode of CBT/MM delivery. Patients in arm 1 receiving ketamine alone will have no CBT/MM as part of the trial design. Patients assigned to CBT/MM alone (Arm 2) will be receiving their intervention sessions remotely rather than in-person for 16 weeks. Patients in Arm 3 will be receiving ketamine on weeks 2, 7, and 12 and in-person CBT/MM at this time. They will also be involved with remote CBT/MM sessions from weeks 1 to 16 (except for weeks 2,7, and 12). This hybrid intervention will allow us to collect data on the feasibility of in-person versus remote psychotherapy for this patient population.

This study will inform the development of a larger-scale multicenter RCT. Our results will help inform the sample size calculation to ensure an adequately powered, definitive RCT. We anticipate that the psychotherapy and ketamine protocols developed in this study will be easily replicable and scalable should they show clinical and statistical benefits in the chronic neuropathic pain population. Furthermore, future studies developed by our research team will aim to study longer-term outcomes associated with KAP and the need for ongoing therapy in this patient subset.

Acknowledgments

This study was partially funded by the Canadian Pain Society in partnership with the Pfizer Early Career Investigator Award, and the St. Michael's Hospital Association Innovation Fund. KL and H Clarke are recipients of Merit Awards administered by

the Department of Anesthesiology and Pain Medicine at the University of Toronto. Joel Katz is supported by a Canadian Institutes of Health Research Canada Research Chair in Health Psychology at York University. PR is currently funded by the Canadian Institutes of Health (2021-2025). He coordinates research with NexJ Health Inc which provides software to convey the programming he develops and assesses.

Authors' Contributions

KL, H Clarke, JK, PR, JPC, ZT, GM, and AG were responsible for conception and design. BK, H Chan, KP, and AG were responsible for drafting the manuscript. All the authors were responsible for revising the manuscript for intellectual content and final approval of the completed manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the Canadian Pain Society in partnership with the Pfizer Early Career Investigator Award.
[PDF File (Adobe PDF File), 742 KB - resprot_v13i1e54406_app1.pdf]

References

1. Canadian Pain Task Force report: june 2019. Government of Canada. 2019. URL: https://www.canada.ca/en/health-canada/corporate/about-health-canada/public-engagement/external-advisory-bodies/canadian-pain-task-force/report-2019.html [accessed 2022-01-30]
2. Mackey S. Future directions for pain management: lessons from the institute of medicine pain report and the national pain strategy. Hand Clin 2016;32(1):91-98 [FREE Full text] [doi: 10.1016/j.hcl.2015.08.012] [Medline: 26611393]
3. Cohen SP, Bhatia A, Buvanendran A, Schwenk ES, Wasan AD, Hurley RW, et al. Consensus guidelines on the use of intravenous ketamine infusions for chronic pain from the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. Reg Anesth Pain Med 2018;43(5):521-546 [FREE Full text] [doi: 10.1097/AAP.0000000000000808] [Medline: 29870458]
4. Amr YM. Multi-day low dose ketamine infusion as adjuvant to oral gabapentin in spinal cord injury related chronic pain: a prospective, randomized, double blind trial. Pain Phys 2010;13(3):245-249 [FREE Full text] [doi: 10.36076/ppj.2010/13/245]
5. Noppers I, Niesters M, Swartjes M, Bauer M, Aarts L, Geleijnse N, et al. Absence of long-term analgesic effect from a short-term S-ketamine infusion on fibromyalgia pain: a randomized, prospective, double blind, active placebo-controlled trial. Eur J Pain 2011;15(9):942-949. [doi: 10.1016/j.ejpain.2011.03.008] [Medline: 21482474]
6. Sigtermans MJ, van Hilten JJ, Bauer MC, Arbous SM, Marinus J, Sarton EY, et al. Ketamine produces effective and long-term pain relief in patients with complex regional pain syndrome type 1. Pain 2009;145(3):304-311. [doi: 10.1016/j.pain.2009.06.023] [Medline: 19604642]
7. Buhrman M, Syk M, Burvall O, Hartig T, Gordh T, Andersson G. Individualized guided internet-delivered cognitive-behavior therapy for chronic pain patients with comorbid depression and anxiety: a randomized controlled trial. Clin J Pain 2015;31(6):504-516. [doi: 10.1097/AJP.0000000000000176] [Medline: 25380222]
8. Knoerl R, Lavoie Smith EM, Weisberg J. Chronic pain and cognitive behavioral therapy: an integrative review. West J Nurs Res 2016;38(5):596-628. [doi: 10.1177/0193945915615869] [Medline: 26604219]
9. Greenway KT, Garel N, Jerome L, Feduccia AA. Integrating psychotherapy and psychopharmacology: psychedelic-assisted psychotherapy and other combined treatments. Expert Rev Clin Pharmacol 2020;13(6):655-670. [doi: 10.1080/17512433.2020.1772054] [Medline: 32478631]
10. Drozdz SJ, Goel A, McGarr MW, Katz J, Ritvo P, Mattina GF, et al. Ketamine assisted psychotherapy: a systematic narrative review of the literature. J Pain Res 2022;15:1691-1706 [FREE Full text] [doi: 10.2147/jpr.s360733]
11. Ocker AC, Shah NB, Schwenk ES, Witkowski TA, Cohen MJ, Viscusi ER. Ketamine and cognitive behavioral therapy for rapid opioid tapering with sustained opioid abstinence: a case report and 1-year follow-up. Pain Pract 2020;20(1):95-100. [doi: 10.1111/papr.12829] [Medline: 31408575]
12. Keizer BM, Roache JD, Jones JR, Kalpinski RJ, Porcerelli JH, Krystal JH. Continuous ketamine infusion for pain as an opportunity for psychotherapy for PTSD: a case series of ketamine-enhanced psychotherapy for PTSD and pain (KEP-P2). Psychother Psychosom 2020;89(5):326-329. [doi: 10.1159/000507095] [Medline: 32248200]
13. Pludwinski S, Ahmad F, Wayne N, Ritvo P. Participant experiences in a smartphone-based health coaching intervention for type 2 diabetes: a qualitative inquiry. J Telemed Telecare 2016;22(3):172-178. [doi: 10.1177/1357633X15595178] [Medline: 26199275]
14. Ritvo P, Ahmad F, El Morr C, Pirbaglou M, Moineddin R, Team MVC. A mindfulness-based intervention for student depression, anxiety, and stress: randomized controlled trial. JMIR Ment Health 2021;8(1):e23491 [FREE Full text] [doi: 10.2196/23491] [Medline: 33264098]

15. El Morr C, Ritvo P, Ahmad F, Moineddin R, Team MVC. Effectiveness of an 8-week web-based mindfulness virtual community intervention for university students on symptoms of stress, anxiety, and depression: randomized controlled trial. JMIR Ment Health 2020;7(7):e18595 [FREE Full text] [doi: 10.2196/18595] [Medline: 32554380]
16. Butcher NJ, Monsour A, Mew EJ, Chan AW, Moher D, Mayo-Wilson E, et al. Guidelines for reporting outcomes in trial reports: the CONSORT-outcomes 2022 extension. JAMA 2022;328(22):2252-2264 [FREE Full text] [doi: 10.1001/jama.2022.21022] [Medline: 36511921]

Abbreviations

CBT: cognitive behavioral therapy
CONSORT: Consolidated Standards of Reporting Trials
GAD-7: Generalized Anxiety Disorder-7
KAP: ketamine-assisted psychotherapy
MM: mindfulness and meditation
PCS: Pain Catastrophizing Scale
PGIC: Patient Global Impression of Change Scale
PHQ-9: Patient Health Questionnaire-9
PROMIS-PI: Patient-Reported Outcomes Measurement Information System
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture

Edited by A Mavragani; submitted 08.11.23; this is a non–peer-reviewed article;accepted 25.01.24; published 17.04.24.

Please cite as:
Goel A, Kapoor B, Chan H, Ladha K, Katz J, Clarke H, Pazmino-Canizares J, Thomas Z, Philip K, Mattina G, Ritvo P
Psychotherapy for Ketamine's Enhanced Durability in Chronic Neuropathic Pain: Protocol for a Pilot Randomized Controlled Trial
JMIR Res Protoc 2024;13:e54406
URL: https://www.researchprotocols.org/2024/1/e54406
doi:10.2196/54406
PMID:38630524

Protocol

Quantifying Bone and Skin Movement in the Residual Limb-Socket Interface of Individuals With Transtibial Limb Loss Using Dynamic Stereo X-Ray: Protocol for a Lower Limb Loss Cadaver and Clinical Study

Jason T Maikos[1*], PhD; John M Chomack[1*], MS; David V Herlihy[2*], BS; David N Paglia[3*], PhD; Charlene Wetterstrand[3*], MS, RT(R)(ARRT); J Patrick O'Connor[3*], PhD; Michael J Hyre[2*], MS; J Peter Loan[4*], MS; Susan E D'Andrea[5*], PhD

[1]Veterans Affairs New York Harbor Healthcare System, New York, NY, United States

[2]Narrows Institute for Biomedical Research and Education, Inc., Brooklyn, NY, United States

[3]Department of Orthopaedics, Rutgers-New Jersey Medical School, Newark, NJ, United States

[4]C-Motion, Inc, Germantown, MD, United States

[5]Department of Kinesiology, College of Health Sciences, University of Rhode Island, Kingston, RI, United States

[*]all authors contributed equally

Corresponding Author:
Jason T Maikos, PhD
Veterans Affairs New York Harbor Healthcare System
423 E. 23rd Street
New York, NY, 10010
United States
Phone: 1 2126867500 ext 7482
Email: jason.maikos@va.gov

Abstract

Background: Relative motion between the residual limb and socket in individuals with transtibial limb loss can lead to substantial consequences that limit mobility. Although assessments of the relative motion between the residual limb and socket have been performed, there remains a substantial gap in understanding the complex mechanics of the residual limb-socket interface during dynamic activities that limits the ability to improve socket design. However, dynamic stereo x-ray (DSX) is an advanced imaging technology that can quantify 3D bone movement and skin deformation inside a socket during dynamic activities.

Objective: This study aims to develop analytical tools using DSX to quantify the dynamic, in vivo kinematics between the residual limb and socket and the mechanism of residual tissue deformation.

Methods: A lower limb cadaver study will first be performed to optimize the placement of an array of radiopaque beads and markers on the socket, liner, and skin to simultaneously assess dynamic tibial movement and residual tissue and liner deformation. Five cadaver limbs will be used in an iterative process to develop an optimal marker setup. Stance phase gait will be simulated during each session to induce bone movement and skin and liner deformation. The number, shape, size, and placement of each marker will be evaluated after each session to refine the marker set. Once an optimal marker setup is identified, 21 participants with transtibial limb loss will be fitted with a socket capable of being suspended via both elevated vacuum and traditional suction. Participants will undergo a 4-week acclimation period and then be tested in the DSX system to track tibial, skin, and liner motion under both suspension techniques during 3 activities: treadmill walking at a self-selected speed, at a walking speed 10% faster, and during a step-down movement. The performance of the 2 suspension techniques will be evaluated by quantifying the 3D bone movement of the residual tibia with respect to the socket and quantifying liner and skin deformation at the socket-residuum interface.

Results: This study was funded in October 2021. Cadaver testing began in January 2023. Enrollment began in February 2024. Data collection is expected to conclude in December 2025. The initial dissemination of results is expected in November 2026.

Conclusions: The successful completion of this study will help develop analytical methods for the accurate assessment of residual limb-socket motion. The results will significantly advance the understanding of the complex biomechanical interactions between the residual limb and the socket, which can aid in evidence-based clinical practice and socket prescription guidelines.

This critical foundational information can aid in the development of future socket technology that has the potential to reduce secondary comorbidities that result from complications of poor prosthesis load transmission.

International Registered Report Identifier (IRRID): DERR1-10.2196/57329

(JMIR Res Protoc 2024;13:e57329) doi:10.2196/57329

KEYWORDS

biplanar fluoroscopy; dynamic stereo x-ray; lower limb loss; transtibial limb loss; prosthetic sockets; amputation; lower extremity

Introduction

Background

For individuals with lower limb loss who use a prosthesis, relative motion between the prosthetic socket and the residual limb, including vertical translation and axial rotation, is a common problem that can lead to skin integrity concerns [1]. Excessive motion between the residual limb and socket can lead to discomfort, pain, and gait deviations that can limit mobility [2], which has been correlated with worse quality of life [3]. Up to 40% of individuals with transtibial limb loss experience issues involving the residual skin and soft tissue, which can be directly attributed to the movement of the residuum relative to the prosthetic socket and liner during dynamic activities [4]. Restricting residual bone motion within the socket may therefore help improve the quality of life and comfort for individuals with lower limb loss. Although some efforts have been made to advance socket technology [5-7] and improve suspension techniques [8], clinical practice has been slow to adopt these new technologies and continues to primarily rely upon unscientific methods for socket fabrication [9,10]. The challenge of developing enhanced socket technology and suspension techniques can be partially attributed to the multifactorial nature of socket fit, which is complicated by the complex mechanical interaction between the residual limb (bone and tissue), the liner, and the socket during dynamic activities. Furthermore, there has traditionally been a lack of accurate analytical techniques to quantify the complex, dynamic biomechanics of the socket-residual limb interface.

Although biomechanical assessments of the relative motion between the residual limb and the prosthetic socket have been performed, the existing data are suboptimal or lack an appropriate resolution. Radiological methods have been widely used to measure the relative motion of the bone and socket in 2 dimensions, but these methods have only provided static analyses of the residual limb-socket relationships [11,12]. Ultrasound has been used to monitor residual limb motion in individuals with above-knee limb loss [13], but the mounting technique has been found to be too cumbersome to implement on a clinical basis. Advanced imaging methods including computed tomography (CT) and spiral x-ray CT offer higher spatial resolution, but imaging must be performed in the supine position, resulting in non–weight-bearing, static assessments [14-16]. Roentgen stereophotogrammetric analyses have been used to characterize the motion between the residual limb and socket in 6 degrees of freedom (DOF) by using biplanar imaging [17]; however, these techniques use static loading protocols. Dynamic assessments of 3D in-socket residual limb-socket kinematics are currently only possible using dynamic stereo x-ray (DSX), which can provide submillimeter bone pose [18-21] and in vivo strain analysis. Currently, only 1 study performed a dynamic investigation of residual tibia motion in participants with transtibial limb loss [10], but the methods relied on subjective input and were time intensive, which can affect accuracy [22] and sample size. In individuals with transfemoral limb loss, Maikos et al [23] used DSX to compare 3D residual femur kinematics between 2 different prosthetic socket types. Gale et al [3] also used DSX for 3D markerless tracking of the residual femur for individuals with transfemoral limb loss during late swing and early stance to calculate the 6 DOF kinematics of the residual femur relative to the socket but did not include terminal stance. DSX may help fill the substantial gap in our understanding of the complex mechanics of the residual limb-socket interaction during dynamic activities that limit the ability to improve prosthetic design.

During the cyclical loading and unloading of the residual limb during the gait cycle, the skin of the residual limb is exposed to nonphysiological stresses and strains, including excessive shear forces [24]. Although the skin is well adapted to compressive force, excessive shear force can be damaging, leading to abrasions, wounds, and ulcers [25,26]. Understanding in-socket skin strain biomechanics is critical for enhancing prosthetic socket fit, limb health, and overall comfort. However, whole-limb skin strain analysis is complicated by the heterogeneous composition of the skin and its anisotropic mechanical properties. Some investigations have used 3D digital image correlation (DIC) to create full-field deformation and strain maps of an unsupported residual limb [27]. Lin et al [28] examined skin strain in a flexed biological residual limb from an individual with transtibial limb loss and showed that the anterior patella region of the limbs exhibited predominantly tensile strains, whereas the posterior patella region exhibited predominately compressive strains. Although 3D DIC evaluations have provided critical data to help improve the mechanical interface of sockets and liners to limit relative motion and shear forces on the skin surface, these investigations only considered strain on an unloaded residual limb. Whole-limb strain fields can drastically change during dynamic, weight-bearing activities while using a prosthetic interface. Furthermore, 3D DIC and other imaging techniques are further complicated by the need for transparent biomechanical interfaces to accurately compute the strain analysis. Other techniques, such as magnetic resonance imaging and CT, can be used to evaluate in vivo strains, but they are also limited by static protocols, low resolution, motion artifacts, and shape distortion [29]. Gale et al [30] used DSX to measure residual limb skin strain and strain rate for individuals with transfemoral limb loss during gait and found that shear strain increased from proximal

to distal regions of the residual limb. The proposed investigation will use time-efficient and highly accurate analytical techniques to measure in-socket residual limb skin strain for individuals with transtibial limb loss during dynamic activities.

Study Objectives and Aims

There remains an unmet need to fill the gap of accurate, biomechanical evaluations of residual limb-socket kinematics, which can then be effectively translated into evidence-based clinical practice. Furthermore, quantifying dynamic shear and tissue deformation is yet to be efficiently evaluated to determine the exact mechanism of tissue strain. Therefore, the objective of this investigation is to develop quantitative, dynamic analytical tools to quantify both 3D bone movement as well as soft tissue and liner deformation at the socket-residual limb interface for individuals with transtibial limb loss. To meet the study objective, the following aims will be addressed: (1) to optimize the DSX procedural setup for the accurate tracking of the prosthetic socket, skeletal kinematics, and tissue and liner deformation; (2) to quantify the relative motion between the residual tibia and the prosthetic socket during dynamic activities; and (3) to measure the deformation of the skin and liner in the prosthetic socket during dynamic activities. The proposed investigation will use a state-of-the-art DSX system to accurately quantify 3D in vivo residual limb-socket kinematics during dynamic activities. To verify the sensitivity of this technique and its relevance to individuals with transtibial limb loss, residual limb-socket kinematics will be evaluated in 2 different socket suspension systems: elevated vacuum (EV) and traditional suction. It is hypothesized that an efficient and highly accurate method to quantify the dynamic interaction between the residual limb and the prosthetic socket will be sensitive enough to distinguish between different types of prosthetic socket suspension systems, which will further enhance the biomechanical understanding of residual limb-socket kinematics.

Methods

Study Overview

To address the study aims, first an iterative cadaver study will be conducted to optimize the placement of an array of radiopaque beads and markers on the socket, liner, and skin to simultaneously assess both dynamic skeletal movement and residual skin and liner deformation. Using a gait simulator, stance phase gait will be simulated using cadaver limbs during each DSX session to induce bone movement as well as skin and liner deformation. The number and placement of markers will be evaluated after each session to refine the marker placement to best track skin and liner deformation and skeletal movement. Once an optimal marker setup is identified, 21 participants with transtibial limb loss will be fitted with a socket capable of being suspended via both EV and traditional suction. Participants will undergo a 4-week acclimation period using the new socket and will then be evaluated at the DSX facility at Rutgers New Jersey Medical School. DSX will be used to track skeletal, skin, and liner motion under both suspension techniques during 3 dynamic activities: treadmill walking at a self-selected speed, treadmill walking at fast walking (10% faster), and a step-down movement. The performance of the 2 suspension techniques (active EV and traditional suction) will be tested by quantifying the 3D bone movement of the residual tibia with respect to the prosthetic socket and quantifying liner and skin deformation at the socket-residuum interface. This study has been registered on ClinicalTrials.gov (NCT05287646).

Cadaver Study to Optimize DSX Setup

The aim of the cadaver study is to optimize the placement of an array of radiopaque beads and markers on the socket, liner, and skin, which will then be used in the human trial to accurately measure the dynamic skeletal movement and residual tissue and liner deformation simultaneously during functional tasks. Five cadaver limbs will be used in an iterative process to develop an optimal marker setup to distinguish markers placed on the socket, liner, and skin as well as to visualize the tibia. The number, size, shape, and placement of markers will be evaluated after each cadaver test to determine the optimal marker set for the measurement of skin and liner deformation and bone movement. The goal is to develop a skin and liner marker set that is free of occlusion during tracking while also not interfering with bone tracking. Although it is understood that the cadaveric tissue may not produce accurate tissue displacement and deformation profiles compared to living tissue, the main intent of cadaver testing is to accurately position the skin and liner markers during an iterative process to reduce or eliminate occlusion during tracking.

Cadaver Preparation and Socket Casting

Five fresh-frozen, whole, lower extremity cadaveric specimens without a history of significant trauma or major surgery at or below the knee will be used. Lower extremity cadaver specimens will be from individuals aged <80 years and with a BMI of <38 kg/m^2 to account for the predicted upper limits of the human trials. Cadavers will be thawed at room temperature for 24 hours and will be transected at the midthigh to keep the knee intact. The cadaver specimens for the initial assessments will be amputated below the knee to a length between 12.5 cm and 17.5 cm below the medial joint line, which is considered an ideal length for transtibial amputation [31]. Myodesis will be performed to stabilize the muscles, and the remaining skin flap will be sutured in place. After initial cadavers of ideal length have been used to determine an optimized marker set, subsequent cadaver limbs will be amputated at shorter lengths to ensure that the marker set does not need to be modified to account for different residual limb lengths. A liner will be placed over the amputated cadaver limbs and then cast with fiberglass to create a negative mold. The negative mold will be filled with plaster to create a positive cast, which will be used to fabricate a ThermoLyn socket. Cadavers will be fitted with the socket and prosthetic componentry, including a pylon and prosthetic foot. A rocker bottom shoe will be placed on the prosthetic foot to aid in simulating dynamic gait.

Cadaver CT Scans

A single CT scan will be acquired for each cadaver experiment. The residual limb will be marked with radiopaque paint. A silicone liner will be applied to the residual limb, and a thermoformed plastic socket marked with solid, 2-mm diameter embedded brass spheres will be placed on the limb before

scanning. The socket will maintain the unloaded 3D shape of the residual limb and the relative positioning of the radiopaque makers. The CT scan will be used to create gray-scale volumes and high-resolution 3D bone surface models required for computing all outcome variables in DSX. CT volume images will be acquired at a resolution of 512×512×0.625 mm^3 (120 kVp; SMART mA).

Experimental Design

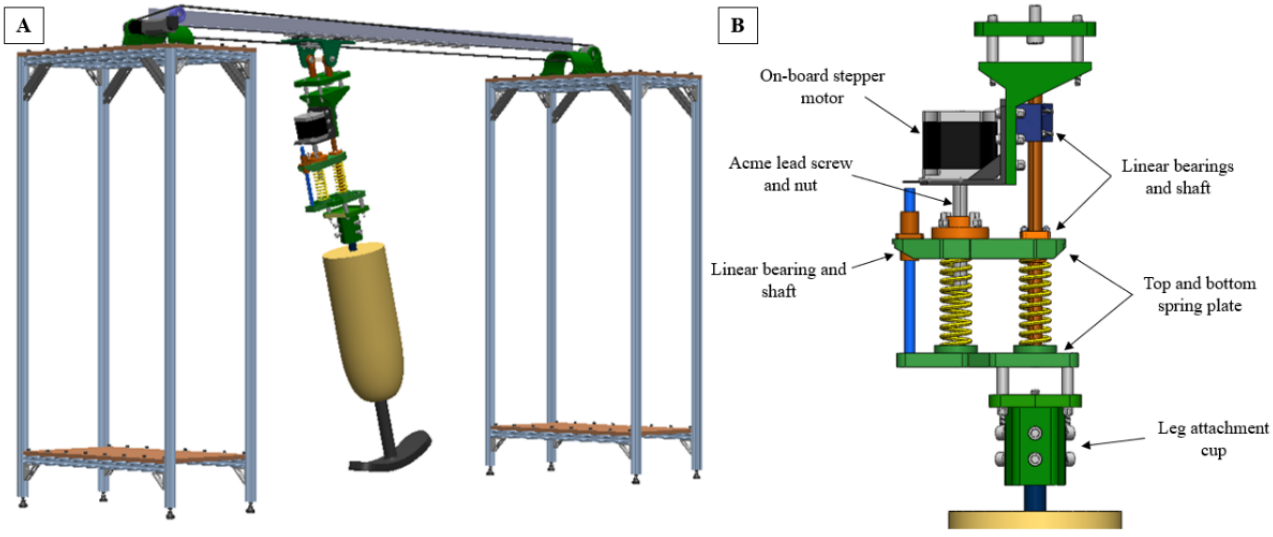
To determine the areas of highest strain on both the skin and inner liner surface (to serve as a starting point for appropriate marker placement), the first cadaver experiment will use a grid of circular radiopaque markers distributed across the circumference of the residual limb and the inner surface of the liner (in separate experiments). Although this grid pattern will cover the entire surface to help quantify areas of highest strain on the liner and skin, the high density of radiopaque markers will make it unlikely to track the movement of the residual tibia, liner, skin, and socket accurately and simultaneously. Therefore, this initial cadaver experiment will serve only to help determine areas of importance for subsequent cadaver studies. However, previously reported skin strain findings from the scientific literature will be considered to ensure that areas of interest are included [10,27]. For clarity, the procedures will be first carried out with markers on the skin and no markers on the liner. The experiment will then be repeated using a liner with no markers on the skin.

A custom grid stencil will be fabricated by cutting specific patterns of circles on a thin vinyl sheet using an electronic die-cutting machine (Cricut, Inc). The circles on the grid will be cut to diameters of either 2 mm or 4 mm and spaced 2 cm apart within each row and column. Each row and column of circles will alternate between the larger and smaller circles, which will help uniquely identify them during marker tracking. The stencil will then be applied to the cadaver limb or liner (in separate experiments), and radiopaque paint will be applied to the pattern to transfer the grid onto the residual limb or liner. The liner will then be placed over the limb, the socket will be donned, and the limb will be placed in the DSX capture volume. Averaging the DSX data collected from 10 to 20 frames from the unloaded-donned socket in the static pose will produce the relative resting grid positions, which will account for any skewness after donning the liner and socket. The circles will then be digitized in dynamic trials to relate their dynamic positions to the resting grid.

Stance Simulation

An electromechanical stance simulator will be designed to apply a compressive load on a cadaver limb through simulated stance phase (Figure 1). The framework will be designed to interface with the DSX system while allowing for remote control of the load and trajectory of a cadaver limb during DSX data capture. Using this setup in conjunction with DSX data capture, simulated stance phase will be performed to determine areas of highest strain on both the skin of a cadaver leg and the inner liner surface, while simultaneously tracking tibial movement during dynamic activities during the clinical trial. To ensure accurate results, the system will be able to apply 100% body weight in compression to induce tissue deformation. The applied load will be monitored using a force plate (AMTI Inc).

Figure 1. Overview of the stance simulator design for simulation of the stance phase for cadaver testing. (A) Isometric view of the stance simulator assembly. (B) Detailed view of the force applicator mechanism.



To avoid interference with the DSX system, the main support structure of the simulator will consist of 2 stands with an angle bar spanning the length between them (Figure 1A). Weights placed on the outer stands will ensure that the system remains fixed despite varied applied loads. A linear track attached to the beam will provide a low friction path for the leg to travel along the plane of forward progression, and the beam will ensure minimal deflection of the track. The leg will pivot around this attachment point, allowing it to attain a full range of motion to mimic heel-strike to toe-off. The drive motor will be placed off-board and will move the leg with a timing belt and pulley. A second, on-board motor will control the deflection of 2 springs to actuate the load applied to the leg. The force applicator mechanism (Figure 1B) will include a stepper motor with a built-in Acme lead screw and nut to add spring compression, allowing for consistent control of applied forces at high loads.

In addition, 3 linear bearings in the assembly allow the assembly to compress without direct control from the on-board motor because of the natural compression of the springs as the leg rolls over in stance under the fixed-height track. The cadaver leg will be placed in extension to limit bending of the knee or the knee will be fixed in place with a titanium rod, increasing the lever arm and ensuring that the springs apply a compressive force. A 3D-printed cup fixture will be secured to the exposed femur of the leg by tightening 6 separate bolts. This attachment method will allow for alignment flexibility, varying the load path through the leg. The entire system will be controlled electronically by 2 separate motor drivers, 1 each for the off-board motor and on-board stepper motor.

Marker Tracking

For each cadaver trial, the images will be analyzed using Locate3D (C-Motion, Inc), which is an application in the DSX suite of software. Locate3D tracks radiopaque markers in x-ray trials by locating the weighted center of circular regions on the images. The circles will be digitized in both the unloaded (resting) and loaded dynamic conditions to relate dynamic positions to the resting grid. Each circle will be tracked throughout the simulated stance phase to calculate the 3D position of each circle in the socket reference frame during dynamic movement. Point clouds will then be calculated in a common frame. Vector fields (ie, movement of the circles) will be computed between the loaded and the resting trial. The distance between each circle and its 8 closest neighbors will be calculated and measured from the resting to the loaded conditions during dynamic trials. From these measurements, the circle clusters that have the largest changes in distance will be determined. The displacement field on the limb surface will be calculated by correlating the time series of images during the dynamic movements. From the correlated skin displacement field, the Green-Lagrange strain and Euler-Almansi strain will be calculated. The areas of the highest strain from these trials will provide a strong estimate of the most appropriate placement of markers on the skin and liner for the human trials.

Subsequent Cadaver Experiments

The results from the initial cadaver experiment will help inform the placement of markers on the liner and skin for subsequent cadaver experiments. Figure 2 illustrates example marker shapes (Figure 2A) and the setup on a cadaver limb (Figure 2B). To track the pose of the socket, brass beads (2 mm diameter) will be secured to the socket. The initial marker shapes on the skin will be lines (10×3 mm) of radiopaque paint that will be placed in a circular pattern (6 cm in diameter—black lines in Figure 2A). Lines organized in the shape of a circle were chosen because the end points of each line in each marker cluster will be able to be independently tracked. However, there is a possibility that there may be a substantial overlap between markers on the surface of the skin, particularly on opposite sides, which would limit their ability to be tracked throughout the movement trials. Therefore, additional shapes (eg, triangles and stars) will also be tested during initial cadaver experiments to determine which marker types are easiest to track throughout the movement trials. Overall, these sizes and shapes were chosen to provide a large surface area on the skin while also permitting visualization of the tibial bone edges. For the inner surface of the liner, radiopaque paint consisting of double lines (10×3 mm) in the shape of a square will be used (Figure 2A). The number of markers, marker shape, placement, and size will be evaluated after each testing session to determine the optimal placement to avoid any overlapping or occlusion of the bone edges. If the markers overlap or interfere with DSX, the sizes will be reduced, the placement of the markers will be changed, or different shapes will be used. An initial, sample cadaver marker set was tested in the DSX system under static conditions to determine if the DSX software had the ability to distinguish markers placed on the socket, skin, and liner (Figure 3). Brass beads were embedded in the socket and radiopaque markers were placed on the skin and liner (similar to that presented in Figure 2). The anteroposterior and oblique x-ray views were fused with the CT imaging into a 3D entity with coregistration of the socket markers, liner markers, skin markers, and bone geometry. It was confirmed that the DSX software could distinguish markers on all surfaces. Subsequent cadaver testing will be performed under dynamic conditions while the skin, liner, and socket markers are tracked in conjunction with bone tracking throughout the simulated stance phase.

Figure 2. Example skin marker shape and setup for the cadaver trials. (A) Circles (lines: 10 mm in length, 3 mm wide) and squares (lines: 10 mm in length, 3 mm wide) will be placed on the skin and liner, respectively. (B) Example marker placement on the skin on a scanned, translucent residual limb in the anterior-lateral view.

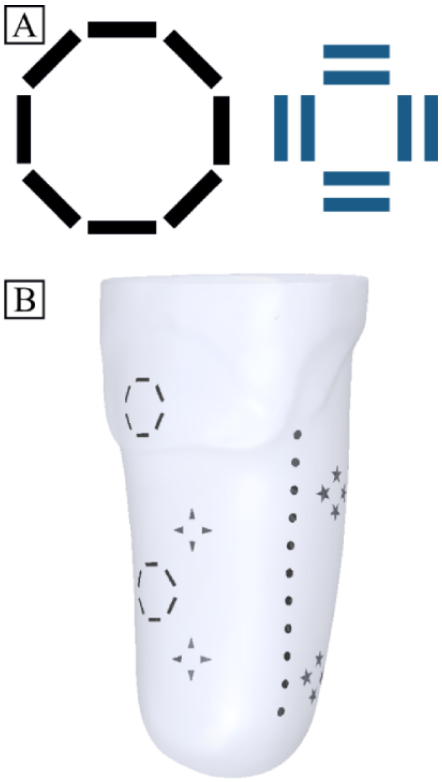
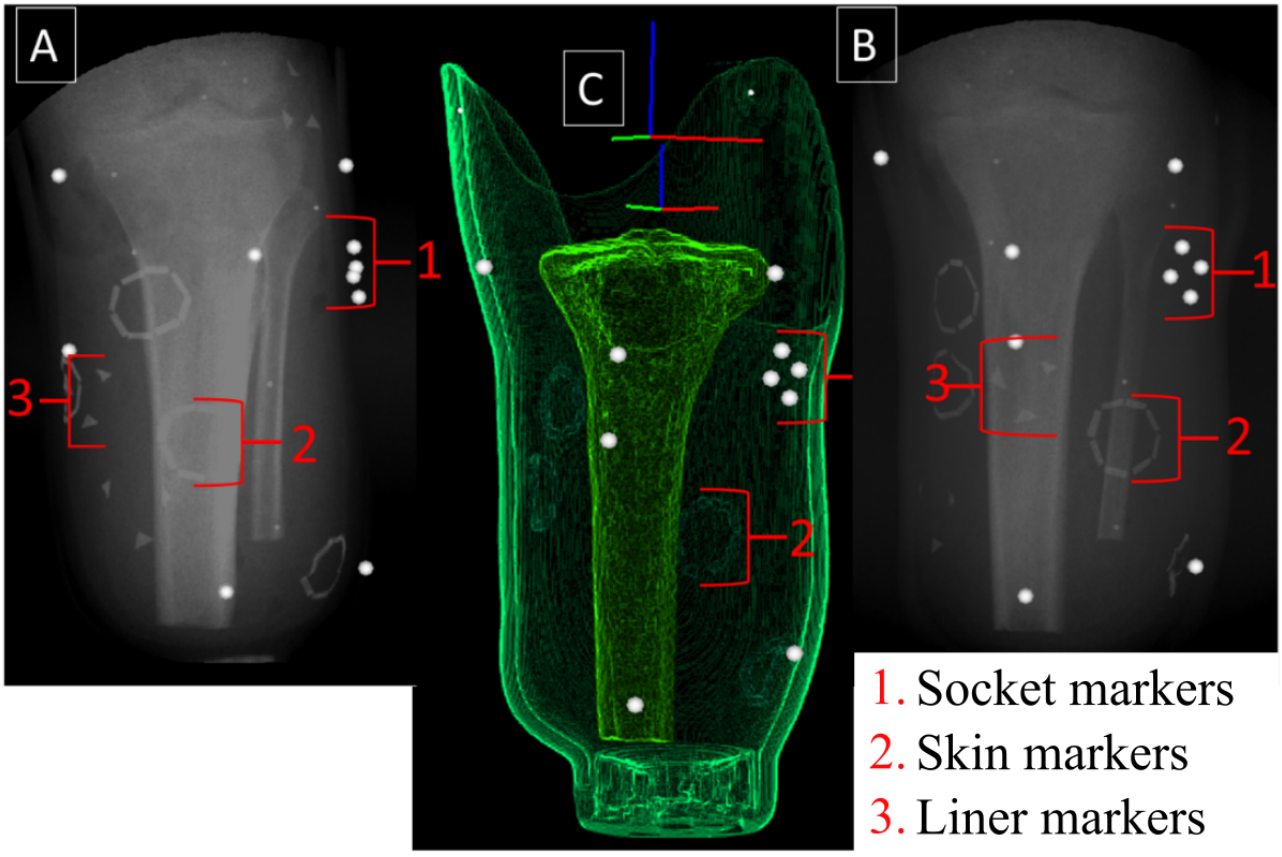


Figure 3. Static testing of a sample cadaver marker set in the dynamic stereo x-ray system. (A) and (B) X-ray images of the residual tibia, socket, and skin markers from the inline and offset x-ray views. Note the cluster of skin (lines in the shape of a circle), liner (triangles), and socket (beads) markers and the bone edges. (C) The x-ray and computed tomography images are fused to create a 3D model with coregistration of the socket and skin markers and bone geometry.



Optimization of the Marker Set

An iterative, heuristic approach will be used with the goal of accurately tracking all end points of each line for the skin and liner marker sets without (or minimal) occlusion while simultaneously tracking the underlying tibial movement. Notably, if there is too much overlap of the lines and tracking is not possible with the lines, additional shapes will be evaluated, and the centroid of each shape will be tracked. Cadaver trials will be sequential, and the marker set will be evaluated through tracking of each marker and performing preliminary deformation analysis after each cadaver trial. Once an acceptable marker protocol has been achieved heuristically, it will be tested on subsequent cadavers to ensure that it is robust for differing anatomies and residual limb lengths. Shorter residual limbs could potentially limit the number of markers that could be applied to the skin. As such, a minimum length may be required for skin and liner marker tracking, which would be then reflected in the inclusion and exclusion criteria.

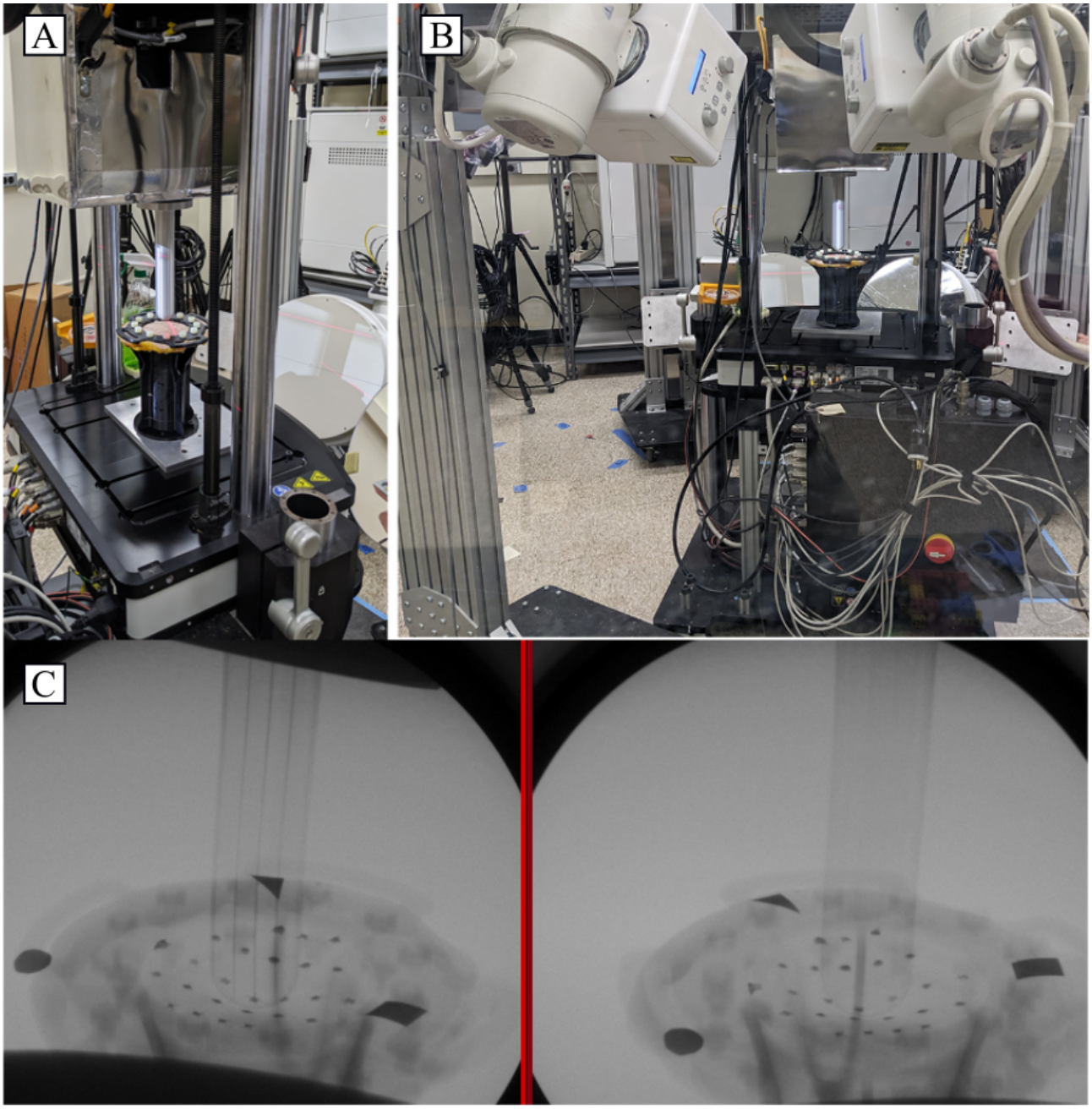
Deformation Analysis

The markers on the cadaver skin and the inner surface of the liner will be tracked during the simulated stance phase, and their trajectories in both the socket and tibia coordinate systems will define the motion of the skin relative to the socket and tibia, respectively. Their positions in the socket and tibia coordinate systems during the static trial will serve as their baseline positions. Visual3D (C-Motion, Inc) contains the tools to define the socket and tibia coordinate systems and track the motion of the skin and liner markers within these reference frames. Two metrics will be used to quantify skin and liner deformation. The first, shear, is defined as the change in angle between the lines painted on the skin and liner from the baseline position. The end points of the lines forming the circles and squares will be digitized, and the 3D trajectories will be used to reconstruct the 3D shape of the line at each time frame. The angles between the lines will be measured in the static pose to quantify the baseline skin shear. The change in angles will be measured during the simulated stance phase. Shear will be measured as the change in angle relative to the angle in the static position. The second, compression, will be quantified by calculating the change in distance between the lines and a neutral position. As with shear, baseline distances will be calculated from the static trial. From these values, 3D strain maps of the highest areas of deformation will be developed for both the liner and the skin.

Validation of DSX Strain Measurements

In conjunction with the cadaver experiments, to validate the accuracy of proposed methods to measure skin deformation, a customized, mechanical testing setup (Acumen 3AT axial-torsion system, MTS Systems Corp), which can directly interface with the DSX system, will be used. This system permits mechanical testing of soft tissue to be simultaneously performed during DSX data captures (Figure 4). This setup will be used to apply displacements to cadaveric lower limb tissue (mimicking tissue deformation in the socket) to validate the measurements from the proposed DSX analysis. To perform this validation test, 5 segments of cadaveric skin and subdermal tissue will be dissected to be mechanically tested in conjunction with DSX imaging. Each tissue sample will be affixed in tension between the opposing rings of a radiolucent plastic fixture with the skin held taut between the rings using radiolucent hardware. To validate the deformation analysis, radiopaque markers used in the cadaver experiments will be painted on the tissue. A CT scan, as previously described, of each tissue sample with applied markers will be obtained before testing to model the tissue specimen and locate the markers in a 3D space. The DSX apparatus will be angled at a maximum of 30° to distinguish the markers on the horizontal surface to avoid occlusion by the metal structures of the mechanical testing system. The mechanical testing compression rings will allow translation while the center of the fixture below the sample will be open to allow the tissue to freely deform with the applied force. Both the plastic circular fixture attachment and compressive bending fixture will be fabricated from polylactic acid thermoplastic, which is radiolucent. The Acumen 3AT axial-torsion system will be used for mechanical testing with a maximum axial testing capacity of 3 kN. To remove the effects of tissue freezing, the samples will be preconditioned at 0.1 mm/s with an axial displacement loading between 0.1 and 0.5 cm, for 50 cycles, based on the results of a previous study [32]. This displacement (0.5 cm) corresponds to the minimum bone-socket displacement associated with patellar straps, sleeves, or suspension liners [11]. Following this, the displacements associated with vacuum (1.3 cm) and traditional suction (1.8 cm) for the bone-socket interface [11] will be tested for 10 cycles each in compression at a displacement rate of 1 mm/s [32]. The axial displacement, axial force, and time will be recorded with high-speed data acquisition while the tissue is simultaneously imaged by the DSX system. A digital input-output connection will be used to synchronize the 2 systems. The compressive force on the skin tissue is proportional to the distance from the origin of the bending load, and the skin strain and shear stress can thus be calculated for a given symmetric, circular geometry. The skin strain will be compared directly to the strain calculations derived from the position of the markers collected by the DSX system. To account for the asymmetry present in the skin, the geometries, boundary conditions, material properties, and the loading regimen will be simulated using finite element analysis (Ansys, Inc). This analysis will be compared to the mechanical testing results along the skin to determine the degree to which the asymmetry of the skin affects the strain measurements.

Figure 4. Validation apparatus setup. (A) The mechanical testing system interfaces with the dynamic stereo x-ray system. (B) Full view of the testing setup showing testing inclination. (C) Single static biplanar x-ray images of the skin deflected during compressive testing.



Clinical Experiment

Upon completion of the cadaver trials, a robust marker set will have been developed to evaluate skin strain and residual tibial movement for human participants as part of the clinical experiments. The residual tibial motion will be compared relative to the prosthetic socket for individuals with transtibial limb loss while separately using 2 suspension methods: EV suspension and traditional suction (EV system not activated). Participants will be assessed while walking at a self-selected speed on a treadmill, at a speed 10% faster, and during a step-down task. These activities were chosen for three distinct reasons: (1) their relevance to normal activities [33], (2) the fact that the forces exerted on the lower limb during stepping and walking can displace the prosthetic socket relative to the residual limb, and (3) these movements are suitable for recording by the DSX system. These 2 common suspension conditions (EV and traditional suction) were chosen because of their clinical relevance and expected measurable differences between these conditions.

Recruitment and Enrollment

The study sample will consist of 21 individuals with unilateral transtibial limb loss recruited from Veterans Affairs New York Harbor Healthcare System. The inclusion and exclusion criteria are presented in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Veteran, service member, or civilian with unilateral transtibial limb loss of any etiology
- Aged ≥18 years
- ≥6 months after limb loss
- Current prosthesis users for ≥6 hours per day

Exclusion criteria

- Inability to tolerate socket suspension
- Length of the residual limb prohibits socket fitting, marker placement, or dynamic stereo x-ray data capture
- Mental impairment that impedes study compliance
- Cognitive deficits or mental health problems that would limit the ability to participate fully in the study protocol
- Skin conditions and those with severe contractures that prevent prior prosthetic wear
- Neuropathy, uncontrolled diabetes, receiving dialysis, insensate feet, severe phantom pain, a history of severe skin ulcers, or any other significant comorbidity that would interfere with the study
- Severe circulatory problems including peripheral vascular disease and pitting edema
- Women who are pregnant or who plan to become pregnant during participation in the study

Ethical Considerations

This study was approved by the Veterans Affairs New York Harbor Healthcare System institutional review board (protocol ID 1655582) and the Rutgers University institutional review board (protocol ID Pro2022001576). All participants will provide informed consent before participating in any study activity. No research data will be acquired until the informed consent form has been signed. The principal investigator or study staff will explain the protocol, and participants will be given adequate time to review and comprehend all information before agreeing to participate in the study. After the informed consent form is signed, the study prosthetist will then screen each participant to confirm all inclusion and exclusion criteria and will inspect the residual limb to ensure that there are no issues that could prevent socket fitting. The appropriate residual limb measurements will be taken, and the residual limb will be cast to prepare for socket fabrication. Each participant's involvement will last approximately 8 weeks, including 4 weeks for socket fabrication and fitting, a 4-week acclimation period, and a data collection visit for CT scans and DSX testing on both socket suspension conditions. Study participants will be compensated US $50 for each of the socket fitting visits (up to 4 maximum) and US $100 for the 1-day data collection and testing at Rutgers. Compensation will be given in the form of a direct deposit voucher, processed through the Veterans Affairs New York Harbor Healthcare System fiscal department.

To protect the privacy and confidentiality of the human participants, each participant will be given a unique identification number that will be used in all study-related paperwork. The specific code system will not contain any personally identifiable information. All information collected throughout the study will be methodically recorded, handled, and stored to allow for accurate reporting, interpretation, and verification. Veterans Affairs (VA) complies with the requirements of the Health Insurance Portability and Accountability Act of 1996 and its privacy regulations and all applicable laws that protect the privacy of research participants. The principal investigator and study staff will ensure that research records are stored in a manner that protects the confidentiality of human participant information. All electronic data collected will be deidentified and will not contain any Health Insurance Portability and Accountability Act identifiers, and the physical study forms (ie, signed consent forms and data collection forms) will be stored in secured and locked filing cabinets at the on-site office of the principal investigator. Computer files will be secured through password protection. Throughout the study, deidentified data (video data and electronic data) will be shared using VA information security office–approved secured VA computer systems with password protection and firewall. The study materials will be stored in accordance with the VA record control schedule.

Prosthetic Suspensions

Individuals with transtibial limb loss will be provided with a prosthesis capable of being suspended via both EV and traditional suction, with the prosthetic ankle-foot devices they currently use. Participants will be tested under 2 conditions: with the EV suspension active and with the EV inactive (traditional suction suspension). The order of the conditions will be counterbalanced.

Socket Fitting and Prosthetic Alignment

Before fitting the prosthetic socket, the study prosthetist will capture measurements of the residual limb (eg, length, circumference, and percentage of the sound limb). The study prosthetist will also document any areas of potential concern on the residual limb (eg, excessive redness, scar tissue, redundant tissue, heterotopic ossification, sensitivities, or evidence of previous wounds). A total of 2 to 3 preliminary "check" sockets will then be fabricated to ensure proper fit before the fabrication of the definitive socket. Each socket will

be fitted with a Harmony vacuum pump (Ottobock Inc). Continued fittings will occur, as needed, to get to a comfortable, consistent daily volumetric fit throughout several consecutive days. Each participant will use their own ankle-foot device. Once a consistent, comfortable fit is achieved, fabrication of a definitive, laminated study socket will occur. Participants will use the study socket for a minimum period of 4 weeks before DSX testing occurs. Participants will be asked to use each suspension method equally during the 4-week acclimation period.

Subjective Surveys

Following the 4-week acclimation period, participants will complete 3 surveys for each suspension method. Participants will complete the Prosthesis Evaluation Questionnaire (PEQ), which is a self-reported visual analog-style survey for individuals with lower limb loss [34]. The PEQ has 9 independent domains as well as separate, non–domain-specific questions that can be evaluated individually. For this investigation, the domains for utility, appearance, sounds, residual limb health, and ambulation will be used. The PEQ questions on satisfaction and pain will also be assessed. In addition, participants will complete the PEQ Addendum, which asks 2 open-ended questions regarding any falls and stumbles that the participant may have experienced over the previous 4 weeks [35]. To specifically assess socket comfort, participants will complete the socket comfort score scale, which is a numerical scale of socket comfort that has shown good repeatability and sensitivity to change [36].

DSX Experimental Design

Following the 4-week acclimation period, the participants will be evaluated at the Rutgers New Jersey Medical School DSX facility. To evaluate the 6 DOF kinematics of the residual limb within the socket, participants will separately walk on a treadmill at a self-selected speed, at a speed 10% faster, and during a step-down task from an 18 cm–high platform. The DSX system will be oriented such that all tasks can be recorded with the same configuration. These movement tasks will be completed under 2 conditions: with the EV suspension active and with the EV system inactive (traditional suction). For testing with the traditional suction suspension (EV inactive), the vacuum connector will be replaced with a PushValve (Ottobock, Inc) [11]. A randomized block, crossover design will be used to evaluate the residual limb-socket fit. A group of 11 participants (group 1) and a group of 10 participants (group 2) will be formed. Participants in group 1 will first be tested in the DSX system with the EV on, and then, they will repeat all procedures with the EV inactive. Participants in group 2 will first be tested in the DSX system with the EV inactive, and then, they will repeat the tasks with the EV active. After each suspension method is applied, participants will be instructed to perform normal daily activities for 2 hours to allow for acclimation and for transient changes (eg, volume loss) to manifest. A period of 2 hours was chosen so that both conditions can be tested on the same day while still capturing 90% of the volume loss during socket use [1]. Up to 4 trials of DSX will be conducted for each task for each socket condition, giving a maximum of 24 trials per participant. For each task, DSX data will be collected and analyzed to determine the underlying bone movement and skin strain with respect to the socket. Separate CT scans of the residual limb and socket will also be captured for each participant to generate participant-specific socket and bone models of the residual limb for tracking kinematics.

DSX technology has a limited field of view (about the size of a basketball). Careful placement of the x-ray sources will permit a view of the knee, tibia, and socket. Because participants will be walking on a treadmill, the DSX setup will likely be able to capture the entire gait cycle; but at a minimum, stance phase will be collected. The 3D kinematics of the thorax, pelvis, lower limbs, and prosthesis will be recorded synchronously using a 6-camera motion capture system (Qualisys Inc). Marker-based motion capture will be used to record the overall position and orientation of the body segments that are out of the viewing volume of the DSX during the movement to establish the participants' overall movement patterns.

Clinical Study CT Scans

After the radiopaque markers have been applied to the residual limb and liner, the socket with embedded brass beads will be donned by the participant and a single CT scan of the residual knee joint and tibia will be acquired while participants lie in the supine position with their socket and liner on and with the knee extended. CT scans provide gray-scale volumes for use with DSX and high-resolution 3D surface models required for computing all outcome variables. CT volume images will be acquired at a resolution of 512×512×0.625 mm^3 (120 kVp; SMART mA). Surface3D (C-Motion Inc) will be used to segment 3D models of the socket, liner, and tibia from the CT volumes.

Quantification of the Relative Motion Between the Residual Bone and the Prosthetic Socket

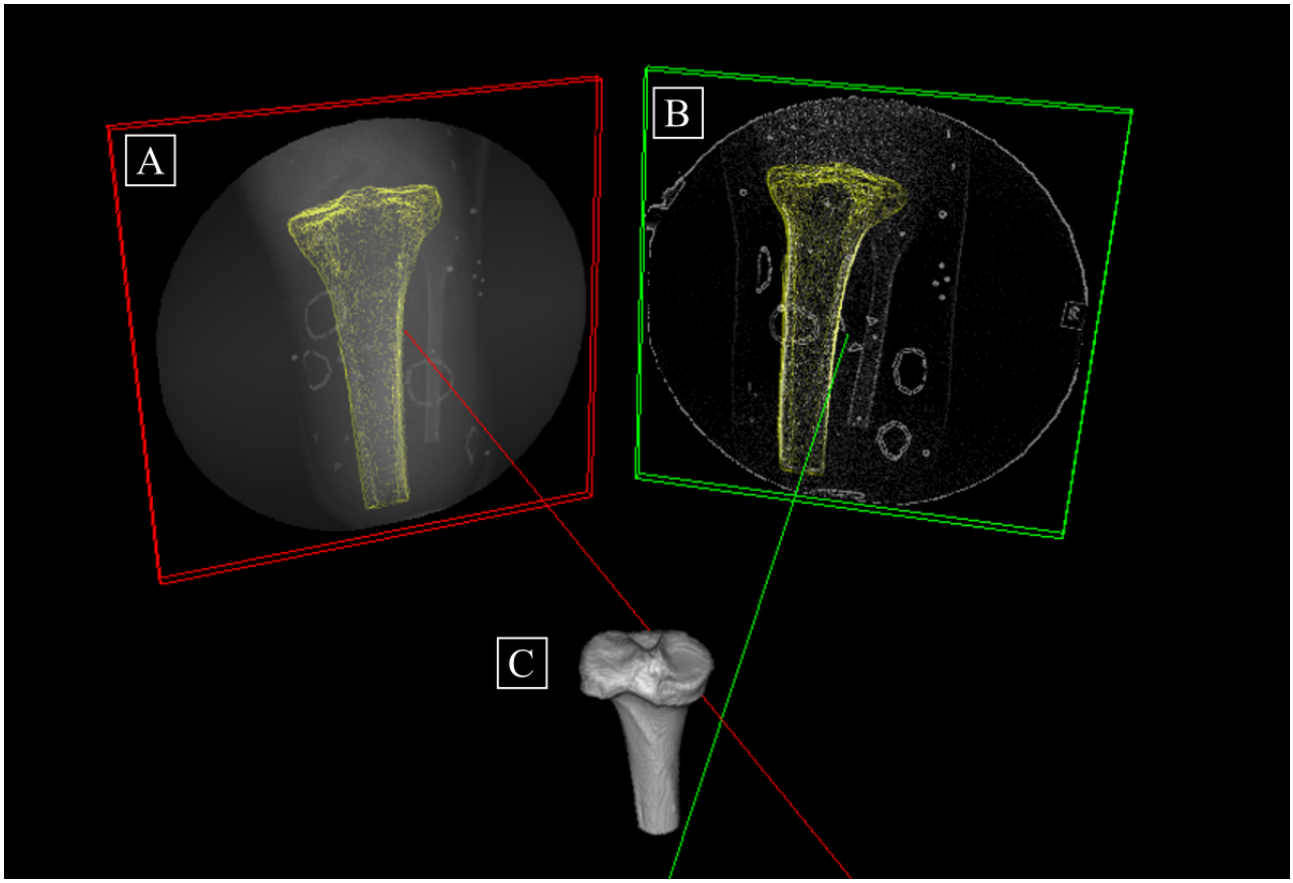
Quantification of the 3D position and orientation of the residual limb has been previously described in detail [23]. In brief, the residual tibia will be tracked throughout the gait cycle, with the coordinate system defined in the CT space using a morphology-based coordinate systems adapted from previous studies [37,38]. These coordinate systems will be registered between Visual3D (C-Motion, Inc) and CT space using the coregistration transformation matrix. The position and orientation (pose) of the socket will also be tracked with 2-mm brass beads secured to the exterior of the prosthetic socket. To provide a context for the relative motion of the residual tibia and socket, 3D infrared motion capture will synchronously be recorded with the DSX data for each participant. Anatomical frames of the thorax, pelvis, and thigh will be constructed by placing retroreflective markers on anatomical locations. Visual3D will be used to establish the anatomical reference frames, estimate the position and orientation of all segments, and compute the kinematics. The reference frames for the socket will be established based on the sagittal plane of the prosthesis. The sagittal plane will be defined by the long axis of the foot. The axial direction will be defined by the pylon. The lateral direction will be perpendicular to the sagittal plane. The anterior direction will be the cross-product of the axial and lateral directions.

To use the same reference frames for both imaging techniques, the global coordinate systems of the optical motion capture and DSX systems will be coregistered by simultaneously capturing the static position of a rigid lattice consisting of 11 radiopaque, spherical markers outfitted with retroreflective tape. The transformation matrix for the coregistration of each global coordinate space will be computed and applied to the respective kinematic data sets. The pose of the socket will be estimated using a standard 6-DOF pose estimation with a set of beads as tracking markers implanted into the socket. The socket reference frame will be established by structural landmarks on the prosthesis in the CT image.

Data Processing

Validation of DSX systems for 3D volumetric model-based tracking has been previously reported [39-41]. For each participant, the residual tibia will be segmented from the CT volume to construct a polygonal mesh of the tibia surface. Digitally reconstructed radiographs (DRRs) created from participant-specific CT scans will be matched to the DSX images in the inline and offset views to calculate the 3D pose of the tibia (Figure 5) [18,41]. DRRs will be generated by positioning the segmented CT volume within a virtual x-ray system and projecting rays through it to create a simulated x-ray image [23]. The optimal position and orientation of the bone will be defined as the pose that maximizes the similarity between the pair of DRR images and their corresponding x-ray images. To track each trial, the tibia will first be manually positioned in every fourth frame of data. Subsequently, a cubic spline will be fitted to the set of manual positions and orientations of the bone, which can be interpolated by the model-based tracking algorithm to determine a pose of the bone in every frame.

Figure 5. A 3D representation of the synchronized x-rays. The inline x-ray image is the red frame (A), whereas the offset x-ray image is the green frame (B). The 3D residual tibia (C) is reconstructed from computed tomography (CT) data. The red and green lines are the perpendiculars from the x-ray image planes to the x-ray sources. The outlines of the tibia (shown in yellow) superimposed over each x-ray image are created by casting rays from each x-ray source through the CT tibia to the x-ray planes.



The algorithm output will be a set of 4×4 transformation matrices representing the pose of the residual tibia. The position and orientation of the socket will be calculated using beads placed on the rigid socket for each time frame. Excursions for relative tibial rotations and translations will be defined as the difference between the maximum and minimum values for each variable within the gait cycle. The differences between the residual bone movement with the EV and traditional suction will be determined in 6 DOF for each participant. Group differences for tibial rotations and translations will be compared at initial contact, toe-off, and swing phase as well as for the total excursions of the residual tibia during the gait cycle.

Quantification of Skin and Liner Deformation

Motion between the bone and the skin (skin deformation) and motion between the skin and the inner surface of the liner will be examined simultaneously with bone movement in the prosthetic socket. Motion between these interfaces can be directly associated with discomfort while wearing a prosthesis [3,30]. In addition, motion between the socket and both the skin

and inner surface of the liner will be examined for a complete understanding of the motion between the limb and the prosthesis.

The results from the cadaver experiments will inform the final placement of markers on the liner and skin. The final number, sizes, shapes, and placement of markers will be based on the results of the cadaver experiments and any potential overlap or bone occlusion. However, the proposed shapes will make identification of the markers in the x-ray images easier and will foster the ability to examine both shear and compression. The ends of each line will be digitized manually from the 2 sets of x-ray images. Reconstruction of the 3D trajectories of the markers will be performed using the DSX software (C-Motion Inc). Visual3D will be used to estimate the deformation of the skin and liner from the relative movement of the markers in the socket reference frame.

Motion of the Skin and Interior of the Liner Relative to the Socket and Residual Tibia

The ends of the lines on the skin and liner will be tracked during the dynamic trials, and their trajectories in the socket coordinate system will define the motion of the skin and liner relative to the socket. Their positions in the socket coordinate system during the static trial will serve as the baseline positions. Visual3D contains the tools to define the socket coordinate system and track the motion of the skin markers within this reference frame. The motion of the lines will also be calculated in the coordinate system of the residual tibia. Their positions in the tibia coordinate system during the stationary trial will serve as their baseline positions. The tibia coordinate system will be defined to track the motion of the skin and liner markers within this reference frame.

Deformation of the Skin

Deformation of the skin will be evaluated in the same way as in the cadaver experiments. In brief, 2 primary metrics will be used to quantify skin deformation: shear and compression. For shear, the end points from the lines will be digitized and the 3D trajectories will be used to reconstruct the 3D shape of the line at each time frame. The angles between the lines will be measured in the static pose to quantify the baseline skin shear. The change in angle will be measured during each dynamic task. Shear will be measured as the change in angle relative to the angle in the static position. Compression will be calculated by the change in distance between lines as well as a neutral position. As with shear, baseline distances will be calculated from the static trial.

Data and Statistical Analysis

Overview

Descriptive statistics will be used to summarize demographic and continuous baseline variables. Median and IQR will be used to classify nonnormal or ordinal data. For the clinical experiment, a between-participant factor at 2 levels (EV on and EV off) will be used. The interaction of the suspension condition (EV on or off) will determine the efficacy of the EV system on the outcome measures.

Bone Movements

The differences between the residual bone movement with the EV and the traditional suction suspension will be determined in 6 DOF for each participant. Briefly, group differences for tibial rotations and translations as well as total excursions of the bone for each suspension condition will be compared during the gait cycle. Paired *t* tests will be performed and a between-participant factor at 2 levels (EV on and EV off) will be used. A hierarchical linear model will be used to evaluate the tibial range of motion (ie, maximum translation and rotation) as a function of tibial position and potential confounding factors (eg, gender, age, etiology, and time since limb loss). The hierarchical linear model will also be used to evaluate the tibial motion path and the effect of rate during the 3 different activities.

Skin and Liner Deformation

The characterization of 3D skin deformation will be performed by comparing the 3D position of the skin markers at rest, or unloaded position, to the 3D positions of the markers when deformed during each task to produce relative strain assessments for marked regions of the residual limb. The characterization of 3D deformation will be measured between the suspension methods. Paired *t* tests will be performed as previously described for bone movements. Linear regression models will be used to evaluate the potential confounding factors.

Power Analysis

Table 1 outlines the sample size estimate required to achieve 90% power for the key variables of interest. A previous pilot investigation for individuals with transfemoral limb loss [23] indicated an effect size of 0.77 for residual femur axial translation. Assuming an α of .05, using paired *t* tests, 21 participants are required to achieve 90% power to detect a 0.5 cm difference in axial translation. Owing to the paucity of highly accurate data on movement between the residual tibia and socket, data from Board et al [1] were used to calculate an effect size for tibia translation (1.75) for suction and EV suspension. Given an effect size of 1.75 and an α of .05 for a paired *t* test, a sample size of 21 will be powered at >99% to detect differences between EV on and off. For skin strain, Gale et al [30] found a maximum shear strain of approximately 0.08. Assuming a shear strain of 0.08 with a moderate effect size of 0.75 (α=.05), a sample size of 21 will be required to achieve 90% power to detect differences between EV on and off.

Table 1. Power analysis.

Measure	Values, mean (SD)	Sample size for achieving 90% power, n
Femur distal translation (cm)	2.0 (0.6)	21
Tibial translation (cm)	4.0 (0.4)	6
Skin shear strain	0.08 (0.02)	21

Results

This study was funded in October 2021. Cadaver testing began in January 2023. Enrollment began in February 2024. Clinical data collection is expected to be completed in December 2025, and the study is expected to be completed in April 2026. Data analysis of the full data set will begin after final data collection. Initial dissemination of results is expected in November 2026, with subsequent publication of secondary analyses in 2027.

Discussion

Expected Outcomes and Anticipated Principal Findings

It is expected that the outcomes of this investigation will significantly contribute to the understanding of the complex mechanics of the residual limb-tissue-socket interfaces during dynamic activities for individuals with lower limb loss. It is also expected that by using DSX in combination with novel mathematical algorithms, relative movement between the residual limb and socket and skin deformation can be accurately measured during dynamic motions for individuals with lower limb loss. Ultimately, this foundational information can be critical for developing a database of biomechanical socket parameters deemed important for socket fit, limb health, and comfort. By using the techniques developed in this investigation to perform future comparative effectiveness research of current prosthetic socket technology, better information about the benefits, risks, and costs of different socket options can be generated to provide health care decision makers (eg, patients, clinicians, and policy makers) with highly accurate, evidence-based information. Furthermore, the methodology detailed in this study should speed up the processing time, which, to date, has been burdensome for researchers. This will allow for faster dissemination of information and greater throughput of data to inform clinical guidelines for prosthetic suspension systems. Finally, this investigation can provide vital foundational information that can be used by leading manufacturers in prosthetic design to create enhanced socket technology that has the potential to reduce long-term secondary physical comorbidities and degenerative changes [42].

As the number of individuals with limb loss continues to grow [43], substantial resources will be required for rehabilitation and prosthetic services for this population. Effective outcomes-based clinical practice will be necessary to reduce long-term disabilities associated with prosthetic use. As such, it is the objective of this investigation to examine the dynamic in vivo kinematics between the residual limb and prosthetic socket in 6 DOF of motion, as well as to quantify residual tissue and liner deformation for individuals with transtibial limb loss.

Dissemination Plan

For large-scale dissemination in the Department of Veterans Affairs and Department of Defense, results will be presented through webinars offered by the Extremity Trauma and Amputation Center of Excellence, which are available across the entire Department of Veterans Affairs and Department of Defense health care networks. These webinars are offered to researchers and health care professionals who provide care for individuals with limb loss. For stakeholders in the civilian health care systems, the outcomes and important techniques developed in this study will be published in highly rated peer-reviewed scientific journals (eg, *Gait & Posture, Clinical Biomechanics, Journal of Biomechanics, Frontiers,* and *Orthotics and Prosthetics International*). The results will also be presented at professional conferences that are specific to clinical limb loss care teams (eg, the American Academy of Orthotists and Prosthetists, American Society of Biomechanics, and Military Health System Research Symposium). The findings and methods of this study will also be directly distributed to industry partners. Because most prosthetic technologies used by veterans and service members with limb loss are developed by industrial entities, sharing new evidence-based information with industry leaders will support the development of future products to better meet the needs of individuals with lower limb loss.

Limitations

The heterogeneity of the population, including varied ages, etiology of limb loss, prosthesis experience, and time since limb loss, may limit the generalizability of the outcomes to a more diverse population. However, the statistical analysis models will adjust for these specific confounding factors. Although participants will use the same type of prosthetic socket, the ankle-foot devices will not be prescribed, which could introduce additional variability. The tibia and skin markers will likely be manually positioned at every fourth to tenth time frame, which may cause intratracker errors that could be improved with automated algorithms. Finally, the limited field of view for DSX may restrict collecting data for the entire gait cycle and will be unable to record the overall position and orientation of the lower limbs and pelvis that are out of view.

Acknowledgments

At the Department of Veterans Affairs New York Harbor Healthcare System, the authors would like to acknowledge Eric Baksh for assisting with socket fabrication and socket alignment during stance simulator testing as well as Kenneth Breuer for his assistance during protocol design. The Rutgers Orthopeadic Department would like to thank the radiology department at the Rutgers School of Dental Medicine for assisting with the preclinical computed tomography (CT) scans. The authors would also like to thank Dr Sheldon Lin, Dr Joe Ippolito, and Dr Joseph Galloway for conducting cadaveric amputation procedures. The authors would like to thank the radiology department at University Hospital for assisting with pre- and postclinical CT scans. Finally, the authors would like to acknowledge the Narrows Institute for Biomedical Research and Education for their assistance in grant management. This work was supported by a Veterans Affairs Merit Review Award (I01 RX003700) from the United States Department of Veterans Affairs, Rehabilitation Research and Development Service. This funding source had no role in

the design of this study and will not have any role during its execution, analyses, and interpretation of the data or in the decision to submit results.

Data Availability

All data generated or analyzed during this study are included in this published paper. The final results will be available via a publicly available data repository.

Disclaimer

The views expressed in this paper are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the US government. The identification of specific products or scientific instrumentation is considered an integral part of the scientific endeavor and does not constitute endorsement or implied endorsement on the part of the authors, the Department of Veterans Affairs, or any component agency.

Authors' Contributions

JTM, JPL, and SED participated in the conceptualization of the study. JTM, JMC, DVH, DNP, CW, JPL, and SED participated in methodology development. JTM, JMC, DVH, DNP, and CW participated in data collection. JTM, JMC, DVH, DNP, CW, JPO, MJH, JPL, and SED participated in writing, review, and editing of the manuscript. JTM, JPO, and MJH participated in project administration. JTM and JPO participated in supervision of the project and staff. JTM, DNP, JPL, and SED participated in funding acquisition. All authors have read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-reviewed summary statement from the Congressionally Directed Medical Research Programs, Orthotics and Prosthetics Outcomes Research Program.
[PDF File (Adobe PDF File), 89 KB - resprot_v13i1e57329_app1.pdf]

References

1. Board WJ, Street GM, Caspers C. A comparison of trans-tibial amputee suction and vacuum socket conditions. Prosthet Orthot Int 2001 Dec;25(3):202-209. [doi: 10.1080/03093640108726603] [Medline: 11860094]
2. Eshraghi A, Osman NA, Gholizadeh H, Karimi M, Ali S. Pistoning assessment in lower limb prosthetic sockets. Prosthet Orthot Int 2012 Mar;36(1):15-24. [doi: 10.1177/0309364611431625] [Medline: 22269941]
3. Gale T, Yang S, McGough R, Fiedler G, Anderst W. Motion of the residual femur within the socket during gait is associated with patient-reported problems in transfemoral amputees. J Biomech 2020 Nov 09;112:110050. [doi: 10.1016/j.jbiomech.2020.110050] [Medline: 33035840]
4. Dudek NL, Marks MB, Marshall SC, Chardon JP. Dermatologic conditions associated with use of a lower-extremity prosthesis. Arch Phys Med Rehabil 2005 Apr;86(4):659-663. [doi: 10.1016/j.apmr.2004.09.003] [Medline: 15827914]
5. Sengeh DM, Herr HM. A variable-impedance prosthetic socket for a transtibial amputee designed from magnetic resonance imaging data. J Prosthet Orthot 2013;25(3):129-137 [FREE Full text] [doi: 10.1097/jpo.0b013e31829be19c]
6. Moerman KM, Solav D, Sengeh D, Herr H. Automated and data-driven computational design of patient-specific biomechanical interfaces. engrXiv. Preprint posted online August 15, 2016 2016 [FREE Full text] [doi: 10.31224/osf.io/g8h9n]
7. Goh JC, Lee PV, Toh SL, Ooi CK. Development of an integrated CAD-FEA process for below-knee prosthetic sockets. Clin Biomech (Bristol, Avon) 2005 Jul;20(6):623-629. [doi: 10.1016/j.clinbiomech.2005.02.005] [Medline: 15927736]
8. Wernke MM, Schroeder RM, Haynes ML, Nolt LL, Albury AW, Colvin JM. Progress toward optimizing prosthetic socket fit and suspension using elevated vacuum to promote residual limb health. Adv Wound Care (New Rochelle) 2017 Jul 01;6(7):233-239 [FREE Full text] [doi: 10.1089/wound.2016.0719] [Medline: 28736683]
9. Mak AF, Zhang M, Boone DA. State-of-the-art research in lower-limb prosthetic biomechanics-socket interface: a review. J Rehabil Res Dev 2001;38(2):161-174 [FREE Full text] [Medline: 11392649]
10. Papaioannou G, Mitrogiannis C, Nianios G, Fiedler G. Assessment of amputee socket-stump-residual bone kinematics during strenuous activities using dynamic roentgen stereogrammetric analysis. J Biomech 2010 Mar 22;43(5):871-878. [doi: 10.1016/j.jbiomech.2009.11.013] [Medline: 20047746]
11. Darter BJ, Sinitski K, Wilken JM. Axial bone-socket displacement for persons with a traumatic transtibial amputation: the effect of elevated vacuum suspension at progressive body-weight loads. Prosthet Orthot Int 2016 Oct;40(5):552-557. [doi: 10.1177/0309364615605372] [Medline: 26423107]

12. Tucker CJ, Wilken JM, Stinner PD, Kirk KL. A comparison of limb-socket kinematics of bone-bridging and non-bone-bridging wartime transtibial amputations. J Bone Joint Surg Am 2012 May 16;94(10):924-930. [doi: 10.2106/JBJS.K.00605] [Medline: 22617921]
13. Convery P, Murray KD. Ultrasound study of the motion of the residual femur within a trans-femoral socket during gait. Prosthet Orthot Int 2000 Dec;24(3):226-232. [doi: 10.1080/03093640008726552] [Medline: 11195358]
14. Commean PK, Brunsden BS, Smith KE, Vannier MW. Below-knee residual limb shape change measurement and visualization. Arch Phys Med Rehabil 1998 Jul;79(7):772-782. [doi: 10.1016/s0003-9993(98)90355-0] [Medline: 9685090]
15. Smith KE, Commean PK, Bhatia G, Vannier MW. Validation of spiral CT and optical surface scanning for lower limb stump volumetry. Prosthet Orthot Int 1995 Aug;19(2):97-107. [doi: 10.3109/03093649509080351] [Medline: 8570386]
16. Smith KE, Commean PK, Vannier MW. Residual-limb shape change: three-dimensional CT scan measurement and depiction in vivo. Radiology 1996 Sep;200(3):843-850. [doi: 10.1148/radiology.200.3.8756942] [Medline: 8756942]
17. Söderberg B, Ryd L, Persson BM. Roentgen stereophotogrammetric analysis of motion between the bone and the socket in a transtibial amputation prosthesis: a case study. J Prosthet Orthot 2003;15(3):95-99. [doi: 10.1097/00008526-200307000-00008]
18. Bey MJ, Zauel R, Brock SK, Tashman S. Validation of a new model-based tracking technique for measuring three-dimensional, in vivo glenohumeral joint kinematics. J Biomech Eng 2006 Aug;128(4):604-609 [FREE Full text] [doi: 10.1115/1.2206199] [Medline: 16813452]
19. Bey MJ, Kline SK, Tashman S, Zauel R. Accuracy of biplane x-ray imaging combined with model-based tracking for measuring in-vivo patellofemoral joint motion. J Orthop Surg Res 2008 Sep 04;3:38 [FREE Full text] [doi: 10.1186/1749-799X-3-38] [Medline: 18771582]
20. Brainerd EL, Baier DB, Gatesy SM, Hedrick TL, Metzger KA, Gilbert SL, et al. X-ray reconstruction of moving morphology (XROMM): precision, accuracy and applications in comparative biomechanics research. J Exp Zool A Ecol Genet Physiol 2010 Jun 01;313(5):262-279. [doi: 10.1002/jez.589] [Medline: 20095029]
21. Zhang J, Lv L, Shi X, Wang Y, Guo F, Zhang Y, et al. 3-D reconstruction of the spine from biplanar radiographs based on contour matching using the Hough transform. IEEE Trans Biomed Eng 2013 Jul;60(7):1954-1964. [doi: 10.1109/TBME.2013.2246788] [Medline: 23412567]
22. Eshraghi A, Gholizadeh H, Abu Osman NA. Comments on "assessment of amputee socket-stump-residual bone kinematics during strenuous activities using dynamic roentgen stereogrammetric analysis" (volume 43, issue 5, 2010). J Biomech 2011 Nov 10;44(16):2851-2852. [doi: 10.1016/j.jbiomech.2011.05.042] [Medline: 21784425]
23. Maikos JT, Chomack JM, Loan JP, Bradley KM, D'Andrea SE. Effects of prosthetic socket design on residual femur motion using dynamic stereo X-ray - a preliminary analysis. Front Bioeng Biotechnol 2021 Aug 10;9:697651 [FREE Full text] [doi: 10.3389/fbioe.2021.697651] [Medline: 34447740]
24. Laszczak P, McGrath M, Tang J, Gao J, Jiang L, Bader D, et al. A pressure and shear sensor system for stress measurement at lower limb residuum/socket interface. Med Eng Phys 2016 Jul;38(7):695-700. [doi: 10.1016/j.medengphy.2016.04.007] [Medline: 27118308]
25. Graser M, Day S, Buis A. Exploring the role of transtibial prosthetic use in deep tissue injury development: a scoping review. BMC Biomed Eng 2020 Jan 29;2(1):2 [FREE Full text] [doi: 10.1186/s42490-020-0036-6] [Medline: 32903320]
26. Meulenbelt HE, Geertzen JH, Dijkstra PU, Jonkman MF. Skin problems in lower limb amputees: an overview by case reports. J Eur Acad Dermatol Venereol 2007 Feb 20;21(2):147-155. [doi: 10.1111/j.1468-3083.2006.01936.x] [Medline: 17243947]
27. Solav D, Moerman KM, Jaeger AM, Herr HM. A framework for measuring the time-varying shape and full-field deformation of residual limbs using 3-D digital image correlation. IEEE Trans Biomed Eng 2019 Oct;66(10):2740-2752 [FREE Full text] [doi: 10.1109/TBME.2019.2895283] [Medline: 30676943]
28. Lin B, Moerman KM, McMahan CG, Pasch KA, Herr HM. Low-cost methodology for skin strain measurement of a flexed biological limb. IEEE Trans Biomed Eng 2017 Dec;64(12):2750-2759. [doi: 10.1109/tbme.2016.2626442]
29. Sanders JE, Fatone S. Residual limb volume change: systematic review of measurement and management. J Rehabil Res Dev 2011;48(8):949-986 [FREE Full text] [doi: 10.1682/jrrd.2010.09.0189] [Medline: 22068373]
30. Gale T, Yang S, McGough R, Fiedler G, Anderst W. Residual limb shear strain during gait is correlated with patient reported outcomes for persons with transfemoral amputation. J Biomech 2021 Dec 02;129:110826. [doi: 10.1016/j.jbiomech.2021.110826] [Medline: 34717161]
31. Crowe CS, Impastato KA, Donaghy AC, Earl C, Friedly JL, Keys KA. Prosthetic and orthotic options for lower extremity amputation and reconstruction. Plast Aesthet Res 2019 Feb 27;6(4). [doi: 10.20517/2347-9264.2018.70]
32. Remache D, Caliez M, Gratton M, Dos Santos S. The effects of cyclic tensile and stress-relaxation tests on porcine skin. J Mech Behav Biomed Mater 2018 Jan;77:242-249 [FREE Full text] [doi: 10.1016/j.jmbbm.2017.09.009] [Medline: 28954243]
33. Gailey R, McFarland LV, Cooper RA, Czerniecki J, Gambel JM, Hubbard S, et al. Unilateral lower-limb loss: prosthetic device use and functional outcomes in servicemembers from Vietnam war and OIF/OEF conflicts. J Rehabil Res Dev 2010;47(4):317-331 [FREE Full text] [doi: 10.1682/jrrd.2009.04.0039] [Medline: 20803401]

34. Legro MW, Reiber GD, Smith DG, del Aguila M, Larsen J, Boone D. Prosthesis evaluation questionnaire for persons with lower limb amputations: assessing prosthesis-related quality of life. Arch Phys Med Rehabil 1998 Aug;79(8):931-938. [doi: 10.1016/s0003-9993(98)90090-9] [Medline: 9710165]
35. Kahle JT, Highsmith MJ, Hubbard SL. Comparison of nonmicroprocessor knee mechanism versus C-Leg on Prosthesis Evaluation Questionnaire, stumbles, falls, walking tests, stair descent, and knee preference. J Rehabil Res Dev 2008;45(1):1-14 [FREE Full text] [doi: 10.1682/jrrd.2007.04.0054] [Medline: 18566922]
36. Hanspal RS, Fisher K, Nieveen R. Prosthetic socket fit comfort score. Disabil Rehabil 2003 Nov 18;25(22):1278-1280. [doi: 10.1080/09638280310001603983] [Medline: 14617445]
37. Miranda DL, Rainbow MJ, Leventhal EL, Crisco JJ, Fleming BC. Automatic determination of anatomical coordinate systems for three-dimensional bone models of the isolated human knee. J Biomech 2010 May 28;43(8):1623-1626 [FREE Full text] [doi: 10.1016/j.jbiomech.2010.01.036] [Medline: 20167324]
38. Rainbow MJ, Miranda DL, Cheung RT, Schwartz JB, Crisco JJ, Davis IS, et al. Automatic determination of an anatomical coordinate system for a three-dimensional model of the human patella. J Biomech 2013 Aug 09;46(12):2093-2096 [FREE Full text] [doi: 10.1016/j.jbiomech.2013.05.024] [Medline: 23791087]
39. Miranda DL, Schwartz JB, Loomis AC, Brainerd EL, Fleming BC, Crisco JJ. Static and dynamic error of a biplanar videoradiography system using marker-based and markerless tracking techniques. J Biomech Eng 2011 Dec;133(12):121002 [FREE Full text] [doi: 10.1115/1.4005471] [Medline: 22206419]
40. Miranda DL, Rainbow MJ, Crisco JJ, Fleming BC. Kinematic differences between optical motion capture and biplanar videoradiography during a jump-cut maneuver. J Biomech 2013 Feb 01;46(3):567-573 [FREE Full text] [doi: 10.1016/j.jbiomech.2012.09.023] [Medline: 23084785]
41. Anderst W, Zauel R, Bishop J, Demps E, Tashman S. Validation of three-dimensional model-based tibio-femoral tracking during running. Med Eng Phys 2009 Jan;31(1):10-16 [FREE Full text] [doi: 10.1016/j.medengphy.2008.03.003] [Medline: 18434230]
42. Mbithi FM, Chipperfield AJ, Steer JW, Dickinson AS. Predictive control for an active prosthetic socket informed by FEA-based tissue damage risk estimation. In: Proceedings of the 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society. 2019 Presented at: EMBC '19; July 23-27, 2019; Berlin, Germany p. 2073-2076 URL: https://ieeexplore.ieee.org/document/8857155 [doi: 10.1109/embc.2019.8857155]
43. Ziegler-Graham K, MacKenzie EJ, Ephraim PL, Travison TG, Brookmeyer R. Estimating the prevalence of limb loss in the United States: 2005 to 2050. Arch Phys Med Rehabil 2008 Mar;89(3):422-429. [doi: 10.1016/j.apmr.2007.11.005] [Medline: 18295618]

Abbreviations

CT: computed tomography
DIC: digital image correlation
DOF: degrees of freedom
DRR: digitally reconstructed radiograph
DSX: dynamic stereo x-ray
EV: elevated vacuum
PEQ: Prosthesis Evaluation Questionnaire
VA: Veterans Affairs

Edited by A Mavragani; submitted 13.02.24; this is a non–peer-reviewed article;accepted 04.03.24; published 26.04.24.

Please cite as:
Maikos JT, Chomack JM, Herlihy DV, Paglia DN, Wetterstrand C, O'Connor JP, Hyre MJ, Loan JP, D'Andrea SE
Quantifying Bone and Skin Movement in the Residual Limb-Socket Interface of Individuals With Transtibial Limb Loss Using Dynamic Stereo X-Ray: Protocol for a Lower Limb Loss Cadaver and Clinical Study
JMIR Res Protoc 2024;13:e57329
URL: https://www.researchprotocols.org/2024/1/e57329
doi:10.2196/57329
PMID:38669065

Protocol

Social Transfers for Exclusive Breastfeeding (STEB) Intervention in Lao People's Democratic Republic: Protocol for a Randomized Controlled Trial

Souliviengkham Sonephet[1], MD; Sengchanh Kounnavong[1], MD, PhD; Lucienne Zinsstag[2], MS; Pascale Vonaesch[3], MPH, MSc, PhD; Somphou Sayasone[1], MSc, PhD; Latsamy Siengsounthone[1], PhD; Peter Odermatt[2,4], MSc, PhD; Günther Fink[2,4], MSc, PhD; Jordyn Tinka Wallenborn[2,4], MPH, PhD

[1]Lao Tropical and Public Health Institute, Vientiane, Lao People's Democratic Republic

[2]Department of Epidemiology and Public Health, Swiss Tropical and Public Health Institute, Allschwil, Switzerland

[3]Department of Fundamental Microbiology, University of Lausanne, Lausanne, Switzerland

[4]University of Basel, Basel, Switzerland

Corresponding Author:
Jordyn Tinka Wallenborn, MPH, PhD
Department of Epidemiology and Public Health
Swiss Tropical and Public Health Institute
Kreuzstrasse 2
Allschwil
Switzerland
Phone: 41 765250183
Email: jordyn.wallenborn@swisstph.ch

Abstract

Background: Children in Lao People's Democratic Republic (Lao PDR) receive suboptimal nutrition because of low breastfeeding rates, undermining their developmental potential. While major public health campaigns have attempted to increase breastfeeding rates, they have been largely unsuccessful. One explanation for these unsuccessful interventions is the economic and financial constraints faced by mothers. A potential solution for alleviating these pressures is providing social transfers to support breastfeeding; defined as a cash or in-kind transfer. Capitalizing on key strategies used in previous social transfer programs, we will assess the effectiveness of social transfer intervention for increasing exclusive breastfeeding rates in Vientiane, Lao PDR.

Objective: This study aims to conduct a randomized controlled trial (RCT) designed to assess whether social transfers can increase exclusive breastfeeding rates in Vientiane Capital, Lao PDR.

Methods: A prospective, parallel cluster-RCT was conducted among 300 mothers who recently gave birth and initiated breastfeeding. Enrolling 100 participants for each intervention arm provided us with 80% power to detect an increase in exclusive breastfeeding from the anticipated 21% in the control arm to 40% in either of the 2 intervention arms. Mother-infant dyads were enrolled at approximately 1 month post partum. Follow-up visits will occur at 6 months, 1 year, 2 years, and 3 years post partum; with the ambition to extend the follow-up period. Mother-infant dyads were enrolled between August 2022 and April 2023 with follow-up until 3 years post partum (2026). A local study team comprised of 2 nurses and 2 laboratory technicians is responsible for enrollment and follow-up of participants. Participants were randomly assigned to one of three groups during the baseline, 1-month visit: (1) control group, no social transfer; (2) intervention group 1, an unconditional social transfer at 6 months post partum; and (3) intervention group 2, a social transfer at 6 months post partum conditional upon mothers exclusively breastfeeding. All groups received educational materials supporting mothers to exclusively breastfeed. The primary end point will be exclusive breastfeeding at 6 months post partum. Secondary end points will include exclusive and complementary breastfeeding duration, childhood wasting and stunting, child growth, maternal and infant stress, predictors of early breastfeeding cessation, intestinal inflammation, anemia, maternal weight loss, maternal blood pressure, maternal anxiety, and GRIT personality score. Questionnaires and physical examinations were used to collect information.

Results: As of November 2023, the study has enrolled 300 participants. Study participation is ongoing until December 2026 at minimum. Over the study lifetime, 93% have completed all visits.

Conclusions: We see potential for a long-term program that may be implemented in other low- or lower-middle-income countries with only minor modifications. The RCT will be used as a basis for observational studies and to investigate the impact of human milk on child fecal microbiota and growth.

Trial Registration: ClinicalTrials.gov NCT05665049; https://clinicaltrials.gov/study/NCT05665049

International Registered Report Identifier (IRRID): DERR1-10.2196/54768

(JMIR Res Protoc 2024;13:e54768) doi:10.2196/54768

KEYWORDS

breastfeeding; lactation; human milk; breastmilk; child; infant; health; growth and development; cash transfer; incentive; intervention

Introduction

Breastfeeding provides important benefits for infants and societies [1,2]. Despite its well-known and widespread benefits, breastfeeding rates remain low in many parts of the world. In Vientiane, the capital of Lao People's Democratic Republic (Lao PDR), only 21% of children aged 0-5 months were exclusively breastfed, and less than half (42.3%) were predominantly breastfed in 2017 [3]. Complying with the World Health Organization's breastfeeding recommendations can help countries meet the United Nation's sustainable development goals with respect to good health and well-being, economic growth, and reduced inequalities [4].

Even though most mothers recognize the benefits of breastfeeding, they also face a complex web of factors that make breastfeeding difficult, including formal labor commitments without sufficient parental leave or breastfeeding support, and television ads promoting infant formula [5,6]. Over the last 30 years, the Ministry of Health in Lao PDR has attempted to increase breastfeeding rates through standard public health behavior change campaigns, including a safe motherhood program and a large United Nations children's fund supported exclusive breastfeeding promotion campaign; however, these programs were largely unsuccessful [5].

One probable explanation for these unsuccessful interventions is the economic and financial constraints faced by mothers. A potential solution for alleviating these pressures is providing social transfers to support breastfeeding; defined as a cash or in-kind transfer. Evidence suggests that social transfers have helped increase breastfeeding rates in other settings. In a previous experiment, Puerto Rican mothers were provided US $25 per month after successful observation of breastfeeding (ie, conditional cash transfer), which resulted in significantly higher breastfeeding rates at 6 months postpartum compared with mothers who did not receive the cash transfer [7]. A similar model providing a social transfer with a letter encouraging mothers to spend time with their infant (ie, labeled social transfer) in a US neonatal intensive care unit increased the daily provision of breastmilk [8]. However, all evidence on social transfer programs for breastfeeding comes from high-income countries. In fact, no study has implemented a social transfer program for breastfeeding promotion in low- or middle-income countries despite a large number of successful social transfer programs targeting other health behaviors in these settings [9].

Capitalizing on key strategies used in previous social transfer programs, we will assess the effectiveness of social transfer programs for increasing breastfeeding rates in Vientiane, Lao PDR. A previous qualitative, community-engaged project in Vientiane focused on identifying breastfeeding norms and social transfers that would support breastfeeding mothers (unpublished data). Using the results from this study, we designed a culturally grounded social transfer program that is responsive to the identified needs of new mothers.

The overall objectives of this project are to assess (1) the effect of social transfers on exclusive and complementary breastfeeding duration and (2) the long-term impacts of breastfeeding on child development.

Methods

Overview

The Social Transfers for Exclusive Breastfeeding (STEB) is a prospective, parallel cluster-randomized trial in the Vientiane Capital, of Lao PDR. Mother-infant dyads will be enrolled at approximately 1 month post partum and followed for 3 years; with the ambition to extend the follow-up period. The study period runs from August 2022 to December 2026.

Participants and Recruitment

Our study is nested within an ongoing birth cohort (the Vientiane Multigenerational Birth Cohort [VITERBI]). Women were recruited for VITERBI if they (1) lived in one of the following districts of Vientiane: Chanthabuly, Sikhottabong, Sangthong, or Mayparkngum; (2) had an expected due date/or gave birth between July 1, 2022, and June 30, 2023; (3) did not plan to permanently move outside the study area; (4) did not have a medical, intellectual, or psychological disability; and (5) agreed to participate and sign an informed consent; if younger than 18 years, a legal representative had to agree to sign the informed consent.

The target sample size for the STEB randomized control trial was 300 mothers and their children. All pregnant women enrolled in VITERBI were eligible to participate in our study if they gave birth within the last 4 weeks, were exclusively breastfeeding at the time of recruitment, had no illnesses that contraindicate breastfeeding, and had a healthy singleton infant of 37 weeks or more gestation with a birth weight of at least 2500 g.

A local study team comprised of 2 nurses and 2 laboratory technicians was responsible for enrollment and follow-up of participants. Using pregnancy records from VITERBI, a list of potential participants was created. In order to identify women

who recently gave birth (≤1 month), the following data were used: (1) approximate due date or (2) weeks gestation when an approximate due date was not provided. When both variables were missing, the average week of gestation was set at 40 weeks and added to the interview date to provide the latest possible birth date. All potential participants were screened on a telephone call to ensure they met the eligibility criteria. If the participant met the inclusion criteria and agreed to participate in the study, a baseline visit was scheduled.

Sample Size Calculation and Power

Enrolling 100 participants for each intervention arm provided us with 80% power to detect an increase in exclusive breastfeeding from the anticipated 21% in the control arm to 40% in either of the 2 intervention arms.

Study Logistics

During the baseline visit, if informed consent was given, a random number was generated within the Open Data Kit (ODK) platform that assigned the mother to a control or intervention group. If they were randomly assigned to an intervention group, mothers were allowed to choose from the following social transfers: (1) money (US $75); (2) developmental toys, clothes, and diapers for the child; or (3), a combination of money and developmental toys, clothes, and diapers for the child (Figure 1). We created a shopping catalog with different toys and clothes for them to choose from. At the end of the visit, the study team encouraged intervention group 1 to meet their breastfeeding goals and told them that the social transfer would be provided at 6 months post partum to show our support for their breastfeeding efforts. Mothers randomly selected for the third intervention arm were told that they would only receive their social transfer if they exclusively breastfed and nurses could observe breastmilk expression at the 6-month visit. All intervention and control groups received educational material about the benefits and recommendations of exclusive breastfeeding.

During a follow-up visit when the child is 6 months of age, nurses will collect an end-line survey from mothers, collect infant fecal samples, and observe breastmilk expression.

Figure 1. Screenshot from shopping catalog for Social Transfers for Exclusive Breastfeeding (STEB) participants.

Data Collection Instruments

Overview

STEB has a total of five questionnaires: (1) a screening questionnaire to assess eligibility; (2) baseline enrollment conducted at approximately 1 month post partum; (3) an endline questionnaire at 6 months post partum; (4) a follow-up visit at 1 year post partum; and (5) a follow-up visit at 2 years post partum. All source documents were created in English and translated into Lao. We briefly describe each questionnaire below.

Screening Questionnaire

A screening questionnaire was conducted on the telephone in order to assess the inclusion and exclusion criteria. A maximum of 10 questions were asked. If an answer to one of the questions rendered them ineligible for the study, no further questions were asked. Questions included date of birth and expected birth date in order to determine prematurity of the infant, birth parity, birthweight, current breastfeeding status, breastfeeding exclusivity, long-term medical problems of the infant, and if the mother experiences galactosemia, human immunodeficiency virus, human T-cell lymphotropic virus type 1 or 2, illicit drug use (ie, cocaine), Ebola, artificial breast implants, or infectious tuberculosis.

Baseline—1 Month Postpartum

The baseline questionnaire is conducted at approximately 1 month post partum and includes employment questions, the short Grit scale [10], family and gender roles, child health and vitamin, mineral or other medicine intakes, breastfeeding and infant feeding, Breastfeeding Self-Efficacy Scale–short form [11], and maternal diet. The Demographic and Health Surveys household characteristics questionnaire. Hemoglobin levels of the mother and infant were taken using the HemoCue Hb 301. Biospecimen samples included infant feces, human milk, and a saliva sample from the mother and infant. Anthropometric measurements of the child included skinfold thickness of the triceps, subscapular, quadriceps, and flank, weight, length, mid-upper arm circumference (MUAC), and head circumference. Anthropometric measurements of the mother included skinfold thickness of the triceps, subscapular, quadriceps, and flank, blood pressure, height, weight, and heart rate.

Endline—6 Months Postpartum

The endline questionnaire is conducted at approximately 6 months post partum and includes employment questions; child health; vitamin, mineral, or other medicine intake; breastfeeding and infant feeding; maternal diet; participation in cultural postpartum activities (eg, hotbeds and mother roasting); perceived stress scale [12]; Postpartum Specific Anxiety Scale [13]; and caregiver-reported early development instruments [14]. A variety of additional health measurements were assessed. Hemoglobin levels of the mother and infant were taken using the HemoCue Hb 301. Biospecimen samples include infant feces, human milk, and a saliva sample from the mother and infant. Anthropometric measurements of the child included skinfold thickness of the triceps, subscapular, quadriceps, and flank, weight, length, MUAC, and head circumference. Anthropometric measurements of the mother included skinfold thickness of the triceps, subscapular, quadriceps, and flank, blood pressure, height, weight, and heart rate.

1- and 2-Year Follow-Up

Visits will occur at 1, 2, and 3 years post partum (SD 1 month). The questionnaire includes child health and vitamin, mineral or other medicine intake; breastfeeding and infant feeding; maternal diet; alcohol consumption; Postpartum Specific Anxiety Scale [13]; Edinburgh Postnatal Depression Scale [15]; and the brief infant sleep questionnaire–short form [16]. At 1 year post partum, child development will be assessed using caregiver-reported early development instruments [14]. At 2 and 3 years post partum, child development will be assessed using the Global Scale for Early Development [17]. Hemoglobin levels of the mother and infant will be taken using the HemoCue Hb 301. Biospecimen samples include infant feces and human milk. Anthropometric measurements of the child included foot length, skinfold thickness of the triceps, subscapular, quadriceps, and flank, weight, length, MUAC, and head circumference. Anthropometric measurements of the mother included skinfold thickness of the triceps, subscapular, quadriceps, and flank, blood pressure, height, weight, and heart rate.

Retention of Participants

In order to reduce participant dropout, we collect a variety of contact information. Participants provide their first and family name, address, phone number, email address, village leader name, temple or religious organization, and the contact information of a family member or close friend. In addition, we provide a small incentive. Immediately after the physical examination, all participants receive the test results for both the mother and child and can track their progress over time at each visit. Test results include blood pressure, hemoglobin levels, and all anthropometric values. Results are explained in person and written on an information pamphlet. All participants who complete the baseline questionnaire receive a small gift that equates to approximately US $1.

Outcomes

The primary end point will be exclusive breastfeeding at 6 months postpartum. Secondary end points will include exclusive and complementary breastfeeding duration, childhood wasting and stunting, child growth (height and weight), maternal and infant stress, predictors of early breastfeeding cessation, intestinal inflammation, anemia, maternal weight loss, maternal blood pressure, maternal anxiety, and GRIT personality score.

Data Management

The ODK is used for all questionnaires and data management. All study staff have access to an Android tablet with the ODK Collect app. Data collection is completed offline on password-protected devices. Data connectivity is only used to send the final questionnaire data.

Project data will only be accessible to authorized personnel who require the data to fulfill their duties within the scope of the research project. On the case report forms and other project-specific documents, participants are only identified by a unique participant number. The unique participant number will be taken directly from VITERBI, and is a combination of

the household number, district, village, and individual within the household. Health-related data will be stored for 15 years, following institutional storage and safety policies. Only samples will be kept for an unidentified amount of time if the separate consent for reuse of health data has been signed. Data storage is on a locally secured server using the ODK Aggregate server and secured via a secure sockets layer.

Biological material in this project is not identified by participant name but by a unique participant number. Biological material is appropriately stored in a restricted area only accessible to authorized personnel. The biological specimens will be stored with their code at Lao TPHI and Swiss TPH.

Ethical Considerations

Ethical approval for the study was obtained from the Ethics Commission of Northwestern and Central Switzerland (EKNZ, 2020-00037) and from the National Ethic Committee for Health Research (044/NECHR; June 30, 2021). This research project will be conducted in accordance with the protocol, the Declaration of Helsinki [3], the Swiss Human Research Act, and the Swiss Human Research Ordinance [1], as well as other locally relevant regulations. Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research. Eligible participants will be visited initially by study staff. The purpose of the study and its procedures will be explained to participants and written informed consent will be obtained. Pregnant women will be giving consent for themselves and their newborns. For minors (aged <18 years), both the pregnant woman and her parents will provide consent. For participants who are illiterate, there will be an additional witness who is not part of the study team. Participation is voluntary and patients have the right to withdraw from the study at any given point in time with no further obligations. If the participant withdraws at any time, all data will be deleted and biospecimen samples destroyed. Confidentiality of information will be assured to the participants. All participants younger than 18 years are considered vulnerable populations according to the Lao PDR legislation. If the respondent is underage and agrees to participate, he or she needs the authorization of a parent or legal guardian, who cosigns the study informed consent.

Results

As of November 2023, the study has enrolled 300 participants. Study participation is ongoing until December 2027 at minimum. Over the study lifetime, 93% have completed all visits. Primary results from the 6-month visit are expected in early 2024.

Discussion

Conditional cash transfer programs have been used in a wide range of settings to reduce poverty, with proven benefits for short- and long-term health [18]. STEB is to our knowledge the first longitudinal and randomized social transfer program evaluation for breastfeeding in a low- or middle-income country. We will follow participants for a minimum of 3 years post partum—providing an excellent platform to investigate the short- and long-term benefits of a breastfeeding social transfer program.

During the first year of the program, we encountered a variety of barriers. To start, enrolling new mothers at approximately 1 month post partum was difficult due to the high rates of infant formula use. We strategically enrolled at 1 month post partum to reduce coercion among mothers who did not want to breastfeed. However, a large majority of mothers provided infant formula before 1 month post partum. Enrolling mothers earlier in the postpartum period who want to exclusively breastfeed may reduce the early introduction of infant formula. Second, distances between the 4 study districts in Vientiane, Lao PDR are large. Transportation of staff to the rural districts is a major challenge because of the time spent traveling and the high burden of transportation costs. For example, during the rainy season, many streets become impassable—reducing the capabilities of the study staff to reach participants. Collection of infant fecal samples at 1-month was also difficult because of the irregularity of bowel movements at this age.

Despite the substantial size of the social transfers made, we believe that interventions that include financial support for breastfeeding can be highly cost-effective in this setting. In 7 Southeast Asian countries alone, the short- and long-term benefits of breastfeeding are estimated at US $1.9 billion a year [1]. We believe that social transfer programs focused on breastfeeding have the potential to be more effective in low- or middle-income countries, where monetary compensation may reduce additional barriers not present in high-income countries.

STEB has some limitations worth noting. The small sample size will prohibit more nuanced data analysis. Enrollment does not occur immediately after birth; instead, all participants are enrolled at 1-month post partum. Many mothers face significant barriers to exclusive breastfeeding during the first month postpartum; therefore, the study population of STEB may be slightly different. Recall of the exact timing of complementary foods provided is likely biased; yet, previous research has shown that recall bias for breastfeeding is minimal.

STEB was designed to provide a unique platform to investigate the short- and long-term impacts of exclusive and complementary breastfeeding on child health and development. Further, the longitudinal sampling of human milk and infant feces provides a unique opportunity to study human milk as a biological system and how this impacts the gut microbiome. If proven effective, we see potential for a long-term program that may be implemented in other low- or lower-middle-income countries with only minor modifications.

Acknowledgments

This work was supported by the Swiss National Science Foundation (grant 208782) and the University of Basel Forschungsfonds (grant 3ZX1407). PV was further supported by an Eccellenza grant from the Swiss National Science Foundation (grant PCEFP3_194545).

Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Authors' Contributions

SK and GF made substantial contributions to the conception and design of the study. S Sonephet, LZ, PV, S Sayasone, PO, and LS contributed to the acquisition of data and revised the manuscript. JTW made a substantial contribution to the conception and design of the study, the acquisition of data, and drafted the manuscript. All authors approve the submitted version and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated, resolved, and the resolution documented in the literature.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report by the Swiss National Science Foundation.
[PDF File (Adobe PDF File), 272 KB - resprot_v13i1e54768_app1.pdf]

References

1. Walters D, Horton S, Siregar AYM, Pitriyan P, Hajeebhoy N, Mathisen R, et al. The cost of not breastfeeding in Southeast Asia. Health Policy Plan 2016;31(8):1107-1116 [FREE Full text] [doi: 10.1093/heapol/czw044] [Medline: 27107295]
2. Wallenborn JT, Levine GA, Dos Santos AC, Grisi S, Brentani A, Fink G. Breastfeeding, physical growth, and cognitive development. Pediatrics 2021;147(5):e2020008029 [FREE Full text] [doi: 10.1542/peds.2020-008029] [Medline: 33888567]
3. Bureau LS. Lao social indicator survey II 2017, survey findings report. Lao Statistics Bureau and UNICEF. Vientiane; 2018. URL: https://dhsprogram.com/pubs/pdf/FR356/FR356.pdf [accessed 2024-04-05]
4. León-Cava N, Lutter C, Ross J, Martin L. Quantifying the Benefits of Breastfeeding: A Summary of the Evidence. Washington, D.C: The Food and Nutrition Program (HPN), Pan American Health Organization (PAHO); 2002.
5. Lee HMH, Durham J, Booth J, Sychareun V. A qualitative study on the breastfeeding experiences of first-time mothers in Vientiane, Lao PDR. BMC Pregnancy Childbirth 2013;13:223 [FREE Full text] [doi: 10.1186/1471-2393-13-223] [Medline: 24304510]
6. Wallenborn JT, Valera CB, Kounnavong S, Sayasone S, Odermatt P, Fink G. Urban-rural gaps in breastfeeding practices: evidence from Lao People's Democratic Republic. Int J Public Health 2021;66:1604062 [FREE Full text] [doi: 10.3389/ijph.2021.1604062] [Medline: 34566553]
7. Washio Y, Humphreys M, Colchado E, Sierra-Ortiz M, Zhang Z, Collins BN, et al. Incentive-based intervention to maintain breastfeeding among low-income Puerto Rican mothers. Pediatrics 2017;139(3):e20163119 [FREE Full text] [doi: 10.1542/peds.2016-3119] [Medline: 28167511]
8. Andrews KG, Martin MW, Shenberger E, Pereira S, Fink G, McConnell M. Financial support to medicaid-eligible mothers increases caregiving for preterm infants. Matern Child Health J 2020;24(5):587-600. [doi: 10.1007/s10995-020-02905-7] [Medline: 32277384]
9. Floate HJ, Marks GC, Durham J. Cash transfer programmes in lower-income and middle-income countries: understanding pathways to nutritional change-a realist review protocol. BMJ Open 2019;9(5):e028314 [FREE Full text] [doi: 10.1136/bmjopen-2018-028314] [Medline: 31133594]
10. Duckworth AL, Quinn PD. Development and validation of the short grit scale (grit-s). J Pers Assess 2009;91(2):166-174. [doi: 10.1080/00223890802634290] [Medline: 19205937]
11. Dennis CL. The breastfeeding self-efficacy scale: psychometric assessment of the short form. J Obstet Gynecol Neonatal Nurs 2003;32(6):734-744. [doi: 10.1177/0884217503258459] [Medline: 14649593]
12. Cohen S, Kamarck T, Mermelstein R. Perceived stress scale. Measuring stress: a guide for health and social scientists 1994;10(2):1-2. [doi: 10.1037/t02889-000]
13. Silverio SA, Davies SM, Christiansen P, Aparicio-García ME, Bramante A, Chen P, et al. A validation of the Postpartum Specific Anxiety Scale 12-item research short-form for use during global crises with five translations. BMC Pregnancy Childbirth 2021;21(1):112 [FREE Full text] [doi: 10.1186/s12884-021-03597-9] [Medline: 33557764]
14. McCoy DC, Waldman M, Fink G. Measuring early childhood development at a global scale: evidence from the caregiver-reported early development instruments. Early Child Res Q 2018;45:58-68. [doi: 10.1016/j.ecresq.2018.05.002]

15. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. development of the 10-item Edinburgh postnatal depression scale. Br J Psychiatry 1987;150:782-786. [doi: 10.1192/bjp.150.6.782] [Medline: 3651732]
16. Sadeh A. A brief screening questionnaire for infant sleep problems: validation and findings for an internet sample. Pediatrics 2004;113(6):e570-e577. [doi: 10.1542/peds.113.6.e570] [Medline: 15173539]
17. Black MM, Bromley K, Cavallera V, Cuartas J, Dua T, Eekhout I, et al. The Global Scale for Early Development (GSED). Early childhood matters 2019;14:80-84 [FREE Full text]
18. Ferraro PJ, Simorangkir R. Conditional cash transfers to alleviate poverty also reduced deforestation in Indonesia. Sci Adv 2020;6(24):eaaz1298 [FREE Full text] [doi: 10.1126/sciadv.aaz1298] [Medline: 32582848]

Abbreviations

Lao PDR: Lao People's Democratic Republic
MUAC: mid-upper arm circumference
ODK: Open Data Kit
RCT: randomized controlled trial
STEB: Social Transfers for Exclusive Breastfeeding
VITERBI: Vientiane Multigenerational Birth Cohort

Edited by A Mavragani; submitted 21.11.23; this is a non–peer-reviewed article;accepted 22.02.24; published 03.05.24.

Please cite as:
Sonephet S, Kounnavong S, Zinsstag L, Vonaesch P, Sayasone S, Siengsounthone L, Odermatt P, Fink G, Wallenborn JT
Social Transfers for Exclusive Breastfeeding (STEB) Intervention in Lao People's Democratic Republic: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2024;13:e54768
URL: https://www.researchprotocols.org/2024/1/e54768
doi:10.2196/54768
PMID:38700928

Protocol

Adaptive Intervention to Prevent Respiratory Illness in Cerebral Palsy: Protocol for a Feasibility Pilot Randomized Controlled Trial

Alyssa Fleischman[1], MD; Carlos Lerner[2], MD, MPhil; Heidi Kloster[1], MD; Paul Chung[3], MD, MS; Thomas Klitzner[2], MD, PhD; Christopher Cushing[4], PhD; Danielle Gerber[1], BA; Barbara Katz[5], MA; Gemma Warner[1], MSSW; Kristina Devi Singh-Verdeflor[1], MPH; Roxana Delgado-Martinez[2], BA; Lorena Porras-Javier[2], MPH; Siem Ia[2], CPNP-PC; Teresa Wagner[6], RN; Mary Ehlenbach[1], MD; Ryan Coller[1], MD, MPH

[1]Department of Pediatrics, University of Wisconsin School of Medicine and Public Health, Madison, WI, United States

[2]Department of Pediatrics, David Geffen School of Medicine at UCLA, Los Angeles, CA, United States

[3]Department of Health Systems Science, Kaiser Permanente School of Medicine, Pasadena, CA, United States

[4]Clinical Child Psychology Program and Schiefelbusch Life Span Institute, University of Kansas, Kansas, KS, United States

[5]Family Voices of Wisconsin, Madison, WI, United States

[6]UW Health Kids American Family Children's Hospital, Madison, WI, United States

Corresponding Author:
Alyssa Fleischman, MD
Department of Pediatrics
University of Wisconsin School of Medicine and Public Health
H6/551 CSC
600 Highland Ave
Madison, WI, 53792
United States
Phone: 1 608 262 9150
Email: afleischman2@wisc.edu

Abstract

Background: This study will pilot-test an innovative just-in-time adaptive intervention to reduce severe respiratory illness among children with severe cerebral palsy (CP). Our intervention program, Respiratory Exacerbation–Plans for Action and Care Transitions (RE-PACT), delivers timely customized action planning and rapid clinical response when hospitalization risk is elevated.

Objective: This study aims to establish RE-PACT's feasibility, acceptability, and fidelity in up to 90 children with severe CP. An additional aim is to preliminarily estimate RE-PACT's effect size.

Methods: The study will recruit up to 90 caregivers of children with severe CP aged 0 to 17 years who are cared for by a respiratory specialist or are receiving daily respiratory treatments. Participants will be recruited from pediatric complex care programs at the University of Wisconsin–Madison (UW) and the University of California, Los Angeles (UCLA). Study participants will be randomly assigned to receive usual care through the complex care clinical program at UW or UCLA or the study intervention, RE-PACT. The intervention involves action planning, rapid clinical response to prevent and manage respiratory illness, and weekly SMS text messaging surveillance of caregiver confidence for their child to avoid hospitalization. RE-PACT will be run through 3 successively larger 6-month trial waves, allowing ongoing protocol refinement according to prespecified definitions of success for measures of feasibility, acceptability, and fidelity. The feasibility measures include recruitment and intervention time. The acceptability measures include recruitment and completion rates as well as intervention satisfaction. The fidelity measures include observed versus expected rates of intervention and data collection activities. The primary clinical outcome is a severe respiratory illness, defined as a respiratory diagnosis requiring hospitalization. The secondary clinical outcomes include hospital days and emergency department visits, systemic steroid courses, systemic antibiotic courses, and death from severe respiratory illness.

Results: The recruitment of the first wave began on April 27, 2022. To date, we have enrolled 30 (33%) out of 90 participants, as projected. The final wave of recruitment will end by October 31, 2023, and the final participant will complete the study by April 30, 2024. We will start analyzing the complete responses by April 30, 2024, and the publication of results is expected at the end of 2024.

Conclusions: This pilot intervention, using adaptive just-in-time strategies, represents a novel approach to reducing the incidence of significant respiratory illness for children with severe CP. This protocol may be helpful to other researchers and health care providers caring for patients at high risk for acute severe illness exacerbations.

Trial Registration: ClinicalTrials.gov NCT05292365; https://clinicaltrials.gov/study/NCT05292365

International Registered Report Identifier (IRRID): DERR1-10.2196/49705

(JMIR Res Protoc 2024;13:e49705) doi:10.2196/49705

KEYWORDS

just-in-time adaptive intervention; respiratory illness; cerebral palsy; action planning; digital health

Introduction

Background

Children with severe cerebral palsy (CP) have spastic quadriplegia and are classified in level IV or V on the Gross Motor Function Classification System (GMFCS), often resulting in little or no independent mobility and serious respiratory consequences [1]. The mechanisms of respiratory illness in severe CP vary, paralleling those of other neuromuscular diseases [2], and include respiratory muscle weakness, recurrent infections and aspiration with inflammatory fibrosis, impaired airway clearance from altered tone, upper airway abnormalities, and poor chest wall compliance [3,4].

Respiratory illness is consistently the leading cause of death and hospitalization in severe CP [5,6]. Respiratory illness accounts for 59% of the deaths [5,7] and 25% of the hospitalizations [8-10] in severe CP. Moreover, respiratory illness strongly predicts future risk: respiratory hospitalization risk is 10-fold higher with a respiratory illness in the past year. Nevertheless, respiratory illness risk factors in severe CP are considered modifiable [11]. The prevention of these events is a significant need and a key to improving the quality of life and decreasing mortality [1,12].

Preventing hospitalization requires the opportunity for families and clinical teams to connect early enough to change trajectory [13-15]. Parents of children with CP have expressed the need for interventions focused on crisis management and self-efficacy [9,13,16]. However, respiratory illness in severe CP has broad comorbid triggers (eg, emesis, dysphagia, aspiration, and seizures). Because of this complexity, simple action plans or coaching alone may not address the breadth of respiratory illness triggers or potential responses; for example, if a parent of a child with severe CP follows an action plan directed toward bronchospasm, it would not effectively address an acute infectious lower respiratory infection. Parents of children with severe CP need comprehensive action planning and coaching; they also need an efficient direct extension to their clinical team for a just-in-time (JIT) adaptive clinical response directed specifically to acute real-time problems.

Currently, difficulty identifying when JIT care is needed is a barrier to effective illness response. Concerns may not reach clinical teams until an emergency department (ED) visit or hospitalization is inevitable. A national expert panel to identify interventions to prevent the hospitalization of children with complex diseases concluded that enhanced access, proactive crisis planning, and support for caregiver technical skills were crucial strategies to lower hospital use [17]. Prior postdischarge research has confirmed that admissions and ED visits could be better predicted by identifying when parents were not confident that their child with chronic conditions could avoid hospitalization or an ED visit than by other clinical or demographic indicators [18,19]. Preliminary work with a cohort that included children with severe CP demonstrated that parent confidence, monitored prospectively and repeatedly by SMS text message, is feasible, is acceptable, and predicts hospitalization within 2 weeks. This program of research will drive care forward by providing JIT care triggered by parents' self-reported period of low confidence, thus matching the intervention to the immediate clinical need and preventing respiratory crisis.

Prior Work

This team developed the earlier Plans for Action and Care Transitions (PACT) intervention to prevent hospitalizations for children with complex chronic diseases, including severe CP. After integrating a systematic literature review [20], parent interviews [21], and a national expert panel [17], each focused on preventing hospitalization, the team designed PACT to leverage evidence-based strategies from different populations: asthma action planning [22-24], health coaching [25-27], and feedback from parent advisory group meetings. The PACT intervention delivered action planning and coaching activities to children with diverse complex diseases, including severe CP, and observed 40% lower hospitalization rates for intervention versus control patients [28]. Simultaneously, our prior multisite research observed that confidence to avoid hospitalization, measured through repeated SMS text messaging, predicted hospitalization over the subsequent 2 weeks. Our clinical team and family partners hypothesized that periods of low confidence might be a useful tailoring variable to prompt intervention delivery [29].

The pact intervention has now been adapted to prevent severe respiratory illness in children with severe CP and to integrate SMS text messaging as a tailoring variable within a JIT adaptive intervention framework [29,30].

Objectives

This pilot study (ClinicalTrials.gov: NCT05292365) is designed to establish the feasibility, acceptability, and fidelity of our intervention program, Respiratory Exacerbation–Plans for Action and Care Transitions (RE-PACT) in up to 90 children with severe CP and to establish a preliminary effect size of RE-PACT to inform a future efficacy study to reduce severe

respiratory illness. This intervention consists of three related parts: (1) universal action planning, (2) an ongoing assessment of hospitalization risk, and (3) an algorithm to determine when to increase clinician contacts and tailor action plans. The study period will be divided into 3 waves; after each wave, feasibility, acceptability, and fidelity data will be reviewed against predefined measures of success to adjust the protocol and overcome implementation barriers. We describe the design and protocol of this trial in the following sections.

Methods

Participants and Setting

This intervention will recruit primary caregivers of children with severe CP. Up to 90 caregivers of children with severe (GMFCS level IV or V) CP aged 0 to 17 years and cared for by a respiratory specialist or receiving daily respiratory treatments will be enrolled. Participants will be recruited from pediatric complex care programs at the University of Wisconsin–Madison (UW) and the University of California, Los Angeles (UCLA). These programs were established to deliver care to children with medical complexity. The key components of each program include pediatric clinicians, care coordinators, and extended visit lengths, which aid in delivering comprehensive care to children with CP. Both clinical programs have been described in more detail elsewhere [28,31].

Inclusion Criteria

Participants are caregivers of children with severe CP. Individuals must meet all inclusion criteria to be eligible to participate in the study. Caregiver criteria include (1) being aged at least 18 years, (2) being the primary caregiver to an eligible child, (3) ability to speak English or Spanish well enough to be interviewed, and (4) having a mobile phone capable of sending and receiving SMS text messages. Child criteria include (1) age 0 to 17 years, (2) GMFCS level IV or V CP [32], and (3) being cared for by a respiratory specialist or receiving daily respiratory treatments (oxygen, ventilation, airway clearance device, and medications).

Exclusion Criteria

During this study, participants are asked to reply to SMS text messages when received at random times during daytime hours and connect with an intervention clinical responder either at home, in person at a mutually agreeable location, by mobile phone, or over the internet. Any individual lacking the ability or willingness to engage in SMS text messaging or clinical responder interactions during the study will be excluded from participation in the study.

Recruitment and Screening

We will recruit caregivers of children with severe CP aged between 0 and 17 years. We will recruit up to 90 participants (n=45, 50% at each site) divided across 3 waves. In each wave, there is a 1- to 2-month enrollment period. We anticipate that approximately 80% of those screened will enroll, requiring approximately 110 individuals to be screened.

Using diagnostic codes for CP (International Classification of Diseases, Tenth Revision [ICD-10]: G80-83), we will identify potential participants by reviewing clinic registries and electronic health record data, which contain detailed information about children and their diagnoses. We will send an *opt-out* letter that alerts families that a research study is being conducted and their child may be eligible, with a contact number to call if they wish to opt out of the research or if they wish to receive additional information or have any questions. Potentially eligible caregivers will be contacted by telephone to screen for eligibility and interest.

If the research team is not notified that a family wishes to opt out of the research, the study research personnel will attempt to call the families (or meet them at an upcoming visit) to complete screening, informed consent, baseline questionnaires, and random group assignment. CP status and additional eligibility criteria will be determined with a reliable and valid parent questionnaire and screener conducted at the beginning of the initial telephone contact [32].

Individuals who do not meet the criteria for participation in this trial (screen failure) because they meet ≥1 exclusion criteria that are likely to change over time may be rescreened. Theoretical examples might include a child developing a need for respiratory treatment or families acquiring a mobile phone capable of sending and receiving SMS text messages.

All study participants will undergo informed consent, including authorization to view the child's medical record and participate in action planning, rapid clinical response, and weekly SMS text message surveillance.

Study Design

This is a 2-site pilot randomized controlled clinical trial to establish the RE-PACT protocol's feasibility, acceptability, and fidelity as well as an estimate of effect size. We anticipate being underpowered to assess the efficacy of the intervention in this pilot study; however, to inform future randomized controlled trial power estimates, we will test differences between the intervention and control groups in primary and secondary clinical outcomes.

Study participants will be randomly assigned to receive usual care through the complex care clinical program at UW or UCLA or the study intervention, RE-PACT. Random allocation will be concealed from the research staff conducting recruitment and will use a 1:1 allocation with random block sizes of 2 and 4. Block randomization will be achieved with a computer-generated random number list prepared by the study biostatistician without clinical involvement in the trial. Randomization will be stratified by site to account for site-specific study characteristics.

RE-PACT will be run through 3 successively larger 6-month trials (*waves*), allowing ongoing protocol refinement between waves, guided by prespecified definitions of success for feasibility, acceptability, and fidelity measures. Each wave has a specific protocol refinement focus (wave 1: onboarding, training, recruitment, and data collection; wave 2: randomization and intervention activities; and wave 3: rapid enrollment and the conduct of all protocol activities with high fidelity). Participants in both groups will undergo assessments of demographic, clinical, and caregiving measures using

questionnaires and medical record review case report forms at baseline and at 6 months after enrollment. Intervention feasibility, acceptability, and fidelity data will be collected from parent reports, medical records, and research team logs using case report forms.

Description of the Intervention

RE-PACT uses a dynamic JIT adaptive intervention design [33] to deliver proactive intervention based on risk modeling and partnership between the care team, patients, and families. Although the causes of respiratory illness in severe CP are modifiable, they are also broad and require distinct responses, even for the same child, over time. RE-PACT assumes that (1) every patient with severe CP has a risk of hospitalization, (2) some risks are knowable via the ecosystem of data generated around patient care, and (3) an intervention delivered when risk is increasing can reduce hospitalizations. RE-PACT's design addresses the changing needs of a child and family. RE-PACT involves action planning, rapid clinical response to prevent and manage respiratory illness, and weekly SMS text messaging surveillance of caregiver confidence for their child to avoid hospitalization.

Action Planning

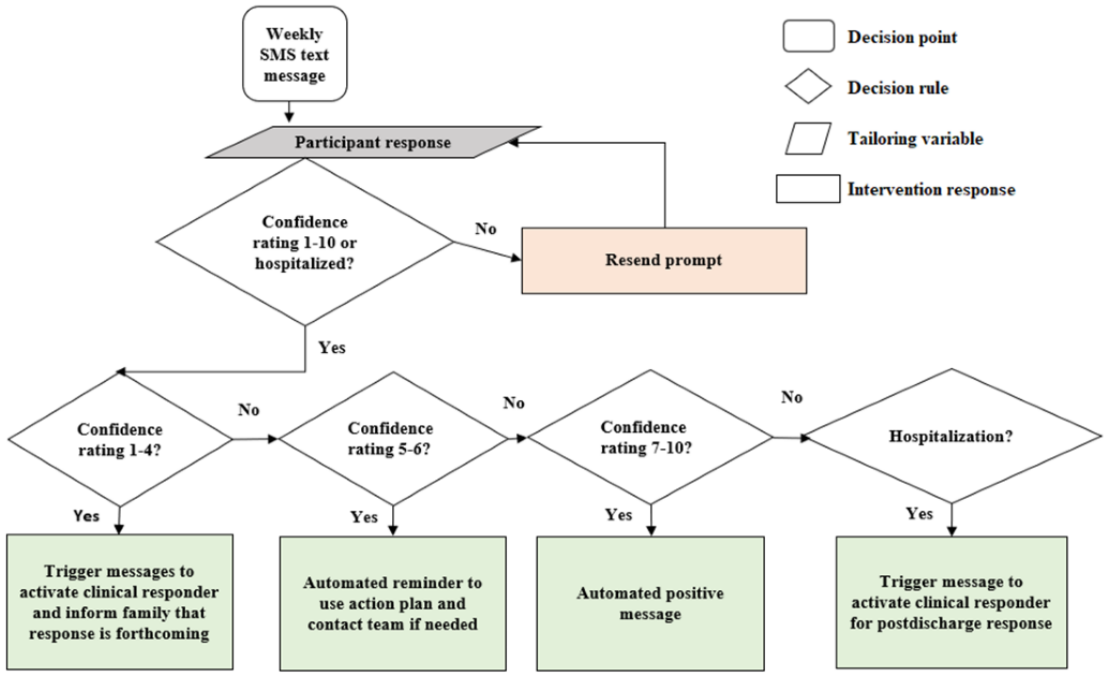
Overview

All intervention families will receive respiratory illness action plans within 1 month of study entry. The action plan format and process are adapted from the original PACT study, and the contents include (at minimum) recognizing, describing, and managing the child's known contributors to respiratory illness. The three main components of the action plans are (1) *focus area* for the action plan (eg, asthma, aspiration, and seizures); (2) *severity levels* corresponding to objective and subjective indicators of baseline (*green*), concerning (*yellow*), and severe (*red*) statuses (eg, >2 L/min of oxygen); and (3) *specific actions* that caregivers should take to manage each status (eg, increase vest therapy, albuterol, suction every 4 hours, and use oxygen up to 4 L/min). As needed, JIT plans are also created at times of low confidence by parent request or by clinician determination during the study period. Any plan created will be developed with families, target an issue that plausibly will recur and lead to respiratory illness–related ED or hospital visit, and, when relevant, be harmonized with prior plans and reflect pulmonologist agreement.

Mobile Health Platform

The mobile health (mHealth) platform is built from an earlier study, *Assessing Confidence at Times of Increased Vulnerability* (ACTIV) [29], which was designed to elicit a SMS text rating of confidence to avoid hospitalization in the next month (ratings range from 1 to 10, where 1 is lowest confidence, and 10 is highest confidence; Figure 1). The platform supports English and Spanish languages. Beginning on the Sunday after enrollment, families will start receiving weekly SMS text messages asking them to rate their confidence for their child to avoid hospitalization in the next month. SMS text messages are programmed to be sent at random days and times to caregivers, averaging once weekly (Sunday to Thursday) between 8 AM and 9 PM (local time). The Sunday-to-Thursday time frame was chosen to support a feasible response during business days and hours. After 2 hours of nonresponse, a reminder is sent, and this is repeated up to 2 times at 2-hour intervals. Clinical responders will receive an email notification in real time if a participant reports low confidence. In addition, clinical responders will receive an SMS text message notification between 9 AM and 6 PM with the report of low confidence. If a response comes outside of these hours, it will be delayed until the next day.

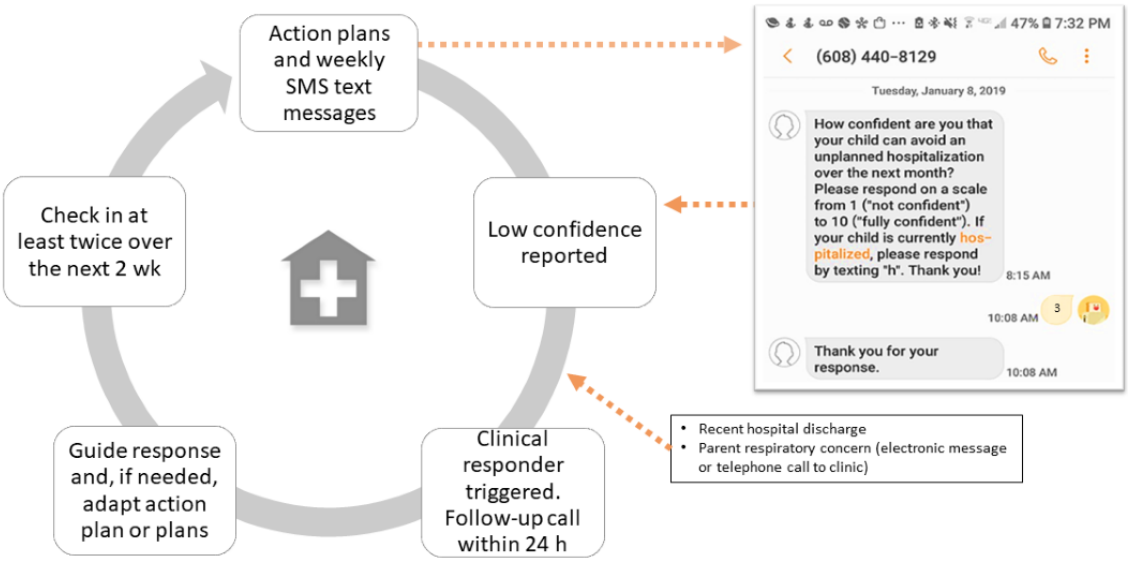
Figure 1. Schematic of the mobile health (mHealth) SMS text message process in which all study participants receive weekly SMS text messages asking them to rate their confidence for their child to avoid hospitalization in the next month.



Rapid Clinical Response

This response is adapted from our prior intervention (PACT) [28]. In RE-PACT, a clinical responder guides the JIT response, adapting to the current child and family situation. Triggers for the clinical responder include (1) low family-reported confidence (a confidence rating of <5) during mHealth messaging, (2) hospital discharge, and (3) family call or electronic message to the clinic owing to acute respiratory concerns (Figure 2). Clinical responders are clinicians, including medical doctors, nurse practitioners, registered nurses, and care coordinators (or equivalent). The same responder intends to work with the family throughout study enrollment.

Figure 2. Summary of the Respiratory Exacerbation–Plans for Action and Care Transitions (RE-PACT) intervention. The figure illustrates low-confidence SMS text messages as the trigger of rapid clinical response. Other triggers include hospital discharge or family-expressed respiratory concerns through telephone call or electronic message to the clinic.



Rapid clinical responses include 3 interactions between family participants and clinical responders. First, a triage contact occurs within 24 hours of a trigger (during business hours). The triage contact goals are to determine the nature of the trigger, whether an action plan exists for the situation, and whether the issue is within the clinical responder's clinical practice scope. If not within the scope, the issue is referred to the relevant support (eg, a specialty physician or clinic social worker). Second, a response planning visit occurs either as a component of the triage contact or at a mutually agreed upon time within 72 hours of the trigger. Third, at least 2 follow-up contacts occur within 2 weeks of the trigger, with additional follow-ups as indicated by ongoing need until the issue is resolved. All contacts can occur through any of the following, at the preference of the family: telephone call, clinical encounter (telehealth, clinic, and hospitalization), or a home visit. The follow-up contacts can occur through electronic communication if the clinical responder and family determine this to be appropriate. At each contact point, there are two goals: (1) ensuring that the family understands red flags, relevant medications, and whom to call and when and keeps notes about the issue; and (2) coaching and skill transfer for the family to generate solutions and lead actions, with the responder intervening if the family is stuck or if clinical needs dictate intervention. Each contact point has scripting to guide the clinical responder as well as electronic health record documentation templates. At the end of a clinical responder event, the responder determines whether the issue affects respiratory health, is likely to recur, and poses a risk for future ED or hospital visits. If all of these are true, the responder either updates existing action plans or creates a new one to address the issue. A participant is considered to have completed the study if they have completed the baseline and 6-month follow-up assessments (Table 1; Figure 3).

Figure 3. Schematic of the study design of Respiratory Exacerbation–Plans for Action and Care Transitions (RE-PACT) intervention enrollment period, enrollment visit, postenrollment evaluation, and protocol refinement. The protocol is refined between each of the 3 waves of the RE-PACT study. JIT: just-in-time; mHealth: mobile health; REDCap: Research Electronic Data Capture; UCLA: University of California, Los Angeles; UW: University of Wisconsin–Madison.

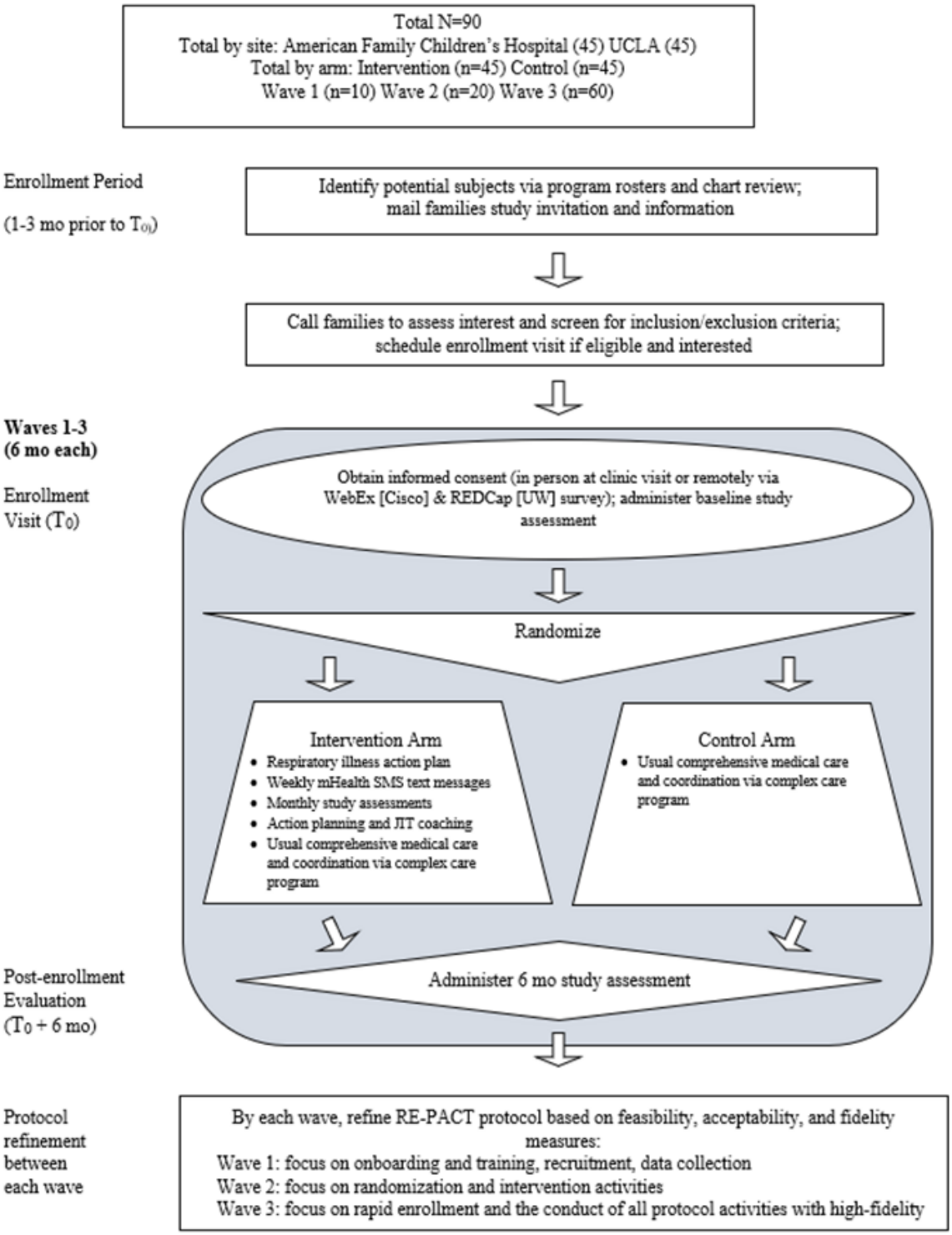


Table 1. Schedule of activities of the Respiratory Exacerbation–Plans for Action and Care Transitions (RE-PACT) intervention throughout the study period, with the depiction of personnel involved.

Activities	Study period (personnel involved)							
	Enrollment visit (research coordinator)	RE-PACT intervention period (clinicians)						Final visit (research coordinator)
	0 (T_0)[a]	1 (T_1)[a]	2 (T_2)[a]	3 (T_3)[a]	4 (T_4)[a]	5 (T_5)[a]	6 (T_6)[a]	End of month 6 (T_7)[a]
Confirm eligibility	✓							
Informed consent	✓							
Baseline assessment	✓							
6-mo assessment								✓
Randomization	✓							
Participant compensation	✓							✓
Usual comprehensive medical care and coordination via complex care program		✓	✓	✓	✓	✓	✓	
Intervention arm only								
SMS text message training	✓							
Weekly mHealth[b] text message and response		✓	✓	✓	✓	✓	✓	
Intervention overview		✓						
Create action plan		✓						
Action planning		✓	✓	✓	✓	✓	✓	
Rapid clinical response when triggered		✓	✓	✓	✓	✓	✓	
Monthly study assessments		✓	✓	✓	✓	✓	✓	

[a]Month (time point).

[b]mHealth: mobile health.

Outcomes

Primary Study End Points: Feasibility, Acceptability, and Fidelity

The specific measures and prespecified definitions of success for primary study end points, including feasibility, acceptability, and fidelity, are listed in Table 2. These measures will be summarized between each of the 3 waves, with protocol adjustments made for any measures that do not meet the definition of success.

Table 2. Primary study end points to evaluate the feasibility, acceptability, and fidelity of Respiratory Exacerbation–Plans for Action and Care Transitions (RE-PACT; n=90).

Measure and measure detail		Success definition
Feasibility		
Recruitment	Days to enroll target, mean (SD)	<14 (1)
Intervention onset	Days between randomization and "T_0[a]" intervention activities, mean (SD)	<7 (1)
Time to action plan	Days to action plan creation	<30
Intervention time	Time logged (min) for action planning and for coaching activities, mean (SD)	N/A[b]
Intervention costs	Mileage and travel costs; personnel salary; training costs; and other incurred costs, total	N/A
Intervention triggers	Number per patient (annualized), both respiratory and nonrespiratory focused	N/A
Acceptability		
Enrollment	Enrollment rate (number of patients enrolled/number approached)	>80%
Consent refusal	Categorized reasons for refusal	N/A
Loss and dropouts	Dropout rate (active or passive) before 6 mo (number of dropouts/number enrolled)	<10%
Action plan, SMS text messaging and clinical responder satisfaction	Do caregivers use the action plan, coaching, and texting? How could it be improved? Would caregivers recommend this to another family?	N/A
Fidelity		
Enrollment duration	Time (mo) of participant enrollment in the study, mean (SD)	6 (1)
Action plan creation	Number of respiratory and overall action plans per patient and action plan focus areas	≥1
Rapid clinical response: home or web-based visit	Success rate (number of visits completed and number expected); stratify by trigger and by "respiratory" and "nonrespiratory"	>80%
mHealth[c] texting	Response rates (number of SMS texts responded and number expected); "respiratory" and "nonrespiratory"	>90%
Crossover	Number of patients inappropriately receiving any intervention component	0
Data collection	Complete entry and exit questionnaire, monthly questionnaire, and chart review data (number of data collection events completed and number of total data collection events)	>95%

[a]a: Enrollment visit

[b]N/A: not applicable.

[c]mHealth: mobile health.

Clinical End Points

The study's secondary objective is to estimate the effect size of RE-PACT. The clinical end points are listed in Textbox 1. The primary clinical end point is severe respiratory illness, defined as a respiratory diagnosis requiring hospitalization. *Respiratory diagnosis* is defined as a discharge diagnosis of any of the following: asthma, pneumonia (community or hospital acquired), bronchiolitis, influenza, upper or lower respiratory tract infection, tracheitis, aspiration pneumonia and pneumonitis, chronic lung disease, and respiratory failure [34]. *Hospitalization* is defined as a nonelective, unscheduled hospital encounter (inpatient or *observation* status), accompanied by both an admission history and physical examination as well as a discharge summary note signed by a physician or advanced practice provider. Field-testing the assessment of this end point with trained research personnel at study sites demonstrated high interrater reliability (κ>0.9).

Textbox 1. Clinical end points of Respiratory Exacerbation–Plans for Action and Care Transitions (RE-PACT).

Primary clinical end point

- Severe respiratory illness, defined as a respiratory diagnosis requiring hospitalization

Secondary clinical end points

- Hospital days during severe respiratory illness
- Systemic steroid courses (systemic steroids [exclude inhaled or topical steroids for the purposes of defining an illness]: hydrocortisone, prednisone, prednisolone, dexamethasone, methylprednisolone, and triamcinolone acetonide; common inhaled steroids: fluticasone, budesonide, mometasone, beclomethasone, and triamcinolone [14-16,35])
- Systemic antibiotic courses (antibiotics: amoxicillin or amoxicillin/ and clavulanate, ampicillin, ampicillin and sulbactam, azithromycin, cefdinir, cefepime, cefixime, cefpodoxime, ceftazidime, ceftriaxone or cefotaxime, ceftibuten, cefuroxime, cephalexin [Keflex], clarithromycin, clindamycin, ciprofloxacin, doxycycline, erythromycin, ertapenem, imipenem, levofloxacin, linezolid, meropenem, metronidazole, moxifloxacin, oseltamivir, penicillin, piperacillin and tazobactam, rifampin, and vancomycin [14-16,35])
- Respiratory emergency department visits
- Death

The secondary clinical outcomes (Textbox 1) include total hospital days during severe respiratory illness; the number of systemic steroid courses, systemic antibiotic courses, and respiratory ED visits; and death. Hospital days are calculated through resolution if admission occurs in the study time frame, even if discharge occurs after the study exit date. *Systemic corticosteroid course* is defined by oral or parenteral corticosteroids prescribed for respiratory diagnosis, including hydrocortisone, prednisone, prednisolone, methylprednisolone at least 1 mg/kg/d (or 30 mg/d) × minimum 3 days, or dexamethasone at least 0.15 mg/kg/d (or 10 mg/d) × ≥1 days. Physiologic or stress replacement doses in adrenal insufficiency are excluded. *Systemic antibiotic course* is defined by oral or parenteral antibiotics prescribed for respiratory diagnosis for a minimum of 3 days. The specific antibiotics are derived from the Infectious Diseases Society of America pediatric pneumonia guidelines [36] and published literature [35]. Respiratory ED visits are any ED visits not resulting in admission and having a discharge respiratory diagnosis.

Exploratory Study End Points

The objectives of the tertiary study are to explore the mediating relationships between RE-PACT and capability, opportunity, motivation, and behavior (COM-B) measures [37]. By blending our foundational research on preventing hospitalizations [17,21] with behavioral intervention theory [38], our conceptual model suggests that decisions to seek care (behaviors) are influenced by capability (family capacity), opportunity (health system and susceptibility), and motivation (confidence). A theorized mechanism of RE-PACT's effect is that combining action planning, mHealth surveillance, and coaching will increase caregiver COM-B measures to manage respiratory illness in severe CP. The tertiary end points are listed in Textbox 2.

Textbox 2. Exploratory study end points of Respiratory Exacerbation–Plans for Action and Care Transitions (RE-PACT).

Capability

- Family Caregiver Activation in Transition (FCAT) tool [39]: mean composite score
- Caregiver General Self-Efficacy Scale (GSES) [40]: mean composite score

Opportunity

- Family Experiences with Care Coordination (FECC) [41]: percentage top-box score for selected items

Motivation

- Confidence responses mobile health SMS text messaging: mean weekly score

Assessment Procedures

Data about research participants (children and their families) will be collected by study research assistants on case report forms using electronic family self-administered questionnaires, structured interviews with research personnel by telephone or in person with enrolled caregivers, and abstraction of child medical record data. Family and child measures will be recorded at baseline, and end points will be recorded at study exit (6 months after the enrollment visit [T_0]). Caregiving measures, which may change as a result of the intervention, will be collected at baseline and study exit. Clinical responders will enter data for intervention group families into a clinical response event case report form.

Feasibility, acceptability, and fidelity end point data will be collected during each of the 3 waves by research personnel reviewing study logs, conducting monthly chart reviews, and administering surveys (by telephone, in person, or sending electronic self-administered links) with caregivers randomized to the intervention. For control group participants, the feasibility

of assessments will be evaluated by completion rates at study exit. In addition, intervention and control participants will be debriefed at study exit on their experiences in the study and asked for feedback on the strengths and weaknesses, as well as any concerns about the protocol. Between each wave and after the third wave, clinical teams at each site will be debriefed on the strengths and weaknesses, as well as concerns about the protocol.

The CP GMFCS measures and all caregiving measures have been well documented as reliable in the literature [39-45]. We have separately established the reliability of identifying respiratory illnesses in our preliminary research (κ>0.9). We will ensure reliability in data collection through direct observation, data auditing, establishing clear data dictionaries and definitions, using uniform variable definitions, and use of a central data repository coordinated and maintained by UW.

Data Collection, Storage, and Protection

Clinical data (including adverse effects) and clinical laboratory data will be entered into Research Electronic Data Capture (REDCap; UW) managed by the University of Wisconsin, a 21 Code of Federal Regulation Part 11–compliant data capture system provided by the UW Institute for Clinical and Translational Research. The data system includes password protection and internal quality checks, such as automatic range checks, to identify inconsistent, incomplete, or inaccurate data. Clinical data will be entered directly from the source documents or entered directly from secure self-administered questionnaires (surveys) sent via REDCap to participants.

Sample Size Considerations

We will enroll up to 90 participants. On the basis of this team's preliminary work, we estimate that half (45/90, 50%) of the participants will experience at least 1 respiratory illness during the enrollment period. We expect to be able to maintain contact and collect data from ≥90% (≥81/90) of the participants at the final follow-up, evenly divided between the intervention and control groups. We assume that this sample will not be powered to establish the efficacy of the intervention; however, it will provide a sufficient sample to determine feasibility and estimate effect sizes, which will be used for power calculations in the future large randomized clinical trial. Attainable power levels were calculated for detecting differences in severe respiratory illness rates (primary clinical outcome) between the study arms at the 2-tailed <.05 significance level based on a negative binomial (NB) regression model with an overdispersion parameter of ϕ=1.0 (Table 3). Hence, large effect sizes with relative risks ranging between 3.0 and 5.0 for comparing the severe respiratory illness rates between the study arms will be detected with 19% to 88% power at the 2-tailed <.05 significance level.

Table 3. Attainable power levels for detecting differences in severe respiratory illness rates between the study arms, assuming a sample size of 45 participants per arm with a missing value rate of ≤10%.

Relative risk (control vs intervention)	Number of severe respiratory illnesses in the intervention arm over the 6-mo follow-up period				
	5 (λ=0.02)[a], %	10 (λ=0.40)[a], %	15 (λ=0.06)[a], %	20 (λ=0.08)[a], %	25 (λ=0.10)[a], %
3.0	19	29	38	45	52
4.0	31	41	59	68	75
5.0	42	62	74	83	88

[a]Severe respiratory illness rate per patient-month.

Statistical Analysis Plan

The primary outcome data will assess the RE-PACT intervention's feasibility, acceptability, and fidelity using descriptive statistics. Categorical variables will be displayed as percentages and continuous variables as means with SDs (if normally distributed) or medians with IQRs (if skewed). We will compare observed values with the prespecified definitions of success for each of our feasibility, acceptability, and fidelity measures. We will also determine overall positive, neutral, and negative reports of feasibility and acceptability using content analysis of qualitative (open-ended comments) data. We will explore any patterns if challenges emerge (eg, enrollment refusal or dropout or low reported use of the intervention activities).

We anticipate being underpowered to assess efficacy using the clinical end points of the intervention in this pilot study. Analyses will also estimate the effect size estimates of clinical end points to allow precise sample size calculations for a future large-scale efficacy trial. We will compare differences between the intervention and active control group outcomes at 6 months. The primary clinical outcome is the severe respiratory illness rate, defined as the total number of severe respiratory illnesses divided by the person-months over the 6-month follow-up period. The severe respiratory illness rate will be analyzed using an NB regression model to account for overdispersion in the count data. For the primary analysis, univariate NB regression analysis will be conducted with a study arm as a predictor variable. The study site will be included as a stratification factor in the primary analysis to account for stratified randomization. The observed effect size of the analysis will be quantified in terms of relative risk and reported along with the corresponding 95% CI. As a secondary analysis, multivariate NB regression analysis will be performed to compare the severe respiratory illness rates between the study arms. This analysis will include clinical and demographic characteristics as covariates in an initial nonparsimonious model. The least absolute shrinkage and selection operator and elastic net penalty methods for NB regression models will be used to identify a parsimonious model with independent covariates.

Longitudinal changes in the severe respiratory illnesses within and between study arms will be evaluated with a generalized linear mixed effects model with a logit link function and

participant-specific random effects. An autoregressive correlation structure will be used to account for within-participant correlations. In this analysis, the presence or absence of severe respiratory illness at the monthly assessments will be the dependent variable, the study arm will be included as a predictor variable, and the study site will be included as a stratification variable to account for the stratified randomization.

The secondary clinical outcomes include total hospital days during severe respiratory illness; the number of systemic steroid courses, systemic antibiotic courses, and respiratory ED visits; and death. The number of systemic steroid courses, systemic antibiotic courses, and respiratory ED visits over the 6-month follow-up period will be analyzed using NB regression analysis as described previously for the primary outcome. Observed effect sizes and the corresponding 95% CIs will be reported. The presence or absence of systemic steroid courses, systemic antibiotic courses, and respiratory ED visits will be documented at the monthly assessments, and longitudinal changes within and between study arms will be analyzed using generalized linear mixed effects modeling with a logit link function and patient-specific random effects. The total number of hospital days over the 6-month follow-up period will be analyzed using ANOVA with the study site as a stratification factor. In a secondary analysis, an analysis of covariance (ANCOVA) will be performed where clinical and demographic baseline characteristics will be included as covariates, and the least absolute shrinkage and selection operator method will be used to identify a parsimonious model. Longitudinal changes in the number of hospital days per hospitalization will be analyzed using a normal mixture linear mixed effects model with patient-specific random effects. The normal mixture component will be included in the model to capture the probabilities of hospitalization at the monthly follow-up. Parameter estimation will be performed using the expectation-maximization algorithm, the standard method for the parameter estimation of mixture models.

Two-tailed *P* values of <.05 will be considered statistically significant. Missing values (eg, owing to loss of follow-up and missing monthly visits) will be evaluated by conducting a sensitivity analysis comparing the results obtained from the complete case analysis with those obtained from imputation-based analyses. Specifically, multiple imputations will be used to impute the missing values of the primary and secondary clinical outcomes. For monotonic missing value data structures, we will use regression-based multiple imputation techniques. By contrast, we will use Markov Chain Monte Carlo–based imputation techniques for nonmonotonic missing value data structure.

Although we anticipate that the intervention and control groups will be similar owing to random assignment, we will adjust for any variables in our analysis that are not equal between the groups, given the small sample size. In addition, we will analyze for any effect of primary home language on the study outcomes because this may affect families' ability to navigate the systems of care in the United States.

Finally, as a planned exploratory analysis, we will test the mediating effect of caregiver COM-B measures on the relationship between intervention and respiratory illness outcomes. The mediating effects will be evaluated by conducting a multistep analysis approach. In the initial step, NB regression analyses will be conducted to examine whether there are differences in respiratory illness outcomes (the number of severe respiratory illnesses, systemic steroid courses, systemic antibiotic courses, and respiratory ED visits) between the intervention and control arms. In the next step, we will conduct a sequence of univariate analyses by regressing each potential mediator variable (caregiver capability COM-B measures) on the binary study arm variable. If significant associations between the potential mediator variables and the study arm are detected, we will regress the respiratory illness outcomes on both the mediator variables and study arm indicator variables using ANCOVA. The mediation effect for each potential mediator variable will then be tested using the Sobel *z* test based on the slope parameter estimates from the corresponding regression models.

Ethical Considerations

This study received initial approval from the UW health system's institutional review board on January 19, 2022 (20211532). All participants will provide informed consent before taking part in the study. Informed consent materials will be provided in private spaces in both written and verbal formats and will review in detail the study design, including random assignment to the intervention and control groups, potential risks of participation, protections against risk, and the rights of human research subjects. The informed consent process will also include review and signing of the Health Insurance Portability and Accountability Act waiver, allowing researchers to review the child's medical records. Parents will be able to decline parts of the study and still participate in other parts and can revoke their consent at any point. Any identifying information kept for the purpose of contacting participants will be kept secure, in REDCap, a locked filing cabinet or in a password-protected electronic file and will be destroyed when the study is complete. The study is monitored by the Data Monitoring Committee at the UW-Madison Institute for Clinical and Translational Research. All participants receive an incentive of US $200, divided in 2 parts: US $100 at enrollment and US $100 after the exit survey, in the form of a gift card, check, or cash.

Results

The recruitment of the first wave began on April 27, 2022. To date, we have enrolled 30 (33%) out of 90 participants, as projected. The final wave of recruitment will end by October 31, 2023, and the final participant will complete the study by April 30, 2024. We will start analyzing the complete responses by April 30, 2024, and the publication of results is expected at the end of 2024.

Discussion

Summary

We describe the protocol for a pilot clinical trial of RE-PACT, a JIT adaptive intervention to reduce respiratory illness in severe

CP. A recent expert consensus statement on preventing and managing respiratory disease in young people with CP highlighted the need for 4 activities: early identification of risk factors; regular assessment of risk; effective partnerships among multidisciplinary teams, families, and individuals with CP; and proactive treatment of respiratory disease [46]. The RE-PACT intervention protocol aligns with each of these 4 critical areas.

For children with severe CP, RE-PACT was designed by families and clinicians from promising earlier interventions to manage health crises with proactive action planning, simple surveillance of family confidence to avoid hospitalization through frequent SMS text messaging, and JIT adaptive rapid clinical responses. This intervention breaks down barriers to equitably connect families and clinical teams precisely when it matters most. This approach is innovative because we tailor the intensity of the response (eg, telephone call and clinic visit) and its content to family- and illness-specific needs. The adaptive nature of the intervention ensures that it meets caregiver needs for that specific instance, flexibly changing for individuals over time in response to each intervention trigger. RE-PACT is also designed to acknowledge that respiratory illness in severe CP is driven by both respiratory and nonrespiratory comorbid and social conditions [11,46] (eg, neuromuscular weakness, seizures, dysphagia, feeding intolerance, health system navigation barriers, and coordination problems).

By conducting successively larger waves of the RE-PACT protocol, we expect to produce a final high-quality protocol that has been developed sufficiently to support the implementation of a large-scale multisite clinical efficacy trial.

Limitations

This study has several limitations. Although we anticipate achieving a feasible, acceptable, and high-fidelity protocol by the end of the third wave, it is possible that some challenges may remain. We anticipate being underpowered to assess intervention efficacy. Despite the randomized design, allocation concealment is not possible. As randomization occurs at the level of the family, inadvertent intervention contamination to nonintervention patients in the same clinical program may occur. This risk will be minimized by having research staff (not clinical staff) manage action planning and SMS text messaging procedures. In future studies, we will consider alternative designs (such as a stepped wedge trial), randomizing at the clinic level to avoid this threat. Threats to external validity will reflect the relatively narrow population of families recruited from 2 complex care programs. Although it is a strength that the intervention will be conducted in English and Spanish, future expansion to populations of children with CP outside of complex care programs and from more geographically and culturally diverse settings will be helpful. As research continues, it will be important to examine whether this intervention design, which relies in part on the use of digital technology, addresses disparities in access to care and inequities in outcomes.

Conclusions

Despite the limitations, our pilot RE-PACT intervention represents an innovative and promising strategy to reduce severe respiratory illness among children with severe CP. RE-PACT operationalizes universal action planning, mobile SMS text messaging, and a JIT adaptive rapid clinical response to deliver timely customized care to families of children with severe CP. This protocol describes detailed methods to assess intervention feasibility, acceptability, and fidelity. This line of research may be relevant to other researchers and health care providers who wish to adopt a similar early intervention strategy for patients with chronic and complex conditions at high risk of future hospitalization.

Acknowledgments

The research reported in this publication was supported by the National Heart, Lung, and Blood Institute of the National Institutes of Health (R34HL153570). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Data Availability

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

Authors' Contributions

RC, the principal investigator of this study, obtained grant funding and conceived the study. CL, HK, TK, PC, CC, DG, BK, ME, and SI participated in the design of the study. AF and RC drafted the manuscript. RC, CL, GW, KH, LP, RD, SI, and TW are responsible for recruitment and major study activities. All authors contributed to the intellectual content of the manuscript and the development of the trial protocol, and all authors have read, revised, and approved the final manuscript.

Conflicts of Interest

None declared.

References

1. Boel L, Pernet K, Toussaint M, Ides K, Leemans G, Haan J, et al. Respiratory morbidity in children with cerebral palsy: an overview. Dev Med Child Neurol 2019 Jun;61(6):646-653 [FREE Full text] [doi: 10.1111/dmcn.14060] [Medline: 30320434]

2. Fitzgerald DA, Follett J, van Asperen PP. Assessing and managing lung disease and sleep disordered breathing in children with cerebral palsy. Paediatr Respir Rev 2009 Mar;10(1):18-24. [doi: 10.1016/j.prrv.2008.10.003] [Medline: 19203740]
3. Murphy N, Such-Neibar T. Cerebral palsy diagnosis and management: the state of the art. Curr Probl Pediatr Adolesc Health Care 2003;33(5):146-169. [doi: 10.1016/s1538-5442(03)00002-6] [Medline: 12738938]
4. Seddon PC, Khan Y. Respiratory problems in children with neurological impairment. Arch Dis Child 2003 Jan;88(1):75-78 [FREE Full text] [doi: 10.1136/adc.88.1.75] [Medline: 12495971]
5. Reid SM, Carlin JB, Reddihough DS. Survival of individuals with cerebral palsy born in Victoria, Australia, between 1970 and 2004. Dev Med Child Neurol 2012 Apr;54(4):353-360 [FREE Full text] [doi: 10.1111/j.1469-8749.2012.04218.x] [Medline: 22329739]
6. Himmelmann K, Sundh V. Survival with cerebral palsy over five decades in western Sweden. Dev Med Child Neurol 2015 Aug;57(8):762-767 [FREE Full text] [doi: 10.1111/dmcn.12718] [Medline: 25694102]
7. Centers for Disease ControlPrevention (CDC). Economic costs associated with mental retardation, cerebral palsy, hearing loss, and vision impairment--United States, 2003. MMWR Morb Mortal Wkly Rep 2004 Jan 30;53(3):57-59 [FREE Full text] [Medline: 14749614]
8. Murphy NA, Hoff C, Jorgensen T, Norlin C, Young PC. Costs and complications of hospitalizations for children with cerebral palsy. Pediatr Rehabil 2006 Jul 10;9(1):47-52. [doi: 10.1080/13638490500079476] [Medline: 16352506]
9. Meehan E, Reid SM, Williams K, Freed GL, Babl FE, Sewell JR, et al. Tertiary paediatric emergency department use in children and young people with cerebral palsy. J Paediatr Child Health 2015 Oct 15;51(10):994-1000. [doi: 10.1111/jpc.12919] [Medline: 25976361]
10. Meehan E, Reid S, Williams K, Freed GL, Sewell JR, Vidmar S, et al. Hospital admissions in children with cerebral palsy: a data linkage study. Dev Med Child Neurol 2017 May;59(5):512-519 [FREE Full text] [doi: 10.1111/dmcn.13350] [Medline: 27900776]
11. Blackmore AM, Bear N, Blair E, Langdon K, Moshovis L, Steer K, et al. Predicting respiratory hospital admissions in young people with cerebral palsy. Arch Dis Child 2018 Dec 19;103(12):1119-1124 [FREE Full text] [doi: 10.1136/archdischild-2017-314346] [Medline: 29555725]
12. Katz RT. Life expectancy for children with cerebral palsy and mental retardation: implications for life care planning. NeuroRehabilitation 2003 Sep 10;18(3):261-270 [FREE Full text] [doi: 10.3233/nre-2003-18310]
13. Raina P, O'Donnell M, Rosenbaum P, Brehaut J, Walter SD, Russell D, et al. The health and well-being of caregivers of children with cerebral palsy. Pediatrics 2005 Jun;115(6):e626-e636. [doi: 10.1542/peds.2004-1689] [Medline: 15930188]
14. Hayles E, Jones A, Harvey D, Plummer D, Ruston S. Delivering healthcare services to children with cerebral palsy and their families: a narrative review. Health Soc Care Community 2015 May;23(3):242-251. [doi: 10.1111/hsc.12121] [Medline: 25175322]
15. Jones M, Morgan E, Shelton JE. Primary care of the child with cerebral palsy: a review of systems (part II). J Pediatr Health Care 2007 Jul;21(4):226-237. [doi: 10.1016/j.pedhc.2006.07.003] [Medline: 17606159]
16. Meehan E, Freed GL, Reid SM, Williams K, Sewell JR, Rawicki B, et al. Tertiary paediatric hospital admissions in children and young people with cerebral palsy. Child Care Health Dev 2015 Nov 30;41(6):928-937. [doi: 10.1111/cch.12263] [Medline: 26032706]
17. Coller RJ, Nelson BB, Klitzner TS, Saenz AA, Shekelle PG, Lerner CF, et al. Strategies to reduce hospitalizations of children with medical complexity through complex care: expert perspectives. Acad Pediatr 2017 May;17(4):381-388. [doi: 10.1016/j.acap.2017.01.006] [Medline: 28108374]
18. Coller RJ, Klitzner TS, Saenz AA, Lerner CF, Nelson BB, Chung PJ. The medical home and hospital readmissions. Pediatrics 2015 Dec;136(6):e1550-e1560. [doi: 10.1542/peds.2015-1618] [Medline: 26527555]
19. Berry J, Ziniel S, Freeman L, Kaplan W, Antonelli R, Gay J, et al. Hospital readmission and parent perceptions of their child's hospital discharge. Int J Qual Health Care 2013 Oct;25(5):573-581 [FREE Full text] [doi: 10.1093/intqhc/mzt051] [Medline: 23962990]
20. Coller RJ, Nelson BB, Sklansky DJ, Saenz AA, Klitzner TS, Lerner CF, et al. Preventing hospitalizations in children with medical complexity: a systematic review. Pediatrics 2014 Dec;134(6):e1628-e1647. [doi: 10.1542/peds.2014-1956] [Medline: 25384492]
21. Nelson BB, Coller RJ, Saenz AA, Chung PJ, Kaplan A, Lerner CF, et al. How avoidable are hospitalizations for children with medical complexity? understanding parent perspectives. Acad Pediatr 2016 Aug;16(6):579-586. [doi: 10.1016/j.acap.2016.04.009] [Medline: 27142492]
22. Zemek RL, Bhogal SK, Ducharme FM. Systematic review of randomized controlled trials examining written action plans in children: what is the plan? Arch Pediatr Adolesc Med 2008 Feb;162(2):157-163. [doi: 10.1001/archpediatrics.2007.34] [Medline: 18250241]
23. Gibson PG, Powell H. Written action plans for asthma: an evidence-based review of the key components. Thorax 2004 Feb;59(2):94-99 [FREE Full text] [doi: 10.1136/thorax.2003.011858] [Medline: 14760143]
24. Bhogal S, Zemek R, Ducharme FM. Written action plans for asthma in children. Cochrane Database Syst Rev 2006 Jul 19(3):CD005306. [doi: 10.1002/14651858.CD005306.pub2] [Medline: 16856090]

25. Coleman EA, Roman SP, Hall KA, Min SJ. Enhancing the care transitions intervention protocol to better address the needs of family caregivers. J Healthc Qual 2015 Jan;37(1):2-11. [doi: 10.1097/01.JHQ.0000460118.60567.fe] [Medline: 26042372]
26. Coleman EA, Smith JD, Frank JC, Min SJ, Parry C, Kramer AM. Preparing patients and caregivers to participate in care delivered across settings: the care transitions intervention. J Am Geriatr Soc 2004 Nov;52(11):1817-1825. [doi: 10.1111/j.1532-5415.2004.52504.x] [Medline: 15507057]
27. Coleman EA, Parry C, Chalmers S, Min SJ. The care transitions intervention: results of a randomized controlled trial. Arch Intern Med 2006 Sep 25;166(17):1822-1828. [doi: 10.1001/archinte.166.17.1822] [Medline: 17000937]
28. Coller R, Klitzner T, Lerner C, Nelson BB, Thompson LR, Zhao Q, et al. Complex care hospital use and postdischarge coaching: a randomized controlled trial. Pediatrics 2018 Aug;142(2):e20174278 [FREE Full text] [doi: 10.1542/peds.2017-4278] [Medline: 29997169]
29. Coller RJ, Lerner CF, Berry JG, Klitzner TS, Allshouse C, Warner G, et al. Linking parent confidence and hospitalization through mobile health: a multisite pilot study. J Pediatr 2021 Mar;230:207-14.e1 [FREE Full text] [doi: 10.1016/j.jpeds.2020.11.049] [Medline: 33253733]
30. Coller RJ, Lerner CF, Chung PJ, Klitzner TS, Cushing CC, Warner G, et al. Caregiving and confidence to avoid hospitalization for children with medical complexity. J Pediatr 2022 Aug;247:109-15.e2 [FREE Full text] [doi: 10.1016/j.jpeds.2022.05.011] [Medline: 35569522]
31. Barreda CB, Ehlenbach ML, Nackers A, Kelly MM, Shadman KA, Sklansky DJ, et al. Complex care program enrollment and change in ED and hospital visits from medical device complications. Pediatr Qual Saf 2021 Aug 26;6(5):e450 [FREE Full text] [doi: 10.1097/pq9.0000000000000450] [Medline: 34476304]
32. McDowell B. The gross motor function classification system--expanded and revised. Dev Med Child Neurol 2008 Oct;50(10):725 [FREE Full text] [doi: 10.1111/j.1469-8749.2008.03104.x] [Medline: 18834382]
33. Nahum-Shani I, Smith SN, Spring BJ, Collins LM, Witkiewitz K, Tewari A, et al. Just-in-time adaptive interventions (JITAIs) in mobile health: key components and design principles for ongoing health behavior support. Ann Behav Med 2018 May 18;52(6):446-462 [FREE Full text] [doi: 10.1007/s12160-016-9830-8] [Medline: 27663578]
34. Nakamura MM, Zaslavsky AM, Toomey SL, Petty CR, Bryant MC, Geanacopoulos AT, et al. Pediatric readmissions after hospitalizations for lower respiratory infections. Pediatrics 2017 Aug;140(2):e20160938. [doi: 10.1542/peds.2016-0938] [Medline: 28771405]
35. Leyenaar JK, Lagu T, Shieh MS, Pekow PS, Lindenauer PK. Management and outcomes of pneumonia among children with complex chronic conditions. Pediatr Infect Dis J 2014 Sep;33(9):907-911 [FREE Full text] [doi: 10.1097/INF.0000000000000317] [Medline: 24732445]
36. Bradley JS, Byington CL, Shah SS, Alverson B, Carter ER, Harrison C, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. Clin Infect Dis 2011 Oct;53(7):e25-e76 [FREE Full text] [doi: 10.1093/cid/cir531] [Medline: 21880587]
37. Keyworth C, Epton T, Goldthorpe J, Calam R, Armitage CJ. Acceptability, reliability, and validity of a brief measure of capabilities, opportunities, and motivations ("COM-B"). Br J Health Psychol 2020 Sep;25(3):474-501 [FREE Full text] [doi: 10.1111/bjhp.12417] [Medline: 32314500]
38. Michie S, van Stralen MM, West R. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. Implement Sci 2011 Apr 23;6:42 [FREE Full text] [doi: 10.1186/1748-5908-6-42] [Medline: 21513547]
39. Coleman EA, Ground KL, Maul A. The Family Caregiver Activation in Transitions (FCAT) tool: a new measure of family caregiver self-efficacy. Jt Comm J Qual Patient Saf 2015 Nov;41(11):502-507. [doi: 10.1016/s1553-7250(15)41066-9] [Medline: 26484682]
40. Luszczynska A, Scholz U, Schwarzer R. The general self-efficacy scale: multicultural validation studies. J Psychol 2005 Sep;139(5):439-457. [doi: 10.3200/JRLP.139.5.439-457] [Medline: 16285214]
41. Measures: family experience with care coordination measure set (FECC). Agency for Healthcare Research and Quality. URL: http://www.ahrq.gov/sites/default/files/wysiwyg/policymakers/chipra/factsheets/chipra_15-p002-ef.pdf [accessed 2023-01-29]
42. Rosenbaum PL, Palisano RJ, Bartlett DJ, Galuppi BE, Russell DJ. Development of the gross motor function classification system for cerebral palsy. Dev Med Child Neurol 2008 Apr;50(4):249-253 [FREE Full text] [doi: 10.1111/j.1469-8749.2008.02045.x] [Medline: 18318732]
43. Palisano RJ, Rosenbaum P, Bartlett D, Livingston MH. Content validity of the expanded and revised gross motor function classification system. Dev Med Child Neurol 2008 Oct;50(10):744-750 [FREE Full text] [doi: 10.1111/j.1469-8749.2008.03089.x] [Medline: 18834387]
44. Brannan AM, Athay MM, de Andrade AR. Measurement quality of the Caregiver Strain Questionnaire-Short Form 7 (CGSQ-SF7). Adm Policy Ment Health 2012 Mar;39(1-2):51-59. [doi: 10.1007/s10488-012-0412-1] [Medline: 22407562]
45. Arroll B, Goodyear-Smith F, Crengle S, Gunn J, Kerse N, Fishman T, et al. Validation of PHQ-2 and PHQ-9 to screen for major depression in the primary care population. Ann Fam Med 2010 Jul;8(4):348-353 [FREE Full text] [doi: 10.1370/afm.1139] [Medline: 20644190]

46. Gibson N, Blackmore AM, Chang AB, Cooper MS, Jaffe A, Kong WR, et al. Prevention and management of respiratory disease in young people with cerebral palsy: consensus statement. Dev Med Child Neurol 2021 Feb;63(2):172-182 [FREE Full text] [doi: 10.1111/dmcn.14640] [Medline: 32803795]

Abbreviations

ACTIV: Assessing Confidence at Times of Increased Vulnerability
ANCOVA: analysis of covariance
COM-B: capability, opportunity, motivation, and behavior
CP: cerebral palsy
ED: emergency department
GMFCS: Gross Motor Function Classification System
***ICD-10*:** *International Classification of Diseases, Tenth Revision*
JIT: just-in-time
mHealth: mobile health
NB: negative binomial
PACT: Plans for Action and Care Transitions
RE-PACT: Respiratory Exacerbation–Plans for Action and Care Transitions
REDCap: Research Electronic Data Capture
UCLA: University of California, Los Angeles
UW: University of Wisconsin–Madison

Edited by A Mavragani; submitted 06.06.23; peer-reviewed by X Zhang, AP Pereira, C Asuzu; comments to author 12.09.23; revised version received 17.09.23; accepted 18.09.23; published 08.01.24.

Please cite as:
Fleischman A, Lerner C, Kloster H, Chung P, Klitzner T, Cushing C, Gerber D, Katz B, Warner G, Singh-Verdeflor KD, Delgado-Martinez R, Porras-Javier L, Ia S, Wagner T, Ehlenbach M, Coller R
Adaptive Intervention to Prevent Respiratory Illness in Cerebral Palsy: Protocol for a Feasibility Pilot Randomized Controlled Trial
JMIR Res Protoc 2024;13:e49705
URL: https://www.researchprotocols.org/2024/1/e49705
doi:10.2196/49705
PMID:38190242

Protocol

Feasibility, Acceptability, and Preliminary Effectiveness of a Combined Digital Platform and Community Health Worker Intervention for Patients With Heart Failure: Protocol for a Randomized Controlled Trial

Jocelyn Carter[1], MD, MPH; Natalia Swack[2], BS; Eric Isselbacher[3], MD, MHCDS; Karen Donelan[4], ScD, EdM; Anne Thorndike[1], MD, MPH

[1]Division of General Internal Medicine, Massachusetts General Hospital, Boston, MA, United States

[2]Department of Medicine, Massachusetts General Hospital, Boston, MA, United States

[3]Corrigan Minehan Heart Center, Massachusetts General Hospital, Boston, MA, United States

[4]Heller School for Policy and Management, Brandeis University, Waltham, MA, United States

Corresponding Author:
Jocelyn Carter, MD, MPH
Division of General Internal Medicine
Massachusetts General Hospital
55 Fruit St, Blake 15
Boston, MA, 02114
United States
Phone: 1 6177262000
Email: jcarter0@partners.org

Abstract

Background: Interventions focused on remote monitoring and social needs care have shown promise in improving clinical outcomes for patients with heart failure (HF). However, patient willingness to use technology as well as concerns about access in underresourced settings have limited digital platform implementation and adoption. There is little research in HF populations examining the effect of a combined digital and social needs care intervention that could enhance patient engagement in digital platform use while closing gaps in care related to social determinants of health. Here, we describe the protocol for a clinical trial of a digitally enabled community health worker intervention designed for patients with HF.

Objective: This study aims to describe the protocol for a randomized controlled trial assessing the acceptability, feasibility, and preliminary effectiveness of an intervention that combines remote monitoring with a digital platform and community health worker (CHW) social needs care for patients with HF who are transitioning from hospital to home. Given the elevated morbidity and mortality, identifying comprehensive and patient-centered interventions at the time of hospital care transitions that can improve clinical outcomes, impact cost, and augment the quality of care for this cohort is a priority.

Methods: This trial randomized adult inpatient participants (n=50) with a diagnosis of HF receiving care at a single academic health care institution to the 30-day intervention (digital platform+CHW pairing+usual care) or the 30-day control (CHW pairing+usual care) arms. All study participants completed baseline questionnaires and 30-day exit interviews and questionnaires. The primary outcomes will be acceptability, feasibility, and preliminary effectiveness.

Results: This clinical trial opened for enrollment in September 2022 and was completed in June 2023. Initial results are expected to be published in the spring of 2024, and analysis is currently underway. Feasibility outcome measures will include the use rates of the biometric sensor (average hours per day), the digital blood pressure monitor (average times per day), the weight scale (average times per day), and the completion of the symptoms questionnaire (average times per day). The acceptability outcome will be measured by the patients' response to the truthfulness of the statement that they would be willing to use the digital platform in the future (response options: very true, somewhat true, or not true). Preliminary effectiveness will be measured by tracking 30-day clinical outcomes (hospital readmissions, emergency room visits, and missed primary care and cardiology appointments).

Conclusions: The results of this investigation are expected to contribute to our understanding of the use of digital interventions and the implementation of supportive home-based social needs care to enhance engagement and the potential effectiveness of

clinically focused digital platforms. These results may inform the construction of a future multi-institutional trial designed to test the true effectiveness of this intervention in HF.

Trial Registration: ClinicalTrials.gov NCT05130008; https://clinicaltrials.gov/study/NCT05130008

International Registered Report Identifier (IRRID): DERR1-10.2196/55687

(JMIR Res Protoc 2024;13:e55687) doi:10.2196/55687

KEYWORDS

heart failure; digital platform; remote monitoring; home-based care; health worker; social needs care; community health worker

Introduction

Background

Heart failure (HF) is one of the most common causes of 30-day readmissions and is a morbid and burdensome disease for patients [1]. Factors related to clinical complexity [2,3] and unmet social needs [4] have been identified as key culprits contributing to rising costs of HF care associated with HF exacerbations and recurrent hospitalizations [5]. While individual interventions focused on digital solutions to augment either clinical care [6-8] or home-based care [9-11] to address unmet social needs have the potential to improve HF clinical outcomes, these interventions are challenged by specific barriers that limit their effectiveness.

Digital platforms with remote monitoring capabilities can track fundamental biometrics, such as heart rate, blood pressure, and body weight, which are critical for the home management of HF [12-15]. These biometrics can be used to evaluate clinical status at home with automated reporting back to patient teams [16-19]. Some platforms also offer daily symptom questionnaires and even embed artificial intelligence algorithms with the ability to tailor alerts to individual patient norms, which can improve platform accuracy and precision [13]. These digital platform capabilities have improved the detection of markers signaling clinical decline (eg, changes in weight, activity tolerance, heart rates, blood pressure, and symptomatology), and a number of studies have demonstrated an early benefit of digital platform use for clinically complex patients, including those managing HF at home [6,8,20,21].

However, the integration of digital platforms among patients with HF has been incremental, at best, for reasons ranging from infrastructure limitations of health care institutions to patient-related barriers [22,23]. Specifically, several patient care barriers have been identified including knowledge gaps, lack of willingness to gain familiarity with technology, reduced health care access, and marginal internet connectivity [22,23]. Concordantly, valid concerns about the exclusion of digital platform use in low-resourced, aging, or less technology-facile populations exist [19]. A number of these challenges could be resolved by integrating a home-based human resource, with basic knowledge of the digital platform who could also deliver social needs care.

Home-based care that focuses on social needs is often delivered by community health workers (CHWs) [24,25]. CHWs, with basic knowledge of chronic conditions, can address unmet social needs and reinforce clinical care plans in ways that improve outcomes by bolstering connections to clinical care teams [26]. Specifically, CHW outreach includes telephone calls; home visits; health care coaching; accompaniment to clinic visits; and identification of low or no-cost resources to close gaps in care related to food insecurity, transportation, rental assistance, or other unmet social needs. CHWs can also provide elbow-to-elbow support with the completion of insurance forms or agency applications. Through motivational interviewing, goal setting, and psychosocial support, CHWs can work closely with patients to identify and address logistical barriers to care [27]. While the evidence base for CHW-focused interventions to improve outcomes and reduce readmissions for patients with chronic diseases including HF is robust [10,11,28-31], CHWs generally rely on one-to-one in-person or phone or text-based patient interactions without symptom or biometric monitoring [32]. In this way, CHW care remains largely siloed without the tools needed to care for larger, clinically complex populations. As such, CHWs inadvertently spend more time with patients who are healthier and engaged in care and less time with patients who are harder to reach and would benefit from early intervention [33,34]. While manageable in smaller cohorts and studies, this can stifle the impact of CHWs on clinical outcomes when scaled.

A combined intervention with a digital platform and CHW care (ie, digitally enabled CHW care) could address important barriers associated with platform use. Specifically, CHW care, through home visits, phone calls, and connections to care teams, can address digital platform knowledge gaps and connectivity issues [27]. CHWs can also act as navigators for digital platforms by encouraging use and engagement that can improve platform usability and adoption. In this way, CHWs are uniquely positioned to enhance the use and reach of digital platforms. In addition, pairing patients at high risk for readmission, especially those with HF, with a CHW and a digital platform could address key barriers to CHW care delivery related to the historical reliance on one-to-one outreach [35]. Digital platforms can better inform the timing and prioritization of CHW outreach with real-time access to streamlined basic biometric data (weights, steps taken per day, or a daily clinical score) and patient response data (collected in a daily questionnaire). This access can augment the ability of CHWs to connect patients to clinical care teams earlier for interventions that can potentially prevent hospital readmissions or emergency department (ED) visits.

This trial, based on a single-arm observational study performed prior [27], will study the effect of a digitally enabled CHW intervention created for patients with HF. In this way, the study addresses a gap in current knowledge of home-based care for patients with HF as one of the first randomized controlled trials

(RCTs) examining the effect of a digital platform combined with social needs care delivery from a CHW in patients with HF. This work is important because it seeks to reduce hospital readmissions for HF, which is imperative for Centers for Medicare and Medicaid stakeholders [36]. This study intervention also occurs at the time of hospital discharge, a particularly vulnerable time point as patients are transitioning out of the hospital. The results of this clinical trial may also contribute to a novel and innovative model for home-based care in a high-risk HF population. Specifically, this study will add value to ongoing conversations about the applications and implementation of digital solutions and unmet social needs, particularly in chronic disease populations with serious illness.

The goal of this trial is to determine if a remote monitoring and social needs care intervention deployed at the time of hospital discharge is feasible, acceptable, and can demonstrate preliminary effectiveness relevant to clinical outcomes (hospital readmissions, ED visits, and missed appointments). We expect to see a higher degree of engagement and adherence to clinical care among those assigned to digitally enabled CHW care compared to those assigned to CHW care alone. The methodology described here will add insight into the implementation of similar digital interventions for patients transitioning from hospital to home with HF.

Primary Objective

The objective of this trial is to assess the acceptability, feasibility, and preliminary effectiveness of a digitally enabled CHW intervention.

Hypothesis

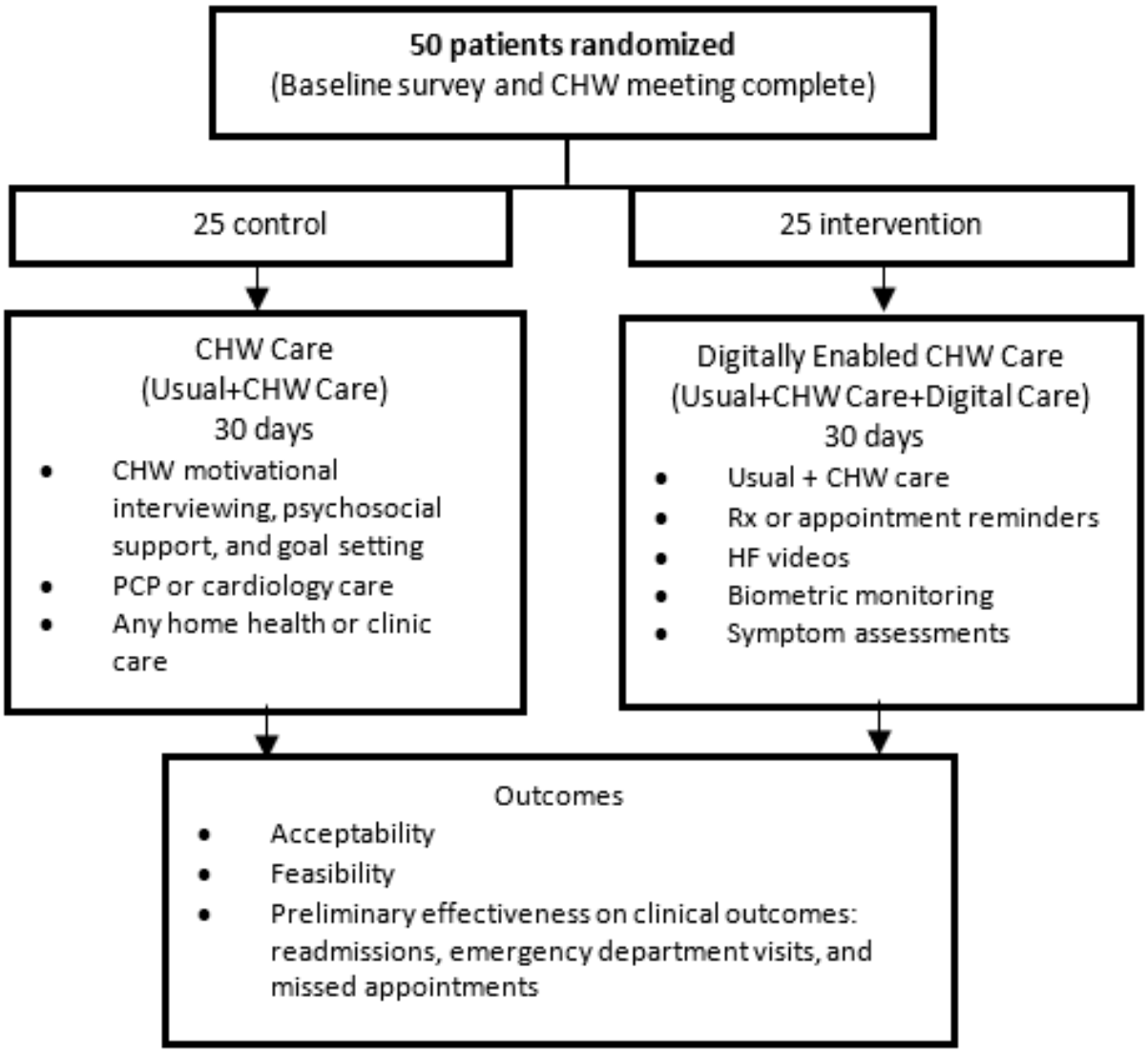
The central hypothesis is that pairing patients with a digitally enabled CHW intervention that addresses clinical, social, and behavioral barriers to HF care will (1) be feasible for patients with HF at home, (2) be acceptable for patients with HF at home, and (3) demonstrate preliminary effectiveness in improving clinical outcomes.

Methods

Study Overview and Design

An RCT design was applied to evaluate the intervention (digital platform+CHW+usual care) group compared to the control (CHW+usual care) group during the 30 days after discharge from the hospital to home. Figure 1 describes the study's procedural flow. Eligible patients were screened via the electronic medical record (EMR) on 8 inpatient study floors (6 internal medicine floors and 2 cardiology floors) in a single health care institution. Research staff approached patients after obtaining permission from bedside nursing. After verifying eligibility and introducing the study design, interested patients completed consent processes and all enrollment questionnaires. Participants were randomized to the intervention or the control arm for the 30-day intervention and study period. Both intervention and control participants were contacted by their assigned CHW within 24 weekday hours of enrollment and received teaching via an American Heart Association–sponsored HF patient education tool (educational control). Intervention participants received study equipment and were oriented to the use of all platform components by research staff prior to hospital discharge. All enrolled participants completed an exit questionnaire and interview via phone at the end of the 30-day intervention.

Figure 1. Trial design, study arm assignment, and outcomes of a pilot randomized controlled trial. CHW: community health worker. PCP: primary care provider. Rx: medical prescription. HF: heart failure.



Clinical Setting of Patient Population

Massachusetts General Hospital (MGH) is a 999-bed academic medical center in Massachusetts with 75,000 to 100,000 hospital admissions each year. The MGH Corrigan Minehan Heart Center serves over 27,000 patients with cardiac disease each year, many of whom have HF. As an accountable care organization and medical home in partnership with the Mass General Brigham system, MGH inpatient teams are comprised of full and part-time staff clinicians, including board-certified internists or cardiologists, residents, fellows, nurses, advanced clinicians (nurse practitioners and physician assistants), and students. The majority of inpatients are supported by Medicare or Medicaid-based insurance products.

Subject Eligibility and Recruitment Strategy

Eligibility criteria were established based on prior clinical trials and qualitative studies focused on care transitions from hospital to home [27,37-39]. Eligibility criteria for participants who were approached and introduced to the study while hospitalized included the following: being 18 years and older, living within a 50-mile radius of MGH, having a diagnosis of HF listed in the EMR problem list, a history of ≥1 hospitalization within the previous 12 months, a clinician managing their HF, cognitive ability to participate in the intervention, and English fluency. Patients were ineligible if they had an active alcohol or substance use disorder, were living in a long-term care facility, were unable to provide consent, had invoked health care proxy, or had prisoner status. Research staff attempted to enroll patients up to 3 times if they were unsure or unable to be engaged in the initial approach.

CHW Training and Supervision

Extensive experience training CHWs gained during our prior CHW clinical trial was applied for CHW training purposes [9]. CHW staff participating in the trial were trained in the core competencies of CHW care delivery for HF and other common diagnoses associated with hospital readmissions (eg, pneumonia, atrial fibrillation, and pulmonary disease). These CHW core competencies included motivational interviewing, behavioral change, and psychosocial support. Additional skill sets and

activity building occurred for medication reconciliation, common management and postdischarge follow-up plans, general American Heart Association guideline–concordant care, patient educational tools, and commonly used community resources. CHW supervision was led by a CHW manager experienced in supervising CHWs caring for clinically, socially, and behaviorally complex patients. Supervision occurred through daily huddles (with the CHW staff supervisors) and weekly meetings with the CHW staff supervisors and the principal investigator (JC). All clinical aspects of CHW care were also supervised by the principal investigator.

For the intervention arm, CHW staff were also trained on the use of the digital platform. The training was fulfilled using participatory methods, case scenarios, and video clips for optimal teaching and application for the patient-facing mobile app as well as the team dashboard. Specific training on the digital platform features (Figure 2) was designed to enhance communication and monitoring in concert with the application of core competencies and skill sets associated with traditional CHW care. This occurred during multicomponent didactics involving feedback, consultation, and supervision. Extensive role play and case studies with simulation experiences for troubleshooting and technology-based challenges were performed over a 14-day period. After training, simulation and behavioral interviewing–based proficiency testing were used to evaluate both CHW best practices and digital platform proficiency. CHW staff were also trained on how to interpret digital platform symptom assessments and biometric monitoring. In the platform, these symptoms and biometrics were translated into a color-coded schematic (Figure 3: green=no new symptoms or biometric variance or clinical symptom score of ≤0.7; yellow=1 new symptom or clinical score of 0.8-0.9; red= more than 1 new symptom or a clinical score of ≥1.0). For any participants with a yellow categorization on any given day, CHWs (1) contacted the participant to verify symptoms and ask probing questions, (2) contacted the participant's designated care clinic, and (3) coordinated a patient visit with CHW staff or a visiting home nurse for expedited clinical evaluation. For participants with a red categorization, all yellow categorization steps were followed and CHWs partnered with the clinical care team to arrange for expedited transfer to MGH or in-home evaluation if clinically indicated per the clinical care team providers.

Figure 2. Procedural workflow overview for study participants. CHW: community health worker.

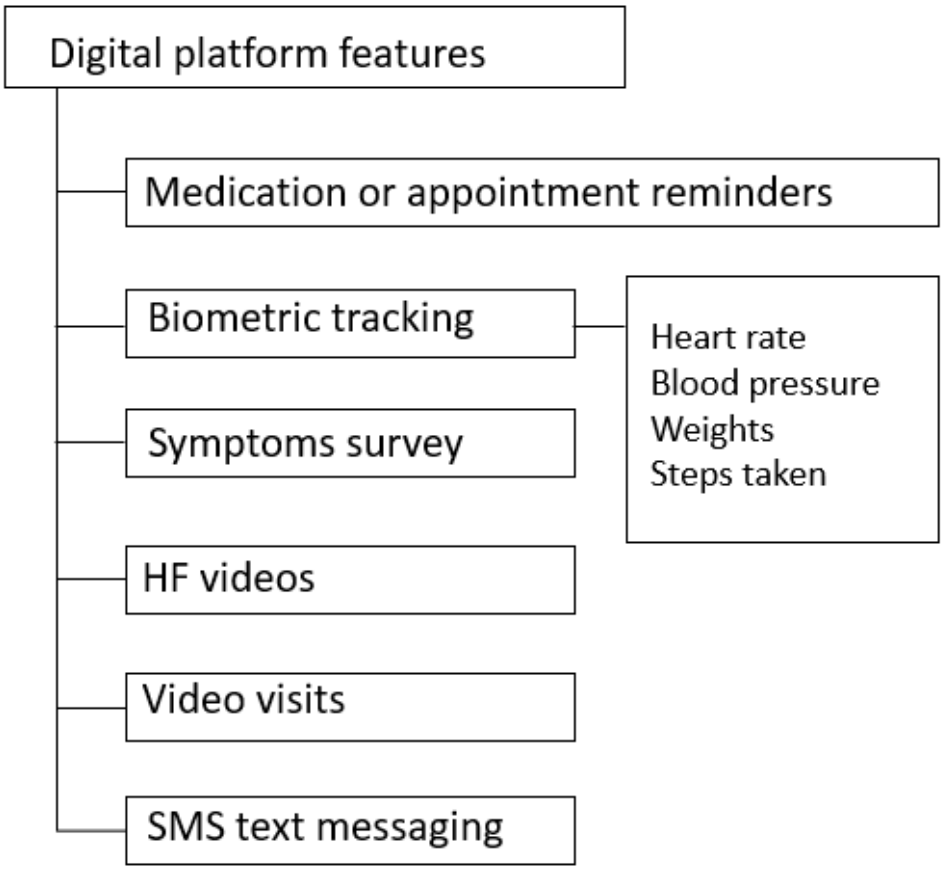


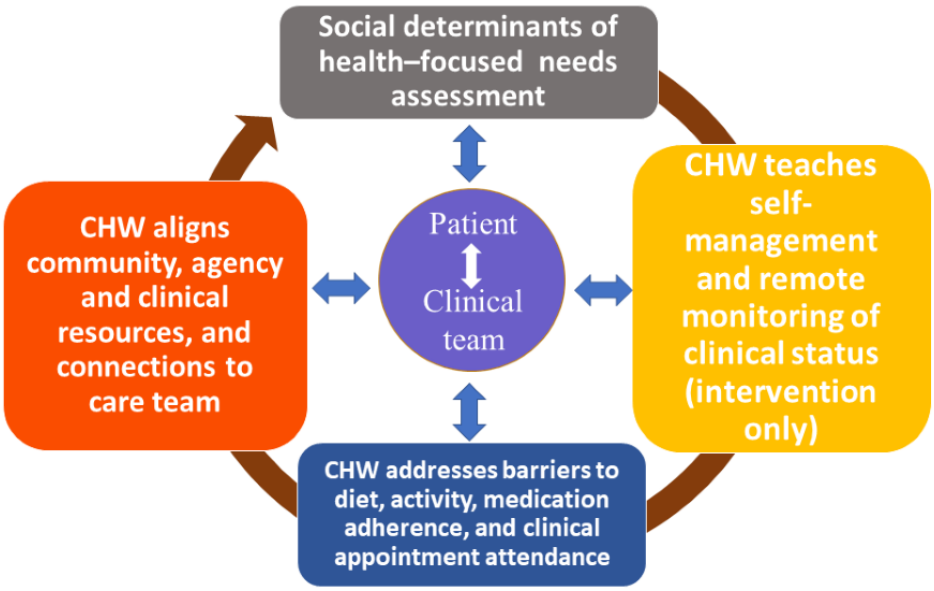
Figure 3. Digital platform components (intervention arm only). HF: heart failure.

Digital platform biometric algorithm			
Digital platform biometric data score and color key			CHW action taken
≤0.7	Green	• No new symptoms or biometric variation	• Continued CHW care
0.8-0.9	Yellow	• 1 new symptom or • 1 biometric variant change by ≤7% baseline	• Contact patient; call clinic care team, arrange for clinical eval with CHW staff
≥1	≥1 Red	• >1 new symptom • ≥1 biometric variant change by >7% baseline	• See "Yellow" action taken + arrange for timely MGH transfer if deemed indicated by providers

Control

Participants were contacted routinely by CHW staff to review medication adherence, nutrition, physical activity, symptoms, and clinic appointments and discuss any unmet social needs. CHW staff (n=1) paired with enrolled participants reviewed individual participant's discharge care plans and integrated the patient's clinical, social, and behavioral goals with clinical care plans. As such, CHWs also identified resources to reduce gaps in care caused by unmet social needs and connected patients to clinical care teams for clinical questions. One CHW with expertise in CHW core competencies [25] (motivational interviewing, goal setting, behavior change, and psychosocial support) delivered the control arm treatment. Daily huddles occurred to discuss patient interactions and plans for goal achievement. CHW staff documented all participant encounters in the EMR. In addition, all CHW interactions were logged in a web-based research team REDCap (Research Electronic Data Capture; Vanderbilt University) database. All social, behavioral, and clinical activities (clinical care team and community agency interactions, as well as time spent engaged in phone, in-person, and email modalities) were tracked. Pre-existing clinical team members were copied on all EMR notes and contacted directly, when necessary, by the CHW or supervisory staff during the intervention. Figure 4 shows an overview of the study participant workflow.

Figure 4. Color schematic depicting the relationship between the biometric clinical status score generated by the digital platform algorithm and the action taken by CHW staff. CHW: community health worker; MGH: Massachusetts General Hospital.



Intervention

Enrolled intervention participants were introduced to the digital platform features prior to hospital discharge: an HF mobile phone app within a smartphone (Android) that included a daily checklist for patients, educational HF videos, a portal CHW video visits, and a daily symptom questionnaire. In addition, participants were given a digital blood pressure monitor, a digital weight scale, and a sensor attached to a lightweight armband to be worn on the nondominant arm tracking basic biometric data (heart rates, oxygenation, and steps taken). As described, CHWs were trained to assist patients with technology setup and troubleshooting. Any unreconciled technical difficulties were addressed by research study staff and the platform vendor as needed. An artificial intelligence algorithm within the mobile app generated a daily score along with alerts sent to the CHW team dashboard, indicating if participants were at or moving away from their clinical baseline in terms of symptoms,

biometrics, and functionality. This team dashboard was used in conjunction with a color schematic described (Figure 3). Any scores or alerts indicating that participants were moving away from their baseline were discussed with a CHW project manager. When indicated, CHWs notified clinical team staff during weekday office hours within 2 hours of a biometric or other clinically related concern (ie, significant change in heart rate, blood pressure, body weight, or patient-reported symptoms). Participants were instructed to engage with clinical care teams or urgent or emergent care as they would normally if they experienced symptomatic changes or other concerns outside weekday hours of operation.

Participants were contacted routinely by CHW staff to review medication adherence, nutrition, physical activity, symptoms, and clinic appointments and discuss any unmet social needs as described in the control treatment arm. All elements of other CHW outreach activities were performed as described in the control arm.

Data Collection and Measures

All study participants completed an enrollment questionnaire focused on health habits and patient experience with home self-care. This questionnaire was developed based on prior patient qualitative interviews and CHW focus groups with those caring for patients with HF [37,38]. These questions were adapted by study investigators for interviewer-assisted administration with inpatients prior to hospital discharge. We used a qualitative process to identify core domains through key informant interviews with patients, community-based primary care physicians, cardiologists, and internal medicine hospitalists. This was coupled with a review of the literature on patient experience in hospitalized settings along with consultations with survey and health services research experts. Draft surveys were pretested with 3 patients with the opportunity for revision prior to study administration. The enrollment questionnaire included 59 items from 7 distinct categories: health-related habits, understanding of the care plan, smartphone knowledge, quality of life (Kansas City Cardiomyopathy Questionnaire) [40], perceptions of physical and mental health, unmet social needs, loneliness (Three-Item Loneliness Scale) [40], and depression (Patient Health Questionnaire-2) [40]. Additional domains included confidence in the ability to perform self-care after discharge and patient-predicted likelihood of readmission within 30 days. Open-ended questions were asked to patients regarding anything that would help them manage their health outside the hospital.

An exit questionnaire administered at the study end (after 30-day enrollment) was also developed. This questionnaire mirrored domains in the enrollment questionnaire to assess any changes (eg, health-related habits and care plan understanding) associated with intervention or control arm assignments. Intervention participants also completed an acceptability questionnaire focused on the digital platform (adapted from components of the Technology Assessment Model Measurement Scales [41] as described by Ben-Zeev et al [42]). Similarly, the exit questionnaire was initially pretested with 3 patients, and no additional changes were made (all pretested questionnaire data will be included in the final analysis).

Separately, participants also completed an exit interview after completion of the 30-day enrollment period. The exit interview was conducted via phone and prompted participants to describe their experience with the digital platform and CHW staff interactions. Specific questions included: *What was it like to work with a CHW for the last month? What was it like using this technology in your home for the last month?* and *Are there things that could have made your time in the study better for you?* Semistructured interviews occurred via phone at times designated by participants and lasted 5-12 minutes. All semistructured interviews were audio-recorded and transcribed verbatim.

Process Measures, Source, and Timeframe Associated With Primary Outcomes of Feasibility, Acceptability, and Primary Effectiveness

The primary outcomes of feasibility, acceptability, and preliminary effectiveness will be tracked (Table 1). We will report feasibility outcome measures including daily use rates of the biometric sensor (mean hours per day), the digital blood pressure monitor (mean times per day), the weight scale (mean times per day), and completion of the symptom questionnaire (mean times per day). The acceptability outcome measure will be patient responses to the truthfulness of a statement indicating willingness to use the intervention in the future (response options: very true, somewhat true, or not true). Preliminary effectiveness will be measured by tracking 30-day clinical outcomes (hospital readmissions, emergency room visits, and missed primary care and cardiology appointments). Demographic data and survey item responses were captured in REDCap. These items will be summarized, and univariate analysis will be completed for any domains connected to the outcomes. Structured medical record review data extracted from the EMR will also be captured in the REDCap database.

Table 1. Outcome measures or covariates for the digitally enabled CHW[a] intervention.

Outcomes and process measures	Source	Timing
Feasibility		
Use of the digital platform (wearing the biosensor[b], use of the blood pressure monitor[c], use of the digital weight scale[c])	Platform database	At 30 days
CHW engagement (number of CHW interactions, types of CHW interactions)	CHW interaction log	At 30 days
Acceptability		
Willingness to use the intervention again	Patient exit questionnaire	At 30 days
Preliminary effectiveness		
30-day readmissions	Electronic health record	At 30 days
Emergency department visits	Electronic health record	At 30 days
Missed appointments	Electronic health record	At 30 days

[a]CHW: community health worker.

[b]Hours worn per day.

[c]Number of times recorded per day.

Statistical Analysis

All standards for trial design, analysis, and reporting will be adhered to per the CONSORT (Consolidated Standards on Reporting Trials) checklist [43]. Univariate analysis will include demographic covariates of participants as well as intervention use frequencies, means, and SDs related to feasibility and acceptability outcomes. For the 30-day clinical outcomes of readmission, ED visits, and missed primary care and specialty appointments, we will use the proportion with any readmissions, emergency visits, or missed clinic visits will be compared between the 2 arms using Pearson ^{2} tests. We will also use a logistic regression model to include other potential predictors of the outcome to improve the precision of the estimate. The number of readmissions, ED visits, or missed appointments will be compared using Poisson models.

For exit interviews, we will use a framework analysis to identify main themes along with verbatim transcription for coding and analysis. Interview transcripts will be uploaded into Dedoose (version 8.3.47b.exe; SocioCultural Research Consultants, LLC). An analytic framework will be developed based on the major domains of the patient interview guide. To help facilitate reliability, 2 members of the research team (JC and NS) will serve as coders and familiarize themselves with the raw transcription data. They will then independently identify key themes raised by respondents. An iterative reapplication of this thematic framework will be used to identify all transcript components mapping to these specific themes. Coders will identify associations between themes, user characteristics, and outcomes for all interviews prior to achieving intercoder reliability. Any discrepancies unable to be resolved through discussion by the 2 coders (JC and NS) will be reviewed by a third researcher with expertise in qualitative data. These methods will be completed in concordance with the COREQ (Consolidated Criteria for Reporting Qualitative Research) checklist standards [44]. All trial procedures will also be in concordance with ClinicalTrials.gov regulations (NCT05130008).

Ethical Considerations

Institutional review board approval (2018P002014) was obtained from the Mass General Brigham Human Research Committee on September 22, 2020. All patients interested in enrollment participated in an informed consent process with the opportunity to ask questions and review all study procedures, data collection, and data analysis processes (primary and secondary) prior to signing an informed consent form. Privacy and protection standards were upheld with secure and password-protected database storage for all study data (which will be presented in deidentified form on publication). All participants were offered US $250 for remuneration for study participation.

Results

Between September 2022 and June 2023, enrollment was completed (n=50) with participants from inpatient general internal medicine and cardiology study floors at the MGH. The analysis is expected to be completed by January 2023, with results published in the spring of 2024. The study was approved by the IRB on June 4, 2019.

Discussion

Anticipated Findings

Here, we describe the protocol of an RCT designed to assess the feasibility, acceptability, and preliminary effectiveness of a novel digitally enabled CHW intervention for patients managing HF at home. The results of this trial are expected to deepen our understanding of experiential barriers patients with HF patients face while living at home and underline the potential value of a home-based CHW-supported digital platform solution. Assessment of the intervention's ability to augment patient engagement, adherence to care plans, and impact clinical outcomes will be addressed. Given the rising cost of care for patients with HF and heightened morbidity and mortality, the findings of this study may also carry important economic lessons in terms of designing value-based care that can assist in avoiding

preventable readmissions for patients with HF who are at high risk for hospitalization.

This study may also add context to our understanding of how digital interventions for patients with HF and other serious illnesses are best implemented. Numerous barriers to adoption have been well documented, and the results generated from this study may aid in the development of a framework, leading to best practices for addressing individual clinical and social barriers that may arise for patients engaging with digital platforms at home. The use of qualitative exit interviews adds to the patient centeredness of the study by highlighting the patient perspective and experience that may generate important solutions for the home management of HF and for unmet social needs. These results may also demonstrate how home-based CHW care can potentially advance patient use and engagement with digital platforms, adherence to clinical care plans, and connections to clinical homes. These study results may be used to strengthen and inform the feasibility and adoption of future digital interventions. Finally, this study also will provide opportunities to clarify our understanding of which types of interactions and resources provided to certain patients with HF by CHWs are most beneficial with regard to clinical outcomes.

Comparison to Prior Work

Remote monitoring studies have shown some improvements in outcomes for patients with HF. In a large trial with 1571 patients randomized to remote monitoring versus usual care, intervention patients had fewer days lost to unplanned cardiovascular admissions (4.88% vs 6.64%; 95% CI 0.65-1.0; *P*=.046) and decreased all-cause death rate (7.86 vs 11.34; hazard ratio 0.70, 95% CI 0.5-0.96; *P*=.028). However, most studies of remote monitoring have demonstrated mixed results [6]. A large study randomized 1437 participants to a combined health coaching and telemonitoring intervention for 180 days but showed no significant difference in readmission (50% vs 49%; *P*=.74) [45]. Similar outcomes were seen in other large-scale studies [46-48]. Nevertheless, systematic reviews have been suggestive of improved outcomes. In a systematic review analysis of 25 studies inclusive of structured telephonic support and telemonitoring (n=9332), telemonitoring reduced all-cause mortality (n=3740; RR 0.80, 95% CI 0.68-0.94) and HF-related hospitalization (n=2148; RR 0.71, 95% CI 0.6-0.83) [20]. However, all-cause 30-day readmission rates were unchanged. Concordantly, in a meta-analysis of 21 analyzed RCTs assigning patients to different remote patient monitoring interventions (n=6317) with medical personnel support or telephone support, results showed that those interventions that included staff delivering some home-based support (either clinically or administratively) reduced mortality (HR 0.77, 95% CI 0.55-1.08) [49].

While the majority of CHW studies are focused on cancer, there is a growing evidence base demonstrating the impact of CHWs on chronic disease and HF populations. In an RCT (n=426) pairing CHWs with patients who have chronic disease insured by Medicaid at the time of hospital discharge, adherence to posthospital care was improved (60% vs 47%; *P*=.02) [10], but no difference in 30-day readmissions was seen. Another RCT that focused on patients with 2 or more chronic diseases (n=322) demonstrated a reduction in systolic blood pressure associated with a 6-month CHW postdischarge intervention (–11.2 mm Hg vs 1.8 mm Hg; overall *P*=.08) [11]; a 28% reduction in 1-year hospitalizations was also seen, although it did not achieve statistical significance. A large RCT (n=525) testing a nurse practitioner and CHW intervention among patients with cardiovascular disease showed reductions in reduced total cholesterol (difference 19.7 mg/dL), low-density lipoprotein cholesterol (difference 15.9 mg/dL), triglycerides (difference 16.3 mg/dL), systolic blood pressure (difference 0.2 mm Hg), and glycated hemoglobin (difference 0.5%), as compared to enhanced usual care [50]. Some smaller studies have also supported these outcomes. In a study with 28 patients with HF paired with CHWs at the time of hospital discharge, participants paired with a CHW for 12 months saw a decrease in HF-related ED visits (0.71 vs 0.18; *P*<.001), and an 89% decrease in HF readmission (0.64 vs 0.07; *P*<.005) [51]. No significant difference in 30-day readmissions or ED visits was seen compared to matched controls. Systematic review data have also been positive. In a meta-analysis of 16 CHW-focused RCTs, 5 RCTs demonstrated a significant reduction in ED visits (23%-51% reduction; *P*=.05), hospitalizations (21%-50% reduction; *P*<.05), and urgent care visits [52]. We expect that this study will build on this knowledge by filling knowledge gaps related to adoption and adherence to a digitally enabled CHW intervention that has yet to be studied in a clinical trial powered to test its effect.

Strengths and Limitations

This methodology describes a small pilot trial performed at a single, urban, academic health care center. Since there are limited survey instruments designed to assess user experience with this particular digital platform, we adapted a prior questionnaire with established generalizability to assess this digital platform [37]. While formal patient-reported outcome measure scales were unable to be incorporated for all patient questionnaire covariates due to burdensome instrument length, Patient Health Questionnaire-2, Kansas City Cardiomyopathy Questionnaire, and the Three-Item Loneliness Scale were included as well as a number of items related to health behaviors and satisfaction used in our previous studies [27]. The study strengths include the RCT design focused on a unique intervention for an at-risk cohort of patients facing a burdensome and morbid condition. We also believe that the inclusion of feasibility as an outcome adds strength to the structure and actionability of the trial methodology in 2 ways: by further informing implementation science and strategic deployment of the intervention and by identifying potential barriers and facilitators of this intervention delivery and engagement for future larger trial performance. Additionally, the use of patient response data gathered from questionnaires and exit interviews adds a quasi-mixed methods design element that not only contributes to our understanding of the patient experience with living with HF at home but can also add depth and context to the study outcomes. While this trial will not be adequately powered to assess the true effectiveness of the intervention and our sample size will be limited to a single academic institution that may not be generalizable to other settings, the methodological quality and integrity of the study performance

may generate preliminary results that may later be tested in a large multisite clinical trial powered to assess the intervention's effect on clinical outcomes in larger populations.

Conclusions and Future Directions

The findings of this trial are expected to contribute to the implementation of digital platforms, as well as the role of CHWs in supporting digital care for a patient with HF. In this way, these findings may improve the performance of a large-scale and multisite RCT and help determine the true effectiveness of this intervention with regard to clinical outcomes. In addition, this trial may answer important questions about what types of CHW interactions can offer the greatest value for patients relevant to demographic, clinical, and social domains. As total medical expenditures for those affected by HF are expected to grow exponentially in the next decade, creating value-based and patient-centered solutions is a fundamental priority for health care institutions and stakeholders alike.

Acknowledgments

The authors especially thank research study team leaders Susan Hassan (BS), Yadira Reyes-Richards (BS), and Anne Walton (RN). The authors also thank Massachusetts General Hospital (MGH) Primary Care, the MGH Corrigan Minehan Heart Center, the MGH Division of General Internal Medicine, and the MGH Department of Medicine. Generative AI tools were not used when writing this paper. This work was supported in part by the National Institutes of Health and the National Heart, Lung, and Blood Institute (NHLBI) (1K23HL150287-01) awarded to JC. AT was also supported by the NHLBI (grant K24 HL163073). The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Availability

The data sets generated and analyzed during this study are not publicly available due to the small number of participants at a single institution but are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

References

1. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Executive summary: heart disease and stroke statistics—2016 update: a report from the American Heart Association. Circulation 2016;133(4):447-454 [FREE Full text] [doi: 10.1161/CIR.0000000000000366] [Medline: 26811276]
2. Heidenreich PA, Albert NM, Allen LA, Bluemke DA, Butler J, Fonarow GC, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. Circ Heart Fail 2013;6(3):606-619 [FREE Full text] [doi: 10.1161/HHF.0b013e318291329a] [Medline: 23616602]
3. Dunlay SM, Shah ND, Shi Q, Morlan B, VanHouten H, Long KH, et al. Lifetime costs of medical care after heart failure diagnosis. Circ Cardiovasc Qual Outcomes 2011;4(1):68-75 [FREE Full text] [doi: 10.1161/CIRCOUTCOMES.110.957225] [Medline: 21139091]
4. White-Williams C, Rossi LP, Bittner VA, Driscoll A, Durant RW, Granger BB, et al. Addressing social determinants of health in the care of patients with heart failure: a scientific statement from the American Heart Association. Circulation 2020;141(22):e841-e863 [FREE Full text] [doi: 10.1161/CIR.0000000000000767] [Medline: 32349541]
5. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. Circulation 2022;145(18):e895-e1032 [FREE Full text] [doi: 10.1161/CIR.0000000000001063] [Medline: 35363499]
6. Koehler F, Koehler K, Deckwart O, Prescher S, Wegscheider K, Kirwan BA, et al. Efficacy of telemedical interventional management in patients with heart failure (TIM-HF2): a randomised, controlled, parallel-group, unmasked trial. Lancet 2018;392(10152):1047-1057 [FREE Full text] [doi: 10.1016/S0140-6736(18)31880-4] [Medline: 30153985]
7. Felker GM, Sharma A, Mentz RJ, She L, Green CL, Granger BB, et al. A randomized controlled trial of mobile health intervention in patients with heart failure and diabetes. J Card Fail 2022;28(11):1575-1583. [doi: 10.1016/j.cardfail.2022.07.048] [Medline: 35882260]
8. Hägglund E, Lyngå P, Frie F, Ullman B, Persson H, Melin M, et al. Patient-centred home-based management of heart failure. Findings from a randomised clinical trial evaluating a tablet computer for self-care, quality of life and effects on knowledge. Scand Cardiovasc J 2015;49(4):193-199 [FREE Full text] [doi: 10.3109/14017431.2015.1035319] [Medline: 25968968]
9. Carter J, Hassan S, Walton A, Yu L, Donelan K, Thorndike AN. Effect of community health workers on 30-day hospital readmissions in an accountable care organization population: a randomized clinical trial. JAMA Netw Open 2021;4(5):e2110936 [FREE Full text] [doi: 10.1001/jamanetworkopen.2021.10936] [Medline: 34014324]

10. Kangovi S, Mitra N, Grande D, White ML, McCollum S, Sellman J, et al. Patient-centered community health worker intervention to improve posthospital outcomes: a randomized clinical trial. JAMA Intern Med 2014;174(4):535-543 [FREE Full text] [doi: 10.1001/jamainternmed.2013.14327] [Medline: 24515422]
11. Kangovi S, Mitra N, Grande D, Huo H, Smith RA, Long JA. Community health worker support for disadvantaged patients with multiple chronic diseases: a randomized clinical trial. Am J Public Health 2017;107(10):1660-1667. [doi: 10.2105/AJPH.2017.303985] [Medline: 28817334]
12. Bhatia A, Maddox TM. Remote patient monitoring in heart failure: factors for clinical efficacy. Int J Heart Fail 2021;3(1):31-50 [FREE Full text] [doi: 10.36628/ijhf.2020.0023] [Medline: 36263114]
13. McBeath KCC, Angermann CE, Cowie MR. Digital technologies to support better outcome and experience of care in patients with heart failure. Curr Heart Fail Rep 2022;19(3):75-108 [FREE Full text] [doi: 10.1007/s11897-022-00548-z] [Medline: 35486314]
14. Killough CM, Madaras A, Phillips C, Hettema J, Ceballos V, Fuentes JE, et al. Community health worker insights on promoting research engagement with diverse populations. Front Public Health 2022;10:959504 [FREE Full text] [doi: 10.3389/fpubh.2022.959504] [Medline: 36711331]
15. Farwati M, Riaz H, Tang WHW. Digital health applications in heart failure: a critical appraisal of literature. Curr Treat Options Cardiovasc Med 2021;23(2):12 [FREE Full text] [doi: 10.1007/s11936-020-00885-z] [Medline: 33488049]
16. Brahmbhatt DH, Cowie MR. Remote management of heart failure: an overview of telemonitoring technologies. Card Fail Rev 2019;5(2):86-92 [FREE Full text] [doi: 10.15420/cfr.2019.5.3] [Medline: 31179018]
17. Mohebali D, Kittleson MM. Remote monitoring in heart failure: current and emerging technologies in the context of the pandemic. Heart 2021;107(5):366-372. [doi: 10.1136/heartjnl-2020-318062] [Medline: 33431425]
18. Krittanawong C, Rogers AJ, Johnson KW, Wang Z, Turakhia MP, Halperin JL, et al. Integration of novel monitoring devices with machine learning technology for scalable cardiovascular management. Nat Rev Cardiol 2021;18(2):75-91 [FREE Full text] [doi: 10.1038/s41569-020-00445-9] [Medline: 33037325]
19. Cowie MR, Lam CSP. Remote monitoring and digital health tools in CVD management. Nat Rev Cardiol 2021;18(7):457-458 [FREE Full text] [doi: 10.1038/s41569-021-00548-x] [Medline: 33824486]
20. Inglis SC, Clark RA, Dierckx R, Prieto-Merino D, Cleland JGF. Structured telephone support or non-invasive telemonitoring for patients with heart failure. Cochrane Database Syst Rev 2015;2015(10):CD007228 [FREE Full text] [doi: 10.1002/14651858.CD007228.pub3] [Medline: 26517969]
21. Wei KS, Ibrahim NE, Kumar AA, Jena S, Chew V, Depa M, et al. Habits heart app for patient engagement in heart failure management: pilot feasibility randomized trial. JMIR Mhealth Uhealth 2021;9(1):e19465 [FREE Full text] [doi: 10.2196/19465] [Medline: 33470941]
22. Zaman SB, Khan RK, Evans RG, Thrift AG, Maddison R, Islam SMS. Exploring barriers to and enablers of the adoption of information and communication technology for the care of older adults with chronic diseases: scoping review. JMIR Aging 2022;5(1):e25251 [FREE Full text] [doi: 10.2196/25251] [Medline: 34994695]
23. Raza MM, Venkatesh KP, Kvedar JC. Promoting racial equity in digital health: applying a cross-disciplinary equity framework. NPJ Digit Med 2023;6(1):3 [FREE Full text] [doi: 10.1038/s41746-023-00747-5] [Medline: 36631555]
24. Abdel-All M, Putica B, Praveen D, Abimbola S, Joshi R. Effectiveness of community health worker training programmes for cardiovascular disease management in low-income and middle-income countries: a systematic review. BMJ Open 2017;7(11):e015529 [FREE Full text] [doi: 10.1136/bmjopen-2016-015529] [Medline: 29101131]
25. Covert H, Sherman M, Miner K, Lichtveld M. Core competencies and a workforce framework for community health workers: a model for advancing the profession. Am J Public Health 2019;109(2):320-327 [FREE Full text] [doi: 10.2105/AJPH.2018.304737] [Medline: 30571307]
26. Hartzler AL, Tuzzio L, Hsu C, Wagner EH. Roles and functions of community health workers in primary care. Ann Fam Med 2018;16(3):240-245 [FREE Full text] [doi: 10.1370/afm.2208] [Medline: 29760028]
27. Carter J, Swack N, Isselbacher E, Donelan K, Thorndike AN. Feasibility and acceptability of a combined digital platform and community health worker intervention for patients with heart failure: single-arm pilot study. JMIR Cardio 2023;7:e47818 [FREE Full text] [doi: 10.2196/47818] [Medline: 37698975]
28. Spencer MS, Kieffer EC, Sinco B, Piatt G, Palmisano G, Hawkins J, et al. Outcomes at 18 months from a community health worker and peer leader diabetes self-management program for latino adults. Diabetes Care 2018;41(7):1414-1422 [FREE Full text] [doi: 10.2337/dc17-0978] [Medline: 29703724]
29. Brownstein JN, Bone LR, Dennison CR, Hill MN, Kim MT, Levine DM. Community health workers as interventionists in the prevention and control of heart disease and stroke. Am J Prev Med 2005;29(5 Suppl 1):128-133. [doi: 10.1016/j.amepre.2005.07.024] [Medline: 16389138]
30. Brownstein JN, Chowdhury FM, Norris SL, Horsley T, Jack L, Zhang X, et al. Effectiveness of community health workers in the care of people with hypertension. Am J Prev Med 2007;32(5):435-447. [doi: 10.1016/j.amepre.2007.01.011] [Medline: 17478270]
31. Ursua RA, Aguilar DE, Wyatt LC, Trinh-Shevrin C, Gamboa L, Valdellon P, et al. A community health worker intervention to improve blood pressure among Filipino Americans with hypertension: a randomized controlled trial. Prev Med Rep 2018;11:42-48 [FREE Full text] [doi: 10.1016/j.pmedr.2018.05.002] [Medline: 29984137]

32. Kangovi S, Asch DA. The community health worker boom. NEJM Catalyst 2018;4(4) [FREE Full text]
33. Kangovi S, Grande D, Trinh-Shevrin C. From rhetoric to reality—community health workers in post-reform U.S. health care. N Engl J Med 2015;372(24):2277-2279 [FREE Full text] [doi: 10.1056/NEJMp1502569] [Medline: 26061832]
34. Liu A, Sullivan S, Khan M, Sachs S, Singh P. Community health workers in global health: scale and scalability. Mt Sinai J Med 2011;78(3):419-435 [FREE Full text] [doi: 10.1002/msj.20260] [Medline: 21598268]
35. Rodrigues SM, Kanduri A, Nyamathi A, Dutt N, Khargonekar P, Rahmani AM. Digital health-enabled community-centered care: scalable model to empower future community health workers using human-in-the-loop artificial intelligence. JMIR Form Res 2022;6(4):e29535 [FREE Full text] [doi: 10.2196/29535] [Medline: 35384853]
36. McIlvennan CK, Eapen ZJ, Allen LA. Hospital readmissions reduction program. Circulation 2015;131(20):1796-1803 [FREE Full text] [doi: 10.1161/CIRCULATIONAHA.114.010270] [Medline: 25986448]
37. Carter J, Donelan K, Thorndike AN. Patient perspectives on home-based care and remote monitoring in heart failure: a qualitative study. J Prim Care Community Health 2022;13:21501319221133672 [FREE Full text] [doi: 10.1177/21501319221133672] [Medline: 36305386]
38. Carter J, Ward C, Wexler D, Donelan K. The association between patient experience factors and likelihood of 30-day readmission: a prospective cohort study. BMJ Qual Saf 2018;27(9):683-690 [FREE Full text] [doi: 10.1136/bmjqs-2017-007184] [Medline: 29146680]
39. Carter J, Ward C, Thorndike A, Donelan K, Wexler DJ. Social factors and patient perceptions associated with preventable hospital readmissions. J Patient Exp 2020;7(1):19-26 [FREE Full text] [doi: 10.1177/2374373518825143] [Medline: 32128367]
40. Spertus JA, Jones PG. Development and validation of a short version of the Kansas City cardiomyopathy questionnaire. Circ Cardiovasc Qual Outcomes 2015;8(5):469-476 [FREE Full text] [doi: 10.1161/CIRCOUTCOMES.115.001958] [Medline: 26307129]
41. Venkatesh V, Davis FD. A theoretical extension of the technology acceptance model: four longitudinal field studies. Manage Sci 2000;46(2):186-204 [FREE Full text] [doi: 10.1287/mnsc.46.2.186.11926]
42. Ben-Zeev D, Brenner CJ, Begale M, Duffecy J, Mohr DC, Mueser KT. Feasibility, acceptability, and preliminary efficacy of a smartphone intervention for schizophrenia. Schizophr Bull 2014;40(6):1244-1253 [FREE Full text] [doi: 10.1093/schbul/sbu033] [Medline: 24609454]
43. Schulz KF, Altman DG, Moher D, CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ 2010;340:c332 [FREE Full text] [doi: 10.1136/bmj.c332] [Medline: 20332509]
44. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. Int J Qual Health Care 2007;19(6):349-357 [FREE Full text] [doi: 10.1093/intqhc/mzm042] [Medline: 17872937]
45. Ong MK, Romano PS, Edgington S, Aronow HU, Auerbach AD, Black JT, et al. Effectiveness of remote patient monitoring after discharge of hospitalized patients with heart failure: the Better Effectiveness After Transition—Heart Failure (BEAT-HF) randomized clinical trial. JAMA Intern Med 2016;176(3):310-318 [FREE Full text] [doi: 10.1001/jamainternmed.2015.7712] [Medline: 26857383]
46. Chaudhry SI, Mattera JA, Curtis JP, Spertus JA, Herrin J, Lin Z, et al. Telemonitoring in patients with heart failure. N Engl J Med 2010;363(24):2301-2309 [FREE Full text] [doi: 10.1056/NEJMoa1010029] [Medline: 21080835]
47. Koehler F, Winkler S, Schieber M, Sechtem U, Stangl K, Böhm M, et al. Impact of remote telemedical management on mortality and hospitalizations in ambulatory patients with chronic heart failure: the telemedical interventional monitoring in heart failure study. Circulation 2011;123(17):1873-1880 [FREE Full text] [doi: 10.1161/CIRCULATIONAHA.111.018473] [Medline: 21444883]
48. Angermann CE, Störk S, Gelbrich G, Faller H, Jahns R, Frantz S, et al. Mode of action and effects of standardized collaborative disease management on mortality and morbidity in patients with systolic heart failure: the Interdisciplinary Network for Heart Failure (INH) study. Circ Heart Fail 2012;5(1):25-35 [FREE Full text] [doi: 10.1161/CIRCHEARTFAILURE.111.962969] [Medline: 21956192]
49. Pandor A, Gomersall T, Stevens JW, Wang J, Al-Mohammad A, Bakhai A, et al. Remote monitoring after recent hospital discharge in patients with heart failure: a systematic review and network meta-analysis. Heart 2013;99(23):1717-1726 [FREE Full text] [doi: 10.1136/heartjnl-2013-303811] [Medline: 23680885]
50. Allen JK, Dennison-Himmelfarb CR, Szanton SL, Bone L, Hill MN, Levine DM, et al. Community Outreach and Cardiovascular Health (COACH) trial: a randomized, controlled trial of nurse practitioner/community health worker cardiovascular disease risk reduction in urban community health centers. Circ Cardiovasc Qual Outcomes 2011;4(6):595-602 [FREE Full text] [doi: 10.1161/CIRCOUTCOMES.111.961573] [Medline: 21953407]
51. Vohra AS, Chua RFM, Besser SA, Alcain CF, Basnet S, Battle B, et al. Community health workers reduce rehospitalizations and emergency department visits for low-socioeconomic urban patients with heart failure. Crit Pathw Cardiol 2020;19(3):139-145 [FREE Full text] [doi: 10.1097/HPC.0000000000000220] [Medline: 32209825]
52. Jack HE, Arabadjis SD, Sun L, Sullivan EE, Phillips RS. Impact of community health workers on use of healthcare services in the United States: a systematic review. J Gen Intern Med 2017;32(3):325-344 [FREE Full text] [doi: 10.1007/s11606-016-3922-9] [Medline: 27921257]

Abbreviations

CHW: community health worker
CONSORT: Consolidated Standards on Reporting Trials
COREQ: Consolidated Criteria for Reporting Qualitative Research
ED: emergency department
EMR: electronic medical record
HF: heart failure
MGH: Massachusetts General Hospital
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture

Edited by A Mavragani; submitted 20.12.23; peer-reviewed by K Chappell; comments to author 27.12.23; revised version received 28.12.23; accepted 11.01.24; published 06.02.24.

Please cite as:
Carter J, Swack N, Isselbacher E, Donelan K, Thorndike A
Feasibility, Acceptability, and Preliminary Effectiveness of a Combined Digital Platform and Community Health Worker Intervention for Patients With Heart Failure: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2024;13:e55687
URL: https://www.researchprotocols.org/2024/1/e55687
doi:10.2196/55687
PMID:38216543

Protocol

Clinical Remote Monitoring of Individuals With Spinal Cord Injury at Risk for Pressure Injury Recurrence Using mHealth: Protocol for a Pilot, Pragmatic, Hybrid Implementation Trial

Melissa M Morrow[1], PhD; Lynne C Hughes[1], PT, PhD; Diane M Collins[1], OT, PhD; Tamara L Vos-Draper[2], OTR, PhD

[1]Department of Physical Therapy & Rehabilitation Sciences, University of Texas Medical Branch, Galveston, TX, United States

[2]College of Pharmacy, Program in Occupational Therapy, University of Minnesota, Minneapolis, MN, United States

Corresponding Author:
Melissa M Morrow, PhD
Department of Physical Therapy & Rehabilitation Sciences
University of Texas Medical Branch
301 University BLVD
Galveston, TX, 77573
United States
Phone: 1 409 266 0344
Email: memorrow@utmb.edu

Abstract

Background: Pressure injuries are one of the most challenging secondary conditions for individuals with spinal cord injuries and related disorders (SCI/D) owing to inherent, lifelong risk factors that include a lack of sensory and motor function below the level of injury and reliance on a wheelchair for daily mobility, resulting in prolonged periods of sitting. Although many factors contribute to the development of pressure injuries, the pressure between the skin and a surface is always a factor and the development of injury is dependent on the magnitude and duration of the pressure. Clinically, broad recommendations for relieving pressure are used because we know very little about the unique day-to-day life patterns of the individual wheelchair user. Typically, it is after the occurrence of a pressure injury that the therapist will check equipment fit and the effectiveness of pressure offloading and ask about other surfaces they sit on in their home and community. This time-lapsed, largely self-reported data are fraught with recall bias and inaccuracies that the therapist incorporates into a plan of care.

Objective: This study's objective is to pilot-test the implementation and clinical effectiveness of a telehealth model of care combined with our mobile health (mHealth) Assisted Weight-Shift device for remote monitoring of factors related to maintaining skin health and wheelchair setup. Our overall hypothesis is that this study will result in an effective implementation plan, and the enhanced connected model of care using remote monitoring of pressure management will result in pilot-level, improved clinical outcomes for adults with spinal cord injury at high risk for pressure injury recurrence.

Methods: For all aims, we will use a mixed methods design using an exploratory, sequential approach to include the strengths of both qualitative and quantitative data. For aims 1 and 2, we will iteratively collect qualitative data from therapists, patients with SCI/D, and other stakeholders. For aim 3, we will perform a hybrid effectiveness-implementation randomized controlled trial to pilot-test the intervention. The projected results include an iteratively developed and tested implementation plan that meets moderate to high levels of acceptability, feasibility, and appropriateness. Additionally, the pilot trial results are expected to show positive trends in relevant clinical outcomes related to reduced pressure injury incidence, recurrence, and improved healing when compared with the standard of care.

Results: Currently, 6 participants have been recruited for our aim-1 qualitative study.

Conclusions: This study will expand upon our previous study to move the Assisted Weight-Shift system into routine clinical care, which was a strong desire of adults with SCI/D for improved individualized care plans to prevent pressure injuries. The results of this study will guide the next steps in a full, hybrid effectiveness-implementation trial with the goal of improving care to prevent pressure injuries.

International Registered Report Identifier (IRRID): DERR1-10.2196/51849

(JMIR Res Protoc 2024;13:e51849) doi:10.2196/51849

KEYWORDS

wheelchair user; seating and mobility; weight shift behavior; pressure injury; mobile phone

Introduction

Background

Pressure injuries are one of the most challenging secondary conditions for individuals with spinal cord injuries and related disorders (SCI/D) owing to inherent lifelong risk factors that include a lack of sensory and motor function below the level of injury and reliance on a wheelchair for daily mobility, resulting in prolonged periods of sitting. A 2022 report stated that the incidence of pressure injuries in adults with SCI/D was 25% to 38%, with incidence increasing with time after SCI/D onset [1,2]. Recurrence rates as high as 80% [3-5] have been reported. Pressure injuries are also the second most common reason for rehospitalization at a rate of 11% to 20%, and these numbers are also increasing with time since SCI/D onset [1]. Pressure injuries are the only secondary condition consistently correlated with mortality risk [1,6], and they cause a significant negative impact on the individual, health care system, and society owing to the costs to manage them once they are present.

Interface Pressure Is a Major Risk Factor for Pressure Injuries

Although many factors contribute to the development of pressure injuries [7,8], the pressure between the skin and a surface is always a factor and the development of injury is dependent on the magnitude and duration of pressure [9,10]. An individual's pressure versus time curve is based on their ability to physiologically tolerate mechanical loads over time [11]. The longer the pressure is applied without mitigation, the higher the risk for tissue damage. Some individuals can tolerate more load over longer periods of time than others; therefore, individualization is important for prevention.

Individualized Solutions Are Necessary for Effective Prevention

Unique risk factors are present for individuals with SCI/D, including motor and sensory impairment; changes to muscle and bone tissues; and for up to 80% of those with SCI/D, the reliance on a wheelchair for mobility [1]. Individuals with more complete injuries have more impaired sensory function [12] and tend to fare worse in their ability to prevent pressure injury over time [13-15]. Movement is a key mechanism in offloading pressure, and there is high variability in daily movement patterns across the SCI/D population [16], which makes it difficult to standardize the recommendations for performing weight shifts. In addition, some individuals are physiologically better able to tolerate more or longer duration of pressure than others [17]. Each person has unique levels of risk awareness, daily routines, habits, and contexts within which they function, and these influence their ability to adhere to preventative behaviors [18]. Thus, for preventative behaviors to be added successfully to daily life, they need to be customizable and individualized to fit within each person's unique scenarios.

Standard of Care for Pressure Injury Prevention Is Individualized but Includes Limited Data About Daily Life

For the occupational or physical therapy seating specialists, care is provided in a client-centered manner such that education, treatments, and recommendations are individualized to the person as much as possible. This client-centered approach includes education about minimizing prolonged pressures under bony areas [3,11,19,20], with movement strategies to redistribute pressures [21-26] that are specific to the individual's injury level, functional level, body habitus, and so on. However, although the wheelchair, seating surface, and mechanism of pressure offloading (leaning or tilt) are specialized to the person, the clinical recommendations for the frequency and duration of skin-protective movement patterns are broadly applied to all people and range from performing weight shifts every 15 minutes to every hour and holding them for up to a 2-minute duration [3,7,19]. Broad recommendations are used because we know very little about the unique day-to-day life patterns of the individual wheelchair user. If a patient returns to their therapist after the occurrence of a pressure injury, the therapist can check equipment fit and the effectiveness of pressure offloading, and they can ask about other surfaces they sit on in their home and community. This time-lapsed, largely self-reported data are fraught with recall bias and inaccuracies that the therapist does their best to incorporate into an effective care plan.

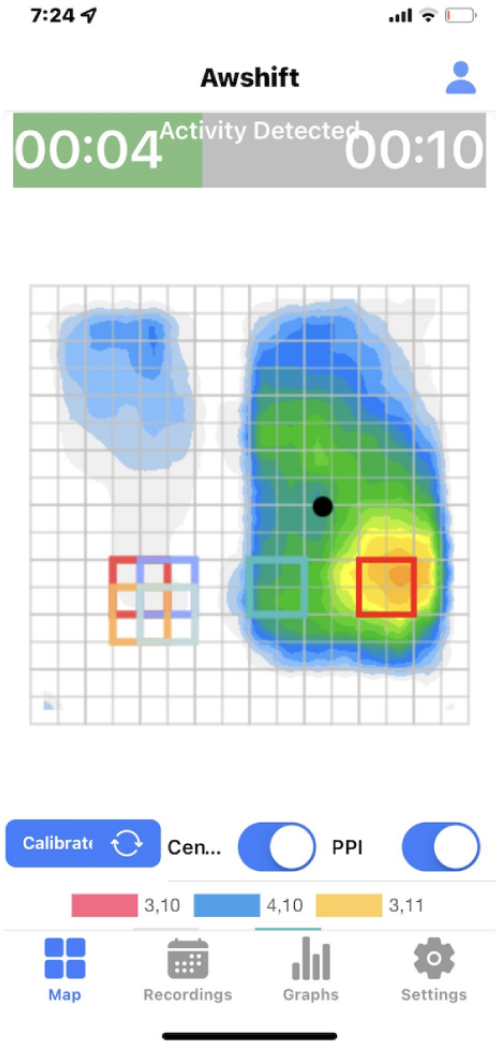
However, based on the rates of pressure injury incidence and recurrence, there is a gap in the care we can provide to individuals with SCI/D. We hypothesize that this gap is largely owing to the limited availability of data about the patient's daily life. On the basis of our own preliminary data, we know that therapists want to know the following objective and contextual data about their patients: (1) frequency and duration of daily pressure offloading behaviors, (2) effectiveness of pressure offloading during their daily weight shifts, and (3) pressure distribution on the other sitting surfaces the patient interacts with (chair, car seat, commode, etc). Without the necessary client-centered data gathered in context, the therapist is significantly limited in developing an individualized care plan.

The Assisted Weight-Shift System Monitors Factors of Individualized Pressure Management

In our Department of Defense (DoD) Spinal Cord Injury Research Program–funded project (W81XWH-15-1-0484), our group, in collaboration with veterans with SCI/D, developed the Assisted Weight-Shift (AW-Shift) system (formerly called the comprehensive mobile assessment of pressure system) to capture objective data regarding pressure management during daily life to be used by the patient or consumer and clinical partners to better prevent pressure injuries [27]. In a current National Institute of Health (NIH)–funded project (R01 AG056255), we have improved the hardware and software design of the AW-Shift system and are performing a clinical trial of the system in a consumer-use model. The AW-Shift system provides real-time pressure mapping visualization

(Figure 1), tracks weight shift behaviors, and provides weight shift reminders and high-pressure alerts. The data provided by the AW-Shift system offer unique, client-centered information to drive individualized goals and intervention plans. With this level of information about daily life, each person's unique daily occupations, routines, and rituals that influence their pressure management profile can be directly integrated into individualized care. Through DoD and NIH funding, we have demonstrated the efficacy of the system in terms of improving pressure injury prevention awareness, self-efficacy, and pressure management behavior in a consumer-use model. The proposed project advances our past studies through implementation of the AW-Shift system and evaluation of its impact on the clinical care of adults with SCI/D.

Figure 1. Assisted Weight-Shift (AW-Shift) real-time pressure map and countdown to next weight shift. PPI: Peak Pressure Index.



Structured Implementation Studies Are Necessary for Clinical Practice Improvement

Implementation research is the study of methods to optimize the systematic uptake of evidence that has been shown to be efficacious (has the intended effect) and effective (has the intended effect in the intended setting). As noted, emerging technologies such as AW-Shift may provide safe, efficient, and effective pressure injury prevention, but additional studies are needed to determine what approaches are optimal for integrating this technology and individualized data into clinical practice. The implementation of the AW-Shift system into routine clinical practice is far more complex than simply providing proof that the system works in a research setting.

Implementation into practice requires the commitment and active involvement of practitioners and patients, collaboration with relevant stakeholders who influence care delivery, and modifications to the intervention that meet the needs of providers and patients in dynamic practice settings. We have designed this project to assess the current clinical practices, iteratively modify the intervention to meet the clinical practice needs, and identify what factors may influence its uptake.

Overall Objective and Specific Aims

Overview

Our long-term objective is to facilitate the effective prevention of seating-related pressure injuries throughout the lifetime of individuals with SCI/D with the use of our evidence-based, real-time pressure management solution, the AW-Shift system (Figure 1). Our short-term objective for this study is to pilot-test the implementation and effectiveness of a telehealth model of care combined with our mobile health (mHealth) AW-Shift

device for remote monitoring of factors related to maintaining skin health and wheelchair setup. Our overall hypothesis is that our development plan will result in an effective implementation plan, and the enhanced connected model of care using remote monitoring of pressure management will result in pilot-level improved clinical outcomes (wound recurrence, early identification of wounds, and wound healing) for adults with spinal cord injury (SCI) at high risk for pressure injury recurrence. We will pursue our objective through the following specific aims.

Aim 1: Clinical System Development (Develop mHealth Report and Integrate Within the Medical Electronic Environment)

The current remote monitoring interface was built for research use. Through a user-centered, mixed methods design, we will engage with patients and clinicians through focus groups, interviews, and surveys to determine the optimized design for the capture and reporting of data to the patient and the clinician through a connected care model. After the capture and reporting method is developed, the data flow will be integrated within electronic medical record infrastructure.

Aim 2: Rapid Cycle Quality Improvement (Integrate System Into Connected Care and Telemedicine Infrastructure)

Using best practices for rapid cycle quality improvement, we will integrate our connected care solution into a current telehealth infrastructure. We will test the ability of our connected care solution to perform patient visits and short-term remote monitoring of pressure management focused on the system integration aspects to cycle through improvements in a 3-month time frame to prepare for aim 3.

Aim 3: Pragmatic, Hybrid Implementation Trial (Implement the Connected Care Solution via a Pilot, Pragmatic Trial Comparing Clinical Outcomes Between the Connected Care Model and Standard Practice)

Patients identified as having high risk for pressure injury recurrence will be randomized to either the connected care model (Figure 2) or the standard model of care for a 1-year follow-up time frame. Our implementation outcomes include important stakeholders' assessment of feasibility, acceptability, appropriateness, costs, and improved monitoring. Our pilot effectiveness outcomes are rate of wound healing for prevalent cases, incidence and recurrence of pressure injuries, early identification of wounds, and hospital admissions or readmissions.

Figure 2. Through a connected care model and the Assisted Weight-Shift mobile health system, the provider guides the patient to change high-risk pressures (phone image on the left) into safe pressures (phone image on the right).

Methods

Study Design

For all aims, we will use a mixed methods design using an exploratory, sequential approach to include the strengths of both qualitative and quantitative data. For aims 1 and 2 of the study, in an iterative manner, we will collect qualitative data from therapists, patients, and other stakeholders. For aim 3, using both qualitative and quantitative data, we will perform a hybrid effectiveness-implementation randomized controlled trial to pilot-test the intervention. For implementation outcomes, we will assess the feasibility, acceptability, and appropriateness for the in-home use by the patients and the feasibility, acceptability, and appropriateness of the previsit information from clinical stakeholders. For pilot effectiveness, we will assess the clinical outcome measures of wound recurrence, early identification of wounds, and wound healing.

Ethical Considerations

All research activities for aims 1 to 3 will be performed under institutional review board (IRB) oversight and with IRB approval. At the time of the writing of this manuscript, aim 1 was approved by the University of Texas Medical Branch IRB (22-0280) as an exempt study that waives the requirement for informed consent. The study is no more than minimal risk and fits the second exemption category (interviews), including recording data in such a manner that the identity of the human participants cannot be readily ascertained through identifiers linked to the participants. IRB approval for aims 2 and 3 will be sought under the minimal risk category. We expect that owing to the iterative nature of aims 2 and 3, modifications will be

required throughout the study to accommodate updates to the protocol and procedures, motivated by study staff and participant experiences and feedback. Participants for aim 1 are compensated for their participation with a gift card worth US $50. Participants for aims 1 and 2 will be compensated for their time with payment commiserate with the time required to complete the study.

Rationale for Hybrid Effectiveness-Implementation Study Design

Hybrid designs were developed to improve efficiency in moving promising interventions along the efficacy-effectiveness-implementation continuum, as implementation research focuses on the adoption of evidence-based interventions by systems of care. Integrating implementation planning into the study design helps to promote the full adoption of an intervention into the practice in which it was tested. We propose to use a hybrid-1 design [28], wherein the study is designed to test a pilot clinical intervention while gathering information about its delivery during the effectiveness trial and about its potential implementation in "the real world" of clinical practice. We will simultaneously plan for implementing AW-Shift into practice while testing its effectiveness in changing clinical outcomes. Our design includes formative evaluations of clinical staff during the study period, which will provide a rigorous assessment of what potential internal and external influences are critical for a successful implementation and add qualitative data to enrich the data analysis and evaluation.

Rationale for Using Consolidated Framework for Implementation Research Implementation Model to Guide Implementation

We propose to use Consolidated Framework for Implementation Research (CFIR) to inform which implementation targets will be critical for successful implementation. CFIR is a meta-theoretical framework that is based on a synthesis of 19 implementation frameworks and models with a goal to "foster knowledge-building into why implementations succeed or fail." It includes 5 domains: outer setting, inner setting, intervention characteristics, individual characteristics, and process. Each domain includes common constructs, 39 in total, associated with successful implementation. The framework does not specify hypotheses or causal pathways, allowing flexibility in evaluating constructs that are unique to a study. It has been described as a "menu of constructs" that enables systematic and comprehensive exploration and identification of potential factors that can influence implementation [29]. In general, the framework helps researchers and interventionists to assess the structural capacity for an intervention, culture for change, perceptions from stakeholders about the need for change, quality of the proposed solution, and way in which the intervention should be planned and executed. Regarding the qualitative work for aim 1, we will explore the potential constructs in each domain (eg, design quality and packaging, patient needs and resources, compatibility, relative priority, leadership engagement, and self-efficacy) from the CFIR model that will inform the efforts for the rapid cycle assessment in aim 2 and pilot trial in aim 3.

Specific Aim-1 Methods: Clinical System Development

The goal of aim 1 is to define the scope of the implementation of the AW-Shift system into a connected care model and operationalize that scope into a testable plan for aim 2. Each step of the plan will be guided by the end users and other key stakeholders through qualitative and survey feedback.

Patient and Clinician Needs Assessment

Overall, 2 focus groups, 1 for adults with SCI/D and 1 for clinicians from the Seating Clinic and Wound Care, will be conducted to determine the needs and priorities of each group for improving the assessment of seating and mobility needs. A focus group guide, drawn from CFIR's Interview Guide Tool [30], will be used for each group to better understand how expanded seating pressure information captured during the daily life of patients could better inform seating and mobility therapy visits. The discussion will include brainstorming of types of information that would be of value and identifying barriers to and facilitators of attaining the information. There will be an emphasis on understanding the concerns about the complexities of a new process as it relates to the outer setting, inner setting, and individual characteristic constructs of the CFIR model [31]. The focus groups will be conducted through a Health Insurance Portability and Accountability Act–compliant web-based meeting format (Zoom; Zoom Video Communications). The discussion will be recorded for analysis.

Qualitative Outcome Measures and Data Analysis

The qualitative data from the focus groups will be transcribed by a transcriptionist. Investigators will import transcripts and field notes into computer-assisted coding software such as NVivo (Lumivero) to structure the transcripts and enable them to be "openly coded" by the researchers. The CFIR constructs will guide the development of the code book, as these constructs are key to effective implementation. Qualitative analysis of the interview transcripts will combine deductive and inductive approaches using an initial coding template structured around the interview guide topics and then refined through full data set coding [32]. The coding template refinement process will include an element of reflexivity owing to clinical expertise of coders, thus offering an efficient process to generate high-value design requirements layered with contextual rationale. Through memo-taking and iterative meetings to discuss data, the team will reach consensus about the code book and the assignment of text segments to particular codes. Investigators will independently review the transcripts and codes to provide a measure of internal validation. A coalescence of major themes from the coders will be used for the interpretation of findings and the subsequent theory development. The survey data will be used to define the areas of strengths and weaknesses of the intervention and implementation plan.

Sample Size

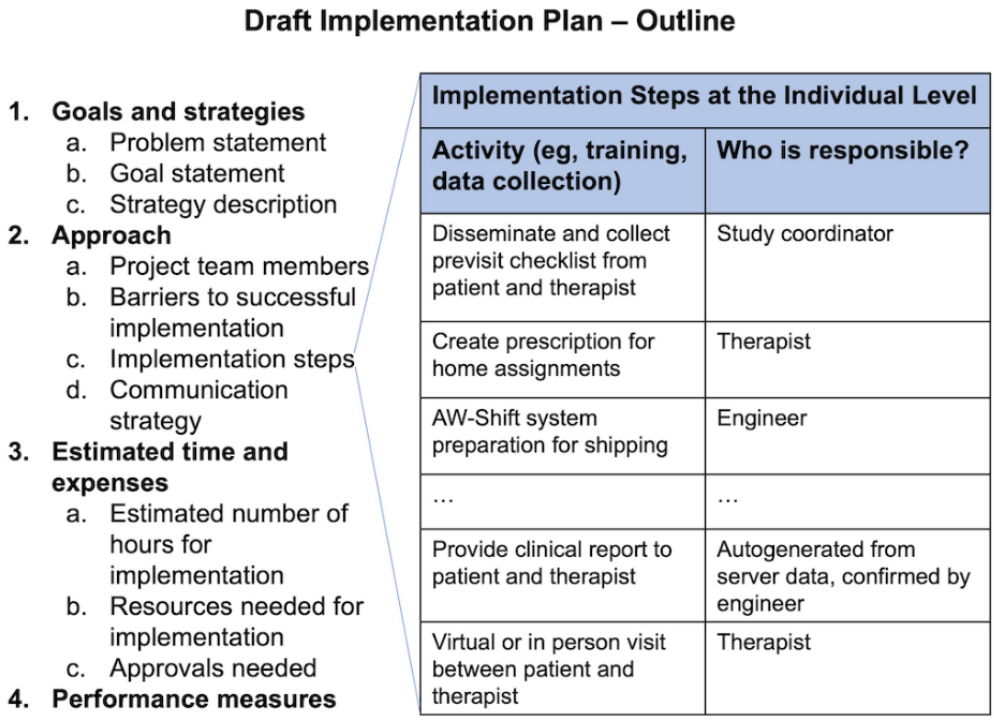
For focus groups, we will follow the recommended practice by having no more than 10 participants per group [33]. For the patient focus group (n=10), we aim to purposively sample patients with various levels of SCI/D, wheelchair type (power and manual), history of pressure injuries, and age to seek a wide breadth of user experiences. For the therapist focus group

(n=10), we aim to purposely sample therapists with a range of years of experience, to seek a breadth of perspectives about providing seating and mobility care to patients with SCI/D.

Draft Plan and Follow-up Focus Group

Needs assessment will be used to refine the draft implementation plan (Figure 3). Following the refinement of the draft plan, a follow-up focus group with clinicians and patients will be conducted, wherein the draft plan will be presented along with a description of the AW-Shift system. Through this focus group, we seek to understand the specific types of data and activities to measure during daily life that can inform the clinical assessment. In addition, the participants may be queried about specific aspects of the plan using survey responses that will likely use a Likert scale for assessing the level of satisfaction or acceptability with aspects of the plan. We will learn from these focus groups and survey responses regarding what needs to be adapted in the draft plan and what data will be used in the mHealth report. We will operationalize the implementation plan based on the participant feedback and use the CFIR constructs to increase the usability and acceptance of the AW-Shift system by participants or patients with SCI/D.

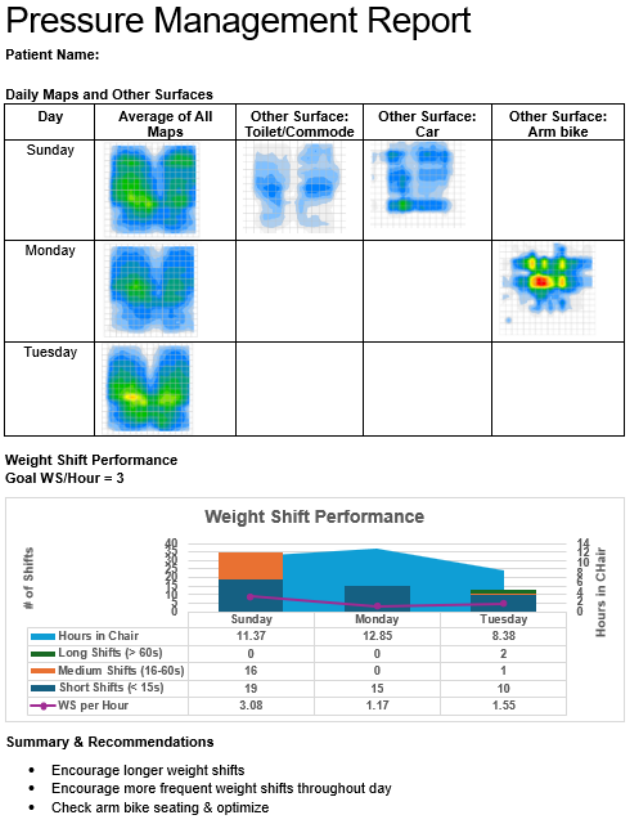
Figure 3. Implementation outline with example implementation steps. AW-Shift: Assisted Weight-Shift.



mHealth Report

The mHealth report will provide summary data and visualizations that provide an informative snapshot of the home testing period (a partial example is shown in Figure 4).

Figure 4. Example of a partial mobile health report. AW-Shift: Assisted Weight-Shift.



Integration of the mHealth Report Into the Clinical Electronic Environment

On the basis of the focus group findings, the team will perform the following tasks in collaboration with necessary stakeholders. We will adapt the current, remote data capture process and infrastructure to meet the patient and therapist priorities and requirements for use during the clinical visit. A likely solution for communication of the data will involve the mHealth report being autogenerated on the server and provided back to the patient through the mobile app before the telehealth visit. The patient, being the ultimate owner of their data, will then send their report to their therapist through a secure patient website or mobile app that allows direct communication to the care team and patient access to their web-based medical record. With this data flow plan, the report would be available to the therapist for easy viewing during their visit. In addition, the patient will have full awareness of the data that the clinician is viewing.

Iterative Process for User-Designed Implementation of the AW-Shift System Into Clinical Care

Through a series of iterative focus groups and further refinement steps, the team, along with the users of the system (patients and therapists), will co-design the full implementation plan that will be ready for testing in aim 2. We estimate this step will take 2 to 3 iterations of focus groups and refinement steps.

Specific Aim-2 Methods: Rapid Cycle Quality Improvement

Overview

Rapid quality improvement assessment of the implementation plan will be completed in aim 2 by testing the plan with an estimated 10 patients with SCI/D. For the first 3 to 5 patient participants, each participant will be run 1 at a time through the implementation plan. Rapid adjustments will be made as each participant goes through the steps of the plan. For the final 6 to 8 participants, participants will be scheduled in pairs such that at least 2 participants will be run in parallel to test the ability of the implementation plan to adjust to concurrent use of the system in the participants' home and community. After each participant set, we will make rapid adjustments to optimize the implementation plan. Owing to participant heterogeneity, we will be mindful about how plans will need to be optimized differently depending on patient characteristics such as injury level and whether a caregiver or personal aid is required by the patient to use the system.

Protocol for Connected Care Model

Although the specific details of this protocol may change, we propose an outline of the procedures that will occur after participant consent and enrollment.

Individualized AW-Shift Prescription

A seating clinic therapist will review the clinical notes of the participant for their seating and mobility history. We presume from our preliminary data from therapists and the knowledge of the clinical team members in this project that a simple initial checklist will be effective in determining the possible "home

assignments" that therapists could give to patients to gather the pertinent information specific to the patient, including recording pressure across different surfaces, using weight shift reminders, and recording weight shifts performed during specific tasks. In addition, the patient will be asked to complete a checklist to identify their seating and mobility concerns including, for example, new areas of concern about their skin, seat cushion, weight shifting habits, pressure on other surfaces, sitting posture, or weight relief quantity or quality. On the basis of the checklist information, an individualized prescription will be developed for the participant to fulfill (with extensive team support) during the 2-week daily life testing period.

System Setup and Prescription Delivery

The participant will be shipped an AW-Shift system and scheduled for a virtual visit to set up the system by the study coordinator. The system will include the hardware components, a user manual, and a study-provided smartphone or tablet if the participant does not have their own device. If the participant is using their own phone, they will be instructed to download the AW-Shift mobile app from the Apple App Store or Google Play Store. During the system setup visit, the participant will be provided with training regarding how to use the AW-Shift system with the study coordinator and engineering and therapy experts on the study team. The team will review the individualized prescription with the participant, and knowledge about system use will be tested to determine sufficient mastery of using the system.

Home and Community Use of the AW-Shift System

Participants will use the system for an estimated 2 weeks before their clinical visit. Participants will have easy access via phone; secure, web-based format; email; and SMS text message for technical and therapy support. A potential prescription could include (but not be limited to) mapping the variety of surfaces the participant sits on in the home and community (the system can be used on any surface), completion of daily weight shift protocols to assess participant positioning on their cushion, measurement of how the participant performs weight shifts with and without reminders provided by AW-Shift, and measurement of the effectiveness of the weight shifts to offload pressure.

Summary Report

Before the telehealth clinic visit, the prepared mHealth report will be delivered via the AW-Shift mobile app to the participant. The participant will be instructed about how to upload the report 1 day before their telehealth clinical visit. The therapist will view the mHealth report via the participant's medical records during the clinical visit.

Telehealth Clinical Visit

During the visit, the therapist will use the standard clinical notes and the data provided on the mHealth report to guide the patient participant through the typical steps of a therapy visit focused on the seating and mobility needs related to pressure injury prevention. The telehealth visit will be completed using the standard Zoom interface. The therapist will use all the information they have available to determine the next steps in the patient's care plan. The clinic visits will be recorded, so that the study team can provide additional observations for use in process improvement. The therapist will ask for confirmation of a skin check performed on the day of the visit with assistance from a caregiver, if necessary.

Assessment

Following the telehealth visit, both the patient participants and the therapists will complete a series of surveys to assess usability (System Usability Survey [34]), acceptability (Unified Theory of Acceptance of Use of Technology [35,36]), feasibility (Feasibility of Intervention Measure [37]), and appropriateness [37] of the procedures, and each of them will participate in a short interview to gather qualitative feedback to improve the implementation plan.

Rapid Assessment Procedure

Rapid assessment procedures are a pragmatic option for producing timely, contextually rich evaluative information about complex interventions implemented into dynamic clinical settings [38]. We will use rapid assessment procedures after each participant in the first 3 to 5 participants or after each pair of the final 6 to 8 participants to improve the plan for the next set of participants.

Stakeholder Input About Case Summaries

The findings from aim 2 will be written as a case summary that will be presented to the patient and therapist focus groups from aim 1 to gather additional stakeholder input about the optimization process. Any points regarding necessary improvement or inconsistencies will be discussed by the research team until consensus is achieved for the final plan for aim 3.

Outcome Measures and Data Analysis

The qualitative data from focus groups and interviews will be managed and analyzed as described for aim 1. The quantitative data from the survey scores will be used to define the areas of strengths and weaknesses of the intervention and implementation plan for further refinement.

Sample Size

For the rapid assessment testing for aim 2, we provide a robust approach by cycling the process through single and paired visits. Similar to the focus groups, we will sample to attain a breadth of user experiences. A total of 10 participants for each round is an effective sample size to be able to narrow down and optimize the process [33].

Data Management

All study data will have unique identifiers removed before the final analysis. Study data will be imported from the various clinical data sets into a central REDCap (Research Electronic Data Capture; Vanderbilt University) database that can be accessed by the study team. The study coordinator managing the database will keep the electronic key secure in accordance with Health Insurance Portability and Accountability Act and patient privacy regulations.

Potential Limitations and Alternative Strategies

Failure of the System in the Field

We will monitor system use and will be available for troubleshooting. We currently have 25 full systems and will be able to accommodate equipment swapping by mail.

Recruitment

We have experienced very little difficulty in reaching our goals for participation in past studies with similar methodology. We will continue to collaborate closely with clinical staff and consumer groups to ensure successful recruitment.

Skin Safety

We will continue to track skin safety during the study and will discontinue use if we notice any signs of skin issues.

Sensing Technology

The current resistive sensors used in the selected pressure map have inherent limitations including a tendency to creep under prolonged loaded states, but we mitigate this through specific calibration protocols. The mat was selected because it stretches and is durable for whole day use.

Specific Aim-3 Methods: Pilot

Pragmatic Hybrid Implementation Trial

The proposed pilot randomized controlled trial will test whether our novel AW-Shift system intervention adds value to the clinical care of adults with SCI/D to inform our next steps in translation.

Study Design

This single-site randomized controlled trial will use a modified intention-to-treat analysis. Randomization will be a stratified, block randomization with stratification based on wheelchair type (manual vs power) and current wound severity (no wound or stage 1 vs stage 2 or stage 3). The intervention group (26/52, 50%) will receive the connected care model that used AW-Shift in combination with telehealth. The control group (26/52, 50%) will receive the standard of care that uses telehealth when appropriate. The statistician will be masked to the group allocation information for the outcome measure analysis.

Randomization

We will stratify based on wheelchair type (2 groups: power and manual), and current wound severity (2 groups: no wound or stage 1 and stage 2 or stage 3). We will block randomize in groups of 4. This randomization scheme will ensure distribution of important confounders between arms of the study. Furthermore, the blocking will ensure equal distribution of group assignment during the study.

Study Population

Adults with SCI/D with high risk of recurring pressure injury who answer "yes" to one of the following questions are eligible: (1) I get pressure ulcers about every couple of years; (2) I get at least 1 pressure ulcer a year; and (3) I always seem to have sores, often requiring surgery or hospitalization [39]. Our rationale for choosing individuals at high risk for recurring injury is that once a person has one pressure injury, their chances are significantly high to have another; hence, it has been recommended that interventions focus on this group of individuals [39].

Initiating and Conducting the Pilot Clinical Trial

The principal investigators (PIs), coinvestigators, and study staff will manage the process of study initiation with a modified standard checklist that covers essential items. Pilot clinical trial initiation meeting will occur early in mid–year 1, wherein all the steps will be reviewed, and the specific timeline will be determined. Standard operating procedures and field guidebooks will be developed to follow throughout the trial period. Weekly phone calls or web-based meetings among all study members will be used for study management. Any urgent communication regarding the pilot clinical trial will be managed with a phone call to the PI made within 18 hours of the event and reported to the IRB.

Study Procedures

For initiation and administration of the intervention, the following procedures will be followed:

1. Project initiation: The project will be initiated following a study initiation checklist by the PI and local site investigators.
2. Staff training for the intervention: Staff will be instructed about how to use the AW-Shift system, view and use the mHealth report, and administer data collection elements as is appropriate for each study role. Data collection procedures will be standardized and tested for consistency across study team members.
3. Participant recruitment: Recruitment and enrollment during year 2 will occur primarily through clinical staff in collaboration with the study coordinator.
4. Intervention study period: The intervention will begin with 2 weeks of AW-Shift use at home by the patient with SCI/D, followed by a web-based clinical visit with a seating clinic therapist. Before mailing AW-Shift to participants, individualized tasks will be assigned by the seating specialist. The tasks are meant to inform the seating assessment process during the clinical visit. Participants and seating specialists will complete surveys after the seating clinic visit and participate in a guided interview.

Intervention Protocol

The planned intervention protocol is similar to that described for aim 2, for the rapid quality assessment as described in the *Protocol for Connected Care Model* section. We expect that the protocol will be improved through the iterative process we are using to optimize the implementation of our intervention. Full demographic variables relevant to SCI/D will be collected during the consent visit. The same surveys and structured interview will be completed after each visit by the intervention group participants and the therapists including assessment of usability (System Usability Survey [34]), acceptability (Unified Theory of Acceptance of Use of Technology [35,36]), feasibility (Feasibility of Intervention Measure [37]), and appropriateness [37] of the procedures.

Control Protocol

If participants are randomized into the control group, the standard of care protocol will be followed as used in the seating clinic. Demographic and additional variables will be collected from participants similar to those in the intervention group, and their clinical visit will be recorded for assessment of the visit.

General Statistical Methods

All tests are 2 sided, with a 0.05 type-1 error rate. Analysis will be conducted using SAS (SAS Institute) and R software (GNU Project). Mean and SD or median and IQR will be reported for all demographic, predictor, and outcome variables, as appropriate. For all outcome measures, the effect of relevant biological variables including sex, age, level of sensation, and pressure injury history will be assessed as covariates in the analysis. In addition, wheelchair type will be included as a covariate. Variables will be transformed as necessary to meet the appropriate distributional assumptions for modeling (eg, normality). For missing data, mixed models can be used to handle missing data naturally, so that all available data points may be analyzed, irrespective of whether the participant had some outcome data missing. However, analyses of data with multiple imputation for missing data may be attempted if the data are likely to be missing at random.

Primary Pilot Clinical Trial Effectiveness Outcomes

The primary effectiveness of the intervention will be captured via the collection of the following clinical outcomes: wound recurrence, early identification of wounds, wound healing, and hospital admission or readmission. The data for these metrics will be abstracted during the full year (365 days) after the study-related clinical visit for both the control and intervention group participants. Then, 2 independent therapist team members will abstract the medical records of each participant to search for the occurrence of an incident wound, stage at which wounds are identified, time frame of wound healing, and occurrence of a hospital admission or readmission directly related to a seating area pressure wound. Comparisons between groups for the primary outcome measures will be made using a 2-tailed *t* test. Additional comparisons will be made with regression and mixed effect models to explore the role of covariates on the study findings.

Secondary Pilot Clinical Trial Effectiveness Outcomes

As a proxy outcome measure for clinical effectiveness, each clinical visit for the control and intervention groups will be assessed using the review of visit checklist shown in Figure 5 by the therapists leading the clinical visit. Then, 2 independent raters, who are seating specialists, will assess the checklist for each participant and will be blinded to the identities of the patients and therapist. The reviewers will rate the visit information on a 5-point Likert scale (eg, “Rate the effect of AW-Shift data on clinical recommendations: (1) significantly diminished, (2) diminished, (3) neither improved nor diminished, (4) improved, or (5) significantly improved”). The reviewer ratings will be analyzed with a 2-sample Mann-Whitney *U* test to determine if the ratings are different between groups to test our hypothesis that the AW-Shift data will significantly improve clinical recommendations. Effectiveness will also be assessed qualitatively in the interviews.

Figure 5. Clinical visit review checklist.

Clinical Visit Checklist

Used for retrospective chart review and for study visit video observation.

Participant ID:

Visit Date:

Does the documentation indicate that:	Yes	No
○ Participant has a concern regarding pressure?		
○ Pressure mapping completed during the visit?		
○ There were concerns about pressure management?		
○ Mention of surfaces other than the seat cushion/wheelchair used during the visit?		
○ There is a need for further evaluation of pressure on other surfaces?		
○ New equipment or modification of current equipment needed?		
○ A change in daily routine or daily activities is needed?		
○ There is a need for change in weight shift practice		
○ Frequency		
○ Duration		
○ Consistency		
○ Method for improved pressure distribution		

Comments (indicate the recommendations and strategies that were documented):

Implementation Outcome Measures

Implementation success will be assessed using feasibility, acceptability, and appropriateness surveys regarding the in-home system use of participants and therapists. This information will guide the broad implementation of the intervention.

Additional Study Variables, Controls, and End Points

Demographic variables relevant to SCI/D will be collected and used in the analysis as appropriate. Additional metrics include self-efficacy in managing pressure, assessed using the Skin Care Belief Scales [40]; consistency of weight shift performance, as measured by the AW-Shift system during home use; and the SCI–Quality of Life scale.

Feasibility Study Variables

For future clinical trial planning, the study variables of screening rate, recruitment rate, enrollment rate, and retention rate will be measured. In addition, the treatment adherence rate and treatment fidelity rates will be measured, and the assessment process will be evaluated. The assessment process includes documenting the planned assessments and data collection instruments that are completed in addition to the duration of the visits.

Sample Size

The sample size for this pilot study (N=52; n=26, 50% per group) is based on guidance that for a trial with 90% power and 2-sided 5% significance, pilot trial sample size of 25 participants per treatment arm is sufficient for an expected small, standardized effect size (0.2) [39]. We do not have the needed data for our primary outcomes to directly determine the power of our planned study design; however, this pilot study will be used to power the full clinical trial. Furthermore, we have used approaches to optimize our statistical power including blocking within the design itself that adjusts for covariates during randomization to reduce imbalance and triangulating the findings of quantitative analyses with qualitative data in mixed methods designs [41].

Potential Limitations and Alternative Strategies

In addition to the potential limitation described for aim 2, aim 3 has the added potential of loss to follow-up. As the long-term follow-up data are passively extracted from the medical record, we acknowledged that patients may seek care outside the original health system they were recruited from. In addition, for participants who have data that we cannot access, we will seek the approval of the participant to access their medical records from other medical systems.

Human Participants

Study Population

Focus groups and structured interviews will be conducted for all aims. Qualitative methods will include adult patients with SCI/D and seating and mobility therapy specialists. Adults with a SCI/D will be the participants for aims 2 and 3. As needed, we will capture additional input from other stakeholders involved in the proposed implementation process to ensure that we are gathering views from a broad range of affected individuals as per the CFIR framework. These individuals may include therapy managers, IT staff, data security staff, scheduling staff, and industry representatives.

Recruitment

Following IRB guidelines, manual and power wheelchair users with traumatic or atraumatic SCI/Ds will be enrolled for the study. The inclusion and exclusion criteria were chosen to include wheelchair users with SCI/D who are at risk for pressure injury development. Recruitment will be purposeful in achieving the desired equal distribution of power and manual wheelchair users and individuals with paraplegia and tetraplegia. For study randomization in aim 3, we will use a stratified, blocked randomization method to ensure even distribution of important predictor and confounding variables in the intervention and control groups. Announcements for participation in this study will be made by personnel directly to patients through mailed letters, phone calls, and word of mouth. Upon determining a person's eligibility, an appointment (via phone or in person) will be made with the study coordinator to explain the research project, confirm eligibility, and collect the necessary demographic data.

Inclusion and Exclusion Criteria

We will enroll adult men and women, aged between 18 and 80 years, with SCI/D at C4 or below, who have a lack or absence of sensation, are primary wheelchair users, and are at high risk for pressure injury. For aims 2 and 3, participants must have had a seating clinic visit or be scheduled for a seating clinic visit. Participants must demonstrate the ability to independently access the AW-Shift system app on a mobile phone or tablet and be able to participate in web-based visits or meetings with the research team. Participants will be excluded if they are unable to consent, have an active stage-4 wound at the seating surface site, do not have adequate resources or support for use of the AW-Shift technology in their home environment, or are currently receiving palliative care. We will enroll current occupational or physical therapy staff for aim-1 qualitative and survey feedback.

Potential Risks

There is the potential for skin irritation from sitting on a pressure mat for long periods. Participants may sit on the pressure mat throughout the day or may simply use it for short periods while performing their prescribed activities. Participants will be instructed to do a skin check every day and log their findings.

Participants are instructed to call the study coordinator if a new area of skin breakdown or wound occurs while they are using the pressure mat or if a current wound worsens. The participant will be asked to remove the mat until the skin breakdown or wound resolves. If the area does not resolve and worsens further, the participant will again contact the study coordinator and will then be referred to their typical clinical care provider in the case of a potential, new-onset incidence of pressure ulcers of stage 3 or 4. Initializing and deploying the AW-Shift system will require performing transfers and weight shifts. Transfers always have some risk of injury or fall, and the participant will be advised to transfer in their usual manner. Weight shifts will include typical functional movements, such as leaning forward and sideways, but participants will be instructed to only perform weight shifts with which they are comfortable. Risks from transferring on their own while the sensors are on the wheelchair are no different than transferring without the sensors present.

Focus Group Guide

Questions were created for the clinicians' structured interviews and focus groups. A sample of the question list is shown in Textbox 1.

Textbox 1. Sample of question list.

- What are some of the challenges you come up against when teaching a patient with spinal cord injuries and related disorders (SCI/D) about pressure relief?
- On the basis of feedback from our patients of how very useful real-time information is to their pressure relieving behavior. What do you think about the having the real-time image available all the time to the patient?
  - Do you think having that image available will assist you in monitoring and teaching seating behavior?
- What other information, or data, would you want to be readily available to you to monitor the patients' learning of pressure injury prevention behaviors?
  - For example, would it help you to know how many pressure reliefs the patient conducted during the previous hour?
- Would you like the data available for you to be in a particular format?
  - For example, an average number of pressure reliefs conducted over the past four hours, or the percentage of offload over a certain period?
  - How far back would you want data available for monitoring or educating pressure relieving behaviors?
  - Do you want the information pushed to you?
- Can you think of any data that would not be helpful for you to be able to access?
  - For example, when reviewing the patients pressure relieving behavior would you find it useful to know the actual peak psi's that occurred over the previous period of monitoring, or would that be too much information?

Implementation Strategies

We developed the draft of our study-specific implementation strategies (Table 1). From this chart, a refined, operational implementation guide would be created.

Table 1. Implementation strategies chart.

Study phase	Implementation strategies
Prestudy	• Conduct local needs assessment • Conduct local consensus discussions • Fund and contract for the clinical innovation • Use an implementation advisor • Develop an implementation glossary • Identify and prepare champions • Identify early adopters • Inform local opinion leaders • Build a coalition • Assess for readiness and identify barriers and facilitators • Promote network weaving • Develop and organize quality monitoring systems • Develop and implement tools for quality monitoring
Aim 1: Clinical system development: define scope of implementation of AW-Shift[a] into a Connected Care model	• Develop a formal implementation blueprint • Build a coalition • Conduct educational meetings • Distribute educational materials • Promote adaptability • Prepare patients or consumers to be active participants • Involve patients or consumers and family members • Obtain and use patients or consumers and family feedback • Shadow other experts • Use data warehousing techniques
Aim 2: Rapid cycle quality improvement: rapid quality improvement assessment of the implementation plan	• Facilitation • Conduct educational meetings • Conduct cyclical small tests of change • Provide ongoing consultation • Provide local technical assistance • Provide clinical supervision • Organize clinician implementation team meetings • Prepare patients or consumers to be active participants • Involve patients or consumers and family members • Purposely reexamine the implementation • Obtain and use patients or consumers and family feedback • Tailor strategies • Remind clinicians • Intervene with patients or consumers to enhance uptake and adherence • Shadow other experts • Facilitate relay of clinical data to providers • Use data warehousing techniques
Aim 3: Hybrid pilot clinical and implementation trial: randomized controlled trial to test whether AW-Shift system adds value to clinical care of people with SCI/D[b]	• Stage implementation scale up • Provide ongoing consultation • Provide local technical assistance • Provide clinical supervision • Remind clinicians • Recruit, designate, and train for leadership • Use data warehousing techniques • Obtain formal commitments

[a]AW-Shift: Assisted Weight-Shift.

[b]SCI/D: spinal cord injuries and related disorders.

Results

This study was funded in January 2023, and the IRB approval for Aim 1 of the study was December 5, 2022. We have recruited 6 participants into the clinician arm of our Aim 1 qualitative study as of manuscript submission. Expected results for Aim 1 to be published in winter 2024.

Discussion

Expected Outcome

Pressure mapping performed in rehabilitation clinics can effectively determine appropriate equipment and positioning in a wheelchair [42-44], but the translation of the same information from daily life into clinical care has not been previously tested. The day-to-day uncertainty of ulceration leads to patient

appointments simply to “be mapped” as a preventative action often involving long distances and, sometimes, with an active pressure injury. A system such as AW-Shift can be integrated into a connected care model to allow for the integration of real-world data into the clinical practice of wheelchair users with SCI/D. The system has the potential to enhance the prevention of pressure injuries. Our mapping system has the ability to address and correct the contributors to pressure ulceration that have been observed in seating and mobility clinics: undetected cushion failures; caregivers who are unexpectedly late or absent, leaving the patient in the chair longer than necessary; frequent caregiver turnover; inexperienced caregivers; and caregivers who struggle with positioning the patient. AW-Shift can provide meaningful information about the daily life of people with SCI/D to the patient, caregivers, and clinicians to significantly improve the management of patient needs.

This project will demonstrate the ability to use an mHealth solution for improvement in pressure injury clinical outcomes. The success of this project will have sustained, powerful influence in the field of SCI/D through enhanced evidence of pressure injury risks that are present in a wheelchair user’s daily routine and environment that are not identifiable through routine, in-person evaluations in the clinic. It will further demonstrate the opportunity for the clinician and individual with SCI/D to work together to plan effective strategies for more expeditious interventions.

We hypothesize that an enhanced connected model of care using remote monitoring of pressure management will result in improved clinical outcomes (wound recurrence, early identification of wounds, and wound healing) for adults with SCI at high risk for pressure injury recurrence. We have performed extensive studies assessing the acceptability, usability, and efficacy of the AW-Shift system with adults with SCI/D. We now need to partner with patients and clinicians (therapists) to capture seating pressure information during daily life to inform clinical visits for individualized seating and skin health recommendations. On the basis of our projects funded by DoD, NIH, and Veterans Administration, we know that adults with SCI/D and therapists who treat them have the strong desire for a visual system and expanded access to data from daily life. Changing current clinical practices will require engagement and collaboration with providers and patients about what information is critical and how it should be used with clinical guidelines. This project will expand upon our previous study to move the AW-Shift system into routine clinical care, which was a high desire of adults with SCI/D for improved individualized care plans to prevent pressure injuries.

Acknowledgments

Funding support for this project is provided through the generous support of the Craig H Neilsen Foundation.

Conflicts of Interest

TLV-D, MMM, and Mayo Clinic have a financial interest related to this study. MMM and TLV-D are inventors of the Assisted Weight-Shift system. The previous study reported in this paper has been reviewed by the University of Minnesota and Mayo Clinic Conflict of Interest Review Board and has been conducted in compliance with both policies.

References

1. The 2022 annual statistical report complete public version for the spinal cord injury model systems. National Spinal Cord Injury Statistical Center. URL: https://www.nscisc.uab.edu/public/AR2022_public%20version.pdf [accessed 2024-01-13]
2. Raghavan P, Raza WA, Ahmed YS, Chamberlain MA. Prevalence of pressure sores in a community sample of spinal injury patients. Clin Rehabil 2003 Dec;17(8):879-884 [FREE Full text] [doi: 10.1191/0269215503cr692oa] [Medline: 14682560]
3. Bates-Jensen BM, Guihan M, Garber SL, Chin AS, Burns SP. Characteristics of recurrent pressure ulcers in veterans with spinal cord injury. J Spinal Cord Med 2009;32(1):34-42 [FREE Full text] [doi: 10.1080/10790268.2009.11760750] [Medline: 19264047]
4. Niazi ZB, Salzberg CA, Byrne DW, Viehbeck M. Recurrence of initial pressure ulcer in persons with spinal cord injuries. Adv Wound Care 1997;10(3):38-42. [Medline: 9306777]
5. Stillman MD, Barber J, Burns S, Williams S, Hoffman JM. Complications of spinal cord injury over the first year after discharge from inpatient rehabilitation. Arch Phys Med Rehabil 2017 Sep;98(9):1800-1805 [FREE Full text] [doi: 10.1016/j.apmr.2016.12.011] [Medline: 28115072]
6. Krause JS, Cao Y, DeVivo MJ, DiPiro ND. Risk and protective factors for cause-specific mortality after spinal cord injury. Arch Phys Med Rehabil 2016 Oct;97(10):1669-1678 [FREE Full text] [doi: 10.1016/j.apmr.2016.07.001] [Medline: 27449321]
7. Posthauer ME, Banks M, Dorner B, Schols JM. The role of nutrition for pressure ulcer management: National Pressure Ulcer Advisory Panel, European Pressure Ulcer Advisory Panel, and Pan Pacific Pressure Injury Alliance white paper. Adv Skin Wound Care 2015 Apr;28(4):175-88; quiz 189-90. [doi: 10.1097/01.ASW.0000461911.31139.62] [Medline: 25775201]
8. Garber SL, Rintala DH. Pressure ulcers in veterans with spinal cord injury: a retrospective study. J Rehabil Res Dev 2003;40(5):433-441 [FREE Full text] [doi: 10.1682/jrrd.2003.09.0433] [Medline: 15080228]

9. Gefen A, Brienza DM, Cuddigan J, Haesler E, Kottner J. Our contemporary understanding of the aetiology of pressure ulcers/pressure injuries. Int Wound J 2022 Mar;19(3):692-704 [FREE Full text] [doi: 10.1111/iwj.13667] [Medline: 34382331]
10. Sprigle S, McNair D, Sonenblum S. Pressure ulcer risk factors in persons with mobility-related disabilities. Adv Skin Wound Care 2020 Mar;33(3):146-154 [FREE Full text] [doi: 10.1097/01.ASW.0000653152.36482.7d] [Medline: 32058440]
11. Coleman S, Gorecki C, Nelson EA, Closs SJ, Defloor T, Halfens R, et al. Patient risk factors for pressure ulcer development: systematic review. Int J Nurs Stud 2013 Jul;50(7):974-1003 [FREE Full text] [doi: 10.1016/j.ijnurstu.2012.11.019] [Medline: 23375662]
12. Rupp R, Biering-Sørensen F, Burns SP, Graves DE, Guest J, Jones L, et al. International standards for neurological classification of spinal cord injury: revised 2019. Top Spinal Cord Inj Rehabil 2021;27(2):1-22. [doi: 10.46292/sci2702-1] [Medline: 34108832]
13. Sumiya T, Kawamura K, Tokuhiro A, Takechi H, Ogata H. A survey of wheelchair use by paraplegic individuals in Japan. Part 2: prevalence of pressure sores. Spinal Cord 1997 Sep;35(9):595-598 [FREE Full text] [doi: 10.1038/sj.sc.3100467] [Medline: 9300965]
14. Defloor T, Grypdonck MF. Pressure ulcers: validation of two risk assessment scales. J Clin Nurs 2005 Mar;14(3):373-382 [FREE Full text] [doi: 10.1111/j.1365-2702.2004.01058.x] [Medline: 15707448]
15. Halfens RJ, van Achterberg T, Bal RM. Validity and reliability of the braden scale and the influence of other risk factors: a multi-centre prospective study. Int J Nurs Stud 2000 Aug;37(4):313-319 [FREE Full text] [doi: 10.1016/s0020-7489(00)00010-9] [Medline: 10760538]
16. Sonenblum SE, Sprigle SH, Martin JS, PE. Everyday sitting behavior of full-time wheelchair users. J Rehabil Res Dev 2016;53(5):585-598 [FREE Full text] [doi: 10.1682/JRRD.2015.07.0130] [Medline: 27898157]
17. Bogie KM, Zhang GQ, Roggenkamp SK, Zeng N, Seton J, Tao S, et al. Individualized clinical practice guidelines for pressure injury management: development of an integrated multi-modal biomedical information resource. JMIR Res Protoc 2018 Sep 06;7(9):e10871 [FREE Full text] [doi: 10.2196/10871] [Medline: 30190252]
18. Carlson M, Vigen CL, Rubayi S, Blanche EI, Blanchard J, Atkins M, et al. Lifestyle intervention for adults with spinal cord injury: results of the USC-RLANRC pressure ulcer prevention study. J Spinal Cord Med 2019 Jan;42(1):2-19 [FREE Full text] [doi: 10.1080/10790268.2017.1313931] [Medline: 28414254]
19. Consortium for Spinal Cord Medicine Clinical Practice Guidelines. Pressure ulcer prevention and treatment following spinal cord injury: a clinical practice guideline for health-care professionals. J Spinal Cord Med 2001;24 Suppl 1:S40-101. [doi: 10.1080/10790268.2001.11753592] [Medline: 11958176]
20. Prevention and treatment of pressure ulcers: quick reference guide. National Pressure Ulcer Advisory Panel, European Pressure Ulcer Advisory Panel and Pan Pacific Pressure Injury Alliance. 2009. URL: https://www.nzwcs.org.nz/images/International_PUG/Quick_Reference_Guide_DIGITAL-PPPIA-Jan2016.pdf [accessed 2024-01-13]
21. Regan MA, Teasell RW, Wolfe DL, Keast D, Mortenson WB, Aubut JA. A systematic review of therapeutic interventions for pressure ulcers after spinal cord injury. Arch Phys Med Rehabil 2009 Feb;90(2):213-231 [FREE Full text] [doi: 10.1016/j.apmr.2008.08.212] [Medline: 19236976]
22. Stinson M, Ferguson R, Porter-Armstrong A. Exploring repositioning movements in sitting with 'at risk' groups using accelerometry and interface pressure mapping technologies. J Tissue Viability 2018 Feb;27(1):10-15 [FREE Full text] [doi: 10.1016/j.jtv.2017.11.001] [Medline: 29268953]
23. Sonenblum SE, Vonk TE, Janssen TW, Sprigle SH. Effects of wheelchair cushions and pressure relief maneuvers on ischial interface pressure and blood flow in people with spinal cord injury. Arch Phys Med Rehabil 2014 Jul;95(7):1350-1357 [FREE Full text] [doi: 10.1016/j.apmr.2014.01.007] [Medline: 24480336]
24. Chen Y, Wang J, Lung CW, Yang TD, Crane BA, Jan YK. Effect of tilt and recline on ischial and coccygeal interface pressures in people with spinal cord injury. Am J Phys Med Rehabil 2014 Dec;93(12):1019-1030 [FREE Full text] [doi: 10.1097/PHM.0000000000000225] [Medline: 25353193]
25. Sprigle S, Sonenblum S. Assessing evidence supporting redistribution of pressure for pressure ulcer prevention: a review. J Rehabil Res Dev 2011;48(3):203-213 [FREE Full text] [doi: 10.1682/jrrd.2010.05.0102] [Medline: 21480095]
26. Coggrave MJ, Rose LS. A specialist seating assessment clinic: changing pressure relief practice. Spinal Cord 2003 Dec;41(12):692-695 [FREE Full text] [doi: 10.1038/sj.sc.3101527] [Medline: 14639449]
27. Olney CM, Vos-Draper T, Egginton J, Ferguson J, Goldish G, Eddy B, et al. Development of a comprehensive mobile assessment of pressure (CMAP) system for pressure injury prevention for veterans with spinal cord injury. J Spinal Cord Med 2019 Nov;42(6):685-694 [FREE Full text] [doi: 10.1080/10790268.2019.1570437] [Medline: 30702395]
28. Curran G, Bauer M, Mittman B, Pyne J, Stetler C. Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact. Med Care 2012 Mar;50(3):217-226 [FREE Full text] [doi: 10.1097/MLR.0b013e3182408812] [Medline: 22310560]
29. Brehaut JC, Eva KW. Building theories of knowledge translation interventions: use the entire menu of constructs. Implement Sci 2012 Nov 22;7:114 [FREE Full text] [doi: 10.1186/1748-5908-7-114] [Medline: 23173596]
30. Welcome to the Interview Guide Tool. The Consolidated Framework for Implementation Research. URL: https://cfirguide.org/guide/app/#/ [accessed 2024-03-05]

31. Damschroder LJ, Aron DC, Keith RE, Kirsh SR, Alexander JA, Lowery JC. Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. Implement Sci 2009 Aug 07;4:50 [FREE Full text] [doi: 10.1186/1748-5908-4-50] [Medline: 19664226]
32. Braun V, Clarke V. Thematic Analysis: A Practical Guide. Thousand Oaks, CA: SAGE Publications; Oct 13, 2021.
33. Krueger RA, Casey · MA. Focus Groups: A Practical Guide for Applied Research. Thousand Oaks, CA: SAGE Publications, Inc; 1988.
34. Bangor A, Kortum PT, Miller JT. An empirical evaluation of the system usability scale. Int J Hum Comput Interact 2008;24(6):574-594 [FREE Full text] [doi: 10.1080/10447310802205776]
35. Venkatesh V, Thong JY, Xu X. Consumer acceptance and use of information technology: extending the unified theory of acceptance and use of technology. MIS Q 2012 Mar;36(1):157-178 [FREE Full text] [doi: 10.2307/41410412]
36. Venkatesh V, Morris MG, Davis GB, Davis FD. User acceptance of information technology: toward a unified view. MIS Q 2003 Sep;27(3):425-478 [FREE Full text] [doi: 10.2307/30036540]
37. Weiner BJ, Lewis CC, Stanick C, Powell BJ, Dorsey CN, Clary AS, et al. Psychometric assessment of three newly developed implementation outcome measures. Implement Sci 2017 Aug 29;12(1):108 [FREE Full text] [doi: 10.1186/s13012-017-0635-3] [Medline: 28851459]
38. Holdsworth LM, Safaeinili N, Winget M, Lorenz KA, Lough M, Asch S, et al. Adapting rapid assessment procedures for implementation research using a team-based approach to analysis: a case example of patient quality and safety interventions in the ICU. Implement Sci 2020 Feb 22;15(1):12 [FREE Full text] [doi: 10.1186/s13012-020-0972-5] [Medline: 32087724]
39. Whitehead AL, Julious SA, Cooper CL, Campbell MJ. Estimating the sample size for a pilot randomised trial to minimise the overall trial sample size for the external pilot and main trial for a continuous outcome variable. Stat Methods Med Res 2016 Jun;25(3):1057-1073 [FREE Full text] [doi: 10.1177/0962280215588241] [Medline: 26092476]
40. King RB, Champion VL, Chen D, Gittler MS, Heinemann AW, Bode RK, et al. Development of a measure of skin care belief scales for persons with spinal cord injury. Arch Phys Med Rehabil 2012 Oct;93(10):1814-1821 [FREE Full text] [doi: 10.1016/j.apmr.2012.03.030] [Medline: 22497804]
41. Brown CH, Curran G, Palinkas LA, Aarons GA, Wells KB, Jones L, et al. An overview of research and evaluation designs for dissemination and implementation. Annu Rev Public Health 2017 Mar 20;38:1-22 [FREE Full text] [doi: 10.1146/annurev-publhealth-031816-044215] [Medline: 28384085]
42. Stinson MD, Porter-Armstrong A, Eakin PA. Pressure mapping systems: reliability of pressure map interpretation. Clin Rehabil 2003 Aug;17(5):504-511 [FREE Full text] [doi: 10.1191/0269215503cr643oa] [Medline: 12952156]
43. Crawford SA, Strain B, Gregg B, Walsh DM, Porter-Armstrong AP. An investigation of the impact of the force sensing array pressure mapping system on the clinical judgement of occupational therapists. Clin Rehabil 2005 Mar;19(2):224-231 [FREE Full text] [doi: 10.1191/0269215505cr826oa] [Medline: 15759539]
44. Norman D. Measuring interface pressure: validity and reliability problems. J Wound Care 2004 Feb;13(2):78-80 [FREE Full text] [doi: 10.12968/jowc.2004.13.2.26576] [Medline: 14999994]

Abbreviations

AW-Shift: Assisted Weight-Shift
CFIR: Consolidated Framework for Implementation Research
DoD: Department of Defense
IRB: institutional review board
mHealth: mobile health
NIH: National Institute of Health
PI: principal investigator
REDCap: Research Electronic Data Capture
SCI/D: spinal cord injuries and related disorders
SCI: spinal cord injury

Edited by A Mavragani; submitted 31.08.23; peer-reviewed by C Baxter, A Van de Winckel; comments to author 05.11.23; revised version received 15.12.23; accepted 16.12.23; published 10.04.24.

Please cite as:
Morrow MM, Hughes LC, Collins DM, Vos-Draper TL
Clinical Remote Monitoring of Individuals With Spinal Cord Injury at Risk for Pressure Injury Recurrence Using mHealth: Protocol for a Pilot, Pragmatic, Hybrid Implementation Trial
JMIR Res Protoc 2024;13:e51849
URL: https://www.researchprotocols.org/2024/1/e51849
doi:10.2196/51849
PMID:38598267

Protocol

Efficacy and Safety of the Natural Killer T Cell–Stimulatory Glycolipid OCH-NCNP1 for Patients With Relapsing Multiple Sclerosis: Protocol for a Randomized Placebo-Controlled Clinical Trial

Tomoko Okamoto[1], MD, PhD; Takami Ishizuka[2], PhD; Reiko Shimizu[2], MD, PhD; Yasuko Asahina[2], PhD; Harumasa Nakamura[2], MD, PhD; Yuko Shimizu[3], MD, PhD; Yoichiro Nishida[4], MD, PhD; Takanori Yokota[4], MD, PhD; Youwei Lin[1,5], MD; Wakiro Sato[5], MD, PhD; Takashi Yamamura[5], MD, PhD

[1]Department of Neurology, National Center Hospital, National Center of Neurology and Psychiatry, Tokyo, Japan

[2]Department of Clinical Research Support, Clinical Research and Education Promotion Division, National Center Hospital, National Center of Neurology and Psychiatry, Tokyo, Japan

[3]Department of Neurology, Tokyo Women's Medical University, Tokyo, Japan

[4]Department of Neurology and Neurological Science, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan

[5]Department of Immunology, National Institute of Neuroscience, National Center of Neurology and Psychiatry, Tokyo, Japan

Corresponding Author:
Takashi Yamamura, MD, PhD
Department of Immunology
National Institute of Neuroscience
National Center of Neurology and Psychiatry
4-1-1 Ogawahigashi-cho, Kodaira
Tokyo, 187-8502
Japan
Phone: 81 42 341 2712 ext 5241
Email: yamamura@ncnp.go.jp

Abstract

Background: Multiple sclerosis (MS) is an autoimmune inflammatory disease of the central nervous system that causes myelin sheath damage and axonal degeneration. The glycolipid (2S, 3*S*, 4*R*)-1-O-(α-d-galactosyl)-2-tetracosanoylamino-1,3,4-nonaetriol (OCH-NCNP1 or OCH) exerts an immunoregulatory action that suppresses T helper (Th)1 cell–mediated immune responses through natural killer T cell activation, selective interleukin-4 production, and Th2 bias induction in human CD4-positive natural killer T cells.

Objective: This trial aims to investigate the efficacy and safety of the immunomodulator OCH in patients with relapsing MS through 24-week repeated administration.

Methods: This protocol describes a double-blind, multicenter, placebo-controlled, randomized phase II clinical trial that was initiated in September 2019. The participants were randomly assigned to either a placebo control group or an OCH-NCNP1 group and the investigational drug (3.0 mg) was orally administered once weekly for the 24-week duration. Major inclusion criteria are as follows: patients had been diagnosed with relapsing MS (relapsing-remitting and/or secondary progressive MS) based on the revised McDonald criteria or were diagnosed with MS by an attending physician as noted in their medical records; patients with at least two medically confirmed clinical exacerbations within 24 months prior to consent or one exacerbation within 12 months prior to consent; patients with at least one lesion suspected to be MS on screening magnetic resonance imaging (MRI); and patients with 7 points or less in the Expanded Disability Status Scale during screening. Major exclusion criteria are as follows: diagnosis of neuromyelitis optica and one of optic neuritis, acute myelitis, and satisfying at least two of the following three items: (1) spinal cord MRI lesion extending across at least three vertebral bodies, (2) no brain MRI lesions during onset (at least four cerebral white matter lesions or three lesions, one of which is around the lateral ventricle), and (3) neuromyelitis optica–immunoglobulin G or antiaquaporin-4 antibody-positive. Outcome measures include the primary outcome of MRI changes (the percentage of subjects with new or newly expanded lesions at 24 weeks on T2-weighted MRI) and the secondary outcomes annual relapse rate

(number of recurrences per year), relapse-free period (time to recurrence), sustained reduction in disability (SRD) occurrence rate, period until SRD (time to SRD occurrence), no evidence of disease activity, and exploratory biomarkers from phase I trials (such as gene expression, cell frequency, and intestinal and oral microbiome).

Results: We plan to enroll 30 patients in the full analysis set. Enrollment was closed in June 2021 and the study analysis was completed in March 2023.

Conclusions: This randomized controlled trial will determine whether OCH-NCNP1 is effective and safe in patients with MS as well as provide evidence for the potential of OCH-NCNP1 as a therapeutic agent for MS.

Trial Registration: ClinicalTrials.gov NCT04211740; https://clinicaltrials.gov/study/NCT04211740

International Registered Report Identifier (IRRID): DERR1-10.2196/46709

(JMIR Res Protoc 2024;13:e46709) doi:10.2196/46709

KEYWORDS

OCH-NCNP1; natural killer cell; multiple sclerosis; clinical study; randomized controlled trial; autoimmune inflammatory disease; degeneration; clinical efficacy; biomarker; relapse; disability; imaging; autoimmune; RCT; Expanded Disability Status Scale; EDSS; neuromyelitis optica; optic neuritis; acute myelitis; Fisher exact test; MRI; magnetic resonance imaging; myelin sheath; demyelinating lesion; aminotransferase; clinicopathology; pathology

Introduction

Multiple sclerosis (MS) is considered to be an autoimmune disease triggered by environmental factors that act on a genetically susceptible host. Both major histocompatibility complex (MHC) and non-MHC genes are risk factors for the development of MS. In addition, environmental factors such as low vitamin D, low ultraviolet radiation exposure, cigarette smoking, obesity, and Epstein-Barr virus exposure can increase the risk for both the development of MS and a more severe disease course. Accumulating evidence suggests that dysregulation of the intestinal microbiome (dysbiosis) constitutes an important factor contributing to MS pathogenesis. The microbiome regulates T cell function, with both regulatory and pathogenic effects, thereby playing an important role in autoimmune responses [1].

MS is a cell-mediated autoimmune disease directed against central nervous system (CNS) myelin antigens involving both CD4+ and CD8+ T cells, especially the so-called pathogenic T helper (Th)17- and Th1-type and CD8 myelin autoreactive T cells. The development of MS is likely triggered or promoted by breakdown of the delicate balance between autoreactive T cells and regulatory lymphocytes [1].

Although MS has historically been considered a demyelinating disease of the CNS and white matter, in recent years, neurodegeneration of the cortical and deep gray matter has been recognized to play a role in the pathogenesis of MS. Cortical atrophy is associated with disease progression, which has emerged as one of the best predictors of neurological disability in MS [1].

According to a recent worldwide epidemiological study, the number of patients with MS is estimated to be 2.8 million, which has been increasing in every world region since 2013 [2]. The estimated total economic burden of MS in the United States is US $85.4 billion, with a direct medical cost of US $63.3 billion and indirect and nonmedical costs of US $22.1 billion [3].

Relapsing-remitting MS (RRMS) initially involves clinical relapses with near or complete recovery; however, recovery over time may be incomplete and disability often worsens [4]. Approximately 20% of patients with RRMS develop a progressive form of MS accompanied by chronic neuroinflammation. Such cases are referred to as secondary progressive MS (SPMS). The term “relapsing MS” (RMS) is used to describe the condition of patients with repeated relapses of either RRMS or SPMS.

As understanding of the pathomechanism of MS progresses, various disease-modifying drugs have been used in clinical practice, including sphingosine-1-phosphate receptor modulators (fingolimod, siponimod), a monoclonal antibody that selectively binds the α4 integrin subunit (natalizumab), and CD20 monoclonal antibodies (ofatumumab, ocrelizumab), resulting in an overall improvement of patient prognosis. However, there are patients for whom current treatments are ineffective and there are cases where current treatments are intolerable due to side effects. Furthermore, progressive MS remains refractory to current drugs and constitutes an unmet medical need [4]. These observations highlight the need for new, safer therapeutic oral agents.

In 1997, Kawano et al [5] reported the discovery of sponge-derived α-galactosylceramide (α-GC) as a glycolipid ligand that stimulates natural killer T (NKT) cells. However, because this glycolipid stimulates NKT cells and induces the production of both interleukin (IL)-4 and interferon (IFN)-γ, a search for glycolipids that selectively induce IL-4 production was initiated to treat Th1 cytokine–dependent autoimmune diseases such as MS. These efforts led to the discovery of (2*S*, 3 *S* , 4*R*)-1-O-(α-d-galactosyl)-2-tetracosanoylamino-1,3,4-nonaetriol (OCH-NCNP1; hereafter referred to as OCH), which was detected during screening for glycolipids that selectively induce the production of Th2 cytokines [6].

OCH is a derivative (synthetic glycolipid) of α-GC with a shortened fatty-acid chain (sphingosine chain). The compound is a white to slightly yellow powder that is extremely insoluble in methanol or ethanol and is practically insoluble in water. OCH exhibits an immunoregulatory action that suppresses Th1 cell–mediated immune responses through NKT cell activation,

selective IL-4 production, and Th2 bias induction in human CD4+ NKT cells [7].

Although the mechanism by which OCH induces Th2 bias in NKT cells is not fully understood, it has been suggested to involve both cell intrinsic and extrinsic factors [8,9]. As a cell intrinsic mechanism, IFN-γ production by NKT cells was reported to be more susceptible to the sphingosine length of the glycolipid ligand compared to IL-4 production, and the length of the sphingosine chain determined the half-life of NKT cell stimulation by CD1d-associated glycolipids. As an extrinsic regulatory mechanism, OCH suppresses the production of IFN-γ, not only by NKT cells but also by NK cells, compared with that of α-GC. OCH induced lower IL-12 production due to ineffective primary IFN-γ and CD40 ligand expression by NKT cells, which resulted in lower secondary IFN-γ induction.

Animal studies verified that OCH can be administered orally to control Th1 cell–mediated autoimmune pathology in mice, with efficacy against autoimmune disease models such as experimental autoimmune encephalomyelitis, collagen-induced myelitis [10], nonobese diabetes [11], and inflammatory enteritis [12].

We here describe a protocol for a feasibility study that will be conducted in patients with RMS to investigate the efficacy and safety of OCH immunomodulators. Through 24 weeks of weekly administration, this trial was performed to confirm changes in exploratory T cell and NK cell biomarkers that fluctuated in the phase I trial [13], as well as measures of efficacy, including recurrence, dysfunction, and magnetic resonance imaging (MRI) changes, and their association with combined endpoints. In alignment with past clinical trials [14,15] and European Medical Agency guidelines, the primary outcome will be the percentage of subjects with new or newly expanded lesions at 24 weeks on T2-weighted MRIs.

Methods

Study Design

This is a double-blind, multicenter, placebo-controlled, randomized phase II clinical trial with a 24-week duration. This trial investigates the efficacy and safety of the immunomodulator OCH in patients with RMS through 24-week repeated administration. The protocol was also designed to confirm exploratory biomarkers of T cells and NK cells that fluctuated in the phase I trial [13], as well as efficacy-related clinical endpoints, including relapses, disability, and MRI changes, and their association with combined endpoints. Recruitment opened in September 2019 and concluded in June 2021, with participants randomly assigned to either a placebo control group or an OCH group using a clinical-based management system (Translational Research Center for Medical Innovation, Kobe, Japan). The researchers were blinded to the participant group assignments, and the packaging appearance of the control and investigational drugs was confirmed to be indistinguishable.

An independent data monitoring committee will regularly audit all available data, including safety, and recommend trial continuation to the principal investigator.

Selection Criteria

Inclusion and exclusion criteria for this study are provided in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Patients who provided written consent for trial participation
- Patients had been diagnosed with relapsed multiple sclerosis (MS), including relapse-remitting MS and/or secondary progressive MS, based on the revised McDonald criteria or were diagnosed with MS by an attending physician as noted in their medical records
- Patients with at least two medically confirmed clinical exacerbations within 24 months prior to consent or one exacerbation within 12 months prior to consent
- Patients with at least one lesion suspected to be MS on screening magnetic resonance imaging (MRI)
- Patients with 7 points or less in the Expanded Disability Status Scale during screening
- Patients who were 20-65 years old at the time of consent
- Patients who can practice contraception until 90 days after final administration of the investigational drug
- Patients with no clinical or test findings suggesting acute recurrence based on evaluation by a neurologist

Exclusion criteria

- Diagnosis of neuromyelitis optica and one of the three following three criteria: optic neuritis, acute myelitis, and satisfied at least two of the following three items: (1) spinal cord MRI lesion extending across at least three vertebral bodies, (2) no brain MRI lesions during onset (at least four cerebral white matter lesions or three lesions, one of which is around the lateral ventricle), and (3) neuromyelitis optica–immunoglobulin G (IgG) or antiaquaporin-4 antibody-positive
- Currently pregnant or nursing
- Contraindication for MRI (eg, those with metal implants or a pacemaker) or cases in which MRI is difficult to perform (eg, claustrophobia)
- History of allergic or hypersensitive reaction to gadolinium contrast
- History of liver disease, including liver transplantation, viral hepatitis, autoimmune hepatitis, cirrhosis, and hepatic malignancies
- Liver dysfunction determined by the screening test or baseline test (alanine aminotransferase, aspartate aminotransferase, γ-guanosine triphosphate, or alkaline phosphatase) exceeding twice the upper limit of normal and total bilirubin exceeding 1.5-fold the upper limit of normal
- History of malignant tumors in the past 5 years (however, patients deemed to have no recurrence for at least 5 years prior to consent can be enrolled)
- Varicella-zoster virus IgG antibody–negative
- Positive for syphilis serum reaction (treponema pallidum latex agglutination, rapid plasma reagin)
- positive for β-D glucan (exceeding the standard value) or T-spot
- positive for antiaquaporin-4 antibody
- history of human immunodeficiency virus infection or who have been confirmed positive by a screening test
- History of hepatitis B infection (hepatitis B surface antigen–positive or hepatitis B core antibody–positive), or patients who have been confirmed positive by a screening test
- History of stem cell transplantation, organ transplantation, and treatment for rejection
- Physical, mental, or social condition affecting the ability to provide consent to or complete the trial
- Participation in other clinical trials that received the investigational drug within 4 months prior to enrollment
- Blood donation (200 mL within 2 months, 400 mL within 3 months) prior to enrollment
- Peripheral blood lymphocyte count <600/mm^3 by screening or baseline examination
- With or suspected of having an infectious disease
- Immunocompromised patients
- Inflammatory bowel disease
- Use of the following prohibited concomitant therapies:

interferon-β preparation (prohibited 1 month before trial enrollment); fingolimod hydrochloride (prohibited 6 months before trial enrollment); natalizumab (prohibited 3 months before trial enrollment); glatiramer acetate (prohibited 1 month before trial enrollment); dimethyl fumarate (prohibited 3 months before trial enrollment); drugs other than azathioprine that have immunosuppressive, immunostimulatory, or myelosuppressive effects (prohibited 3 months before trial enrollment); pulse therapy using corticosteroids (prohibited 1 month before clinical trial registration, except when MS recurs); plasmapheresis, immunoadsorption therapy, lymphocyte depletion therapy (prohibited from the time of consent acquisition); immunoglobulin preparation (prohibited 2 months before trial enrollment); vaccines (prohibited 1 month before trial enrollment, except when permitted by the investigator); other investigational drugs (prohibited 4 months before trial enrollment); nonsteroidal anti-inflammatory drug (liver damage at the time of screening should be checked, and for patients who take it regularly, this drug can be used in combination by fixing the dosage and administration. Additionally, when used for adverse events, it should be possible to use this drug within the minimum necessary range)

Additional exclusion criteria:

- Patients with evident prolongation of the QT/QTc interval prior to the trial (eg, patients with repeating QTc interval>450 ms)
- Patients with a history of other risk factors for torsades de pointes (eg, family history of heart failure, hypokalemia, and long QT syndrome)
- History of severe drug or food allergy
- Patients with drug or alcohol dependence in the past or present
- Asthma (excluding patients with no history of treatment or attack for at least 10 years)
- Diagnosis of epilepsy or patients with a history of seizures (excluding febrile seizures)
- Other pathological symptoms, illnesses, or history that may affect this trial
- Other factors resulting in unsuitability for this trial as deemed by the principal investigator; if such exclusion occurs, the specific rationale will be described in the trial results

Sample Size Estimate

The target number of participants was 30 (15 per group) based on feasibility. The detection power was calculated when the primary outcome (proportion of subjects with new or enlarged existing lesions detected on T2-weighted images) was compared using the Fisher exact test. With 60% of patients placed in the placebo group based on the results of the domestic phase II study (D1201 study) at the time of fingolimod development [16] and assuming a 5% proportion in the OCH group, the detection power was 86.5%. Furthermore, when the OCH group was set to 10%, the detection power was 74.6% (the significance level was set to 5% using a two-tailed test).

Patient Clinicodemographic Characteristics

The following clinicodemographic information was recorded for each participant: (1) subject background (eg, birth date, sex, body height, body weight); (2) urine pregnancy test; (3) infectious disease or antibody test; (4) vital signs (blood pressure, pulse rate, body temperature, and breathing rate); (5) neurological symptoms rating scale (Expanded Disability Status Scale [EDSS] or functional disability scale); (6) clinical tests (hematological test, hematobiochemical test, or urine test); (7) 12-lead electrocardiogram; (8) echocardiography; (9) chest or abdominal X-ray; (10) abdominal computed tomography; (11) MRI; (12) peripheral blood gene expression level (reverse transcription–polymerase chain reaction); (13) frequencies of NK, NKT, T cells, or other lymphocyte subsets; (14) frequencies of Th1, Th2, or Th17 cells; (15) intestinal and oral microbiome; (16) adverse events; (17) combination drugs and important nondrug therapies; and (18) Columbia Suicide Severity Rating Scale.

Outcome Measurements and Study Timeline

The outcomes that will be measured repeatedly throughout the trial and the corresponding time points are shown in Multimedia Appendix 1. The main outcome is MRI changes (the percentage of subjects with new or newly expanded lesions on T2-weighted MRI). In addition, the annual relapse rate, cumulative number of new or newly expanded lesions on T2-weighted MRI, percentage of subjects who did not have lesions at 12 and 24 weeks on T2-weighted images of head MRI compared to those at the preobservation period at 24 weeks, brain atrophy in T1-3D images, percentage of subjects with no contrast-enhanced lesions on gadolinium-enhanced T1-weighted images, number of contrast-enhanced lesions on gadolinium-enhanced T1-weighted images, changes in volume of demyelinating lesions on fluid-attenuated inversion recovery 3D images, diffusion tensor imaging changes in myelin sheath lesions, and changes in myelin sheath lesions by a myelin map will be assessed. Additional outcomes include the relapse-free period (from randomization to earliest relapse), sustained reduction in disability occurrence rate, period until sustained reduction in disability (from randomization), no evidence of disease activity, and exploratory biomarkers from phase I trials (peripheral blood gene expression, frequencies of lymphocyte subsets, and intestinal and oral microbiome) [13].

Adverse Events

Adverse events, defined as any undesired or unintended sign (including abnormal fluctuations in each test value), symptoms, or illness that occurs between the start of investigational drug administration and end or discontinuation of the investigational drug (regardless of its association with the study drug), will be recorded. The recordings will include the degree of symptoms on a 1-5 scale (1=asymptomatic or mild adverse events, 5=death due to the adverse event), outcomes from 1 to 6 (1=event disappeared or normalized, 6=death), and association with the

investigational drug from 1 to 4 (1=associated, 4=not associated).

Discontinuation Criteria

Discontinuation of involvement in the clinical trial may occur for any patient because of voluntary withdrawal or for any of the following reasons: (1) serious adverse events; (2) pregnancy; (3) alanine aminotransferase and aspartate aminotransferase >5-fold higher than the standard value upper limit; (4) total bilirubin exceeding 2.0 mg/dL; (5) number of peripheral blood lymphocytes <500/mm^3 and administration of the investigational drug is stopped three times in a row without recovery, even after three tests; (6) occurrence of a grade-3 event based on Common Terminology Criteria for Adverse Events v4.0-JCOG; (7) new neurological symptoms with unpredictable MRI findings observed from the course of MS; (8) more than one recurrence of MS; (9) at least three courses of pulse steroid therapy performed; (10) an important management problem is discovered (subject noncompliance); (11) significant deviation from the protocol; (12) administration of the investigational drug is stopped at least three times, regardless of the reason; and (13) at the discretion of the principal investigator. If discontinuation occurs because of this final criterion, justification will be provided in the results report.

Administration of Trial Compound

The investigational drug OCH (3.0 mg) in the form of granules (total of 0.3 g) or placebo granules alone (0.3 g) was orally administered with approximately 150 mL of water 30 min before breakfast once weekly for the 24-week trial duration. The white granules were composed of crystalline cellulose, mannitol, sodium croscarmellose, low-substituted hydroxypropyl cellulose, and polysorbate 80.

Statistical Methods

Patient clinicopathological data will be summarized using descriptive statistics for each group. The proportion of subjects with new or enlarged existing lesions on T2-weighted MRIs in each group will be calculated and compared using the Fisher exact test with 95% CIs. The proportion of data between groups related to the primary endpoint will also be compared using the Fisher exact test with 95% CIs. For time-to-event data such as relapse-free periods, Kaplan-Meier estimates will be calculated for each group and groups will be compared using the log-rank test. The expression rates of safety-related outcomes and adverse events will be calculated for each group. For various test values, a list of measured values will be created for each group. The summary statistics for each group and measurement time point will also be calculated.

Patient and Public Involvement

Patients were first involved in this study during the recruitment and screening processes. Based on previous experiences with patients with MS, the importance of the outcomes measured in this study was evaluated and determined based on their medical importance and impact on the patients' quality of life. The patients recruited for the study agreed to the methods of disseminating the aggregate results when providing informed consent.

Ethical Considerations

This study was conducted in compliance with the Declaration of Helsinki and all applicable local and national regulatory laws with approval from the National Center of Neurology and Psychiatry institutional review board (approval number II-013). The legal representatives of each patient provided written informed consent prior to participation in the study. Copayment reduction fees were paid to the trial participants in accordance with the regulations of the implementing medical institution.

Dissemination

The results will be disseminated in peer-reviewed journals and presented at relevant conferences.

Results

The first patient completed registration in December 2019 and the last patient completed registration in June 2021. The full analysis set comprised 30 cases and the study analysis was completed in March 2023. Preliminary analysis suggests that OCH may be effective for RMS (particularly SPMS).

Discussion

Principal Results

This will be the first randomized double-blind placebo-controlled trial to study the efficacy and safety of OCH. This randomized controlled trial will determine whether OCH is effective and safe in patients with MS. The results of this trial are expected to provide evidence for the potential of using OCH as a therapeutic agent for MS.

A single-dose trial (STEP 1) trial was conducted in healthy adults from November 2012 to July 2013 and a repeated-dose trial (STEP 2) was conducted in patients with RRMS from March 2014 to August 2017 [13]. In a phase I trial consisting of STEP 1 and STEP 2, OCH was administered to 28 patients (STEP 1: 3 patients×5 groups in all cohorts, STEP 2: 7 patients×1 group in a cohort, 3 patients×2 groups in a cohort).

Grade-1 adverse events and side effects were noted in STEP 1 and there were no serious adverse events or discontinuations. In STEP 2, serious side effects (acidosis and altered state of consciousness, depression, muscle weakness, and malaise) were reported in three patients in the 0.3 and 3 mg groups. Two patients discontinued treatment; however, all patients recovered. No other serious events were observed, confirming that the patients tolerated doses of 0.3, 1, and 3 mg. After OCH administration, there was no significant change in the neurological symptom evaluation scale score (EDSS or functional disability scale) even in STEP 2 because of the short observation period. MRI revealed clinically significant abnormalities in one patient in the 0.3 mg group; this patient discontinued the study.

A phase I physician-led clinical trial, conducted as an early exploratory clinical trial, determined that the dose was likely to have pharmacological action (fluctuations in some biomarkers) in humans. The dose at which pharmacological action was observed in experimental autoimmune

encephalomyelitis model mice was 0.4-0.5 mg/kg. Considering that the area under the curve $(AUC)_{0-\infty}$ following oral administration of 5 mg/kg to mice was 2922 ng·h/mL, the $AUC_{0-\infty}$ following oral administration of 0.5 mg/kg (dose at which pharmacological action was observed) was estimated as 292.2 ng h/mL. Assuming a correlation between systemic exposure ($AUC_{0-\infty}$) and pharmacological effects and systemic exposure in monkeys ($AUC_{0-\infty}$ after oral administration of 10 mg/kg was 2376, SD 1164 ng), pharmacological action may be expected in humans if at least approximately 1.2 mg/kg is orally administered.

In STEP 1 of the phase I trial, administration of OCH at doses of 0.3, 1, 3, 10, 30, 100, and 300 mg to healthy adults was planned. However, STEP 1 was completed at 30 mg; in the subsequent STEP 2, OCH at 0.3, 1, and 3 mg was administered to patients with MS. Importantly, no tolerability problems were noted.

The following changes in exploratory biomarkers were observed. In analysis of the immune cell subsets using flow cytometry, (1) inhibitory T cells (Foxp3+T cells) and effector regulatory T cells (CD45RA-$FoxP3^{high}$ T cells) tended to increase and (2) granulocyte-macrophage colony-stimulating factor–producing Th cells transiently decreased in both healthy subjects and patients with MS. Recently, granulocyte-macrophage colony-stimulating factor–producing Th cells were identified as pathogenic cells in MS [17]. These changes suggest that oral OCH administration can correct the proinflammatory changes linked with disease activity in MS. Moreover, by conducting DNA microarray analysis of whole blood cells, we identified upregulation of several immunoregulatory genes and downregulation of several inflammatory genes in both healthy subjects and patients with MS, further supporting the immunoregulatory effect of OCH.

Based on the above safety profile and biomarker analysis results, a dose of 3 mg was selected as the investigational dose for this trial.

Limitations

The primary limitation of our trial design is the small sample size. The sample size in this study was determined to be 30 participants based on the results of the previous phase I study. This study was limited to a small cohort of patients over a 24-week timeline and involved weekly administration of one dose of OCH. Although necessary in this early stage of the investigation, the small sample size could limit the ability to identify potential adverse events that may be rare or related to specific clinicodemographic traits of patients not captured in this study. However, the robust and clinically relevant nature of our primary outcome measure and sample size determined in prior studies are expected to provide indications of drug efficacy.

Conclusions

This article describes an NKT cell–stimulatory glycolipid (OCH) protocol. This randomized controlled trial will determine whether OCH is effective and safe in patients with MS. The results of the trial are expected to provide evidence for the potential of OCH as a therapeutic agent for MS.

Acknowledgments

Editorial support—in the form of medical writing and assembling tables based on authors' detailed directions, collating author comments, copyediting, fact checking, and referencing—was provided by Editage (Cactus Communications). This study was supported by the Japan Agency for Medical Research and Development (grant number 20ek0109342h0003). EA Pharma Co, Ltd (Tokyo, Japan) provided monitoring and audit costs. The study was designed, conducted, analyzed, and interpreted by the investigators independently from EA Pharma Co, Ltd. Generative artificial intelligence was not used in the ideation or writing process.

Data Availability

Data are not included in this protocol, but will be presented in an upcoming paper summarizing the results of this clinical trial. The data sets are available from the corresponding author upon reasonable request taking into account our patent strategy.

Authors' Contributions

TO, TI, RS, YA, HN, WS, and T Yamamura conceived and designed the study and were involved in protocol development. TI, RS, YA, and HN were involved in administrative and regulatory aspects of the study. TI and HN wrote the first draft of the manuscript. YS and YN were involved in patient recruitment. TO, YN, T Yokota, YL, and WS were responsible for data acquisition.

Conflicts of Interest

TO, WS, and T Yamamura disclose that royalties were received from EA Pharma Co, Ltd based on a license agreement. The other authors have no conflicts of interest to declare.

Multimedia Appendix 1
Observation, examination, and survey schedule.
[DOCX File , 26 KB - resprot_v13i1e46709_app1.docx]

References

1. Baecher-Allan C, Kaskow BJ, Weiner HL. Multiple sclerosis: mechanisms and immunotherapy. Neuron 2018 Feb 21;97(4):742-768 [FREE Full text] [doi: 10.1016/j.neuron.2018.01.021] [Medline: 29470968]
2. Walton C, King R, Rechtman L, Kaye W, Leray E, Marrie RA, et al. Rising prevalence of multiple sclerosis worldwide: insights from the Atlas of MS, third edition. Mult Scler 2020 Dec 11;26(14):1816-1821 [FREE Full text] [doi: 10.1177/1352458520970841] [Medline: 33174475]
3. Bebo B, Cintina I, LaRocca N, Ritter L, Talente B, Hartung D, et al. The economic burden of multiple sclerosis in the United States: estimate of direct and indirect costs. Neurology 2022 May 03;98(18):e1810-e1817 [FREE Full text] [doi: 10.1212/WNL.0000000000200150] [Medline: 35418457]
4. McGinley MP, Goldschmidt CH, Rae-Grant AD. Diagnosis and treatment of multiple sclerosis: a review. JAMA 2021 Feb 23;325(8):765-779. [doi: 10.1001/jama.2020.26858] [Medline: 33620411]
5. Kawano T, Cui J, Koezuka Y, Toura I, Kaneko Y, Motoki K, et al. CD1d-restricted and TCR-mediated activation of valpha14 NKT cells by glycosylceramides. Science 1997 Nov 28;278(5343):1626-1629. [doi: 10.1126/science.278.5343.1626] [Medline: 9374463]
6. Miyamoto K, Miyake S, Yamamura T. A synthetic glycolipid prevents autoimmune encephalomyelitis by inducing TH2 bias of natural killer T cells. Nature 2001 Oct 04;413(6855):531-534. [doi: 10.1038/35097097] [Medline: 11586362]
7. Araki M, Kondo T, Gumperz J, Brenner M, Miyake S, Yamamura T. Th2 bias of CD4+ NKT cells derived from multiple sclerosis in remission. Int Immunol 2003 Feb;15(2):279-288. [doi: 10.1093/intimm/dxg029] [Medline: 12578858]
8. Oki S, Chiba A, Yamamura T, Miyake S. The clinical implication and molecular mechanism of preferential IL-4 production by modified glycolipid-stimulated NKT cells. J Clin Invest 2004 Jun;113(11):1631-1640. [doi: 10.1172/JCI20862] [Medline: 15173890]
9. Oki S, Tomi C, Yamamura T, Miyake S. Preferential T(h)2 polarization by OCH is supported by incompetent NKT cell induction of CD40L and following production of inflammatory cytokines by bystander cells in vivo. Int Immunol 2005 Dec;17(12):1619-1629. [doi: 10.1093/intimm/dxh342] [Medline: 16291659]
10. Chiba A, Oki S, Miyamoto K, Hashimoto H, Yamamura T, Miyake S. Suppression of collagen-induced arthritis by natural killer T cell activation with OCH, a sphingosine-truncated analog of alpha-galactosylceramide. Arthritis Rheum 2004 Jan;50(1):305-313 [FREE Full text] [doi: 10.1002/art.11489] [Medline: 14730629]
11. Mizuno M, Masumura M, Tomi C, Chiba A, Oki S, Yamamura T, et al. Synthetic glycolipid OCH prevents insulitis and diabetes in NOD mice. J Autoimmun 2004 Dec;23(4):293-300. [doi: 10.1016/j.jaut.2004.09.008] [Medline: 15571923]
12. Ueno Y, Tanaka S, Sumii M, Miyake S, Tazuma S, Taniguchi M, et al. Single dose of OCH improves mucosal T helper type 1/T helper type 2 cytokine balance and prevents experimental colitis in the presence of valpha14 natural killer T cells in mice. Inflamm Bowel Dis 2005 Jan;11(1):35-41. [doi: 10.1097/00054725-200501000-00005] [Medline: 15674111]
13. Sato W, Noto D, Araki M, Okamoto T, Lin Y, Yamaguchi H, et al. First-in-human clinical trial of the NKT cell-stimulatory glycolipid OCH in multiple sclerosis. Ther Adv Neurol Disord 2023 Mar 23;16:17562864231162153 [FREE Full text] [doi: 10.1177/17562864231162153] [Medline: 36993937]
14. Dhib-Jalbut S, Marks S. Interferon-beta mechanisms of action in multiple sclerosis. Neurology 2010 Jan 05;74(Suppl 1):S17-S24. [doi: 10.1212/WNL.0b013e3181c97d99] [Medline: 20038758]
15. Fletcher J, Lalor S, Sweeney C, Tubridy N, Mills K. T cells in multiple sclerosis and experimental autoimmune encephalomyelitis. Clin Exp Immunol 2010 Oct;162(1):1-11 [FREE Full text] [doi: 10.1111/j.1365-2249.2010.04143.x] [Medline: 20682002]
16. Committee for Medicinal Products for Human Use. Assessment Report Gilenya (international non-proprietary name: FINGOLIMOD) EMA/CHMP/549382/2015. European Medicines Agency. 2015 Sep. URL: https://www.ema.europa.eu/en/documents/variation-report/gilenya-h-c-2202-ii-0034-epar-assessment-report-variation_en.pdf [accessed 2023-12-20]
17. Galli E, Hartmann FJ, Schreiner B, Ingelfinger F, Arvaniti E, Diebold M, et al. GM-CSF and CXCR4 define a T helper cell signature in multiple sclerosis. Nat Med 2019 Aug 22;25(8):1290-1300 [FREE Full text] [doi: 10.1038/s41591-019-0521-4] [Medline: 31332391]

Abbreviations

α-GC: α-galactosylceramide
AUC: area under the curve
CNS: central nervous system
EDSS: expanded disability status scale
IFN: interferon
IL: interleukin
MHC: major histocompatibility complex
MRI: magnetic resonance imaging
MS: multiple sclerosis
NKT: natural killer T cells

OCH: (2S, 3S, 4R)-1-O-(α-d-galactosyl)-2-tetracosanoylamino-1,3,4-nonaetriol
RMS: relapsing multiple sclerosis
RRMS: relapsing-remitting multiple sclerosis
SPMS: secondary progressive multiple sclerosis
Th: T helper

Edited by A Mavragani; submitted 23.02.23; peer-reviewed by Y Tomizawa, P Lei, M Katsuichi; comments to author 24.09.23; revised version received 14.11.23; accepted 23.11.23; published 15.01.24.

Please cite as:
Okamoto T, Ishizuka T, Shimizu R, Asahina Y, Nakamura H, Shimizu Y, Nishida Y, Yokota T, Lin Y, Sato W, Yamamura T
Efficacy and Safety of the Natural Killer T Cell–Stimulatory Glycolipid OCH-NCNP1 for Patients With Relapsing Multiple Sclerosis: Protocol for a Randomized Placebo-Controlled Clinical Trial
JMIR Res Protoc 2024;13:e46709
URL: https://www.researchprotocols.org/2024/1/e46709
doi:10.2196/46709
PMID:38224478

Protocol

Transcranial Magnetic Stimulation of the Default Mode Network to Improve Sleep in Individuals With Insomnia Symptoms: Protocol for a Double-Blind Randomized Controlled Trial

Lindsey Hildebrand[1*], MA; Alisa Huskey[1*], PhD; Natalie Dailey[1], PhD; Samantha Jankowski[1], BS; Kymberly Henderson-Arredondo[1], BS; Christopher Trapani[2], BS; Salma Imran Patel[3], MD; Allison Yu-Chin Chen[2], MD, PhD; Ying-Hui Chou[2], ScD; William D S Killgore[1], PhD

[1]Department of Psychiatry, University of Arizona, Tucson, AZ, United States

[2]Department of Psychology, University of Arizona, Tucson, AZ, United States

[3]Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, University of Arizona, Tucson, AZ, United States

[*]these authors contributed equally

Corresponding Author:
Lindsey Hildebrand, MA
Department of Psychiatry
University of Arizona
1501 N Campbell Ave
Tucson, AZ, 85724
United States
Phone: 1 651 410 9663
Email: hildebrandll@arizona.edu

Abstract

Background: Cortical hyperarousal and ruminative thinking are common aspects of insomnia that have been linked with greater connectivity in the default mode network (DMN). Therefore, disrupting network activity within the DMN may reduce cortical and cognitive hyperarousal and facilitate better sleep.

Objective: This trial aims to establish a novel, noninvasive method for treating insomnia through disruption of the DMN with repetitive transcranial magnetic stimulation, specifically with continuous theta burst stimulation (cTBS). This double-blind, pilot randomized controlled trial will assess the efficacy of repetitive transcranial magnetic stimulation as a novel, nonpharmacological approach to improve sleep through disruption of the DMN prior to sleep onset for individuals with insomnia. Primary outcome measures will include assessing changes in DMN functional connectivity before and after stimulation.

Methods: A total of 20 participants between the ages of 18 to 50 years with reported sleep disturbances will be recruited as a part of the study. Participants will then conduct an in-person screening and follow-on enrollment visit. Eligible participants then conduct at-home actigraphic collection until their first in-residence overnight study visit. In a double-blind, counterbalanced, crossover study design, participants will receive a 40-second stimulation to the left inferior parietal lobule of the DMN during 2 separate overnight in-residence visits. Participants are randomized to the order in which they receive the active stimulation and sham stimulation. Study participants will undergo a prestimulation functional magnetic resonance imaging scan and a poststimulation functional magnetic resonance imaging scan prior to sleep for each overnight study visit. Sleep outcomes will be measured using clinical polysomnography. After their first in-residence study visit, participants conduct another at-home actigraphic collection before returning for their second in-residence overnight study visit.

Results: Our study was funded in September 2020 by the Department of Defense (W81XWH2010173). We completed the enrollment of our target study population in the October 2022 and are currently working on neuroimaging processing and analysis. We aim to publish the results of our study by 2024. Primary neuroimaging outcome measures will be tested using independent components analysis, seed-to-voxel analyses, and region of interest to region of interest analyses. A repeated measures analysis of covariance (ANCOVA) will be used to assess the effects of active and sham stimulation on sleep variables. Additionally, we will correlate changes in functional connectivity to polysomnography-graded sleep.

Conclusions: The presently proposed cTBS protocol is aimed at establishing the initial research outcomes of the effects of a single burst of cTBS on disrupting the network connectivity of the DMN to improve sleep. If effective, future work could determine the most effective stimulation sites and administration schedules to optimize this potential intervention for sleep problems.

Trial Registration: ClinicalTrials.gov NCT04953559; https://clinicaltrials.gov/ct2/show/NCT04953559

International Registered Report Identifier (IRRID): DERR1-10.2196/51212

(JMIR Res Protoc 2024;13:e51212) doi:10.2196/51212

KEYWORDS

continuous theta burst stimulation; transcranial magnetic stimulation; default mode network; sleep; insomnia; cTBS; randomized controlled trial

Introduction

Overview

The sleep disturbances of insomnia include difficulty falling asleep, staying asleep, or inability to fall back to sleep after premature awakenings, or any combination of these, along with daytime sleepiness and dysfunction. Difficulty falling and remaining asleep affected nearly 30% of the US population, with approximately 20% of the general population experiencing occasional difficulties and an additional 10% meeting the clinical criteria for an insomnia disorder [1]. However, this protocol was conducted during the COVID pandemic, when the prevalence of insomnia symptoms increased to 53% and insomnia disorder prevalence jumped from 10% to 17% [2]. Insomnia symptoms have been linked with poorer health across multiple domains and exacts a high societal cost in the workplace, on the health care system, and on an individual's and family's quality of life [3-5]. Moreover, side effects from medications used to manage insomnia increase these factors in some cases. Novel approaches that facilitate sleep are critically needed, and some potential neural mechanisms of insomnia create a viable treatment target [6].

The most widely accepted theory of primary insomnia is the hyperarousal hypothesis, which suggests that problems with sleep initiation and maintenance are due largely to the disruptive effects of somatic or cognitive hyperarousal [7,8]. In particular, cortical hyperarousal can emerge from excessive focus on repetitive negative thoughts, including intensive problem-solving, self-reflective rumination, and worry [9-11]. Subjectively, people who struggle with insomnia often make comments such as "I wish I could just turn my mind off" or "I just keep replaying conversations over in my head." In fact, one of the major features of insomnia is the tendency toward self-reflective rumination and worry [9,12-15]. This internal dialogue contributes to a cycle of self-referential thought and hyperarousal that appears to hinder sleep onset and maintenance [9,16-18]. In fact, worry and sleep disruptions are associated in the general population [3]. In individuals with insomnia, cortical hyperarousal contributes to difficulty initiating and maintaining sleep [19].

Neuroimaging research has shown that internally focused self-reflective processes of this type tend to activate an interconnected system within the brain known as the default mode network (DMN) [20,21]. Moreover, negative ruminative thinking is associated with changes in DMN connectivity and other brain regions associated with cognitive arousal or negative emotion [22]. Patients with insomnia often show abnormalities in the functioning of the DMN that are consistent with the hyperarousal hypothesis [23-25]. The core nodes of the DMN typically include the medial prefrontal cortex, posterior cingulate cortex, precuneus, and bilateral inferior parietal cortex regions but can also include several ancillary smaller regions, including the hippocampus, medial temporal lobes, and other subcortical structures [26]. Individuals with insomnia disorder tend to have increased resting-state functional connectivity (FC) between spatially segregated nodes of the DMN [27,28]. Increased connectivity and activation of the DMN could contribute to the ongoing self-referential processing and internal dialogue that maintains a hyperaroused state and perpetuates difficulties falling and remaining asleep [27,29]. Individuals with insomnia disorder show greater activation of the DMN compared with healthy controls while viewing word lists associated with past, present, and future worries, particularly when the words are self-referential [29].

Mainstream approaches to treating primary insomnia include cognitive behavioral therapy for insomnia and pharmacologic sleep aids, such as hypnotic sedatives [30-33]. While cognitive behavioral therapy for insomnia often helps to reduce ruminative cognitions and is effective at improving sleep for many individuals, there are many who fail to achieve meaningful benefits [34,35]. Similarly, pharmacologic sleep aids also tend to have modest effect sizes [36] and are often associated with unwanted side effects (eg, daytime drowsiness and memory problems) and health-related morbidities [37]. Various noninvasive neuromodulatory approaches have been shown to improve insomnia symptoms, including repetitive transcranial magnetic stimulation (rTMS) [38]. However, low-frequency rTMS has a cortical inhibition effect that has been shown to improve insomnia symptoms, which may be due to hyperarousal across multiple psychological and physiological domains [39].

The proposed protocol aims to bridge the gap between cognitive and neuromodulatory interventions to facilitate sleep onset and longer maintenance by temporarily inhibiting the brain FC that is associated with cortical hyperarousal and presleep ruminative cognitions. Our proposed approach will involve using rTMS prior to bedtime to briefly disrupt the strength of FC among cortical regions of the DMN. As we propose to inhibit connectivity within the DMN, we will use continuous theta burst stimulation (cTBS), which induces long-term depression of cortical neural firing following a sustained stimulation period of 40 seconds [40]. Thus, we hypothesize that the application

of cTBS to an easily accessible node of the DMN will suppress the local neural activity of that node and propagate inhibition throughout the DMN, thereby reducing ruminative thinking and worry prior to sleep onset. Decreased DMN connectivity is expected to improve sleep quality and quantity. An increase in slow-wave and rapid eye movement sleep stages has been proposed as mechanisms of rTMS in increasing restorative sleep in individuals with insomnia, so polysomnography (PSG) parameters are the primary outcome measures in the outlined protocol [41]. This phase 1 clinical trial will be the first study to investigate the effects of cTBS targeted to the left inferior parietal node of the DMN on objectively measured sleep outcomes.

Research Aims and Hypotheses

This study aims to explore the effects of cTBS on (1) the activation and connectivity of the DMN and (2) sleep outcomes. We hypothesize that modulating the DMN by stimulating a targeted region of the left inferior parietal lobule with a single cTBS administration will decrease FC within the DMN and thereby improve sleep parameters (ie, PSG) relative to an identical sham administration.

Study Design and Randomization

This phase 1 clinical trial (ClinicalTrials.gov NCT04953559) will be conducted with a randomized, double-blind, sham-controlled, counterbalanced, crossover design. Participants serve as their own controls as they undergo 2 identical study sessions separated by at least 5 days (ie, washout period). Participants and study personnel who interact with the participants will be blind to the specific condition (active cTBS vs sham) the participant receives during each study visit. Using a prespecified, equally balanced, block randomization procedure, participants will be assigned to the order in which they receive active cTBS and sham stimulation conditions. The randomization list will be generated by a computer random number generator, with the constraint that half of the participants of each biological sex will receive sham first and half will receive the active cTBS first. This design will allow us to examine the intraindividual effects of the active cTBS and establish the superiority of active cTBS compared with sham stimulation in improving PSG sleep outcomes.

Methods

Study Procedures Overview

The study procedures were completed over 3 separate visits. Screening to determine eligibility and baseline assessments was conducted during visit 1. Eligible participants were asked to wear a wrist actigraph for at least 5 days prior to their first in-laboratory overnight visit (visit 2). Based on a preestablished counterbalanced crossover randomization schedule, participants were then assigned to receive either the active cTBS or sham stimulation for their first overnight visit (visit 2) followed by the alternative intervention during their second overnight visit (visit 3) at least 5 days later. As shown in Figure 1, each in-laboratory session lasted 18 hours, including a 2-hour cognitive testing block, 1 hour of preintervention magnetic resonance imaging (MRI), followed by either active cTBS or sham stimulation, and a postintervention hour of neuroimaging. Participants were then fitted with PSG electrodes and were permitted 8 hours of sleep while undergoing PSG sleep monitoring in the lab. The next morning, participants completed another 2-hour cognitive testing block before being released.

The full study execution takes approximately 38-40 hours with 2-3 hours allocated for baseline screening and enrollment (visit 1) and 18 hours allocated for each overnight visit (visits 2 and 3). Table 1 presents the specific assessment measures administered at each visit.

Figure 1. Overview of the pilot randomized controlled trial study design. Participants first complete a web-based eligibility survey screening for sleep disturbances. Potentially eligible volunteers complete an in-lab enrollment process and baseline assessment (visit 1) at a large Southwestern University medical research center. Participants are then randomized to a stimulation order condition. After at least 5 days with actigraphically measured sleep, participants return for an 18-hour overnight session involving 2 MRI scans and overnight sleep (visit 2) at the medical research center. Depending on their condition assignment order, they either receive active cTBS or sham intervention. Participants then undergo a washout period of at least 5 days that includes actigraphically measured sleep. They then return for an identical overnight visit that involves the alternate intervention condition. cTBS: continuous theta burst stimulation; MRI: magnetic resonance imaging.

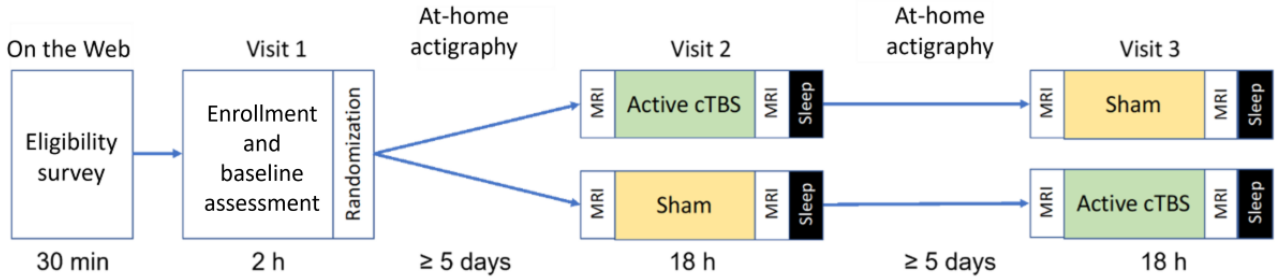


Table 1. List of study activities and assessments performed during study visits during a pilot randomized controlled trial evaluating the preliminary effectiveness of continuous theta burst stimulation in improving sleep in individuals with reported sleep disturbances.

Study activities and assessments	Baseline screening and enrollment (visit 1)	At home	Overnight visits (visits 2 and 3)
Screening			
Consent form	✓		
Eligibility screening (TMS[a], health background, MRI[b], PSQI[c], ISI[d], and ESS[e])	✓		
Pregnancy test	✓		
Covariates			
Demographics	✓		
Anxiety (STAI-S[f] and STAI-T[g])	✓		✓
Depression (BDI-II[h])	✓		✓
Sleep preoccupation (SPS[i] and GCTI[j])	✓		✓[k]
Caffeine consumption questionnaire	✓		
Intelligence (WASI-II[l])	✓		
Actigraphy (Phillips Actiwatch)		✓	
Sleep quality (Sleep diaries)		✓	
Primary Outcomes			
Functional connectivity in DMN[m]			✓
Sleep (PSG[n])			✓
Secondary Outcomes			
Information processing speed (GNG[o])			✓
Attention (PVT[p])			✓
Verbal memory (CVLT-3[q])			✓
Immediate and delayed memory (RBANS[r])			✓
Self-reported sleepiness (KSS[s])			✓
Mood (VAMS[t])			✓
Side effects (pre- and post-TMS assessment)			✓

[a]TMS: transcranial magnetic stimulation.
[b]MRI: magnetic resonance imaging.
[c]PSQI: Pittsburgh Sleep Quality Index.
[d]ISI: Insomnia Severity Index.
[e]ESS: Eppworth Sleepiness Scale.
[f]STAI-S: State-Trait Anxiety Inventory-State.
[g]STAI-T: State-Trait Anxiety Inventory-Trait.
[h]BDI-II: Beck Depression Inventory.
[i]SPS: Sleep Preoccupation Scale.
[j]GCTI: Glasgow Content of Thoughts Inventory.
[k]Only GCTI.
[l]WASI-II: Wechsler Abbreviated Scale of Intelligence.
[m]DMN: default mode network.
[n]PSG: polysomnography.
[o]GNG: go/no-go task.
[p]PVT: psychomotor vigilance task.

[q]CVLT-3: California Verbal Learning Task 3.

[r]RBANS: repeatable battery for the assessment of neuropsychological status.

[s]KSS: Karolinska Sleepiness Scale.

[t]VAMS: Visual Analogue Mood Scale.

Ethical Considerations

All study activities and study personnel were approved by the University of Arizona's Institutional Review Board (IRB) and by the Department of Defense Office of Human Research Oversight (OHRO) in March 2021 (approval 2007900971). Any protocol amendments and reportable new information were disseminated to both IRB and OHRO. All participant information was deidentified for confidentiality. Participants were compensated 500 dollars via check for their participation in the study if they were fully compliant with the study procedures. The study team maintains dissemination control of the final deidentified data set. Final results will only report cumulative population data to respective regulatory and scientific reporting agencies and along with peer-reviewed publications. Access to the deidentified data set will be available upon request to the principal investigator and in conjunction with proper regulatory requirement.

Participants and Recruitment

A total of 20 otherwise healthy adults with self-reported sleep disturbances were recruited from the greater Tucson and Phoenix metropolitan areas. Recruitment strategies include flyers posted on community boards, advertisements in local newspapers, sponsored social media posts, and email lists at local universities. Individuals who were recruited from the community were directed to complete a web-based survey in a HIPAA (Health Insurance Portability and Accountability Act)–compliant server. If participants met the initial inclusion criteria, a study member then completed a preliminary phone screening with the participant. Study personnel then scheduled an in-person screening visit for eligible individuals.

Power Analyses

During the study design, we conducted a power analysis to determine the sample size necessary to compare mean changes in DMN connectivity before and after cTBS using a within-subjects ANOVA approach. From prior cited work on transcranial magnetic stimulation (TMS) and FC, a total sample of 20 was found to have sufficient power to answer the research questions to include analysis of 2 groups (within-subject active and sham), 2 repeated measurements (before and after TMS), and a correlation between the change in DMN activation and sleep outcome metrics [42,43].

Inclusion and Exclusion Criteria

Individuals between the ages of 18-50 years with reported sleep disturbances were included in the study. Individuals were excluded if they reported or exhibited any health conditions beyond insomnia-related symptoms. Exclusionary criteria were based on one or more of the following considerations: the criterion in question is (1) known to alter sleep, (2) known to substantially increase interparticipant variability, (3) known to put the volunteer outside the range of what is considered healthy, or (4) required by regulation. Detailed inclusion and exclusion criteria are referenced in Textbox 1.

Textbox 1. A detailed description of inclusion and exclusion criteria of a pilot randomized controlled trial evaluating the preliminary effectiveness of continuous theta burst stimulation in improving sleep in individuals with reported sleep disturbances.

Inclusion criteria

- 18-50 years old
- Self-reported sleep disturbances on 2 of 3 inventories:
  - Pittsburgh Sleep Quality Index ≥6
  - Insomnia Severity Index ≥15
  - Epworth Sleepiness Scale ≥11

Exclusion criteria

- Unwillingness to provide informed consent
- Presence of a metal implant or medical device which poses a safety risk for magnetic resonance imaging or transcranial magnetic stimulation
- Self-reported past or present medical diagnosis of sleep- or breathing-related disorders
- Travel outside the time zone within 1 week prior to the enrollment visit or while active during the study
- Self-reported major medical or neurological problems
- Self-reported past or present history of cardiovascular disease
- Self-reported past or present history or first-degree family history of any seizures or seizure disorders
- Self-reported underlying acute or chronic pulmonary disease
- Self-reported history of fainting spells or syncope
- Self-reported past or present psychiatric problems
- Self-reported suicidal ideation
- Self-reported current use of prescription medications
- Self-reported current use of supplements that affect sleep
- Self-reported caffeine use in excess of 300 mg per day on average
- Self-reported regular nicotine use
- Self-reported or suspected heavy alcohol indicated on the Alcohol Use Disorders Identification Test (AUDIT) as greater than or equivalent to 14 drinks a week for male individuals and 7 drinks a week for female individuals
- Self-reported use of illicit drugs
- Speaking English as a nonprimary language
- Less than a ninth-grade education
- Engaged in overnight shift work
- Female individuals only: positive urine pregnancy test
- Female individuals only: self-reported current breast-feeding or collecting breast milk

Study Activities

Enrollment and Baseline Assessment (Visit 1)

Eligible participants were invited for an in-person screening and baseline data collection session lasting approximately 2-3 hours. After participant consent was obtained by trained study staff members, the participants underwent a baseline assessment, including measurement of intellectual capacity with the Wechsler Abbreviated Scale of Intelligence by a certified administrator, subjective sleep assessment including the Pittsburgh Sleep Quality Index and Insomnia Severity Index, and other cognitive assessments.

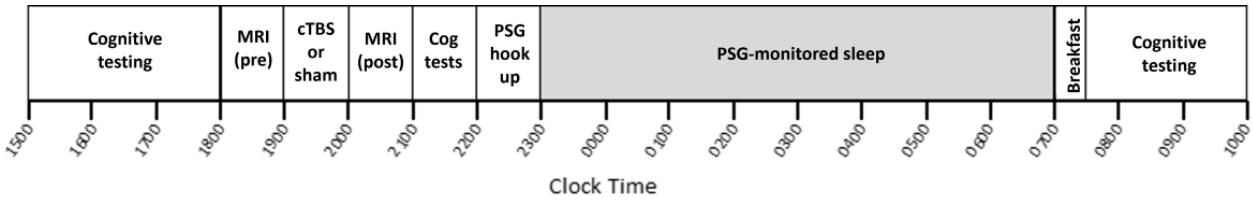
At-Home Actigraphy Week

Upon the completion of the enrollment visit, participants were fitted with a wrist actigraphic sleep monitor that they wear for at least 5 days prior to returning for the in-laboratory assessment sessions and continued to wear the device during the intervening washout week between the 2 in-residence laboratory stays. Participants also completed a web-based sleep diary each morning. Throughout the entire period of enrollment, participants were required to maintain a regular sleep schedule and were not permitted to use caffeine products for 48 hours prior to the in-laboratory overnight stays.

Overnight In-Residence Laboratory Sessions (Visits 2 and 3)

Participants completed 2 overnight in-residence laboratory stays according to a double-blind counterbalanced crossover design, with each session separated by at least 5 days. Figure 2 provides a graphical overview of the in-residence laboratory activities.

Figure 2. Timeline of the in-residence laboratory testing for the pilot randomized controlled trial. Participants arrive at the lab at 1500 and undergo cognitive testing followed by a preintervention MRI scan. The intervention is administered between 1900 and 2000 and is randomly assigned as either active cTBS stimulation or an identical appearing sham condition. After stimulation, participants complete a postintervention series of MRI scans, followed by a brief cognitive testing battery. At 2200, they are escorted to the sleep lab and PSG electrodes are applied. Lights out occur at 2300 and the participant is provided with an 8-hour undisturbed period for PSG-monitored sleep. Following wake-up at 0700 the next morning, the participant is provided a light breakfast and completes a final battery of cognitive tests. This procedure is repeated on separate weeks for the active cTBS and placebo conditions. cTBS: continuous theta burst stimulation; MRI: magnetic resonance imaging; PSG: polysomnography.



Cognitive Testing Block

Participants arrived at 3 PM and completed approximately 3 hours of cognitive testing with a trained and certified administrator, including the 10-minute psychomotor vigilance testing (PVT) and Karolinska Sleepiness Scale (KSS) at 3 time points separated by an hour, in addition to the Visual Analog Mood Scale, State-Trait Anxiety Inventory-State only (STAI-S), Beck Depression Inventory (BDI-II), California Verbal Learning Task 3 (CVLT3), go/no-go task (GNG), repeatable battery for the assessment of neuropsychological status (RBANS) symbol digit test, RBANS digit span, RBANS story memory test, and Glasgow Content of Thoughts Inventory (GCTI).

Prestimulation Neuroimaging

MRI scans were collected on a Siemens MAGNETOM Skyra 3T scanner (Siemens) using a 32-channel head coil. Participants completed a series of scans that included structural (magnetization-prepared rapid gradient-echo), functional (10-min eyes open) resting state, and proton magnetic resonance spectroscopy (^{1}H MRS) scans, with voxels placed in (1) the anterior cingulate gyrus and (2) posterior cingulate or precuneus. Functional MRI data will be preprocessed with standard neuroimaging packages, including statistical parametric mapping 12, FSL, and the functional connectivity toolbox (CONN v17f or later; focusing on DMN network connectivity) following standard published pipelines [44].

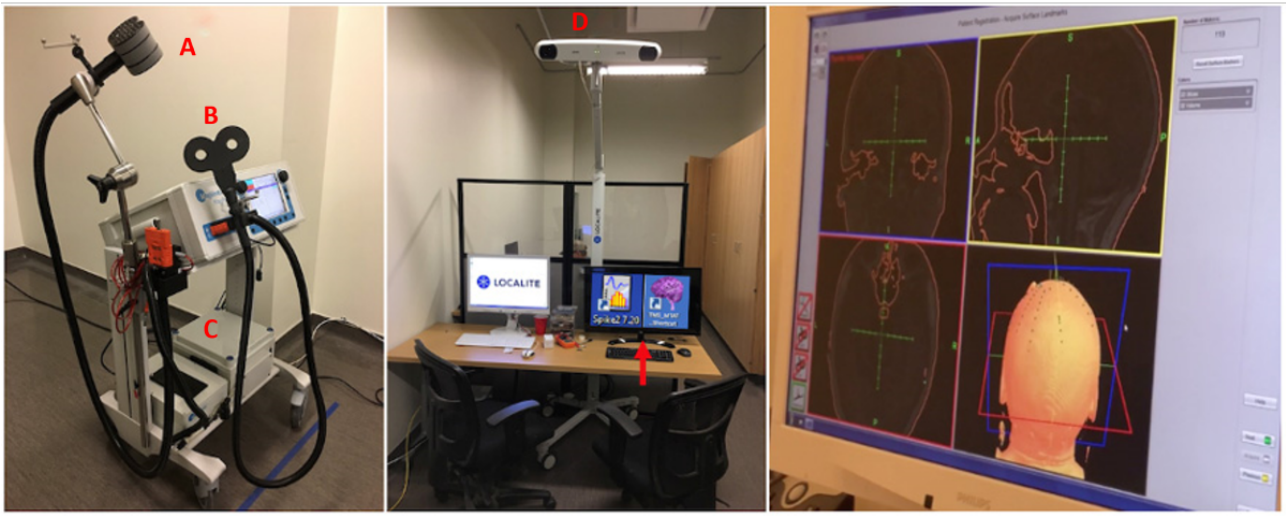
Intervention: cTBS Versus Sham

Following the first MRI scan, participants exited the scanner and underwent either cTBS stimulation or sham stimulation according to their preassigned double-blinded condition. The stimulator was preprogrammed prior to the start of the session and the participants and technicians that administered the stimulation procedure were blind to the administered condition. Each individual was expected to have a different sensitivity to the magnetic fields generated by the stimulation coil, and the stimulation intensity was adjusted based on each individual's resting motor threshold (RMT). The real-time, motor-evoked potential of muscle contraction is provided to ensure consistent force production. Once the RMT was identified, the stimulation intensity for TBS was set to 70% of each participant's RMT.

For primary rTMS stimulation, we located a predetermined node in the inferior parietal lobe, localized by coregistering the participant's head, structural T1-weighted MRI image, and TMS coil in the same space using a TMS 3D Neuronavigation System. Once coregistration was complete, the Neuronavigation system provided real-time feedback on the TMS coil location and recorded the coil position and orientation relative to the head. The cTBS was applied using a figure-of-8 coil with an active cooling system connected to the MagPro magnetic stimulator (MagVenture Cool-B65). The same coil has 2 sides, 1 designed for active TMS stimulation, and the other is equipped with a magnetic shield that effectively blocks any stimulation and is used for the sham condition. The rTMS setup is shown in Figure 3.

For this project, we selected an easily accessible node of the DMN located on the left lateral parietal (LLP) cortex. The exact spatial location for stimulation is based on the Yeo et al [45] probability atlas. We downloaded this atlas into the Mango 4.1 visualization program (and identified the centroid of the LLP node of the DMN at the MNI coordinates of x (–48), y (–61.5), and z (32.5). These coordinates are converted into the same stereotaxic space as the participant's brain to allow precision localization of the LLP node as the target for stimulation. Once this site was localized for the participants, a 40-second cTBS stimulation train (600 stimuli/session) or identically matched sham stimulation was administered using a MagVenture MagPro X100 stimulator (MagVenture Inc) connected with a figure-of-8 magnetic coil with active cooling.

Figure 3. Transcranial magnetic intervention system set-up for the pilot randomized controlled trial. Left: (A) the continuous theta burst stimulation is administered with a MagVenture Cool-B65 stimulator that included an active and sham side; (B) the resting motor threshold was determined using a MagPro X100 stimulator with a figure-of-8 coil; (C) the transcranial magnetic stimulation system is maintained at a constant temperature using an active cooling system. Middle: the stimulation is directed by a computerized system that detected the orientation of the head in space using (D) an antenna camera and correlate it with the individual's coregistered magnetic resonance imaging scan. Right: An image showing the Neuronavigation system used to administer the transcranial magnetic stimulation to the precise default mode network locations.



Poststimulation Neuroimaging

Immediately following the cTBS or sham stimulation period, each participant underwent a second neuroimaging session that was identical to the prestimulation MRI session previously described.

PSG Recording

Participants slept undisturbed in a light- and temperature-controlled private bedroom while continuously monitored by a trained technician with a Nihon Kohden JE-921 PSG recording system using standard 10-20 electrode placement. Data from PSG were scored using Polysmith software according to the standard Rechtschaffen and Kales approach by a trained and certified sleep technician who was blind to the participant's condition and status. The primary outcome metrics include sleep onset latency (SOL), latency to N1, N2, N3, and REM, total sleep time (TST), sleep efficiency (SE), wake after sleep onset (WASO), and number of awakenings and arousals, as well as time and percentage of time spent in each sleep stage.

Monitoring

Participants were assessed both prior to stimulation and after receiving stimulation for any adverse somatic, cognitive, or physical symptoms. Any presence of symptoms was logged in a HIPAA-compliant server and the participant was assessed by the study physician to determine if enrollment needed to be discontinued. All adverse events were reported to both IRB and OHRO. All study activity was subject to independent, random auditing from the Department of Psychiatry at the University of Arizona and study sponsors.

Data Management

All collected data were deidentified and stored within HIPAA-compliant, password-protected servers immediately after collection. Study data were only accessible to IRB-approved study staff. All data were checked and double-entered by study personnel no more than 1 week after data collection. Data quality checks were conducted every quarter by staff members for additional data assurance. Any data collected after participants' consent were included in the study database for both compliant and noncompliant participants. However, following a per-protocol analysis, we are only using data from participants who fully completed the study due to within-subjects analysis.

Primary Outcomes: FC Changes in the DMN

We hypothesize that active cTBS will disrupt the within-network and between-network connectivity of the DMN. This hypothesis will be assessed from a 10-minute resting-state FC scan and analyzed using standard procedures in the CONN (v17f or higher). Standard pipelines for preprocessing will be used. Within-network connectivity will be determined by first conducting an independent components analysis of the intrinsic activation patterns across the brain. Twenty independent components will be extracted. Mean activation clusters from each component will be examined for intercorrelation to determine within-network connectivity. Additionally, between-network, region-to-region, and seed-to-voxel analyses will be conducted to compare changes in FC between the 2 stimulation conditions.

Analysis Plan

FC Changes to the DMN

First-level whole brain connectivity analyses will be undertaken in CONN for each subject at each of the 4 sessions (ie, active prestimulation, active poststimulation, sham prestimulation, and sham poststimulation). This will result in an FC map for each participant at each session, indicating the magnitude and direction of intrinsic correlation between each seed region (eg, lateral parietal cortex of the DMN) and all other voxels in the brain. For our primary analysis, we will estimate the effects of active cTBS on FC within the DMN using multimodal neuroimaging data including resting state FC. Raw NifTI images

will be preprocessed using standard functional preprocessing pipelines in CONN [46].

The first-level connectivity maps will be combined in subsequent second-level analyses in CONN to explore the effects of cTBS stimulation on brain connectivity to include (1) independent components analysis, (2) seed-to-voxel analyses, and (3) region of interest to region of interest analyses [44]. Statistically significant differences in FC of the DMN between sham and active conditions will be the minimal important change to confirm the primary hypothesis. Next, PSG parameters measuring sleep stage duration and onsets, arousals, and awakenings will be added as covariates of FC change from before to after stimulation, comparing sham and active cTBS conditions.

PSG Analysis

We will assess the effects of active cTBS on sleep and whether participants demonstrated greater sleep quality during their active cTBS session compared with their sham stimulation session. Analyses will be conducted on sleep variables including total sleep time; N1 latency; N2 latency; N3 latency; REM latency; SOL; persistent SOL; SE; WASO; total number of awakenings; spontaneous arousals; wake duration; and stage duration for N1, N2, N3, and REM. Analyses will include repeated measures ANOVA controlling for covariates. Statistically significant difference between sham and active conditions will be the minimal important change to confirm this hypothesis.

Exploratory Analysis

We will examine the effects of active cTBS on secondary outcomes of cognitive performance, mood, and side effects compared with sham stimulation using repeated measures ANOVAs and nonparametric tests accordingly.

Results

Our study was funded in September 2020 by the Department of Defense (W81XWH2010173). We completed the enrollment of our target population of 20 participants in October 2022. As of July 2023, we will initiate extensive neuroimaging data analysis and anticipate that the full results of the study will be published by 2024.

Discussion

Study Rationale

With a growing number of people reporting greater sleep disturbances, identifying effective nonpharmacological interventions is an important step in providing more innovative and noninvasive approaches for improving sleep outcomes. While the sample size for this study is small, this is the first study to investigate cTBS effects on the DMN to improve sleep outcomes.

Experimental Clinical Design Rationale

Double-blind randomized controlled trials are the gold standard for scientific inquiry. Therefore, each participant will serve as their own control in a counterbalanced crossover design. Implementing a crossover design in which every participant receives both active and sham cTBS stimulation permits comparison of intraindividual differences in DMN connectivity and sleep quality parameters, as each participant acts as their own control. Because the goal was to examine the effects of cTBS on individuals with sleep problems, no healthy control samples were recruited or necessary to test our hypotheses. Blinding study personnel to the TMS condition also reduces systematic differences in the administration of the stimulation interventions and ostensibly reduces the influence of expectations about treatment effects.

Brief cTBS of the LLP Lobule

Continuous theta burst was selected as the intervention based on its previously demonstrated inhibitory effects on the cortex [47]. A single 40-second cTBS session inhibits, or suppresses, neural excitability in the cortex for up to 50 minutes or longer [47]. Stimulation of a single node of the DMN is expected to inhibit local activity, with further suppression of cortical excitability propagating throughout the network overall. Inhibition of the left inferior parietal lobule was selected for two primary reasons: (1) prior research showed reduced metabolic activity in this region when individuals were falling asleep and (2) this region facilitates an easy-to-access node of the posterior DMN [48].

The localization of specific brain regions requires prestimulation imaging to account for individual variability in brain structure. For this reason, a critical element of that project was to show that stimulation of a single, easily accessible surface node of the larger DMN could lead to significant alterations in FC within this network. Prior investigations using cTBS have focused primarily on the stimulation of brain regions associated with the prefrontal areas of the DMN. Sleep-related parameters have rarely been collected as outcome measures for cTBS. One prior study examining rTMS effects on the right parietal cortex showed reduced anxiety and insomnia symptoms [49]. However, that study used a stimulation session (of three 1-Hz stimulations every 10 minutes) spread across 10 days. The presently proposed cTBS protocol is aimed at establishing initial research outcomes of the effects of a single burst of cTBS on disrupting network connectivity of the DMN to improve sleep. Thus, only a single stimulation session of both active cTBS and sham is needed to identify the intraindividual effects of cTBS on sleep outcomes.

Limitations and Future Directions

Targeting a single node of the DMN and conducting only 1 stimulation session are limitations of this protocol to sufficiently answer the research questions and aims proposed regarding DMN and insomnia improvement. Future work could determine the most effective stimulation sites within the DMN and the optimal number of pulses and administrations to optimize this potential intervention for sleep problems. Larger samples are also needed than the small pilot sample collected for this protocol to examine the effects of sex observed in previous studies [38].

Summary and Conclusions

Insomnia symptoms linked with many other psychiatric and physiological morbidities have become an increasingly prevalent

and important health care and societal concern. Noninvasive neuromodulation can be inexpensive and is a technique accessible to many types of treatment providers. The protocol presented here unifies the prominent aspects of insomnia—physiological and psychological hyperarousal—by targeting a unique neural network, known to be associated with proposed mechanisms of insomnia [8,50].

Acknowledgments

This study was funded by the United States Army Medical Research and Development Command (W81XWH2010173; primary investigator: WDSK).

Authors' Contributions

LH carried out the data collection, data management, wrote the initial draft of the manuscript, and contributed to revisions. AH contributed equally to the initial drafting of the manuscript, provided revisions, and contributed to the ongoing statistical analysis of the study. ND assisted with the study design and executed data collection. SJ and KHA contributed to data collection, data management, and regulatory reporting, and reviewed drafts of the manuscript. CT, YCC, and YHC provided training in transcranial magnetic stimulation (TMS), provided the TMS study equipment, and oversaw TMS data collection. WDSK was responsible for the initial conceptualization and design of the project, obtaining the research funding, providing oversight of the study, contributing to ongoing statistical analysis and interpretation of the findings, and contributing to initial drafting and revisions of the manuscript.

Conflicts of Interest

None declared.

References

1. Morin CM, Vézina-Im LA, Ivers H, Micoulaud-Franchi JA, Philip P, Lamy M, et al. Prevalent, incident, and persistent insomnia in a population-based cohort tested before (2018) and during the first-wave of COVID-19 pandemic (2020). Sleep 2022;45(1):zsab258 [FREE Full text] [doi: 10.1093/sleep/zsab258] [Medline: 34698868]
2. AlRasheed MM, Fekih-Romdhane F, Jahrami H, Pires GN, Saif Z, Alenezi AF, et al. The prevalence and severity of insomnia symptoms during COVID-19: a global systematic review and individual participant data meta-analysis. Sleep Med 2022;100:7-23 [FREE Full text] [doi: 10.1016/j.sleep.2022.06.020] [Medline: 36030616]
3. Clancy F, Prestwich A, Caperon L, Tsipa A, O'Connor DB. The association between worry and rumination with sleep in non-clinical populations: a systematic review and meta-analysis. Health Psychol Rev 2020;14(4):427-448 [FREE Full text] [doi: 10.1080/17437199.2019.1700819] [Medline: 31910749]
4. Bramoweth AD, Taylor DJ. Chronic insomnia and health care utilization in young adults. Behav Sleep Med 2012;10(2):106-121. [doi: 10.1080/15402002.2011.587067] [Medline: 22468929]
5. Taylor DJ, Lichstein KL, Durrence HH. Insomnia as a health risk factor. Behav Sleep Med 2003;1(4):227-247. [doi: 10.1207/S15402010BSM0104_5] [Medline: 15600216]
6. Taddei-Allen P. Economic burden and managed care considerations for the treatment of insomnia. Am J Manag Care 2020;26(Suppl 4):S91-S96 [FREE Full text] [doi: 10.37765/ajmc.2020.43008] [Medline: 32282179]
7. Bonnet MH, Arand DL. Hyperarousal and insomnia. Sleep Med Rev 1997;1(2):97-108. [doi: 10.1016/s1087-0792(97)90012-5] [Medline: 15310517]
8. Kay DB, Buysse DJ. Hyperarousal and beyond: new insights to the pathophysiology of insomnia disorder through functional neuroimaging studies. Brain Sci 2017;7(3):23 [FREE Full text] [doi: 10.3390/brainsci7030023] [Medline: 28241468]
9. Tousignant OH, Taylor ND, Suvak MK, Fireman GD. Effects of rumination and worry on sleep. Behav Ther 2019;50(3):558-570. [doi: 10.1016/j.beth.2018.09.005] [Medline: 31030873]
10. Benham G. Bedtime repetitive negative thinking moderates the relationship between psychological stress and insomnia. Stress Health 2021;37(5):949-961. [doi: 10.1002/smi.3055] [Medline: 33904245]
11. Zagaria A, Ottaviani C, Lombardo C, Ballesio A. Perseverative cognition as a mediator between perceived stress and sleep disturbance: a structural equation modeling meta-analysis (meta-SEM). Ann Behav Med 2023;57(6):463-471. [doi: 10.1093/abm/kaac064] [Medline: 36409327]
12. Carney CE, Harris AL, Moss TG, Edinger JD. Distinguishing rumination from worry in clinical insomnia. Behav Res Ther 2010;48(6):540-546 [FREE Full text] [doi: 10.1016/j.brat.2010.03.004] [Medline: 20362977]
13. Palagini L, Moretto U, Dell'Osso L, Carney C. Sleep-related cognitive processes, arousal, and emotion dysregulation in insomnia disorder: the role of insomnia-specific rumination. Sleep Med 2017;30:97-104. [doi: 10.1016/j.sleep.2016.11.004] [Medline: 28215272]
14. Kalmbach DA, Roth T, Cheng P, Ong JC, Rosenbaum E, Drake CL. Mindfulness and nocturnal rumination are independently associated with symptoms of insomnia and depression during pregnancy. Sleep Health 2020;6(2):185-191 [FREE Full text] [doi: 10.1016/j.sleh.2019.11.011] [Medline: 32146168]

15. Yu J, Liu K, Liu S. Relationship between coping style and insomnia in college students: the mediating effect of rumination. Nan Fang Yi Ke Da Xue Xue Bao 2020;40(1):137-141 [FREE Full text] [doi: 10.12122/j.issn.1673-4254.2020.01.22] [Medline: 32376569]
16. Mamede A, Merkelbach I, Noordzij G, Denktas S. Mindfulness as a protective factor against depression, anxiety and psychological distress during the COVID-19 pandemic: emotion regulation and insomnia symptoms as mediators. Front Psychol 2022;13:820959 [FREE Full text] [doi: 10.3389/fpsyg.2022.820959] [Medline: 35432084]
17. Kalmbach DA, Buysse DJ, Cheng P, Roth T, Yang A, Drake CL. Nocturnal cognitive arousal is associated with objective sleep disturbance and indicators of physiologic hyperarousal in good sleepers and individuals with insomnia disorder. Sleep Med 2020;71:151-160 [FREE Full text] [doi: 10.1016/j.sleep.2019.11.1184] [Medline: 32247571]
18. Kalmbach DA, Cuamatzi-Castelan AS, Tonnu CV, Tran KM, Anderson JR, Roth T, et al. Hyperarousal and sleep reactivity in insomnia: current insights. Nat Sci Sleep 2018;10:193-201 [FREE Full text] [doi: 10.2147/NSS.S138823] [Medline: 30046255]
19. Fernandez-Mendoza J, Li Y, Vgontzas AN, Fang J, Gaines J, Calhoun SL, et al. Insomnia is associated with cortical hyperarousal as early as adolescence. Sleep 2016;39(5):1029-1036 [FREE Full text] [doi: 10.5665/sleep.5746] [Medline: 26951400]
20. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. Proc Natl Acad Sci U S A 2001;98(2):676-682 [FREE Full text] [doi: 10.1073/pnas.98.2.676]
21. Zhou HX, Chen X, Shen YQ, Li L, Chen NX, Zhu ZC, et al. Rumination and the default mode network: meta-analysis of brain imaging studies and implications for depression. Neuroimage 2020;206:116287 [FREE Full text] [doi: 10.1016/j.neuroimage.2019.116287] [Medline: 31655111]
22. Ehrlich TJ, Bhat J, Horwege AM, Mathalon DH, Glover GH, Roach BJ, et al. Ruminative reflection is associated with anticorrelations between the orbitofrontal cortex and the default mode network in depression: implications for repetitive transcranial magnetic stimulation. Brain Imaging Behav 2022;16(3):1186-1195 [FREE Full text] [doi: 10.1007/s11682-021-00596-4] [Medline: 34860349]
23. O'Byrne JN, Rosa MB, Gouin JP, Dang-Vu TT. Neuroimaging findings in primary insomnia. Pathol Biol (Paris) 2014;62(5):262-269. [doi: 10.1016/j.patbio.2014.05.013] [Medline: 25129873]
24. Yu S, Guo B, Shen Z, Wang Z, Kui Y, Hu Y, et al. The imbalanced anterior and posterior default mode network in the primary insomnia. J Psychiatr Res 2018;103:97-103. [doi: 10.1016/j.jpsychires.2018.05.013] [Medline: 29804003]
25. Schiel JE, Holub F, Petri R, Leerssen J, Tamm S, Tahmasian M, et al. Affect and arousal in insomnia: through a lens of neuroimaging studies. Curr Psychiatry Rep 2020;22(9):44 [FREE Full text] [doi: 10.1007/s11920-020-01173-0] [Medline: 32661938]
26. Alves PN, Foulon C, Karolis V, Bzdok D, Margulies DS, Volle E, et al. An improved neuroanatomical model of the default-mode network reconciles previous neuroimaging and neuropathological findings. Commun Biol 2019;2:370 [FREE Full text] [doi: 10.1038/s42003-019-0611-3] [Medline: 31633061]
27. Marques DR, Gomes AA, Caetano G, Castelo-Branco M. Insomnia disorder and brain's default-mode network. Curr Neurol Neurosci Rep 2018;18(8):45. [doi: 10.1007/s11910-018-0861-3] [Medline: 29886515]
28. Regen W, Kyle SD, Nissen C, Feige B, Baglioni C, Hennig J, et al. Objective sleep disturbances are associated with greater waking resting-state connectivity between the retrosplenial cortex/ hippocampus and various nodes of the default mode network. J Psychiatry Neurosci 2016;41(5):295-303 [FREE Full text] [doi: 10.1503/jpn.140290] [Medline: 26809225]
29. Marques DR, Gomes AA, Clemente V, dos Santos JM, Duarte IC, Caetano G, et al. Self-referential dysfunction and default-mode hyperactivation in psychophysiological insomnia patients. J Psychophysiol 2018;32(3):140-155. [doi: 10.1027/0269-8803/a000194]
30. Bramoweth AD, Germain A. Deployment-related insomnia in military personnel and veterans. Curr Psychiatry Rep 2013;15(10):401 [FREE Full text] [doi: 10.1007/s11920-013-0401-4] [Medline: 24005883]
31. Good CH, Brager AJ, Capaldi VF, Mysliwiec V. Sleep in the United States military. Neuropsychopharmacology 2020;45(1):176-191 [FREE Full text] [doi: 10.1038/s41386-019-0431-7] [Medline: 31185484]
32. Jacobs GD, Pace-Schott EF, Stickgold R, Otto MW. Cognitive behavior therapy and pharmacotherapy for insomnia: a randomized controlled trial and direct comparison. Arch Intern Med 2004;164(17):1888-1896 [FREE Full text] [doi: 10.1001/archinte.164.17.1888] [Medline: 15451764]
33. Taylor DJ, Peterson AL, Pruiksma KE, Hale WJ, Young-McCaughan S, Wilkerson A, et al. Impact of cognitive behavioral therapy for insomnia disorder on sleep and comorbid symptoms in military personnel: a randomized clinical trial. Sleep 2018;41(6):zsy069 [FREE Full text] [doi: 10.1093/sleep/zsy069] [Medline: 29618098]
34. Baron KG, Hooker S. Next steps for patients who fail to respond to Cognitive Behavioral Therapy for Insomnia (CBT-I): the perspective from behavioral sleep medicine psychologists. Curr Sleep Medicine Rep 2017;3(4):327-332. [doi: 10.1007/s40675-017-0096-x]
35. Grandner MA, Esquivel DR, Dawson S. Chapter 19—CBT-I for people who failed CBT-I. In: Cuddihy L, Grandner MA, Nowakowski S, Garland S, editors. Adapting Cognitive Behavioral Therapy for Insomnia. London: Elsevier Science; 2022:403-435.

36. Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: an American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med 2017;13(02):307-349. [doi: 10.5664/jcsm.6470] [Medline: 27998379]
37. Vermeeren A, Coenen AML. Effects of the use of hypnotics on cognition. Prog Brain Res 2011;190:89-103. [doi: 10.1016/B978-0-444-53817-8.00005-0] [Medline: 21531246]
38. Ma H, Lin J, He J, Lo DHT, Tsang HWH. Effectiveness of TES and rTMS for the treatment of insomnia: meta-analysis and meta-regression of randomized sham-controlled trials. Front Psychiatry 2021;12:744475 [FREE Full text] [doi: 10.3389/fpsyt.2021.744475] [Medline: 34744835]
39. Holbert RC, Carr BR, Bussing R. An open label pilot trial of sequential bifrontal low frequency r-TMS in the treatment of primary insomnia. Psychiatry Res 2023;324:115194 [FREE Full text] [doi: 10.1016/j.psychres.2023.115194] [Medline: 37054553]
40. Chung SW, Hill AT, Rogasch NC, Hoy KE, Fitzgerald PB. Use of theta-burst stimulation in changing excitability of motor cortex: a systematic review and meta-analysis. Neurosci Biobehav Rev 2016;63:43-64. [doi: 10.1016/j.neubiorev.2016.01.008] [Medline: 26850210]
41. Sun N, He Y, Wang Z, Zou W, Liu X. The effect of repetitive transcranial magnetic stimulation for insomnia: a systematic review and meta-analysis. Sleep Med 2021;77:226-237. [doi: 10.1016/j.sleep.2020.05.020] [Medline: 32830052]
42. Eldaief MC, Halko MA, Buckner RL, Pascual-Leone A. Transcranial magnetic stimulation modulates the brain's intrinsic activity in a frequency-dependent manner. Proc Natl Acad Sci U S A 2011;108(52):21229-21234 [FREE Full text] [doi: 10.1073/pnas.1113103109] [Medline: 22160708]
43. Luber B, Stanford AD, Bulow P, Nguyen T, Rakitin BC, Habeck C, et al. Remediation of sleep-deprivation-induced working memory impairment with fMRI-guided transcranial magnetic stimulation. Cereb Cortex 2008;18(9):2077-2085 [FREE Full text] [doi: 10.1093/cercor/bhm231] [Medline: 18203694]
44. Nieto-Castanon A, Whitfield-Gabrieli S. CONN functional connectivity toolbox (RRID: SCR_009550), version 21. Hilbert Press. 2021. URL: https://www.hilbertpress.org/link-nieto-castanon2021 [accessed 2024-01-05]
45. Yeo BTT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, et al. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. J Neurophysiol 2011;106(3):1125-1165 [FREE Full text] [doi: 10.1152/jn.00338.2011] [Medline: 21653723]
46. Nieto-Castanon A. Handbook of Functional Connectivity Magnetic Resonance Imaging Methods in CONN. Boston, MA: Hilbert Press; 2020.
47. Wischnewski M, Schutter DJLG. Efficacy and time course of theta burst stimulation in healthy humans. Brain Stimul 2015;8(4):685-692. [doi: 10.1016/j.brs.2015.03.004] [Medline: 26014214]
48. Braun AR, Balkin TJ, Wesenten NJ, Carson RE, Varga M, Baldwin P, et al. Regional cerebral blood flow throughout the sleep-wake cycle. an H2(15)O PET study. Brain 1997;120(Pt 7):1173-1197. [doi: 10.1093/brain/120.7.1173] [Medline: 9236630]
49. Huang Z, Li Y, Bianchi MT, Zhan S, Jiang F, Li N, et al. Repetitive transcranial magnetic stimulation of the right parietal cortex for comorbid generalized anxiety disorder and insomnia: a randomized, double-blind, sham-controlled pilot study. Brain Stimul 2018;11(5):1103-1109. [doi: 10.1016/j.brs.2018.05.016] [Medline: 29871798]
50. Fasiello E, Gorgoni M, Scarpelli S, Alfonsi V, Strambi LF, De Gennaro L. Functional connectivity changes in insomnia disorder: a systematic review. Sleep Med Rev 2022;61:101569. [doi: 10.1016/j.smrv.2021.101569] [Medline: 34902821]

Abbreviations

ANCOVA: analysis of covariance
BDI-II: Beck Depression Inventory
CONN: Functional Connectivity Toolbox
cTBS: continuous theta burst stimulation
CVLT-3: California Verbal Learning Task 3
DMN: default mode network
FC: functional connectivity
GCTI: Glasgow Content of Thoughts Inventory
HIPAA: Health Insurance Portability and Accountability Act
IRB: Institutional Review Board
LLP: left lateral parietal
MRI: magnetic resonance imaging
OHRO: Office of Human Research Oversight
PSG: polysomnography
PVT: psychomotor vigilance task
RBANS: Repeatable Battery for the Assessment of Neuropsychological Status
RMT: resting motor threshold

rTMS: repetitive transcranial magnetic stimulation
SE: sleep efficiency
SOL: sleep onset latency
TMS: transcranial magnetic stimulation
TST: total sleep time
WASO: wake after sleep onset

Edited by A Mavragani; submitted 24.07.23; peer-reviewed by Q Chen, A Tavares; comments to author 04.12.23; revised version received 24.12.23; accepted 26.12.23; published 26.01.24.

Please cite as:
Hildebrand L, Huskey A, Dailey N, Jankowski S, Henderson-Arredondo K, Trapani C, Patel SI, Chen AYC, Chou YH, Killgore WDS Transcranial Magnetic Stimulation of the Default Mode Network to Improve Sleep in Individuals With Insomnia Symptoms: Protocol for a Double-Blind Randomized Controlled Trial
JMIR Res Protoc 2024;13:e51212
URL: https://www.researchprotocols.org/2024/1/e51212
doi:10.2196/51212
PMID:38277210

Protocol

Psychostimulant Medications for Physical Function and Spasticity in Children With Cerebral Palsy: Protocol for a Randomized Controlled Trial

Mansour Alotaibi[1,2*], MBA, PT, PhD; Anwar B Almutairi[3*], PT, PhD; Saleh Alhirsan[4*], PT, PhD; Afrah Alkazemi[5*], BCPS, MSc, PharmD; Maha Alharbi[5*], BCPS, MSc, PharmD; Naif Alrashdi[6,7], MSRS, PT, PhD; Ahmad Taqi[5], MSc, PharmD; Bibi Alamiri[8], MD, SCD; Laura Vogtle[9], PhD; Mohammed M Alqahtani[10,11], RRT-NPS, PhD

[1]Department of Rehabilitation, Faculty of Applied Medical Sciences, Northern Border University, Arar, Saudi Arabia

[2]Center for Health Research, Northern Border University, Arar, Saudi Arabia

[3]Department of Physical Therapy, Faculty of Allied Health, Kuwait University, Kuwait City, Kuwait

[4]Department of Physical Therapy, College of Applied Medical Sciences, Jouf University, Aljouf, Saudi Arabia

[5]Department of Pharmacy Practice, College of Pharmacy, Kuwait University, Kuwait City, Kuwait

[6]Department of Physical Therapy and Health Rehabilitation, College of Applied Medical Sciences, Majmaah University, Al-Majmaah, Saudi Arabia

[7]The Health and Scientific Research Center, Majmaah University, Majmaah, Saudi Arabia

[8]Kuwait Center for Mental Health, Public Authority for Disability Affairs, Almanara, Kuwait

[9]Department of Occupational Therapy, School of Health Professions, University of Alabama at Birmingham, Birmingham, AL, United States

[10]Department of Respiratory Therapy, College of Applied Medical Sciences, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia

[11]King Abdullah International Medical Research Center, Riyadh, Saudi Arabia

[*]these authors contributed equally

Corresponding Author:
Mansour Alotaibi, MBA, PT, PhD
Department of Rehabilitation
Faculty of Applied Medical Sciences
Northern Border University
4636 Jawhara Dist
Arar, 73551
Saudi Arabia
Phone: 966 558811790
Email: mansour.alotaibi@nbu.edu.sa

Abstract

Background: Cerebral palsy (CP) is a prevalent nonprogressive disorder that leads to impaired movement (ie, spasticity), posture, and balance, which affects functions such as walking and upper extremity tasks. Current medical treatments show efficacy in improving motor performance but have considerable side effects. Emerging off-label use of central nervous system (CNS) medications for improving motor performance has shown promising results in children with CP and other populations.

Objective: The aim of this study is to describe a protocol for a pilot randomized controlled trial (RCT) to examine the safety, tolerability, and efficacy of methylphenidate (MPH) and modafinil on spasticity and motor performance in children with CP.

Methods: This will be a protocol study for a pilot, triple-masked, placebo-controlled RCT (a class I trial following the American Academy of Neurology criteria) with blinded patients, outcome assessors, and intervention delivery team. Eligible children should be diagnosed with CP levels I or II based on the Gross Motor Function Classification System and be aged between 7 and 12 years. Thirty-six children with CP will be randomized into 3 groups to receive (1) MPH (2.5 mg of MPH + 100 mg placebo), (2) modafinil (100 mg modafinil + 2.5 mg placebo), or (3) a placebo (2.5 mg placebo + 100 mg placebo), in addition to physical therapy for 12 weeks. Primary outcomes include the Gross Motor Function Measure–66 and the Modified Ashworth Scale. Secondary outcomes include the Timed Up and Go test, 5 Time Sit to Stand test, Modified Clinical Test for Sensory Interaction of Balance, and 10-Meter Walk Test.

Results: The protocol has been accepted by Kuwait University (VDR/EC-225) and the Ministry of Health of Kuwait (2022/2157). The inclusion of participants will start in June 2024.

Conclusions: The combination of CNS stimulant medications and controlling for rehabilitation has not been studied yet. The findings of this study may determine if using CNS stimulant medications is beneficial for the reduction of spasticity and improvement of physical function in children with spastic CP.

Trial Registration: ClinicalTrials.gov NCT05675098; https://clinicaltrials.gov/study/NCT05675098

International Registered Report Identifier (IRRID): PRR1-10.2196/53728

(JMIR Res Protoc 2024;13:e53728) doi:10.2196/53728

KEYWORDS

cerebral palsy; CNS stimulants; spasticity; motor performance; gross motor function; psychostimulant; medications; physical function; CP; children; child; pediatrics; pediatric; impairment; movement; central nervous system; safety; tolerability; efficacy; methylphenidate; modafinil; Kuwait; rehabilitation; physical therapy

Introduction

Background

Cerebral palsy (CP) is a group of disorders that cause permanent, nonprogressive damage to the developing brain [1], leading to impairments in movement and posture, as well as balance deficits [2,3]. These impairments could affect gross motor skills [4], such as gait [5], upper limb tasks (eg, reaching) [6], and oral motor function (eg, eating and swallowing) [7], which could contribute to limitations across a variety of life domains, including self-care, education and work, and recreational activities [8].

CP is one of the leading causes of disability [2], affecting about 1 in 500 children, with estimated prevalence of 17 million individuals globally [9]. CP can be classified into different categories based on motor impairments, including spasticity (increased muscle excitability) [10], dyskinesia (uncontrollable random movement) [11], ataxia (impaired coordination) [12], or mixed movement disorders [3].

Spastic disorders are the most common type of CP that affects motor activities essential for activities of daily living (ADL) [3]. Treatment of CP spastic disorders includes pharmacological medications (oral and injected), surgical therapy, and nonpharmacological therapy (ie, rehabilitation or constraint-induced movement therapy [13,14]). Pharmacological medications with different mechanisms of action can be used to reduce spasticity in children with CP. For instance, using botulinum toxin type A (BoNT-A) injections is efficacious in reducing spasticity of the upper extremities (UEs) [15] and lower extremities (LEs) [16], which helps in improving the overall motor function in children with CP [17]. BoNT-A inhibits acetylcholine production from the presynaptic terminal, causing a decrease in muscle excitability [17]. Based on the current CP clinical practice guidelines, BoNT-A is considered a safe and effective intervention for spasticity in children and adolescents with CP [18-21]. However, BoNT-A effects are peripheral, targeting specific muscles, and have a temporary influence on spasticity [15,16]. Importantly, BoNT-A has been criticized due to its potential to induce muscle weakness in a condition that is characterized by motor impairments [17].

Other pharmacological medications can reduce spasticity in children with CP, such as baclofen (tablets or intrathecal injections) and diazepam (tablets) [20]. These medications reduce spasticity by improving the affinity of gamma-amino butyric acid (GABA) on its receptors, which in turn blocks excitatory neurotransmitters [22,23]. Notably, these medications have shown effectiveness in both reducing spasticity and improving motor performance in children with CP [24,25]. Nevertheless, baclofen and diazepam have potential side effects that could impact their use, including drowsiness and potential muscle weakness [20]. These medications counter a key factor in improving motor performance by decreasing the rate of motor firing [20]. Therefore, there is a critical need to explore the effects of medications that could both improve motor performance and reduce spasticity but also exhibit minimal side effects in children with CP.

In the past 2 decades, central nervous system (CNS) stimulants such as methylphenidate (MPH) have been reported to improve motor performance when used in children with attention-deficit/hyperactivity disorder (ADHD) [26,27]. Furthermore, a case report documented that a woman aged 44 years with CP (mixed type—choreoathetosis with spasticity) consumed another CNS stimulant (amphetamine) recreationally and observed a remarkable reduction in her spasticity, which encouraged her physician to prescribe MPH for spasticity reduction [28]. This woman had a considerable long-term decline in spasticity and choreoathetosis with MPH use [28]. Another CNS stimulant (modafinil) showed improvements in gait and spasticity among children with CP [29-31]. Nevertheless, the effects of modafinil on spasticity and motor improvement have been inconsistent [32]. Consequently, potential CNS stimulants such as MPH and modafinil are hypothesized to reduce spasticity and improve motor performance in children with CP due to alteration in neurochemicals in the brain (ie, changes in neuroplasticity) [33].

Rehabilitation interventions for children with CP produce changes in neuroplasticity [34], which could lead to long-term improvements in motor function. Specifically, early interventions for spasticity and motor function may be associated with improved motor performance due to enhancement of sensory feedback plasticity [35]. Sensory feedback is an essential modifiable factor for motor learning by iteration, which alters

connections between primary motor and somatosensory cortices [36,37]. Therefore, the use of CNS stimulants, in addition to rehabilitation interventions, could offer long-term improvements in spasticity and motor performance in children with CP. Using CNS stimulants may offer advantages over existing pharmacological treatments, primarily because they do not induce muscle weakness [17]. Given the limited studies that have examined the effects of CNS stimulants on motor performance, with or without rehabilitation, in children with CP, a pilot experimental research study is warranted.

Objective

We designed a triple-masked pilot randomized controlled trial (RCT) that aims to examine the safety and tolerability of MPH and modafinil (aim 1) as well as to assess trends in changes in gross motor function and spasticity with the use of MPH and modafinil in children with CP (aim 2). In this placebo-controlled study, participants will be randomized into 3 groups that will receive MPH, modafinil, or placebo tablets. We hypothesize that using MPH or modafinil will be tolerable and safe for children with CP. We also hypothesize that there will be trends toward improvement in gross motor function and spasticity in children with CP.

Methods

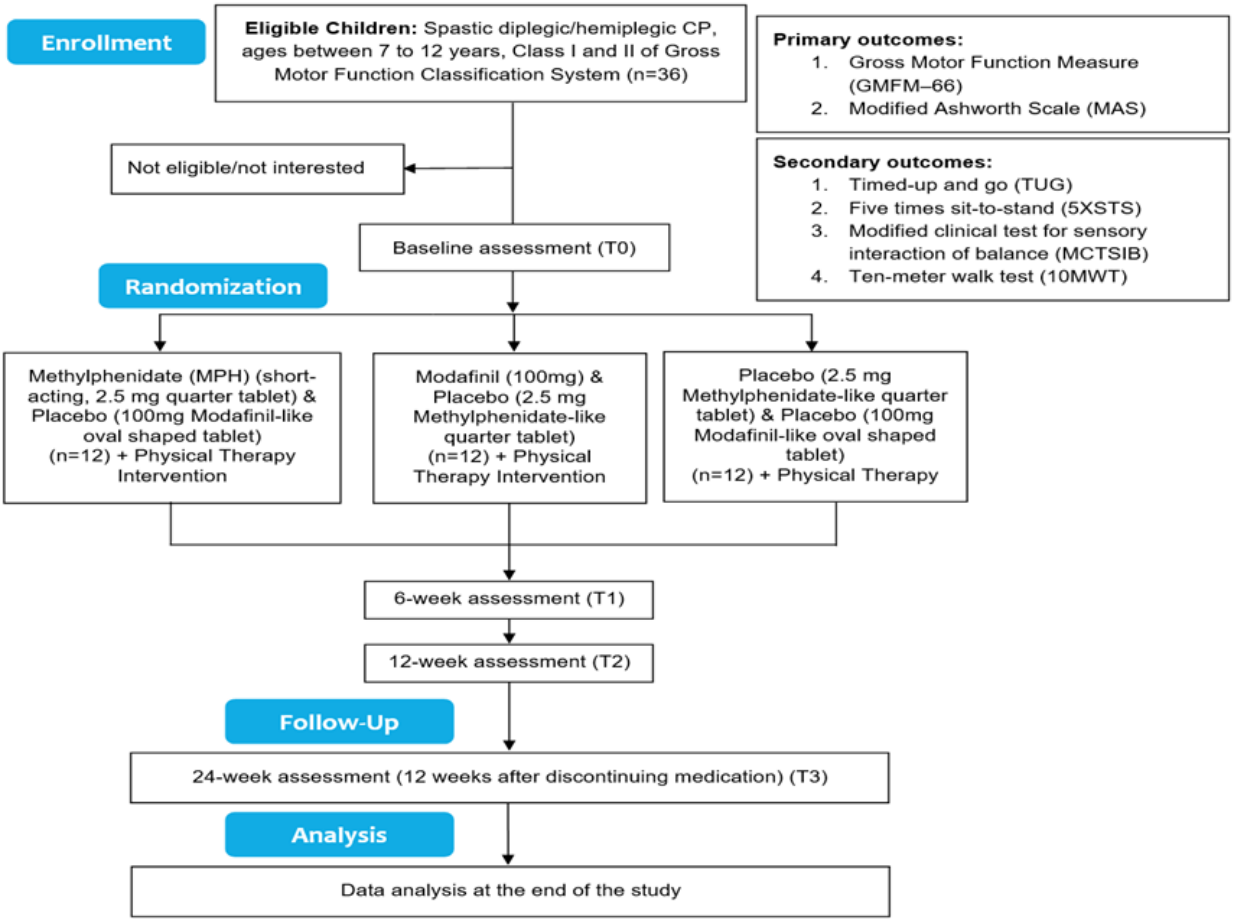
Ethical Considerations

Ethical approval for this study has been obtained from Kuwait University (VDR/EC-225) and the Ministry of Health of Kuwait (2022/2157). Prior to initiation of this study, participants and their legal guardians will be informed about the study and written consent and assent will be obtained from each participant. We followed the SPIRIT (Standard Protocol Items: Recommendation for Interventional Trials) guidelines for the preparation of this protocol [38]. The SPIRIT guidelines are a 33-item checklist that allows researchers to draft and plan high-quality RCTs and describe elements of the content of the RCT. The protocol of this study has been registered at ClinicalTrials.gov (NCT05675098).

Study Design

This study will be a single-center, prospective, triple-masked, placebo-controlled pilot RCT. The study design is informed by the American Academy of Neurology (AAN) criteria for evidence classification as a class I study [39]. To meet these criteria, this study will (1) be triple-masked (blinded) to minimize the risk of bias (ie, patients and legal guardians, treatment providers, and outcome assessors will be blinded), (2) use the intent-to-treat principle to account for dropouts, (3) have only 2 primary outcomes (the Gross Motor Function Measure [GMFM] and Modified Ashworth Scale [MAS]), (4) have a prespecified minimal clinical detectable change in the primary outcomes, and (5) use a powerful method to correct for multiple comparisons for secondary outcomes. This study will also use a placebo-control group as an active control; this is due to the fact that there are no medications that possess CNS-stimulant qualities that have been tested for the purpose of the study. This study will examine the effects of a 12-week administration of MPH, modafinil, or placebo with the GMFM and MAS, with a testing session in the middle of the study period (ie, at the 6-week mark). This is integral, as it will allow for monitoring changes in the primary outcomes at multiple time points. The study will also examine the long-lasting effects of these medications (MPH and modafinil) at 12 weeks after the conclusion of the intervention (ie, at 24 weeks) to assess if any detected trends of improvement last beyond the period of the intervention. This study will be guided by the CONSORT (Consolidated Standards of Reporting Trials) guidelines for recruitment (Figure 1).

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flowchart of the proposed randomized controlled trial.



Recruitment

Participants

Formal power calculation will not be carried out because this is a pilot study. Children with CP (N=36) aged 7 to 12 years will be enrolled (ie, 12 children per group). Children will be recruited from hospitals around Kuwait using several advertisement methods, including flyers, email notifications to health care providers, and social media advertisements (eg, on X, formerly known as Twitter). Additionally, we will use the snowball recruitment method for this study. The study will be conducted at Jaber Al-Ahmad Hospital, Kuwait.

Inclusion Criteria

Children will be screened and considered for eligibility if they are diagnosed with spastic diplegic or hemiplegic CP by a pediatric neurologist with at least 5 years of experience with this population, aged 7 to 2 years, male or female, classified as level I or II on the Gross Motor Function Classification System (GMFCS), (ie, they are able to walk independently with or without limitation) [40], and have received physical therapy for at least 3 months. GMFCS level will be determined by the treating therapist of the participant according to the expanded and revised version of the GMFCS [41]. If eligible, participants will only follow the rehabilitation intervention described in this protocol. Medicine management will continue as prescribed by the treating physician.

Exclusion Criteria

Children will be excluded if they have had a seizure in the past 6 months, have been diagnosed with ADHD, have had any surgery within the last 6 months, use medications that interfere with spasticity (eg, baclofen), are unable to follow simple commands, or have LE (hip, knee, and ankle) contractures determined by the passive range of motion (ROM). Contracture measurement will follow the CP Follow-up Program (CPUP) measurement manual, based on the guidelines of Norkin and White [42]. Measurements will be done using a universal goniometer and in standardized positions. Decreases in passive ROM are considered contractures if they fall within the red level of the “traffic light” system of the CPUP [42]. For the hip joint, abduction and extension ROM will be measured with the Ely test [43]. For the knee joint, extension along with popliteal angle will be measured [44]. Finally, for the ankle joint, dorsiflexion with knee flexed and extended along with plantarflexion will be measured. Assessors will be consistent across data collection points (screening, baseline, at 6 weeks, at 12 weeks, and at 24 weeks). Interrater reliability will be measured on 25% of the sample, chosen randomly to ensure consistency among assessors.

Randomization

Match or pair randomization will be used in this study to control for confounding effects of sex and GMFCS level. Children will be allocated to the MPH, modafinil, or placebo group using a concealed centralized electronic allocation application. Children

will be matched for sex (male or female) and GMFCS (level I or II).

Sample Size

This study will include 12 children in each group (N=36). Due to the design of the study (ie, a pilot trial), power calculation will not be performed to estimate the sample size. Upon the completion of this study, our findings will provide effect sizes that are essential for future studies to conduct a power analysis.

Blinding Procedures

This study will be triple-masked (blinded), where treatment providers, outcome assessors, and participants (children and their legal guardians) will be unaware of the study group allocation. Two pharmacists and 1 study coordinator will be the only personnel exposed to the group allocation. The 2 pharmacists will carry out the randomization process and prepare the medication using a concealed nontransparent envelope and send it to the nursing staff, who will provide the treatment approximately 90 minutes before the physical therapy session. The study coordinator will track group allocation and deliver the prescriptions to the nursing staff before the administration of the drug. Physicians who prescribe MPH, modafinil, or placebo will use a customized sham form to ensure blinding. All primary and secondary outcomes will be collected by 2 physical therapists (PTs), who will be also blinded to the group allocation.

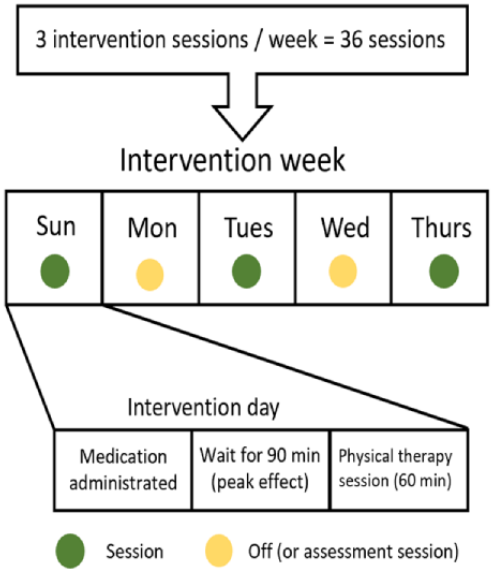
Intervention

Medication

Participants will receive 2 medications based on their group assignment. The MPH group will receive a quarter tablet of short-acting MPH (2.5 mg) and an oval-shaped placebo (100 mg) tablet that looks like a modafinil tablet. The modafinil group will receive a modafinil (100-mg) tablet and a circle-shaped quarter tablet of placebo that looks like an MPH tablet (2.5 mg). The placebo group (the active control) will receive 2 placebo tablets (a circle-shaped quarter tablet of MPH placebo and an oval-shaped tablet of modafinil placebo). All delivered medications (MPH, modafinil, and placebo) will be administered approximately 90 minutes before the physical therapy session, to use the peak medication effect to augment the outcomes of physical therapy [45]. The medication will be administered by a registered nurse and will be controlled by the pharmacy department at Jaber Al-Ahmed Hospital. The medication will be only prescribed on the day of a physical therapy session, which means that children will receive 3 medication doses per week over 12 consecutive weeks (the duration of the study). Since children need to receive the medication 90 minutes before their PT session, appointments will be scheduled on Sundays, Tuesdays, and Thursdays during the daytime (ie, from 8 AM to 1 PM; Figure 2). Any missed appointment will be documented, and the prescribed medication will be returned to the pharmacy. After 12 weeks of medication administration, participants will stop receiving the prescribed medication in this study, whether it was the active agent or placebo. A follow-up assessment session will be performed 12 weeks after the discontinuation of medication to examine the potential for long-lasting benefits from the received medication. Further analysis will be done to compare compliant versus noncompliant children.

All MPH (Ritalin, 10 mg; Novartis), modafinil (Provigil, 100 mg; Apotex), and placebo (circle-shaped MPH placebo, 10 mg; oval-shaped modafinil placebo, 100 mg; Kuwait Saudi Pharmaceutical Industries Co) bottles that will be used in this study will adhere to labeling requirements to ensure traceability and accountability, containing the following information: (1) the full name of the supplier of the medication and placebo bottles, (2) the batch number, and (3) the manufacturing and expiration dates. In addition, the medication and placebo tablets will be extracted from their original bottles and secured in individual containers with the aforementioned information and a patient identifier. The study coordinator is responsible for ensuring compliance with these labeling requirements, which will be recorded and will be made available for inspection upon request.

Figure 2. Illustration of the timing of the administration of the medication and physical therapy sessions.



Physical Therapy Intervention

The physical therapy intervention will include therapeutic exercises that target different domains of the International Classification of Functioning, Health, and Disability (ICF), including body structure, activity, and participation. The dose of the physical therapy intervention will be as follows: (1) the frequency will be 3 sessions per week for 12 weeks; (2) the session time will be 60 minutes; (3) the type and intensity will be treatment activities that focus on joint ROM and muscle strength (body structure domain), locomotion training (body structure [endurance], activity [gait training], and participation [locomotive abilities] domains), reaching training (activity and participation domain), and motor control and motor learning training (activity and participation domain) (Table 1). A detailed manual will be provided to the treating PTs to ensure consistency in the treatment delivered to each child. After 12 weeks of receiving the physical therapy intervention, participants are entitled to enroll into any other rehabilitation program. At week 24, participants will complete an assessment session and provide information on whether they received rehabilitation after stopping the medication, if any, including duration of the session per day, frequency of sessions per week, and compliance to these sessions in the past 12 weeks.

Table 1. Detailed physical therapy plan.

ICF[a] domain and type	Details
Body structure and function	
Joint range of motion	• Active and passive stretching (eg, squats and stepping up)
Muscle strength	• Active and resistive training (85% of 1-repetition maximum—build up to 3 sets of 10 repetitions)
Activity	
Locomotion training	• Treadmill walking—build up to 1.2 m/s with a 0.2 m/s increase per week or as tolerated • Overground walking—over and around obstacles for 10 m or as tolerated
Reaching training	• Bimanual activities—reaching in all directions (with both hands or switching between hands)
Postural control	• Equilibrium reaction training— moving from a stable to an unstable surface with eyes open, then repeated with eyes closed
Participation	
Motor control and learning	• Training for activities of daily living—standing progression, walking progression, and higher function progression (stair climbing, running, and jumping)

[a]ICF: International Classification of Functioning, Health, and Disability.

Implementation of the Intervention

Data collection sessions (assessment data points) will be held on Sundays, Tuesdays, and Thursdays during the daytime (ie, 8 AM to 1 PM). Two PTs will be assigned to deliver physical therapy interventions throughout the study. Each PT will treat a range of 3 to 6 children per intervention period (n=36 intervention sessions). Two experienced investigators will supervise the physical therapy treatment and track the participants' compliance. The expected time commitment for each child for each session is about 2 to 2.5 hours, with the first hour waiting for the medication's peak effect and the remaining time for the physical therapy intervention.

Outcomes

Primary Outcomes

After obtaining the consent and assent forms, caregivers will complete a questionnaire on demographic information, followed by a body weight and height assessment of each child. The primary outcomes of this study will be the GMFM-66 and MAS scores for the LEs and UEs to assess changes in functional motor performance and spasticity, respectively. The assessment session will be done by a trained PT who is different from the PTs that will deliver the intervention. There will be 4 examination sessions (baseline, at 6 weeks, at 12 weeks, and at 24 weeks) that will last approximately 2 hours—for both primary and secondary outcomes. These assessment sessions will be scheduled separately from the intervention sessions. The GMFM-66 is designed to examine gross motor activities in five domains: (1) lying and rolling, (2) sitting, (3) crawling and kneeling, (4) standing, and (5) walking, running, and jumping [46]. The GMFM-66 scores range between 0 to 3, where 0 corresponds to "does not initiate," 1 corresponds to "initiates," 2 corresponds to "partially completes," and 3 corresponds to "completes" [46]. Items that a child refuses to perform or that are not administered are scored as "not tested" [46]. Scoring will be done using the Gross Motor Ability Estimator (GMAE), where each score is entered and then converted into an internal level to calculate the total score for each child's gross motor function. The GMFM-66 is a valid and reliable tool to assess gross motor function in children with CP [47]. In addition, we will use the MAS for the LE (hip extensors and adductors and ankle plantar flexors) and UE (shoulder internal rotators and flexors and elbow flexors) musculature as the second primary outcome. The MAS scores range from 0 (no increase in resistance to stretch) to 4 (complete rigidity) [48]. Children will lay supine on a flat bed with their head at midline and the arm beside the trunk [48]. Each extremity will be examined

separately. The examiner will rapidly move the child's extremity throughout the range within 1 second [48]. The examiner will determine the MAS score after applying 3 passive movements [48]. This MAS has been shown to have a good intrarater reliability for the LEs (intraclass correlation [ICC]=0.644; Cohen κ=0.488) [49]. The minimum clinically important differences (MCIDs) for the GMFM-66 are 1.7 and 1.0 for GMFCS levels I and II, respectively [50].

Secondary Outcomes

The secondary outcomes will include the Timed Up and Go (TUG) test, 5 Times Sit to Stand (5XSTS) test, Modified Clinical Test for Sensory Interaction of Balance (MCTSIB), and 10-Meter Walk Test (10MWT). For the TUG, participants will stand up from a 45-cm height armchair, walk at their typical, comfortable pace around a cone that will be placed 3 meters away from the chair, then walk back to the chair and sit down. Time(s) to complete the task will be recorded as the score of this test using a stopwatch. The TUG has excellent test-retest reliability in children with CP (ICC=0.91-0.99) and MCIDs of 0.36 and 0.87 for GMFCS levels I and II, respectively (ie, a large effect size) [51].

For the 5XSTS, participants will stand up from a 45-cm armchair and sit down as fast as they can. Time(s) will be used for scoring this test. This test has excellent test-retest reliability in children with CP (ICC=0.91) [52]. Of note, MCID data are not available for children with CP; however, the minimal detectable change for this test is 0.06 seconds [53].

The MCTSIB measures balance in 4 conditions, measured for a maximum of 3 trials of 30 seconds for each condition: firm floor with eyes open, then closed; and foam (unstable surface) with eyes open, then closed [54]. This test has excellent test-retest reliability (ICC=0.91) [54].

For the 10MWT, participants will be instructed to walk at their comfortable pace for 10 meters; time(s) will be recorded as the score of this test. This test is to measure gait speed and variability and has fair test-retest reliability (ICC=0.81) [55].

Statistical Analysis

SPSS (version 29; IBM Corp) will be used to conduct all the data analyses in this study. For changes in the primary outcomes, we will use a repeated-measures ANOVA to examine changes in the GMFM-66 between the 3 intervention groups across all testing time points (ie, baseline, at 6 weeks, at 12 weeks, and at 24 weeks). To examine changes in MAS between the 3 intervention groups, we will use Kruskal-Wallis *H* test because MAS is an ordinal scale. Finally, we will use multivariate linear mixed models to determine changes in the associated secondary outcomes between the 3 intervention groups.

Adverse Events

At the beginning of each intervention week, a questionnaire will be administered by the PTs inquiring about adverse effects. Any adverse events will be addressed immediately by the research team. Any potential risks of using CNS medications will be recorded in the informed consent and assent forms and will be explained to the caregiver of each child. In case of an adverse event, we will refer the participant directly to the emergency department to receive medical care and record the incident of the adverse event. Additionally, we will notify the institutional review board office at Kuwait University and the Ministry of Health of Kuwait about any potential incidents. Finally, should we encounter 2 or more incidents per medication group, we will stop the intervention for that specific group and document it in our records.

Data Collection and Management

Data collection will be performed at baseline (before randomization), 6 weeks, and 12 weeks, as well as at 24 weeks (as a test of long-lasting effects) after starting the intervention. A data monitoring committee (DMC) will be assigned that will include a research assistant and a pharmacist. Members of the DMC will be exposed to the randomization process and will manage adverse events throughout the protocol. Compliance to medication and physical therapy will be collected every session by the PTs, using an online Google form; Microsoft Excel sheets and participant ID numbers will be used to identify each participant. Only the DMC members will have access to this sheet, in which no identifiable information of participants will be included.

Confidentiality

All identifiable data of participants will be protected and decoded in the data collection sheet. After agreement to participate, signed consent and assent forms will be stored in a locked locker at the principal investigator's office. All other study documents (eg, data collection sheet, randomization and mediation prescriptions, and demographic data questionnaires) will use a participant ID number that will replace the name of the child.

Ancillary and Posttrial Care

Due to the pilot nature of this study, the results will not provide definite findings regarding the effectiveness of CNS stimulant medications in reducing spasticity and improving motor function in children with CP. Therefore, we are unable to recommend the prescribing of any CNS medication for children with CP until the findings of advanced phases of this project indicate their efficacy and effectiveness.

Results

The protocol has been accepted by Kuwait University (VDR/EC-225) and the Ministry of Health of Kuwait (2022/2157). The inclusion of participants will start in June 2024. The findings of this study are intended to be disseminated at several scientific meetings, including the American Academy of Cerebral Palsy and Developmental Medicine and the AAN annual meetings. Additionally, the findings of this study will be submitted for publication to scientific journals specialized in the field of CP and developmental medicine.

Discussion

Principal Findings

This study protocol details the background and design of a pilot RCT to determine changes in motor performance and spasticity

as a result of the use of CNS stimulant medications in children with CP. We expect the findings of this study to document the safety and tolerability of using these medications in children with CP. We also expect that there will be a trend of improvements in the GMFM-66 and MAS in the CNS stimulant groups (ie, MPH and modafinil) compared to the placebo group. We anticipate that these changes will impact quality of life and the overall function of children with CP, demonstrated by improvement trends in secondary outcomes, where these improvements could document positive effects of CNS stimulants in improving the health of patients with CP.

The findings of this study will be shared and disseminated through multiple scientific mediums, including annual conferences and scientific meetings, as well as peer-reviewed scientific journals. The functional and motor improvements that could result from using CNS stimulants in this population could reduce the consequences of impairments associated with CP. Therefore, using CNS stimulants could help in reducing the financial burden associated with treating CP functional impairments on the health care system.

Limitations

The complexity of CP and the heterogeneity of motor impairments may contribute to variations in response to medication in this study. However, we limited participation in this study to participants with GMFCS levels I and II to minimize the effect of severe motor impairments. Although not an issue in pilot studies, dropout across the study groups may occur. Nevertheless, this concern could be mitigated by providing physical therapy sessions to all groups in addition to medications. Regardless, CP motor treatment is valued across parents of children with CP and could help in reducing attrition. Finally, information obtained from the physical therapy intervention will be important for revising the conceptual model for the intervention and will inform the next step of the trial.

Conclusions

Evidence suggests promising results of using CNS stimulant medications for reducing spasticity and improving physical function in children with spastic CP. The combination of CNS stimulant medications and controlling for rehabilitation has not been studied yet. The findings of this study may suggest positive effects of using CNS stimulant medications for reducing spasticity and improving physical function in children with spastic CP.

Acknowledgments

The authors extend their appreciation to the Deanship of Scientific Research at Northern Border University, Arar, Saudi Arabia, for funding this research work through project NBU-FFR-2024-2508-02.

Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Authors' Contributions

M Alotaibi and ABA conceptualized the idea and methodology and contributed to manuscript preparation and revision. SA and NA improved the methodology, provided an overall framework, and revised the manuscript. AA, M Alharbi, and AT managed the pharmacological planning and placebo design in accordance with the study requirements and revised the manuscript. BA, LV, and MMA helped refine the protocol and provided critical feedback for improving the quality of this protocol. All authors have read and approved the manuscript.

Conflicts of Interest

None declared.

References

1. Vitrikas K, Dalton H, Breish D. Cerebral palsy: an overview. Am Fam Physician 2020 Feb 15;101(4):213-220 [FREE Full text] [Medline: 32053326]
2. Cerebral palsy. US Centers for Disease Control and Prevention. URL: https://www.cdc.gov/ncbddd/cp/index.html [accessed 2024-02-16]
3. O'Shea T. Diagnosis, treatment, and prevention of cerebral palsy. Clin Obstet Gynecol 2008 Dec;51(4):816-828 [FREE Full text] [doi: 10.1097/GRF.0b013e3181870ba7] [Medline: 18981805]
4. Woollacott M, Burtner P. Neural and musculoskeletal contributions to the development of stance balance control in typical children and in children with cerebral palsy. Acta Paediatr Suppl 1996 Oct;416(s416):58-62. [doi: 10.1111/j.1651-2227.1996.tb14279.x] [Medline: 8997450]
5. Liao H, Hwang A. Relations of balance function and gross motor ability for children with cerebral palsy. Percept Mot Skills 2003 Jun;96(3 Pt 2):1173-1184. [doi: 10.2466/pms.2003.96.3c.1173] [Medline: 12929770]

6. van der Heide JC, Begeer C, Fock JM, Otten B, Stremmelaar E, van Eykern LA, et al. Postural control during reaching in preterm children with cerebral palsy. Dev Med Child Neurol 2004 Apr;46(4):253-266 [FREE Full text] [doi: 10.1017/s0012162204000416] [Medline: 15077703]
7. Larnert G, Ekberg O. Positioning improves the oral and pharyngeal swallowing function in children with cerebral palsy. Acta Paediatr 1995 Jun;84(6):689-692. [doi: 10.1111/j.1651-2227.1995.tb13730.x] [Medline: 7670257]
8. Dewar R, Love S, Johnston LM. Exercise interventions improve postural control in children with cerebral palsy: a systematic review. Dev Med Child Neurol 2015 Jun;57(6):504-520 [FREE Full text] [doi: 10.1111/dmcn.12660] [Medline: 25523410]
9. Graham HK, Rosenbaum P, Paneth N, Dan B, Lin J, Damiano DL, et al. Cerebral palsy. Nat Rev Dis Primers 2016 Jan 07;2:15082 [FREE Full text] [doi: 10.1038/nrdp.2015.82] [Medline: 27188686]
10. Patel DR, Neelakantan M, Pandher K, Merrick J. Cerebral palsy in children: a clinical overview. Transl Pediatr 2020 Feb;9(Suppl 1):S125-S135 [FREE Full text] [doi: 10.21037/tp.2020.01.01] [Medline: 32206590]
11. Richards C, Malouin F. Cerebral palsy: definition, assessment and rehabilitation. Handb Clin Neurol 2013;111:183-195. [doi: 10.1016/B978-0-444-52891-9.00018-X] [Medline: 23622163]
12. Musselman KE, Stoyanov CT, Marasigan R, Jenkins ME, Konczak J, Morton SM, et al. Prevalence of ataxia in children: a systematic review. Neurology 2014 Jan 07;82(1):80-89 [FREE Full text] [doi: 10.1212/01.wnl.0000438224.25600.6c] [Medline: 24285620]
13. Dong VA, Fong KNK, Chen Y, Tseng SSW, Wong LMS. 'Remind-to-move' treatment versus constraint-induced movement therapy for children with hemiplegic cerebral palsy: a randomized controlled trial. Dev Med Child Neurol 2017 Feb;59(2):160-167 [FREE Full text] [doi: 10.1111/dmcn.13216] [Medline: 27503605]
14. DeLuca S, Case-Smith J, Stevenson R, Ramey S. Constraint-induced movement therapy (CIMT) for young children with cerebral palsy: effects of therapeutic dosage. J Pediatr Rehabil Med 2012;5(2):133-142. [doi: 10.3233/PRM-2012-0206] [Medline: 22699104]
15. Delgado MR, Tilton A, Carranza-Del Río J, Dursun N, Bonikowski M, Aydin R, et al. Efficacy and safety of abobotulinumtoxinA for upper limb spasticity in children with cerebral palsy: a randomized repeat-treatment study. Dev Med Child Neurol 2021 May;63(5):592-600 [FREE Full text] [doi: 10.1111/dmcn.14733] [Medline: 33206382]
16. Dursun N, Bonikowski M, Dabrowski E, Matthews D, Gormley M, Tilton A, et al. Efficacy of repeat abobotulinumtoxina (Dysport) injections in improving gait in children with spastic cerebral palsy. Dev Neurorehabil 2020 Aug;23(6):368-374. [doi: 10.1080/17518423.2019.1687602] [Medline: 31691605]
17. Multani I, Manji J, Hastings-Ison T, Khot A, Graham K. Botulinum toxin in the management of children with cerebral palsy. Paediatr Drugs 2019 Aug;21(4):261-281 [FREE Full text] [doi: 10.1007/s40272-019-00344-8] [Medline: 31257556]
18. Strobl W, Theologis T, Brunner R, Kocer S, Viehweger E, Pascual-Pascual I, et al. Best clinical practice in botulinum toxin treatment for children with cerebral palsy. Toxins (Basel) 2015 May 11;7(5):1629-1648 [FREE Full text] [doi: 10.3390/toxins7051629] [Medline: 25969944]
19. Whelan MA, Delgado MR. Practice parameter: pharmacologic treatment of spasticity in children and adolescents with cerebral palsy (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy Of Neurology and the Practice Committee of the Child Neurology Society. Neurology 2010 Aug 17;75(7):669. [doi: 10.1212/WNL.0b013e3181ec670b] [Medline: 20713958]
20. Novak I, Morgan C, Fahey M, Finch-Edmondson M, Galea C, Hines A, et al. State of the evidence traffic lights 2019: systematic review of interventions for preventing and treating children with cerebral palsy. Curr Neurol Neurosci Rep 2020 Feb 21;20(2):3 [FREE Full text] [doi: 10.1007/s11910-020-1022-z] [Medline: 32086598]
21. Bohn E, Goren K, Switzer L, Falck-Ytter Y, Fehlings D. Pharmacological and neurosurgical interventions for individuals with cerebral palsy and dystonia: a systematic review update and meta-analysis. Dev Med Child Neurol 2021 Sep;63(9):1038-1050 [FREE Full text] [doi: 10.1111/dmcn.14874] [Medline: 33772789]
22. Hägglund G, Hollung SJ, Ahonen M, Andersen GL, Eggertsdóttir G, Gaston MS, et al. Treatment of spasticity in children and adolescents with cerebral palsy in Northern Europe: a CP-North registry study. BMC Neurol 2021 Jul 12;21(1):276 [FREE Full text] [doi: 10.1186/s12883-021-02289-3] [Medline: 34253183]
23. Goyal V, Laisram N, Wadhwa RK, Kothari SY. Prospective randomized study of oral diazepam and baclofen on spasticity in cerebral palsy. J Clin Diagn Res 2016 Jun;10(6):RC01-RC05 [FREE Full text] [doi: 10.7860/JCDR/2016/17067.7975] [Medline: 27504360]
24. Yadav S, Chand S, Majumdar R, Sud A. Effect of botulinum toxin type-A in spasticity and functional outcome of upper limbs in cerebral palsy. J Clin Orthop Trauma 2020;11(2):208-212 [FREE Full text] [doi: 10.1016/j.jcot.2020.01.002] [Medline: 32099281]
25. Flemban A, Elsayed W. Effect of combined rehabilitation program with botulinum toxin type A injections on gross motor function scores in children with spastic cerebral palsy. J Phys Ther Sci 2018 Jul;30(7):902-905 [FREE Full text] [doi: 10.1589/jpts.30.902] [Medline: 30034093]
26. Stray L, Stray T, Iversen S, Ruud A, Ellertsen B. Methylphenidate improves motor functions in children diagnosed with hyperkinetic disorder. Behav Brain Funct 2009 May 13;5(1):21 [FREE Full text] [doi: 10.1186/1744-9081-5-21] [Medline: 19439096]

27. Jacobi-Polishook T, Shorer Z, Melzer I. The effect of methylphenidate on postural stability under single and dual task conditions in children with attention deficit hyperactivity disorder - a double blind randomized control trial. J Neurol Sci 2009 May 15;280(1-2):15-21. [doi: 10.1016/j.jns.2009.01.007] [Medline: 19217632]
28. Boogerd W, Beijnen JH. Methylphenidate for cerebral palsy with choreoathetosis. Ann Intern Med 2000 Mar 21;132(6):510. [doi: 10.7326/0003-4819-132-6-200003210-00023] [Medline: 10733460]
29. Hurst DL, Lajara-Nanson W. Use of modafinil in spastic cerebral palsy. J Child Neurol 2002 Mar;17(3):169-172. [doi: 10.1177/088307380201700303] [Medline: 12026230]
30. Hurst DL, Lajara-Nanson WA, Dinakar P, Schiffer RB. Retrospective review of modafinil use for cerebral palsy. J Child Neurol 2004 Dec;19(12):948-951. [doi: 10.1177/088307380401901207 01] [Medline: 15704868]
31. Hurst DL, Lajara-Nanson WA, Lance-Fish ME. Walking with modafinil and its use in diplegic cerebral palsy: retrospective review. J Child Neurol 2006 Apr;21(4):294-297. [doi: 10.1177/08830738060210042001] [Medline: 16900924]
32. Murphy AM, Milo-Manson G, Best A, Campbell KA, Fehlings D. Impact of modafinil on spasticity reduction and quality of life in children with CP. Dev Med Child Neurol 2008 Jul;50(7):510-514 [FREE Full text] [doi: 10.1111/j.1469-8749.2008.03019.x] [Medline: 18611200]
33. Nyberg F. Structural plasticity of the brain to psychostimulant use. Neuropharmacology 2014 Dec;87:115-124. [doi: 10.1016/j.neuropharm.2014.07.004] [Medline: 25018041]
34. Reid LB, Rose SE, Boyd RN. Rehabilitation and neuroplasticity in children with unilateral cerebral palsy. Nat Rev Neurol 2015 Jul;11(7):390-400. [doi: 10.1038/nrneurol.2015.97] [Medline: 26077839]
35. Matusz PJ, Key AP, Gogliotti S, Pearson J, Auld ML, Murray MM, et al. Somatosensory plasticity in pediatric cerebral palsy following constraint-induced movement therapy. Neural Plast 2018;2018:1891978 [FREE Full text] [doi: 10.1155/2018/1891978] [Medline: 30532772]
36. Ostry DJ, Gribble PL. Sensory plasticity in human motor learning. Trends Neurosci 2016 Feb;39(2):114-123 [FREE Full text] [doi: 10.1016/j.tins.2015.12.006] [Medline: 26774345]
37. Alhirsan SM, Capó-Lugo CE, Brown DA. Effects of different types of augmented feedback on intrinsic motivation and walking speed performance in post-stroke: A study protocol. Contemp Clin Trials Commun 2021 Dec;24:100863 [FREE Full text] [doi: 10.1016/j.conctc.2021.100863] [Medline: 34841123]
38. Chan A, Tetzlaff J, Altman D, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med 2013 Feb 05;158(3):200-207 [FREE Full text] [doi: 10.7326/0003-4819-158-3-201302050-00583] [Medline: 23295957]
39. Gronseth GS, Cox J, Gloss D. Clinical Practice Guideline Process Manual. Minneapolis, MN: American Academy of Neurology; 2017.
40. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol 1997 Apr;39(4):214-223 [FREE Full text] [doi: 10.1111/j.1469-8749.1997.tb07414.x] [Medline: 9183258]
41. Palisano RJ, Rosenbaum P, Bartlett D, Livingston MH. Content validity of the expanded and revised Gross Motor Function Classification System. Dev Med Child Neurol 2008 Oct;50(10):744-750 [FREE Full text] [doi: 10.1111/j.1469-8749.2008.03089.x] [Medline: 18834387]
42. Norkin CC, White DJ. Measurement of Joint Motion: A Guide to Goniometry (4th Edition). F. A. Davis Company: Philadelphia, PA; 2009.
43. Peeler J, Anderson J. Reliability of the Ely's test for assessing rectus femoris muscle flexibility and joint range of motion. J Orthop Res 2008 Jun;26(6):793-799 [FREE Full text] [doi: 10.1002/jor.20556] [Medline: 18186129]
44. Fosdahl MA, Jahnsen R, Pripp AH, Holm I. Change in popliteal angle and hamstrings spasticity during childhood in ambulant children with spastic bilateral cerebral palsy. A register-based cohort study. BMC Pediatr 2020 Jan 08;20(1):11 [FREE Full text] [doi: 10.1186/s12887-019-1891-y] [Medline: 31914961]
45. Childress AC, Komolova M, Sallee FR. An update on the pharmacokinetic considerations in the treatment of ADHD with long-acting methylphenidate and amphetamine formulations. Expert Opin Drug Metab Toxicol 2019 Nov;15(11):937-974. [doi: 10.1080/17425255.2019.1675636] [Medline: 31581854]
46. Russell DJ, Wright M, Rosenbaum PL, Avery LM. Gross Motor Function Measure (GMFM-66 and GMFM-88) User's Manual, 3rd Edition. MacKeith Press: London, UK; 2021.
47. Brunton L, Bartlett D. Validity and reliability of two abbreviated versions of the Gross Motor Function Measure. Phys Ther 2011 Apr;91(4):577-588. [doi: 10.2522/ptj.20100279] [Medline: 21350032]
48. Ansari NN, Naghdi S, Arab TK, Jalaie S. The interrater and intrarater reliability of the Modified Ashworth Scale in the assessment of muscle spasticity: limb and muscle group effect. NeuroRehabilitation 2008;23(3):231-237. [Medline: 18560139]
49. Meseguer-Henarejos A, Sánchez-Meca J, López-Pina JA, Carles-Hernández R. Inter- and intra-rater reliability of the Modified Ashworth Scale: a systematic review and meta-analysis. Eur J Phys Rehabil Med 2018 Aug;54(4):576-590 [FREE Full text] [doi: 10.23736/S1973-9087.17.04796-7] [Medline: 28901119]

50. Oeffinger D, Bagley A, Rogers S, Gorton G, Kryscio R, Abel M, et al. Outcome tools used for ambulatory children with cerebral palsy: responsiveness and minimum clinically important differences. Dev Med Child Neurol 2008 Dec;50(12):918-925 [FREE Full text] [doi: 10.1111/j.1469-8749.2008.03150.x] [Medline: 19046185]
51. Carey H, Martin K, Combs-Miller S, Heathcock J. Reliability and responsiveness of the timed up and go test in children with cerebral palsy. Pediatr Phys Ther 2016;28(4):401-408. [doi: 10.1097/PEP.0000000000000301] [Medline: 27661230]
52. Kumban W, Amatachaya S, Emasithi A, Siritaratiwat W. Five-times-sit-to-stand test in children with cerebral palsy: reliability and concurrent validity. NeuroRehabilitation 2013;32(1):9-15. [doi: 10.3233/NRE-130818] [Medline: 23422454]
53. Wang T, Liao H, Peng Y. Reliability and validity of the five-repetition sit-to-stand test for children with cerebral palsy. Clin Rehabil 2012 Jul;26(7):664-671. [doi: 10.1177/0269215511426889] [Medline: 22080526]
54. Almutairi A, Christy J, Vogtle L. Psychometric properties of clinical tests of balance and vestibular-related function in children with cerebral palsy. Pediatr Phys Ther 2020 Apr;32(2):144-150. [doi: 10.1097/PEP.0000000000000682] [Medline: 32218079]
55. Thompson P, Beath T, Bell J, Jacobson G, Phair T, Salbach NM, et al. Test-retest reliability of the 10-metre fast walk test and 6-minute walk test in ambulatory school-aged children with cerebral palsy. Dev Med Child Neurol 2008 May;50(5):370-376 [FREE Full text] [doi: 10.1111/j.1469-8749.2008.02048.x] [Medline: 18355340]

Abbreviations

10MWT: 10-Meter Walk Test
5XSTS: 5 Times Sit to Stand
AAN: American Academy of Neurology
ADHD: attention-deficit/hyperactivity disorder
ADL: activity of daily living
BoNT-A: botulinum toxin type A
CONSORT: Consolidated Standards of Reporting Trials
CP: cerebral palsy
CPUP: cerebral palsy follow-up program
CNS: central nervous system
GABA: gamma-amino butyric acid
GMAE: Gross Motor Ability Estimator
GMFCS: Gross Motor Function Classification System
GMFM: Gross Motor Function Measure
ICC: intraclass correlation
ICF: International Classification of Functioning, Health, and Disability
LE: lower extremity
MAS: Modified Ashworth Scale
MCID: minimum clinically important difference
MCTSIB: Modified Clinical Test for Sensory Interaction of Balance
MPH: methylphenidate
PT: physical therapist
RCT: randomized controlled trial
ROM: range of motion
SPIRIT: Standard Protocol Items: Recommendation for Interventional Trials
TUG: Timed Up and Go
UE: upper extremity

Edited by A Mavragani; submitted 17.10.23; peer-reviewed by X Zhang; comments to author 25.01.24; revised version received 06.02.24; accepted 09.02.24; published 05.03.24.

Please cite as:
Alotaibi M, Almutairi AB, Alhirsan S, Alkazemi A, Alharbi M, Alrashdi N, Taqi A, Alamiri B, Vogtle L, Alqahtani MM
Psychostimulant Medications for Physical Function and Spasticity in Children With Cerebral Palsy: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2024;13:e53728
URL: https://www.researchprotocols.org/2024/1/e53728
doi:10.2196/53728
PMID:38441919

Original Paper

Design and Rationale of Prolonged Nightly Fasting for Multiple Myeloma Prevention (PROFAST): Protocol for a Randomized Controlled Pilot Trial

David J Lee[1,2,3], MD, MPH, MMSc; Elizabeth K O'Donnell[2,3,4], MD; Noopur Raje[1,3], MD; Cristina Panaroni[1,3], PhD; Robert Redd[5], MS; Jennifer Ligibel[2,3], MD; Dorothy D Sears[6], PhD; Omar Nadeem[2,3,4], MD; Irene M Ghobrial[2,3,4], MD; Catherine R Marinac[2,3,4], PhD

[1]Department of Medicine, Massachusetts General Hospital, Boston, MA, United States

[2]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, United States

[3]Harvard Medical School, Boston, MA, United States

[4]Center for Early Detection and Interception of Blood Cancers, Dana-Farber Cancer Institute, Boston, MA, United States

[5]Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, MA, United States

[6]College of Health Solutions, Arizona State University, Phoenix, AZ, United States

Corresponding Author:
David J Lee, MD, MPH, MMSc
Department of Medicine
Massachusetts General Hospital
55 Fruit St.
Boston, MA, 02114
United States
Phone: 1 6177242450
Fax: 1 6177247441
Email: DJLee@mgh.harvard.edu

Abstract

Background: Obesity is an established, modifiable risk factor of multiple myeloma (MM); yet, no lifestyle interventions are routinely recommended for patients with overweight or obesity with MM precursor conditions. Prolonged nightly fasting is a simple, practical dietary regimen supported by research, suggesting that the synchronization of feeding-fasting timing with sleep-wake cycles favorably affects metabolic pathways implicated in MM. We describe the design and rationale of a randomized controlled pilot trial evaluating the efficacy of a regular, prolonged nighttime fasting schedule among individuals with overweight or obesity at high risk for developing MM or a related lymphoid malignancy.

Objective: We aim to investigate the effects of 4-month prolonged nightly fasting on body composition and tumor biomarkers among individuals with overweight or obesity with monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM), or smoldering Waldenström macroglobulinemia (SWM).

Methods: Individuals with MGUS, SMM, or SWM aged ≥18 years and a BMI of ≥25 kg/m^2 are randomized to either a 14-hour nighttime fasting intervention or a healthy lifestyle education control group. Participants' baseline diet and lifestyle patterns are characterized through two 24-hour dietary recalls: questionnaires querying demographic, comorbidity, lifestyle, and quality-of-life information; and wrist actigraphy measurements for 7 days. Fasting intervention participants are supported through one-on-one telephone counseling by a health coach and automated SMS text messaging to support fasting goals. Primary end points of body composition, including visceral and subcutaneous fat (by dual-energy x-ray absorptiometry); bone marrow adiposity (by bone marrow histology); and tumor biomarkers, specifically M-proteins and serum free light-chain concentrations (by gel-based and serum free light-chain assays), are assessed at baseline and after the 4-month study period; changes therein from baseline are evaluated using a repeated measures mixed-effects model that accounts for the correlation between baseline and follow-up measures and is generally robust to missing data. Feasibility is assessed as participant retention (percent dropout in each arm) and percentage of days participants achieved a ≥14-hour fast.

Results: The PROlonged nightly FASTing (PROFAST) study was funded in June 2022. Participant recruitment commenced in April 2023. As of July 2023, six participants consented to the study. The study is expected to be completed by April 2024, and data analysis and results are expected to be published in the first quarter of 2025.

Conclusions: PROFAST serves as an important first step in exploring the premise that prolonged nightly fasting is a strategy to control obesity and obesity-related mechanisms of myelomagenesis. In evaluating the feasibility and impact of prolonged nightly fasting on body composition, bone marrow adipose tissue, and biomarkers of tumor burden, this pilot study may generate hypotheses regarding metabolic mechanisms underlying MM development and ultimately inform clinical and public health strategies for MM prevention.

Trial Registration: ClinicalTrials.gov NCT05565638; http://clinicaltrials.gov/ct2/show/NCT05565638

International Registered Report Identifier (IRRID): DERR1-10.2196/51368

(JMIR Res Protoc 2024;13:e51368) doi:10.2196/51368

KEYWORDS

MGUS; smoldering myeloma; cancer prevention; intermittent fasting; fasting; myeloma; cancer; oncology; oncological; overweight; weight; obese; obesity; tumor; tumors; RCT; randomized; controlled trial; controlled trials; body mass index; BMI; blood; hematology; hematological; gammopathy; eating; diet; dietary

Introduction

Multiple myeloma (MM) is the second most common hematologic malignancy in the United States and is preceded by well-defined precursor conditions called monoclonal gammopathy of undetermined significance (MGUS) and smoldering MM (SMM) [1,2]. MGUS and SMM are asymptomatic conditions that have an annual progression rate to overt MM of 1% and 10%, respectively, but can be as high as 58% in 20 years in certain risk groups [3,4]. Despite the increasingly strong interest in intervening at the precursor stage for the early interception and prevention of MM, safe and cost-effective interventions are lacking. Although clinical trials have shown that earlier initiation of anti-MM therapies at the precursor stage (eg, lenalidomide-based regimen for high-risk SMM [5]) may alter the natural disease course and improve survival [5,6], early treatment remains highly controversial due to high costs and toxicity risks to patients, limiting its use to only a subset of patients at the highest risk strata [7-10].

Lifestyle interventions targeting excess adiposity and metabolic health in precursor patients may have an important role in MM prevention. Obesity is a well-established, potentially modifiable risk factor of MM [11], and there is accumulating evidence that obesity may also increase the risk of MGUS and its progression to overt MM [12-14]. Although current dietary and weight control guidelines for cancer prevention focus largely on calorie restriction and optimizing intake of specific food groups [15], challenges related to their integration into individuals' daily lives for a sustained period of time remain a consideration [16-19]. Time-restricted feeding, a form of intermittent fasting whereby ad libitum energy consumption is constrained to a window of time (typically between 4 and 12 hours daily), may be a simple, feasible alternative for weight loss and cancer risk reduction [16,20]. When food intake timing occurs during the wake phase of the 24-hour day, time-restricted feeding may benefit metabolic health and cancer risk by synchronizing feeding-fasting regimens with daily circadian rhythms, which, in turn, improve oscillations in the circadian clock expression of numerous genes important for glucose metabolism and overall cellular homeostasis (eg, autophagy and DNA damage repair) [16,21,22].

The PROlonged nightly FASTing (PROFAST) study is a randomized controlled pilot trial investigating the clinical benefit of a 4-month prolonged nightly fasting regimen in individuals with overweight or obesity with MGUS, those with SMM, and those with smoldering Waldenström macroglobulinemia (SWM). The intervention is supported by evidence that prolonged nighttime fasting is not only a simple and sustainable behavior change [16,23] but also improves metabolism and body weight regulation [24-29]. Here, we describe the study design, rationale, and framework for assessing the potential clinical significance of a low-risk, cost-effective lifestyle intervention in patients with MM precursor conditions.

Methods

Design of PROFAST

PROFAST is a pilot randomized controlled trial of our 4-month prolonged nightly fasting intervention in patients with overweight or obesity with MGUS, SMM, or SWM. The goal of the trial is to acquire preliminary outcome data for the efficacy of prolonged nightly fasting on body composition and clinical markers of disease progression in precursor patients. Participants are randomly assigned to (1) a theory-based intervention designed to promote a 14-hour fast during the nighttime hours or (2) the healthy lifestyle education control group.

Ethical Considerations

All study procedures and materials have been approved by the institutional review board at the Dana-Farber Cancer Institute (22-071).

Participants and Eligibility

Eligible participants are at least 18 years old, have a BMI of ≥25 kg/m^2, and have a documented diagnosis of MGUS, SMM, or SWM via the review of their electronic medical records. As shown in Textbox 1, inclusion criteria include individuals who (1) are currently fasting for <14 hours per night as assessed via

self-report and using 24-hour food recalls and (2) own a cell phone and are capable of sending and receiving SMS text messages comfortably. Exclusion criteria are patients with (1) overt MM; (2) other cancers requiring active therapy; (3) diabetes mellitus, which may increase the risk of hypoglycemia with a prolonged fast, unless the physician who manages their clinical care provides consent that they may enroll; or (4) any other condition or circumstance that, in the investigators' judgment, would be a contraindication to nightly fasting or interfere with trial participation (eg, night shift work, night eating syndrome, taking weight loss medication, and participation in another weight loss program). Participants are primarily recruited from the Dana-Farber Cancer Institute Center for Early Detection and Interception of Blood Cancers, a clinic focused on evaluating patients diagnosed with precursor conditions of hematologic malignancies and which works with patients to manage their risk of disease progression.

Textbox 1. Study eligibility criteria.

Inclusion criteria

- Age ≥18 years
- BMI ≥25 kg/m^2
- Diagnosis of monoclonal gammopathy of undetermined significance, smoldering multiple myeloma, or smoldering Waldenström macroglobulinemia
- Currently fasting for <14 hours per night, as assessed by 24-hour food recalls
- Owns a cell phone capable of sending and receiving SMS text messages comfortably
- Ability to understand and willing to sign a written informed consent document

Exclusion criteria

- Diagnosis of overt multiple myeloma
- Diagnosis of another malignancy requiring active therapy
- Diagnosis of diabetes mellitus, unless consent from the patient's physician managing the participant's clinical care
- Any medical or lifestyle condition contraindicated in or would interfere with study intervention (eg, night eating syndrome and night shift work)
- Currently taking medications intended for weight loss or participating in other weight loss programs

Clinic Visits and Randomization

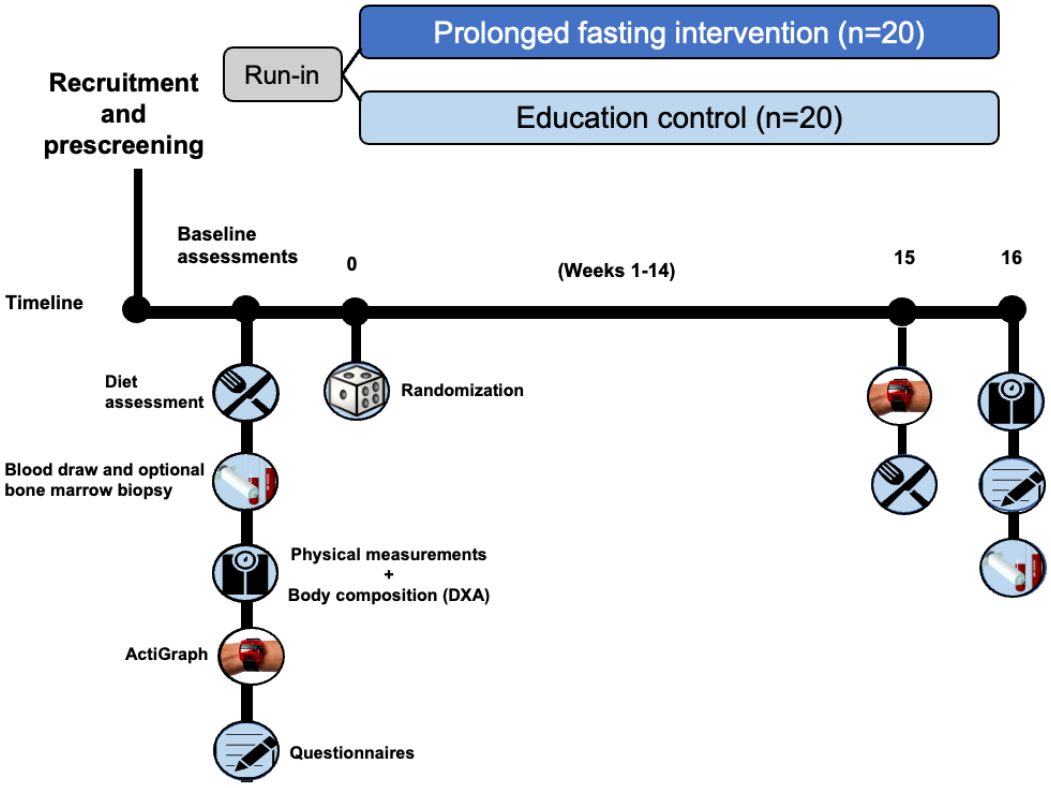
On completion of the consent form, participants attend a baseline clinic visit that includes laboratory, self-report, and physical assessments, as shown in Figure 1. In particular, participants have their height and weight measured and receive a dual-energy x-ray absorptiometry (DXA) scan to evaluate body composition. Participants provide biospecimen samples (ie, blood and bone marrow aspirate or biopsy). For each blood draw, approximately 30 to 60 mL of blood per participant is collected into EDTA and serum separator tubes for immediate plasma and serum preparation, respectively, and aliquots of plasma and serum in 1.8-mL cryovials are placed in a –80 °C freezer for storage. As for bone marrow samples, approximately 20 mL of bone marrow is collected into EDTA tubes for immediate processing, and the processed samples are placed in cryovials in a slow freezing cryostorage for 1 to 7 days before moving to storage in a liquid nitrogen tank.

Participants' current diet and lifestyle patterns are characterized through two 24-hour dietary recalls: (1) questionnaires ascertaining demographic, comorbidity, lifestyle, and quality-of-life information; and (2) the wearing of an ActiGraph accelerometer (GT3XP-BTLE; ActiGraph Corp) on their wrists for 7 days for baseline assessment of sleep, physical activity, and circadian rhythm.

Within 28 days of completing baseline assessments, participants are randomized in a 1:1 manner to either the nighttime 14-hour fast intervention group or the healthy lifestyle education comparison group. Once randomized, participants initiate the intervention or control condition ideally no later than 28 days of baseline screening assessments.

A clinic visit is scheduled 4 months after initiating and ideally within 7 days of completing the intervention or control condition. At this final visit, participants' weight, biospecimens and clinical labs, DXA scan, and self-reported outcome measures are reobtained.

Figure 1. Schematic of the study design. Timeline of participant recruitment, baseline visit, randomization to intervention or control arm, and end-of-study visit, with assessments that include tumor biomarkers, body composition, 24-hour food recalls, quality-of-life and lifestyle survey, and ActiGraph.



Details of the Intervention

The intervention's goal is to achieve a 14-hour nightly fast. Fasting goals during the initial weeks of the study are individualized, allowing participants to gradually adopt a 14-hour fasting duration on or before the third week of study. A 14-hour window was selected because it has been demonstrated to be an achievable intervention target in other populations of adults with chronic health conditions, and studies to date suggest that it is a sustainable intervention target [29,30]. Specifically, previous interventions have reported elective continuation of the intervention beyond the intervention period, resulting in sustained health benefits including weight loss [29,30]. The overnight fasting period is defined as the longest interval of time overnight in which no calorie-containing foods or beverages are consumed. Given prior findings that fasting may be more beneficial when aligned with the biological night [26], participants are encouraged to begin their nightly fast by 8 PM. To maximize acceptability and adherence to the intervention protocol, participants are allowed to consume noncaloric beverages including water, plain coffee, plain tea, zero-calorie sodas, and calorie-free sweeteners.

The intervention delivery consists of one-on-one telephone counseling by a health coach and an SMS text messaging system to support this target. Participants are supported through telephone counseling during the initial phase (weeks 1-3) of the interventional period and gradually transition to activities that promote self-reliance for behavioral maintenance from week 4 until the end of the study. The intervention incorporates a number of theory-based behavior change strategies in its design [31-33], including those grounded in social cognitive theory and its central tenet of self-efficacy [31].

SMS Text Messaging System

An SMS text messaging system was developed in collaboration with Mosio, Inc, and is introduced to participants during week 3 of the study for the purpose of self-monitoring, tracking adherence, and encouraging maintenance of prolonged nightly fasting. Participants are asked to text the study team to indicate when they began and ended their overnight fast. Participants receive an automated response to their SMS text messages, with positive reinforcement if the fasting goal was successfully achieved or corrective tools, such as a behavioral strategy, that may help them achieve a longer fast. The messages sent back to participants also contain feedback about their cumulative adherence to the prolonged overnight fasting pattern, calculated as the percentage of the successful overnight fasts during the past week. Participants also receive an SMS text message each day to remind them of their target end time of the overnight fast as well as encouraging SMS text messages to promote adherence that are customized to past performance. An example of SMS text messages sent to and received from participants through the automated SMS text messaging system is provided in Table 1.

Table 1. Example of an interaction in which a participant in the intervention arm submits SMS text messages to indicate the beginning and end of overnight fast and, in turn, is provided with automated, encouraging messages promoting cumulative adherence and achievement of the fasting goal.

Time stamp	Message status	Message content
February 17, 2013, 6:00 PM	Sent	Remember: Calories break a fast! Once you start, you need be calorie-free
February 17, 2013, 7:28 PM	Received	FAST
February 17, 2013, 7:29 PM	Response	Thanks! You are now running calorie free! Check back in the morning for your end time.
February 18, 2013, 7:00 AM	Sent	Your fast ends at 9.28 am. You can do it!
February 18, 2013, 9:55 AM	Received	EAT
February 17, 2013, 10:05 AM	Response	Congratulations! Your success rate is 100%. Nice work!

Healthy Lifestyle Education Control

Participants in the control arm receive educational information regarding healthy lifestyle to enhance retention of participants randomized to this group. At baseline, control participants receive an educational session with the health coach and a workbook containing brief information about topics about a healthy lifestyle (eg, sun safety, sleep, hydration, and sitting less). It is notable that research indicates that a single education session has only modest and temporary impacts on behaviors among most individuals [34,35]. To support sustained engagement throughout the 4-month study period, control group participants also receive 1 email and 1 SMS text message per week by the same SMS text messaging system used for participants in the interventional arm. These SMS text messages contain a mixture of educational information and potential personalized touch points to help participants feel valued.

Primary End Points

A challenge in assessing the clinical benefit of short-term interventions in MGUS, SMM, and SWM is that precursor patients are expected to have a relatively small number of progression events over months to years, limiting the ability to evaluate these events as the outcome. In this study, we focus on body composition, bone marrow adipose tissue, and biomarkers of tumor burden, which are accessible outcome measures in evaluating the efficacy of our lifestyle intervention.

Body Composition and Bone Marrow Adiposity

Most investigations evaluating the association of obesity and MGUS and MM have used BMI as a surrogate measure of obesity [12,13,36,37], and although BMI is a convenient, inexpensive measurement [38], it has low specificity for identifying excess adipose tissue and does not account for the type and distribution of fat (visceral and subcutaneous fat) [39,40]. These shortcomings of BMI limit our understanding of the relationship between obesity and the development of MM, as different adipose tissue compartments are known to have differential influences on obesity-related diseases [41-43]. For example, visceral fat is a metabolically active tissue type that releases fatty acids and proinflammatory substances and, in comparison with subcutaneous tissue, is more strongly associated with components of metabolic syndrome [41-43]. Thus, in our study, DXA scan (Horizon W DXA; Hologic, Inc) is used to measure body composition, differentiating not only fat mass from lean mass but also among adipose tissue types (visceral and subcutaneous fat). Furthermore, bone marrow adipose tissue is an understudied adipose depot with endocrine and paracrine signaling functions linked with the proliferation of nearby MM cells [44]. In our study, total marrow lipid content is quantified in bone marrow aspirate samples. Adipocyte-lipid content is analyzed using histology, flow cytometry, and lipidomics on adipocyte-enriched fractions. By measuring and comparing these adiposity measures between baseline and end of study, our study is able to evaluate whether prolonged nightly fasting possibly improves the body composition profile of participants.

Clinically Available Tumor Biomarkers

Serum protein electrophoresis supplemented by immunofixation (SPEP/IFX) and serum-free light chains (SFLCs) are the most commonly used clinical tests used to monitor patients at all stages of the disease continuum (MGUS, SMM, and MM). Monoclonal immunoglobulin (M-protein) and light-chain concentrations, as measured by SPEP/IFX and SFLCs, correlate with overall tumor burden and importantly decrease after treatment with a range of mild and aggressive MM therapies [45-47]. These biomarkers are sensitive and measurable variables of tumor response to treatment [48] and, therefore, serve as clinically relevant disease end points for our lifestyle-related intervention pilot study.

Other End Points

Metabolomics

Metabolomics—the high-throughput identification and quantification of small-molecule metabolites—is the study of metabolic changes in biological systems and provides the small-molecule fingerprints that reflect the complex relationships among diet, lifestyle (obesity), genes, and disease processes [49]. Metabolomics can yield novel insights into pathogenesis and risk of cancer and chronic disease [49,50]. Particularly important categories of metabolites in cancer and metabolic disease are metabolites of glycolysis and the tricarboxylic acid cycle [51,52]. These are of interest to this study because of their critical role in tumor growth and because they have been shown to be related to obesity [53]. Metabolomics-based data of MGUS, SMM, and MM are limited to only a small number of studies, including one by Ludwig et al [54] that identified 25 bone marrow metabolites that differed between 10 patients with MGUS and 10 patients with MM [55-59]. Of all molecular entities in the body (eg, genes, transcripts, proteins, and metabolites), metabolites as the final products of biochemical processing have the closest relationship

to expressed phenotype [60]. Thus, we believe that metabolomics offers a unique lens to study progression of MM precursors.

Quality of Life

Given the high rates of anxiety and distress document in individuals with MGUS and SMM and lack of evidence-based risk reduction strategies available for preventing disease progression to MM [61,62], we aim to evaluate the psychosocial benefits of offering a low-risk lifestyle intervention to this patient population as an exploratory objective. Quality of life is assessed using the well-validated PROMIS (Patient-Reported Outcomes Measurement Information System) global health survey [63-65]. Cancer worry is assessed using a 4-item scale adapted from Lerman et al [66].

Baseline Dietary and Lifestyle Assessment

Participants undergo two 24-hour dietary recalls to assess food and beverage consumption (ideally for 1 weekday and 1 weekend day), which are conducted through the Behavioral Measurement and Interventions Shared Resource at the University of Arizona Cancer Center. Participants also complete a baseline survey querying sociodemographic variables (eg, age, sex, race, ethnicity, highest level of education attained, and annual family income), medical comorbidities (eg, hypertension, hyperlipidemia, and diabetes mellitus), and lifestyle factors (eg, smoking, physical activity, sleep impairment, and disturbance) measured by well-validated instruments [67-72]. Finally, participants are asked to wear an ActiGraph accelerometer (GT3XP-BTLE; ActiGraph Corp) on their wrists for 7 days for a baseline assessment of physical activity, sleep, and circadian rhythm parameters [73-75].

Feasibility, Acceptability, Fidelity, and Safety

Feasibility is assessed as participant retention (percent dropout in each arm) and percentage of days participants achieved a ≥14-hour fast. Acceptability is assessed as perceived effectiveness of intervention components, plans to continue to engage in a prolonged nightly fast, elements of intervention liked or disliked, and satisfaction with program delivery and staff. Items are rated on a scale from 1 to 5. Finally, fidelity is assessed as percentage of days participants recorded fasting duration via the SMS text messaging system, percentage of SMS text messages read, and percentage of calls with the health coach.

Safety is monitored and assessed by the number and severity of adverse events, according to the revised National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Individuals with any medical or lifestyle condition (eg, diabetes mellitus) that is deemed to elevate their risk of adverse events from the intervention are excluded from the study (Textbox 1). Participants are informed of expected side effects related to fasting (eg, lightheadedness, headaches, restlessness, irritability, and low blood glucose), and adverse events that vary in nature, intensity, and frequency from what is expected are reported.

Analysis Plan

The key outcomes evaluated in this trial are changes in body composition (with a focus on visceral and subcutaneous adiposity), M-protein concentrations, and bone marrow adiposity. Changes in these end points are evaluated from baseline to follow-up in the 2 groups using a repeated measures mixed-effects model that accounts for the correlation between baseline and follow-up measures and is generally robust to missing data. The baseline values of the dependent variables (eg, weight and M-protein level) and disease subtype are included as covariates in the regression models. Group-by-time interaction terms are included as fixed effects in the regression model. Model fit is assessed using standard methods.

Results

The PROFAST Study was funded in June 2022. Participant recruitment commenced in April 2023, after developing and testing the text messaging system. As of July 2023, a total of 6 participants consented to the study. The study is expected to be completed by April 2024, and data analysis and results are expected to be published in the first quarter of 2025.

Discussion

The PROFAST study provides important preliminary data regarding the impact of prolonged nightly fasting on body composition, bone marrow adipose tissue, and biomarkers of tumor burden (SPEP/IFX and SFLCs) in patients with MM precursor conditions, thereby generating hypotheses on how targeting obesity-related mechanisms of carcinogenesis may help prevent MM development.

Obesity is a well-established, potentially modifiable risk factor of MM [11], and there is accumulating evidence that obesity may also increase the risk of MGUS and its progression to overt MM [12-14]. A study of 3 large prospective cohorts of US-based adults followed over 5 million person-years observed a 17% increase in MM risk per 5 kg/m^2 increase in BMI [36]. In another study of 7818 patients with MGUS in the US Veterans Health Administration database, being overweight and obese were associated with an increased risk of transformation to MM (hazard ratio [HR] for overweight 1.55, 95% CI 1.16-2.06; HR for obesity 1.98, 95% CI 1.47-2.68) [12]. Concordant with these findings, a more recent analysis of patients with MGUS identified through a population-based screening study in Olmstead County, Minnesota, between 1995 and 2003 observed that having a BMI ≥25 was also associated with increased progression to MM or other plasma cell or lymphoid disorders in univariate analysis (HR 2.14, 95% CI 1.05-4.36) and in a multivariable model accounting for clinical factors [13].

These epidemiological studies are supported by mechanistic evidence that obesity may lead to chronic low-grade inflammation and dysregulation of endogenous growth factors linked to myelomagenesis [76,77], together suggesting that weight control may be an effective MM prevention strategy. Indeed, according to a compelling 2016 consensus statement, an expert panel convened by the International Agency for Research on Cancer concluded that there is sufficient

mechanistic evidence that a preventative relationship has been established between the "absence of body fatness" and MM [76]. In obesity, adipose tissue, including adipocytes in the bone marrow, is altered in ways that may promote carcinogenesis, including by creating an unfavorable tumor microenvironment in which MM can engraft and grow [44,78]. Notably, the adipose tissue of obese individuals leads to excess free fatty acids as well as altered levels of proinflammatory cytokines (eg, tumor necrosis factor α and interleukin 6), adipokines (eg, adiponectin and leptin), and metabolic peptide hormones (eg, insulin and insulin-like growth factor 1) [44,78,79]. Dysregulated levels of these biological compounds may fuel tumor initiation and influence the genetic characteristics of MM cells in ways that increase cell proliferation [80], reduce apoptosis [81], and contribute to immune cell evasion [82,83]. The implication of these factors is that weight loss may curb the contribution that excess adiposity-associated chronic inflammation and metabolic dysregulation have on MM development.

Beyond weight loss, the PROFAST study tests the hypothesis that "when we eat," not just "what or how much we eat," is relevant to cancer prevention [24,25,84,85]. There is evidence suggesting that chronic exposure to circadian rhythm disturbances may lead to metabolic dysregulation, upregulation of proinflammatory cytokines, and abnormal cell proliferation [21,86]. As food intake contributes to the setting of circadian clock rhythms in peripheral organs, such as by inducing changes in body temperature and through the action of hormones such as insulin and nutrient-sensing enzymatic and nuclear receptor signaling systems [21,87], the synchronization of feeding-fasting patterns with circadian rhythms may be important for preventing chronic diseases [24,26,27]. This hypothesis is supported by a large prospective study of patients with early-stage breast cancer, which observed that a short nightly fasting duration (<13 hours per night), compared with a nightly fasting of ≥13 hours, was associated with an increased risk of breast cancer recurrence [25]. In that same study, each 2-hour increase in the nightly fasting duration was associated with lower hemoglobin A_{1c} levels and a longer duration of nighttime sleep [25]. These findings are consistent with the results of population-based studies [24,26,27], including a large case-control study in Spain that observed that diurnal eating patterns, specifically in maintaining longer time intervals between the last meal of the day and initiation of sleep, were inversely associated with risk of breast and prostate cancer [27]. Similarly, two US-based studies of 2009-2010 National Health and Nutrition Examination Survey data evaluating biomarkers of breast cancer risk observed that a longer duration of nighttime fasting was associated with improved measures of glycemic control and systemic inflammation [24,26], aligning with pathophysiological mechanisms underlying cancer risk [76].

Results from these human observational studies are consistent with rodent studies demonstrating that mice subjected to a time-restricted (16-hour) fasting regimen of a high-fat diet during the sleep phase were protected against weight gain, abnormal glucose metabolism, and inflammation, all of which were associated with cancer outcomes [22,88-91]. Notably, protective effects were observed despite these mice having the same caloric intake as those that had ad libitum access to food and ate frequently throughout day and night [22], suggesting that the beneficial effects of this fasting regimen were partly mediated through mechanisms independent of calorie restriction. Together, these data provide a strong basis of our intervention aimed to curb the inflammatory and metabolic mechanisms shown to contribute to myelomagenesis [44,77].

Finally, and importantly, prolonged nightly fasting represents a lifestyle modification that is safe, practical, and acceptable for patients who otherwise are managed by a "watchful waiting" strategy. Patients with MM precursor conditions are reported to have diminished quality of life, increased comorbidities, and heighted anxiety and a sense of loss of control regarding their MM risk [61,62,92,93]. There is, therefore, a need to identify lifestyle-based interventions that patients can safely and practically adopt into their daily lifestyles and ultimately help curb disease progression. Fasting, as a practice, developed independently among different people groups and religions (eg, Ramadan in Islam) around the world [94], and intermittent fasting has become one of the most common dietary patterns reported in the United States [95]. Prolonged nightly fasting is attractive because of its simplicity and feasibility, as supported by evidence from clinical trials of time-restricted eating strategies [16,23], and, thus, may be a potentially effective disease prevention strategy at the population level [16].

The limitations of this study include the relatively small sample size of the study and the potential lack of sociodemographic and geographic diversity of participants due to recruitment occurring at a single academic institution, thus, possibly impacting generalizability of findings. Also, participants willing to participate in a 4-month prolonged overnight fasting intervention may not be representative of the general population of patients with overweight or obesity with MM precursors, and selection bias for patients who are motivated to participate in PROFAST could increase the study adherence rate. Furthermore, although participants in the intervention group are prescribed solely a prolonged overnight fasting regimen with no other recommendations regarding lifestyle patterns, it is theoretically possible that participants may change their dietary, physical activity, and sleep habits due to paying closer attention to the timing of their eating and evaluations of their body composition before and after the intervention. These changes may also impact outcomes.

In summary, the study described herein serves as an important first step in exploring the premise that prolonged nightly fasting is a practical, effective strategy to control obesity and intercept disease progression in individuals with MM precursor conditions. By evaluating the impact of this lifestyle intervention on relevant biomarkers of excess adiposity and myeloma tumor burden, this pilot study may generate hypotheses and inform further investigations in identifying clinical and public health strategies for MM prevention.

Acknowledgments

This study was funded in part by the National Institutes of Health (R25AI147393, R38HL150212, R21 CA256644, K22 CA251648, R25 AI147393, R38 HL150212) and the Paula and Roger Riney Foundation.

Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Conflicts of Interest

IMG has served as a consultant for AbbVie, Adaptive, Amgen, Aptitude Health, Bristol-Myers Squibb, GlaxoSmithKline, Janssen, Menarini Silicon Biosystems, Novartis, Pfizer, Regeneron, Sanofi, Standard Biotools, Takeda, The Binding Site, and Window Therapeutics; received honoraria from Vor Biopharma and CurioScience; and received support for attending meetings from Amgen, Bristol-Myers Squibb, Novartis, Menarini Silicon Biosystems, and Pfizer. IMG's spouse, William Savage, is Chief Medical Officer and equity holder at Disc Medicine.

References

1. Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Altekruse SF, et al. Previous version: SEER cancer statistics review, 1975-2013. National Cancer Institute: Surveillance, Epidemiology, and End Results Program. Bethesda, MD: National Cancer Institute; 2016. URL: https://seer.cancer.gov/archive/csr/1975_2013/ [accessed 2023-12-15]
2. Kyle RA, Therneau TM, Rajkumar SV, Larson DR, Plevak MF, Offord JR, et al. Prevalence of monoclonal gammopathy of undetermined significance. N Engl J Med 2006 Mar 30;354(13):1362-1369 [FREE Full text] [doi: 10.1056/NEJMoa054494] [Medline: 16571879]
3. Landgren O. Monoclonal gammopathy of undetermined significance and smoldering multiple myeloma: biological insights and early treatment strategies. Hematology Am Soc Hematol Educ Program 2013;2013:478-487 [FREE Full text] [doi: 10.1182/asheducation-2013.1.478] [Medline: 24319222]
4. Kyle RA, Durie BGM, Rajkumar SV, Landgren O, Blade J, Merlini G, International Myeloma Working Group. Monoclonal gammopathy of undetermined significance (MGUS) and smoldering (asymptomatic) multiple myeloma: IMWG consensus perspectives risk factors for progression and guidelines for monitoring and management. Leukemia 2010 Jun;24(6):1121-1127 [FREE Full text] [doi: 10.1038/leu.2010.60] [Medline: 20410922]
5. Mateos MV, Hernández MT, Giraldo P, de la Rubia J, de Arriba F, López Corral L, et al. Lenalidomide plus dexamethasone for high-risk smoldering multiple myeloma. N Engl J Med 2013 Aug 01;369(5):438-447 [FREE Full text] [doi: 10.1056/NEJMoa1300439] [Medline: 23902483]
6. Korde N, Roschewski M, Zingone A, Kwok M, Manasanch EE, Bhutani M, et al. Treatment with carfilzomib-lenalidomide-dexamethasone with lenalidomide extension in patients with smoldering or newly diagnosed multiple myeloma. JAMA Oncol 2015 Sep;1(6):746-754 [FREE Full text] [doi: 10.1001/jamaoncol.2015.2010] [Medline: 26181891]
7. Caers J, Fernández de Larrea C, Leleu X, Heusschen R, Zojer N, Decaux O, et al. The changing landscape of smoldering multiple myeloma: a European perspective. Oncologist 2016 Mar;21(3):333-342 [FREE Full text] [doi: 10.1634/theoncologist.2015-0303] [Medline: 26921288]
8. Ghobrial IM, Landgren O. How I treat smoldering multiple myeloma. Blood 2014 Nov 27;124(23):3380-3388 [FREE Full text] [doi: 10.1182/blood-2014-08-551549] [Medline: 25298034]
9. Rajkumar SV, Landgren O, Mateos MV. Smoldering multiple myeloma. Blood 2015 May 14;125(20):3069-3075 [FREE Full text] [doi: 10.1182/blood-2014-09-568899] [Medline: 25838344]
10. Kumar SK. Timing of treatment of smoldering myeloma: delay until progression. Blood Adv 2018 Nov 13;2(21):3050-3053 [FREE Full text] [doi: 10.1182/bloodadvances.2018021238] [Medline: 30425069]
11. Castaneda-Avila MA, Ulbricht CM, Epstein MM. Risk factors for monoclonal gammopathy of undetermined significance: a systematic review. Ann Hematol 2021 Apr;100(4):855-863 [FREE Full text] [doi: 10.1007/s00277-021-04400-7] [Medline: 33416902]
12. Chang SH, Luo S, Thomas TS, O'Brian KK, Colditz GA, Carlsson NP, et al. Obesity and the transformation of monoclonal gammopathy of undetermined significance to multiple myeloma: a population-based cohort study. J Natl Cancer Inst 2017;109(5):djw264 [FREE Full text] [doi: 10.1093/jnci/djw264] [Medline: 28040690]
13. Kleinstern G, Larson DR, Allmer C, Norman AD, Muntifering G, Sinnwell J, et al. Body mass index associated with Monoclonal Gammopathy of Undetermined Significance (MGUS) progression in Olmsted County, Minnesota. Blood Cancer J 2022;12(4):67 [FREE Full text] [doi: 10.1038/s41408-022-00659-9] [Medline: 35440099]
14. Thordardottir M, Lindqvist EK, Lund SH, Costello R, Burton D, Korde N, et al. Obesity and risk of monoclonal gammopathy of undetermined significance and progression to multiple myeloma: a population-based study. Blood Adv 2017;1(24):2186-2192 [FREE Full text] [doi: 10.1182/bloodadvances.2017007609] [Medline: 29296866]

15. Rock CL, Thomson C, Gansler T, Gapstur SM, McCullough ML, Patel AV, et al. American Cancer Society guideline for diet and physical activity for cancer prevention. CA Cancer J Clin 2020;70(4):245-271 [FREE Full text] [doi: 10.3322/caac.21591] [Medline: 32515498]
16. Patterson RE, Laughlin GA, LaCroix AZ, Hartman SJ, Natarajan L, Senger CM, et al. Intermittent fasting and human metabolic health. J Acad Nutr Diet 2015;115(8):1203-1212 [FREE Full text] [doi: 10.1016/j.jand.2015.02.018] [Medline: 25857868]
17. Donaldson MS. Nutrition and cancer: a review of the evidence for an anti-cancer diet. Nutr J 2004;3:19 [FREE Full text] [doi: 10.1186/1475-2891-3-19] [Medline: 15496224]
18. Tsofliou F, Vlachos D, Hughes C, Appleton KM. Barriers and facilitators associated with the adoption of and adherence to a mediterranean style diet in adults: a systematic review of published observational and qualitative studies. Nutrients 2022;14(20):4314 [FREE Full text] [doi: 10.3390/nu14204314] [Medline: 36296998]
19. Clifton KK, Ma CX, Fontana L, Peterson LL. Intermittent fasting in the prevention and treatment of cancer. CA Cancer J Clin 2021;71(6):527-546 [FREE Full text] [doi: 10.3322/caac.21694] [Medline: 34383300]
20. Liu D, Huang Y, Huang C, Yang S, Wei X, Zhang P, et al. Calorie restriction with or without time-restricted eating in weight loss. N Engl J Med 2022;386(16):1495-1504 [FREE Full text] [doi: 10.1056/NEJMoa2114833] [Medline: 35443107]
21. Sulli G, Lam MTY, Panda S. Interplay between circadian clock and cancer: new frontiers for cancer treatment. Trends Cancer 2019;5(8):475-494 [FREE Full text] [doi: 10.1016/j.trecan.2019.07.002] [Medline: 31421905]
22. Hatori M, Vollmers C, Zarrinpar A, DiTacchio L, Bushong EA, Gill S, et al. Time-restricted feeding without reducing caloric intake prevents metabolic diseases in mice fed a high-fat diet. Cell Metab 2012;15(6):848-860 [FREE Full text] [doi: 10.1016/j.cmet.2012.04.019] [Medline: 22608008]
23. Termannsen AD, Varming A, van Elst C, Bjerre N, Nørgaard O, Hempler NF, et al. Feasibility of time-restricted eating in individuals with overweight, obesity, prediabetes, or type 2 diabetes: a systematic scoping review. Obesity (Silver Spring) 2023;31(6):1463-1485 [FREE Full text] [doi: 10.1002/oby.23743] [Medline: 37203334]
24. Marinac CR, Natarajan L, Sears DD, Gallo LC, Hartman SJ, Arredondo E, et al. Prolonged nightly fasting and breast cancer risk: findings from NHANES (2009-2010). Cancer Epidemiol Biomarkers Prev 2015;24(5):783-789 [FREE Full text] [doi: 10.1158/1055-9965.EPI-14-1292] [Medline: 25896523]
25. Marinac CR, Nelson SH, Breen CI, Hartman SJ, Natarajan L, Pierce JP, et al. Prolonged nightly fasting and breast cancer prognosis. JAMA Oncol 2016;2(8):1049-1055 [FREE Full text] [doi: 10.1001/jamaoncol.2016.0164] [Medline: 27032109]
26. Marinac CR, Sears DD, Natarajan L, Gallo LC, Breen CI, Patterson RE. Frequency and circadian timing of eating may influence biomarkers of inflammation and insulin resistance associated with breast cancer risk. PLoS One 2015;10(8):e0136240 [FREE Full text] [doi: 10.1371/journal.pone.0136240] [Medline: 26305095]
27. Kogevinas M, Espinosa A, Castelló A, Gómez-Acebo I, Guevara M, Martin V, et al. Effect of mistimed eating patterns on breast and prostate cancer risk (MCC-Spain Study). Int J Cancer 2018;143(10):2380-2389 [FREE Full text] [doi: 10.1002/ijc.31649] [Medline: 30016830]
28. Wang JB, Patterson RE, Ang A, Emond JA, Shetty N, Arab L. Timing of energy intake during the day is associated with the risk of obesity in adults. J Hum Nutr Diet 2014;27(Suppl 2):255-262 [FREE Full text] [doi: 10.1111/jhn.12141] [Medline: 23808897]
29. Wilkinson MJ, Manoogian ENC, Zadourian A, Lo H, Fakhouri S, Shoghi A, et al. Ten-hour time-restricted eating reduces weight, blood pressure, and atherogenic lipids in patients with metabolic syndrome. Cell Metab 2020;31(1):92-104.e5 [FREE Full text] [doi: 10.1016/j.cmet.2019.11.004] [Medline: 31813824]
30. Gill S, Panda S. A smartphone app reveals erratic diurnal eating patterns in humans that can be modulated for health benefits. Cell Metab 2015;22(5):789-798 [FREE Full text] [doi: 10.1016/j.cmet.2015.09.005] [Medline: 26411343]
31. Bandura A. Social Foundations of Thought and Action: A Social Cognitive Theory. Englewood Cliffs, NJ: Prentice Hall; 1986.
32. Carver CS, Scheier MF. Control theory: a useful conceptual framework for personality-social, clinical, and health psychology. Psychol Bull 1982;92(1):111-135 [FREE Full text] [Medline: 7134324]
33. Patrick K, Marshall SJ, Davila EP, Kolodziejczyk JK, Fowler JH, Calfas KJ, et al. Design and implementation of a randomized controlled social and mobile weight loss trial for young adults (project SMART). Contemp Clin Trials 2014;37(1):10-18 [FREE Full text] [doi: 10.1016/j.cct.2013.11.001] [Medline: 24215774]
34. Dansinger ML, Tatsioni A, Wong JB, Chung M, Balk EM. Meta-analysis: the effect of dietary counseling for weight loss. Ann Intern Med 2007;147(1):41-50 [FREE Full text] [doi: 10.7326/0003-4819-147-1-200707030-00007] [Medline: 17606960]
35. Tsai AG, Wadden TA. Treatment of obesity in primary care practice in the United States: a systematic review. J Gen Intern Med 2009;24(9):1073-1079 [FREE Full text] [doi: 10.1007/s11606-009-1042-5] [Medline: 19562419]
36. Marinac CR, Birmann BM, Lee IM, Rosner BA, Townsend MK, Giovannucci E, et al. Body mass index throughout adulthood, physical activity, and risk of multiple myeloma: a prospective analysis in three large cohorts. Br J Cancer 2018;118(7):1013-1019 [FREE Full text] [doi: 10.1038/s41416-018-0010-4] [Medline: 29527008]

37. Shah UA, Whiting K, Devlin S, Ershler R, Kanapuru B, Lee DJ, et al. Extreme body mass index and survival in newly diagnosed multiple myeloma patients. Blood Cancer J 2023;13(1):13 [FREE Full text] [doi: 10.1038/s41408-022-00782-7] [Medline: 36631444]
38. de Gonzalez AB, Hartge P, Cerhan JR, Flint AJ, Hannan L, MacInnis RJ, et al. Body-mass index and mortality among 1.46 million white adults. N Engl J Med 2010;363(23):2211-2219 [FREE Full text] [doi: 10.1056/NEJMoa1000367] [Medline: 21121834]
39. Prentice AM, Jebb SA. Beyond body mass index. Obes Rev 2001;2(3):141-147 [FREE Full text] [doi: 10.1046/j.1467-789x.2001.00031.x] [Medline: 12120099]
40. Heymsfield SB, Peterson CM, Thomas DM, Heo M, Schuna JM. Why are there race/ethnic differences in adult body mass index-adiposity relationships? A quantitative critical review. Obes Rev 2016;17(3):262-275 [FREE Full text] [doi: 10.1111/obr.12358] [Medline: 26663309]
41. Zhang M, Hu T, Zhang S, Zhou L. Associations of different adipose tissue depots with insulin resistance: a systematic review and meta-analysis of observational studies. Sci Rep 2015;5(1):18495 [FREE Full text] [doi: 10.1038/srep18495] [Medline: 26686961]
42. Després JP, Lemieux I. Abdominal obesity and metabolic syndrome. Nature 2006;444(7121):881-887 [FREE Full text] [doi: 10.1038/nature05488] [Medline: 17167477]
43. De Larochellière E, Côté J, Gilbert G, Bibeau K, Ross MK, Dion-Roy V, et al. Visceral/epicardial adiposity in nonobese and apparently healthy young adults: association with the cardiometabolic profile. Atherosclerosis 2014;234(1):23-29 [FREE Full text] [doi: 10.1016/j.atherosclerosis.2014.01.053] [Medline: 24589564]
44. Falank C, Fairfield H, Reagan MR. Signaling interplay between bone marrow adipose tissue and multiple myeloma cells. Front Endocrinol (Lausanne) 2016;7:67 [FREE Full text] [doi: 10.3389/fendo.2016.00067] [Medline: 27379019]
45. Golombick T, Diamond TH, Manoharan A, Ramakrishna R. Monoclonal gammopathy of undetermined significance, smoldering multiple myeloma, and curcumin: a randomized, double-blind placebo-controlled cross-over 4g study and an open-label 8g extension study. Am J Hematol 2012;87(5):455-460 [FREE Full text] [doi: 10.1002/ajh.23159] [Medline: 22473809]
46. Ross DM, To LB, Horvath N. Assessment of early paraprotein response to vincristine-doxorubicin-dexamethasone chemotherapy may help guide therapy in multiple myeloma. Intern Med J 2004;34(9-10):576-578. [doi: 10.1111/j.1445-5994.2004.00689.x] [Medline: 15482273]
47. Schaar CG, Kluin-Nelemans JC, le Cessie S, Franck PFH, te Marvelde MC, Wijermans PW. Early response to therapy and survival in multiple myeloma. Br J Haematol 2004;125(2):162-166 [FREE Full text] [doi: 10.1111/j.1365-2141.2004.04884.x] [Medline: 15059138]
48. Shah J, Bladé J, Sonneveld P, Harousseau JL, Lantz K, Londhe A, et al. Rapid early monoclonal protein reduction after therapy with bortezomib or bortezomib and pegylated liposomal doxorubicin in relapsed/refractory myeloma is associated with a longer time to progression. Cancer 2011;117(16):3758-3762 [FREE Full text] [doi: 10.1002/cncr.25937] [Medline: 21328327]
49. Kim YS, Maruvada P, Milner JA. Metabolomics in biomarker discovery: future uses for cancer prevention. Future Oncol 2008;4(1):93-102 [FREE Full text] [doi: 10.2217/14796694.4.1.93] [Medline: 18241004]
50. Beger RD. A review of applications of metabolomics in cancer. Metabolites 2013;3(3):552-574 [FREE Full text] [doi: 10.3390/metabo3030552] [Medline: 24958139]
51. Anderson NM, Mucka P, Kern JG, Feng H. The emerging role and targetability of the TCA cycle in cancer metabolism. Protein Cell 2018;9(2):216-237 [FREE Full text] [doi: 10.1007/s13238-017-0451-1] [Medline: 28748451]
52. Hsu PP, Sabatini DM. Cancer cell metabolism: warburg and beyond. Cell 2008;134(5):703-707 [FREE Full text] [doi: 10.1016/j.cell.2008.08.021] [Medline: 18775299]
53. Doerstling SS, O'Flanagan CH, Hursting SD. Obesity and cancer metabolism: a perspective on interacting tumor-intrinsic and extrinsic factors. Front Oncol 2017;7:216 [FREE Full text] [doi: 10.3389/fonc.2017.00216] [Medline: 28959684]
54. Ludwig C, Williams DS, Bartlett DB, Essex SJ, McNee G, Allwood JW, et al. Alterations in bone marrow metabolism are an early and consistent feature during the development of MGUS and multiple myeloma. Blood Cancer J 2015;5(10):e359 [FREE Full text] [doi: 10.1038/bcj.2015.85] [Medline: 26473531]
55. Piszcz J, Lemancewicz D, Dudzik D, Ciborowski M. Differences and similarities between LC-MS derived serum fingerprints of patients with B-cell malignancies. Electrophoresis 2013;34(19):2857-2864 [FREE Full text] [Medline: 24228264]
56. Kuliszkiewicz-Janus M, Baczyński S. Chemotherapy-associated changes in 31P MRS spectra of sera from patients with multiple myeloma. NMR Biomed 1995;8(3):127-132 [FREE Full text] [doi: 10.1002/nbm.1940080308] [Medline: 8580000]
57. Lodi A, Tiziani S, Khanim FL, Günther UL, Viant MR, Morgan GJ, et al. Proton NMR-based metabolite analyses of archived serial paired serum and urine samples from myeloma patients at different stages of disease activity identifies acetylcarnitine as a novel marker of active disease. PLoS One 2013;8(2):e56422 [FREE Full text] [doi: 10.1371/journal.pone.0056422] [Medline: 23431376]
58. Puchades-Carrasco L, Lecumberri R, Martínez-López J, Lahuerta JJ, Mateos MV, Prósper F, et al. Multiple myeloma patients have a specific serum metabolomic profile that changes after achieving complete remission. Clin Cancer Res 2013;19(17):4770-4779 [FREE Full text] [doi: 10.1158/1078-0432.CCR-12-2917] [Medline: 23873687]

59. Steiner N, Müller U, Hajek R, Sevcikova S, Borjan B, Jöhrer K, et al. The metabolomic plasma profile of myeloma patients is considerably different from healthy subjects and reveals potential new therapeutic targets. PLoS One 2018;13(8):e0202045 [FREE Full text] [doi: 10.1371/journal.pone.0202045] [Medline: 30096165]
60. Rattray NJW, Deziel NC, Wallach JD, Khan SA, Vasiliou V, Ioannidis JPA, et al. Beyond genomics: understanding exposotypes through metabolomics. Hum Genomics 2018;12(1):4 [FREE Full text] [doi: 10.1186/s40246-018-0134-x] [Medline: 29373992]
61. Maatouk I, He S, Hummel M, Hemmer S, Hillengass M, Goldschmidt H, et al. Patients with precursor disease exhibit similar psychological distress and mental HRQOL as patients with active myeloma. Blood Cancer J 2019;9(2):9 [FREE Full text] [doi: 10.1038/s41408-019-0172-1] [Medline: 30664623]
62. Hildebrandt MAT, Callender RA, Belachew AA, Classen C, Lee HC, Patel KK, et al. Quality of life and cancer worry in a follow-up cohort of patients with asymptomatic monoclonal gammopathies. J Clin Oncol 2018;36(15_suppl):-8049 [FREE Full text] [doi: 10.1200/jco.2018.36.15_suppl.8049]
63. Shim J, Hamilton DF. Comparative responsiveness of the PROMIS-10 global health and EQ-5D questionnaires in patients undergoing total knee arthroplasty. Bone Joint J 2019;101-B(7):832-837 [FREE Full text] [doi: 10.1302/0301-620X.101B7.BJJ-2018-1543.R1] [Medline: 31256677]
64. Wilford J, Osann K, Hsieh S, Monk B, Nelson E, Wenzel L. Validation of PROMIS emotional distress short form scales for cervical cancer. Gynecol Oncol 2018;151(1):111-116 [FREE Full text] [doi: 10.1016/j.ygyno.2018.07.022] [Medline: 30078504]
65. Schalet BD, Pilkonis PA, Yu L, Dodds N, Johnston KL, Yount S, et al. Clinical validity of PROMIS depression, anxiety, and anger across diverse clinical samples. J Clin Epidemiol 2016;73:119-127 [FREE Full text] [doi: 10.1016/j.jclinepi.2015.08.036] [Medline: 26931289]
66. Lerman C, Schwartz MD, Lin TH, Hughes C, Narod S, Lynch HT. The influence of psychological distress on use of genetic testing for cancer risk. J Consult Clin Psychol 1997 Jun;65(3):414-420. [doi: 10.1037//0022-006x.65.3.414] [Medline: 9170764]
67. Hoos T, Espinoza N, Marshall S, Arredondo EM. Validity of the Global Physical Activity Questionnaire (GPAQ) in adult Latinas. J Phys Act Health 2012;9(5):698-705 [FREE Full text] [doi: 10.1123/jpah.9.5.698] [Medline: 22733873]
68. Armstrong T, Bull F. Development of the World Health Organization Global Physical Activity Questionnaire (GPAQ). J Public Health 2006;14(2):66-70 [FREE Full text] [doi: 10.1007/s10389-006-0024-x]
69. Bull FC, Maslin TS, Armstrong T. Global physical activity questionnaire (GPAQ): nine country reliability and validity study. J Phys Act Health 2009;6(6):790-804 [FREE Full text] [doi: 10.1123/jpah.6.6.790] [Medline: 20101923]
70. Kenfield SA, Wei EK, Rosner BA, Glynn RJ, Stampfer MJ, Colditz GA. Burden of smoking on cause-specific mortality: application to the Nurses' Health Study. Tob Control 2010;19(3):248-254 [FREE Full text] [doi: 10.1136/tc.2009.032839] [Medline: 20501499]
71. Cao Y, Willett WC, Rimm EB, Stampfer MJ, Giovannucci EL. Light to moderate intake of alcohol, drinking patterns, and risk of cancer: results from two prospective US cohort studies. BMJ 2015;351:h4238 [FREE Full text] [doi: 10.1136/bmj.h4238] [Medline: 26286216]
72. Patient Reported Outcomes Measurement Information System (PROMIS). URL: https://www.healthmeasures.net/explore-measurement-systems/promis [accessed 2023-01-11]
73. Mitchell JA, Quante M, Godbole S, James P, Hipp JA, Marinac CR, et al. Variation in actigraphy-estimated rest-activity patterns by demographic factors. Chronobiol Int 2017;34(8):1042-1056 [FREE Full text] [doi: 10.1080/07420528.2017.1337032] [Medline: 28650674]
74. Quante M, Mariani S, Weng J, Marinac CR, Kaplan ER, Rueschman M, et al. Zeitgebers and their association with rest-activity patterns. Chronobiol Int 2019;36(2):203-213 [FREE Full text] [doi: 10.1080/07420528.2018.1527347] [Medline: 30365354]
75. Feliciano EMC, Quante M, Weng J, Mitchell JA, James P, Marinac CR, et al. Actigraphy-derived daily rest-activity patterns and body mass index in community-dwelling adults. Sleep 2017;40(12):zsx168 [FREE Full text] [doi: 10.1093/sleep/zsx168] [Medline: 29029250]
76. Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K, International Agency for Research on Cancer Handbook Working Group. Body fatness and cancer—viewpoint of the IARC Working Group. N Engl J Med 2016;375(8):794-798 [FREE Full text] [doi: 10.1056/NEJMsr1606602] [Medline: 27557308]
77. Carson KR, Bates ML, Tomasson MH. The skinny on obesity and plasma cell myeloma: a review of the literature. Bone Marrow Transplant 2014;49(8):1009-1015 [FREE Full text] [doi: 10.1038/bmt.2014.71] [Medline: 24820216]
78. van Kruijsdijk RCM, van der Wall E, Visseren FLJ. Obesity and cancer: the role of dysfunctional adipose tissue. Cancer Epidemiol Biomarkers Prev 2009;18(10):2569-2578 [FREE Full text] [doi: 10.1158/1055-9965.EPI-09-0372] [Medline: 19755644]
79. Singla P, Bardoloi A, Parkash AA. Metabolic effects of obesity: a review. World J Diabetes 2010;1(3):76-88 [FREE Full text] [doi: 10.4239/wjd.v1.i3.76] [Medline: 21537431]

80. Sprynski AC, Hose D, Kassambara A, Vincent L, Jourdan M, Rossi JF, et al. Insulin is a potent myeloma cell growth factor through insulin/IGF-1 hybrid receptor activation. Leukemia 2010;24(11):1940-1950 [FREE Full text] [doi: 10.1038/leu.2010.192] [Medline: 20844560]
81. Reseland JE, Reppe S, Olstad OK, Hjorth-Hansen H, Brenne AT, Syversen U, et al. Abnormal adipokine levels and leptin-induced changes in gene expression profiles in multiple myeloma. Eur J Haematol 2009;83(5):460-470. [doi: 10.1111/j.1600-0609.2009.01311.x] [Medline: 19572994]
82. Brocke-Heidrich K, Kretzschmar AK, Pfeifer G, Henze C, Löffler D, Koczan D, et al. Interleukin-6-dependent gene expression profiles in multiple myeloma INA-6 cells reveal a Bcl-2 family-independent survival pathway closely associated with Stat3 activation. Blood 2004;103(1):242-251 [FREE Full text] [doi: 10.1182/blood-2003-04-1048] [Medline: 12969979]
83. Colotta F, Allavena P, Sica A, Garlanda C, Mantovani A. Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. Carcinogenesis 2009;30(7):1073-1081 [FREE Full text] [doi: 10.1093/carcin/bgp127] [Medline: 19468060]
84. Hutchison AT, Heilbronn LK. Metabolic impacts of altering meal frequency and timing—does when we eat matter? Biochimie 2016;124:187-197 [FREE Full text] [doi: 10.1016/j.biochi.2015.07.025] [Medline: 26226640]
85. Mattson MP, Allison DB, Fontana L, Harvie M, Longo VD, Malaisse WJ, et al. Meal frequency and timing in health and disease. Proc Natl Acad Sci U S A 2014;111(47):16647-16653 [FREE Full text] [doi: 10.1073/pnas.1413965111] [Medline: 25404320]
86. Zhou L, Zhang Z, Nice E, Huang C, Zhang W, Tang Y. Circadian rhythms and cancers: the intrinsic links and therapeutic potentials. J Hematol Oncol 2022;15(1):21 [FREE Full text] [doi: 10.1186/s13045-022-01238-y] [Medline: 35246220]
87. Mayeuf-Louchart A, Zecchin M, Staels B, Duez H. Circadian control of metabolism and pathological consequences of clock perturbations. Biochimie 2017;143:42-50 [FREE Full text] [doi: 10.1016/j.biochi.2017.07.017] [Medline: 28778719]
88. Chaix A, Zarrinpar A, Miu P, Panda S. Time-restricted feeding is a preventative and therapeutic intervention against diverse nutritional challenges. Cell Metab 2014;20(6):991-1005 [FREE Full text] [doi: 10.1016/j.cmet.2014.11.001] [Medline: 25470547]
89. Das M, Ellies LG, Kumar D, Sauceda C, Oberg A, Gross E, et al. Time-restricted feeding normalizes hyperinsulinemia to inhibit breast cancer in obese postmenopausal mouse models. Nat Commun 2021;12(1):565 [FREE Full text] [doi: 10.1038/s41467-020-20743-7] [Medline: 33495474]
90. Yan L, Sundaram S, Mehus AA, Picklo MJ. Time-restricted feeding attenuates high-fat diet-enhanced spontaneous metastasis of lewis lung carcinoma in Mice. Anticancer Res 2019;39(4):1739-1748 [FREE Full text] [doi: 10.21873/anticanres.13280] [Medline: 30952713]
91. Sundaram S, Yan L. Time-restricted feeding mitigates high-fat diet-enhanced mammary tumorigenesis in MMTV-PyMT mice. Nutr Res 2018;59:72-79 [FREE Full text] [doi: 10.1016/j.nutres.2018.07.014] [Medline: 30442235]
92. Jean-Baptiste M, Gries KS, Lenderking WR, Fastenau J. Symptom burden and health-related quality of life impacts of smoldering multiple myeloma: the patient perspective. J Patient Rep Outcomes 2020;4(1):95 [FREE Full text] [doi: 10.1186/s41687-020-00253-2] [Medline: 33165677]
93. Lomas OC, Mouhieddine TH, Tahri S, Ghobrial IM. Monoclonal gammopathy of undetermined significance (MGUS)—not so asymptomatic after all. Cancers (Basel) 2020;12(6):1554 [FREE Full text] [doi: 10.3390/cancers12061554] [Medline: 32545521]
94. Kerndt PR, Naughton JL, Driscoll CE, Loxterkamp DA. Fasting: the history, pathophysiology and complications. West J Med 1982;137(5):379-399 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1274154/ [FREE Full text] [Medline: 6758355]
95. 2023 Food and Health Survey. International Food Information Council. 2023. URL: https://foodinsight.org/2023-food-and-health-survey/ [accessed 2023-12-15]

Abbreviations

CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events
DXA: dual-energy x-ray absorptiometry
HR: hazard ratio
MGUS: monoclonal gammopathy of undetermined significance
MM: multiple myeloma
PROFAST: PROlonged nightly FASTing
PROMIS: Patient-Reported Outcomes Measurement Information System
SFLC: serum-free light chain
SMM: smoldering multiple myeloma
SPEP/IFX: serum protein electrophoresis supplemented by immunofixation
SWM: smoldering Waldenström macroglobulinemia

Edited by A Mavragani; submitted 31.07.23; peer-reviewed by W Demark-Wahnefried, S Chakraborty, S Chaudhry; comments to author 13.10.23; revised version received 17.11.23; accepted 23.11.23; published 11.03.24.

Please cite as:
Lee DJ, O'Donnell EK, Raje N, Panaroni C, Redd R, Ligibel J, Sears DD, Nadeem O, Ghobrial IM, Marinac CR
Design and Rationale of Prolonged Nightly Fasting for Multiple Myeloma Prevention (PROFAST): Protocol for a Randomized Controlled Pilot Trial
JMIR Res Protoc 2024;13:e51368
URL: https://www.researchprotocols.org/2024/1/e51368
doi:10.2196/51368
PMID:38466984

Protocol

Effects of Electronic Nicotine Delivery Systems Substitution on Body Weight Status: Protocol for a Systematic Review and Meta-Analysis

Giusy Rita Maria La Rosa[1,2], DDS, PhD; Maria Ahmed Qureshi[1,2], MD; Lucia Frittitta[1,2,3], MD, PhD; Erika Anastasi[4], BA; Riccardo Polosa[1,2,5], MD, PhD

[1]Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy

[2]Centre of Excellence for the Acceleration of Harm Reduction, University of Catania, Catania, Italy

[3]Diabetes and Obesity Center, Garibaldi Hospital, Catania, Italy

[4]ECLAT Srl, Spin-off of the University of Catania, Catania, Italy

[5]Centre for the Prevention and Treatment of Tobacco Addiction, University Hospital, University of Catania, Catania, Italy

Corresponding Author:
Giusy Rita Maria La Rosa, DDS, PhD
Department of Clinical and Experimental Medicine
University of Catania
Via S. Sofia, 89
Catania, 95123
Italy
Phone: 39 095 4781124
Email: g_larosa92@live.it

Abstract

Background: Weight gain following smoking cessation is a well-documented concern, often attributed to the absence of nicotine's metabolic influence. The adoption of Electronic Nicotine Delivery Systems (ENDS) has been used to achieve smoking cessation, with claims of aiding weight control. However, existing reviews present conflicting conclusions on ENDS' impact on weight status, necessitating a rigorous evaluation.

Objective: We aim to conduct a systematic review with meta-analysis to assess the actual impact of ENDS on weight status in individuals who have ceased or reduced conventional smoking. The primary goal is to provide clinicians with evidence-based insights into the potential effects of ENDS use as a smoking substitute on weight control.

Methods: Adhering to PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) guidelines, our systematic review will analyze randomized and nonrandomized controlled trials, clinical trials (quasi-experimental), and prospective or retrospective cohort studies on the weight status effects of ENDS among individuals who have either quit or reduced smoking. Searches will include PubMed, Scopus, and Cochrane Library, covering the period from 2010 to January 2024. A gray literature search and supplementary searches will be performed. Data will be extracted independently by 2 reviewers and quality assessments will be conducted concurrently. Quality assessments will use Joanna Briggs Institute tools, 2020 version, along with bias assessments for internal validity and reporting bias based on the Catalogue of Bias. The included studies will be examined for any internal data reporting discrepancies by using Puljak's checklist. Meta-analysis and subgroup analyses (ie, general ENDS usage, ENDS use coupled with a reduction in smoking exceeding 50%, and exclusive ENDS use for achieving smoking cessation) are planned. Certainty of evidence will be evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework.

Results: The protocol has been registered in PROSPERO (CRD42023494974) and the entire systematic review is expected to be completed by April 2024. The main goal of this review is to retrieve all current human research studies investigating the influence of ENDS on weight management among individuals who have quit or reduced smoking. Furthermore, the review will assess the quality of these studies and examine potential biases to identify the most dependable evidence available. Dissemination strategies will include traditional journal publications, social media announcements, and a white paper. The latter, available for download and distributed at conferences, aims to reach a broad audience, including clinicians and ENDS users.

Conclusions: The review will address the importance of informing health care professionals and patients about the current and robust evidence regarding the effects of transitioning to ENDS for smoking cessation on weight status.

Trial Registration: PROSPERO CRD42023494974; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=494974
International Registered Report Identifier (IRRID): PRR1-10.2196/56324

(JMIR Res Protoc 2024;13:e56324) doi:10.2196/56324

KEYWORDS

Electronic Nicotine Delivery Systems; body weight; smoking cessation; tobacco harm reduction; systematic review; meta-analysis

Introduction

Background

The phenomenon of weight gain following smoking cessation is a well-documented concern in scientific research [1]. Typically, individuals who quit smoking experience an average weight increase ranging from 4.67 to 4.8 kg after 1 year, with more than 10% experiencing a rise exceeding 10 kg [2,3]. This weight gain can primarily be attributed to the lack of nicotine's influence on metabolic processes, which includes appetite suppression and alterations to both lipolysis and lipogenesis [4,5].

In the past few years, there has been a notable increase in the adoption of Electronic Nicotine Delivery Systems (ENDS), commonly known as e-cigarettes, among individuals attempting to cease tobacco use [6]. Some who use ENDS do so for weight loss or weight management. The use of ENDS for weight loss was most prevalent among individuals with eating disorders, at 32% (n=178) [7]. This usage drops considerably in the general ENDS-using population. In the United States, 15% (13/84) of college students and 13.5% (62/459) of adults reported using ENDS for weight control [8,9]. Among US military recruits, 5.1% (11/223) of males and 6.0% (4/61) of females have used ENDS for this purpose [10]. In England, the figure stands at 4.6% (18/394) of current ENDS users [3].

Observational studies have also noted the practice of using vaping as a dietary substitution, where individuals vape flavored liquids to mitigate food cravings. This behavior, while less prevalent in England [3], has been reported in various surveys and interviews conducted in the United States [11,12].

Commercial entities have recognized these consumer patterns, resulting in the development and marketing of vaping products that claim to support weight loss. Numerous patents have been filed globally, and several companies have marketed vapor devices that propose to offer benefits such as fat burning, appetite suppression, and rapid weight loss [13,14]. These claims, often promoted through online sites and aggressive marketing strategies [13,15], are claims that have not been verified.

Previous Reviews

Recent reviews assert that there is insufficient evidence to draw definitive conclusions on the impact of ENDS on weight control in people who have ceased or reduced conventional smoking. The systematic review of Hod et al [16] of human and in vitro studies concluded that ENDS use is prevalent among the obese, although the authors state that causality cannot be determined due to the cross-sectional design of human studies. Moreover, the data are conflicting, with in vivo studies suggesting weight loss effects, but in vitro studies do not support this claim Thus, the authors underlined the need for further investigation to determine the impact of ENDS on weight control [16]. Another review by Hartmann-Boyce et al [17] found 2 ENDS studies, 1 involving ENDS as an adjunct to nicotine replacement therapy and the other comparing them to varenicline, both with wide CIs at all measurement time points. The CIs of weight change (kg) at the end of the treatment and 12 months encompassed both clinically significant weight loss and weight gain [17]. Therefore, the authors stated that "data are needed on whether using e-cigarettes to quit smoking affects post-cessation weight change" [17].

Research Question

Given the rise of ENDS as an alternative to traditional smoking, and their associated perceived benefits for weight control, we aim to rigorously evaluate the actual impact of ENDS on weight status in individuals who have ceased or reduced conventional smoking. For this purpose, we intend to conduct a systematic review with meta-analysis to analyze human clinical studies that provide longitudinal data on body weight among participants who have replaced cigarette smoking with ENDS use.

Population, Intervention, Comparator, and Outcomes Criteria

The research strategy follows the Population, Intervention, Comparator, and Outcome (PICO) approach as follows: population—adults who smoke cigarettes, intervention—complete or partial substitution of ENDS for cigarettes, comparator—within-subject changes baseline to the end of the study, and outcomes—changes in body weight.

Objectives

We will conduct a systematic review with a meta-analysis to critically assess and synthesize available human studies on the weight status effects of ENDS among individuals who have either quit or reduced smoking. Our goal is to critically evaluate and synthesize the available evidence to offer clinicians high-quality insights into the potential effects of ENDS use as a substitute for smoking, specifically concerning weight control. Thus, our aim is to equip clinicians with robust evidence to enhance their treatment recommendations and strategies for individuals who smoke, aiding them in making informed decisions and plans.

Methods

Overview

In adherence to the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) requirements

[18], this protocol is registered with PROSPERO (CRD42023494974), and any deviations will be transparently reported within the review. The review team (GRMLR, MAQ, LF, EA, and RP), led by RP, has substantial expertise in conducting literature reviews and an expert background in tobacco control, tobacco harm reduction, and ENDS.

Database Search and Secondary Searches

The databases to be included are PubMed, Scopus, and CENTRAL Cochrane Library. Using the keywords specific to each database (ie, weight, BMI, "body mass index," "electronic cigarette," "e-cigarette," and "electronic nicotine"), searches will be performed in the title and abstract fields in PubMed, and in the title, abstract, and keywords in Scopus. Cochrane Library will be searched for trials. The search will include the period from 2010 to January 2024, in line with the date of the first peer-reviewed research studies on ENDS. Language restrictions will not be applied. In compliance with PRISMA-P, the search strategy example is detailed in Multimedia Appendix 1. Retrievals will be downloaded into EndNote (Clarivate), and duplicates will be removed.

A secondary search of the existing reviews, conducted independently by 2 reviewers, will be conducted to identify any additional studies. Next, the references of the included studies will be scrutinized to identify additional studies. Finally, the included studies will be citation chased (ie, snowball search) through Google Scholar. The studies excluded during the thorough full-paper review will be documented.

The list of selected studies will be forwarded to 2 medical experts to validate that all pertinent studies have been included. In addition, a comprehensive gray literature search will be conducted on the websites of 16 weight-related medical organizations (Multimedia Appendix 1).

Inclusion and Exclusion Criteria

The selected study designs will include randomized and nonrandomized controlled trials, clinical trials (quasi-experimental), and prospective or retrospective cohort studies. The initial exclusion will be based on titles and abstracts reviewed. Exclusion criteria will be by publication types (ie, editorials, letters, commentaries, protocols, narrative reviews, conference abstracts, and dissertations), study designs (ie, vitro, animal studies, inhalation toxicology, biomarker studies, surveys, and qualitative studies), adolescent populations, and studies lacking baseline or follow-up weight data. A total of 2 reviewers will independently conduct the exclusion process, with any discrepancies resolved through discussion.

The next process will involve a thorough review of full papers, guided by 3 inclusion criteria, including study designs, availability of data before and after testing participants who substituted ENDS for smoking, and outcome data on weight. All 3 criteria will have to be satisfied for a study to be included.

Review team members will undergo training on the inclusion criteria through analysis of 3 included studies. Two independent reviewers will then conduct the inclusion and exclusion assessments on the studies, resolving any disparities through discussion. The objective is to attain a high level of agreement between reviewers on the study selection process. The project leader will make the final decision regarding the inclusion and assessment of the studies.

Data Extraction

Using a standardized form derived from Joanna Briggs Institute (JBI) and Cochrane Collaboration inventories [19,20], data extraction will be conducted by 2 reviewers independently, followed by cross-checking for accuracy. The full data extraction form is provided in Multimedia Appendix 1. The data extraction form includes bibliographic details, study population demographics, intervention descriptions, and weight measurements. The form will be pilot-tested and revised as necessary.

In cases where the published data are insufficient or absent, an email requesting additional details will be sent to the corresponding author. Findings from the included studies will be reported in a dual format. First, individual studies will be summarized with a concise narrative description. Second, study tables will be formulated incorporating elements derived from the data extraction and quality assessments (refer to the subsequent section).

Quality Assessment and Risk of Bias

Quality assessments will use JBI tools, 2020 version [21], along with bias assessments for internal validity and reporting bias based on the Catalogue of Bias [22] (Multimedia Appendix 1). Examination of studies for any internal data reporting discrepancies will be conducted using the checklist proposed by Puljak et al [23] (Multimedia Appendix 1). The data extraction forms will be pilot-tested and revised if necessary. The comprehensive evaluation of study quality will involve calculating an overall rating through a rubric that integrates the JBI score and biases checklist. The overall study quality will be categorized according to the Cochrane guidelines—low risk of bias, some concerns, and high risk of bias [20]. Quality assessment will be conducted concurrent with the data extraction, and 2 reviewers will independently perform assessments. Discrepancies will be resolved through discussion or decided by the project leader.

No studies will be excluded on the basis of their quality assessment or bias. Studies deviating from the JBI quality assessment criteria or exhibiting biases will be documented in the study table. These limitations will be explicitly identified during the data analysis and referenced in the discussion section of the review.

Data Analysis and Synthesis

Studies will be categorized by risk of bias, and summaries will include study design, participant and intervention characteristics, and main findings. A meta-analysis of change scores is planned, where the change score is defined as mean kg at the end of the study minus mean kg at the baseline. Three subgroup analyses will be performed, focusing on (1) general ENDS usage, (2) ENDS use coupled with a reduction in smoking exceeding 50%, and (3) exclusive ENDS use with the goal of smoking cessation. Publication bias will be assessed if a minimum of 10 studies are included.

Grading of Recommendations Assessment, Development, and Evaluation

Certainty of evidence will be evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework [24].

Results

The protocol has been registered in PROSPERO (CRD42023494974) and the entire systematic review is expected to be completed by April 2024. The primary objective of this review is to compile all existing human research studies concerning the impact of ENDS on weight control in people who ceased or reduced smoking. In addition, the review will rigorously evaluate the quality of these studies and scrutinize potential biases to emphasize the most reliable and available evidence. The planned review will also identify studies that may exhibit reporting bias, thereby enabling a more accurate representation of the effects of ENDS on weight control within the ongoing discourse on tobacco harm reduction.

Discussion

Principal Findings

This protocol is intended to provide the methodological framework for a systematic review and meta-analysis of the actual impact of ENDS on weight status in individuals who have ceased or reduced conventional smoking.

Many research protocols lack comprehensive planning for dissemination and knowledge translation activities beyond the conventional approach of publishing the review in a peer-reviewed journal and presenting findings at conferences. Naturally, this review will be disseminated through these traditional channels. Following an approach previously described [25], some additional strategies will be adopted. Briefly, upon acceptance, the project protocol will be published in JMIR Research Protocols and the final review with meta-analysis will be published in a peer-reviewed journal. In addition, efforts will be made to translate the review's abstract into several languages. To enhance visibility, the availability of the review will be disseminated via social media platforms.

A white paper will be produced and made available for download on a dedicated website, and we anticipate disseminating it to medical associations and distributing it at conferences. The goal is to ensure the widespread of findings among clinicians and individuals currently using or considering ENDS. Given that a significant number of physicians and health care providers harbor misconceptions regarding the health impacts of nicotine [26,27], the white paper will incorporate a dedicated section focusing on nicotine. Infographics drawn from the white paper will be disseminated to current and potential ENDS users via user advocacy organizations [25]. Traditional review publication methods may not effectively reach the stakeholders who will benefit from clear and accessible updated sources of information. The objective of these activities is to ensure broad dissemination of the review findings to multiple audiences.

It is crucial to acknowledge the potential limitations arising from both the number and the quality of the studies that will be included in this systematic review. The limited quantity of available studies can restrict the scope and depth of conclusions drawn, leading to gaps in understanding and potentially biasing the overall assessment. Furthermore, the quality of the studies significantly impacts the reliability of the review's conclusions. If the included studies exhibit methodological flaws, biases, or insufficient rigor, the overall evidence may be weakened, resulting in tentative or inconclusive findings.

Conclusions

In conclusion, tobacco consumption constitutes a significant public health burden. Electronic cigarettes may represent a viable option for those attempting to quit smoking. Furthermore, there is a growing interest in these devices due to their potential benefits for weight control, especially for counteracting the short-term weight gain associated with smoking cessation. Therefore, it is essential to inform both patients and health care professionals about the most current and robust evidence regarding the effects of switching to electronic cigarettes for smoking cessation on weight status. This review, including meta-analysis, aims to contribute to this objective.

Acknowledgments

This investigator-initiated study was sponsored by ECLAT srl, a research-based spin-off company of the University of Catania, with the help of a grant from the Foundation for a Smoke-Free World, Inc a US nonprofit 501(3)(c) private foundation and a bursary from the Dipartimento di Medicina Clinica e Sperimentale at the University of Catania Italy (Bando N 1355 2020 Borsa di Ricerca). The contents, selection, and presentation of facts, as well as any opinions expressed herein are the sole responsibility of the authors and under no circumstances shall be regarded as reflecting the positions of the funders.

Data Availability

Data sharing is not applicable to this study as no data sets were generated or analyzed during this study.

Authors' Contributions

GRMLR, MAQ, and RP designed the study and wrote the original draft. LF and EA contributed to the study and reviewed the final study for accuracy and completeness. All authors have read and approved the final study.

Conflicts of Interest

GRMLR, MAQ, LF, and EA declare no conflicts of interest. RP is full tenured professor of Internal Medicine at the University of Catania (Italy) and Medical Director of the Institute for Internal Medicine and Clinical Immunology at the same University. He has received grants from Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes (U-BIOPRED) and AIR-PROM (Airway Disease Predicting Outcomes through Patient Specific Computational Modelling), Integral Rheumatology and Immunology Specialists Network (IRIS), Foundation for a Smoke Free World, Pfizer, GlaxoSmithKline, CV Therapeutics, NeuroSearch A/S, Sandoz, Merk Sharp and Dohme, Boehringer Ingelheim, Novartis, Arbi Group srl, Duska Therapeutics, Forest Laboratories, Ministero dell Universita' e della Ricerca (MUR) Bando Piano Nazionale di Ripresa e Resilienza (PNRR) 3277/2021 (CUP E63C22000900006) and 341/2022 (CUP E63C22002080006), funded by NextGenerationEU of the European Union (EU), and the ministerial grant PON REACT-EU 2021 GREEN- Bando 3411/2021 by Ministero dell Universita' e (MUR)—PNRR EU Community. He is founder of the Center for Tobacco Prevention and Treatment (CPCT) at the University of Catania and of the Center of Excellence for the Acceleration of Harm Reduction at the same university. He receives consultancy fees from Pfizer, Boehringer Ingelheim, Duska Therapeutics, Forest Laboratories, CV Therapeutics, Sermo Inc, GRG Health, Clarivate Analytics, Guidepoint Expert Network, and Gerson Lehrman Group (GLG) Group. He receives textbooks royalties from Elsevier. He is also involved in a patent application for ECLAT srl. He is a pro bono scientific advisor for Lega Italiana Anti Fumo (LIAF) and the International Network of Nicotine Consumers Organizations (INNCO); and he is Chair of the European Technical Committee for Standardization on "Requirements and test methods for emissions of electronic cigarettes" (CEN/TC 437; WG4).

Multimedia Appendix 1
(A) Sample PubMed bibliographic search. (B) Weight medical organizations grey literature search. (C) Data extraction form. (D) Data discrepancies form. (E) Bias report. (F) PRISMA-P 2015 checklist.
[DOCX File , 39 KB - resprot_v13i1e56324_app1.docx]

References

1. Pebley K, Bursac Z, Klesges RC, Ebbert JO, Womack CR, Graber J, et al. A randomized controlled trial to reduce post-cessation weight gain. Int J Obes (Lond) 2023;47(6):471-478 [FREE Full text] [doi: 10.1038/s41366-023-01286-5] [Medline: 36841886]
2. Aubin HJC, Farley A, Lycett D, Lahmek P, Aveyard P. Weight gain in smokers after quitting cigarettes: meta-analysis. BMJ 2012;345:e4439 [FREE Full text] [doi: 10.1136/bmj.e4439] [Medline: 22782848]
3. Jackson SE, Brown J, Aveyard P, Dobbie F, Uny I, West R, et al. Vaping for weight control: a cross-sectional population study in England. Addict Behav 2019;95:211-219 [FREE Full text] [doi: 10.1016/j.addbeh.2019.04.007] [Medline: 30981033]
4. Driva S, Korkontzelou A, Tonstad S, Tentolouris N, Katsaounou P. The effect of smoking cessation on body weight and other metabolic parameters with focus on people with type 2 diabetes mellitus. Int J Environ Res Public Health 2022;19(20):13222 [FREE Full text] [doi: 10.3390/ijerph192013222] [Medline: 36293800]
5. Harris KK, Zopey M, Friedman TC. Metabolic effects of smoking cessation. Nat Rev Endocrinol 2016;12(5):299-308 [FREE Full text] [doi: 10.1038/nrendo.2016.32] [Medline: 26939981]
6. Carpenter MJ, Heckman BW, Wahlquist AE, Wagener TL, Goniewicz ML, Gray KM, et al. A naturalistic, randomized pilot trial of e-Cigarettes: uptake, exposure, and behavioral effects. Cancer Epidemiol Biomarkers Prev 2017;26(12):1795-1803 [FREE Full text] [doi: 10.1158/1055-9965.EPI-17-0460] [Medline: 29127080]
7. Morean ME, L'Insalata A. Electronic cigarette use among individuals with a self-reported eating disorder diagnosis. Int J Eat Disord 2018;51(1):77-81. [doi: 10.1002/eat.22793] [Medline: 29076176]
8. Napolitano MA, Lynch SB, Stanton CA. Young adult e-Cigarette users: perceptions of stress, body image, and weight control. Eat Weight Disord 2020;25(2):487-495. [doi: 10.1007/s40519-018-0627-6] [Medline: 30554326]
9. Morean ME, Wedel AV. Vaping to lose weight: predictors of adult e-Cigarette use for weight loss or control. Addict Behav 2017;66:55-59. [doi: 10.1016/j.addbeh.2016.10.022] [Medline: 27875790]
10. Fahey MC, Little MA, Klesges RC, Talcott GW, Richey PA, Mehmet K, et al. Use of tobacco for weight control across products among young adults in the U.S. military. Subst Use Misuse 2021;56(1):153-161 [FREE Full text] [doi: 10.1080/10826084.2020.1846196] [Medline: 33183122]
11. Kechter A, Ceasar RC, Simpson KA, Schiff SJ, Dunton GF, Bluthenthal RN, et al. A chocolate cake or a chocolate vape? Young adults describe their relationship with food and weight in the context of nicotine vaping. Appetite 2022;175:106075. [doi: 10.1016/j.appet.2022.106075] [Medline: 35525332]
12. Goldberg RL, Cataldo JK. Using an e-Cigarette is like eating tofu when you really want meat. Am J Health Behav 2018;42(5):54-64 [FREE Full text] [doi: 10.5993/AJHB.42.5.5] [Medline: 30688641]
13. Singh H, Kennedy RD, Lagasse LP, Czaplicki LM, Cohen JE. E-cigarettes and weight loss-product design innovation insights from industry patents. Nicotine Tob Res 2018;20(8):1010-1014 [FREE Full text] [doi: 10.1093/ntr/ntx112] [Medline: 28525609]
14. Lose your cravings!. perfectvapordiet. URL: https://www.perfectvapordiet.com/index.php [accessed 2023-06-23]

15. Basáñez T, Majmundar A, Cruz TB, Allem JP, Unger JB. e-Cigarettes are being marketed as "Vitamin delivery" devices. Am J Public Health 2019;109(2):194-196. [doi: 10.2105/AJPH.2018.304804] [Medline: 30649935]
16. Hod R, Nor NHM, Maniam S. Systematic review on e-Cigarette and its effects on weight gain and adipocytes. PLoS One 2022;17(7):e0270818 [FREE Full text] [doi: 10.1371/journal.pone.0270818] [Medline: 35788209]
17. Hartmann-Boyce J, Theodoulou A, Farley A, Hajek P, Lycett D, Jones LL, et al. Interventions for preventing weight gain after smoking cessation. Cochrane Database Syst Rev 2021;10(10):CD006219 [FREE Full text] [doi: 10.1002/14651858.CD006219.pub4] [Medline: 34611902]
18. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015;350:g7647 [FREE Full text] [doi: 10.1136/bmj.g7647] [Medline: 25555855]
19. Aromataris E, Munn Z. JBI manual for evidence synthesis. 2020. URL: https://synthesismanual.jbi.global [accessed 2024-01-05]
20. Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al. Cochrane handbook for systematic reviews of interventions version 6.1. Cochrane Training. 2020. URL: https://training.cochrane.org/handbook/archive/v6.1 [accessed 2024-01-05]
21. Critical appraisal tools. JBI Global. 2020. URL: https://jbi.global/critical-appraisal-tools [accessed 2023-12-15]
22. Catalogue of bias. Centre for Evidence Based Medicine. 2019. URL: https://catalogofbias.org/ [accessed 2023-12-13]
23. Puljak L, Riva N, Parmelli E, González-Lorenzo M, Moja L, Pieper D. Data extraction methods: an analysis of internal reporting discrepancies in single manuscripts and practical advice. J Clin Epidemiol 2020;117:158-164 [FREE Full text] [doi: 10.1016/j.jclinepi.2019.09.003] [Medline: 31541692]
24. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. rating the quality of evidence. J Clin Epidemiol 2011;64(4):401-406 [FREE Full text] [doi: 10.1016/j.jclinepi.2010.07.015] [Medline: 21208779]
25. O'Leary R, Qureshi MA, La Rosa GRM, Vernooij RWM, Odimegwu DC, Bertino G, et al. Respiratory and cardiovascular health effects of e-Cigarette substitution: protocol for two living systematic reviews. JMIR Res Protoc 2021;10(5):e29084 [FREE Full text] [doi: 10.2196/29084] [Medline: 34042601]
26. Manderski MTB, Steinberg MB, Wackowski OA, Singh B, Young WJ, Delnevo CD. Persistent misperceptions about nicotine among US physicians: results from a randomized survey experiment. Int J Environ Res Public Health 2021;18(14):7713 [FREE Full text] [doi: 10.3390/ijerph18147713] [Medline: 34300168]
27. Shi R, Feldman R, Liu J, Clark PI. The dilemma of correcting nicotine misperceptions: nicotine replacement therapy versus electronic cigarettes. Health Commun 2021;36(14):1856-1866 [FREE Full text] [doi: 10.1080/10410236.2020.1800288] [Medline: 32762261]

Abbreviations

ENDS: electronic nicotine delivery systems
GRADE: Grading of Recommendations Assessment, Development, and Evaluation
JBI: Joanna Briggs Institute
PICO: Population, Intervention, Comparator, and Outcome
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols

Edited by A Mavragani; submitted 12.01.24; this is a non–peer-reviewed article;accepted 01.02.24; published 26.03.24.

Please cite as:
La Rosa GRM, Qureshi MA, Frittitta L, Anastasi E, Polosa R
Effects of Electronic Nicotine Delivery Systems Substitution on Body Weight Status: Protocol for a Systematic Review and Meta-Analysis
JMIR Res Protoc 2024;13:e56324
URL: https://www.researchprotocols.org/2024/1/e56324
doi:10.2196/56324
PMID:38530329

Protocol

Epidemiology of Syphilis in Pregnancy and Congenital Syphilis in Brazil and the Risk or Associated Factors: Protocol for a Systematic Review

Yago Tavares Pinheiro[1], PhD; Janmilli da Costa Dantas[1], PhD; Jose Rebberty Rodrigo Holanda[2], MD; Ankilma do Nascimento Andrade Feitosa[3], PhD; Richardson Augusto Rosendo da Silva[1], PhD

[1]Federal University of Rio Grande do Norte, Natal, Brazil

[2]Federal University of Rio Grande do Norte, Caicó, Brazil

[3]University Center Santa Maria, Cajazeiras, Brazil

Corresponding Author:
Yago Tavares Pinheiro, PhD
Federal University of Rio Grande do Norte
Lagoa Nova
Natal, 59078-900
Brazil
Phone: 55 (83) 99664 7797
Fax: 55 (83) 99664 7797
Email: yagostavares5@gmail.com

Abstract

Background: Syphilis in pregnancy and congenital syphilis are growing public health issues worldwide. Several factors can influence their occurrence in the population. Therefore, understanding the epidemiology of this condition and the factors that influence its occurrence is fundamental for decision-making by clinicians and health managers. However, so far, no systematic review has summarized and analyzed data on the incidence, prevalence, and predictors of these diseases in Brazilian cities, considering different sociocultural, demographic, economic, sanitary, and spatial-temporal characteristics presented across locations.

Objective: We propose a systematic review protocol to gather and analyze data on the incidence, prevalence, and risk or associated factors of syphilis in pregnancy and congenital syphilis in Brazil, taking into account different local or regional contexts.

Methods: Searches will be conducted in CINAHL, MEDLINE, LILACS, Embase, and Web of Science databases. We will include observational studies (ie, cross-sectional, longitudinal, or case-control studies), analyzing the incidence, prevalence, and risk or associated factors of syphilis in pregnancy and congenital syphilis in Brazil from primary data. The diagnosed syphilis will be assessed based on direct pathogen detection tests or through immunological, treponemal or nontreponemal tests, following Brazilian protocols for diagnosing syphilis. The studies are currently undergoing screening in the databases, and after this step, 2 reviewers will perform all identified documents. The Newcastle-Ottawa Scale and the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) system will be used to assess methodological quality and quality of evidence of studies, respectively. The Kappa coefficient will assess the agreement between researchers in each study stage. Cochran Q test will assess the heterogeneity among studies. Then, a random-effects meta-analysis will be performed.

Results: Results will be discussed based on subgroup analysis, which is as follows: (1) type of syphilis (in pregnancy or congenital), (2) type of study (case-control and cross-sectional studies for analysis of associated factors and longitudinal studies for risk factors), and (3) contextual factors (ie, region of country, socioeconomic and demographic characteristics, and year of study). This systematic review is expected to be completed by December 2023, and our results will be disseminated through publication in peer-reviewed journals and scientific events.

Conclusions: This systematic review aims to assist health care managers and professionals in their decision-making to control these diseases in Brazil, considering location heterogeneity. Furthermore, countries with health systems and demographic and socioeconomic contexts similar to those of Brazil may benefit from this information.

International Registered Report Identifier (IRRID): DERR1-10.2196/50702

(JMIR Res Protoc 2024;13:e50702) doi:10.2196/50702

KEYWORDS

sexually transmitted diseases; epidemiology; prevalence; incidence; Brazil; syphilis; pregnancy; sociocultural; economic; congenital syphilis; heterogeneity; decision-making

Introduction

Syphilis is a sexually transmitted infection caused by *Treponema pallidum* and is a major public health issue worldwide [1]. Despite the efforts of health care professionals to control this infection in Brazil, cases of syphilis have increased in recent years [2-4], impacting public and private health care systems and highlighting the need to improve disease surveillance [5,6]. Globally, 2 million out of 36 million syphilis infections occur in pregnant women [7], resulting in congenital syphilis (infection of the fetus) and adverse events (eg, early fetal death, stillbirth, premature birth, low birth weight, and neonatal death) [8,9].

Recently, an outbreak of syphilis has been observed among men and women in more economically developed countries, which can be explained by changes in the sexual behavior of individuals and increased exposure to the risk of infection due to a false sense of security stemming from new treatments and an increased search for sexual partners over the internet [10]. In this context, understanding the epidemiology and control of this disease becomes more complex and difficult.

Syphilis in pregnancy and congenital syphilis can be controlled with health care measures, such as access to prevention services, early diagnosis, and treatment [4,11,12]. Conversely, these measures require the analysis of epidemiological data and predictors [4,11]. Although studies in Brazilian cities analyzed the incidence, prevalence, and predictors of syphilis in pregnancy and congenital syphilis [13-17], each city presented different sociocultural, demographic, economic, sanitary, and spatial-temporal characteristics, hindering data extrapolation to the national territory.

Summarizing and analyzing the incidence, prevalence, and risk or associated factors of syphilis in pregnancy and congenital syphilis must take into account location heterogeneity. This type of analysis enables a broader understanding of the problem, improves control strategies and equity in disease management, and establishes reference data to help disease screening efforts in Brazil. Despite the relevance of the theme, no systematic review has been conducted to date on the epidemiological data of gestational and congenital syphilis or its predictors, subgrouping and analyzing this information from different contexts.

Thus, we propose a systematic review protocol to gather and analyze data on the incidence, prevalence, and risk or associated factors of syphilis in pregnancy and congenital syphilis in Brazil, taking into account different local or regional contexts.

Methods

Study Design

This systematic review protocol was developed according to PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) [18], which will also guide the systematic review. The protocol has been registered in PROSPERO (CRD42022329329).

Eligibility Criteria

Observational studies whose sample comprised cases of syphilis in pregnant women or newborns in Brazil will be included in the systematic review. Table 1 [2,19,20] presents the eligibility criteria used in the review.

Table 1. Eligibility criteria for the systematic review.

Variables	Inclusion criteria	Exclusion criteria
Study design	• Cross-sectional, longitudinal, or case-control studies conducted in Brazil • Studies based on primary data	• Reviews, opinion articles, editorials, or publications without primary data or not peer-reviewed • The most complete and recent data will be used if studies report the same data in multiple sources [19,20].
Population and location	• Studies in which the sample involved pregnant women or newborns with syphilis • Studies with residents in Brazil	• Studies with samples involving other populations (non-pregnant women or men)
Outcomes	• Studies reporting the prevalence or incidence of Treponema pallidum (syphilis) infection or its risk or associated factors in pregnant women or neonates • Studies that diagnosed syphilis based on direct pathogen detection tests or through immunological, treponemal, or non-treponemal tests, in accordance with Brazilian protocols for diagnosing syphilis [2]	• Studies presenting the incidence or prevalence of combined infections (ie, syphilis with other sexually transmitted infections) and not allowing isolated analysis
Language	—[a]	• No restriction regarding language or year of publication
Time frame	—	• No restriction regarding to year in which the study was carried out or published

[a]Not applicable.

Study Selection

Textbox 1 presents the search strategy. Searches will be conducted in the CINAHL, MEDLINE, LILACS, Embase, and Web of Science databases. Grey literature will be also searched using the reference lists of relevant studies in addition to using databases such as Open Gray and Google Scholar. Further, reports with epidemiological data on syphilis in the country will be screened in the electronic database of the Brazilian Ministry of Health.

Two researchers will independently search, identify potentially eligible studies, and remove duplicates. Then, inclusion and exclusion criteria will be applied to titles and abstracts, eligible studies will be read in full, and reasons for exclusion will be recorded. Disagreements between researchers will be resolved by discussion or with a third researcher. The flowchart of the study selection is described in Figure 1.

Textbox 1. Search strategy.

#1 “syphilis” [Title/Abstract] OR “congenital syphilis” [Title/Abstract] OR “treponemal infections” [Title/Abstract] OR “T. pallidum” [Title/Abstract] OR “pallidum” [Title/Abstract] OR “serosyphilis” [Title/Abstract] OR “sexually transmitted diseases” [Title/Abstract]

#2 “pregnant” [Title/Abstract] OR “women” [Title/Abstract] OR “congenital” [Title/Abstract]

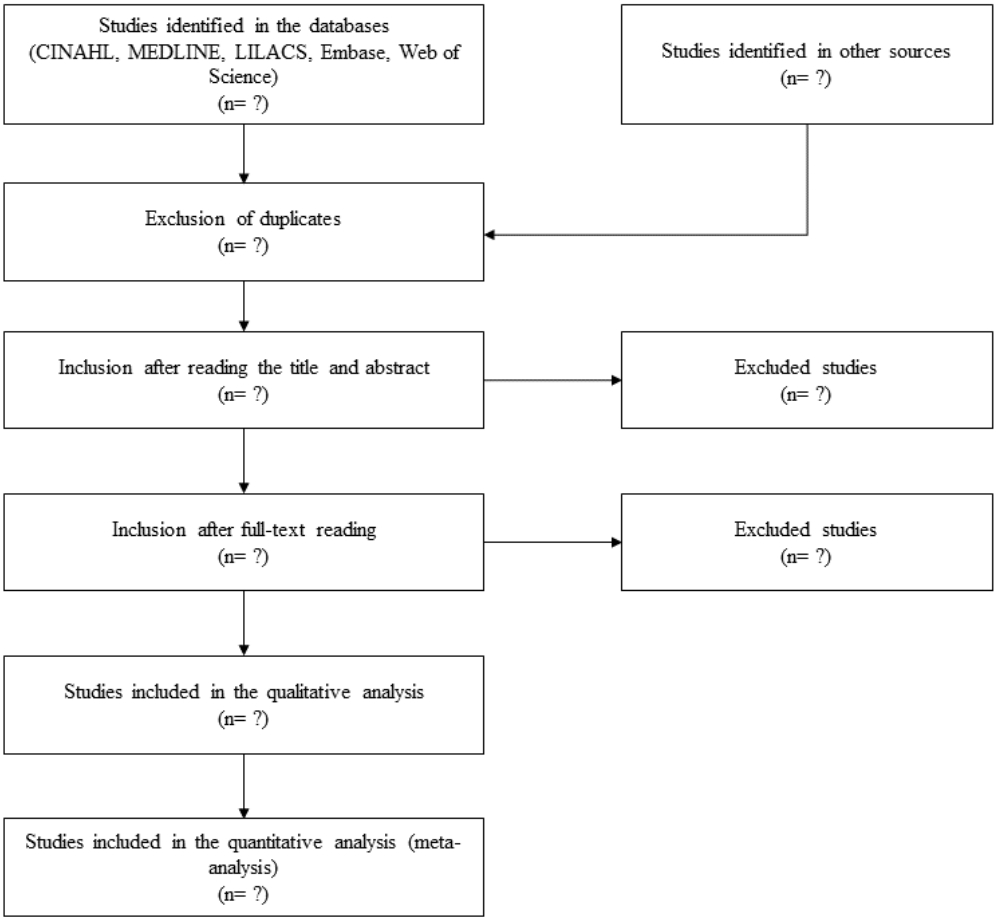
#3 “incidence” [Title/Abstract] OR “prevalence” [Title/Abstract] OR “prevalence study” [Title/Abstract] OR “cross-sectional study” [Title/Abstract] OR “observational study” [Title/Abstract]

#4 “risk factors” [Title/Abstract] OR “associated factors” [Title/Abstract] OR “measures of association, exposure, risk or outcome” [Title/Abstract]

#5 “brazil” [Title/Abstract] OR “brazilian” [Title/Abstract]

#6 #1 AND #2 AND #3 OR #4 AND #5

Figure 1. Flowchart of the study. The numbers are to be confirmed.



Assessment of Methodological Quality and Quality of Evidence

The Newcastle-Ottawa Scale will be used to assess the methodological quality of studies [21]. This scale includes 8 items categorized into 3 domains (ie, selection, comparability, and outcome or exposure) to assess the risk of bias in nonrandomized studies. The Newcastle-Ottawa Scale has specific tools for cohort and case-control studies. Thus, adaptations will be made to allow the proper assessment of the potential sources of bias in cross-sectional studies. In addition, quality of evidence will be analyzed using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) system, which classifies evidence as high, moderate, low, and very low [22,23].

Data Extraction and Synthesis

The following data will be extracted and entered into a Microsoft Excel spreadsheet: first author, year of publication, type of study (eg, longitudinal, cross-sectional, or case-control), type of syphilis (eg, in pregnancy or congenital), the diagnostic method used, study location (eg, city and state), participants (eg, sample size, age, type of population, and presence of co-infection), population setting (eg, community, health care centers, schools, neighborhoods, and the environmental context of the participants), date of data collection, sampling method, and main results (eg, incidence, prevalence, and risk or associated factors).

After summarizing the studies, results will be discussed based on subgroup analysis, as follows: (1) type of syphilis (eg, in pregnancy or congenital), (2) type of study (eg, case-control and cross-sectional for analysis of associated factors and longitudinal for risk factors), and (3) contextual factors (eg, region of country, socioeconomic and demographic characteristics, and year of study).

Statistical Planning

Kappa coefficient will assess the agreement between researchers [24]. The unadjusted incidence or prevalence and the standard error will be recalculated based on the numerator and denominator values presented in each study. Furthermore, the prevalence or incidence may be reported using the direct method of standardization, adjusted for the variables of age, study location, and presence of co-infection. If the study does not provide data for calculating adjusted incidence or prevalence, the researchers will request this information from the study authors.

Additionally, a meta-analysis will be performed using a random-effects model due to the potential heterogeneity among studies. The random-effects model is applied when the aim is to combine several studies that have similar objectives but are conducted in different ways (ie, exhibiting methodological

heterogeneity) [25]. Moreover, the Freeman-Tukey double arcsine transformation will stabilize variances to maintain the estimates of individual effects of each study [26]. Cochran Q test will assess the heterogeneity among studies [27]. I^2 values of 25%, 50%, and 75% will represent low, medium, and high heterogeneity, respectively [28].

Studies will undergo a subgroup analysis using clustering variables (eg, study location, study population, method of syphilis diagnosis, mean sample size, year of data collection, sampling methods, and methodological quality) to investigate possible sources of heterogeneity [20].

Analyzes will be performed using the Review Manager (RevMan) software (version 5.4; Cochrane Collaboration) and the R software (R Core Team), considering a 95% CI.

Results

The protocol has been registered in PROSPERO (CRD42022329329). The screening of the studies in the databases has already started, and the entire systematic review is expected to be completed by December 2023. The results of the study will provide evidence that can support decision-making regarding strategies to control syphilis in Brazil and countries with similar health, demographic, and socioeconomic profiles. Results will be disseminated through publication in peer-reviewed journals and presentation at scientific events.

Discussion

Expected Results and Practical Implications

After a preliminary search, we found studies in Brazilian cities that analyzed epidemiological data and predictors of syphilis in pregnancy and congenital syphilis [13-17,29]. However, no study has organized and summarized data to perform a broader analysis of this public health issue.

Summarizing local studies will allow the analysis and discussion of epidemiology and risk or associated factors of syphilis in pregnancy and congenital syphilis, considering sociocultural, demographic, spatial-temporal, economic, and sanitary differences in each location. Thus, this systematic review will help in the decision-making of health care managers and professionals to control these diseases in Brazil according to location heterogeneity.

Limitations

Some limitations that may compromise the quality of evidence can be found in the systematic review, such as heterogeneity among studies, wide CIs, and uncertainty of estimated effects.

Acknowledgments

The authors would like to thank Probatus Academic Services for providing scientific language translation and revision.

This study was supported by the Coordination for the Improvement of Higher Education Personnel (CAPES), Brazil (finance code 001).

Data Availability

All data generated and analyzed in this study are available upon request from the corresponding author.

Authors' Contributions

YTP, JCD, and ANAF designed the study and wrote the original draft; JRRH and RARS designed the study and approved the final manuscript.

Conflicts of Interest

None declared.

References

1. Kojima N, Klausner J. An update on the global epidemiology of syphilis. Curr Epidemiol Rep 2018 Mar;5(1):24-38 [FREE Full text] [doi: 10.1007/s40471-018-0138-z] [Medline: 30116697]
2. Gaspar PC, Bigolin A, Alonso Neto JB, Pereira E, Bazzo M. Brazilian Protocol for Sexually Transmitted Infections 2020: syphilis diagnostic tests. Rev Soc Bras Med Trop 2021;54(suppl 1):e2020630 [FREE Full text] [doi: 10.1590/0037-8682-630-2020] [Medline: 34008728]
3. Domingues CSB, Duarte G, Passos M, Sztajnbok DDN, Menezes M. Brazilian Protocol for Sexually Transmitted Infections, 2020: congenital syphilis and child exposed to syphilis. Rev Soc Bras Med Trop 2021;54(suppl 1):e2020597 [FREE Full text] [doi: 10.1590/0037-8682-597-2020] [Medline: 34008719]
4. Freitas FLS, Benzaken A, Passos MD, Coelho I, Miranda A. Brazilian Protocol for Sexually Transmitted Infections 2020: acquired syphilis. Rev Soc Bras Med Trop 2021;54(suppl 1):e2020616 [FREE Full text] [doi: 10.1590/0037-8682-616-2020] [Medline: 34008726]

5. Brasil. Ministério da Saúde—Departamento de Informática do Sistema Único de Saúde do Brasil. Sífilis em gestante - Casos confirmados notificados no Sistema de Informação de Agravos de Notificação - Brasil. 2021. URL: http://tabnet.datasus.gov.br/cgi/tabcgi.exe?sinannet/cnv/sifilisgestantebr.def [accessed 2023-12-12]
6. Ribeiro AF. Concordância dos Dados de Mortalidade por Doenças de Notificação Compulsória no Sistema de Informação sobre Mortalidade- Sim e Sistema de Informação de Agravos de Notificação-SINAN, Brasil 2007 a 2015. RGSS 2017 Aug 01;6(2):173-183. [doi: 10.5585/rgss.v6i2.345]
7. Peeling RW, Mabey D, Kamb M, Chen X, Radolf J, Benzaken A. Syphilis. Nat Rev Dis Primers 2017 Oct 12;3:17073 [FREE Full text] [doi: 10.1038/nrdp.2017.73] [Medline: 29022569]
8. Milanez H. Syphilis in pregnancy and congenital syphilis: why can we not yet face this problem? Rev Bras Ginecol Obstet 2016 Sep;38(9):425-427 [FREE Full text] [doi: 10.1055/s-0036-1593603] [Medline: 27756083]
9. D'Aiuto C, Valderrama A, Byrns M, Boucoiran I. Sexually transmitted and blood-borne infections in pregnant women and adverse pregnancy outcomes. J Obstet Gynaecol Can 2020 Aug;42(8):977-983 [FREE Full text] [doi: 10.1016/j.jogc.2020.01.023] [Medline: 32418858]
10. Mercuri SR, Moliterni E, Cerullo A, Di Nicola MR, Rizzo N, Bianchi V, et al. Syphilis: a mini review of the history, epidemiology and focus on microbiota. New Microbiol 2022 Jan;45(1):28-34 [FREE Full text] [Medline: 35403844]
11. Bezerra M, Fernandes F, de Oliveira Nunes JP, de Araújo Baltar SLSM, Randau K. Congenital syphilis as a measure of maternal and child healthcare, Brazil. Emerg Infect Dis 2019 Aug;25(8):1469-1476 [FREE Full text] [doi: 10.3201/eid2508.180298] [Medline: 31310223]
12. Domingues C, Duarte G, Passos M, Sztajnbok DDN, Menezes M. Protocolo Brasileiro para Infecções Sexualmente Transmissíveis 2020: sífilis congênita e criança exposta à sífilis. Epidemiol Serv Saúde 2021;30(spe1):e2020597 [FREE Full text] [doi: 10.1590/s1679-4974202100005.esp1]
13. Neto PLF, Fonseca RDS, Avelino MDS, Vilhena E, Barbosa MDADA, Lopes C, et al. Prevalence and factors associated with syphilis in people living with HIV/AIDS in the State of Pará, Northern Brazil. Front Public Health 2021;9:646663 [FREE Full text] [doi: 10.3389/fpubh.2021.646663] [Medline: 34434909]
14. da Silva Santana R, Kerr L, Mota R, Kendall C, Rutherford G, McFarland W. Lifetime syphilis prevalence and associated risk factors among female prisoners in Brazil. Sexual Trans Dis 2019 Dec 18;47(2):105-110 [FREE Full text] [doi: 10.1097/olq.0000000000001113]
15. Cavalcante P, Pereira RDL, Castro J. Syphilis in pregnancy and congenital syphilis in Palmas, Tocantins State, Brazil, 2007-2014. Epidemiol Serv Saude 2017;26(2):255-264 [FREE Full text] [doi: 10.5123/S1679-49742017000200003] [Medline: 28492767]
16. Soares M, Aquino R. Completude e caracterização dos registros de sífilis gestacional e congênita na Bahia, 2007-2017. Epidemiol Serv Saúde 2021;30(4):e20201148 [FREE Full text] [doi: 10.1590/s1679-49742021000400018]
17. Amorim E, Matozinhos F, Araújo L, Silva T. Tendência dos casos de sífilis gestacional e congênita em Minas Gerais, 2009-2019: um estudo ecológico. Epidemiol Serv Saúde 2021;30(4):e2021128 [FREE Full text] [doi: 10.1590/s1679-49742021000400006]
18. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015 Jan 02;350(jan02 1):g7647-g7647 [FREE Full text] [doi: 10.1136/bmj.g7647] [Medline: 25555855]
19. Kitayama E, Segura E, Lake J, Perez-Brumer A, Oldenburg C, Myers B, et al. Syphilis in the Americas: a protocol for a systematic review of syphilis prevalence and incidence in four high-risk groups, 1980-2016. Syst Rev 2017 Oct 10;6(1):195 [FREE Full text] [doi: 10.1186/s13643-017-0595-3] [Medline: 29017552]
20. Kebede KM, Abateneh D, Belay A, Manaye G. The epidemiology of syphilis in Ethiopia: a protocol for systematic review and meta-analysis covering the last three decades. Syst Rev 2019 Aug 22;8(1):210 [FREE Full text] [doi: 10.1186/s13643-019-1136-z] [Medline: 31439009]
21. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa Hospital Research Institute. URL: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp [accessed 2023-12-12]
22. Iorio A, Spencer FA, Falavigna M, Alba C, Lang E, Burnand B, et al. Use of GRADE for assessment of evidence about prognosis: rating confidence in estimates of event rates in broad categories of patients. BMJ 2015 Mar 16;350(mar16 7):h870-h870 [FREE Full text] [doi: 10.1136/bmj.h870] [Medline: 25775931]
23. Atkins D, Best D, Briss P, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. BMJ 2004 Jun 19;328(7454):1490 [FREE Full text] [doi: 10.1136/bmj.328.7454.1490] [Medline: 15205295]
24. Hsu L, Field R. Interrater Agreement Measures: Comments on Kappa, Cohen's Kappa, Scott's π, and Aickin's α. Understanding Statistics 2003;2(3):205-219 [FREE Full text] [doi: 10.1207/s15328031us0203_03]
25. Spineli LM, Pandis N. Meta-analysis: random-effects model. Am J Orthod Dentofacial Orthop 2020;157(2):280-282 [FREE Full text] [doi: 10.1016/j.ajodo.2019.10.007] [Medline: 32005481]

26. Mansfield KE, Sim J, Jordan J, Jordan K. A systematic review and meta-analysis of the prevalence of chronic widespread pain in the general population. Pain 2016;157(1):55-64 [FREE Full text] [doi: 10.1097/j.pain.0000000000000314] [Medline: 26270591]
27. Cochran WG. The combination of estimates from different experiments. Biometrics 1954;10:101 [FREE Full text] [doi: 10.2307/3001666]
28. Higgins JPT, Thompson S. Quantifying heterogeneity in a meta-analysis. Stat Med 2002 Jun 15;21(11):1539-1558 [FREE Full text] [doi: 10.1002/sim.1186] [Medline: 12111919]
29. Torres RG, Mendonça ALN, Montes G, Manzan J, Ribeiro J, Paschoini M. Syphilis in pregnancy: the reality in a public hospital. Rev Bras Ginecol Obstet 2019 Feb;41(2):90-96 [FREE Full text] [doi: 10.1055/s-0038-1676569] [Medline: 30786305]

Abbreviations

GRADE: Grading of Recommendations, Assessment, Development, and Evaluations
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols

Edited by A Mavragani; submitted 10.07.23; peer-reviewed by C Shah; comments to author 11.10.23; revised version received 13.10.23; accepted 14.10.23; published 04.01.24.

Please cite as:
Pinheiro YT, Dantas JDC, Holanda JRR, Feitosa ADNA, Augusto Rosendo da Silva R
Epidemiology of Syphilis in Pregnancy and Congenital Syphilis in Brazil and the Risk or Associated Factors: Protocol for a Systematic Review
JMIR Res Protoc 2024;13:e50702
URL: https://www.researchprotocols.org/2024/1/e50702
doi:10.2196/50702
PMID:38175689

Protocol

Blockchain-Based Dynamic Consent and its Applications for Patient-Centric Research and Health Information Sharing: Protocol for an Integrative Review

Wendy M Charles[1,2], PhD; Mark B van der Waal[3,4], PhD; Joost Flach[3], PhD; Arno Bisschop[3], MD, PhD; Raymond X van der Waal[3], MSc; Hadil Es-Sbai[3], MSc; Christopher J McLeod[5], MBChB, PhD

[1]Health Administration Program, Business School, University of Colorado, Denver, Denver, CO, United States

[2]Healthcare Informatics Program, University of Denver, Denver, CO, United States

[3]Triall, Maarssen, Netherlands

[4]Athena Institute, Vrije Universiteit Amsterdam, Amsterdam, Netherlands

[5]Department of Cardiovascular Medicine, Mayo Clinic, Jacksonville, FL, United States

Corresponding Author:
Wendy M Charles, PhD
Health Administration Program
Business School
University of Colorado, Denver
1475 Lawrence Street
Denver, CO, 80202
United States
Phone: 1 303 250 1148
Email: wendy.charles@cuanschutz.edu

Abstract

Background: Blockchain has been proposed as a critical technology to facilitate more patient-centric research and health information sharing. For instance, it can be applied to coordinate and document dynamic informed consent, a procedure that allows individuals to continuously review and renew their consent to the collection, use, or sharing of their private health information. Such has been suggested to facilitate ethical, compliant longitudinal research, and patient engagement. However, blockchain-based dynamic consent is a relatively new concept, and it is not yet clear how well the suggested implementations will work in practice. Efforts to critically evaluate implementations in health research contexts are limited.

Objective: The objective of this protocol is to guide the identification and critical appraisal of implementations of blockchain-based dynamic consent in health research contexts, thereby facilitating the development of best practices for future research, innovation, and implementation.

Methods: The protocol describes methods for an integrative review to allow evaluation of a broad range of quantitative and qualitative research designs. The PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) framework guided the review's structure and nature of reporting findings. We developed search strategies and syntax with the help of an academic librarian. Multiple databases were selected to identify pertinent academic literature (CINAHL, Embase, Ovid MEDLINE, PubMed, Scopus, and Web of Science) and gray literature (Electronic Theses Online Service, ProQuest Dissertations and Theses, Open Access Theses and Dissertations, and Google Scholar) for a comprehensive picture of the field's progress. Eligibility criteria were defined based on PROSPERO (International Prospective Register of Systematic Reviews) requirements and a criteria framework for technology readiness. A total of 2 reviewers will independently review and extract data, while a third reviewer will adjudicate discrepancies. Quality appraisal of articles and discussed implementations will proceed based on the validated Mixed Method Appraisal Tool, and themes will be identified through thematic data synthesis.

Results: Literature searches were conducted, and after duplicates were removed, 492 articles were eligible for screening. Title and abstract screening allowed the removal of 312 articles, leaving 180 eligible articles for full-text review against inclusion criteria and confirming a sufficient body of literature for project feasibility. Results will synthesize the quality of evidence on blockchain-based dynamic consent for patient-centric research and health information sharing, covering effectiveness, efficiency, satisfaction, regulatory compliance, and methods of managing identity.

Conclusions: The review will provide a comprehensive picture of the progress of emerging blockchain-based dynamic consent technologies and the rigor with which implementations are approached. Resulting insights are expected to inform best practices for future research, innovation, and implementation to benefit patient-centric research and health information sharing.

Trial Registration: PROSPERO CRD42023396983; http://tinyurl.com/cn8a5x7t

International Registered Report Identifier (IRRID): DERR1-10.2196/50339

(JMIR Res Protoc 2024;13:e50339) doi:10.2196/50339

KEYWORDS

best practices; blockchain; clinical trial; data reuse; data sharing; dynamic consent; health care data; integrative research review; scientific rigor; technology implementation

Introduction

Rationale

Blockchain has been proposed as a critical technology to advance patient engagement and facilitate a shift toward improved patient centricity in health research [1]. For instance, in addition to being used as a means to enhance the integrity and transparency of data in clinical trials [2,3], research indicates that it can be applied to coordinate and document dynamic consent for patient-centric health information sharing [4,5] in which patients' needs, wants, and perspectives are optimally considered [6].

Dynamic consent is a procedure that allows patients and research participants to continuously review and renew their consent to use their private health information. Compared to conventional one-time obtainment and documentation of informed consent, dynamic consent strives to give individuals greater control over their data and to ensure their preferences are respected throughout their participation [7,8]. Moreover, dynamic consent can facilitate ongoing engagement for the secondary use of data (ie, for purposes other than the initial purposes for which consent was given). Thus, dynamic consent may open up novel opportunities for ethical and compliant research, data sharing, and longitudinal researcher-patient engagement beyond the scope of the original agreement [9].

Blockchain technology offers functionality and efficiencies that are difficult to achieve with traditional data systems. First, it can be applied to facilitate dynamic consent by establishing a privacy-preserving, universally verifiable, and immutable record of the consent process [9]. The decentralized nature of blockchain ensures that these records cannot be altered by a single party, safeguarding the integrity of the participant's documented consent independent of any 1 system or device. Moreover, blockchain offers means for mathematical and privacy-preserving verification of (consent) records and associated user identities, with no dependence on trusted intermediaries for reliable recordkeeping [10]. Such can be used for decentralized authentication and authorization, bolstering individual autonomy. In addition, using blockchain in dynamic consent can enhance the transparency of the process. Research participants can track how their data are used and can be provided with means to readily revise their consent [11]. The use of dynamic consent can inspire more people to participate in clinical research by fostering trust between participants and researchers [8]. Additionally, dynamic consent allows for continuous engagement and communication with research participants throughout and after a study, registry, or repository participation [12]. Last, blockchain technologies are currently used to automate downstream researcher access to data based on individuals' preferences without the burden and expense of manual curation [9].

While promising, dynamic consent based on blockchain technology is a relatively new concept, and it is unclear how well it functions in real-world health research environments. Although numerous studies and pilot projects have been conducted to describe the potential application of blockchain technology to facilitate dynamic consent capabilities [13-15], it is necessary to critically evaluate the articles' scientific methodology and results. Further, there are few best practices published about implementation methodology for blockchain-based dynamic consent. Moreover, there is a need for critical appraisal of approaches that capitalize on blockchain's abilities to empower individuals in managing their digital data and identities. For example, self-sovereign identity (SSI) seems particularly pertinent for ongoing authentication and authorization in patient-centric research collaborations [16].

Yet, as of December 2022, the authors could not locate any published systematic or scoping review to examine the current state of blockchain-based dynamic consent features and implementations. Additionally, no reviews of blockchain-based dynamic consent are currently registered as "in progress" with PROSPERO (International Prospective Register of Systematic Reviews), the systematic review registry [17]. Therefore, there is a need for a systematic review to capture a wide range of literature to establish the scope and quality of evidence for blockchain-based dynamic consent features and implementations in clinical settings.

Objectives

We aim to conduct a systematic integrative research review to synthesize a wide range of evidence regarding blockchain-based dynamic consent solutions, thereby informing future innovation research and practice in this domain. The goal is to identify blockchain-based dynamic consent implementations, the technology's impact, and potential best practices for research, innovation, and implementation.

Research Questions

The following research questions (RQs) will be used to guide the analysis and critical appraisal:

- RQ1: What are the current implementations of dynamic consent involving blockchain and their objectives for health information sharing and health research? What empirical evidence is provided for these implementations?
- RQ2: What are the risks, challenges, and opportunities of applying blockchain-based dynamic consent for health information sharing and health research?
- RQ3: What are the technical, spatial, and temporal aspects of SSI for different blockchain-based dynamic consent systems for health information sharing and health research?
- RQ4: What are the future research directions for research, innovation, and implementation of blockchain-based dynamic consent systems for health information sharing and health research?

A summary of how RQs are addressed by the various research methods is provided in Table 1.

Table 1. Research questions and methods to address them.

Research questions	Associated research methods
RQ1: What are the current implementations of dynamic consent involving blockchain and their objectives for health information sharing and health research? What empirical evidence is provided for these implementations?	• Include only publication years since 2016 (current), and only Technology Readiness Level 6 or higher (actual implementations). • Use integrative design that considers different sources and varied research methodologies. • Perform systematic data extraction and evaluation on implementations' development status and empirical evidence.
RQ2: What are the risks, challenges, and opportunities of applying blockchain-based dynamic consent for health information sharing and health research?	• Perform systematic data extraction and evaluation on implementations' effectiveness, efficiency, satisfaction, compliance, challenges, and limitations.
RQ3: What are the technical, spatial, and temporal aspects of self-sovereign identity for different blockchain-based dynamic consent systems for health information sharing and health research?	• Perform systematic data extraction and evaluation on implementations' consideration of self-sovereign identity standards and capabilities.
RQ4: What are the future research directions for designing, implementing, and validating blockchain-based dynamic consent systems for health information sharing and health research?	• Systematic data extraction and evaluation of articles' future research suggestions and description of best practices regarding design, implementation, and validation. • Critical appraisal and synthesis of collected data from RQ1-4 into best practices for research and innovation.

Methods

Protocol and Registration

This protocol demonstrates a priori development of the research plan. It was registered at PROSPERO on February 15, 2023 (registration number CRD42023396983) [18], before initiating literature review activities. In addition, a timestamped and immutable cryptographic record of the protocol was generated using blockchain-anchoring technology by Triall (Clinblocks BV), allowing for indisputable and independent verification of the protocol and its exact contents at the registered time.

The PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) checklist [19,20] was referenced to prepare this protocol.

Study Design

The review will accumulate and synthesize the global published literature about blockchain-based dynamic consent, including quantitative, qualitative, and mixed methods research articles. We will use integrative research review methodology for a comprehensive review of diverse literature [21]. Specifically, integrative reviews aim to provide a comprehensive and holistic understanding of a particular phenomenon or problem by synthesizing evidence from diverse research methodologies. For example, an integrative review may include case studies, observational studies, mixed methods, and qualitative methods that inform theory. By synthesizing a combination of diverse research methodologies, an integrative review allows researchers to develop new theories or models as well as identify gaps in the literature that need to be addressed by future research [22,23]. We plan to identify literature gaps and suggest methods for strengthening future research designs accordingly [24]. By critically appraising current implementations of blockchain-based dynamic consent, we also plan to inform best practices for future innovation and implementation.

To ensure precision, we will adopt the following definitions:

A blockchain is a decentralized, distributed ledger that records information about transactions or activities across a network of computers. Blocks consist of interconnected, encrypted groups of records [25].

Dynamic consent is a method of electronic consent that is flexible, configurable, and can honor an individual's consent preferences across a spectrum of choices over time [7,8].

The protocol is organized to use the integrative review methodology proposed by Whittemore and Knafl [21] and augmented by the PRISMA-P checklist [19,20].

Problem Identification

To progress with blockchain-based dynamic consent, it is critical to advance high-quality research and establish guidance for innovation and implementation. However, most papers to date

have concentrated on theoretical applications and proofs of concept. Despite the acknowledged requirement for high-quality data and scientific rigor [26], evidence collection has received little attention.

Literature Search

The integrative review will focus on published articles about blockchain-based dynamic consent. Databases selected to search the indexed peer-reviewed academic literature include CINAHL, Embase, Ovid MEDLINE, PubMed, Scopus, and Web of Science (all databases). Gray literature (which is described in various ways but typically includes nearly everything not published in a peer-reviewed journal [27]) will be included in the literature review because a significant portion of relevant research and innovation in this fast-moving field takes place outside of academia. Further, gray literature allows for a more comprehensive assessment of the field's progress [28]. While gray literature can be captured in some of the indices listed above, additional search engines selected to identify gray literature include Electronic Theses Online Service, ProQuest Dissertations and Theses, Open Access Theses and Dissertations, and Google Scholar.

Eligibility Criteria

Eligibility criteria reflect PROSPERO questions and requirements [29]. Not all PROSPERO data fields are pertinent for this integrative review. The eligibility criteria are summarized and presented in Textbox 1.

Textbox 1. Article inclusion and exclusion eligibility criteria.

Inclusion criteria

- Original research articles (architecture, system designs, framework, scheme, model, platform, approach, protocols, test results, and algorithms)
- Any type of research methodology, including quantitative, qualitative, mixed methods, and descriptive narratives
- Describes an actual blockchain-based dynamic consent system (technology readiness level 6 or higher)
- Solutions are implemented in, or intended for, human health-oriented care or research contexts
- Publication years since 2016
- English language articles

Additional sources of gray literature for inclusion criteria

- Scientific or government reports
- Books and book chapters
- Conference papers or proceedings
- Theses

Exclusion criteria

- Review articles that summarize a body of existing literature (although review articles will be examined to perform backward literature tracking)
- Abstracts only
- Letters to the Editor
- Non-English articles
- Secondary research where an author describes work from another publication
- Articles discussing only proposed, potential, or theoretical applications of blockchain-based dynamic consent
- Articles unrelated to the topic

Additional sources of gray literature for exclusion criteria

- Magazine publications
- Interviews
- White papers
- Patents
- Preprints self-posted by the author

Types of Articles to Be Included

Inclusion and exclusion criteria reflect academic and gray literature sources to capture a vast body of literature for the integrative review. These criteria are deliberately broad because few empirical studies are available for inclusion. Therefore, we will include quantitative, qualitative, mixed methods, and descriptive articles from various sources. Further, review articles are included to permit backward citation tracking. A population,

intervention, control, and outcomes format was used to guide the article selection criteria as follows.

Participants and Population

Articles must feature participants who would use a blockchain-based dynamic consent solution. Populations may include—but are not limited to—patients, research participants, providers, staff members, and research administrators. Some studies may not assess the actual users.

Interventions and Exposures

Rather than a health intervention, participant exposure involves interaction with a dynamic consent solution. The blockchain-based dynamic consent solution must demonstrate sufficient development progress for evaluation. We evaluated the technology described in each article using a modified Technology Readiness Level (TRL) framework that includes technology descriptions from both the US Government Accountability Office [30] and the US Department of Defense [31]. TRL frameworks provide guidelines about the nature of evidence and progress expected for each level of technology development on a scale of 1 (idea formulation and review of scientific literature) to 9 (ready for full-scale production and commercialization). Government Accountability Office guidelines allow consideration and early negotiation with vendors whose products meet the criteria of TRL 6 (representative model or prototype in a relevant environment) or higher. Therefore, for this integrative review, descriptions of dynamic consent solutions must meet the criteria for TRL 6 or higher for inclusion. Our preliminary examination of the full-text articles has confirmed a sufficient body of literature with blockchain-based dynamic consent products at and above this threshold.

Comparators and Control

While we would like to capture comparisons of blockchain-based systems to other comparator systems, we are unaware of any published head-to-head comparisons. Therefore, we included studies without comparators if they meet all other eligibility criteria.

Context

The studies must apply to a health research context, which is, they must describe intended or actual application to the sharing and use of health information for research purposes. Publication years must be 2016 or later to capture the modern implementations of blockchain in this context.

Main Outcome

The review is intended to capture evidence of progress with blockchain, and dynamic consent technology related to health research. Several components will be collected about the implementation or commercialization stage, effectiveness, efficiency, satisfaction, regulatory compliance, and methods of managing identity.

Search Terms

The search strategies were determined through team discussion and were reviewed by an experienced academic librarian at the University of Colorado Denver Auraria Library.

The blockchain-based dynamic consent search strategy includes 2 primary blocks of search terms: “blockchain” and “dynamic consent” within a health care or health research setting. The blocks of terms include synonyms and related concepts, such as using the search term “distributed ledger” for “blockchain.”

Because exact terms, such as “dynamic consent,” may not be used in the desired articles, a list of synonyms was generated for “dynamic,” including: “progressive,” “personalized,” “customized,” “interactive,” “modify,” “modifiable,” “revocation,” “revocable,” and “revoking.” These synonyms will be searched within the proximity of other pertinent terms. For example, we propose using synonyms of “dynamic” within 5 words of terms representing “consent” as a verb or noun, including: “consent,” “permission,” “grant,” “authorize,” “authorization,” “allow,” “agree,” and “agreement.”

Search strategies used character substitutions, such as “decentrali?ed,” to capture American and British English spelling variations (eg, decentralized and decentralised, respectively). Further, word truncations were used to capture related word endings, such as “consent*,” to capture “consent,” “consents,” and “consenting.” The search strategy was customized for each index or database’s unique syntax and capabilities. The complete search terms and syntax are presented for a sample MEDLINE search in Multimedia Appendix 1.

Additional scientific articles were identified using manual backward and forward citation tracking of review articles obtained during the search. Backward citation tracking, also referred to as “backward chaining,” “footnote chasing,” and “reference list searching,” is an umbrella term for finding articles directly or indirectly from the reference section of articles being reviewed [28]. Forward citation tracking, also called “forward chaining,” aims to identify additional literature among the articles that cite one of the selected articles [32]. These additional abstracts were obtained and reviewed for inclusion.

Several gray literature articles were incidentally identified using the search process described above. Theses and dissertations were identified with iterations of the search terms to augment the gray literature search process. Google Scholar was searched using the advanced search screen and Boolean operators. Forward citation tracking was facilitated by clicking the “cited by” option.

Article Selection and Screening

Search results were imported and deduplicated using Covidence Systematic Review Management software (Veritas Health Innovation Ltd). A total of 2 reviewers (WMC and MBW) independently reviewed titles and abstracts (and keywords, when applicable) to determine potential eligibility for inclusion in the review. Any abstracts considered too ambiguous or where reviewers disagreed were resolved by a third reviewer (JF) or by examining the full text.

To facilitate full-text review and abstraction, Covidence automatically imported the open-access articles, and the remaining articles were manually imported. The articles selected for abstraction were also imported into EndNote (version X9; Clarivate) citation management software to facilitate manuscript preparation.

Full-Text Review

A total of 2 reviewers (WMC and MBW) will independently review the publications to verify that eligibility criteria are met. While the articles do not specify a TRL level, the reviewers will attempt to discern whether the blockchain-based dynamic consent technologies described in the articles meet the criteria for TRL 6 or higher. Any reviewer disagreement will be resolved by a third reviewer (JF) or by discussions between reviewers.

Data Extraction and Evaluation

Although integrative reviews do not typically include a quality appraisal, we have elected to use the validated Mixed Method Appraisal Tool (MMAT) [33] to capture data on the studies' quality. This aligns with established guidelines for organizing and synthesizing a wide range of literature [22,23]. Moreover, we recognize that there is an increased risk of bias in articles where the authors describe their own products with the goal of future commercialization. The MMAT is brief (only 5 yes or no questions per article) and is designed to assess the methodological strength of studies with diverse designs, consistent with an integrative review. Questions pertain to methodological quality, interpretations, and risks of bias. This tool has been assessed and updated for reliability [34] and content validity [35]. A total of 2 reviewers (WMC and MBW) will independently address the MMAT quality appraisal questions of the eligible literature and will extract all pertinent information from each article. A third reviewer (JF) will integrate the reviews from the 2 reviewers or request collaborative discussions among all reviewers.

The remaining data extraction questions were developed by WMC and MBW and refined by the other team members. Questions were programed into Covidence and tracked with an audit trail. Key information planned for extraction includes: (1) article characteristics: author or authors, year of publication, title, and journal; (2) context and setting for actual or intended blockchain-based dynamic consent implementation: country of intended implementation, setting of implementations (eg, hospital, clinic, or research organization), and intended users; (3) details about blockchain-based dynamic consent solution: name given to the technology (if any), stated purposes or objectives of the product, blockchain platform used (if specified), capabilities of integrations with other data sources, maturity of the technology, stated compliance with regulations, SSI capabilities; (4) evidence about the blockchain-based dynamic consent solution: comparisons with other technologies, evaluation with patients or research participants, nature, and scope of evidence presented; and (5) additional questions about scientific integrity and future research: descriptions of challenges and limitations, whether evidence is presented objectively, descriptions of best practices, and recommendations for future research.

Data Synthesis

Categorical data will be summarized by the percentage of articles or blockchain-based dynamic consent products by category.

Information pertaining to the research questions will be organized using qualitative summary narratives—comparing and contrasting blockchain-based dynamic consent approaches [36]. If necessary, a coding manual will be developed to increase the consistency of coding categorization and the synthesis of subthemes [37,38]. The interpretations will consider article quality, representativeness, and bias or objectivity [36].

Results

Article Selection and Screening

Using the search strategies and databases described above, 637 articles were identified. A total of 145 duplicates were removed, resulting in 492 articles eligible for preliminary screening. Title and abstract screening removed 312 articles. A total of 180 articles are available for full-text review against inclusion criteria, confirming a sufficient body of literature for project feasibility.

Presentation

The review will present data as a narrative, supported by tables and graphs to display the characteristics of included articles and implementations of blockchain-based dynamic consent. The structure of the narrative synthesis will reflect the objective and research questions. The flow of information through the review phases will be generated by Covidence and displayed as a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 flow diagram [39].

Discussion

Key Findings

While the results will not be known until we complete the integrative review, we plan to interpret the findings and their implications in the context of the 4 research questions. In discussing findings and implications, we will refer to the subthemes synthesized by evaluating data extracted from the articles.

Potential Impact of the Review

Individual patients and research participants are increasingly given more rights to control the uses of their data through privacy regulations [40-42] and health information interoperability requirements [43,44]. In addition, patient-centric research initiatives are considered by industry, academia, and regulatory stakeholders globally as a promising means to overcome clinical research and development delays, inefficiencies, and high failure rates [45]. Therefore, technologies that facilitate patient-centricity, such as blockchain-based dynamic consent, are increasingly relevant for health care and health research organizations. It underscores the importance of rigorously reviewing these technologies and their impact, elevating scientific rigor, and establishing best practices for research, innovation, and implementation.

Elucidating Technology Benefits

Extant studies that suggest blockchain-based technologies for health care settings typically involve prototypes, proof-of-concept technologies, or minimum viable products, where nearly all purported results are theoretical [46]. This protocol and subsequent integrative review publication highlight

the relevance and methods for evaluating technology readiness and empirical evidence. Similarly, some studies promote blockchain products and possible benefits but do not explain how products are designed to address specific problems. For example, Durneva et al [47] performed a systematic review of blockchain-based systems for health care and examined how well-proposed solutions aligned with organizational goals. In their review, the authors noted that only 10% (7/70) of products were designed to reduce inefficiencies. As organizations publish more literature about these technology developments, this protocol provides methodology that facilitates critical appraisal of studies and presented evidence.

With the recognition that it is necessary to manage users' identities for a digital consent solution used over time [48]—and possibly across multiple devices—we believe this literature review will also shed light on the identity management features that blockchain could underpin.

Elevating Scientific Rigor

This work can inform and improve future research designs on blockchain-based dynamic consent. In 2019, Treiblmaier [26] noted that the quality of blockchain research was lagging, and he offered guidelines for designing and publishing case studies to improve evidence quality. Years later, authors still emphasize that blockchain research must have more scientific rigor for the work to be respected [49-51]. When addressing blockchain-based dynamic consent literature quality, we will offer deeper insight into gaps, weaknesses, and ways to address these.

Offering Best Practices

This integrative review is expected to identify optimal approaches to implementing and evaluating the effectiveness of blockchain-based dynamic consent technologies. While blockchain products are being developed for health research environments, few implementation models exist [52]. Additionally, few articles describe their products' limitations or weaknesses, contributing to narrow and unrealistic perspectives [53]. Based on the data, we plan to discuss how blockchain-based dynamic consent solutions must be designed to address specific issues in health information sharing and health research. This review will aggregate all information from the articles about strengths and weaknesses—plus draw from our real-world experience—to offer best practices for blockchain technology implementation in this domain. To enhance understanding and practical relevance, we intend to discuss these best practices in an exemplary implementation case, for example, blockchain-based dynamic consent for collecting and exchanging health information and managing informed consent across research centers in the context of longitudinal cardiovascular research projects with extensive and diverse participant cohorts.

Limitations

This integrative research review has several limitations. First, we acknowledge that this is a relatively new area of research and innovation. As a result, the literature base is still relatively small and may not facilitate a comprehensive understanding of the technology and its potential applications. Another limitation is that many published studies on blockchain-based dynamic consent describe early stages of development rather than being based on real-world implementations [14]. This means that they may not reflect the challenges and limitations encountered in practical applications of the technology. Last, some published studies on blockchain-based dynamic consent may be based on small-scale or pilot projects, which may not represent how the technology would perform in a larger, more complex health research setting [47]. To mitigate these limitations, we have conducted a preliminary full-text examination of eligible articles to confirm a sufficient body of literature on implementations at a sufficiently progressed technology readiness level (ie, TRL 6 or higher). The quality of studies and their focal implementations will be appraised systematically using the MMAT. Besides, the early stages of this research arguably increase the relevance of critically evaluating current approaches and synthesizing best practices for future research, innovation, and implementation.

Conclusions

The review will provide a comprehensive picture of the progress of emerging blockchain-based dynamic consent technologies and the rigor with which implementations are approached. Resulting insights are expected to inform best practices for future research, innovation, and implementation to benefit patient-centric research and health information sharing.

Acknowledgments

The authors gratefully acknowledge the support and assistance of Geoff Johnson at the University of Colorado Denver Auraria Library for assisting with the literature search strategies and syntax.

Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PubMed Search Syntax.
[DOCX File , 15 KB - resprot_v13i1e50339_app1.docx]

References

1. Hang L, Chen C, Zhang L, Yang J. Blockchain for applications of clinical trials: taxonomy, challenges, and future directions. IET Comms 2022;16(20):2371-2393 [FREE Full text] [doi: 10.1049/cmu2.12488]
2. Benchoufi M, Altman D, Ravaud P. From clinical trials to highly trustable clinical trials: blockchain in clinical trials, a game changer for improving transparency? Front. Blockchain 2019;2:23 [FREE Full text] [doi: 10.3389/fbloc.2019.00023]
3. Charles W, editor. Blockchain in Life Sciences. Singapore: Springer Nature; 2022.
4. Qu Y, Chen S, Gao L, Cui L, Sood K, Yu S. Personalized privacy-preserving medical data sharing for blockchain-based smart healthcare networks. 2022 Presented at: ICC 2022 - IEEE International Conference on Communications; May 16-20, 2022; Seoul, South Korea URL: https://ieeexplore.ieee.org/abstract/document/9839288/ [doi: 10.1109/icc45855.2022.9839288]
5. Wang L, Jiang Z, Wang Y. Data sharing method for heterogeneous medical and health databases with blockchain technology. Int J Eng Innov Manag 2020;10(1):8-13 [FREE Full text]
6. Yeoman G, Furlong P, Seres M, Binder H, Chung H, Garzya V, et al. Defining patient centricity with patients for patients and caregivers: a collaborative endeavour. BMJ Innov 2017;3(2):76-83 [FREE Full text] [doi: 10.1136/bmjinnov-2016-000157] [Medline: 28890797]
7. Budin-Ljøsne I, Teare HJA, Kaye J, Beck S, Bentzen HB, Caenazzo L, et al. Dynamic consent: a potential solution to some of the challenges of modern biomedical research. BMC Med Ethics 2017;18(1):4 [FREE Full text] [doi: 10.1186/s12910-016-0162-9] [Medline: 28122615]
8. Kaye J, Whitley EA, Lund D, Morrison M, Teare H, Melham K. Dynamic consent: a patient interface for twenty-first century research networks. Eur J Hum Genet 2015;23(2):141-146 [FREE Full text] [doi: 10.1038/ejhg.2014.71] [Medline: 24801761]
9. Charles WM. Accelerating life sciences research with blockchain. In: Namasudra S, Deka GC, editors. Applications of Blockchain in Healthcare. Singapore: Springer Nature; 2021:221-252.
10. Huh KY, Jeong SU, Moon SJ, Kim MJ, Yang W, Jeong M, et al. METORY: development of a demand-driven blockchain-based dynamic consent platform tailored for clinical trials. Front Med (Lausanne) 2022;9:837197 [FREE Full text] [doi: 10.3389/fmed.2022.837197] [Medline: 35646983]
11. Leon-Sanz P. Key points for an ethical evaluation of healthcare big data. Processes 2019;7(8):493 [FREE Full text] [doi: 10.3390/pr7080493]
12. Silva P, Dahlke DV, Smith ML, Charles W, Gomez J, Ory MG, et al. An idealized clinicogenomic registry to engage underrepresented populations using innovative technology. J Pers Med 2022;12(5):713 [FREE Full text] [doi: 10.3390/jpm12050713] [Medline: 35629136]
13. Albalwy F, Brass A, Davies A. A blockchain-based dynamic consent architecture to support clinical genomic data sharing (ConsentChain): proof-of-concept study. JMIR Med Inform 2021;9(11):e27816 [FREE Full text] [doi: 10.2196/27816] [Medline: 34730538]
14. Mamo N, Martin GM, Desira M, Ellul B, Ebejer JP. Dwarna: a blockchain solution for dynamic consent in biobanking. Eur J Hum Genet 2020;28(5):609-626 [FREE Full text] [doi: 10.1038/s41431-019-0560-9] [Medline: 31844175]
15. Shah M, Li C, Sheng M, Zhang Y, Xing C. CrowdMed: a blockchain-based approach to consent management for health data sharing. 2019 Presented at: Smart Health: International Conference, ICSH 2019; July 1–2, 2019; Shenzhen, China p. 345-356 URL: https://link.springer.com/chapter/10.1007/978-3-030-34482-5_31 [doi: 10.1007/978-3-030-34482-5_31]
16. Satybaldy A, Subedi A, Nowostawski M. A framework for online document verification using self-sovereign identity technology. Sensors (Basel) 2022;22(21):8408 [FREE Full text] [doi: 10.3390/s22218408] [Medline: 36366105]
17. PROSPERO. National Institute for Health Research.: University of York; 2023. URL: https://www.crd.york.ac.uk/prospero/ [accessed 2023-01-01]
18. Charles W, van der Waal M, Flach J. The emergence of blockchain-based dynamic consent in health information sharing and health research: an integrative review and instructions for future research and innovation. National Institute for Health Research. 2023. URL: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023396983 [accessed 2023-12-21]
19. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4(1):1 [FREE Full text] [doi: 10.1186/2046-4053-4-1] [Medline: 25554246]
20. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015;350:g7647 [FREE Full text] [doi: 10.1136/bmj.g7647] [Medline: 25555855]
21. Whittemore R, Knafl K. The integrative review: updated methodology. J Adv Nurs 2005;52(5):546-553 [FREE Full text] [doi: 10.1111/j.1365-2648.2005.03621.x] [Medline: 16268861]
22. Toronto CE, Remington R, editors. A Step-by-Step Guide to Conducting an Integrative Review. Cham, Switzerland: Springer International Publishing; 2020.
23. Torraco RJ. Writing integrative reviews of the literature: methods and purposes. Int J Adult Vocat Ed 2016;7(3):62-70. [doi: 10.4018/ijavet.2016070106]

24. Tricco AC, Antony J, Soobiah C, Kastner M, Cogo E, MacDonald H, et al. Knowledge synthesis methods for generating or refining theory: a scoping review reveals that little guidance is available. J Clin Epidemiol 2016;73:36-42 [FREE Full text] [doi: 10.1016/j.jclinepi.2015.11.021] [Medline: 26891951]
25. Yaga D, Mell P, Roby N, Scarfone K. Blockchain technology overview. National Institute of Standards and Technology. 2018. URL: https://doi.org/10.6028/NIST.IR.8202 [accessed 2019-03-03]
26. Treiblmaier H. Toward more rigorous blockchain research: recommendations for writing blockchain case studies. Front Blockchain 2019;2(3):1-15. [doi: 10.3389/fbloc.2019.00003]
27. Rothstein H, Hopewell S. In: Cooper H, Hedges LV, Valentine JC, editors. The Handbook of Research Synthesis and Meta-Analysis, 2nd Edition. New York: Russell Sage Foundation; 2009:103-125.
28. Hirt J, Nordhausen T, Appenzeller-Herzog C, Ewald H. Using citation tracking for systematic literature searching - study protocol for a scoping review of methodological studies and a delphi study. F1000Res 2020;9:1386 [FREE Full text] [doi: 10.12688/f1000research.27337.3] [Medline: 34631036]
29. PROSPERO: registration record details. National Institute for Health Research.: University of York; 2023. URL: https://www.crd.york.ac.uk/prospero/#aboutpage [accessed 2023-01-01]
30. Persons TM, Mackin M. Technology readiness assessment guide: best practices for evaluating the readiness of technology for use in acquisition programs and projects. U.S. Government Accountability Office. 2020. URL: https://www.gao.gov/assets/gao-20-48g.pdf [accessed 2023-03-18]
31. National Research Council, Institute of Medicine, Board on Life Sciences, Board on Health Sciences Policy. In: Hook-Barnard I, Alper J, Norris SMP, editors. Technologies to Enable Autonomous Detection for BioWatch: Ensuring Timely and Accurate Information for Public Health Officials: Workshop Summary. Washington, D.C: The National Academies Press; 2014:141-144.
32. Cribbin TF. Augmenting citation chain aggregation with article maps. 2014 Presented at: CEUR Workshop Proceedings, First Workshop on Knowledge Maps and Information Retrieval (KMIR 2014); September 11, 2014; London, UK p. 31-39 URL: https://bura.brunel.ac.uk/handle/2438/9989
33. Pluye P, Hong QN. Combining the power of stories and the power of numbers: mixed methods research and mixed studies reviews. Annu Rev Public Health 2014;35(1):29-45 [FREE Full text] [doi: 10.1146/annurev-publhealth-032013-182440] [Medline: 24188053]
34. Souto RQ, Khanassov V, Hong QN, Bush PL, Vedel I, Pluye P. Systematic mixed studies reviews: updating results on the reliability and efficiency of the mixed methods appraisal tool. Int J Nurs Stud 2015;52(1):500-501 [FREE Full text] [doi: 10.1016/j.ijnurstu.2014.08.010] [Medline: 25241931]
35. Hong QN, Pluye P, Fàbregues S, Bartlett G, Boardman F, Cargo M, et al. Improving the content validity of the mixed methods appraisal tool: a modified e-delphi study. J Clin Epidemiol 2019;111:49-59.e1 [FREE Full text] [doi: 10.1016/j.jclinepi.2019.03.008] [Medline: 30905698]
36. Miles MB, Huberman AM, Saldana J. Qualitative Data Analysis: A Methods Sourcebook. 3rd Edition. Thousand Oaks, Californinia: SAGE Publications, Inc; 2014.
37. Saldana J. The Coding Manual for Qualitative Researchers. London: SAGE Publications Ltd; 2009.
38. Thomas J, Harden A. Methods for the thematic synthesis of qualitative research in systematic reviews. BMC Med Res Methodol 2008;8(1):45 [FREE Full text] [doi: 10.1186/1471-2288-8-45] [Medline: 18616818]
39. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. PLoS Med 2021;18(3):e1003583 [FREE Full text] [doi: 10.1371/journal.pmed.1003583] [Medline: 33780438]
40. Children's online privacy protection rule: a six-step compliance plan for your business. Federal Trade Commission. 2019. URL: https://www.ftc.gov/tips-advice/business-center/guidance/childrens-online-privacy-protection-rule-six-step-compliance [accessed 2019-06-03]
41. California Consumer Privacy Act (CCPA). State of California Department of Justice Office of the Attorney General. 2018. URL: https://oag.ca.gov/privacy/ccpa [accessed 2023-12-22]
42. European Parliament and the Council of the European Union. General Data Protection Regulation. 2016. URL: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32016R0679 [accessed 2018-05-01]
43. Introduction to the Trusted Exchange Framework and Common Agreement (TEFCA). Office of the National Coordinator for Health Information Technology.: Department of Health and Human Services; 2019. URL: https://www.healthit.gov/sites/default/files/page/2019-04/FINALTEFCAQTF41719508version.pdf [accessed 2019-06-12]
44. Department of Health and Human Services. 21st Century Cures Act: interoperability, information blocking, and the ONC health IT certification program. Fed Regist 2020;85(85):25642-25961 [FREE Full text]
45. Stergiopoulos S, Michaels DL, Kunz BL, Getz KA. Measuring the impact of patient engagement and patient centricity in clinical research and development. Ther Innov Regul Sci 2020;54(1):103-116 [FREE Full text] [doi: 10.1007/s43441-019-00034-0] [Medline: 32008233]
46. Justinia T. Blockchain technologies: opportunities for solving real-world problems in healthcare and biomedical sciences. Acta Inform Med 2019;27(4):284-291 [FREE Full text] [doi: 10.5455/aim.2019.27.284-291] [Medline: 32055097]

47. Durneva P, Cousins K, Chen M. The current state of research, challenges, and future research directions of blockchain technology in patient care: systematic review. J Med Internet Res 2020;22(7):e18619 [FREE Full text] [doi: 10.2196/18619] [Medline: 32706668]
48. Kakarlapudi PV, Mahmoud QH. A systematic review of blockchain for consent management. Healthcare (Basel) 2021;9(2):137 [FREE Full text] [doi: 10.3390/healthcare9020137] [Medline: 33535465]
49. Kölbel T, Dann D, Weinhardt C. Giant or dwarf? A literature review on blockchain-enabled marketplaces in business ecosystems. 2023 Presented at: International Conference on Wirtschaftsinformatik; February 21-23, 2022; Nürnberg, Germany URL: https://aisel.aisnet.org/cgi/viewcontent.cgi?article=1087&context=wi2022
50. Sabbagh P, Pourmohamad R, Elveny M, Beheshti M, Davarpanah A, Metwally ASM, et al. Evaluation and classification risks of implementing blockchain in the drug supply chain with a new hybrid sorting method. Sustainability 2021;13(20):11466 [FREE Full text] [doi: 10.3390/su132011466]
51. Sai AR, Vranken H. Promoting rigor in blockchain energy and environmental footprint research: a systematic literature review. ArXiv 2022 Oct 21;2210:11664 [FREE Full text] [doi: 10.1016/j.bcra.2023.100169]
52. Akbar MA, Leiva V, Rafi S, Qadri SF, Mahmood S, Alsanad A. Towards roadmap to implement blockchain in healthcare systems based on a maturity model. J Software Evolu Process 2022;34(12):e2500 [FREE Full text] [doi: 10.1002/smr.2500]
53. Hughes L, Dwivedi YK, Misra SK, Rana NP, Raghavan V, Akella V. Blockchain research, practice and policy: applications, benefits, limitations, emerging research themes and research agenda. Int J Inf Manag 2019;49:114-129 [FREE Full text] [doi: 10.1016/j.ijinfomgt.2019.02.005]

Abbreviations

MMAT: Mixed Method Appraisal Tool
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PROSPERO: International Prospective Register of Systematic Reviews
RQ: research question
SSI: self-sovereign identity
TRL: Technology Readiness Level

Edited by A Mavragani; submitted 27.06.23; peer-reviewed by F Albalwy, Y Zhuang, G Ertek; comments to author 12.09.23; revised version received 01.12.23; accepted 07.12.23; published 05.02.24.

Please cite as:
Charles WM, van der Waal MB, Flach J, Bisschop A, van der Waal RX, Es-Sbai H, McLeod CJ
Blockchain-Based Dynamic Consent and its Applications for Patient-Centric Research and Health Information Sharing: Protocol for an Integrative Review
JMIR Res Protoc 2024;13:e50339
URL: https://www.researchprotocols.org/2024/1/e50339
doi:10.2196/50339
PMID:38315514

Protocol

The Effectiveness of Digital Health Lifestyle Interventions on People With Prediabetes: Protocol for a Systematic Review, Meta-Analysis, and Meta-Regression

Tanja Fredensborg Holm[1,2], MSc; Flemming Witt Udsen[1], PhD; Kristine Færch[3,4], PhD; Morten Hasselstrøm Jensen[1,3], PhD; Bernt Johan von Scholten[3], DMSc; Ole Kristian Hejlesen[1], PhD; Stine Hangaard[1,2], PhD

[1]Department of Health Science and Technology, Aalborg University, Gistrup, Denmark

[2]Steno Diabetes Center North Jutland, Aalborg University Hospital, Aalborg, Denmark

[3]Data Science, Novo Nordisk A/S, Søborg, Denmark

[4]Clinical Research, Copenhagen University Hospital – Steno Diabetes Center Copenhagen, Herlev, Denmark

Corresponding Author:
Tanja Fredensborg Holm, MSc
Department of Health Science and Technology
Aalborg University
Selma Lagerløfs vej 249
Gistrup, 9260
Denmark
Phone: 45 23459792
Email: tfh@hst.aau.dk

Abstract

Background: There has been an increasing interest in the use of digital health lifestyle interventions for people with prediabetes, as these interventions may offer a scalable approach to preventing type 2 diabetes. Previous systematic reviews on digital health lifestyle interventions for people with prediabetes had limitations, such as a narrow focus on certain types of interventions, a lack of statistical pooling, and no broader subgroup analysis of intervention characteristics. The identified limitations observed in previous systematic reviews substantiate the necessity of conducting a comprehensive review to address these gaps within the field. This will enable a comprehensive understanding of the effectiveness of digital health lifestyle interventions for people with prediabetes.

Objective: The objective of this systematic review, meta-analysis, and meta-regression is to systematically investigate the effectiveness of digital health lifestyle interventions on prediabetes-related outcomes in comparison with any comparator without a digital component among adults with prediabetes.

Methods: This systematic review will include randomized controlled trials that investigate the effectiveness of digital health lifestyle interventions on adults (aged 18 years or older) with prediabetes and compare the digital interventions with nondigital interventions. The primary outcome will be change in body weight (kg). Secondary outcomes include, among others, change in glycemic status, markers of cardiometabolic health, feasibility outcomes, and incidence of type 2 diabetes. Embase, PubMed, CINAHL, and CENTRAL (Cochrane Central Register of Controlled Trials) will be systematically searched. The data items to be extracted include study characteristics, participant characteristics, intervention characteristics, and relevant outcomes. To estimate the overall effect size, a meta-analysis will be conducted using the mean difference. Additionally, if feasible, meta-regression on study, intervention, and participant characteristics will be performed. The Cochrane risk of bias tool will be applied to assess study quality, and the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach will be used to assess the certainty of evidence.

Results: The results are projected to yield an overall estimate of the effectiveness of digital health lifestyle interventions on adults with prediabetes and elucidate the characteristics that contribute to their effectiveness.

Conclusions: The insights gained from this study may help clarify the potential of digital health lifestyle interventions for people with prediabetes and guide the decision-making regarding future intervention components.

Trial Registration: PROSPERO CRD42023426919; http://tinyurl.com/d3enrw9j

International Registered Report Identifier (IRRID): PRR1-10.2196/50340

(JMIR Res Protoc 2024;13:e50340) doi:10.2196/50340

KEYWORDS

digital health; effectiveness; lifestyle intervention; meta-analysis; meta-regression; prediabetic state; systematic review; type 2 diabetes prevention; weight loss

Introduction

Diabetes is a major global health care challenge. In 2021, an estimated 10.5% of the world's population aged between 20 and 79 years had diabetes, and the prevalence is expected to increase to 12.2% by 2045 [1]. Type 2 diabetes (T2D) is the predominant form of diabetes, representing approximately 90% of diabetes cases worldwide, and is one of the most common metabolic disorders [1,2]. T2D results in abnormally high levels of plasma glucose due to insulin resistance and gradual impairment of pancreatic beta-cell function [2,3]. Continuously high levels of plasma glucose can lead to several micro- and macrovascular complications, such as retinopathy, nephropathy, and cardiovascular diseases, increasing the risk of premature mortality, morbidity, and reduced quality of life [2,3]. This poses a major economic burden to the health care system and society [3-5].

The development of T2D is affected by both environmental and genetic factors but living with overweight and having a sedentary lifestyle are prominent risk factors [2,6]. Before the diagnosis of T2D, an intermediate stage of elevated plasma glucose usually exists [7,8]. This intermediate stage, where a person has abnormally high glucose levels but not high enough to be diagnosed with T2D, is called prediabetes [1,9]. Prediabetes is characterized by impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or elevated hemoglobin A_{1c} (HbA_{1c}) levels [9,10]. Depending on the organization, diagnostic test, and cutoff criteria used, different definitions of prediabetes exist, which makes global prevalence estimates challenging and varying [8,11]. According to the International Diabetes Federation, an estimated 10.6% of the global population aged between 20 and 79 years had IGT in 2021 and an estimated 6.2% of adults had IFG, based on the criteria established by the World Health Organization. The global prevalence of IGT and IFG is expected to increase to 11.4% and 6.9%, respectively, by 2045 [1].

Most people with prediabetes are unaware of the condition, as it is frequently asymptomatic [10]. People with prediabetes are at increased risk of developing T2D. Approximately 70% of people with prediabetes will develop T2D during their lifetime and about 25% will progress to T2D within 3-5 years [10,11]. Additionally, elevated plasma glucose in the range of prediabetes leads to an increased risk of developing micro- and macrovascular complications usually associated with T2D [12-14]. Several studies have demonstrated that progression from prediabetes (mainly IGT) to T2D, as well as complications, can be prevented and delayed through intensive lifestyle interventions that focus on diet and physical activity [15-18]. These studies have found that intensive lifestyle interventions reduced the risk of progression to T2D by 28%-58% over a 2.5- to 6-year period [15-18]. Prediabetes thus represents a time of opportunity to prevent or delay progression to T2D, potentially slowing down the increase in the prevalence of people with T2D [10,11,19].

Despite the effect of resource-intensive lifestyle interventions observed in clinical trials, these interventions may not be scalable and accessible in clinical practice because of restricted health care resources [8,20,21]. Digital health interventions have the potential to reduce the resources of intensive lifestyle interventions and thereby make them more scalable and accessible in clinical practice [21-23]. Digital health defines the use of digital technologies in support of health care and includes technologies such as mobile apps, videos, websites, and wearable devices [24,25]. Previous reviews have demonstrated that digital health interventions are effective in reducing body weight among people with overweight or obesity [26,27] and reducing HbA_{1c} among people with diabetes [28-30]. These findings indicate that digital health interventions have the potential to improve various health-related outcomes. However, more research is still required to determine whether digital health lifestyle interventions can effectively improve prediabetes-related outcomes (eg, weight loss and glycemic status) to clarify their potential for people with prediabetes. In addition, an evaluation of characteristics associated with effects on outcomes is crucial to guide the development of future interventions and inform decision-making on intervention components.

Previous systematic reviews have investigated the effect of digital health lifestyle interventions on people with prediabetes [20,21,31-33]. However, the reviews had limitations. They focused on specific types of digital interventions [32], including a relatively small number of data sources [32,33], lacking a meta-analysis [20,21,33], or pooling results from different study designs [31]. Furthermore, previous meta-analyses did not include a broader subgroup analysis exploring the association between intervention characteristics and effects on outcomes [31,32]. As a result, the specific characteristics that are associated with effects on prediabetes-related outcomes remain relatively unknown. Additionally, given the rapid development of digital interventions, several new research papers have likely emerged since the conduct of previous reviews.

The considerations mentioned above indicate the need for an updated and comprehensive systematic review, meta-analysis, and meta-regression in the field to synthesize and evaluate the effectiveness of digital health lifestyle interventions on people with prediabetes.

Methods

Study Design

The conduct and reporting of this review will follow the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [34]. The review process will

be conducted based on this review protocol, which adheres to the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) checklist [35]. The protocol was registered on PROSPERO (International Prospective Register of Systematic Reviews) on July 5, 2023 (CRD42023426919), in accordance with the PRISMA guidelines.

Objective

The objective of this systematic review, meta-analysis, and meta-regression is to systematically investigate the effectiveness of digital health lifestyle interventions on weight loss and other prediabetes-related secondary outcomes in comparison with any comparator without a digital component among adults with prediabetes.

Review Questions

This systematic review, meta-analysis, and meta-regression is guided by the following research questions: What is the effectiveness of digital health lifestyle interventions on weight loss and other prediabetes-related outcomes among adults with prediabetes, and how do variations across study, intervention, and participant characteristics contribute to differences in the observed effect?

Inclusion Criteria

Participants

Studies including adults aged 18 years or older meeting criteria indicative of prediabetes will be considered for inclusion in this systematic review, meta-analysis, and meta-regression. The criteria for meeting prediabetes will be defined by the presence of IFG, IGT, or raised HbA_{1c}. According to the criteria of the American Diabetes Association, IFG is defined as fasting plasma glucose levels between 5.6-6.9 mmol/L, IGT as 2-hour plasma glucose (75-gram oral glucose tolerance test) between 7.8-11.0 mmol/L, and raised HbA_{1c} as HbA_{1c} levels between 39-47 mmol/mol [9].

Studies that are restricted to adults with T2D, type 1 diabetes, or gestational diabetes will be excluded. In addition, studies that investigate the effect of a combined lifestyle and pharmacological intervention will be excluded. Studies that examine combined age groups (eg, adults and adolescents) will also be excluded unless the data for the adult population are reported transparently and separately. Similarly, studies that do not report separate data when considering prediabetes in conjunction with any type of diabetes (eg, T2D) or metabolic syndrome will also be excluded.

Interventions

Studies that examined the effectiveness of digital health lifestyle interventions (diet or physical activity interventions) on adults with prediabetes will be considered for inclusion. These studies may encompass both independent digital solutions and interventions that combine in-person meetings with a digital component. The digital component may include different technologies such as SMS text messaging, smartphone apps, email, automated phone calls, mobile phones, websites, computer-based programs, and video. Studies will be deemed ineligible for inclusion if the intervention does not incorporate a digital component.

Comparators

This systematic review, meta-analysis, and meta-regression will examine studies that compare digital health lifestyle interventions to any comparator without a digital component.

Settings

Studies investigating the effectiveness of digital health lifestyle interventions on adults with prediabetes will be considered without any restrictions on the setting.

Outcomes

Studies that report the effectiveness on relevant outcomes related to prediabetes (eg, weight loss, glycemic status, and incidence of T2D) will be considered in this systematic review, meta-analysis, and meta-regression. The primary outcome will be a change in body weight (kg). Secondary outcomes will include changes in the following variables: (1) glycemic status, (2) body composition, (3) incidence of T2D, (4) markers of cardiometabolic health (eg, blood pressure and lipids), (5) patient-reported outcomes (eg, quality of life), and (6) feasibility outcomes (eg, differential retention rate, adherence, and acceptance).

Study Types

Randomized controlled trials with a parallel design will be eligible for inclusion in the systematic review, meta-analysis, and meta-regression. Additionally, studies will be eligible for inclusion if the researchers assess that the study was conducted using a parallel randomized controlled trial design, regardless of whether the paper itself describes the design using a different terminology. Systematic reviews or meta-analyses will be excluded but inspected for potentially eligible studies. Only full-text studies that have undergone peer review and are available in English, Norwegian, Danish, or Swedish will be included. The present review will not impose any restrictions on the publication year of included studies, as older as well as more recent interventions will be evaluated to offer valuable insights.

Search Strategy

The systematic search will be conducted by the first author (TFH) across various databases with the aim of systematically identifying studies investigating the effectiveness of digital health lifestyle interventions for adults with prediabetes. The following bibliographic databases will be searched: Embase, PubMed, CINAHL, and CENTRAL (Cochrane Central Register of Controlled Trials). Assistance in the performance of the systematic search will be provided by a research librarian experienced in systematic review searching.

To identify search terms of relevance, encompassing controlled vocabulary and keywords, an initial limited search will be conducted in PubMed and Embase. The systematic search will involve the identification and incorporation of related terms and synonyms associated with the identified search terms. Additionally, a series of search functions, such as truncation and phrase search, will be used, and the identified search terms

will be combined using Boolean operators. The systematic search approach will be tailored and adjusted to suit each database included in the study. The complete search strategy for PubMed is presented in the Multimedia Appendix 1. If relevant, for example, in case of inaccessibility of a study or questions during the selection process, the authors of the study in question will be contacted.

Reference search and citation tracking of eligible studies will be performed to identify additional potentially relevant studies. Citation tracking will be conducted in Web of Science and SCOPUS.

A follow-up search will be conducted in each included database before final submission to prevent selection bias and to ensure that all newly published papers are included.

Study Selection

The identified studies will be collected and imported into RefWorks. First, any duplicate studies will be removed in RefWorks. Second, the titles and abstracts of remaining studies will be screened for inclusion against the review eligibility criteria by the first author. Third, the studies that meet eligibility criteria, as well as those where uncertainty persists, will undergo full-text screening. The first author will assess their inclusion against the predetermined eligibility criteria with assistance from a coauthor. In case of any disagreement between the reviewers regarding study selection, the reviewers will engage in discussion to resolve the issue. If necessary, a third coauthor will be involved to reach a consensus. Data extraction, quality assessment, and, if feasible, statistical analysis will be conducted for all eligible studies.

A PRISMA flowchart [34] will be used to demonstrate the screening process for each stage and the results of the systematic search, as depicted in the Multimedia Appendix 2. The PRISMA flowchart will also comprise exclusion reasons of full-text studies.

Risk of Bias Assessment

The Cochrane risk of bias tool will be applied to facilitate the quality assessment of the included studies by the first author with assistance from a coauthor. In case of disagreements, the reviewers will resolve them through discussion, and a third coauthor may be involved if needed. If necessary, for example, if items are missing or unclear for the risk of bias assessment, the authors of the studies in question will be contacted.

Data Extraction

A standardized spreadsheet in Excel (Microsoft Corporation) will be used to extract data from included studies, facilitating data synthesis and analysis while ensuring consistent data extraction. The first author will perform the data extraction with assistance from a coauthor. In case of any disagreement between the reviewers regarding data extraction, the reviewers will engage in discussion to resolve the issue. If necessary, a third coauthor will be involved to reach a consensus.

The data items that will be extracted include the following four categories:

1. Study characteristics, including first author, year of publication, study design, and country.
2. Baseline characteristics of study participants, including sample size of each group, percentage male participants, ethnicity, age, body weight, BMI, HbA_{1c}, and fasting plasma glucose.
3. Outcomes of the study intervention and control group, including primary and/or secondary outcomes when available.
4. Characteristics of the digital health lifestyle intervention, including duration of follow-up, setting, resources used, intervention components, mode of delivery, provider, contact type (eg, face-to-face, fully automated, or remote), and frequency of contact.

Data Synthesis

A statistical meta-analysis will be conducted using Stata (version 17; StataCorp 2021) by pooling data from included studies to estimate the overall effect size of digital health lifestyle interventions on adults with prediabetes. The mean difference between the digital intervention group and the comparator group will be used to present the effect size for continuous data, along with a 95% CI. Primary outcomes presented in other units will be scaled to the same unit if possible (eg, a change in body weight reported as percentage or in pounds will be transformed into kilograms). Standardized mean difference will be used to present the effect size for secondary outcomes presented in different units unless it is possible to scale them to the same unit. Traditional methods will be used to convert results reported as medians and interquartile ranges into means and SDs [36]. For dichotomous data, the effect size will be presented as an odds ratio with a 95% CI. In cases where statistical pooling is impossible, the results will be presented narratively, accompanied by tables and figures where applicable. Feasibility outcomes will also be summarized narratively, eventually supported by tables and figures.

Both qualitative and statistical assessments will be conducted to evaluate the heterogeneity of the included studies. Qualitative assessment will involve comparing the characteristics of the studies, while the I^2 test will be used for statistical analysis. If heterogeneity is present, as determined by an I^2 value of more than 50%, a random-effects model will be used to statistically pool the data. Otherwise, a fixed-effect model will be used. The results of the meta-analysis will be presented in a forest plot. If possible, meta-regression on study characteristics (eg, variations across countries), intervention characteristics (eg, human-to-human interventions vs fully automated interventions), and participant characteristics (eg, gender) will be conducted to uncover common patterns among effective interventions and identify knowledge gaps within the research field. If conducting a meta-regression is impossible due to data limitations, alternative subgroup analyses based on study-, intervention-, and participant characteristics will be performed.

To visually evaluate the potential presence of publication bias, a funnel plot will be created and included in the presentation of the results. If the number of studies included in the meta-analysis is more than 10, a statistical test (Egger test) will be performed to detect funnel plot asymmetry.

Certainty of Evidence Assessment

The certainty of evidence will be assessed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach [37]. The assessment will consider the risk of bias, inconsistency, indirectness, imprecision, and publication bias. Based on these considerations, the evidence will be classified as high, moderate, low, or very low certainty. A summary of findings table will be generated using the web-based software GRADEpro Guideline Development Tool to summarize the strength and reliability of the evidence [38].

Results

The results of this review intend to provide insights into both the overall effectiveness of digital health lifestyle interventions and the characteristics that contribute to their effectiveness. The results will undergo peer review and be submitted for publication.

Discussion

This systematic review, meta-analysis, and meta-regression will review current evidence to address a lack of comprehensive research within the field of digital health lifestyle interventions for people with prediabetes.

As this publication represents a preliminary stage of the systematic review, specific comparisons with key studies are currently lacking. However, the protocol emphasizes conducting a comprehensive review of relevant literature to allow for meaningful comparisons once the results are obtained. Furthermore, the forthcoming discussion aims to assess the applicability of the findings in clinical practice and their potential implications for real-world implementation. Evaluating the resources used in the included interventions may be crucial for this assessment, considering their potential limitations in expanding digital health lifestyle interventions into real-world settings.

The insight gained from this study may help clarify the potential of digital health lifestyle interventions in the management of prediabetes and offer guidance for future development decisions. The planned systematic evidence assessment, using the GRADE methodology, is expected to indirectly inform and guide future recommendations and development decisions for digital health solutions [39]. These recommendations will be enriched by insights obtained from the meta-regression or subgroup analysis. We intend to explore these aspects in the forthcoming discussion.

However, it is crucial to acknowledge the anticipated limitations within this review. Studies investigating digital health interventions are expected to vary in factors such as mode of delivery, intervention type, population, and duration, resulting in notable heterogeneity among the included studies. This diversity might complicate the comparison and statistical pooling of results. Moreover, the upcoming discussion intends to highlight additional limitations and knowledge gaps identified during the review, with the aim of informing and enhancing further work in this field.

Acknowledgments

The authors would like to express their gratitude to research librarian Conni Skrubbeltrang for competent assistance with the search strategy and the literature search. No specific funding will be allocated to support this systematic review, meta-analysis, and meta-regression.

Authors' Contributions

The protocol was drafted by TFH. TFH and SH constructed the search strategy in collaboration with a research librarian experienced in systematic review searching. All authors contributed to the developed eligibility criteria and data extraction strategy. FWU provided statistical expertise. All authors contributed to the final manuscript by reading it, providing feedback, and critically revising it for important intellectual content. The final protocol was approved by all authors.

Conflicts of Interest

KF and BJvS are full-time employees and own shares at Novo Nordisk A/S (joint-stock company). MHJ owns shares at Novo Nordisk A/S. No conflicts of interest were declared by the remaining authors.

Multimedia Appendix 1
Search strategy.
[DOCX File , 17 KB - resprot_v13i1e50340_app1.docx]

Multimedia Appendix 2
Study selection process.
[DOCX File , 59 KB - resprot_v13i1e50340_app2.docx]

References

1. Magliano D, Boyko EJ. IDF Diabetes Atlas, 10th Edition. Brussels: International Diabetes Federation; 2021.

2. Galicia-Garcia U, Benito-Vicente A, Jebari S, Larrea-Sebal A, Siddiqi H, Uribe KB, et al. Pathophysiology of type 2 diabetes mellitus. Int J Mol Sci 2020;21(17):6275 [FREE Full text] [doi: 10.3390/ijms21176275] [Medline: 32872570]
3. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nat Rev Endocrinol 2018;14(2):88-98. [doi: 10.1038/nrendo.2017.151] [Medline: 29219149]
4. Yip WCY, Sequeira IR, Plank LD, Poppitt SD. Prevalence of pre-diabetes across ethnicities: a review of Impaired Fasting Glucose (IFG) and Impaired Glucose Tolerance (IGT) for classification of dysglycaemia. Nutrients 2017 22;9(11):1273 [FREE Full text] [doi: 10.3390/nu9111273] [Medline: 29165385]
5. Ng CS, Lee JYC, Toh MP, Ko Y. Cost-of-illness studies of diabetes mellitus: a systematic review. Diabetes Res Clin Pract 2014;105(2):151-163. [doi: 10.1016/j.diabres.2014.03.020] [Medline: 24814877]
6. Palermo A, Maggi D, Maurizi AR, Pozzilli P, Buzzetti R. Prevention of type 2 diabetes mellitus: is it feasible? Diabetes Metab Res Rev 2014 Mar;30 Suppl 1:4-12. [doi: 10.1002/dmrr.2513] [Medline: 24353270]
7. Faerch K, Borch-Johnsen K, Holst JJ, Vaag A. Pathophysiology and aetiology of impaired fasting glycaemia and impaired glucose tolerance: does it matter for prevention and treatment of type 2 diabetes? Diabetologia 2009;52(9):1714-1723 [FREE Full text] [doi: 10.1007/s00125-009-1443-3] [Medline: 19590846]
8. Echouffo-Tcheugui JB, Selvin E. Prediabetes and what it means: the epidemiological evidence. Annu Rev Public Health 2021;42:59-77 [FREE Full text] [doi: 10.1146/annurev-publhealth-090419-102644] [Medline: 33355476]
9. American Diabetes Association Professional Practice Committee. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2022. Diabetes Care 2022;45(Suppl 1):S17-S38 [FREE Full text] [doi: 10.2337/dc22-S002] [Medline: 34964875]
10. Rett K, Gottwald-Hostalek U. Understanding prediabetes: definition, prevalence, burden and treatment options for an emerging disease. Curr Med Res Opin 2019;35(9):1529-1534. [doi: 10.1080/03007995.2019.1601455] [Medline: 30935247]
11. Hostalek U. Global epidemiology of prediabetes—present and future perspectives. Clin Diabetes Endocrinol 2019;5:5 [FREE Full text] [doi: 10.1186/s40842-019-0080-0] [Medline: 31086677]
12. Gottwald-Hostalek U, Gwilt M. Vascular complications in prediabetes and type 2 diabetes: a continuous process arising from a common pathology. Curr Med Res Opin 2022;38(11):1841-1851 [FREE Full text] [doi: 10.1080/03007995.2022.2101805] [Medline: 35833523]
13. Palladino R, Tabak AG, Khunti K, Valabhji J, Majeed A, Millett C, et al. Association between pre-diabetes and microvascular and macrovascular disease in newly diagnosed type 2 diabetes. BMJ Open Diabetes Res Care 2020;8(1):e001061 [FREE Full text] [doi: 10.1136/bmjdrc-2019-001061] [Medline: 32332069]
14. Brannick B, Wynn A, Dagogo-Jack S. Prediabetes as a toxic environment for the initiation of microvascular and macrovascular complications. Exp Biol Med (Maywood) 2016;241(12):1323-1331 [FREE Full text] [doi: 10.1177/1535370216654227] [Medline: 27302176]
15. Pan XR, Li GW, Hu YH, Wang JX, Yang WY, An ZX, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and diabetes study. Diabetes Care 1997;20(4):537-544 [FREE Full text] [doi: 10.2337/diacare.20.4.537] [Medline: 9096977]
16. Tuomilehto J, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, Ilanne-Parikka P, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001;344(18):1343-1350 [FREE Full text] [doi: 10.1056/NEJM200105033441801] [Medline: 11333990]
17. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346(6):393-403 [FREE Full text] [doi: 10.1056/NEJMoa012512] [Medline: 11832527]
18. Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar AD, Vijay V, Indian Diabetes Prevention Programme (IDPP). The Indian diabetes prevention programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). Diabetologia 2006;49(2):289-297 [FREE Full text] [doi: 10.1007/s00125-005-0097-z] [Medline: 16391903]
19. Schlesinger S, Neuenschwander M, Barbaresko J, Lang A, Maalmi H, Rathmann W, et al. Prediabetes and risk of mortality, diabetes-related complications and comorbidities: umbrella review of meta-analyses of prospective studies. Diabetologia 2022;65(2):275-285 [FREE Full text] [doi: 10.1007/s00125-021-05592-3] [Medline: 34718834]
20. Van Rhoon L, Byrne M, Morrissey E, Murphy J, McSharry J. A systematic review of the behaviour change techniques and digital features in technology-driven type 2 diabetes prevention interventions. Digit Health 2020;6:2055207620914427 [FREE Full text] [doi: 10.1177/2055207620914427] [Medline: 32269830]
21. Grock S, Ku JH, Kim J, Moin T. A review of technology-assisted interventions for diabetes prevention. Curr Diab Rep 2017;17(11):107. [doi: 10.1007/s11892-017-0948-2] [Medline: 28942537]
22. Khokhar B, Jones J, Ronksley PE, Armstrong MJ, Caird J, Rabi D. Effectiveness of mobile electronic devices in weight loss among overweight and obese populations: a systematic review and meta-analysis. BMC Obes 2014;1:22 [FREE Full text] [doi: 10.1186/s40608-014-0022-4] [Medline: 26217509]
23. Fukuoka Y, Gay CL, Joiner KL, Vittinghoff E. A novel diabetes prevention intervention using a mobile app: a randomized controlled trial with overweight adults at risk. Am J Prev Med 2015;49(2):223-237 [FREE Full text] [doi: 10.1016/j.amepre.2015.01.003] [Medline: 26033349]

24. Wienert J, Jahnel T, Maaß L. What are digital public health interventions? First steps toward a definition and an intervention classification framework. J Med Internet Res 2022;24(6):e31921 [FREE Full text] [doi: 10.2196/31921] [Medline: 35763320]
25. Guo C, Ashrafian H, Ghafur S, Fontana G, Gardner C, Prime M. Challenges for the evaluation of digital health solutions-a call for innovative evidence generation approaches. NPJ Digit Med 2020;3:110 [FREE Full text] [doi: 10.1038/s41746-020-00314-2] [Medline: 32904379]
26. Schippers M, Adam PCG, Smolenski DJ, Wong HTH, de Wit JBF. A meta-analysis of overall effects of weight loss interventions delivered via mobile phones and effect size differences according to delivery mode, personal contact, and intervention intensity and duration. Obes Rev 2017;18(4):450-459. [doi: 10.1111/obr.12492] [Medline: 28187246]
27. Lyzwinski LN. A systematic review and meta-analysis of mobile devices and weight loss with an intervention content analysis. J Pers Med 2014;4(3):311-385 [FREE Full text] [doi: 10.3390/jpm4030311] [Medline: 25563356]
28. Liang X, Wang Q, Yang X, Cao J, Chen J, Mo X, et al. Effect of mobile phone intervention for diabetes on glycaemic control: a meta-analysis. Diabet Med 2011;28(4):455-463. [doi: 10.1111/j.1464-5491.2010.03180.x] [Medline: 21392066]
29. Lee SWH, Ooi L, Lai YK. Telemedicine for the management of glycemic control and clinical outcomes of type 1 diabetes mellitus: a systematic review and meta-analysis of randomized controlled studies. Front Pharmacol 2017;8:330 [FREE Full text] [doi: 10.3389/fphar.2017.00330] [Medline: 28611672]
30. Wang X, Shu W, Du J, Du M, Wang P, Xue M, et al. Mobile health in the management of type 1 diabetes: a systematic review and meta-analysis. BMC Endocr Disord 2019;19(1):21 [FREE Full text] [doi: 10.1186/s12902-019-0347-6] [Medline: 30760280]
31. Bian RR, Piatt GA, Sen A, Plegue MA, De Michele ML, Hafez D, et al. The effect of technology-mediated diabetes prevention interventions on weight: a meta-analysis. J Med Internet Res 2017;19(3):e76 [FREE Full text] [doi: 10.2196/jmir.4709] [Medline: 28347972]
32. Joiner KL, Nam S, Whittemore R. Lifestyle interventions based on the diabetes prevention program delivered via eHealth: a systematic review and meta-analysis. Prev Med 2017;100:194-207 [FREE Full text] [doi: 10.1016/j.ypmed.2017.04.033] [Medline: 28456513]
33. Villegas V, Shah A, Manson JE, Tobias DK. Prevention of type 2 diabetes through remotely administered lifestyle programs: a systematic review. Contemp Clin Trials 2022;119:106817. [doi: 10.1016/j.cct.2022.106817] [Medline: 35691488]
34. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71 [FREE Full text] [doi: 10.1136/bmj.n71] [Medline: 33782057]
35. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4(1):1 [FREE Full text] [doi: 10.1186/2046-4053-4-1] [Medline: 25554246]
36. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 2014;14:135 [FREE Full text] [doi: 10.1186/1471-2288-14-135] [Medline: 25524443]
37. Schünemann H, Brożek J, Guyatt G, Oxman A. GRADE handbook for grading quality of evidence and strength of recommendations. GRADE Work Group. 2013. URL: https://gdt.gradepro.org/app/handbook/handbook.html [accessed 2023-05-15]
38. GRADEpro GDT: GRADEpro Guideline Development Tool. McMaster University and Evidence Prime. 2022. URL: https://www.gradepro.org/ [accessed 2023-05-15]
39. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011;64(4):383-394 [FREE Full text] [doi: 10.1016/j.jclinepi.2010.04.026] [Medline: 21195583]

Abbreviations

A/S: joint-stock company, in Danish
CENTRAL: Cochrane Central Register of Controlled Trials
GRADE: Grading of Recommendations Assessment, Development and Evaluation
HbA_{1c}: hemoglobin A_{1c}
IFG: impaired fasting glucose
IGT: impaired glucose tolerance
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PROSPERO: International Prospective Register of Systematic Reviews
T2D: type 2 diabetes

Edited by A Mavragani; submitted 06.07.23; peer-reviewed by B Breznen, A Al; comments to author 02.12.23; revised version received 15.12.23; accepted 17.12.23; published 09.02.24.

Please cite as:
Holm TF, Udsen FW, Færch K, Jensen MH, von Scholten BJ, Hejlesen OK, Hangaard S
The Effectiveness of Digital Health Lifestyle Interventions on People With Prediabetes: Protocol for a Systematic Review, Meta-Analysis, and Meta-Regression
JMIR Res Protoc 2024;13:e50340
URL: https://www.researchprotocols.org/2024/1/e50340
doi:10.2196/50340
PMID:38335018

Protocol

Implementation of Chatbot Technology in Health Care: Protocol for a Bibliometric Analysis

Zhao Ni[1,2], BMed, PhD; Mary L Peng[3], MPH; Vimala Balakrishnan[4], PhD; Vincent Tee[5], MD; Iskandar Azwa[5,6], MD; Rumana Saifi[5], PhD; LaRon E Nelson[1,2], PhD; David Vlahov[1,2], PhD; Frederick L Altice[2,5,7,8], MA, MD

[1]School of Nursing, Yale University, Orange, CT, United States

[2]Center for Interdisciplinary Research on AIDS, Yale University, New Haven, CT, United States

[3]Department of Global Health and Social Medicine, Harvard Medical School, Harvard University, Boston, MA, United States

[4]Department of Information Systems, Faculty of Computer Science and Information Technology, Unversity of Malaya, Kuala Lumpur, Malaysia

[5]Centre of Excellence for Research in AIDS, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

[6]Infectious Disease Unit, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

[7]Section of Infectious Disease, Department of Internal Medicine, Yale School of Medicine, New Haven, CT, United States

[8]Division of Epidemiology of Microbial Diseases, Yale School of Public Health, New Haven, CT, United States

Corresponding Author:
Zhao Ni, BMed, PhD
School of Nursing
Yale University
400 West Campus Drive
Orange, CT, 06477
United States
Phone: 1 2037373039
Email: zhao.ni@yale.edu

Abstract

Background: Chatbots have the potential to increase people's access to quality health care. However, the implementation of chatbot technology in the health care system is unclear due to the scarce analysis of publications on the adoption of chatbot in health and medical settings.

Objective: This paper presents a protocol of a bibliometric analysis aimed at offering the public insights into the current state and emerging trends in research related to the use of chatbot technology for promoting health.

Methods: In this bibliometric analysis, we will select published papers from the databases of CINAHL, IEEE Xplore, PubMed, Scopus, and Web of Science that pertain to chatbot technology and its applications in health care. Our search strategy includes keywords such as "chatbot," "virtual agent," "virtual assistant," "conversational agent," "conversational AI," "interactive agent," "health," and "healthcare." Five researchers who are AI engineers and clinicians will independently review the titles and abstracts of selected papers to determine their eligibility for a full-text review. The corresponding author (ZN) will serve as a mediator to address any discrepancies and disputes among the 5 reviewers. Our analysis will encompass various publication patterns of chatbot research, including the number of annual publications, their geographic or institutional distribution, and the number of annual grants supporting chatbot research, and further summarize the methodologies used in the development of health-related chatbots, along with their features and applications in health care settings. Software tool VOSViewer (version 1.6.19; Leiden University) will be used to construct and visualize bibliometric networks.

Results: The preparation for the bibliometric analysis began on December 3, 2021, when the research team started the process of familiarizing themselves with the software tools that may be used in this analysis, VOSViewer and CiteSpace, during which they consulted 3 librarians at the Yale University regarding search terms and tentative results. Tentative searches on the aforementioned databases yielded a total of 2340 papers. The official search phase started on July 27, 2023. Our goal is to complete the screening of papers and the analysis by February 15, 2024.

Conclusions: Artificial intelligence chatbots, such as ChatGPT (OpenAI Inc), have sparked numerous discussions within the health care industry regarding their impact on human health. Chatbot technology holds substantial promise for advancing health care systems worldwide. However, developing a sophisticated chatbot capable of precise interaction with health care consumers, delivering personalized care, and providing accurate health-related information and knowledge remain considerable challenges.

This bibliometric analysis seeks to fill the knowledge gap in the existing literature on health-related chatbots, entailing their applications, the software used in their development, and their preferred functionalities among users.

International Registered Report Identifier (IRRID): PRR1-10.2196/54349

(JMIR Res Protoc 2024;13:e54349) doi:10.2196/54349

KEYWORDS

artificial intelligence; AI; bibliometric analysis; chatbots; health care; health promotion

Introduction

Chatbots are software applications that use computerized algorithms to simulate conversations with human users through text or voice interactions [1,2]. Since their inception in the 1960s, chatbots have found applications in various settings, such as airlines, banks, hotel chains, and information technology companies, serving as digital agents to handle and streamline customers' queries and needs [3]. Compared to human agents, chatbots can efficiently respond to a large number of users simultaneously, conserving human effort and time while still providing users with a sense of human interaction [4]. Due to this advantageous feature, chatbots have been implemented in health care settings to automatically resolve or deflect repetitive calls, thereby reducing waiting times for health care consumers and enabling health care professionals to focus on more complex cases. Driven by the evolution of Industry 4.0, characterized by the integration of digital technologies, data, and automation to create more efficient and responsive societal systems, the future of high-quality health care hinges on the automation and digitalization of data exchange. Against this social-technological backdrop, artificial intelligence (AI) chatbots, also known as conversational AI, hold substantial promise as innovative tools for advancing our health care systems [5].

AI chatbots have been developed to automate and streamline various tasks for health care consumers, including retrieving health information, providing digital health support, and offering therapeutic care [6]. The literature reveals that AI chatbots commonly fulfill roles such as assisting individuals in scheduling medical appointments, identifying health clinics, and providing health educational information [7,8]. Research has also shown that health care professionals, patients, and families exhibit favorable attitudes toward the use of chatbot technology to enhance health outcomes [7,9-12].

While AI chatbots hold considerable potential to drive significant advancements and improvements in health care [13,14], their application in health care is still in its early stages. A significant barrier to the deployment of chatbot technology in health care systems is the lack of sophisticated AI algorithms capable of facilitating precise and personalized human-chatbot interactions to meet the expectations of health care providers or fulfill the needs of health care consumers [11]. For instance, in the United States, health-related chatbots have been developed to monitor the health status of patients with chronic heart failure [15], screen for osteoporosis in menopausal women [16], and detect colorectal cancer in the general population [17]. However, their effectiveness in clinical trials was found to be limited when compared to health professional assessments. To fully realize the potential of chatbot technology in health care systems, more studies are needed to develop more sophisticated AI algorithms that are culturally tailored, theoretically informed, and trained based on clinical needs [18-21]. Creating such sophisticated AI chatbots presents a challenge for both health scientists and chatbot engineers, necessitating iterative collaboration between the 2 [22]. Specifically, after chatbot engineers develop a chatbot prototype, health scientists evaluate it and provide feedback for further refinement. Chatbot engineers then upgrade the chatbot, followed by health scientists testing the updated version, training it, and conducting further assessments. This iterative cycle can impose significant demands in terms of time and funding before a chatbot is equipped with the necessary knowledge and language skills to deliver precise responses to its users.

Bibliometric analysis is a quantitative research method to discern publication patterns within a specific timeframe [23]. Scholars use this type of analysis to elucidate the intellectual structure of a particular area within the realm of existing literature [24]. Despite the increasing popularity of health-related chatbots, no bibliometric analysis has been conducted to examine their application. Studies on the coverage of health-related chatbot research have predominantly been conducted in the form of scoping or systematic reviews [19,25,26]. The current body of research papers lacks the breadth of a comprehensive scientific performance mapping analysis. Hence, this bibliometric analysis aims to identify the current status and emerging trends in chatbot technology research, serving as an initial stride for researchers worldwide to gain a comprehensive understanding on the landscape of health-related chatbots. This overview will facilitate the identification of areas for improvement and promote the integration of chatbot technology into health care systems.

Chatbot technology should be promoted in the health care system because many digital health interventions have proven effective but are not implemented in real clinical settings, as they often require high-intensity and sustained human inputs. For example, they often require researchers to regularly and manually send personalized reminders, provide real-time guidance, and initiate referrals [27,28]. To bring population-level effects, digital health intervention needs to be automating personalized messages, modifying them based on responses, and providing new outputs in real time [29]. AI chatbots have the potential to achieve these goals. For example, our previous formative research indicates a high level of acceptance toward the use of chatbot technology among vulnerable populations who are at high risk for HIV [2]. Additionally, we have conducted beta testing for chatbot technology in promoting HIV testing and prevention and found that participants believed chatbot technology provided them with a platform to protect their safety and privacy. This was particularly important in

environments where stigma and discrimination toward HIV exist, and where same-sex behaviors are criminalized. Compared with the conventional health care use model, where people need to face stigma and discrimination from health care providers, chatbots can provide them with a safe platform to ask questions and receive consulting services. Therefore, promoting chatbot technology holds significance for enhancing the current health care system and an anonymous user setting in chatbots is necessary to protect health consumers' privacy [2].

Methods

Bibliographic Search

We will conduct searches in the following databases: CINAHL (EBSCOHost), IEEE Xplore (IEEE), PubMed, Scopus (Elsevier), and Web of Science (Clarivate) to ensure a comprehensive coverage of research on health-related chatbots. We have identified a set of consensus search keywords related to chatbots and health care through a review of previous systematic reviews [18-21] and consultations with university librarians who possess expertise in informatics and digital health. Our search strategy includes keywords such as "chatbot," "virtual agent," "virtual assistant," "conversational agent," "conversational AI," "interactive agent," "health," and "healthcare." A retrieval search string, including the keywords with Boolean operators listed in Multimedia Appendix 1, will be used.

Selection of Studies

We will include papers on chatbots that are used to promote health outcomes. All interventional and observational studies published as journal papers or conference proceedings will be included. To offer a holistic view of the evolving usage of chatbots in health care, we will not set restrictions on the year of publication. Moreover, we will not exclude papers published in non–English language to incorporate research findings from low- and middle-income countries [30]. Studies that do not discuss the use of chatbots to promote health or wellness will be excluded. Systematic reviews pertaining only to chatbot designs and development, purposes, or features will be excluded. Papers such as editorials, dissertations, preprints, and letters to the editor will also be excluded.

Search results from each database will be imported into Covidence (Veritas Health Innovation Ltd), a systematic review management software. Duplicate papers will be identified and removed. Five researchers will independently screen the titles and abstracts of all papers and categorize them as either "include," "exclude," or "unsure" based on the following inclusion criteria related to (1) chatbot and (2) health promotion. To provide a comprehensive overview of the current research on health-related chatbots, we will include papers about chatbots designed for various populations, including patients, clinicians, policy makers, or the general population. We will not exclude papers based on their study design. Papers marked as "unsure" will be downloaded and assessed for eligibility. The eligibility assessment will be performed by 2 authors (VB and VT) who are an AI consultant and a clinician. In the event of disagreements, the 2 authors will discuss in team meetings with the corresponding author (ZN) to reach a consensus.

Data Extraction

Selected studies will be downloaded from Covidence and imported into VOSViewer (version 1.6.19; Leiden University), a Java-based bibliometric analysis visualization software application. We will use VOSViewer to analyze data related to chatbot publication patterns, encompassing the number of annual publications, the distribution of countries and institutions involved in chatbot research, the number of annual grants that supported chatbot research, the number of funders, the number of journals publishing chatbot research, the number of journal citations, the most prolific authors in the field of chatbots, author network maps, and the most frequently used keywords related to chatbots. Additionally, using Excel (Microsoft Corp), we will manually extract data regarding the number of interventional and observational studies, the methodologies used in creating chatbots, the number of chatbots deployed worldwide, and the usage of chatbots.

Data Analysis

Research Characteristics

In this bibliometric analysis, we will analyze the characteristics of chatbot research based on the topics of the selected studies, identified through their reported keywords, such as primary functions and disease domains. We will report the frequency and percentage of the top keywords and topics by following the framework in previous research to measure the centrality of a keyword using its frequency scores [31].

Publication Patterns

We will report the trend of yearly number of publications and showcase the growth rate of publication by computing the monthly publication rate each year from the earliest publication selected to the latest. To control for the "publication noise," a surge in publications following the releases of ChatGPT, we will stratify the data by publication date before and after the emergence of ChatGPT and conduct sensitivity analyses to distinguish between the direct impact of ChatGPT and other trends in chatbot research. This approach will help to ensure that our findings reflect the broader trends in chatbot technology research and are not disproportionately influenced by the recent increase in publications related to a single event or development. We will calculate the frequencies and percentages of publications for each journal and country in each publication year, whereby we identify the countries and institutions associated with the publication based on the affiliations of the corresponding authors. We will report the trend of research support by identifying the number of grants and funders as reported under each study's source of funding. Moreover, we will compute the distribution of the following two indicators including (1) the methodology used to create chatbots and (2) the implementation of health chatbots.

Research Hot Spot and Connectedness

We will use the number of journal citations to construct bursts, whereby clusters will be sorted by the keywords used by the study. We will further report the most prolific authors based on a combined metric of the number of publications and citation frequency. We will present 2 author network maps using author names and research institutions affiliated with the listed authors.

Authors and affiliated institutions will be the nodes within each network connected by edges representing the coauthorship of publications [32]. Edges will be weighted by the number of coauthorships between the same listed authors and their affiliated institutions.

Ethical Considerations

This analysis does not involve recruiting human participants or providing interventions; therefore, ethical review and consent forms are not required. We hope that the findings from the manuscript will aid researchers, engineers, health professionals, funders, and policy makers in their future implementation of chatbot technology to facilitate innovative and efficient health care systems.

Results

The preparation for the bibliometric analysis began on December 3, 2021, with the initial steps involving the research team familiarizing themselves with VOSViewer and CiteSpace, followed by digital consultations with 3 librarians from Yale University. Tentative searches in the databases yielded a total of 2340 papers. The official search phase began on July 27, 2023. Our goal is to complete the screening of papers and perform the analysis by February 15, 2024. We anticipate a significant increase in chatbot research following the emergence of ChatGPT.

Discussion

AI chatbots hold strong potential to transform the field of health care. For example, ChatGPT, an AI chatbot developed by OpenAI, has sparked numerous discussions within the health care industry regarding the impact of AI chatbots on human health [13,14,33-38]. Our team has been developing an AI chatbot since June 2019, and we have discovered that developing a sophisticated AI chatbot capable of precise interaction with health care consumers, delivering personalized care, and providing accurate health-related information and knowledge remains a considerable challenge. One of the major obstacles faced by health scientists interested in chatbot research is their lack of familiarity with chatbots' underlying technologies, such as the computational systems, software platforms, and underlying algorithms that train chatbots and enable their automation and individualization. Similarly, chatbot engineers may have limited insight into the challenges faced by patients and health care providers in real-world clinical settings, making it difficult for them to fully grasp the nuances and directions of chatbot technology. Such information asymmetry in interdisciplinary collaboration hinders health-advancing chatbot technology from reaching its full potential. More literature that can offer diverse stakeholders, ranging from health scientists, health care providers, to chatbot developers, insights into a holistic roadmap to creating effective chatbots to meet health care needs is thus urgently needed to facilitate such interdisciplinary endeavors.

Chatbot technology holds immense potential to enhance health care quality for both patients and professionals through streamlining administrative processes and assisting with assessment, diagnosis, and treatment. Used for health information acquisition, chatbot-powered search, as we anticipate, will become an important complement to traditional web-based searches. This trend is primarily driven by the convenience of chatbot-powered search for users, as it eliminates the need for users to manually sift through search results as required in traditional web-based searches. However, no recognized standards or guidelines have been established for creating health-related chatbots. We believe that with theory-informed and well-trained algorithms, chatbots can also be used as health care digital assistants to provide consumers and patients with quick, precise, and individualized answers. As demonstrated by the widespread adoption of ChatGPT in recent times, it is reasonable to anticipate that the development and implementation of AI chatbots will substantially enhance the efficiency and convenience of health care consumers' information search. Existing studies have also shown that AI chatbots can increase health appointment volume by automating the scheduling process for health care consumers, achieved through a user-friendly platform that enables appointment scheduling, verification, and cancellation with ease, further leading to reduced no-show rates. For example, Weill Cornell Medicine reported a 47% increase in appointments booked digitally through the use of AI chatbots [39]. Moreover, chatbot technology can enhance the work efficiency of nurses, physicians, and other health care professionals by delivering prompt responses to inquiries related to clinical practice standards, eliminating the need to navigate prolonged websites or extensive clinical guidelines for specific information.

Despite the obvious benefits of chatbot technology in health care, several potential risks of using chatbots exist, including breaching privacy, providing misinformation, and generating systematically biased responses [2,7-9]. These risks are relevant to the nature of chatbot technology, in which chatbot developers need to maximize a personalized experience and enable chatbots to provide users with precision answers through training chatbots [12]. However, training chatbots requires chatbot technology to have access to a wealth of users' personal data. This poses a major threat to using chatbots in health care. To address privacy issues, chatbot developers and researchers must ensure that users' data are protected using encryption during human-chatbot interactions or when a chatbot needs to retrieve backend data [2]. Second, misinformation originates from the immature or flaws of the chatbot algorithms. Training a chatbot is an iterative process that demands a large data set and vetting of the outputs by researchers. During a chatbot creation, the earlier versions of the chatbot often provide redundant and impersonalized information that may prevent users from using the chatbot. To increase chatbot usability, a chatbot must be precise enough in its communications with users or can connect users to a human agent if necessary [11,12]. Third, even well-trained chatbots can provide biased responses or solutions to users [13]. This is particularly true if the data sets used to train chatbots are biased. To minimize these risks of using chatbots in health care, it is necessary for researchers to validate chatbot outputs and reduce biases in the data sets used to train a chatbot. Only by adopting this approach, quality chatbots with high usability can be used to promote health care.

To fully realize the potential of chatbot technology in improving health outcomes for everyone, sustained collaborative efforts from an interdisciplinary research team comprising chatbot engineers and health scientists are essential. To the best of our knowledge, this is the first study aimed at summarizing the current status and future trends of chatbots in the health care field. This study will provide a broad overview of publications on health-related chatbot research and bridge the knowledge gap in the existing literature, including software used for chatbot development, popular functionalities, and chatbots' applications in health care. This study includes papers published since the inception of the chatbot and is not confined by the language of publication. Consequently, it offers a global perspective on the evolution of chatbots within the health care domain. One limitation of this study is its nature as a bibliometric analysis, which does not explore topics in the same depth as a systematic review.

Acknowledgments

This work was supported by grants from the National Institutes of Health (R21TW011663 and R33TW011663 for ZN and FLA; and D43TW011324 for FLA and RS) and faculty research funds from Yale University School of Nursing for ZN.

We extend our sincere thanks to Janene Batten and other librarians at Yale University for their invaluable assistance and guidance in preparing for this bibliometric analysis

Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Authors' Contributions

ZN, VT, MLP, and VB conceived the study and wrote the first draft of the manuscript. MLP and VB helped to develop the bibliographic search and bibliometric analysis. All authors contributed to the development of the study protocol, revised the subsequent version of the manuscript, and approved the submitted version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
A retrieval search string.
[DOCX File , 15 KB - resprot_v13i1e54349_app1.docx]

References

1. Kate B, Scardina J. What is a chatbot? Techtarget. 2019. URL: https://searchcustomerexperience.techtarget.com/definition/chatbot [accessed 2021-09-01]
2. Peng ML, Wickersham JA, Altice FL, Shrestha R, Azwa I, Zhou X, et al. Formative evaluation of the acceptance of HIV prevention artificial intelligence Chatbots by men who have sex with men in Malaysia: focus group study. JMIR Form Res 2022;6(10):e42055 [FREE Full text] [doi: 10.2196/42055] [Medline: 36201390]
3. Coheur L. From Eliza to Siri and beyond. In: Lesot MJ, Vieira S, Reformat MZ, Carvalho JP, Wilbik A, Bouchon-Meunier B, et al, editors. Information Processing and Management of Uncertainty in Knowledge-Based Systems: 18th International Conference, IPMU 2020, Lisbon, Portugal, June 15–19, 2020, Proceedings, Part I, Vol 1237. Cham: Springer International Publishing; 2020:29-41.
4. Luxton DD. Ethical implications of conversational agents in global public health. Bull World Health Organ 2020;98(4):285-287 [FREE Full text] [doi: 10.2471/BLT.19.237636] [Medline: 32284654]
5. Milne-Ives M, de Cock C, Lim E, Shehadeh MH, de Pennington N, Mole G, et al. The effectiveness of artificial intelligence conversational agents in health care: systematic review. J Med Internet Res 2020;22(10):e20346 [FREE Full text] [doi: 10.2196/20346] [Medline: 33090118]
6. Mesko B. The top 12 health Chatbots. The Medical Futurist. 2021. URL: https://medicalfuturist.com/top-12-health-chatbots/ [accessed 2021-11-18]
7. Palanica A, Flaschner P, Thommandram A, Li M, Fossat Y. Physicians' perceptions of Chatbots in health care: cross-sectional web-based survey. J Med Internet Res 2019;21(4):e12887 [FREE Full text] [doi: 10.2196/12887] [Medline: 30950796]
8. Koman J, Fauvelle K, Schuck S, Texier N, Mebarki A. Physicians' perceptions of the use of a Chatbot for information seeking: qualitative study. J Med Internet Res 2020;22(11):e15185 [FREE Full text] [doi: 10.2196/15185] [Medline: 33170134]

9. Abd-Alrazaq AA, Alajlani M, Ali N, Denecke K, Bewick BM, Househ M. Perceptions and opinions of patients about mental health chatbots: scoping review. J Med Internet Res 2021;23(1):e17828 [FREE Full text] [doi: 10.2196/17828] [Medline: 33439133]
10. Miles O, West R, Nadarzynski T. Health chatbots acceptability moderated by perceived stigma and severity: a cross-sectional survey. Digit Health 2021;7:1-7 [FREE Full text] [doi: 10.1177/20552076211063012] [Medline: 34917391]
11. Nadarzynski T, Miles O, Cowie A, Ridge D. Acceptability of artificial intelligence (AI)-led chatbot services in healthcare: a mixed-methods study. Digit Health 2019;5:1-12 [FREE Full text] [doi: 10.1177/2055207619871808] [Medline: 31467682]
12. Oh YJ, Zhang J, Fang ML, Fukuoka Y. A systematic review of artificial intelligence chatbots for promoting physical activity, healthy diet, and weight loss. Int J Behav Nutr Phys Act 2021;18(1):160 [FREE Full text] [doi: 10.1186/s12966-021-01224-6] [Medline: 34895247]
13. Wang X, Sanders HM, Liu Y, Seang K, Tran BX, Atanasov AG, et al. ChatGPT: promise and challenges for deployment in low- and middle-income countries. Lancet Reg Health West Pac 2023;41:100905 [FREE Full text] [doi: 10.1016/j.lanwpc.2023.100905] [Medline: 37731897]
14. No Authors. Will ChatGPT transform healthcare? Nat Med 2023;29(3):505-506 [FREE Full text] [doi: 10.1038/s41591-023-02289-5] [Medline: 36918736]
15. Galescu L, Allen J, Ferguson G, Quinn J, Swift M. Speech recognition in a dialog system for patient health monitoring. 2009 Presented at: 2009 IEEE International Conference on Bioinformatics and Biomedicine Workshop; November 1-4, 2009; Washington, DC, USA. [doi: 10.1109/bibmw.2009.5332111]
16. Heyworth L, Kleinman K, Oddleifson S, Bernstein L, Frampton J, Lehrer M, et al. Comparison of interactive voice response, patient mailing, and mailed registry to encourage screening for osteoporosis: a randomized controlled trial. Osteoporos Int 2014;25(5):1519-1526. [doi: 10.1007/s00198-014-2629-1] [Medline: 24566584]
17. Simon SR, Zhang F, Soumerai SB, Ensroth A, Bernstein L, Fletcher RH, et al. Failure of automated telephone outreach with speech recognition to improve colorectal cancer screening: a randomized controlled trial. Arch Intern Med 2010;170(3):264-270 [FREE Full text] [doi: 10.1001/archinternmed.2009.522] [Medline: 20142572]
18. Hoermann S, McCabe KL, Milne DN, Calvo RA. Application of synchronous text-based dialogue systems in mental health interventions: systematic review. J Med Internet Res 2017;19(8):e267 [FREE Full text] [doi: 10.2196/jmir.7023] [Medline: 28784594]
19. de Cock C, Milne-Ives M, van Velthoven MH, Alturkistani A, Lam C, Meinert E. Effectiveness of conversational agents (virtual assistants) in health care: protocol for a systematic review. JMIR Res Protoc 2020;9(3):e16934 [FREE Full text] [doi: 10.2196/16934] [Medline: 32149717]
20. Geoghegan L, Scarborough A, Wormald JCR, Harrison CJ, Collins D, Gardiner M, et al. Automated conversational agents for post-intervention follow-up: a systematic review. BJS Open 2021;5(4):zrab070 [FREE Full text] [doi: 10.1093/bjsopen/zrab070] [Medline: 34323916]
21. Luo TC, Aguilera A, Lyles CR, Figueroa CA. Promoting physical activity through conversational agents: mixed methods systematic review. J Med Internet Res 2021;23(9):e25486 [FREE Full text] [doi: 10.2196/25486] [Medline: 34519653]
22. Corti K, Gillespie A. A truly human interface: interacting face-to-face with someone whose words are determined by a computer program. Front Psychol 2015;6:634 [FREE Full text] [doi: 10.3389/fpsyg.2015.00634] [Medline: 26042066]
23. Linnenluecke MK, Marrone M, Singh AK. Conducting systematic literature reviews and bibliometric analyses. Aust J Manag 2019;45(2):175-194 [FREE Full text] [doi: 10.1177/0312896219877678]
24. Naveen D, Satish K, Debmalya M, Nitesh P, Lim WM. How to conduct a bibliometric analysis: an overview and guidelines. J Bus Res 2021;133:285-296 [FREE Full text] [doi: 10.1016/j.jbusres.2021.04.070]
25. Car LT, Dhinagaran DA, Kyaw BM, Kowatsch T, Joty S, Theng YL, et al. Conversational agents in health care: scoping review and conceptual analysis. J Med Internet Res 2020;22(8):e17158 [FREE Full text] [doi: 10.2196/17158] [Medline: 32763886]
26. Gaffney H, Mansell W, Tai S. Conversational agents in the treatment of mental health problems: mixed-method systematic review. JMIR Ment Health 2019;6(10):e14166 [FREE Full text] [doi: 10.2196/14166] [Medline: 31628789]
27. Ni Z, Liu C, Wu B, Yang Q, Douglas C, Shaw RJ. An mHealth intervention to improve medication adherence among patients with coronary heart disease in China: development of an intervention. Int J Nurs Sci 2018;5(4):322-330 [FREE Full text] [doi: 10.1016/j.ijnss.2018.09.003] [Medline: 31406843]
28. Ni Z, Wu B, Yang Q, Yan LL, Liu C, Shaw RJ. An mHealth intervention to improve medication adherence and health outcomes among patients with coronary heart disease: randomized controlled trial. J Med Internet Res 2022;24(3):e27202 [FREE Full text] [doi: 10.2196/27202] [Medline: 35262490]
29. Holloway IW, Winder TJ, Lea CH, Tan D, Boyd D, Novak D. Technology use and preferences for mobile phone-based HIV prevention and treatment among Black young men who have sex with men: exploratory research. JMIR Mhealth Uhealth 2017;5(4):e46 [FREE Full text] [doi: 10.2196/mhealth.6436] [Medline: 28408360]
30. Walpole SC. Including papers in languages other than english in systematic reviews: important, feasible, yet often omitted. J Clin Epidemiol 2019;111:127-134. [doi: 10.1016/j.jclinepi.2019.03.004] [Medline: 30951800]
31. Vega-Oliveros DA, Gomes PS, Milios EE, Berton L. A multi-centrality index for graph-based keyword extraction. Inform Process Manag 2019;56(6):102063. [doi: 10.1016/j.ipm.2019.102063]

32. Bender ME, Edwards S, von Philipsborn P, Steinbeis F, Keil T, Tinnemann P. Using co-authorship networks to map and analyse global neglected tropical disease research with an affiliation to Germany. PLoS Negl Trop Dis 2015;9(12):e0004182 [FREE Full text] [doi: 10.1371/journal.pntd.0004182] [Medline: 26719978]
33. Sallam M. ChatGPT utility in healthcare education, research, and practice: systematic review on the promising perspectives and valid concerns. Healthcare (Basel) 2023;11(6):887 [FREE Full text] [doi: 10.3390/healthcare11060887] [Medline: 36981544]
34. Cascella M, Montomoli J, Bellini V, Bignami E. Evaluating the feasibility of ChatGPT in healthcare: an analysis of multiple clinical and research scenarios. J Med Syst 2023;47(1):33 [FREE Full text] [doi: 10.1007/s10916-023-01925-4] [Medline: 36869927]
35. Sajjad M, Saleem R. Evolution of healthcare with ChatGPT: a word of caution. Ann Biomed Eng 2023;51(8):1663-1664. [doi: 10.1007/s10439-023-03225-x] [Medline: 37219697]
36. Zheng Y, Wang L, Feng B, Zhao A, Wu Y. Innovating healthcare: the role of ChatGPT in streamlining hospital workflow in the future. Ann Biomed Eng Preprint posted online on July 18, 2023. [FREE Full text] [doi: 10.1007/s10439-023-03323-w] [Medline: 37464178]
37. Howard A, Hope W, Gerada A. ChatGPT and antimicrobial advice: the end of the consulting infection doctor? Lancet Infect Dis 2023;23(4):405-406 [FREE Full text] [doi: 10.1016/S1473-3099(23)00113-5] [Medline: 36822213]
38. Li H, Moon JT, Purkayastha S, Celi LA, Trivedi H, Gichoya JW. Ethics of large language models in medicine and medical research. Lancet Digit Health 2023;5(6):e333-e335 [FREE Full text] [doi: 10.1016/S2589-7500(23)00083-3] [Medline: 37120418]
39. Feng H, Zou Z, Zhang Q, Wang L, Ouyang YQ, Chen Z, et al. The effect of the group-based Otago exercise program on frailty among nursing home older adults with cognitive impairment. Geriatr Nurs 2021;42(2):479-483. [doi: 10.1016/j.gerinurse.2021.02.012] [Medline: 33714906]

Abbreviations

AI: artificial intelligence

Edited by A Mavragani; submitted 07.11.23; peer-reviewed by J Wang, A Gerada; comments to author 01.12.23; revised version received 07.12.23; accepted 16.01.24; published 15.02.24.

Please cite as:
Ni Z, Peng ML, Balakrishnan V, Tee V, Azwa I, Saifi R, Nelson LE, Vlahov D, Altice FL
Implementation of Chatbot Technology in Health Care: Protocol for a Bibliometric Analysis
JMIR Res Protoc 2024;13:e54349
URL: https://www.researchprotocols.org/2024/1/e54349
doi:10.2196/54349
PMID:38228575

Protocol

Nutritional Interventions for the Prevention of Cognitive Decline in Patients With Mild Cognitive Impairment and Alzheimer Disease: Protocol for a Network Meta-Analysis of Randomized Controlled Trials

Qian He[1], MPH; Kevin Chun Hei Wu[1], BSc; Adam N Bennett[1], PhD; Jia Yue Zhang[1], BSc; Kei Hang Katie Chan[1,2,3], MPH, PhD

[1]Department of Biomedical Sciences, City University of Hong Kong, Hong Kong, China

[2]Department of Electrical Engineering, City University of Hong Kong, Hong Kong, China

[3]Department of Epidemiology, Centre for Global Cardiometabolic Health, Brown University, Providence, RI, United States

Corresponding Author:
Kei Hang Katie Chan, MPH, PhD
Department of Electrical Engineering
City University of Hong Kong
1A-313 To Yuen Building
Hong Kong, 999077
China
Phone: 86 34426661
Email: kkhchan@cityu.edu.hk

Abstract

Background: Mild cognitive impairment (MCI) is the stage between cognitive decline due to physiological aging and the severity of decline seen in neurodegenerative disorders like Alzheimer disease (AD), which is among the most prevalent neurodegenerative disorders characterized by cognitive impairment. People with MCI are at increased risk of developing AD. Although MCI and AD are incurable, nutritional interventions can potentially delay or prevent their onset. Consequently, effective interventions used to decelerate or alleviate the progress of cognitive impairment in older people are a significant focus in geriatric care. Given the synergistic effects of nutrition on health, assessing the effectiveness of nutritional supplements or dietary composition in preventing MCI or AD is essential for developing interventional strategies.

Objective: Our study aims to assess the effectiveness of various nutritional interventions, including special dietary types, dietary patterns, specific foods, nutritional intake, and nutritional supplements, in preventing cognitive decline among patients diagnosed with MCI or AD. To achieve this, we will use a comprehensive approach, including network meta-analysis, pairwise meta-analysis, and systematic review of randomized controlled trials (RCTs).

Methods: The review will follow the Population, Intervention, Comparison, Outcome (PICO) model and the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) guidelines. Two investigators will independently search PubMed electronically. Data extraction will follow the inclusion criteria, and data will be assessed for risk of bias using a revised tool. Additionally, evidence quality will be evaluated using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework. The outcomes of interest are assessing the cognitive outcomes in patients with MCI or AD. A systematic literature search will be conducted, identifying randomized controlled trials that investigate the impact of these nutritional interventions on cognitive function decline in individuals with MCI and AD. Network meta-analyses (random-effects model) and pairwise meta-analyses will then estimate the relative effectiveness of different nutritional interventions.

Results: We included 51 studies, published between 1999 and 2023 (27 studies for AD and 24 studies for MCI) and involving 8420 participants. We completed data extraction for all 51 studies by December 2023. Currently, we are actively engaged in data analysis and manuscript preparation. We plan to finalize the manuscript and publish the comprehensive results by the end of 2024.

Conclusions: Our study holds significant clinical relevance given the rising prevalence of AD and the potential influence of nutritional interventions on cognitive function in individuals with MCI and AD. By investigating this relationship, our research aims to inform evidence-based decision-making in the development of prevention strategies for MCI and AD. The outcomes are

expected to contribute to the establishment of reliable recommendations for MCI or AD management, providing substantial support in the field.

Trial Registration: PROSPERO CRD42022331173; http://tinyurl.com/3snjp7a4

International Registered Report Identifier (IRRID): PRR1-10.2196/47196

(JMIR Res Protoc 2024;13:e47196) doi:10.2196/47196

KEYWORDS

network meta-analysis; cognitive impairment; Alzheimer disease; Alzheimer; neurodegenerative disorders; geriatric care; nutritional interventions; older patient; geriatric; cognitive decline; aging; older people; nutrition; cognitive; aging; intervention; Alzheimer disease; dementia; acute confusional senile dementia; Elder Nutritional Physiological Phenomena; Nutrition Physiology; nutrition; meta-analysis; meta-analyses; systematic review; systematic reviews

Introduction

Cognitive decline, particularly associated with mild cognitive impairment (MCI) and Alzheimer disease (AD), represents a significant and growing public health concern worldwide [1]. As the aging population continues to increase, the prevalence of MCI and AD is also on the rise, leading to substantial personal, societal, and economic burdens [2]. One study indicated that the occurrence of MCI was higher than 22.5 per 1000 person-years among people aged 75 years and older [3]. Patients with MCI are also at a high risk of developing AD [4,5]. Therefore, identifying effective interventions to prevent or delay cognitive decline in individuals with MCI and AD is of utmost importance.

Currently, MCI and AD are incurable; however, delay and prevention of MCI or AD are possible [6]. Modifiable factors such as metabolic conditions (eg, diabetes), vascular issues (eg, hypertension), mental health concerns (eg, depression), social factors (eg, isolation), and lifestyle choices (eg, nutritional intake [7], dietary type [8], and physical inactivity) have been frequently linked with the risk of MCI and AD [9]. As such, it is critical to understand how modulating health and lifestyle factors may prevent cognitive decline. In recent decades, nutritional interventions have gained attention as potential strategies for cognitive decline prevention [10,11]. Various nutrients, dietary patterns, and dietary supplements have been investigated for their potential benefits in cognitive function and neuroprotection. Multiple types of intervention have been applied to these populations to reduce the decline of cognitive function, such as the Mediterranean diet and the ketogenic diet as well as the regulation of fatty acids, antioxidants, vitamins, and micronutrients [12-15]. Andrews et al [16] conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) to evaluate the effect of dietary patterns, food, and nutritional supplements on cognitive function in individuals with MCI. The findings of this review demonstrated that few nutritional interventions convincingly improved the cognition of individuals with MCI [16]. Vlachos et al [17] conducted a systematic review and found folate, vitamin E, omega-3 fatty acids, and certain multinutrient formulations have shown some preliminary promising results [17]. However, the evidence regarding the effectiveness of different nutritional interventions remains inconclusive, with conflicting findings reported across individual RCTs.

To address the limitations of traditional pairwise meta-analyses and provide a comprehensive synthesis of the available evidence, we propose conducting a network meta-analysis (NMA). An NMA is a type of meta-analysis that extends beyond regular meta-analyses [18,19]. By using this approach, we aim to provide more precise and robust estimates of the effects of different nutritional interventions on cognitive decline in patients with MCI and AD. In this protocol, we outline the methodology for conducting an NMA of RCTs on nutritional interventions for the prevention of cognitive decline in patients with MCI and AD.

Methods

Experimental Approach

This protocol was developed following the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) 2015 checklist [20]. This protocol has been registered with the PROSPERO database (CRD42022331173).

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria will be determined according to the principle of the Population, Intervention, Comparison, Outcome (PICO) design. The inclusion and exclusion criteria are presented briefly in Table 1.

Table 1. Inclusion and exclusion criteria for studies in the meta-analysis.

Variables	Inclusion criteria	Exclusion criteria
Study design	RCTs[a] reported as comparing one nutritional intervention with another or a placebo	Non-RCTs
Participants	Participants with MCI[b] or AD[c] older than 50 years	Participants with vascular dementia; Parkinson disease–related dementia; delirium; depression and other mental illnesses; congenital brain function hypoplasia, such as Down syndrome; or subarachnoid hemorrhage
Diagnosis of MCI or AD	Diagnosis according to NINCDS-ADRDA[d] DSM[e] or assessed by MMSE[f] with scores between 10 and 26	N/A[g]
Nutritional intervention assessment	Any type of nutritional intervention, such as special dietary type, dietary pattern, food, nutritional intake, and nutritional supplements at all doses or ingested amounts with a duration of more than 12 weeks	No definitive preventative impact was evaluated, or the effects were evaluated for less than 12 weeks.
Outcome measurement	The primary outcome will be assessed by the MMSE. The secondary outcomes will be assessed with other scales like the ADAS-Cog[h], CDR[i], and WAIS-R[j] scores.	N/A

[a]RCTs: randomized controlled trials.

[b]MCI: mild cognitive impairment.

[c]AD: Alzheimer disease.

[d]NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association.

[e]DSM: Diagnostic and Statistical Manual of Mental Disorders.

[f]MMSE: Mini-Mental State Examination.

[g]N/A: not applicable.

[h]ADAS-Cog: Alzheimer's Disease Assessment Scale cognitive subscale.

[i]CDR: Clinical Dementia Rating Scale.

[j]WAIS-R: Wechsler Adult Intelligence Scale-Revised.

Inclusion Criteria

Type of Study

All RCTs that compared one nutritional intervention with another or a placebo for the prevention of cognitive decline in patients with MCI or AD will be included.

Participants

Participants with MCI or AD older than 50 years, regardless of gender, ethnicity or race, geography, dwelling, or chronic diseases, will be included in the analysis.

Inclusion of Patients With Different Degrees of MCI or AD

Participants will be considered as having AD by fulfilling the requirement of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) or the Diagnostic and Statistical Manual of Mental Disorders (DSM) [21,22]. Participants will be evaluated for MCI using the Mini-Mental State Examination (MMSE) [23].

Nutritional Interventions Assessment

Experimental interventions included any type of nutritional intervention, such as special dietary type, dietary pattern, food, nutritional intake, and nutritional supplements at all doses or ingested amounts. Interventions lasted more than 12 weeks and were with or without medication as cointervention. The control group received a placebo intervention.

Outcome Measurements

Both the primary outcome and secondary outcomes involve the assessment of the cognitive function. The primary outcome will be assessed by the MMSE and the Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-Cog). The secondary outcomes will be assessed using other scales, such as the Clinical Dementia Rating Scale (CDR), and the Wechsler Adult Intelligence Scale-Revised (WAIS-R). The standard mean difference (SMD; Cohen *d*) will assess the effect sizes of the continuous variables. A small-sample (n<20) correction will be applied to SMD, leading to an effect size called Hedges *g*.

Exclusion Criteria

The following studies were excluded:

- Studies were non-RCTs or in the form of a letter, editorial, commentary, or case report.
- There was no definitive preventative impact evaluated, or the effects were evaluated for less than 12 weeks.
- Participants had vascular dementia; Parkinson disease–related dementia; delirium; depression and other mental illnesses; congenital brain function hypoplasia, such as Down syndrome; or subarachnoid hemorrhage.

Search Strategy

Two investigators (QH and KCHW) will independently perform the search strategy, and disagreements will be resolved by discussion or by a third investigator (JYZ). We will search for all the relevant citations published from the date of the respective database onset until Dec 31, 2023, in 3 English databases (ie, PubMed, Embase, and Cochrane Library). We will establish search strategies that combine keywords and indexed terms indicative of MCI or AD, nutritional intervention, and RCTs. Furthermore, the reference lists of the listed papers will be manually examined to seek new studies that are related. Any controversies will be resolved through dialogue. Multimedia Appendix 1 includes the search techniques.

Data Extraction

Two investigators (QH and KCHW) will independently extract the data from all eligible studies published in English using standardized spreadsheets that are predefined. Any discrepancies will be resolved through consensus by discussion between the 2 investigators or, if necessary, arbitrated by a third investigator (JYZ). The following information will be extracted from every study: first author, publication year, detailed trial information (ie, randomization, sequence concealment, blinding, nutritional intervention protocols, number of treatment arms, as well as the dose and frequency of interventions), the diagnosis criteria, characteristics of the patient (eg, age, gender, race, and baseline MMSE or ADAS-Cog scores), sample size, follow-up MMSE or ADAS-Cog scores, number of completed interventions, as well as the duration of the intervention and follow-up. We will contact the authors via email to obtain the raw data when the data on outcomes are incomplete in the original article; otherwise, we will not include studies lacking such data. At last, 2 investigators will cross-check all retrieved data to verify their accuracy.

Quality Assessment

The quality of the included studies will be evaluated by the Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB2) [24]. Various biases, such as selection bias (randomized sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (dealing with incomplete outcome data), reporting bias (selective reporting), and overall biases will be assessed in our study. The trials will be categorized into 3 types: low risk of bias, unclear risk of bias, and high risk of bias. Assessment of bias of the trials will be conducted by 2 investigators (QH and KCHW), and disagreements will be resolved through discussion with a third investigator (JYZ). Moreover, we will contact the authors asking for detailed allocation concealment and other characteristics when they are not available in the study.

Statistical Synthesis

Characteristics of Included Studies and Information Flow in the Network

For the eligible trials included in our analysis, we will generate descriptive statistics to provide a comprehensive overview of the population characteristics and key variables across all trials. These descriptive statistics will encompass factors such as age, disease subtype, and other relevant risk factors that may impact the outcomes of interest. To visually represent the network of evidence, we will construct a network diagram. The edges connecting different interventions will be depicted with widths proportional to the inverse of the variance of the summary impact for each direct treatment comparison. The size of the nodes in the diagram will correspond to the quantity of evidence accumulated for each treatment, represented by the total number of studies contributing to that node. In addition, we will use a contribution matrix to explore the direct comparisons that have a substantial influence on the relative effects within the network [21,22]. This matrix will help identify the specific comparisons that contribute significantly to the overall findings.

Assessment of the Transitivity Assumption

The transitivity assumption will be assessed by evaluating the distribution of modifiable variables, such as age and mean baseline cognitive function, between the intervention and the control group [23].

Pairwise Meta-Analyses and Network Meta-Analyses

By conducting the pairwise meta-analysis, we can quantitatively assess the effectiveness of interventions that have direct evidence. This analysis allows for a comparison of the treatment effects within individual studies, providing valuable insights into the efficacy of each intervention. To ensure transparency and facilitate interpretation, we will present the results of the pairwise meta-analysis using forest plots.

The NMA will be conducted using a Bayesian framework, pooling data from all included studies [24]. To provide a visual representation of the network of evidence, we will generate network plots, which summarize the geometry of the network. These plots will help illustrate the connections between different interventions and highlight the available evidence for each comparison. For the estimation of effect sizes, we will use contrast-based methods within the NMA framework. The surface under the cumulative ranking curve will be used to estimate the relative rank of the different nutritional interventions [25].

All data will be analyzed using the R 4.0.3 (R Core Team) software, specifically using the gemtc package. Estimates will be reported as SMDs and 95% credible intervals (CrIs). We will use 3 Markov chains with 100,000 iterations after an initial thinning of 10,000 and a thinning of 10. The convergence of the model will be estimated by checking trace plots and the Brooks-Gelman-Rubin statistical value.

A systematic review will be considered when studies are scarce, typically involving less than 2 available studies. Additionally, if the heterogeneity observed among the included studies is exceptionally high, typically exceeding 95%, a systematic review approach will be adopted.

Assessment of Inconsistency for Network Meta-Analysis (NMA)

Consistency refers to the statistical manifestation of transitivity while a lack thereof is known as inconsistency [26]. Inconsistency suggests a disagreement between these estimates and indicates potential issues with the consistency of evidence

across the network of studies. We will use the node-splitting method to assess inconsistency [27,28]. The presence of inconsistency between different estimates using direct and indirect evidence can be evaluated by assessing the *P* value. Inconsistency in the network is indicated by $P<.05$.

Assessment of Heterogeneity and Sensitivity Analyses

To quantify between-study heterogeneity, we will calculate the I^2 statistics with 95% CrI and τ^2 to convey the heterogeneity. τ^2 represents the variability in intervention effects across studies, while I^2 quantifies the proportion of total variability that is due to heterogeneity rather than chance. If I^2 >50%, it will be considered as moderate to substantial heterogeneity; in such cases, the effect sizes will be estimated using a random-effects model [29]. Moreover, we will estimate the outlier and influential study when I^2>50%, and then, we will perform the NMA or pairwise meta-analysis again, excluding the outliers and influential studies. Study-specific estimates and 95% CrIs, will be presented by forest plots. Subgroup meta-analyses and meta-regression analysis will be performed to estimate the source of heterogeneity. Subgroup analyses by different groups allow us to test specific hypotheses and describe why certain types of studies produce lower or higher effects than others. Performing subgroup analysis would help estimate if the interventional effects for the primary outcomes are robust. Meta-regression analysis could help quantify the effects by including covariates in the network meta-analysis models, if suitable. Then we will run subgroup and meta-regression with the following criteria: cognitive dysfunction severity at baseline, study year, sample size, risk of bias, duration of intervention, and number of recruiting centers (ie, single-center or multicentric studies).

Sensitivity analyses will be conducted to assess the robustness of the primary outcome results in the meta-analysis. These analyses will involve examining the impact of outliers, influential studies, risk of bias, and sample size by using the leave-one-out method. Specifically, each study will be systematically removed from the meta-analysis, and the pooled effect will be re-evaluated both in pairwise meta-analysis and NMA for each iteration. Studies with changes in the effect size exceeding 10% will be noted.

Assessment of Publication Bias

The comparison-adjusted [26] and contour-enhanced funnel plots [30] will be used to find out whether the results in imprecise trials differ from more precise trials. In addition, network meta-regression models and the Egger test will be performed to detect the effects between study size and effect size and to assess the asymmetry of the funnel plot, respectively.

Results

The initial search yielded 30,269 citations, of which 248 articles were identified as potentially eligible and will undergo evaluation for eligibility. Among these, a total of 197 articles were excluded for various reasons. This exclusion consisted of 3 duplicates, 39 articles without full-text availability, 45 articles lacking an assessment of cognitive function, 40 articles not meeting the criteria of being RCTs, 28 articles not in English, and 42 articles unrelated to the study objective. Ultimately, 51 studies meeting the inclusion criteria were included in our NMA. These studies, published between 1999 and 2023, consisted of 27 studies focusing on AD and 24 studies focusing on MCI. In total, these studies involved 8420 participants. We completed data extraction for all 51 studies by December 2023. Currently, we are actively engaged in data analysis and manuscript preparation. We plan to finalize the manuscript and publish the comprehensive results by the end of 2024.

Ethical approval was not required in the meta-analysis. Our study is merely based on the published literature, for which ethical approval has been obtained. To disseminate the evidence obtained, we will publish our results in an international peer-reviewed journal to improve preventive applications with scientific evidence.

Discussion

The global phenomenon of population aging has led to a significant increase in the prevalence of cognitive impairment, particularly AD and MCI [31]. This demographic shift has garnered substantial attention from health care providers, researchers, and policy makers due to the immense personal, societal, and economic implications [32]. As the current treatments for MCI and AD are limited and primarily focused on symptom management, identifying effective preventive strategies is of paramount importance [15]. The potential benefits of nutritional interventions for cognitive health have been a subject of considerable interest [2]. Various nutrients, dietary patterns, and dietary supplements have been investigated for their potential neuroprotective effects and cognitive function improvement. Therefore, through this study, we aim to consolidate the available evidence and provide a rigorous and comprehensive synthesis using the NMA approach. Moreover, identifying the most effective interventions will help guide future research efforts and resource allocation toward the most promising strategies.

It is important to acknowledge the limitations of this study. Although an NMA provides a robust statistical framework for synthesizing evidence, it is reliant on the quality and availability of data from included RCTs. Furthermore, potential sources of bias and heterogeneity among the studies may affect the robustness of the results.

In conclusion, the findings of this study will have significant implications for clinical practices as well as for informing public health strategies and policy making.

Acknowledgments

The authors would like to thank Dr Qing Xia and Yubo Ma for their helpful advice on this protocol.

This work is supported by the City University of Hong Kong New Research Initiatives Support from Central (APRC; grant 9610401).

Authors' Contributions

QH and KCHW participated in the study design and data collection; they also analyzed the data and wrote the manuscript. ANB participated in the discussion of the study design and data analysis; he also edited the manuscript. JYZ participated in the independent quality checking of all data included in the analysis. KHKC conceived the study, designed and coordinated the study, and revised the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search techniques.
[PDF File (Adobe PDF File), 60 KB - resprot_v13i1e47196_app1.pdf]

References

1. Petersen RC, Caracciolo B, Brayne C, Gauthier S, Jelic V, Fratiglioni L. Mild cognitive impairment: a concept in evolution. J Intern Med 2014 Mar 08;275(3):214-228 [FREE Full text] [doi: 10.1111/joim.12190] [Medline: 24605806]
2. Tahami Monfared AA, Byrnes MJ, White LA, Zhang Q. The humanistic and economic burden of Alzheimer's disease. Neurol Ther 2022 Jun 22;11(2):525-551 [FREE Full text] [doi: 10.1007/s40120-022-00335-x] [Medline: 35192176]
3. Mitchell AJ, Shiri-Feshki M. Rate of progression of mild cognitive impairment to dementia--meta-analysis of 41 robust inception cohort studies. Acta Psychiatr Scand 2009 Apr;119(4):252-265. [doi: 10.1111/j.1600-0447.2008.01326.x] [Medline: 19236314]
4. Morris JC, Storandt M, Miller JP, McKeel DW, Price JL, Rubin EH, et al. Mild cognitive impairment represents early-stage Alzheimer disease. Arch Neurol 2001 Mar 01;58(3):397-405. [doi: 10.1001/archneur.58.3.397] [Medline: 11255443]
5. Collie A, Maruff P. The neuropsychology of preclinical Alzheimer's disease and mild cognitive impairment. Neurosci Biobehav Rev 2000 May;24(3):365-374. [doi: 10.1016/s0149-7634(00)00012-9] [Medline: 10781696]
6. Rabinovici GD, Karlawish J, Knopman D, Snyder HM, Sperling R, Carrillo MC. Testing and disclosures related to amyloid imaging and Alzheimer's disease: common questions and fact sheet summary. Alzheimers Dement 2016 Apr;12(4):510-515. [doi: 10.1016/j.jalz.2016.03.002] [Medline: 27103054]
7. Coley N, Vaurs C, Andrieu S. Nutrition and cognition in aging adults. Clin Geriatr Med 2015 Aug;31(3):453-464. [doi: 10.1016/j.cger.2015.04.008] [Medline: 26195103]
8. Rosenberg A, Mangialasche F, Ngandu T, Solomon A, Kivipelto M. Multidomain interventions to prevent cognitive impairment, Alzheimer's disease, and dementia: from FINGER to world-wide FINGERS. J Prev Alzheimers Dis 2020;7(1):29-36. [doi: 10.14283/jpad.2019.41] [Medline: 32010923]
9. Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, et al. Dementia prevention, intervention, and care. Lancet 2017 Dec 16;390(10113):2673-2734. [doi: 10.1016/S0140-6736(17)31363-6] [Medline: 28735855]
10. McGrattan A, van Aller C, Narytnyk A, Reidpath D, Keage H, Mohan D, et al. Nutritional interventions for the prevention of cognitive impairment and dementia in developing economies in East-Asia: a systematic review and meta-analysis. Crit Rev Food Sci Nutr 2022 Dec 18;62(7):1838-1855. [doi: 10.1080/10408398.2020.1848785] [Medline: 33337250]
11. Xu Z, Sun W, Zhang D, Chung VC, Sit RW, Wong SY. Comparative effectiveness of interventions for global cognition in patients with mild cognitive impairment: a systematic review and network meta-analysis of randomized controlled trials. Front Aging Neurosci 2021 Jun 18;13:653340 [FREE Full text] [doi: 10.3389/fnagi.2021.653340] [Medline: 34220484]
12. Liu Y, Gao X, Na M, Kris-Etherton PM, Mitchell DC, Jensen GL. Dietary pattern, diet quality, and dementia: a systematic review and meta-analysis of prospective cohort studies. J Alzheimers Dis 2020;78(1):151-168. [doi: 10.3233/JAD-200499] [Medline: 32955461]
13. Hill E, Goodwill AM, Gorelik A, Szoeke C. Diet and biomarkers of Alzheimer's disease: a systematic review and meta-analysis. Neurobiol Aging 2019 Apr;76:45-52. [doi: 10.1016/j.neurobiolaging.2018.12.008] [Medline: 30682676]
14. Chen L, Xu X, Cao H, Li H. Comparison of effects of different dietary interventions on cognitive function in Alzheimer's disease: protocol for systematic review and network meta-analysis. BMJ Open 2021 Jan 15;11(1):e042997 [FREE Full text] [doi: 10.1136/bmjopen-2020-042997] [Medline: 33452198]
15. García-Casares N, Gallego Fuentes P, Barbancho M, López-Gigosos R, García-Rodríguez A, Gutiérrez-Bedmar M. Alzheimer's disease, mild cognitive impairment and mediterranean diet. a systematic review and dose-response meta-analysis. J Clin Med 2021 Oct 10;10(20):4642 [FREE Full text] [doi: 10.3390/jcm10204642] [Medline: 34682764]

16. Andrews V, Zammit G, O'Leary F. Dietary pattern, food, and nutritional supplement effects on cognitive outcomes in mild cognitive impairment: a systematic review of previous reviews. Nutr Rev 2023 Oct 10;81(11):1462-1489 [FREE Full text] [doi: 10.1093/nutrit/nuad013] [Medline: 37027832]
17. Vlachos GS, Scarmeas N. Dietary interventions in mild cognitive impairment and dementia. Dialogues Clin Neurosci 2019 Mar;21(1):69-82 [FREE Full text] [doi: 10.31887/DCNS.2019.21.1/nscarmeas] [Medline: 31607782]
18. Caldwell DM, Ades AE, Higgins JPT. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. BMJ 2005 Oct 15;331(7521):897-900 [FREE Full text] [doi: 10.1136/bmj.331.7521.897] [Medline: 16223826]
19. Salanti G, Marinho V, Higgins JP. A case study of multiple-treatments meta-analysis demonstrates that covariates should be considered. J Clin Epidemiol 2009 Aug;62(8):857-864. [doi: 10.1016/j.jclinepi.2008.10.001] [Medline: 19157778]
20. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015 Jan 01;4:1 [FREE Full text] [doi: 10.1186/2046-4053-4-1] [Medline: 25554246]
21. Chaimani A, Higgins JPT, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. PLoS One 2013;8(10):e76654 [FREE Full text] [doi: 10.1371/journal.pone.0076654] [Medline: 24098547]
22. Furukawa TA, Miura T, Chaimani A, Leucht S, Cipriani A, Noma H, et al. Using the contribution matrix to evaluate complex study limitations in a network meta-analysis: a case study of bipolar maintenance pharmacotherapy review. BMC Res Notes 2016 Apr 14;9(1):218 [FREE Full text] [doi: 10.1186/s13104-016-2019-1] [Medline: 27074861]
23. Guyot P, Pandhi S, Nixon R, Iqbal A, Chaves R, Karabis A, et al. AB0837 efficacy and safety of diclofenac in osteoarthritis (OA): results of a network meta-analysis (NMA) of legacy studies. Ann Rheum Dis 2015 Jun 09;74(Suppl 2):1180.1-111180. [doi: 10.1136/annrheumdis-2015-eular.2375]
24. Schwingshackl L, Chaimani A, Hoffmann G, Schwedhelm C, Boeing H. Impact of different dietary approaches on blood pressure in hypertensive and prehypertensive patients: protocol for a systematic review and network meta-analysis. BMJ Open 2017 Apr 26;7(4):e014736. [doi: 10.1136/bmjopen-2016-014736] [Medline: 28446526]
25. Salanti G, Ades AE, Ioannidis JPA. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol 2011 Feb;64(2):163-171. [doi: 10.1016/j.jclinepi.2010.03.016] [Medline: 20688472]
26. Salanti G, Del Giovane C, Chaimani A, Caldwell DM, Higgins JPT. Evaluating the quality of evidence from a network meta-analysis. PLoS One 2014 Jul 3;9(7):e99682 [FREE Full text] [doi: 10.1371/journal.pone.0099682] [Medline: 24992266]
27. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol 1997 Jun;50(6):683-691. [doi: 10.1016/s0895-4356(97)00049-8] [Medline: 9250266]
28. Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. Stat Med 2010 Mar 30;29(7-8):932-944. [doi: 10.1002/sim.3767] [Medline: 20213715]
29. Muñoz Fernández SS, Ivanauskas T, Lima Ribeiro SM. Nutritional strategies in the management of alzheimer disease: systematic review with network meta-analysis. J Am Med Dir Assoc 2017 Oct 01;18(10):897.e13-897.e30. [doi: 10.1016/j.jamda.2017.06.015] [Medline: 28807434]
30. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. J Clin Epidemiol 2008 Oct;61(10):991-996. [doi: 10.1016/j.jclinepi.2007.11.010] [Medline: 18538991]
31. Chen P, Cai H, Bai W, Su Z, Tang Y, Ungvari GS, et al. Global prevalence of mild cognitive impairment among older adults living in nursing homes: a meta-analysis and systematic review of epidemiological surveys. Transl Psychiatry 2023 Mar 11;13(1):88 [FREE Full text] [doi: 10.1038/s41398-023-02361-1] [Medline: 36906613]
32. Fang EF, Xie C, Schenkel JA, Wu C, Long Q, Cui H, et al. A research agenda for ageing in China in the 21st century (2nd edition): focusing on basic and translational research, long-term care, policy and social networks. Ageing Res Rev 2020 Dec;64:101174 [FREE Full text] [doi: 10.1016/j.arr.2020.101174] [Medline: 32971255]

Abbreviations

AD: Alzheimer disease
ADAS-Cog: Alzheimer's Disease Assessment Scale cognitive subscale
CDR: Clinical Dementia Rating Scale
CrI: credible interval
DSM: Diagnostic and Statistical Manual of Mental Disorders
GRADE: Grading of Recommendations, Assessment, Development and Evaluation
MCI: mild cognitive impairment
MMSE: Mini-Mental State Examination
NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
NMA: network meta-analysis

PICO: Population, Intervention, Comparison, Outcome
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
RCT: randomized controlled trial
SMD: standard mean difference
WAIS-R: Wechsler Adult Intelligence Scale-Revised

Edited by A Mavragani; submitted 11.03.23; peer-reviewed by M Danovska, H Li; comments to author 13.10.23; revised version received 18.10.23; accepted 23.11.23; published 28.02.24.

Please cite as:
He Q, Wu KCH, Bennett AN, Zhang JY, Chan KHK
Nutritional Interventions for the Prevention of Cognitive Decline in Patients With Mild Cognitive Impairment and Alzheimer Disease: Protocol for a Network Meta-Analysis of Randomized Controlled Trials
JMIR Res Protoc 2024;13:e47196
URL: https://www.researchprotocols.org/2024/1/e47196
doi:10.2196/47196
PMID:38416536

Protocol

The Effectiveness of a Telenutrition Intervention to Improve Dietary Behavior and Physical Activity Among Adolescents With Obesity: Protocol for a Systematic Review

Muhammad Ridwan Ansari[1,2], MSc; Nurul Kodriati[3], PhD; Ariani Arista Putri Pertiwi[4], DNP; Fatwa Sari Tetra Dewi[5], PhD

[1]Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia

[2]Department of Nutrition, Faculty of Public Health, Universitas Ahmad Dahlan, Yogyakarta, Indonesia

[3]Departement of Public Health, Faculty of Public Health, Universitas Ahmad Dahlan, Yogyakarta, Indonesia

[4]Department of Basic Nursing and Emergency, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia

[5]Department of Health Behavior, Environment and Social Medicine, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia

Corresponding Author:
Fatwa Sari Tetra Dewi, PhD
Department of Health Behavior, Environment and Social Medicine
Faculty of Medicine, Public Health and Nursing
Universitas Gadjah Mada
IKM building 3rd Fl
Farmako Street, North Sekip
Yogyakarta, 55281
Indonesia
Phone: 62 274 551409
Fax: 62 274 551410
Email: fatwasari@ugm.ac.id

Abstract

Background: The global obesity pandemic among adolescents is becoming a public health issue throughout the world. Telehealth use has significantly increased during and after the COVID-19 pandemic, including its application in adolescent obesity prevention and treatment.

Objective: This review aims to synthesize the evidence on the effectiveness of telenutrition in improving dietary behavior and physical activity in adolescents with obesity.

Methods: The PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols) guideline will be used to structure this protocol. The focus of the systematic review is guided by the population, intervention, comparator, and outcome (PICO) framework. A systematic search of Science Direct, PubMed, Cochrane, Embase, JMIR, ProQuest, and Google scholar databases will be conducted. Two authors will screen the titles and abstracts of identified studies independently and select studies according to the eligibility criteria. The full-text reading will be done independently by 2 reviewers to assess final eligibility. Any discrepancies will then be discussed and resolved. The Cochrane Collaboration Risk of Bias tool was used to assess the risk of bias; a descriptive analysis will summarize the effectiveness of the telenutrition or any type of telehealth intervention used.

Results: The systematic review is expected to be completed by the end of March 2024. The ongoing screening and review of the articles are currently being conducted.

Conclusions: This systematic review aims to summarize the effectiveness, features, design process, usability, and coherence of a telenutrition intervention using behavior change theory to improve dietary patterns and physical activity among adolescents with obesity. It will identify areas for improvement and best practices, informing the development of more useful and engaging telenutrition interventions for adolescents.

Trial Registration: PROSPERO CRD42023458336; http://tinyurl.com/cp46fjj9

International Registered Report Identifier (IRRID): DERR1-10.2196/53282

(JMIR Res Protoc 2024;13:e53282) doi:10.2196/53282

KEYWORDS

telehealth; obesity; telenutrition; adolescent; behavior change; virtual counseling; teenager; young adult; food intake; dietary pattern; intervention

Introduction

The global obesity pandemic is becoming a public health issue, particularly among children and adolescents aged 5 to 19 years [1]. Between 2013 and 2018, the trend of adolescent obesity nearly doubled in Indonesia [2,3]. Obesity is caused by unhealthy lifestyles, such as most adolescents not meeting the daily fruit and vegetable recommendation and engaging in less physical activity; additionally, approximately 65% of adolescents skip breakfast, and 56% of adolescents aged 15-19 years have regular daily consumption of sugar-sweetened beverages [4,5].

To address this issue, various programs and interventions have been implemented. Nutrition literacy interventions combined with behavior change communication interventions in a school-based setting have shown to be promising for improving BMI and reducing unhealthy food choices. The school environment has been identified as a strategic channel for health promotion among school-age adolescents [6,7]. However, certain gaps have been identified that explain why health and nutrition programs in school settings in Indonesia have not been as effective as desired. Some schools encountered competing priorities in supporting the program, such as a lack of teachers and time due to teaching constraints. Additionally, 21% of adolescents were not going to school, compounded by insufficient parental support [8,9].

Telehealth is an alternative method for increasing access to adolescents, as the target population, and their parents. A previous systematic review revealed that there is great potential in digital platforms for universal health promotion, especially among school-age children and adolescents [10]. Digital nutrition literacy combined with a behaviour change program delivered via a telehealth platform could be a promising solution to bridge the gap. The International Organization for Standardization defines telehealth intervention for children as "the use of telecommunication techniques for the purpose of providing telemedicine, medical education, and health education over a distance" [11]. A review was carried out to assess the use of digital health interventions, such as websites, short-text messages, gamification, social media, and multidigital component interventions, aimed at improving adolescent diet and physical activity. The review revealed that website interventions can influence behavior change in adolescent diet and physical activity. However, due to variability in engagement, these changes often are not sustained in the medium or long term [12]. Meanwhile, there is less evidence supporting the effectiveness of other digital platforms, such as apps, text messages, and social media [12].

During and after the COVID-19 pandemic, there has been an increase in evidence supporting the impact of telehealth interventions in improving health [13,14]. This medium provides more engagement features compared to other forms of digital intervention. Therefore, a systematic review is required to address the following:

- Synthesize the evidence on the effectiveness of telenutrition in improving dietary behavior and physical activity in adolescents with obesity.
- Identify specific intervention components that characterize the more successful telenutrition intervention, particularly in adolescent populations.

Methods

Overview

We will use the population, intervention, comparator, and outcome (PICO) framework to identify appropriate Medical Subject Headings (MeSH) terms for the literature search. Meanwhile, the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols) 2015 guideline will be used as the standard reporting protocol guideline checklist. The PRISMA-P 2015 guideline will aid in describing the rationale, hypothesis, and planned methods of the review [15]. The checklist is provided in Multimedia Appendix 1.

This systematic review will comprise a literature search, article selection, data extraction, quality appraisal, data analysis, and data synthesis. The protocol of this systematic review was prospectively registered on PROSPERO (CRD42023458336).

Eligibility Criteria

The PICO framework presented in Table 1 is derived from the research questions previously mentioned.

Table 1. The eligibility criteria based on the population, intervention, comparator, and outcome (PICO) framework.

Criteria	Detailed information
Population	Adolescents or young adults aged 13-18 years with overweight or obesity.
Intervention	Any digital health promotion intervention with any type of telehealth (including but not limited to either educational or personalized feedback or monitoring services).
Comparator	Other digital health promotion interventions delivered by other methods, such as social media, websites, and short-text messengers or studies with control groups without an intervention.
Outcomes	Healthy behavior and nutritional outcome, such as changes in dietary behavior, physical activity level, and BMI.

Search Strategy

We will search the following databases: Science Direct, PubMed, Cochrane, Embase, JMIR, ProQuest, and Google Scholar. Key terms relating to telehealth and telenutrition were extracted from an initial review of the literature. Specific search terms, such as "obesity," "adolescent," "dietary behaviors," and "physical activity," were identified in a preliminary scan of the literature and chosen in consultation with a medical librarian. Search terms will include MeSH terms and related keywords and are grouped into 3 themes presented in Table 2. All the MeSH terms and Keywords are included in Table 2 with the following structure: Obesity (MeSH OR keywords) AND Adolescent (MeSH OR keywords) AND Telenutrition (MeSH OR keywords). To broaden the scope of the article collection, we will not limit the publication period or language of publication in our search strategy. In addition to exploring these databases, a manual search will be performed to identify the reference lists of included studies. Authors of conference and poster abstracts selected for inclusion will be contacted to see if a full text is available to be included.

Table 2. Search terms.

Number	Category	MeSH[a] terms and keywords in titles or abstracts
1	Obesity	"Obesity"[Mesh] OR "Pediatric Obesity"[Mesh] OR "overweight"[MeSH Terms] OR "overweight"[All Fields]
2	Adolescent	("Adolescent" OR "Adolescent Behavior" OR "Adolescent Health" OR adolesce*)
3	Telenutrition	("Telenutrition" OR "Mobile Health" OR "mHealth" OR "Telehealth" OR "eHealth" OR "Short Message Service" OR "SMS" OR "Text Messag*" OR "cell phone" OR "telephone" OR "smartphone" OR "cellular" OR "mobile" OR "social media" OR "social network")
4	All categories	1 AND 2 AND 3

[a]MeSH: Medical Subject Headings.

Inclusion Criteria

Only human intervention studies, either quasi-experimental studies or randomized controlled trials, will be included in this review. This review will evaluate original research articles using digital health promotion interventions delivered via any type of telehealth and involving adolescents aged 13-18 years with overweight or obesity. Overweight and obesity among adolescents aged 5-19 years are defined by their BMI per age *z* score, as outlined in the World Health Organization growth chart references [16]. We will include any study that categorizes participants with a BMI per age *z* score >1 SD as overweight and those with a BMI >2 SD as obese.

Exclusion Criteria

The review focused mainly on the changes in healthy behaviors and nutritional outcomes, including dietary behavior, physical activity levels, and BMI. Any outcomes other than these will be excluded from our review. In addition, articles for which full texts cannot be obtained despite requests to the corresponding authors will be excluded.

Screening and Article Selection

All articles found through database searches will be saved in the citation and article management software Mendeley and Rayyan AI, which will be used to eliminate duplicates and screening. The titles and abstracts of all studies will be reviewed independently by 2 reviewers. Studies that do not meet the eligibility criteria will be excluded, and any disagreements will be discussed until a consensus is reached. The full text of the remaining studies will then be examined by 2 reviewers independently to determine final eligibility, with any disagreements resolved by a third and fourth reviewer. A PRISMA flow diagram will be used to record the details of the screening and selection process so that the study can be replicated.

Data Extraction and Management

One reviewer will read the full text of all the papers included in the final selection to extract the predetermined outcomes, which will be validated by a second reviewer. The outcomes will be extracted into a standard extraction form, which will be designed in Covidence (Veritas Health Innovation). The detailed extraction custom-built form is summarized in Table 3. Disagreements will be resolved through discussion, and if consensus cannot be reached, a third and fourth reviewer will be consulted. Missing data will be considered in the risk of bias assessment, but due to time constraints, authors will not be contacted.

Table 3. Summary of the data extraction template.

Information	Detail extraction
General study information	• Year of publication • Study setting (including the time frame before or after the COVID-19 pandemic, if available) • Analyzing the sample size • Sample demographics (including age, gender, and target population) • Intervention design information (including type, duration, and follow-up periods, if any)
Behavioral and nutrition literacy intervention	• Target health behaviors and intervention focus • Theory of the intervention • Behavior change technique
Telehealth and telenutrition	• Area of health care used • Name of the platform • Developers • Media platform • Design process or steps • Component and design features (ie, gamification, families' involvement, and SMS reminder)
Evaluation	• The outcomes measured • Any kind of effectiveness measurement • Participant health outcomes • Participant engagement or adherence rates (including participation or drop-out rates) • Feasibility and usability • Challenges and limitations (including ethical concerns and barriers during the experiment)

Quality Appraisal and Risk of Bias Assessment

Following the final selection of studies, 2 reviewers will independently assess the risk of bias in all papers included in the final selection. If there is a disagreement in judgment, the reviewers will discuss it before consulting the third and fourth reviewers. The Cochrane Collaboration Risk of Bias tool will be used to assess the randomized controlled trials included in the review and assign low, unclear, or high risk to the studies for each of the potential biases [17]. Studies will be classified as low risk if the identified bias is unlikely to significantly alter the results, and they are classified as high risk if the bias clearly has the potential to significantly alter the results. Unclear risk occurs when the bias imposes some doubt on the outcome. The risk of bias assessment will cover 6 domains: selection, performance, detection, attrition, reporting, and other bias [17].

Meanwhile, ROBINS-I (Risk Of Bias In Non-randomized Studies of Interventions) will be used for evaluating the risk of bias in estimates of the comparative effectiveness of interventions from studies that did not use randomization to allocate units to comparison groups [18]. A table will be created that summarizes the quality of all included studies.

Data Analysis and Synthesis

A meta-analysis is unlikely to be conducted due to the expected diversity of study aims, methods, and reported outcomes. As a result, we will conduct a descriptive analysis to summarize the extracted data. Each outcome will be coded as having no (0), some (+), or significant evidence (++) of effectiveness in both outcomes. Significant evidence will be coded only when the intervention (ie, nutritional literacy and behavior change communication via telehealth delivery) outperforms a comparator or control. The intervention will be considered to have some evidence of effectiveness if there is a significant difference over time but not between groups or a significant improvement in only a subgroup of the population. Studies will be grouped by target health behavior (eg, dietary pattern only, physical activity only, or both) and analyzed together to describe the effectiveness of telehealth or telenutrition interventions in general for both those target behaviors; in particular, the analysis will focus on either dietary pattern or physical activity. The discussion will synthesize the data to describe specific intervention components that characterize a successful telenutrition intervention, such as the type of digital platform, engagement features, theory, method, and behavior change strategy used. The theory, method, and behavior change strategy will be analyzed and presented based on the intervention mapping approach and its taxonomy, as described by Bartholomew et al [19] and Kok et al [20]. Furthermore, the information regarding the identified barriers and challenges of telehealth interventions will be summarized to give directions for future research and development.

Ethical Considerations

There will be no involvement from patients or the public in this study. This study synthesizes data from studies that were already peer reviewed and published. Thus, no ethical approval will be required.

Results

The systematic review is expected to be completed by the end of March 2024. The ongoing review and data extraction of the articles is currently being conducted. The findings of this study will be outlined in the following subsections: (1) study selection,

(2) study characteristics, (3) synthesis of results (behavior change strategy and method or telehealth development and intervention), as well as (4) impact and evaluation, including challenges and barriers of study implementation.

Discussion

A systematic and transparent review of the literature will provide a better understanding of the current state-of-the-art telehealth or telenutrition approaches, how they are used, and their effectiveness. Strengths, limitations, and implications for the interaction of technology and behavioral health management will help inform and improve the development, acceptability, and effectiveness of future telehealth approaches in managing adolescent obesity for clinicians, telehealth providers, and relevant stakeholders. Based on the data, we will outline the conclusions, the strengths and limitations of our systematic review, and important directions for future research. Telehealth has grown over the past decade, with its popularity increasing during the COVID-19 pandemic. In addition, our review aims to differentiate findings between before and after the COVID-19 pandemic, if possible. Furthermore, the findings will be interpreted carefully, taking into consideration the potential scalability to other areas or countries with similar contexts. Our study has some potential limitations due to limited resources; we were unable to conduct manual searching and identification of reference lists of included studies. The review also could not provide a clear effect estimate between the telehealth intervention and health outcomes, as a meta-analysis could not be conducted.

Acknowledgments

The authors would like to thank the Faculty of Medicine, Public Health and Nursing of the Universitas Gadjah Mada and the Faculty of Public Health of the Universitas Ahmad Dahlan, Indonesia, for their support of this study. Our special thanks goes to Herman Herman, PhD, from the Faculty of Information and Technology at Universitas Ahmad Dahlan for the useful discussion during our protocol design.

Authors' Contributions

MRA and FSTD conceived the study topic and designed the review protocol. MRA and NK performed article screening, reviewed by AAPP and FSTD. MRA prepared the first draft of the protocol, and revisions were made by NK, AAPP, and FSTD. The manuscript was submitted after all authors reviewed and agreed to it.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols) checklist.
[PDF File (Adobe PDF File), 150 KB - resprot_v13i1e53282_app1.pdf]

References

1. Barata CO, Barquera S, Baur L. World obesity atlas 2022. World Obesity. 2022 Mar 04. URL: https://www.worldobesity.org/resources/resource-library/world-obesity-atlas-2022 [accessed 2023-10-19]
2. Balitbangkes RI. Laporan Nasional Riset Kesehatan Dasar 2013 (National Basic Health Research Report 2013). Kementerian Kesehatan RI. Jakarta, Indonesia: Lembaga Penerbit Badan Penelitian dan Pengembangan Kesehatan; 2013. URL: https://repository.badankebijakan.kemkes.go.id/id/eprint/4467/1/Laporan_riskesdas_2013_final.pdf [accessed 2023-10-19]
3. Balitbangkes RI. Laporan Nasional Riset Kesehatan Dasar 2018 (National Basic Health Research Report 2018). Kementerian Kesehatan RI. Jakarta, Indonesia: Lembaga Penerbit Badan Penelitian dan Pengembangan Kesehatan RI; 2018. URL: https://repository.badankebijakan.kemkes.go.id/id/eprint/3514/1/Laporan%20Riskesdas%202018%20Nasional.pdf [accessed 2023-10-19]
4. Rachmi CN, Jusril H, Ariawan I, Beal T, Sutrisna A. Eating behaviour of Indonesian adolescents: a systematic review of the literature. Public Health Nutr 2020 Sep 10;24(S2):s84-s97. [doi: 10.1017/s1368980020002876]
5. Sartika RAD, Atmarita A, Duki MIZ, Bardosono S, Wibowo L, Lukito W. Consumption of sugar-sweetened beverages and its potential health implications in Indonesia. Kesmas: Jurnal Kesehatan Masyarakat Nasional 2022 Feb 01;17(1). [doi: 10.21109/kesmas.v17i1.5532]
6. O'Brien KM, Barnes C, Yoong S, Campbell E, Wyse R, Delaney T, et al. School-based nutrition interventions in children aged 6 to 18 years: an umbrella review of systematic reviews. Nutrients 2021 Nov 17;13(11):4113 [FREE Full text] [doi: 10.3390/nu13114113] [Medline: 34836368]
7. Jacob CM, Hardy-Johnson PL, Inskip HM, Morris T, Parsons CM, Barrett M, et al. A systematic review and meta-analysis of school-based interventions with health education to reduce body mass index in adolescents aged 10 to 19 years. Int J Behav Nutr Phys Act 2021 Jan 04;18(1):1 [FREE Full text] [doi: 10.1186/s12966-020-01065-9] [Medline: 33397403]

8. Octaria Y, Apriningsih A, Dwiriani CM, Februhartanty J. School readiness to adopt a school-based adolescent nutrition intervention in urban Indonesia. Public Health Nutr 2020 May 07;24(S2):s72-s83. [doi: 10.1017/s1368980020001299]
9. Liu KSN, Chen JY, Ng MYC, Yeung MHY, Bedford LE, Lam CLK. How does the family influence adolescent eating habits in terms of knowledge, attitudes and practices? a global systematic review of qualitative studies. Nutrients 2021 Oct 22;13(11):3717. [doi: 10.3390/nu13113717]
10. Oh C, Carducci B, Vaivada T, Bhutta Z. Digital interventions for universal health promotion in children and adolescents: a systematic review. Pediatrics 2022 May 01;149(Suppl 5):A. [doi: 10.1542/peds.2021-053852H] [Medline: 35503335]
11. Chai LK, Collins CE, May C, Brown LJ, Ashman A, Burrows TL. Fidelity and acceptability of a family-focused technology-based telehealth nutrition intervention for child weight management. J Telemed Telecare 2019 Aug 07;27(2):98-109. [doi: 10.1177/1357633x19864819]
12. Rose T, Barker M, Maria Jacob C, Morrison L, Lawrence W, Strömmer S, et al. A systematic review of digital interventions for improving the diet and physical activity behaviors of adolescents. J Adolesc Health 2017 Dec;61(6):669-677 [FREE Full text] [doi: 10.1016/j.jadohealth.2017.05.024] [Medline: 28822682]
13. Shaver J. The state of telehealth before and after the COVID-19 pandemic. Prim Care 2022 Dec;49(4):517-530 [FREE Full text] [doi: 10.1016/j.pop.2022.04.002] [Medline: 36357058]
14. Suran M. Increased use of medicare telehealth during the pandemic. JAMA 2022 Jan 25;327(4):313. [doi: 10.1001/jama.2021.23332] [Medline: 35076683]
15. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015 Jan 01;4:1 [FREE Full text] [doi: 10.1186/2046-4053-4-1] [Medline: 25554246]
16. BMI-for-age (5-19 years). World Health Organization. URL: https://www.who.int/tools/growth-reference-data-for-5to19-years/indicators/bmi-for-age [accessed 2024-02-14]
17. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Cochrane Bias Methods Group, Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011 Oct 18;343(oct18 2):d5928-d5928 [FREE Full text] [doi: 10.1136/bmj.d5928] [Medline: 22008217]
18. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016 Oct 12;355:i4919 [FREE Full text] [doi: 10.1136/bmj.i4919] [Medline: 27733354]
19. Bartholomew Eldredge LK, Parcel GS, Kok G, Gottlieb NH, FernÃ¡ndez ME. Planning Health Promotion Programs: An Intervention Mapping Approach. 3rd Edition. Hoboken, NJ: Jossey-Bass; 2011.
20. Kok G, Gottlieb NH, Peters GY, Mullen PD, Parcel GS, Ruiter RAC, et al. A taxonomy of behaviour change methods: an Intervention Mapping approach. Health Psychol Rev 2016 Sep;10(3):297-312 [FREE Full text] [doi: 10.1080/17437199.2015.1077155] [Medline: 26262912]

Abbreviations

MeSH: Medical Subject Heading
PICO: population, intervention, comparator, and outcome
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols
ROBINS-I: Risk Of Bias In Non-randomized Studies of Interventions

Edited by A Mavragani; submitted 02.10.23; peer-reviewed by S Mitra, AC Hovadick; comments to author 02.12.23; revised version received 02.01.24; accepted 02.02.24; published 05.03.24.

Please cite as:
Ansari MR, Kodriati N, Pertiwi AAP, Dewi FST
The Effectiveness of a Telenutrition Intervention to Improve Dietary Behavior and Physical Activity Among Adolescents With Obesity: Protocol for a Systematic Review
JMIR Res Protoc 2024;13:e53282
URL: https://www.researchprotocols.org/2024/1/e53282
doi:10.2196/53282
PMID:38441950

Protocol

Patients' Experiences of Digital Health Interventions for the Self-Management of Chronic Pain: Protocol for a Systematic Review and Thematic Synthesis

Ashleigh Main[1], BSc, MSc; Haruno McCartney[1], BSc; Maryam Ibrar[1], MA, MSc; Harleen Kaur Rai[1], BSc, MSc, PhD; Fiona Muirhead[2], BSc, MSc, PhD; Alexandra Mavroeidi[3], BSc, MSc, PhD; Roma Maguire[1], BSc, MSc, PhD

[1]Department of Computer and Information Sciences, University of Strathclyde, Glasgow, United Kingdom

[2]Physical Activity for Health, School of Psychological Sciences and Health, University of Strathclyde, Glasgow, United Kingdom

[3]Department of Occupational Therapy and Human Nutrition and Dietetics, School of Health & Life Sciences, Glasgow Caledonian University, Glasgow, United Kingdom

Corresponding Author:
Ashleigh Main, BSc, MSc
Department of Computer and Information Sciences
University of Strathclyde
26 Richmond Street
Glasgow, G1 1XH
United Kingdom
Phone: 44 (0)141 552 4400
Email: ashleigh.main@strath.ac.uk

Abstract

Background: Chronic pain is a highly prevalent condition that requires multidisciplinary treatment. However, in the United Kingdom, access to specialist pain clinics where patients can receive medical multidisciplinary treatment is limited, and provision varies between health boards. As such, self-management of chronic pain using digital tools has been gaining traction recently, but evidence of its effectiveness from clinical-based trials focuses mainly on quantitative outcomes.

Objective: This systematic review aims to identify, appraise, and synthesize qualitative evidence on patients' experiences with digital health interventions (DHIs) for the management of chronic pain.

Methods: This systematic review will consider qualitative and mixed methods studies that explore the experience of patients (aged 18 years and older) with chronic pain engaging in DHIs to manage their pain. MEDLINE Ovid, PubMed, Embase, CINAHL, PsycINFO, and Scopus databases will be searched for published studies. The systematic review will be conducted in accordance with the ENTREQ (Enhancing Transparency in Reporting the Synthesis of Qualitative Research) guidelines. Following the 3-step thematic synthesis methodology of Thomas and Harden, titles and abstracts will be screened by 2 independent reviewers (AM and HM), and a third reviewer (MI or FM) will resolve any conflict that arises before the full-text screening. The Critical Appraisal Skills Programme checklist tool will be used to critically appraise the included studies. The extracted data will be imported to NVivo (QSR International), where thematic synthesis will be used to derive analytical themes from the included studies.

Results: Themes that encapsulate the patient experience will be identified from qualitative evidence, and these themes will shed light on the perceived benefits and disadvantages, usability, acceptability, and the overall impact digital tools can have on the lives of those with chronic pain.

Conclusions: This systematic review will identify, appraise, and synthesize the overall experience of patients engaging in DHI to manage a diverse range of chronic pain conditions. By elaborating the patient experience through qualitative analysis, the findings from this review will enhance our current understanding of the experiences of patients with chronic pain using digital tools for the self-management of their pain and highlight what person-centered elements are essential for future DHI development.

Trial Registration: PROSPERO CRD42023445100; http://tinyurl.com/4z77khfs

International Registered Report Identifier (IRRID): DERR1-10.2196/52469

(JMIR Res Protoc 2024;13:e52469) doi:10.2196/52469

KEYWORDS

chronic pain; digital health; digital tool; digital health intervention; mHealth; eHealth; pain-management; person-centered; experience; protocol; patients' experiences; patient experiences; self-management; systematic review; thematic synthesis; protocol.

Introduction

Background

Chronic pain is a major public health condition affecting more than 30% of the world's population [1]. Defined as pain that persists beyond the expected recovery period of 12 weeks [2], chronic pain is a complex phenomenon, and the root causes are only partially understood [3]. Following recent developments, the *International Classification of Diseases* has adapted its definition of chronic pain to encompass both primary and secondary chronic pain. Chronic secondary pain is initially regarded as a symptom caused by an underlying condition or disease (such as cancer, rheumatoid arthritis, or endometriosis), whereas in chronic primary pain, pain emerges without any history of an injury or operation (eg, fibromyalgia, headache, and musculoskeletal pain) [2].

Chronic pain is a complex condition pertaining to biological, psychological, and social components [4]. A UK-based population study found that of 28 million adults affected by chronic pain, around 12% of people described their pain to be moderately or severely disabling [5]. In addition to the physical burden, psychological challenges are frequently associated with chronic pain with many individuals reporting a significantly deteriorated quality of life [6]. Chronic pain can also have a considerable socioeconomic impact, with pain impacting work effectiveness, which in many cases leads to unemployment [7].

To successfully manage the multifaceted nature of chronic pain, a multidisciplinary treatment approach is required. Substantial evidence supports that combining approaches across disciplines is the most effective treatment in addressing the biopsychosocial nature of chronic pain [8-12], although access to evidence-based multidisciplinary treatment is not always readily available [13]. Many patients with chronic pain rely on their general practitioner for advice [14], and those who do get referred to specialist pain clinics can wait months to years for assessment and treatment [13].

A means of overcoming the barriers of accessibility to multidisciplinary health care could be the delivery of self-management strategies using digital tools, which have become more prevalent than ever since the COVID-19 pandemic. Digitization has transformed the health care landscape by offering more accessible alternatives to conventional medical treatment [15]. Digital health interventions (DHIs) use a range of digital tools, such as smartphone apps, websites, and social media campaigns, to deliver self-management programs remotely [16]. Self-management strategies for chronic pain management include symptom tracking, physical activity, education, relaxation techniques, and cognitive behavioral therapy [17-20]. According to the Office of National Statistics, approximately 90% of private UK households have computers and mobile phones in 2022; therefore, digital health is accessible to almost everyone [21].

Research regarding the impact of digital tools has grown exponentially in recent years. A number of systematic reviews have evaluated the effectiveness of digital tools in areas such as chronic pain in general [16,22], specific chronic pain conditions [23,24], the impact of individual modalities such as smartphones [25,26], and specific age groups [27]. It is widely considered that such tools are effective in improving clinical outcomes such as pain intensity, pain interference, and improvements in quality of life [28].

Although there is substantial evidence on the positive effect digital tools can have on chronic pain patients' symptoms, most research focuses on quantitative outcomes. Quantitative research is essential in supporting evidence-based practice, which emphasizes findings from well-designed research to provide high-quality patient care [29]. However, it has been argued that quantitative evidence from clinical trials does not take into account patients' individual experiences, thus overlooking the complex nature of chronic pain [30]. In response to standard evidence-based practice, there has been a shift to person-centered care, which has transformed the health care system. Person-centered care was first described as "understanding the patient as a unique human being" [31], where the sole focus is on the individual, and treatment can be tailored to a patient's needs. The World Health Organization (WHO) guidelines advise person-centered care as a core element of good quality health care [2], and studies have shown that person-centered care significantly improves clinical outcomes [32].

A systematic review of qualitative studies by Fernandes et al [33] evaluated enablers and barriers to telehealth interventions for individuals with musculoskeletal pain, and Svendsen et al [34] explored engagement strategies, facilitators, and barriers to the use of DHIs for low back pain management. However, both qualitative reviews focus on barriers and facilitators to DHI engagement rather than overall patient experience, and both studies target a specific condition as opposed to a diverse range of chronic pain conditions. Despite the abundance of qualitative literature exploring the experiences of patients with chronic pain with DHIs, the evidence that encapsulates the experience as a whole has yet to be synthesized.

To address this gap in the research, this review will identify, appraise, and synthesize qualitative data, through a thematic synthesis approach, to provide a detailed account of how patients with chronic pain experience DHIs, and if and why they experience changes and improvements in patient-reported outcomes. Thematic synthesis was developed to address questions concerning intervention need, appropriateness, and acceptability and can produce results that have the potential to inform the design and practice of interventions [35]. Descriptive explanations of patients with chronic pain views could uncover a better understanding of DHI lived experiences from the point of view of the end user—for whom the treatment is designed. Therefore, the findings from this review could have the potential

to enhance our understanding of how DHIs impact patients with chronic pain and emphasize what patient-centered aspects are important for future DHI development.

Objectives

This review aims to identify, appraise, and synthesize existing qualitative evidence on patients' experiences with a DHI for the self-management of chronic pain.

Methods

Overview

The proposed review will be conducted in accordance with "ENTREQ (Enhancing Transparency in Reporting the Synthesis of Qualitative Research) guidelines [36].

Search Strategy

The search strategy and eligibility criteria will be based on the SPIDER (Sample, Phenomenon of Interest, Design, Evaluation and Research) framework [37]. This framework was deemed the most suitable for answering the research question as it has been adapted for clarity in nonquantitative research by outlining key characteristics of qualitative research questions [37].

Keywords used in the search strategy adhere to each of the key characteristics of the SPIDER framework. These include chronic pain as the sample ("fibromyalgia" and "rheumatoid arthritis"), DHIs as the phenomenon of interest ("mHealth" and "telemedicine"), qualitative methods as the design and research type ("qualitative" and "thematic analysis"), and patient experience as the evaluated outcomes ("patient satisfaction" and "patient attitudes").

The search strategy will involve an initial search of electronic databases, followed by the analysis of keywords in the titles and abstracts of each database search. The search will then continue to the reference lists of selected articles to identify additional studies not located through the electronic database search. The strategy will aim to locate published articles—gray literature and unpublished articles will be excluded from the review. Due to the rapidly evolving nature of digital technology, the search will be limited to articles published within the last 10 years in order to capture the most relevant literature (2013-2023). The search will also be limited to articles published in the English language. The search strategy will be adapted for each electronic database. A detailed search strategy for each database is presented in Multimedia Appendix 1.

Information Sources

A literature search for qualitative and mixed methods studies will be conducted on the following electronic databases: Embase, MEDLINE, PubMed, CINAHL, PsycINFO, and Scopus. These databases have been chosen as they encompass nursing, medicine, social sciences, and psychology literature, which are deemed the most appropriate for answering the research question concerning patient experience and chronic pain.

Eligibility Criteria

Inclusion criteria will follow the SPIDER [37] framework. Textbox 1 shows the list of inclusion and exclusion criteria.

Textbox 1. Inclusion and exclusion criteria based on the SPIDER (Sample, Phenomenon of Interest, Design, Evaluation and Research) framework.

Inclusion criteria

- Papers reporting on participants (aged ≥18 years old) with a diagnosis of chronic pain
- Papers that report on digital health interventions to deliver self-management strategies for chronic pain
- Qualitative studies and mixed methods studies with a qualitative component
- Papers that report on patient experience of participating in a digital health intervention through qualitative data
- Papers published in the English language

Exclusion criteria

- Papers reporting on participants <18 years old
- Papers that have not specified that the participants have a chronic pain diagnosis
- Papers that include participants with chronic pain that does not exceed 12 weeks
- Papers that report on digital health interventions that incorporate external involvement
- Quantitative studies, quantitative components from mixed methods studies, gray literature, protocols, dissertations, and other reviews
- Papers that report data from participants who did not actively participate in the intervention
- Papers published in a language other than English

Sample

The review will include studies that involve patients older than age of 18 years with a diagnosis of chronic pain, who have participated in a DHI that delivered self-management strategies. Studies exploring the experience of children, adolescents, clinicians, or health professionals will be excluded. The definition of chronic pain will be aligned with the revised *International Classification of Diseases, 11th Revision* classification: pain that persists or recurs for more than 3 months [2], including both primary and secondary chronic pain. The included conditions are based on the National Institute for Health

and Care Excellence guidelines for assessing and managing both primary and secondary chronic pain [3].

Phenomenon of Interest

The phenomenon of interest explored in this review will be DHIs that deliver self-management strategies for chronic pain. Digital interventions regardless of platform (eg, telephone, web-based smartphone app, and social media) or self-management strategy (eg, exercise, education, relaxation, and meditation) will be included. Due to the terminological inconsistency existent in the current literature, the review will not distinguish among telehealth, telemedicine, eHealth, mobile health, or other similar terms. This review will use the term "digital health" to encompass all related terms.

Design and Research Type

The review will consider studies that explore patients' experiences of participating in a DHI. Qualitative data regarding patient experience collected through surveys, questionnaires, focus groups, group and individual interviews, and observational data will be examined, and this may have been collected remotely or face-to-face or in a group or one-to-one setting. Mixed methods studies with a qualitative component will be included; the quantitative data from these studies will not be used in this review. Protocols, dissertations, gray literature, and other reviews will be excluded.

Evaluated Outcomes

The outcome evaluated in this review will be patients' experiences of participating in DHIs. This will be in the form of qualitative data collected via questionnaires, focus groups, surveys, observational data, and interviews. Patients must have participated in the intervention either entirely or partially, for example, patients who started a digital intervention and followed through until completion, and patients who started a digital intervention and did not complete it in its entirety. Studies exploring patients' opinions or perceptions of what an intervention should involve without active participation will be excluded.

Data Extraction

Articles identified from the database search will be uploaded to EndNote (version 20; Clarivate), and any duplicates will be removed. Two independent reviewers (AM and HM) will then screen the titles and abstracts in Rayyan for papers that meet the inclusion criteria. The data extracted will adhere to the SPIDER tool, specifically outlining the sample, phenomenon of interest, and outcomes of significance to the objective of this review [37]. Any uncertainty between reviewers will be resolved by discussion, and if necessary, a third reviewer (MI or FM) will be requested to resolve any disagreements that persist. This process will be repeated for the papers included for full-text screening. Subsequently, the remaining papers will be included in the review. Each paper will be uploaded to NVivo (version 12) as this will facilitate the researcher's ability to perform data synthesis systematically and rigorously. The full data extraction table will include the author, year of publication, country design, data collection method, participant characteristics, type and description of the intervention, and potential themes.

Strategy for Data Synthesis

The results and discussion section of each included paper will be imported verbatim to NVivo, where a 3-step thematic synthesis approach based on the methodology described by Thomas and Harden will be used [38].

1. The first step will involve line-by-line coding of the results and discussion sections to identify contextual information on patient experiences with DHIs for the self-management of chronic pain.
2. Subsequently, similarly coded data will be clustered together to generate "descriptive themes." Descriptive themes will be based on verbatim data from the selected studies. Reviewers will reassess these codes to ensure the data are captured accurately.
3. Consequently, using inductive reasoning to make inferences from previous codes, reviewers will identify "analytical themes" about the experiences captured in the descriptive themes. These themes will be relevant to the key aim of this meta-synthesis. These themes are comprised based on inferences made from the data and, therefore, will be conducted independently by 1 reviewer (AM).

Risk of Bias or Critical Appraisal for Included Studies

The Critical Appraisal Skills Programme (CASP) checklist tool will be used to assess the methodological quality of the included studies. The CASP tool was deemed appropriate for the context of this review as it is endorsed by Cochrane and the WHO [39] and is the most frequently used tool for quality appraisal in health-related qualitative evidence syntheses [40]. Two reviewers (AM and HM) will assess the quality of the included papers independently, and any discrepancies that arise between reviewers will be resolved through discussion. If an agreement is not met, an additional reviewer (MI or FM) will be consulted until a consensus has been reached.

Ethical Considerations

Ethical approval is not required for conducting the systematic review as the research does not directly involve human participants or access to personal or identifiable data. The findings from this review will be disseminated to a broad range of stakeholders, including academics, clinicians, and policy makers. The findings will also be published in accredited peer-reviewed journals. This protocol is part of a larger PhD project; therefore, the findings will also be included as part of the thesis.

Results

This review will synthesize qualitative literature on patients' experiences of participating in a DHI for the self-management of chronic pain. Using thematic synthesis, an adapted version of Braun and Clark's thematic analysis developed for the purpose of secondary data synthesis [38,41], analytical themes will be derived from the included studies. We anticipate that the results from this review will characterize the patient experience of DHIs for the self-management of chronic pain and explain the impact digital tools have on the lives of those with chronic pain. These findings will emphasize what patient-centered aspects are essential for future DHI

development, such as how they engaged with DHIs, perceived advantages and disadvantages, which aspects of DHIs they felt worked well and which could be improved, and insights on acceptability and usability. Evidence-based practice emphasizes evidence from well-designed research. However, it has been argued that this approach does not value individual experience and subsequently does not effectively represent the complexity of the chronic pain experience [38]. The results of this qualitative systematic review will enhance our understanding of the way patients experience DHIs for the self-management of chronic pain by emphasizing individual experience from a person-centered approach.

Discussion

Principal Findings

Previous systematic reviews have demonstrated the effectiveness of DHIs in improving patients' outcomes across various health conditions, including chronic pain in general [16,22] as well as specific chronic pain conditions like musculoskeletal pain [23]. However, there is a lack of research evaluating qualitative studies that explore how patients with chronic pain experience such improvements in DHIs. A qualitative exploration of experiences has the potential to generate an in-depth, representative, conceptual understanding of how patients exhibit such improvements in outcomes. Themes that characterize the patient experience of participating in DHIs for the self-management of chronic pain will be identified to capsulate the impact DHIs have on individuals living with chronic pain.

Strengths and Limitations

The comprehensive systematic approach to the current review is a major strength of this research. The search strategy and inclusion criteria are based on SPIDER, a framework adapted for clarity in qualitative research by defining crucial characteristics of qualitative research questions [37]. The search strategies for each database were developed with the help of 2 specialist librarians (see Multimedia Appendix 1), and search terms regarding chronic pain were taken from the National Institute for Health and Care Excellence guidelines for the management of chronic pain [3]. The review will be guided by the ENTREQ checklist to ensure a rigorous systematic approach is taken to synthesize the qualitative evidence [36]. The quality of included studies will be assessed using the CASP checklist tool, which has been endorsed by Cochrane and the WHO [39]. Following the 3-step thematic synthesis approach based on the methodology described by Thomas and Harden, extracted data will be reviewed by 2 independent researchers (AM and HM), and a third reviewer (MI or FM) will be consulted to resolve any issues that arise.

Limitations of this review include the exclusion of studies published in a language other than English, as well as gray literature, both of which could have valuable contributions to the research outcomes. Furthermore, although thematic synthesis is a powerful method that can draw overall conclusions on a specific topic, the raw data from each included study are not analyzed, which could undermine the richness of the data from each primary study.

Conclusions

This systematic review will be the first to synthesize the overall experience of patients engaging in DHIs to manage a diverse range of chronic pain conditions. The in-depth analysis provided by qualitative data will enhance our current knowledge, representing the point of view of the end user—for whom the digital interventions are designed to treat. By elaborating the patient experience through qualitative analysis, the findings from this review have the potential to inform the future development of DHIs by highlighting which person-centered aspects are crucial to effectively manage symptoms of chronic pain.

Acknowledgments

The authors thank the University of Strathclyde librarians Elaine Blair from the Faculty of Science and Sarah Kevill from Humanities and Social Sciences for their support in developing the search strategies for this review. This systematic review is part of a PhD studentship funded by the Dr David Stirling Health Research Fund to support research into Chronic Pain.

Data Availability

Data sharing is not applicable to the current article as no data were generated or analyzed during this study.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy for each database.
[DOCX File , 17 KB - resprot_v13i1e52469_app1.docx]

References

1. Cohen SP, Vase L, Hooten WM. Chronic pain: an update on burden, best practices, and new advances. Lancet 2021;397(10289):2082-2097. [doi: 10.1016/S0140-6736(21)00393-7] [Medline: 34062143]

2. ICD-11: International Classification of Diseases (11th revision). World Health Organization. URL: https://icd.who.int/ [accessed 2023-06-16]
3. Chronic pain (primary and secondary) in over 16s: assessment of all chronic pain and management of chronic primary pain. National Institute for Health and Care Excellence. 2021. URL: https://www.nice.org.uk/guidance/ng193 [accessed 2023-06-20]
4. El-Metwally A, Shaikh Q, Aldiab A, Al-Zahrani J, Al-Ghamdi S, Alrasheed AA, et al. The prevalence of chronic pain and its associated factors among Saudi Al-Kharj population; a cross sectional study. BMC Musculoskelet Disord 2019;20(1):177 [FREE Full text] [doi: 10.1186/s12891-019-2555-7] [Medline: 31027485]
5. Fayaz A, Croft P, Langford RM, Donaldson LJ, Jones GT. Prevalence of chronic pain in the UK: a systematic review and meta-analysis of population studies. BMJ Open 2016;6(6):e010364 [FREE Full text] [doi: 10.1136/bmjopen-2015-010364] [Medline: 27324708]
6. Cragg JJ, Warner FM, Shupler MS, Jutzeler CR, Cashman N, Whitehurst DGT, et al. Prevalence of chronic pain among individuals with neurological conditions. Health Rep 2018;29(3):11-16 [FREE Full text] [Medline: 29561565]
7. Adams G, Salomons TV. Attending work with chronic pain is associated with higher levels of psychosocial stress. Can J Pain 2021;5(1):107-116 [FREE Full text] [doi: 10.1080/24740527.2021.1889925] [Medline: 34189394]
8. Hooten WM. Chronic pain and mental health disorders: shared neural mechanisms, epidemiology, and treatment. Mayo Clin Proc 2016;91(7):955-970 [FREE Full text] [doi: 10.1016/j.mayocp.2016.04.029] [Medline: 27344405]
9. Takahashi N, Kasahara S, Yabuki S. Development and implementation of an inpatient multidisciplinary pain management program for patients with intractable chronic musculoskeletal pain in Japan: preliminary report. J Pain Res 2018;11:201-211 [FREE Full text] [doi: 10.2147/JPR.S154171] [Medline: 29391827]
10. Takahashi N, Takatsuki K, Kasahara S, Yabuki S. Multidisciplinary pain management program for patients with chronic musculoskeletal pain in Japan: a cohort study. J Pain Res 2019;12:2563-2576 [FREE Full text] [doi: 10.2147/JPR.S212205] [Medline: 31686898]
11. Vanhaudenhuyse A, Gillet A, Malaise N, Salamun I, Grosdent S, Maquet D, et al. Psychological interventions influence patients' attitudes and beliefs about their chronic pain. J Tradit Complement Med 2018;8(2):296-302 [FREE Full text] [doi: 10.1016/j.jtcme.2016.09.001] [Medline: 29736385]
12. Staudt MD. The multidisciplinary team in pain management. Neurosurg Clin N Am 2022;33(3):241-249. [doi: 10.1016/j.nec.2022.02.002] [Medline: 35718393]
13. Deslauriers S, Déry J, Proulx K, Laliberté M, Desmeules F, Feldman DE, et al. Effects of waiting for outpatient physiotherapy services in persons with musculoskeletal disorders: a systematic review. Disabil Rehabil 2021;43(5):611-620. [doi: 10.1080/09638288.2019.1639222] [Medline: 31304824]
14. Mitra F, Woolley T. Links between perceived general practitioner support and the wellbeing of Australian patients with persistent pain. Aust J Gen Pract 2020;49(4):221-225 [FREE Full text] [doi: 10.31128/AJGP-06-19-4959] [Medline: 32233349]
15. Abernethy A, Adams L, Barrett M, Bechtel C, Brennan P, Butte A, et al. The promise of digital health: then, now, and the future. NAM Perspect 2022;2022:1-24 [FREE Full text] [doi: 10.31478/202206e] [Medline: 36177208]
16. Hussain A, Haroon H, Ahmed A, Gilani SA. Digital technologies in management of chronic pain—a systematic review. J Pak Med Assoc 2022;72(6):1158-1165 [FREE Full text] [doi: 10.47391/JPMA.3885] [Medline: 35751328]
17. Grasaas E, Helseth S, Fegran L, Stinson J, Småstuen M, Lalloo C, et al. App-based intervention among adolescents with persistent pain: a pilot feasibility randomized controlled trial. Pilot Feasibility Stud 2022;8(1):158 [FREE Full text] [doi: 10.1186/s40814-022-01113-0] [Medline: 35897086]
18. Sandal LF, Bach K, Øverås CK, Svendsen MJ, Dalager T, Jensen JSD, et al. Effectiveness of app-delivered, tailored self-management support for adults with lower back pain-related disability: a selfBACK randomized clinical trial. JAMA Intern Med 2021;181(10):1288-1296 [FREE Full text] [doi: 10.1001/jamainternmed.2021.4097] [Medline: 34338710]
19. Huber S, Priebe JA, Baumann KM, Plidschun A, Schiessl C, Tölle TR. Treatment of low back pain with a digital multidisciplinary pain treatment app: short-term results. JMIR Rehabil Assist Technol 2017;4(2):e11 [FREE Full text] [doi: 10.2196/rehab.9032] [Medline: 29203460]
20. Shebib R, Bailey JF, Smittenaar P, Perez DA, Mecklenburg G, Hunter S. Randomized controlled trial of a 12-week digital care program in improving low back pain. NPJ Digit Med 2019;2:1 [FREE Full text] [doi: 10.1038/s41746-018-0076-7] [Medline: 31304351]
21. Percentage of homes and individuals with technological equipment. Office for National Statistics. 2022. URL: https://www.ons.gov.uk/aboutus/transparencyandgovernance/freedomofinformationfoi/percentageofhomesandindividualswithtechnologicalequipment#:~:text=Table%20A45%20shows%20that%20for,mobile%20phone%20are%20not%20collected) [accessed 2023-06-20]
22. Moreno-Ligero M, Moral-Munoz JA, Salazar A, Failde I. mHealth intervention for improving pain, quality of life, and functional disability in patients with chronic pain: systematic review. JMIR Mhealth Uhealth 2023;11:e40844 [FREE Full text] [doi: 10.2196/40844] [Medline: 36729570]
23. Valentijn PP, Tymchenko L, Jacobson T, Kromann J, Biermann CW, AlMoslemany MA, et al. Digital health interventions for musculoskeletal pain conditions: systematic review and meta-analysis of randomized controlled trials. J Med Internet Res 2022;24(9):e37869 [FREE Full text] [doi: 10.2196/37869] [Medline: 36066943]

24. Hewitt S, Sephton R, Yeowell G. The effectiveness of digital health interventions in the management of musculoskeletal conditions: systematic literature review. J Med Internet Res 2020;22(6):e15617 [FREE Full text] [doi: 10.2196/15617] [Medline: 32501277]
25. Pfeifer AC, Uddin R, Schröder-Pfeifer P, Holl F, Swoboda W, Schiltenwolf M. Mobile application-based interventions for chronic pain patients: a systematic review and meta-analysis of effectiveness. J Clin Med 2020;9(11):3557 [FREE Full text] [doi: 10.3390/jcm9113557] [Medline: 33167300]
26. Slattery BW, Haugh S, O'Connor L, Francis K, Dwyer CP, O'Higgins S, et al. An evaluation of the effectiveness of the modalities used to deliver electronic health interventions for chronic pain: systematic review with network meta-analysis. J Med Internet Res 2019;21(7):e11086 [FREE Full text] [doi: 10.2196/11086] [Medline: 31317869]
27. Dunham M, Bonacaro A, Schofield P, Bacon L, Spyridonis F, Mehrpouya H. Smartphone applications designed to improve older people's chronic pain management: an integrated systematic review. Geriatrics (Basel) 2021;6(2):40 [FREE Full text] [doi: 10.3390/geriatrics6020040] [Medline: 33917697]
28. Hadjiat Y, Arendt-Nielsen L. Digital health in pain assessment, diagnosis, and management: overview and perspectives. Front Pain Res (Lausanne) 2023;4:1097379 [FREE Full text] [doi: 10.3389/fpain.2023.1097379] [Medline: 37139342]
29. Scott K, McSherry R. Evidence-based nursing: clarifying the concepts for nurses in practice. J Clin Nurs 2009;18(8):1085-1095 [FREE Full text] [doi: 10.1111/j.1365-2702.2008.02588.x] [Medline: 19077021]
30. Neergaard MA, Olesen F, Andersen RS, Sondergaard J. Qualitative description—the poor cousin of health research? BMC Med Res Methodol 2009;9:52 [FREE Full text] [doi: 10.1186/1471-2288-9-52] [Medline: 19607668]
31. Balint E. The possibilities of patient-centered medicine. J R Coll Gen Pract 1969;17(82):269-276 [FREE Full text] [Medline: 5770926]
32. Kuipers SJ, Cramm JM, Nieboer AP. The importance of patient-centered care and co-creation of care for satisfaction with care and physical and social well-being of patients with multi-morbidity in the primary care setting. BMC Health Serv Res 2019;19(1):13 [FREE Full text] [doi: 10.1186/s12913-018-3818-y] [Medline: 30621688]
33. Fernandes LG, Devan H, Fioratti I, Kamper SJ, Williams CM, Saragiotto BT. At my own pace, space, and place: a systematic review of qualitative studies of enablers and barriers to telehealth interventions for people with chronic pain. Pain 2022;163(2):e165-e181. [doi: 10.1097/j.pain.0000000000002364] [Medline: 34433776]
34. Svendsen MJ, Wood KW, Kyle J, Cooper K, Rasmussen CDN, Sandal LF, et al. Barriers and facilitators to patient uptake and utilisation of digital interventions for the self-management of low back pain: a systematic review of qualitative studies. BMJ Open 2020;10(12):e038800 [FREE Full text] [doi: 10.1136/bmjopen-2020-038800] [Medline: 33310794]
35. Barnett-Page E, Thomas J. Methods for the synthesis of qualitative research: a critical review. BMC Med Res Methodol 2009;9:59 [FREE Full text] [doi: 10.1186/1471-2288-9-59] [Medline: 19671152]
36. Tong A, Flemming K, McInnes E, Oliver S, Craig J. Enhancing transparency in reporting the synthesis of qualitative research: ENTREQ. BMC Med Res Methodol 2012;12:181 [FREE Full text] [doi: 10.1186/1471-2288-12-181] [Medline: 23185978]
37. Cooke A, Smith D, Booth A. Beyond PICO: the SPIDER tool for qualitative evidence synthesis. Qual Health Res 2012;22(10):1435-1443. [doi: 10.1177/1049732312452938] [Medline: 22829486]
38. Thomas J, Harden A. Methods for the thematic synthesis of qualitative research in systematic reviews. BMC Med Res Methodol 2008;8:45 [FREE Full text] [doi: 10.1186/1471-2288-8-45] [Medline: 18616818]
39. Noyes J, Booth A, Flemming K, Garside R, Harden A, Lewin S, et al. Cochrane qualitative and implementation methods group guidance series-paper 3: methods for assessing methodological limitations, data extraction and synthesis, and confidence in synthesized qualitative findings. J Clin Epidemiol 2018;97:49-58 [FREE Full text] [doi: 10.1016/j.jclinepi.2017.06.020] [Medline: 29247700]
40. Long HA, French DP, Brooks JM. Optimising the value of the Critical Appraisal Skills Programme (CASP) tool for quality appraisal in qualitative evidence synthesis. Res Meth Med Health Sci 2020;1(1):31-42 [FREE Full text] [doi: 10.1177/2632084320947559]
41. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol 2006;3(2):77-101.

Abbreviations

CASP: Critical Appraisal Skills Programme
DHI: digital health intervention
ENTREQ: Enhancing Transparency in Reporting the Synthesis of Qualitative Research
SPIDER: Sample, Phenomenon of Interest, Design, Evaluation and Research
WHO: World Health Organization

Edited by A Mavragani; submitted 04.09.23; peer-reviewed by AM Aliosi, C Baxter, Z Galavi; comments to author 25.01.24; revised version received 12.02.24; accepted 14.02.24; published 07.03.24.

Please cite as:
Main A, McCartney H, Ibrar M, Rai HK, Muirhead F, Mavroeidi A, Maguire R
Patients' Experiences of Digital Health Interventions for the Self-Management of Chronic Pain: Protocol for a Systematic Review and Thematic Synthesis
JMIR Res Protoc 2024;13:e52469
URL: https://www.researchprotocols.org/2024/1/e52469
doi:10.2196/52469
PMID:38451694

Protocol

AI as a Medical Device for Ophthalmic Imaging in Europe, Australia, and the United States: Protocol for a Systematic Scoping Review of Regulated Devices

Ariel Yuhan Ong[1,2], MBChB; Henry David Jeffry Hogg[1,3], MBBS, MRes; Aditya U Kale[4,5], MBChB; Priyal Taribagil[1], MBBS; Ashley Kras[6], MD; Eliot Dow[7], MD, PhD; Trystan Macdonald[4,5,8], MBChB; Xiaoxuan Liu[4,5,8,9], PhD; Pearse A Keane[1,10,11], MD; Alastair K Denniston[4,5,8,9], PhD

[1]Moorfields Eye Hospital NHS Foundation Trust, London, United Kingdom

[2]Oxford Eye Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom

[3]Population Health Sciences Institute, Faculty of Medical Sciences, Newcastle University, Newcastle, United Kingdom

[4]Department of Ophthalmology, Queen Elizabeth Hospital Birmingham, University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom

[5]Institute of Inflammation and Ageing, University of Birmingham, Birmingham, United Kingdom

[6]Sydney Eye Hospital, Sydney, Australia

[7]Retinal Consultants Medical Group, Sacramento, CA, United States

[8]NIHR Birmingham Biomedical Research Centre, Birmingham, United Kingdom

[9]Centre for Regulatory Science and Innovation, Birmingham Health Partners, Birmingham, United Kingdom

[10]Institute of Ophthalmology, University College London, London, United Kingdom

[11]NIHR Moorfields Biomedical Research Centre, London, United Kingdom

Corresponding Author:
Alastair K Denniston, PhD
Institute of Inflammation and Ageing
University of Birmingham
College of Medical and Dental Sciences
Edgbaston
Birmingham, B15 2TT
United Kingdom
Phone: 44 01213716905
Email: a.denniston@bham.ac.uk

Abstract

Background: Artificial intelligence as a medical device (AIaMD) has the potential to transform many aspects of ophthalmic care, such as improving accuracy and speed of diagnosis, addressing capacity issues in high-volume areas such as screening, and detecting novel biomarkers of systemic disease in the eye (oculomics). In order to ensure that such tools are safe for the target population and achieve their intended purpose, it is important that these AIaMD have adequate clinical evaluation to support any regulatory decision. Currently, the evidential requirements for regulatory approval are less clear for AIaMD compared to more established interventions such as drugs or medical devices. There is therefore value in understanding the level of evidence that underpins AIaMD currently on the market, as a step toward identifying what the best practices might be in this area. In this systematic scoping review, we will focus on AIaMD that contributes to clinical decision-making (relating to screening, diagnosis, prognosis, and treatment) in the context of ophthalmic imaging.

Objective: This study aims to identify regulator-approved AIaMD for ophthalmic imaging in Europe, Australia, and the United States; report the characteristics of these devices and their regulatory approvals; and report the available evidence underpinning these AIaMD.

Methods: The Food and Drug Administration (United States), the Australian Register of Therapeutic Goods (Australia), the Medicines and Healthcare products Regulatory Agency (United Kingdom), and the European Database on Medical Devices (European Union) regulatory databases will be searched for ophthalmic imaging AIaMD through a snowballing approach. PubMed and clinical trial registries will be systematically searched, and manufacturers will be directly contacted for studies investigating

the effectiveness of eligible AIaMD. Preliminary regulatory database searches, evidence searches, screening, data extraction, and methodological quality assessment will be undertaken by 2 independent review authors and arbitrated by a third at each stage of the process.

Results: Preliminary searches were conducted in February 2023. Data extraction, data synthesis, and assessment of methodological quality commenced in October 2023. The review is on track to be completed and submitted for peer review by April 2024.

Conclusions: This systematic review will provide greater clarity on ophthalmic imaging AIaMD that have achieved regulatory approval as well as the evidence that underpins them. This should help adopters understand the range of tools available and whether they can be safely incorporated into their clinical workflow, and it should also support developers in navigating regulatory approval more efficiently.

International Registered Report Identifier (IRRID): DERR1-10.2196/52602

(JMIR Res Protoc 2024;13:e52602) doi:10.2196/52602

KEYWORDS

AIaMD; artificial intelligence as a medical device; artificial intelligence; deep learning; machine learning; ophthalmic imaging; regulatory approval

Introduction

Overview

There is a growing capacity-demand mismatch within ophthalmology, increasing the risk of sight loss from treatment delays [1,2]. Artificial intelligence (AI) has the potential to help address these challenges. AI's strength lies in its ability to produce high-throughput analyses and glean meaningful insights from complex multimodal and multidimensional data sets through pattern recognition. This is well aligned with ophthalmology services, where disease diagnosis and management depend heavily on multimodal imaging [3]. AI therefore has the potential to help improve speed and access to care at reduced costs.

However, despite the exponential increase in the number of AI as a medical device (AIaMD) being developed and receiving regulatory approval, relatively few have been seamlessly integrated into routine clinical practice [4-6]. This so-called "AI chasm" limits the deployment of AIaMD to achieve patient benefit at scale [7]. This AI chasm results from a wide range of interdependent factors at the policy, organizational, and individual levels [8-13]. Key elements include ensuring adequate clinical evaluation to support regulatory decisions, such that the evidence base underpinning such tools is aligned with their intended use and is safe for the target population, and also clarifying how these regulatory requirements align with commissioners' needs.

The evidential requirements for software (including AIaMD) may be more ambiguous compared to more established interventions, making it more difficult for AI developers to explicitly understand the nature and extent of evidence they need to generate to gain regulatory approval. Attempts to study regulator approved AIaMD are impeded by the usability of public databases as well as the private nature of much of the information submitted by applicants, making it difficult for researchers, clinicians, or commissioners attempting to understand the evidence underpinning approved AIaMD. A review of Food and Drug Administration (FDA) approvals in the United States found that few submissions included comparisons between AI and human performance and that only a small proportion reported prospective data [14]. The reporting of sample size and number of sites in the validation studies was generally poor. The review did not assess whether participant characteristics such as gender and ethnicity were reported. Although guidelines for performing and presenting AI studies have been developed [15-18], there is no clear "best practice" for providers to ensure the safety and effectiveness of the AIaMD they adopt [14].

Review Objectives

This scoping review will focus on AIaMD that contributes to clinical decision-making (relating to screening, diagnosis, prognosis, and treatment) using ophthalmic imaging as an input. The aim is to identify and characterize AIaMD for ophthalmic imaging, which have received regulatory approval in 4 countries with established regulatory pathways for clinical use, in order to support providers in procurement decisions and developers in generating evidence to support applications to regulators.

The objectives are as follows:

1. To identify regulator-approved AIaMD for ophthalmic imaging in Europe, Australia, and the United States
2. To report the characteristics of those AIaMD and the regulatory approvals granted to them
3. To report the available evidence for the effectiveness and efficacy of approved AIaMD

Methods

Protocol Registration and Reporting

The protocol and subsequent review will adhere to the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) [19] and PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) [20] reporting guidelines, respectively (note that PRISMA-AI [21] is still in development). The protocol was registered with the Open Science Framework's website.

Eligibility Criteria

This review will focus on AIaMD for ophthalmic imaging that helps inform clinical management. All AIaMD for ophthalmic

imaging where the AIaMD or its manufacturer are recorded in the US FDA, Medicines and Healthcare products Regulatory Agency (MHRA), European Database on Medical Devices (EUDAMED), or Australian Register of Therapeutic Goods (ARTG) databases will be included. All 4 countries are members of the International Medical Regulators Device Forum and have a track record of admitting AIaMD to their markets. No restrictions will be placed on the type of ophthalmic imaging modality involved or the intended use of the AIaMD.

The AIaMD will have a partial or fully data-led mechanism (eg, regression modeling, random forest, or convolutional neural networks). Any AIaMD that exclusively uses rule-based mechanisms (eg, a priori decision trees, best practice alerts, and normal or abnormal threshold alerts) will be excluded.

With regard to the evidence underpinning each AIaMD, only original research that comprises a clinical evaluation of the AIaMD in human participants will be included. This may include randomized controlled trials or prospective or retrospective observational studies. Systematic reviews and meta-analyses, case series, case reports, commentaries, and expert opinions will not be eligible. No date or language restrictions will be applied to the electronic search.

Search Strategy and Sources of Information

To identify potentially eligible AIaMD, the FDA (United States), ARTG (Australia), MHRA (United Kingdom), and EUDAMED (European Union) regulatory databases will be searched through a snowballing approach [22]. This will involve an exhaustive review of the product class codes and predicate devices (if applicable) with which each known eligible device is associated. This strategy has been adopted due to limitations in the search functionality of these databases. No AI tools will be used to assist the search.

The snowball search will commence with a list of 15 AIaMD for ophthalmic imaging (Textbox 1). This represents the sum of the authors' awareness of regulated products and a pragmatic search of relevant academic literature [23].

Textbox 1. Initial list of ophthalmic imaging artificial intelligence as a medical device (AIaMD) used in snowball search.

Ophthalmic imaging AIaMD

- LumineticsCore (previously known as IDx-DR), Digital Diagnostics
- Eyeart, Eyenuk Inc
- RetmarkerDR, Retmarker SA
- SELENA+, eyRIS Pte Ltd
- Automated Retinal Disease Assessment, Verily Life Sciences
- Medios AI, Remidio
- OphtAI, Evolucare, ACDIS
- RetCAD, Thirona Retina B.V.
- DeepDee AI, DeepDee
- MONA DR, MONA
- Eyetelligence, Eyetelligence Pty Ltd
- CARA, Diagnos
- RetinaLyze, RetinaLyze System A/S (Ltd)

Next, PubMed, ClinicalTrials.gov, and the International Clinical Trials Registry Platform will be systematically searched for each eligible AIaMD and its manufacturer by combining both search terms with an "OR" Boolean operator. These searches will be limited to relevant ophthalmology-specific studies using relevant key terms such as "retin*" for AIaMD relating to diabetic retinopathy screening.

In addition, manufacturers' websites will also be reviewed for any peer-reviewed publications. The manufacturers of all eligible AIaMD will be contacted directly for clarification and as an additional source of peer-reviewed publications and ongoing studies. A preliminary scoping search highlighted that not all studies mention the AI device name or manufacturer, and some devices undergo a name change from one version to the next. Hence, this additional search will ensure that the data captured are as comprehensive as possible.

Study Selection

Two authors will search the regulatory databases independently. They will come to a consensus decision about the eligibility of any AIaMD identified. Any unresolved disagreements will be arbitrated by a third author. There may be instances where an AIaMD's eligibility or its regulatory approval status cannot be determined with publicly available evidence, as eligible devices may use proprietary AI that is kept confidential. If this is the case, correspondence with the manufacturer will be undertaken to seek clarification. If further clarification is not possible, the ambiguity about the AIaMD's eligibility and the rationale for including or excluding it will be recorded.

The search for evidence will be undertaken by an independent author. After deduplication, the titles and abstracts will be independently screened by 2 authors to assess their relevance to the eligible AIaMD. Discrepancies will be resolved by discussion and by arbitration with an additional author if

necessary. The full texts will be screened, and a further round of arbitration will take place as needed.

Data Extraction

Data extraction will be undertaken in 2 phases, using standardized data extraction forms designed and piloted for the purposes of this review.

Phase 1

The characteristics of each eligible AIaMD for ophthalmic imaging with regulatory approval in Europe, Australia, and the United States at the time of the search will be obtained. Where available, this will include:

1. Type of regulator approval and date of approval
2. Class assigned under FDA, TGA, UK MDR (Medical Devices Regulations 2002) and/or EU MDR (Regulation (EU) 2017/745)
3. Intended use statement
4. Ophthalmic imaging modality
5. Model type and architecture (eg, deep learning with machine learning)
6. Recall indications on the regulatory databases, as available

Some AIaMD may be approved in 2 or more jurisdictions, and the data will be extracted accordingly. Google searches will be used to supplement data extraction if the required data are unavailable from the FDA, EUDAMED, MHRA, or ARTG databases.

Phase 2

Published evidence underpinning the effectiveness and efficacy of each eligible AIaMD will be obtained. The following data will be extracted from each included study:

1. Study characteristics: title, author name, publication status, funding source, conflicts of interest, and author affiliations with manufacturers
2. Study methodology: study duration, study design (randomized, prospective observational, and retrospective observational), etc
3. Validation: external validation, reference standards, and comparison between AI and humans
4. Data set or cohort details: source of data set, size of data set or number of participants, setting, number of countries, number of centers, and participant demographics (age, gender, and ethnicity)
5. Model performance: metrics including sensitivity, specificity, area under the curve, etc, with 95% CIs; clinical outcomes as described

Assessment of Methodological Quality

Two review authors will independently assess the methodological quality of each included clinical validation study. Appropriate quality assessment tools will be used for each study type, for example, the QUADAS-2 tool for evaluating the risk of bias and applicability of primary diagnostic accuracy studies [24], the Cochrane risk of bias-2 tool for randomized controlled trials [25], and the ROBINS-I (Risk of Bias in Nonrandomized Studies of Interventions) tool for nonrandomized studies [26]. QUADAS-AI (quality assessment tool for artificial intelligence-centered diagnostic test accuracy studies) [27] and PROBAST-AI (Prediction Model Risk of Bias Assessment Tool for Artificial Intelligence) [28] are under development at the time of writing but will be used where appropriate if available. Any disagreements will be resolved through discussion or by involving a third reviewer where consensus cannot be reached.

Data Synthesis

Study-Level Data

The extracted data will be synthesized using narrative and tabular approaches. A summary of the findings will be presented, using descriptive statistics to describe the characteristics of the included studies. For example, mean and SD will be used to describe continuous variables, while percentages will be used to describe proportions. If appropriate, a meta-analysis of AIaMD diagnostic accuracy will be considered, but this may not be feasible if there is significant heterogeneity in study methods and AI methodology.

AIaMD-Level Data

The data for each AIaMD will be synthesized to give an overview of the characteristics of its regulatory approval or approvals and its clinical validation studies, again through narrative and tabular approaches.

Ethical Considerations

Ethical approval is not required, as this is a protocol for a systematic scoping review. All relevant data have been published, and no primary or proprietary data will be collected. This decision has been verified with the Newcastle University Ethics Committee.

Results

Preliminary searches were conducted in February 2023, and screening is underway. Data extraction, data synthesis, and assessment of methodological quality commenced in October 2023. We anticipate that the scoping review will be completed and submitted for peer review by April 2024.

Discussion

This will be the first review to examine and synthesize evidence on AIaMD for ophthalmic imaging. The key aim is to better understand the landscape of AIaMD for ophthalmic imaging on the market and the level of evidence that supports their regulatory approval.

Strengths and Limitations

Due to the limited and variable functionality of regulatory databases, it was not possible to conduct searches with standard systematic review methodologies based on research databases. This has necessitated several design considerations. We have sought to minimize publication bias and improve the completeness of the search process by undertaking a snowballing approach informed by expert knowledge, in combination with a database search. This was necessitated by limitations in the search functionality of the regulatory databases, but we

acknowledge that this approach facilitates the mitigation rather than the removal of these limitations. In addition, our PubMed search strategy may be hampered by incomplete reporting or no mention of the AI device's name or manufacturer. We have attempted to mitigate this by supplementing our search with reviewing manufacturers' websites, corresponding with manufacturers, and performing adjunct searches of major clinical trial registries in order to ensure that our search is as comprehensive as possible.

Strengths include the international scope of the review. We recognize that there may be differences in regulatory requirements across territories (and in the transparency of reporting of data supporting those applications) and have therefore included 4 major jurisdictions. We have also assembled an international team of authors with representation from the United States, Europe, and Australia to support the interpretation of the data. The inclusion of critical appraisal to identify any methodological variations or shortcomings of existing clinical validation studies is a further strength not common to previous regulatory reviews of AIaMDs, and will help guide any future improvements.

Conclusion

We describe the protocol for a systematic scoping review that seeks to map and examine AIaMD for ophthalmic imaging that has received regulatory approvals for commercial use. We anticipate that our findings may be of interest to ophthalmic professionals, AI model developers, health care commissioners, and policy makers, with the overall aim of improving transparency to help inform safe AIaMD implementation, thereby optimizing patient care.

Data Availability

Data sharing is not applicable to this article, which is a protocol for a scoping review, as no data sets were generated or analyzed.

Conflicts of Interest

HDJH is funded by the National Institute for Health Research through a doctoral fellowship award (NIHR301467) and is on the advisory board for Siloton, an optical coherence tomography imaging equipment manufacturer. PAK has received personal fees from AbbVie, Google Health, Roche, Apellis, Novartis, RetinAI, Bitfount, and nonfinancial support from Bayer outside the submitted work. The remaining authors do not have any conflicts of interest or financial disclosures to declare.

References

1. Foot B, MacEwen C. Surveillance of sight loss due to delay in ophthalmic treatment or review: frequency, cause and outcome. Eye (Lond) 2017 May;31(5):771-775 [FREE Full text] [doi: 10.1038/eye.2017.1] [Medline: 28128796]
2. Facing workforce shortages and backlogs in the aftermath of COVID-19: the 2022 census of the ophthalmology consultant, trainee and SAS workforce. The Royal College of Ophthalmologists. 2023. URL: https://www.rcophth.ac.uk/wp-content/uploads/2023/03/2022-Ophthalmology-census-Facing-workforce-shortages-and-backlogs-in-the-aftermath-of-COVID-19.pdf [accessed 2024-02-22]
3. Ringel MJ, Tang EM, Tao YK. Advances in multimodal imaging in ophthalmology. Ther Adv Ophthalmol 2021;13:25158414211002400 [FREE Full text] [doi: 10.1177/25158414211002400] [Medline: 35187398]
4. Zhang J, Whebell S, Gallifant J, Lertvittayakumjorn P, Mattie H, Budhdeo S, et al. AI for Human Health—Dashboard. URL: https://aiforhealth.app/ [accessed 2023-03-11]
5. Guo Y, Hao Z, Zhao S, Gong J, Yang F. Artificial intelligence in health care: bibliometric analysis. J Med Internet Res 2020;22(7):e18228 [FREE Full text] [doi: 10.2196/18228] [Medline: 32723713]
6. FDA. Artificial Intelligence and Machine Learning (AI/ML)-enabled medical devices. U.S. Food and Drug Administration. 2022. URL: https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-aiml-enabled-medical-devices [accessed 2023-02-19]
7. Keane PA, Topol EJ. With an eye to AI and autonomous diagnosis. NPJ Digit Med 2018;1:40 [FREE Full text] [doi: 10.1038/s41746-018-0048-y] [Medline: 31304321]
8. Tseng RMWW, Gunasekeran DV, Tan SSH, Rim TH, Lum E, Tan GSW, et al. Considerations for artificial intelligence real-world implementation in ophthalmology: providers' and patients' perspectives. Asia Pac J Ophthalmol (Phila) 2021;10(3):299-306 [FREE Full text] [doi: 10.1097/APO.0000000000000400] [Medline: 34383721]
9. Ibrahim H, Liu X, Zariffa N, Morris AD, Denniston AK. Health data poverty: an assailable barrier to equitable digital health care. Lancet Digit Health 2021;3(4):e260-e265 [FREE Full text] [doi: 10.1016/S2589-7500(20)30317-4] [Medline: 33678589]
10. Aristidou A, Jena R, Topol EJ. Bridging the chasm between AI and clinical implementation. Lancet 2022;399(10325):620. [doi: 10.1016/S0140-6736(22)00235-5] [Medline: 35151388]
11. Muehlematter UJ, Daniore P, Vokinger KN. Approval of artificial intelligence and machine learning-based medical devices in the USA and Europe (2015-20): a comparative analysis. Lancet Digit Health 2021 Mar;3(3):e195-e203 [FREE Full text] [doi: 10.1016/S2589-7500(20)30292-2] [Medline: 33478929]
12. Kramer DB, Xu S, Kesselheim AS. How does medical device regulation perform in the United States and the European union? A systematic review. PLoS Med 2012;9(7):e1001276 [FREE Full text] [doi: 10.1371/journal.pmed.1001276] [Medline: 22912563]

13. Taribagil P, Hogg HJ, Balaskas K, Keane PA. Integrating artificial intelligence into an ophthalmologist's workflow: obstacles and opportunities. Expert Rev Ophthalmol 2023;18(1):45-56 [FREE Full text] [doi: 10.1080/17469899.2023.2175672]
14. Wu E, Wu K, Daneshjou R, Ouyang D, Ho DE, Zou J. How medical AI devices are evaluated: limitations and recommendations from an analysis of FDA approvals. Nat Med 2021;27(4):582-584. [doi: 10.1038/s41591-021-01312-x] [Medline: 33820998]
15. Liu X, Cruz Rivera S, Moher D, Calvert MJ, Denniston AK. Reporting guidelines for clinical trial reports for interventions involving artificial intelligence: the CONSORT-AI extension. Nat Med 2020 Sep;26(9):1364-1374 [FREE Full text] [doi: 10.1038/s41591-020-1034-x] [Medline: 32908283]
16. Rivera SC, Liu X, Chan AW, Denniston AK, Calvert MJ, SPIRIT-AI and CONSORT-AI Working Group. Guidelines for clinical trial protocols for interventions involving artificial intelligence: the SPIRIT-AI Extension. BMJ 2020 Sep 09;370:m3210 [FREE Full text] [doi: 10.1136/bmj.m3210] [Medline: 32907797]
17. Vasey B, Nagendran M, Campbell B, Clifton DA, Collins GS, Denaxas S, et al. Reporting guideline for the early-stage clinical evaluation of decision support systems driven by artificial intelligence: DECIDE-AI. Nat Med 2022;28(5):924-933 [FREE Full text] [doi: 10.1038/s41591-022-01772-9] [Medline: 35585198]
18. Sounderajah V, Ashrafian H, Golub RM, Shetty S, De Fauw J, Hooft L, et al. Developing a reporting guideline for artificial intelligence-centred diagnostic test accuracy studies: the STARD-AI protocol. BMJ Open 2021;11(6):e047709 [FREE Full text] [doi: 10.1136/bmjopen-2020-047709] [Medline: 34183345]
19. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, PRISMA-P Group. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015 Jan 02;350:g7647 [FREE Full text] [doi: 10.1136/bmj.g7647] [Medline: 25555855]
20. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med 2018 Oct 02;169(7):467-473 [FREE Full text] [doi: 10.7326/M18-0850] [Medline: 30178033]
21. Cacciamani GE, Chu TN, Sanford DI, Abreu A, Duddalwar V, Oberai A, et al. PRISMA AI reporting guidelines for systematic reviews and meta-analyses on AI in healthcare. Nat Med 2023;29(1):14-15. [doi: 10.1038/s41591-022-02139-w] [Medline: 36646804]
22. Wohlin C, Kalinowski M, Romero Felizardo KR, Mendes E. Successful combination of database search and snowballing for identification of primary studies in systematic literature studies. Inf Softw Technol 2022;147:106908 [FREE Full text] [doi: 10.1016/j.infsof.2022.106908]
23. Grzybowski A, Brona P. Approval and certification of ophthalmic AI devices in the European Union. Ophthalmol Ther 2023 Apr;12(2):633-638 [FREE Full text] [doi: 10.1007/s40123-023-00652-w] [Medline: 36652171]
24. Whiting PF, Rutjes AWS, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011 Oct 18;155(8):529-536 [FREE Full text] [doi: 10.7326/0003-4819-155-8-201110180-00009] [Medline: 22007046]
25. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019 Aug 28;366:l4898 [FREE Full text] [doi: 10.1136/bmj.l4898] [Medline: 31462531]
26. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016 Oct 12;355:i4919 [FREE Full text] [doi: 10.1136/bmj.i4919] [Medline: 27733354]
27. Sounderajah V, Ashrafian H, Rose S, Shah NH, Ghassemi M, Golub R, et al. A quality assessment tool for artificial intelligence-centered diagnostic test accuracy studies: QUADAS-AI. Nat Med 2021;27(10):1663-1665. [doi: 10.1038/s41591-021-01517-0] [Medline: 34635854]
28. Collins GS, Dhiman P, Navarro CLA, Ma J, Hooft L, Reitsma JB, et al. Protocol for development of a reporting guideline (TRIPOD-AI) and risk of bias tool (PROBAST-AI) for diagnostic and prognostic prediction model studies based on artificial intelligence. BMJ Open 2021;11(7):e048008 [FREE Full text] [doi: 10.1136/bmjopen-2020-048008] [Medline: 34244270]

Abbreviations

AI: artificial intelligence
AIaMD: artificial intelligence as a medical device
ARTG: Australian Register of Therapeutic Goods
EUDAMED: European Database on Medical Devices
FDA: Food and Drug Administration
MHRA: Medicines and Healthcare products Regulatory Agency
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
PROBAST-AI: Prediction Model Risk of Bias Assessment Tool for Artificial Intelligence
QUADAS-AI: quality assessment tool for artificial intelligence–centered diagnostic test accuracy studies

ROBINS-I: Risk of Bias in Nonrandomized Studies of Interventions

Edited by A Mavragani; submitted 09.09.23; peer-reviewed by H Demir, B Jacob, JJ Beunza, D Chrimes; comments to author 17.12.23; revised version received 10.02.24; accepted 20.02.24; published 14.03.24.

Please cite as:
Ong AY, Hogg HDJ, Kale AU, Taribagil P, Kras A, Dow E, Macdonald T, Liu X, Keane PA, Denniston AK
AI as a Medical Device for Ophthalmic Imaging in Europe, Australia, and the United States: Protocol for a Systematic Scoping Review of Regulated Devices
JMIR Res Protoc 2024;13:e52602
URL: https://www.researchprotocols.org/2024/1/e52602
doi:10.2196/52602
PMID:38483456

Protocol

Factors Underlying Vaccine Hesitancy and Their Mitigations in Saudi Arabia: Protocol for a Systematic Review

Mohammed Kanan[1*], PharmD; Samar Abdulrahman[2*], PharmD; Abdulaziz Alshehri[3*], PharmD; Renad AlSuhaibani[4*], PharmD; Nawaf M Alotaibi[5*], PhD; Azhar Alsaleh[6*]; Bushra Nasser[7], PharmD; Rana Baowaydhan[8], MB; Ibrahim Alredaini[9], PharmD; Taif Khalid[10], MLB; Fatima Almukhtar[11], MB; Nourah Altoaimi[12], PharmD; Almaha Alhneshel[13], MB; Shouq Alanazi[14*], MB; Shahad Algmaizi[15], MB

[1]Department of Clinical Pharmacy, King Fahad Medical City, Riyadh, Saudi Arabia
[2]Department of Pharmacy, Second Health Cluster, Riyadh, Saudi Arabia
[3]Department of Pharmacy, Security Forces Hospital, Riyadh, Saudi Arabia
[4]Department of Medicine, Imam Mohammed Ibn Saud Islamic University, Riyadh, Saudi Arabia
[5]Department of Clinical Pharmacy, Northern Border University, Rafha, Saudi Arabia
[6]Department of Nursing, Prince Saud Bin Jalawi Hospital, Alhasa, Saudi Arabia
[7]Department of Clinical Pharmacy, King Khalid University, Abha, Saudi Arabia
[8]Department of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia
[9]Department of Pharmacy, Qassim University, Buraydah, Saudi Arabia
[10]Department of Clinical Laboratory, Al-Jawf University, Al-Jawf, Saudi Arabia
[11]Department of Medicine, Ministry of Health, Dammam, Saudi Arabia
[12]Department of Pharmacy, Qassim University, Qassim, Saudi Arabia
[13]Department of Medicine, Suliman Alrajhi University, Qassim, Saudi Arabia
[14]Department of Medicine, Northern Border University, Northern Borders, Arar, Saudi Arabia
[15]Department of Medicine, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia
[*]these authors contributed equally

Corresponding Author:
Mohammed Kanan, PharmD
Department of Clinical Pharmacy
King Fahad Medical City
2642, Makkah Al Mukarramah Br Rd, As Sulimaniyah
Riyadh, 12231
Saudi Arabia
Phone: 966 508564504
Email: ii_kanan101@outlook.com

Abstract

Background: Vaccine hesitancy is a growing concern in Saudi Arabia, impacting even well-educated parents. The decision-making process involves various factors such as accessibility, trustworthy information, and the influence of social networks, reflecting a complex interplay of emotional, cultural, social, spiritual, and political dimensions.

Objective: This review seeks to evaluate the prevalence and trends of vaccine hesitancy, identify contributing factors, and explore potential solutions to enhance immunization rates. This review aligns with global concerns, as the World Health Organization has identified vaccine hesitancy as a top global health threat.

Methods: Our systematic review will follow the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and PICOS (Population, Intervention, Comparison, Outcomes, and Study) criteria for comprehensive assessment. We will conduct a thorough search across various databases, encompassing a wide range of vaccines, and pay special attention to vaccination campaigns and refusals. Inclusion criteria involve descriptive, observational, and analytical studies focusing on factors influencing vaccine acceptance or hesitancy. The study will use the Crowe Critical Appraisal Tool for quality assessment and perform a narrative synthesis to summarize findings thematically.

Results: This systematic review is expected to unveil the prevalence and trends of vaccine hesitancy in diverse populations in Saudi Arabia, shedding light on cultural, religious, and social factors contributing to hesitancy. It aims to assess the effectiveness of implemented strategies, enable regional and global comparisons, and provide implications for tailored vaccination policies. Additionally, the review may pinpoint research gaps, guiding future investigations to address and mitigate vaccine hesitancy effectively.

Conclusions: The findings are expected to have direct policy implications and guide interventions to strengthen vaccination programs and improve public health outcomes.

International Registered Report Identifier (IRRID): PRR1-10.2196/54680

(JMIR Res Protoc 2024;13:e54680) doi:10.2196/54680

KEYWORDS

acceptance; campaigns; effectiveness; factors; hesitancy; immunization rates; immunization; intervention; literature analysis; misinformation; mitigations; prevention; protocol; public health; review methodology; review methods; Saudi Arabia; search; searching; syntheses; synthesis; systematic review; systematic; vaccination; vaccine hesitancy; vaccine

Introduction

Vaccines have consistently proven to be among the safest and most effective methods for preventing a wide range of infectious diseases [1,2]. Despite the proven safety and effectiveness of vaccines, vaccine-preventable diseases continue to persist in various parts of the world. In recent years, there have been outbreaks of infectious diseases, even when effective vaccines are available to combat them. One significant contributing factor to this phenomenon is “vaccine hesitancy” [3,4]. Vaccine hesitancy is defined as a reluctance or delay in accepting or agreeing to receive vaccines, even when vaccination services are readily available. Vaccine hesitancy is a complex and multifaceted phenomenon influenced by a wide range of factors. These factors encompass cognitive, psychological, sociodemographic, political, and cultural elements, among others. Moreover, the specific factors contributing to vaccine hesitancy can vary significantly across different populations and communities [5]. The reasons for vaccine hesitancy are intricate and can vary over time, across different locations, and depending on the specific type of vaccine in question. Similarly, vaccine hesitancy arises from a multitude of factors, including religious beliefs, geographic barriers, the quality of the parent-provider relationship, concerns about adverse events of immunization, limited knowledge about vaccination, and perceptions of disease risk [6].

In 2019, the World Health Organization (WHO) identified vaccine hesitancy as one of the top 10 global health threats [7]. Vaccine hesitancy refers to the reluctance of certain individuals or communities to accept vaccines, and it poses a substantial challenge to public health efforts. This reluctance is influenced by various factors, including misinformation, distrust in health care systems, personal beliefs, and a perceived low risk of vaccine-preventable diseases [7,8]. Vaccine hesitancy is not a recent challenge in disease prevention. It has been a significant issue for years, and examples of it can be found in the context of seasonal influenza vaccination and the response to the 2009 H1N1 pandemic [9-11]. Recent research in the literature over the past decade has indicated a concerning trend: vaccine hesitancy appears to be on the rise among various populations, including health care workers [12,13]. According to Olive et al [14], a social movement opposing public health vaccines has been gaining traction in the United States. This movement, among various other factors, has played a role in the increasing percentage of the population in both the United States and Europe that is refusing vaccination efforts in recent years [14]. Vaccine hesitancy indeed poses a substantial challenge to public health experts as it leads to significantly reduced vaccination rates within populations. This challenge becomes even more critical in the context of combating infectious diseases [1]. According to a survey conducted by the WHO and UNICEF (United Nations Children’s Fund), vaccine hesitancy started to emerge as a significant concern approximately a decade ago [15]. This trend of vaccine hesitancy has been observed in several countries around the world, including the United Kingdom, the United States, and India [16,17]. Vaccine hesitancy across Gulf Cooperation Council countries varied between 11% and 71%, with notable discrepancies observed based on the type of vaccine, with the highest reported hesitancy recorded for the COVID-19 vaccine at 70.6% [18].

Vaccine hesitancy has also become a concern in Saudi Arabia. According to Alabbad et al [19], 17% of their study population expressed hesitance to receive the influenza vaccine. Additionally, Alsubaie et al [20] found that vaccine hesitancy among Saudi parents reached 20%. Even well-educated parents have the same behavior. Alzahrani and Alghamdi [21] reported a vaccine hesitancy rate 20%-27 % against COVID-19 immunization [21]. A study conducted by Thabit et al [22] determined that factors such as the convenience of receiving the vaccine, the availability of trustworthy information from authorities, and the positive influence of family and friends played significant roles in motivating the public to get vaccinated. Al-Mohaithef and Padhi [23] reported that concerns about vaccine safety (17%), worries about potential side effects (35%), and perceptions of receiving too many injections (28%) are critical factors contributing to vaccine hesitancy. Alaamri et al [24] conducted a cross-sectional study in Saudi Arabia, which stated that decision-making for vaccination is a multifaceted process that encompasses emotional, cultural, social, spiritual, and political dimensions. These various aspects can significantly influence an individual’s or a community’s choice regarding vaccination. In-depth literature analysis reveals the current absence of a systematic review on vaccine hesitancy factors specific to Saudi Arabia. This review aims to (1) assess

the prevalence and trends of vaccine hesitancy, (2) identify factors contributing to vaccine hesitancy, and (3) explore potential solutions to enhance immunization rates.

These findings will be instrumental in shaping a comprehensive vaccination policy for Saudi Arabia.

Methods

Basic Strategy

This systematic review will adhere to the quality standards outlined in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) reporting guidelines [25,26] and will be structured according to the PICOS (Population, Intervention, Comparison, Outcomes, and Study) criteria for comprehensive and transparent reporting [27], as given in Textbox 1 and Table 1. Before conducting this review, the protocol will be submitted to PROSPERO (the International Prospective Register of Systematic Reviews) for approval [28,29].

A comprehensive search will be conducted across multiple databases, including Cochrane, PubMed (MEDLINE), Web of Science, Google Scholar, Scopus, Science Direct, and Springer Links, to identify peer-reviewed literature. The search will not be limited by a specific time period because no previous review on the factor has been conducted. If it is time-limited, there is a chance of missing some factor that may affect the prospective work. It will also encompass literature with search terms present in the title, abstract, and full text. Furthermore, the search will be restricted to publications available in the English language.

Textbox 1. Title and checklist items for the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist.

Title

- Determine whether the report is categorized as a systematic review, a meta-analysis, or a combination of both.

Background: objectives

- The research inquiry encompasses elements such as comparators, interventions, outcomes, and participants.

Methods: eligibility criteria

- Criteria for inclusion are based on the characteristics of the study and the report.

Methods: sources of information

- The databases that were searched and the dates of those searches.

Methods: potential for bias

- Methods for evaluating the potential for bias in research studies.

Results: studies inclusion

- The quantity and nature of incorporated research studies, the participants involved, and pertinent attributes of these studies.

Results: report of findings

- Summary of primary results, ideally with a breakdown of the number of studies and participants for each outcome.

Results: description of the effect

- The direction of the impact (ie, which group benefits) and the magnitude of the effect expressed in terms that are meaningful to health care professionals and patients.

Discussion: limitations and strengths of available evidences

- Concise overview of the advantages and drawbacks of the evidence, including factors like inconsistency, imprecision, indirectness, or risk of bias, along with any corroborating or conflicting evidence.

Discussion: interpretation

- Overall interpretation of the findings and significant implications.

Table 1. PICOS (Population, Intervention, Comparison, Outcomes, and Study) inclusion and exclusion criteria.

PICOS criteria	Inclusion criteria	Exclusion criteria
Participants	The community of Saudi Arabia	Research studies will intentionally exclude certain subgroups, such as those with comorbidities, complex patients, or health care providers
Intervention	The qualitative and quantitative studies and randomized controlled trials	Studies pertaining to other topics and those involving statistical, mathematical, or predictive methods will not be covered in this context
Comparison	When applicable, this comparison of specific subgroups may also extend to studies conducted in multiple cities or locations	N/A[a]
Outcomes	To assess the factors that influence individuals' decisions regarding vaccine acceptance or vaccine hesitancy	Studies that do not aim to identify or analyze the factors influencing vaccine acceptance or hesitancy
Study design	Observational or descriptive and analytical studies conducted at a national level, or those with an adequately justified sample size and calculations	Pilot studies for tool assessment or improper sampling

[a]N/A: Not applicable.

Searching Approaches

To optimize search results and ensure comprehensive coverage, a combination of medical subject headings and natural language keywords will be used. Boolean and proximity operators will also be used to refine search queries and uncover relevant studies. Additionally, truncation (*) and wildcards ($) will be used to account for variations in search terms and enhance the chances of identifying a wide range of relevant literature.

The search strategy has been configured to align with the specific vocabularies and indexing systems used by each database, ensuring that the search is optimized for each platform's unique structure and content. This approach enhances the precision and relevance of search results within each database.

The search strategy will be formulated using the vocabularies and indexing systems specific to each database. This tailored approach ensures that the search is optimized for the unique characteristics and content of each database. The terms "vaccine," "immunization," "vaccine hesitancy," "vaccine trust," "vaccine resistance," "vaccine concern," "vaccination," "vaccine intervention," "vaccine side effects," "vaccine confidence," "vaccine impact," "vaccine strategy," "vaccine hesitant," "vaccine refusal," "adverse effect of vaccines," and "vaccine rejection" will be applied alone or combined as operators.

Eligibility Criteria

While conducting our search for vaccine hesitancy, we will take into account universally recommended vaccines for individuals across various age groups, including children, adolescents, and adults. These vaccines encompass a range of preventable diseases and include: "seasonal influenza vaccine," "hepatitis B vaccine," "tuberculosis (Bacillus Calmette-Guerin [BCG] vaccine)," "measles, mumps, and rubella (MMR) vaccine," "diphtheria-pertussis-tetanus (DPT) vaccine," "Haemophilus influenzae type b (Hib) vaccine," "human papillomavirus (HPV) vaccine," "poliomyelitis vaccine," "oral polio vaccine," "varicella vaccine," "meningococcal vaccine," "pneumococcal vaccine," and "COVID-19 vaccine." These vaccines are typically recommended as part of immunization programs to protect individuals from various infectious diseases. In addition, we will pay particular attention to the results of vaccination campaigns aimed at promoting and expanding vaccination programs in Saudi Arabia. This will also involve a detailed examination of the various campaigns, their objectives, strategies, and outcomes, as well as their impact on increasing vaccine coverage and public health in the region.

In this review, we will include both descriptive and analytical studies that provide insights into the impact of strategies aimed at addressing vaccine hesitancy. These studies should offer a clear description of the strategies used and their effects on vaccine hesitancy.

However, we will exclude studies that are opinion-based or studies that do not primarily focus on populations eligible to receive vaccines or their parents. Additionally, studies that do not allow for the extraction of relevant information related to vaccination will also be excluded from our analysis.

Selection of Studies and Critical Appraisal

Our research review process should be robust, and it should be designed to ensure the quality and relevance of the studies included in the analysis [30]. The following sections provide a summary of the key steps.

Initial Screening

A total of 2 researchers will independently review the titles, abstracts, and keywords of the identified studies. This step will ensure the segregation of eligible studies from those that are not relevant.

Full-Text Retrieval and Screening

After the initial screening, studies that pass this stage will have their full texts retrieved and reviewed. This allows for a more detailed assessment of their eligibility.

Data Extraction

A total of 2 researchers will independently perform data extraction from the selected studies. This process involves extracting relevant information and data from the studies.

Consensus on Unmatched Studies

In cases where there is a disagreement between the 2 researchers regarding the inclusion or exclusion of a study, a third researcher will be involved to reach a consensus. This ensures that the final selection of studies is based on consensus and reduces bias.

This screening process, along with independent data extraction and consensus resolution, will help to enhance the reliability and validity of our research findings. It also minimizes the potential for bias in the selection and extraction of data from the identified studies.

Quality Assessment

This study will undergo quality assessment using the Crowe Critical Appraisal Tool (CCAT) [31,32]. This tool focuses on 8 domains for evaluating quality, encompassing preliminaries (title, abstract, and text), introduction (background and objective), design (research design, intervention, treatment, exposure, outcome, output, predictor, measure, and bias), sampling (sampling method, sample size, sampling protocol), data collection (collection method, collection protocol), ethical considerations (participant ethics, researcher ethics), results (analysis, integration, interpretation method, essential analysis, outcome, output, predictor analysis), and discussion (interpretation, generalization, and concluding remarks). The CCAT tool will be used to evaluate the quality of all the included articles across these 8 domains. A cumulative score will be computed for each article and then converted into a percentage. The percentage scores will be categorized into three groups: (1) high quality (≥80%), (2) medium quality (60%-79%), and (3) poor quality (<60%). This assessment of quality will be carried out independently by the authors, with any disagreements being resolved through consensus.

Analysis and Synthesis

According to the methodological nature of our systematic review, conducting a narrative synthesis of the results will be a suitable approach. A narrative synthesis will involve summarizing and interpreting the findings of the included studies. This approach is common when the included studies are diverse in terms of methodology, outcome measures, or data presentation [33].

Thematic Analysis

We will organize the findings thematically. Focus on the common themes, patterns, or trends across the studies. We will create categories, themes, and subthemes that capture the key aspects of vaccine hesitancy and the impact of strategies.

Narrative Description and Synthesis

We will describe the findings of each study within the context of the identified themes that provide a clear and concise summary of each study. We will synthesize the findings by drawing connections between different studies and themes.

Results

We can anticipate potential results that may emerge from this systematic review.

Prevalence and Trends of Vaccine Hesitancy

The review is expected to reveal the prevalence and trends of vaccine hesitancy among different populations. It may show whether vaccine hesitancy rates have been increasing or decreasing over time and how this compares to global trends.

Factors Contributing to Vaccine Hesitancy

Identification of specific factors contributing to vaccine hesitancy in the Saudi Arabian context. Insights into cultural, religious, and social influences on vaccine hesitancy within Saudi Arabia.

Impact of Strategies on Vaccine Hesitancy

Evaluation of the effectiveness of strategies implemented to address vaccine hesitancy and the identification of successful interventions and areas where improvements are needed.

Regional and Global Comparisons

Discover potential comparisons between vaccine hesitancy factors and strategies in Saudi Arabia and those in other countries, particularly within the Middle East region, and understand whether Saudi Arabia faces unique challenges or shares common issues with other nations.

Implications for Vaccination Policy

The review is likely to have implications for public health policy in Saudi Arabia and provide recommendations for tailored vaccination strategies to improve acceptance rates and combat vaccine hesitancy.

Identifying Research Gaps

The review may identify gaps in the existing literature on vaccine hesitancy in Saudi Arabia and highlight areas where further research is needed or not to address vaccine hesitancy.

Discussion

Impact

Vaccine hesitancy poses a substantial threat to public health worldwide [34], and Saudi Arabia is no exception [19-24]. Understanding the prevalence and factors contributing to vaccine hesitancy in Saudi Arabia is crucial for developing targeted interventions to increase vaccination rates and prevent outbreaks of vaccine-preventable diseases [35,36]. Moreover, the causes of vaccine hesitancy and its consequences will be helpful to mitigate [37].

Like the United States, the findings will help tailor an individualized educational program for vaccine-hesitant parents [38]. Alternatively, childhood vaccination will increase, as it is reported to be very low in Saudi Arabia [39-41]. Delays in vaccination were influenced by factors such as parental education, nutrition preferences, and vaccine-related beliefs, while prematurity was associated with a decreased likelihood of delays. As a mandatory requirement, children in Saudi Arabia are expected to be fully vaccinated before starting school at the age of 6 years [42].

In Saudi Arabia, the vaccination program commenced in 1979 with the administration of DTP vaccines, and it has since been

expanded to encompass a broader range of vaccines [20]. The Saudi National Immunization Program advises administering several vaccines within the first 24 months of life. These vaccines include the hepatitis B vaccine at birth, as well as the pneumococcal conjugate, rotavirus, inactivated poliovirus vaccine (IPV), meningococcal vaccine (MCV), diphtheria, tetanus, polio, Hib vaccine, BCG vaccine, MMR vaccine, and hepatitis A vaccines [20,42].

According to the WHO, vaccination coverage rates in Saudi Arabia have shown significant variation in recent years. In 2019, the coverage rate for BCG vaccination was reported to be 52%, a notable decrease from the 98% coverage rate observed in 2018 [42,43]. While in 2022, it was similar to 2022 [44]. On the other hand, the coverage rates for DPT and MMR vaccines remained high, with rates of 98% and 96%, respectively. Despite the generally high immunization rates, there were concerning numbers of reported cases in 2019. Measles, for instance, had 1035 reported cases, mumps had 187 reported cases, pertussis had 326 reported cases, and rubella had 62 reported cases. These figures indicate that, despite high vaccination coverage rates for some vaccines, there are still significant challenges in preventing these vaccine-preventable diseases in certain populations or regions within Saudi Arabia [42,43].

The study aligns with global concerns about vaccine hesitancy, which the WHO identified as a top 10 global health threat [7]. By exploring vaccine hesitancy in Saudi Arabia, this research contributes to the global understanding of this phenomenon and may shed light on whether Saudi Arabia faces unique challenges or shares common issues with other nations [45,46].

By analyzing the predictors from different stakeholders [47-51], the study's findings are likely to have direct policy implications. Tailored vaccination strategies can be developed based on the identified factors contributing to vaccine hesitancy [41-43,52]. Policy recommendations can help improve acceptance rates and strengthen vaccination programs in Saudi Arabia, ultimately enhancing public health outcomes. Identifying specific factors contributing to vaccine hesitancy in Saudi Arabia is essential for designing targeted interventions. For instance, if religious beliefs are a significant factor [53,54], interventions may involve engaging religious leaders to promote vaccination [55].

Conclusions

This systematic review will investigate Saudi Arabia's vaccine hesitancy, examining prevalence, trends, and contributing factors across diverse populations. It evaluates the effectiveness of implemented strategies and draws regional and global comparisons, shedding light on unique challenges or shared issues within the Middle East. The findings hold implications for Saudi public health policy, suggesting tailored vaccination strategies to combat hesitancy. Additionally, by identifying research gaps, the review provides direction for future studies, pinpointing areas where further investigation is crucial for a comprehensive understanding of vaccine hesitancy in Saudi Arabia.

Conflicts of Interest

None declared.

References

1. Cascini F, Pantovic A, Al-Ajlouni Y, Failla G, Ricciardi W. Attitudes, acceptance and hesitancy among the general population worldwide to receive the COVID-19 vaccines and their contributing factors: a systematic review. EClinicalMedicine 2021;40:101113 [FREE Full text] [doi: 10.1016/j.eclinm.2021.101113] [Medline: 34490416]
2. Orenstein WA, Ahmed R. Simply put: vaccination saves lives. Proc Natl Acad Sci U S A 2017;114(16):4031-4033 [FREE Full text] [doi: 10.1073/pnas.1704507114] [Medline: 28396427]
3. Dubé E, Gagnon D, Nickels E, Jeram S, Schuster M. Mapping vaccine hesitancy—country-specific characteristics of a global phenomenon. Vaccine 2014;32(49):6649-6654 [FREE Full text] [doi: 10.1016/j.vaccine.2014.09.039] [Medline: 25280436]
4. MacDonald NE, SAGE Working Group on Vaccine Hesitancy. Vaccine hesitancy: definition, scope and determinants. Vaccine 2015;33(34):4161-4164 [FREE Full text] [doi: 10.1016/j.vaccine.2015.04.036] [Medline: 25896383]
5. Sallam M. COVID-19 vaccine hesitancy worldwide: a concise systematic review of vaccine acceptance rates. Vaccines (Basel) 2021;9(2):160 [FREE Full text] [doi: 10.3390/vaccines9020160] [Medline: 33669441]
6. Singh P, Dhalaria P, Kashyap S, Soni GK, Nandi P, Ghosh S, et al. Strategies to overcome vaccine hesitancy: a systematic review. Syst Rev 2022;11(1):78 [FREE Full text] [doi: 10.1186/s13643-022-01941-4] [Medline: 35473819]
7. Ten threats to global health in 2019. World Health Organization. URL: https://www.who.int/news-room/spotlight/ten-threats-to-global-health-in-2019 [accessed 2024-02-21]
8. Patel MK, Goodson JL, Alexander JP, Kretsinger K, Sodha SV, Steulet C, et al. Progress toward regional measles elimination—worldwide, 2000-2019. MMWR Morb Mortal Wkly Rep 2020;69(45):1700-1705 [FREE Full text] [doi: 10.15585/mmwr.mm6945a6] [Medline: 33180759]
9. Mesch GS, Schwirian KP. Social and political determinants of vaccine hesitancy: lessons learned from the H1N1 pandemic of 2009-2010. Am J Infect Control 2015;43(11):1161-1165 [FREE Full text] [doi: 10.1016/j.ajic.2015.06.031] [Medline: 26521933]

10. Buchan SA, Kwong JC. Trends in influenza vaccine coverage and vaccine hesitancy in Canada, 2006/07 to 2013/14: results from cross-sectional survey data. CMAJ Open 2016;4(3):E455-E462 [FREE Full text] [doi: 10.9778/cmajo.20160050] [Medline: 27975047]
11. Schmid P, Rauber D, Betsch C, Lidolt G, Denker ML. Barriers of influenza vaccination intention and behavior—a systematic review of influenza vaccine hesitancy, 2005-2016. PLoS One 2017;12(1):e0170550 [FREE Full text] [doi: 10.1371/journal.pone.0170550] [Medline: 28125629]
12. Yaqub O, Castle-Clarke S, Sevdalis N, Chataway J. Attitudes to vaccination: a critical review. Soc Sci Med 2014;112:1-11 [FREE Full text] [doi: 10.1016/j.socscimed.2014.04.018] [Medline: 24788111]
13. Maltezou HC, Theodoridou K, Ledda C, Rapisarda V, Theodoridou M. Vaccination of healthcare workers: is mandatory vaccination needed? Expert Rev Vaccines 2019;18(1):5-13. [doi: 10.1080/14760584.2019.1552141] [Medline: 30501454]
14. Olive JK, Hotez PJ, Damania A, Nolan MS. The state of the antivaccine movement in the United States: a focused examination of nonmedical exemptions in states and counties. PLoS Med 2018;15(6):e1002578 [FREE Full text] [doi: 10.1371/journal.pmed.1002578] [Medline: 29894470]
15. Larson HJ, Jarrett C, Schulz WS, Chaudhuri M, Zhou Y, Dube E, et al. Measuring vaccine hesitancy: the development of a survey tool. Vaccine 2015;33(34):4165-4175 [FREE Full text] [doi: 10.1016/j.vaccine.2015.04.037] [Medline: 25896384]
16. Jarrett C, Wilson R, O'Leary M, Eckersberger E, Larson HJ, SAGE Working Group on Vaccine Hesitancy. Strategies for addressing vaccine hesitancy—a systematic review. Vaccine 2015;33(34):4180-4190 [FREE Full text] [doi: 10.1016/j.vaccine.2015.04.040] [Medline: 25896377]
17. Streefland P, Chowdhury AM, Ramos-Jimenez P. Patterns of vaccination acceptance. Soc Sci Med 1999;49(12):1705-1716. [doi: 10.1016/s0277-9536(99)00239-7] [Medline: 10574240]
18. Algabbani A, AlOmeir O, Algabbani F. Vaccine hesitancy in the Gulf Cooperation Council countries. East Mediterr Health J 2023;29(5):402-411 [FREE Full text] [doi: 10.26719/emhj.23.064] [Medline: 37306176]
19. Alabbad AA, Alsaad AK, Al Shaalan MA, Alola S, Albanyan EA. Prevalence of influenza vaccine hesitancy at a tertiary care hospital in Riyadh, Saudi Arabia. J Infect Public Health 2018;11(4):491-499 [FREE Full text] [doi: 10.1016/j.jiph.2017.09.002] [Medline: 28988776]
20. Alsubaie SS, Gosadi IM, Alsaadi BM, Albacker NB, Bawazir MA, Bin-Daud N, et al. Vaccine hesitancy among Saudi parents and its determinants. Result from the WHO SAGE working group on vaccine hesitancy survey tool. Saudi Med J 2019;40(12):1242-1250 [FREE Full text] [doi: 10.15537/smj.2019.12.24653] [Medline: 31828276]
21. Alzahrani AA, Alghamdi AN. Vaccine hesitancy among parents and its determinants during the era of COVID-19 in Taif City, Saudi Arabia. Cureus 2023;15(6):e40404 [FREE Full text] [doi: 10.7759/cureus.40404] [Medline: 37456420]
22. Thabit AK, Badr AF, Jad L, Jose J, Kaae S, Jacobsen R, et al. Views and perceptions of the public toward COVID-19 vaccine in Saudi Arabia. Saudi Pharm J 2023;31(6):942-947 [FREE Full text] [doi: 10.1016/j.jsps.2023.05.001] [Medline: 37197386]
23. Al-Mohaithef M, Padhi BK. Determinants of COVID-19 vaccine acceptance in Saudi Arabia: a web-based national survey. J Multidiscip Healthc 2020;13:1657-1663 [FREE Full text] [doi: 10.2147/JMDH.S276771] [Medline: 33262600]
24. Alaamri O, Okmi EA, Suliman Y. Vaccine hesitancy in Saudi Arabia: a cross-sectional study. Trop Med Infect Dis 2022;7(4):60 [FREE Full text] [doi: 10.3390/tropicalmed7040060] [Medline: 35448835]
25. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339:b2700 [FREE Full text] [doi: 10.1136/bmj.b2700] [Medline: 19622552]
26. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6(7):e1000097 [FREE Full text] [doi: 10.1371/journal.pmed.1000097] [Medline: 19621072]
27. Amir-Behghadami M, Janati A. Population, Intervention, Comparison, Outcomes and Study (PICOS) design as a framework to formulate eligibility criteria in systematic reviews. Emerg Med J 2020;37(6):387. [doi: 10.1136/emermed-2020-209567] [Medline: 32253195]
28. Schiavo JH. PROSPERO: an international register of systematic review protocols. Med Ref Serv Q 2019;38(2):171-180. [doi: 10.1080/02763869.2019.1588072] [Medline: 31173570]
29. Pieper D, Rombey T. Where to prospectively register a systematic review. Syst Rev 2022;11(1):8 [FREE Full text] [doi: 10.1186/s13643-021-01877-1] [Medline: 34998432]
30. Porritt K, Gomersall J, Lockwood C. JBI's systematic reviews: study selection and critical appraisal. Am J Nurs 2014;114(6):47-52 [FREE Full text] [doi: 10.1097/01.NAJ.0000450430.97383.64] [Medline: 24869584]
31. Crowe M, Sheppard L, Campbell A. Comparison of the effects of using the Crowe Critical Appraisal Tool versus informal appraisal in assessing health research: a randomised trial. Int J Evid Based Healthc 2011;9(4):444-449. [doi: 10.1111/j.1744-1609.2011.00237.x] [Medline: 22093394]
32. Crowe M, Sheppard L, Campbell A. Reliability analysis for a proposed critical appraisal tool demonstrated value for diverse research designs. J Clin Epidemiol 2012;65(4):375-383. [doi: 10.1016/j.jclinepi.2011.08.006] [Medline: 22078576]
33. Munn Z, Tufanaru C, Aromataris E. JBI's systematic reviews: data extraction and synthesis. Am J Nurs 2014;114(7):49-54 [FREE Full text] [doi: 10.1097/01.NAJ.0000451683.66447.89] [Medline: 25742352]

34. Galagali PM, Kinikar AA, Kumar VS. Vaccine hesitancy: obstacles and challenges. Curr Pediatr Rep 2022;10(4):241-248 [FREE Full text] [doi: 10.1007/s40124-022-00278-9] [Medline: 36245801]
35. Frew PM, Lutz CS. Interventions to increase pediatric vaccine uptake: an overview of recent findings. Hum Vaccin Immunother 2017;13(11):2503-2511 [FREE Full text] [doi: 10.1080/21645515.2017.1367069] [Medline: 28949819]
36. Kreuter MW, Caburnay CA, Chen JJ, Donlin MJ. Effectiveness of individually tailored calendars in promoting childhood immunization in urban public health centers. Am J Public Health 2004;94(1):122-127 [FREE Full text] [doi: 10.2105/ajph.94.1.122] [Medline: 14713709]
37. Salmon DA, Dudley MZ, Glanz JM, Omer SB. Vaccine hesitancy: causes, consequences, and a call to action. Am J Prev Med 2015;49(6 Suppl 4):S391-S398. [doi: 10.1016/j.amepre.2015.06.009] [Medline: 26337116]
38. Gowda C, Schaffer SE, Kopec K, Markel A, Dempsey AF. A pilot study on the effects of individually tailored education for MMR vaccine-hesitant parents on MMR vaccination intention. Hum Vaccin Immunother 2013;9(2):437-445 [FREE Full text] [doi: 10.4161/hv.22821] [Medline: 23291937]
39. Opel DJ, Mangione-Smith R, Taylor JA, Korfiatis C, Wiese C, Catz S, et al. Development of a survey to identify vaccine-hesitant parents: the parent attitudes about childhood vaccines survey. Hum Vaccin 2011;7(4):419-425 [FREE Full text] [doi: 10.4161/hv.7.4.14120] [Medline: 21389777]
40. Williams SE, Rothman RL, Offit PA, Schaffner W, Sullivan M, Edwards KM. A randomized trial to increase acceptance of childhood vaccines by vaccine-hesitant parents: a pilot study. Acad Pediatr 2013;13(5):475-480 [FREE Full text] [doi: 10.1016/j.acap.2013.03.011] [Medline: 24011750]
41. Alamer F, Alamir A, AlJohani S, AlSumih N, Hiji F, Alhammadi M, et al. Childhood vaccination hesitancy in Saudi Arabia: a time for action. J Infect Public Health 2022;15(1):94-99 [FREE Full text] [doi: 10.1016/j.jiph.2021.11.009] [Medline: 34838473]
42. Alghofaili MA, Aljuaid SO, Alqahtani N, Alghufaili M, Abd-Ellatif EE. Factors contributing to the delayed vaccination among children in Riyadh City, Saudi Arabia: a cross-sectional study. Cureus 2023;15(8):e43188 [FREE Full text] [doi: 10.7759/cureus.43188] [Medline: 37692740]
43. Saudi MOH: immunization schedule. MOH. 2018. URL: https://www.moh.gov.sa/_LAYOUTS/15/MOH/Internet/New/404/error.html [accessed 2023-09-11]
44. Bacillus Calmette-Guérin (BCG) vaccination coverage. World Health Organization. URL: https://immunizationdata.who.int/pages/coverage/BCG.html?CODE=SAU&YEAR= [accessed 2023-02-04]
45. Magadmi RM, Kamel FO. Beliefs and barriers associated with COVID-19 vaccination among the general population in Saudi Arabia. BMC Public Health 2021;21(1):1438 [FREE Full text] [doi: 10.1186/s12889-021-11501-5] [Medline: 34289817]
46. Sheerah HA, Almuzaini Y, Khan A. Public health challenges in Saudi Arabia during the COVID-19 pandemic: a literature review. Healthcare (Basel) 2023;11(12):1757 [FREE Full text] [doi: 10.3390/healthcare11121757] [Medline: 37372875]
47. Al Nufaiei ZF, Alshenkiti A, Sallam FN, Badraig NS, Al Zhranei RM, Alshamrani KM, et al. Assessment of the knowledge and opinions of undergraduate health care students concerning influenza vaccination in Saudi Arabia: a cross-sectional study. J Multidiscip Healthc 2023;16:2681-2690 [FREE Full text] [doi: 10.2147/JMDH.S415745] [Medline: 37720268]
48. Altulahi N, AlNujaim S, Alabdulqader A, Alkharashi A, AlMalki A, AlSiari F, et al. Willingness, beliefs, and barriers regarding the COVID-19 vaccine in Saudi Arabia: a multiregional cross-sectional study. BMC Fam Pract 2021;22(1):247 [FREE Full text] [doi: 10.1186/s12875-021-01606-6] [Medline: 34911441]
49. Aedh AI. Parents' attitudes, their acceptance of the COVID-19 vaccines for children and the contributing factors in Najran, Saudi Arabia: a cross-sectional survey. Vaccines (Basel) 2022;10(8):1264 [FREE Full text] [doi: 10.3390/vaccines10081264] [Medline: 36016152]
50. Maqsood MB, Islam MA, Al Qarni A, Nisa ZU, Ishaqui AA, Alharbi NK, et al. Assessment of COVID-19 vaccine acceptance and reluctance among staff working in public healthcare settings of Saudi Arabia: a multicenter study. Front Public Health 2022;10:847282 [FREE Full text] [doi: 10.3389/fpubh.2022.847282] [Medline: 35712310]
51. Al-Ghuraibi M, Dighriri IM, Elrggal ME, Obaid NA. The socio-cultural factors behind the Saudi attitude toward COVID-19 vaccination: a survey-based study. Front Public Health 2022;10:1026252 [FREE Full text] [doi: 10.3389/fpubh.2022.1026252] [Medline: 36699886]
52. Alsubaie SS, Gosadi IM, Alsaadi BM, Albacker NB, Bawazir MA, Bin-Daud N, et al. Vaccine hesitancy among Saudi parents and its determinants. Result from the WHO SAGE working group on vaccine hesitancy survey tool. Saudi Med J 2019;40(12):1242-1250 [FREE Full text] [doi: 10.15537/smj.2019.12.24653] [Medline: 31828276]
53. Alsuwaidi AR, Hammad HAAK, Elbarazi I, Sheek-Hussein M. Vaccine hesitancy within the Muslim community: Islamic faith and public health perspectives. Hum Vaccin Immunother 2023;19(1):2190716 [FREE Full text] [doi: 10.1080/21645515.2023.2190716] [Medline: 36914409]
54. Volet AK, Scavone C, Catalán-Matamoros D, Capuano A. Vaccine hesitancy among religious groups: reasons underlying this phenomenon and communication strategies to rebuild trust. Front Public Health 2022;10:824560 [FREE Full text] [doi: 10.3389/fpubh.2022.824560] [Medline: 35198525]

55. Ruijs WLM, Hautvast JLA, Kerrar S, van der Velden K, Hulscher MEJL. The role of religious leaders in promoting acceptance of vaccination within a minority group: a qualitative study. BMC Public Health 2013;13:511 [FREE Full text] [doi: 10.1186/1471-2458-13-511] [Medline: 23711160]

Abbreviations

BCG: Bacillus Calmette-Guerin
CCAT: Crowe Critical Appraisal Tool
DPT: diphtheria-pertussis-tetanus
Hib: Haemophilus influenzae type b
HPV: human papillomavirus
IPV: inactivated poliovirus vaccine
MCV: meningococcal vaccine
MMR: measles, mumps, and rubella
PICOS: Population, Intervention, Comparison, Outcomes, and Study
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO: International Prospective Register of Systematic Reviews
UNICEF: United Nations Children's Fund
WHO: World Health Organization

Edited by A Mavragani; submitted 18.11.23; peer-reviewed by S Awaidy; comments to author 12.01.24; revised version received 05.02.24; accepted 07.02.24; published 22.03.24.

Please cite as:
Kanan M, Abdulrahman S, Alshehri A, AlSuhaibani R, Alotaibi NM, Alsaleh A, Nasser B, Baowaydhan R, Alredaini I, Khalid T, Almukhtar F, Altoaimi N, Alhneshel A, Alanazi S, Algmaizi S
Factors Underlying Vaccine Hesitancy and Their Mitigations in Saudi Arabia: Protocol for a Systematic Review
JMIR Res Protoc 2024;13:e54680
URL: https://www.researchprotocols.org/2024/1/e54680
doi:10.2196/54680
PMID:38517463

Protocol

Applications of Artificial Intelligence in Emergency Departments to Improve Wait Times: Protocol for an Integrative Living Review

Bahareh Ahmadzadeh[1], BSc, MSc; Christopher Patey[2,3], MD; Oliver Hurley[1], BSc, MEnvSc; John Knight[4,5], PhD; Paul Norman[2], BN; Alison Farrell[6], MLIS; Stephen Czarnuch[7,8], PEng, PhD; Shabnam Asghari[1], MPH, MD, PhD

[1]Centre for Rural Health Studies, Faculty of Medicine, Memorial University of Newfoundland, St. John's, NL, Canada

[2]Eastern Health, Carbonear Institute for Rural Reach and Innovation by the Sea, Carbonear General Hospital, Carbonear, NL, Canada

[3]Faculty of Medicine, Memorial University of Newfoundland, St. John’s, NL, Canada

[4]Data and Information Services, Digital Health, NL Health Services, St. John’s, NL, Canada

[5]Division of Community Health and Humanities, Faculty of Medicine, Memorial University of Newfoundland, St. John’s, NL, Canada

[6]Health Sciences Library, Memorial University of Newfoundland, St. John’s, NL, Canada

[7]Department of Electrical and Computer Engineering, Faculty of Engineering and Applied Science, Memorial University of Newfoundland, St. John’s, NL, Canada

[8]Discipline of Emergency Medicine, Faculty of Medicine, Memorial University of Newfoundland, St. John’s, NL, Canada

Corresponding Author:
Shabnam Asghari, MPH, MD, PhD
Centre for Rural Health Studies
Faculty of Medicine
Memorial University of Newfoundland
300 Prince Philip Drive
St. John's, NL, A1B3V6
Canada
Phone: 1 709 777 2142
Fax: 1 709 777 6118
Email: sasghari@mun.ca

Abstract

Background: Long wait times in the emergency department (ED) are a major issue for health care systems all over the world. The application of artificial intelligence (AI) is a novel strategy to reduce ED wait times when compared to the interventions included in previous research endeavors. To date, comprehensive systematic reviews that include studies involving AI applications in the context of EDs have covered a wide range of AI implementation issues. However, the lack of an iterative update strategy limits the use of these reviews. Since the subject of AI development is cutting edge and is continuously changing, reviews in this area must be frequently updated to remain relevant.

Objective: This study aims to provide a summary of the evidence that is currently available regarding how AI can affect ED wait times; discuss the applications of AI in improving wait times; and periodically assess the depth, breadth, and quality of the evidence supporting the application of AI in reducing ED wait times.

Methods: We plan to conduct a living systematic review (LSR). Our strategy involves conducting continuous monitoring of evidence, with biannual search updates and annual review updates. Upon completing the initial round of the review, we will refine the search strategy and establish clear schedules for updating the LSR. An interpretive synthesis using Whittemore and Knafl’s framework will be performed to compile and summarize the findings. The review will be carried out using an integrated knowledge translation strategy, and knowledge users will be involved at all stages of the review to guarantee applicability, usability, and clarity of purpose.

Results: The literature search was completed by September 22, 2023, and identified 17,569 articles. The title and abstract screening were completed by December 9, 2023. In total, 70 papers were eligible. The full-text screening is in progress.

Conclusions: The review will summarize AI applications that improve ED wait time. The LSR enables researchers to maintain high methodological rigor while enhancing the timeliness, applicability, and value of the review.

International Registered Report Identifier (IRRID): DERR1-10.2196/52612

(JMIR Res Protoc 2024;13:e52612) doi:10.2196/52612

KEYWORDS

emergency department; ED; wait time; artificial intelligence; AI; living systematic review; LSR

Introduction

Background

Extended emergency department (ED) wait times are a major health care system problem worldwide [1-4]. Long wait times in the ED can threaten patients' well-being, leading them to depart the ED without receiving the essential care they require. Additionally, this situation contributes to overcrowding within the ED and fosters a sense of dissatisfaction among both patients and ED personnel [2]. Previous studies have investigated many initiatives to reduce ED wait times. Among them, a new approach is the use of artificial intelligence (AI) [3,4].

AI is one of the most important technological advancements of the Fourth Industrial Revolution [5]. AI refers to the use of technology and computers to mimic human-like critical thinking and intelligent behavior. In 1956, the word AI was first used by John McCarthy to refer to the science and engineering of creating intelligent machines AI refers to the use of technology and computers to mimic human-like critical thinking and intelligent behavior. As mentioned by Amisha et al [6], John McCarthy used the word AI for the first time in 1956 to refer to the science and engineering of creating intelligent machines. Recent years have seen exponential growth in the technological and scientific aspects of AI as well as machine learning, one of its main subcategories [7]. Notable benefits include increased productivity and innovation. Significant progress has been made to date in several fields, including computer vision, natural language processing, audio analysis, smart sensing, and many more [8]. Therefore, modeling based on AI is the key to creating automated, intelligent, and smart systems that meet today's needs. Different forms of AI, including analytical, functional, interactive, textual, and visual AI, can be used to improve an application's intelligence and capabilities to solve problems in the real world [5]. Although many of AI's practical applications are still in the early stages and require further research and development, the technology has the potential to revolutionize medicine in ways that have not yet been considered [6].

Harnessing the power of AI holds promising potential to improve the quality of care within EDs by effectively tackling challenges such as overcrowding by offering advanced clinical decision-making tools [9,10]. By developing an AI-assisted module, a significant reduction in wait times for outpatient services was demonstrated in the ED, according to a retrospective cohort study [4]. Furthermore, a prospective study revealed a notable decrease in the wait time for receiving care services through digital automation [11].

All AI methods that enable computers to learn from data without explicit programming are included in machine learning [12]. An Italian study used 2 large data sets of EDs to test several machine learning methods using predictive analytics. The findings demonstrate the viability of a real-time performance monitoring system that supports operational decision-making and has major practical implications for EDs and hospitals [13]. An Australian study showed that wait time forecasts for low-acuity ED patients assigned to the waiting room were improved through machine learning techniques and a wide range of queuing and service flow features. Machine learning models surpass the best rolling average in terms of mean absolute prediction error using queuing and service flow characteristics along with knowledge of daily fluctuations, and quantile regression lowers the proportion of patients with significantly underestimated wait times [14].

Deep learning is a subclass of machine learning defined primarily by neural network models with more layers and, in general, more neurons than typical machine learning neural networks. Additionally, deep networks, relative to traditional neural networks, achieve increased performance with increasingly large amounts of data, becoming practically realizable due to modern advances in computing power [15]. In a study conducted in Saudi Arabia, deep learning was used to forecast the length of time patients would wait in the ED's queue system. The findings of this study demonstrated the applicability of deep learning models for predicting patient wait times in the ED [16].

By looking at current developments in ED operations and clinical patient management, the authors of a review paper summarized the applications of AI in emergency medicine. They came to the view that the areas of prehospital emergency management, patient acuity, triage, and disposition, prediction of medical diseases and conditions, and ED management are where AI applications in ED are most prevalent [2]. Another systematic review study sought to show how AI was applied in ED and how it changed how ED practitioners' work was organized. Most AI applications, according to the study's findings, involved AI-based tools to support clinical judgment and reduce the pressure on overburdened EDs. Additionally, AI support was primarily provided during triage, the decision-making stage that determines a patient's course, and there is strong evidence that AI-based apps could enhance clinical decision-making [10].

Based on our understanding of the literature, the systematic reviews that encompassed studies involving AI applications in the context of EDs were comprehensive and addressed diverse aspects of AI implementation. However, these reviews were limited in their usefulness due to the absence of a plan for regular updates on AI progress, rendering them less applicable across some contexts. It is crucial to recognize that AI development is a revolutionary field with a rapidly evolving landscape. As such, reviews in this domain must undergo frequent updates to stay relevant. As a result of AI, computer programs can answer questions intelligently and infer facts based on real-world data. AI will become a core component of all contemporary decision-making in the immediate future. To keep up with the ongoing changes and revolutions in this field, we plan to conduct living systematic reviews (LSRs). Our

review will be regularly updated. We will incorporate relevant new evidence when it is available.

Study Goals and Objective

The study aims to summarize the available evidence on how AI can impact ED wait times; describe the applications of AI in reducing wait times; and examine the depth, breadth, and quality of evidence related to the application of AI in reducing wait time in the ED.

Methods

Rationale for LSR

LSR enables researchers to maintain high methodological rigor while enhancing the timeliness, applicability, and value of the review. Our strategy involves conducting continuous monitoring of evidence, with biannual search updates and annual review updates. Upon completing the initial round of the review, we will refine the search strategy and establish clear schedules for updating the LSR.

Type of Review

This will be an integrative review. Integrative reviews stand out as the most exhaustive form of systematic review methodology. They offer the flexibility of diverse sampling strategies and a broad scope of objectives, enabling them to provide a comprehensive representation of complex ideas, theories, or significant health care issues [17]. We selected this type of review since we aimed to examine the full breadth of techniques, methods, algorithms, and modalities of AI used to improve wait time in EDs from various academic sources. As mentioned by Hopia et al [18], according to Whittemore and Knafl's methodological steps, the integrated review method can use diverse data sources, thereby creating a comprehensive understanding of the topic of interest by presenting the state of the science and contributing to theory development. Whittemore and Knafl [17] approach consists of 5 stages and is based on Cooper's theoretical framework, which is one of the methodological approaches used in integrative reviews. These steps generally include problem identification, literature search, data evaluation, data analysis, and presentation [17].

Systematic Review Team

Research team members participating in the systematic review include researchers, physicians, and nurses with expertise in emergency medicine, librarians, learners, patients, AI specialists, and review methodologists.

Patient Engagement

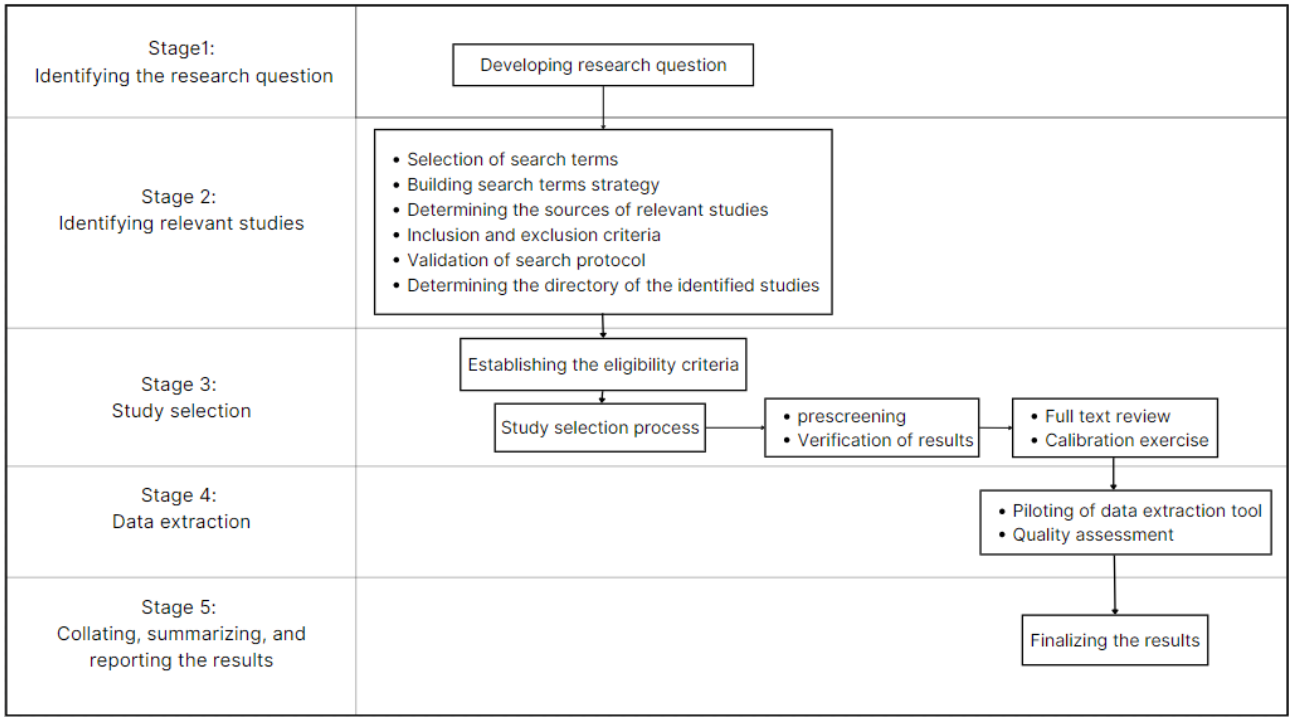
Our research plan and related materials will be showcased to SurgeCon's [19] patient engagement working group, comprising individuals from diverse backgrounds, including people of different gender identities residing in urban and rural areas of Newfoundland and Labrador. This approach aims to comprehensively gather the needs, desires, and firsthand experiences of those who stand to gain from the implementation of AI in improving ED wait times.

Protocol of the Integrative Review

Overview

Our designed integrative review protocol will include 5 stages summarized in Figure 1, which will be explained in the following. Furthermore, to ensure transparent and accurate reporting, we will use PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines in this review [20].

Figure 1. Visual representation of the 5 key stages in an integrative review protocol.



Stage 1: Identifying the Research Question

Our research questions will be developed and refined by a team of researchers and clinicians, including physicians and nurses with expertise in emergency medicine, patients, and librarians. "How does the application of AI reduce ED wait times, as supported by evidence from current literature?"

Stage 2: Identifying Relevant Studies

Selection of Search Terms

The search terms will be developed by content experts and patients. These terms include general variations on "ED," "wait times," "AI," "machine learning," "deep learning," and any more specific terms related to algorithms and methods used in the field of AI and indicators related to wait times in the ED. Once completed, the research question's key terms will be chosen by relevant stakeholders, which will be compiled alongside a list of potential synonyms or other terms identified by a librarian. The optimal search phrases will be determined by searching for Medical Subject Heading (MeSH) terms, the MeSH tree, and related words in keywords and references.

Building Search Terms Strategy

A librarian will assist in exploring various word combinations in databases to discover the most effective search method. When searching relevant literature, search phrases are iteratively improved by evaluating various terms, merging new terms, and finding new relevant citations. The MeSH and keywords will be combined in the search. For other data sets, different search techniques will be applied as needed.

Sources of Relevant Studies

We initiate the review process by conducting a comprehensive examination of peer-reviewed papers cited in electronic databases. This meticulous approach allows us to identify and encompass all relevant, available information sources. A librarian will provide support in completing the search for research studies in the following databases for studies that were published between January 1, 1946, and August 17, 2023: Embase, MEDLINE via Ovid, CINAHL, Cochrane, and Scopus. The search strategy for MEDLINE is available in Multimedia Appendix 1.

Inclusion and Exclusion Criteria

During our search for relevant research papers, we will incorporate peer-reviewed papers and published PhD dissertations from reputable repositories. Studies that focus on AI-related concepts, including AI algorithms and techniques, in the context of EDs to improve wait times will undergo a full-text review. We have categorized all the AI-related concepts and terminology we want to explore in reducing ED wait times in Multimedia Appendix 2. Since AI and its applications are evolving, we will reevaluate the inclusion and exclusion criteria in the next review to ensure new terminologies for AI will be included in our research. Our inclusion criteria will consist of studies that specifically concentrate on the application of AI techniques in the ED to decrease wait times. These studies must include wait times as an outcome measure and present relevant results. We will exclude studies that do not directly address the use of AI or do not primarily focus on reducing wait times in the ED. Additionally, master theses and conference abstracts will also be excluded from our selection.

Validation of the Search Protocol

The gold standard papers and journals recommended by subject matter experts will be used to test the search methodology and calibrate our search technique. The eligibility requirements will be changed as necessary. The search strategy for this LSR will be iteratively revised, and new search terms may supplement future searches if required.

Directory of Identified Studies

Covidence software (Veritas Health Innovation) will be used to manage the review and build a directory of publications.

Stage 3: Study Selection

Overview

The process of inclusion studies will be iterative and involve searching the literature, adjusting the search strategy, determining eligibility, prescreening, reviewing the full text of the literature for inclusion, and keeping only studies that discuss the use of AI to reduce ED wait times.

Eligibility Criteria

Members of our team who are knowledgeable about AI and ED and who will be blinded to the study results in question will make decisions about the review process methodology. Inclusion criteria will ensure a wide range of literature from various sources.

We will include patients, regardless of gender or age, who have been analyzed by AI algorithms. Audits or anecdotal information, planning-stage research, pilot studies, undergraduate dissertations, book reviews, gray literature, such as unpublished theses and reports from relevant websites, and policy assessments are among the exclusion criteria. We will look at both qualitative and quantitative studies. If the paper is a systematic review, all included studies in the review will be examined, and the related ones will be included in our review. In addition, we will conduct backward and forward citations of all studies eligible for data extraction in our review.

Study Selection Process

Prescreening

Papers will be digitally stored and managed in Covidence software, and duplicates will be removed by Covidence software. After training team members, they will independently review the titles and abstracts of all publications found through database searches to determine eligibility. Conflicts will be resolved through a discussion between the 2 reviewers (BA and AG); a third team (SA) member will provide feedback when necessary. If studies or abstracts do not address the topic of the search, or if the studies are commentaries or editorials, they will be deemed unrelated and excluded.

Verification of Results

One of the 2 reviewers (BA and AG) will then reevaluate a random sample of 5% (n=875) of the papers that were rejected based on title and abstract to make sure that all pertinent studies were considered. All excluded papers will be reexamined if

more than 5% (n=44) of the sample is determined to be relevant. We will also provide reviewers with retraining as needed.

Full-Text Review

Two research team members (BA and AG) will independently review all full texts. Only English papers are subject to full-text reviews, although the total number of studies considered appropriate by title, abstract, and full text will be noted for future use.

Calibration Exercise

We will conduct a calibration exercise before the process begins and then continue the calibration exercise throughout the review. Five percent of the listed citations will be randomly chosen. Two reviewers (BA and AG) will independently assess the full text against the eligibility criteria provided in Covidence. They will then discuss their rationale for including or excluding each article, and a third team member (SA) will provide feedback if necessary. Using an iterative process, if the level of agreement between the 2 reviewers is low (0.5), the eligibility criteria for screening and full-text review and the exclusion criteria for full-text review will be revised on Covidence. Then, the remaining citations will be evaluated by the reviewers (BA and AG), and a third reviewer (SA) will settle any disagreements. Furthermore, we will schedule biweekly team meetings to assess the review process. We will examine the reviewers' understanding of the eligibility criteria during these meetings and provide training if needed. The reviewers need to maintain a 0.8 agreement during the process.

Stage 4: Data Extraction

Overview

A data extraction tool for systematic data gathering from the indicated studies will be prepared in Excel (Microsoft Corporation). The tool will be made to extract data based on citation type (eg, original research), country, study date, study methodological features, study design, study population, sample size, AI techniques used, input variables, wait time metrics, outcomes measured, results performance, performance measure, and any limitations or challenges reported by the authors.

Piloting of the Data Extraction Tool

The team evaluates the data extraction tool by using a random sample of 5% (2) of the included studies. If required, the data extraction tool will also undergo frequent revisions. The data will be reviewed and extracted separately by 2 independent reviewers (BA and AG).

Quality Assessment

A scoring system for systematic reviews of mixed research will be used to evaluate the quality of primary studies (both quantitative and qualitative) [21]. The goal of the quality assessment is to determine the overall caliber of the studies in the sample rather than to identify or reject weaker studies. The quality of the screened studies will be reported.

Stage 5: Collating, Summarizing, and Reporting the Results

We will use a complex strategy to understand and combine the results of many studies for an interpretive synthesis. A descriptive summary of the identified and relevant studies will be reported. The frequency of research with study designs that match the criteria included in the data extraction tool will be provided [22]. In addition to collecting results, we seek to uncover underlying meaning, patterns, and relationships in the data. The framework developed by Whittemore and Knafl [17] is a useful resource for accomplishing this interpretative synthesis. Detailing the documented outcomes of AI interventions and the kinds of AI methods used by our data extraction tool's specifications will be part of the interpretive synthesis. We aim to identify commonalities or patterns in the studies by categorizing their results according to their impact on various wait time metrics. We will classify the findings of the identified research according to how they affect different wait time metrics in the ED using interpretive synthesis. These metrics include length of stay, number of patients leaving without being seen by a physician or their delegate, time to the initial physician assessment, and others. We will list the reported effects of AI interventions and the types of AI techniques implemented based on the criteria included in our data extraction tool. For an in-depth visual representation, the outcomes of the interpretative synthesis will be presented using descriptive tables, frequency tables, and diagrams. To develop a combined estimate of the effectiveness of AI initiatives in lowering ED wait times, the integrative review will evaluate the included papers' suitability for conducting a meta-analysis. If the selected studies show sufficient homogeneity in their methods and findings, a meta-analysis could be possible and provide a quantitative synthesis of the findings. We improve the breadth and clarity of this study's results by integrating these components into our interpretive synthesis approach, offering a robust analysis of the effect of AI interventions on ED wait times.

Knowledge-User Consultation

The review will be carried out using an integrated knowledge translation strategy, and knowledge users will be involved at all stages of the review to guarantee applicability, usability, and clarity of purpose. This strategy aims to engage content experts and the community advisory committee within our team through multiple consultations. The objective is to actively involve them in shaping the study's outcomes, action plan, and research agenda while also fostering opportunities for knowledge exchange [22,23]. We will organize regular meetings with the knowledge users' group to provide an opportunity to receive their feedback throughout the review. In addition, we will regularly update the progress of the review to notify them. By adopting these strategies, we can ensure that feedback from consultations is systematically integrated into the integrative review process, enhancing the relevance and applicability of the study outcomes. This team includes researchers and clinicians, including physicians and nurses with expertise in emergency medicine, learners, patients, AI specialists, and review methodologists. A practical understanding of the difficulties and possible advantages of applying AI to reduce wait times can be gained by speaking with ED physicians, nurses, administrators, and other health care workers who have firsthand experience working in the ED. Speaking with those in charge of planning the ED system and allocating resources

can give us an understanding of the broader effects of using AI in the ED. They can provide viewpoints on financing priorities, legislative considerations, and the viability of incorporating AI solutions into current health care systems. Speaking with professionals involved in the development and application of AI in similar contexts will help us comprehend the technical facets and capabilities of AI systems on a deeper level. These professionals can offer perceptions of the promise of AI technologies, the difficulties in putting them into practice, and factors to consider for successful integration into the ED environment. This LSR aims to provide updated information on the application of AI to improve ED wait times. Initial review findings will be regularly communicated to our team to validate our conclusions and help direct the completion of the review [22]. In addition to scientific papers and academic presentations, a summary of potential clinical practice implications will be created using the study's findings, including any areas that might call for medium- or long-term action. The summary will be distributed in our biweekly meetings with ED stakeholders to generate ideas, formulate research questions, and decide on suitable approaches for the SurgeCon ED wait time improvement team in Newfoundland and Labrador, Canada.

Results

The literature search was completed by September 22, 2023. We identified 17,569 studies. The title and abstract screening was started independently by 2 reviewers (BA and AG) on September 23, 2023, and ended on December 9, 2023. The full-text review phase started with 70 eligible papers on January 22, 2024, and is in progress.

Discussion

Recognizing the dynamic nature of AI research and its impact on health care decision-making in emergency medicine, we propose the use of LSRs. The major goal of LSRs is to keep our reviews up-to-date and relevant by including new information and revolutions in the field of AI as they become available. Using LSRs, we propose a methodological innovation that maintains rigor and assures that reviews remain relevant and applicable over time, reflecting the continual progress of AI applications in EDs.

Our research aimed to analyze the published studies examining AI applications in EDs, with a particular emphasis on reducing wait times. The analysis of the literature found that studies of AI applications in EDs to improve wait times cover a wide range of topics in emergency medicine [4,9,11,13,14,16]. We also found a few systematic reviews showing that scholars and specialists in the field have been proactive in synthesizing the available knowledge [2,10]. Despite their comprehensiveness, these systematic assessments have 1 significant limitation: no plan for regular updates. Since the field of AI is characterized by rapid change and continual progress, this issue jeopardizes the use of these studies in future settings. AI technologies are continually improving, and their applications in health care, including EDs, are no exception.

The study has several limitations. Implementing an LSR strategy may necessitate changes to existing review procedures as well as potential challenges in gathering and synthesizing constantly emerging data. Furthermore, the feasibility and practicality of conducting living reviews must be carefully considered. In addition, like other types of systematic reviews, the LSR is prone to publication bias, and the quality of the synthesis could be affected by the quality of the included studies.

In conclusion, our study illuminates the current state of AI applications in EDs and addresses a crucial gap in systematic review methods. LSRs emerge as a timely solution to the challenge of obsolescence amid rapid AI growth and advancements. Embracing LSRs ensures timely information for health care decision makers and sets a precedent for enhancing review techniques in the dynamic realm of AI research. As major technological shifts loom, our study highlights the methodological evolution needed to fully harness AI's potential in health care.

Acknowledgments

The work outlined in this protocol is supported by the Canadian Institutes of Health Research and provincial sponsors, including the Newfoundland and Labrador Provincial Government (Department of Industry, Energy and Technology), Newfoundland and Labrador Health Services, and the Trinity Conception Placentia Health Foundation. We acknowledge the use of ChatGPT (GPT-3.5, August 2023) for cross-validating a list of AI-related concepts and terminology. The original ChatGPT transcript is made available in Multimedia Appendix 3. Furthermore, we used AI-powered writing assistant tools, QuillBot for document editing and grammar checking, and Grammarly for proper referencing and improving readability. We thank Aswathy Geetha Manukumar for her role as one of the two reviewers in the in-progress integrative living review.

Data Availability

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

Conflicts of Interest

None declared.

Multimedia Appendix 1

Search strategy.
[PDF File (Adobe PDF File), 76 KB - resprot_v13i1e52612_app1.pdf]

Multimedia Appendix 2
Related concepts and terms.
[DOCX File , 17 KB - resprot_v13i1e52612_app2.docx]

Multimedia Appendix 3
The original ChatGPT transcript.
[DOCX File , 17 KB - resprot_v13i1e52612_app3.docx]

References

1. Wilper AP, Woolhandler S, Lasser KE, McCormick D, Cutrona SL, Bor DH, et al. Waits to see an emergency department physician: U.S. trends and predictors, 1997-2004. Health Aff (Millwood) 2008;27(2):w84-w95. [doi: 10.1377/hlthaff.27.2.w84] [Medline: 18198184]
2. Tang KJW, Ang CKE, Constantinides T, Rajinikanth V, Acharya UR, Cheong KH. Artificial intelligence and machine learning in emergency medicine. Biocybern Biomed Eng 2021;41(1):156-172. [doi: 10.1016/j.bbe.2020.12.002]
3. Chenais G, Lagarde E, Gil-Jardiné C. Artificial intelligence in emergency medicine: viewpoint of current applications and foreseeable opportunities and challenges. J Med Internet Res 2023;25:e40031 [FREE Full text] [doi: 10.2196/40031] [Medline: 36972306]
4. Li X, Tian D, Li W, Dong B, Wang H, Yuan J, et al. Artificial intelligence-assisted reduction in patients' waiting time for outpatient process: a retrospective cohort study. BMC Health Serv Res 2021;21(1):237 [FREE Full text] [doi: 10.1186/s12913-021-06248-z] [Medline: 33731096]
5. Sarker IH. AI-based modeling: techniques, applications and research issues towards automation, intelligent and smart systems. SN Comput Sci 2022;3(2):158 [FREE Full text] [doi: 10.1007/s42979-022-01043-x] [Medline: 35194580]
6. Amisha, Malik P, Pathania M, Rathaur VK. Overview of artificial intelligence in medicine. J Family Med Prim Care 2019;8(7):2328-2331 [FREE Full text] [doi: 10.4103/jfmpc.jfmpc_440_19] [Medline: 31463251]
7. Al Ka'Bi A. Challenges encountered by artificial intelligence applications in today's interconnected world. 2022 Presented at: 2022 International Conference on Electrical, Computer and Energy Technologies (ICECET); July 20-22, 2022; Prague, Czech Republic p. 1-6. [doi: 10.1109/icecet55527.2022.9873465]
8. Chen Z, Wu M, Chan A, Li X, Ong YS. Survey on AI sustainability: emerging trends on learning algorithms and research challenges [review article]. IEEE Comput Intell Mag 2023;18(2):60-77. [doi: 10.1109/mci.2023.3245733]
9. Kirubarajan A, Taher A, Khan S, Masood S. Artificial intelligence in emergency medicine: a scoping review. J Am Coll Emerg Physicians Open 2020;1(6):1691-1702 [FREE Full text] [doi: 10.1002/emp2.12277] [Medline: 33392578]
10. Boonstra A, Laven M. Influence of artificial intelligence on the work design of emergency department clinicians a systematic literature review. BMC Health Serv Res 2022;22(1):669 [FREE Full text] [doi: 10.1186/s12913-022-08070-7] [Medline: 35585603]
11. Bin KJ, Melo AAR, da Rocha JGMF, de Almeida RP, Junior VC, Maia FL, et al. The impact of artificial intelligence on waiting time for medical care in an urgent care service for COVID-19: single-center prospective study. JMIR Form Res 2022;6(2):e29012 [FREE Full text] [doi: 10.2196/29012] [Medline: 35103611]
12. Samuel AL. Some studies in machine learning using the game of checkers. IBM J Res Dev 1959;3(3):210-229 [FREE Full text] [doi: 10.1147/rd.33.0210]
13. Benevento E, Aloini D, Squicciarini N. Towards a real-time prediction of waiting times in emergency departments: a comparative analysis of machine learning techniques. Int J Forecast 2023;39(1):192-208. [doi: 10.1016/j.ijforecast.2021.10.006]
14. Pak A, Gannon B, Staib A. Predicting waiting time to treatment for emergency department patients. Int J Med Inform 2021;145:104303. [doi: 10.1016/j.ijmedinf.2020.104303] [Medline: 33126060]
15. Sarker IH. Deep learning: a comprehensive overview on techniques, taxonomy, applications and research directions. SN Comput Sci 2021;2(6):420 [FREE Full text] [doi: 10.1007/s42979-021-00815-1] [Medline: 34426802]
16. Hijry H, Olawoyin R. Predicting patient waiting time in the queue system using deep learning algorithms in the emergency room. Int J Ind Eng Oper Manag 2021;03(01):33-45. [doi: 10.46254/j.ieom.20210103]
17. Whittemore R, Knafl K. The integrative review: updated methodology. J Adv Nurs 2005;52(5):546-553. [doi: 10.1111/j.1365-2648.2005.03621.x] [Medline: 16268861]
18. Hopia H, Latvala E, Liimatainen L. Reviewing the methodology of an integrative review. Scand J Caring Sci 2016;30(4):662-669. [doi: 10.1111/scs.12327] [Medline: 27074869]
19. Mariathas HH, Hurley O, Anaraki NR, Young C, Patey C, Norman P, et al. A quality improvement emergency department surge management platform (SurgeCon): protocol for a stepped wedge cluster randomized trial. JMIR Res Protoc 2022;11(3):e30454 [FREE Full text] [doi: 10.2196/30454] [Medline: 35323121]

20. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71 [FREE Full text] [doi: 10.1136/bmj.n71] [Medline: 33782057]
21. Pluye P, Gagnon MP, Griffiths F, Johnson-Lafleur J. A scoring system for appraising mixed methods research, and concomitantly appraising qualitative, quantitative and mixed methods primary studies in mixed studies reviews. Int J Nurs Stud 2009;46(4):529-546. [doi: 10.1016/j.ijnurstu.2009.01.009] [Medline: 19233357]
22. Asghari S, Maybank A, Hurley O, Modir H, Farrell A, Marshall Z, et al. Perspectives of people living with HIV on access to health care: protocol for a scoping review. JMIR Res Protoc 2016;5(2):e71 [FREE Full text] [doi: 10.2196/resprot.5263] [Medline: 27193076]
23. Kastner M, Tricco AC, Soobiah C, Lillie E, Perrier L, Horsley T, et al. What is the most appropriate knowledge synthesis method to conduct a review? Protocol for a scoping review. BMC Med Res Methodol 2012;12:114 [FREE Full text] [doi: 10.1186/1471-2288-12-114] [Medline: 22862833]

Abbreviations

AI: artificial intelligence
ED: emergency department
LSR: living systematic review
MeSH: Medical Subject Heading
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Edited by A Mavragani; submitted 13.09.23; peer-reviewed by D Kohen; comments to author 25.01.24; revised version received 14.02.24; accepted 01.03.24; published 12.04.24.

Please cite as:
Ahmadzadeh B, Patey C, Hurley O, Knight J, Norman P, Farrell A, Czarnuch S, Asghari S
Applications of Artificial Intelligence in Emergency Departments to Improve Wait Times: Protocol for an Integrative Living Review
JMIR Res Protoc 2024;13:e52612
URL: https://www.researchprotocols.org/2024/1/e52612
doi:10.2196/52612
PMID:38607662

Protocol

Effectiveness and Experiences of Quality Improvement Interventions in Older Adult Care: Protocol for a Mixed Methods Systematic Review

Md Shafiqur Rahman Jabin[1], PhD; Ray Samuriwo[2,3], PhD; Marcus Chilaka[2], PhD; Emilia Vann Yaroson[4], PhD

[1]Department of Medicine and Optometry, Linnaeus University, Växjö, Sweden

[2]Faculty of Health Studies, University of Bradford, Bradford, United Kingdom

[3]School of Health and Social Care, Edinburgh Napier University, Edinburgh, United Kingdom

[4]Logistics, Transport, Operations and Analytics, Huddersfield Business School, University of Huddersfield, Huddersfield, United Kingdom

Corresponding Author:
Md Shafiqur Rahman Jabin, PhD
Department of Medicine and Optometry
Linnaeus University
Linnéuniversitetet Box 451
Växjö, 351 06
Sweden
Phone: 44 07915673612
Email: mjabin@bradford.ac.uk

Abstract

Background: Quality improvement (QI) interventions are designed to resolve the recurring challenges of care for older individuals, such as working conditions for staff, roles of older individuals in their own care and their families, and relevant stakeholders. Therefore, there is a need to map the impacts of QI interventions in older adult care settings and further improve health and social care systems associated with older adults.

Objective: This review aims to compile and synthesize the best available evidence regarding the effectiveness of policy and practice QI interventions in older adult care. The secondary aim is to understand the care of older individuals and QI intervention-related experiences and perspectives of stakeholders, care providers, older individuals, and their families.

Methods: The mixed methods review will follow the standard methodology used by Joanna Briggs Institute. The published studies will be searched through CINAHL, MEDLINE, PsycINFO, ASSIA, and Web of Science, and the unpublished studies through Mednar, Trove, OCLC WorldCat, and Dissertations and Theses. This review included both qualitative and quantitative analyses of patients undergoing older adult care and any health and care professionals involved in the care delivery for older adults; a broad range of QI interventions, including assistive technologies, effects of training and education, improved reporting, safety programs, and medical devices; the experiences and perspectives of staff and patients; the context of older adult care setting; and a broad range of outcomes, including patient safety. The standard procedure for reporting, that is, PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, will be followed.

Results: A result-based convergent synthesis design will be used in which both quantitative and qualitative studies will be analyzed separately, and the results of both syntheses will be then integrated during a final (convergent) synthesis. The integration will compare the findings of quantitative and qualitative evidence using tables in light of the results of both syntheses.

Conclusions: This comprehensive review is expected to reflect on the insights into some QI interventions and their impact, outline some common challenges of quality for older adult care, and benefit both the practical usefulness of care service activities and the society at large.

International Registered Report Identifier (IRRID): PRR1-10.2196/56346

(JMIR Res Protoc 2024;13:e56346) doi:10.2196/56346

KEYWORDS

patient safety; acceptability; accessibility; appropriateness; timeliness; equitability; social care

Introduction

Overview

Quality improvement (QI) intervention has been defined as "a systematic and continuous approach that designs, tests and implements changes using real-time measurements to improve the safety, effectiveness and experience of care" [1]. There are QI interventions designed to illuminate and resolve the current challenges in the care of older individuals that arise within health care and social care systems. This may include the challenges regarding working conditions for staff and the organization as a whole [2]; the roles of older individuals in their own care, including support from their relatives and families [3]; and the roles of clinical and public health researchers, academics, engineers and planning experts [4-7] to make changes in improving health and social care systems for older adults [4,8]. For the readers' convenience, the definition of QI will be used throughout this protocol to indicate the care of older individuals associated with health and social care systems.

The older population worldwide is growing with increased life expectancy and improving public health. These individuals are expected to live longer with multiple needs and circumstances [9]. Despite the challenge regarding adequate funding, care for older individuals in Sweden has been established because everyone should have equal access to care services [10]. Over 18% of the Swedish population is 65 years or older, and this number is expected to grow and be over 20% by the year 2030 and 25% by 2040 [11]. Sweden's health and care burden was moved to homecare in 1992 by implementing the ÄDEL reform, which focuses on minimizing complications for older adult care. Even though this strategy turned out to be a success for the Swedish health and social care system, achieving better accessibility by providing home health services to 90% of the aging population [10,12], the challenges around older adult care still remain. For example, a Swedish study found that while government agencies were very positive about the implementation of new technology in older adult care, the unstructured implementation process (without proper planning) and incoherent evaluation model (without compatible designing) indicated inequality of access to such new technology [13,14].

Several QI programs have shown promising results in improving the aging population's health and social care quality. For example, the QI program, that is, Acute Care for Elders, improved the outcomes for older adults, that is, significant reductions in cost and length of stay with greater comorbidity scores [15]. Other QI interventions, such as education sessions/toolkits, improved the impact of accurate and suitable medicines supply to the residents of residential aged-care facilities [16]. A discharge planning intervention increased the feasibility and effectiveness of facilitating the transition of older adults from hospitals to their homes [17]. An intervention comprising technical and social components reduced preventable harm in care homes [18,19]. Such QI programs may also involve collaboration between geriatricians and primary care physicians, further reducing hospitalization risk and total health and care costs among vulnerable older adults [20].

The review will consider various dimensions of care quality, such as accessibility, appropriateness, safety, efficacy, effectiveness, timeliness, patient-centeredness, and equitability [21,22]. Each subsection will also be covered to obtain a comprehensive insight into health and care quality. For example, the 5 dimensions of accessibility, that is, approachability, acceptability, availability and accommodation, affordability, and appropriateness, will be considered and explored [23,24]. This is because the care provided should be adequate for all these dimensions, that is, 1 or more missing aspects of the care do not complete the entirety of the quality [25,26]. For instance, providing inappropriate or ineffective care should be unacceptable even if it is safe and provided in a timely manner [27,28].

A recent comprehensive or mixed methods systematic review of QI interventions in the radiology setting has demonstrated expected results, that is, improvements in outcomes, such as improved workflow efficiency, report turnaround time, and teamwork and communication [29,30]. We believe that a similar review in the setting of older adult care would develop new knowledge for the health and social care system as well as for older individuals and care providers. Therefore, the findings of the review will generate insights that have wider relevance in creating a model for improved older adult care systems and to meet today's societal challenges.

Several systematic reviews have been performed for older adult care focusing on health and care quality and its dimensions, such as patient safety [31], appropriateness [32], and accessibility [23], including recent reviews on the interventions of eHealth [33] and training [34]. However, none of these reviews constitutes a comprehensive systematic review focusing on both quantitative and qualitative studies for looking through multiple lenses into the health and social care system of older adult care with broader perspectives that would further facilitate analyzing the issues and devising recommendations. A preliminary search has been performed on Campbell Systematic Reviews, the Cochrane Database of Systematic Reviews, PROSPERO (International Prospective Register of Systematic Reviews), and Joanna Briggs Institute (JBI) evidence synthesis, and we have not identified any systematic reviews on QI interventions in older adult care settings using either qualitative or quantitative methodology.

Aim and Review Questions

The primary purpose of this review is to compile and synthesize the best available evidence regarding the effectiveness of QI interventions in older adult care. Provided that QI initiatives ultimately target the beliefs and perspectives of clinicians, in a broader sense, the organization and its resources, the secondary objective of this review is to understand the experiences and perspectives of care providers, older individuals and their families, and relevant stakeholders undergoing a QI initiative. Specifically, the review questions are as follows:

- What kind of QI interventions have been used to improve the quality of older adult care?
- How effective are interventions in relation to policy and practice that target improvements in the quality of older adult care?

- What are the experiences and perspectives of care providers, older individuals and their families, and relevant stakeholders about these interventions?

Methods

The proposed scoping review will be conducted in accordance with the JBI methodology for systematic (mixed methods) reviews [35].

Search Strategy

Databases will be searched for both published and unpublished studies. The approach to searching for studies for a scoping review will follow the standard 3-step method. The first step will be an initial limited search of a selection of relevant databases, followed by an analysis of text words in the title and abstract and the index terms used to describe the article. The search for published studies will include a 2-way search strategy. One is to search the journal and reference databases, such as CINAHL, MEDLINE, PsycINFO, ASSIA, and Web of Science. Another is to search article-based (journal) databases, such as ACM digital library, IEEE Xplore, and BMJ Journals. The search for unpublished studies (gray literature) will include Mednar, Trove, OCLC WorldCat, and Dissertations and Theses. A second search using all identified keywords (see Textbox 1) and index terms will be undertaken across all included databases. Additional search strategies, that is, citation search—specific researcher or article (for example, gold-standard article), and chain search—review reference list of the systematically selected articles will be included to complement the search for published and unpublished papers. Studies, such as reviews (systematic, scoping, umbrella) and editor letters, will be excluded. Any studies that lack ethical concerns will also be excluded.

Textbox 1. A list of keywords for search strategy.

Participants: Old people (patient), older people (patient), elderly people (patient), elderly people (patient), elderlies, aging population, geriatricians, social workers, and domiciliary workers (Using OR Boolean operator).

Context: elderly care, aged care, primary care, private hospital, public hospital, clinic, geriatric ward, old-age home, nursing homes, domiciliary care, and home care (Using OR Boolean operator).

Interventions: Technology, training, education, staff arrangement, incident reporting, peer review, clinical audit, teamwork intervention, communication intervention, team training, safety checklist, local governance, and quality improvement intervention. (Using OR Boolean operator).

Outcomes: Patient safety, incident, event, near miss, adverse event, safety culture, safety effectiveness, timeliness, patient-centeredness, equitability, decision-making, communication, teamwork, leadership, report turnaround, patient experience, patient perspective, staff experience, and staff perspective. (Using OR Boolean operator).

Types of Studies: Randomized controlled trials, cluster randomized controlled trials, quasi-experimental, controlled before and after trials, interrupted time series analysis, qualitative, grounded theory, ethnography, phenomenology, case study, narrative model, and historical model (Using OR Boolean operator).

Studies published in English will be considered. Studies published from 1990 onward (when the first substantive patient safety research study, "Harvard Medical Practice," was published) [36,37] will be considered for inclusion in this review. The search strategy results will be depicted through the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram [38].

Inclusion Criteria

Research Background

The inclusion criteria of this review will follow the mnemonics of PICO (for quantitative studies) and PICo (for qualitative studies)—which stands for Population, Phenomena of Interest, and Context. These mnemonics are used as a guide (not policy); therefore, the inclusion criteria of this systematic review will include a detailed description of types of participants/population, types of interventions, phenomena of interest, context, outcomes, as well as types of studies, search strategies, assessment of methodological quality, and synthesis of results.

Types of Participants/Population

This review will include studies of older individuals (65 years or older) undergoing older adult care irrespective of gender and diversity, including age, ethnicity, socioeconomic status, and disability, and any health and care professionals (care providers) and stakeholders involved in the care delivery for older individuals, such as nurse practitioners, registered nurses, enrolled nurses, specialist nurses, and geriatricians.

Types of Interventions

The included studies should concentrate on the implementation of a QI intervention, that is, defined as the systematic and continuous approach that designs, tests, and implements changes using real-time measurements to improve the safety, effectiveness, and experience of older adult care. Given the complexities of the health and social care system, a range of QI interventions will be included in this review. The interventions will include but not are limited to ton technology; training and education; improved reporting and management; safety programs; changes in staffing arrangements (staffing levels, and skill, grade and qualification mix); improved regulation; peer review; and revalidation, clinical audit, and changes to local governance.

Phenomena of Interest

The phenomena of interest will be the effects on outcomes and workflow processes and the experiences and perspectives of care providers and older individuals undergoing or being exposed to the QI interventions. These experiences or perspectives included descriptions of the quality and safety concerns, the contexts and cultures of the workplaces (including factors such as conflict and how it was managed, teamwork

behaviors, and the attitudes of care providers), and the management of adverse events and near misses.

Context

The systematic review will consider studies in older adult care settings, such as geriatric wards of primary health care, hospitals or clinics, old-age homes, nursing homes, and home care facilities for older people.

Outcomes

The outcomes will include validated measures of safety culture decision-making, communication, teamwork, leadership, report turnaround time, and timeliness of care. Further outcomes will be patient satisfaction and patients' perceptions of the quality of older adult care [39].

Types of Studies

Quantitative and qualitative studies will be included to report empirical evidence and the human experience. Quantitative studies include randomized controlled trials or Cluster Randomized Controlled trials; nonrandomized controlled trials; quasi-experimental, controlled before-after trials; and interrupted time series studies. Qualitative studies included interpretive work focusing on, but not limited to, designs such as content analysis, phenomenology, grounded theory, ethnography, case study, narrative model, and historical model. Mixed methods and descriptive studies will also be eligible for inclusion.

Assessment of Methodological Quality

Two independent reviewers for methodological validity prior to inclusion will assess selected quantitative and qualitative papers for retrieval, reducing the risk of methodological issues, such as subjective bias. This will be done using the standardized critical appraisal criteria from the critical appraisal instruments by the JBI. Any discrepancies that may arise between reviewers' assessments will be resolved by consensus through discussion.

A critical appraisal of the selected papers will be conducted after screening. The formal process of GRADE (Grading of Recommendations Assessment, Development, and Evaluation) and the GRADE-CERQual (Confidence in the Evidence from Reviews of Qualitative Research) will be used to rate the quality of scientific evidence and confidence to place in findings from systematic reviews of both quantitative and qualitative studies, respectively. For example, 3 grades of quality may be used for each study, based on the score achieved in the critical appraisals: low quality (less than 33% or equal to 33%), medium quality (34%-66%), and high quality (more than 66%).

Data Extraction

Quantitative data will be extracted from papers included in the review using the standardized JBI data extraction tool. Qualitative data will be extracted from papers included in the review using the standardized JBI data extraction tool. The data extracted for quantitative and qualitative studies will include specific details about the interventions, populations, study methods, and outcomes of significance to the review question and specific objectives.

Results

A result-based convergent synthesis design [40] will be used in which quantitative and qualitative studies will be analyzed separately, and the results of both syntheses will be then integrated during a final (convergent) synthesis. The integration will compare the quantitative and qualitative evidence findings using tables in light of the results of both syntheses. This will help us address overall review questions with subquestions (if possible).

Quantitative papers will, where possible, be pooled in a statistical meta-analysis using the appropriate JBI tool. All results will be subject to double data entry. Effect sizes expressed as odds ratio (for categorical data) and weighted mean differences (for continuous data) and their 95% CIs will be calculated for analysis. Heterogeneity will be assessed statistically using the standard chi-square and I-square. It will also be explored using subgroup analyses based on the different quantitative study designs included in this review. Where statistical pooling is impossible, the findings will be presented in narrative form, including tables and figures, to aid in data presentation where appropriate.

Qualitative research findings will, where possible, be pooled using the appropriate JBI tool. This will involve the aggregation or synthesis of findings to generate a set of statements that represent that aggregation through assembling the findings rated according to their quality and categorizing them based on similarity in meaning. These categories are then subjected to a meta-synthesis to produce a single comprehensive set of synthesized findings that can be used as a basis for evidence-based practice. Where textual pooling is impossible, the findings will be presented in narrative form.

Discussion

Principal Findings

Health and social care systems embrace welfare broadly and include institutions, organizations, and resources to maintain or promote health and social care. The resources may consist of funds for the training and education of care providers and welfare technologies used for older adult care services [41,42]. During the COVID-19 pandemic, the quality and safety of care for older individuals have been a top priority [43]. A future pandemic situation can be overcome through sustainable health and social care systems for older individuals by dealing with the challenges found at the system and organizational levels.

This review is designed to be a mixed methods systematic review that will contain evidence of and bring together the results of single-method reviews (including quantitative and qualitative), which has the potential to produce reviews of direct relevance to policy makers and practitioners. As this review covers a wide range of interventions and outcomes and the experiences and perspectives of both care providers and older individuals, the results are expected to reflect on and offer insights into some QI interventions and their impact and some common quality challenges for older adult care. The challenges may include accommodation and availability, the role of the

families, friends, and relatives; working conditions and staffing arrangements; and the practical usefulness of the patients and care service activities and the society at large.

It is essential to cover a diversity perspective in the review; for example, older individuals of different cultural backgrounds may have different needs for QI. As we cover as many health and care quality dimensions as possible, we believe that issues of diverse perspectives will be included in the literature. For example, the dimension of "acceptability" is defined as the relationship between clients' attitudes about personal and practice characteristics of existing providers, including age, sex, location, and type of facility or religious affiliation of the provider or facility, as well as provider attitudes about acceptable personal characteristics of clients, including ethnicity and source of payment [23,24,44].

This review will include studies of individuals undergoing older adult care irrespective of gender, diversity, ethnicity, socioeconomic status, and disability. This review will evaluate if older adult care facilities worldwide are equipped enough to deal with the challenges of gender sensitivity and cultural diversity. For example, the review may cover the issues of gender sensitivity, especially when a family experiences feelings of shame when receiving care from a nonfamily member or the opposite gender [23,45].

Strengths and Limitations of the Review

The results of this systematic review will need to be treated with caution since our search is restricted to language and publication period. To minimize the effect of such limitations, a comprehensive strategy, that is, a standard 3-step method, will be followed. For example, the inclusion of gray literature will provide additional insights into the review findings. There may be other limitations, for instance, the possibility pertaining to the results associated with limited included studies, introducing a layer of bias for the selected studies. The evidence-based practice center methods guide proposed by the Agency for Health Care Research and Quality will be used to risk the risk of bias in individual studies [46].

To ensure the review produces generalizable findings, discussions with older adults and their families and the relevant public will be channeled to support the interpretation and dissemination of the review findings.

Conclusion

No current or underway systematic reviews on the topic were identified. This comprehensive review will uncover the shreds of evidence requiring diligent attention to address the effectiveness of interventions in relation to policy and practice in older adult care settings. The review will also reflect on the insights into the impact of QI interventions, outline some common challenges of quality for older adult care, and benefit both the practical usefulness of care service activities and the society at large.

Acknowledgments

The authors thank the librarians from Linnaeus University and the University of Bradford for their guidance and assistance in this research. This study is being undertaken without external funding. A publishing grant has been received from Linnaeus University as a part of the University Library's research support. No generative artificial intelligence was used in any portion of the manuscript writing.

Data Availability

All data generated or analyzed during this study will be included in this published article and its supplementary information files.

Conflicts of Interest

None declared.

References

1. Quality improvement-training for better outcomes. Academy of Medical Royal Collages. 2016. URL: https://gmpcb.org.uk/wp-content/uploads/Quality_improvement_training_better_outcomes_140316-2.pdf [accessed 2024-02-21]
2. Ede L, Rantakeisu U. Managing organized insecurity: the consequences for care workers of deregulated working conditions in elderly care. Nord J Work Life Stud 2015;5(2):55-70 [FREE Full text] [doi: 10.19154/njwls.v5i2.4793]
3. Tinetti ME, Naik AD, Dindo L, Costello DM, Esterson J, Geda M, et al. Association of patient priorities-aligned decision-making with patient outcomes and ambulatory health care burden among older adults with multiple chronic conditions: a nonrandomized clinical trial. JAMA Intern Med 2019;179(12):1688-1697 [FREE Full text] [doi: 10.1001/jamainternmed.2019.4235] [Medline: 31589281]
4. Alavi K, Sutan R, Shahar S, Manaf MRA, Jaafar MH, Maulud KNA, et al. Connecting the dots between social care and healthcare for the sustainability development of older adult in Asia: a scoping review. Sustainability 2022;14(5):2573 [FREE Full text] [doi: 10.3390/su14052573]
5. Jabin MSR, Nilsson E, Nilsson A, Bergman P, Jokela P. Digital health testbeds in Sweden: an exploratory study. Digit Health 2022;8:20552076221075194 [FREE Full text] [doi: 10.1177/20552076221075194] [Medline: 35186314]

6. Jabin MSR, Pan D. Software-related challenges in Swedish healthcare through the lens of incident reports: a desktop study. Digit Health 2023;9:20552076231203600 [FREE Full text] [doi: 10.1177/20552076231203600] [Medline: 37744748]
7. Jabin MSR. Operational disruption in healthcare associated with software functionality issue due to software security patching: a case report. Front Digit Health 2024;6:1367431 [FREE Full text] [doi: 10.3389/fdgth.2024.1367431]
8. Jabin MSR, Steen M, Wepa D, Bergman P. Assessing the healthcare quality issues for digital incident reporting in Sweden: incident reports analysis. Digit Health 2023;9:20552076231174307 [FREE Full text] [doi: 10.1177/20552076231174307] [Medline: 37188073]
9. Fors S, Wastesson JW, Morin L. Growing income-based inequalities in old-age life expectancy in Sweden, 2006-2015. Demography 2021;58(6):2117-2138 [FREE Full text] [doi: 10.1215/00703370-9456514] [Medline: 34528078]
10. Healthcare in Sweden. Sweden Sverige. 2020. URL: https://sweden.se/society/health-care-in-sweden/ [accessed 2024-08-06]
11. Lennartsson C, Heimerson I. Elderly people's health: health in Sweden: the national public health report 2012. chapter 5. Scand J Public Health 2012;40(9 Suppl):95-120 [FREE Full text] [doi: 10.1177/1403494812459468] [Medline: 23238403]
12. Sweden: a role model for elderly care. Global Health Aging. 2014. URL: https://globalhealthaging.org/2014/08/03/sweden-a-role-model-for-elderly-care/ [accessed 2020-08-08]
13. Frennert S, Baudin K. The concept of welfare technology in Swedish municipal eldercare. Disabil Rehabil 2021;43(9):1220-1227 [FREE Full text] [doi: 10.1080/09638288.2019.1661035] [Medline: 31503509]
14. Tapuria A, Porat T, Kalra D, Dsouza G, Xiaohui S, Curcin V. Impact of patient access to their electronic health record: systematic review. Inform Health Soc Care 2021;46(2):192-204 [FREE Full text] [doi: 10.1080/17538157.2021.1879810] [Medline: 33840342]
15. Brennan MJ, Knee AB, Leahy EJ, Ehresman MJ, Courtney HA, Coffelt P, et al. An acute care for elders quality improvement program for complex, high-cost patients yields savings for the system. J Hosp Med 2019;14(9):527-533 [FREE Full text] [doi: 10.12788/jhm.3198] [Medline: 31112495]
16. Gilmartin JFM, Marriott JL, Hussainy SY. Improving Australian care home medicine supply services: evaluation of a quality improvement intervention. Australas J Ageing 2016;35(2):E1-E6. [doi: 10.1111/ajag.12236] [Medline: 26489372]
17. Dedhia P, Kravet S, Bulger J, Hinson T, Sridharan A, Kolodner K, et al. A quality improvement intervention to facilitate the transition of older adults from three hospitals back to their homes. J Am Geriatr Soc 2009;57(9):1540-1546. [doi: 10.1111/j.1532-5415.2009.02430.x] [Medline: 19694865]
18. Marshall M, Pfeifer N, de Silva D, Wei L, Anderson J, Cruickshank L, et al. An evaluation of a safety improvement intervention in care homes in England: a participatory qualitative study. J R Soc Med 2018;111(11):414-421 [FREE Full text] [doi: 10.1177/0141076818803457] [Medline: 30235053]
19. Marasinghe KM, Chaurasia A, Adil M, Liu QY, Nur TI, Oremus M. The impact of assistive devices on community-dwelling older adults and their informal caregivers: a systematic review. BMC Geriatr 2022;22(1):897 [FREE Full text] [doi: 10.1186/s12877-022-03557-8] [Medline: 36424533]
20. Fenton JJ, Levine MD, Mahoney LD, Heagerty PJ, Wagner EH. Bringing geriatricians to the front lines: evaluation of a quality improvement intervention in primary care. J Am Board Fam Med 2006;19(4):331-339 [FREE Full text] [doi: 10.3122/jabfm.19.4.331] [Medline: 16809646]
21. Quality of Care: A Process for Making Strategic Choices in Health Systems. Geneva: World Health Organization; 2006.
22. King A. Improving quality (IQ): a systems approach for the New Zealand health and disability sector. N Z Med J 2003;116(1182):U599. [Medline: 14581951]
23. van Gaans D, Dent E. Issues of accessibility to health services by older Australians: a review. Public Health Rev 2018;39:20 [FREE Full text] [doi: 10.1186/s40985-018-0097-4] [Medline: 30027001]
24. Penchansky R, Thomas JW. The concept of access: definition and relationship to consumer satisfaction. Med Care 1981;19(2):127-140. [doi: 10.1097/00005650-198102000-00001] [Medline: 7206846]
25. Jabin MSR, Magrabi F, Hibbert P, Schultz T, Runciman W. Identifying clusters and themes from incidents related to health information technology in medical imaging as a basis for improvements in practice. : IEEE; 2019 Presented at: 2019 IEEE International Conference on Imaging Systems and Techniques (IST); December 09-10, 2019; Abu Dhabi, United Arab Emirates p. 1-16. [doi: 10.1109/ist48021.2019.9010280]
26. Jabin MSR, Pan D, Nilsson E. Characterizing patient details-related challenges from health information technology-related incident reports from Swedish healthcare. Front Digit Health 2024;6:1260521 [FREE Full text] [doi: 10.3389/fdgth.2024.1260521] [Medline: 38380372]
27. Jabin MSR, Mandel C, Schultz T, Hibbert P, Magrabi F, Runciman W. Identifying and characterizing the 18 steps of medical imaging process workflow as a basis for targeting improvements in clinical practice. : IEEE; 2019 Presented at: 2019 IEEE International Conference on Imaging Systems and Techniques (IST); December 09-10, 2019; Abu Dhabi, United Arab Emirates p. 1-6. [doi: 10.1109/ist48021.2019.9010117]
28. Jabin MSR. Identifying and characterising problems arising from interactions between medical imaging and health information technology as a basis for improvements in practice. Australian Institute for Precision Health. Adelaide: University of South Australia; 2019. URL: https://find.library.unisa.edu.au/discovery/fulldisplay?vid=61USOUTHAUS_INST:UNISA&tab=LIBCOLL&docid=alma9916366810901831&context=L&lang=en [accessed 2024-03-27] [WebCite Cache ID 9916366810901831]

29. Jabin MSR, Schultz T, Mandel C, Bessen T, Hibbert P, Wiles L, et al. A mixed-methods systematic review of the effectiveness and experiences of quality improvement interventions in radiology. J Patient Saf 2022;18(1):e97-e107. [doi: 10.1097/PTS.0000000000000709] [Medline: 32433438]
30. Jabin SR, Schultz T, Hibbert P, Mandel C, Runciman W. Effectiveness of quality improvement interventions for patient safety in radiology: a systematic review protocol. JBI Database System Rev Implement Rep 2016;14(9):65-78 [FREE Full text] [doi: 10.11124/JBISRIR-2016-003078] [Medline: 27755318]
31. Long SJ, Brown KF, Ames D, Vincent C. What is known about adverse events in older medical hospital inpatients? a systematic review of the literature. Int J Qual Health Care 2013;25(5):542-554 [FREE Full text] [doi: 10.1093/intqhc/mzt056] [Medline: 23925507]
32. Niehoff KM, Mecca MC, Fried TR. Medication appropriateness criteria for older adults: a narrative review of criteria and supporting studies. Ther Adv Drug Saf 2019;10:2042098618815431 [FREE Full text] [doi: 10.1177/2042098618815431] [Medline: 30719279]
33. Buyl R, Beogo I, Fobelets M, Deletroz C, Van Landuyt P, Dequanter S, et al. e-Health interventions for healthy aging: a systematic review. Syst Rev 2020;9(1):128 [FREE Full text] [doi: 10.1186/s13643-020-01385-8] [Medline: 32493515]
34. Lopez P, Pinto RS, Radaelli R, Rech A, Grazioli R, Izquierdo M, et al. Benefits of resistance training in physically frail elderly: a systematic review. Aging Clin Exp Res 2018;30(8):889-899. [doi: 10.1007/s40520-017-0863-z] [Medline: 29188577]
35. Peters MDJ, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. Int J Evid Based Healthc 2015;13(3):141-146 [FREE Full text] [doi: 10.1097/XEB.0000000000000050] [Medline: 26134548]
36. Leape LL, Brennan TA, Laird N, Lawthers AG, Localio AR, Barnes BA, et al. The nature of adverse events in hospitalized patients. results of the Harvard medical practice study II. N Engl J Med 1991;324(6):377-384 [FREE Full text] [doi: 10.1056/NEJM199102073240605] [Medline: 1824793]
37. Brennan TA, Leape LL, Laird NM, Hebert L, Localio AR, Lawthers AG, et al. Incidence of adverse events and negligence in hospitalized patients. results of the Harvard Medical Practice Study I. N Engl J Med 1991;324(6):370-376 [FREE Full text] [doi: 10.1056/NEJM199102073240604] [Medline: 1987460]
38. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Int J Surg 2021;88:105906 [FREE Full text] [doi: 10.1016/j.ijsu.2021.105906] [Medline: 33789826]
39. Owens DJ, Batchelor C. Patient satisfaction and the elderly. Soc Sci Med 1996;42(11):1483-1491. [doi: 10.1016/0277-9536(95)00234-0] [Medline: 8771631]
40. Hong QN, Pluye P, Bujold M, Wassef M. Convergent and sequential synthesis designs: implications for conducting and reporting systematic reviews of qualitative and quantitative evidence. Syst Rev 2017;6(1):61 [FREE Full text] [doi: 10.1186/s13643-017-0454-2] [Medline: 28335799]
41. Calnan M. Health and welfare systems. In: Dingwall R, Quah SR, Cockerham WC, editors. The Wiley Blackwell Encyclopedia of Health, Illness, Behavior, and Society. Chichester: Wiley Blackwell; 2014:1120-1127.
42. Marasinghe KM. Assistive technologies in reducing caregiver burden among informal caregivers of older adults: a systematic review. Disabil Rehabil Assist Technol 2016;11(5):353-360. [doi: 10.3109/17483107.2015.1087061] [Medline: 26371519]
43. Ministry of Health and Social Affairs. About the COVID-19 virus: for older people, people with health conditions and health and social care staff. Government Offices of Sweden. 2020. URL: https://www.government.se/speeches/2020/04/speech-by-minister-for-health-and-social-affairs-lena-hallengren-at-who-briefing-23-april/ [accessed 2024-06-11]
44. Perski O, Short CE. Acceptability of digital health interventions: embracing the complexity. Transl Behav Med 2021;11(7):1473-1480 [FREE Full text] [doi: 10.1093/tbm/ibab048] [Medline: 33963864]
45. Iriarte EG, McConkey R, Vilda D. Family experiences of personalised accommodation and support for people with intellectual disability. J Intellect Disabil 2021;25(4):476-489. [doi: 10.1177/1744629520905207] [Medline: 32065010]
46. Viswanathan M, Patnode CD, Berkman ND, Bass EB, Chang S, Hartling L, et al. Assessing the risk of bias of individual studies in systematic reviews of health care interventions. In: Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville, MD: Agency for Healthcare Research and Quality (US); 2012.

Abbreviations

CERQual: Confidence in the Evidence from Reviews of Qualitative Research
GRADE: Grading of Recommendations Assessment, Development and Evaluation
JBI: Joanna Briggs Institute
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO: International Prospective Register of Systematic Reviews
QI: quality improvement

Edited by A Mavragani; submitted 13.01.24; peer-reviewed by M Casella Jean-Baptiste, A Hall; comments to author 05.02.24; revised version received 08.02.24; accepted 26.02.24; published 18.04.24.

Please cite as:
Jabin MSR, Samuriwo R, Chilaka M, Yaroson EV
Effectiveness and Experiences of Quality Improvement Interventions in Older Adult Care: Protocol for a Mixed Methods Systematic Review
JMIR Res Protoc 2024;13:e56346
URL: https://www.researchprotocols.org/2024/1/e56346
doi:10.2196/56346
PMID:38635311

Protocol

Impact of Digital Interventions on the Treatment Burden of Patients With Chronic Conditions: Protocol for a Systematic Review

Manria Polus[1,2], MSc; Pantea Keikhosrokiani[1,2], PhD; Olli Korhonen[1], PhD; Woubshet Behutiye[1], PhD; Minna Isomursu[1,2], PhD

[1]Faculty of Information Technology and Electrical Engineering, University of Oulu, Oulu, Finland

[2]Faculty of Medicine, University of Oulu, Oulu, Finland

Corresponding Author:
Manria Polus, MSc
Faculty of Information Technology and Electrical Engineering
University of Oulu
Pentti Kaiteran Katu 1
Oulu, 90570
Finland
Phone: 358 294 48 0000
Email: manria.polus@oulu.fi

Abstract

Background: There is great potential for delivering cost-effective, quality health care for patients with chronic conditions through digital interventions. Managing chronic conditions often includes a substantial workload required for adhering to the treatment regimen and negative consequences on the patient's function and well-being. This treatment burden affects adherence to treatment and disease outcomes. Digital interventions can potentially exacerbate the burden but also alleviate it.

Objective: The objective of this review is to identify, summarize, and synthesize the evidence of how digital interventions impact the treatment burden of people with chronic conditions.

Methods: The search, selection, and data synthesis processes were designed according to the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) 2015. A systematic search was conducted on October 16, 2023, from databases PubMed, Scopus, Web of Science, ACM, PubMed Central, and CINAHL.

Results: Preliminary searches have been conducted, and screening has been started. The review is expected to be completed in October 2024.

Conclusions: As the number of patients with chronic conditions is increasing, it is essential to design new digital interventions for managing chronic conditions in a way that supports patients with their treatment burden. To the best of our knowledge, the proposed systematic review will be the first review that investigates the impact of digital interventions on the treatment burden of patients. The results of this review will contribute to the field of health informatics regarding knowledge of the treatment burden associated with digital interventions and practical implications for developing better digital health care for patients with chronic conditions.

Trial Registration: PROSPERO CRD42023477605; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=477605

International Registered Report Identifier (IRRID): DERR1-10.2196/54833

(JMIR Res Protoc 2024;13:e54833) doi:10.2196/54833

KEYWORDS

chronic illness; treatment burden; eHealth; mHealth; digital health; mobile health

Introduction

Background

Digital technologies are now commonly used in daily life, bringing many new possibilities for connecting people and providing services. The use of mobile- and web-based digital health care interventions has increased during the COVID-19 pandemic and has been found to have high efficacy, accessibility, and cost-effectiveness in the self-management of chronic diseases [1-3].

As the global population is growing, the prevalence of chronic diseases has increased significantly [4]. The World Health Organization [4] has estimated that if this trend continues, by 2050 chronic diseases will be the cause of 86% of the 90 million deaths each year. This means a 90% increase in absolute numbers since 2019. Therefore, there is a continuous need for new interventions for the management of chronic diseases.

Chronic diseases often require regular long-term management, which requires patients to not only cope with their symptoms but also navigate services, interact with health professionals, and adhere to treatments, creating a significant burden for many patients [5]. Treatment burden is defined as both the workload required for self-management of disease and the impact treatment regimens have on the patient's function and well-being [5]. Treatment burden can affect many domains: burden of taking medications, traveling to appointments, financial burden, impact on social life and emotions, and burden of accessing health care services [6,7]. A high treatment burden has been associated with poor adherence and worse disease outcomes [6].

The variety of available digital interventions can be tailored to meet the diverse needs of patients. For example, telemedicine and remote visits can reduce the need for traveling to medical appointments [8]. Mobile health apps, wearable technologies, and remote monitoring systems can track patients' health data and alert health care professionals (HCPs) if intervention is required [9,10]. Electronic health records offer a central repository for patients' history to minimize the paperwork and speed up the adherence process [11], while electronic prescription management improves patient safety as well as the efficiency and costs of prescribing medications [12]. Furthermore, patients' portals, web-based support groups, and forums provide emotional and social support for patients [13].

The World Health Organization Classification of Digital Interventions, Services and Applications in Health [14] highlights a variety of digital health technologies for different types of services. In this study, we will focus on the point of service category of digital interventions. The point of service category includes those digital interventions that facilitate and deliver health care services to the patients, making it easier to see the connection between the treatment burden of the patient and the digital intervention. This category includes communication systems, community-based information systems, decision support systems, diagnostics information systems, electronic medical record systems, laboratory information systems, personal health records, pharmacy information systems, and a variety of telehealth systems. These digital interventions can include many different components, such as monitoring tools, decision aids, behavior change support, communication with HCPs, and web-based peer support groups.

Digital interventions may affect the treatment burden in multiple ways. With limited resources, digital interventions may be used to reduce the burden on the health care system, and staff end up offloading the burden to patients [15-18]. Patients may also find digital systems inaccessible or difficult to use [19] and struggle with digital stress [20]. However, digital interventions can expedite and simplify health care processes in a way that patients may receive treatment more efficiently, reducing the treatment burden for patients. For example, they can reduce the need for medical appointments and travel to hospitals [8] and make self-management easier and more motivating for patients [21,22].

Many systematic reviews have been conducted to investigate the treatment burden on patients with chronic conditions [6,7,23-26]. These reviews have provided insights into the definition, prevention, and patient's experience of treatment burden. In addition, recent systematic and umbrella reviews about digital interventions have found that most digital interventions in health care are mobile- or computer-based [27-29]. The findings of the recent research are mostly focused on effectiveness, and the largest targeted condition group is mental illnesses [27,29]. However, we have observed a gap in the literature regarding systematic reviews combining these 3 concepts: treatment burden, digital interventions, and chronic conditions.

Objective

The aim of this review is to identify gaps in the literature and summarize and synthesize currently available evidence of how digital interventions impact the treatment burden of people with chronic conditions. The impact can be a positive or negative effect on any domain of treatment burden. We aim to investigate if the results differ between chronic conditions with different levels of treatment burden or between interventions with different components.

Research Questions

We have two primary research questions: (1) How can digital interventions impact the treatment burden on people with chronic conditions? (2) What kind of support can digital interventions provide for people with chronic conditions with their treatment burden?

Methods

Ethical Considerations

We followed the University of Oulu ethics process as defined in the guidelines from the Ethics Committee of Human Sciences [30]. According to the guidelines, an ethics board review is not needed for this protocol.

Study Design

This protocol is reported according to the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) 2015 [31]. We registered the protocol on the International Prospective Register of Systematic Reviews (PROSPERO CRD42023477605).

The systematic review will use a convergent design for systematic mixed studies reviews [32]. The mixed method approach was selected because qualitative results can help us to understand the phenomenon of treatment burden in the context of digital health care, and quantitative results can be used to generalize the qualitative findings by measuring their magnitude, trends, causes, and effects [33]. The convergent design was

most suitable for this review since the research questions can be answered by both qualitative and quantitative findings.

Information Sources and Search Strategy

A systematic search for papers published between January 1, 2013, and October 16, 2023, was conducted from bibliographical databases PubMed, Scopus, Web of Science, ACM, PubMed Central, and CINAHL. The following search string was used: ("Chronic illness" OR "chronic disease" OR "chronic diseases" OR "chronic illnesses" OR "chronically ill" OR "diabetes" OR "asthma" OR "cancer" OR "cystic fibrosis" OR "epilepsy" OR "rheumatoid arthritis" OR "HIV" OR "patient") AND ("Digital" OR "Remote" OR "Mobile" OR "smartphone" OR "smartwatch" OR "smart ring" OR "smart device" OR "smart devices" OR "app" OR "mHealth" OR "eHealth" OR "web-based") AND ("Treatment burden" OR "Burden of treatment" OR "Treatment impact" OR "Treatment workload" OR "Treatment inconvenience" OR "Treatment acceptability" OR "Illness burden" OR "Burden of illness" OR "Medication burden"). To identify relevant papers, a search strategy was conducted in an iterative way. The creation of the search strings for treatment burden was informed by previous systematic reviews on the topic [23,24]. Scoping searches were conducted in several potential databases focusing on health and biomedicine, information technology, nursing, psychology, or multiple disciplines (PubMed, Scopus, Web of Science, ACM, PubMed Central, CINAHL, IEEE, and APA PsycINFO). Scoping searches were conducted on October 15, 2023, in CINAHL and on October 12, 2023, in other databases. Searches conducted on IEEE and APA PsycINFO databases revealed no relevant results, so databases were excluded from the search strategy. Including only certain chronic conditions, for example, epilepsy or neurological conditions, was considered, but there was a limited number of studies found during the initial scoping searches. For example, in the scoping search for epilepsy conducted on October 12, 2023, only 3 relevant papers were identified. Therefore, we decided to keep the scope wide and include all chronic conditions in the search string.

The MeSH term "chronic disease" and search terms "coronary heart disease," "heart disease," "MS," and "multiple sclerosis" were tested during a scoping search in PubMed, but they brought no new results and therefore were removed from the search terms. A supplementary search will be conducted from the citations contained in systematic literature reviews and scoping reviews that were found during the literature searches.

Inclusion Criteria

We have included original publications written in English and accepted in peer-reviewed journals or conference proceedings. Qualitative, quantitative, and mixed method studies are included. The studies can be clinical trials, nonrandomized controlled trials, cross-sectional studies, longitudinal studies, observational studies, case studies, and other types of qualitative studies. Study design will be classified based on the tool from Grimes and Schulz [34]. Conference proceedings are included, but reviews, protocols, and book chapters are excluded.

We limited our search to publications after 2013 to include the last 10 years of research. Although digital health technology has developed quickly in recent years, the use of digital interventions in health care for chronic conditions goes farther than 10 years [35]. To the best of our knowledge, there are no previous systematic reviews relating to both digital health and treatment burden. However, studies before 2013 referred mostly to apps created only for research purposes, which were not available to the public at that time. Therefore, we decided to include papers published after 2013 to cover all relevant publications.

The study population in the included publications must consist of patients who have a chronic condition, their caregivers, or HCPs treating patients with chronic conditions. All ages and ethnicities are included. Only studies with outcomes regarding treatment burden for the patients are included. Studies that do not specifically mention the phrase "treatment burden" or "burden of treatment" but still discuss the impact of health care on the workload and burden for patients are also included. Only studies regarding a digital intervention that facilitates and delivers health care services to patients with chronic conditions are included.

Selection of Studies

After the searches, all titles and abstracts from search results were uploaded to a web-based Covidence screening tool (Veritas Health Innovation), where duplicate records will be removed. All titles and abstracts were screened and selected for inclusion independently by 2 authors (MP and PK or OK). Full-text papers from the selected papers will also be screened and selected for inclusion independently by 2 authors (MP and PK or OK). Disagreements will be resolved by discussion.

Data Extraction

Data on population characteristics, study design, aims, intervention characteristics, measures, and main results will be extracted using a predefined data extraction form in Covidence. Study design will be classified based on the tool from Grimes and Schulz [34]. Before proceeding with data extraction, MP will pilot the data extraction form with 5 papers to identify possible adjustment needs. Data extraction will be performed independently by 2 reviewers (MP and PK or OK). Disagreements will be resolved by discussion.

Risk of Bias

The quality of the included studies will be assessed using Joanna Briggs Institute Critical Appraisal tools. Two reviewers (MP and PK or OK) will assess the quality of each included study independently. Based on the design of the eligible studies, we will use Joanna Briggs Institute checklists designed for randomized controlled trials, quasi-experimental studies, analytical cross-sectional studies, case-control studies, case series, and qualitative studies.

Data Synthesis

A convergent integrated approach to synthesis and integration will be used [32]. This involves converting quantitative data into qualitative data followed by integration of the qualitative and quantitative evidence [36].

Results

Currently, we have performed searches in the 6 selected databases, and 241 studies have been identified. Screening based on title and abstract excluded 192 studies. Overall, 69 studies have been included in the second round of study selection, which is ongoing. The review is expected to be completed in 2024.

Discussion

This systematic review is performed to investigate the impact of digital health care on the treatment burden of patients with chronic conditions. This review is important because the world is currently facing increasing amounts of chronic diseases, and digital solutions are needed to improve the management of chronic diseases, which pose a significant burden on both health care systems and the patients themselves. However, it is essential to design the digital interventions in a way that helps patients to deal with their existing treatment burden and avoids further increasing the treatment burden. To the best of our knowledge, this will be the first review that covers the impact of digital health care on the treatment burden of patients with chronic conditions. The outcomes are expected to cover the positive and negative impacts of digital interventions on treatment burden and the different types of support digital interventions can provide to people with chronic conditions struggling with treatment burden. We aim to categorize different types of interventions and their components and find potential differences between interventions with different components and chronic conditions with different levels of treatment burden.

For the limitations of this review, the findings will depend on the number of eligible studies we will be able to identify and the quality of these studies. In addition, the studies identified for this review may be heterogeneous in terms of design, interventions, participant groups, and outcomes. Furthermore, our search will be restricted to peer-reviewed studies published in English.

Authors' Contributions

MP developed the initial research questions; design of the review, search, and selection strategies; and drafted the paper. PK and OK contributed to the refining of the research questions; design of the review, search, and selection strategies; and writing and editing of the paper. WB and MI contributed to the editing and approved the final paper.

Conflicts of Interest

None declared.

References

1. Blandford A, Wesson J, Amalberti R, AlHazme R, Allwihan R. Opportunities and challenges for telehealth within, and beyond, a pandemic. Lancet Glob Health 2020;8(11):e1364-e1365 [FREE Full text] [doi: 10.1016/S2214-109X(20)30362-4] [Medline: 32791119]
2. Portnoy J, Waller M, Elliott T. Telemedicine in the era of COVID-19. J Allergy Clin Immunol Pract 2020;8(5):1489-1491 [FREE Full text] [doi: 10.1016/j.jaip.2020.03.008] [Medline: 32220575]
3. Sim I. Mobile devices and health. N Engl J Med 2019;381(10):956-968. [doi: 10.1056/NEJMra1806949] [Medline: 31483966]
4. World health statistics 2023: monitoring health for the SDGs, sustainable development goals. World Health Organization. 2023. URL: https://www.who.int/publications/i/item/9789240074323 [accessed 2024-04-03]
5. Eton DT, de Oliveira DR, Egginton JS, Ridgeway JL, Odell L, May CR, et al. Building a measurement framework of burden of treatment in complex patients with chronic conditions: a qualitative study. Patient Relat Outcome Meas 2012;3:39-49 [FREE Full text] [doi: 10.2147/PROM.S34681] [Medline: 23185121]
6. Demain S, Gonçalves AC, Areia C, Oliveira R, Marcos AJ, Marques A, et al. Living with, managing and minimising treatment burden in long term conditions: a systematic review of qualitative research. PLoS One 2015;10(5):e0125457 [FREE Full text] [doi: 10.1371/journal.pone.0125457] [Medline: 26024379]
7. Sav A, King MA, Whitty JA, Kendall E, McMillan SS, Kelly F, et al. Burden of treatment for chronic illness: a concept analysis and review of the literature. Health Expect 2015;18(3):312-324 [FREE Full text] [doi: 10.1111/hex.12046] [Medline: 23363080]
8. Kelley LT, Phung M, Stamenova V, Fujioka J, Agarwal P, Onabajo N, et al. Exploring how virtual primary care visits affect patient burden of treatment. Int J Med Inform 2020;141:104228. [doi: 10.1016/j.ijmedinf.2020.104228] [Medline: 32683311]
9. Hamine S, Gerth-Guyette E, Faulx D, Green BB, Ginsburg AS. Impact of mHealth chronic disease management on treatment adherence and patient outcomes: a systematic review. J Med Internet Res 2015;17(2):e52 [FREE Full text] [doi: 10.2196/jmir.3951] [Medline: 25803266]
10. Mattison G, Canfell O, Forrester D, Dobbins C, Smith D, Töyräs J, et al. The influence of wearables on health care outcomes in chronic disease: systematic review. J Med Internet Res 2022;24(7):e36690 [FREE Full text] [doi: 10.2196/36690] [Medline: 35776492]
11. Tinetti ME, Naik AD, Dindo L, Costello DM, Esterson J, Geda M, et al. Association of patient priorities-aligned decision-making with patient outcomes and ambulatory health care burden among older adults with multiple chronic

conditions: a nonrandomized clinical trial. JAMA Intern Med 2019;179(12):1688-1697 [FREE Full text] [doi: 10.1001/jamainternmed.2019.4235] [Medline: 31589281]
12. Klepser D, Lanham A, Cochran G. Electronic prescriptions: opportunities and challenges for the patient and pharmacist. Adv Health Care Technol 2016;2:1-11 [FREE Full text] [doi: 10.2147/ahct.s64477]
13. Schwartz CE, Zhang J, Michael W, Eton DT, Rapkin BD. Reserve-building activities attenuate treatment burden in chronic illness: the mediating role of appraisal and social support. Health Psychol Open 2018;5(1):2055102918773440 [FREE Full text] [doi: 10.1177/2055102918773440] [Medline: 29785278]
14. Classification of digital interventions, services and applications in health: a shared language to describe the uses of digital technology for health, 2nd Edition. World Health Organization. 2023. URL: https://www.who.int/publications-detail-redirect/9789240081949#:~:text=The%20WHO%20Classification%20of%20digital,needs%20and%20advance%20health%20goals [accessed 2024-04-03]
15. May CR, Eton DT, Boehmer K, Gallacher K, Hunt K, MacDonald S, et al. Rethinking the patient: using Burden of Treatment Theory to understand the changing dynamics of illness. BMC Health Serv Res 2014;14:281 [FREE Full text] [doi: 10.1186/1472-6963-14-281] [Medline: 24969758]
16. Eton DT, Ridgeway JL, Egginton JS, Tiedje K, Linzer M, Boehm DH, et al. Finalizing a measurement framework for the burden of treatment in complex patients with chronic conditions. Patient Relat Outcome Meas 2015;6:117-126 [FREE Full text] [doi: 10.2147/PROM.S78955] [Medline: 25848328]
17. Mair FS, Montori VM, May CR. Digital transformation could increase the burden of treatment on patients. BMJ 2021;375:n2909 [FREE Full text] [doi: 10.1136/bmj.n2909] [Medline: 34824093]
18. Hardman R, Begg S, Spelten E. Healthcare professionals' perspective on treatment burden and patient capacity in low-income rural populations: challenges and opportunities. BMC Fam Pract 2021;22(1):50 [FREE Full text] [doi: 10.1186/s12875-021-01387-y] [Medline: 33750306]
19. Henni SH, Maurud S, Fuglerud KS, Moen A. The experiences, needs and barriers of people with impairments related to usability and accessibility of digital health solutions, levels of involvement in the design process and strategies for participatory and universal design: a scoping review. BMC Public Health 2022;22(1):35 [FREE Full text] [doi: 10.1186/s12889-021-12393-1] [Medline: 34991540]
20. Steele RG, Hall JA, Christofferson JL. Conceptualizing digital stress in adolescents and young adults: toward the development of an empirically based model. Clin Child Fam Psychol Rev 2020;23(1):15-26. [doi: 10.1007/s10567-019-00300-5] [Medline: 31392451]
21. Allam A, Kostova Z, Nakamoto K, Schulz PJ. The effect of social support features and gamification on a web-based intervention for rheumatoid arthritis patients: randomized controlled trial. J Med Internet Res 2015;17(1):e14 [FREE Full text] [doi: 10.2196/jmir.3510] [Medline: 25574939]
22. Comello MLG, Qian X, Deal AM, Ribisl KM, Linnan LA, Tate DF. Impact of game-inspired infographics on user engagement and information processing in an eHealth program. J Med Internet Res 2016;18(9):e237 [FREE Full text] [doi: 10.2196/jmir.5976] [Medline: 27658469]
23. Alsadah A, van Merode T, Alshammari R, Kleijnen J. A systematic literature review looking for the definition of treatment burden. Heliyon 2020;6(4):e03641 [FREE Full text] [doi: 10.1016/j.heliyon.2020.e03641] [Medline: 32300666]
24. Sheehan OC, Leff B, Ritchie CS, Garrigues SK, Li L, Saliba D, et al. A systematic literature review of the assessment of treatment burden experienced by patients and their caregivers. BMC Geriatr 2019;19(1):262 [FREE Full text] [doi: 10.1186/s12877-019-1222-z] [Medline: 31604424]
25. Gallacher K, Smyth R, May C, Mair F. A systematic review of the use of Burden of Treatment Theory: systematic review, meta-analysis, or scoping review. Ann Fam Med 2023;21(Suppl 1):3641 [FREE Full text] [doi: 10.1370/afm.21.s1.3641]
26. Matthews KS, Rennoldson SC, Fraser SD. Influence of health-system change on treatment burden: a systematic review. Br J Gen Pract 2022;73(726):e59-e66 [FREE Full text] [doi: 10.3399/bjgp.2022.0066]
27. Taylor ML, Thomas EE, Vitangcol K, Marx W, Campbell KL, Caffery LJ, et al. Digital health experiences reported in chronic disease management: an umbrella review of qualitative studies. J Telemed Telecare 2022;28(10):705-717 [FREE Full text] [doi: 10.1177/1357633X221119620] [Medline: 36346938]
28. Xiong S, Lu H, Peoples N, Duman EK, Najarro A, Ni Z, et al. Digital health interventions for non-communicable disease management in primary health care in low-and middle-income countries. NPJ Digit Med 2023;6(1):12 [FREE Full text] [doi: 10.1038/s41746-023-00764-4] [Medline: 36725977]
29. Ibrahim MS, Yusoff HM, Bakar YIA, Aung MMT, Abas MI, Ramli RA. Digital health for quality healthcare: a systematic mapping of review studies. Digit Health 2022;8:20552076221085810 [FREE Full text] [doi: 10.1177/20552076221085810] [Medline: 35340904]
30. Ethics Committee of Human Sciences. University of Oulu. URL: https://www.oulu.fi/en/university/faculties-and-units/eudaimonia-institute/ethics-committee-human-sciences [accessed 2024-01-09]
31. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015;350:g7647 [FREE Full text] [doi: 10.1136/bmj.g7647] [Medline: 25555855]

32. Stern C, Lizarondo L, Carrier J, Godfrey C, Rieger K, Salmond S, et al. Methodological guidance for the conduct of mixed methods systematic reviews. JBI Evid Implement 2021;19(2):120-129 [FREE Full text] [doi: 10.1097/xeb.0000000000000282]
33. Pluye P, Hong QN. Combining the power of stories and the power of numbers: mixed methods research and mixed studies reviews. Annu Rev Public Health 2014;35:29-45 [FREE Full text] [doi: 10.1146/annurev-publhealth-032013-182440] [Medline: 24188053]
34. Grimes DA, Schulz KF. An overview of clinical research: the lay of the land. Lancet 2002;359(9300):57-61. [doi: 10.1016/s0140-6736(02)07283-5]
35. Eland-de Kok P, van Os-Medendorp H, Vergouwe-Meijer A, Bruijnzeel-Koomen C, Ros W. A systematic review of the effects of e-health on chronically ill patients. J Clin Nurs 2011;20(21-22):2997-3010. [doi: 10.1111/j.1365-2702.2011.03743.x] [Medline: 21707807]
36. Voils CI, Sandelowski M, Barroso J, Hasselblad V. Making sense of qualitative and quantitative findings in mixed research synthesis studies. Field Methods 2008;20(1):3-25 [FREE Full text] [doi: 10.1177/1525822x07307463]

Abbreviations

HCP: health care professional
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols

Edited by A Mavragani; submitted 24.11.23; peer-reviewed by KL Mauco, C Baxter; comments to author 02.02.24; revised version received 20.02.24; accepted 13.03.24; published 23.04.24.

Please cite as:
Polus M, Keikhosrokiani P, Korhonen O, Behutiye W, Isomursu M
Impact of Digital Interventions on the Treatment Burden of Patients With Chronic Conditions: Protocol for a Systematic Review
JMIR Res Protoc 2024;13:e54833
URL: https://www.researchprotocols.org/2024/1/e54833
doi:10.2196/54833
PMID:38652531

Protocol

Connecting Actors With the Introduction of Mobile Technology in Health Care Practice Placements (4D Project): Protocol for a Mixed Methods Study

Carlos Martínez-Gaitero[1], PhD; Sebastian Maximilian Dennerlein[2], PhD; Beata Dobrowolska[3], PhD; Angela Fessl[4,5], PhD; Daniel Moreno-Martínez[6], PhD; Stephanie Herbstreit[7], Prof Dr Med; Gilbert Peffer[8], MEng; Esther Cabrera[1], Prof Dr; 4D Project Consortium[9]

[1]Tecnocampus, Pompeu Fabra University, Mataró, Spain

[2]Faculty of Behavioural, Management and Social Sciences, University of Twente, Enschede, Netherlands

[3]Faculty of Health Sciences, Medical University of Lublin, Lublin, Poland

[4]Institute of Interactive Systems and Data Science, Graz University of Technology, Graz, Austria

[5]Know-Center GmbH, Graz, Austria

[6]Germans Trias i Pujol Research Institute, Hospital Germans Trias i Pujol Institut Català de la Salut, Badalona, Spain

[7]Medical Faculty, University of Duisburg-Essen, Essen, Germany

[8]Kubify, Utrecht, Netherlands

[9]see Acknowledgments

Corresponding Author:
Carlos Martínez-Gaitero, PhD
Tecnocampus
Pompeu Fabra University
Avinguda d'Ernest Lluch, 32
Mataró, 08302
Spain
Phone: 34 931 696 501 ext 10341
Email: cmartinezga@tecnocampus.cat

Abstract

Background: The learning process in clinical placements for health care students is a multifaceted endeavor that engages numerous actors and stakeholders, including students, clinical tutors, link teachers, and academic assessors. Successfully navigating this complex process requires the implementation of tasks and mentorships that are synchronized with educational and clinical processes, seamlessly embedded within their respective contexts. Given the escalating number of students and the rising demand for health care services from the general population, it becomes imperative to develop additional tools that support the learning process. These tools aim to simplify day-to-day clinical practice, allowing a concentrated focus on value-based activities. This paper introduces a project funded by the European Commission that involves 5 European countries. The project's objective is to comprehensively outline the entire process of development and ultimately implement mobile technology in practice placements. The project tackles the existing gap by constructing tailored mobile apps designed for students, teachers, tutors, and supervisors within each participating organization. This approach leverages practice-based learning, mobile technology, and technology adoption to enhance the overall educational experience.

Objective: This study aims to introduce mobile technology in clinical practice placements with the goal of facilitating and enhancing practice-based learning. The objective is to improve the overall effectiveness of the process for all stakeholders involved.

Methods: The "4D in the Digitalization of Learning in Practice Placement" (4D Project) will use a mixed methods research design, encompassing 3 distinct study phases: phase 1 (preliminary research), which incorporates focus groups and a scoping review, to define the problem, identify necessities, and analyze contextual factors; phase 2 (collaborative app development), which involves researchers and prospective users working together to cocreate and co-design tailored apps; and phase 3, which involves feasibility testing of these mobile apps within practice settings.

Results: The study's potential impact will primarily focus on improving communication and interaction processes, fostering connections among stakeholders in practice placements, and enhancing the assessment of training needs. The literature review

and focus groups will play a crucial role in identifying barriers, facilitators, and factors supporting the integration of mobile technology in clinical education. The cocreation process of mobile learning apps will reveal the core values and needs of various stakeholders, including students, teachers, and health care professionals. This process also involves adapting and using mobile apps to meet the specific requirements of practice placements. A pilot study aimed at validating the app will test and assess mobile technology in practice placements. The study will determine results related to usability and design, learning outcomes, student engagement, communication among stakeholders, user behavior, potential issues, and compliance with regulations.

Conclusions: Health care education, encompassing disciplines such as medicine, nursing, midwifery, and others, confronts evolving challenges in clinical training. Essential to addressing these challenges is bridging the gap between health care institutions and academic settings. The introduction of a new digital tool holds promise for empowering health students and mentors in effectively navigating the intricacies of the learning process.

International Registered Report Identifier (IRRID): DERR1-10.2196/53284

(JMIR Res Protoc 2024;13:e53284) doi:10.2196/53284

KEYWORDS

practice-based learning; practice placement; technology enhanced learning; mobile learning; co-design; cocreation; higher education; health professionals; health students.

Introduction

Background

Practice-based learning encompasses the educational process in which students acquire knowledge within a service delivery environment tailored to their educational level and competencies. Health profession students, such as nurses, physicians, and physiotherapists, cultivate skills through hands-on experience in various settings. Learning occurs through observation and subsequent participation in clinical tasks.

Conceptually, learners in practice settings acquire "knowledge-in-action" [1] through interaction with experienced professionals, patients/clients, and their peers. For health profession students, practice-based learning provides an opportunity for direct engagement with "real" patients in authentic settings where actual health care is delivered. Health profession students cannot grasp the full complexity of the health care environment until they acquire the specific knowledge, skills, and attitudes that demonstrate competency in their area of practice [2].

The learning process in clinical placements typically involves a diverse array of individuals, including tutors, supervisors, mentors, teachers, and students. Throughout this intricate process, tasks and mentorships must be implemented in a manner that aligns with both educational and clinical processes and is well-embedded in the respective contexts [3].

The learning process, connecting the academic environment with health care centers, encompasses a broad variety of scenarios and contexts. Numerous factors are involved in this complex and challenging practical training for health profession students, affecting both the respective actors and institutions. These factors can result in an inefficient process, causing dissatisfaction and frustration. Much of the effort is directed toward coordinating the involved parties rather than focusing on the learning process itself and its quality.

The interplay between learning and education at the university, along with practical training in placements, constitutes core elements of health care degree programs at universities, such as nursing or medicine [4]. The purpose of education in practice placements is to equip future professionals with the ability to manage their learning, make decisions that enable effective action in their future professional practice, and enhance the quality of care provision [5]. To attain these objectives, practice-based learning becomes indispensable as it necessitates students to scrutinize and assess their patient care, evaluate and integrate scientific evidence, and consistently enhance patient care through ongoing self-evaluation. Students are expected to cultivate skills and habits that enable the practical application of clinical and transversal competencies acquired at the university.

Practice-based learning in health care settings is defined and characterized by several key aspects [6]. These include the contexts in which practices occur [7], their purpose or objective [8], the methods used to assess students [9], the overall commitment within health care degree programs, the practice education model [10-13], and the various actors involved [3,14].

Elements of Practice Placement in Health Care Education

According to Jokelainen et al [15], the 2 fundamental aspects of mentorship in practice placement involve establishing a supportive learning environment and addressing aspects related to the mentorship process itself. Delving into the establishment of learning support environments, 2 elements are identified as facilitators of learning and indicators of clinical practice environments. These elements are (1) the preparation of the practice setting for learning, which involves planning the training and practice placement, ensuring the implementation of training in the practice setting, and providing opportunities for individualized support during placement; and (2) the organization of interpersonal learning practices, encompassing becoming familiar with the workplace as a work environment, promoting equal participation in practices through teamwork, and collaborating with other stakeholders involved in training.

In delving into the mentorship process within a practice placement, 2 elements that serve as facilitators of learning and indicators of clinical practice placement are recognized. These are (1) facilitating student learning by establishing a supportive

learning environment and fostering individualized learning processes; and (2) enhancing the professionalism of students by encouraging the development of professional attributes and identity, ultimately improving the attainment of professional competence.

Furthermore, Thomson et al [16], in a qualitative phenomenological study, identified 5 significant aspects of the experience in tutoring and follow-up in nursing student practice environments. These mentoring and follow-up aspects were (1) being more independent, (2) receiving support, (3) a sense of belonging to the profession, (4) feedback on the learning process, and (5) anticipatory anxiety.

In this intricate scenario involving various actors, institutions, placement contexts, and mentoring approaches, among others, numerous processes are undertaken, requiring substantial resources and time investments. Given that the primary goal of practice-based learning is student learning and the enhancement of their clinical practice, it becomes crucial to develop innovative approaches that can enable more efficient resource management. In this context, the integration of mobile technology in practice settings has the potential to support and enhance students' learning process while concurrently reducing the resources required for administrative processes in practice placements.

Introducing Mobile Technology in the Learning Process

Contemporary health systems are shifting toward more integrated and person-centered care models [17], with the use of technology becoming increasingly common in various processes related to care provision. Within this context, health care higher education institutions are incorporating technology into their degree programs with the goal of equipping students with essential skills in digital health [18] and preparing them for their future workplaces. The integration of mobile technologies, coupled with advancements in digital literacy, is expected to empower professionals to confront the intricate challenges presented by contemporary health systems [19]. Additionally, these technologies should facilitate student learning, particularly during clinical practice periods. The education of health students is grounded in the preparation of future professionals capable of navigating this evolving context. Therefore, a key objective of training and learning is the transition from acquiring established knowledge to educating for an unknown future. This shift in learning necessitates the adoption of new approaches and the utilization of innovative teaching and learning technologies [20]. Hence, the utilization of information and communication technologies and Web 2.0 environments in the context of learning during practice placements plays a pivotal role in preparing for this uncertain future in education. Technology-enhanced learning encompasses the application of technology to support any learning-related activity, concentrating on various pedagogical domains that leverage technology [21-23].

The evolution of the Web 2.0 concept has seen a shift in learning from eLearning to mobile learning (mLearning). mLearning is characterized as learning that occurs in diverse contexts, involving social interactions and content consumption, using personal electronic devices as a means of distance education. In this approach, mLearners (students) use educational technology through mobile devices [24] at their convenience [25]. The application and utilization of mLearning in education are contingent on the specific learning needs, context, and objectives to be accomplished [26,27].

In practice placements, where the learning needs involve reinforcing and applying competencies acquired at the university, mLearning serves as a valuable tool for consulting reference materials. Its accessibility virtually anywhere and anytime allows students to enhance their understanding. Furthermore, students can share experiences and knowledge gained in the practice setting with mentors and peers, enabling instant feedback and suggestions. This highly interactive process has demonstrated a 22% reduction in abandonment rates in technical environments, accompanied by an increase in evaluation scores from the 50th percentile to the 70th percentile [28]. In the context of mobility, mLearning facilitates student movement, offering excellent content portability by replacing traditional books and notes with small, personalized devices filled with learning materials. Its convenience stems from its accessibility from almost anywhere.

To effectively tackle current issues in teaching and learning, integrate technologies into their respective practices, and enhance user acceptance, mLearning solutions must be collaboratively designed with all stakeholders. This includes researchers, teachers, students, and administrative staff. Achieving a sustainable digitization and transformation of higher education demands a human-centered approach [29,30] that fosters adoption and ensures a lasting impact on practices. Applying this approach to the digitization and transformation of practice-based learning in health care can aid in comprehending the determinants and factors contributing to the successful introduction of mLearning in practice placements. To bridge the gap between the various actors in these learning contexts (university and clinical practice placement) and enhance the overall experience in practice-based learning in health care settings, it becomes essential to implement mLearning approaches in practice placements and gain insights into their tangible benefits and optimal usage strategies.

This paper outlines the protocol for a study focused on the implementation of mobile technology in practice placements. The study protocol aligns with the research vision of an innovation project in higher education known as the "4D in the Digitalization of Learning in Practice Placement" (4D Project; Multimedia Appendices 1 and 2), involving participants from 5 European countries, namely, Spain, Germany, The Netherlands, Austria, and Poland [31] (Multimedia Appendix 3).

The project aims to fill this gap by creating personalized mobile apps for students, teachers, tutors, and supervisors in each participating organization. This will be achieved through the integration of practice-based reflective learning, mobile technology, and the adoption of technology. The aims are as follows:

- To determine the key factors (barriers, facilitators, and solutions) to introduce mobile technology in practice placements.
- To cocreate design learning practices, materials, and adapt or adopt mLearning technology in practice placements using various co-design methods. This approach aims to respect users' core values and address their needs.
- To test and assess the introduction of this mobile technology in practice placements in 3 different health institutions in European countries.

Methods

Study Design and Methodological Framework

The research will follow a mixed methods research design, incorporating 3 distinct study phases, each utilizing different methodologies.

In phase 1, the focus is on comprehending the facilitators and barriers associated with the integration of mobile technology into clinical education during practice placements for medical and health care students. The goal is to identify potential strategies and approaches to overcome the identified barriers.

During phase 2, the emphasis is on collaborative creation and design with users, involving various design methods. The objective is to cocreate and co-design an mLearning technology specifically tailored for practice placements. This phase aims to incorporate user input and preferences into the development process.

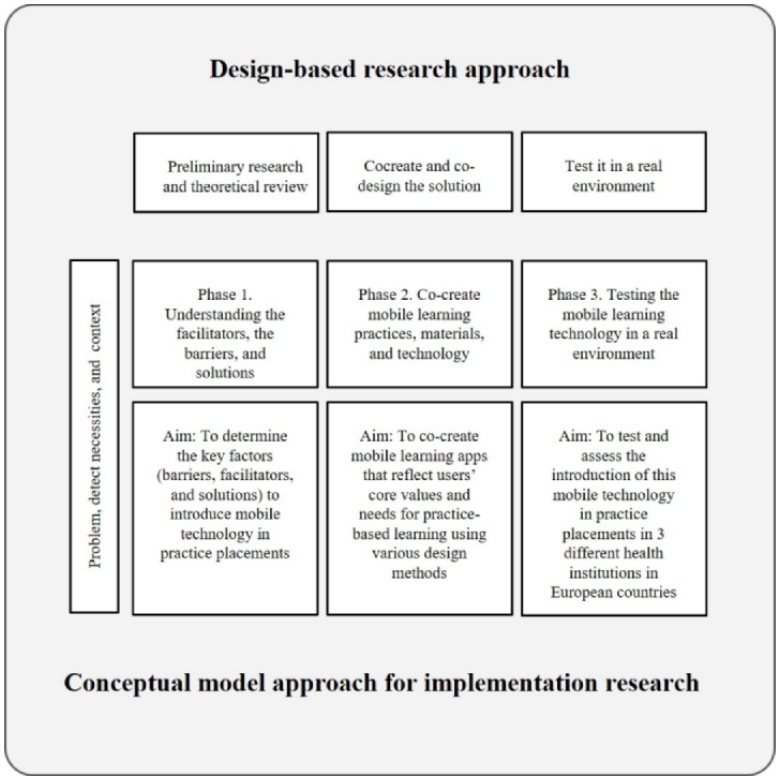
In phase 3, the research moves to the practical testing of the mLearning technology in a real-world environment. The focus is on evaluating the impact, usability, design effectiveness, interactive learning features, and overall user satisfaction. This phase involves assessing how well the developed technology performs in a real setting and gathering feedback to refine and improve its functionality.

Theoretical Framework

The study will be guided by a design-based research framework, which aligns with the principles of design-based research [32-34]. This framework acknowledges that initial research and theoretical review are essential for understanding the problem, identifying needs, and analyzing the context (as seen in phase 1). Subsequently, during the next phase, researchers actively engage in the cocreation of the solution using various design methods (as in phase 2). The final phase involves testing the solution in a real-world environment to assess its impact on students' learning (as in phase 3). This iterative process allows for the continuous refinement and improvement of the developed solution. The study includes a reflecting phase that directs researchers to reflect on the outcomes and use this reflection to redesign the solution. The iterative research process involves designing, testing, evaluating, and reflecting, leading to a new research cycle aimed at refining and redesigning the solution [35] (Figure 1). This cyclical approach allows for continuous improvement and adaptation based on the insights gained from each iteration.

The following sections detail methodological considerations for each phase:

Figure 1. 4D Project conceptual model approach for implementation research [35].



Phase 1: Understanding the Facilitators, the Barriers, and Solutions

Overview

During this initial phase, the primary objective is to comprehend the facilitators and barriers associated with the integration of mobile technology into clinical education during practice placements for medical and health care students. The focus is on identifying potential solutions to overcome the identified barriers, laying the foundation for subsequent phases of the research.

Aim

The aim of this phase is to determine the key factors (barriers, facilitators, and solutions) to introduce mobile technology in practice placements. We describe 3 research questions to ensure and support the objective's consecution:

- What are the facilitators for introducing mobile technology into clinical education in the practice placement of medical and health care students?
- What are the barriers to introducing mobile technology into clinical education in the practice placement of medical and health care students?
- What are the solutions to overcome barriers for introducing mobile technology into clinical education in the practice placement of medical and health care students?

Research Design

To carry out the assessment, we will use 2 methods. First, a scoping literature review will analyze and synthesize existing research evidence. Simultaneously, focus groups will be conducted to capture the perspectives of undergraduate health profession students and stakeholders on the barriers and facilitators associated with the introduction of mobile devices in practice placements. The scoping literature review adheres to the recommendations of the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) statement [36]. The review process follows the framework established by Arksey and O'Malley [37], further refined by Levac and colleagues [38], encompassing the following stages: (1) identification of research questions; (2) identification of relevant studies; (3) selection of studies; (4) data charting; and (5) collation, summarization, and reporting of results.

Focus groups will be conducted to analyze the barriers, facilitators, and needs associated with introducing mobile technology in practical training for future health care students. This qualitative data collection method aims to offer an in-depth understanding of the phenomena. The findings will be reported following the guidelines outlined in the COREQ (Consolidated Criteria for Reporting Qualitative Research) checklist [39]. The content for the focus groups will be collaboratively developed through consensus among the research team and subject matter experts. Research questions have been formulated in alignment with the research's purpose by experts representing all partners involved in the 4D Project. This collaborative approach ensures a comprehensive and well-informed set of questions for the focus groups.

Sampling Procedures of Focus Groups

Participants for the focus groups will include undergraduate health care students and stakeholders from Tecnocampus, Pompeu Fabra University, the Medical University of Lublin (Poland), the University of Duisburg Essen (Germany), and the Germans Trias i Pujol University Hospital (Spain). The selection of participants will be carried out using purposive sampling with the aim of achieving maximum variation. Students eligible for participation should be enrolled in degree programs such as nursing, medicine, physiotherapy, or midwifery. Stakeholders will also be included based on the following criteria: involvement in the practical training of future nurses, midwives, physiotherapists, or doctors in roles such as clinical mentors; link teachers; practical training coordinators; hospital ward managers; or staff in the nursing, midwifery, and medical fields.

In each country, we have scheduled 2 focus groups with 8-10 participants each. Overall, we plan to conduct 3 focus groups with undergraduate students (nurses, physiotherapists, midwives, or medical students) and 3 focus groups with stakeholders, including clinical mentors, link teachers, practical training coordinators, hospital ward managers, staff, and other relevant stakeholders.

Analysis

In the scoping literature review, the study screening will follow a structured process [40] involving a sequential review by title, abstract, and full text. Two pairs (pair 1: BD and Agnieszka Chrzan-Rodak; pair 2: Cristina Casanovas Cuéllar and Ariadna Huertas Zurriaga) of experienced researchers will participate in this screening process. Initially, study titles will undergo independent screening by paired reviewers to identify studies that meet the inclusion criteria. Subsequently, researchers will assess the abstracts for inclusion, reviewing a distinct group of articles from the previous step. Following this, the researchers will rigorously evaluate the full text of the remaining articles, strictly adhering to the inclusion and exclusion criteria. In each round, a third researcher will scrutinize the work of each reviewing pair for potential errors. In case of any disagreement between the paired researchers, the document will be referred to the next researcher in the process to mitigate deselection bias. The third researcher will additionally assess the level of agreement between review pairs for both the title and abstract phases, aiming for a 95% agreement level.

The analysis of focus group data will adhere to Koole's FRAME (Framework for the Rational Analysis of Mobile Education) model [41]. The FRAME model delineates 3 principal aspects influencing mLearning and specifies factors (device usability, interaction learning, and social technology) that impact the successful integration of these aspects. For this study, the FRAME model will be adapted to encompass all the findings generated throughout the research.

The initial phase of analysis involves 1 of the researchers (BD) reading the transcripts multiple times to gain familiarity with the content and identify initial units of meaning. Subsequently, the texts will be coded using descriptive codes based on their content. These codes will then be organized into categories according to similarities in the codes. At this juncture, the

preliminary results will be discussed within the research group. Through reflective thinking and critical reasoning, adjustments will be made until a consensus is reached. The themes derived from the analysis will be organized under the learning aspects outlined in Koole's original model. Subsequently, the resulting report will be discussed with 2 participants to validate the meaning and coherence of the interpretations. To enhance the trustworthiness of the data, considerations will be given to credibility, dependability, conformability, and transferability [42]. The participants for this discussion will be selected through purposive sampling with maximum variation to bolster credibility. The information from the focus groups will undergo thorough examination by at least two members (SH and CMG) of the research team, and the results will be compared to evaluate dependability. To ensure conformability, all information provided by participants will be presented transparently. For the transferability of the study's data, a comprehensive and detailed description of the data and context will be provided.

Phase 2: Cocreate Mobile Learning Practices, Materials, and Technology

Overview

This phase is dedicated to collaboratively creating mLearning practices, materials, and technology for practice-based learning using various (co-)design methods.

Aim

The objective is to cocreate mLearning apps that align with users' core values and needs for practice-based learning. This involves collaborative design and production of mLearning practices and materials. Additionally, it includes the adaptation and appropriation of existing mobile apps to bridge the gap between the academic and practice contexts in health care practice placements.

Research Design

This section of the study utilizes collaborative design methods to comprehend the core values and needs of health care students and stakeholders. The goal is to develop embedded mLearning apps for practice placements. To facilitate the coordination of the innovation process within the design team and with domain representatives, the university innovation canvas (UIC) is used. The UIC elucidates the key factors fostering digital transformation and sustainable innovation. This will help to plan the selection and application of more specific co-design methods and tools such as the value proposition canvas (VPC), personas, storytelling, and use case definitions.

University Innovation Canvas and Value Proposition Canvas

The UIC draws inspiration from the business model canvas by Osterwalder and Pigneur [43] and the lean canvas by Maurya [44]. While the business model canvas primarily explores the creation of value for businesses, the UIC [30] is designed to reflect how "value" is generated within a university setting. This adaptation aligns the canvas with the specific context and objectives of fostering innovation within the university environment. In our scenario, the aim is to establish a shared understanding of enhancing collaboration between universities and their affiliated practice placement organizations, involving all relevant stakeholders (eg, students, teachers, and nurses). The UIC comprises 11 elements organized into 3 dimensions: the technology-enhanced learning concept (value creation), stakeholder relationships (value delivery), and foundation and scaling (value capture). This framework provides a structured approach to addressing key aspects of innovation and value creation in the university setting. The specific elements and dimensions within the canvas serve as tools for various stakeholders from diverse contexts to refine their collective focus. They facilitate reflection on crucial factors related to planned sustainable innovation, particularly in the context of enhancing practice placements. The canvas provides a structured framework that encourages stakeholders to align their perspectives and contribute to the development of innovative solutions.

To precisely define the value proposition within the UIC and align it with the technologies available for adoption within the consortium, we opted for the VPC [45]. This tool concentrates on how to generate value for all stakeholders involved (eg, students, teachers, nurses), or more precisely, how these stakeholders can benefit from the anticipated learning intervention. The VPC offers a structured approach to articulate and understand the unique value that the proposed innovations bring to each stakeholder. The VPC consists of 2 parts: First, the *stakeholder profile*, which aims at (1) describing the things or tasks they must do during their work; (2) related pains during the work including risks, potential bad outcomes, or obstacles related to their job; and (3) desired gains including the outcomes and benefits they would like to have. Second, the *value map*, which aims at creating value for the stakeholders by identifying the following: (1) pain relievers in the form of an innovation to reduce/eliminate the stakeholder's pains, (2) innovations that could be built around the value proposition, and (3) gain creators that describe how the innovation creates gains for the stakeholders.

Participants

The participants involved in this process are all members of the 4D Project partner teams, particularly those working at universities or in hospitals. This inclusive approach aims to gather perspectives and insights from both the education side at the university and the practice placements, ensuring a comprehensive representation of stakeholders involved in the project.

Procedure and Analysis

The application of the UIC and VPC will follow a 2-step approach, commencing with a "top-down" approach and subsequently transitioning to a "bottom-up" approach. In the initial step ("top-down" approach), the UIC will be distributed to all 4 distinct practice placements. The stakeholders engaged in the practice placements will receive an introduction to the UIC along with a clear explanation of the purpose behind this activity. The objective is to illuminate the addressed problems, identify value propositions and measures, and identify all involved stakeholders from various perspectives. After the completion of the UICs for each of the 4 practice placements,

the analysis will focus on uncovering commonalities across all of them. In the subsequent step (ie, the "bottom-up" approach), 3 of the identified commonalities will undergo a more detailed analysis. Hence, in a face-to-face setting, the pertinent stakeholders will be invited to vote for the most significant commonalities and collaboratively complete the VPC. The objective is to explore, from a value proposition perspective, how potential innovations could assist them in creating value for their stakeholders (eg, students, lecturers, and nurses). After the completion of the VPCs, the input will be analyzed and used to generate new UICs. This process aims to establish a shared understanding of possible solutions that align with all 4 practice placements and to emphasize how such innovations can be applied across all 4 settings. Based on the outcomes, subsequent co-design activities using personas, storytelling, and use case definition will be used to further refine the elicited innovation. This may involve creating mock-ups and developing application scenarios in practice. The process includes collaborative efforts to cocreate mLearning practices, materials, and suitable tools within the consortium and with all stakeholders. The overarching goal is to support the practice-based learning of health care professionals in education through innovative and tailored solutions.

Phase 3: Testing the Mobile Learning Technology in a Real Environment

Overview

This phase is dedicated to testing the mLearning technology in a real environment, evaluating its impact, usability, design, interactive learning, social technology, and overall satisfaction.

Aim

The objective is to test and assess the introduction of this mobile technology in practice placements within 3 distinct health institutions located in Spain, Germany, and Poland.

Research Design

In this phase of the study, the descriptive method, specifically a survey, will be used. The underlying premise is that the primary users, namely, the students and clinical mentors, can provide valuable information on aspects related to the use of mobile devices in a practice placement.

The proposed data collection method involves designing and crafting a questionnaire to ensure a comprehensive exploration of the subject. A self-administered questionnaire will be formulated, comprising distinct sections, including a participant information sheet; consent form; demographics information; and segments focusing on usability, design interaction, learning, social technology, and satisfaction. The questionnaire has been created by the authors of the study and draws upon the insights gained from the literature review [41,46,47] and the outcomes obtained in phase 2. Response options will consist of a 5-point Likert scale (ranging from 5=strongly agree to 1=strongly disagree), short responses, or free-text answer options. To assess the feasibility of the questionnaire, it will undergo a pilot phase with a group of students and stakeholders engaged in clinical education. Subsequently, the questionnaire will be revised, if necessary, based on the feedback received during the pilot testing. All participants will be provided with information about the study, including the study protocol, a digital consent form, and a questionnaire. Only those who agree to participate in the study will be directed to the questionnaire. Participants retain the right to withdraw from the study at any point. The online survey is estimated to take approximately 15 minutes to complete. The collected data will be securely stored on a password-protected computer, with access restricted to designated research staff or other authorized personnel who are obligated to maintain the confidentiality of the information. It is important to note that the data will be anonymized.

Participants

The study sample will consist of participants from Tecnocampus, Pompeu Fabra University (Spain), the Medical University of Lublin (Poland), the University of Duisburg Essen (Germany), and the Germans Trias i Pujol University Hospital (Spain). The questionnaire will be completed by students, teachers, tutors, and supervisors who use the developed apps. Moreover, all other individuals engaged in clinical education (practice placement) will be invited to participate in the study.

Analysis

The survey will be designed and implemented using REDCap (Research Electronic Data Capture), a secure, web-based application specifically designed to facilitate data capture for research studies [48].

The analysis in this phase will use inferential statistics to draw conclusions regarding the integration of mobile technology in practical placements. The statistical package used for this analysis will be SPSS, version 23.0 (SPSS Inc.). However, we do not exclude the possibility of using MS Excel (Microsoft Corporation) to facilitate and expedite the data collection and analysis process.

The methodology for describing and analyzing open free-text answers (unstructured data) will involve the use of Dcipher Studio (Dcipher Analytics), an artificial intelligence–powered tool designed to identify topics and sentiments in free-form text responses [49]. Using sentiment analysis and tonality detection will prove valuable in quantifying the emotional tones expressed in the responses.

The analysis of mobile app usage will involve reviewing computer-generated event logs to identify bugs and security threats, ensuring compliance with regulations, and gaining insights into user behavior.

Ethical Issues

At every stage of the planned research, strict adherence to the ethical principles outlined in the Declaration of Helsinki will be maintained. In research involving individuals, such as students and stakeholders, each partner will submit an application containing a comprehensive description of the research protocol to the relevant Ethics Committee. The focus groups and questionnaire studies will adhere to the principles of voluntary participation, anonymity, and respect for the decision to withdraw from the study at any stage. The gathered data will be used solely for purposes associated with the implementation of the 4D Project.

Ethics Approval

The study has received approval from the ethics committees of the respective institutes in each country: the Bioethical Commission at the Medical University of Lublin in Poland (protocol code KE-0254/152/06/2022 approved on June 30, 2022), the University of Duisburg Essen's Ethics Committee in Germany (protocol code 22-10783-BO approved on October 19, 2022), and the Fundació Tecnocampus Mataró-Maresme's Ethics Committee in Spain (protocol code CEI2/2022 approved on October 7, 2022). Informed consent will be obtained from all study participants.

Results

Phase 1: Understanding Facilitators and Barriers

The scoping literature review commenced in April 2022 and concluded in July 2022, while the focus groups were conducted from October to December 2022. It is anticipated that the outcomes of phase 1 will reveal (1) the identification of factors supporting the successful integration of mobile technology in clinical education for medical and health care students; (2) the acknowledgment of obstacles and challenges impeding the effective use of mobile technology in practice placements; (3) practical solutions proposed to address the identified barriers and challenges, and (4) insights derived from the focus groups, which will provide a deep understanding of the perspectives and experiences of health care students and stakeholders regarding the integration of mobile technology.

Phase 2: Cocreating Mobile Learning Practices

The design process commenced in July 2022 and concluded in November 2023. The outcomes of phase 2 revealed (1) the development of innovative and customized mLearning apps that resonate with the core values and requirements of health care students and stakeholders; (2) the adaptation and proficient utilization of preexisting mobile apps to fulfill the distinct needs of practice placements; and (3) the recognition of how collaboratively crafted mLearning practices can yield value for a diverse range of stakeholders, encompassing students, educators, and health care professionals.

Phase 3: Testing Mobile Learning Technology

The pilot study is set to commence in January 2024. It is anticipated that the outcomes of phase 3 will reveal (1) results pertaining to the usability and design of the collaboratively created mLearning apps obtained through surveys; (2) the impact of mobile technology integration on various aspects including learning outcomes, student engagement, and communication among stakeholders; (3) an examination of the emotional tones expressed by participants in relation to the implementation of mobile technology; and (4) findings from the analysis of computer-generated event logs from mobile apps, providing insights into user behavior, identifying potential issues, and ensuring compliance with regulations.

Discussion

Principal Findings

The primary objective of this study is to bridge the gap in practice-based learning by developing personalized mobile apps tailored for diverse actors and stakeholders. The study aims to assess the integration of mobile technology in practice placements within European health care institutions.

This study aims to showcase the transformative potential of mobile technology in reshaping practice placements within health care education. Through targeted efforts to overcome significant barriers, engaging stakeholders in co-design processes, and integrating mobile apps, the study will concentrate on enhancing both the learning and administrative aspects of practice placement. The overarching goal is to ensure the effective clinical education of health care students in higher education.

Identifying key factors, including barriers, facilitators, and potential solutions, for the introduction of mobile technology in practice placements will unveil a spectrum of elements. Literature reviews and insights from focus groups suggest that factors facilitating the use of mLearning in practice placements may include improved access to clinical resources; enhanced communication and collaboration among health care professionals, students, and stakeholders; and the facilitation of self-directed learning. Barriers to the integration of mobile technology in practice placements are concerns about the design of the product being beyond the control of learners and their teaching staff. Additionally, challenges arise when cultural acceptance and adherence to social norms regarding the use of mobile devices in clinical settings are not taken into account. Moreover, the absence of clear policies further contributes to impediments in this context [50-52].

The co-design of an mLearning app, aligning with users' core values and needs, is crucial for the effective adoption of mobile technology in practice-based learning [53]. The outcomes will offer valuable insights into users' needs, values, and preferences, guiding the design process to ensure a user-centered application [54].

Ultimately, the testing and assessment of mobile technology in clinical practice placements are poised to yield promising results across various dimensions, including usability and design, learning outcomes, student engagement, communication among stakeholders, user behavior, identification of potential issues, and compliance with regulations. The integration of mobile apps holds the potential to have a positive impact on the learning process, streamlining day-to-day clinical practice, and enhancing value-based activities.

The impact of this study underscores the necessity for sustained investment in technology-enhanced learning and the crucial role of user-centered design in health care education. Extending beyond the immediate scope of this study, the findings will emphasize broader implications for health care education, particularly in clinical practice placements.

Limitations

It is important to note that the findings of this study may have limited generalizability beyond the participating European countries due to variations in educational contexts and health care systems. Moreover, the assessment of learning outcomes and intervention effectiveness in complex educational settings poses challenges, potentially impacting the comprehensiveness and quantifiability of our results.

Conclusions

The 4D Project endeavors to address the existing gap between academic contexts and clinical placements in higher education. Its objective is to introduce mobile technology as a solution to enhance the learning process in this context. The project actively supports the examination of communication and interaction processes among various stakeholders within and across different organizations and countries. This is achieved through a meticulous methodology used in the design of a mobile app.

The study will use a multiphase approach. Initially, a systematic review and qualitative methodology involving focus groups will be used to identify barriers and facilitators to the introduction of mobile technology in practice placements. Subsequently, a design-based research methodology will be implemented, enabling the cocreation of mLearning apps that align with users' core values and needs for practice-based learning. Finally, a pilot study using both quantitative and qualitative methods will be conducted to validate and test the mLearning technology in a real-world environment. This phase will evaluate its impact, usability, design, interactive learning, social technology aspects, and user satisfaction.

The long-term benefits of the "4D Project" are centered around improving communication, interaction, and collaboration among the diverse stakeholders engaged in the educational process. By addressing current challenges in practice placements, the project aims to fortify the connection between these stakeholders in the digital era. It seeks to foster new forms of collaboration through the strategic integration of mobile technology.

Health care education, encompassing disciplines such as medicine, nursing, midwifery, and others, encounters ongoing challenges in clinical training. The imperative task of bridging the divide between health care institutions and academic settings is crucial. The introduction of a novel digital tool holds the potential to empower health students and mentors, providing a means to navigate the complexities inherent in the learning process.

Acknowledgments

The authors thank the work and dedication of the 4D Project Consortium. The members of the 4D Project Consortium are Esther Cabrera (Tecnocampus, Pompeu Fabra University, Barcelona, Spain), Carlos Martínez-Gaitero (Tecnocampus, Pompeu Fabra University, Barcelona, Spain), Carles Garcia (Tecnocampus, Pompeu Fabra University, Barcelona, Spain), Sebastian Dennerlein (University of Twente, Enschede, The Netherlands), Beata Dobrowolskaa (Faculty of Health Sciences, Medical University of Lublin, Lublin, Poland), Agnieszka Chrzan-Rodak (Faculty of Health Sciences, Medical University of Lublin, Lublin, Poland), Gilbert Peffer (Kubify BV, Utrecht, The Netherlands), Raymond Elferink (Kubify BV, Utrecht, The Netherlands), Daniel Moreno-Martinez (Germans Trias i Pujol Research Institute, Badalona, Spain), Cristina Casanovas-Cuéllar (Germans Trias i Pujol Research Institute, Badalona, Spain), Ariadna Huertas-Zurriaga (Germans Trias i Pujol Research Institute, Badalona, Spain), Stephanie Herbstreit (Medical Faculty, University of Duisburg-Essen, Duisburg, Germany), Cynthia Szalai (Medical Faculty of the University of Duisburg-Essen, Duisburg, Germany), Daniela Mäker (Medical Faculty of the University of Duisburg-Essen, Duisburg, Germany), and Angela Fessl (Graz University of Technology and the Know-Center GmbH, Graz, Austria). The Know-Center is funded within COMET (Competence Centers for Excellent Technologies) under the auspices of the Austrian Federal Ministry of Transport, Innovation and Technology, the Austrian Federal Ministry of Economy, Family and Youth, and by the State of Styria. COMET is managed by the Austrian Research Promotion Agency FFG. This project has been funded with support from the European Union, Programme Erasmus+ Action Type KA220-HED—Cooperation partnerships in higher education Call 2021 Round 1.

Authors' Contributions

All authors have had substantial intellectual contributions to this protocol. CMG and EC conceptualized this study and wrote the first and final drafts of the protocol. All the authors participated in writing, reviewing, and editing the protocol. All authors have contributed to revising the protocol for intellectual content. All authors have read and approved the final manuscript and given final approval for the manuscript to be published.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Selected projects 2021-KA220-HED-s.
[PDF File (Adobe PDF File), 1271 KB - resprot_v13i1e53284_app1.pdf]

Multimedia Appendix 2
Eligibility outcome for the 4D Project. 4D Project: 4D in the Digitalization of Learning in Practice Placement.
[PDF File (Adobe PDF File), 68 KB - resprot_v13i1e53284_app2.pdf]

Multimedia Appendix 3
4D Project grant agreement. 4D Project: 4D in the Digitalization of Learning in Practice Placement.
[PDF File (Adobe PDF File), 1360 KB - resprot_v13i1e53284_app3.pdf]

References

1. Gherardi S. Practice-based theorizing on learning and knowing in organizations. Organization 2016 Aug 17;7(2):211-223. [doi: 10.1177/135050840072001]
2. Thistlethwaite JE. Practice-based learning across and between the health professions: a conceptual exploration of definitions and diversity and their impact on interprofessional education. International Journal of Practice-based Learning in Health and Social Care 2013 Jun;1(1):15-28. [doi: 10.11120/pblh.2013.00003]
3. Dobrowolska B, McGonagle I, Kane R, Jackson CS, Kegl B, Bergin M, et al. Patterns of clinical mentorship in undergraduate nurse education: a comparative case analysis of eleven EU and non-EU countries. Nurse Educ Today 2016 Jan;36:44-52. [doi: 10.1016/j.nedt.2015.07.010] [Medline: 26254673]
4. Directive 2005/36/EC, European Parliament and of the Council of 7 September 2005 on the recognition of professional qualifications, consolidated version of 24 march 2011. European Union (EU). URL: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32005L0036 [accessed 2022-11-04]
5. Council Directive 77/453/EEC of 27 June 1977 concerning the coordination of provisions laid down by law, regulation or administrative action in respect of the activities of nurses responsible for general care. European Union (EU). URL: http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31977L0453:EN:HTML [accessed 2022-11-04]
6. Mallik M, McGowan B. Issues in practice based learning in nursing in the United Kingdom and the Republic of Ireland: results from a multi professional scoping exercise. Nurse Educ Today 2007 Jan;27(1):52-59. [doi: 10.1016/j.nedt.2006.02.007] [Medline: 16624453]
7. Saarikoski M. The main elements of clinical learning in healthcare education. In: Saarikoski M, Strandell-Laine C, editors. The CLES-Scale: An Evaluation Tool for Healthcare Education. 1st ed. Cham, Switzerland: Springer; 2018:7-15.
8. Ryan G, Toohey S, Hughes C. The purpose, value and structure of the practicum in higher education: a literature review. High Educ 1996 Apr;31(3):355-377. [doi: 10.1007/bf00128437]
9. Bray L, Nettleton P. Assessor or mentor? Role confusion in professional education. Nurse Educ Today 2007 Nov;27(8):848-855. [doi: 10.1016/j.nedt.2006.11.006] [Medline: 17293009]
10. Nyoni CN, Dyk LH, Botma Y. Clinical placement models for undergraduate health professions students: a scoping review. BMC Med Educ 2021 Dec 04;21(1):598 [FREE Full text] [doi: 10.1186/s12909-021-03023-w] [Medline: 34863178]
11. Pedregosa S, Fabrellas N, Risco E, Pereira M, Dmoch-Gajzlerska E, Şenuzun F, et al. Effective academic-practice partnership models in nursing students' clinical placement: a systematic literature review. Nurse Educ Today 2020 Dec;95:104582. [doi: 10.1016/j.nedt.2020.104582] [Medline: 33049559]
12. Chuan OL, Barnett T. Student, tutor and staff nurse perceptions of the clinical learning environment. Nurse Educ Pract 2012 Jul;12(4):192-197. [doi: 10.1016/j.nepr.2012.01.003] [Medline: 22277167]
13. Budgen C, Gamroth L. An overview of practice education models. Nurse Educ Today 2008 Apr;28(3):273-283. [doi: 10.1016/j.nedt.2007.05.005] [Medline: 17629596]
14. Lambert V, Glacken M. Clinical support roles: a review of the literature. Nurse Education in Practice 2004 Sep;4(3):177-183. [doi: 10.1016/s1471-5953(03)00039-8]
15. Jokelainen M, Turunen H, Tossavainen K, Jamookeeah D, Coco K. A systematic review of mentoring nursing students in clinical placements. J Clin Nurs 2011 Oct;20(19-20):2854-2867. [doi: 10.1111/j.1365-2702.2010.03571.x] [Medline: 21429055]
16. Thomson R, Docherty A, Duffy R. Nursing students' experiences of mentorship in their final placement. Br J Nurs 2017 May 11;26(9):514-521. [doi: 10.12968/bjon.2017.26.9.514] [Medline: 28493780]
17. World Health Organization (WHO). Framework on integrated, people-centred health services. WHO. Geneva, Switzerland: WHO; 2016. URL: https://apps.who.int/gb/ebwha/pdf_files/WHA69/A69_39-en.pdf [accessed 2022-11-04]
18. Huston C. Technology in the healthcare workplace: benefits, limitations, and challenges. In: Huston C, editor. Professional Issues in Nursing: Challenges and Opportunities. 3rd ed. Philadelphia, PA: Lippincott, Williams, & Wilkins; 2014:214-227.
19. Institute of Medicine (US) Committee on the Robert Wood Johnson Foundation Initiative on the Future of Nursing, at the Institute of Medicine. The Future of Nursing: Leading Change, Advancing Health. Washington, DC: National Academies Press (US); 2011.
20. Council Conclusions of 12 May 2009 on a strategic framework for European cooperation in education and training (ET 2020). Council of the European Union. Brussels, Belgium: Council of the European Union; 2009. URL: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:119:0002:0010:en:PDF [accessed 2022-11-04]

21. Ward JP, Gordon J, Field MJ, Lehmann HP. Communication and information technology in medical education. The Lancet 2001 Mar;357(9258):792-796. [doi: 10.1016/s0140-6736(00)04173-8]
22. Kirkwood A, Price L. Technology-enhanced learning and teaching in higher education: what is 'enhanced' and how do we know? A critical literature review. Learning, Media and Technology 2013 Feb 20;39(1):6-36. [doi: 10.1080/17439884.2013.770404]
23. Traxler J. Current state of mobile learning. IRRODL 2007 Jun 15;8(2):9-24 [FREE Full text] [doi: 10.19173/irrodl.v8i2.346]
24. Crompton H. Historical overview of mobile learning: toward learner-centered education. In: Berge ZL, Muilenburg LY, editors. Handbook of Mobile Learning. 1st ed. Florence, KY: Routledge; 2013:3-14.
25. Crescente ML, Lee D. Critical issues of m-learning: design models, adoption processes, and future trends. Journal of the Chinese Institute of Industrial Engineers 2011 Mar;28(2):111-123. [doi: 10.1080/10170669.2010.548856]
26. O'Connor S, Andrews T. Mobile technology and its use in clinical nursing education: a literature review. J Nurs Educ 2015 Mar;54(3):137-144. [doi: 10.3928/01484834-20150218-01] [Medline: 25693246]
27. Mackay B, Anderson J, Harding T. Mobile technology in clinical teaching. Nurse Educ Pract 2017 Jan;22:1-6. [doi: 10.1016/j.nepr.2016.11.001] [Medline: 27871040]
28. Saylor M. The mobile wave: how mobile intelligence will change everything. In: Creswell JW, Clark VLP, editors. Designing and Conducting Mixed Methods Research. 2nd ed. Thousand Oaks, CA: Perseus Books/Vanguard Press; 2012:176.
29. Dennerlein SM, Tomberg V, Treasure-Jones T, Theiler D, Lindstaedt S, Ley T. Co-designing tools for workplace learning. ILS 2020 Apr 25;121(3/4):175-205. [doi: 10.1108/ils-09-2019-0093]
30. Dennerlein S, Pammer-Schindler V, Ebner M, Getziner G, Ebner E. Designing a sandpit- and co-design-informed innovation process for scaling TEL research in higher education. 2020 Mar 9 Presented at: 15th International Conference on Wirtschaftsinformatik 2020; March 8-11, 2020; Potsdam, Germany URL: https://research.utwente.nl/en/publications/designing-a-sandpit-and -co-design-informed-innovation-process-for/> [doi: 10.30844/wi_2020_s4-dennerlein]
31. 4D Project: digitalization of learning in practice placement. TecnoCampus. 2022. URL: https://4d.tecnocampus.cat/ [accessed 2022-11-04]
32. Edelson DC. Balancing innovation and risk. In: van den Akker JJH, editor. Educational Design Research. London, UK: Routledge; 2006:100-106.
33. van den Akker DAJ, Bannan B, Kelly AE, Nieveen N, Plomp T. An introduction to educational design research. University of Twente.: https://ris.utwente.nl/ws/portalfiles/portal/14472302/Introduction_20to_20education_20design_20research.pdf; 2007. URL: https://ris.utwente.nl/ws/portalfiles/portal/14472302/Introduction_20to_20education_20design_20research.pdf [accessed 2024-01-09]
34. McKenney S, Reeves TC. Systematic review of design-based research progress. Educational Researcher 2013 Mar 01;42(2):97-100. [doi: 10.3102/0013189x12463781]
35. Wademan M. Utilizing development research to guide people capability maturity model adoption considerations: instructional design, development and evaluation [Doctoral dissertation]. Syracuse, NY: Syracuse University; 2005. URL: https://surface.syr.edu/idde_etd/12 [accessed 2022-11-04]
36. Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, PRISMA-S Group. PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. Syst Rev 2021 Jan 26;10(1):39 [FREE Full text] [doi: 10.1186/s13643-020-01542-z] [Medline: 33499930]
37. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. International Journal of Social Research Methodology 2005 Feb;8(1):19-32. [doi: 10.1080/1364557032000119616]
38. Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. Implement Sci 2010 Sep 20;5:69 [FREE Full text] [doi: 10.1186/1748-5908-5-69] [Medline: 20854677]
39. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. Int J Qual Health Care 2007 Dec;19(6):349-357. [doi: 10.1093/intqhc/mzm042] [Medline: 17872937]
40. Porritt K, Gomersall J, Lockwood C. JBI's systematic reviews: study selection and critical appraisal. Am J Nurs 2014 Jun;114(6):47-52. [doi: 10.1097/01.NAJ.0000450430.97383.64] [Medline: 24869584]
41. Koole M, Buck R, Anderson K, Laj D. A comparison of the uptake of two research models in mobile learning: the FRAME model and the 3-level evaluation framework. Education Sciences 2018 Aug 07;8(3):114. [doi: 10.3390/educsci8030114]
42. Lincoln YS, Guba EG. Naturalistic Inquiry. Newbury Park, CA: Sage Publications; 1985.
43. Osterwalder A, Pigneur Y. Business Model Generation: A Handbook for Visionaries, Game Changers, and Challengers. Hoboken, NJ: John Wiley & Sons; 2010.
44. Maurya A. Running Lean: Iterate From Plan A to A Plan That Works. Sebastopol, CA: O'Reilly Media, Inc; 2012.
45. Osterwalder A, Pigneur Y, Bernarda G, Smith A. Value Proposition Design: How to Create Products and Services Customers Want. Hoboken, NJ: John Wiley & Sons., Inc; 2015.
46. Sauro J, Zarolia P. SUPR-Qm: a questionnaire to measure the mobile app user experience. J Usability Stud 2017;1(13):17-37 [FREE Full text]

47. Zhou L, Bao J, Setiawan IMA, Saptono A, Parmanto B. The mHealth App Usability Questionnaire (MAUQ): development and validation study. JMIR Mhealth Uhealth 2019 Apr 11;7(4):e11500 [FREE Full text] [doi: 10.2196/11500] [Medline: 30973342]
48. Patridge EF, Bardyn TP. Research Electronic Data Capture (REDCap). jmla 2018 Jan 12;106(1):142-144. [doi: 10.5195/jmla.2018.319]
49. Analyzing free-form text responses in surveys: a 6-step guide. Dcipher Analytics. 2021. URL: https://bit.ly/3GdpLZz [accessed 2022-11-09]
50. Strandell-Laine C, Leino-Kilpi H, Löyttyniemi E, Salminen L, Stolt M, Suomi R, et al. A process evaluation of a mobile cooperation intervention: a mixed methods study. Nurse Educ Today 2019 Sep;80:1-8. [doi: 10.1016/j.nedt.2019.05.037] [Medline: 31175963]
51. Scott KM, Nerminathan A, Alexander S, Phelps M, Harrison A. Using mobile devices for learning in clinical settings: a mixed‐methods study of medical student, physician and patient perspectives. Brit J Educational Tech 2015 Sep 22;48(1):176-190. [doi: 10.1111/bjet.12352]
52. Rashid-Doubell F, Mohamed S, Elmusharaf K, O'Neill CS. A balancing act: a phenomenological exploration of medical students' experiences of using mobile devices in the clinical setting. BMJ Open 2016 May 03;6(5):e011896 [FREE Full text] [doi: 10.1136/bmjopen-2016-011896] [Medline: 27142860]
53. Durall E, Bauters M, Hietala I, Leinonen T, Kapros E. Co-creation and co-design in technology-enhanced learning: innovating science learning outside the classroom. IxD&A 2019 Sep 20;42:202-226. [doi: 10.55612/s-5002-042-010]
54. Hanington B, Martin B. Universal Methods of Design Expanded and Revised: 125 Ways to Research Complex Problems, Develop Innovative Ideas, and Design Effective Solutions. Beverly, MA: Rockport Publishers Inc; Sep 25, 2014:222-224.

Abbreviations

4D Project: 4D in the Digitalization of Learning in Practice Placement
COREQ: Consolidated Criteria for Reporting Qualitative Research
FRAME: Koole's Framework for the Rational Analysis of Mobile Education
mLearning: mobile learning
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
REDCap: Research Electronic Data Capture
UIC: university innovation canvas
VPC: value proposition canvas

Edited by A Mavragani; submitted 02.10.23; this is a non–peer-reviewed article;accepted 23.11.23; published 08.02.24.

Please cite as:
Martínez-Gaitero C, Dennerlein SM, Dobrowolska B, Fessl A, Moreno-Martínez D, Herbstreit S, Peffer G, Cabrera E, 4D Project Consortium
Connecting Actors With the Introduction of Mobile Technology in Health Care Practice Placements (4D Project): Protocol for a Mixed Methods Study
JMIR Res Protoc 2024;13:e53284
URL: https://www.researchprotocols.org/2024/1/e53284
doi:10.2196/53284
PMID:38329786

Protocol

Digital Knowledge Translation Tools for Disseminating Sexual and Reproductive Health Information to Adolescents: Protocol for an Evidence Gap Map Review

Salima Meherali[1], PhD; Soumyadeep Bhaumik[2], PhD; Sobia Idrees[1], RN, MN; Megan Kennedy[3], MLIS; Zohra S Lassi[4], PhD

[1]Faculty of Nursing, College of Health Sciences, University of Alberta, Edmonton, AB, Canada

[2]Meta-research and Evidence Synthesis Unit, Health Systems Science, George Institute for Global Health, Sydney, Australia

[3]Health Science Library, University of Alberta, Edmonton, AB, Canada

[4]Robinson Research Institute, Helen Mayo North, Adelaide, Australia

Corresponding Author:
Sobia Idrees, RN, MN
Faculty of Nursing
College of Health Sciences
University of Alberta
5-021 Edmonton Clinic Health Academy
11405 – 87 Avenue
Edmonton, AB, T6G 1C9
Canada
Phone: 1 7806559335
Fax: 1 7804922551
Email: sidrees@ualberta.ca

Abstract

Background: Digital or eHealth knowledge translation (KT) interventions have been identified as useful public health tools, particularly to advance sexual and reproductive health (SRH) among adolescents. Existing literature reviews on digital health interventions for adolescents' SRH demonstrate limitations, including shortcomings in reporting and comprehensiveness that limit the utility and trustworthiness of findings. However, there is a lack of evidence synthesis on the effectiveness of available digital or mobile health KT tools to promote SRH interventions for adolescents.

Objective: We aim to identify, map, and describe existing empirical evidence on the digital KT tools developed to improve adolescent SRH outcomes globally.

Methods: This study will be conducted using an evidence gap map (EGM) approach to address the objectives, including reviewing relevant literature and a landscape analysis of the outcomes of interest. The following electronic databases will be searched for retrieval of literature: MEDLINE (1946-present), Embase (1974-present), and Global Health (1910-present) via OVID; CINAHL (1936-present) via EBSCOhost; Scopus (1976-present); and Cochrane Library (1993-present) via Wiley. We will include only those studies that focused on adolescents aged 10-19 years and addressed SRH outcomes. We will include experimental studies (randomized or cluster randomized and nonrandomized controlled trials, including quasi-randomized, controlled before-after, and interruptive time series) and observational studies, that is, including prospective cohort and case-control studies. The experimental and observational studies will only be included in the presence of control or comparison arms. Studies with a historical control arm will be excluded. The systematic review software, Covidence (Ventas Health Innovation), will be used to screen and select the studies. Further, 2 independent reviewers will complete the first and second levels of screening of studies and any conflicts arising will be resolved by consensus between the 2 reviewers or by involving the third reviewer. We will conduct the quality assessment of all included studies using the Risk of Bias tool for randomized controlled trials and nonrandomized controlled trials, and AMSTAR2 for systematic reviews.

Results: Papers screening, data extraction, and synthesis will be completed by March 2024. We will use EPPI-Mapper (The International Public Policy Observatory) software to generate an online evidence map and to produce the tables and figures for the descriptive report. This EGM review will identify areas with high-quality, evidence-based digital KT tools (for immediate scale and spread) and areas where few or no KT tools exist (for targeted KT tool development and research or policy prioritization).

Conclusions: This protocol focused on mapping eHealth KT tools that have been used in the literature to address SRH among adolescents. This will be the first EGM exercise to map digital KT tools to promote adolescents' SRH and will incorporate a range of published sources.

International Registered Report Identifier (IRRID): DERR1-10.2196/55081

(JMIR Res Protoc 2024;13:e55081) doi:10.2196/55081

KEYWORDS

adolescents; sexual and reproductive health; digital tools; knowledge translation; mobile phone

Introduction

Background

Adolescence is a critical period in the transition from childhood into adulthood, during which young individuals aged 10 to 19 years experience substantial physical, psychological, social, and emotional changes [1]. Adolescents are vulnerable because of their age-related psychosocial and biological changes and the challenges associated with navigating these changes [2]. As part of their physical, psychological, and social development, it is common for adolescents to explore their sexual orientations and feelings through sexual experimentation [3]. Depending on their knowledge about sexuality and social support, some may experience unintended consequences such as unplanned pregnancy and sexually transmitted infections. Neglect of specific adolescents' sexual and reproductive health (SRH) needs can affect their physical and mental health, future employment, economic well-being, and ability to reach their full potential [4-6].

SRH issues pose serious concerns for adolescents including the lesbian, gay, bisexual, transgender, queer, and gender diverse population. Adolescents have the highest rates of contracting sexually transmitted infections, including HIV [7,8]. Approximately 16 million girls aged 15-19 years and 2 million girls younger than 15 years become pregnant each year around the world [9]. Pregnancy-related complications are the second leading cause of death among girls aged 15-19 years [10]. Furthermore, adolescents have less access to information and services. Access to contraception also remains low among females 15-24 years compared to women older than 30 years [11]. This is primarily due to a lack of awareness, social stigma, policies, and procedures inhibiting the provision of contraception and abortion services to girls, and judgmental attitudes of health care professionals [12-14]. Young people have special SRH education needs that remain unmet, and to address these specific SRH needs, innovative and novel approaches are required to ensure access to evidence-based SRH information and acceptable SRH services [13].

To maximize health system resources and improve SRH outcomes for adolescents, it is increasingly important to close the research-practice gap by ensuring that research knowledge translates into action—a process called knowledge translation (KT). KT is the synthesis, exchange, and application of knowledge to improve the health of individuals, provide more effective health information, services, and products, and strengthen health care systems [15]. KT is the process of translating knowledge into action to provide more effective health services and strengthen the health care system [15,16]. The goal of KT is to ensure that individuals, such as patients, health professionals, and policymakers, can access and use research evidence to inform their health-related decision-making [17].

KT is a dynamic process that uses tools and methods to increase the use of evidence in decision-making while considering policy rationales in the process of generating evidence [18]. On the other hand, KT tools are a subgroup of KT interventions that facilitate moving research-based information to clinicians and patients or health care consumers in user-friendly language and formats to provide explicit recommendations or meet knowledge or information needs [16,17,19]. KT tools to transfer health information to health care consumers can be presented using a multitude of formats, including but not limited to videos, infographics, apps, practice guidelines, and decision-aiding tools to aid consumers in the synthesis, dissemination, and implementation of research [19]. Digital KT tools offer a promising approach to improving health literacy and communicating complex health information to health care consumers. Digital KT tools such as mobile phone websites, mobile apps, mobile health (mHealth), SMS text messaging, and social media platforms have been identified as useful public health tools, particularly to promote SRH among adolescents. The use of digital technology for SRH promotion offers privacy [20-25], access to personalized information [20,22,24,26], and convenience [20,25,27] making it a valuable way to provide accurate information about sexual health to adolescents [20-24].

Several research studies tested the effect of technology-based tools on improving adolescents' knowledge, attitudes, and practices regarding sexual health [22-27]. Cornelius and Lawrence [23] used text messaging through mobile phone technology to increase awareness of adolescents to prevent sexually transmitted infections (HIV) and improve safe sexual practices [28]. The study reported that adolescents found text messaging to be an excellent source of information exchange and a reminder to have safe sex practices [27]. Another study evaluated the prevalence and effectiveness of using chatbot (chat agent) inquiries related to sex, drugs, and alcohol use among adolescents. The study reported that adolescents found chatbots a confidential and user-friendly tool to answer their queries related to topics around sex and sexual activities [28]. Additionally, Guse and colleagues [21] conducted a systematic review to summarize evidence on the effectiveness of digital media-based sexual health intervention for adolescents aged 13-24 years [29]. The review included 10 studies in total, while the majority of the included studies were conducted in the United States. The findings of the review study reported the

effectiveness of digital media-based interventions in improving sexual behavior and health among adolescents.

However, despite the availability of digital KT tools, there is a lack of evidence of synthesis on the available digital or mHealth KT tools to promote SRH interventions for adolescents. Not all KT tools are equally effective and trustworthy sources of SRH information. Therefore, this study using an evidence gap map (EGM) exercise aims to synthesize evidence on the usefulness of digital KT tools to improve adolescents' SRH. EGM is an emerging approach to mapping and synthesizing evidence from empirical studies to implement effective strategies and inform policymakers [30]. EGM is a systematic way of gathering scientific evidence and summarizing the evidence in a graphical format for researchers and practitioners to understand what is known and where the gap is in a particular sector. Another key advantage of using the EGM framework is that this guide is designed for nonspecialist audiences to distill key findings and provide implications for practice and policy [30].

Study Purpose and Objective

This review aims to identify, map, and describe existing empirical evidence on the digital KT tools developed to improve adolescent SRH outcomes globally. In this EGM, we will assess and report on empirical studies describing the development, implementation, or evaluation of SRH digital KT tools to identify current aims, processes, methods, frameworks, tools, user roles, disciplinary and geographic domains of application, as well as to document existing knowledge gaps. The specific objectives of this EGM are to, first, identify, assess, and report on empirical studies of any design that describe the development, implementation, or evaluation of adolescent SRH digital KT tools; second, to identify current uses, purposes, and methods in the development of digital KT tools; third, to describe the characteristics of digital KT tools; and finally, to identify research gaps in the literature.

We will conduct an EGM to address the objectives, including reviewing relevant literature and a landscape analysis of the outcomes of interest. The EGM will be presented on a web-based platform and accompanied by a published paper with an analysis of the available evidence. An EGM aims to establish what we know and do not know about the effects of interventions in a thematic area [31]. The map is populated through systematic searching, screening, and data extraction of all relevant completed, and ongoing, impact evaluations and systematic reviews.

Methods

Study Design

This study is conducted in alignment with standard methodologies for the development of EGM [30]. The protocol for this work is registered with PROSPERO (CRD42022373970). We started this review in May 2023 and will complete it by April 2024.

Scope of EGM

The scope of the EGM was determined through a consultative workshop organized by SM to discuss the interventions and strategies to improve the adolescents' SRH and rights and on how to meet the information needs of adolescents related to SRH. We invited the stakeholders from Option for Sexual Health and Action Canada for Sexual Health and Rights to the consultative workshops for research team members of World Universities Network and members of the Contraception and Abortion Research Team. This workshop identified the need for the EGM and informed the general inclusion criteria and the framework of the EGM. We found EGM as the most appropriate and suitable framework for this review as we aim to map the available evidence on the effectiveness of digital interventions in the form of a table or matrix that provides a visual presentation of the evidence [32].

Eligibility Criteria

The eligibility criteria for the evidence map are summarized in Textbox 1 and detailed below:

- *Study types:* We will include experimental studies (randomized or cluster randomized and nonrandomized controlled trials, including quasi-randomized, controlled before-after, and interruptive time series) and observational studies, that is, including prospective cohort and case-control studies. The experimental and observational studies will only be included in the presence of control or comparison arms. Studies with a historical control arm will be excluded. Studies such as cross-sectional studies, case reports and series, editorials, commentaries, and narrative reviews will not be included.
- *Topics of interest:* We will include studies that have reported KT tools on SRH topics such as family planning and contraception use, healthy timings and spacing of pregnancy, teenage pregnancy, abortion, HIV and AIDS and other sexually transmitted infections, intimate partner violence or dating violence, menstruation, feminine hygiene, child marriage, and female genital mutilation associated with the above topics.
- *Population:* We will include primary studies conducted on adolescents aged 10-19 years. Studies and reviews on populations younger and older than adolescents but inclusive of adolescents will be included if they separately report outcomes on adolescents. We will report the studies separately if they do not report outcomes on adolescents separately.
- *Exposure or intervention:* We will include studies assessing digital KT tools for disseminating SRH information to adolescents. If a digital KT tool is meant for dissemination in wider age groups, it will be included, and these KT tools will consist of websites, mobile apps, mHealth, SMS text messaging, pamphlets, and brochures over email, podcasts, mass media such as radio messages or videos on television, and social media such as Instagram, TikTok, Facebook, Twitter, YouTube, and over-the-top platforms.
- *Comparison:* We will include studies comparing the abovementioned KT tools with no interventions, the standard of care, or other interventions.
- *Setting:* We will include studies conducted globally regardless of the settings or context of its conduct.

Textbox 1. Eligibility criteria for the evidence map.

Population

- Adolescents aged 10-19 years

Exposure or intervention

- Digital knowledge translation tools for disseminating sexual and reproductive health information such as websites, mobile apps, mobile health (mHealth), SMS text messaging, pamphlets, and brochures over email, podcasts, radio messages, videos on television, and social media such as Instagram, TikTok, Facebook, and Twitter

Comparison

- Any comparison is eligible

Geography

- Global evidence, that is, studies from high-income and low- and middle-income countries

Topics of interest

- Family planning and contraception use
- Healthy timings and spacing of pregnancy
- Teenage pregnancy
- Abortion
- HIV and AIDS and other sexually transmitted infections
- Intimate partner violence or dating violence
- Menstruation and feminine hygiene
- Child marriage
- Female genital mutilation
- Rights, norms, education, and empowerment associated with the above topics

Study type

- Experimental and observational studies, including systematic reviews

Timeframe

- Studies and reports published from 2010 onwards as internet and digital or social media usage increased from 2010

Language

- English language only given the prominence of the English language in science

Search Strategy

The search strategy for this review will be reported in adherence to the PRISMA-S (Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Searching) extension [33]. The search strategy will be developed by an experienced health sciences librarian (MK) in consultation with the research team. The following databases will be searched individually from inception to present: MEDLINE (1946-present), Embase (1974-present), and Global Health (1910-present) via OVID; CINAHL (1936-present) via EBSCOhost; Scopus (1976-present); and Cochrane Library (1993-present) via Wiley.

The search strategy will be derived from four main concepts: (1) adolescents, teenagers, or young adults; (2) SRH or health services including vocabulary related to contraception, family planning, pregnancy, sexually transmitted infections, and gender-based violence; (3) digital communication tools such as websites, web-based messaging, smartphones, mobile apps, social media, podcasts, television, or digital information; and (4) KT including vocabularies such as information dissemination, research innovation, knowledge transfer, implementation science, research into practice, knowledge into practice, and evidence-based practice. Bibliographic databases will be searched using a combination of natural language (keywords) and subject headings, such as Medical Subject Headings, wherever they are available. Items such as books, book chapters, editorials, conference materials, and opinion pieces will be removed from the results and a publication date limit of 2010 to the present will be applied. A preliminary search for OVID Medline was developed and executed in October 2022 to determine the feasibility of this project and test the scope (see Multimedia Appendix 1 for the MEDLINE search strategy). The systematic review software, Covidence, will be used to manage this review. Covidence will be used for the

deduplication of database search results and will be used to facilitate the title or abstract screening and full-text screening phases.

Screening and Extraction

All the studies identified from the databases will be imported to Covidence (a digital screening software), and 2 independent reviewers will screen the studies in title or abstract and full-text stages. Disagreements, if any, will be resolved by consensus. The reference list of all the included studies will be scanned and searched to include any relevant study that may have been missed during the search of databases. The final list of included studies will be subject to forwarding and backward citation chaining to ensure no relevant eligible papers have been missed. A diagram showing the flow of literature will be produced and reported by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [33]. For data extraction, we will use a standardized data extraction form to extract descriptive data from all studies meeting our inclusion criteria. Data extracted from each study will include bibliographic details, KT tool types and descriptions, outcome types and descriptions, study design, context or geographical information, and details on the outcome and quality of the KT tool. Further, 2 review authors will independently extract data, and discrepancies will be resolved through discussion until consensus has been achieved or by consulting a third reviewer if required. Attempts will be made to contact the authors of the included studies to obtain clarifications or additional data. We will extract data on the following study characteristics presented in Textbox 2:

Textbox 2. Extraction of data on this study's characteristics.

Publication information

- Journal, publication year, study location, and study setting

Population

- Number of participants, sex, mean age, age range, and sociodemographic status

Digital knowledge translation (KT) tool

- Digital KT tool description, purpose, setting, and any other important detail

Intervention (if studies used digital KT tool as an intervention to improve sexual and reproductive health [SRH] information and outcome of adolescents)

- Intervention description, the composition of the intervention, duration of intervention, a platform for delivery (school-based or community-based, peer-support, mobile health [mHealth]), and comparison group description

Control

- Standard of care or control

Outcomes

- Outcomes specified earlier, time points of outcomes reported, and evaluation methods used

Study design

- Type of study design

Other information

- Funding sources, study limitations, and conflicts of interest

Data Synthesis

Data from the review will be visually synthesized in an EGM using EPPI-Mapper [34] with an accompanying narrative. Rows of the EGM list digital KT strategies and columns components of outcomes and other relevant data coding. Each cell shows the number and quality of evidence for digital KT strategies. We will conduct the quality assessment of the included studies using Risk of Bias for interventional studies including randomized controlled trials and nonrandomized controlled trials and AMSTAR2 tool for systematic reviews [31,35]. The EGM identifies areas with high-quality, evidence-based digital KT tools (for immediate scale and spread) and areas where few or no KT tools exist (for targeted KT tool development and research or policy prioritization) An example of the layout of the evidence map matrix can be found in Multimedia Appendix 2 (developed in consultation and discussion with experts in the area of adolescents SRH).

Patient and Public Involvement

Patients will not be involved in the design, conduct, reporting, or dissemination of the EGM exercise.

Ethical Considerations

No ethical review was required, as we included published data which is accessible and available for the public in this review. We will disseminate findings from the EGM through summary reports and publications; present our findings at conferences to

facilitate research reach; list project descriptions and associated outputs on investigator-affiliated websites and professional web-based accounts; and concurrent dissemination through professional social media accounts. The EGM has the potential to inform researchers and decision makers about user-centered innovation by highlighting current practices and opportunities for further KT tools development. Findings will inform the development of future projects with the principal investigators and coprincipal investigators' research program aimed at developing, implementing, and evaluating digital KT tools and associated projects in various receptive adolescent SRH contexts. Findings will directly inform a concurrent project by the lead investigator (SM) focused on co-designing a mobile app to improve the SRH of immigrant adolescents in Canada.

Results

Overview

Paper screening, data extraction, and synthesis will be completed by March 2024. We will use EPPI-Mapper software to generate a digital evidence map and to produce the tables and figures for the descriptive report. EPPI-Mapper will consist of rows representing digital KT interventions and column components presenting outcomes. Each cell shown within the matrix will present the number and quality of evidence for digital KT strategies. This EGM review will identify areas with high-quality, evidence-based digital KT tools (for immediate scale and spread) and areas where few or no KT tools exist (for targeted KT tool development and research or policy prioritization). This EGM exercise will offer a novel knowledge synthesis tool (a web-based EGM), mapping all of the digital KT tools currently available to promote the SRH of adolescents. The information will be available in a usable format to enable efficient and effective use by multi-stakeholder audiences.

Discussion

Principal Findings

The purpose of this review is to create an EGM to guide multi-sectoral stakeholders regarding digital KT tools to better understand and use the evidence-based digital KT tools to improve the SRH of adolescents. Digital KT tools have the potential to advance the SRH of adolescents, yet there is a dearth of knowledge regarding the quality and uptake of these digital KT tools. Digital technologies have the potential to facilitate innovative, efficient ways of meeting growing global health needs. A global 2019 report [36] indicated that over 5 billion mobile phone users, 4 billion internet users, and 3 billion active social media users, with most accessing the internet through mobile devices. The anonymity, convenience, and accessibility afforded by SMS, web access, and video streaming enhance the potential for SRH interventions to reach persons disconnected from mainstream SRH services.

Existing literature reviews on digital health interventions for adolescents' SRH demonstrate limitations, including shortcomings in reporting and comprehensiveness that limit the utility and trustworthiness of findings. An EGM of digital KT tools is therefore warranted. Innovative ways to deliver sexual health information and services are more important than ever before due to the impact of the COVID-19 pandemic on access to SRH services globally [37]. Interruptions in SRH information and service delivery seriously impact vulnerable adolescents' health and well-being. The absence of adolescent SRH services from "essential" health services during COVID-19 amplifies the potential role of technology in meeting the SRH needs of vulnerable groups like adolescents. Amidst the pandemic, technology has primarily provided the means to support the recalibration of health systems, service provision, and information delivery [38]. Digital health tools play an important role in preserving the continuity of SRH services for adolescents and youth during a crisis. Using digital health tools in the pandemic and climate change context would improve adolescents' access to information which might support them in having the knowledge and motivation to access services.

Guidelines and policies are increasingly focused on adolescents as a specific population for modifying health behaviors [39], and the global community is calling for further research in this area [40]. However, it is important to first map out all the available digital KT tools for improving behavior related to SRH among adolescents. Digital or eHealth KT interventions have been identified as useful public health tools, particularly to advance SRH among adolescents. The use of digital technology for SRH promotion offers privacy [21-26], access to personalized information [21,23,25,27], and convenience [21,26,28] making it a valuable way to provide accurate information about SRH to adolescents [21-26].

Despite the high level of SRH information consumption via a digital platform, evidence of the successful use of SRH digital KT tools is limited. EGM provides a novel knowledge synthesis approach that can accelerate the uptake of digital KT tools to promote adolescent SRH outcomes. This study will map all the digital KT tools currently available and identify the key evidence gaps in digital KT tools that may not be obvious from quick snapshots of the literature. Systematically mapping evidence for digital KT tools will provide valuable insights to inform practice, policy, research, or investment for future adolescent SRH research agendas.

Strengths and Limitations of This Study

This will be the first EGM exercise to map digital KT tools to promote adolescents' SRH and will incorporate a range of published literature sources. An independent dual-reviewer process will be used throughout to reduce the risk of bias and increase the likelihood of comprehensive study identification and inclusion. The 2D matrix of interventions and outcomes will help identify and inform policy and funding agencies for further specific areas of research. Publication bias is a possible limitation as non-English and gray literature will be excluded, which may underrepresent the digital KT tools available and used across geographically diverse contexts.

Conclusions

This project will offer a novel knowledge synthesis tool (a digital EGM), mapping all of the digital KT tools currently available to promote the SRH of adolescents. The information will be available in a usable format to enable efficient and

effective use by multi-stakeholder audiences. This work is timely as innovative ways to deliver SRH information are more important than ever before due to the impact of digital media on accessing SRH information and services globally. In addition, key policies will be enacted to encourage and support research initiatives in underrepresented regions as this would promote a more comprehensive global understanding of SRH among adolescents. This review will report on the gaps identified in the research and quality assessment of included studies and recommendations will be set forth for future robust research studies. We will disseminate the findings of our study, via community symposiums, and public training sessions, and present at academic conferences and publish in open-access, peer-reviewed journals, advancing the body of knowledge on available digital KT tools to promote SRH and the rights of adolescents.

Acknowledgments

Thank you to stakeholders from Option for Sexual Health and Action Canada for Sexual Health for providing their expert feedback in preparing an evidence map matrix for this study. This study is funded through an Endowment Fund for the Future: Support for the Advancement of Scholarship (EFF-SAS) Research Fund (ZLD 23).

Authors' Contributions

SM and ZSL conceptualized this study, including leading the associated grant application and drafting this study's protocol. All authors contributed to the protocol and will be involved in conducting the proposed research. All authors provided final approval of this paper before submission and agree to be accountable for all aspects of this study as described here.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Preliminary Medline search strategy.
[PDF File (Adobe PDF File), 27 KB - resprot_v13i1e55081_app1.pdf]

Multimedia Appendix 2
Example evidence map matrix.
[DOCX File , 23 KB - resprot_v13i1e55081_app2.docx]

References

1. Kuzma EK, Peters RM. Adolescent vulnerability, sexual health, and the NP's role in health advocacy. J Am Assoc Nurse Pract 2016;28(7):353-361 [FREE Full text] [doi: 10.1002/2327-6924.12331] [Medline: 26688465]
2. Making health services adolescent friendly: developing national quality standards for adolescent friendly health services. World Health Organization. 2012. URL: https://iris.who.int/bitstream/handle/10665/75217/9789241503594_eng.pdf [accessed 2024-01-10]
3. Adolescent development. U. S. National Library of Medicine. 2018. URL: https://medlineplus.gov/ency/article/002003.htm [accessed 2024-01-10]
4. Herbenick D, Reece M, Schick V, Sanders SA, Dodge B, Fortenberry JD. Sexual behaviors, relationships, and perceived health status among adult women in the United States: results from a national probability sample. J Sex Med 2010;7(Suppl 5):277-290 [FREE Full text] [doi: 10.1111/j.1743-6109.2010.02010.x] [Medline: 21029385]
5. Hensel DJ, Nance J, Fortenberry JD. The association between sexual health and physical, mental, and social health in adolescent women. J Adolesc Health 2016;59(4):416-421 [FREE Full text] [doi: 10.1016/j.jadohealth.2016.06.003] [Medline: 27491340]
6. Defining sexual health: report of a technical consultation on sexual health. World Health Organization. 2006. URL: https://www.who.int/teams/sexual-and-reproductive-health-and-research-(srh)/areas-of-work/sexual-health#:~:text=WHO%20defines%20sexual%20health%20as%20%E2%80%9Ca%20state%20of,merely%20the%20absence%20of%20disease%2C%20dysfunction%20or%20infirmity [accessed 2024-01-10]
7. Division of STD Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention. Sexually transmitted disease surveillance, 2016. Centers for Disease Control and Prevention. 2017. URL: https://www.cdc.gov/std/stats16/CDC_2016_STDS_Report-for508WebSep21_2017_1644.pdf [accessed 2024-01-10]
8. Adolescents and young adults. Centers for Disease Control and Prevention. 2016. URL: https://www.cdc.gov/std/life-stages-populations/adolescents-youngadults.htm [accessed 2024-01-10]
9. Family, health promotion and life course. World Health Organization. URL: https://www.paho.org/en/family-health-promotion-and-life-course [accessed 2024-01-10]

10. Ganchimeg T, Ota E, Morisaki N, Laopaiboon M, Lumbiganon P, Zhang J, et al. Pregnancy and childbirth outcomes among adolescent mothers: a World Health Organization multicountry study. BJOG 2014 Mar;121 Suppl 1:40-48. [doi: 10.1111/1471-0528.12630] [Medline: 24641534]
11. Loaiza E, Liang M. Adolescent Pregnancy: A Review of the Evidence. New York: UNFPA; 2013.
12. Feroz AS, Ali NA, Khoja A, Asad A, Saleem S. Using mobile phones to improve young people sexual and reproductive health in low and middle-income countries: a systematic review to identify barriers, facilitators, and range of mHealth solutions. Reprod Health 2021;18(1):9 [FREE Full text] [doi: 10.1186/s12978-020-01059-7] [Medline: 33453723]
13. Meherali S, Salami B, Okeke-Ihejirika P, Vallianatos H, Stevens G. Barriers to and facilitators of South Asian immigrant adolescents' access to sexual and reproductive health services in Canada: a qualitative study. Can J Hum Sex 2021;30(3):329-338 [FREE Full text] [doi: 10.3138/cjhs.2020-0056]
14. Flicker S, Travers R, Flynn S, Larkin J, Guta A, Salehi R, et al. Sexual health research for and with urban youth: the Toronto Teen Survey story. Can J Hum Sex 2010;19(4):133-144 [FREE Full text]
15. Knowledge translation definition. Canadian Institutes of Health Research. 2015. URL: http://www.cihr-irsc.gc.ca/e/29418.html#2 [accessed 2015-03-18]
16. Graham ID, Logan J, Harrison MB, Straus SE, Tetroe J, Caswell W, et al. Lost in knowledge translation: time for a map? J Contin Educ Health Prof 2006;26(1):13-24 [FREE Full text] [doi: 10.1002/chp.47] [Medline: 16557505]
17. Straus SE, Tetroe JM, Graham ID. Knowledge translation is the use of knowledge in health care decision making. J Clin Epidemiol 2011;64(1):6-10 [FREE Full text] [doi: 10.1016/j.jclinepi.2009.08.016] [Medline: 19926445]
18. Meijers K, van der Kwaak A, Aqel I, Borst R, Jenniskens F, Radyowijati A, et al. Using a rapid knowledge translation approach for better sexual and reproductive health and rights in Bangladesh, Burundi, Indonesia, and Jordan. Glob Health Sci Pract 2022;10(2):e2100461 [FREE Full text] [doi: 10.9745/GHSP-D-21-00461] [Medline: 35487555]
19. Knowledge translation tools. Knowledge Translation Program. 2016. URL: https://knowledgetranslation.net/kt-tools/ [accessed 2024-01-10]
20. L'Engle KL, Mangone ER, Parcesepe AM, Agarwal S, Ippoliti NB. Mobile phone interventions for adolescent sexual and reproductive health: a systematic review. Pediatrics 2016;138(3):e20160884 [FREE Full text] [doi: 10.1542/peds.2016-0884] [Medline: 27553221]
21. Guse K, Levine D, Martins S, Lira A, Gaarde J, Westmorland W, et al. Interventions using new digital media to improve adolescent sexual health: a systematic review. J Adolesc Health 2012;51(6):535-543 [FREE Full text] [doi: 10.1016/j.jadohealth.2012.03.014] [Medline: 23174462]
22. Boyar R, Levine D, Zensius N. TECHsex USA: youth sexuality and reproductive health in the digital age. Youth Tech Health. Oakland: ISIS; 2011. URL: https://www.yth.org/wp-content/uploads/YTH-youth-health-digital-age.pdf [accessed 2024-01-10]
23. Cornelius JB, St Lawrence JS. Receptivity of African American adolescents to an HIV-prevention curriculum enhanced by text messaging. J Spec Pediatr Nurs 2009;14(2):123-131 [FREE Full text] [doi: 10.1111/j.1744-6155.2009.00185.x] [Medline: 19356206]
24. Cornelius JB, St Lawrence JS, Howard JC, Shah D, Poka A, McDonald D, et al. Adolescents' perceptions of a mobile cell phone text messaging-enhanced intervention and development of a mobile cell phone-based HIV prevention intervention. J Spec Pediatr Nurs 2012;17(1):61-69 [FREE Full text] [doi: 10.1111/j.1744-6155.2011.00308.x] [Medline: 22188273]
25. Crutzen R, Peters GJY, Portugal SD, Fisser EM, Grolleman JJ. An artificially intelligent chat agent that answers adolescents' questions related to sex, drugs, and alcohol: an exploratory study. J Adolesc Health 2011;48(5):514-519 [FREE Full text] [doi: 10.1016/j.jadohealth.2010.09.002] [Medline: 21501812]
26. Collins RL, Martino SC, Shaw R. Influence of new media on adolescent sexual health: evidence and opportunities. RAND Health. 2011. URL: https://www.rand.org/pubs/working_papers/WR761.html [accessed 2024-01-10]
27. Perry RCW, Kayekjian KC, Braun RA, Cantu M, Sheoran B, Chung PJ. Adolescents' perspectives on the use of a text messaging service for preventive sexual health promotion. J Adolesc Health 2012;51(3):220-225 [FREE Full text] [doi: 10.1016/j.jadohealth.2011.11.012] [Medline: 22921131]
28. Devine S, Bull S, Dreisbach S, Shlay J. Enhancing a teen pregnancy prevention program with text messaging: engaging minority youth to develop TOP ® plus text. J Adolesc Health 2014;54(3 Suppl):S78-S83 [FREE Full text] [doi: 10.1016/j.jadohealth.2013.12.005] [Medline: 24560081]
29. Lin WY, Zhang X, Cao B. How do new media influence youths' health literacy? Exploring the effects of media channel and content on safer sex literacy. Int J Sex Health 2018;30(4):354-365. [doi: 10.1080/19317611.2018.1509921]
30. Snilstveit B, Vojtkova M, Bhavsar A, Stevenson J, Gaarder M. Evidence and gap maps: a tool for promoting evidence informed policy and strategic research agendas. J Clin Epidemiol 2016;79:120-129 [FREE Full text] [doi: 10.1016/j.jclinepi.2016.05.015] [Medline: 27387966]
31. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ 2017;358:j4008 [FREE Full text] [doi: 10.1136/bmj.j4008] [Medline: 28935701]

32. Saran A, White H, Kuper H. Evidence and gap map of studies assessing the effectiveness of interventions for people with disabilities in low-and middle-income countries. Campbell Syst Rev 2020;16(1):e1070 [FREE Full text] [doi: 10.1002/cl2.1070] [Medline: 37131970]
33. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med 2018;169(7):467-473 [FREE Full text] [doi: 10.7326/M18-0850] [Medline: 30178033]
34. Mapper E. International Initiative for Impact Evaluation. URL: https://www.3ieimpact.org/evidence-hub/evidence-gap-maps/open-access-egm [accessed 2024-01-10]
35. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898 [FREE Full text] [doi: 10.1136/bmj.l4898] [Medline: 31462531]
36. Kemp S. Digital in 2019: global internet use accelerates. We Are Social. 2019. URL: https://wearesocial.com/uk/blog/2019/01/digital-in-2019-global-internet-use-accelerates/#:~:text=We%20Are%20Social%20and%20Hootsuite's,Next%20Billion%20Users'%20now%20online [accessed 2024-01-10]
37. Chen E, Mangone ER. A systematic review of apps using Mobile Criteria for Adolescent Pregnancy Prevention (mCAPP). JMIR Mhealth Uhealth 2016 Nov 10;4(4):e122 [FREE Full text] [doi: 10.2196/mhealth.6611] [Medline: 27833070]
38. Tang K, Gaoshan J, Ahonsi B, Ali M, Bonet M, Broutet N, et al. Sexual and reproductive health (SRH): a key issue in the emergency response to the coronavirus disease (COVID- 19) outbreak. Reprod Health 2020;17(1):59 [FREE Full text] [doi: 10.1186/s12978-020-0900-9] [Medline: 32326943]
39. The Global Strategy for Women's, Children's and Adolescents' Health (2016-2030). World Health Organization. 2018. URL: https://www.who.int/publications/i/item/A71-19 [accessed 2024-01-10]
40. Chandra-Mouli V, Akwara E, Engel D, Plessons M, Asnake M, Mehra S, et al. Progress in adolescent sexual and reproductive health and rights globally between 1990 and 2016: what progress has been made, what contributed to this, and what are the implications for the future? Sex Reprod Health Matters 2020;28(1):1741495 [FREE Full text] [doi: 10.1080/26410397.2020.1741495] [Medline: 32254004]

Abbreviations

EGM: evidence gap map
KT: knowledge translation
mHealth: mobile health
PRISMA-S: Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Searching
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SRH: sexual and reproductive health

Edited by A Mavragani; submitted 01.12.23; this is a non–peer-reviewed article;accepted 07.01.24; published 13.02.24.

Please cite as:
Meherali S, Bhaumik S, Idrees S, Kennedy M, Lassi ZS
Digital Knowledge Translation Tools for Disseminating Sexual and Reproductive Health Information to Adolescents: Protocol for an Evidence Gap Map Review
JMIR Res Protoc 2024;13:e55081
URL: https://www.researchprotocols.org/2024/1/e55081
doi:10.2196/55081
PMID:38349722

Protocol

The Impact of the Ecosystem on Health Literacy Among Rural Communities in Protected Areas: Protocol for a Mixed Methods Study

Nor Aziah Abd Kadir[1,2], MA; Amirah Azzeri[1], PhD; Hafiz Jaafar[1], PhD; Mohd Iqbal Mohd Noor[2,3], PhD; Zurina Kefeli[4], PhD

[1]Faculty of Medicine and Health Sciences, Universiti Sains Islam Malaysia, Negeri Sembilan, Malaysia

[2]Faculty of Business and Management, Universiti Teknologi MARA Cawangan Pahang, Kampus Raub, Raub, Malaysia

[3]Institute for Biodiversity and Sustainability Development, Universiti Teknologi MARA, Shah Alam, Malaysia

[4]Faculty of Economics and Muamalat, Universiti Sains Islam Malaysia, Negeri Sembilan, Malaysia

Corresponding Author:
Amirah Azzeri, PhD
Faculty of Medicine and Health Sciences
Universiti Sains Islam Malaysia
Bandar Baru Nilai
Negeri Sembilan, 71800
Malaysia
Phone: 60 132088543
Email: amirah.azzeri@usim.edu.my

Abstract

Background: Protected areas are crucial for the maintenance of human health and well-being. They aim to preserve biodiversity and natural resources to secure various ecosystem services that are beneficial to human health. Their ecological characteristics can influence local health literacy. Typically, communities surrounding protected areas have limited economic opportunities due to restriction policies to protect the ecosystem, resulting in socioeconomic disparities. The local community faces obstacles in gaining access to health care facilities and health information due to these limitations. It is difficult for them to locate, comprehend, and apply information and services to make better health-related decisions for themselves and others.

Objective: This study protocol examines the impact of the ecosystem on health literacy among rural communities in protected areas.

Methods: This study comprises 5 phases. In phase 1, we conduct a systematic review to identify the issue of health literacy in protected areas. In phase 2, we will collect data from stakeholders in a protected area of Pahang National Park and analyze the results using Net-Map analysis. In phase 3, we will conduct a survey among the adult community in Pahang National Park related to health literacy, socioeconomic status, health expenditure, and quality of life. In phase 4, informed by the results of the survey, we will determine suitable intervention programs to improve health literacy through a focus group discussion. Finally, in phase 5, we will conduct a costing analysis to analyze which intervention program is the most cost-effective.

Results: This study was funded by Universiti Sains Islam Malaysia (USIM) and strategic research partnership grants, and enrollment is ongoing. The first results are expected to be submitted for publication in 2024.

Conclusions: This is one of the first studies to explore health literacy among rural communities in protected areas and will provide the first insights into the overall level of health literacy in the protected community, potential determinants, and a suitable intervention program with expected cost analysis. The results can be used to promote health literacy in other protected areas and populations.

Trial Registration: International Standard Randomized Controlled Trial Number Registry ISRCTN40626062; http://tinyurl.com/4kjxuwk5

International Registered Report Identifier (IRRID): PRR1-10.2196/51851

(JMIR Res Protoc 2024;13:e51851) doi:10.2196/51851

KEYWORDS

ecosystem; health literacy; protected areas; Net-Map; quality of life; rural communities; protocol

Introduction

Good health and well-being can be achieved with adequate health literacy [1,2]. Adequate health literacy indicates that the individual can obtain, process, understand, and apply basic health information and services needed to make appropriate health decisions [3]. Higher levels of health literacy allow people to make better health decisions [4], be more committed, and do their jobs more efficiently [5]. Patients must have enough information about their health to leverage it and make well-informed decisions regarding getting health treatments and medicine. In the context of preventive health care, an adequate level of health literacy helps ensure that patients get the most out of their health investments and make the best use of resources [6]. According to the World Health Organization (WHO), people residing in rural areas often experience socioeconomic inequity and lower educational attainment due to imperfect living conditions. These areas are cut off from urban centers and have limited facilities [7,8]. The varying ecosystems within the population may influence different levels of health literacy.

People living in the protected areas often have limited health literacy [9]. The government designates protected areas for conservation purposes. Thus, less emphasis is placed on new land development for farming, housing, and infrastructure [10-12]. As a result, populations encounter challenges in gaining better access to networks, health facilities, the internet, and other resources. This limitation, in turn, adversely affects their quality of life [9]. The health outcomes, living conditions, and education levels of the population residing in rural areas lag significantly behind those living near urban centers. This disparity places people in rural areas at a disadvantage when it comes to making informed health decisions, as they have limited knowledge in this regard.

Accordingly, policy makers are putting in place and advocating for health programs and awareness campaigns to improve the health literacy status among populations in rural and protected areas [13]. However, this strategy is hard to implement in communities that live in protected areas as they have limited educational backgrounds. They struggle to access, obtain, understand, and apply health information in their daily lives. Moreover, they are often unable to access health information when they are sick. Indigenous people often turn to traditional remedies, consult shamans, or opt for inaction with the hopes that the illness will recover on its own [14]. The limited knowledge of hygiene among indigenous people has prompted the government to develop a specialized syllabus for indigenous children at primary school. This curriculum focuses on teaching essential practices, such as washing hands, proper toilet usage, and dental hygiene. Understanding the impact of protected areas on health literacy in local communities is crucial to sustaining their way of life and health. However, the level of health literacy and its response to protected areas varies, depending on factors such as the type of protected area, how policies are planned, and how they are implemented [15].

Research on health literacy among people who live in protected areas is important for understanding their needs for access to health care, disease prevention, health promotion, and health care. It will also help elucidate how to meet these needs in the best and most effective way. Nevertheless, thus far, there has been limited research on health literacy and health issues among people in protected areas considering 4 perspectives (ie, that of government entities, knowledge institutions, civil agencies, and local communities). Accordingly, this paper proposes a study that will examine health literacy and health status of communities in protected areas. The study protocol can serve as a model for similar investigations in protected areas in other countries.

Based on the available evidence, this study aims to (1) conduct a systematic review to understand the health literacy status among rural communities surrounding protected areas; (2) explore stakeholders' perceptions of health literacy status among rural communities surrounding protected areas; (3) determine the health literacy status and its associated factors among rural communities located near protected areas; (4) develop a new health literacy intervention program for rural communities near protected areas; and (5) conduct a cost structure analysis of the new health literacy intervention programs for rural communities surrounding protected areas.

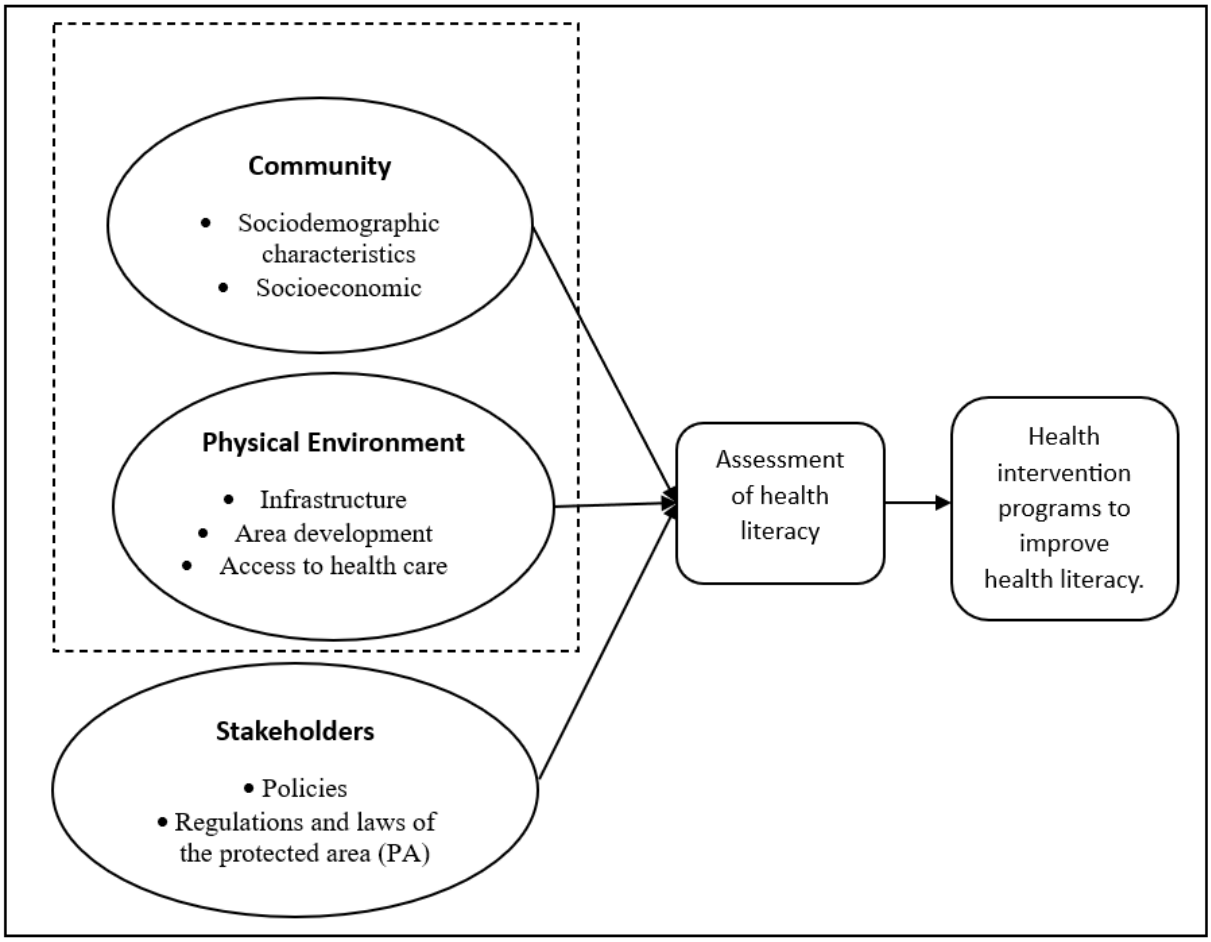
Methods

Background and Conceptual Model

This study adopts a mixed methods approach to investigate health literacy.

Our understanding of health literacy is underpinned by the four core dimensions of the Health Literacy Model [16]: (1) accessing, (2) understanding, (3) appraising, and (4) applying health information. Based on this model, this study will explore the impact of the ecosystem on health literacy among rural communities in protected areas. Figure 1 explains the conceptual model for this study.

Figure 1. Conceptual model of the study.



Study Site

This study comprises one of Malaysia's protected areas, Pahang National Park (PNP). There are 53 national and state parks in Malaysia, with PNP being among the country's most important and best-protected conservation areas. The region has diverse populations, including Malay and indigenous communities. As per the Jabatan Kemajuan Orang Asli (JAKOA; translated to Department of Orang Asli Development) [17], Pahang has the highest number of indigenous communities (37.9%) in Malaysia. Because the PNP site fulfills the criteria for this research (ie, the implementation of a protected area and the presence of legal or other formal mechanisms promoting such an area), we selected it as our study area.

Research Design

This study contains 5 phases consisting of identifying the health literacy issues in this area, confirming the issues, testing the issues, and preventing and analyzing the issues. The 5 phases will be carried out based on the 5 objectives.

Phase 1: Identifying Issues Through a Systematic Review

Overview

In phase 1, we will review the literature to understand the health literacy status among rural communities surrounding protected areas. This phase will involve conducting a systematic review following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

Approach

The systematic review will use a standard search string using the PICO (Population, Intervention, Comparison, and Outcome) structure. For the keyword search, we will use PubMed, Scopus, and Web of Science databases. Later, 2 reviewers will be appointed to appraise all selected studies. The result will compile the highest quality studies relevant to the study objectives.

Eligibility

The selection of results will be based on the following eligibility criteria: (1) full articles written in English and (2) articles published between 2012 and 2022. The exclusion criteria include (1) gray literature and (2) articles outside the scope of our research. The screening process will consider the qualifying requirements established.

Quality Assessment

First, 2 reviewers will conduct a quality assessment using a set of study quality assessments checklist. The checklist consists of eight evaluation criteria: (1) research goals, (2) study design, (3) study outcomes, (4) sample size calculations, (5) analysis of findings, (6) variance estimates for the primary results, (7) adequate reported results, and (8) conclusions. A quality score is one way to incorporate quality into the review process [18]. The reviewers will assign 2 points to articles that meet all

criteria, 1 point if they fulfill some requirements, and 0 points if they do not. Subsequently, the quality score will be calculated by aggregating all elements from the quality assessment tool to provide an overall single score. In case of disagreements, a third reviewer will be appointed.

Data Coding and Analysis

This study employs a thematic synthesis, utilizing a 2-step coding procedure wherein reviewers will code each line of text from the articles separately for its meaning and substance. Before finishing this step, we will analyze every text associated with a particular code to ensure that the interpretation is consistent.

Phase 2: Exploring Stakeholders' Perceptions of Health Literacy Status in Rural Communities Surrounding Protected Areas

Overview

Phase 2 will use focus group discussions (FGDs) and in-depth interviews to achieve objective 2, which is to obtain stakeholders' opinions on health literacy issues among the community in PNP. The results will support the findings for objective 1.

Sample Selection

The selection of the stakeholders will be based on 3 categories, namely, government entities, knowledge-generating institutions, and civil society organizations [19,20]. However, the number of these actors will vary. This method will use purposive sampling to obtain a precise sample size. The expected actors can nominate any other actors with potential contributions to PNP's health literacy issue. This process will be halted when the answers given by the respondents are saturated [21].

Data Coding and Analysis

Data extraction and coding will be done for all Net-Map exercises, with a focus on thematic analysis utilizing information from the interviews. This analysis will mainly involve mapping activities and explaining the impact of protected areas on health literacy. The thematic analysis will follow a 2-step coding process. First, a line-by-line review of the interview data will be conducted to identify the key impacts related to the study objectives. Subsequently, each article will be assigned a code label to cluster all the information into a common theme.

Phase 3: Identifying Health Literacy and Its Associated Factors in Rural Communities Surrounding Protected Areas

Participants and Sampling

This study will focus on the PNP. It covers 2477 square kilometers and was the country's first national park established in Malaysia between 1938 and 1939, originally known as the King George V National Park. Following Malaysia's independence from British rule in 1957, the park was renamed. It is comprised of 3 protected areas in the states of Pahang, Kelantan, and Terengganu to form the central spine of Peninsular Malaysia. The national park has a reputation for being one of the world's oldest tropical rainforests, with an estimated age of 130 million years and a size of 4343 square kilometers.

Local communities in PNP are composed of Malay and Orang Asli (Batek and Semak Beri ethnicities). This location meets the criteria for this study because a protected area has been established and legal and other institutional measures have been established to promote them. The Pahang Department of Wildlife and National Parks (PERHILITAN) manages the PNP. The area is not open to the public except for those who have received prior approval from the authority for research purposes and minimal tourism activity at Kuala Tahan. Currently, the wildlife reserve contains a single research center that serves 2 distinct goals. The national park was originally established at Ulu Tembeling, with the first superintendent's office situated at Kuala Tahan. The southern section of PNP features a river boundary of over 80 kilometers along Sungai Tembeling, the Hulu Tembeling basin's principal river. Indigenous people inhabit the national park, while the Malay community resides near the river. For this study, respondents were drawn from the Malay and indigenous communities from the provinces of Hulu Tembeling and Tembeling Tengah. Table 1 shows the total number of respondents.

Respondents aged 18 years and above may vary in health status, including those with disabilities. A stratified random sampling approach (based on villages) will be employed for both the Hulu Tembeling and Tembeling Tengah provinces. All villages will be identified and visited. The choice of houses in the village will be selected randomly based on the number of houses given by the head of the village (Tok Empat and Tok Batin) and the inclusion criteria among the respondents, such as being able to read, having no cognitive disabilities, and being willing to participate in the survey.

Table 1. The total number of respondents and sample in Pahang National Park (PNP).

Name of village	Race	Province	Head of households (N=2525), n (%)	Sample (N=400), n (%)
Kg Pagi	Malay	Hulu Tembeling	95 (3.8)	15 (3.8)
Kg Kuala Sat	Malay	Hulu Tembeling	142 (5.6)	22 (5.6)
Kg Bantal	Malay	Hulu Tembeling	155 (6.1)	25 (6.1)
Kg Gusai	Malay	Hulu Tembeling	70 (2.8)	11 (2.8)
Kg Bukit Mat Daling	Malay	Hulu Tembeling	141 (5.6)	22 (5.6)
Kg Kuala Tahan	Malay	Tembeling Tengah	657 (26.0)	104 (26.0)
Kg Gol/Lik	Malay	Tembeling Tengah	40 (1.6)	6 (1.6)
Kg Merting/Lubok Payung	Malay	Tembeling Tengah	111 (4.4)	18 (4.4)
Kg Labu/Jong Berlabuh	Malay	Tembeling Tengah	163 (6.5)	26 (6.5)
Kg Pasir Sia/Air Hitam	Malay	Tembeling Tengah	86 (3.4)	14 (3.4)
Kg Selimbar/Chebong	Malay	Tembeling Tengah	58 (2.3)	9 (2.3)
Felda Sg Retang	Malay	Tembeling Tengah	509 (20.2)	81 (20.2)
Kuala Atok	Batek	Tembeling Tengah	35 (1.4)	6 (1.4)
Sungai Tiang	Semoq Beri	Tembeling Tengah	60 (2.4)	10 (2.4)
Sungai Tekal	Semoq Beri	Tembeling Tengah	83 (3.3)	13 (3.3)
Bukit Gam	Batek	Tembeling Tengah	22 (0.9)	3 (0.9)
Sg Keniam	Batek	Tembeling Tengah	35 (1.4)	6 (1.4)
Jeram Aur	Batek	Tembeling Tengah	13 (0.5)	2 (0.5)
Jeram Dedari	Batek	Tembeling Tengah	17 (0.7)	3 (0.7)
Sungai Yong	Batek	Tembeling Tengah	18 (0.7)	3 (0.7)
Sg Tabung/ Teresek	Batek	Tembeling Tengah	15 (0.6)	2 (0.6)

Sample Size

Two approaches will be considered to calculate the optimal sample size (ie, using the odds ratio [OR] and prevalence). The selection will be based on the method producing the higher sample size. For the OR, the sample size will be calculated using the OR of health literacy in Malaysia [22], identified as 3.41 with a 95% CI. We will use the Open Epi Software (version 3.01) to calculate the sample size. With an OR of 3.41, the estimated sample size is 310 as shown in Table 2. Furthermore, Table 3 shows the comparison of sample sizes for exposed and nonexposed groups in Kelsey and Fleiss methods.

In contrast, the second method uses prevalence. In Malaysia, the health literacy prevalence among individuals aged 18 years and above is 35.5% [23]. Using this percentage, the minimum sample size calculated for this study is 323 people for a 95% CI. Since the prevalence sample size is higher than the OR, we decided to use it as our sample size. Considering a dropout probability of approximately 10%, the total sample size needed for this study is about 355 people. However, we will distribute a sample size of 400 people based on the ratio calculated. We estimate that out of 400 adults, approximately 200 households will need to be interviewed based on the assumption that 1 household has 2 adults. To ensure that the provinces within the national park are well represented, the percentage of the selected population is determined to be 24%, 64%, and 12% for Malay in Hulu Tembeling, Tembeling Tengah, and indigenous people, respectively. Using the stratified random sampling techniques, the number of samples allocated for each village is outlined in Table 1.

Table 2. The estimated sample size.

Variables	Values, n
Sample size, n	310
Two-sided significance level (1-alpha)	95
Power (1-beta, % chance of detecting)	80
Ratio of sample size, unexposed/exposed	1
Percent of unexposed with outcome	5
Percent of exposed with outcome	15
Odds ratio	3.4
Risk/prevalence ratio	3
Risk/Prevalence difference	10

Table 3. Comparison of sample sizes for exposed and nonexposed groups in Kelsey and Fleiss methods.

Variables	Kelsey (n=274), n (%)	Fleiss (n=272), n (%)	Fleiss with CC[a] (n=310), n (%)
Sample size, exposed	137 (50)	136 (50)	155 (50)
Sample size, nonexposed	137 (50)	136 (50)	155 (50)

[a]CC: continuity correction.

Inclusion and Exclusion Criteria

Participants in this study are required to be adults aged 18 or above and will be recruited after providing consent. Age verification will be based on their ID cards. Potential respondents may either be healthy or have various physical disabilities and demonstrate a willingness to participate. Additionally, they must be able to communicate in the Malay language. However, people with cognitive impairments will be excluded from the study.

Tools and Instruments

This study will comprise 3 evaluations: health literacy, health, and socioeconomic status. There are 8 parts to the questionnaire, which are outlined in Table 4.

Table 4. Components of the questionnaire.

Component	Description
Part 1: Housing and the environment (head of household only)	Part 1 will capture family structure, household transportation, and water supply.
Part 2: Household income (head of household only)	Part 2 will record the household's annual income from all sources.
Part 3: Sociodemographic characteristics (all household members, including the head of household)	Part 3 will capture sociodemographic information such as date of birth, ethnicity, education, employment status, relationship status, and so on.
Part 4: Health care expenditure and utilization (all household members, including the head of household)	Part 4 questions will capture data on health payments, health care service utilization, traditional and complementary medicine practice, and health care expenditure.
Part 5: Modifiable lifestyle factors (all household members, including the head of household)	Part 5 will ask about tobacco consumption, nutrition, physical activity, and medical conditions.
Part 6: Medical information (all household members, including the head of household)	Part 6 will measure the height, weight, waist circumference, and hip circumference. The calibrated vertical SECA portable 217 stadiometer (SECA GmBH & Co KG) will be used to measure respondents' height, the calibrated SECA 813 digital electronic weighing scale will measure weight, and the SECA 201 ergonomic measuring tape will measure waist (abdominal) and hip circumferences.
Part 7: Quality of life (all household members, including the head of household)	Questions in part 7 will assess the participant's quality of life using standard and generic methods.
Part 8: Health literacy status	Health literacy status will be determined using the HLS-SF-Q12[a] [24]. The perceived difficulty of each health-related task is rated on a 4-point Likert scale (1=*very difficult*, 2=*difficult*, 3=*easy*, and 4=*very easy*), with a possible lowest mean score of 1 and a possible highest mean score of 4. The questions consider the 4 competencies of an individual when dealing with health-relevant information (access/obtain, understand, appraise/judge/evaluate, and apply/use health information) to form a judgment and make health-related decisions for the 3 domains of health care, disease prevention, and health promotion.

[a]HLS-SF-Q12: 12-item Short-Form Health Literacy Questionnaire.

Reliability, Validity, and Trustworthiness

Reliability indicates whether the results can be consistently reproduced or not. In this study, internal consistency is evaluated through the Cronbach α value, with a threshold set at greater than or equal to .70 for satisfactory reliability. At the same time, validity will measure the validity and accuracy of the questionnaire. Face and content validity will be used to measure the validity of the questionnaire. Notably, this study incorporates established questionnaires with preestablished reliability and validity from different sources [22,25].

Data Collection Procedure

A total of 8 interviewers will be required to conduct the survey, working in pairs. For security and dialect reasons, a local representative will be appointed to accompany each team. Before the data collection, the ground staff will introduce the interviewers to the household members to ensure that the head of the household and other members are present and grant permission for the interviewers to enter their personal premises. Once approval is obtained, the interviewer will explain the nature of the study based on the participants' information sheet, which outlines the key details. Subsequently, the information sheet will be provided to the participants for their reference. In addition, the interviewers will reassure the participants that the information provided in the study will remain confidential and their participation is entirely voluntary. The face-to-face interview will begin shortly after the head of the household and other household members have signed the consent form. During the interview, the respondents' height and weight will be measured, contingent on suitability and participant preference. If the head of the household is absent during the visit, the house will be marked on the map, and a second visit will be arranged for the next day. However, the house will be excluded if the head of the household is still not present during the second visit.

Data Analysis Procedure

The data analysis procedure will involve both descriptive and analytical analyses. Initially, a descriptive analysis will focus on the sociodemographic characteristics of the study population. We will examine the distribution of study variables by calculating frequency and percentage, along with reporting mean and SD. Since the outcome of interest is categorical, nonparametric tests will be used. Following the approach outlined in [26], responses categorized as inadequate and problematic will be grouped as inadequate (0), while those categorized as sufficient and excellent will be classified as adequate (1) during the analysis.

For the analytical analysis, we will carry out both bivariate and multivariate analyses to explore the determinants of health literacy among both the study population residing whining the

PNP and the population living outside the PNP. This comparative approach will aim to determine which ecosystem has adequate health literacy. The significance level has been set to $P<.05$. The analytical analysis will be conducted using SPSS software (version 28.0, IBM Corp).

Phase 4: Developing a New Health Literacy Intervention Program for Rural Communities in the Protected Area

Overview

Phase 4 will be conducted via FGD discussion among the stakeholders.

Data Collection Procedure

The data collection process will be based on the opinions of the stakeholders and field experts. We will invite them to the seminar and sharing session to discuss the sustainability of the community near PNP. An invitation letter will be sent to the stakeholders and experts to confirm their willingness to participate in the discussion. They will include representatives from the Ministry of Health, JAKOA, Department of Wildlife and National Parks, heads of villages (Tok Empat and Tok Batin), nongovernmental agencies (NGOs), and academicians who are Taman Negara community health experts. During the seminar and sharing session, they will discuss mitigation measures that are suitable and effective in enhancing the health literacy status of the rural community.

Eligibility

The eligibility criteria for the intervention programs will be based on several factors, including the capacity of these programs, the financial support they received, their geographical location, prior experience in conducting health literacy programs, and willingness to participate. To account for differences in intervention activities, epidemiology, and target populations, we will limit our selection to only interventions that target communities located within the protected areas.

Data Analysis Procedure

During the discussion session, stakeholders will provide information regarding suitable intervention programs to improve health literacy at PNP using Logical Framework Analysis (LFA). The core components of LFA are outlined in Table 5.

Table 5. The core components of Logical Framework Analysis (LFA).

Component	Description
General objectives (goal)	This is the project's overarching goal. The project's benefits are laid forth in the objective goal for the beneficiaries.
Project purpose	The target group's plan of action to effect the desired change is expressed in the purpose. The project purpose frequently refers to modifying the target group's behavior because they use the services or goods the project offers.
Output	The project offers the products, services, and goods to the intended audience. The project is accountable for these outputs.
Activities	The project's processes for delivering the various goods, services, and products are outlined.

Phase 5: Conducting a Cost Structure Analysis of the New Health Literacy Intervention Programs for Rural Communities Surrounding the Protected Area

Overview

Phase 5 is a continuation of Phase 4. We will conduct a cost analysis for every intervention program listed in Phase 4.

Data Collection Procedure

The cost structure will be prepared based on advice from experienced agencies or individuals in the field. A list of intervention activities will be presented as an alternative to the policy makers or any agencies who are interested in improving health literacy among the PNP community.

Economic data on providers' costs will be collected for the financial year 2021 to 2022. The data obtained will contain information on the costs incurred at the intervention and funding agency levels. When valuing economic costs, the opportunity cost of each resource will be considered, encompassing all resources used in the intervention, including those that are donated or subsidized. This approach ensures a uniform method of data collection, enabling reliable cost comparisons among the various interventions.

Data Analysis Procedure

The cost analysis will analyze expenses based on the cost unit, source data, and frequency, with comparisons made across the intervention programs. The cost unit pertains to the expenses associated with each intervention per patient per year. Simultaneously, the sources of data serve as evidence for the interventions, and frequency refers to the number of interventions required annually.

Data Management and Analysis

Data Security

At the end of each day of data collection, the project manager will gather all interviewers and conduct a postmortem session. Any loopholes identified during the process will be addressed immediately to avoid further mistakes and invalidate the collected data. In addition, the project manager will verify if the number of answer booklets corresponds with the number of households surveyed. Upon verification, the answer booklets will be placed in a safe box, while the consent form will be kept in a separate secure box to avoid any information breach. Only the project manager and the principal investigator have access to these secured boxes. Similarly, all recorded videos and voices from FGD and interviews will be safely placed in a Dropbox (Evenflow Inc) for analysis.

Data Entry and Analysis

Data entry from the survey form will be completed within 2 to 4 weeks after completing the groundwork, depending on the number of respondents. Once all data have been entered into SPSS software, we will perform a random cross-checking of the data set to maintain data accuracy. The cross-checking will be set at 20% of the overall questionnaires entered [25]. Data analysis will comprise both descriptive and analytical analyses. Descriptive analysis will be performed on the population's sociodemographic characteristics, BMI measurements, expenditure, utilization of health care goods and services, modifiable lifestyle factors, and reported quality of life. The analytical examination will be conducted to determine the association between sociodemographic characteristics, health status, and socioeconomic status with health literacy status. The results will be analyzed using SPSS software. The data and results will be presented to and validated by field experts and stakeholders of PNP in the form of reports and seminar-sharing sessions.

Ethical Considerations

Ethics approval for this study was granted by the Universiti Sains Islam Malaysia (USIM) Research Ethics Committee (USIM/JKEP/2022-216). Each respondent will sign a written informed consent form before the interview. Academic journals, conferences, and stakeholder seminars will be used to communicate the findings of this research. The protocol received approval from the International Standard Randomized Controlled Trial Number Registry (ISRCTN; 40626062).

Results

The project was funded by USIMl and strategic research partnership grants. Enrollment for the overall project is ongoing. We are conducting a systematic review of health literacy in protected areas and conducting a cross-sectional study based on the survey results to determine the determinants of health literacy in protected areas. Findings from this study will be used to develop a sustainable health intervention module with an effective cost that may be adopted in all protected areas in Malaysia. The first results are expected to be submitted for publication in 2024.

Discussion

Anticipated Findings

The conservation policy of the protected areas has limited opportunities for local communities to harvest natural resources from the ecosystem. Their quality of life has been affected due to inferior education, health, and living conditions compared to communities living in urban areas. This disparity has resulted in challenges for the community in accessing health facilities and infrastructure, thereby limiting their health literacy level. Their remote location and distance from main roads have contributed to this low health literacy. To our knowledge, few studies have been conducted on health literacy and health issues among individuals in protected areas from 4 perspectives: government entities, knowledge institutions, civil agencies, and local communities. Accordingly, this paper proposes a study to investigate the health literacy and health status of communities within and near PNP. In accordance with the recommendations made by the PNP shareholders, this study aims to develop a health intervention program that is efficient and appropriate for community implementation. Health literacy research among people living in protected areas is essential for a deeper understanding of their needs for access to health care, illness prevention, health promotion, and health care. This understanding will guide the development of effective strategies to meet these requirements.

Strengths and Limitations

This study’s strength lies in its mixed methods analysis, employing a triangulation process to converge and validate both qualitative and quantitative data [27]. Moreover, this study will be conducted in multiple phases to discuss the issue comprehensively. This structured approach facilitates incremental progress [28]. Phases 1 and 2 are conceptual phases where the issue is identified and validated through a systematic review by stakeholders in PNP, such as government agencies, knowledge institutions, and civil society organizations. Phase 3 will design and plan the questionnaire and examine the health literacy status and its influencing factors among the community. The stakeholders in the FGD in phase 4 will validate the results of phases 1 to 3. Using these results, the stakeholders will discuss and design an effective health literacy intervention program. Finally, phase 5 will involve the dissemination of the health literacy intervention program to improve the health literacy status in the community. Moreover, a cost analysis will be calculated to analyze the cost of the program.

The study’s limitations became apparent during the FGD session with the stakeholders, as the invited participants did not attend. Consequently, we missed capturing unique macro-level perspectives. Another limitation is that the stakeholders’ views may not be representative of all who live inside or near the protected area in Malaysia or globally. Additionally, the study did not address the distinctions between locals and outsiders. Access to rural areas is difficult logistically, and the potential presence of wildlife, such as tigers, elephants, and bears, further complicates the research process.

Conclusions

In conclusion, this study will determine how different ecosystems, especially in protected areas, impact the health literacy of the local community using a mixed methods approach. The phases of the data collection process, incorporating both qualitative and quantitative methods, aim to comprehensively address the issue of health literacy in the local community. We will use these findings to disseminate a health intervention program, along with a cost structure, to improve health literacy among the protected area's community. The mixed methods study serves as a structured investigative model for evaluating and improving health literacy, health status, and well-being among all protected areas and communities worldwide.

Acknowledgments

This research is funded by an institutional grant from the Universiti Sains Islam Malaysia (USIM; PPI/FPSK/0122/USIM/13722), as well as a strategic research partnership grant USIM/MG/UiTM/FPSK/SEPADAN-K/73622).

We are highly grateful to students of Universiti Teknologi MARA (UiTM) Cawangan Pahang Kampus Raub for their commitment to being part of this project for the data collection, the Jabatan Kemajuan Orang Asli (JAKOA) Jerantut for serving as a mediator between the researchers and the indigenous people, and the communities of the Pahang National Park (PNP).

Data Availability

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

Authors' Contributions

The conceptualization of the project was led by AA, MHJ, and MIMN. The data collection was led by NAAK, and the development of the questionnaire was a collaborative effort involving NAAK, AA, MHJ, and MIMN. Supervision was provided by AA, MHJ, MIMN, and ZK. NAAK wrote the original draft, which was then reviewed by AA and MIMN.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review reports from the Universiti Sains Islam Malaysia (USIM).
[PDF File (Adobe PDF File), 520 KB - resprot_v13i1e51851_app1.pdf]

References

1. Levin-Zamir D, Leung AYM, Dodson S, Rowlands G. Health literacy in selected populations: Individuals, families, and communities from the international and cultural perspective. Inf Serv Use 2017 Jun 26;37(2):131-151. [doi: 10.3233/isu-170834]
2. Jandorf S, Krogh Nielsen M, Sørensen K, Sørensen TL. Low health literacy levels in patients with chronic retinal disease. BMC Ophthalmol 2019 Aug 08;19(1):174 [FREE Full text] [doi: 10.1186/s12886-019-1191-1] [Medline: 31395040]
3. Schillinger D. The intersections between social determinants of health, health literacy, and health disparities. Stud Health Technol Inform 2020 Jun 25;269:22-41 [FREE Full text] [doi: 10.3233/SHTI200020] [Medline: 32593981]
4. Samerski S. Health literacy as a social practice: Social and empirical dimensions of knowledge on health and healthcare. Soc Sci Med 2019 Apr;226:1-8. [doi: 10.1016/j.socscimed.2019.02.024] [Medline: 30831555]
5. Vamos S, Okan O, Sentell T, Rootman I. Making a case for "education for health literacy": an international perspective. Int J Environ Res Public Health 2020 Feb 24;17(4):1436 [FREE Full text] [doi: 10.3390/ijerph17041436] [Medline: 32102271]
6. Kruk ME, Gage AD, Arsenault C, Jordan K, Leslie HH, Roder-DeWan S, et al. High-quality health systems in the Sustainable Development Goals era: time for a revolution. Lancet Glob Health 2018 Nov;6(11):e1196-e1252 [FREE Full text] [doi: 10.1016/S2214-109X(18)30386-3] [Medline: 30196093]
7. Health promotion. World Health Organization. URL: https://www.who.int/teams/health-promotion/enhanced-wellbeing/ninth-global-conference/health-literacy [accessed 2024-01-22]
8. Mali: Health literacy and people with diabetes in low-resource settings. World Health Organization. URL: https://apps.who.int/iris/bitstream/handle/10665/364206/9789240055391-eng.pdf?sequence=1 [accessed 2024-01-22]
9. Jiricka-Pürrer A, Tadini V, Salak B, Taczanowska K, Tucki A, Senes G. Do protected areas contribute to health and well-being? A cross-cultural comparison. Int J Environ Res Public Health 2019 Apr 01;16(7):1172 [FREE Full text] [doi: 10.3390/ijerph16071172] [Medline: 30939833]
10. Qin S, Golden Kroner RE, Cook C, Tesfaw AT, Braybrook R, Rodriguez CM, et al. Protected area downgrading, downsizing, and degazettement as a threat to iconic protected areas. Conserv Biol 2019 Dec 17;33(6):1275-1285 [FREE Full text] [doi: 10.1111/cobi.13365] [Medline: 31192510]
11. Schulze K, Knights K, Coad L, Geldmann J, Leverington F, Eassom A, et al. An assessment of threats to terrestrial protected areas. Conserv Lett 2018 Jan 15;11(3). [doi: 10.1111/conl.12435]
12. Alemohammad S, Yavari A, Malek-Mohammadi B, Salehi E, Amiri M. Landscape conservation and protected areas (case of Dena, Iran). Environ Monit Assess 2022 Jan 05;194(2):54. [doi: 10.1007/s10661-021-09696-6] [Medline: 34988699]
13. Salim H, Young I, Lee PY, Shariff-Ghazali S, Pinnock H, RESPIRE collaboration. Insights into how Malaysian adults with limited health literacy self-manage and live with asthma: A Photovoice qualitative study. Health Expect 2022 Feb 12;25(1):163-176 [FREE Full text] [doi: 10.1111/hex.13360] [Medline: 34514689]

14. Ghani EK, Muhammad K, Hassan R. Understanding the influence of remoteness on culture and socio-economic of the Orang Asli in Malaysia. PalArch's J Archaeol 2020;17(2):366-376 [FREE Full text]
15. Lanzas M, Hermoso V, de-Miguel S, Bota G, Brotons L. Designing a network of green infrastructure to enhance the conservation value of protected areas and maintain ecosystem services. Sci Total Environ 2019 Feb 15;651(Pt 1):541-550. [doi: 10.1016/j.scitotenv.2018.09.164] [Medline: 30245410]
16. Sørensen K, Van DBS, Fullam J, Doyle G, Pelikan J, Slonska Z, et al. Health literacy and public health: a systematic review and integration of definitions and models. BMC Public Health 2012;12:80 [FREE Full text] [doi: 10.1186/1471-2458-12-80] [Medline: 22276600]
17. Data terbuka sektor awam. Department of Orang Asli Development (JAKOA). URL: https://www.jakoa.gov.my [accessed 2023-11-12]
18. Cox LA. Modernizing the Bradford Hill criteria for assessing causal relationships in observational data. Crit Rev Toxicol 2018 Sep 15;48(8):682-712. [doi: 10.1080/10408444.2018.1518404] [Medline: 30433840]
19. Bhagavan M, Virgin I. Generic aspects of institutional capacity development in developing countries. World Health Organization. 2004. URL: http://tinyurl.com/5n99u9b7 [accessed 2024-01-22]
20. Desalegn A, Solomon N. The impacts of institutional capacity, infrastructure governance, and equity on state-and-nation-building processes in Ethiopia. Manag Theory Stud Ru 2021;43(4):484-499 [FREE Full text] [doi: 10.15544/mts.2021.44]
21. Weller SC, Vickers B, Bernard HR, Blackburn AM, Borgatti S, Gravlee CC, et al. Open-ended interview questions and saturation. PLoS One 2018;13(6):e0198606. [doi: 10.1371/journal.pone.0198606] [Medline: 29924873]
22. Duong TV, Aringazina A, Kayupova G, Nurjanah, Pham TV, Pham KM, et al. Development and validation of a new Short-Form Health Literacy Instrument (HLS-SF12) for the general public in six Asian countries. Health Lit Res Pract 2019 Apr;3(2):e91-e102 [FREE Full text] [doi: 10.3928/24748307-20190225-01] [Medline: 31294310]
23. Jaafar N, Perialathan K, Krishnan M, Juatan N, Ahmad M, Mien TYS, et al. Malaysian health literacy: scorecard performance from a national survey. IJERPH 2021 May 28;18(11):5813. [doi: 10.3390/ijerph18115813]
24. Duong TV, Nguyen TTP, Pham KM, Nguyen KT, Giap MH, Tran TDX, et al. Validation of the Short-Form Health Literacy Questionnaire (HLS-SF12) and its determinants among people living in rural areas in Vietnam. Int J Environ Res Public Health 2019 Sep 11;16(18):3346 [FREE Full text] [doi: 10.3390/ijerph16183346] [Medline: 31514271]
25. Dahlui M, Azzeri A, Zain MA, Mohd Noor MI, Jaafar H, Then AYH, et al. Health status, healthcare utilisation, and quality of life among the coastal communities in Sabah: Protocol of a population-based survey. Medicine (Baltimore) 2020 Sep 11;99(37):e22067 [FREE Full text] [doi: 10.1097/MD.0000000000022067] [Medline: 32925742]
26. Sørensen K, Pelikan JM, Röthlin F, Ganahl K, Slonska Z, Doyle G, et al. Health literacy in Europe: comparative results of the European Health Literacy Survey (HLS-EU). Eur J Public Health 2015 Dec;25(6):1053-1058 [FREE Full text] [doi: 10.1093/eurpub/ckv043] [Medline: 25843827]
27. Wasti SP, Simkhada P, van Teijlingen E, Sathian B, Banerjee I. The growing importance of mixed-methods research in health. Nepal J Epidemiol 2022 Mar 31;12(1):1175-1178 [FREE Full text] [doi: 10.3126/nje.v12i1.43633] [Medline: 35528457]
28. Smith S, Mörelius E. Principle-based concept analysis methodology using a phased approach with quality criteria. Int J Qual Methods 2021 Nov 23;20:160940692110579. [doi: 10.1177/16094069211057995]

Abbreviations

FGD: focus group discussion
ISRCTN: International Standard Randomized Controlled Trial Number Registry
JAKOA: Jabatan Kemajuan Orang Asli
LFA: Logical Framework Analysis
NGO: nongovernmental agency
OR: odds ratio
PERHILITAN: Pahang Department of Wildlife and National Parks
PICO: Population, Intervention, Comparison, and Outcome
PNP: Pahang National Park
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
USIM: Universiti Sains Islam Malaysia

Edited by A Mavragani; submitted 15.08.23; this is a non–peer-reviewed article;accepted 19.08.23; published 29.01.24.

Please cite as:
Abd Kadir NA, Azzeri A, Jaafar H, Mohd Noor MI, Kefeli Z
The Impact of the Ecosystem on Health Literacy Among Rural Communities in Protected Areas: Protocol for a Mixed Methods Study
JMIR Res Protoc 2024;13:e51851
URL: https://www.researchprotocols.org/2024/1/e51851
doi:10.2196/51851
PMID:38285500

Proposal

Meaningful Social Inclusion and Mental Well-Being Among Autistic Adolescents and Emerging Adults: Protocol for a Community-Based Mixed Methods Study

Darcy Jones McMaughan[1], PhD; Casey Lewis[1], MS; Amy McGehee[1], MS; Dani Noreen[2], BS; Elliot Parker[1], BA; Michael M Criss[1], PhD

[1]Human Development and Family Science, Oklahoma State University, Stillwater, OK, United States
[2]Neurodiversity Unbound, Aurora, CO, United States

Corresponding Author:
Casey Lewis, MS
Human Development and Family Science
Oklahoma State University
Stillwater, OK
United States
Phone: 1 1 405 385 9754
Email: clewi28@okstate.edu

Abstract

Background: In the United States, autistic people face high rates of co-occurring mental illnesses and premature death due to self-harm, which are indicators of threats to mental well-being. Social inclusion may enhance mental well-being and resilience among autistic people. According to Simplican and colleague's (2015) model of social inclusion for people with intellectual and developmental disabilities, social inclusion is an interaction between community participation and interpersonal relationships. There is limited research on social inclusion that includes the integration of interpersonal relationships and community participation among autistic people or the impact of social inclusion on the well-being of autistic people. Additionally, little evidence exists regarding how autistic people prefer to be included in the community or form interpersonal relationships.

Objective: The long-term objective of this project is to improve social inclusion factors to support the mental well-being of autistic people. This protocol describes a community-based, mixed methods pilot study to develop a definition of meaningful social inclusion for autistic people and to understand the relationship between meaningful social inclusion and mental well-being among autistic adolescents and emerging adults.

Methods: The project uses a community-based, sequential mixed methods design with a formative phase (Phase 1) that informs a survey phase (Phase 2) and concludes with a process evaluation of the community engagement process (Phase 3). During Phase 1, we will recruit 10 community partners (autistic adults and stakeholders) and conduct sharing sessions to cocreate a definition of meaningful social inclusion and a survey of meaningful social inclusion and well-being. During Phase 2, we will recruit 200 participants (100 autistic adolescents and emerging adults and 100 caregivers) to complete the survey. We will examine whether meaningful social inclusion predicts well-being given sociodemographic factors using ordered logistic regression, with well-being categorized as low, medium, and high. During Phase 3, the community partners from Phase 1 will complete a survey on their experiences with the project.

Results: Ethics approval was obtained for this project in March 2023. We have recruited community partners and started the Phase 1 focus groups as of September 2023. Phase 2 and Phase 3 have not yet started. We expect to complete this study by March 2025.

Conclusions: Using a community-based, mixed methods approach, we intended to develop a definition of meaningful social inclusion for autistic people and understand the role meaningful social inclusion plays in the well-being of autistic people.

International Registered Report Identifier (IRRID): PRR1-10.2196/52658

(JMIR Res Protoc 2024;13:e52658) doi:10.2196/52658

KEYWORDS

autism; community-based; mixed methods; social inclusion; well-being

Introduction

Overview

Mental well-being is a holistic conceptualization of mental health characterized by a lack of symptoms of mental conditions and the presence of positive feelings [1]. Compared to nonautistic people, autistic people often experience poor mental well-being [2], reduced quality of life [3], higher rates of suicidality and premature death due to suicide [4-6], and greater rates of mental health conditions [7-9]. Worldwide, across decades, and across age groups, autistic people have a twofold increase in mental health issues compared to people without autism. For example, rates of mental health issues among the general population in the United States hit an all-time high during the COVID-19 pandemic, with an estimated 40% reporting mental health challenges [10], while rates of co-occurring mental health issues among autistic adolescents and emerging adults during a "typical" time period are as high as 82% [11]. The total size of the autistic population is unknown due to women, gender-diverse people, and people of color being historically underdiagnosed and adult-diagnosed autistic people not being captured in prevalence rates. Even so, current estimates suggest that 1 in 44 children in the United States are diagnosed with autism [12]. The impact of poor mental well-being among autistic people impacts a substantial proportion of the US youth population. The burden of poor mental well-being in the autistic community increases with age [13,14] and shortens life expectancy [5].

A complex interplay of internal and external factors may explain disparities in mental well-being between autistic people and nonautistic people. While endogenous factors such as genetics and neurology play a role, systemic, compounding stressors exogenous to the autistic person can also influence mental well-being. These modifiable, external factors include experiences such as being bullied, masking, and feeling accepted. Autistic people experience higher rates of bullying compared to nonautistic people, and these experiences are linked to a greater risk of mental health issues [15]. Masking (also known as camouflaging) describes the efforts of autistic people to hide autistic traits and avoid negative experiences such as bullying. Similar to bullying, masking is also associated with poorer mental well-being [16-19]. Conversely, when autistic people feel accepted, they report better mental well-being. Higher levels of acceptance by nonautistic people are associated with lower levels of mental distress [20]. Contrary to stereotypes of autistic people, research confirms that interpersonal relationships are important to the autistic well-being [20], and higher levels of community participation are associated with better mental well-being [21,22].

However, current research suggests that autistic people face individual-level social inclusion barriers [20,23] and are less likely to participate in the community [24] or form interpersonal relationships [25] compared to nonautistic people. Additionally, this literature primarily focuses on how autistic people should change to adapt to communities and other people, rather than on how communities and other people could adapt to include autistic people [26]. Because they do not center on the experiences of autistic people, many of these studies focus on independence rather than autonomy and conformity to neurotypical standards as criteria for social inclusion and enforced normalization. Given the historic emphasis on children [7], it is imperative to focus on the mental well-being of autistic adolescents and emerging adults. Social inclusion may hold the key to implementing sweeping changes to improve mental well-being for autistic adolescents and emerging adults [23,27], particularly as identification with social groups is associated with higher levels of mental well-being among autistic people [1]. Social inclusion and mental well-being are research priorities for the autistic community [28], as is shifting the focus from "fixing" the individual to addressing systemic issues external to the autistic person [29].

To the best of our knowledge, no study has integrated both aspects of social inclusion, included the voices of autistic people, and focused on mental well-being. These 2 relationship contexts (interpersonal relationships and community participation) are instrumental in promoting adaptive mental and physical health among autistic people. Interpersonal relationships are important to the well-being of autistic people [20], and higher levels of community participation are associated with better mental well-being [21,22]. This project fills a critical need to develop an understanding of meaningful social inclusion that includes both interpersonal relationships and community participation for autistic people and use this to understand the impact of social inclusion on mental well-being. Without an understanding of how social inclusion factors shape mental well-being, we cannot identify and implement effective and efficient community-level change to improve the well-being and quality of life of autistic people. In the absence of this knowledge, rates of co-occurring mental health conditions, the resulting diminished quality of life, and premature deaths will remain high. Filling this gap with this study is critical, as this information is necessary for policy and planning to improve mental health parity among autistic people.

Conceptual Framework

There is no agreed-upon conceptual framework for social inclusion. However, the ecological model of social inclusion for people with intellectual and developmental disabilities by Simplican and colleagues [30] provides a road map for understanding, measuring, and modifying social inclusion. According to this model, social inclusion is defined as the interaction of interpersonal relationships (family, staff, friends, acquaintances, and partners) and community participation (leisure activities, political and civic activities, employment and education, access to goods and services, and religious and cultural activities).

Study Aims

The long-term objective of this project is to improve social inclusion factors to support the mental well-being of people with autism. Our goal is to address the problem of high rates of poor mental well-being by understanding how social inclusion is associated with this phenomenon. We focus on adolescence and emerging adulthood because this is a key developmental period for autistic people and a challenging time for mental well-being [31,32]. We will meet our goal through two specific

aims: Aim 1: develop a working definition of meaningful social inclusion for autistic people living in the community that is cocreated with the autistic community; and Aim 2: delineate variation in mental well-being by social inclusion (interpersonal relationships and community participation) among autistic adolescents and emerging adults. Our hypothesis is that higher levels of social inclusion will be associated with higher rates of mental well-being.

Methods

All protocols and materials will follow the Academic Autism Spectrum Partnership in Research and Education practice-based guidelines for research coproduced with autistic people [33].

Study Design

Overview

The project uses a community-based, sequential mixed methods design with a primary formative phase that will inform a subsequent secondary survey phase [34] and a tertiary phase that consists of a process evaluation of the community engagement process. This design has been used successfully to capture community member experiences and influence policy changes [35]. In Phase 1, we will conduct sharing sessions with members of the autistic community to cocreate (1) a working definition of meaningful social inclusion and (2) an adaptation of a survey of social inclusion and well-being. In Phase 2, we will deploy the cocreated survey in the autistic community to gather data on their level of social inclusion and mental well-being. In Phase 3, we will evaluate the research processes. Findings from each phase will be integrated using triangulation with the autistic community. We will consider where findings from each part agree (convergence), result in complementary information (complementarity), or disagree (discrepancy).

Phase 1: Formative Research

Sharing sessions will be held virtually through Zoom (Zoom Video Communications), recorded, and transcribed for analysis. Sharing sessions will be facilitated through a series of open-ended questions developed to capture the lived experiences of meaningful social inclusion of autistic community members. Community members participating in the sharing sessions will be provided with informed consent, a 1-page description of the study, the open-ended questions, the draft survey, and the background of the research team. Multiple meetings will be scheduled to (1) develop an understanding of meaningful social inclusion, (2) select and refine survey items, (3) review analysis results, and (4) determine the best ways to disseminate the results that align with the community's agenda. Over the course of the project, the timing, number, and format of the meetings will be negotiated with community partners [36].

Phase 2: Adapted Survey of Social Inclusion and Mental Well-Being

This aspect of the project follows a cross-sectional survey design in which data are captured at a single point in time. Autistic adults living in the community will report on social inclusion and mental well-being using adaptations of existing survey instruments created with community members during the sharing sessions. Data will be gathered through an anonymous web-based questionnaire hosted through the Qualtrics (Silver Lake) platform.

Phase 3: Process Evaluation

Satisfaction with community engagement will be measured by asking community partners at the end of the study to report on their experiences with the community engagement process.

Measures

Overview

Our main variables of interest are meaningful social inclusion and mental well-being. We will measure the identity of autistic people and address potentially confounding variables through sociodemographic variables associated with social inclusion and mental well-being. Whenever possible, short-form versions of instruments will be used to reduce the burden on participants. Items will also be adapted for completion by caregivers reporting on autistic adolescents and emerging adults in their care. Caregivers will be asked if the autistic adolescents and emerging adults in their care also completed the survey to create a subgroup of caregivers providing proxy responses and caregivers providing additional responses.

Identity of Autistic People

The identity of autistic people will be measured using current guidelines for establishing rigor to generalize to autistic people [37], through self-identification, age at diagnosis, diagnosis status (self vs community), and the Ritvo Autism Asperger Diagnostic Scale-14 [38]. This measure will be used for autistic people who will complete the survey. Caregivers will be asked if they care for an autistic adolescent or emerging adult, whether the autistic adolescent or emerging adult was professionally diagnosed, the current age of the person they provide care for, and the age the person was diagnosed.

Social Inclusion

Social inclusion will be assessed using adaptations of the Temple University Community Participation (TUCP) measure [39] for community participation and the Friendship Questionnaire (FQ) for interpersonal relationships [40]. The TUCP contains 26 items that measure independent and self-directed community participation over the last 30 days in the following domains: community activities, employment, education, and volunteering. The TUCP asks (1) for the number of days in the past 30 days that the person engaged in a community activity (0-30); (2) if the activity is important to the person (1=yes or 0=no); and (3) if the activity was done enough, not enough, or too much (−1=not enough, 0=enough, or 1=too much). Although initially created for use with people with complex and chronic mental health conditions, the TUCP has been used to assess community participation among autistic adults [24,41,42].

The FQ contains 35 items that measure multiple aspects of interpersonal relationships, such as having best friends ("I have one or two particular best friends") and the characteristics of friends ("In terms of interests, how similar to your friends do you tend to be?"). The FQ was designed for use with nonautistic and autistic adults [40].

Mental Well-Being

Mental well-being will be captured through the Warwick-Edinburgh Mental Well-being Scale (WEMWBS) [43] and the Depression Anxiety Stress Scales-21 (DASS-21) [44]. The WEMWBS is a 14-item questionnaire measuring positive mental well-being through positive emotions, positive mental health, and psychological functioning. Each item is a positively worded statement (eg, "I've been feeling good about myself") with a 5-point Likert-type scale (1=none of the time to 5=all the time) indicating how often the statement applied to the person over the past 2 weeks. An overall score is calculated by totaling the scores for each item. Higher scores indicate higher levels of mental well-being. The WEMWBS has good content and construct validity, face validity, cross-cultural validity, test-retest reliability (intraclass correlation =.83), and internal consistency, with Cronbach α ranging from 0.89 to 0.93 [43,45]. The WEMWBS has been extensively used to measure mental well-being among autistic adults [1,46]. The DASS-21 contains 3 self-report scales measuring depression, anxiety, and stress. The DASS-21 has been found to function well as a measure of psychological distress among autistic people [47].

Sociodemographic Variables

Sociodemographic variables will include age, gender, race and ethnicity, rurality, income, education, employment status, co-occurring conditions, level of support need, and social functioning using the Social Functioning Questionnaire [48]. Gender, education, race and ethnicity, and co-occurring conditions are items derived from the National Survey on Health and Disability. Gender will include options for gender-diverse people. Employment status is based on items used in the 2021 Behavioral Risk Factor Surveillance System. Participants will be asked to estimate their household income and will be presented with multiple-choice income options. The level of support needed will be determined using items representing assistance needed for activities of daily living and instrumental activities of daily living.

Rurality will be identified using the self-reported residence zip code of the participant's permanent residence and categorized based on Rural-Urban Commuter Area (RUCA) codes. RUCA codes classify US census tracts on a continuum of rural to urban categories using patterns of daily commuting, population density, and measures of urbanization. Whether a participant originated from a rural community will be determined based on residence in a zip code associated with large rural, small rural, or isolated RUCA codes.

Satisfaction With Community Engagement

Satisfaction with community engagement will be measured by asking community partners who participated in the sharing sessions to complete a Community Engagement Questionnaire [36] describing their experiences with the project: (1) What has been your experience with participating in this research study? (2) How satisfied were you with your contribution to this research study? (3) How could your experience be improved? and (4) Is there anything else you would like to add?

Study Participants and Recruitment

Participants will be recruited on the web through groups such as the Autism Foundation of Oklahoma, Autistic Adults of Oklahoma, AutismStillwater's website, AutismOKC's website, tribal organizations, and state department health services caseworkers. Our community partners will leverage their community contacts in each of these groups for the recruitment of participants for the study.

The intended participants for Phase 1 are autistic adults and caregivers of autistic young people. The participants will be older than 18 years and reside in Oklahoma. For Phase 2, the intended participants are (1) autistic adolescents (aged between 10 and 18 years) and emerging adults (aged between 19 and 25 years) residing in Oklahoma, fluent in English, who have a community diagnosis of autism or meet the Ritvo Autism Asperger Diagnostic Scale-14 cutoff for autism and (2) caregivers of autistic adolescents and emerging adults. Phase 3 participants are the same participants from Phase 1. Exclusion criteria include communication impairment and an inability to consent.

For Phase 1 and Phase 3, we will recruit up to 10 autistic community partners to participate in the sharing sessions, and each partner will be paid US $400 for their participation. For Phase 2, we will recruit 100 autistic adolescents and emerging adults living in the community and 100 caregivers to complete the adapted survey. The most recent electronic survey deployed by the Autism Foundation of Oklahoma resulted in 270 respondents. Based on this, we believe 200 respondents is feasible. We will not incentivize the survey. Recent web-based surveys deployed by the research team that were incentivized (ie, had a gift card raffle) resulted in a high number of bots and scammers completing the survey for monetary gain. This, combined with the relatively high number of participants the Autism Foundation of Oklahoma had on their surveys who were not incentivized, led the research team to drop the use of incentives.

Data Analysis

Phase 1: Formative Research and Phase 3: Process Evaluation

The data from the sharing sessions and community engagement questionnaire will be analyzed and interpreted using iterative inductive and deductive thematic analyses. Data will be developed through verbatim transcription of audio recordings, analyzed using Dedoose (SocioCultural Research Consultants), and transformed into concept maps. The transcripts and texts will be reviewed several times and coded based on themes to reduce and display the data and draw conclusions. This process involves (1) familiarizing the research team with the data, (2) coding the data, (3) using the codes to develop initial themes, (4) reviewing the themes as a team, (5) defining the themes, and (6) writing up the results. Inductive codes will be based on emerging codes from the data, and deductive codes will be based on the literature and the open-ended sharing session and process evaluation questions. The credibility of the outcomes will be verified with community members to help ensure we capture the experiences of the community members.

Phase 2: An Adapted Survey of Social Inclusion and Mental Well-Being

We will examine whether meaningful social inclusion predicts well-being given sociodemographic factors using ordered logistic regression, with well-being categorized as low, medium, and high [49]. Models will be adjusted using participant characteristics to hold influences outside of social inclusion constant.

Power Analysis

Qualitative data will be collected until saturation is reached. For quantitative analysis, logistic regression is a nonlinear model, and thus, probability at the mean and 1 SD above the mean is necessary for the power analysis. These values are not available in the literature. We will develop these probabilities through this pilot study for use in a larger study. However, in general, a sample size over 100 with cell counts over 10 is necessary for logistic regression.

Ethical Considerations

Ethics approval for Phase 1 was obtained for this project in March 2023 from the Institutional Review Board of Oklahoma State University (IRB-23-46). Phase 2 and Phase 3 of this protocol will be reviewed and approved, and electronic informed consent or assent, where appropriate, will be attained before beginning any aspect of the study.

Results

The study was funded by Oklahoma Center for the Advancement of Science and Technology in January 2023. Ethics approval was obtained for this project in March 2023. We have developed Phase 1 materials, recruited community partners, developed a draft of the survey, and started the Phase 1 focus groups as of September 2023. Phase 2 and Phase 3 have not started yet. We expect to complete this study by March 2025.

Discussion

Expected Outcomes and Potential Impact

The expected outcomes of this protocol include a definition of meaningful social inclusion for autistic people and an enhanced understanding of the role meaningful social inclusion plays in the well-being of autistic people. The research findings may generate new knowledge on meaningful social inclusion that addresses community-level needs and limited social inclusion among autistic adolescents and emerging adults. This project could advance our understanding of how to improve social inclusion, reduce poor mental well-being among autistic adolescents and emerging adults, and advance our scientific understanding of facilitating social inclusion and integration of autistic people in communities.

Results will be integrated into the Autism Foundation of Oklahoma's training and awareness programs on, for example, employment, education, and criminal justice. The results will also be used to develop new training and awareness programs focused on social inclusion. The proposed study will provide preliminary data for developing interventions for testing (eg, modifying the Autism Foundation of Oklahoma's current training program for employers to hire autistic people) and lay the groundwork for larger studies on enhancing quality of life and social inclusion factors such as interpersonal relationships and community participation for autistic adolescents and emerging adults.

Potential Difficulties and Limitations

We assume that social inclusion is associated with better mental well-being. However, it could be that better mental well-being is associated with higher levels of social inclusion; that is, better mental well-being leads to more social inclusion. This is an issue of endogeneity—when the outcome variable is a predictor and not simply a response (simultaneity bias). We can test for this relationship using the Hausman test for endogeneity, and we also included variables that can be used as statistical instruments should we need to use an instrumental variable analysis to control for endogeneity.

Strength of the Study

Most research on social inclusion and autistic people focuses on exclusion rather than inclusion. This research is typically conducted on autistic children in primary school settings and often excludes the lived experiences of autistic people. This can result in outcomes and recommendations that do not align with the experiences and goals of the autistic community. As such, several strengths of this study lie in our focus on social inclusion rather than exclusion, our centering of the experiences of autistic adolescents and emerging adults, and our use of a community-based mixed methods approach to engage the autistic community. By focusing on the lived experiences of autistic people, we increase the likelihood that the outcomes of this project will have a meaningful impact on the well-being of autistic people.

Acknowledgments

This research project was funded by the Oklahoma Center for the Advancement of Science and Technology (HR23-062) awarded to DJM and MC. The content of this manuscript is solely the responsibility of the authors. Oklahoma Center for the Advancement of Science and Technology does not review or require approval of manuscripts for publication.

Authors' Contributions

DJM and MC designed the study protocol and wrote the manuscript. DN provided content experience. EP and DJM developed the community member engagement materials. DJM, EP, AM, and CL are leading community member engagement and focus

groups. All authors are developing the survey. CL programed the draft survey. All authors provided input for the study protocol, reviewed the manuscript, and will participate in implementing the study protocol.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review reports.
[PDF File (Adobe PDF File), 171 KB - resprot_v13i1e52658_app1.pdf]

References

1. Maitland CA, Rhodes S, O'Hare A, Stewart ME. Social identities and mental well-being in autistic adults. Autism 2021;25(6):1771-1783 [FREE Full text] [doi: 10.1177/13623613211004328] [Medline: 34011188]
2. Kamio Y, Inada N, Koyama T. A nationwide survey on quality of life and associated factors of adults with high-functioning autism spectrum disorders. Autism 2013;17(1):15-26. [doi: 10.1177/1362361312436848] [Medline: 22399449]
3. Mason D, McConachie H, Garland D, Petrou A, Rodgers J, Parr JR. Predictors of quality of life for autistic adults. Autism Res 2018;11(8):1138-1147 [FREE Full text] [doi: 10.1002/aur.1965] [Medline: 29734506]
4. Guan J, Li G. Injury mortality in individuals with autism. Am J Public Health 2017;107(5):791-793. [doi: 10.2105/AJPH.2017.303696] [Medline: 28323463]
5. Hirvikoski T, Mittendorfer-Rutz E, Boman M, Larsson H, Lichtenstein P, Bölte S. Premature mortality in autism spectrum disorder. Br J Psychiatry 2016;208(3):232-238 [FREE Full text] [doi: 10.1192/bjp.bp.114.160192] [Medline: 26541693]
6. Kirby AV, Bakian AV, Zhang Y, Bilder DA, Keeshin BR, Coon H. A 20-year study of suicide death in a statewide autism population. Autism Res 2019;12(4):658-666 [FREE Full text] [doi: 10.1002/aur.2076] [Medline: 30663277]
7. Hossain MM, Khan N, Sultana A, Ma P, McKyer ELJ, Ahmed HU, et al. Prevalence of comorbid psychiatric disorders among people with autism spectrum disorder: an umbrella review of systematic reviews and meta-analyses. Psychiatry Res 2020;287:112922. [doi: 10.1016/j.psychres.2020.112922] [Medline: 32203749]
8. Lai MC, Kassee C, Besney R, Bonato S, Hull L, Mandy W, et al. Prevalence of co-occurring mental health diagnoses in the autism population: a systematic review and meta-analysis. Lancet Psychiatry 2019;6(10):819-829. [doi: 10.1016/S2215-0366(19)30289-5] [Medline: 31447415]
9. McMaughan DJD, Imanpour S, Mulcahy A, Jones J, Criss MM. Mental health-related hospitalizations among adolescents and emerging adults with autism in the United States: a retrospective, cross-sectional analysis of national hospital discharge data. Autism 2023;27(6):1702-1715. [doi: 10.1177/13623613221143592] [Medline: 36597938]
10. Czeisler M, Lane RI, Petrosky E, Wiley JF, Christensen A, Njai R, et al. Mental health, substance use, and suicidal ideation during the COVID-19 pandemic—United States, june 24-30, 2020. MMWR Morb Mortal Wkly Rep 2020;69(32):1049-1057 [FREE Full text] [doi: 10.15585/mmwr.mm6932a1] [Medline: 32790653]
11. Lever AG, Geurts HM. Psychiatric co-occurring symptoms and disorders in young, middle-aged, and older adults with autism spectrum disorder. J Autism Dev Disord 2016;46(6):1916-1930 [FREE Full text] [doi: 10.1007/s10803-016-2722-8] [Medline: 26861713]
12. CDC. Autism and Developmental Disabilities Monitoring (ADDM) Network. Centers for Disease Control and Prevention. 2022. URL: https://www.cdc.gov/ncbddd/autism/addm.html [accessed 2022-09-14]
13. Mandell DS. Psychiatric hospitalization among children with autism spectrum disorders. J Autism Dev Disord 2008;38(6):1059-1065 [FREE Full text] [doi: 10.1007/s10803-007-0481-2] [Medline: 17975720]
14. Bishop-Fitzpatrick L, Rubenstein E. The physical and mental health of middle aged and older adults on the autism spectrum and the impact of intellectual disability. Res Autism Spectr Disord 2019;63:34-41 [FREE Full text] [doi: 10.1016/j.rasd.2019.01.001] [Medline: 31768189]
15. Rodriguez G, Drastal K, Hartley SL. Cross-lagged model of bullying victimization and mental health problems in children with autism in middle to older childhood. Autism 2021;25(1):90-101 [FREE Full text] [doi: 10.1177/1362361320947513] [Medline: 32921150]
16. Cage E, Troxell-Whitman Z. Understanding the reasons, contexts and costs of camouflaging for autistic adults. J Autism Dev Disord 2019;49(5):1899-1911 [FREE Full text] [doi: 10.1007/s10803-018-03878-x] [Medline: 30627892]
17. Cook J, Hull L, Crane L, Mandy W. Camouflaging in autism: a systematic review. Clin Psychol Rev 2021;89:102080. [doi: 10.1016/j.cpr.2021.102080] [Medline: 34563942]
18. Hull L, Levy L, Lai MC, Petrides KV, Baron-Cohen S, Allison C, et al. Is social camouflaging associated with anxiety and depression in autistic adults? Mol Autism 2021;12(1):13 [FREE Full text] [doi: 10.1186/s13229-021-00421-1] [Medline: 33593423]
19. Mandy W. Social camouflaging in autism: is it time to lose the mask? Autism 2019;23(8):1879-1881 [FREE Full text] [doi: 10.1177/1362361319878559] [Medline: 31552745]

20. Cage E, Di Monaco J, Newell V. Experiences of autism acceptance and mental health in autistic adults. J Autism Dev Disord 2018;48(2):473-484 [FREE Full text] [doi: 10.1007/s10803-017-3342-7] [Medline: 29071566]
21. Bishop-Fitzpatrick L, Smith DaWalt L, Greenberg JS, Mailick MR. Participation in recreational activities buffers the impact of perceived stress on quality of life in adults with autism spectrum disorder. Autism Res 2017;10(5):973-982 [FREE Full text] [doi: 10.1002/aur.1753] [Medline: 28244233]
22. Stacey TL, Froude EH, Trollor J, Foley KR. Leisure participation and satisfaction in autistic adults and neurotypical adults. Autism 2019;23(4):993-1004. [doi: 10.1177/1362361318791275] [Medline: 30132680]
23. Kapp SK. Social support, well-being, and quality of life among individuals on the autism spectrum. Pediatrics 2018;141(Suppl 4):S362-S368. [doi: 10.1542/peds.2016-4300N] [Medline: 29610418]
24. Song W, Shea L, Nonnemacher SL, Brusilovskiy E, Townley G, Salzer MS. Community participation comparison between adults on the autism spectrum and adults in the general population. J Autism Dev Disord 2022;52(4):1610-1621. [doi: 10.1007/s10803-021-05059-9] [Medline: 33966134]
25. Magiati I, Tay XW, Howlin P. Cognitive, language, social and behavioural outcomes in adults with autism spectrum disorders: a systematic review of longitudinal follow-up studies in adulthood. Clin Psychol Rev 2014;34(1):73-86. [doi: 10.1016/j.cpr.2013.11.002] [Medline: 24424351]
26. Jones SC, Gordon CS, Akram M, Murphy N, Sharkie F. Inclusion, exclusion and isolation of autistic people: community attitudes and autistic people's experiences. J Autism Dev Disord 2022;52(3):1131-1142. [doi: 10.1007/s10803-021-04998-7] [Medline: 33884534]
27. Lai MC, Szatmari P. Resilience in autism: research and practice prospects. Autism 2019;23(3):539-541 [FREE Full text] [doi: 10.1177/1362361319842964] [Medline: 30971108]
28. Roche L, Adams D, Clark M. Research priorities of the autism community: a systematic review of key stakeholder perspectives. Autism 2021;25(2):336-348. [doi: 10.1177/1362361320967790] [Medline: 33143455]
29. Benevides TW, Shore SM, Palmer K, Duncan P, Plank A, Andresen ML, et al. Listening to the autistic voice: mental health priorities to guide research and practice in autism from a stakeholder-driven project. Autism 2020;24(4):822-833 [FREE Full text] [doi: 10.1177/1362361320908410] [Medline: 32429818]
30. Simplican SC, Leader G, Kosciulek J, Leahy M. Defining social inclusion of people with intellectual and developmental disabilities: an ecological model of social networks and community participation. Res Dev Disabil 2015;38:18-29. [doi: 10.1016/j.ridd.2014.10.008] [Medline: 25543997]
31. Gadke DL, McKinney C, Oliveros A. Autism spectrum disorder symptoms and comorbidity in emerging adults. Child Psychiatry Hum Dev 2016;47(2):194-201. [doi: 10.1007/s10578-015-0556-9] [Medline: 25995020]
32. Simonoff E, Pickles A, Charman T, Chandler S, Loucas T, Baird G. Psychiatric disorders in children with autism spectrum disorders: prevalence, comorbidity, and associated factors in a population-derived sample. J Am Acad Child Adolesc Psychiatry 2008;47(8):921-929. [doi: 10.1097/CHI.0b013e318179964f] [Medline: 18645422]
33. Nicolaidis C, Raymaker D, Kapp SK, Baggs A, Ashkenazy E, McDonald K, et al. The AASPIRE practice-based guidelines for the inclusion of autistic adults in research as co-researchers and study participants. Autism 2019;23(8):2007-2019 [FREE Full text] [doi: 10.1177/1362361319830523] [Medline: 30939892]
34. Creswell JW, Plano Clark VL. Designing and Conducting Mixed Methods Research, Third Edition. Los Angeles: SAGE Publications; 2017.
35. McMaughan DJ, Ozmetin JP, Welch ML, Mulcahy A, Imanpour S, Beverly JG, et al. Framing the front door: co-creating a home health care assessment of service need for children with disabilities. Home Health Care Serv Q 2021;40(3):231-246. [doi: 10.1080/01621424.2021.1952132] [Medline: 34315352]
36. Beighton C, Victor C, Carey IM, Hosking F, DeWilde S, Cook DG, et al. 'I'm sure we made it a better study…': experiences of adults with intellectual disabilities and parent carers of patient and public involvement in a health research study. J Intellect Disabil 2019;23(1):78-96 [FREE Full text] [doi: 10.1177/1744629517723485] [Medline: 28812949]
37. Bal VH, Taylor JL. Advancing understanding of adults: the role of diagnostic confirmation and sample description. Autism 2019;23(4):807-810 [FREE Full text] [doi: 10.1177/1362361319847547] [Medline: 31044599]
38. Eriksson JM, Andersen LM, Bejerot S. RAADS-14 screen: validity of a screening tool for autism spectrum disorder in an adult psychiatric population. Mol Autism 2013;4(1):49 [FREE Full text] [doi: 10.1186/2040-2392-4-49] [Medline: 24321513]
39. Salzer MS, Burns-Lynch B. Peer facilitated community inclusion toolkit. Temple University Collaboration on Community Inclusion for Individuals with Psychiatric Disabilities. Philadelphia, PA; 2016. URL: https://tucollaborative.org/ [accessed 2024-01-23]
40. Baron-Cohen S, Wheelwright S. The friendship questionnaire: an investigation of adults with Asperger syndrome or high-functioning autism, and normal sex differences. J Autism Dev Disord 2003;33(5):509-517. [doi: 10.1023/a:1025879411971] [Medline: 14594330]
41. Shea LL, Verstreate K, Nonnemacher S, Song W, Salzer MS. Self-reported community participation experiences and preferences of autistic adults. Autism 2021;25(5):1295-1306. [doi: 10.1177/1362361320987682] [Medline: 33491462]
42. Song W, Salzer MS, Nonnemacher SL, Miller KK, Shea LL. Living arrangements and community participation among autistic adults: exploring the possible influences of living alone or with others. Res Dev Disabil 2022;124:104213. [doi: 10.1016/j.ridd.2022.104213] [Medline: 35290949]

43. Tennant R, Hiller L, Fishwick R, Platt S, Joseph S, Weich S, et al. The Warwick-Edinburgh Mental Well-being Scale (WEMWBS): development and UK validation. Health Qual Life Outcomes 2007;5:63 [FREE Full text] [doi: 10.1186/1477-7525-5-63] [Medline: 18042300]
44. Lovibond PF, Lovibond SH. The structure of negative emotional states: comparison of the Depression Anxiety Stress Scales (DASS) with the Beck Depression and Anxiety Inventories. Behav Res Ther 1995;33(3):335-343. [doi: 10.1016/0005-7967(94)00075-u] [Medline: 7726811]
45. Lloyd K, Devine P. Psychometric properties of the Warwick-Edinburgh Mental Well-being Scale (WEMWBS) in Northern Ireland. J Ment Health 2012;21(3):257-263. [doi: 10.3109/09638237.2012.670883] [Medline: 22574955]
46. Muniandy M, Richdale AL, Arnold SRC, Trollor JN, Lawson LP. Inter-relationships between trait resilience, coping strategies, and mental health outcomes in autistic adults. Autism Res 2021;14(10):2156-2168. [doi: 10.1002/aur.2564] [Medline: 34184818]
47. McKernan EP, Russo N. Investigating the structure of the CESD-R and DASS-21 across adults with low and high levels of autistic traits. J Autism Dev Disord 2023. [doi: 10.1007/s10803-023-05944-5] [Medline: 36959520]
48. Tyrer P, Nur U, Crawford M, Karlsen S, MacLean C, Rao B, et al. The social functioning questionnaire: a rapid and robust measure of perceived functioning. Int J Soc Psychiatry 2005;51(3):265-275. [doi: 10.1177/0020764005057391] [Medline: 28095167]
49. Stranges S, Samaraweera PC, Taggart F, Kandala NB, Stewart-Brown S. Major health-related behaviours and mental well-being in the general population: the Health Survey for England. BMJ Open 2014;4(9):e005878 [FREE Full text] [doi: 10.1136/bmjopen-2014-005878] [Medline: 25239293]

Abbreviations

DASS-21: Depression Anxiety Stress Scales-21
FQ: Friendship Questionnaire
RUCA: Rural-Urban Commuter Area
TUCP: Temple University Community Participation
WEMWBS: Warwick-Edinburgh Mental Well-being Scale

Edited by A Mavragani; submitted 12.09.23; this is a non–peer-reviewed article;accepted 29.11.23; published 14.03.24.

Please cite as:
McMaughan DJ, Lewis C, McGehee A, Noreen D, Parker E, Criss MM
Meaningful Social Inclusion and Mental Well-Being Among Autistic Adolescents and Emerging Adults: Protocol for a Community-Based Mixed Methods Study
JMIR Res Protoc 2024;13:e52658
URL: https://www.researchprotocols.org/2024/1/e52658
doi:10.2196/52658
PMID:38483470

Protocol

Nonspecific Effects of the Bacillus Calmette-Guérin Vaccine in Portuguese Children Under 5 Years of Age: Protocol for a Population-Based Historical Birth Cohort Study

Ines Fronteira[1,2], MSc, PhD, Hab; Matilde Pacheco[1,3], MSc; Frederik Schaltz-Buchholzer[4], PhD; Paulo Ferrinho[2], MSc, PhD, Hab

[1]NOVA National School of Public Health, Public Health Research Center, Comprehensive Health Research Center, NOVA University, Lisbon, Portugal

[2]Global Health and Tropical Medicine, GHTM, Associate Laboratory in Translation and Innovation Towards Global Health, LA-REAL, Instituto de Higiene e Medicina Tropical, IHMT, Universidade Nova de Lisboa, UNL, Lisbon, Portugal

[3]Instituto de Higiene e Medicina Tropical, Universidade Nova de Lisboa, Lisbon, Portugal

[4]Bandim Health Project, OPEN, Department of Clinical Research, University of Southern Denmark and Odense University Hospital, Odensen, Denmark

Corresponding Author:
Ines Fronteira, MSc, PhD, Hab
NOVA National School of Public Health
Public Health Research Center, Comprehensive Health Research Center
NOVA University
Avenida Padre Cruz
Lisbon, 1600-560
Portugal
Phone: 351 919745584
Email: ines.fronteira@ensp.unl.pt

Abstract

Background: The Bacillus Calmette-Guérin vaccine (BCG) against tuberculosis (TB) shows beneficial nonspecific effects, which are likely related to innate immune training. Until 2016, a single BCG dose was administered to all newborns in Portugal. In July 2016, a clinical guideline established that only children under 6 years belonging to high-risk groups should receive BCG. This might have prevented nonvaccinated children from developing trained immunological responses as effectively as BCG-vaccinated children.

Objective: This study aims to investigate if there is variation in TB-related and all-cause mortality, and severe, moderate, or mild morbidity in children under 5 years of age, and whether such variation might be explained by the BCG vaccination policy change in 2016.

Methods: This population-based historical birth cohort study includes children under 5 years of age born in Portugal between July 1, 2010, and June 30, 2021. Newborns with low birth weight, premature status, or known or suspected HIV infection are excluded. The follow-up period is until the completion of 5 years of age or the end of follow-up (June 30, 2021). The study will use secondary data from the National Health Service user registry, death certificate database, vaccination registry, communicable diseases surveillance system, TB surveillance system, diagnosis-related group information system for hospital admissions and emergency department visits, and primary health care information system. The data will be linked. Primary outcomes include person-time incidence rates of death (all causes and TB), TB diagnosis, and all causes and some specific causes of severe, moderate, or mild morbidity, and the incidence rate ratio of nonvaccinated to BCG-vaccinated children. We will compare the probability of surviving the first and fifth years of life or of not having severe, moderate, or mild morbidity during the follow-up period according to exposure (BCG vaccinated or nonvaccinated, number of doses, and time from birth until the first dose), using the log-rank test for assessing differences in survival rates between exposed and nonexposed children and hazard ratios for quantifying the differences. Moreover, we will perform a proportional hazards regression analysis.

Results: Ethics approval has been obtained. In March 2022, database owners were contacted to present the project and discuss the request for data. A unique identifier will be used. In July 2023, a process of redefinition of the variables per database was initiated. Data were received in October and November 2023. In November 2023, further work was conducted. By April 2024, we expect to start analyzing the full data set.

Conclusions: The results will contribute to the accumulating body of knowledge and might have relevance to guide global BCG vaccination policy. Data linkage can contribute to a swifter mechanism to use available health data to conduct population-based studies and inform policy decision-making.

Trial Registration: ClinicalTrials.gov NCT05471167; https://clinicaltrials.gov/study/NCT05471167

International Registered Report Identifier (IRRID): DERR1-10.2196/55332

(JMIR Res Protoc 2024;13:e55332) doi:10.2196/55332

KEYWORDS

BCG; Bacillus Calmette-Guérin vaccine; policy; Portugal; nonspecific effects; vaccines; heterologous immunity

Introduction

Background

Immunization has led to a significant decrease in mortality in children under 5 years of age. Several studies have demonstrated that the reduction in mortality and morbidity due to vaccination extends beyond the targeted infections. This seems to result from broader nonspecific effects (also termed heterologous immunity) stemming from the synergistic effects of several live vaccines [1-4]. The vaccines demonstrated to have nonspecific effects include the Bacillus Calmette-Guérin vaccine (BCG), polio vaccine, and measles vaccine [5]. Overall, the nonspecific effects of vaccines vary according to age, sex, time to administration, last vaccine administration, previous and concurrent infections and immunizations, interval between vaccines, genetic factors, nutritional state, season, and co-administration of other immunomodulating agents [1].

BCG is a live attenuated vaccine against tuberculosis (TB), which is administered to newborns ideally at birth or before the seventh day of life. Despite its low efficacy for preventing primary infection or reactivation of latent pulmonary infection and TB infection, BCG is effective against childhood tuberculous meningitis and miliary disease [6]. Hence, BCG at birth is recommended in settings with a high incidence of TB, and it is parsimoniously administered in countries with a low incidence and has been removed from routine vaccination schemes in high-income countries with a low TB incidence [7].

BCG was introduced in the 1920s in Sweden, where it quickly became apparent that the all-cause mortality was lower in BCG-vaccinated children than in those not vaccinated [8]. In England and the United States, the same pattern was observed between the late 1940s and early 1960s, where a reduction in mortality from diseases other than TB was estimated in 25% of vaccinated children (95% CI 6%-41%) [1,9]. Later studies showed the same pattern in infant mortality and morbidity [10], as well as in morbidity in the neonatal period [11]. Furthermore, BCG is used as a standard treatment for carcinoma of the bladder and influences the natural history of infectious and neoplastic diseases [1]. More recently, the effect of BCG was tested in viremia after SARS-CoV-2 exposure [12].

Further studies in children from Denmark and Greenland failed to show a decrease in hospitalization due to infectious diseases in vaccinated children [13,14]. On the contrary, a cohort study of children from 19 different countries revealed that BCG-vaccinated children under 5 years of age had a lower risk of suspected acute lower respiratory infection [15]. In Spain, hospitalization rates due to respiratory infection were lower in BCG-vaccinated children, with an attributable fraction of 32% for children under 1 year of age, and a similar finding was noted for sepsis, with an attributable fraction of 53% [16].

A systematic review concluded that BCG has a beneficial effect on mortality in children, with differential effects according to age (earlier administration of the vaccine is associated with greater effects) [5]. Nevertheless, there has been a call for more research on the nonspecific effects of BCG [5,17]. Currently, studies are seeking to further investigate the nonspecific effects of BCG [18] in terms of the effects on allergy and infection [7], severe morbidity, nonaccidental hospital admission, and all-cause consultation in children under 5 years of age [19].

BCG Vaccination in Portugal

In Portugal, BCG began to be routinely administered to all newborn children in 1965. Until 2016, a single BCG dose was administered to all newborns, typically before discharge from the maternity ward (most births in Portugal are hospital-based) or as early as possible thereafter [20].

In June 2016, a clinical guideline established that only children under 6 years of age who belong to high-risk groups (those originating from countries with high TB incidence; having contact with active cases or persons under prophylaxis; having HIV-positive mothers; having parents with a alcohol or drug abuse problem and antecedents of TB; having parents who have been in prison in the last 5 years; living in high-risk TB communities; or traveling to high-incidence countries) should be vaccinated as close to birth as possible [21]. Some of these risks were not considered individually but by proxy, with some parishes (freguesias) thus considered high risk for the criteria defined.

In 2016, 42% of children under 1 year of age had received BCG (compared to 98% in the previous year) [20]. Between 2016 and 2018, the incidence of TB increased by 16% in children under 1 year of age (from 7.0 to 8.1 per 100,000 inhabitants) and 192% in children aged 1 to 5 years (from 2.6 to 7.6 per 100,000 inhabitants) [20].

Between the adoption of the high-risk strategy for BCG vaccination in 2016 and 2018, the infant mortality rate (IMR) remained stable at 3.2‰ to 3.3‰, with important variations between the considered years [20]. In 2019, there was a decrease to 2.8‰. The mortality rate in children under 5 years of age decreased from 3.4‰ in 2016 to 3.0‰ in 2019, but not constantly in this period (eg, during 2018 it was 3.5‰) [20]. No death in children under 5 years of age has been attributable

to TB since the implementation of the high-risk strategy for BCG [20]. Nevertheless, the number of severe cases of TB in children under 5 years of age decreased in 2020 compared to 2018 (4 cases) and 2019 (7 cases), with just 1 case registered in a child without BCG vaccination [22].

Evaluation of the BCG Vaccination Policy

Since the implementation of the high-risk strategy for BCG in 2016, no assessment has been conducted regarding the impact of the BCG policy shift on severe, moderate, or mild morbidity and on mortality in children. It is a common problem that vaccination practices are changed without evaluating the overall health effects of the change and that the nonspecific effects of vaccines are not included in the considerations regarding vaccine policies.

In 2021, the first cohort of children not vaccinated for BCG completed the fifth year of life, and evidence is needed regarding the impact of this strategy, especially given fluctuations in the IMR, a decline in the TB notification rate not accompanied by a decline in the incidence, a higher TB incidence in greater metropolitan areas, and a high median number of days from symptoms to diagnosis [22].

No data have been gathered on overall hospital admissions and morbidity patterns. Similarly, no data have been compiled on the BCG strains used in the country and their differences in terms of efficacy. This evidence will have a bearing on the continuity of the current strategy.

The need for more and better evidence is paramount, especially given that besides deciding on the inclusion of BCG in the country's immunization plan, arguments on the nonspecific effects of vaccines (and not only of BCG) can help overcome vaccine hesitancy. In high-income countries, including Portugal, vaccine hesitancy has been responsible for a decline in coverage rates and for the re-emergence of severe cases of vaccine-preventable diseases such as measles [23,24].

Hypothesis

Given the described effects of BCG on overall mortality, immune and atopic conditions including asthma, and incidence of respiratory tract infections; its nonspecific protection against nonrelated pathogens; and its protective effects that are apparent shortly after immunization and sustained for at least 1 year [2,25], we hypothesize that some of the variations in mortality among children under 5 years of age, in the incidence of TB, and in severe, moderate, and mild morbidity among children under 5 years of age might be partially explained by a reduction in the coverage rate of BCG since 2016. The reduction in the coverage rate of BCG, which resulted from only high-risk children receiving BCG at birth, might have prevented nonvaccinated children from developing trained immunological responses as effectively as BCG-vaccinated children.

Objectives

We aim to investigate the incidence of the specific and nonspecific effects of BCG by comparing the incidences of TB disease and infection; mild, moderate, and severe morbidity; and mortality in the first 5 years of life among children born in Portugal between 2010 and 2021, according to their BCG status.

Methods

Study Design

This population-based historical (retrospective) birth cohort study will compare the incidence of all-cause mortality (including due to TB disease); TB disease; and severe, moderate, and mild morbidity between BCG-vaccinated and nonvaccinated children born between July 1, 2010, and June 30, 2021.

Setting

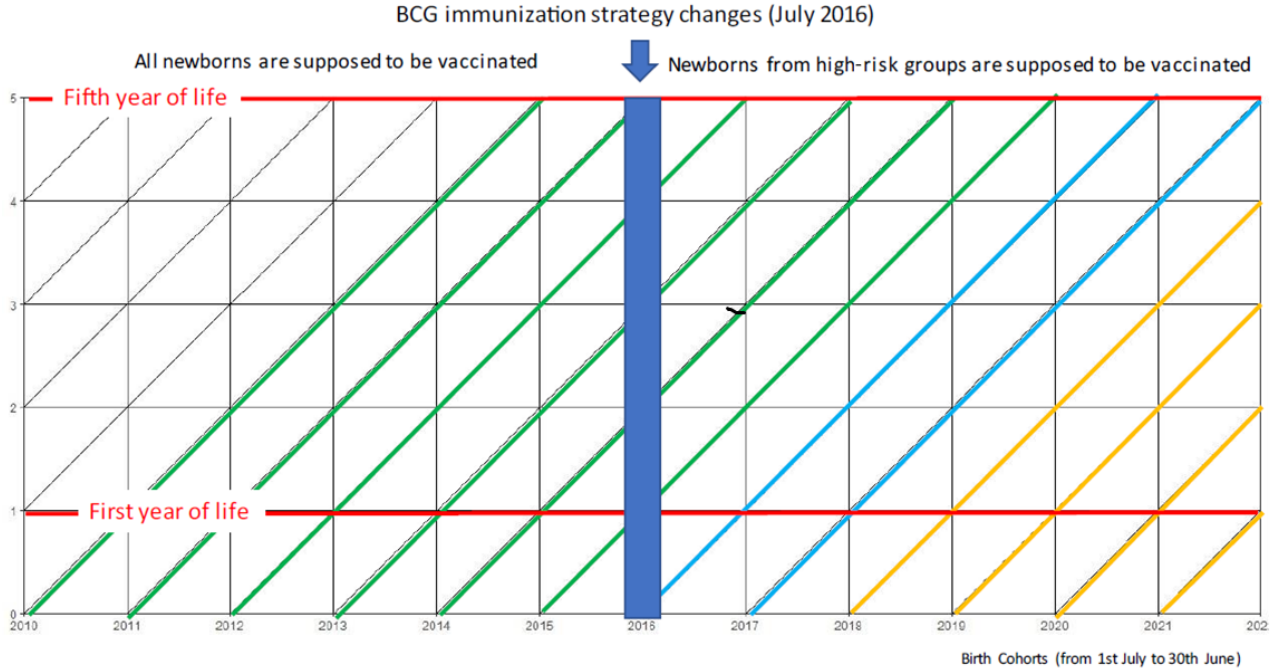
This study will investigate the specific and nonspecific effects of BCG based on the shift in the BCG vaccination policy that occurred in Portugal in July 2016, when a consistently low incidence of TB led to the revision of the National Immunization Plan. Since then, BCG has been administered only to newborns considered to be at higher risk of TB infection, thus creating an opportunity to compare BCG-vaccinated and nonvaccinated children.

The approach adopted by Portuguese public health authorities to define the high risk for TB was based on geographical risk, with, for instance, all children born in some parishes in the metropolitan areas of Lisbon and Porto being offered BCG independent of socioeconomic status, country of origin, or vulnerability. We believe that this type of risk definition has guaranteed enough variability between BCG-vaccinated and nonvaccinated children, thus allowing comparisons of health outcomes between exposed and nonexposed children.

Participants

The study will include children under 5 years of age born and registered in Portugal between July 1, 2010, and June 30, 2021. We have chosen this period because it will allow us to (1) compare the cohorts before and after the change in the BCG immunization strategy (Figure 1); (2) characterize children not vaccinated with BCG and their health outcomes (when universal BCG at birth was recommended); and (3) compare children exposed and not exposed to BCG after the 2016 change in the BCG vaccination strategy.

Figure 1. Lexis graph. BCG: Bacillus Calmette-Guérin vaccine.



Eligibility Criteria

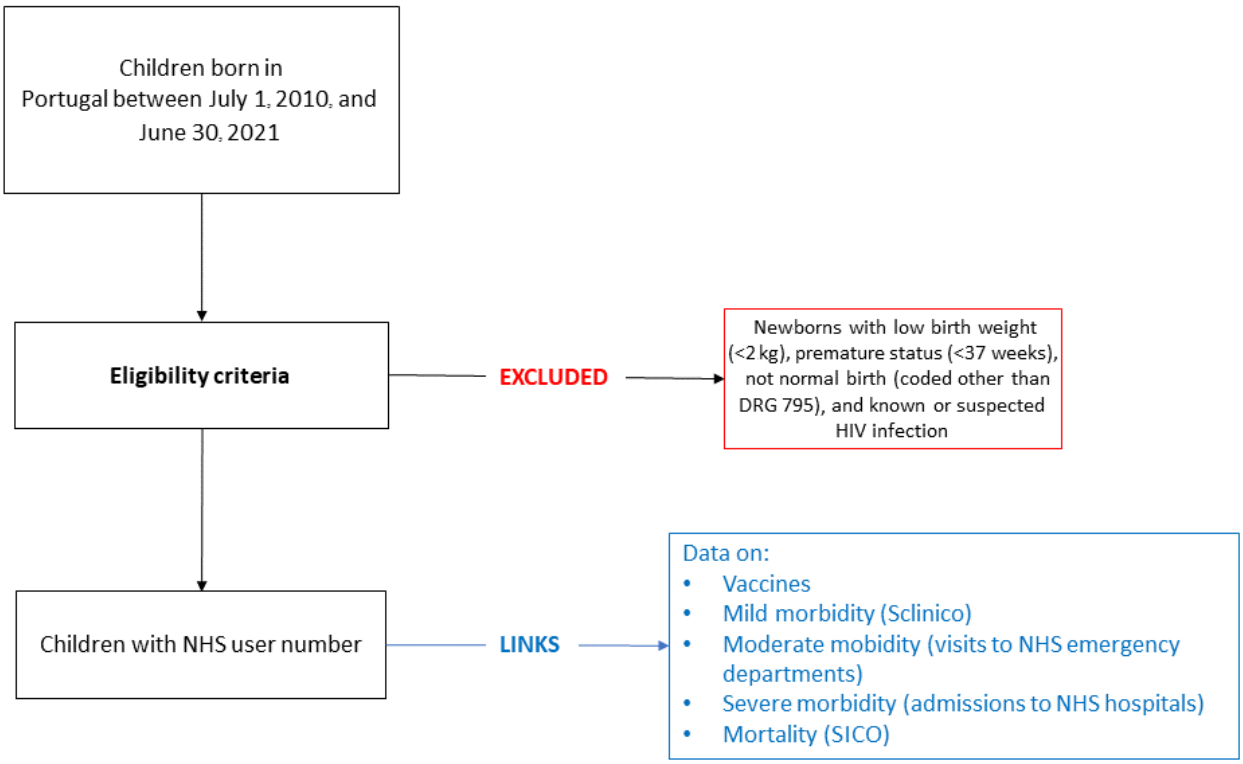
The study will include children born alive in Portugal (births coded as diagnosis-related group [DRG] 795 [normal newborn]).

Exclusion Criteria

The study will exclude newborns who have a weight of <2 kg, are premature (<37 weeks of gestation), or are known or suspected to have HIV infection.

The follow-up period will be until the completion of 5 years of age or the end of follow-up (June 30, 2021) (Figure 2).

Figure 2. Flowchart. DRG: diagnosis-related group; NHS: National Health Service.



Data Sources

The study will be based solely on secondary data. The data sources are the National Health Service (NHS) user registry (RNU), Death Certificate Information System (SICO), vaccination registry, communicable diseases surveillance system (Sistema Nacional de Vigilancia Epidemiologica [SINAVE]), surveillance information system for TB (Svig-TB), DRG information system for hospital admissions and visits to the emergency department (Base de Dados de Morbilidade Hospitalar [BDMH]), and primary health care (PHC) information system (SClínico) of children born between July 1, 2010, and June 30, 2021.

The birth registry database (RNU) contains data on gender, age, PHC center where the child is to be followed up, nationality, and place of residence. The SICO database provides data on the cause and date of death. The vaccination registry includes data on the vaccines administered, date of vaccination, and place of residence. The BDMH database gathers data on hospital admissions and emergency department visits to NHS hospitals, including the date of admission and discharge, diagnosis, type of admission, motive for admission, weight at birth, DRG code, major diagnostic category (MDC) code, complications of pregnancy and delivery, and type and place of delivery. Data from admissions at private hospitals are not included. The SClínico database contains data on socioeconomic status and visits (including motive and diagnosis) to NHS PHC units. Svig-TB is a database for notification and follow-up of TB cases, and SINAVE is the general surveillance information system for communicable diseases, including TB, and regarding TB, it contains data on symptoms at presentation, date of diagnosis, type of treatment, other diseases before TB, risk groups, and outcomes of the infection.

Measurements

Exposure is defined as having received the BCG vaccine during the first year of life and is measured using the vaccination registry. Variables include BCG (yes or no, and number of doses) and time from birth to BCG (in days).

Outcomes

Primary Outcomes

In this study, the primary outcomes for BCG-vaccinated and nonvaccinated infants and children under 5 years of age include the incidence of all-cause death and death due to TB; the incidence of mild, moderate, and severe morbidity; and respective relative risks.

The primary outcomes will be measured as person-time incidence rates of death (all causes and TB); TB diagnosis; and severe, moderate, and mild morbidity in the follow-up period, and the incidence rate ratio of nonvaccinated to BCG-vaccinated children (Table 1). For the outcome of death, data will include death (yes or no), age at the time of death (in days), and cause of death (eg, diseases of the respiratory system and diseases of the skin and subcutaneous tissue). Data on TB diagnosis will include confirmed case (yes or no), presentation of TB, age at diagnosis (in days), duration of treatment, and outcomes of treatment. Severe and moderate morbidity will be measured based on hospitalization and visits to the emergency department of the NHS. Outcomes will be characterized by age at presentation (in days), frequency of admissions or visits to the emergency department, length of stay for hospital admission (in nights), and MDC code for hospitalization and emergency department visits. We will include the outcome of hospital admission (discharged alive or died) in case fatality risk analyses. The outcome of mild morbidity is defined as contact with a medical doctor or nurse at a PHC unit owing to disease or ill health during the follow-up, as well as contact related to a recommended child surveillance scheme or other reasons besides health. It will be characterized through visits to the PHC center owing to disease or ill health (yes or no, and number), age at the visits (in days), and diagnosis (International Classification of Primary Care-2 [ICPC-2]). Mortality and morbidity pertaining to external causes and accidents will not be included in the analysis.

Table 1. Predictable analysis per cohort and outcome.

Analysis[a]	Outcomes
Exposed children in birth cohorts 2010 to 2015 compared to nonexposed children in birth cohorts 2010 to 2015, 2016, 2017, 2018, 2019, 2020, and 2021	Primary outcomes in the first year of life
Exposed children in birth cohorts 2010 to 2015 compared to nonexposed children in birth cohorts 2010 to 2015, 2016, and 2017	Primary outcomes in the first 5 years of life
Exposed children in birth cohorts 2016, 2017, 2018, 2019, 2020, and 2021 compared to nonexposed children in birth cohorts 2016, 2017, 2018, 2019, 2020, and 2021	Primary outcomes in the first year of life
Exposed children in birth cohorts 2016 and 2021 compared to nonexposed children in birth cohorts 2016 and 2017	Primary outcomes in the first 5 years of life
Nonexposed children in birth cohorts 2010 to 2015 compared to nonexposed children in birth cohorts 2016 to 2021	Secondary outcome profile of nonvaccinated children before and after the 2016 BCG[b] vaccination change
Children in birth cohorts 2010 to 2015, 2016, and 2017	Secondary outcomes of the mortality and morbidity profile of children under 5 years of age, and NHS[c] hospital and primary health care utilization profiles
Exposed children in birth cohorts 2010 to 2015 compared to exposed children in birth cohorts 2016, 2017, 2018, 2019, 2020, and 2021	Secondary outcomes of the mortality and morbidity incidence according to BCG strains administered per cohort in the first 5 years of life and first year of life
Exposed children in birth cohorts 2010 to 2015 compared to exposed children in birth cohorts 2016 and 2017	Secondary outcomes of the mortality and morbidity incidence according to BCG strains administered per cohort in the first 5 years of life

[a]Between 2010 and 2015, Bacillus Calmette-Guérin vaccine (BCG) coverage varied between 98.2% and 98.4%. In 2016, BCG coverage was 41.6%.

[b]BCG: Bacillus Calmette-Guérin vaccine.

[c]NHS: National Health Service.

Secondary Outcomes

The secondary outcomes include the mortality and morbidity profiles of children under 5 years of age between 2010 and 2021, including causes of death and morbidity, the profiles of nonvaccinated children, and the NHS hospital and PHC utilization profiles of children under 5 years of age before and after 2016 (Table 1).

Statistical Methods

Through data linkage, we will create a single database that links data from the birth registry, SICO, vaccination registry, SINAVE, Svig-TB, BDMH, and PHC database (SClínico) to reconstruct chronological sequences of morbidity and mortality events from birth until the completion of 5 years of life or the end of follow-up (for the 2018 cohort onwards).

In each of the databases, we will identify the data needed and whether a unique identifier (UI) exists and can be provided with the data set. After having access to the requested data and in case a UI is provided (and common to all databases), we will combine information based on that UI.

In case a UI is not provided, we will link data from several data sets using a range of proxy identifiers (eg, date and place of birth, sex, and place of residence) to identify probable matches.

The type of data linkage method to be used will depend on the type and quality of the linkage variables available in the data sets. However, we anticipate having to use a combination of deterministic and probabilistic methods. Before applying linkage methods, we will clean and standardize the data, thus identifying and removing errors and inconsistencies. Given the expected size of the data sets, we will then select sets of block attributes (eg, sex, date of birth, and initials) and compare record pairs with the same matched attributes within blocks. Subsequently, record pairs will be compared for each linkage variable, and an agreement score will be computed. This score will be used to weigh the probability of a record pair belonging to the same child [26,27].

After obtaining the final database, we will compute person-time incidence rates for primary outcomes in BCG-vaccinated and nonvaccinated children. Using the Kaplan-Meier method, we will compute and compare the probability of surviving the first and fifth years of life or of not having a hospitalization, emergency department visit, or mild morbidity episode during the follow-up period according to exposure. Additionally, we will use a log-rank test for assessing differences in survival rates between exposed and nonexposed children and hazard ratios (and corresponding CIs) for quantifying the differences. To explore the effects of several variables on the survival outcomes, we will use proportional hazards regression analysis. If missing data are below 5%, we will use complete case analysis. Otherwise, the frequency and patterns of missing data will be analyzed, and if appropriate, we will use multiple imputation techniques.

Confounders to be measured and controlled for are sex, health unit, completeness and timeliness of vaccination status and scheme, socioeconomic status, and BCG strain (over the years, administered BCG has been provided by different producers, with different strains).

Ethical Considerations

This study has received ethical approval from the Ethics Committee of Instituto de Higiene e Medicina Tropical (IHMT) – Instituto de Tecnologia Química e Biológica António Xavier (ITQB) NOVA – NOVA School of Law (NSL) – Instituto Gulbenkian de Ciência (IGC) (11.23) [28].

The project protocol was submitted to the Ethics Committee of IHMT – ITQB NOVA (11.23), which issued a conditional authorization in July 2022 [29] that became definitive in December 2023.

Results

This project was approved as an exploratory project by the Portuguese Foundation for Science and Technology in the 2021 competitive call for R&D projects (reference: EXPL/SAU-EPI/0067/2021). It was granted approximately €50,000 (US$ 53,869) and was started in January 2022.

During the first month of the project's implementation, administrative and financial activities were carried out, with a summary of the project sent to members of the Scientific Advisory Board, including the planned activities.

In March 2022, database owners were contacted to present the project and discuss how to officially request the data. A document detailing all the data needed to carry out the study was prepared and sent to the Directorate General of Health. After approval from this body, Serviços Partilhados do Ministério da Saúde (SPMS) and Administração Central do Sistema de Saúde (ACSS) also had to provide authorization to access the data, with the last authorization given in October 2023.

We were informed that a UI would be provided for each database, based on the NHS user number, from the RNU, thus allowing direct linkage of records. However, some of the requested variables had to be reviewed and replaced given the Data Protection Law. In July 2023, a process of redefinition of the variables per database was initiated, with some of the variables requested not being supplied owing to legal restrictions (eg, date of birth had to be replaced by days from birth until the event and information if the child had been born before or after 2016) (Multimedia Appendix 1).

Data were received during October and November 2023. By mid-December, data from SINAVE had not yet been provided. No data were obtained from Svig-TB as we were not granted access. Some of the variables requested from this database were replaced by equivalent or proxy variables from SINAVE (Multimedia Appendix 1).

In November 2023, work was conducted in the databases already provided to restructure the databases, perform quality checks and cleaning, compute exposure variables, transform string variables into numeric variables, and perform coding.

By April 2024, we expect to start analyzing the full data set, which is expected to include around 970,000 children.

Discussion

Principal Findings

If the change in the BCG strategy in 2016 is proven to influence the health outcomes of children in their first year of life and during the first 5 years of life, it would further contribute to evidence that BCG primes the immune system against unrelated pathogens and even other health conditions, strengthening the arguments regarding the nonspecific effects of BCG. Additionally, it would provide evidence of the impact of the high-risk strategy for BCG vaccination and inform future decisions regarding BCG vaccination for children in Portugal and other high-income countries. The results will contribute to the accumulating body of knowledge and might have relevance to guide global BCG vaccination policy.

The use of data linkage can also contribute to a swifter mechanism to use available health data to conduct population-based studies and inform policies. The project will demonstrate the feasibility of conducting large-scale epidemiological register-based vaccine studies in Portugal.

Limitations

The main limitation of this project involves the use of secondary data collected for purposes other than research. The RNU database, which provides the basis for creating a UI, only includes children who have a user number for the NHS. The user number is assigned to each person to identify them when accessing the services of the public health care units of the NHS. People with Portuguese citizenship obtain their user number automatically when they apply for a Citizen's Card. Foreigners with a residence or stay permit in Portugal have to apply for an NHS user number. Most but not all infants are registered shortly after birth.

In August 2016, the Portuguese government created the program "Nascer Utente" (translated to "Born as a User") that allowed for immediate registration in the RNU database, assigning the respective user number. This process is conducted by the hospital (public and private) where the child is born, immediately after birth [30]. We therefore expect a bias toward children born after this date in the RNU database.

The electronic registry of vaccines was started in 2017, and all data before this point had to be back introduced in the database, which could have increased the number of typing errors and other issues. We can again have a bias toward the most recent years in terms of the quality of data.

The number of deaths of children under 5 years of age might be underestimated since very young children tend not to have an NHS user number, especially before August 2016. In this case, we can also expect to have a bias in the age of children who died between July 1, 2010, and June 30, 2021, toward older ones.

The BDMH database only pertains to public hospitals. It does not include data from emergency department visits or hospital admissions in the private sector. The same is true for SClínico, which contains data from PHC centers in the NHS. Children using the private sector are not captured by this database.

Additionally, the case mix (severity) of admissions in public hospitals is usually greater than that in private hospitals, which might introduce a bias toward higher case fatality rates in hospital admissions.

In 2020, 32% of Portuguese people had voluntary health insurance (in 2010, the proportion was less than 20%), and the proportion is dependent on household income, with those in higher income groups showing a higher probability of having voluntary health insurance. As such, we expect a bias toward lower income groups, especially in the last years of the study period [31].

Comparison With Prior Work

This is one of the first studies conducted in Portugal linking several databases. During the COVID-19 pandemic, several data linkage studies were conducted [32,33].

To our knowledge, this is the first population-based study that gathers data on mild, moderate, and severe morbidity and mortality among children under 5 years of age and addresses the nonspecific effects of BCG.

In Portugal, this is the first study to assess the impact of the BCG vaccination policy change on the health of children.

Conclusions

The results will contribute to the accumulating body of knowledge and might have relevance to guide global BCG vaccination policy. The use of data linkage can also contribute to a swifter mechanism to use available health data to conduct population-based studies and inform policy decision-making.

Acknowledgments

The Portuguese Foundation for Science and Technology provided funds to Global Health and Tropical Medicine (UID/04413/2020) and Comprehensive Health Research Center (UIDP/04923/2020). This project was funded by a grant from the Portuguese Foundation for Science and Technology (reference number: EXPL/SAU-EPI/0067/2021).

Data Availability

The data sets analyzed during this study are not publicly available owing to Portuguese Law but are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Data on variables (variables requested per database, variables provided per database, number of records in original data sets, actions taken, and final number of records to be linked).
[DOCX File , 30 KB - resprot_v13i1e55332_app1.docx]

Multimedia Appendix 2
Peer-review report from the Fundação para a Ciência e Tecnologia.
[PDF File (Adobe PDF File), 196 KB - resprot_v13i1e55332_app2.pdf]

References

1. Shann F. The non-specific effects of vaccines. Arch Dis Child 2010 Sep;95(9):662-667 [FREE Full text] [doi: 10.1136/adc.2009.157537] [Medline: 20716675]
2. Higgins JPT, Soares-Weiser K, López-López J, Kakourou A, Chaplin K, Christensen H, et al. Association of BCG, DTP, and measles containing vaccines with childhood mortality: systematic review. BMJ 2016 Oct 13;355:i5170 [FREE Full text] [doi: 10.1136/bmj.i5170] [Medline: 27737834]
3. Kjærgaard J. Bacillus Calmette-Guérin vaccination at birth: Effects on early childhood infections, growth, and development. Dan Med J 2016 Nov;63(11):B5304. [Medline: 27808041]
4. de Bree L, Koeken VA, Joosten LA, Aaby P, Benn CS, van Crevel R, et al. Non-specific effects of vaccines: Current evidence and potential implications. Semin Immunol 2018 Oct;39:35-43. [doi: 10.1016/j.smim.2018.06.002] [Medline: 30007489]
5. Roth A, Garly ML, Jensen H, Nielsen J, Aaby P. Bacillus Calmette-Guérin vaccination and infant mortality. Expert Rev Vaccines 2006 Apr 09;5(2):277-293. [doi: 10.1586/14760584.5.2.277] [Medline: 16608427]
6. Aaby P, Roth A, Ravn H, Napirna B, Rodrigues A, Lisse I, et al. Randomized trial of BCG vaccination at birth to low-birth-weight children: beneficial nonspecific effects in the neonatal period? J Infect Dis 2011 Jul 15;204(2):245-252. [doi: 10.1093/infdis/jir240] [Medline: 21673035]

7. Hollm-Delgado M, Stuart E, Black R. Acute lower respiratory infection among Bacille Calmette-Guérin (BCG)-vaccinated children. Pediatrics 2014 Jan;133(1):e73-e81. [doi: 10.1542/peds.2013-2218] [Medline: 24379224]
8. de Castro M, Pardo-Seco J, Martinón-Torres F. Nonspecific (Heterologous) Protection of Neonatal BCG Vaccination Against Hospitalization Due to Respiratory Infection and Sepsis. Clin Infect Dis 2015 Jun 01;60(11):1611-1619. [doi: 10.1093/cid/civ144] [Medline: 25725054]
9. McGovern M, Canning D. Vaccination and all-cause child mortality from 1985 to 2011: global evidence from the Demographic and Health Surveys. Am J Epidemiol 2015 Nov 01;182(9):791-798 [FREE Full text] [doi: 10.1093/aje/kwv125] [Medline: 26453618]
10. Flanagan KL, van Crevel R, Curtis N, Shann F, Levy O, Optimmunize Network. Heterologous ("nonspecific") and sex-differential effects of vaccines: epidemiology, clinical trials, and emerging immunologic mechanisms. Clin Infect Dis 2013 Jul 09;57(2):283-289 [FREE Full text] [doi: 10.1093/cid/cit209] [Medline: 23572484]
11. Netea M, Domínguez-Andrés J, Barreiro L, Chavakis T, Divangahi M, Fuchs E, et al. Defining trained immunity and its role in health and disease. Nat Rev Immunol 2020 Jun;20(6):375-388 [FREE Full text] [doi: 10.1038/s41577-020-0285-6] [Medline: 32132681]
12. BCG Vaccine Fact Sheet. CDC. URL: https://www.cdc.gov/tb/publications/factsheets/prevention/bcg.htm [accessed 2024-02-14]
13. Messina NL, Gardiner K, Donath S, Flanagan K, Ponsonby A, Shann F, et al. Study protocol for the Melbourne Infant Study: BCG for Allergy and Infection Reduction (MIS BAIR), a randomised controlled trial to determine the non-specific effects of neonatal BCG vaccination in a low-mortality setting. BMJ Open 2019 Dec 15;9(12):e032844 [FREE Full text] [doi: 10.1136/bmjopen-2019-032844] [Medline: 31843845]
14. Curtis N, Sparrow A, Ghebreyesus TA, Netea MG. Considering BCG vaccination to reduce the impact of COVID-19. The Lancet 2020 May;395(10236):1545-1546. [doi: 10.1016/s0140-6736(20)31025-4]
15. Stensballe L, Ravn H, Birk N, Kjærgaard J, Nissen T, Pihl G, et al. BCG Vaccination at Birth and Rate of Hospitalization for Infection Until 15 Months of Age in Danish Children: A Randomized Clinical Multicenter Trial. J Pediatric Infect Dis Soc 2019 Jul 01;8(3):213-220. [doi: 10.1093/jpids/piy029] [Medline: 29635419]
16. Haahr S, Michelsen S, Andersson M, Bjorn-Mortensen K, Soborg B, Wohlfahrt J, et al. Non-specific effects of BCG vaccination on morbidity among children in Greenland-an answer to a relevant question. Int J Epidemiol 2017 Jun 01;46(3):1073-1074. [doi: 10.1093/ije/dyx044] [Medline: 28402471]
17. Kandasamy R, Voysey M, McQuaid F, de Nie K, Ryan R, Orr O, et al. Non-specific immunological effects of selected routine childhood immunisations: systematic review. BMJ 2016 Oct 13;355:i5225 [FREE Full text] [doi: 10.1136/bmj.i5225] [Medline: 27737830]
18. Aaby P, Benn C. Developing the concept of beneficial non-specific effect of live vaccines with epidemiological studies. Clin Microbiol Infect 2019 Dec;25(12):1459-1467 [FREE Full text] [doi: 10.1016/j.cmi.2019.08.011] [Medline: 31449870]
19. Thysen SM, Jensen AKG, Rodrigues A, Borges IDS, Aaby P, Benn C, et al. Can earlier BCG vaccination reduce early infant mortality? Study protocol for a cluster randomised trial in Guinea-Bissau. BMJ Open 2019 Sep 24;9(9):e025724 [FREE Full text] [doi: 10.1136/bmjopen-2018-025724] [Medline: 31551370]
20. Base de Dados. Instituto Nacional de Estatística. URL: https://www.ine.pt/xportal/xmain?xpid=INE&xpgid=ine_base_dados [accessed 2024-02-14]
21. Estratégia de vacinação contra a tuberculose com a vacina BCG norma 006/2016. Direção Geral da Saúde. URL: https://www.backoffice.dgs.pt/upload/DGSv9/ficheiros/i030231.pdf [accessed 2024-02-14]
22. Relatório de Vigilância e Monitorização da Tuberculose em Portugal - Dados definitivos 2018-2019. Lisbon, Portugal: Direção-Geral da Saúde; 2020.
23. The Lancet Child Adolescent Health. Vaccine hesitancy: a generation at risk. Lancet Child Adolesc Health 2019 May;3(5):281 [FREE Full text] [doi: 10.1016/S2352-4642(19)30092-6] [Medline: 30981382]
24. Petrelli F, Contratti C, Tanzi E, Grappasonni I. Vaccine hesitancy, a public health problem. Ann Ig 2018;30(2):86-103 [FREE Full text] [doi: 10.7416/ai.2018.2200] [Medline: 29465146]
25. Kleinnijenhuis J, Quintin J, Preijers F, Benn CS, Joosten LA, Jacobs C, et al. Long-lasting effects of BCG vaccination on both heterologous Th1/Th17 responses and innate trained immunity. J Innate Immun 2014 Oct 30;6(2):152-158 [FREE Full text] [doi: 10.1159/000355628] [Medline: 24192057]
26. Shlomo N. Overview of Data Linkage Methods for Policy Design and Evaluation. In: Crato N, Paruolo P, editors. Data-Driven Policy Impact Evaluation. Cham: Springer; 2019:47-65.
27. Pacheco AG, Saraceni V, Tuboi SH, Moulton LH, Chaisson RE, Cavalcante SC, et al. Validation of a hierarchical deterministic record-linkage algorithm using data from 2 different cohorts of human immunodeficiency virus-infected persons and mortality databases in Brazil. Am J Epidemiol 2008 Dec 01;168(11):1326-1332 [FREE Full text] [doi: 10.1093/aje/kwn249] [Medline: 18849301]
28. Ethics Committee approval. IHMT. URL: https://www.ihmt.unl.pt/wp-content/uploads/2023/12/Parecer-11.23.pdf [accessed 2024-02-14]
29. Projetos submetidos à Comissão de ética. IHMT. URL: https://www.ihmt.unl.pt/wp-content/uploads/2023/02/Projetos-com-pareceres-emitidos-em-2022.pdf [accessed 2024-02-14]

30. Despacho n.º 10440/2016. Diário da República. 2016. URL: https://files.diariodarepublica.pt/2s/2016/08/159000000/2609326093.pdf [accessed 2024-02-14]
31. Seguros de saúde privados no sistema de saúde português: mitos e factos - Observatório da Despesa em Saúde | 02. Nova School of Business and Economics. URL: https://www.novasbe.unl.pt/Portals/0/Files/Social%20Equity%20Initiative/02%20Observatorio%20da%20despesa%20em%20saude_v5.pdf [accessed 2024-02-14]
32. Machado A, Kislaya I, Rodrigues A, Sequeira D, Lima J, Cruz C, et al. COVID-19 vaccine effectiveness against symptomatic SARS-CoV-2 infections, COVID-19 related hospitalizations and deaths, among individuals aged ≥65 years in Portugal: A cohort study based on data-linkage of national registries February-September 2021. PLoS One 2022;17(9):e0274008 [FREE Full text] [doi: 10.1371/journal.pone.0274008] [Medline: 36099273]
33. Machado A, Kislaya I, Soares P, Magalhães S, Rodrigues A, Franco R, et al. Bivalent mRNA vaccine effectiveness against COVID-19 infections, hospitalisations and deaths in Portugal: a cohort study based on electronic health records, September 2022 to May 2023. medRxiv. URL: https://www.medrxiv.org/content/10.1101/2023.09.05.23295025v1 [accessed 2024-02-14]

Abbreviations

BCG: Bacillus Calmette-Guérin vaccine
BDMH: Base de Dados de Morbilidade Hospitalar
DRG: diagnosis-related group
IHMT: Instituto de Higiene e Medicina Tropical
IMR: infant mortality rate
ITQB: Instituto de Tecnologia Química e Biológica António Xavier
MDC: major diagnostic category
NHS: National Health Service
PHC: primary health care
SINAVE: Sistema Nacional de Vigilancia Epidemiologica
TB: tuberculosis
UI: unique identifier

Edited by A Mavragani; submitted 09.12.23; this is a non–peer-reviewed article;accepted 30.01.24; published 14.03.24.

Please cite as:
Fronteira I, Pacheco M, Schaltz-Buchholzer F, Ferrinho P
Nonspecific Effects of the Bacillus Calmette-Guérin Vaccine in Portuguese Children Under 5 Years of Age: Protocol for a Population-Based Historical Birth Cohort Study
JMIR Res Protoc 2024;13:e55332
URL: https://www.researchprotocols.org/2024/1/e55332
doi:10.2196/55332
PMID:38328938

Protocol

Personalized Deep Learning for Substance Use in Hawaii: Protocol for a Passive Sensing and Ecological Momentary Assessment Study

Yinan Sun[1], MA; Ali Kargarandehkordi[1], MSc; Christopher Slade[1], MSc; Aditi Jaiswal[1], MSc; Gerald Busch[2], MPH, MD; Anthony Guerrero[2], MD; Kristina T Phillips[3], PhD; Peter Washington[1], PhD

[1]Department of Information and Computer Sciences, University of Hawaii at Manoa, Honolulu, HI, United States

[2]Department of Psychiatry, University of Hawaii at Manoa, Honolulu, HI, United States

[3]Center for Integrated Health Care Research, Kaiser Permanente Hawaii, Honolulu, HI, United States

Corresponding Author:
Peter Washington, PhD
Department of Information and Computer Sciences
University of Hawaii at Manoa
1680 East-West Road
Honolulu, HI, 96822
United States
Phone: 1 5126800926
Email: pyw@hawaii.edu

Abstract

Background: Artificial intelligence (AI)–powered digital therapies that detect methamphetamine cravings via consumer devices have the potential to reduce health care disparities by providing remote and accessible care solutions to communities with limited care solutions, such as Native Hawaiian, Filipino, and Pacific Islander communities. However, Native Hawaiian, Filipino, and Pacific Islander communities are understudied with respect to digital therapeutics and AI health sensing despite using technology at the same rates as other racial groups.

Objective: In this study, we aimed to understand the feasibility of continuous remote digital monitoring and ecological momentary assessments in Native Hawaiian, Filipino, and Pacific Islander communities in Hawaii by curating a novel data set of longitudinal Fitbit (Fitbit Inc) biosignals with the corresponding craving and substance use labels. We also aimed to develop personalized AI models that predict methamphetamine craving events in real time using wearable sensor data.

Methods: We will develop personalized AI and machine learning models for methamphetamine use and craving prediction in 40 individuals from Native Hawaiian, Filipino, and Pacific Islander communities by curating a novel data set of real-time Fitbit biosensor readings and the corresponding participant annotations (ie, raw self-reported substance use data) of their methamphetamine use and cravings. In the process of collecting this data set, we will gain insights into cultural and other human factors that can challenge the proper acquisition of precise annotations. With the resulting data set, we will use self-supervised learning AI approaches, which are a new family of machine learning methods that allows a neural network to be trained without labels by being optimized to make predictions about the data. The inputs to the proposed AI models are Fitbit biosensor readings, and the outputs are predictions of methamphetamine use or craving. This paradigm is gaining increased attention in AI for health care.

Results: To date, more than 40 individuals have expressed interest in participating in the study, and we have successfully recruited our first 5 participants with minimal logistical challenges and proper compliance. Several logistical challenges that the research team has encountered so far and the related implications are discussed.

Conclusions: We expect to develop models that significantly outperform traditional supervised methods by finetuning according to the data of a participant. Such methods will enable AI solutions that work with the limited data available from Native Hawaiian, Filipino, and Pacific Islander populations and that are inherently unbiased owing to their personalized nature. Such models can support future AI-powered digital therapeutics for substance abuse.

International Registered Report Identifier (IRRID): DERR1-10.2196/46493

(JMIR Res Protoc 2024;13:e46493) doi:10.2196/46493

KEYWORDS

machine learning; precision health; Indigenous data sovereignty; substance use; personalized artificial intelligence; wearables; ecological momentary assessments; passive sensing; mobile phone

Introduction

Background

Methamphetamine abuse is highly prevalent in Hawaii, especially among Indigenous Pacific Peoples [1]. Since the 1980s, Hawaii has been considered the methamphetamine capital of the United States. Data from the Pacific Health Analytics Collaborative show that from 2015 to 2018, in total, 1.5% of Hawaiian residents used methamphetamine annually [2]. This was more than twice the national rate of 0.6%. According to the Bureau of Alcohol, Tobacco, Firearms, and Explosives, 71% of all drug cases in Hawaii were related to methamphetamine [3]. There are major methamphetamine-related disparities between Native Hawaiian, Filipino, and Pacific Islander individuals and people of other races in Hawaii, with Native Hawaiian, Filipino, and Pacific Islander individuals exhibiting elevated rates of illicit substance abuse [4]. According to the Centers for Disease Control and Prevention, Native Hawaiian and Pacific Islander high school students exhibited lifetime methamphetamine use of 7.7% versus 3.7% in White students, 2.7% in Black students, 3.1% in Asian students, and 5.7% in Hispanic and Latino students, and these disparities continued into adulthood [5]. Digital interventions powered by artificial intelligence (AI) have the potential to reduce these disparities by aiding clinicians in remotely providing care and monitoring patients between visits, especially among populations living in rural areas in Hawaii. Furthermore, such technology could be useful in relapse prevention for those hoping to maintain abstinence. In Hawaii in 2021, a total of 96% of residents possessed at least 1 piece of hardware with internet capacity, with only 4% lacking access to such equipment, indicating widespread internet access among the population [6].

AI-based detection of substance abuse using biometric signals measured by wearables is an active field of research across several research laboratories globally, as documented in a 2022 review paper by Rumbut et al [7]. Studies in this field tend to collect prediction labels through the remote administration of an ecological momentary assessment (EMA), a methodology in which participants are periodically asked to answer questions about their psychiatric or behavioral state while living as usual [8-10]. Notably, previous AI models suffered from clinically unacceptable performance. The primary reason for this lackluster performance is that prior methods attempted to train models using data from many patients, which is the status quo in deep learning because of the requirement of massive data sets for successful training. In contrast to these prior works, we will develop personalized AI models using a method developed in PW's laboratory, which are capable of learning baseline patterns of human behavior and transferring this knowledge to prediction tasks with very few labeled examples to learn from.

Our research laboratory is particularly qualified to carry out this project as we are already developing computer science methods to support the personalization of AI models for large and mostly unlabeled data streams, with promising preliminary data and publications in preparation supporting this methodology. As a T1 (covering basic discovery) or T2 (initial human trials) project, our proposed study is significant both in terms of equitable substance abuse therapeutics and as a general methodology for clinical and translational research in other domains. There are countless situations in health care where vast amounts of unlabeled data are collected from a single patient. Annotations for the event of interest (eg, substance abuse) are frequently sparsely dispersed. The development of predictive supervised models is infeasible in such circumstances because classical approaches cannot handle the complexity of data, and modern deep learning approaches require vast amounts of data.

Innovation

To support machine learning (ML) development in situations where vast longitudinal data are collected with minimal human-provided annotations, we propose the development of personalized ML models, which are trained solely on an individual's unlabeled data to learn feature representations that are specific to their baseline temporal dynamics. We are creating a novel method and framework that has never been explored in health care, consisting of pretraining neural networks to learn the temporal dynamics of a patient's biosignals. This method will enable deep networks to be trained using relatively small data sets, which would not be possible without the self-supervised approach proposed in this study. This technique is particularly well-suited for massive data sets with few labels.

The application of personalized AI to a diverse population of persons using substances is unique. Native Hawaiian, Filipino, and Pacific Islander communities have been understudied and could benefit from novel treatments to address methamphetamine use. Although we will apply this technological innovation toward the prediction of methamphetamine use, multimodal time-series personalization can be applied to a variety of other biological and health problems where (1) multiple signals are sparsely emitted, (2) the baseline signal patterns are specific to each individual, and (3) it is infeasible to acquire the vast amounts of labels required to train a supervised deep learning model.

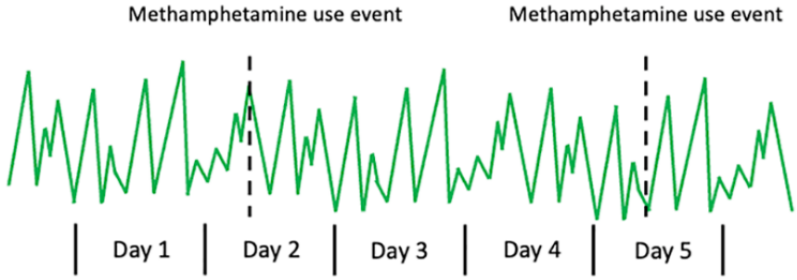
This method has the potential to dramatically advance the field of precision health care by enabling reliable AI predictions from massive but mostly unlabeled data sets, which are trained in a self-supervised manner on data from a single user. This setting of large, unlabeled data sets with sparse supervision appears frequently in the field of digital health care. Notable examples include passive mobile sensing studies for mental health and well-being [11-20], digital therapeutics for children with autism spectrum disorder that record videos of the child [21-37], and passive brain sensors for brain-computer interfaces [38-46]. As such, this study protocol can be considered as one of the first tests of a broader emerging paradigm in precision health.

Methods

Overview

The long-term methodological goal of the proposed work is to develop novel AI methodologies for predicting health events (eg, methamphetamine use and cravings) using biosensors in a personalized manner. This technical innovation will be applied toward the detection of drug use events from wearable device sensors. The inputs to the proposed AI models are Fitbit (Fitbit Inc [47]) biosensor readings, and the outputs are predictions of methamphetamine use or craving (Figure 1). The methods developed can be applied to a variety of biomedical domains.

Figure 1. In many biomedical domains, there exist large data sets with sparse annotations of health events. We propose a "personalized self-supervised learning" method that can support the training of deep neural networks in such scenarios. We will evaluate our method primarily on the prediction of methamphetamine use events using biosignal data from a Fitbit device.



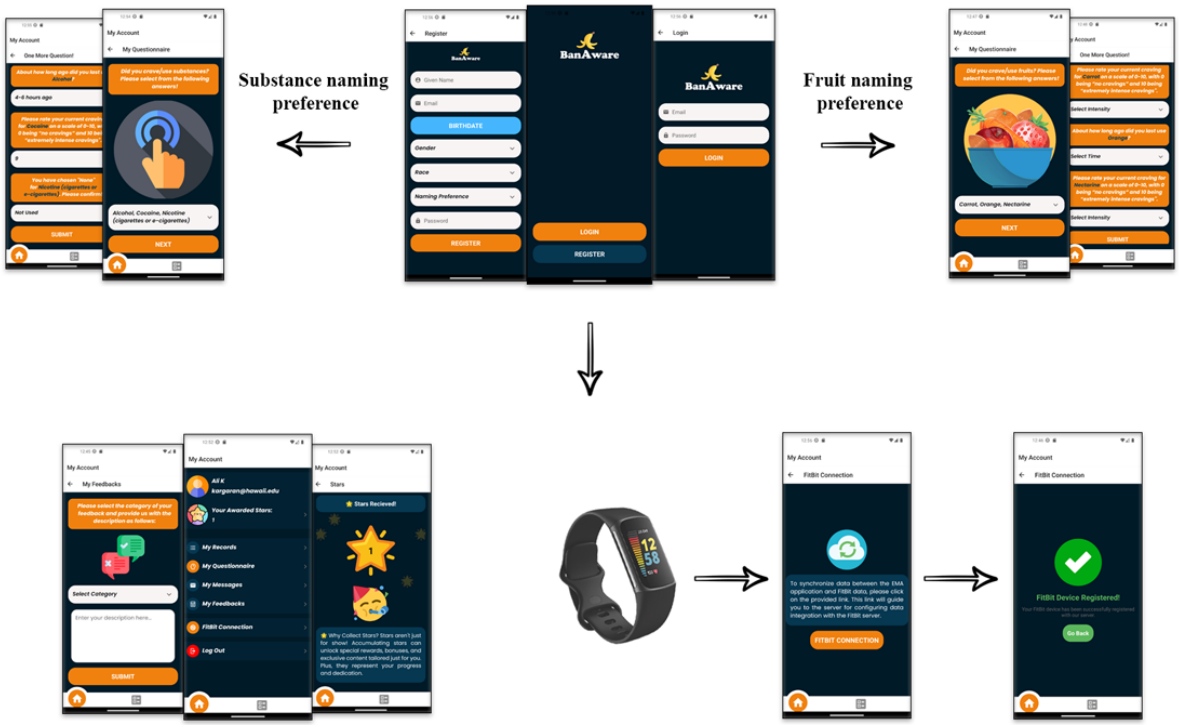
Diagnostic ML models are typically trained and deployed at a population level. In this traditional scenario, a single model is developed to make predictions for all individuals within a population. However, in several health contexts, an event of interest occurs repeatedly for an individual. For example, patients with diabetes have repeated blood glucose spikes, and chronically stressed individuals might have repeated blood pressure spikes. In these cases, ML models can be developed by conducting supervised training on the individual's data only, resulting in a separate personalized model per individual. Although deep learning models have achieved state-of-the-art performance in a variety of health contexts, neural networks require massive data sets that are infeasible to collect for an individual. However, recent advances in self-supervised learning (SSL), or the subfield of ML focusing on pretraining models without any human-provided labels, have made it possible to realize the personalized ML diagnostics paradigm using deep learning by pretraining the weights of a neural network such that it can learn the baseline temporal dynamics without any labels. The pretrained model can then use transfer learning on relatively few labels that are acquired solely from the individual in question. This methodology can work particularly well in scenarios where massive amounts of unlabeled data are collected, such as with continuously worn devices.

Aim 1: To Understand the Feasibility of Remote Digital Monitoring and EMAs in Native Hawaiian, Filipino, and Pacific Islander Communities by Curating Longitudinal Fitbit Biosignals With the Corresponding Substance Use and Craving Labels

Description

We will recruit 40 carefully selected Native Hawaiian, Filipino, and Pacific Islander participants who are either in treatment or have received services from one of our community partners to participate in a 4-week remote Fitbit data collection and concurrent EMA study. EMA studies, which involve periodic digital self-reports about psychiatric and behavioral outcomes *in the wild*, have often been used to understand substance abuse [48], including among persons who use methamphetamine [49]. We expect ≥80% complete data from approximately 25% (10/40) of the participants (refer to the *Recruitment* section for justification). Each participant will wear a study-provided Fitbit Charge 5 watch during all waking hours for at least 15 hours each day. Apart from wearing the device and periodically recording an EMA about their methamphetamine use via a mobile smartphone app (Figure 2), participants will be asked to follow their normal routine throughout the study.

Figure 2. User interface of the ecological monitoring app provided to participants.



Participant Recruitment and Management

We will recruit participants from a combination of sites, including the Hawaii Health and Harm Reduction Center and other sites where the clinical collaborators have connections (ie, Hina Mauka). Potential participants will be eligible for the study if they (1) are aged ≥18 years, (2) self-report consumption of methamphetamine on ≥2 different days per week on average, (3) have no plans to leave Oahu for at least 1 month, and (4) own a smartphone with either a data plan or regular access to a Wi-Fi connection. Potential participants will be excluded if they (1) are homicidal or suicidal, (2) cannot provide informed consent, (3) are not able to complete interviews in English, (4) are expecting incarceration or plan to leave Oahu within the next month, or (5) are unable to provide names and contact information for at least 2 verifiable locator persons for retention purposes.

We will recruit 40 participants in total. A secondary analysis of EMAs for methamphetamine abuse monitoring measured the percentage of participants who reached ≥80% compliance at different frequencies of methamphetamine use, finding that approximately 50% of persons who use methamphetamine 1 to 3 times per month met this 80% compliance bar, and 40% using 1 to 2 days per week met the bar, and 25% using 3 to 4 days per week met the bar [50]. Therefore, we anticipated that approximately 25% (10/40) of the participants will reach ≥80% compliance rate, which is sufficient to demonstrate the feasibility of our AI method, as a separate analysis will be conducted for each participant (ie, 1 model per participant).

Data Collection

We will leverage the existing application programming interface provided by Fitbit to record the user's watch sensor readings and upload the data to the cloud. The Fitbit application programming interface provides access to heart rate (HR), gyroscope and accelerometer readings, breathing rate, blood oxygen saturation (SpO_2) level, and skin temperature sensor readings. These biosensors have previously been used to predict substance abuse and cravings using AI [51-55]. The data will be managed on each participant's smartphone device through an app, implemented for both iOS and Android, which we are actively developing. The study team will install the app on the user's smartphone and configure the Fitbit device during study onboarding.

We will run the study with 8 (20%) of the 40 participants at a time as we have 8 Fitbit Charge 5 devices, resulting in 5 batches of data collection periods. We will record background characteristics, substance use, and treatment history during study intake, and we will record questions pertaining to the tolerability and obtrusiveness of the app during study outtake (Textbox 1). The smartphone app will record EMA responses from the participants throughout the 1-month study period (Textbox 1). At each EMA, we will ask participants to list the approximate times (eg, date, hour, and minute) of their methamphetamine intake in the past 24 hours via a user interface on the smartphone app. Participants will be asked to do the same for cravings. Participants will be prompted to provide EMA responses both when drastic signal changes are detected (ie, event-triggered EMA) and every 24 hours (ie, fixed-interval EMA).

Textbox 1. Study intake and outtake measures and ecological momentary assessment (EMA) questions collected from each participant.

Background characteristics (intake)

- To better describe the sample, participants will be asked about their gender, sexual orientation, age, race or ethnicity, marital status, education, income, employment, housing, and health insurance status.

Substance use and treatment history (intake)

- Questions will be developed to assess current and history of substance use and participation in treatment services.

Tolerability (study conclusion)

- How comfortable was the device?

Obtrusiveness (study conclusion)

- Did the device change your daily routine? Do you have any concerns with continuously Fitbit usage?

Methamphetamine use (EMA)

- Have you used meth since the last time we contacted you?
- Approximately what time did you last use meth?
- How did you use meth the last time you used?

Craving (EMA)

- Please rate your current craving or desire to use methamphetamine at this exact moment on a scale of 0-10, with 0 being “no cravings” and 10 being “extremely intense cravings.”

We will institute procedures to reduce the burden associated with EMA and increase compliance as suggested by Burke et al [56]. To reduce the burden related to time commitment, we are compensating for every signal-contingent response and providing additional compensation when participants respond to >80% of prompts. Participants will be trained extensively on the EMA protocol at baseline, and if they experience any technology-related issues, our research assistants will help troubleshoot these issues remotely. Participants who experience technology-related problems will not have their compensation reduced because of missing prompts.

We will store the curated data from each participant (Figure 2) on a centralized server hosted on Amazon Web Services (AWS; Amazon). Data uploaded from both wearable systems and the smartphone will first run through a preprocessing server hosted on an elastic cloud computing (EC2) instance with data stored on DynamoDB (Amazon). Each table will have columns for the participant ID and timestamp. To ensure privacy and Health Insurance Portability and Accountability Act (HIPAA) compliance, we will encrypt all server-side data and require secret access keys for data access. DynamoDB tables are automatically encrypted on the server side. To add an additional layer of security, we will implement client-side encryption on the mobile app, ensuring encrypted data transmission across an https connection to move data between the devices and AWS. The data will not be accessible without a secret access key. All data will be anonymized.

An anonymized version of participant data will be made available to other computational researchers as a publicly available data set. This data set will be stored on AWS on a HIPAA-compliant server and will be password protected. Researchers will only gain access to this data set by signing a data use agreement. Such data sets exist for activity and emotion recognition from wearable data, but the prediction of methamphetamine use from these measurements will be a challenging task, and other ML practitioners can improve upon our initial AI models with the release of the deidentified data set. This will be the first publicly available data set that includes substance use self-reports alongside wearable sensor readings.

Data Analysis and Interpretation

We will measure the success rate of the remote data collection procedure using the response rate to EMA notifications. We hypothesize that we will observe higher compliance rates with event-triggered EMAs than fixed-interval EMAs. Furthermore, we will document qualitative challenges with the data collection process, tolerability, and unobtrusiveness (Textbox 1). We will conduct an interview with the participants at the study conclusion when the devices are returned. The research team will qualitatively code interview responses to derive recurring themes and design insights.

Potential Pitfalls and Mitigation Strategies

This analysis plan is uniquely robust to incomplete data collection because a separate AI model will be trained and evaluated for each participant. There is no requirement for equivalent data streams between participants nor will the analysis be prevented if the full 28-day data collection period is not achieved. The ML strategy can work with only a few logged methamphetamine use events. We expect approximately 25% (10/40) of the participants to complete the study at a sufficient level of compliance to support personalized ML analysis. This will provide sufficient data to demonstrate the feasibility of personalized ML analysis.

We have budgeted a 4-month buffer period beyond the 5 months required for complete data collection to account for participant delays and no-shows. Because participant data will be uploaded to AWS daily, we will remotely monitor participants through an automated tracking system already developed in our research laboratory and will cease the study if compliance is not logged after 4 days. Another possible issue is Fitbit theft or loss. To minimize this risk, participants will be compensated a minimum of US $135 for study completion and a maximum of US $210, which will be paid when the Fitbit device is returned. In the case of Fitbit device breakage or loss, our laboratory will purchase additional devices with funds separated from Center for Pacific Innovations, Knowledge, and Opportunities, up to a limit of 6 additional devices along the course of the study period.

Aim 2: To Develop Real-Time Personalized AI Models Predicting Methamphetamine Use and Craving With Fitbit Sensor Data

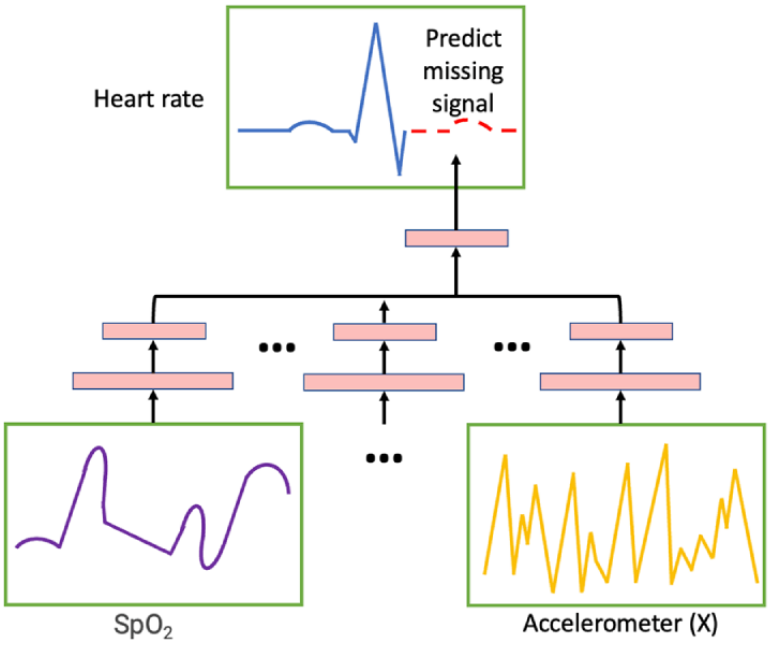
Description

On the basis of extensive support from prior literature, we hypothesize that AI solutions can detect periods of both methamphetamine use and cravings with high sensitivity through the personalization of ML models. Such models will achieve high performance on a single individual through the finetuning of each model using only the data curated from the person of interest for model training. These personalized predictions can trigger the onset of digital therapy. We will develop two AI models per participant: (1) a model that detects methamphetamine use in real time and (2) a model that predicts methamphetamine craving in real time. We hypothesize that model personalization using novel self-supervised pretraining strategies will outperform traditional state-of-the-art AI techniques with <5% of the required label data.

ML Model Training

The inputs to the models will consist of a separate 1D convolutional backbone pretrained for each biometric modality. The convolutional features will be fused upstream into a shared joint dense representation space and finally a dense prediction layer with linear activation for regression prediction (Figure 3). We will implement all models using TensorFlow (Google Brain) [57].

Figure 3. The key methodological computer science innovation of this protocol is the personalization of machine learning models that make predictions from biosignals time-series data without user-provided labels. In this figure, we depict a neural network that is trained to predict a heart rate signal given SpO_2 levels and accelerometer signals from a single participant. SpO_2: blood oxygen saturation.



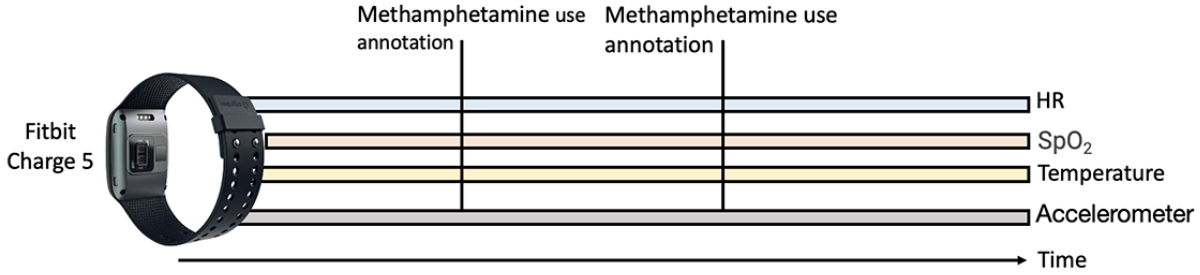
The data augmentation techniques that we apply to the signals will be domain specific, keeping in mind the inherent dynamics of each sensor. For example, for accelerometer data, rotations simulate different sensor placements, and cropping is used to diminish the dependency on event locations [58]. Across several modalities, sensor noise can be simulated through scaling, magnitude warping, and jittering [58]. We will be careful not to apply augmentation strategies that might change the meaning of the underlying signal.

Model Personalization

SSL is usually used to pretrain an entire data set with no explicit labeling by humans to guide the supervision task. We propose to redesign the SSL paradigm toward the task of model personalization. By pretraining a model only on the vast amounts of data curated from a single individual, the weights of the neural network will learn to make predictions using the inherent structure of each participant's biosignals. This is essential because baseline HR, SpO_2, skin temperature, and movement patterns, regardless of stress, will vary drastically across individuals, limiting the performance of general-purpose ML models.

We plan to exploit the multimodal time-series nature of the collected data to perform novel SSL pretraining. We will use ≥1 signal to predict the value of another signal source (Figure 4). The motivation for this approach is that the biometrics of interest recorded by Fitbit are correlated [59-62].

Figure 4. Depiction of the proposed data set, consisting of continuous Fitbit Charge 5 sensor readings and the corresponding methamphetamine use and craving annotations from 20 participants collected over a 4-week period. HR: heart rate; SpO_2: blood oxygen saturation.



Data Analysis and Interpretation

We will train the model on the first 75% of the data (by time) and calculate the balanced accuracy, precision, recall, F_1-score, and area under the receiver operating characteristic curve for the final 25%. This evaluation pattern mimics real-world use, where a model will be calibrated by a user before real-world deployment. It is important to emphasize that we will train and test a separate personalized ML model for each individual (up to 40 separate models).

In a manner similar to our preliminary data, we will evaluate the models by comparing the performance with respect to the number of labeled examples used for supervised finetuning. A plot of this comparison will elucidate the number of methamphetamine annotations required for model calibration to an individual. We will create a separate plot for each study participant as the ML portion of this protocol tests the personalization of ML models rather than a general-purpose one-size-fits-all ML model, which is more typical in ML evaluations.

Feasibility

Self-supervised pretraining has been successfully demonstrated in several contexts in computer science and even health care [59,63,64], although not in the personalized context that we will explore, except for preliminary results that we have recently published [65-68]. Multimodal SSL has demonstrated success in prior literature [69-72], although not in the personalized manner in which we will innovate.

Ethical Considerations

This protocol was approved by the University of Hawaii Institutional Review Board (protocol #2022-01030). In addition, this study has received further scrutiny and approval from the University of Hawaii Data Governance Process (request #230410-3).

Informed consent will be provided by the participants on paper during the intake session of the study.

Participants will provide information about their substance use on a smartphone app that we have created and will install on the phones of each participant. Because Fitbit is owned by Google, participants' Fitbit data will be uploaded directly to Google's cloud servers, which uses the same level of security as other Google products, such as Gmail.

Access to each participant's Fitbit data on Google's cloud servers is implemented through OAuth, which provides clients with secure delegated access to server resources on behalf of a resource owner (ie, the participants of this study). This mechanism is used by companies such as Amazon, Google, Facebook, Microsoft, and X (X Corp, formerly known as Twitter) to permit the users to share information about their accounts with third-party apps or websites. In this case, the "third party" is the study team.

Access to each participant's annotations of substance use and craving from their smartphone app will be immediately uploaded to our secure and encrypted server on AWS, which is HIPAA compliant [73]. The participant's data will be immediately removed from their smartphone after successful uploading to AWS.

All participant data will be analyzed on AWS. A fully anonymized version of the data set will be released to researchers who sign a data use agreement, which will be approved by the University of Hawaii Data Governance Office.

As a precaution, the interface on the app will not be labeled as "substance consumption" and "substance use" but rather as "banana consumption" and "banana use." Furthermore, our data will be stored and labeled as "fruit" rather than "substance use."

The participant's data that will be accessible to the study team will include biometrics data from Fitbit, labels of "banana consumption" and "banana use" with the corresponding timestamps, and a unique participant ID. Digital data will only contain participant IDs rather than identifiable information. A paper copy of the participant's mapping from the participant ID to the name and contact information will be stored on paper and securely locked in a lockbox hidden in PW's desk. The lockbox in PW's desk is secured with a key that only PW has access to, and his desk is in his office, which is secured with another key that only PW has access to. PW's office is located within a suite of offices, which is secured by a third key that only professors in the Information and Computer Sciences Department have access to and which currently only PW has access to.

We will anonymize all the collected data. We will be provided with a Federal Certificate of Confidentiality from the National Institutes of Health, which will protect participants and assure confidentiality and privacy. KTP, a member of the mentorship and community teams, has found that having a Certificate of Confidentiality helps retain participants in lengthy projects.

Compensation Type and Amount

We will provide the participants with US $135 for participation in the study. This amount is commensurate compensation for the requested work (wearing a smartwatch during all waking hours of the day for 4 weeks while continuously annotating their craving events). In addition, this compensation amount is above the market rate of a Fitbit device, helping to mitigate the risk of device theft by study participants.

US $20 will be provided to the participants to cover their transportation expenses for attending 2 in-person meetings on campus.

Furthermore, we will use snowball sampling as a form of recruitment, where participants can choose to refer their acquaintances to the study. Enrolled participants will be encouraged to refer other eligible participants to the study and will receive US $5 each for up to 3 referrals who enroll. The participants will be given 3 recruitment cards to distribute to eligible participants. When a new and eligible enrollee presents the card, the recruiting participant will receive US $5 compensation. If the recruiting participant has already completed the study, they will be contacted via their assigned study phone number (eg, by phone or SMS text messaging) or email to receive the compensation. If this proves unsuccessful, we will reach out to locator contacts or send a letter notifying the participant that they are eligible for the additional compensation.

Finally, we can compensate participants an extra US $40 as an incentive for providing responses on schedule and consistently throughout the study period.

Results

Starting from November 2023, a total of 5 participants visited our laboratory and received Fitbit devices, including 4 (80%) male individuals and 1 (20%) female individual, aged between 22 and 63 years, representing 3 different ethnicities: 3 (60%) are White, 1 (20%) is Mexican, and 1 (20%) is Filipino Hawaiian.

Among the 5 participants, 178 logs have been collected. They completed an average of 8.6 days of EMA activity reporting, with each participant logging their data approximately 4 times per day. In total, the participants reported 40 instances of substance craving and 61 instances of substance use, including methamphetamine, alcohol, cannabis, and nicotine.

Fitbit devices recorded sensor data, including HR, number of steps, SpO_2, HR variability, and breathing rate. HR and number of steps were tracked throughout the day, whereas SpO_2 level, HR variability, and breathing rate were monitored during sleep.

Challenges related to EMA prompt reception were initially experienced by 1 (20%) of the 5 participants, but these were promptly resolved by the research team. In addition, labor-intensive reporting of simultaneous substance use and documenting of constant nicotine use posed difficulties for this participant. Another participant noted increased awareness of substance-related thoughts owing to EMA prompts.

Discussion

Preliminary Findings

To our knowledge, this is the first study to evaluate the feasibility of using a mobile app–based EMA to prospectively capture substance use among the Native Hawaiian, Filipino, and Pacific Islander population. Despite challenges, this study provides evidence to support the feasibility and acceptability of using EMA methods for collecting data on substance use in this population.

Following our research protocol, we successfully recruited 5 participants for our study in the first month of recruitment. Our research protocol, which included 4 scheduled prompts per day, was designed to represent a lower to moderate participant burden [74,75]. Each participant consistently provided an average of 4 logs per day. We received no significant issues or complaints from the participants, and their logging activities have been continuous. This partially aligns with prior studies by Phillips et al [76], Turner et al [50], and Hanson et al [77], who found that it is feasible and acceptable to use EMA to evaluate substances (eg, alcohol and methamphetamine) with people who come from historically marginalized groups.

Meanwhile, 1 (20%) of the 5 participants showed hesitancy regarding privacy concerns when discussing certain types of substances, as reported in the study by Han et al [78] that substance use can still be associated with social stigma. This suggests that building and maintaining a trusting relationship with the participants throughout the study, and even afterward, is crucial.

Despite concerns raised by Adams et al [79] about the potential impact of busy schedules on response rates, no significant problems were encountered in this regard as long as participants initiated their study. However, instances were experienced in which eligible individuals needed to reschedule their meetings because of their demanding work schedules. To accommodate their availability, the research team maintained a flexible schedule to encourage these individuals to visit the laboratory at their convenience. Weekly check-ins were conducted by the research team with the participants to ensure effective participation and promptly address any issues that arose.

Although prior studies, such as those by Cao et al [80] and Rodrigues et al [81], have successfully used Fitbit devices to collect sleep data, one challenge encountered by the research team is the absence of those data (eg, SpO_2 level, HR variability, and breathing rate) that can only be collected while participants are asleep, despite the participants' claims that they wear the Fitbit devices during sleep. To address this issue, the research team recommended that participants activate the sensitive mode for sleep sensitivity in the Fitbit app settings and ensure that they wear the devices tightly or close enough to their wrists. However, this recommendation might negatively affect the

participants' sleep quality, particularly for those who have self-reported sleeping problems.

This research protocol provides compensation to participants for reporting substance use events. However, this approach might lead to an increase in data noise, as observed when 1 (20%) participant provided 7 logs in a single day. The research team will diligently review these data to ensure their effectiveness and minimize potential noise.

None of the participants have reported participation exhaustion owing to the research protocol so far, despite such findings reported by Yang et al [75] and Semborski et al [82] in their studies. This may be attributed to the fact that many participants are still in their first or second weeks of the study. However, the research team observed that contacting participants >2 times per week could induce stress, particularly when technical issues persist without resolution. In response to these observations, the research team has currently limited their contact with each participant to a maximum of 2 times per week to mitigate participant exhaustion. Future studies may benefit from reducing contact frequency and providing clear and efficient instructions whenever such issues arise. Another issue related to participation fatigue or dropout is the extended waiting time for study entry. Despite the research team's efforts to maintain contact with individuals who registered as early as May 2023, some of them may no longer be available or interested after several months of waiting. Future studies should minimize the waiting period to prevent potential disengagement.

One (20%) of the 5 participants expressed concerns about the increased contemplation of substances when responding to EMA prompts. Similarly, Fridberg et al [74] noted a slight increase in self-reported alcohol consequences in their EMA study. One plausible explanation is that certain EMA protocols may induce stress [82], potentially triggering substance use [83]. This study is in its initial stages and cannot provide any conclusions. The research team will closely monitor this participant and conduct weekly check-ins to ensure that there are no adverse effects.

This study has several limitations. Given the small sample size, the preliminary findings do not have enough statistical power to provide any significant findings on participants' substance use and craving patterns or sociocultural factors that might affect those activities. The EMA prompts primarily collect quantitative data related to the scale, timing, or dates of substance use or cravings, excluding information on social and cultural factors that may trigger or influence substance cravings or use. For instance, we could not capture the presence of others during these moments using EMA prompts. Meanwhile, incorporating these questions into EMA prompts as self-reported data could have imposed cognitive demands on the participants, potentially impacting response rates and causing participation fatigue. To address this limitation, we plan to conduct in-depth semistructured interviews to explore the social and cultural factors.

One (20%) of the 5 participants highlighted the challenge of logging multiple substance use instances simultaneously and recommended the implementation of a more user-friendly feature in such situations. Currently, the research team is actively working to enhance this feature. In future studies, it is advisable to consider providing a more intuitive design when requiring participants to submit multiple logs in a more streamlined manner.

Our target population consisted of Native Hawaiian, Filipino, and Pacific Islander individuals; however, none of the team members belonged to this community, despite some team members having lived in Hawaii for >5 years. To address this limitation, the research team will work closely with the local partners, such as Hawaii Health and Harm Reduction Center and Hina Mauka, to ensure that key social and cultural factors are not overlooked.

Another limitation of our study is the exclusion of potentially eligible individuals who do not own a mobile phone or lack internet access. Future research endeavors could enhance inclusivity by considering the provision of mobile phones with a data plan for individuals who lack these resources.

Conclusions

An EMA using smartphone apps offers a broad scope of research perspectives. Its capacity to capture phenomena instantaneously within real-life contexts grants the EMA a promising vantage point for understanding methamphetamine use and cravings among the Native Hawaiian, Filipino, and Pacific Islander population and other racial groups in Hawaii who have experienced methamphetamine-related disparities from the 1980s. Given the dearth of research on this issue within the targeted, historically marginalized group, sharing and presenting a standardized and innovative protocol for conducting EMA studies on methamphetamine use is crucial, which is the primary objective of this study.

We anticipate that this study will yield valuable insights into the feasibility of using EMA methods in this particular population and the sociocultural factors that can affect precise data acquisition. Furthermore, it will enable the development of personalized AI models for predicting methamphetamine-related behaviors within this demographic group. To date, our preliminary findings indicate promising outcomes associated with the use of EMA methods for data collection.

Acknowledgments

This protocol described was supported by grant U54GM138062 from the National Institute of General Medical Sciences, a component of the National Institutes of Health, and its contents are solely the responsibility of the author and do not necessarily represent the official view of the National Institute of General Medical Sciences or the National Institutes of Health.

Conflicts of Interest

None declared.

References

1. Kenneth I. Reducing Demand For Crystal Meth in Hawaii: "Ohana" Involvement. Saarbrücken, Germany: Lambert Academic Publishing; 2015.
2. Pasia N. A look at Hawaii's underfunded meth epidemic. State of Reform. 2021 Sep 15. URL: https://stateofreform.com/news/2021/09/a-look-at-hawaiis-underfunded-meth-epidemic/ [accessed 2024-01-24]
3. Earles D, DeCosta G. Hawaii Meth Project staff interview (2014). 2014. URL: https://scholar.google.com/scholar_lookup?author=D.+Earles&author=G.+DeCosta&title=%E2%80%9CHawaii+Meth+Project+staff+interview&publication_year=2014&journal=Honolulu%2C+Hawaii# [accessed 2024-01-24]
4. Monick B, Rehuher D, Wilczek K, Helm S. Supplemental material for eliminating disparities in youth substance use among native Hawaiian, Micronesian, and sex and gender minorities: a qualitative needs assessment from interviews with public service leaders. Psychol Serv 2022 Jan 31;20(S1):103-116. [doi: 10.1037/ser0000609.supp]
5. Behavioral Health Barometer United States, Volume 5: Indicators as measured through the 2017 National Survey on Drug Use and Health and the National Survey of Substance Abuse Treatment Services. Rockville, MD: Substance Abuse and Mental Health Services Administration (US); 2019.
6. Kirsch I, Sands A, Robbins S, Goodman M, Rannenbaum R. Hawaii digital literacy and readiness study. National Association of State Workforce Agencies. 2021 Sep. URL: https://library.naswa.org/doi/10.5555/20.500.11941/4491 [accessed 2024-01-23]
7. Rumbut J, Fang H, Carreiro S, Smelson D, Boyer E. An overview of wearable biosensor systems for real-time substance use detection. IEEE Internet Things J 2022 Dec 1;9(23):23405-23415. [doi: 10.1109/jiot.2022.3207090]
8. Ferreri F, Bourla A, Mouchabac S, Karila L. e-Addictology: an overview of new technologies for assessing and intervening in addictive behaviors. Front Psychiatry 2018 Mar 1;9:51 [FREE Full text] [doi: 10.3389/fpsyt.2018.00051] [Medline: 29545756]
9. Jacobson NC, Bhattacharya S. Digital biomarkers of anxiety disorder symptom changes: personalized deep learning models using smartphone sensors accurately predict anxiety symptoms from ecological momentary assessments. Behav Res Ther 2022 Feb;149:104013 [FREE Full text] [doi: 10.1016/j.brat.2021.104013] [Medline: 35030442]
10. Tutunji R, Kogias N, Kapteijns B, Krentz M, Krause F, Vassena E, et al. Using wearable biosensors and ecological momentary assessments for the detection of prolonged stress in real life. BioRxiv. Preprint posted online on May 18, 2022 [FREE Full text] [doi: 10.1101/2021.06.29.450360]
11. Adler DA, Wang F, Mohr DC, Choudhury T. Machine learning for passive mental health symptom prediction: generalization across different longitudinal mobile sensing studies. PLoS One 2022 Apr 27;17(4):e0266516 [FREE Full text] [doi: 10.1371/journal.pone.0266516] [Medline: 35476787]
12. Spathis D, Servia-Rodriguez S, Farrahi K, Mascolo C, Rentfrow J. Passive mobile sensing and psychological traits for large scale mood prediction. In: Proceedings of the 13th EAI International Conference on Pervasive Computing Technologies for Healthcare. 2019 Presented at: PervasiveHealth'19; May 20-23, 2019; Trento, Italy. [doi: 10.1145/3329189.3329213]
13. Lind MN, Byrne ML, Wicks G, Smidt AM, Allen NB. The Effortless Assessment of Risk States (EARS) tool: an interpersonal approach to mobile sensing. JMIR Ment Health 2018 Aug 28;5(3):e10334 [FREE Full text] [doi: 10.2196/10334] [Medline: 30154072]
14. Trifan A, Oliveira M, Oliveira JL. Passive sensing of health outcomes through smartphones: systematic review of current solutions and possible limitations. JMIR Mhealth Uhealth 2019 Aug 23;7(8):e12649 [FREE Full text] [doi: 10.2196/12649] [Medline: 31444874]
15. Rabbi M, Ali S, Choudhury T, Berke E. Passive and in-situ assessment of mental and physical well-being using mobile sensors. In: Proceedings of the 13th International Conference on Ubiquitous Computing. 2011 Presented at: UbiComp '11; September 17-21, 2011; Beijing, China. [doi: 10.1145/2030112.2030164]
16. Boonstra TW, Nicholas J, Wong QJ, Shaw F, Townsend S, Christensen H. Using mobile phone sensor technology for mental health research: integrated analysis to identify hidden challenges and potential solutions. J Med Internet Res 2018 Jul 30;20(7):e10131 [FREE Full text] [doi: 10.2196/10131] [Medline: 30061092]
17. Young AS, Choi A, Cannedy S, Hoffmann L, Levine L, Liang LJ, et al. Passive mobile self-tracking of mental health by veterans with serious mental illness: protocol for a user-centered design and prospective cohort study. JMIR Res Protoc 2022 Aug 05;11(8):e39010 [FREE Full text] [doi: 10.2196/39010] [Medline: 35930336]
18. Wen H, Sobolev M, Vitale R, Kizer J, Pollak JP, Muench F, et al. mPulse mobile sensing model for passive detection of impulsive behavior: exploratory prediction study. JMIR Ment Health 2021 Jan 27;8(1):e25019 [FREE Full text] [doi: 10.2196/25019] [Medline: 33502330]
19. Wang R, Wang W, daSilva A, Huckins JF, Kelley WM, Heatherton TF, et al. Tracking depression dynamics in college students using mobile phone and wearable sensing. Proc ACM Interact Mob Wearable Ubiquitous Technol 2018 Mar 26;2(1):1-26. [doi: 10.1145/3191775]

20. Wang R, Aung MS, Abdullah S, Brian R, Campbell AT, Choudhury T, et al. CrossCheck: toward passive sensing and detection of mental health changes in people with schizophrenia. In: Proceedings of the 2016 ACM International Joint Conference on Pervasive and Ubiquitous Computing. 2016 Presented at: UbiComp '16; September 12-16, 2016; Heidelberg, Germany. [doi: 10.1145/2971648.2971740]
21. Banerjee A, Mutlu OC, Kline A, Surabhi S, Washington P, Wall DP. Training and profiling a pediatric facial expression classifier for children on mobile devices: machine learning study. JMIR Form Res 2023 Mar 21;7:e39917 [FREE Full text] [doi: 10.2196/39917] [Medline: 35962462]
22. Daniels J, Haber N, Voss C, Schwartz J, Tamura S, Fazel A, et al. Feasibility testing of a wearable behavioral aid for social learning in children with autism. Appl Clin Inform 2018 Jan 21;9(1):129-140 [FREE Full text] [doi: 10.1055/s-0038-1626727] [Medline: 29466819]
23. Daniels J, Schwartz JN, Voss C, Haber N, Fazel A, Kline A, et al. Exploratory study examining the at-home feasibility of a wearable tool for social-affective learning in children with autism. NPJ Digit Med 2018 Aug 02;1(1):32 [FREE Full text] [doi: 10.1038/s41746-018-0035-3] [Medline: 31304314]
24. Kalantarian H, Jedoui K, Washington P, Wall DP. A mobile game for automatic emotion-labeling of images. IEEE Trans Games 2020 Jun;12(2):213-218 [FREE Full text] [doi: 10.1109/tg.2018.2877325] [Medline: 32551410]
25. Kalantarian H, Washington P, Schwartz J, Daniels J, Haber N, Wall D. A gamified mobile system for crowdsourcing video for autism research. 2018 Presented at: IEEE International Conference on Healthcare Informatics (ICHI); June 04-07, 2018; New York, NY. [doi: 10.1109/ichi.2018.00052]
26. Kalantarian H, Jedoui K, Dunlap K, Schwartz J, Washington P, Husic A, et al. The performance of emotion classifiers for children with parent-reported autism: quantitative feasibility study. JMIR Ment Health 2020 Apr 01;7(4):e13174 [FREE Full text] [doi: 10.2196/13174] [Medline: 32234701]
27. Kalantarian H, Jedoui K, Washington P, Tariq Q, Dunlap K, Schwartz J, et al. Labeling images with facial emotion and the potential for pediatric healthcare. Artif Intell Med 2019 Jul;98:77-86 [FREE Full text] [doi: 10.1016/j.artmed.2019.06.004] [Medline: 31521254]
28. Kalantarian H, Washington P, Schwartz J, Daniels J, Haber N, Wall DP. Guess what?: towards understanding autism from structured video using facial affect. J Healthc Inform Res 2019 Oct 2;3(1):43-66 [FREE Full text] [doi: 10.1007/s41666-018-0034-9] [Medline: 33313475]
29. Kline A, Voss C, Washington P, Haber N, Schwartz H, Tariq Q, et al. Superpower glass. GetMobile Mob Comput Commun 2019 Nov 14;23(2):35-38. [doi: 10.1145/3372300.3372308]
30. Penev Y, Dunlap K, Husic A, Hou C, Washington P, Leblanc E, et al. A mobile game platform for improving social communication in children with autism: a feasibility study. Appl Clin Inform 2021 Oct 17;12(5):1030-1040 [FREE Full text] [doi: 10.1055/s-0041-1736626] [Medline: 34788890]
31. Varma M, Washington P, Chrisman B, Kline A, Leblanc E, Paskov K, et al. Identification of social engagement indicators associated with autism spectrum disorder using a game-based mobile app: comparative study of gaze fixation and visual scanning methods. J Med Internet Res 2022 Feb 15;24(2):e31830 [FREE Full text] [doi: 10.2196/31830] [Medline: 35166683]
32. Voss C, Schwartz J, Daniels J, Kline A, Haber N, Washington P, et al. Effect of wearable digital intervention for improving socialization in children with autism spectrum disorder: a randomized clinical trial. JAMA Pediatr 2019 May 01;173(5):446-454 [FREE Full text] [doi: 10.1001/jamapediatrics.2019.0285] [Medline: 30907929]
33. Voss C, Washington P, Haber N, Kline A, Daniels J, Fazel A, et al. Superpower glass: delivering unobtrusive real-time social cues in wearable systems. In: Proceedings of the 2016 ACM International Joint Conference on Pervasive and Ubiquitous Computing: Adjunct. 2016 Presented at: UbiComp '16; September 12-16, 2016; Heidelberg, Germany. [doi: 10.1145/2968219.2968310]
34. Washington P, Park N, Srivastava P, Voss C, Kline A, Varma M, et al. Data-driven diagnostics and the potential of mobile artificial intelligence for digital therapeutic phenotyping in computational psychiatry. Biol Psychiatry Cogn Neurosci Neuroimaging 2020 Aug;5(8):759-769 [FREE Full text] [doi: 10.1016/j.bpsc.2019.11.015] [Medline: 32085921]
35. Washington P, Voss C, Haber N, Tanaka S, Daniels J, Feinstein C, et al. A wearable social interaction aid for children with autism. In: Proceedings of the 2016 CHI Conference Extended Abstracts on Human Factors in Computing Systems. 2016 Presented at: CHI EA '16; May 7-12, 2016; San Jose, CA. [doi: 10.1145/2851581.2892282]
36. Washington P, Kalantarian H, Kent J, Husic A, Kline A, Leblanc E, et al. Improved digital therapy for developmental pediatrics using domain-specific artificial intelligence: machine learning study. JMIR Pediatr Parent 2022 Apr 08;5(2):e26760 [FREE Full text] [doi: 10.2196/26760] [Medline: 35394438]
37. Washington P, Voss C, Kline A, Haber N, Daniels J, Fazel A, et al. SuperpowerGlass: a wearable aid for the at-home therapy of children with autism. Proc ACM Interact Mob Wearable Ubiquitous Technol 2017 Sep 11;1(3):1-22. [doi: 10.1145/3130977]
38. Ahn M, Lee M, Choi J, Jun SC. A review of brain-computer interface games and an opinion survey from researchers, developers and users. Sensors (Basel) 2014 Aug 11;14(8):14601-14633 [FREE Full text] [doi: 10.3390/s140814601] [Medline: 25116904]
39. Al-Hudhud G, Alqahtani L, Albaity H, Alsaeed D, Al-Turaiki I. Analyzing passive BCI signals to control adaptive automation devices. Sensors (Basel) 2019 Jul 10;19(14):3042 [FREE Full text] [doi: 10.3390/s19143042] [Medline: 31295908]

40. Bagheri M, Power SD. Simultaneous classification of both mental workload and stress level suitable for an online passive brain-computer interface. Sensors (Basel) 2022 Jan 11;22(2):535 [FREE Full text] [doi: 10.3390/s22020535] [Medline: 35062495]
41. Chen WC, Lee CW, Kiourti A, Volakis JL. A multi-channel passive brain implant for wireless neuropotential monitoring. IEEE J Electromagn RF Microw Med Biol 2018 Dec;2(4):262-269. [doi: 10.1109/jerm.2018.2877330]
42. Estepp JR, Christensen JC. Electrode replacement does not affect classification accuracy in dual-session use of a passive brain-computer interface for assessing cognitive workload. Front Neurosci 2015 Mar 09;9:54 [FREE Full text] [doi: 10.3389/fnins.2015.00054] [Medline: 25805963]
43. Park S, Han CH, Im CH. Design of wearable EEG devices specialized for passive brain-computer interface applications. Sensors (Basel) 2020 Aug 14;20(16):4572 [FREE Full text] [doi: 10.3390/s20164572] [Medline: 32824011]
44. Sciaraffa N, Di Flumeri G, Germano D, Giorgi A, Di Florio A, Borghini G, et al. Evaluation of a new lightweight EEG technology for translational applications of passive brain-computer interfaces. Front Hum Neurosci 2022 Jul 14;16:901387 [FREE Full text] [doi: 10.3389/fnhum.2022.901387] [Medline: 35911603]
45. Zander TO, Andreessen LM, Berg A, Bleuel M, Pawlitzki J, Zawallich L, et al. Evaluation of a dry EEG system for application of passive brain-computer interfaces in autonomous driving. Front Hum Neurosci 2017 Feb 28;11:78 [FREE Full text] [doi: 10.3389/fnhum.2017.00078] [Medline: 28293184]
46. Zander TO, Jatzev S. Detecting affective covert user states with passive brain-computer interfaces. 2009 Presented at: 3rd International Conference on Affective Computing and Intelligent Interaction and Workshops; September 10-12, 2009; Amsterdam, The Netherlands. [doi: 10.1109/acii.2009.5349456]
47. Web API reference. Fitbit. URL: https://dev.fitbit.com/build/reference/web-api/ [accessed 2024-01-25]
48. Shiffman S. Ecological momentary assessment (EMA) in studies of substance use. Psychol Assess 2009 Dec;21(4):486-497 [FREE Full text] [doi: 10.1037/a0017074] [Medline: 19947783]
49. Galloway GP, Didier R, Garrison K, Mendelson J. Feasibility of ecological momentary assessment using cellular telephones in methamphetamine dependent subjects. Subst Abuse 2008 Feb 10;1:9-14 [FREE Full text] [doi: 10.4137/sart.s428] [Medline: 19997532]
50. Turner CM, Coffin P, Santos D, Huffaker S, Matheson T, Euren J, et al. Race/ethnicity, education, and age are associated with engagement in ecological momentary assessment text messaging among substance-using MSM in San Francisco. J Subst Abuse Treat 2017 Apr;75:43-48 [FREE Full text] [doi: 10.1016/j.jsat.2017.01.007] [Medline: 28237053]
51. Carreiro S, Chintha KK, Shrestha S, Chapman B, Smelson D, Indic P. Wearable sensor-based detection of stress and craving in patients during treatment for substance use disorder: a mixed methods pilot study. Drug Alcohol Depend 2020 Apr 01;209:107929 [FREE Full text] [doi: 10.1016/j.drugalcdep.2020.107929] [Medline: 32193048]
52. Mahmud MS, Fang H, Wang H, Carreiro S, Boyer E. Automatic detection of opioid intake using wearable biosensor. 2018 Presented at: International Conference on Computing, Networking and Communications (ICNC); March 05-08, 2018; Maui, HI. [doi: 10.1109/iccnc.2018.8390334]
53. Natarajan A, Parate A, Gaiser E, Angarita GA, Malison RT, Marlin BM, et al. Detecting cocaine use with wearable electrocardiogram sensors. In: Proceedings of the 2013 ACM International Joint Conference on Pervasive and Ubiquitous Computing. 2013 Presented at: UbiComp '13; September 8-12, 2013; Zurich, Switzerland. [doi: 10.1145/2493432.2493496]
54. Rumbut J, Singh D, Fang H, Wang H, Carreiro S, Boyer E. Poster abstract: detecting kratom intoxication in wearable biosensor data. 2019 Presented at: IEEE/ACM International Conference on Connected Health: Applications, Systems and Engineering Technologies (CHASE); September 25-27, 2019; Arlington, VA. [doi: 10.1109/chase48038.2019.00028]
55. Shi R, Chen Z, Wang H, Sun P, Trull T, Shang Y. mAAS -- a mobile ambulatory assessment system for alcohol craving studies. 2015 Presented at: IEEE 39th Annual Computer Software and Applications Conference; July 01-05, 2015; Taichung, Taiwan. [doi: 10.1109/compsac.2015.242]
56. Burke LE, Shiffman S, Music E, Styn MA, Kriska A, Smailagic A, et al. Ecological momentary assessment in behavioral research: addressing technological and human participant challenges. J Med Internet Res 2017 Mar 15;19(3):e77 [FREE Full text] [doi: 10.2196/jmir.7138] [Medline: 28298264]
57. Abadi M, Barham P, Chen J, Chen Z, Davis A, Dean J, et al. TensorFlow: a system for large-scale machine learning. In: Proceedings of the 12th USENIX conference on Operating Systems Design and Implementation. 2016 Presented at: OSDI'16; November 2-4, 2016; Savannah, GA.
58. Um TT, Pfister FM, Pichler D, Endo S, Lang M, Hirche S, et al. Data augmentation of wearable sensor data for Parkinson's disease monitoring using convolutional neural networks. In: Proceedings of the 19th ACM International Conference on Multimodal Interaction. 2017 Presented at: ICMI '17; November 13-17, 2017; Glasgow, UK. [doi: 10.1145/3136755.3136817]
59. Chowdhury A, Rosenthal J, Waring J, Umeton R. Applying self-supervised learning to medicine: review of the state of the art and medical implementations. Informatics 2021 Sep 10;8(3):59. [doi: 10.3390/informatics8030059]
60. Lan X, Ng D, Hong S, Feng M. Intra-inter subject self-supervised learning for multivariate cardiac signals. Proc AAAI Conf Artif Intell 2022 Jun 28;36(4):4532-4540. [doi: 10.1609/aaai.v36i4.20376]
61. Li Y, Wei D, Chen J, Cao S, Zhou H, Zhu Y, et al. Efficient and effective training of COVID-19 classification networks with self-supervised dual-track learning to rank. IEEE J Biomed Health Inform 2020 Oct;24(10):2787-2797. [doi: 10.1109/jbhi.2020.3018181]

62. Tiu E, Talius E, Patel P, Langlotz CP, Ng AY, Rajpurkar P. Expert-level detection of pathologies from unannotated chest X-ray images via self-supervised learning. Nat Biomed Eng 2022 Dec 15;6(12):1399-1406 [FREE Full text] [doi: 10.1038/s41551-022-00936-9] [Medline: 36109605]
63. Krishnan R, Rajpurkar P, Topol EJ. Self-supervised learning in medicine and healthcare. Nat Biomed Eng 2022 Dec 11;6(12):1346-1352. [doi: 10.1038/s41551-022-00914-1] [Medline: 35953649]
64. Shurrab S, Duwairi R. Self-supervised learning methods and applications in medical imaging analysis: a survey. PeerJ Comput Sci 2022 Jul 19;8:e1045 [FREE Full text] [doi: 10.7717/peerj-cs.1045] [Medline: 36091989]
65. Islam T, Washington P. Individualized stress mobile sensing using self-supervised pre-training. Appl Sci 2023 Nov 04;13(21):12035. [doi: 10.3390/app132112035]
66. Eom S, Eom S, Washington P. SIM-CNN: self-supervised individualized multimodal learning for stress prediction on nurses using biosignals. medRxiv. Preprint posted online August 28, 2023 [FREE Full text] [doi: 10.1101/2023.08.25.23294640]
67. Kargarandehkordi A, Kaisti M, Washington P. Personalization of affective models to enable neuropsychiatric digital precision health interventions: a feasibility study. arXiv. Preprint posted online on September 21, 2023 [FREE Full text]
68. Li J, Washington P. A comparison of personalized and generalized approaches to emotion recognition using consumer wearable devices: machine learning study. arXiv. Preprint posted online on August 28, 2023 .
69. Akbari H, Yuan L, Qian R, Chuang WH, Chang SF, Cui Y, et al. VATT: transformers for multimodal self-supervised learning from raw video, audio and text. arXiv. Preprint posted online on April 22, 2021 [FREE Full text]
70. Lee MA, Zhu Y, Srinivasan K, Shah P, Savarese S, Fei-Fei L, et al. Making sense of vision and touch: self-supervised learning of multimodal representations for contact-rich tasks. 2019 Presented at: International Conference on Robotics and Automation (ICRA); May 20-24, 2019; Montreal, QC. [doi: 10.1109/icra.2019.8793485]
71. Taleb A, Lippert C, Klein T, Nabi M. Multimodal self-supervised learning for medical image analysis. In: Proceedings of the International Conference on Information Processing in Medical Imaging. 2021 Presented at: IPMI 2021; June 28-30, 2021; Online. [doi: 10.1007/978-3-030-78191-0_51]
72. Wang L, Luc P, Recasens A, Alayrac JB, van den Oord A. Multimodal self-supervised learning of general audio representations. arXiv. Preprint posted online on April 26, 2021 .
73. HIPAA Compliance. Amazon Web Services. URL: https://aws.amazon.com/compliance/hipaa-compliance/ [accessed 2024-01-25]
74. Fridberg DJ, Faria J, Cao D, King AC. Real-time mobile monitoring of drinking episodes in young adult heavy drinkers: development and comparative survey study. JMIR Mhealth Uhealth 2019 Nov 20;7(11):e13765 [FREE Full text] [doi: 10.2196/13765] [Medline: 31746774]
75. Yang C, Linas B, Kirk G, Bollinger R, Chang L, Chander G, et al. Feasibility and acceptability of smartphone-based ecological momentary assessment of alcohol use among African American men who have sex with men in Baltimore. JMIR Mhealth Uhealth 2015 Jun 17;3(2):e67 [FREE Full text] [doi: 10.2196/mhealth.4344] [Medline: 26085078]
76. Phillips KT, Phillips MM, Lalonde TL, Prince MA. Does social context matter? an ecological momentary assessment study of marijuana use among college students. Addict Behav 2018 Aug;83:154-159. [doi: 10.1016/j.addbeh.2018.01.004] [Medline: 29329753]
77. Hanson JD, Harris A, Gilbertson RJ, Charboneau M, O'Leary M. Feasibility and acceptability of using ecological momentary assessment to evaluate alcohol use with American Indian women. Int J Environ Res Public Health 2023 Jun 07;20(12):6071 [FREE Full text] [doi: 10.3390/ijerph20126071] [Medline: 37372658]
78. Han H, Zhang JY, Hser YI, Liang D, Li X, Wang SS, et al. Feasibility of a mobile phone app to support recovery from addiction in China: secondary analysis of a pilot study. JMIR Mhealth Uhealth 2018 Feb 27;6(2):e46 [FREE Full text] [doi: 10.2196/mhealth.8388] [Medline: 29487040]
79. Adams L, Igbinedion G, DeVinney A, Azasu E, Nestadt P, Thrul J, et al. Assessing the real-time influence of racism-related stress and suicidality among Black men: protocol for an ecological momentary assessment study. JMIR Res Protoc 2021 Oct 20;10(10):e31241 [FREE Full text] [doi: 10.2196/31241] [Medline: 34668869]
80. Cao R, Azimi I, Sarhaddi F, Niela-Vilen H, Axelin A, Liljeberg P, et al. Accuracy assessment of Oura ring nocturnal heart rate and heart rate variability in comparison with electrocardiography in time and frequency domains: comprehensive analysis. J Med Internet Res 2022 Jan 18;24(1):e27487 [FREE Full text] [doi: 10.2196/27487] [Medline: 35040799]
81. Rodrigues E, Lima D, Barbosa P, Gonzaga K, Guerra RO, Pimentel M, et al. HRV monitoring using commercial wearable devices as a health indicator for older persons during the pandemic. Sensors (Basel) 2022 Mar 04;22(5):2001 [FREE Full text] [doi: 10.3390/s22052001] [Medline: 35271148]
82. Semborski S, Henwood B, Redline B, Dzubur E, Mason T, Intille S. Feasibility and acceptability of ecological momentary assessment with young adults who are currently or were formerly homeless: mixed methods study. JMIR Form Res 2022 Mar 25;6(3):e33387 [FREE Full text] [doi: 10.2196/33387] [Medline: 35333187]
83. Zorrilla EP, Logrip ML, Koob GF. Corticotropin releasing factor: a key role in the neurobiology of addiction. Front Neuroendocrinol 2014 Apr;35(2):234-244 [FREE Full text] [doi: 10.1016/j.yfrne.2014.01.001] [Medline: 24456850]

Abbreviations

AI: artificial intelligence
AWS: Amazon Web Services
EMA: ecological momentary assessment
HIPAA: Health Insurance Portability and Accountability Act
HR: heart rate
ML: machine learning
SpO_2: blood oxygen saturation
SSL: self-supervised learning

Edited by A Mavragani; submitted 25.08.23; peer-reviewed by W LaMendola, J Zhu; comments to author 03.11.23; revised version received 08.12.23; accepted 11.12.23; published 07.02.24.

Please cite as:
Sun Y, Kargarandehkordi A, Slade C, Jaiswal A, Busch G, Guerrero A, Phillips KT, Washington P
Personalized Deep Learning for Substance Use in Hawaii: Protocol for a Passive Sensing and Ecological Momentary Assessment Study
JMIR Res Protoc 2024;13:e46493
URL: https://www.researchprotocols.org/2024/1/e46493
doi:10.2196/46493
PMID:38324375

Protocol

Digitally Diagnosing Multiple Developmental Delays Using Crowdsourcing Fused With Machine Learning: Protocol for a Human-in-the-Loop Machine Learning Study

Aditi Jaiswal[1], MS; Ruben Kruiper[1], PhD; Abdur Rasool[1], PhD; Aayush Nandkeolyar[1], BTECH; Dennis P Wall[2,3,4], PhD; Peter Washington[1], PhD

[1]Department of Information and Computer Sciences, University of Hawaii at Manoa, Honolulu, HI, United States

[2]Department of Pediatrics (Systems Medicine), Stanford University School of Medicine, Stanford, CA, United States

[3]Department of Biomedical Data Science, Stanford University School of Medicine, Stanford, CA, United States

[4]Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, United States

Corresponding Author:
Aditi Jaiswal, MS
Department of Information and Computer Sciences
University of Hawaii at Manoa
Room 312, Pacific Ocean Science and Technology (POST)
1680 East-West Road
Honolulu, HI, 96822
United States
Phone: 1 8088296359
Email: ajaiswal@hawaii.edu

Abstract

Background: A considerable number of minors in the United States are diagnosed with developmental or psychiatric conditions, potentially influenced by underdiagnosis factors such as cost, distance, and clinician availability. Despite the potential of digital phenotyping tools with machine learning (ML) approaches to expedite diagnoses and enhance diagnostic services for pediatric psychiatric conditions, existing methods face limitations because they use a limited set of social features for prediction tasks and focus on a single binary prediction, resulting in uncertain accuracies.

Objective: This study aims to propose the development of a gamified web system for data collection, followed by a fusion of novel crowdsourcing algorithms with ML behavioral feature extraction approaches to simultaneously predict diagnoses of autism spectrum disorder and attention-deficit/hyperactivity disorder in a precise and specific manner.

Methods: The proposed pipeline will consist of (1) gamified web applications to curate videos of social interactions adaptively based on the needs of the diagnostic system, (2) behavioral feature extraction techniques consisting of automated ML methods and novel crowdsourcing algorithms, and (3) the development of ML models that classify several conditions simultaneously and that adaptively request additional information based on uncertainties about the data.

Results: A preliminary version of the web interface has been implemented, and a prior feature selection method has highlighted a core set of behavioral features that can be targeted through the proposed gamified approach.

Conclusions: The prospect for high reward stems from the possibility of creating the first artificial intelligence–powered tool that can identify complex social behaviors well enough to distinguish conditions with nuanced differentiators such as autism spectrum disorder and attention-deficit/hyperactivity disorder.

International Registered Report Identifier (IRRID): PRR1-10.2196/52205

(JMIR Res Protoc 2024;13:e52205) doi:10.2196/52205

KEYWORDS

machine learning; crowdsourcing; autism spectrum disorder; ASD; attention-deficit/hyperactivity disorder; ADHD; precision health

Introduction

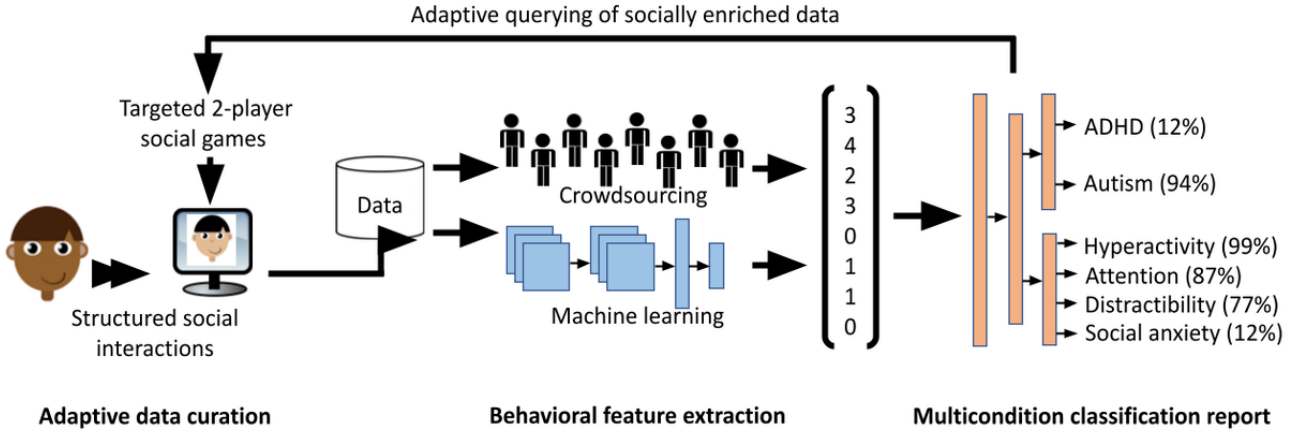
Background

Approximately 17% of minors in the United States aged 3 to 17 years have a diagnosis of ≥1 developmental or psychiatric conditions [1], with the true prevalence likely being higher because of underdiagnosis in rural areas and for minority populations [2]. Unfortunately, timely diagnostic services are inaccessible to a large portion of the United States and global population owing to cost, distance, and clinician availability. Digital phenotyping tools have the potential to shorten the time to diagnosis and bring diagnostic services to more people by enabling accessible evaluations. Although automated machine learning (ML) approaches for the detection of pediatric psychiatric conditions have garnered increased research attention in recent years, existing approaches use a limited set of social features for the prediction task and focus on a single binary prediction.

Many psychiatric conditions affecting adolescents contain overlapping etiologies and phenotypic characteristics. A major difficulty preventing the expansion of computational methods into the simultaneous prediction of multiple related conditions stems from heavy similarities between their phenotypes, creating barriers to achieving specificity and precision. Although some of the key overlapping and distinct features of these conditions are related to behaviors that can be automatically detected with ML methods, such as eye gaze patterns and facial emotion evocation, the majority are too complex for current ML techniques to classify precisely. For example, the degree to which a child enjoys participating in social games and interactions is one of the most salient behavioral features for autism spectrum disorder (ASD) diagnosis [3]. However, building an ML model for behavioral features is infeasible because of outliers and irrelevant, noisy features. These factors contribute to poor data generalization and increase the risk of overfitting. Furthermore, the constraints of existing benchmark data sets, characterized by a limited number of participants, pose challenges for deep learning (DL) models that thrive on substantial, diverse, and representative data to capture complex and nuanced features accurately [4]. By contrast, humans can naturally identify complex and nuanced behaviors by observing their peers. Crowdsourcing, or the use of distributed human workers toward a common goal, has the potential to bridge this gap by enabling rapid feature tagging of complex behaviors on demand. Although crowdsourcing has traditionally been used for public health studies and labeling ML training data, we plan to explore the incorporation of human labels into the feature extraction process. The intuition behind the proposed paradigm is that although nonprofessionals may be unable to directly identify psychiatric diagnoses from videos, many can tag behaviors that are relevant to a diagnosis.

We propose to develop a novel paradigm for accessible and scalable multicondition digital diagnostics of neuropsychiatric conditions by fusing traditional ML with novel human-in-the-loop crowdsourcing approaches. Although this approach (Figure 1) can be applied toward classification between any set of psychiatric conditions, we will focus on attention-deficit/hyperactivity disorder (ADHD) and ASD to maintain feasibility. The approach will comprise (1) developing gamified web applications to curate videos of social interactions adaptively based on needs of the diagnostic system, (2) innovative behavioral feature extraction techniques consisting of automated ML methods and novel crowdsourcing algorithms, and (3) ML models that classify several conditions simultaneously and that adaptively request additional information based on uncertainties about the data. We will collaborate with Dr Dennis Wall, who will provide domain expertise for pediatric developmental delays and methodological guidance for innovative biomedical data science solutions.

Figure 1. Overview of the proposed crowd-powered diagnostic system comprising adaptive gamified data curation, behavioral feature extraction by both crowd workers and computational workflows, and machine learning models for multicondition classification that also output individual symptom estimates and dynamically query participants based on crowd ratings. Each of these 3 major steps is independent yet can be combined to produce a synergistic improvement in remote and accessible diagnostics for pediatric psychiatry. ADHD: attention-deficit/hyperactivity disorder.



The proposed project involves the integration of multiple data modalities for its diagnostic tasks, including from ML and from crowd workers. In our prior work, we have worked with several sources of information such as facial emotion [5,6], body movements [7,8], audio streams [9], and crowd worker ratings [10,11], all of which were used toward the singular goal of digital ASD diagnostics. For this protocol, we hypothesize that the complex and heterogeneous nature of the conditions that

we plan to study requires multimodal data analysis to achieve a clinically acceptable level of performance, and this protocol will involve testing this theory.

Related Work

Psychiatric conditions are widespread globally across demographic groups and geographical boundaries. The prevalence of ADHD is 2.5% in children and 5% in adults [3]. The prevalence of ASD is approximately 1% [3]. Approximately 50% to 70% of individuals diagnosed with ASD also have comorbid ADHD. Access to diagnostics, and therefore care, is limited for populations with low income or large geographic distances from clinicians. Although diagnostic modalities based on biomarkers are promising, they can be inaccessible to underserved populations. By contrast, a large and rapidly expanding portion of the global population has access to digital devices. As psychiatric conditions are fundamentally diagnosed based on behaviors, digital methods to measure behavior have the potential to bring diagnostic services to populations that have been traditionally neglected in health care.

A psychiatrist's diagnostic evaluation process involves identifying ≥1 condition from a large set of possibilities defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth edition (DSM-5). However, current approaches to digital diagnostics tend to focus on binary predictions. A major bottleneck complicating the pursuit of multiclass psychiatric diagnostics is that behavioral conditions often have overlapping presentations (Table 1), severely complicating the use of purely automated methods.

Table 1. Overlap of a small subset of the core behavioral symptoms of ASD[a] and ADHD[b]. Overlap is determined according to the DSM-5[c] diagnostic criteria [3].

Behavioral symptom	ADHD	ASD
Difficulty with social skills	✓	✓
Concentration issues	✓	
Hyperfixation	✓	✓
Restrictive and repetitive behaviors		✓
High distractibility	✓	
Impulsivity	✓	
Hyperactivity	✓	

[a]ASD: autism spectrum disorder.

[b]ADHD: attention-deficit/hyperactivity disorder.

[c]DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth edition.

In addition, each condition is heterogeneous, and all defining behavioral symptoms do not have to be present to warrant a diagnosis. Psychiatric conditions can either be comorbid (eg, ADHD and ASD) or not (eg, only ADHD or only ASD), creating a diagnosis space that scales combinatorially with each additional condition considered. For feasibility, we will only study 2 conditions to maintain a reasonably sized output space of 4.

The proposed research addresses a critical need in the field of pediatric neuropsychiatric diagnostics, focusing on the challenges posed by the prevalence of developmental and psychiatric conditions among minors in the United States. Current diagnostic practices face limitations in accessibility, particularly concerning cost, distance, and the availability of clinicians [10,12-14]. The *Background* section highlights the potential of digital phenotyping tools to overcome these challenges and expedite the diagnostic process through ML approaches. The field of digital phenotyping is vast and broad. A nonexhaustive list of National Institutes of Health–funded projects for developmental diagnostics includes the work by Guillermo Sapiro (NIH grant number R01MH120093) developing active closed-loop data collection for gaze and motor features for ASD as well as ADHD [15-22], work by James Rehg (NIH grant number R01MH114999) modeling nonverbal communication in atypical and typical development [23,24], work by Robert Schultz (NIH grant number R01MH118327) involving diagnostic computer vision analyses of motor movements displayed in videos of dyadic social interactions involving children with ASD [25], and work by Dennis Wall (NIH grant number R01LM013364) exploring the use of mobile games to acquire computer vision data for DL prediction of individual ASD-related behaviors [26-41].

Previous studies [4,12,42,43] have recognized the potential of ML techniques for detecting pediatric psychiatric conditions. However, a notable limitation of the existing approaches is their reliance on a limited set of social features for prediction tasks, often concentrating on a single binary prediction. For instance, in 2019, Carette et al [12] meticulously analyzed eye-tracking scanpath data using preprocessing procedures such as feature extraction via principal component analysis. The paper delineates comprehensive guidelines for the acquisition of the scanpath image data set. ML models were implemented, including support vector machine, logistic regression, random forest, and artificial neural network with diverse layers. The outcomes underscored the identification of a Childhood Autism Rating Scale score threshold of ≥36 as indicative of severe ASD. Notably, the single-layer artificial neural network model exhibited an improved area under the curve, outperforming support vector machine, which attained 77%. Despite the noteworthy findings, the study conscientiously recognized certain limitations, including a confined participant pool and shorter video scenarios, suggesting avenues for prospective

investigations. This limitation raises concerns about the specificity and precision of these models, particularly when dealing with the overlapping etiologies and phenotypic characteristics inherent in many psychiatric conditions affecting adolescents [44].

The literature [14] underscores the complexity of overlapping psychiatric conditions, such as ADHD and ASD, and the challenges in achieving specificity and precision in their simultaneous prediction. Key behavioral features, such as eye gaze patterns and facial emotion evocation, present opportunities for automated ML methods, but the majority remain too complex for precise classification [10]. For example, a study [45] centered on analyzing eye-tracking image data using a clustering approach with 2 distinct algorithms, K-means and an autoencoder. The findings revealed that 33% of individuals were categorized into cluster 1, indicating the presence of ASD, whereas a higher prevalence of 85% was observed in cluster 2. However, the study lacks clarity on the specific feature extraction technique and parameter settings applied during the clustering process. Therefore, our study introduces a novel paradigm that integrates traditional ML with human-in-the-loop crowdsourcing approaches to address the limitation of feature annotation. The motivation behind this paradigm lies in the belief that although nonprofessionals may struggle to identify psychiatric diagnoses directly, they can effectively tag behaviors relevant to a diagnosis. This shift toward a crowdsourced, human-annotated feature space is a novel approach in the context of pediatric neuropsychiatric diagnostics.

In addition, ML models incorporating both human-annotated and automatically extracted features are hypothesized to outperform models using only 1 type of feature; there is a notable gap in the literature regarding the integration of human-annotated features through crowdsourcing for the specific purpose of enhancing diagnostic accuracy in pediatric psychiatry [4,42,46]. Mauro et al [13] introduced a model to extract sensory features from consumer feedback reviews, considering user preferences and compatibility information. The efficacy of their model was assessed across individuals considered autistic and neurotypical through integration into the recommendation algorithm. However, because the perception of places is inherently subjective, there exists a potential for bias in the feature values derived from explicitly crowdsourced data. Consequently, the authors recommended a comprehensive evaluation of the features through multimodal analysis to enhance the precision and accuracy of the proposed algorithm.

Our proposed research protocol fills a critical gap in the literature by combining automated ML methods with innovative crowdsourcing algorithms, aiming to create a diagnostic system with greater discriminative power than previously achievable in precision psychiatry.

Methods

Overview

In contrast to prior inspirational National Institutes of Health–funded efforts and others like them, we propose an approach to digital phenotyping that expands the possible feature vectors used to classify psychiatric conditions with complex and nuanced social features that only humans can identify using a novel *crowd-powered precision diagnostics* approach. The primary high-risk and high-reward differentiators from prior work are (1) the incorporation of a novel crowdsourcing pipeline into a precision diagnostic system to enable quantification of more complex social features, (2) the adaptive querying of the participant in question within a 2-player game-based system using active learning algorithms that exploit crowdsourced responses, and (3) the differential diagnosis of ASD and ADHD simultaneously. Differentiators (2) and (3) would not be possible without (1). The addition of targeted crowdsourcing into the diagnostic process creates several technical challenges that we will address, including automating the preservation of privacy of participants, efficiently and intelligently quantifying the behavioral feature–tagging ability of crowd workers, and creating algorithms for dynamically assigning workers to new data streams and tasks. Although prior projects have attained successful performances >90% using purely automated DL approaches to differentiate ASD from neurotypical peers [47], our preliminary data show that human-in-the-loop crowdsourced feature tagging of targeted behavioral features results in classification sensitivity, specificity, and accuracy >95%, even when privacy-preserving alternations are made to the video streams [42,48,49]. We hypothesize that incorporating both human observations, which are beyond the current and foreseeable abilities of ML, into the feature extraction process will provide enough social information for automated models to classify each condition using the same video data.

We hypothesize that diagnostic ML models that incorporate both human-annotated features acquired through crowdsourcing (to generate a complex feature space with respect to social human behavior) and automatically extracted features (to provide objectivity when possible) will outperform models that use only automatically extracted features or only human-provided features, as there will likely be nonlinear interactions between features. This complex feature space will allow the classification model to simultaneously distinguish 4 possible outcomes: only ASD, only ADHD, both ASD and ADHD, or neither condition. To support efficient and reliable feature tagging by workers, we will develop novel crowdsourcing algorithms for quantifying the behavioral tagging strengths and weaknesses of each worker. The algorithms will dynamically assign workers to tasks based on their tagging history. We will alter each video to provide privacy protection for the participants while still allowing reliable tagging. To facilitate the acquisition of sufficiently structured data, we will develop a broadly accessible gamified web platform for curating socially enriched video and audio clips in a targeted manner. We will use active learning algorithms to adaptively query for additional data in cases where the presence of a particular symptom is unclear from the current set of ML features and crowdsourced ratings. Each of these innovations (crowdsourcing algorithms, privacy-preserving video alterations, gamified social data capture systems, and active learning algorithms to dynamically query needed data), although useful for the field of precision psychiatry individually, will be combined to create a novel diagnostic system with greater discriminative power than previously possible.

Achieving the precision required to distinguish between ASD, ADHD, both ASD and ADHD, or neither from videos of social interaction using ML at clinically acceptable levels requires a complex social feature space that is not necessarily impossible but highly infeasible with purely automated methods. In contrast, untrained human annotators can identify nuanced social features but are prone to error because of the subjective nature of the task. Combining features extracted by both nonexpert human raters and computational programs can enable precise diagnostics and quantification of behaviors by creating a rich diagnostic feature space. There are several challenges to accomplishing targeted crowdsourcing in a precision health context, which we will address, including privacy preservation, quantifying crowd worker capabilities, and developing algorithms for matchmaking crowd workers with incoming data streams. The rich social feature space provided by crowdsourcing enables improvements to the other aspects of the digital behavioral diagnostics pipeline, including the adaptive assignment of participants to data collection games using active learning crowdsourcing metrics. Although we will focus on ASD and ADHD in particular, the crowd-powered methods we will develop have the potential to benefit diagnostics for any condition primarily evaluated through behavioral observation.

Ethical Considerations

This study has been approved by the University of Hawaii Institutional Review Board (IRB; 2022-00909). We will only collect data from voluntary participants who sign an informed consent (parents) and assent (children) document during the intake session of the study. Participants whose videos will be shared for the 20 crowdsourcing tasks used to filter workers will be contacted by the study team to have a thorough discussion about the planned use of those videos. Workers who are qualified to rate the remaining videos for ≥1 question will be required to complete The Health Insurance Portability and Accountability Act training and The Collaborative Institutional Training Initiative training and will be required to encrypt their laptops using whole disk encryption. These workers will be added to the IRB protocol and will become official members of the study team after thorough training.

Although we will require participants to consent to sharing videos with crowd workers who have undergone thorough training, the clinical translation of this diagnostic system will require a more scalable approach that is sensitive to privacy concerns. We will experiment with privacy-preserving alterations to the curated videos to obfuscate identifiable information from the videos without degrading the feature-tagging performance of workers. Examples include pitch shifting the audio, which will allow workers to understand the content of the speech, and pixelating the video, which will obscure the participant's background and face but would still allow workers to observe body movement patterns. We will measure the extent to which each privacy-preserving mechanism degrades the answers to each question.

We will deidentify the participant data and anonymize any personally identifiable information. All the data will be immediately uploaded to our secure and encrypted server on Amazon Web Services (AWS) [50], which is Health Insurance Portability and Accountability Act–compliant. A fully anonymized version of the data set will be released to researchers only after signing a data use agreement, which will be approved by the University of Hawai'I Data Governance Office.

To ensure that the annotation task is manageable for crowd workers, each 15-minute video will be segmented into five 3-minute clips. During the profiling phase, crowd workers will be compensated US $0.50 per 3-minute video segment rated. Workers who are selected to continue rating videos in the primary portion of the study will be compensated US $0.05 per question answered per video segment, with the opportunity of a bonus of US $0.05 per question if the answer aligns with the clinician ratings for that question. These payment rates are consistent with practices in crowdsourcing research studies in the field of human-computer interaction, and our preliminary studies have shown that the retention rate for this level of compensation is >90% [10,42,49].

Gamified Data Curation

Description

We will develop novel gamified social experiences to curate video data containing diagnostically rich information. Each of these games will impose the structure required to extract salient behavioral features that are comparable across peers. Each game will involve 2 participants interacting on the web application through both the game itself and socially through live video and audio. During gameplay, each participant's camera and microphone will be turned on, and their video and audio will be displayed in a Zoom-style [51] feed to the other participant. The video and audio feeds will be recorded during each session, in addition to keyboard strokes and mouse movements.

Each game will correspond to a subset of targeted behaviors for data capture. The existing literature on "serious games" has documented the usefulness of certain games to capture behaviors related to psychiatric diagnostics, although these games are usually single player. An example is a Go/No-Go game, where the player presses the spacebar in response to a timed "go" prompt in the presence of auditory and visual distractions. This game has been shown to be a reliable estimate of attention, impulsivity, hyperactivity, and executive functioning when recording gaze behavior, response time, and correct reaction rate [52]. We will modify the game so that the "go" prompts are initiated by the social game partner rather than an automated computer, allowing for the capture of socially relevant features. The field of "serious games" for the assessment of psychiatric behaviors is vast, and therefore, we will base all games on previously published literature. However, many behavioral features that we will study will not be tied to a particular game but will rather be observable as a by-product of the social interactions between participants (eg, social anxiety).

One of 7 possible games will be administered each day. A complete list of games and the corresponding behaviors that each game is designed to measure is shown in Table 2.

Table 2. List of previously validated data capture games that have successfully generated data relevant for distinguishing the targeted psychiatric conditions from neurotypical controls.

Game[a]	Targeted behaviors
Go/No-Go [52]	Concentration, impulsivity, hyperactivity, executive functioning, and reaction time
AULA Nesplora [52]	Process speed and motor activity
Plan-It Commander [52]	Planning and organization
Braingame Brian [52]	Working memory, cognition flexibility, and impulsivity
Charades [6]	Emotion evocation and recognition and restrictive and repetitive behaviors
Balloon Popping [53]	Visual motor coordination
Spot The Eyes and Face [53]	Eye contact and face gaze
Free-form conversation[b]	Social anxiety, difficulty with social skills, speech delays, and language narrative

[a]As the games themselves are not central to the innovation of this proposal, details of the gameplay can be found in corresponding references [6,52,53].
[b]Free-form conversation will naturally occur across all games.

The design of the games will be conducted in consultation with a team of practicing clinical psychiatrists at the University of Hawai‘i School of Medicine, including Dr Anthony Guerrero, who is the chair of the Department of Psychiatry and who specializes in digital technologies for pediatric and adolescent psychiatry, as well as Dr Gerald Busch, who is an assistant professor in the Department of Psychiatry and who has experience with digital health solutions for psychiatry.

A minimum of 15 minutes of gameplay will be required each day, although participants may elect to participate for longer. To facilitate consistent data capture across possible computer, microphone, and camera configurations, a pertinent step for enabling comparisons across participants, a calibration program will be developed that will require each participant to align the camera's zoom and their body position before each session. We will extensively test the calibration procedure before the study.

Participant Recruitment and Management

We plan to recruit a total of 400 study participants, comprising 100 individuals formally diagnosed with ADHD, another 100 diagnosed with ASD, a further 100 diagnosed with both ASD and ADHD, and 100 individuals evaluated and confirmed to not have any socially related psychiatric conditions. Our inclusion criteria are as follows: (1) adolescents aged between 14 and 18 (inclusive) years and (2) formally evaluated for ADHD and ASD by a licensed clinician with available documentation. The selection of the final 400 participants that comprise our core data set will be based on the personal information that participants are asked to disclose. Such metadata will be used to ensure a data set that is balanced with respect to race, ethnicity, and gender. The number of participants is based on testing the ability of our system to discriminate between groups of participants. As these groups are balanced, we set the prevalence for binary classification between each condition to 50%. Following a CI of 95%, an estimated theta of 95% [42,48,49], and a width of 15%, the sample size to compute the area under the receiver operating characteristic curve (AUROC) should be 37 [54]. Considering that we have 400 participants, with 100 participants per group, this enables us to follow a common 60:20:20 (train, validation and test ratio respectively) randomized split on the data. That is, we have a sample size (test set) of 40 participants to verify the system's ability to discriminate between the neurotypical participants and the participants who were diagnosed with either ASD, ADHD, or comorbid ASD and ADHD.

Although formal and well-established methods to perform power calculations for ML analyses have yet to be established, most digital diagnostics studies for conditions such as ASD include <100 participants per class in binary classification [47]. We aim to maintain a similar sample size per diagnostic category. The digital social experiences will be delivered to study participants for 15 minutes each day for a 3-week duration, with a single game out of the 7 possible delivered each day. At least 3 distinct 15-minute sessions will be collected per game for each participant, allowing for comparisons across days for analysis of within-peer consistency.

Given the remote delivery of the data collection, a critical challenge will be to ensure that all participants will have a social partner when logging into the study system. The participants will be asked to log in at a particular time each day to be scheduled in advance of the first day of the study. We will host 10 separate time slots and 3 makeup time slots every day of the study, and participants will be automatically matched with a partner during log-in.

Evaluation

We will evaluate the data curation system for (1) compliance of participants with respect to the study procedures during each session and (2) global participation rates. To measure compliance, we will run computer vision face detection algorithms in conjunction with skeletal pose estimation using MediaPipe [55] Python library to ensure that each participant's face, upper torso, and shoulders are fully visible and will calculate the percentage of valid frames across sessions per participant. To measure participation across sessions, we will record the total number of sessions with both participants and the mean session time. In addition to these quantitative analyses, we will run qualitative pilot user studies to understand participants' experiences about the data collection game process, including questions about the entertainment value provided by

the games, the usability of the participant matching and scheduling system, and open-ended feedback.

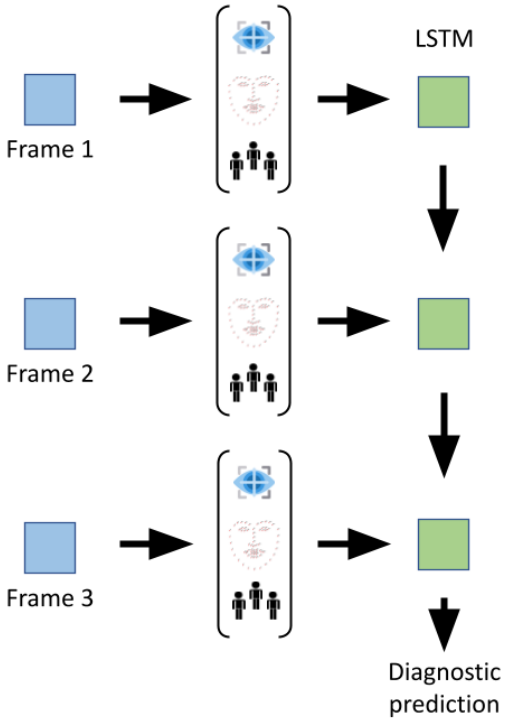
Novel Crowd-Powered and Traditional ML-Based Feature Extraction

Description

We will create 2 pipelines for converting raw video and audio data into interpretable feature vectors that quantify social behavior relevant to ADHD and ASD diagnostics. For behaviors that can be feasibly quantified using computational methods, we will use existing toolkits. For highly complex and nuanced social behaviors that are beyond the scope of current ML tools but that are highly relevant to psychiatric classification, we will use a novel crowdsourcing pipeline to match crowd workers to labeling tasks.

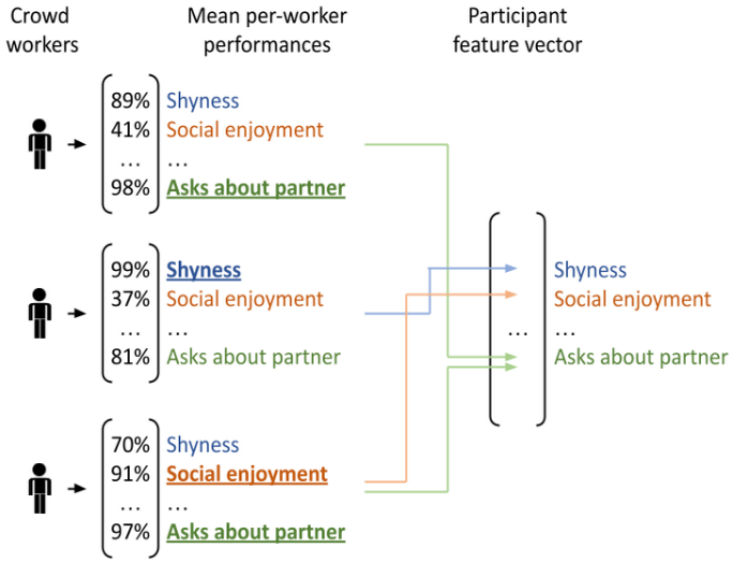
We will perform automatic feature extraction for behaviors potentially related to diagnoses such as the percentage of total conversation time contributed by the participant, eye gaze patterns during the gameplay including the proportion of gaze directed toward the game versus the live video feed of the other participant, vocal prosody and intonation during conversation, natural language processing analysis of the content of the conversation after converting raw audio to text using speech-to-text programs, and breaks in task flow as measured by pauses in game-related keystrokes and mouse movements. The extracted information will be stored for each frame at a sampling rate of 5 frames per second. As depicted in Figure 2, each of these features will be concatenated into a temporal feature vector and used to train a time series DL model such as a long short-term memory recurrent neural network or an attention-based model (eg, transformers). There are existing Python libraries that enable the proposed automatic behavioral feature extraction such as OpenFace [56] and MediaPipe for eye gazing. For facial emotion recognition, we will use Amazon Rekognition [57], an AWS service that provides recognition of disgust, happiness, surprise, anger, confusion, calmness, and sadness in addition to other relevant facial features such as whether the eyes and mouth are open. In the audio domain, pitch will be extracted using the Convolutional Representation for Pitch Estimation library [58], and waveforms will be processed using the librosa library [59].

Figure 2. Feature extraction and quantification of behaviors relevant to neuropsychiatric diagnostics. LSTM: Long Short-Term Memory network.



For complex social features beyond the scope of automated ML-powered computational processing, we will deploy a novel crowdsourcing framework consisting of a crowd worker profiling phase, followed by a study data tagging step. In the first phase, we will post 20 tasks on Amazon Mechanical Turk, each presenting a video acquired through pilot testing of the gamified social data collection platform, followed by a series of multiple-choice questions corresponding to items from the diagnostic criteria for ADHD and ASD, as defined by the DSM-5. Each task will correspond to a separate video, and there will be 4 videos per diagnostic category used to quantify worker abilities. Worker responses will be compared against the Clinical Global Impression gold standard ratings provided by our collaborators in the Department of Psychiatry at the University of Hawai‘i. Crowd workers who align with the ratings of clinical experts on at least 1 behavioral feature, where alignment is defined as <1 categorical ordinal deviation per 2 videos, will be recruited to label the final study data from 400 participants. Recruited workers will only label those features for which their alignment with clinicians was demonstrated during the profiling phase as shown in Figure 3.

Figure 3. Crowd worker assignment to labeling tasks. Each crowd worker will only be asked to label those features for which they agreed with clinicians during a worker profiling step performed before the primary study.



A valuable by-product of this process will be the generation of large behavioral multimedia data sets for ML of complex social features, enabling improved artificial intelligence modeling of human behavior more broadly. With explicit permission from study participants on a per-video basis, we will package and publish the collected data into novel computer vision, audio, and natural language processing data sets for ML. These labeled data sets will be released publicly, providing a stepping stone toward improved automated methods for quantifying complex human behavior.

Evaluation

To assess the effectiveness of the crowdsourcing pipeline, we will compare the performance of crowd workers before and after their recruitment. The preliminary data show that crowd workers who answer similarly to clinicians during filtering continue to perform in a similar manner on new, unseen videos. We will also measure crowdsourcing metrics such as latency to starting a task, interrater reliability, any decline in performance with increased ratings, and the completion rate for all assigned tasks. To evaluate the privacy-preserving mechanisms, we will randomly assign each worker to a single privacy condition per video, only asking them to rate the unaltered videos after the ratings for the privacy condition have been provided. We will measure the mean deviation from clinician answers per privacy condition for each question.

Multicondition Diagnostics With Adaptive Input Querying

Description

We will develop DL models for the multilabel classification of ADHD and ASD, which can emit four possible outcomes: (1) ADHD, (2) ASD, (3) ADHD and ASD, and (4) neither condition. The models will also output the behavioral characteristics that led to the final classification decision by producing the 95% CI of each behavior as derived from both crowd workers and automated computational models. This will involve synthesizing multiple sources of inputs and communicating the result to the end user in a manner that is understandable to the patient or the caregiver. The confidence scores will enable the model to adaptively request more data from the patient and to be specific about which types of data are needed.

To derive an interpretable quantification of each behavioral feature, we will collect clinical categorical ratings of each behavior by licensed psychiatrists at the University of Hawai‘i at Mānoa. We will compensate the psychiatrists for their service and will use the mean of the crowd worker responses as a baseline method for deriving the interpretable quantification of each behavior. Although this method could be sufficient, it is possible that crowd workers have varying levels of rating abilities depending on the qualities of the video and the qualities of the crowd workers themselves. Therefore, we will explore the use of the crowdsourced ratings themselves combined with crowdsourcing metrics derived from worker performance and the computationally generated behavioral features as collective inputs into an ML model for each behavior. Such metrics will include the time spent by each worker providing the annotations for the video, worker rating history for each question, and variability in the worker's answers across videos and within a particular video. It has been previously shown that these crowdsourcing metrics and similar metrics have predictive power in a crowd worker's annotation quality [11]. We will test whether the ML model is a better predictor than the crowdsourced ratings alone. The loss function for the ML model for individual behaviors will optimize with respect to the mean clinician rating per behavior.

To model the multilabel classification problem, we will create separate binary classifiers for ASD and ADHD. Each model will be optimized separately. In comparison with training distinct binary classifiers, a single model trained in a multitask learning setup is able to share parameters between the classification tasks. This helps the model focus on distinguishing features between conditions and has been found to reduce overfitting. We expect that the multitask setting will decrease the number

of false-positive predictions by helping the model recognize features that overlap between conditions.

Using a sigmoid activation function for each independent classifier, the classification system will output a probability score for each diagnostic possibility as well as each of the behaviors defined by the DSM-5, which will be quantified by the system.

Using the output scores of the DL model, an active learning system will be developed that queries for additional data from the user in a targeted manner by suggesting the next game for the participant to play. For each participant, the algorithm will measure the confidence score of each behavioral symptom and produce a list of games for the user to play, sorted by the classifier's mean uncertainty of the behavioral symptoms each game is designed to curate data for. Classifier uncertainty will be measured by the entropy of each classifier's output vector. As neural networks are inherently uncalibrated, we will apply a method published by Kuleshov et al [60] based on isotonic regression to calibrate the probability estimates before measuring uncertainty.

Evaluation

The diagnostic ML model will be evaluated using balanced classification metrics including AUROC, area under the precision-recall curve, balanced accuracy, precision, recall (sensitivity), F_1-score, and specificity. Performance and CIs will be derived through Monte Carlo cross-validation, with each data split consisting of 300 participants in the training set, 50 participants in the validation set, and 50 participants in the test set. All splits will contain a balance with respect to the 5 diagnostic classes, age, gender, race, and ethnicity.

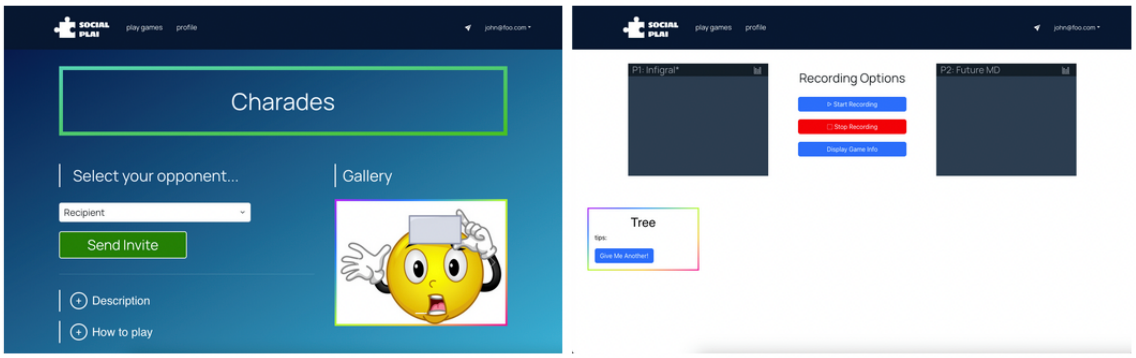
To evaluate the effectiveness of the active learning querying system, we will run post hoc simulations comparing the random selection of new data against targeted requests using active learning. We will train the classification system with 12 sessions of data, hold out the remaining 9 sessions, and plot the performance of each metric against the number of additional samples acquired using both active learning and random selection of data segments.

Results

Gamified Data Curation

A preliminary version of the web interface has been implemented (Figure 4). We are finalizing the features corresponding to video and metadata recording for downstream ML analysis. Over the course of this 5-year study, our objectives are to complete the development of the study's web system by the end of year 1, begin initial recruitment in year 2, and concurrently conduct human-in-the-loop ML analysis while continuing recruitment from years 3 to 5.

Figure 4. Preliminary interface for the study's central web platform. (A) Users who are not a part of the core user study where participant matchmaking occurs can select their game play partner. (B) One of the implemented games, Charades.



Novel Crowd-Powered and Traditional ML-Based Feature Extraction

We have conducted a series of preliminary studies testing the use of crowdsourcing for precision behavioral health, demonstrating that although there is a high degree of variability in crowd workers' innate ability to rate complex social behaviors in unstructured home videos [10], there exists a small fraction of crowd workers on platforms such as Amazon Mechanical Turk who consistently rate in alignment with licensed clinical experts [48,49]. In a study, we demonstrated that a group of 40 crowd workers filtered from an original pool of >1000 workers was able to rate behaviors that, when fed into a classifier trained on clinician records, achieved an AUROC of 0.9904 for one set of features and 0.9872 for another feature set [42]. Our experience of receiving approval from university IRBs and data privacy offices as well as obtaining consent from families to share their videos with crowd workers mitigates any risks related to this novel process.

After applying privacy-preserving modifications to the videos, such as pitch shifting the audio downward and using face detection to box out the child's face, the performance of the model remained >0.95 for both AUROC and area under the precision-recall curve [42]. Although these results show promise for predicting autism in a binary task, they are likely to decline in accuracy when expanding to include ADHD as a diagnosis too. These studies provide strong evidence to support the proposed worker matching procedure, which will enable the more nuanced feature space required for multicondition classification. The prior experience in developing automated

pipelines for managing crowd workers will help streamline the development of the crowd management scripts.

The feasibility of the automatic feature extraction steps comes from the existing packaging of the required functionalities into Python libraries and the high documented performance of these tools. All the ML-powered feature extractors we have used are well documented.

Multicondition Diagnostics With Adaptive Input Querying

In 1 of our preliminary experiments involving 4-way ASD or ADHD classification (only ASD vs only ADHD vs both vs none) using publicly available survey data, a decision tree classifier achieved an F_1-score of 0.75 and Hamming loss of 0.23. The final data set consisted of 270,978 data points and 60 columns, with which we attempted multiple feature selection methods such as recursive feature elimination, decision tree feature importance scores, and logistic regression coefficients to quantify the strength of the relationship between the predictor variables and target variables. Across all 3 methods, the highlighted behavioral features were difficulty in making or keeping friends; difficulty in dressing or bathing; having behavioral problems; having difficulty concentrating, remembering, or making decisions; having anxiety; arguing too much; and sharing ideas or talking about things that really matter. On the basis of these observations, we believe that the games targeting behavioral and motor skills, mentioned in Table 2, can support the research findings and generate relevant data. We will modify the currently implemented games to specifically target these newly identified behavioral features.

The feasibility of DL models relies on the underlying data used to train them. DL has the capacity to learn any discriminative function, provided it has a large enough model and adequate computational power to train a large model. University of Hawai‘i at Mānoa has provided us with a dedicated Nvidia v100 graphics processing unit node and a dedicated Nvidia RTX5000 [61] for computationally intensive research. In addition, the Hawai‘i Data Science Institute has shared computing resources consisting of 346 nodes (8500 cores) with 63.19 terabyte of RAM, 120 graphics processing units, and >1 petabyte of storage. These resources are free to use for University of Hawai‘i laboratories. Collectively, these resources are more than sufficient to train DL models for the proposed data set size.

We have previously trained DL models for making a binary prediction of ASD (Table 3).

Table 3. Preliminary data supporting the use of multimedia data from social games to predict autism spectrum disorder.

Data modality	Prediction performance
Audio	AUROC[a]: 0.815 (0.077 or −0.077)
Facial emotion	Balanced accuracy: 71%
Eye gaze	Recall: 66.2%; precision: 63.5%

[a]AUROC: area under the receiver operating characteristic curve.

Although each of these models used a single data modality (audio, facial emotion expression, or eye gaze), their performances were on par with prior literature [47]. We hypothesize that incorporating additional modalities will not only allow for increased performance within a single class but will also enhance discriminative power across diagnostic categories.

Discussion

Principal Findings

There is a great need for improved, scalable, and accessible diagnostic assessments for neuropsychiatric conditions that require accurate and extensive evaluations. We propose to use a multimodal ML model to study heterogeneous psychiatric conditions through human-in-the-loop computing. Although DL models have been able to successfully classify participants with ASD from their neurotypical peers in prior work, the human-in-the-loop observations can help extract a more nuanced feature subset for the diagnosis of similar yet distinct conditions. We have deployed an initial set of games on the web interface targeting behavioral features, and we have extracted a subset of core behavioral features that aligns with the proposed games and can thus help us to effectively target our digital diagnostic. The crowd worker ratings appear to be of high quality based on our prior studies, aligning with the computationally extracted features and clinician's records, even after the videos are modified. Moreover, the reduced feature subset extracted using preliminary studies from multiclass classification of publicly available survey data has helped us identify the core behavioral features that we intend to target through our gamified approach.

This study aligns with multiple previous works [1,2,5-11,15-41] where the researchers worked with single-modality data to capture the phenotypic behaviors of ASD, ADHD or both. These studies were not only limited by the availability of social features but also by the small size and lack of diversity in the data set [1]. By contrast, our study encompasses several sources of information such as facial emotion, body movements, audio streams, and crowd worker ratings that will improve the predictive capability of the model for comorbid diagnosis and capture the overlapping features. Through this study, we aim to bridge the gap posed by diagnostic and therapeutic challenges in psychiatry using ML techniques. Such noninvasive studies can better use the complex social behaviors to characterize behaviors specific to ASD and ADHD.

The technical aspects of the project are highly feasible, with modest development requirements compared with modern real-time computer gaming systems. The web server will be developed using the Django Python framework [62] and hosted on an Elastic Compute Cloud (EC2) instance [63] on AWS, with extensive existing functionality and documentation existing

for all technologies used. Extensive codes are available on the internet for implementing the video and audio chat features. A full-time developer, an engineering or computer science student, or a postdoctoral researcher can implement the entire system within the span of 4 person-months.

Limitations

Although our initial findings are optimistic, there are some limitations to the study. The primary challenge will be the recruitment and retention of 400 study participants, including the formal clinical validation of the diagnosis for each participant. Although this study can be successfully completed with fewer participants, smaller data sets can affect the model's learning capability, leading to overfitting, noisy outliers, or sample bias. To help manage this recruitment effort, we will hire a full-time clinical research coordinator to recruit and manage the participants. We will work with the clinical collaborators in the Department of Psychiatry to recruit in Hawai i's psychiatric clinics, where our collaborators and their colleagues practice. This will be supplemented with web-based recruitment using targeted advertisements on social media. We have discussed this recruitment plan and desired study size with our collaborators in the Department of Psychiatry, and we hold recurring monthly meetings to strategize about participant recruitment using both our existing access to several clinics in Hawai i and web-based targeted recruitment. In addition, our former mentor and collaborator, Dr Dennis Wall at Stanford University, has access to hundreds of families with adolescent children diagnosed with ASD as well as comorbid ADHD. He is the founder of Cognoa [53,64-69], an artificial intelligence–based digital diagnostic tool for studying early childhood development and pediatric behavior.

There might be technical challenges associated with web applications or user interfaces, which may occur at later stages of the study. The proposed data curation game platform may lack qualities that would garner repeated participant engagement over a 3-week period, such as poor user interface design, poor design of the automated notification system, or poor entertainment quality of the individual games. To mitigate this risk, we will run several iterative design sessions regarding proper implementation of the design process to maximize both user engagement and high-fidelity data collection. We will run several pilot studies to obtain both qualitative and quantitative measures of engagement before running the primary data collection study.

The other potential pitfalls are compliance and tardiness. We will run automated computer vision checks in real time to ensure participant compliance with camera calibration requirements. Another script will send automated text messages and email reminders to late participants, assigning them to makeup sessions. If these mitigation steps fail or if recruitment is unsuccessful and there are <100 participants with valid data per diagnostic category, the study can still be successful with as few as 20 participants per class, as ML studies with approximately 20 participants per diagnostic category have frequently been published in the field [47].

There are also limitations associated with crowdsourcing based on the expertise of the crowd workers or their temporal availability. Although this never occurred during preliminary data collection, a potential pitfall is that some questions may have no workers who consistently rate them in accordance with clinicians. If this occurs, then that question will be removed from any further components of the study (ie, removed as a feature for the diagnostic classifier).

In crowdsourcing, scaling the number of workers does not correlate with the time spent on recruitment. However, to ensure high-quality annotations, we do anticipate spending a considerable amount of time recruiting crowd workers. As mentioned previously, we plan a crowd worker profiling phase based on 20 tasks and data collected through pilot studies with our data-gathering platform. By periodically posing a gold-annotated question and providing a monetary bonus for correctly answering such questions, we incentivize workers to provide high-quality answers. On the basis of our prior studies, we expect that the level of compensation will lead to a worker retention rate of >90%. Furthermore, to account for the loss of workers, we will recruit 3 times more crowd workers than is minimally required for the study. With regard to the number of crowd workers required, we follow the study by Roitero et al [70]. As such, the recommended number of workers will be estimated based on a small amount of data collected during our pilot studies.

When verifying the automatically extracted computational features manually, it is possible that some features will be incorrect. Computational feature extraction approaches are not perfect and are not necessarily robust to unforeseen conditions (eg, dim lighting, obfuscation of certain body parts, and unfamiliar accents). If any feature is consistently unreliable across several participants, then we will remove that feature from the study. There are sufficient features available, so if some do not function as intended, the study can still proceed.

It is possible that the large number of features used to train the DL classification models will be overfitted to the training set, as a data set of 400 samples (of which approximately 300/400, 75% would be in the training set) is relatively small for ML and is unlikely to capture all the intricacies of social behavior that can be expressed with the feature space. If this happens, we will run feature selection and dimensionality reduction algorithms to reduce the number of features used in the model to a minimum viable set and to summarize the feature space in a low-dimensional manner, respectively. The feature selection will enable interrogations into which features are most useful in the differentiation of each condition.

Conclusions

Given the complex nature of neuropsychiatric conditions, ML models can greatly reduce time to diagnosis, for example, by identifying salient information in support of establishing a diagnosis through a low-cost and remote data collection approach. Multimodal data with human-in-the-loop crowdsourcing may improve not only digital diagnostics but also our understanding of the complexity of the conditions. The crowd workers' annotation can also provide data for other computer vision tasks, serving as a promising tool for genetic association, psychological, and kinematic studies.

Acknowledgments

This project is funded by the NIH Director's New Innovator Award (DP2) from the National Institutes of Health (award DP2-EB035858).

Data Availability

The authors intend to create approved subsets of the data that can be shared with other researchers.

Conflicts of Interest

None declared.

References

1. Zablotsky B, Black LI, Maenner MJ, Schieve LA, Danielson ML, Bitsko RH, et al. Prevalence and trends of developmental disabilities among children in the United States: 2009-2017. Pediatrics 2019 Oct;144(4):e20190811 [FREE Full text] [doi: 10.1542/peds.2019-0811] [Medline: 31558576]
2. Magaña S, Parish SL, Rose RA, Timberlake M, Swaine JG. Racial and ethnic disparities in quality of health care among children with autism and other developmental disabilities. Intellect Dev Disabil 2012 Aug;50(4):287-299. [doi: 10.1352/1934-9556-50.4.287] [Medline: 22861130]
3. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Washington, DC: American Psychiatric Association Publishing; 2022.
4. Yaneva V, Ha LA, Eraslan S, Yesilada Y, Mitkov R. Detecting high-functioning autism in adults using eye tracking and machine learning. IEEE Trans Neural Syst Rehabil Eng 2020 Jun;28(6):1254-1261. [doi: 10.1109/tnsre.2020.2991675]
5. Washington P, Kalantarian H, Kent J, Husic A, Kline A, Leblanc E, et al. Training affective computer vision models by crowdsourcing soft-target labels. Cognit Comput 2021 Sep;13(5):1363-1373 [FREE Full text] [doi: 10.1007/s12559-021-09936-4] [Medline: 35669554]
6. Washington P, Kalantarian H, Kent J, Husic A, Kline A, Leblanc E, et al. Improved digital therapy for developmental pediatrics using domain-specific artificial intelligence: machine learning study. JMIR Pediatr Parent 2022 Apr 08;5(2):e26760 [FREE Full text] [doi: 10.2196/26760] [Medline: 35394438]
7. Washington P, Kline A, Mutlu OC, Leblanc E, Hou C, Stockham N, et al. Activity recognition with moving cameras and few training examples: applications for detection of autism-related headbanging. In: Proceedings of the Extended Abstracts of the 2021 CHI Conference on Human Factors in Computing Systems. 2021 Presented at: CHI '21: CHI Conference on Human Factors in Computing Systems; May 8-13, 2021; Yokohama, Japan. [doi: 10.1145/3411763.3451701]
8. Lakkapragada A, Kline A, Mutlu OC, Paskov K, Chrisman B, Stockham N, et al. The classification of abnormal hand movement to aid in autism detection: machine learning study. JMIR Biomed Eng 2022 Jun;7(1):e33771 [FREE Full text] [doi: 10.2196/33771]
9. Chi NA, Washington P, Kline A, Husic A, Hou C, He C, et al. Classifying autism from crowdsourced semistructured speech recordings: machine learning model comparison study. JMIR Pediatr Parent 2022 Apr 14;5(2):e35406 [FREE Full text] [doi: 10.2196/35406] [Medline: 35436234]
10. Washington P, Leblanc E, Dunlap K, Penev Y, Kline A, Paskov K, et al. Precision telemedicine through crowdsourced machine learning: testing variability of crowd workers for video-based autism feature recognition. J Pers Med 2020 Aug 13;10(3):86 [FREE Full text] [doi: 10.3390/jpm10030086] [Medline: 32823538]
11. Washington P, Leblanc E, Dunlap K, Penev Y, Varma M, Jung JY, et al. Selection of trustworthy crowd workers for telemedical diagnosis of pediatric autism spectrum disorder. Pac Symp Biocomput 2021;26:14-25 [FREE Full text] [Medline: 33691000]
12. Carette R, Elbattah M, Cilia F, Dequen G, Guerin JL, Bosche J. Learning to predict autism spectrum disorder based on the visual patterns of eye-tracking scanpaths. In: Proceedings of the 12th International Conference on Health Informatics. 2019 Presented at: 12th International Conference on Health Informatics; February 22-24, 2019; Prague, Czech Republic URL: https://www.scitepress.org/Link.aspx?doi=10.5220/0007402601030112
13. Mauro N, Ardissono L, Cocomazzi S, Cena F. Using consumer feedback from location-based services in PoI recommender systems for people with autism. Expert Syst Appl 2022 Aug;199:116972. [doi: 10.1016/j.eswa.2022.116972]
14. Seernani D, Damania K, Ioannou C, Penkalla N, Hill H, Foulsham T, et al. Visual search in ADHD, ASD and ASD + ADHD: overlapping or dissociating disorders? Eur Child Adolesc Psychiatry 2021 Apr;30(4):549-562 [FREE Full text] [doi: 10.1007/s00787-020-01535-2] [Medline: 32314021]
15. Bovery M, Dawson G, Hashemi J, Sapiro G. A scalable off-the-shelf framework for measuring patterns of attention in young children and its application in autism spectrum disorder. IEEE Trans Affect Comput 2021;12(3):722-731 [FREE Full text] [doi: 10.1109/taffc.2018.2890610] [Medline: 35450132]

16. Campbell K, Carpenter KL, Hashemi J, Espinosa S, Marsan S, Borg JS, et al. Computer vision analysis captures atypical attention in toddlers with autism. Autism 2019 Apr;23(3):619-628 [FREE Full text] [doi: 10.1177/1362361318766247] [Medline: 29595333]
17. Carpenter KL, Hahemi J, Campbell K, Lippmann SJ, Baker JP, Egger HL, et al. Digital behavioral phenotyping detects atypical pattern of facial expression in toddlers with autism. Autism Res 2021 Mar;14(3):488-499 [FREE Full text] [doi: 10.1002/aur.2391] [Medline: 32924332]
18. Chang Z, Di Martino JM, Aiello R, Baker J, Carpenter K, Compton S, et al. Computational methods to measure patterns of gaze in toddlers with autism spectrum disorder. JAMA Pediatr 2021 Aug 01;175(8):827-836 [FREE Full text] [doi: 10.1001/jamapediatrics.2021.0530] [Medline: 33900383]
19. Dawson G, Sapiro G. Potential for digital behavioral measurement tools to transform the detection and diagnosis of autism spectrum disorder. JAMA Pediatr 2019 Apr 01;173(4):305-306 [FREE Full text] [doi: 10.1001/jamapediatrics.2018.5269] [Medline: 30715131]
20. Hashemi J, Spina TV, Tepper M, Esler A, Morellas V, Papanikolopoulos N, et al. A computer vision approach for the assessment of autism-related behavioral markers. In: Proceedings of the 2012 IEEE International Conference on Development and Learning and Epigenetic Robotics (ICDL). 2012 Presented at: 2012 IEEE International Conference on Development and Learning and Epigenetic Robotics (ICDL); November 7-9, 2012; San Diego, CA. [doi: 10.1109/devlrn.2012.6400865]
21. Isaev DY, Major S, Murias M, Carpenter KL, Carlson D, Sapiro G, et al. Relative average look duration and its association with neurophysiological activity in young children with autism spectrum disorder. Sci Rep 2020 Feb 05;10(1):1912 [FREE Full text] [doi: 10.1038/s41598-020-57902-1] [Medline: 32024855]
22. Major S, Isaev D, Grapel J, Calnan T, Tenenbaum E, Carpenter K, et al. Shorter average look durations to dynamic social stimuli are associated with higher levels of autism symptoms in young autistic children. Autism 2022 Aug;26(6):1451-1459 [FREE Full text] [doi: 10.1177/13623613211056427] [Medline: 34903084]
23. Rehg JM, Abowd GD, Rozga A, Romero M, Clements MA, Sclaroff S, et al. Decoding children's social behavior. In: Proceedings of the IEEE Conference on Computer Vision and Pattern Recognition. 2013 Presented at: IEEE Conference on Computer Vision and Pattern Recognition; June 23-28, 2013; Portland, OR URL: https://ieeexplore.ieee.org/document/6619282
24. Rehg JM. Behavior imaging and the study of autism. In: Proceedings of the 15th ACM on International conference on multimodal interaction. 2013 Presented at: ICMI '13: 2013 International Conference on Multimodal Interaction; December 9-13, 2013; Sydney, Australia. [doi: 10.1145/2522848.2532203]
25. Fein D, Barton M, Eigsti IM, Kelley E, Naigles L, Schultz RT, et al. Optimal outcome in individuals with a history of autism. J Child Psychol Psychiatry 2013 Feb;54(2):195-205 [FREE Full text] [doi: 10.1111/jcpp.12037] [Medline: 23320807]
26. Daniels J, Schwartz JN, Voss C, Haber N, Fazel A, Kline A, et al. Exploratory study examining the at-home feasibility of a wearable tool for social-affective learning in children with autism. NPJ Digit Med 2018 Aug 02;1:32 [FREE Full text] [doi: 10.1038/s41746-018-0035-3] [Medline: 31304314]
27. Daniels J, Haber N, Voss C, Schwartz J, Tamura S, Fazel A, et al. Feasibility testing of a wearable behavioral aid for social learning in children with autism. Appl Clin Inform 2018 Jan;9(1):129-140 [FREE Full text] [doi: 10.1055/s-0038-1626727] [Medline: 29466819]
28. Deveau N, Washington P, Leblanc E, Husic A, Dunlap K, Penev Y, et al. Machine learning models using mobile game play accurately classify children with autism. Intell Based Med 2022;6:100057 [FREE Full text] [doi: 10.1016/j.ibmed.2022.100057] [Medline: 36035501]
29. Hou C, Kalantarian H, Washington P, Dunlap K, Wall DP. Leveraging video data from a digital smartphone autism therapy to train an emotion detection classifier. medRxiv. Preprint posted online August 01, 2021 2023 [FREE Full text] [doi: 10.1101/2021.07.28.21260646]
30. Kalantarian H, Jedoui K, Washington P, Wall DP. A mobile game for automatic emotion-labeling of images. IEEE Trans Games 2020 Jun;12(2):213-218 [FREE Full text] [doi: 10.1109/tg.2018.2877325] [Medline: 32551410]
31. Kalantarian H, Washington P, Schwartz J, Daniels J, Haber N, Wall D. A gamified mobile system for crowdsourcing video for autism research. In: Proceedings of the 2018 IEEE International Conference on Healthcare Informatics (ICHI). 2018 Presented at: 2018 IEEE International Conference on Healthcare Informatics (ICHI); June 4-7, 2018; New York, NY. [doi: 10.1109/ichi.2018.00052]
32. Kalantarian H, Jedoui K, Washington P, Tariq Q, Dunlap K, Schwartz J, et al. Labeling images with facial emotion and the potential for pediatric healthcare. Artif Intell Med 2019 Jul;98:77-86 [FREE Full text] [doi: 10.1016/j.artmed.2019.06.004] [Medline: 31521254]
33. Kalantarian H, Washington P, Schwartz J, Daniels J, Haber N, Wall DP. Guess what?: towards understanding autism from structured video using facial affect. J Healthc Inform Res 2019;3(1):43-66 [FREE Full text] [doi: 10.1007/s41666-018-0034-9] [Medline: 33313475]
34. Kalantarian H, Jedoui K, Dunlap K, Schwartz J, Washington P, Husic A, et al. The performance of emotion classifiers for children with parent-reported autism: quantitative feasibility study. JMIR Ment Health 2020 Apr 01;7(4):e13174 [FREE Full text] [doi: 10.2196/13174] [Medline: 32234701]

35. Kline A, Voss C, Washington P, Haber N, Schwartz H, Tariq Q, et al. Superpower glass. GetMobile Mob Comp Commun 2019 Nov 14;23(2):35-38. [doi: 10.1145/3372300.3372308]
36. Penev Y, Dunlap K, Husic A, Hou C, Washington P, Leblanc E, et al. A mobile game platform for improving social communication in children with autism: a feasibility study. Appl Clin Inform 2021 Oct;12(5):1030-1040 [FREE Full text] [doi: 10.1055/s-0041-1736626] [Medline: 34788890]
37. Surabhi S, Shah B, Washington P, Mutlu OC, Leblanc E, Mohite P, et al. TikTok for good: creating a diverse emotion expression database. In: Proceedings of the 2022 IEEE/CVF Conference on Computer Vision and Pattern Recognition Workshops (CVPRW). 2022 Presented at: 2022 IEEE/CVF Conference on Computer Vision and Pattern Recognition Workshops (CVPRW); June 19-20, 2022; New Orleans, LA. [doi: 10.1109/cvprw56347.2022.00279]
38. Voss C, Schwartz J, Daniels J, Kline A, Haber N, Washington P, et al. Effect of wearable digital intervention for improving socialization in children with autism spectrum disorder: a randomized clinical trial. JAMA Pediatr 2019 May 01;173(5):446-454 [FREE Full text] [doi: 10.1001/jamapediatrics.2019.0285] [Medline: 30907929]
39. Voss C, Washington P, Haber N, Kline A, Daniels J, Fazel A, et al. Superpower glass: delivering unobtrusive real-time social cues in wearable systems. In: Proceedings of the 2016 ACM International Joint Conference on Pervasive and Ubiquitous Computing: Adjunct. 2016 Presented at: UbiComp '16: The 2016 ACM International Joint Conference on Pervasive and Ubiquitous Computing; September 12-16, 2016; Heidelberg, Germany. [doi: 10.1145/2968219.2968310]
40. Washington P, Voss C, Haber N, Tanaka S, Daniels J, Feinstein C, et al. A wearable social interaction aid for children with autism. In: Proceedings of the 2016 CHI Conference Extended Abstracts on Human Factors in Computing Systems. 2016 Presented at: CHI'16: CHI Conference on Human Factors in Computing Systems; May 7-12, 2016; San Jose, CA. [doi: 10.1145/2851581.2892282]
41. Washington P, Voss C, Kline A, Haber N, Daniels J, Fazel A, et al. SuperpowerGlass: a wearable aid for the at-home therapy of children with autism. Proc ACM Interact Mob Wearable Ubiquitous Technol 2017 Sep 11;1(3):1-22. [doi: 10.1145/3130977]
42. Washington P, Tariq Q, Leblanc E, Chrisman B, Dunlap K, Kline A, et al. Crowdsourced privacy-preserved feature tagging of short home videos for machine learning ASD detection. Sci Rep 2021 Apr 07;11(1):7620 [FREE Full text] [doi: 10.1038/s41598-021-87059-4] [Medline: 33828118]
43. Duda M, Daniels J, Wall DP. Clinical evaluation of a novel and mobile autism risk assessment. J Autism Dev Disord 2016 Jun;46(6):1953-1961 [FREE Full text] [doi: 10.1007/s10803-016-2718-4] [Medline: 26873142]
44. Chen ZS, Kulkarni PP, Galatzer-Levy IR, Bigio B, Nasca C, Zhang Y. Modern views of machine learning for precision psychiatry. Patterns (N Y) 2022 Nov 11;3(11):100602 [FREE Full text] [doi: 10.1016/j.patter.2022.100602] [Medline: 36419447]
45. Elbattah M, Carette R, Cilia F, Guérin JL, Dequen G. Chapter 5 - Applications of machine learning methods to assist the diagnosis of autism spectrum disorder. In: El-Baz AS, Suri JS, editors. Neural Engineering Techniques for Autism Spectrum Disorder. Cambridge, MA: Academic Press; 2023.
46. Kanhirakadavath MR, Chandran MS. Investigation of eye-tracking scan path as a biomarker for autism screening using machine learning algorithms. Diagnostics (Basel) 2022 Feb 17;12(2):518 [FREE Full text] [doi: 10.3390/diagnostics12020518] [Medline: 35204608]
47. Washington P, Park N, Srivastava P, Voss C, Kline A, Varma M, et al. Data-driven diagnostics and the potential of mobile artificial intelligence for digital therapeutic phenotyping in computational psychiatry. Biol Psychiatry Cogn Neurosci Neuroimaging 2020 Aug;5(8):759-769 [FREE Full text] [doi: 10.1016/j.bpsc.2019.11.015] [Medline: 32085921]
48. Washington P, Kalantarian H, Tariq Q, Schwartz J, Dunlap K, Chrisman B, et al. Validity of online screening for autism: crowdsourcing study comparing paid and unpaid diagnostic tasks. J Med Internet Res 2019 May 23;21(5):e13668 [FREE Full text] [doi: 10.2196/13668] [Medline: 31124463]
49. Washington P, Chrisman B, Leblanc E, Dunlap K, Kline A, Mutlu C, et al. Crowd annotations can approximate clinical autism impressions from short home videos with privacy protections. Intell Based Med 2022;6:None [FREE Full text] [doi: 10.1016/j.ibmed.2022.100056] [Medline: 35634270]
50. Welcome to AWS documentation. Amazon Web Services. URL: https://docs.aws.amazon.com/ [accessed 2024-01-17]
51. Zoom home page. Zoom Video Communications, Inc. URL: https://zoom.us/ [accessed 2024-01-17]
52. Peñuelas-Calvo I, Jiang-Lin LK, Girela-Serrano B, Delgado-Gomez D, Navarro-Jimenez R, Baca-Garcia E, et al. Video games for the assessment and treatment of attention-deficit/hyperactivity disorder: a systematic review. Eur Child Adolesc Psychiatry 2022 Jan;31(1):5-20. [doi: 10.1007/s00787-020-01557-w] [Medline: 32424511]
53. Kosmicki JA, Sochat V, Duda M, Wall DP. Searching for a minimal set of behaviors for autism detection through feature selection-based machine learning. Transl Psychiatry 2015 Feb 24;5(2):e514 [FREE Full text] [doi: 10.1038/tp.2015.7] [Medline: 25710120]
54. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982 Apr;143(1):29-36. [doi: 10.1148/radiology.143.1.7063747] [Medline: 7063747]
55. google/mediapipe. GitHub. URL: https://github.com/google/mediapipe [accessed 2024-01-08]

56. Amos B, Ludwiczuk B, Satyanarayanan M. OpenFace: a general-purpose face recognition library with mobile applications. School of Computer Science, Carnegie Mellon University. 2016 Jun. URL: https://elijah.cs.cmu.edu/DOCS/CMU-CS-16-118.pdf [accessed 2024-01-08]
57. Amazon rekognition. Amazon Web Services. URL: https://aws.amazon.com/rekognition/ [accessed 2024-01-16]
58. Kim JW, Salamon J, Li P, Bello JP. CREPE: a convolutional representation for pitch estimation. arXiv. Preprint posted online February 17, 2018 2023 [FREE Full text]
59. McFee B, Raffel C, Liang D, Ellis D, Mcvicar M, Battenberg E, et al. librosa: audio and music signal analysis in python. In: Proceedings of the Python in Science Conference. 2015 Presented at: Python in Science Conference; July 6-12, 2015; Austin, TX URL: https://www.researchgate.net/publication/328777063_librosa_Audio_and_Music_Signal_Analysis_in_Python [doi: 10.25080/majora-7b98e3ed-003]
60. Kuleshov V, Fenner N, Ermon S. Accurate uncertainties for deep learning using calibrated regression. In: Proceedings of the 35th International Conference on Machine Learning. 2018 Presented at: 35th International Conference on Machine Learning; July 10-15, 2018; Stockholm, Sweden URL: https://arxiv.org/abs/1807.00263
61. Cloud and data center. NVIDIA Corporation. URL: https://www.nvidia.com/en-us/data-center/ [accessed 2024-01-17]
62. Django documentation. Django. URL: https://docs.djangoproject.com/en/5.0/ [accessed 2024-01-08]
63. Amazon elastic compute cloud documentation. Amazon Web Services. URL: https://docs.aws.amazon.com/ec2 [accessed 2023-12-14]
64. Levy S, Duda M, Haber N, Wall DP. Sparsifying machine learning models identify stable subsets of predictive features for behavioral detection of autism. Mol Autism 2017 Dec 19;8:65 [FREE Full text] [doi: 10.1186/s13229-017-0180-6] [Medline: 29270283]
65. Abbas H, Garberson F, Liu-Mayo S, Glover E, Wall DP. Multi-modular AI approach to streamline autism diagnosis in young children. Sci Rep 2020 Mar 19;10(1):5014 [FREE Full text] [doi: 10.1038/s41598-020-61213-w] [Medline: 32193406]
66. Abbas H, Garberson F, Glover E, Wall DP. Machine learning approach for early detection of autism by combining questionnaire and home video screening. J Am Med Inform Assoc 2018 Aug 01;25(8):1000-1007 [FREE Full text] [doi: 10.1093/jamia/ocy039] [Medline: 29741630]
67. Wall DP, Liu-Mayo S, Salomon C, Shannon J, Taraman S. Optimizing a de novo artificial intelligence-based medical device under a predetermined change control plan: improved ability to detect or rule out pediatric autism. Intell Based Med 2023;8:100102. [doi: 10.1016/j.ibmed.2023.100102]
68. Megerian J, Dey S, Melmed RD, Coury DL, Lerner M, Nicholls CJ, et al. Evaluation of an artificial intelligence-based medical device for diagnosis of autism spectrum disorder. NPJ Digit Med 2022 May 05;5(1):57 [FREE Full text] [doi: 10.1038/s41746-022-00598-6] [Medline: 35513550]
69. Wall DP, Dally R, Luyster R, Jung JY, Deluca TF. Use of artificial intelligence to shorten the behavioral diagnosis of autism. PLoS One 2012;7(8):e43855 [FREE Full text] [doi: 10.1371/journal.pone.0043855] [Medline: 22952789]
70. Roitero K, Barbera DL, Soprano M, Demartini G, Mizzaro S, Sakai T. How many crowd workers do I need? On statistical power when crowdsourcing relevance judgments. ACM Trans Inf Syst 2023 Aug 18;42(1):1-26. [doi: 10.1145/3597201]

Abbreviations

ADHD: attention-deficit/hyperactivity disorder
ASD: autism spectrum disorder
AUROC: area under the receiver operating characteristic curve
AWS: Amazon Web Services
DL: deep learning
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
IRB: institutional review board
ML: machine learning

Edited by A Mavragani; submitted 25.08.23; peer-reviewed by M Zubairi, F Alam, R Alpers; comments to author 06.11.23; revised version received 17.12.23; accepted 26.12.23; published 08.02.24.

Please cite as:
Jaiswal A, Kruiper R, Rasool A, Nandkeolyar A, Wall DP, Washington P
Digitally Diagnosing Multiple Developmental Delays Using Crowdsourcing Fused With Machine Learning: Protocol for a Human-in-the-Loop Machine Learning Study
JMIR Res Protoc 2024;13:e52205
URL: https://www.researchprotocols.org/2024/1/e52205
doi:10.2196/52205
PMID:38329783

Protocol

Telehealth-Delivered Program and Accompanying Patients to Enhance the Clinical Condition of Patients Throughout a Liver Transplant: Protocol for a Mixed Methods Study

Marie-Pascale Pomey[1,2,3], MD, PhD; Enora Le Roux[1,4,5], PhD; Nathalie Nadon[1], MSc; Jessie Perron[1,6], MSc; Angèle Barry[1,7,8], MSc; Chantal Bémeur[9], PhD; Thomas G Poder[2,10], PhD; Fernand Duford[11]; Louise Laviolette[11]; Johanne Tétrault-Lassonde[11], MSc; Cécile Vialaron[1], MSc; Manuel J Escalona[1], PhD; Louise Normandin[1], PhD; Geneviève Huard[7,11], MD; Catherine Girardin[7,11], MD; Christopher Rose[9], PhD; Kathy Malas[1], MSc; Denis Ouellet[12], MSc; Catherine Vincent[7,11], MD

[1]Carrefour de l'Innovation, Centre de recherche du Centre hospitalier de l'Université de Montréal, Montréal, QC, Canada

[2]Département de gestion, évaluation et politique de santé, école de santé publique, Université de Montréal, Montreal, QC, Canada

[3]Centre d'excellence sur le partenariat avec les patients et le public, Montreal, QC, Canada

[4]Université Paris Cité, ECEVE UMR 1123, Inserm, Faculté de Médecine, Paris, France

[5]AP-HP.Nord-Université Paris Cité, Hôpital Universitaire Robert Debré, Unité d'épidémiologie clinique, Inserm, CIC 1426, Paris, France

[6]Regroupement cardio-vasculaire, hépatologie et transplantation, Centre hospitalier de l'Université de Montréal, Montreal, QC, Canada

[7]Axe immunopathologie, Centre de recherche du Centre hospitalier de l'Université de Montréal, Montreal, QC, Canada

[8]Réseau transplantation et cliniques externes de transplantation et d'hépatologie, Centre hospitalier de l'Université de Montréal, Montreal, QC, Canada

[9]Axe Cardiométabolique, Centre de recherche du Centre hospitalier de l'Université de Montréal, Montreal, QC, Canada

[10]Centre de recherche de l'IUSMM, CIUSSS de l'Est de l'Île de Montréal, Montreal, QC, Canada

[11]Département d'hépatologie, Centre hospitalier universitaire de Montréal (CHUM), Montreal, QC, Canada

[12]Direction de la biovigilance et de la biologie médicale, Ministère de la Santé et des Services sociaux du Québec, Montreal, QC, Canada

Corresponding Author:
Marie-Pascale Pomey, MD, PhD
Carrefour de l'Innovation
Centre de recherche du Centre hospitalier de l'Université de Montréal
850, rue Saint-Denis (bureau S01.124)
Montréal, QC, H2X 0A9
Canada
Phone: 1 514 890 8000 ext 14302
Email: marie-pascale.pomey@umontreal.ca

Abstract

Background: Liver transplantation (LT) is indicated in patients with severe acute or chronic liver failure for which no other therapy is available. With the increasing number of LTs in recent years, liver centers worldwide must manage their patients according to their clinical situation and the expected waiting time for transplantation. The LT clinic at the Centre hospitalier de l'Université de Montréal (CHUM) is developing a new health care model across the entire continuum of pre-, peri-, and posttransplant care that features patient monitoring by an interdisciplinary team, including an accompanying patient; a digital platform to host a clinical plan; a learning program; and data collection from connected objects.

Objective: This study aims to (1) evaluate the outcomes following the implementation of a patient platform with connected devices and an accompanying patient, (2) identify implementation barriers and facilitators, (3) describe service outcomes in terms of health outcomes and the rates and nature of contact with the accompanying patient, (4) describe patient outcomes, and (5) assess the intervention's cost-effectiveness.

Methods: Six types of participants will be included in the study: (1) patients who received transplants and reached 1 year after transplantation before September 2023 (historical cohort or control group), (2) patients who will receive an LT between December 2023 and November 2024 (prospective cohort/intervention group), (3) relatives of those patients, (4) accompanying patients who have received an LT and are interested in supporting patients who will receive an LT, (5) health care professionals, and (6) decision makers. To describe the study sample and collect data to achieve all the objectives, a series of validated questionnaires,

accompanying patient logbooks, transcripts of interviews and focus groups, and clinical indicators will be collected throughout the study.

Results: In total, 5 (steering, education, clinical-technological, nurse prescription, and accompanying patient) working committees have been established for the study. Recruitment of patients is expected to start in November 2023. All questionnaires and technological platforms have been prepared, and the clinicians, stakeholders, and accompanying patient personnel have been recruited.

Conclusions: The implementation of this model in the trajectory of LT recipients at the CHUM may allow for better monitoring and health of patients undergoing transplantation, ultimately reducing the average length of hospital stay and promoting better use of medical resources. In the event of positive results, this model could be transposed to all transplant units at the CHUM and across Quebec (potentially affecting 888 patients per year) but could also be applied more widely to the monitoring of patients with other chronic diseases. The lessons learned from this project will be shared with decision makers and will serve as a model for other initiatives involving accompanying patients, connected objects, or digital platforms.

International Registered Report Identifier (IRRID): PRR1-10.2196/54440

(JMIR Res Protoc 2024;13:e54440) doi:10.2196/54440

KEYWORDS

liver transplantation; accompanying patients; connected objects; health care model; digital platform

Introduction

Background

Liver transplantation (LT) is a surgical procedure to remove a diseased or injured liver that results in liver failure and replaces it with a healthy liver from a donor. LT is indicated in patients with severe acute or chronic liver failure for which no other therapy is available or with hepatocellular carcinoma. Acute liver failure has several causes, including viral (most commonly hepatitis B and C) and drug-induced hepatitis. Chronic liver failure can also have several causes, such as alcoholic liver disease, autoimmune liver disease, and fatty liver disease. LT offers an opportunity to improve not only the health-related quality of life but also the life span of patients living with chronic liver disease and its associated complications.

Liver failure is now the seventh leading cause of death worldwide, with 1.4 million deaths per year. In Europe, >5000 LTs are performed per year, with >140,000 LTs performed over the past 6 years [1] for a European population of 751 million. In the United States, 8906 LTs were performed in 2020 alone, with a total of 24,936 candidates listed for LTs that same year [2]. In Canada, liver failure is the 12th leading cause of death, particularly among the population aged between 25 and 64 years. Cumulative LT activity in Canada has reached 27,488 patients, including 498 transplants from living donors since 1998. In 2020, a total of 565 LTs were reported, with the transplantation rate increasing by 22% over the past 10 years [3]. However, the growing need for LTs also increases the number of candidates on the waiting list, which is greater than the number of viable livers. As a result, the waiting time for transplantations can vary from a few days to >1 year depending on the patient's condition [1].

With the growing number of LTs, liver centers worldwide must manage their patients according to their clinical situation and the expected waiting time for transplants. Moreover, the LT procedure and postoperative period adversely affect the patient's well-being. Therefore, patients should be carefully prepared both physically and mentally to undergo transplantation. Proper management of patients on the waiting list is essential to avoid death or dropout because of deterioration of their condition, as well as to ensure that patients are in the best possible physical, psychological, and social condition before the procedure. These factors are key to the success of the postoperative course [1]. Moreover, the organization of outpatient care is characterized by a certain number of dysfunctions, such as numerous medical consultations with several specialists, which require that patients travel several times to appointments. This is particularly the case with pretransplant assessments, for which patients may need to meet with numerous specialists and undergo several biological, clinical, and imaging tests. These numerous trips put a heavy burden on patients, often resulting in outdated examination results such that patients then have to retake them, unnecessary consultations, and a significant mobilization of caregivers.

However, implementing a model that will meet these requirements is costly and requires the availability of all qualified professionals involved in the LT process. Given the limited human resources in care services, follow-up tools such as mobile apps and web-based platforms may strengthen patient adherence and help empower patients who have undergone transplantation [4]. The mobilization of patients who have undergone transplantation or former patients to provide additional support may also improve patients' motivation and engagement in care [5]. Finally, involving professionals with a mission of health promotion may have an impact on the immediate and long-term health of patients with liver disease. Given this context, the University of Montréal Health Center (*Centre hospitalier de l'Université de Montréal*; CHUM) has decided to implement an innovative health care model to speed up pretransplant assessments, provide interdisciplinary support, and implement social and technological innovations that will enhance patient health.

Aims and Objectives

Drawing on implementation science, this mixed methods pilot study will evaluate the implementation of a new health care model to enhance the clinical condition of patients throughout

their LT experience. In line with the outcome categories proposed for implementation research [6], this study's specific objectives are to (1) quantitatively evaluate the implementation outcomes of a patient platform through connected devices and accompaniment by a former patient (in terms of predefined benchmarks for acceptability, usability, response burden, feasibility [recruitment and retention], and fidelity), (2) identify implementation barriers and facilitators through semistructured interviews with stakeholders, (3) describe service outcomes in terms of health outcomes and the rates and nature of contact with the accompanying patient, (4) describe patient outcomes (based on daily self-reported health data, including symptoms, use of health services beyond the intervention, and patient satisfaction with teleconsultations if received), and (5) assess the cost-effectiveness of the intervention.

Intervention Implementation Strategy

Overview of the Strategy

This study draws on implementation sciences [7] that are intended to foster the adoption or implementation of an intervention. The selected strategies are presented based on the main corresponding implementation phase: preimplementation, implementation, and postimplementation phase. Central to our implementation strategy is our intention to involve patients and stakeholders through various engagement approaches. Our stakeholder engagement strategy is implemented by an interdisciplinary research team that includes not only researchers (MPP, ELR, CB, TP, CV, CR, and MJE), clinicians (CV, AB, GH, and CG), managers (NN and JP), and decision makers (KM and DO) but also patient coresearchers and former patients (FD, LL, and JTL) [8-11]. Our research and intervention development processes are based on a coconstruction methodology that respects the knowledge and responsibility of the stakeholders based on their values, expertise, and perspectives concerning a health condition and its associated care [12,13]. By involving all stakeholders in this project from the outset, we seek not only to detect and address the challenges associated with recruitment, accessibility, acceptability, and the comprehensibility of procedures and instruments [14] but also to enhance the relevance and meaningfulness of our research results [12].

At the CHUM, certain sectors of activity have been prioritized, including the LT clinic, to improve the patient pathway. The LT clinic constitutes a great target for work on a new model of outpatient care as the medical and nonmedical teams are highly motivated; the number of patients is manageable (60 patients undergoing transplants per year); and the clinic offers a platform where it is possible to integrate and coordinate several medical specialties, such as hepatology, nephrology, cardiology, endocrinology, and even psychiatry.

Overview of the Intervention

The proposed intervention is complex; it "comprises multiple interacting components, although additional dimensions of complexity include the difficulty of their implementation and the number of organizational levels they target" [15]. This new health care model is called Transplant'Action Connected in Liver Transplant (TAC) and includes five components implemented before, during, and after LT: (1) clinical team and technical support; (2) a kinesiology-based intervention plan; (3) a nutritional intervention plan; (4) peer support; and (5) the use of a digital platform, including an interface containing the intervention plans with support videos as well as the association of connected objects (COs; ie, a blood pressure monitor, scale, bracelet, and glucometer [if necessary]) to monitor patients' biological variables and physical activity.

Before Transplantation

In the regular care at the CHUM, patients who could potentially benefit from a transplant are assessed by the CHUM's *guichet rapide d'investigation en transplantation du foie* (rapid LT assessment service; GRIT-F), which provides a 1-week pretransplant assessment on an outpatient basis. GRIT-F usually includes a clinical team composed of hepatologists, a pretransplant nurse, and a cardiologist if necessary. Following this assessment, if the results are favorable, the patient is placed on the transplant waiting list. The patient is then monitored exclusively by the hepatologist every 3 months (or more often if the patient presents signs of deterioration). No systematic follow-up by a nurse or other health care professionals (HCPs) is provided during this period.

In the new TAC health care model, the GRIT-F will include additional professionals, such as a kinesiologist, nutritionist, psychologist, cardiologist (if needed), social worker, and accompanying patients. This team assesses not only the patient's clinical situation but also the patient's knowledge and understanding of the disease, living with the disease, the transplant, and drug treatments, as well as their digital literacy. If the patient is placed on the transplant list, the patient benefits from a 1-day individual meeting with the CHUM pretransplant team, consisting of the clinical team (hepatologist, nurse, nutritionist, kinesiologist, and accompanying patient) and the digital health specialist. During this day, an intervention plan is coconstructed with the patient that includes activities to be carried out as well as the fitness and nutritional goals to be achieved. To support them in implementing this intervention plan, the patient receives COs (ie, a blood pressure monitor, scale, bracelet to measure physical activity, and glucometer) as well as access to a digital platform that provides physical exercises and nutritional recommendations. This digital platform tracks the data collected by the COs and provides access to videos. A support plan is also implemented. It includes a follow-up by the transplant nurse every 4 weeks via teleconsultation, by the accompanying patient every month, and by the nutritionist and kinesiologist every month for the first 2 months and upon request thereafter. Technological support is also provided throughout this phase.

During Transplantation

In the regular care provided at the CHUM, the patient is followed by the medical team and the transplant floor nurse and is seen by the pharmacist for medication education. In addition, the services of a physiotherapist and a nutritionist are available on the transplant floor.

In the new TAC health care model, other professionals, such as psychologists, kinesiologists, and nutritionists, will intervene according to the patient's needs. However, the patient who undergoes transplantation continues to benefit from the support

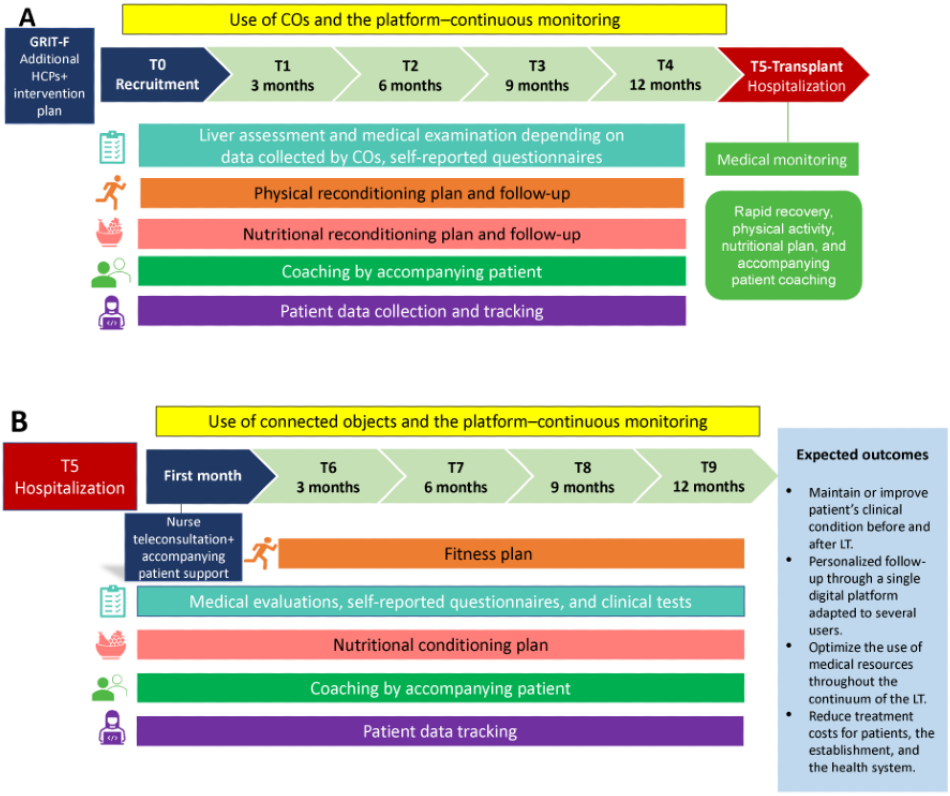
of an accompanying patient. Depending on their clinical condition, the patient can perform kinesiology exercises using a bicycle adapted to the bed. The use of COs during this phase is left to the patient's discretion.

After Transplantation

As part of the regular care at the CHUM, the patient is followed only by the hepatologist and posttransplant follow-up nurse in the months following the transplant.

As part of the new TAC health care model, upon returning home, the patient continues to receive weekly support via videoconference from the nurse and the accompanying patient during the first month and then monthly for 1 year, as well as in-person meetings with the clinical team. The patient resumes the use of COs at any time, and the nutritional plan is adapted as needs emerge. When allowed by the patient's general condition (eg, healing and muscular strength), a new physical exercise plan is proposed in the first 3 to 6 months after transplantation and carried out under the supervision of the kinesiologist and accompanying patient. An overview of the TAC health care model is presented in Figure 1.

Figure 1. Overall view of the intervention indicating key time points for data collection during (A) the pretransplant period and (B) the posttransplant period. CO: connected object; GRIT-F: guichet rapide d'investigation en transplantation du foie (rapid liver transplant assessment service); HCP: health care professional; LT: liver transplant.



Strategies During the Implementation Phase

All the HCPs and accompanying patients will be trained in therapeutic education and motivational interviewing to support the patients throughout their treatment, as well as in the use of the digital platform and COs. The team's role is to provide recommendations on the use of the digital platform, the procedures to follow as part of their intervention plan, the procedures for remote monitoring using the COs, the patient's daily self-assessment, and information on the educational material to be provided to participants through the patient portal.

When patients receive their COs, they will be supported by the digital platform developers and by the CHUM telehealth coordination center. To centralize technical support, the CHUM telehealth coordinator will communicate with the digital platform development team (ML and ECN) to maintain, configure, and update the patient portal for the duration of the project. Regular meetings will be held to discuss the configuration of the digital platform to ensure that it integrates stakeholder recommendations as obtained from engaged HCPs, accompanying patients, and patients. RdP will also be available to provide technical assistance to patients via email throughout the study.

To ensure that the patients' needs are met, the accompanying patients and HCPs will be regularly consulted to obtain their feedback on the proposed procedures for remote monitoring and research material (eg, informed consent documents and all the data collection instruments, including the self-assessment). This will help ensure the relevance, comprehensibility, and comprehensiveness of the results.

To effect cyclical change, MPP is planning 4 prototype tests with engaged HCPs (ie, the clinical team), accompanying patients, and a sample of patients. For each test, the members will receive training on the digital platform; use it for 4 days; and then meet to discuss their experiences, report any problems, and make recommendations. Furthermore, a test is planned of

the patient app portal involving 5 participants to adjust the intervention as required before the project begins with the patients. During that time, all HCPs, accompanying patients, and researchers will be trained on how to use the platform.

Once the platform is ready, patients will be registered to use it. Participants will be guided by a member of the research staff (CV or ME), who will confirm their identity and explain platform functionalities. The remote registration system will send a unique verification code to the user's smartphone with a link to the registration page, where the code will be entered. This is to ensure the security and privacy of patient information.

Strategy During the Postimplementation Phase

Our strategy is to re-examine the implementation phase by analyzing the participants' and stakeholders' views on implementation barriers and facilitators after implementation (based on qualitative interviews).

Methods

Study Design

A single-center pilot study will be conducted following the guidance provided by the CONSORT (Consolidated Standards of Reporting Trials) statement for pilot and feasibility studies [16,17]. It uses a mixed methods embedded design, with quantitative methods to measure the outcome and output and qualitative methods to extend the analysis of the implementation process [18].

Participants

To attain the study objectives, six types of participants will be included in the study: (1) patients who underwent transplantation 2 years before and received regular care (historical cohort or control group); (2) patients who will receive an LT during the next year under the new health care model (prospective cohort/intervention group); (3) relatives of the patients who will receive an LT; (4) accompanying patients who have already received an LT and are interested in supporting patients who will receive an LT; (5) HCPs, including proximity managers; and (6) decision makers.

Eligibility Criteria

Patient Population

All patients selected for an LT at the CHUM who are aged >18 years at the time of registration on the transplant waiting list and are fluent in French or English (written and spoken) will be considered for participation in the study. In addition, patients in the prospective cohort who will receive an LT will have to be able to use COs and remote monitoring platforms. The exclusion criterion for persons in the intervention group is not having a relative who can provide support in their use of the platform and the COs.

Other Population

Persons aged >18 years who are fluent in French or English (written and spoken) and linked to the study will be considered for participation.

Recruitment and Sample

Patient Population (Control Group)

This comprises patients *not exposed* to the new health care model. It consists of a historical cohort focused on the last 50 patients who underwent transplantation and reached 1 year after transplantation before September 2023. They will be identified through the hospital archive department.

Patient and Relative Population (Intervention Group)

This comprises patients (and their relatives) who will receive an LT from December 2023 to November 2024. Knowing that 60 patients receive an LT at the CHUM each year and that it is expected that 80% of these patients will be selected for the research project, we expect that 48 patients will be enrolled. This percentage is an estimate made by the clinical team based on their knowledge of the target population. During the week of the GRIT-F review, the research project will be presented to patients by the accompanying patient and the nurse. On the day that the patient is listed to receive an LT, the research assistant (CV or ME) will meet with the patient to present the project, give the informed consent form, answer their questions, and collect their consent or refusal to participate in the study. Patients who refuse to participate in the study will have the team's support without access to the digital platform and will not have any data collected in addition to what is routinely collected at the clinic.

Accompanying Patients and HCPs

This includes all the persons in these categories involved in patient care.

Decision Makers

This includes all persons involved in facilitating the implementation of the new health care model. It comprises the chairman and chief executive officer, the deputy chairman and chief executive officer, the director of medical affairs or their representative, the director of nursing or their representative, the director of multidisciplinary care or their representative, the director of the Information Technologies and Telecommunications Department or their representative, the director of the Technological Integration and Interoperability Operationalization Centers Department or their representative, the director of the Network Coordination Department or their representative, and the director of research or their representative.

Procedures

Table 1 presents all the study procedures and clinical and output indicators for patient data collection and evaluation to be used in the study. Table 2 details the data collection procedures to be used for accompanying patients, HCPs, and decision makers throughout the study.

Table 1. Clinical and output indicators for patient data collection and evaluation.

Data source and description	Collection time
Clinical examinations	
Hepatic encephalopathy using the Stroop test	Every 3 months (during the medical visit)
Liver Frailty Index	Every 3 months (during the medical visit)
6MWT[a]	During the personal meeting day
Calf circumference	During the personal meeting day
Clavien-Dindo score (eg, presence of infectious complications, presence of wound dehiscence, and revision surgery) [1]	At the end of hospitalization
COs[b]	
Blood pressure	3 times a week
Weight	3 times a week
Capillary glucose (if needed)	3 times a week
Pulse	3 times a week
Number of steps and type of exercise	Continuously (ie, 3 times per day, 7 days per week)
Number of false alerts	Continuously
Number of interventions to solve problems related to COs	Continuously
Replacement of COs because of technological problems	Continuously
Medical records	
Number of medical visits (hepatologist, nephrologist, cardiologist, endocrinologist, psychiatrist, medical specialist in addiction, and dentist; via telephone or in person)	Continuously
Number of nonmedical visits (via telephone or in person)	Continuously
Number of emergency room visits	Continuously
Number of hospitalization days while waiting for the transplant and the reasons for these hospitalizations	Continuously
Number of days between registration on the transplant list and transplant	Continuously
Average length of stay (hospitalization days) for the transplant	At the end of hospitalization
Number of rehospitalizations in the first year after the transplant (average duration, location [eg, intensive care], and reasons for these hospitalizations)	Continuously
Surgical revision	Continuously

[a]6MWT: 6-Minute Walk Test.

[b]CO: connected object.

Table 2. Data collection and procedures for accompanying patients, health care professionals, and decision makers throughout the study.

Data source	Description	Collection time
Accompanying patients		
Documents	• Logbook	Continuously
Questionnaires	• Compassion fatigue risk test [19]	At the beginning and end of the study
Focus group or interview	• Perception of the contribution of the new health care model to follow-up and user experience	At the beginning and end of the study
Health care professionals		
Questionnaires and focus group	• Workplace Ethical Climate Scale [20] • Ability to work with accompanying patients [21] • Contributions of this model of care to improving the patient journey and appropriate use of specialized medical resources+evaluation of technical difficulties and the user-friendliness of the data accessed from medical records	At the beginning and end of the study
Decision makers		
Interview	• Contributions of this model of care and its limits and impact on the service	At the beginning and end of the study

Study Data Collection and Metrics

Platform and Connected Device Implementation Questionnaires

To assess the implementation outcomes (for objective 1), a series of interviews will be conducted 1 and 6 months before the transplant and 6 and 12 months after the transplant. These interviews will include questions on acceptability, response burden, and usability.

To evaluate the effort required to complete the questionnaires and further evaluate acceptability, the perceived response burden measure [22] will be used. It consists of a single question on a 5-point response scale adapted from a survey question from the UK Office for National Statistics.

Usability (the extent to which users can achieve the specific goal of a product) and acceptability (how agreeable, pleasant, or satisfactory the intervention is to the stakeholders [6]) are considered important aspects of implementation outcomes [23]. Both aspects will be assessed using the System Usability Scale questionnaire [24], which consists of 10 items rated on a 5-point Likert scale that are then averaged to produce a total score from 1 to 5. The participants' scores for each question are converted to a new number, added together, and then multiplied by 2.5 to convert the original scores from a scale from 0 to 40 to a scale from 0 to 100. A System Usability Scale score of >68 will indicate that the technology is considered to have an important impact and be useful and easy to use.

Satisfaction with teleconsultations (for objective 4) will be evaluated using the Telemedicine Satisfaction Questionnaire [25], which will be sent to patients after each teleconsultation.

Clinical Questionnaires

To describe the study sample and collect the data needed to achieve the study objectives, a series of validated questionnaires will be completed by all patients. The questionnaires will cover patient characteristics, the assessment of the partnership relationship between patients and professionals (CADICEE) [26], quality of life (SF-6Dv2) [27], the ability to engage in one's own care (PAM) [28], the perception of one's ability to change one's lifestyle habits [29], monitoring of compliance with medication treatments [30], internet-based 24-hour recall (dietary assessment) [31], the Subjective Global Assessment [32], out-of-pocket costs by patients for health care (CoPaQ) [33], and medical visits and consultations. Table 3 presents a summary of the timing and frequency of data collection. The secure internet-based platform REDCap (Research Electronic Data Capture; Vanderbilt University), an application for building and managing web-based surveys and databases, will be used to administer the questionnaires, organize the data collection, and analyze the data.

Table 3. Validated questionnaires for patient data collection and evaluation.

Domain and questionnaire	Dimensions	Number of items	Response scale	Time of measurement
Patient information				
Sociodemographic, medical, and capacity for use of COs[a] questionnaire	• Gender, age group, highest level of education, marital status, native language, ethnicity, and employment status • Medical background, smoking habits, other medical conditions, and chronic diseases (other than chronic liver disease) • Use of COs during a research study in the past	11 items	Varied	T0[b]
Emotional evaluation				
CADICEE questionnaire	• Evaluates the foundations of the partnership relationship between patients and health care professionals • Identifies potential gaps in the partnership	27 items	Varied	T0, T2[c], hospitalization, T7[d], and T9[e]
SF-6Dv2 Health Utility Survey	• Measures of health for QALY[f] calculations • Provides keen insights into patient healing by measuring 6 health domains: physical functioning, role limitations, social functioning, pain, mental health, and vitality	7 items	5-point Likert scale (1=not at all; 5=nearly all the time)	T0, T4[g], T6[h], and T9
Treatment monitoring and lifestyle habits				
PAM-13	• Ascertains the patient's self-reported knowledge, skills, and confidence in the self-management of their health	13 items	4-point Likert scale (1=strongly disagree; 4=strongly agree)	T0, T4, T6, and T9
Monitoring compliance with medication treatments	• Explores the intention or the need for help with current treatment plans	8 items	5-point Likert scale (1=strongly disagree; 5=strongly agree)	T0, T1[i], T2, T4, T6, T7, T8[j], and T9
Financial monitoring				
Out-of-pocket costs of health care for patients (CoPaQ)	• Collects net costs related to the patient's state of health that are not reimbursed by their insurers	33 items	Varied	T0, T1, T2, T4, T6, T7, T8, and T9
Clinical and health condition monitoring				
Online 24-hour recall	• Retrospective method that monitors and assesses an individual's food and drink consumption during the previous day	Electronic interface (images)	Varied	T0, T1, T2, T4, T6, T7, T8, and T9
SGA[k]	• Diagnose malnutrition and identify those who would benefit from nutrition care • History of recent intake, weight change, gastrointestinal symptoms, and a clinical evaluation	Clinical assessment	Varied	T0, T1, T2, T4, T6, T7, T8, and T9
Medical visits and consultations	• Continuous monitoring of medical visits or consultations and the reasons for them	Continuous medical monitoring	Varied	T0, T1, T2, T4, T6, T7, T8, and T9
Hospital care				
Quality of care in hospitalization scale (ESQ-H)	• Self-reported questionnaire with 2 domains measuring patient satisfaction with the quality of medical and nursing care in hospitals • It contains 2 domains: quality of medical information and the relationship with staff and daily routine	18 items	5-point Likert scale (1=poor; 5=excellent)	Hospitalization

[a]CO: connected object.

[b]T0: recruitment.
[c]T2: 6 months after recruitment.
[d]T7: 6 months after transplantation.
[e]T9: 12 months after transplantation.
[f]QALY: quality-adjusted life year.
[g]T4: 12 months after recruitment.
[h]T6: 3 months after transplantation.
[i]T1: 3 months after recruitment.
[j]T8: 9 months after transplantation.
[k]SGA: Subjective Global Assessment.

Clinical Indicators

Clinical indicators will be determined by the physician in charge of the patient or the team's kinesiologist. Among the clinical tests specific to this study, the physician will explore signs of hepatic encephalopathy (ie, deterioration of brain function that occurs in people with severe liver failure) using the Stroop test [34] to assess psychomotor speed and cognitive flexibility by recording the response time to interference between recognizing color fields and writing color names performed at different time points during the study (Table 3). Other clinical tests include the Liver Frailty Index [35], which consists of 3 tests representing 3 major components of the multidimensional construct of frailty in patients with cirrhosis: grip strength, chair stands (muscle weakness), and balance (altered neuromotor coordination). Moreover, the 6-Minute Walk Test (6MWT) [36], which assesses aerobic capacity and endurance, will be performed by the team's kinesiologist during the initial patient assessment (baseline) and every 3 months after the LT. The 6MWT measures the distance covered in 6 minutes (outcome) and will be used to identify changes in performance capacity. In conjunction with the 6MWT, the kinesiologist will also measure calf circumference [37], a representative anthropometric index used to screen for sarcopenia and in patient follow-up to adapt nutritional and exercise plans to meet each patient's needs throughout the posttransplant period. Other clinical indicators will be collected using COs: blood pressure, weight, pulse, number of steps/type of exercise, and capillary glucose (if needed).

In addition, to monitor the platform's reliability, we will look at the number of false alerts, the number of interventions required to solve problems related to COs, and the replacement of COs because of technological problems.

Output indicators will also be collected: number of medical visits (hepatologist, nephrologist, cardiologist, endocrinologist, psychiatrist, medical specialist in addiction, and dentist; via telephone, on the platform, or in person), number of nonmedical visits (via telephone, on the platform, or in person), number of emergency room visits, number of hospitalization days while waiting for the transplant and the reasons for these hospitalizations, number of days between registration on the transplant list and the transplant, number of hospitalization days during the transplant, surgical revisions, and number of hospitalization days after the transplant and the reasons for these hospitalizations.

Accompanying Patient Logbook

All accompanying patients participating in the study will document each of the meetings carried out with the patient in a logbook that will be available to all researchers and medical personnel in the project as well as in the REDCap application. In the logbook, the accompanying patient will provide information about the patient (last name and first name), the context of the meeting (health care facility, date of the meeting, start and end time of the meeting, person who requested the meeting, meeting number, and people present during the meeting), the stage of the patient's trajectory (pre-, peri-, or posttransplant stage), meeting method (in person or remotely and location of the meeting), the themes addressed (general aspects, organizational aspects, consequences on daily and family life, and clinical aspects), the accompanying patient's perceptions of the contribution to the patient and of the relationship with the patient, the difficulties encountered by the accompanying patient, unanswered questions, feedback to the clinical team and planned follow-ups, and any other comments deemed relevant by the accompanying patient. The accompanying patient's logbook can be found in Multimedia Appendix 1.

Coordinator Logbook

The coordinator logbook will capture qualitative and feasibility data that include entries on the following: (1) questions or challenges reported by the participants during consent and baseline educational meetings; (2) details about participant recruitment and fidelity throughout the intervention; (3) the recruitment rate (ie, the proportion of contacted eligible individuals who are included in the study); and (4) the retention rate, defined as the proportion of included participants who are retained over the full follow-up period. Fidelity, or the degree to which the intervention was implemented as intended, will be measured as the proportion of included patients who complete their daily self-assessments over the full follow-up period. The reasons for each of these activities will also be categorized and described based on the detailed information recorded in the coordinator logbook.

Interviews and Focus Groups

All qualitative interviews and focus groups will be conducted individually, preferably in person and, if not, via videoconference or phone. Each interview and focus group will be recorded and follow a semistructured guide with open-ended questions and specific prompts. Although adapted to each stakeholder group, the interview guide includes broad questions on the individual's experience of and thoughts on using the

digital platform follow-up, with prompts on challenges and facilitators [38] as well as open questions to identify information and education needs during the study. The interview guides for each stakeholder group can be found in Multimedia Appendix 2.

With the agreement of patients, accompanying patients, HCPs, managers, and decision makers, all interviews and focus groups will be recorded and transcribed to ensure the reliability of the information collected. The recordings will be transcribed and uploaded into the QDA Miner software (Provalis Research) for further analysis and to identify expected and emerging themes.

Data Analysis

All statistical analyses will be conducted using the R software (R Foundation for Statistical Computing) [39]. For the accompanying patient and coordinator logbooks, descriptive statistics (medians, means, and SDs) will be calculated. Economic analysis will be conducted using the Stata software (StataCorp).

Concerning the various questionnaires, descriptive statistics (medians, means, and SDs), chi-square tests, and 2-tailed *t* tests will be calculated on the populations studied for the sociodemographic characteristics of the patients (eg, age, sex, and characteristics of the care pathway) as well as on all the data obtained at each measurement time (ie, at T0 [assessment to be on the transplant waiting list] and then at 3, 6, 9, and 12 months). Medians, means, and SDs will be calculated for all patients.

For individual nutritional and physical conditioning optimization plans, an analysis will be conducted of the gaps between what was proposed and what was achieved. Statistical analyses will also be used to compare the patient's ability to follow the plan before and after the LT. In addition, multivariate analyses will be conducted based on the intensity of the support provided by the accompanying patients.

For qualitative data, a thematic analysis will be conducted. Coding will be carried out independently by a research agent, students, and the researchers to (1) identify points of convergence and divergence in what is said by the different stakeholders, (2) codify the data using the QDA Miner software to systematize the analysis, (3) build emerging themes, and (4) highlight the convergences and divergences of the intervention.

The quantitative and qualitative data will be compared and analyzed to improve our understanding of the intervention [18]. The barriers and facilitators identified through semistructured interviews with the stakeholders (objective 2) will be used to interpret the findings on patient outcomes, the implementation, and the health services (objectives 1, 3, and 4).

Specific Analysis for Each Objective

Objective 1: To Quantitatively Evaluate the Implementation Outcomes of a Patient Platform With Connected Devices and Accompaniment by a Former Patient

Implementation outcomes will be summarized using descriptive statistics. Acceptability and usability will be evaluated using a linear mixed model for each corresponding outcome. The evaluation of perceived response burden and fidelity will be conducted using a generalized linear mixed model for each corresponding outcome, which is appropriate when the dependent variable is not continuous. For all these calculations, the dependent variable of each model will be the outcome, and the independent variables will be the different time points of data collection (Table 3), 3 sociodemographic variables that are reported to influence patient portal use (gender [man or woman], age [≤50 or ≥50 years], and ethnicity), clinical data from the Stroop test, and the presence or absence of relatives during the transplantation process. The goals of testing each model are to determine whether the outcome's mean score changes significantly over time and whether it differs significantly between the groups represented by the sociodemographic variables over time.

Thus, for acceptability and usability, if at each time point the outcome's mean score is greater than or equal to the predefined success threshold, then the target will be considered met. If it is below the threshold, we will use a unilateral *t* test to test the null hypothesis of threshold attainment as being slightly below this mark does not imply failure given the sample mean's variability. To evaluate threshold attainment during the evaluation of perceived response burden and fidelity, if the observed proportion is under the predefined success threshold, a unilateral *z* test will be conducted as it is appropriate for hypothesis testing with proportions. Finally, an evaluation of feasibility will be conducted by comparing the observed recruitment and retention rates with the predefined success thresholds at the end of the recruitment period and at the 1-year patient follow-up, respectively. If the observed rates are greater than or equal to the success threshold, the target will be considered met. If they are under the success threshold, we will use a unilateral *z* test to test the null hypothesis of threshold attainment.

Objective 2: To Identify Implementation Barriers and Facilitators Based on Semistructured Interviews With Stakeholders

To identify implementation facilitators and barriers and their proposed solutions, 2 analysts will conduct an analysis of the content extracted during the study. The source materials will include semistructured interview and focus group transcripts with the HCPs and the accompanying patients' logbook entries. The analysis will be conducted in three phases [40]: (1) the preparation phase, or the period during which the analysts become familiarized with the data set; (2) the organization phase, when the analysts systematically code the data using the QDA Miner software to identify implementation facilitators and barriers while remaining open to any possible emerging categories; and (3) the reporting phase, which consists of presenting and discussing the identified categories during monthly team meetings with the clinical and research teams to identify discrepancies either in coding or interpretation, ensuring data reliability.

Objective 3: To Describe Service Outcomes in Terms of Health Outcomes and the Rates and Nature of Contact With the Accompanying Patient

A qualitative analysis will be conducted of the patients' health status, including visits to emergency rooms and continuous clinical monitoring as well as the reasons underlying participant contact with the team of HCPs (Table 1). This information will be monitored continuously and extracted from the medical records. Moreover, a content analysis will be conducted to assess the nature of contact with the accompanying patient based on the data collected in the accompanying patient logbooks. In addition, a content analysis will be conducted to assess expectations and experience with the health care model as well as the user experience with the digital platform and COs using data collected during interviews and from discussion groups (Multimedia Appendix 1).

Objective 4: To Describe Patient Outcomes Based on the Daily Self-Reported Health Data, Including Symptoms, Use of Health Services Beyond the Intervention, and Patient Satisfaction With Teleconsultations if Received

Descriptive statistics will be used to report patient outcomes collected from medical records (Table 1), daily health data self-reported through the use of COs, self-reported questionnaires completed throughout the study (Table 3), and patient satisfaction with teleconsultations and tools. For the analysis, each patient constitutes their own reference and comparison. Thus, δ calculations will be conducted, derived by comparing individual questionnaire results with outcomes from the same questionnaires at other time points throughout the study (ie, baseline vs time points before and after transplantation). For continuous outcomes, the mean, SD, minimum, and maximum values will be reported. For ordinal and nominal qualitative outcomes, absolute and relative frequencies (proportions) will be reported. Descriptive statistics will also be presented by gender and age group.

Objective 5: To Assess the Cost-Effectiveness of the Intervention

A cost minimization analysis will be used to meet this objective. The out-of-pocket costs for the patient and the caregiver will be measured using the cost for patient questionnaire, which was developed and validated in Quebec [41,42]. The costs for the health care institution will be measured using the PowerHealth software (PowerHealth Solutions) used at the CHUM, which combines financial data with data in patient clinical files. The costs for the health care system will include the costs borne by the institution, including physician remuneration. To identify these costs, a questionnaire on medical visits and consultations will be sent to the patient every 3 months so that the patient can indicate the number and nature of these events. The *Régie de l'assurance maladie du Québec* pricing manual will then be used to identify these costs.

Ethical Considerations

Approval and Consent

Ethics approval was obtained from the research ethics board at the Centre hospitalier de l'Université de Montréal (CHUM), Quebec, Canada (study ID: 20-5185). The research team and principal investigators at the hospital are responsible for recruitment and monitoring of participants. Any major modifications or protocol deviations are discussed with the other principal investigators during monthly meetings, and any major protocol modifications are reported and submitted to the ethics board for approval. Participants will be approached by the project medical team and then by the research team to inform them about the objectives, benefits, and risks of the research. If the participant is accepted for LT, the research team will meet with the patient and have them sign the consent form.

Safety and Anticipated Risks

There are no direct risks to participants in this study. Data security risks will be addressed through numerous measures, such as copying data to the CHUM Research Centre (CRCHUM) server and protecting them with a user code and password. Moreover, the study questionnaires, semistructured interviews, and accompanying patient logbook sessions may lead to distress related to the transplant procedure or follow-up, the economic details collected, or depression and anxiety explorations. Therefore, these research tasks carry a risk of emotional vulnerability. Individuals who experience psychological distress because of their involvement in the study will be instructed to inform a member of the study staff. Regular psychological assessments or support services will be provided by the team's psychologist throughout the study.

Confidentiality, Data Management, and Cybersecurity

All collected data and personal information will be deidentified (coded) and kept in computer format at the CRCHUM. No identification of individual participants in any images of the manuscripts or supplementary materials will be possible. When the study results are released, participants will not be identifiable. The project's principal investigator (MPP) and coinvestigators will have access to the data and study results. All computer data will be copied to the CRCHUM server and protected by a user code and password. Research data will be retained for 10 years after project closure. The person in charge will be the principal investigator of the study, MPP. To join the scientific community, peer-reviewed scientific publications will be recommended.

Compensation

No financial compensation is offered for participating in this study. However, patients will have access at no cost to all COs and follow-up consultations.

Results

Several study-related activities have already been carried out from July 2022 to October 2023 concerning the intervention implementation, research, and the platform promoter, in addition to funding. Some steps are ongoing.

Implementation Status

To complete the GRIT-F clinical team and strengthen the capacity to monitor patients at the pre-, peri-, and posttransplant stage, a nutritionist, a nurse, a kinesiologist, and a psychologist have been recruited. A total of 5 accompanying patients have

been recruited and, along with the clinical team, trained on their roles and how to work together. A certain number of working committees have also been set up, including the following:

1. A steering committee comprising the physician responsible for the transplant clinic, the nursing comanager, the principal researcher, the 2 research assistants, and 3 accompanying patients. This committee meets every week to oversee the implementation of the project.
2. An education committee was also created in September 2023 to develop the tools needed to carry out the educational assessment, including identification of the patient's LT pathway, and the skills that patients and relatives can develop throughout the LT pathway. This committee also helps identify the resources that can be mobilized to support patients and their relatives and integrate these resources into the life course of the patients on the digital platform. This committee consists of not only the 5 accompanying patients but also all the members of the clinical team, the principal investigator, and representatives of the digital platform, as well as specialists in therapeutic education and health literacy. The committee meets every 15 days.
3. A clinical-technological committee ensures that the development of the platform is aligned with the clinical context and patient experience. This committee comprises the clinical team, accompanying patients, and digital platform representatives. It meets every 2 weeks.
4. A committee on prescriptions and nursing roles has also been set up to develop collective prescriptions to give nurses greater flexibility in their activities.
5. Finally, an accompanying patient community of practice has been formed, bringing together the 5 accompanying patients each week to discuss these practices and react to the research tools intended for them.

Research Status

In total, 2 research assistants and a PhD student have been recruited for ethics monitoring, development of the data collection plan and collection tools, recruitment of participants, and analysis of the data, as well as to ensure adherence to deadlines. This study will be conducted in a tertiary hospital. Written informed consent will be obtained from all participants before any study activities begin. Patient recruitment is expected to start in November 2023. All questionnaires; technological platforms; and clinicians, stakeholders, and accompanying patient personnel have been recruited for this study. The protocol was presented at the Canadian Association for Health Services and Policy Research conference in May 2023. In addition, the researchers will meet monthly to discuss the research plan, including the economic evaluation.

Platform Status

A contract has been signed between a digital platform developer and the CHUM, and 2 members of the company have been specifically designated to the project. Personalized training was offered by the company to all members of the clinical team, the accompanying patients, and the research team.

Funding Status

This study secured funding from the *Institut de la pertinence des actes médicaux* in June 2022.

Discussion

Expected Findings

Through this study, the CHUM LT clinic aims to explore the effects of a new health care model, called TAC, on the patient trajectory in LT. The project will be implemented in three phases: (1) a rapid investigation window model in pretransplant assessment will be developed with the introduction of COs and the mobilization of a kinesiologist, a nutritionist, a pharmacist, 2 nurses, a psychologist, a social worker, a computer technician, and accompanying patients; (2) the model will then be implemented throughout the care pathway, including after transplantation, through the integration of an digital platform that includes not only monitoring via COs but also access to educational material coconstructed with patients; and (3) data from the platform will be integrated into the electronic medical record and the CHUM computerized clinical file. Adjustments will also be made to the digital platform to ensure optimal follow-up with the COs as well as for access to personalized medication and nutritional and physical exercise treatment plans.

To our knowledge, this study will be the first to investigate and attempt a reorganization of the care pathway in LTs by optimizing trips to the hospital, reducing the time required for the patient to be registered on the transplant list, engaging an interdisciplinary team to cocreate strategies that encourage patient commitment to their own health promotion, mobilizing each health professional in a relevant manner, and establishing the use of COs to monitor health progression as well as the use of accompanying patients who have already undergone a transplant at the CHUM. Although many studies have brought to light the key roles played by patient monitoring throughout an intervention [43-45] and the inclusion of educational programs provided by HCPs to patients [46-48] in intervention effectiveness over time, this is the first study to integrate both components while also involving an interdisciplinary team to support and explore their application by combining them into a single health care model. The originality of this study lies in the fact that it integrates accompanying patients as full-fledged members of the clinical LT team to assess the potential effects at the clinical and organizational levels, as well as integrating them into the process of creating educational programs for the patients. This study introduces the use of multiple COs, which could have a major impact on patient plans by closely monitoring the patient's health status. This may lead to modifications in personalized nutritional and physical exercise treatment plans that will improve recovery rates after LTs. Moreover, the mixed methods nature of this study allows us to explore the variability between settings to delineate various clinical scenarios and document patients' economic, emotional, and personal realities during the transplant process.

If this new health care model is relevant, it might maintain or improve the clinical condition of patients before and after all types of transplantation through a more personalized and closely monitored follow-up, allowing for the creation of a single

platform adapted to several users and cases. The model would also optimize the use of medical resources throughout the continuum of the LT process as well as reduce treatment costs for patients, the health care facility, and the health system.

Limitations and Challenges of This Research

This study, as complex and multidisciplinary research, is not without its limitations and challenges. Some of these challenges and solutions are, first, the management of a large interdisciplinary team and the standardization of peer support. To be able to overcome any difficulties related to the cohesion of the team, regular committee meetings will be held once a month to inform the HCPs, researchers, stakeholders, and accompanying patients about progress in the study; redirect guidelines; and discuss participant's cases to achieve a better cohesion among the members of the interdisciplinary team. Another limitation is the large number of questionnaires in addition to the introduction of COs (which increases the difficulty of training and use) as it may increase the burden on patients, which may lead to compliance issues. Some ways to reduce this workload are to select the questionnaires that are strictly necessary at each point during the study and use simpler versions of the questionnaires that require more time to complete. Participants will be informed beforehand of their consent to the tasks and the burden that this might carry. Moreover, the digital platform and CO provider will continuously monitor any difficulty using the COs, providing support and maintenance at all times, thus decreasing the burden on the patient.

Barriers to the generalization of research findings also need to be considered. This study is implemented by capturing data from deconditioned patients and factors specific to the liver failure context. However, if the results of the study are positive, our analysis of the implementation outcomes will shed light on the best conditions for implementing the model in other transplant care trajectories within the CHUM (ie, kidney and lung transplantations).

Finally, as this study will collect a large quantity of data from various medical and nonmedical sources, the data management platform REDCap will be used to apply, manage, and integrate all data collected.

Conclusions

By implementing this new health care model in the trajectory of LT recipients at the CHUM, it can be tested in an environment where the clinical team is motivated and united and where the number of patients is manageable. This new model has the potential to ensure that patients reach their transplantation in better health. This would ultimately reduce the average length of hospital stay and nursing unit care as well as promote better use of medical resources. In the event of positive results, this model could be transposed to all transplant units at the CHUM and across Quebec (potentially affecting 888 patients per year), but it could also be applied more widely to the monitoring of patients with chronic diseases. The lessons learned from this project will be shared with decision makers and serve as a model for other initiatives involving COs or digital platforms.

Acknowledgments

The authors would like to thank their granting agency, the *Institut de la pertinence des actes médicaux*. They would also like to thank Jim Kroening for English revision services. This paper is original work and is not under review at any other publication.

Data Availability

The data sets generated during and/or analyzed during this study are available from the corresponding author (MPP) on reasonable request.

Authors' Contributions

In no order of contribution, MPP conceptualized the study. AB, CV, ELR, FD, NN, and JP were involved in planning and supervising the work. MPP, ELR, and MJE drafted the manuscript and designed the figure and tables. All authors critically reviewed the manuscript and approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Accompanying patient logbook.
[DOCX File , 1001 KB - resprot_v13i1e54440_app1.docx]

Multimedia Appendix 2
Qualitative interview guides for each of the stakeholder groups.
[DOCX File , 1844 KB - resprot_v13i1e54440_app2.docx]

References

1. Samuel D, Coilly A. Management of patients with liver diseases on the waiting list for transplantation: a major impact to the success of liver transplantation. BMC Med 2018 Aug 01;16(1):113 [FREE Full text] [doi: 10.1186/s12916-018-1110-y] [Medline: 30064414]
2. Kwong AJ, Ebel NH, Kim WR, Lake JR, Smith JM, Schladt DP, et al. OPTN/SRTR 2020 annual data report: liver. Am J Transplant 2022 Mar;22 Suppl 2:204-309 [FREE Full text] [doi: 10.1111/ajt.16978] [Medline: 35266621]
3. Congly SE, Marquez V, Bhanji RA, Bhat M, Wong P, Huard G, et al. Exception points for liver transplantation: a Canadian review. Can Liver J 2023 Jul 26;6(2):201-214 [FREE Full text] [doi: 10.3138/canlivj-2022-0026] [Medline: 37503519]
4. Duettmann W, Naik MG, Zukunft B, Osmonodja B, Bachmann F, Choi M, et al. eHealth in transplantation. Transpl Int 2021 Jan 27;34(1):16-26 [FREE Full text] [doi: 10.1111/tri.13778] [Medline: 33111393]
5. Pomey MP, Gallego FB, Affdal A, Fortin MC. Peer mentoring as an avenue to explore in kidney transplantation: kidney transplant recipients' perspectives on peer mentoring. Transplant Direct 2021 Mar;7(3):e672 [FREE Full text] [doi: 10.1097/TXD.0000000000001130] [Medline: 34104710]
6. Proctor E, Silmere H, Raghavan R, Hovmand P, Aarons G, Bunger A, et al. Outcomes for implementation research: conceptual distinctions, measurement challenges, and research agenda. Adm Policy Ment Health 2011 Mar 19;38(2):65-76 [FREE Full text] [doi: 10.1007/s10488-010-0319-7] [Medline: 20957426]
7. Powell BJ, Waltz TJ, Chinman MJ, Damschroder LJ, Smith JL, Matthieu MM, et al. A refined compilation of implementation strategies: results from the Expert Recommendations for Implementing Change (ERIC) project. Implement Sci 2015 Feb 12;10:21 [FREE Full text] [doi: 10.1186/s13012-015-0209-1] [Medline: 25889199]
8. Carman KL, Dardess P, Maurer M, Sofaer S, Adams K, Bechtel C, et al. Patient and family engagement: a framework for understanding the elements and developing interventions and policies. Health Aff (Millwood) 2013 Feb 04;32(2):223-231. [doi: 10.1377/hlthaff.2012.1133] [Medline: 23381514]
9. Domecq JP, Prutsky G, Elraiyah T, Wang Z, Nabhan M, Shippee N, et al. Patient engagement in research: a systematic review. BMC Health Serv Res 2014 Feb 26;14:89 [FREE Full text] [doi: 10.1186/1472-6963-14-89] [Medline: 24568690]
10. Pomey MP, Flora L, Karazivan P, Dumez V, Lebel P, Vanier MC, et al. Le « Montreal model » : enjeux du partenariat relationnel entre patients et professionnels de la santé. Sante Publique 2015;1 Suppl:41-50. [Medline: 26414256]
11. Shippee ND, Domecq Garces JP, Prutsky Lopez GJ, Wang Z, Elraiyah TA, Nabhan M, et al. Patient and service user engagement in research: a systematic review and synthesized framework. Health Expect 2015 Oct;18(5):1151-1166 [FREE Full text] [doi: 10.1111/hex.12090] [Medline: 23731468]
12. Patient engagement. Canadian Institutes of Health Research. URL: https://cihr-irsc.gc.ca/e/45851.html [accessed 2023-10-26]
13. Doria N, Condran B, Boulos L, Curtis Maillet DG, Dowling L, Levy A. Sharpening the focus: differentiating between focus groups for patient engagement vs. qualitative research. Res Involv Engagem 2018;4:19 [FREE Full text] [doi: 10.1186/s40900-018-0102-6] [Medline: 29983994]
14. Morgan H, Thomson G, Crossland N, Dykes F, Hoddinott P, 'BIBS' study team. Combining PPI with qualitative research to engage 'harder-to-reach' populations: service user groups as co-applicants on a platform study for a trial. Res Involv Engagem 2016 Mar 24;2(1):7 [FREE Full text] [doi: 10.1186/s40900-016-0023-1] [Medline: 29062508]
15. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M, Medical Research Council Guidance. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ 2008 Sep 29;337(sep29 1):a1655 [FREE Full text] [doi: 10.1136/bmj.a1655] [Medline: 18824488]
16. Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, PAFS consensus group. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ 2016 Oct 24;355:i5239 [FREE Full text] [doi: 10.1136/bmj.i5239] [Medline: 27777223]
17. Thabane L, Hopewell S, Lancaster GA, Bond CM, Coleman CL, Campbell MJ, et al. Methods and processes for development of a CONSORT extension for reporting pilot randomized controlled trials. Pilot Feasibility Stud 2016 May 20;2(1):25 [FREE Full text] [doi: 10.1186/s40814-016-0065-z] [Medline: 27965844]
18. Schoonenboom J, Johnson RB. How to construct a mixed methods research design. Kolner Z Soz Sozpsychol 2017;69(Suppl 2):107-131 [FREE Full text] [doi: 10.1007/s11577-017-0454-1] [Medline: 28989188]
19. Charles R. Test d'Usure de Compassion (Tuc). Café citoyen UPS. URL: https://claudeyacoub.com/wp-content/uploads/2019/05/CC3-TUC.pdf [accessed 2024-01-29]
20. Olson LL. Hospital nurses' perceptions of the ethical climate of their work setting. Image J Nurs Sch 1998 Oct 02;30(4):345-349. [doi: 10.1111/j.1547-5069.1998.tb01331.x] [Medline: 9866295]
21. Readiness to partner with patient and family advisers - patient and family engagement in the surgical environment module. Agency for Healthcare Research and Quality. URL: https://www.ahrq.gov/hai/tools/ambulatory-surgery/sections/implementation/training-tools/readiness.html [accessed 2022-02-03]
22. Hedlin D, Dale T, Haraldsen G, Jones J. Developing methods for assessing perceived response burden. Office for National Statistics, UK. 2005. URL: https://ec.europa.eu/eurostat/documents/64157/4374310/10-DEVELOPING-METHODS-FOR-ASSESSING-PERCEIVED-RESPONSE-BURDEN.pdf/1900efc8-1a07-4482-b3c9-be88ee71df3b [accessed 2024-01-29]
23. Grady TG. Stakeholder engagement essential to health information technology project success. Radiol Technol 2015;86(6):682-683. [Medline: 26199442]

24. Hajesmaeel-Gohari S, Khordastan F, Fatehi F, Samzadeh H, Bahaadinbeigy K. The most used questionnaires for evaluating satisfaction, usability, acceptance, and quality outcomes of mobile health. BMC Med Inform Decis Mak 2022 Jan 27;22(1):22 [FREE Full text] [doi: 10.1186/s12911-022-01764-2] [Medline: 35081953]
25. Yip MP, Chang AM, Chan J, MacKenzie AE. Development of the telemedicine satisfaction questionnaire to evaluate patient satisfaction with telemedicine: a preliminary study. J Telemed Telecare 2003 Jun 24;9(1):46-50. [doi: 10.1258/135763303321159693] [Medline: 12641893]
26. Pomey MP, Clavel N, Normandin L, Del Grande C, Philip Ghadiri D, Fernandez-McAuley I, et al. Assessing and promoting partnership between patients and health-care professionals: co-construction of the CADICEE tool for patients and their relatives. Health Expect 2021 Aug 05;24(4):1230-1241 [FREE Full text] [doi: 10.1111/hex.13253] [Medline: 33949739]
27. Touré M, Kouakou CR, Poder TG. Dimensions used in instruments for QALY calculation: a systematic review. Int J Environ Res Public Health 2021 Apr 21;18(9):4428 [FREE Full text] [doi: 10.3390/ijerph18094428] [Medline: 33919471]
28. Hibbard JH, Stockard J, Mahoney ER, Tusler M. Development of the Patient Activation Measure (PAM): conceptualizing and measuring activation in patients and consumers. Health Serv Res 2004 Aug;39(4 Pt 1):1005-1026 [FREE Full text] [doi: 10.1111/j.1475-6773.2004.00269.x] [Medline: 15230939]
29. Markland D, Tobin V. A modification to the behavioural regulation in exercise questionnaire to include an assessment of amotivation. J Sport Exerc Psychol 2004 Jun;26(2):191-196. [doi: 10.1123/jsep.26.2.191]
30. DiMatteo MR, Hays RD, Gritz ER, Bastani R, Crane L, Elashoff R, et al. Patient adherence to cancer control regimens: scale development and initial validation. Psychol Assess 1993 Mar;5(1):102-112. [doi: 10.1037/1040-3590.5.1.102]
31. Subar AF, Potischman N, Dodd KW, Thompson FE, Baer DJ, Schoeller DA, et al. Performance and feasibility of recalls completed using the automated self-administered 24-hour dietary assessment tool in relation to other self-report tools and biomarkers in the interactive diet and activity tracking in AARP (IDATA) study. J Acad Nutr Diet 2020 Nov;120(11):1805-1820 [FREE Full text] [doi: 10.1016/j.jand.2020.06.015] [Medline: 32819883]
32. da Silva Fink J, Daniel de Mello P, Daniel de Mello E. Subjective global assessment of nutritional status – a systematic review of the literature. Clin Nutr 2015 Oct;34(5):785-792. [doi: 10.1016/j.clnu.2014.12.014] [Medline: 25596153]
33. Drolet M. CoPaQ: mesure des coûts supportés par les patient(e)s pour des soins de santé. Unité soutien SSA Québec. URL: https://ssaquebec.ca/nouvelles/co-paq/ [accessed 2023-04-14]
34. Albaret JM, Migliore L. Test de Stroop. Paris, France: ECPA, les Éditions du centre de psychologie appliquée; 1999.
35. Wang CW, Lebsack A, Chau S, Lai JC. The range and reproducibility of the liver frailty index. Liver Transpl 2019 Jun 29;25(6):841-847 [FREE Full text] [doi: 10.1002/lt.25449] [Medline: 30884128]
36. Enright PL. The six-minute walk test. Respir Care 2003 Aug;48(8):783-785 [FREE Full text] [Medline: 12890299]
37. Rose Berlin Piodena-Aportadera M, Lau S, Chew J, Lim JP, Ismail NH, Ding YY, et al. Calf circumference measurement protocols for sarcopenia screening: differences in agreement, convergent validity and diagnostic performance. Ann Geriatr Med Res 2022 Sep;26(3):215-224 [FREE Full text] [doi: 10.4235/agmr.22.0057] [Medline: 36031936]
38. Evans C, Lewis J. Analysing Semi-Structured Interviews Using Thematic Analysis: Exploring Voluntary Civic Participation Among Adults. Thousand Oaks, CA: Sage Publications; 2018.
39. R Core Team. The R project for statistical computing. R Foundation. URL: https://www.r-project.org/ [accessed 2023-10-23]
40. Elo S, Kyngäs H. The qualitative content analysis process. J Adv Nurs 2008 Apr;62(1):107-115. [doi: 10.1111/j.1365-2648.2007.04569.x] [Medline: 18352969]
41. Laberge M, Coulibaly LP, Berthelot S, Borges da Silva R, Guertin JR, Strumpf E, et al. Development and validation of an instrument to measure health-related out-of-pocket costs: the cost for patients questionnaire. Value Health 2021 Aug;24(8):1172-1181 [FREE Full text] [doi: 10.1016/j.jval.2021.03.016] [Medline: 34372983]
42. Poder TG, Coulibaly LP, Hassan AI, Conombo B, Laberge M. Test-retest reliability of the cost for patients questionnaire. Int J Technol Assess Health Care 2022 Jul 11;38(1):e65. [doi: 10.1017/S0266462322000460] [Medline: 35811410]
43. Chaney AJ, Heckman MG. The benefit of supplemental nutrition education for severely malnourished patients awaiting liver transplant. Prog Transplant 2018 Dec;28(4):390-393 [FREE Full text] [doi: 10.1177/1526924818800052] [Medline: 30244656]
44. Brady TJ, Murphy LB, O'Colmain BJ, Hobson RD. Do program implementation factors or fidelity affect chronic disease self-management education programs' outcomes? Am J Health Promot 2017 Sep;31(5):422-425 [FREE Full text] [doi: 10.1177/0890117116664704] [Medline: 27597794]
45. Dennis SM, Harris M, Lloyd J, Powell Davies G, Faruqi N, Zwar N. Do people with existing chronic conditions benefit from telephone coaching? A rapid review. Aust Health Rev 2013 Jun;37(3):381-388 [FREE Full text] [doi: 10.1071/AH13005] [Medline: 23701944]
46. Cinar S, Ozdogan OC, Alahdab Y. Impact of education provided by nurses on quality of life, anxiety, and depression in patients receiving hepatitis C virus therapy. Gastroenterol Nurs 2015;38(5):343-347. [doi: 10.1097/SGA.0000000000000130] [Medline: 26166422]
47. North CS, Pollio DE, Sims OT, Jain MK, Brown GR, Downs DL, et al. An effectiveness study of group psychoeducation for hepatitis C patients in community clinics. Eur J Gastroenterol Hepatol 2017 Jun;29(6):679-685 [FREE Full text] [doi: 10.1097/MEG.0000000000000860] [Medline: 28195874]

48. Correia JC, Waqas A, Assal JP, Davies MJ, Somers F, Golay A, et al. Effectiveness of therapeutic patient education interventions for chronic diseases: a systematic review and meta-analyses of randomized controlled trials. Front Med (Lausanne) 2022;9:996528 [FREE Full text] [doi: 10.3389/fmed.2022.996528] [Medline: 36760883]

Abbreviations

6MWT: 6-Minute Walk Test
CHUM: Centre hospitalier de l'Université de Montréal (University of Montréal Health Center)
CO: connected object
CONSORT: Consolidated Standards of Reporting Trials
CRCHUM: Centre hospitalier de l'Université de Montréal Research Centre
GRIT-F: *guichet rapide d'investigation en transplantation du foie* (rapid liver transplant assessment service)
HCP: health care professional
LT: liver transplantation
REDCap: Research Electronic Data Capture
TAC: Transplant'Action Connected in Liver Transplant

Edited by A Mavragani; submitted 16.11.23; peer-reviewed by Y Zhang; comments to author 28.01.24; revised version received 02.02.24; accepted 05.02.24; published 22.03.24.

Please cite as:
Pomey MP, Le Roux E, Nadon N, Perron J, Barry A, Bémeur C, Poder TG, Duford F, Laviolette L, Tétrault-Lassonde J, Vialaron C, Escalona MJ, Normandin L, Huard G, Girardin C, Rose C, Malas K, Ouellet D, Vincent C
Telehealth-Delivered Program and Accompanying Patients to Enhance the Clinical Condition of Patients Throughout a Liver Transplant: Protocol for a Mixed Methods Study
JMIR Res Protoc 2024;13:e54440
URL: https://www.researchprotocols.org/2024/1/e54440
doi:10.2196/54440
PMID:38517464

Protocol

N-of-1 Trials of Antimicrobial Stewardship Interventions to Optimize Antibiotic Prescribing for Upper Respiratory Tract Infection in Emergency Departments: Protocol for a Quasi-Experimental Study

Hersh Attal[1*], MBBS; Zhilian Huang[2*], MPH, PhD; Win Sen Kuan[3,4], MBBS, MRCS, MCI; Yanyi Weng[5], MBBS, MCEM; Hann Yee Tan[6], MBBS, MMed, MRCEM; Eillyne Seow[6], MBBS; Li Lee Peng[3,4], MBBS, MPCP; Hoon Chin Lim[1], MBBS, MRCS; Angela Chow[2,7,8], MBBS, MMed, MS, PhD

[1]Accident & Emergency Department, Changi General Hospital, Singapore, Singapore

[2]Department of Preventive and Population Medicine, Office of Clinical Epidemiology, Analytics, and Knowledge, Tan Tock Seng Hospital, Singapore, Singapore

[3]Department of Emergency Medicine, National University Hospital, Singapore, Singapore

[4]Department of Surgery, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore

[5]Department of Emergency Medicine, Tan Tock Seng Hospital, Singapore, Singapore

[6]Acute and Emergency Care Department, Khoo Teck Puat Hospital, Singapore, Singapore

[7]Saw Swee Hock School of Public Health, National University of Singapore, Singapore, Singapore

[8]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore

[*]these authors contributed equally

Corresponding Author:
Angela Chow, MBBS, MMed, MS, PhD
Department of Preventive and Population Medicine
Office of Clinical Epidemiology, Analytics, and Knowledge
Tan Tock Seng Hospital
11 Jalan Tan Tock Seng
Singapore, 308433
Singapore
Phone: 65 63577477
Email: Angela_Chow@ttsh.com.sg

Abstract

Background: Antimicrobial stewardship programs attempting to optimize antibiotic therapy and clinical outcomes mainly focus on inpatient and outpatient settings. The lack of antimicrobial stewardship program studies in the emergency department (ED) represents a gap in tackling the problem of antimicrobial resistance as EDs treat a substantial number of upper respiratory tract infection cases throughout the year.

Objective: We intend to implement two evidence-based interventions: (1) patient education and (2) providing physician feedback on their prescribing rates. We will incorporate evidence from a literature review and contextualizing the interventions based on findings from a local qualitative study.

Methods: Our study uses a quasi-experimental design to evaluate the effects of interventions over time in the EDs of 4 public hospitals in Singapore. We will include an initial control period of 18 months. In the next 6 months, we will randomize 2 EDs to receive 1 intervention (ie, patient education) and the other 2 EDs to receive the alternative intervention (ie, physician feedback). All EDs will receive the second intervention in the subsequent 6 months on top of the ongoing intervention. Data will be collected for another 6 months to assess the persistence of the intervention effects. The information leaflets will be handed to patients at the EDs before they consult with the physician, while feedback to individual physicians by senior doctors is in the form of electronic text messages. The feedback will contain the physicians' antibiotic prescribing rate compared with the departments' overall antibiotic prescribing rate and a bite-size message on good antibiotic prescribing practices.

Results: We will analyze the data using segmented regression with difference-in-difference estimation to account for concurrent cluster comparisons.

Conclusions: Our proposed study assesses the effectiveness of evidence-based, context-specific interventions to optimize antibiotic prescribing in EDs. These interventions are aligned with Singapore's national effort to tackle antimicrobial resistance and can be scaled up if successful.

Trial Registration: ClinicalTrials.gov NCT05451863; https://clinicaltrials.gov/study/NCT05451836

International Registered Report Identifier (IRRID): DERR1-10.2196/50417

(JMIR Res Protoc 2024;13:e50417) doi:10.2196/50417

KEYWORDS

antibiotic resistance; emergency department; upper respiratory tract infection; N-of-1 trials; prescribing feedback; feedback; emergency; upper respiratory tract; respiratory; antibiotic; antimicrobial stewardship; antimicrobials; antibiotics; hospital; experimental study; antibiotic therapy; URTI; evidence-based intervention; evidence-based; patient education; prescribing rates; patient literacy; Singapore; regression analysis; regression

Introduction

Background

The discovery of antibiotics is among the most important public health achievements in the 20th century [1]. However, inappropriate antibiotic use has driven a rapid increase in antibiotic resistance, and with the drying up of the pipeline of new antibiotics, a postantibiotic era is imminent [2-4]. Hence, there is a need to reduce antibiotic use by changing physicians' antibiotic prescribing practices and reducing patient demand through antimicrobial stewardship programs (ASPs).

Despite the presence of ASPs in various settings, their effects are modest, as antibiotic prescribing practices have been difficult to change [5]. Systematic reviews of interventions to improve physicians' antibiotic prescribing practices have suggested that the traditional isolated forms of physician education (eg, didactic presentations or printed education materials alone) have only produced slight improvements in prescribing practices [6,7]. However, interventions such as educational outreach or training of local opinion leaders [8,9], as well as behavioral "nudges" in the form of public commitment devices [10] and peer comparison [11], were more effective in improving physician prescribing behaviors. In a systematic review evaluating information leaflets on common infections in general practice, 3 out of 4 studies on antibiotic use showed significant reductions in antibiotic prescriptions [12]. Another study using patient education in the form of an information leaflet regarding antibiotics for bronchitis showed a significant reduction (49% vs 63%) in antibiotic use compared with the control group [13].

Rationale for the Study

There is a need for more studies to assess the effectiveness of ASP in emergency departments (EDs) [14]. Antibiotics are often prescribed for upper respiratory tract infection (URTI) in the ED, although the routine use of antibiotics for URTI is not recommended [15,16]. A mixed methods study involving 8 EDs in 3 cities in the United States found that the fast-paced environment of the ED encouraged unnecessary antibiotic use [17]. In Singapore, URTIs also accounted for a substantial proportion of attendances at EDs and were associated with frequent ED attendance, as EDs were popular choices for primary care [18]. A previous study at an adult general hospital reported that 35% of adult patients presenting to the ED for URTI were prescribed antibiotics [19].

A physician's likelihood to prescribe antibiotics for a patient is complex and determined by many factors. The determinants of antibiotic prescribing may include the physician's worry about complications arising in the patient [20], busy clinical practice [17], insufficient physicians' knowledge [21], underestimation of the effect of inappropriate antibiotic prescribing leading to antimicrobial resistance (AMR) [22], and perception of the patient's expectations for an antibiotic [19]. Furthermore, decision fatigue can reduce the physician's ability to resist ordering inappropriate treatments and increase inappropriate antibiotic prescribing [23].

Given the multifactorial nature of inappropriate antibiotic prescribing, a single approach will unlikely work for all physicians [24]. Furthermore, different patient populations may warrant a variety of interventions. Hence, there is a need for interventions tailored to physicians and patients to promote the judicious use of antibiotics. We describe the protocol of a quasi-experimental study on 2 antibiotic stewardship interventions in the ED according to the SPIRIT (Standard Protocol Items: Recommendations for International Trials) checklist [25].

Hypothesis and Objectives

We hypothesize that (1) patient education via tailored information leaflets (addressing knowledge, perception, and belief gaps of the local patient population on antibiotic use for URTI) distributed while waiting for consultation with the physician can improve patient knowledge and change patients' expectations for antibiotics. The change in patients' expectations of antibiotics would reduce unnecessary antibiotic prescribing by physicians in response to patient demand in time-pressured EDs. (2) Surveillance of antibiotic prescribing rates and physician feedback enables physicians to reflect on their prescribing practices. Physician feedback by senior ED physicians, coupled with education on good antibiotic prescribing practices, serves as a reminder for physicians to improve their antibiotic prescribing practices.

Hence, we aim to evaluate the effectiveness of 2 tailored antimicrobial stewardship interventions in optimizing antibiotic prescribing for uncomplicated URTI cases in 4 adult EDs in Singapore. The two interventions are (1) patient information leaflets on appropriate antibiotic use and AMR. The ED triage nurses will provide pamphlets to patients suspected of URTI prior to their consultation with the physician. The pamphlets

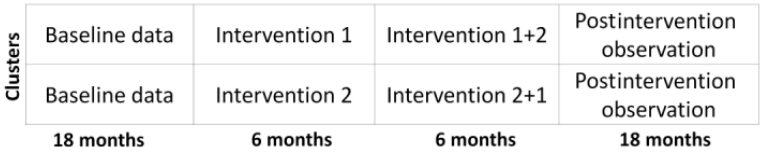
are available in Singapore's 4 official languages. (2) Feedback to physicians on their antibiotic prescribing rates. A senior ED doctor will send a personalized SMS text message to each physician who has seen at least 1 patient in the ED in the previous month at 2 monthly intervals. The feedback will contain the physicians' antibiotic prescribing rate compared with the departments' antibiotic prescribing rate and a bite-size message on good antibiotic prescribing practices.

Methods

Study Design

Our study uses a quasi-experimental design to evaluate the effects of interventions over time. The entire study period is from January 2021 to December 2023. All 4 EDs will be exposed to 2 interventions over 12 months, with the introduction of each intervention in a 6-month interval. The study will include an initial control period of 18 months, with none of the 4 hospitals exposed to any intervention. In the first 6 months, we will randomly assign 2 EDs to receive 1 intervention (ie, patient education), while the other 2 will receive the second intervention (ie, physician feedback). All EDs will subsequently receive the other intervention in the subsequent 6 months on top of the ongoing intervention. Data will be collected for another 6 months to assess the persistence of the intervention effects (Figure 1).

Figure 1. Quasi-experimental study of 2 tailored antimicrobial stewardship interventions in 4 emergency departments.



Study Population

The study population includes physicians working in the adult EDs of 4 public hospitals in Singapore.

Intervention

We will implement 2 interventions tailored to the context of EDs in Singapore. The interventions were selected based on a literature review of the effectiveness of ASP [12,26] and designed with input from ED physicians within our population via a qualitative study. We consulted senior ED physicians from our study sites to adjust the intervention to the local ED context and to facilitate buy-in prior to study implementation.

Patient Education

Patient information leaflets were designed to educate patients on appropriate antibiotic use and AMR. The design of the leaflets was based on the information from the United States Centers for Disease Control and Prevention patient educational materials [27] and tailored to the local ED context.

Patient leaflets (Multimedia Appendix 1) were made available at the EDs of the participating sites. ED triage nurses identified patients presenting to the ED with URTI symptoms and provided these patients with the leaflet prior to their consultation with the physician. The leaflets were made available in Singapore's 4 official languages—English, Chinese, Malay, and Tamil.

Feedback to Individual ED Physicians by Senior Doctors

A senior ED physician in the department will send the feedback messages to the ED physicians in the institution. The feedback message will contain the physicians' personal antibiotic prescribing rate and the department's average prescribing rate in the past month and will be administered at 2 monthly intervals. Bite-sized information on tips to reduce antibiotic prescribing for URTI, obtained from evidence-based sources and adjusted based on inputs from senior ED physicians of our study sites, will be sent together with the personalized message. The feedback will be delivered via Tiger Text, a messaging platform used by employees of Singapore's public health care institutions.

An example of the message is shown in Textbox 1.

Textbox 1. Example of a personalized physician feedback message.

Dear Dr X,

I would like to share with you the following feedback regarding antibiotic prescribing rates for URTI in TTSH ED.

Last month, 200 patients that visited TTSH ED were diagnosed with URTI (primary or secondary diagnosis) and discharged from the ED. Among these patients, 100 (50%) were prescribed with antibiotics.

You were the primary physician of 10 patients and 5 (50%) of them were prescribed with antibiotics.

I hope this feedback would be useful for your practice. Thank you for being our antibiotic guardian!

(Note: Common cold or non-specific upper respiratory tract infection (prominent symptoms include fever, cough, rhinorrhoea, nasal congestion, postnasal drip, sore throat, headache, and myalgia) are caused by at least 200 types of viruses. The receipt of antibiotics for common cold does not reduce the duration of symptoms.)

The medication and visit records of patients diagnosed with uncomplicated URTI will be extracted from the ED's electronic medical records over 36 months (18 months before and 18 months after the intervention). Patient particulars were

deidentified prior to data processing in the R software (R Foundation for Statistical Computing). The medications given to these patients will be identified, and their primary physicians will be given feedback on the antibiotic prescribing rates for the patients they have seen.

Uncomplicated URTI includes but is not limited to acute nasopharyngitis and acute URTI of multiple or unspecified sites (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] 460 and 465); acute pharyngitis, tonsillitis, laryngitis, and tracheitis (ICD-9-CM 462, and 463, and 464); and acute or unspecified bronchitis and bronchiolitis (ICD-9-CM 466 and 490). The listed ICD-9-CM codes are for acute respiratory tract infection diagnoses for which antibiotics are not usually indicated [28].

Outcome Measure

The primary outcome measure of interest is physicians' monthly antibiotic prescribing rate. The antibiotic prescribing rate will be computed by dividing the number of patients prescribed antibiotics by the total number of patients with URTI seen by the physician in the month.

Sample Size

At the end of 12 months, all hospitals will be exposed to both interventions. Assuming 80 physicians per ED and an average of 1200 patients with URTI per ED over a 6-month period, a total of 640 physicians and 9600 patients will be exposed to the interventions in the 12-month intervention period.

Statistical Analysis

We will analyze the data using segmented regression models. Segmented regression models allow adjustments to confounding factor and slope changes at various time points but do not account for cluster differences. The inclusion of cluster differences will increase the robustness of the model [29]. The equation of the model is shown as follows:

$\beta 1$ measures the preintervention slope, $\beta_{2,4,6,8}$ measures the immediate change in mean outcome from the previous level, while $\beta_{3,5,7,9}$ measures the difference in slopes pre-post compared with the previous level. β_{11} measures the differences in groups or clusters at the preintervention level, $\beta_{12,14}$ measures the differences in groups or clusters on changes at the start of the intervention, while $\beta_{13,15}$ measures the differences in groups or clusters on changes in slope due to the intervention. Statistical software such as SPSS (IBM Corp), STATA (StataCorp), and R will be used for analysis.

Ethical Considerations

This study was approved by the National Healthcare Group Domain Specific Review Board in Singapore (2019/00174). Informed consent was waived by the review board as all individual-level data were extracted from the electronic medical records and deidentified by the respective institutions' independent trusted third parties. Data extraction does not interfere with the standard care the patients receive and does not pose more than minimal risk to the participants. No compensation is provided to the participants and the data team does not collect more data than required.

Results

The results are expected to be achieved by January 2024. The data analysis and manuscript are expected to be completed by the end of 2024. The results will be presented at scientific meetings and published in international peer-reviewed journals.

Discussion

Principal Findings

Our protocol describes the design and implementation of a context-based, 2-pronged approach to tackle the issue of antibiotic misuse and overuse in the ED setting. Many ASPs have had limited success due to the lack of vital personnel involvement (ie, senior physician), misalignment with the local context, and lack of physician involvement [30]. We plan to have senior physicians deliver the feedback messages to increase physicians' receptivity to the messages.

Hence, we designed the intervention with a rigorous review of evidence from the literature and considered the factors that contributed to the success of ASP. Our interventions were also tailored to the local ED context by considering the inputs of ED physicians via qualitative interviews and obtaining buy-in from senior physicians from the EDs.

Although randomized controlled trials are the most robust way of evaluating interventions, this approach is often not feasible in the health service setting in terms of blinding participants from interventions and preventing cross-contamination between the control and intervention groups. Quasi-experimental designs serve as a more practical option to evaluate health service interventions without compromising data robustness. Therefore, this study will provide an excellent opportunity for us to assess the effectiveness of a large-scale, context-based ASP in the ED.

With established processes already in place to store and distribute the pamphlets in the EDs involved in this study, we have received buy-in and will be able to re-engage the heads of departments of these EDs to continue our interventions or expand to other EDs in the long term if the intervention is shown to be effective.

Potential Limitations

The antibiotic prescribing feedback may not be accurate if the primary physician is not the prescribing physician. Furthermore, patients attending the ED may have multiple complaints and may receive antibiotics for conditions unrelated to URTI. Hence, the feedback message had to be adjusted to reflect an accurate interpretation of the data. There may also be a lack of continuity of feedback should junior physicians rotate out of the ED. The lack of feedback continuity may affect the statistical effectiveness of feedback intervention, although physicians who received the intervention may have positive spillover effects to other departments upon rotating out of the ED.

Some patients may also miss the pamphlets when the triage nurses are overburdened with a high patient load and forget to

hand out the pamphlets to them. We have placed the pamphlets in the ED waiting areas for patients to pick up the pamphlets should they be interested in the topic. The ED nurses will help to perform periodic checks to replenish the pamphlets when the stock is low.

Conclusions

The lack of ASP in the ED represents a missed opportunity in a collective effort to tackle AMR nationally. Our protocol described a study that assesses the effectiveness of evidence-based, context-specific interventions to optimize antibiotic prescribing in EDs. These interventions are aligned with Singapore's national effort to tackle AMR and can be scaled up to other EDs if successful.

Acknowledgments

We would like to acknowledge Karthiga Natarajan for her assistance in the literature review. Generative artificial intelligence was not used to create any portion of this protocol.

Data Availability

Data sharing not applicable to this article as no data sets were generated or analyzed for this protocol.

Authors' Contributions

ZH and AC conceived the manuscript. HA and ZH drafted the manuscript and contributed equally to the work. HA, ZH, and AC reviewed and edited the manuscript. AC provided support and funding for the study. ZH administrated the study. All authors critically reviewed the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
English version of patient leaflet.
[PDF File (Adobe PDF File), 723 KB - resprot_v13i1e50417_app1.pdf]

References

1. Ten great public health achievements—United States, 1900-1999. Centers for Disease Control and Prevention. 1999. URL: https://www.cdc.gov/mmwr/preview/mmwrhtml/00056796.htm [accessed 2024-02-01]
2. Silver LL. Challenges of antibacterial discovery. Clin Microbiol Rev 2011;24(1):71-109 [FREE Full text] [doi: 10.1128/CMR.00030-10] [Medline: 21233508]
3. Tenover FC, Hughes JM. The challenges of emerging infectious diseases. Development and spread of multiply-resistant bacterial pathogens. JAMA 1996;275(4):300-304. [Medline: 8544270]
4. Antimicrobial Resistance: Global Report on Surveillance. World Health Organization. 2014. URL: https://apps.who.int/iris/handle/10665/112642 [accessed 2024-02-09]
5. Flottorp S, Oxman AD, Håvelsrud K, Treweek S, Herrin J. Cluster randomised controlled trial of tailored interventions to improve the management of urinary tract infections in women and sore throat. BMJ 2002;325(7360):367 [FREE Full text] [doi: 10.1136/bmj.325.7360.367] [Medline: 12183309]
6. Giguère A, Zomahoun HTV, Carmichael PH, Uwizeye CB, Légaré F, Grimshaw JM, et al. Printed educational materials: effects on professional practice and healthcare outcomes. Cochrane Database Syst Rev 2020;8(8):CD004398 [FREE Full text] [doi: 10.1002/14651858.CD004398.pub4] [Medline: 32748975]
7. Forsetlund L, O'Brien MA, Forsén L, Reinar LM, Okwen MP, Horsley T, et al. Continuing education meetings and workshops: effects on professional practice and healthcare outcomes. Cochrane Database Syst Rev 2021;9(9):CD003030 [FREE Full text] [doi: 10.1002/14651858.CD003030.pub3] [Medline: 34523128]
8. Flodgren G, O'Brien MA, Parmelli E, Grimshaw JM. Local opinion leaders: effects on professional practice and healthcare outcomes. Cochrane Database Syst Rev 2019;6(6):CD000125 [FREE Full text] [doi: 10.1002/14651858.CD000125.pub5] [Medline: 31232458]
9. O'Brien MA, Rogers S, Jamtvedt G, Oxman AD, Odgaard-Jensen J, Kristoffersen DT, et al. Educational outreach visits: effects on professional practice and health care outcomes. Cochrane Database Syst Rev 2007;2007(4):CD000409 [FREE Full text] [doi: 10.1002/14651858.CD000409.pub2] [Medline: 17943742]
10. Meeker D, Knight TK, Friedberg MW, Linder JA, Goldstein NJ, Fox CR, et al. Nudging guideline-concordant antibiotic prescribing: a randomized clinical trial. JAMA Intern Med 2014;174(3):425-431 [FREE Full text] [doi: 10.1001/jamainternmed.2013.14191] [Medline: 24474434]

11. Meeker D, Linder JA, Fox CR, Friedberg MW, Persell SD, Goldstein NJ, et al. Effect of behavioral interventions on inappropriate antibiotic prescribing among primary care practices: a randomized clinical trial. JAMA 2016;315(6):562-570 [FREE Full text] [doi: 10.1001/jama.2016.0275] [Medline: 26864410]
12. de Bont EGPM, Alink M, Falkenberg FCJ, Dinant GJ, Cals JWL. Patient information leaflets to reduce antibiotic use and reconsultation rates in general practice: a systematic review. BMJ Open 2015;5(6):e007612 [FREE Full text] [doi: 10.1136/bmjopen-2015-007612] [Medline: 26041493]
13. Macfarlane J, Holmes W, Gard P, Thornhill D, Macfarlane R, Hubbard R. Reducing antibiotic use for acute bronchitis in primary care: blinded, randomised controlled trial of patient information leaflet. BMJ 2002;324(7329):91-94 [FREE Full text] [doi: 10.1136/bmj.324.7329.91] [Medline: 11786454]
14. Losier M, Ramsey TD, Wilby KJ, Black EK. A systematic review of antimicrobial stewardship interventions in the emergency department. Ann Pharmacother 2017;51(9):774-790. [doi: 10.1177/1060028017709820] [Medline: 28539060]
15. Kenealy T, Arroll B. Antibiotics for the common cold and acute purulent rhinitis. Cochrane Database Syst Rev 2013;2013(6):CD000247 [FREE Full text] [doi: 10.1002/14651858.CD000247.pub3] [Medline: 23733381]
16. Gonzales R, Bartlett JG, Besser RE, Cooper RJ, Hickner JM, Hoffman JR, et al. Principles of appropriate antibiotic use for treatment of acute respiratory tract infections in adults: background, specific aims, and methods. Ann Intern Med 2001;134(6):479-486. [doi: 10.7326/0003-4819-134-6-200103200-00013] [Medline: 11255524]
17. May L, Gudger G, Armstrong P, Brooks G, Hinds P, Bhat R, et al. Multisite exploration of clinical decision making for antibiotic use by emergency medicine providers using quantitative and qualitative methods. Infect Control Hosp Epidemiol 2014;35(9):1114-1125 [FREE Full text] [doi: 10.1086/677637] [Medline: 25111919]
18. Paul P, Heng BH, Seow E, Molina J, Tay SY. Predictors of frequent attenders of emergency department at an acute general hospital in Singapore. Emerg Med J 2010;27(11):843-848. [doi: 10.1136/emj.2009.079160] [Medline: 20472703]
19. Tan R, Huang Z, Guo H, Weng Y, Chow A. Antibiotic expectations of patients attending an emergency department with upper respiratory tract infections: clinical and behavioural determinants of antibiotic use. Int J Antimicrob Agents 2022;59(2):106511. [doi: 10.1016/j.ijantimicag.2021.106511] [Medline: 34971727]
20. Kumar S, Little P, Britten N. Why do general practitioners prescribe antibiotics for sore throat? Grounded theory interview study. BMJ 2003;326(7381):138 [FREE Full text] [doi: 10.1136/bmj.326.7381.138] [Medline: 12531847]
21. Vazquez-Lago JM, Lopez-Vazquez P, López-Durán A, Taracido-Trunk M, Figueiras A. Attitudes of primary care physicians to the prescribing of antibiotics and antimicrobial resistance: a qualitative study from Spain. Fam Pract 2012;29(3):352-360 [FREE Full text] [doi: 10.1093/fampra/cmr084] [Medline: 22016323]
22. Vasoo S, Singh K, Hsu LY, Chiew YF, Chow C, Lin RTP, et al. Increasing antibiotic resistance in streptococcus pneumoniae colonizing children attending day-care centres in Singapore. Respirology 2011;16(8):1241-1248. [doi: 10.1111/j.1440-1843.2011.02036.x] [Medline: 21848708]
23. Linder JA, Doctor JN, Friedberg MW, Nieva HR, Birks C, Meeker D, et al. Time of day and the decision to prescribe antibiotics. JAMA Intern Med 2014;174(12):2029-2031 [FREE Full text] [doi: 10.1001/jamainternmed.2014.5225] [Medline: 25286067]
24. Arnold SR, Straus SE. Interventions to improve antibiotic prescribing practices in ambulatory care. Cochrane Database Syst Rev 2005;2005(4):CD003539 [FREE Full text] [doi: 10.1002/14651858.CD003539.pub2] [Medline: 16235325]
25. Des Jarlais DC, Lyles C, Crepaz N, TREND Group. Improving the reporting quality of nonrandomized evaluations of behavioral and public health interventions: the TREND statement. Am J Public Health 2004;94(3):361-366 [FREE Full text] [doi: 10.2105/ajph.94.3.361] [Medline: 14998794]
26. Hallsworth M, Chadborn T, Sallis A, Sanders M, Berry D, Greaves F, et al. Provision of social norm feedback to high prescribers of antibiotics in general practice: a pragmatic national randomised controlled trial. Lancet 2016;387(10029):1743-1752 [FREE Full text] [doi: 10.1016/S0140-6736(16)00215-4] [Medline: 26898856]
27. Get smart for healthcare. Know when antibiotics work. Centers for Disease Control and Prevention. URL: https://www.cdc.gov/antibiotic-use/healthcare/pdfs/getsmart-healthcare.pdf [accessed 2023-02-07]
28. Barlam TF, Soria-Saucedo R, Cabral HJ, Kazis LE. Unnecessary antibiotics for acute respiratory tract infections: association with care setting and patient demographics. Open Forum Infect Dis 2016;3(1):ofw045 [FREE Full text] [doi: 10.1093/ofid/ofw045] [Medline: 27006968]
29. Mascha EJ, Sessler DI. Segmented regression and difference-in-difference methods: assessing the impact of systemic changes in health care. Anesth Analg 2019;129(2):618-633 [FREE Full text] [doi: 10.1213/ANE.0000000000004153] [Medline: 31008746]
30. O'Sullivan CE. Antimicrobial stewardship failure: time for a new model. J Antimicrob Chemother 2020;75(5):1087-1090 [FREE Full text] [doi: 10.1093/jac/dkaa006] [Medline: 32068845]

Abbreviations

AMR: antimicrobial resistance
ASP: antimicrobial stewardship program
ED: emergency department

ICD-9-CM: International Classification of Diseases, 9th Revision, Clinical Modification
SPIRIT: Standard Protocol Items: Recommendations for International Trials
URTI: upper respiratory tract infection

Edited by A Mavragani; submitted 30.06.23; peer-reviewed by K Schwartz; comments to author 25.01.24; revised version received 27.01.24; accepted 29.01.24; published 21.02.24.

Please cite as:
Attal H, Huang Z, Kuan WS, Weng Y, Tan HY, Seow E, Peng LL, Lim HC, Chow A
N-of-1 Trials of Antimicrobial Stewardship Interventions to Optimize Antibiotic Prescribing for Upper Respiratory Tract Infection in Emergency Departments: Protocol for a Quasi-Experimental Study
JMIR Res Protoc 2024;13:e50417
URL: https://www.researchprotocols.org/2024/1/e50417
doi:10.2196/50417
PMID:38381495

Proposal

Assessment of Patient Safety in a Low-Resource Health Care System: Proposal for a Multimethod Study

Ghazal Haque[1], MBBS, MPH; Fozia Asif[1], MBBS, MBA, MHQS; Fasih Ali Ahmed[1], MD; Farwa Ayub[1], MD; Sabih ul Hassan Syed[1], MBBS; Nousheen Akber Pradhan[2], BScN, MSc; Malika Hameed[3], MBBS; Muhammad Muneeb Ullah Siddiqui[2], MBBS; Shafaq Mahmood[2], MBBS; Tahani Zaidi[2], MBBS; Sameen Siddiqi[2], MBBS, MSc, PhD; Asad Latif[1,3], MD, MPH

[1]Center for Patient Safety, Aga Khan University, Karachi, Pakistan

[2]Department of Community Health Sciences, Aga Khan University, Karachi, Pakistan

[3]Department of Anesthesiology, Aga Khan University Medical College, Karachi, Pakistan

Corresponding Author:
Asad Latif, MD, MPH
Department of Anesthesiology
Aga Khan University Medical College
Stadium Road
Karachi, 74800
Pakistan
Phone: 92 2134864639
Email: asad.latif@aku.edu

Abstract

Background: The high prevalence of adverse events (AEs) globally in health care delivery has led to the establishment of many guidelines to enhance patient safety. However, patient safety is a relatively nascent concept in low- and middle-income countries (LMICs) where health systems are already overburdened and underresourced. This is why it is imperative to study the nuances of patient safety from a local perspective to advocate for the judicious use of scarce public health resources.

Objective: This study aims to assess the status of patient safety in a health care system within a low-resource setting, using a multipronged, multimethod approach of standardized methodologies adapted to the local setting.

Methods: We propose purposive sampling to include a representative mix of public and private, rural and urban, and tertiary and secondary care hospitals, preferably those ascribed to the same hospital quality standards. Six different approaches will be considered at these hospitals including (1) focus group discussions on the status quo of patient safety, (2) Hospital Survey on Patient Safety Culture, (3) Hospital Consumer Assessment of Healthcare Providers and Systems, (4) estimation of incidence of AEs identified by patients, (5) estimation of incidence of AEs via medical record review, and (6) assessment against the World Health Organization's Patient Safety Friendly Hospital Framework via thorough reviews of existing hospital protocols and in-person surveys of the facility.

Results: The abovementioned studies collectively are expected to yield significant quantifiable information on patient safety conditions in a wide range of hospitals operating within LMICs.

Conclusions: A multidimensional approach is imperative to holistically assess the patient safety situation, especially in LMICs. Our low-budget, non–resource-intensive research proposal can serve as a benchmark to conduct similar studies in other health care settings within LMICs.

International Registered Report Identifier (IRRID): PRR1-10.2196/50532

(JMIR Res Protoc 2024;13:e50532) doi:10.2196/50532

KEYWORDS

patient safety; health systems; quality assessment; safety culture; assessment; healthcare delivery; health system; hospital; low-middle-income countries; research methodology

Introduction

Background

Adverse events (AEs) are instances of injury or harm to patients as a result of medical care and not their underlying medical condition [1]. They are ubiquitous, with some estimates saying that up to 1 in 10 hospitalizations involve medical errors [2]. Underreported and often overlooked, they take a heavy toll on health systems globally. In the United States alone, an estimated 250,000 deaths are attributed to AEs annually, making them the third leading cause of mortality in the country [3]. Moreover, anywhere from 25% to 80% of these errors—some of which lead to a loss of life or permanent disability—are entirely preventable [4,5]. Due to a myriad of factors including but not limited to, understaffing, resource availability and use, and lack of health literacy, health systems within low- and middle-income countries (LMICs) are estimated to experience far more AEs, with an incidence rate ranging between 2.5% and 18.4% [5].

Given these facts, it is understandable why the domain of patient safety and harm reduction gained traction around the world. Of note, the publication of the Institute of Medicine's report "To Err is Human" in 2000 served as a benchmark in establishing the relevance of this aspect of health care delivery [6]. Since then, it has become increasingly apparent that it is a complex issue requiring a multidimensional approach. This school of thought is also linked to the relatively recent emergence of the "systems thinking" concept. This concept emphasizes recognizing the importance of a systems approach in studying the causes of patient harm and advocates for designing an error-proof system. Such an environment is aimed at preventing human errors and focuses on mitigation rather than the elimination of human factors in health care provision [7]. Additionally, an open and transparent environment where a culture of patient safety is prevalent is also imperative in fostering safe health care systems, which ultimately reduce the chances of errors and AEs. This safety culture can be nurtured by upholding safety beliefs, values, and attitudes among the majority of the workforce [8].

Moreover, viewing patient safety through a systems lens is a low-resource exercise since it mainly requires a shift in cultural and systemic perspectives. By considering patient safety problems as a product of the interaction between human and system factors, clinicians can evaluate the factors contributing to patient safety issues without the need for expensive or time-consuming resources [7]. This is particularly important for LMICs where large groups of the population are catered to using precious scarce resources and more often than not, have fewer human resources available per capita. The low cost of these measures makes the establishment of a patient safety culture a near-ideal step in achieving the provision of safe health care delivery and maximizing the quality and impact of health care services [9]. The cost-effectiveness of patient safety culture and a systems approach is reflected in the idea that prevention of AEs is much less resource-intensive than treating the complications that arise from them and which impose a heavy burden on already strained health systems [1,10].

Knowledge Gap

Though sparse, the existing literature from LMICs suggests that there are considerable knowledge gaps in the patient safety domain despite a general awareness of its importance [11,12]. However, global awareness of patient safety has also resulted in a shift of focus toward improvement in the quality of care in LMICs [13,14]. The Global Patient Safety Collaborative is one such initiative established by the joint efforts of the World Health Organization (WHO) and the governments of the United Kingdom and Northern Ireland to scale up global efforts to prioritize patient safety and improve the safety of health systems at a country level [15].

Similarly, the WHO's Global Patient Safety Action Plan for 2021-2030 [16] outlines some key points in eliminating preventable harm in health care through their defined goals of completely eliminating avoidable harm and ensuring the delivery of safe clinical processes, building reliable health systems to protect patients' rights to safe and quality care, empowering both health care providers and patients by engaging in productive dialogue to influence patient safety policies, and ensuring effective information and knowledge sharing among health systems and partners to promote multidisciplinary involvement in patient safety. Therefore, to achieve a holistic understanding of the status of patient safety within a health care system, it is necessary to approach the problem simultaneously from multiple perspectives such as the health care provider's view of patient safety, the health care consumer's view of patient safety and AEs, the estimated incidence of AEs happening within a health care setting, and the infrastructure available to cater to these problems. To our knowledge, a unified framework that addresses all such facets of patient safety has not been used at scale, hence our proposal is unique in its approach.

As mentioned above, to establish a proper culture of safety, it is imperative to first assess the existing culture of safety within health systems [17]. The most commonly used tool for this assessment is the United States Agency for Healthcare Research and Quality's (AHRQ) Hospital Survey on Patient Safety Culture (HSOPSC), which has been implemented in many countries [18-21], translated into several different languages, and can be adapted to fit the local context of most countries [22]. Similarly, the AHRQ's Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) questionnaire is used globally to assess the patient perspective on health care provision and service delivery. Standards such as the Joint Commission International Accreditation and the WHO's Patient Safety Friendly Hospital Framework (PSFHF) serve as benchmarks against which health care settings can be measured on their quality indicators.

LMICs can greatly benefit from initiatives like the Global Patient Safety Collaborative and PSFHF and from using tools such as the HSOPSC and HCAHPS, to perform comprehensive risk assessments of their hospitals, deliver patient safety education and training, establish a culture of safety, and expand the capacity for patient safety within their hospitals [23]. The generalizability of these standardized, validated tools makes them easily adaptable to the local context and can help evaluate patient safety standards across varying health systems. However,

there is a considerable dearth of research in this domain in LMICs and to our knowledge, a comprehensive study on patient safety has not been undertaken so far in Pakistan.

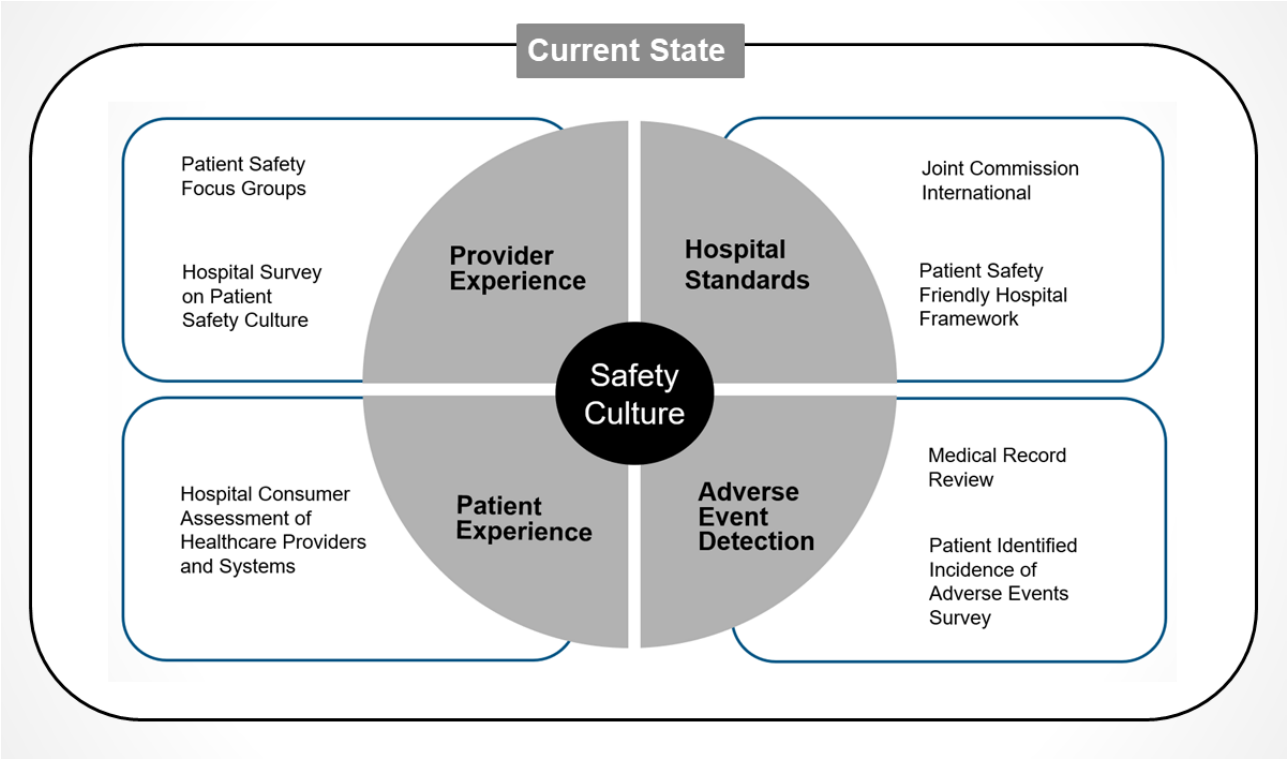
With this proposal, our goals are to evaluate, develop, and implement evidence-based patient safety assessment policies and recommend patient safety strategies and plans that can be replicated across low-resource settings. In order to achieve these goals we aim to perform a comprehensive assessment of the patient safety problem at a sample of hospitals in each province in the country. Additionally, we seek to analyze the results of these assessments to establish the status of patient safety problems in local hospitals, in order to recommend practical steps and policy guidelines for improvement.

Methods

Patient Safety Assessment Framework

To better comprehend the range of patient safety problems and their contributing factors at a variety of hospitals across the country, we propose a multifaceted, multimethod approach with the goal of developing a holistic understanding of patient safety issues within the local health care system. For this purpose, we have devised a conceptual framework for the holistic assessment of the patient safety status across variable health settings. Our framework for the assessment of patient safety (Figure 1) in a low-resource setting approaches the problem from a systems thinking lens. We aim to evaluate each hospital setting on its safety culture, the incidence of AEs, and existing infrastructural standards against a minimum, preset standard. After the study sites are identified and all necessary approvals are obtained, multiple methodologies will be used to analyze the patient safety situation at these sites within 3 interconnected domains: patient safety culture, AE detection, and patient safety infrastructure. We shall use 6 different approaches that can be variably used in either a multicenter study design or in individual health care settings.

Figure 1. Framework for patient safety assessment.



Study Site Selection

In our proposal, a cross-section of public and private hospitals providing varying levels of care to urban or rural populations will be considered for these assessments. Since there is not a single electronic health record network or a unique quality standard implemented across all hospitals in Pakistan, our aim would be to include hospitals participating in the World Health Organization's Patient Safety Friendly Hospital Initiative. The Patient Safety Friendly Hospital Initiative involves a basic, easily implemented framework for hospital quality standards developed by the WHO Regional Office for the Eastern Mediterranean and has been successfully piloted in 7 countries including Pakistan [24]. Attempts will be made to include 1 secondary or tertiary hospital from each province to accommodate for regional variations in a decentralized health system. Following this, key personnel will be identified from the selected centers and stakeholder meetings will be conducted to get the appropriate permissions from all relevant parties on board for subsequent hospital assessments.

Ethical Considerations

Prior to data collection, separate approvals will be obtained from the institutional research review board or an equivalent body of each participating institute. An overarching approval will also be obtained from the institution conducting the research. For study components requiring individual responses, an informed consent form in either English or a certified Urdu

translation will be obtained per the respondent's preference. Each respondent will also be offered a blank copy of the consent form.

For study components requiring medical record access, a review of the participating health center's policy on data governance and sharing will be conducted before any medical records are requested for the study. Consent will be obtained from all relevant institutional authorities prior to medical record reviews. All identifying information will be coded to ensure strict patient confidentiality and anonymity. The collected data will be stored on secure servers with limited access provided only to authorized research personnel. All information generated will be used exclusively for research purposes in accordance with local regulations.

Safety Culture

Focus Group Discussions

To assess the existing infrastructure and culture of patient safety and quality improvement at the study sites, focus groups will be conducted with teams comprising each hospital's leadership, unit-level management, and frontline health care workers. Administrative staff, physicians, nurses, and technicians will be targeted for responses in representative proportions. During these discussions, in-depth interviews will be conducted to try to capture informal methods of health care delivery that might be in practice at each institute, to get an idea of the local understanding of patient safety, and to identify the problems associated with it. A qualitative analysis will be performed following these interviews to identify the relevant codes and themes pertaining to the patient safety situation in these hospitals. Textbox 1 shows a sample of the prompts that will be used for these interviews.

Textbox 1. Interview prompts for focus group discussions among health care providers on the status of patient safety.

Prompt:

- What is your understanding of quality and patient safety?
- What processes/activities/mechanism currently exist at your hospital for quality improvement and patient safety?
- Please share the last unexpected/adverse event that you have encountered/observed at your hospital
- What activities (if any) are planned for initiating/strengthening the existing quality and patient safety culture at the hospital?
- What are your suggestions to improve/strengthen patient safety at your hospital?

Evaluation of Existing Patient Safety Culture

To evaluate the existing safety culture in the participating hospitals, a survey will be conducted using the Agency for Healthcare Research and Quality's HSOPSC [25]. HSOPSC is a standardized, validated tool consisting of 42 items that assess patient safety culture across 12 basic dimensions (Textbox 2). For this survey, a minimum of 2 available personnel belonging to five categories—doctors, nurses, technicians, hospital management, and hospital aides—will be included via quota sampling from the participating hospitals, with a minimum of 10 personnel per hospital. Responses to most items in this survey will be based on a Likert scale, some of which will be dichotomized during analysis to be measured against the predefined composites listed in Textbox 2.

Textbox 2. Hospital Survey on Patient Safety Culture (HSOPSC) survey items and composite measures.

Item

- Teamwork
- Staffing and work pace
- Organizational learning—continuous improvement
- Response to error
- Supervisor, manager, or clinical leader support for patient safety
- Communication about error
- Communication openness
- Reporting patient safety events
- Hospital management support for patient safety
- Hands-off and information exchange
- Number of events reported
- Patient safety rating

Note: Survey items included in the HSOPSC are grouped by safety culture composite measures [25].

Inpatient Hospital Experience Survey

To measure the quality of the inpatient hospital experience from the patients' perspective, a modified version of the AHRQ's Hospital Consumer Assessment of Healthcare Providers and Systems questionnaire will be used to conduct an interview-based survey. The HCAHPS is a widely used standardized survey used to measure patient satisfaction with in-hospital care [26]. The standard HCAHPS survey contains 29 questions split into 7 discrete categories, which measure the patient's experience during their hospital stay in specific areas of inpatient health care delivery. As a standard practice, it should be administered randomly to adult patients between 48 hours and 6 weeks after discharge from the hospital and a minimum of 300 patients should be surveyed per hospital, from 1 calendar year.

Our modified HCAHPS questionnaire adds one more category with additional questions on pain management, adapted from the Qatar Ministry of Public Health's Patient Experience Survey for Hospitals (Textbox 3). Using quota sampling for this survey, we aim to target a minimum of 20 patients being discharged from each participating hospital. Most responses in the HCAHPS are measured with a 4-point Likert scale, which during analysis, will be dichotomized into binary values to elicit the highest positive responses to the items—the so-called "top box percentages."

Textbox 3. Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) survey question categories.

Item:

- Nurse communication
- Doctor communication
- Hospital environment
- In-hospital care experience
- Pain management
- Discharge or transfer information
- Overall hospital rating
- Understanding your care transition upon discharge

Note: Survey categories are based on a standard HCAHPS survey form modified to include questions on pain management [26].

Adverse Event Detection

Patient–Reported Incidence of AE

To understand the patients' perspective of AEs during health care delivery, we propose a questionnaire-based survey to assess patient safety–related issues including patients' understanding and experiences of AEs, preventable harm, and local reporting. This survey is adapted from a tool implemented by Southwick et al [27] to suit the local health care setting. The original study design surveyed almost 700 patients in nearly a 4-year period through a web-based form.

To account for low digital literacy within LMICs we propose using quota sampling to screen patients within the outpatient departments at the study sites to survey those who have availed health care services. Participants will be requested to recall potential AEs experienced during health care delivery using the standardized questionnaire, and the responses will be recorded by a member of the investigating team. The results will be analyzed descriptively to determine the nature and severity of AEs, and their effects as perceived by patients who have received medical care. At least 50 respondents will be interviewed at each study site.

Medical Record–Based Incidence of AEs

To calculate the incidence of AEs during hospitalization, a review of medical records will be performed at each hospital. The sample size for this study will be calculated based on the annual inpatient volume at each hospital with a 5% significance, a precision of 3%, and an estimated 10% dropout rate due to unavailability or poor quality of medical records. A range of prevalence of 10%-18% will be assumed as representative of the population. A team of investigators will also perform a data quality check of the existing medical records against a standardized checklist prior to the review [28].

Following this, a retrospective chart review of the medical records will be conducted in a 2-step process. In the first step, all charts will be screened using a standardized AE screening form, "Review Form 1" (RF1) to identify any potential AEs. All AEs identified using RF1 will then be evaluated using "Review Form 2" (RF2) to establish the nature, causality, and the factors contributing to these AEs. Both review forms have been adapted from the WHO patient safety research tools for data-poor hospitals and contain extensive screening and investigative questions to assess and analyze "harmful incidents" or "adverse events" [29]. The incidence of AEs will be calculated using the following formula:

Additionally, a descriptive analysis will be performed on the types of AEs, their potential causes, and the likely systemic and human factors contributing to the event.

Patient Safety Infrastructure Assessment Against the WHO's Patient Safety Friendly Hospital Framework

The PSFHF is based primarily on 5 domains and 22 standards [30], which together comprise 134 criteria that are prioritized into critical, core, and developmental categories (Table 1).

The 25 critical criteria are the basic minimum requirements that hospitals are encouraged to achieve in terms of quality improvement. To assess each hospital's standing against the PSFHF criteria, members of the investigating team will conduct in-person surveys of the facilities to observe the implementation of standards. They will also review standard operating procedures and existing hospital protocol documents, and check for the existence of an AE reporting system. Interviews with staff members and patients will also be conducted. All these observations will be recorded against the existing standard criteria set within the PSFHF and after a comprehensive review, a list of recommendations will be provided by the investigators in light of their findings.

Table 1. Attributes of the Patient Safety Friendly Hospital Network (PSFHF).

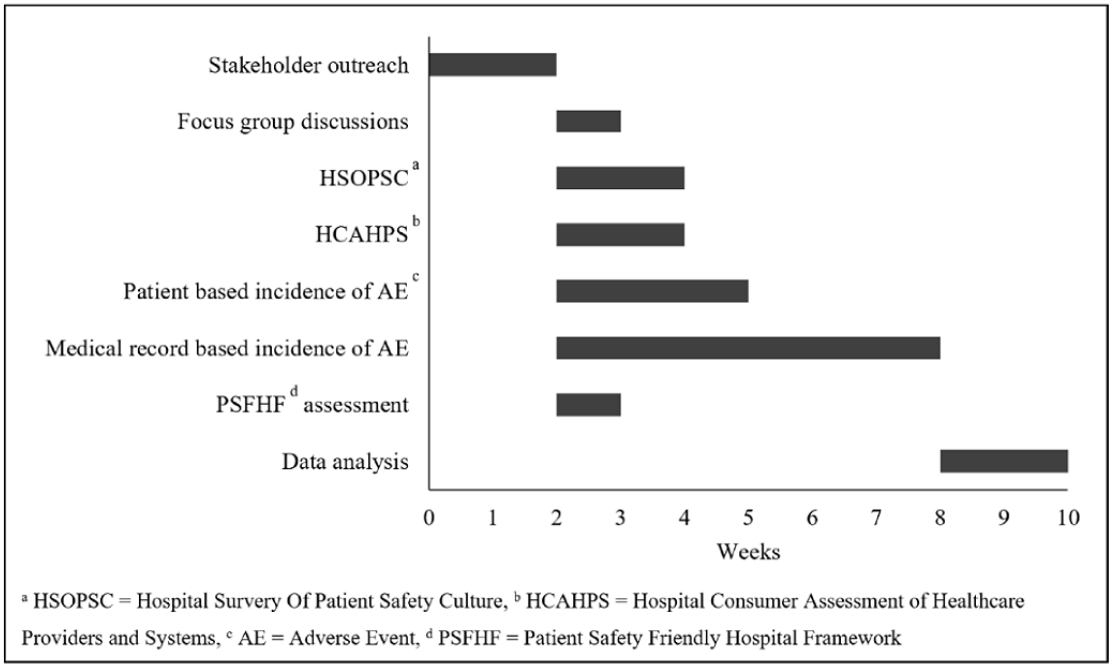
Domain	Standards, n	Critical criteria, n	Core criteria, n	Developmental criteria, n	Total criteria, n
Leadership and management	6	7	26	3	36
Patient and public involvement	7	2	22	7	31
Safe evidence–based clinical practice	4	14	24	2	40
Safe environment	2	1	20	1	22
Lifelong learning	3	1	2	2	5
Total	22	25	94	15	134

Project Execution

In order to conduct all the above study components in an organized and timely manner, the investigating team will comprise health care professionals recruited from the core team and regional partners, who will be trained in conducting each survey. All survey instruments will be developed and recorded in English, whereas the written consent forms for participant recruitment will be translated into the local language as well. The interviewers will be fluent in both languages. The proposed timeline of events for conducting each component of the assessment is given in Figure 2.

It should be noted that as part of a theoretical framework, this proposed timeline includes a timeframe for the completion of each part of this multimodal approach, carried out simultaneously by multiple teams at each site. However, the authors understand that various levels of care within various health care systems require different facets of evaluation. Thus, it is recommended that the approach within this framework be modified according to the local organizational and operational structures and the given limitations of the health care setting being assessed. Subsequently, the project timeline can vary depending on the number of assessments being conducted.

Figure 2. Proposed project timeline of events for a single study site.



Results

A thorough quantitative and qualitative analysis will be conducted which will be aimed for publication in the form of a technical report.

Discussion

Overview

Patient safety culture is an essential component of health care provision and can significantly impact patient outcomes. The beliefs, attitudes, and behaviors of health care providers can significantly affect their understanding of and commitment to ensuring patient safety [10]. Research has consistently shown that a positive patient safety culture leads to improved patient outcomes, increased staff satisfaction, and reduced health care costs [31]. Conversely, a lack of an open, transparent culture focused on patient safety can result in medical errors, AEs, and poor patient outcomes [17]. LMICs in particular fall behind in prioritizing patient safety due to a lack of practical policies and procedures, inadequate education and training, and lacking a culture of transparency and open communication to ensure the best possible patient outcomes [5]. These are largely attributed to the chronically depleted health resources in the region, however, establishing a culture of safety does not necessarily require high-cost interventions. Additionally, in order to establish a sustainable culture of safety, it is essential to first identify the gaps that lie within this system.

Studying the incidence and prevalence of AEs within a health system is an effective way to gauge the status of patient safety. Historically, this has been achieved using incident reporting systems and retrospective chart reviews to record error prevalence [32,33], health consumer and provider surveys [19,23,34], and by studying medical litigation cases [35]. There is a considerable amount of literature from high-income countries that highlights the incidence and impact of AEs in health care [2,27,36], however, the same is not true for LMICs [5]. Moreover, patient safety problems are multifactorial and therefore require a diverse yet intertwined approach to obtain a comprehensive understanding of the problems involved, such as system-based issues, which tend to be locally unique at the unit, hospital, or even regional level. For example, an inpatient hospital setup might have patient safety concerns due to culture issues, while the emergency room at the same hospital might have patient safety concerns due to inadequate resources for their volumes. Similarly, the same type of work area in variably resourced settings, such as the intensive care unit in a public versus a private hospital might have vastly different reasons for gaps in patient safety. Therefore, a comprehensive risk assessment of factors contributing to patient safety concerns is the first step in identifying these issues and subsequently addressing them.

Therefore, our proposed multimodal methodology for assessing patient safety issues in the Pakistani health care system is a pragmatic approach to the problem. With the participation of local and federal stakeholders, the application of our research proposal is easily achievable at a very low cost to the health system. Estimating the incidence of AEs from retrospective chart reviews and patient interviews, assessing the presence of a safety culture within hospitals by interviewing health care providers, learning from patient experiences within the hospital through surveys, and examining hospital compliance to quality improvement measures are all technically sound methods to ascertain the dynamics and challenges within patient safety culture.

Challenges and Solutions

However, even with a less resource-intensive approach such as ours, the local health system still poses many challenges. Implementation of patient safety protocols for quality health care provision in LMICs is limited, mainly due to the unavailability of resources and proper infrastructure. A significant number of health care facilities in Pakistan lack essential equipment, life-saving medications, and adequately trained staff to provide safe and effective care to patients [37]. Additionally, given the diversity in the local population in terms of language and regional lifestyle differences, health care providers can encounter cultural and linguistic barriers that hinder their ability to communicate effectively with patients, which can subsequently compromise patient safety.

Furthermore, the lack of access to continuing medical and nursing education and training opportunities results in poor understanding and implementation of patient safety protocols among health care providers. Additionally, a decentralized health care system paired with political instability and poor governance frequently results in inadequate funding [37] and a dearth of regulations for implementing patient safety protocols effectively. Consequently, health care providers in Pakistan continually navigate these multifaceted challenges while striving for the provision of safe, effective, and quality care for their patients [38].

We anticipate all these issues to surface during our research project as well. To begin with, a significant challenge in collaborative risk assessments in a decentralized health system is to have all the various stakeholders agree on a singular model. Additionally, the lack of a common understanding of the concept of patient safety risk assessment results in discrepancies in the identification and management of risks by the health care providers at different institutions. Moreover, limited channels of communication among the local health care systems also mean that effective collaboration and information sharing among health care providers is almost nonexistent.

Another significant challenge in our research will likely be the absence or inadequacy of medical records within the local hospitals. Poor medical records result in incomplete or incorrect information about medical histories, leading to inaccurate diagnoses, inappropriate treatment, and consequently, AEs. Predictably, poor medical records might limit our ability to track patient progress and treatment outcomes, which can hinder the identification and management of AEs in a retrospective analysis of medical errors and near-misses.

In order to mitigate these problems head-on, we shall aim to diligently communicate with all federal and provincial stakeholders, listen to their concerns, and with the help of our subject matter experts, express our research ideas, intentions,

and expected outcomes as transparently as possible. Additionally, the investigating team will include regional partners who can provide valuable cultural and linguistic context to the data collection process. To streamline the project focus, we shall invite all the major stakeholders to a brainstorming session where their perceptions and practices regarding patient safety will be discussed and incorporated within the data analysis. To combat the problem of poor quality of medical records, all reviewed charts will undergo a quality assessment [28] before they are included in the data set and a wider margin for dropouts will be adjusted in the sample size calculation if needed. Finally, given the law-and-order situation in the country, all efforts will be made to ensure the physical security of the investigating team and the project data.

Our patient- and provider-centered approach to patient safety assessment incorporates the Global Patient Safety Action Plan goals [16] of empowering patients, encouraging health care workers to participate in fostering a culture of safety, sharing valuable information across health systems, promoting transparency in incidence event reporting and making health care delivery safer to produce better outcomes. Building on this knowledge of the patient safety status in Pakistan, we hope to inform and inspire policy making and strive to align local patient safety standards with global recommendations.

Strengths and Limitations

Our research proposal has many strengths. Given the proposed diversity of health care facilities in our study sample, and their varying capacities for health care provision, no single assessment tool can provide an exhaustive description of the patient safety situation in these hospitals. Hence, our diverse multimethod approach is not only unique within patient safety research in LMICs, but it will also provide a comprehensive assessment of the situation. The inclusion of patient safety and quality experts within the research group is also a unique feature for a survey of this magnitude. The relatively low cost of our proposed methodology and short execution time will encourage stakeholder interest in the project. Moreover, our final analysis is expected to provide a first-of-its-kind perspective on the patient safety situation, particularly within the public health care system.

Some of the limitations of our study include the significant disparity in the perception of health economics and literacy in the study population. This can result in a wide shift in the perception of quality indicators in health care between high and low-income countries. This requires adjusting the existing global standards in quality health care delivery against the local perception of it. Moreover, the reliance on retrospective chart reviews limits information availability, while patient interviews introduce the possibility of respondent recall bias in assessing the incidence of AEs. Additionally, some geographical areas of interest for our study might not be logistically or politically feasible for inclusion. There might also be concerns among the participating hospitals regarding data sharing with other institutions. However, all efforts will be made to ensure compliance with confidentiality standards.

Conclusions

Our multidimensional, multimethod research proposal to assess and analyze the patient safety situation on a large scale within the Pakistani health care system is a unique approach to broaching the domain of patient safety in the country. We are confident that our methodology will produce good quality data so that we can use our study results in writing situation analyses, offering policy recommendations, and hopefully, instigating some real change in prioritizing and implementing a safety culture in Pakistani hospitals. Moreover, our research proposal can be easily implemented in other LMICs with a few minor adjustments in the local context.

Acknowledgments

All authors declared that they had insufficient or no funding to support open access publication of this manuscript, including from affiliated organizations or institutions, funding agencies, or other organizations. JMIR Publications provided article processing fee (APF) support for the publication of this article.

Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Authors' Contributions

AL, F Asif, and SS contributed to the conceptualization and design of the study. GH drafted the manuscript. AL, F Asif, FAA, F Ayub, SHS, NAP, MH, MMUS, SM, and TZ reviewed and edited the manuscript.

Conflicts of Interest

None declared.

References

1. Rodziewicz TL, Houseman B, Hipskind JE. Medical error reduction and prevention. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2023. [Medline: 29763131]

2. de Vries EN, Ramrattan MA, Smorenburg SM, Gouma DJ, Boermeester MA. The incidence and nature of in-hospital adverse events: a systematic review. Qual Saf Health Care 2008 Jun;17(3):216-223 [FREE Full text] [doi: 10.1136/qshc.2007.023622] [Medline: 18519629]
3. Makary MA, Daniel M. Medical error-the third leading cause of death in the US. BMJ 2016 May 03;353:i2139. [doi: 10.1136/bmj.i2139] [Medline: 27143499]
4. Schwendimann R, Blatter C, Dhaini S, Simon M, Ausserhofer D. The occurrence, types, consequences and preventability of in-hospital adverse events - a scoping review. BMC Health Serv Res 2018 Jul 04;18(1):521 [FREE Full text] [doi: 10.1186/s12913-018-3335-z] [Medline: 29973258]
5. Wilson RM, Michel P, Olsen S, Gibberd RW, Vincent C, El-Assady R, et al. Patient safety in developing countries: retrospective estimation of scale and nature of harm to patients in hospital. BMJ 2012 Mar 13;344:e832 [FREE Full text] [doi: 10.1136/bmj.e832] [Medline: 22416061]
6. Institute of Medicine Committee on Quality of Health Care in America. In: Kohn LT, Corrigan JM, Donaldson MS, editors. To Err is Human: Building a Safer Health System. Washington (DC): National Academies Press (US); 2000. [doi: 10.17226/9728]
7. Carayon P, Wooldridge A, Hoonakker P, Hundt AS, Kelly MM. SEIPS 3.0: Human-centered design of the patient journey for patient safety. Appl Ergon 2020 Apr;84:103033 [FREE Full text] [doi: 10.1016/j.apergo.2019.103033] [Medline: 31987516]
8. Guldenmund FW. (Mis)understanding safety culture and its relationship to safety management. Risk Anal 2010 Oct;30(10):1466-1480. [doi: 10.1111/j.1539-6924.2010.01452.x] [Medline: 20626685]
9. Kaur G, Prinja S, Lakshmi PVM, Downey L, Sharma D, Teerawattananon Y. Criteria used for priority-setting for public health resource allocation in low- and middle-income countries: a systematic review. Int J Technol Assess Health Care 2019;35(6):474-483. [doi: 10.1017/S0266462319000473] [Medline: 31307561]
10. Bates DW, Singh H. Two decades since to err is human: an assessment of progress and emerging priorities in patient safety. Health Aff (Millwood) 2018 Nov;37(11):1736-1743 [FREE Full text] [doi: 10.1377/hlthaff.2018.0738] [Medline: 30395508]
11. Nabilou B, Feizi A, Seyedin H. Patient safety in medical education: students' perceptions, knowledge and attitudes. PLoS One 2015;10(8):e0135610 [FREE Full text] [doi: 10.1371/journal.pone.0135610] [Medline: 26322897]
12. Shah N, Jawaid M, Shah N, Ali SM. Patient safety: perceptions of medical students of Dow Medical College, Karachi. J Pak Med Assoc 2015 Dec;65(12):1261-1265. [Medline: 26627504]
13. Patient Safety: Making Health Care Safer. World Health Organization. 2017. URL: https://www.who.int/publications/i/item/WHO-HIS-SDS-2017.11 [accessed 2022-12-10]
14. The Lancet. The struggle for universal health coverage. Lancet 2012 Sep 08;380(9845):859 [FREE Full text] [doi: 10.1016/S0140-6736(12)61485-8] [Medline: 22959368]
15. Global patient safety collaborative. World Health Organization. 2019. URL: https://www.who.int/initiatives/global-patient-safety-collaborative [accessed 2022-12-06]
16. Global Patient Safety Action Plan 2021-2030: Towards Eliminating Avoidable Harm in Health Care. World Health Organization. 2021. URL: https://www.who.int/teams/integrated-health-services/patient-safety/policy/global-patient-safety-action-plan [accessed 2023-01-20]
17. Hellings J, Schrooten W, Klazinga N, Vleugels A. Challenging patient safety culture: survey results. Int J Health Care Qual Assur 2007;20(7):620-632. [doi: 10.1108/09526860710822752] [Medline: 18030963]
18. El-Jardali F, Jaafar M, Dimassi H, Jamal D, Hamdan R. The current state of patient safety culture in Lebanese hospitals: a study at baseline. Int J Qual Health Care 2010 Oct;22(5):386-395 [FREE Full text] [doi: 10.1093/intqhc/mzq047] [Medline: 20699233]
19. Chen IC, Li HH. Measuring patient safety culture in Taiwan using the Hospital Survey on Patient Safety Culture (HSOPSC). BMC Health Serv Res 2010 Jun 07;10:152 [FREE Full text] [doi: 10.1186/1472-6963-10-152] [Medline: 20529246]
20. Waterson P, Griffiths P, Stride C, Murphy J, Hignett S. Psychometric properties of the hospital survey on patient safety culture: findings from the UK. Qual Saf Health Care 2010 Oct;19(5):e2 [FREE Full text] [doi: 10.1136/qshc.2008.031625] [Medline: 20211960]
21. Bodur S, Filiz E. Validity and reliability of Turkish version of "Hospital Survey on Patient Safety Culture" and perception of patient safety in public hospitals in Turkey. BMC Health Serv Res 2010 Jan 28;10:28 [FREE Full text] [doi: 10.1186/1472-6963-10-28] [Medline: 20109186]
22. Palmieri PA, Leyva-Moral JM, Camacho-Rodriguez DE, Granel-Gimenez N, Ford EW, Mathieson KM, et al. Hospital survey on patient safety culture (HSOPSC): a multi-method approach for target-language instrument translation, adaptation, and validation to improve the equivalence of meaning for cross-cultural research. BMC Nurs 2020;19:23 [FREE Full text] [doi: 10.1186/s12912-020-00419-9] [Medline: 32308560]
23. Ahmed FA, Asif F, Munir T, Halim MS, Feroze Ali Z, Belgaumi A, et al. Measuring the patient safety culture at a tertiary care hospital in Pakistan using the Hospital Survey on Patient Safety Culture (HSOPSC). BMJ Open Qual 2023 Mar;12(1):e002029 [FREE Full text] [doi: 10.1136/bmjoq-2022-002029] [Medline: 36931633]

24. Siddiqi S, Elasady R, Khorshid I, Fortune T, Leotsakos A, Letaief M, et al. Patient safety friendly hospital initiative: from evidence to action in seven developing country hospitals. Int J Qual Health Care 2012 Apr;24(2):144-151 [FREE Full text] [doi: 10.1093/intqhc/mzr090] [Medline: 22302070]
25. Yount N, Sorra J, Famolaro T, Gray L, Rockville W. Hospital Survey on Patient Safety Culture Version 2.0: User's Guide. Rockville, MD: Agency for Healthcare Research and Quality; 2021. URL: https://www.ahrq.gov/sops/surveys/hospital/index.html [accessed 2024-02-07]
26. Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS). Baltimore, MD: Centers for Medicare & Medicaid Services URL: https://hcahpsonline.org/ [accessed 2023-05-11]
27. Southwick FS, Cranley NM, Hallisy JA. A patient-initiated voluntary online survey of adverse medical events: the perspective of 696 injured patients and families. BMJ Qual Saf 2015 Oct;24(10):620-629 [FREE Full text] [doi: 10.1136/bmjqs-2015-003980] [Medline: 26092166]
28. Joint Commission International Accreditation Standards for Hospitals: Including Standards for Academic Medical Center Hospitals. Joint Commission International. 2020. URL: https://www.jointcommissioninternational.org/-/media/jci/jci-documents/accreditation/hospital-and-amc/jci-errata-standards-only_7th-ed-hospital.pdf [accessed 2023-01-17]
29. Assessing and Tackling Patient Harm: A Methodological Guide for Data-Poor Hospitals. World Health Organization. 2010. URL: https://iris.who.int/bitstream/handle/10665/77100/9789241500388_eng.pdf?sequence=1 [accessed 2023-06-11]
30. Patient Safety Assessment Manual: Third Edition. World Health Organization Regional Office for the Eastern Mediterranean. 2020. URL: https://applications.emro.who.int/docs/9789290223221-eng.pdf [accessed 0000-00-00]
31. Meterko M, Mohr DC, Young GJ. Teamwork culture and patient satisfaction in hospitals. Med Care 2004 May;42(5):492-498. [doi: 10.1097/01.mlr.0000124389.58422.b2] [Medline: 15083111]
32. de Feijter JM, de Grave WS, Muijtjens AM, Scherpbier AJJA, Koopmans RP. A comprehensive overview of medical error in hospitals using incident-reporting systems, patient complaints and chart review of inpatient deaths. PLoS One 2012;7(2):e31125 [FREE Full text] [doi: 10.1371/journal.pone.0031125] [Medline: 22359567]
33. Zanetti ACB, Gabriel CS, Dias BM, Bernardes A, Moura AA, Gabriel AB, et al. Assessment of the incidence and preventability of adverse events in hospitals: an integrative review. Rev Gaucha Enferm 2020;41:e20190364 [FREE Full text] [doi: 10.1590/1983-1447.2020.20190364] [Medline: 32667424]
34. Kiaei MZ, Ziaee A, Mohebbifar R, Khoshtarkib H, Ghanati E, Ahmadzadeh A, et al. Patient safety culture in teaching hospitals in Iran: assessment by the Hospital Survey on Patient Safety Culture (HSOPSC). Health Manag Inf Sci 2016;3(2):51-56 [FREE Full text]
35. Oyebode F. Clinical errors and medical negligence. Med Princ Pract 2013;22(4):323-333 [FREE Full text] [doi: 10.1159/000346296] [Medline: 23343656]
36. Rafter N, Hickey A, Conroy RM, Condell S, O'Connor P, Vaughan D, et al. The Irish National Adverse Events Study (INAES): the frequency and nature of adverse events in Irish hospitals-a retrospective record review study. BMJ Qual Saf 2017 Feb;26(2):111-119 [FREE Full text] [doi: 10.1136/bmjqs-2015-004828] [Medline: 26862223]
37. Kurji Z, Premani ZS, Mithani Y. Analysis of the health care system of Pakistan: lessons learnt and way forward. J Ayub Med Coll Abbottabad 2016;28(3):601-604 [FREE Full text] [Medline: 28712245]
38. Bashir S, Nasir M, Grasic K, Moulin M, Ali S. Association between efficiency and quality of care of public healthcare facilities: evidence from Pakistan. Int J Health Plann Manage 2022 Jul;37(4):2240-2255. [doi: 10.1002/hpm.3465] [Medline: 35340046]

Abbreviations

AE: adverse event
AHRQ: Agency for Healthcare Research and Quality
HCAHPS: Hospital Consumer Assessment of Healthcare Providers and Systems
HSOPSC: Hospital Survey on Patient Safety Culture
LMIC: low and middle–income country
PSFHF: Patient Safety Friendly Hospital Framework
RF1: review form 1
RF2: review form 2
WHO: World Health Organization

Edited by A Mavragani; submitted 15.08.23; peer-reviewed by F Al Dhabbari, M Letaief; comments to author 02.12.23; revised version received 09.01.24; accepted 19.01.24; published 27.03.24.

Please cite as:
Haque G, Asif F, Ahmed FA, Ayub F, Syed SUH, Pradhan NA, Hameed M, Siddiqui MMU, Mahmood S, Zaidi T, Siddiqi S, Latif A
Assessment of Patient Safety in a Low-Resource Health Care System: Proposal for a Multimethod Study
JMIR Res Protoc 2024;13:e50532
URL: https://www.researchprotocols.org/2024/1/e50532
doi:10.2196/50532
PMID:38536223

Protocol

Exploring Shared Implementation Leadership of Point of Care Nursing Leadership Teams on Inpatient Hospital Units: Protocol for a Collective Case Study

Sonia Angela Castiglione[1], RN, MScA; Mélanie Lavoie-Tremblay[2], RN, PhD; Kelley Kilpatrick[1], RN, PhD; Wendy Gifford[3], RN, PhD; Sonia Elizabeth Semenic[1], RN, PhD

[1]Ingram School of Nursing, McGill University, Montreal, QC, Canada

[2]Faculty of Nursing, Université de Montréal, Montreal, QC, Canada

[3]Faculty of Health Sciences, University of Ottawa, Ottawa, ON, Canada

Corresponding Author:
Sonia Angela Castiglione, RN, MScA
Ingram School of Nursing
McGill University
#1800
680 Rue Sherbrooke O
Montreal, QC, H3A 2M7
Canada
Phone: 1 514 398 4144
Email: sonia.castiglione@mcgill.ca

Abstract

Background: Nursing leadership teams at the point of care (POC), consisting of both formal and informal leaders, are regularly called upon to support the implementation of evidence-based practices (EBPs) in hospital units. However, current conceptualizations of effective leadership for successful implementation typically focus on the behaviors of individual leaders in managerial roles. Little is known about how multiple nursing leaders in formal and informal roles share implementation leadership (IL), representing an important knowledge gap.

Objective: This study aims to explore shared IL among formal and informal nursing leaders in inpatient hospital units. The central research question is as follows: How is IL shared among members of POC nursing leadership teams on inpatient hospital units? The subquestions are as follows: (1) What IL behaviors are enacted and shared by formal and informal leaders? (2) What social processes enable shared IL by formal and informal leaders? and (3) What factors influence shared IL in nursing leadership teams?

Methods: We will use a collective case study approach to describe and generate an in-depth understanding of shared IL in nursing. We will select nursing leadership teams on 2 inpatient hospital units that have successfully implemented an EBP as instrumental cases. We will construct data through focus groups and individual interviews with key informants (leaders, unit staff, and senior nurse leaders), review of organizational documents, and researcher-generated field notes. We have developed a conceptual framework of shared IL to guide data analysis, which describes effective IL behaviors, formal and informal nursing leaders' roles at the POC, and social processes generating shared leadership and influencing contextual factors. We will use the Framework Method to systematically generate data matrices from deductive and inductive thematic analysis of each case. We will then generate assertions about shared IL following a cross-case analysis.

Results: The study protocol received research ethics approval (2022-8408) on February 24, 2022. Data collection began in June 2022, and we have recruited 2 inpatient hospital units and 25 participants. Data collection was completed in December 2023, and data analysis is ongoing. We anticipate findings to be published in a peer-reviewed journal by late 2024.

Conclusions: The anticipated results will shed light on how multiple and diverse members of the POC nursing leadership team enact and share IL. This study addresses calls to advance knowledge in promoting effective implementation of EBPs to ensure high-quality health care delivery by further developing the concept of shared IL in a nursing context. We will identify strategies to strengthen shared IL in nursing leadership teams at the POC, informing future intervention studies.

International Registered Report Identifier (IRRID): DERR1-10.2196/54681

(JMIR Res Protoc 2024;13:e54681) doi:10.2196/54681

KEYWORDS

case study; evidence-based practices; implementation leadership; inpatient hospital units; nursing leadership; point of care

Introduction

Overview

Leadership is a key factor in generating conducive contexts for the successful implementation of evidence-based practices (EBPs) in health care settings [1]. Developing effective point of care (POC) nursing leadership for implementation, or implementation leadership (IL), has the potential to create optimal climates for implementation and improve patient outcomes [2]. However, the current understanding of IL in nursing is limited and does not consider the diversity of formal and informal leadership roles that are involved in implementation [3]. In addition, formal and informal nurse leaders work within nursing leadership teams to lead implementation efforts, yet how nursing leaders share in this process has not yet been described. The exploration of IL in nursing is important since it is well known that successful implementation of EBPs in nursing continues to be elusive, contributing to persistent quality gaps in care delivery. Furthermore, within the existing culture of continuous and relentless change, failed implementation efforts may intensify nurses' experiences of physical and emotional sequelae of "change fatigue" including exhaustion, apathy, powerlessness, and burnout, which in turn threaten their engagement in further change initiatives [4].

This study will explore and deepen a relational view of IL, called shared IL, which resonates with the number and variety of nursing roles involved in implementation at the POC. Specifically, this study will describe the leadership behaviors of nurses in formal managerial and nonmanagerial leadership roles at the POC, including nurse managers (NMs), assistant nurse managers (ANMs), nursing professional development educators (NPDEs), and advanced practice nurses (APNs), as well as informal leaders such as champions in the change process who are often appointed to support local implementation efforts. In addition, this study will explore the social processes where shared IL emerges among the various leaders. Finally, the contextual factors that enable shared IL will be highlighted. A more holistic understanding of shared IL in nursing can support the development of effective leadership for implementation.

Background

IL is a nascent concept in implementation science literature that provides guidance on what POC leadership behaviors need to be developed and performed to support successful implementation [5]. IL describes strategic leadership behaviors based on transformational and effective leadership behavior theories whereby leaders are visibly committed, supportive of POC staff, and engaged at the granular level to prepare for and facilitate implementation [6,7]. These behaviors are posited to strengthen implementation climates, which consist of "employees' shared perceptions of the policies, practices, procedures and behaviors that are rewarded, supported and expected in order to facilitate effective EBP implementation and use" [8]. Recent evidence from a nonnursing longitudinal study in mental health clinics supports a link between the enactment of IL behaviors by POC clinical managers with higher levels of implementation climate and self-reported adoption of EBPs by clinicians, reinforcing the critical role of POC leaders in creating the conditions for implementation to succeed [9].

IL has been typically conceptualized as an approach that is manifested through the behaviors of individual leaders, in particular leaders who hold managerial positions at the POC [3]. Indeed, a growing body of research describes NMs as playing a vital role contributing to implementation success. In an updated systematic review, Gifford et al [10] found that NMs enacted change-, relational-, and task-oriented behaviors that included communicating organizational priorities for change, establishing partnerships with nursing and interprofessional colleagues, participating in planning for implementation, and providing resources. These behaviors indicated to staff that the use of the EBP in clinical practice was important and served to "inspire, encourage and provide tangible incentives to staff" to adopt EBPs [10]. Birken et al [11] similarly found that middle managers (including POC NMs) played multiple roles, which consisted of encouraging and enabling frontline staff to overcome obstacles, addressing concerns, coaching, and providing incentives to shape an implementation-conducive climate. These reviews suggest that NMs take on multidimensional leadership behaviors that consist of both enabling and enforcing roles to generate contexts supportive of implementation. In contrast, no studies were found on the role of ANMs in implementation despite their day-to-day involvement in the operations and care processes in a care setting.

Nonmanagerial nursing leaders at the POC also have responsibilities for engaging in processes that aim to optimize the health system, including research, leadership, and education [12]. However, in contrast to research on the role and behaviors enacted by NMs, no studies were found that explicitly explored the IL behaviors of these other types of nurse leaders. Rather, formal nonmanagerial leaders including NPDEs and APNs such as clinical nurse specialists and nurse practitioners, have typically been described in the literature as internal facilitators [13]. Facilitators use strategies that exert social influence to support behavior change including encouragement, role modeling, information sharing, peer-to-peer coaching, delivering formal and informal education, practice surveillance, demonstrating a commitment to the goal, and planning and goal setting among others [14-16]. Similarly, informal nurse leaders can take on champion roles in implementation, and like internal facilitators use a wide range of strategies that are congruent with their professional knowledge, skills, and practice expectations to support change [14]. While it appears that both leadership and facilitation are needed to support implementation,

there is considerable overlap in these processes. In addition, it is unclear how the adoption of either facilitation or leadership roles and behaviors is influenced by the type of nursing leader position held, suggesting an important area for clarification and exploration.

Nursing leaders at the POC level may need better training to take on their leadership roles, and in particular to develop strategic IL behaviors to support implementation [17]. In a study by Lunden et al [18], nursing staff perceived weakness in the way their managers enabled implementation, particularly around providing resources, mitigating obstacles to implementation, and engaging in discussions about EBPs. When measuring IL-specific behaviors, Shuman et al [2] found NMs in acute care units only exhibited these behaviors moderately and suggested that interventions to strengthen IL were needed. However, it is unknown whether formal nonmanagerial nurse leaders also have similar performance gaps enacting IL. Some studies were found that described the development and feasibility testing of IL interventions as an implementation strategy and these were directed mainly at POC NMs to support the adoption of a clinical practice guideline [19,20]. A greater understanding of nursing leaders' behaviors and their interactions is needed to inform how these IL interventions could be adapted to address a team of diverse nursing leaders at the POC involved in implementation.

Nursing leadership to support implementation at the POC resonates with collective leadership models such as shared leadership, which moves away from a perspective of leadership that resides within an individual with formal authority and influencing power [21]. In contrast, shared leadership is a dynamic and collaborative relational process where influence is distributed among a number of networked individuals to achieve team or organizational goals [22,23]. A shared leadership model is viewed as a strength for teams completing complex tasks such as change and improvement in health care contexts and acts as a facilitator for organizations engaged in large-scale transformative change [24,25].

Research exploring the relational processes among nursing leaders that contributed to the successful implementation of EBPs is very limited. In a Canadian study evaluating the feasibility of an IL educational intervention, formal and informal leaders assigned greater value to generating collective versus individual action plans to implement a fall prevention guideline in residential facilities [19]. In another Canadian study, Fleiszer et al [26] described long-term and routine use of clinical practice guidelines in acute care units where the POC nurse leadership team worked cohesively and collaboratively to integrate implementation and sustainability strategies. However, these studies only alluded to the notion of shared leadership in implementation, as an attribute of effective leadership in nursing. In a study examining relational processes among NM and clinical leader dyads to implement urinary incontinence guidelines, van der Zijpp et al [27] concluded that implementation progressed when these leaders were "in sync." Further, this study pointed to the influence of the organizational culture on POC leaders, suggesting that leaders were reluctant to engage in their implementation role due to specific context factors including the challenges of managing competing priorities, hierarchical leadership structures, and the emphasis on top-down compliance to practice standards [27]. This indicates that more research is needed to explore factors influencing the enactment of IL by different formal and informal nurse leaders as a collective activity at the POC.

In summary, the conceptualization of IL is at odds with nursing leadership at the POC, where multiple leaders in distinct roles are called to lead the implementation of EBPs. Similarly, empirical work to date related to IL in nursing has focused predominately on the NM role, whereas how POC nursing leadership consisting of various formal and informal leaders is enacted to support the implementation of EBPs has been relatively unexplored. This represents an important knowledge gap in the field of implementation science and an area of conceptual evolution for IL. Moreover, how these various leaders work together to support implementation and what influences these processes has not been explicitly researched in depth.

Methods

Research Questions

The central research question is as follows: How is IL shared among members of the POC nursing leadership team in inpatient hospital units? The subquestions are as follows: (1) What IL behaviors are enacted and shared by POC formal and informal leaders? (2) What social processes enable shared IL by formal and informal POC leaders? and (3) What factors influence shared IL among the POC nursing leadership team?

Design

We will use a collective case study approach within the constructivist paradigm to answer the research questions [28]. Collective case study is an approach to inquiry where the researcher explores the particularities of multiple, contemporary, and real-life bounded systems (the cases) in order to generate an in-depth understanding of a social phenomenon [29]. In this study, the cases will include POC nursing leadership teams on 2 inpatient hospital units at a university health network where the implementation of an EBP was successful. In line with the research questions for this study, a case study answers "how" questions by disentangling complex relationships among various factors and processes, which emerge as a function of context both within and external to the case [29]. Case studies are also useful in exploring phenomena that have not been extensively researched, such as shared IL [30]. The emphasis on context distinguishes case studies from other qualitative approaches and promotes the use of multiple data sources and collection methods to develop a holistic understanding of the phenomenon [31]. The selection of multiple cases can generate a greater and more nuanced understanding of how effective shared IL is manifested in different environments, offering the potential to develop an explanatory framework of IL in POC nursing leadership teams [28].

Constructivist Paradigm

Applied widely across different disciplines, the methodological choices in the design of case studies can be approached from different ontological and epistemological orientations [32,33].

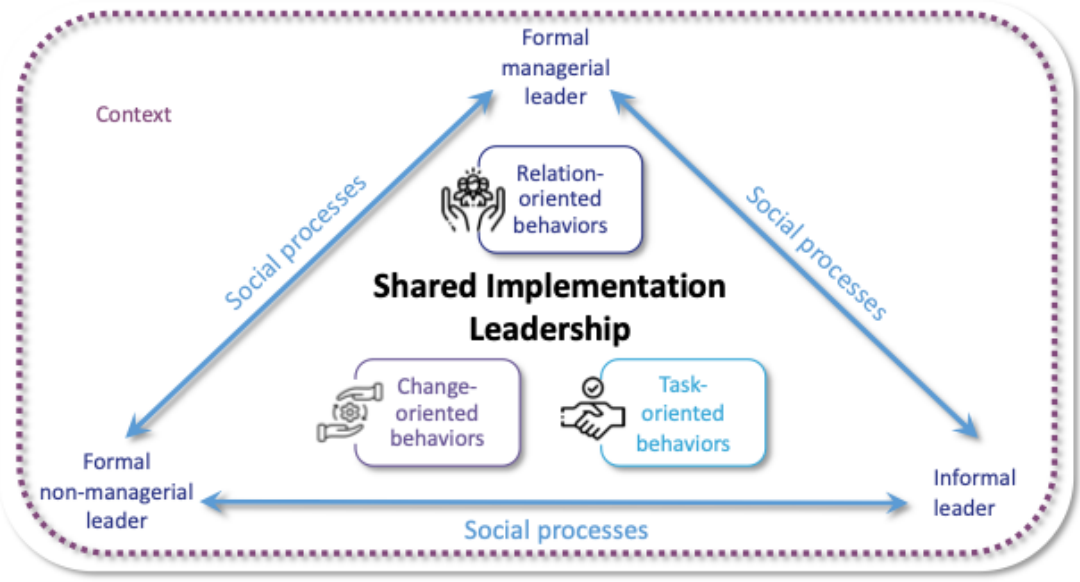
Constructivism, based on a relativist ontology, ascribes to the belief that knowledge of the world is socially constructed [34]. A constructivist orientation to the case study assumes that understanding of a phenomenon such as shared IL in the social world occurs through the perspectives of individuals experiencing it, their shared meanings, and the interactive processes within a given context [35]. For this study, we understand leadership, as constructed through the interactions between grouped individuals, influenced by context and not merely assigned to formalized roles. The focus of this inquiry will be to explore these leaders' IL behaviors and the social processes that support shared IL from the perspectives and collective experiences of POC nurse leaders in inpatient hospital units. To meet the epistemic commitment to constructivism, the theorizations by Stake [34] characterizing case study as a holistic, empirical, interpretive, and empathic research approach will shape our methodological decisions, the role of the researcher in data coconstruction and interpretation, notions of data validation (eg, triangulation), and implications for knowledge generation.

Conceptual Framework

We developed a conceptual framework to guide the selection of key informants and frame the analytical and interpretive focus to explore shared IL among POC nursing leadership team members (Figure 1). A description of the terms can be found in Textbox 1.

This study will build on the dimensions of IL behaviors described in the Ottawa Model of Implementation Leadership, an empirically informed theoretical model in nursing developed over a decade of research [7]. The Ottawa Model of Implementation Leadership describes three meta-categories of leader behaviors to facilitate implementation and support the adoption of EBPs at the POC: (1) relations-oriented behaviors that include supporting, developing, recognizing, and empowering behaviors; (2) change-oriented behaviors that include advocating and envisioning change, encouraging innovation, and facilitating collective learning; and (3) task-oriented behaviors that involve planning, clarifying, monitoring, and problem-solving behaviors. This model is featured in the center of the conceptual framework to describe the specific IL behaviors that are enacted by the different leaders at the POC. Positioned around the IL behaviors are the formal and informal nursing leaders, to integrate the notion that IL behaviors are distributed among a diversity of leaders at the POC. The different leaders are linked to highlight their grouping as a leadership team and social processes where shared IL emerges. Social processes are the patterns of social interactions, that is, the actions and activities occurring over time, and are embedded in a dynamic context, that shapes how IL is shared and the activities across phases of an implementation project [36].

Figure 1. Conceptual framework of shared implementation leadership.



Textbox 1. Description of terms (conceptual framework).

Implementation leadership

- Effective leadership behaviors facilitate the implementation and adoption of evidence-based practices at the point of care.
- Meta-categories of leadership behaviors described in the Ottawa Model of Implementation Leadership [7]:
  - Relation-oriented behaviors: Supporting, developing skills, and recognizing others and their contributions to increasing trust and cooperation.
  - Change-oriented behaviors: Integrating a vision, demonstrating commitment, building coalitions to support change, and creating a sense of need.
  - Task-oriented behaviors: Planning, clarifying roles, monitoring performance, and efficiently using resources.

Leaders

- Formal managerial: Individuals with appointed administrative and management roles with explicit and legitimate authority on the unit (eg, nurse manager and assistant nurse manager).
- Formal nonmanagerial: Individuals with formally recognized clinical leadership and professional development roles in the organization (eg, advanced practice nurses and nursing professional development educators).
- Informal: Individuals with a staff nursing position on the unit are viewed among peers and formal leadership groups as credible. Formalized in the role of nursing champion in the context of an implementation project.

Social processes

- Patterns of social interaction within the team (ie, the individual and collective actions and activities) over time where point of care leaders mutually influence each other for shared implementation leadership to emerge [36].

Context

- The structural, political, cultural, and historical environments of the inpatient unit and health care organization shape features of the social processes.

Sampling and Recruitment

Cases

Stake [34] defines a case as a "bounded system" from which much can be learned. With multiple cases, each case is unique and studied in detail, but it is the phenomenon expressed within each case and across cases that is of interest [28]. We will select 2 instrumental and bounded cases from a large bilingual teaching health network in Montreal, Canada to gain a broad appreciation of shared IL, the phenomenon of interest (or "quintain") in this study [28]. The case will be operationally defined as an inpatient unit in which the POC nursing leadership team has successfully implemented a specified EBP. Inpatient units are socially distinct microsystems that interact with external features, such as the larger organizational hospital context [37,38]. Therefore, inpatient units are considered individual cases, but embedded within the broader clinical and administrative organization and health care contexts. The cases will be bounded as follows: (1) spatially by the physical location, (2) purposefully, by the local clinical mission of the unit, where members of the POC nursing leadership team are assigned responsibility for and have supported the successful implementation of a specified EBP, and (3) temporally by the phases and timeline boundaries of the implementation project.

Case Selection

We will select individual cases based on their relevance to the quintain, the diversity of contexts, and access [28]. To identify potential cases, we will seek advisement from the senior leaders at the health network who are responsible for coordinating EBP project implementations and knowledgeable of implementation outcomes of potential cases. The first case (case A) will be purposively selected and based on predetermined criteria: (1) The successful implementation of the EBP project on the unit within the previous 6 months and senior NMs perception of a "strong" nursing leadership team on the unit, (2) the presence of diverse leaders at the POC, and (3) the availability of the nursing leadership team on the unit to participate in the study. In light of emerging findings as the study unfolds, we will use maximum variation sampling to identify the second case (case B) in consideration of different contextual elements influencing the case (eg, nursing leadership team factors such as composition and tenure, clinical mission, hospital site, and implementation project) [39].

Data Sources

A variety of data sources including key informants and documents will provide breadth and depth to understanding the quintain. We will purposively select key informants for their perspective of firsthand experiences in sharing IL including POC nursing leadership team members consisting of formal managerial and nonmanagerial leaders (ie, the NM, ANMs, NPDE, or APNs) who are assigned responsibility to the inpatient unit and were present during the implementation of the specified EBP; and informal leaders (ie, staff nurse who worked on the unit and were selected as a champion for the specific EBP implementation project). Through purposive and snowball sampling, we will also recruit key informants from the unit and organizational level, who interacted with or observed POC nurse leaders during the implementation, had a role in influencing the

process of shared IL, or can offer a perspective on the contextual influences on shared IL (eg, interdisciplinary team members, staff nurses, and senior-level nursing administrators) [40]. Key informants are considered within the boundaries of the case if they are directly involved in the social processes where shared IL emerges. On the other hand, they will be considered external to the case if they are observers or influencers of the process. Participants will be identified iteratively as the study unfolds with the aim of sampling as many key informants as possible to acquire saturation and depth in understanding the quintain as manifested for each case [41]. Recruitment of POC nursing leadership team members will be completed first and facilitated by senior leaders in the health network. The total number of anticipated key informants recruited will range from 10 to 19 per case.

The documents collected for this study will provide background and historical information and will serve as a proxy for observations [42]. The content and information contained within documents may be useful in describing the quintain over time and can extend, clarify, support, or contradict the perspectives of the key informants. Documents may also provide insight into leadership roles in implementation-specific events, point to instances and processes of leadership being negotiated and distributed, and establish formal expectations for POC leadership in implementation [29]. These insights will inform ongoing data collection by including new interview questions and identifying other documents to gather [42]. Moreover, the documents themselves can be viewed as serving a specific function within the setting [43]. For example, documents created by the setting and using a particular form and structure can give insight into the context of unit and organizational values influencing the social processes among leaders. Examples of documentary sources for this study can include written organizational documents (eg, job descriptions, project charters, protocols, meeting notes, and annual reports), electronic material (eg, email messages and presentations), and physical objects (eg, “war rooms” or “quality boards”, bulletin/whiteboards, and unit layout schematics).

Data Generation

Interviews

We will conduct focus groups with the POC nursing leadership team first. As a pre-existing socially constructed group, participants will be able to draw on their shared experiences and individual group members’ recollections to construct a deeper understanding of the quintain [44]. Data collected from this facilitated discussion can highlight whether accounts and experiences are perceived similarly or differently across team members [45]. Due to the retrospective nature of the case, a facilitated discussion between team members may offer an approximation of their natural group interactions and provide insight into the nature of their relationships (eg, power differentials and conformity) and social processes (eg, reaching consensus and groupthink) [46]. As group interactions are largely nonverbal, observations of group dynamics, including forms of communication, patterns of discussion, group norms, and body language will be collected in the form of descriptive field notes [45-47].

We will conduct individual interviews with key informants for each case to acquire a breadth of perspectives to shape our understanding of shared IL and factors that influence the social processes of shared IL. Complementary to the focus group, individual interviews will yield granular accounts of the case, including greater depth into issues raised during the focus groups, perceptions of shared IL processes and influence, and to check assertions about the group dynamic [48]. Individual interviews with other key informants will clarify their interactions with members of the POC nursing leadership team, and their perceptions of how the POC nursing leadership team supported implementation and influencing factors. The principle of data saturation will guide the total number of interviews conducted for each case [41]. Minimally, 1 focus group interview (possibly over 2 sessions) and 1 individual interview with key informants (n=10-19) will be conducted per case. Additional interviews (focus group and individual) will likely be needed and will serve to validate the analysis (ie, member checking), discuss interview transcripts, clarify ideas, or explore emerging notions gleaned from other data [49].

For both focus group and individual interviews, we will offer face-to-face, in-person or digital interviews, at the convenience of the participants. Interviews will be audio-recorded to capture verbal content data. Prior to the interviews, all participants will complete a sociodemographic questionnaire (Multimedia Appendix 1), which will enable the reporting of details of the key informants in the case description. Interviews will be semistructured to foster an emic approach in line with the constructivist view. We developed an interview guide (Multimedia Appendix 2), with open-ended questions linked to key concepts in the conceptual framework, to explore topic areas aligned with the focus of inquiry while responding to emerging issues emanating from the participants’ experiences of the case [37]. The main questions in the interviews will relate to a description of the EBP project on the unit, the interviewee’s involvement in the EBP implementation, IL behaviors that were distributed or collectively enacted by POC nursing leaders throughout the implementation phases, activities that enabled the POC nursing leadership team to share IL, and the perception of factors related to the context that facilitated or constrained how POC leaders shared IL. In addition, the guide incorporates elements aimed at developing rapport with participants such as broad open-ended questions, with prompts and probes to encourage information sharing and to clarify points [47]. The interview guide concludes with ending questions to promote member checking by summarizing and clarifying what was discussed and asking participants to refer to other sources of information [30]. Throughout the course of inquiry, the interview guide may be adapted in light of emerging ideas and notions from other sources (eg, documents) [47]. Interview guides will be piloted for clarity and comprehension prior to the first interview.

We will identify documents in relation to each case by searching organizational papers and web-based databases, and by direct request of key informants. In addition, SAC will make unit site visits (brief 30-minute tours of the units guided by a leader on the unit to identify other relevant documents) and capture observations about the case through researcher-generated field

notes. Identified documents will be scanned, digitally photographed, saved electronically in a secure study database, and logged. A document intake form will be used to log the characteristics of the document (eg, when, how, and from whom the documents were retrieved), the authenticity of the document, and key themes from the document that relate to the study questions (Multimedia Appendix 3 [40]).

We will generate several types of field notes throughout the course of data collection to accurately describe the research process and achieve an in-depth and credible interpretation of the findings [50,51]. Jottings of ideas, impressions, and brief details of observations will be noted sporadically on a paper notepad to serve as a memory jogger. A daily log of anticipated and actual data collection activities, activities that are being considered, and brief profiles of key informants will be kept electronically. Descriptive observational field notes will be written on separate electronic documents immediately following the case selection meetings, interviews, and unit site visits. Methodological field notes will capture reflections on the techniques and methods used, their perceived success, and adaptations in future data collection. Analytic memos will be used to develop ideas and interpretations of the data collected. Finally, a personal reflexive journal will be kept recording thoughts, feelings, and biases noticed throughout the research process.

Data Analysis

A 2-phase data analysis process will be conducted to ultimately deepen our understanding of the quintain: Within- and cross-case analysis [28]. A within-case analysis will generate an in-depth description of each case, the context and case-based themes, and will occur simultaneously with data collection so that emerging data can iteratively inform the selection of the second case, the pursuit of additional key informant perspectives, and direct lines of inquiry [29]. The Framework Method for the analysis of qualitative data will guide a structured, interconnected, and transparent flow of activities for an in-depth thematic analysis of the data and is aligned with the phases of case analysis described by Stake [34] (ie, case description, categorical aggregation, pattern recognition, and naturalistic generalization) [52]. Similarly, the Framework Method integrates inductive and deductive approaches to analysis, capitalizing on a balance of etic and emic constructions of the case. This approach generates matrix outputs where a large amount of diverse textual data (eg, interviews, documents, and field notes) are systematically reduced, summarized, and displayed facilitating a team approach to analysis [53,54].

The Framework Method moves through five stages: (1) familiarization with the data to form hunches about emerging issues or concepts that correspond with the conceptual framework for each case, (2) developing and iterative refinement of a thematic framework through deductive and inductive coding from a set of a priori codes and subcodes derived from the conceptual framework, (3) indexing the remaining data with the thematic framework, (4) charting of the indexed data into a matrix to allow for data from the entire case to be viewed, and (5) mapping of patterns among categories and interpretation of the data. This final step will be carried through a back-and-forth process between data categories, raw data, and analytic memos toward understanding the case and establishing relationships between case themes and the context.

The case reports generated from the within-case analyses will build toward a cross-case analysis, which aims to identify commonalities and differences of themes across the corpus of cases, and how these are influenced by the variations in contexts to make assertions about the quintain [28]. Assertions constructed about the shared IL may support or suggest modifications to the conceptual framework initially proposed for the study. An updated framework will inform the conceptual structure for the final cross-case report and will be examined against existing research and theory.

Ethical Considerations

The study protocol received research ethics approval (2022-8408) on February 24, 2022, and renewal on February 21, 2023. The study will undergo a research ethics review. There is minimal risk of harm to participants in this study. Potential participants will be informed about the study (eg, study purpose, nature of their involvement, potential risks, and benefits) and will be required to provide written consent prior to embarking on the study. The right to refuse to participate and withdraw at any time during the study without consequence will be explained. The anonymity of study participants will be ensured by identifying transcripts with a numerical code, with the code key kept separately; storage of data files in secured physical and electronic locations; and limited access to data files by the research team [30]. Due to the nature of case study research and its use of thick description to report on the uniqueness of the case, there is a risk of deductive disclosure especially as the POC leaders are known to all staff [55]. In addition, confidentiality will be impossible to maintain for group interviews. Therefore, additional safeguards will be put into place to ensure confidentiality and build rapport with participants. These include (1) a discussion with interviewees following data collection about the anticipated audiences for dissemination of the study results, (2) offering participants the opportunity to review interview transcripts, (3) consulting with participants on how to treat text that may be identifying in nature for the purposes of data analysis and dissemination, and (4) in group interview circumstances, reminding participants not to share any details of the discussion outside of the group context [55]. As interviews with participants will be held during work hours, compensation will not be provided.

Reflexivity and Rigor

SAC will conduct this study to partially fulfill the requirements toward a PhD in nursing degree. She will conduct this study as a trainee with the research institute in the setting and will be partially subsidized by the nursing directorate. SAC is a registered nurse and has worked in the study setting as a clinical nurse specialist and then as an advisor for EBP. As a function of these roles across different sites within the setting, SAC believes she has earned credibility and trust from colleagues, particularly nurses in leadership roles. SAC maintains a strong connection with senior leaders as well as with other colleagues. As a research trainee and recent previous employee with the setting, SAC believes to be positioned as an insider, due to the

"lived familiarity" with the participants in the research and a priori knowledge of the setting and potentially of the cases as well [56]. As an insider, she collaborated with senior leaders in the conceptualization of the study, to strengthen the feasibility and alignment of the study plan with departmental expectations. SAC's insider status also raises questions about the implications of power with respect to data collection, disclosure of confidential knowledge and perspectives, and reporting that may negatively influence the site, participants, and herself [29]. In addition to the strategies mentioned above, SAC will strive to be transparent in interactions with the individuals in her role as a researcher and demonstrate openness to address any concerns in the field [29].

Integrated into the design of this study proposal are strategies that enhance the trustworthiness of a naturalistic inquiry and meet the criteria for a good case study report [34,35]. The strategies encompass researcher behaviors, inquiry, and reporting processes to promote confidence in the findings presented on shared IL (credibility criteria), that accepted research practices were followed in exploring shared IL (dependability criteria), that the findings are grounded in an emic perspective (confirmability criteria) and that there is sufficient contextual information presented in the reporting of this study on shared IL for readers to deliberate over the findings for applicability in other contexts (transferability) [57]. Table 1 details the compendium of strategies planned for each quality criterion.

Table 1. Methodological rigor criteria, definitions, and strategies.

Rigor criteria [58]	Definitions [57]	Strategies to enhance rigor	Criteria described by Stake [34] for a good case study report (adapted)
Credibility	The extent to which the reader has "confidence that [the researchers] have accurately recorded the phenomenon under scrutiny" [57]	• Adequate engagement in the field to generate data [40] • Triangulation to promote variation in views and ways of constructing data • Establishing rapport in interactions with key informants [57,59] • Member checking to validate the accuracy and interpretation of data [34] • Debriefing sessions with research team to discuss and challenge data construction • Transparency in data construction by engaging in reflective commentary [57]	• Data sources are well chosen and in sufficient numbers. • Observations and interpretations appear to be triangulated. • Sound assertions appear to be made, neither over- nor under-interpreting. • Individuals were not put at risk during the inquiry.
Transferability	The extent to which the reader has been provided sufficient contextual information by the researchers to apply the findings elsewhere	• Thick case description [57] • Maximum variation [40]	• Case adequately defined. • Reader is provided with some vicarious experience (sense of story). • Adequate attention paid to various contexts.
Dependability	The extent to which the reader can assess that the proper research practices have been followed	• In-depth methodological description [60]	• Final report is easy to read and edited well. • Research questions and themes developed in a serious and scholarly way.
Confirmability	The extent to which the reader can determine that the findings are based on an emic perspective, "rather than the characteristics and preferences of the researcher" [57]	• Researcher reflexivity [57] • Demonstration of an audit trail [44,57]	• Findings have a conceptual structure (ie, themes). • Quotations are used effectively. • Tables and figures are used effectively. • Sufficient raw data are presented. • The role of the researcher is apparent. • Empathy is shown. • Researcher's personal intentions are examined

Results

Data collection began in June 2022, and we have recruited 2 inpatient hospital units and 24 participants to date. We experienced several challenges locating and recruiting key informants (ie, no longer employed at the hospital) or delays in scheduling focus group interviews with nursing leadership teams and individual interviews with key informants due to high levels of workload during the COVID-19 pandemic. We amended the study protocol (approval received on July 18, 2022), with the research ethics board to be able to recruit employees no longer working at the hospital. We anticipate data collection to be completed by January 2024 and findings to be published in a peer-reviewed journal by late 2024.

Discussion

Significance and Anticipated Contributions

Over, the next 10 years, Canada has committed to advancing the science of knowledge mobilization to generate more capable, effective, and humane health systems and to improve the health of individuals and populations [61]. The aims of this study address this priority by exploring more deeply how nursing leadership facilitates the successful implementation of EBPs to ensure high quality care delivery. Further, as nurses represent the largest regulated health professional group in health systems worldwide and are recognized as key drivers in care quality, the findings of this study will be an important contribution to this goal [62,63]. This study will answer calls for further research investigating how leadership as a complex contextual factor interacts with the implementation process and will add to the growing body of knowledge on POC leader roles in implementation [64]. By expanding the conceptual understanding of IL as behaviors enacted by a single managerial leader, we will be able to articulate in detail the specific contributions of formal and informal nurse leaders at the POC fostering implementation climates. This study will be the first one to hold a relational lens to IL, explore the social processes of an intradisciplinary team at the POC, and demystify the characteristics of effective leadership teams in facilitating evidence-based changes in nursing.

The knowledge generated from study findings can inform the development of tailored implementation strategies that seek to bolster nursing leadership at the POC, such as how to adapt interventions aimed at single POC managers for POC nursing leadership teams. Other nursing scholars in implementation are similarly exploring ways to "prepare context" that easily adapts to regular and ongoing implementation efforts and poses "fewer barriers to change" [65]. By equipping nurse leaders to engage staff and support consistent success in implementation efforts, we may lessen the cost of failed implementation efforts and generate healthier work environments for nurses [66]. Nursing leadership is distinguished from other health care professionals through its multiple and diverse leadership roles at the POC, yet little is known about their specific contributions in implementation, specifically ANMs. The findings may help to inform nursing administrators about what organizational supports are needed to strengthen effective IL at the POC and to facilitate the development of emerging nurse leaders. In addition, during the COVID-19 pandemic, NMs reported that their roles and responsibilities had expanded and sometimes changed altogether with little or no preparation and training [67]. NMs may be increasing their reliance on other POC leaders to distribute specific leadership tasks in order to support implementation and the quality of care in their units. This study is timely and can offer much-needed clarity for policymakers on the present-day contribution of formal and informal roles in nursing to the provision of quality care.

Limitations

One of the limitations of this study is the generalizability of the findings to other inpatient hospital units or health care settings, due to the idiosyncratic nature of the qualitative case study approach and exploration of 2 cases in 1 setting [29]. However, the in-depth focus on the particular and unique aspects of the cases will illuminate the complexity of leadership supporting implementation in nursing and the importance of context in shaping its manifestation [34]. There may be concerns about social desirability bias limiting what POC nursing leaders discuss and disclose during interviews, given the legitimate power relationships across leader types (ie, manager and subordinate relationship) and their ongoing working relationship [68]. Yet, it is the analysis of this social context (eg, group norms) that is of interest to this study. Increases in workload, shifted priorities due to the ongoing COVID-19 pandemic and the nursing workforce shortage in the wake of the acute pandemic phase presented challenges with recruitment and availability of POC nurse leaders, and other key informants in the health setting. We are offering digital interviews to improve the likelihood of participation by teams and individuals. POC nursing leaders may be accustomed to communicating with each other digitally because of the pandemic and therefore may approximate their interactions in the natural setting.

Conclusion

Implementation of EBPs drives and sustains high-quality nursing practice, where effective nursing leadership at the POC is integral to its success. This protocol for a collective case study aims to conceptualize IL through a shared leadership lens in nursing. The study findings will have broad implications for ongoing research in the fields of implementation science and nursing leadership; leadership practice by providing a model for leadership that enables successful implementation; developing leadership education competencies for current and emerging nursing leaders; and informing structural and cultural policy changes that support nursing leader roles in the health system.

Acknowledgments

SAC is a scholar with the Canadian Nurses Foundation and has received student funding from the Fonds de recherche du Québec–Santé, the Quebec Network on Nursing Intervention Research (RRISIQ), the Ordre des infirmière et infirmiers du Québec, the Newton Foundation, and McGill University. The proposal was reviewed by the Doctoral Comprehensive Examination Committee on November 16, 2021. Comments made by the reviewers were taken into consideration for this manuscript.

Data Availability

The data sets generated or analyzed during this study will not be publicly available due to the small sample size and risk of participant identification in this study, and in adherence to the requirements of confidentiality in line with the present ethics permission.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Sociodemographic questionnaire.
[DOCX File , 17 KB - resprot_v13i1e54681_app1.docx]

Multimedia Appendix 2
Semistructured interview guide.
[DOCX File , 19 KB - resprot_v13i1e54681_app2.docx]

Multimedia Appendix 3
Document intake form.
[DOCX File , 15 KB - resprot_v13i1e54681_app3.docx]

Multimedia Appendix 4
Peer-review report by the McGill University Doctoral Comprehensive Examination Committee.
[PDF File (Adobe PDF File), 231 KB - resprot_v13i1e54681_app4.pdf]

References

1. Li SA, Jeffs L, Barwick M, Stevens B. Organizational contextual features that influence the implementation of evidence-based practices across healthcare settings: a systematic integrative review. Syst Rev 2018;7(1):72 [FREE Full text] [doi: 10.1186/s13643-018-0734-5] [Medline: 29729669]
2. Shuman CJ, Powers K, Banaszak-Holl J, Titler MG. Unit leadership and climates for evidence-based practice implementation in acute care: a cross-sectional descriptive study. J Nurs Scholarsh 2019;51(1):114-124 [FREE Full text] [doi: 10.1111/jnu.12452] [Medline: 30552736]
3. Castiglione SA. Implementation leadership: a concept analysis. J Nurs Manag 2020;28(1):94-101. [doi: 10.1111/jonm.12899] [Medline: 31705769]
4. McMillan K, Perron A. Change fatigue in nurses: a qualitative study. J Adv Nurs 2020;76(10):2627-2636. [doi: 10.1111/jan.14454] [Medline: 32542846]
5. Moullin JC, Ehrhart MG, Aarons GA. The role of leadership in organizational implementation and sustainment in service agencies. Res Soc Work Pract 2018;28(5):558-567. [doi: 10.1177/1049731517718361]
6. Aarons GA, Ehrhart MG, Farahnak LR. The Implementation Leadership Scale (ILS): development of a brief measure of unit level implementation leadership. Implement Sci 2014;9(1):45 [FREE Full text] [doi: 10.1186/1748-5908-9-45] [Medline: 24731295]
7. Gifford W, Graham ID, Ehrhart MG, Davies BL, Aarons GA. Ottawa model of implementation leadership and implementation leadership scale: mapping concepts for developing and evaluating theory-based leadership interventions. J Healthc Leadersh 2017;9:15-23 [FREE Full text] [doi: 10.2147/JHL.S125558] [Medline: 29355212]
8. Aarons GA, Ehrhart MG, Farahnak LR, Sklar M. Aligning leadership across systems and organizations to develop a strategic climate for evidence-based practice implementation. Annu Rev Public Health 2014;35:255-274 [FREE Full text] [doi: 10.1146/annurev-publhealth-032013-182447] [Medline: 24641560]
9. Williams NJ, Wolk CB, Becker-Haimes EM, Beidas RS. Testing a theory of strategic implementation leadership, implementation climate, and clinicians' use of evidence-based practice: a 5-year panel analysis. Implement Sci 2020;15(1):10 [FREE Full text] [doi: 10.1186/s13012-020-0970-7] [Medline: 32033575]
10. Gifford WA, Squires JE, Angus DE, Ashley LA, Brosseau L, Craik JM, et al. Managerial leadership for research use in nursing and allied health care professions: a systematic review. Implement Sci 2018;13(1):127 [FREE Full text] [doi: 10.1186/s13012-018-0817-7] [Medline: 30261927]
11. Birken S, Clary A, Tabriz AA, Turner K, Meza R, Zizzi A, et al. Middle managers' role in implementing evidence-based practices in healthcare: a systematic review. Implement Sci 2018;13(1):149 [FREE Full text] [doi: 10.1186/s13012-018-0843-5] [Medline: 30541596]
12. Advanced practice nursing. a pan-Canadian framework. Canadian Nurses Association. 2019. URL: https://www.cna-aiic.ca/en/nursing/advanced-nursing-practice [accessed 2024-01-30]

13. Harvey G, Kitson A. Promoting action on research implementation in health services: the integrated-PARIHS framework. In: Nilsen P, Birken SA, editors. Handbook on Implementation Science. Cheltenham, UK: Edward Elgar Publishing; 2020.
14. Cranley LA, Cummings GG, Profetto-McGrath J, Toth F, Estabrooks CA. Facilitation roles and characteristics associated with research use by healthcare professionals: a scoping review. BMJ Open 2017;7(8):e014384 [FREE Full text] [doi: 10.1136/bmjopen-2016-014384] [Medline: 28801388]
15. Goedken CC, Livorsi DJ, Sauder M, Vander Weg MW, Chasco EE, Chang NC, et al. "The role as a champion is to not only monitor but to speak out and to educate": the contradictory roles of hand hygiene champions. Implement Sci 2019;14(1):110 [FREE Full text] [doi: 10.1186/s13012-019-0943-x] [Medline: 31870453]
16. Shea CM. A conceptual model to guide research on the activities and effects of innovation champions. Implement Res Pract 2021;2:2633489521990443 [FREE Full text] [doi: 10.1177/2633489521990443] [Medline: 34541541]
17. McGarity T, Reed C, Monahan L, Zhao M. Innovative frontline nurse leader professional development program. J Nurses Prof Dev 2020;36(5):277-282 [FREE Full text] [doi: 10.1097/NND.0000000000000628] [Medline: 32890182]
18. Lunden A, Kvist T, Teräs M, Häggman-Laitila A. Readiness and leadership in evidence-based practice and knowledge management: a cross-sectional survey of nurses' perceptions. Nord J Nurs Res 2020;41(4):187-196 [FREE Full text] [doi: 10.1177/2057158520980687]
19. Gifford W, Davies B, Edwards N, Griffin P, Lybanon V. Managerial leadership for nurses' use of research evidence: an integrative review of the literature. Worldviews Evid Based Nurs 2007;4(3):126-145. [doi: 10.1111/j.1741-6787.2007.00095.x] [Medline: 17850494]
20. Tistad M, Palmcrantz S, Wallin L, Ehrenberg A, Olsson CB, Tomson G, et al. Developing leadership in managers to facilitate the implementation of national guideline recommendations: a process evaluation of feasibility and usefulness. Int J Health Policy Manag 2016;5(8):477-486 [FREE Full text] [doi: 10.15171/ijhpm.2016.35] [Medline: 27694661]
21. Yammarino FJ, Salas E, Serban A, Shirreffs K, Shuffler ML. Collectivistic leadership approaches: putting the "We" in leadership science and practice. Ind organ psychol 2015;5(4):382-402. [doi: 10.1111/j.1754-9434.2012.01467.x]
22. Pearce CL, Conger JA, editors. All those years ago. The historical underpinnings of shared leadership. In: Shared Leadership: Reframing the Hows and Whys of Leadership. Thousand Oaks, CA: Sage Publications; 2003.
23. Kocolowski MD. Shared leadership: is it time for a change? ELJ 2010;3(1):22-23 [FREE Full text]
24. Castiglione SA, Lavoie-Tremblay M. An integrative review of organizational factors influencing successful large-scale changes in healthcare. J Nurs Adm 2021;51(5):264-270. [doi: 10.1097/NNA.0000000000001011] [Medline: 33882554]
25. Khan S, Vandermorris A, Shepherd J, Begun JW, Lanham HJ, Uhl-Bien M, et al. Embracing uncertainty, managing complexity: applying complexity thinking principles to transformation efforts in healthcare systems. BMC Health Serv Res 2018;18(1):192 [FREE Full text] [doi: 10.1186/s12913-018-2994-0] [Medline: 29562898]
26. Fleiszer AR, Semenic SE, Ritchie JA, Richer MC, Denis JL. Nursing unit leaders' influence on the long-term sustainability of evidence-based practice improvements. J Nurs Manag 2016;24(3):309-318. [doi: 10.1111/jonm.12320] [Medline: 26081157]
27. van der Zijpp TJ, Niessen T, Eldh AC, Hawkes C, McMullan C, Mockford C, et al. A bridge over turbulent waters: illustrating the interaction between managerial leaders and facilitators when implementing research evidence. Worldviews Evid Based Nurs 2016;13(1):25-31. [doi: 10.1111/wvn.12138] [Medline: 26788694]
28. Stake RE. Multiple Case Study Analysis. New York, NY: Guilford Press; 2006.
29. Creswell JW. Qualitative Inquiry & Research Design: Choosing Among Five Approaches. Thousand Oaks, CA: Sage Publications; 2013.
30. Polit DF, Beck CT. Nursing Research: Generating and Assessing Evidence for Nursing Practice. Philadephia PA: Wolters Kluwer Health; 2017.
31. Brogan P, Hasson F, McIlfatrick S. Lessons learnt: examining the use of case study methodology for nursing research in the context of palliative care. J Res Nurs 2019;24(6):446-459 [FREE Full text] [doi: 10.1177/1744987119867737] [Medline: 34394560]
32. Hyett N, Kenny A, Dickson-Swift V. Methodology or method? a critical review of qualitative case study reports. Int J Qual Stud Health Well-being 2014;9:23606 [FREE Full text] [doi: 10.3402/qhw.v9.23606] [Medline: 24809980]
33. VanWynsberghe R, Khan S. Redefining case study. Int J Qual Methods 2007;6(2):80-94 [FREE Full text] [doi: 10.1177/160940690700600208]
34. Stake RE. The Art of Case Study Research. Thousand Oaks, CA: Sage Publications; 1995.
35. Guba EG, Lincoln YS. Fourth Generation Evaluation. Newbury Park, CA: Sage Publications; 1989.
36. Pettigrew AM. What is a processual analysis? Scand J Manag 1997;13(4):337-348. [doi: 10.1016/s0956-5221(97)00020-1]
37. Abma TA, Stake RE. Science of the particular: an advocacy of naturalistic case study in health research. Qual Health Res 2014;24(8):1150-1161. [doi: 10.1177/1049732314543196] [Medline: 25028158]
38. Braddock CH, Szaflarski N, Forsey L, Abel L, Hernandez-Boussard T, Morton J. The TRANSFORM patient safety project: a microsystem approach to improving outcomes on inpatient units. J Gen Intern Med 2015;30(4):425-433 [FREE Full text] [doi: 10.1007/s11606-014-3067-7] [Medline: 25348342]
39. Stake RE. Case studies. In: Denzin NK, Lincoln YS, editors. Handbook of Qualitative Research. Thousand Oaks, CA: Sage Publications; 2000.

40. Merriam SB, Tisdell EJ. Qualitative Research: A Guide to Design and Implementation. San Francisco, CA: John Wiley & Sons; 2016.
41. Saunders B, Sim J, Kingstone T, Baker S, Waterfield J, Bartlam B, et al. Saturation in qualitative research: exploring its conceptualization and operationalization. Qual Quant 2018;52(4):1893-1907 [FREE Full text] [doi: 10.1007/s11135-017-0574-8] [Medline: 29937585]
42. Bowen GA. Document analysis as a qualitative research method. Qual Res checklist 2009;9(2):27-40. [doi: 10.3316/qrj0902027]
43. Coffey A. Analysing documents. In: Flick U, editor. The SAGE Handbook of Qualitative Data Analysis. London, UK: SAGE Publications; 2014.
44. Green J, Thorogood N. Qualitative Methods for Health Research. Los Angeles, CA: Sage Publications; 2018.
45. Kitzinger J. Focus group research: using group dynamics. In: Holloway I, editor. Qualitative Research in Health Care. Maidenhead, UK: McGraw-Hill Education; 2005.
46. Farnsworth J, Boon B. Analysing group dynamics within the focus group. Qual Res 2010;10(5):605-624. [doi: 10.1177/1468794110375223]
47. Dicicco-Bloom B, Crabtree BF. The qualitative research interview. Med Educ 2006;40(4):314-321 [FREE Full text] [doi: 10.1111/j.1365-2929.2006.02418.x] [Medline: 16573666]
48. Lambert SD, Loiselle CG. Combining individual interviews and focus groups to enhance data richness. J Adv Nurs 2008;62(2):228-237. [doi: 10.1111/j.1365-2648.2007.04559.x] [Medline: 18394035]
49. Read BL. Serial interviews: when and why to talk to someone more than once. Int J Qual Methods 2018;17(1):160940691878345 [FREE Full text] [doi: 10.1177/1609406918783452]
50. Brodsky AE. Fieldnotes. In: Given LM, editor. The SAGE Encyclopedia of Qualitative Research Methods. Thousand Oaks, CA: SAGE Publications; 2008.
51. Bernard HR, editor. Fieldnotes: how to take them, code them, manage them. In: Research Methods in Anthropology: Qualitative and Quantitative Approaches. 3rd Edition. Walnut Creek, CA: AltaMira Press; 2002.
52. Gale NK, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. BMC Med Res Methodol 2013;13(1):117 [FREE Full text] [doi: 10.1186/1471-2288-13-117] [Medline: 24047204]
53. Ward DJ, Furber C, Tierney S, Swallow V. Using framework analysis in nursing research: a worked example. J Adv Nurs 2013;69(11):2423-2431. [doi: 10.1111/jan.12127] [Medline: 23517523]
54. Parkinson S, Eatough V, Holmes J, Stapley E, Midgley N. Framework analysis: a worked example of a study exploring young people's experiences of depression. Qual Res Psychol 2015;13(2):109-129. [doi: 10.1080/14780887.2015.1119228]
55. Kaiser K. Protecting respondent confidentiality in qualitative research. Qual Health Res 2009;19(11):1632-1641 [FREE Full text] [doi: 10.1177/1049732309350879] [Medline: 19843971]
56. Holmes AGD. Researcher positionality—a consideration of its influence and place in qualitative research—a new researcher guide. Shanlax Int J Edu 2020;8(4):1-10. [doi: 10.34293/education.v8i4.3232]
57. Shenton AK. Strategies for ensuring trustworthiness in qualitative research projects. Educ Inf 2004;22(2):63-75. [doi: 10.3233/EFI-2004-22201]
58. Guba EG. Criteria for assessing the trustworthiness of naturalistic inquiries. ECTJ 1981;29(2):75. [doi: 10.1007/bf02766777]
59. Knapik M. The qualitative research interview: participants' responsive participation in knowledge making. Int J Qual Methods 2016;5(3):77-93 [FREE Full text] [doi: 10.1177/160940690600500308]
60. Lauckner H, Paterson M, Krupa T. Using constructivist case study methodology to understand community development processes: proposed methodological questions to guide the research process. Qual Rep 2015;17:1-22 [FREE Full text] [doi: 10.46743/2160-3715/2012.1790]
61. CIHR strategic plan 2021-2031. Canadian Institutes of Health Research. URL: https://cihr-irsc.gc.ca/e/52331.html [accessed 2024-01-30]
62. Regulated nurses, 2016. Canadian Institutes for Health Information. 2017. URL: https://www.cihi.ca/sites/default/files/document/regulated-nurses-2016-report-en-web.pdf [accessed 2024-01-30]
63. Thomas TW, Seifert PC, Joyner JC. Registered nurses leading innovative changes. Online J Issues Nurs 2016;21(3):3 [FREE Full text] [doi: 10.3912/OJIN.Vol21No03Man03] [Medline: 27856917]
64. Bauer MS, Kirchner J. Implementation science: what is it and why should i care? Psychiatry Res 2020;283:112376 [FREE Full text] [doi: 10.1016/j.psychres.2019.04.025] [Medline: 31036287]
65. Cassidy CE, Flynn R, Shuman CJ. Preparing nursing contexts for evidence-based practice implementation: where should we go from here? Worldviews Evid Based Nurs 2021;18(2):102-110 [FREE Full text] [doi: 10.1111/wvn.12487] [Medline: 33493388]
66. Wei H, Sewell KA, Woody G, Rose MA. The state of the science of nurse work environments in the United States: a systematic review. Int J Nurs Sci 2018;5(3):287-300 [FREE Full text] [doi: 10.1016/j.ijnss.2018.04.010] [Medline: 31406839]
67. Jackson J, Nowell L. 'The office of disaster management' nurse managers' experiences during COVID-19: a qualitative interview study using thematic analysis. J Nurs Manag 2021;29(8):2392-2400 [FREE Full text] [doi: 10.1111/jonm.13422] [Medline: 34270140]

68. Bergen N, Labonté R. "Everything is perfect, and we have no problems": detecting and limiting social desirability bias in qualitative research. Qual Health Res 2020;30(5):783-792. [doi: 10.1177/1049732319889354] [Medline: 31830860]

Abbreviations

ANM: assistant nurse manager
APN: advanced practice nurse
EBP: evidence-based practice
IL: implementation leadership
NM: nurse manager
NPDE: nursing professional development educator
POC: point of care

Edited by A Mavragani; submitted 01.12.23; this is a non–peer-reviewed article;accepted 25.01.24; published 19.02.24.

Please cite as:
Castiglione SA, Lavoie-Tremblay M, Kilpatrick K, Gifford W, Semenic SE
Exploring Shared Implementation Leadership of Point of Care Nursing Leadership Teams on Inpatient Hospital Units: Protocol for a Collective Case Study
JMIR Res Protoc 2024;13:e54681
URL: https://www.researchprotocols.org/2024/1/e54681
doi:10.2196/54681
PMID:38373024

Protocol

Innovative Design and Development of Personalized Ankle-Foot Orthoses for Survivors of Stroke With Equinovarus Foot: Protocol for a Feasibility and Comparative Trial

Rui Silva[1,2], MSc; Pedro Morouço[3], PhD; Jorge Lains[4,5], MD; Paula Amorim[4], MD; Nuno Alves[1], PhD; António Prieto Veloso[2], PhD

[1]Centre for Rapid and Sustainable Product Development, Polytechnic University of Leiria, Marinha Grande, Portugal

[2]CIPER, Faculdade de Motricidade Humana, Lisboa, Portugal

[3]Escola Superior de Educação e Ciências Sociais, Polytechnic University of Leiria, Leiria, Portugal

[4]Centro de Medicina de Reabilitação da Região Centro–Rovisco Pais, Tocha, Portugal

[5]Faculty of Medicine, University Coimbra, Coimbra, Portugal

Corresponding Author:
Rui Silva, MSc
Centre for Rapid and Sustainable Product Development
Polytechnic University of Leiria
Rua de Portugal - Zona Industrial
Marinha Grande, 2430-028
Portugal
Phone: 351 244 569 441
Email: rui.d.silva@ipleiria.pt

Abstract

Background: Ankle-foot orthoses (AFOs) are vital in gait rehabilitation for patients with stroke. However, many conventional AFO designs may not offer the required precision for optimized patient outcomes. With the advent of 3D scanning and printing technology, there is potential for more individualized AFO solutions, aiming to enhance the rehabilitative process.

Objective: This nonrandomized trial seeks to introduce and validate a novel system for AFO design tailored to patients with stroke. By leveraging the capabilities of 3D scanning and bespoke software solutions, the aim is to produce orthoses that might surpass conventional designs in terms of biomechanical effectiveness and patient satisfaction.

Methods: A distinctive 3D scanner, complemented by specialized software, will be developed to accurately capture the biomechanical data of leg movements during gait in patients with stroke. The acquired data will subsequently guide the creation of patient-specific AFO designs. These personalized orthoses will be provided to participants, and their efficacy will be compared with traditional AFO models. The qualitative dimensions of this experience will be evaluated using the Quebec User Evaluation of Satisfaction With Assistive Technology (QUEST) assessment tool. Feedback from health care professionals and the participants will be considered throughout the trial to ensure a rounded understanding of the system's implications.

Results: Spatial-temporal parameters will be statistically compared using paired *t* tests to determine significant differences between walking with the personalized orthosis, the existing orthosis, and barefoot conditions. Significant differences will be identified based on *P* values, with $P<.05$ indicating statistical significance. The Statistical Parametric Mapping method will be applied to graphically compare kinematic and kinetic data across the entire gait cycle. QUEST responses will undergo statistical analysis to evaluate patient satisfaction, with scores ranging from 1 (not satisfied) to 5 (very satisfied). Satisfaction scores will be presented as mean and SD values. Significant variations in satisfaction levels between the personalized and existing orthosis will be assessed using a Wilcoxon signed rank test. The anticipation is that the AFOs crafted through this innovative system will either match or outperform existing orthoses in use, with higher patient satisfaction rates.

Conclusions: Embracing the synergy of technology and biomechanics may hold the key to revolutionizing orthotic design, with the potential to set new standards in patient-centered orthotic solutions. However, as with all innovations, a balanced approach, considering both the technological possibilities and individual patient needs, will be paramount to achieving optimal outcomes.

International Registered Report Identifier (IRRID): PRR1-10.2196/52365

(JMIR Res Protoc 2024;13:e52365) doi:10.2196/52365

KEYWORDS

3D printing; 3D scanner; ankle foot orthosis; biomechanical analysis; equinovarus foot

Introduction

Overview

Stroke, often termed a cerebrovascular accident, poses a monumental global health issue and stands as the second leading cause of mortality worldwide [1]. In addition to the grave concern of mortality, survivors of stroke frequently grapple with substantial morbidity, most notably neurological impairments that substantially hamper their quality of life. Among these impairments, a prevalent issue is equinovarus foot, a symptom characterized by the foot being plantarflexed (downward) and inverted (turned inward), often resulting from muscle imbalances or neurological impairments [2,3]

In the management and rehabilitation of the equinovarus foot, ankle-foot orthoses (AFOs) serve as a foundational element, supporting and aligning the ankle and foot, suppressing spastic and overpowering muscles, and assisting weak or paralyzed muscles [4]. While these devices are indispensable in aiding patients to regain some semblance of normal gait, they come with their own sets of limitations. Broadly speaking, AFOs are categorized into 2 primary types: traditional off-the-shelf models and custom-crafted versions. Traditional AFOs, designed for a broad patient demographic, offer widespread accessibility but often miss the mark in addressing the unique biomechanical needs of each patient. This one-size-fits-all approach has drawn criticism for its rigidity and lack of individual customization [5]. Conversely, custom-made AFOs are meticulously tailored to fit a specific patient's anatomical structure. While they provide a more individualized fit, the process of creating these orthoses is time-consuming and very laborious. In addition, the process is also wasteful of materials, as plaster molds and other excess fabrication materials are discarded during the fabrication process [6]. This gap between age-old craftsmanship and cutting-edge precision sets the stage for technological intervention, aiming to meld the advantages of both approaches.

The concept of reverse engineering in orthotics involves capturing a patient's limb anatomy in great detail, translating this information into a digital model, and then crafting an orthotic device to perfectly align with the individual's biomechanical demands [7,8]. Using 3D scanning techniques allows for a highly accurate representation of human anatomy. This digital replica serves as a blueprint upon which orthotic devices can be meticulously designed, thereby ensuring that the device is tailored to an individual's unique biomechanical requirements. Nevertheless, the integration of 3D scanning technology into the orthotic field is fraught with challenges. Capturing a comprehensive scan, particularly of the plantar region of the foot, proves to be problematic. The quality of the scan is often compromised due to patient movements, exacerbated by the extended duration needed for the scanning process [9]. This prolonged duration can be uncomfortable for the patient, thereby leading to unintended movements and consequential errors in the scan data. Moreover, there are ongoing debates over the computational workload and adaptability of the resulting digital models. Such pitfalls, whether arising from anatomical complexities, patient movements, or technological limitations, could culminate in an improperly fitting orthotic device.

The science of photogrammetry, which involves making measurements based on photographs, offers a potential solution. Initially used for mapping and topographical studies [10], its application in the medical realm, particularly in orthotics and prosthetics, has only recently been explored. The capacity to transform photographs into intricate 3D models offers quicker scan times and could minimize errors induced by patient movements [11]. However, the full-scale integration of this promising technology into the orthopedic field is still in its infancy [12-16]. Ensuring that the resulting 3D models are an accurate reflection of patient anatomy and that the resultant devices are both functional and comfortable remains a challenge. Furthermore, orthopedics is a multidisciplinary field that includes physicians, physical therapists, and engineers. Consequently, any new technological adoption must be orchestrated carefully to ensure effective use across all these professions [17]. Armed with these technological advancements, the field of orthotics is poised for a transformative evolution—a shift toward a more patient-centric and technologically integrated paradigm. This fusion of traditional orthotic craftsmanship with cutting-edge computational tools heralds a new era in patient care, targeting both precision and broad accessibility.

Goal of This Study

This research protocol delineates our approach to developing a next-generation AFO system tailored to meet the specific needs of survivors of stroke. The primary objective is to harness advanced scanning tools and bespoke software for a holistic orthotic solution. By innovatively integrating technology and medical expertise, we envision a transformation in the rehabilitation journey, creating a more refined and effective recovery pathway for individuals with poststroke motor challenges. Our methodological framework will guide us from the initial stages of scanner and software development to a culminating phase of validation, where the proposed orthotic devices will undergo rigorous patient trials. Through this initiative, we aim to chart a progressive path in the realm of poststroke orthotic care.

Methods

Study Design

This nonrandomized feasibility study aims to harness advanced scanning technologies and innovative software for the design and refinement of orthotics tailored specifically to the unique anatomical and biomechanical needs of survivors of stroke presenting with equinovarus deformity. Following a noninferiority trial design for biomechanical outcomes and a superiority trial design for qualitative outcomes, our methodology focuses on the development of a novel AFO

system. The goal is to ensure its biomechanical performance is at least as effective as off-the-shelf AFOs while also enhancing patient satisfaction. Feedback from patients and clinical observations will serve as the primary indicators of success.

Ethical Considerations

The approval for the protocol of this study was granted by the Health Ethics Committee of the Centro de Medicina de Reabilitação da Região Centro–Rovisco Pais (Tocha, Portugal) in August 2022.

Consent to Participate and Consent for Publication

Overview

A document was developed at the request of the health ethics committee for informed, clear, and voluntary consent for participation in research studies. The document outlines the research study's objective and assures that there will be no detriment to treatments and clinical follow-up should the patient choose to withdraw. It also guarantees the anonymity and confidentiality of all collected data, including photographs, results from the Quebec User Evaluation of Satisfaction With Assistive Technology (QUEST) [18], and biomechanical analysis data. The consent form must be signed by both the attending physician and the patient.

This protocol was prepared according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 checklist for reporting a protocol study [19].

Eligibility Criteria and Recruitment Procedures

The inclusion criteria for this study have been defined with precision to select the most suitable candidates in alignment with the study objectives. We are targeting survivors of stroke, both male and female, aged between 18 and 75 years, who exhibit equinovarus foot secondary to hemiparesis, affecting either the left or right side. A prerequisite for potential participants is their current use of AFOs. Furthermore, the concurrent use of any assistive technologies such as tripods, crutches, or canes is deemed acceptable. Essential criteria include the capacity to provide informed consent and the ability to ambulate, either independently or with the support of the aforementioned devices. Conversely, candidates with concomitant neurological or orthopedic conditions that might confound the study outcomes, those with active dermatological conditions, or those with severe communication impairments potentially hindering consistent participation will be excluded.

The recruitment process will be at the Centro de Medicina de Reabilitação da Região Centro. Attending physicians will review patient profiles to identify individuals meeting the stipulated criteria. Those aligning with our research parameters will be briefed on the study's aims and subsequently provided with a detailed consent document. Upon granting written consent, these individuals will be enlisted as participants, ensuring a systematic and ethically rigorous approach to data acquisition and feedback.

Clinical Outcomes

In the pursuit of developing an optimized orthotic design system, an array of clinical metrics is implemented to gauge its efficiency, efficacy, and the comfort it bestows on both patients and health care professionals. Ensuring a comfortable experience for the patient during the photography process is paramount, given its pivotal role in orthotic design. This precision not only benefits the patient but also ensures that the system health care professionals navigate is intuitive.

Biomechanical assessments use the Qualisys Miqus M3 system, paired with Bertec force platforms. Patients will wear the Calibrated Anatomical System Technique lower body marker set, which consists of 36 reflective markers, as prescribed by Cappozzo et al [20]. Observations cover 3 walking conditions for each participant: unaided (where possible), with the current orthosis, and with the newly designed orthosis. This methodology provides an in-depth understanding of the orthosis's efficacy, drawing from 10 walking cycles for each leg, and analyzing both kinematics and kinetics.

The biomechanical data under scrutiny spans temporal-spatial parameters, which capture walking speed, gait cycle duration, step length, step time, time in stance, and time in swing. Kinematic parameters delve into pelvic movements such as anterior tilt, up obliquity, and internal rotation. Hip parameters include flexion, adduction, and internal rotation, while knee parameters assess flexion, varus, and internal rotation. Ankle and foot evaluations note dorsiflexion, inversion, pitch, and internal progression. Kinetic parameters are marked by the internal moments at the hip (extensor and valgus), knee (extensor and valgus), and ankle (plantarflexor and extensor), accompanied by the vertical ground reaction force.

The qualitative patient analysis will also incorporate the QUEST assessment. QUEST focuses on understanding the user's satisfaction with assistive technology. It evaluates a range of aspects, from device functionality to user confidence. This offers insights into patients' perceptions and benefits derived from the new orthosis in comparison to conventional models. Incorporating QUEST ensures the orthosis not only meets clinical requirements but also aligns with patient preferences and comfort levels.

Through these comprehensive evaluations, the study aims to offer an enriched perspective on the potential and effectiveness of the innovative orthotic system.

Data Analysis

The forthcoming data analysis is designed to provide an in-depth understanding of the impact of personalized orthoses on gait parameters in relation to both preexisting orthosis and barefoot walking. The sample size was estimated at a prespecified power of 90%, while the α value was set at <.05. The primary outcomes will be represented through spatial-temporal data tables and normalized gait graphs, spanning from 0% to 100% of the gait cycle for the left and right legs.

Spatial-temporal parameters will undergo statistical comparisons using paired *t* tests. This will discern any significant differences between walking with the personalized orthosis, the preexisting orthosis, and walking barefoot. Significant distinctions will be recognized based on *P* values, with a threshold set at 95% indicating statistical significance.

Graphical comparisons of kinematic and kinetic data will use the Statistical Parametric Mapping (SPM) method. SPM is tailored for the analysis of 1D biomechanical data series, such as kinematic curves, yielding a nuanced understanding of differences across the entire gait cycle rather than mere isolated time points. The analysis will leverage the *SPM1D* script. By using SPM1D, it becomes feasible to pinpoint regions in the gait cycle where palpable differences between conditions (existing orthosis, personalized orthosis, and barefoot) arise. This rigorous method offers a continuous evaluation over the entire time or space continuum, safeguarding against missing subtle yet clinically pivotal variations.

Simultaneously, the QUEST responses will be statistically analyzed to evaluate patient satisfaction. Scores from the QUEST, which range from 1 (not satisfied) to 5 (very satisfied), will be presented as mean and SD values for each question. A 1-sample *t* test will be used to determine if the mean satisfaction scores significantly differ from a neutral value. Additionally, a Wilcoxon signed rank test may be used to determine differences in satisfaction levels between using the personalized orthosis and the preexisting orthosis. Any statistically significant variations in user satisfaction between the 2 orthoses will provide insight into the preferential use and comfort of the personalized design.

In essence, this multifaceted statistical approach aims to quantify not only the possible biomechanical advantages of personalized orthoses over standard ones but also the subjective satisfaction of users, ensuring a holistic assessment of the new system's efficacy.

Results

The methodology and approach of this research harbor specific expectations concerning its outcomes. We will use the Qualisys Track Manager from Qualisys to capture biomechanical data with unparalleled accuracy. Once gathered, the data will be processed and analyzed rigorously. With the integration of the Project Automation Framework from Qualisys and Visual 3D from C-Motion, the raw biomechanical data will be transformed into actionable insights that promise to inform and refine orthotic design.

One of the primary quantitative expectations is that the orthosis developed through the new system will either match or surpass the performance of the patient's current orthosis. This benchmark stems from the belief that the integration of state-of-the-art technology and personalized biomechanical data can achieve superior orthotic design. On the qualitative front, using the QUEST assessment, the expectation leans toward higher satisfaction rates with the new orthosis. Since the orthosis is tailored specifically to the patient's leg, it is anticipated that its unique design will resonate more with patients, ensuring better fit, comfort, and overall user experience. To ensure comprehensive results, feedback from health care professionals and participants will be actively sought throughout the trial phases. This blend of qualitative and quantitative data aims to present a holistic perspective on the impact of the new orthotic design, setting the stage for potential breakthroughs in patient-centered orthotic solutions. In summary, while this research protocol lays out the groundwork and anticipated outcomes, the subsequent study will seek to not just present numbers but to demonstrate the tangible and intangible benefits of a personalized orthotic approach.

Discussion

Over the years, the field of gait rehabilitation has witnessed significant advancements, with orthoses taking center stage in many innovative solutions. As such, they have played a pivotal role in enhancing gait and laying the foundation for more customized interventions [21,22]. In the chronicle of medical interventions, the present times showcase a blend of time-tested traditional methods coexisting with avant-garde technologies. It is within this dynamic backdrop that the new system emerges, positioning itself as a game changer in the realm of orthoses. With a design methodology that captures the transformative essence of technology, this system aims to usher in a new epoch where AFOs are no longer generic but are sculpted based on the detailed biomechanical nuances of individual patients [23].

A key component of this innovation lies in the use of 3D scanning and 3D printing techniques. Particularly, AFOs crafted through such state-of-the-art processes have been thrust under the academic microscope. In recent years, various studies have examined multiple outcomes with the use of these technologies for the fabrication of AFOs. Belokar et al [24] and Cha et al [25] conducted numerous mechanical tests to understand the strength and deformation of the AFO, while other studies focused on gait analysis [26-28], while others on a qualitative analysis of patient comfort [16,29]. The allure of these techniques is evident, offering unparalleled precision coupled with the prospect of personalization. However, as with all innovations, there is a spectrum of opinions. While numerous research endeavors highlight the undeniable advantages of 3D methodologies, others have voiced concerns—touching upon biomechanical compatibility, the robustness of materials used, and the overall comfort on prolonged usage studies [8].

While contrasting the biomechanics of barefoot walking with orthotic-assisted gait yields valuable insights, our central focus is on the differences between traditionally designed orthoses and those created using the novel system. Contemporary research reinforces the merits of tailored medical interventions, suggesting that custom orthoses can lead to enhanced foot function, pain relief, and overall improved mobility [30,31]. For patients, the benefits of this approach are substantial. Custom-made orthoses, derived from comprehensive biomechanical analyses, not only promise greater comfort but also accelerate gait rehabilitation and minimize complications arising from poorly fitted orthoses [6,7,25]. Such initiatives are in tune with the broader shift in health care toward patient-centered treatments, ensuring holistic and efficacious therapeutic outcomes [32].

Nonetheless, potential limitations exist. While the novel system promises tailored orthoses, individual patient responses, adaptation periods, and unique rehabilitation timelines could present challenges. The variability in individual reactions to orthoses, both in terms of comfort and therapeutic outcomes, remains a critical factor to consider.

This proposed research protocol marks a pivotal juncture between technology and biomechanics in the health care landscape. It signals a shift in orthotic design, embracing recent advancements and a nuanced understanding of biomechanics. The endeavors are not merely about gait rehabilitation recovery but also about setting a new benchmark for precision and efficacy in patient care.

Acknowledgments

The authors would like to acknowledge the support of the Portuguese Foundation for Science and Technology through the following projects: SFRH/BD/145292/2019, UIDB/04044/2020, UIDP/04044/2020, and PAMI ROTEIRO/0328/2013 (CENTRO2020: N 22158); and the support of the National Innovation Agency through the project ReinventO (POCI-01-0247-FEDER-040021) and project INOV.AM–Innovation in Additive Manufacturing (02-C05-i01.01-2022.PC644865234-00000004), funded by European Union–Next Generation EU, PRR-Plano de Recuperação e Resiliência.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report.
[PDF File (Adobe PDF File), 84 KB - resprot_v13i1e52365_app1.pdf]

References

1. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016;388(10053):1545-1602 [FREE Full text] [doi: 10.1016/S0140-6736(16)31678-6] [Medline: 27733282]
2. Ward AB. Managing spastic foot drop after stroke. Eur J Neurol 2014;21(8):1053-1054. [doi: 10.1111/ene.12404] [Medline: 24628965]
3. Fietzek UM, Kossmehl P, Schelosky L, Ebersbach G, Wissel J. Early botulinum toxin treatment for spastic pes equinovarus—a randomized double-blind placebo-controlled study. Eur J Neurol 2014;21(8):1089-1095. [doi: 10.1111/ene.12381] [Medline: 24754350]
4. Cakar E, Durmus O, Tekin L, Dincer U, Kiralp MZ. The ankle-foot orthosis improves balance and reduces fall risk of chronic spastic hemiparetic patients. Eur J Phys Rehabil Med 2010;46(3):363-368 [FREE Full text] [Medline: 20927002]
5. Zhang M, Davies TC, Xie S. Effectiveness of robot-assisted therapy on ankle rehabilitation: a systematic review. J Neuroeng Rehabil 2013;10:30 [FREE Full text] [doi: 10.1186/1743-0003-10-30] [Medline: 23517734]
6. Liu Z, Zhang P, Yan M, Xie YM, Huang GZ. Additive manufacturing of specific ankle-foot orthoses for persons after stroke: a preliminary study based on gait analysis data. Math Biosci Eng 2019;16(6):8134-8143 [FREE Full text] [doi: 10.3934/mbe.2019410] [Medline: 31698659]
7. Lunsford C, Grindle G, Salatin B, Dicianno BE. Innovations with 3-dimensional printing in physical medicine and rehabilitation: a review of the literature. PM R 2016;8(12):1201-1212. [doi: 10.1016/j.pmrj.2016.07.003] [Medline: 27424769]
8. Silva R, Veloso A, Alves N, Fernandes C, Morouço P. A review of additive manufacturing studies for producing customized ankle-foot orthoses. Bioengineering (Basel) 2022;9(6):249 [FREE Full text] [doi: 10.3390/bioengineering9060249] [Medline: 35735492]
9. Gefen A. Plantar soft tissue loading under the medial metatarsals in the standing diabetic foot. Med Eng Phys 2003;25(6):491-499. [doi: 10.1016/s1350-4533(03)00029-8] [Medline: 12787987]
10. Magnani M, Douglass M, Schroder W, Reeves J, Braun DR. The digital revolution to come: photogrammetry in archaeological practice. Am Antiq 2020;85(4):737-760. [doi: 10.1017/aaq.2020.59]
11. Grazioso S, Selvaggio M, Caporaso T, Di Gironimo G. A digital photogrammetric method to enhance the fabrication of custom-made spinal orthoses. J Prosthet Orthot 2019;31(2):133-139 [FREE Full text] [doi: 10.1097/jpo.0000000000000244]
12. Weigert MC, Poier PH, Rosenmann GC, Foggiatto JA, Volpato N, Okimoto MLLR. Indirect 3D scanning of the foot plant—comparison between a medium and low-cost tools. Adv Transdiscipl Eng 2016;4:614-621. [doi: 10.3233/978-1-61499-703-0-614]
13. Ciobanu O, Ciobanu G, Rotariu M. Photogrammetric scanning technique and rapid prototyping used for prostheses and ortheses fabrication. Appl Mech Mater 2013;371:230-234. [doi: 10.4028/www.scientific.net/amm.371.230]
14. Grazioso S, Selvaggio M, Di Gironimo G. Design and development of a novel body scanning system for healthcare applications. Int J Interact Des Manuf 2017;12(2):611-620. [doi: 10.1007/s12008-017-0425-9]

15. Munhoz R, da Costa Moraes CA, Tanaka H, Kunkel ME. A digital approach for design and fabrication by rapid prototyping of orthosis for developmental dysplasia of the hip. Res Biomed Eng 2016;32(1):63-73 [FREE Full text] [doi: 10.1590/2446-4740.00316]
16. Dal Maso A, Cosmi F. 3D-printed ankle-foot orthosis: a design method. Mater Today Proc 2019;12:252-261. [doi: 10.1016/j.matpr.2019.03.122]
17. Dickinson A, Donovan-Hall M, Kheng S, Wiegand S, Wills G, Ostler C, et al. Technologies to enhance quality and access to prosthetics and orthotics: the importance of a multidisciplinary, user-centred approach. World Health Organization. 2019. URL: https://eprints.soton.ac.uk/433135/ [accessed 2024-03-11]
18. Demers L, Weiss-Lambrou R, Ska B. Development of the Quebec User Evaluation of Satisfaction with Assistive Technology (QUEST). Assist Technol 1996;8(1):3-13. [doi: 10.1080/10400435.1996.10132268] [Medline: 10159726]
19. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med 2013;158(3):200-207 [FREE Full text] [doi: 10.7326/0003-4819-158-3-201302050-00583] [Medline: 23295957]
20. Cappozzo A, Catani F, Croce UD, Leardini A. Position and orientation in space of bones during movement: anatomical frame definition and determination. Clin Biomech (Bristol, Avon) 1995;10(4):171-178. [doi: 10.1016/0268-0033(95)91394-t] [Medline: 11415549]
21. Hurwitz DE, Ryals AB, Case JP, Block JA, Andriacchi TP. The knee adduction moment during gait in subjects with knee osteoarthritis is more closely correlated with static alignment than radiographic disease severity, toe out angle and pain. J Orthop Res 2002;20(1):101-107 [FREE Full text] [doi: 10.1016/S0736-0266(01)00081-X] [Medline: 11853076]
22. Menz HB, Morris ME, Lord SR. Foot and ankle characteristics associated with impaired balance and functional ability in older people. J Gerontol A Biol Sci Med Sci 2005;60(12):1546-1552 [FREE Full text] [doi: 10.1093/gerona/60.12.1546] [Medline: 16424286]
23. Oosterwaal M, Telfer S, Tørholm S, Carbes S, van Rhijn LW, Macduff R, et al. Generation of subject-specific, dynamic, multisegment ankle and foot models to improve orthotic design: a feasibility study. BMC Musculoskelet Disord 2011;12:256 [FREE Full text] [doi: 10.1186/1471-2474-12-256] [Medline: 22074482]
24. Belokar RM, Banga HK, Kumar R. A novel approach for ankle foot orthosis developed by three dimensional technologies. IOP Conf Ser Mater Sci Eng 2017;280:012030 [FREE Full text] [doi: 10.1088/1757-899x/280/1/012030]
25. Cha YH, Lee KH, Ryu HJ, Joo IW, Seo A, Kim D, et al. Ankle-foot orthosis made by 3D printing technique and automated design software. Appl Bionics Biomech 2017;2017:9610468 [FREE Full text] [doi: 10.1155/2017/9610468] [Medline: 28827977]
26. Choi H, Peters KM, MacConnell MB, Ly KK, Eckert ES, Steele KM. Impact of ankle foot orthosis stiffness on Achilles tendon and gastrocnemius function during unimpaired gait. J Biomech 2017;64:145-152. [doi: 10.1016/j.jbiomech.2017.09.015] [Medline: 29037441]
27. Lin YC, Lin KW, Chen CS. Evaluation of the walking performance between 3D-printed and traditional fabricated ankle-foot orthoses—a prospective study. Gait Posture 2017;57:366-367. [doi: 10.1016/j.gaitpost.2017.06.471]
28. Chae DS, Kim DH, Kang KY, Kim DY, Park SW, Park SJ, et al. The functional effect of 3D-printing individualized orthosis for patients with peripheral nerve injuries: three case reports. Medicine (Baltimore) 2020;99(16):e19791 [FREE Full text] [doi: 10.1097/MD.0000000000019791] [Medline: 32311991]
29. Mavroidis C, Ranky RG, Sivak ML, Patritti BL, DiPisa J, Caddle A, et al. Patient specific ankle-foot orthoses using rapid prototyping. J Neuroeng Rehabil 2011;8:1 [FREE Full text] [doi: 10.1186/1743-0003-8-1] [Medline: 21226898]
30. Shih A, Park DW, Yang YY, Chisena R, Wu D. Cloud-based design and additive manufacturing of custom orthoses. Procedia CIRP 2017;63:156-160 [FREE Full text] [doi: 10.1016/j.procir.2017.03.355]
31. Jin Y, Plott J, Chen R, Wensman J, Shih A. Additive manufacturing of custom orthoses and prostheses—a review. Procedia CIRP 2015;36:199-204 [FREE Full text] [doi: 10.1016/j.procir.2015.02.125]
32. Epstein RM, Street RL. The values and value of patient-centered care. Ann Fam Med 2011;9(2):100-103 [FREE Full text] [doi: 10.1370/afm.1239] [Medline: 21403134]

Abbreviations

AFO: ankle-foot orthosis
QUEST: Quebec User Evaluation of Satisfaction With Assistive Technology
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
SPM: Statistical Parametric Mapping

Edited by A Mavragani; submitted 31.08.23; this is a non–peer-reviewed article;accepted 23.11.23; published 02.04.24.

Please cite as:
Silva R, Morouço P, Lains J, Amorim P, Alves N, Veloso AP
Innovative Design and Development of Personalized Ankle-Foot Orthoses for Survivors of Stroke With Equinovarus Foot: Protocol for a Feasibility and Comparative Trial
JMIR Res Protoc 2024;13:e52365
URL: https://www.researchprotocols.org/2024/1/e52365
doi:10.2196/52365
PMID:38564249

Protocol

Experimentally Induced Reductions in Alcohol Consumption and Brain, Cognitive, and Clinical Outcomes in Older Persons With and Those Without HIV Infection (30-Day Challenge Study): Protocol for a Nonrandomized Clinical Trial

Robert L Cook[1], MD, MPH; Veronica L Richards[1,2], PhD; Joseph M Gullett[1], PhD; Brenda D G Lerner[3], PsyD, RN; Zhi Zhou[1], DDS, MPH; Eric C Porges[4], PhD; Yan Wang[1], PhD; Christopher W Kahler[5], PhD; Nancy P Barnett[5], PhD; Zhigang Li[1], PhD; Suresh Pallikkuth[6], PhD; Emmanuel Thomas[6], MD, PhD; Allan Rodriguez[6], MD; Kendall J Bryant[7], PhD; Smita Ghare[8], PhD; Shirish Barve[8], PhD; Varan Govind[6], PhD; Jessy G Dévieux[3], PhD; Ronald A Cohen[4], PhD; The 30-Day Challenge Research Team[9]

[1]Southern HIV and Alcohol Research Consortium, University of Florida, Gainesville, FL, United States

[2]Edna Bennett Pierce Prevention Research Center, The Pennsylvania State University, University Park, PA, United States

[3]Florida International University, Miami, FL, United States

[4]Center for Cognitive Aging and Memory, University of Florida, Gainesville, FL, United States

[5]Department of Behavioral and Social Sciences, Center for Alcohol and Addiction Studies, Brown University School of Public Health, Providence, RI, United States

[6]Miami Center for AIDS Research, University of Miami Miller School of Medicine, Miami, FL, United States

[7]National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD, United States

[8]Department of Medicine, University of Louisville, Louisville, KY, United States

[9]See Acknowledgments, Gainesville, FL, United States

Corresponding Author:
Robert L Cook, MD, MPH
Southern HIV and Alcohol Research Consortium
University of Florida
2004 Mowry Road
Department of Epidemiology
Gainesville, FL, 32610
United States
Phone: 1 3522735869
Email: cookrl@ufl.edu

Abstract

Background: Both alcohol consumption and HIV infection are associated with worse brain, cognitive, and clinical outcomes in older adults. However, the extent to which brain and cognitive dysfunction is reversible with reduction or cessation of drinking is unknown.

Objective: The 30-Day Challenge study was designed to determine whether reduction or cessation of drinking would be associated with improvements in cognition, reduction of systemic and brain inflammation, and improvement in HIV-related outcomes in adults with heavy drinking.

Methods: The study design was a mechanistic experimental trial, in which all participants received an alcohol reduction intervention followed by repeated assessments of behavioral and clinical outcomes. Persons were eligible if they were 45 years of age or older, had weekly alcohol consumption of 21 or more drinks (men) or 14 or more drinks (women), and were not at high risk of alcohol withdrawal. After a baseline assessment, participants received an intervention consisting of contingency management (money for nondrinking days) for at least 30 days followed by a brief motivational interview. After this, participants could either resume drinking or not. Study questionnaires, neurocognitive assessments, neuroimaging, and blood, urine, and stool samples were collected at baseline, 30 days, 90 days, and 1 year after enrollment.

Results: We enrolled 57 persons with heavy drinking who initiated the contingency management protocol (mean age 56 years, SD 4.6 years; 63%, n=36 male, 77%, n=44 Black, and 58%, n=33 people with HIV) of whom 50 completed 30-day follow-up

and 43 the 90-day follow-up. The planned study procedures were interrupted and modified due to the COVID-19 pandemic of 2020-2021.

Conclusions: This was the first study seeking to assess changes in brain (neuroimaging) and cognition after alcohol intervention in nontreatment-seeking people with HIV together with people without HIV as controls. Study design strengths, limitations, and lessons for future study design considerations are discussed. Planned analyses are in progress, after which deidentified study data will be available for sharing.

Trial Registration: ClinicalTrials.gov NCT03353701; https://clinicaltrials.gov/study/NCT03353701

International Registered Report Identifier (IRRID): DERR1-10.2196/53684

(JMIR Res Protoc 2024;13:e53684) doi:10.2196/53684

KEYWORDS

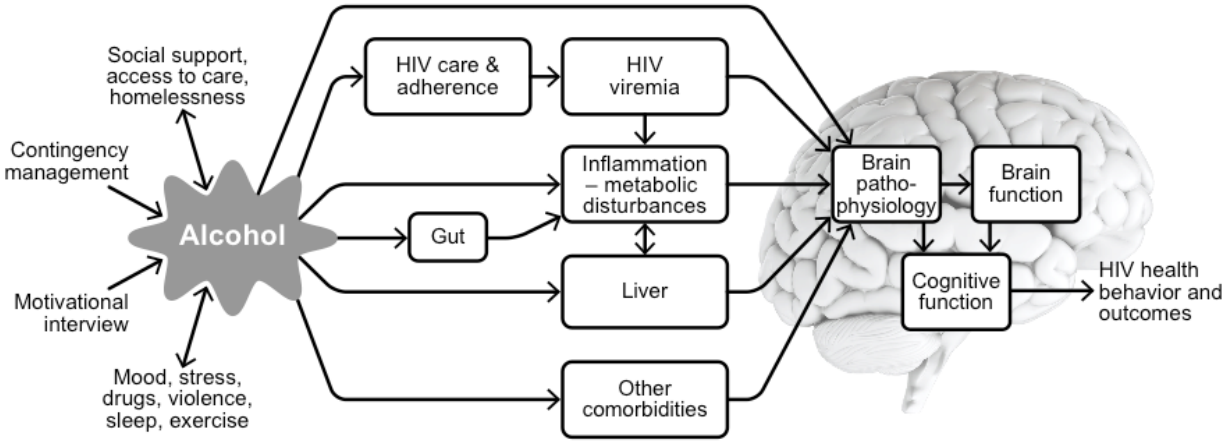
alcohol; contingency management; biosensor; HIV infection; cognitive function

Introduction

Alcohol misuse, or drinking in a manner that could cause harm to the user or those around them [1], is associated with poor HIV-related health outcomes (eg, lower rates of HIV viral suppression and suboptimal adherence to antiretroviral therapy) [2,3]. Alcohol consumption can contribute to a multitude of additional deleterious health effects, such as reductions in brain functioning, cognitive decline, liver disease, and systemic inflammation [4-8]. People with HIV tend to experience worse outcomes, including all-cause mortality, associated with alcohol misuse compared to persons without HIV [9]. Of additional concern is the combination of alcohol misuse and aging among people with HIV, as approximately 58% of people with HIV in the United States are at least 50 years of age [10]. Even mild cognitive impairments have detrimental functional effects and health outcomes that worsen as people with HIV age.

Several mechanisms have been proposed to explain how alcohol consumption could impact chronic disease outcomes. One of the most common is related to the gut-liver-brain axis (see Figure 1), and proposes that alcohol consumption can result in both alterations of the gut microbiota (dysbiosis) as well as microbial translocation, with resulting systemic inflammation that then impacts the liver and brain [11]. While several studies have shown chronic alcohol use to be associated with negative cognitive effects, if any current cognitive effects are due to current brain inflammation, then a reduction in drinking could result in a reduction in inflammation and improved cognition. However, the extent to which these cognitive effects are reversible versus permanent is not known. Since people with HIV also have increased rates of cognitive decline and chronic systemic inflammation, they may be especially vulnerable to the impact of alcohol and might benefit the most from alcohol reduction.

Figure 1. Conceptual model of the possible mechanisms by which alcohol could influence HIV-related health outcomes via the gut-brain axis.



The true causal effect of alcohol consumption on these health outcomes can be difficult to tease out with observational studies. While it is not ethical to challenge persons to engage in ongoing heavy drinking to determine its adverse effects, removing alcohol consumption from heavy drinkers could help to identify whether certain health aspects are reversible when drinking is removed. Therefore, the research team designed a study to determine whether cessation of drinking or significant reduction would be associated with improved brain function, cognition, and HIV clinical outcomes. The study design would also examine whether these outcomes got worse again with any resumption of drinking and would examine potential biological mechanisms related to gut microbial dysbiosis, intestinal permeability, biomarkers of systemic inflammation, liver function, and brain pathology.

In order to experimentally reduce drinking, the research team proposed contingency management (CM), a well-established intervention for treating alcohol use disorder [12,13] that

provides financial payments to encourage individuals to abstain from alcohol use [14]. In order to monitor daily drinking status, the research team used transdermal alcohol sensors, because these can continuously and noninvasively monitor alcohol use [15,16]. Specifically, the Secure Continuous Remote Alcohol Monitor Continuous Alcohol Monitoring (SCRAM CAM; Alcohol Monitoring Systems, Inc), a sensor locked onto the ankle, has effectively been used in CM trials [12,17-20]. The sensor data can be used to determine whether reinforcement should be provided and can be used as an objective evidence of reduction. Motivational interviewing (MI) is another intervention with a demonstrated ability to reduce alcohol consumption [21,22] and was proposed as a booster intervention to help maintain alcohol reduction after CM was removed. The purpose of this study was not to evaluate the effectiveness of either CM or MI as alcohol interventions (since these are already known to be effective), but rather to use the interventions as a method of experimental manipulation to produce maximal drinking reduction in the short term (30-90 days) and provide objective verification of that reduction in order to study the effects of these changes in drinking on the body.

The primary aims of the study were to determine whether CM-induced alcohol reduction would improve cognitive performance and brain function among people with HIV in as little as 30 days and up to 1 year. If the impact of alcohol on systemic and cerebral inflammation is temporary, then reducing or eliminating alcohol consumption could dramatically improve cognitive function and indices of brain health, even among people who have consumed alcohol for many years. We sought to focus the research on people with HIV, because the potential benefits from alcohol cessation may be even greater due to the interactive effects. A smaller group of persons without HIV was included as a control population. Secondary aims were (1) to determine the impact of alcohol reduction on HIV clinical status, markers of systemic inflammation, and liver fat and fibrosis; (2) to investigate factors associated with success in reducing or stopping drinking; (3) to identify mechanisms linking drinking changes to HIV-related behavior and clinical outcomes; and (4) to identify the optimal measures of individual alcohol consumption using biosensors, biomarkers, and self-report.

Methods

Study Design and Overview

This was a nonrandomized, single-arm clinical trial that used a pre-post comparison with extended follow-up. The majority of participants would be people with HIV but a subset of persons without HIV were also included as controls and to allow for subgroup comparisons. After confirming eligibility, all participants provided preintervention data and then received a CM intervention to stop or reduce drinking for 30 to 90 days, and a MI intervention 30 days after baseline. Detailed clinical and behavioral assessments were collected at baseline, 30 days, 90 days, and 12 months after enrollment. The first participant was enrolled in December 2017 and final participant data were collected in April 2022. The study procedures were modified after study initiation to include additional data related to the gut microbiome and to adapt to the COVID-19 pandemic in 2020-2022.

Ethical Considerations

Ethics approval was obtained from the institutional review boards at Florida International University (FIU; IRBSITE00000291), the University of Florida (UF; CED000000011), and the University of Miami (UM, 20170396). The study was registered at ClinicalTrials.gov (NCT03353701) in November 2017.

Recruitment and Informed Consent

Participants were recruited in the Miami Metropolitan region (Florida) from HIV clinics, community outreach, and a contract registry. Recruitment advertisements were placed on public transportation and in local HIV clinics. Potential participants were screened over the phone or in person and those initially eligible were invited to attend an enrollment visit to review procedures, obtain consent, and confirm eligibility.

Enrollment Visit

Potential participants were informed that one of the major goals of the study was to examine changes in the body after drinking reduction, and therefore they were asked to participate in a "30-Day Challenge," in which they would try to reduce or stop drinking for at least 30 days. After informed consent was obtained, participants completed a detailed assessment to determine whether they were eligible to continue with the study.

The inclusion criteria were age 45-75 years, 21 or more drinks per week for men or 14 or more drinks per week for women, confirmed HIV status (for those who reported being HIV positive), English speaking, willingness to participate in CM, and wear an alcohol biosensor for at least 30 days. Exclusion criteria included neurological disorders (eg, dementia, stroke, seizures, and traumatic brain injury); past opportunistic infection; major psychiatric disturbance (eg, severe major depression); unstable medical conditions (eg, cancer); magnetic resonance imaging (MRI) contraindications (eg, pregnancy, severe claustrophobia, metal implants, and physical impairment precluding motor response or lying still); inability to demonstrate an understanding of key aspects of the study; and currently participating in other alcohol research.

Additional assessments used to determine eligibility at this enrollment visit included the Montreal Cognitive Assessment (MoCA) [23], the Alcohol Withdrawal Symptom Checklist (AWSC) [24], and a 30-Day Drug and Alcohol Timeline Followback (TLFB) [25]. Participants with MoCA scores lower than 17 were discussed with the investigators and allowed to proceed if they could clearly discuss the study goals and purpose with the research assistants. Those with AWSC scores greater than 8 were excluded due to the high risk of alcohol withdrawal. The TLFB was used to determine the average number of drinks per week, and persons with less than 21 drinks per week (men) or 14 drinks per week (women) were also excluded from the clinical intervention at this point.

Pre-CM Test Week

At the enrollment visit, those who appeared to be eligible had the SCRAM CAM biosensor placed on their ankle. The monitor

strap has a specialized clip that prevents removal without breaking the clip or cutting the ankle strap (and any removal sends an alert to SCRAM Systems and is viewable by the research team). The purpose of participants wearing the monitor for this week was to confirm that they did drink (for at least 3 days), they could go at least 24 hours without drinking and without withdrawal symptoms, they could tolerate wearing the SCRAM CAM, and they would communicate as expected with the research assistant. During this pre-CM phase, participants were instructed to drink as they normally would, except for at least 1 day of required abstinence (for persons who drink every day). Participants were given instructions about the monitor, including not submerging the device in water, avoiding using alcohol-based items, and not wearing socks under the monitor. A research assistant called the participant every other day to collect information on self-reported drinking and compared this information to that obtained by remote download from a cloud server from the SCRAM website. This ensured that for each participant, the monitor could accurately distinguish drinking from nondrinking days. During this pre-CM test week, participants received incentive payments for providing self-reports but no incentive for drinking behavior itself. During this pre-CM test week, some participants chose to withdraw, mostly due to not wanting to wear the ankle biosensor, and some were excluded because they did not drink enough or were not able to follow study procedures. All other people were scheduled to attend an in-person baseline assessment and to choose a specific date on which they would start the 30-Day Challenge.

Baseline Assessment

The baseline assessment included a study questionnaire, neurocognitive assessments, neuroimaging assessments, liver Fibroscan, and collection of blood, urine, and stool samples. The baseline questionnaire was completed either during the enrollment visit (before the test week) or at the baseline assessment. Participants were required to have a 0 breathalyzer reading in order to proceed with the baseline questionnaire. The primary domains of the measures and the administration schedule are in Table 1. The study questionnaire items are available from the research team upon request.

Table 1. Summary of items assessed by study questionnaires for the 30-Day Challenge study at baseline and follow-up visits.

Domain (source)	Baseline	30 days	90 days	1 year
Sociodemographics				
Age, country of origin, race or ethnicity, sex at birth, gender, sexual orientation, education, and incarceration history	✓			
Marital status, homelessness, insurance, employment, income, and disability	✓			✓
Quality of life				
Quality of life (SF-12[a] Health Survey v1) [26]	✓	✓	✓	✓
Physical activity (Godin-Shephard Leisure-Time Physical Activity Questionnaire) [27]	✓	✓	✓	✓
HIV care and medical history				
HIV/AIDS status, ART[b] treatment adherence, and drinking impact on medication adherence	✓	✓	✓	✓
Year of first HIV positive test and HIV medications	✓			
Self-reported medical conditions and current medications	✓			
COVID-19 diagnosis history and vaccination status	✓			
Symptoms				
General symptoms (Veterans Aging Cohort Study Survey) [28]	✓	✓	✓	✓
Sleep quality-2 items (Pittsburgh Sleep Quality Assessment) [29]	✓	✓	✓	✓
Pain (Brief Pain Inventory Short Form) [30] and self-reported current and past pain treatments	✓	✓	✓	✓
Alcohol use for pain and effectiveness of alcohol use for pain	✓			
Mental health				
Anxiety (Generalized Anxiety Disorder-7) [31]	✓	✓	✓	✓
Depression (Patient Health Questionnaire-8) [32]	✓	✓	✓	✓
Posttraumatic stress disorder (PTSD; Primary Care PTSD Screen) [33]	✓	✓	✓	✓
Emotion regulation (difficulties in emotional regulation scale) [34]	✓		✓	
Childhood trauma 4 items (Childhood Traumatic Events Scale) [35]	✓			
Self-reported cognitive functioning (MOS[c] Mental Health) [36]	✓	✓	✓	✓
Substance use				
30-day alcohol and drug use timeline follow-back [25]	✓	✓	✓	✓
AUDIT-C[d] [37]	✓			✓
Alcohol use disorder assessment DSMV[e] Alcohol Assessment [38]	✓			✓
Drinking motives (Drinking Motive Questionnaire) [39]	✓			
Alcohol use of important persons (3 items), age of drinking onset, previous alcohol treatment, and expectancies about quitting drinking	✓			
Open-ended questions about expectancies and outcomes related to the 30-day challenge and any changes in drinking	✓	✓	✓	
Drug use frequency, including tobacco, readiness to quit smoking, injection drug use, noninjection drug use (Medical Monitoring Project survey) [40]	✓	✓	✓	✓
Lifetime alcohol use and alcohol drinking related to COVID-19 (adapted version of KMSK)[f,g,h] [41]	✓			
Sexual history				
Sexual behaviors (VACS[i] Patient Survey) [28] and substance use before sex	✓	✓	✓	✓
Sexual function and satisfaction—4 items (PROMIS[j] sexual function and satisfaction measures) [42]	✓	✓	✓	✓

[a]SF-12: Short Form Health Survey.

[b]ART: antiretroviral treatment.

[c]MOS: medical outcomes study.

[d]AUDIT-C: Alcohol Use Disorders Identification Test for Consumption.

[e]DSMV: Diagnostic and Statistical Manual-V.

[f]KMSK: Kreek-McHugh-Schluger-Kellogg.

[g]Newly added to the study in revisions.

[h]Administered at other timepoints if baseline completed.

[i]VACS: Veterans Aging Cohort Study.

[j]PROMIS: Patient-Reported Outcomes Measurement Information System.

Neurocognitive Assessments

A comprehensive battery of neuropsychological measures was administered to all participants (Table 2). The National Institutes of Health (NIH) toolbox (cognition battery) was given to participants to obtain an estimate of their crystalized (2 assessments) and fluid intellect (5 assessments) [43]. Uncorrected summary scores were created for the NIH toolbox crystalized and fluid scores and further analyses of these index scores included demographic factors such as age, race, and education in the models. For follow-up cognitive assessments, we used different forms when available, because this helps reduce the magnitude of practice effects.

Due to reported participant fatigue in the early phases of the research, the initial battery was refined to be completed in 1 hour or less (we dropped the California Computerized Assessment Package [CALCAP], Wechsler Adult Intelligence Scale-Fourth Edition [WAIS-IV], Brief Visuospatial Memory Test-Revised [BVMT-R]). Research assistants met with the team neuropsychologist regularly to ensure the best practices to maintain rapport and participant engagement. Reminders were given that the tests were purposefully created to be difficult, breaks were offered when somnolence was observed, and the research staff documented when people appeared to be providing limited effort. A summary of the specific neurocognitive tests and neuroimaging assessments obtained at their respective timepoints is included in Table 2.

For data analysis, the primary outcome for neurocognitive assessments is the change in performance on the 5 measures comprising the Fluid Cognition index from the NIH toolbox, which includes memory, attention, cognitive flexibility, processing speed, and executive functioning. Secondary outcomes of cognition will include changes in the other neuropsychological measures.

Table 2. Battery of neurocognitive tests for participants in the 30-Day Challenge study[a].

Test name	Comments	Cognitive domain
NIH[b] toolbox—Fluid [43]	• Dimensional change card sort • Flanker inhibitory control and attention • Picture sequence memory • List sorting • Pattern comparison	• Executive function • Executive function and attention • Episodic memory • Working memory • Processing speed
NIH toolbox—Crystalized[c] [43]	• Picture vocab • Oral reading recognition	• Premorbid intellect
Montreal Cognitive Assessment[c] [23]	• N/A[d]	• General screen cognitive function
Trail Makings Test, Part A [44]	• Cognitive flexibility	• Graphomotor processing speed
Trail Makings Test, Part B [44]	• N/A	• Graphomotor processing speed and executive function
Stroop Test [45]	• Cognitive flexibility	• General processing speed and inhibitory function
Hopkins Verbal Learning Test-Revised (HVLT-R) [46]	• Included 3 learning trials, a delayed recall, and a recognition trial	• Verbal learning and memory
Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV) [47]	• Symbol search • Digit span • Letter number sequencing	• Graphomotor processing speed • Auditory attention • Working memory
Adaptive Rate Continuous Performance Test (AR-CPT)[e] [48]	• N/A	• Maintained attention and inhibitory control
Controlled Oral Word Association Test [49]	• FAS or CFL[f]	• Language function, processing speed, and verbal fluency
Animal Fluency [50]	• N/A	• Semantic verbal fluency
Card Sorting Task[g] [51]	• N/A	• Novel problem-solving and set-shifting
Grooved Pegboard Test [52]	• N/A	• Fine motor dexterity

[a]Unless otherwise indicated, assessments were done at baseline, 30 days, 90 days, and 1 year after enrollment.

[b]NIH: National Institutes of Health.

[c]The Montreal Cognitive Assessment and the NIH Crystalized measures were only obtained at baseline.

[d]N/A: not applicable.

[e]Some participants did the California Computerized Assessment Package (CALCAP) at baseline and then switched to Adaptive Rate Continuous Performance Test at follow-ups (30 did the Adaptive Rate Continuous Performance Test at baseline).

[f]CFL: Measure of spontaneous production of words beginning with 3 letters (FAS or CFL).

[g]The Wisconsin Card Sorting Task was collected as part of the COVID-19 supplement and was completed by 20 participants.

Neuroimaging Assessments

Participants who had no contraindications underwent MRI neuroimaging at all 4 time points. Prior to the first MRI, participants were provided with instructions on the 2 functional MRI tasks. For example, they were administered the 2-back test, which required participants to view alphabets in English (ie, a stimulus) on a computer screen and indicate by clicking a button on a device held in their hand whether the currently displayed letter was the same or different from the letter that appeared 2 preceding times ago (ie, 2-back). The MRI protocol used for all 4 timepoints of this study is shown in Table 3. The total time to complete all the sequences in the MRI protocol was approximately 65 minutes.

Table 3. Neuroimaging protocol used at all 4 timepoints for participants in the 30-Day Challenge study.

Sequence	Purpose	Measure	Anatomical coverage
T1[a] MRI[b]	To measure brain morphometric changes	Anatomical and tissue volumes and cortical thickness	Whole-brain
FLAIR[c] MRI	Identification of incidental brain pathologies	Pathology type and its volume	Whole-brain
MEGA-PRESS[d] Single-voxel MRS[e] [53]	Quantitation of changes in GABA[f] and other brain metabolites	Concentration of GABA, NAA[g], Cre[h], Cho[i], and m-Ins[j], and their ratios with Cre	Single voxel at the anterior mid-cingulate gyrus
2-back task-based fMRI[k]	Working memory	2-back alphabet letters	Whole-brain
Resting state fMRI	For assessment of changes in neural networks involved in the brain functional-segregation and functional-integration [54]	Functional connectivity measures for 5 major brain networks	Whole-brain
Diffusion tensor and kurtosis imaging [55]	To evaluate tissue microstructural changes	Diffusivities (axial, radial, and mean); fractional anisotropy (FA); free water fraction; kurtoses (axial, radial, and mean); kurtosis FA	Whole-brain
Whole-brain proton MR[l] spectroscopic imaging [56]	Quantitation of changes in NAA, Cre, Cho, and m-Ins metabolites	Concentration of NAA, Cre, Cho, and m-Ins, and their ratios with Cre	Whole-brain

[a]T1: spin-lattice relaxation time.

[b]MRI: magnetic resonance imaging.

[c]FLAIR: fluid attenuated inversion recovery.

[d]MEGA-PRESS: Meshcher-Garwood Point Resolved Spectroscopy.

[e]MRS: magnetic resonance spectroscopy.

[f]GABA: γ-aminobutyric acid.

[g]NAA: N-acetyl aspartate.

[h]Cre: total creatine.

[i]Cho: total choline.

[j]m-Ins: myo-inositol.

[k]fMRI: functional magnetic resonance imaging.

[l]MR: magnetic resonance.

The primary outcome from neuroimaging assessments is changes in brain inflammation from baseline to subsequent timepoints at the regional, tissue-type (ie, gray matter and white matter), and whole-brain levels. This outcome will be assessed from the quantitation of cerebral metabolite markers of neuroinflammation (ie, total choline and myo-inositol) and extracellular free water fraction (a measure determined from diffusion tensor imaging data). The above neuroinflammation markers will be quantified from the brain regions including the basal ganglia, thalamus, and frontal lobe that are primarily involved in HIV infection, alcohol use disorders, and their interaction [57-59]. Changes in brain function from functional magnetic resonance imaging and resting-state connectivity data will be measured for 5 major networks, that is, the default mode network, the dorsal attention network, the salience network, the limbic network, and the fronto-parietal control network.

Blood and Urine Testing

Blood samples were collected at each timepoint. Part of these were sent to a commercial laboratory for measurements of complete blood count with differential, comprehensive metabolic panel, hepatitis C antibody, HIV antibody (to confirm HIV status), HIV-1 RNA (only for people with HIV), and CD4 lymphocyte count (only for people with HIV). A dried blood spot was collected to measure phosphatidylethanol, an alcohol biomarker. We used these samples and performed measurements of cytokines, inflammatory biomarkers, adhesion molecules, and markers of intestinal permeability and microbial translocation. Additional blood samples are stored in a biorepository at the University of Louisville, where there is planned testing related to gut microbiome and gut-derived metabolites (metabolomics). Urine tests were performed at each timepoint for ethyl glucuronide (an alcohol biomarker), drug screen, and (after approximately 1 year) urine specific gravity. Urine-specific gravity was collected to ensure any potential changes in free water–based neuroinflammation (Table 4) were not solely due to brain rehydration after abstinence from alcohol.

Table 4. Summary of additional laboratory and clinical assessments conducted during the 30-Day Challenge study[a].

Domain	Specific measures
Blood	• All participants: complete blood count, comprehensive metabolic panel, phosphatidylethanol (alcohol biomarker), hepatitis C antibody (once), HCV[b] viral load (tested in 2/5 who were HCV antibody positive). • HIV-related: HIV antibody (for those who self-reported HIV-negative). HIV viral load and CD4 lymphocyte count (for HIV-positive). • Cytokines and biomarkers of inflammation: TNF-RII[c], TNFα[d], IL-6[e], IL-10[f], IFN-γ[g] NFL[h], sCD163[i], VCAM-1, ICAM-1, sCD14, CRP[j], and LBP[k]. • COVID-19[l]: RBD[m] IgG[n] and nucleocapsid IgG (in those RBD ab positive).
Urine	• Drug screen (cocaine, methamphetamine, THC[o], MDMA[p], opioid, oxycodone, PCP[q], barbiturates, and benzodiazepines). • Specific gravity. • Urine ethyl glucuronide (at each visit and to confirm self-reported abstinence with positive alcohol biosensor).
Stool	• Gut microbiome: 16S rRNA[r] gene sequencing, relative abundance, Firmicutes/Bacteroidota ratio (F/B)
Fibroscan	• Controlled attenuation parameter (fatty liver), liver stiffness measurement (fibrosis and stiffness).

[a]Unless otherwise indicated, assessments were done at each timepoint.

[b]HCV: hepatitis C virus.

[c]TNF-RII: tumor necrosis factor receptor 2.

[d]TNFα: tumor necrosis factor α.

[e]IL-6: interleukin 6.

[f]IL-10: interleukin 10.

[g]IFNγ: interferon-γ.

[h]NFL: neurofilament light chain.

[i]sCD163: soluble CD163.

[j]CRP: C-reactive protein.

[k]LBP: lipopolysaccharide-binding protein.

[l]COVID-19 antibodies were tested on all blood samples obtained after March 1, 2020.

[m]RBD: receptor-binding domain.

[n]IgG: immunoglobulin G.

[o]THC: tetrahydrocannabinol.

[p]MDMA: methylenedioxymethamphetamine.

[q]PCP: phencyclidine.

[r]16S rRNA: 16S ribosomal RNA (or 16S ribosomal ribonucleic acid).

Stool Samples for Gut Microbiome Assessments (Metagenomic Analysis)

During the first year of the study, the research team received additional funding to add a collection of stool samples for gut microbiome assessment and to measure additional blood biomarkers related to systemic inflammation (U01AA026225). These assessments, together with a food frequency questionnaire [60], were added after 17 participants had been enrolled, but 11 provided this information at a follow-up visit. Stool samples were sent to the University of Louisville for 16S rRNA gene sequencing processing, taxonomic evaluation, and determination of longitudinal changes in bacterial composition and diversity.

A Fibroscan liver test was obtained on all participants (Fibroscan 502 Touch, EchoSens, Paris, and France with the XL probe). The 2 scores were calculated using an average of 10 assessments, fat or controlled attenuation parameter score and fibrosis or liver stiffness measurement.

Alcohol Interventions

Contingency Management

The CM period began after the completion of the baseline assessment. Initially, we sought to maintain abstinence for up to 90 days using CM payments based on reports from the ankle biosensor. After approximately 10 participants enrolled, we modified the protocol to include CM payments and ankle monitoring for only 30 days because the participants did not like to wear the SCRAM, and because the costs for both participant payments and SCRAM monitoring would exceed the awarded budget. The payment protocol followed recommended CM methods as well as prior research using the SCRAM [12,15] and incorporated information obtained from focus groups prior to initiating the study [61]. Participants would receive money for each day they were abstinent and additional bonus payments for completing 7 days of abstinence in a row. Abstinence was determined on a daily basis through ankle biosensor reports with payment amounts increasing for consecutive days. Specifically, on the first day of abstinence, a

participant would receive US $5. For each consecutive day of abstinence thereafter (up to 7 in a row), the daily payout increased by US $1, meaning that after 7 days of abstinence, participants received a total of US $56 in daily payments plus a bonus of US $25 for maintaining abstinence for 7 consecutive days. Bonus payments increased by US $20 every 7 days up to a maximum weekly bonus of US $85. Participants received US $0 on any drinking day and the daily payment for abstinence restarted at US $5 after any drinking day. The maximum amount paid for maintaining abstinence throughout the CM period (30 days) was US $440. Participants were provided their payment as often as they wished but commonly chose to receive payments approximately once a week.

The alcohol biosensor provided data on transdermal alcohol concentration (TAC) assessed every 30 minutes. The specific TAC criteria used to differentiate a drinking day from a nondrinking day are based on several factors including peak TAC, absorption rate (rise rate), and fall rate (elimination rate). Different criteria can be used to minimize both false positives (for example, if alcohol is spilled on the device) and false negatives (for example, a participant may drink but not enough to reach a threshold level TAC). Our research team used the software (Transdermal Alcohol Sensor Data Macro [TASMAC] [62]) developed to identify drinking episodes on any given day (6 AM-6 AM), using more sensitive criteria than SCRAM Systems to detect drinking days (ie, peak TAC of at least 0.02 g/dL and either an absorption rate for the episode <0.05 g/dL per hour or an elimination rate for the episode <0.025 g/dL per hour [when peak <0.15 g/dL] and less than 0.035 g/dL per hour [when peak >0.15 g/dL]) [15]. If participants reported abstinence when alcohol was detected via the biosensor, the participants were given the opportunity to provide a negative in-person urine sample using dipstick ethyl glucuronide testing within 2 days of the SCRAM positive reading to maintain their CM payments.

Motivational Interview

During the 30-day visit, participants completed a single session of MI by videoconference using a computer within the clinical research setting. The MI was provided by a male, masters-level trained counselor at Brown University who had undergone over 20 hours of training in MI and had prior experience delivering MI. The MI session included a discussion of initial motivations for participating in the study, a review of the participant's drinking behavior prior to and during the 30-Day Challenge, a discussion of the perceived benefits of changing drinking, steps taken to reduce drinking successfully during CM, and creation of a change plan, which included discussion of future goals around drinking and brief problem-solving around meeting those goals. The MI assessments took approximately 30-45 minutes and were recorded and transcribed for further analysis. Every other week, a clinical supervisor with over 10 years of experience supervising MI counselors would listen to a session, if available, and provide feedback on MI counseling skills.

Follow-Up

Safety and Fidelity Monitoring

Several safety monitoring procedures were included in the protocol. A research assistant contacted participants on the first 3 days of CM to monitor for alcohol withdrawal symptoms. Research staff also collected self-reported data on drinking several times a week and helped with adjustments of the SCRAM monitor for comfort when needed. A study physician reviewed all laboratory results and participants were notified and referred to their physician for the occasional clinically significant laboratory finding. Potential adverse events were discussed with the research team and study principal investigators on a regular basis. During the first 3 years of the study, if research assistants noted anything that looked suspicious on neuroimaging, a radiologist was consulted, and participants were provided with information to discuss with their physician. For post–COVID-19 assessments, a clinical neuroradiologist reviewed every scan for clinically significant findings. No participants experienced serious alcohol withdrawal, and 1 participant was referred to their physician due to an abnormality found on brain MRI. To monitor fidelity to the research protocol, all research staff completed training and demonstrated the ability to do each of the study assessments. A senior research coordinator from our central coordinating team in Gainesville provided site monitoring in Miami 2-3 times per year.

Follow-Up Visits

Participants returned for in-person assessments at 30 days, 90 days, and 1 year. At each timepoint, updated alcohol consumption data were obtained, and the majority of the baseline measures were repeated (see Tables 2-4). The SCRAM monitor was removed at the 30-day visit for most participants (n=47), whereas 10 participants wore if for 90 days. Stool samples for gut microbiome assessments were obtained at baseline (n=40), 30 days (n=36), 90 days (n=36), and 1 year (n=23).

Procedures to Enhance Follow-Up

The study research staff communicated with participants regularly during the first 30 days (during the CM period) and scheduled follow-up visits in advance. Reminder calls were made to enhance adherence to follow-ups, which included additional participant incentives. The window period around each follow-up included at least 1 week before and 2 weeks after the scheduled appointment period.

Modifications After Study Initiation

Duration of CM

Prior to study initiation, the research team was encouraged by NIH peer grant reviewers and a scientific advisory board to extend the CM (and ankle biosensor monitoring) to 90 days, because it was not known whether any benefits of alcohol cessation or reduction would be fully achieved by 30 days or if a longer period would result in further improvements. A total of 10 of the initial participants chose to continue CM payments and ankle monitoring for 90 days, but many declined to continue monitoring and nearly every participant complained about some aspect of wearing the ankle biosensor. Also, extending the CM from 30 to 90 days added substantially to the cost of the study (participant payments and SCRAM monitoring fees), and with input from an external scientific advisory board, the research team modified the protocol to its original plan of CM payments only to 30 days.

COVID-19–Related Modifications

All in-person research activities were halted for 3 months starting in March 2020, with limited in-person data collection beginning again in June 2020, and MRI studies resuming in July 2020. Study procedures were modified to include remote data collection, and 3 participants provided follow-up data remotely during this period. An NIH COVID-19 funding supplement supported the collection of qualitative data from a subset of participants, additional post–COVID-19 study assessments for interested participants, pilot-testing of remote neurocognitive assessments, and the testing of participant blood samples for COVID-19 antibodies. The research team ultimately decided that remote neurocognitive assessments could not be directly compared to the same assessments conducted face-to-face, and thus neurocognitive and neuroimaging data are missing from some participants at timepoints early during the COVID-19 pandemic in 2020.

Planned Data Analysis

Overview

For our primary exposure variable (change in alcohol consumption), the primary assessment will focus on the average self-reported number of drinks per week during the 4-weeks prior to each timepoint (baseline, 30 days, 90 days, and 1 year), and in changes in self-reported number of drinks per week. Secondary metrics of drinking at each time point will include the number of heavy drinking days (previous 30 days), and categorical definitions of drinking status based on current National Institute on Alcohol Abuse and Alcoholism (NIAAA)–recommended drinking amounts (heavy, mild or moderate drinking, and no drinking). We plan to validate the self-reported measures with other measures of alcohol consumption, especially the SCRAM TAC readings (only collected for 7 days preintervention through 30 days for most participants).

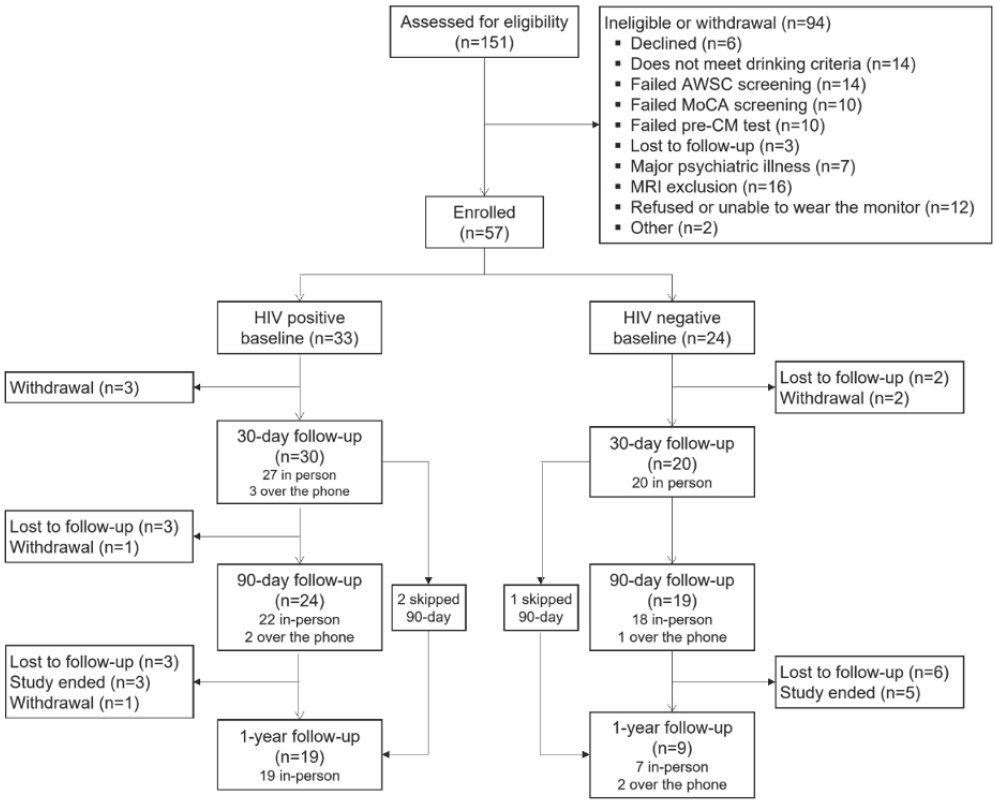
Cross-sectional analyses are planned to compare characteristics of persons at baseline (eg, people with HIV vs controls), and to determine the association of alcohol consumption and potential confounding variables with key outcomes including gut microbial dysbiosis, neurocognition, neuroinflammation, biomarkers of systemic inflammation, Fibroscan liver scores, and HIV-related outcomes.

Longitudinal analyses will assess the relationships between changes in drinking and changes in each of the main clinical outcomes. For each main outcome, we will consider potential confounding variables and whether those are fixed or changing over time. Baseline values will be controlled in the longitudinal analyses. Multiple testing will be adjusted by the false discovery rate approach [63]. Missing data that are considered to be missing at random will be handled by multiple imputation or EM algorithms. Missing data that are considered to be nonignorable missing or missing not at random will be handled with pattern-mixture models.

Sample Size

This study was originally approved to recruit 180 participants (140 people with HIV and 40 without HIV). However, the COVID-19 pandemic, availability of research staff and neuroimaging appointments, and reluctance of people to wear the ankle biosensor substantially impacted recruitment. Final enrollment numbers are detailed in Figure 2 and input from the scientific advisory board was obtained prior to cessation of enrollment and data collection.

Figure 2. Flowchart of participants evaluated and enrolled in the 30-Day Challenge study. AWSC: Alcohol Withdrawal Symptom Checklist; CM: contingency management; MoCA: Montreal Cognitive Assessment; MRI: magnetic resonance imaging.



Results

Recruitment of participants began in December 2017 and ended in October 2021. Data collection was completed in April 2022. Baseline characteristics of 57 participants who initiated the 30-day challenge, including persons with and without HIV, are presented in Table 5. Of the 57 participants who initiated the 30-Day Challenge, 88% completed the 30-day follow-up, 75% completed the 90-day follow-up, and 49% completed the 1-year follow-up.

Table 5. Participant baseline characteristics in the 30-Day Challenge study (N=57).

Characteristics	Total (N=57)	Persons with HIV (n=33)	Persons without HIV (n=24)
Gender, n (%)			
Man	36 (63)	19 (58)	17 (80)
Woman	20 (35)	13 (39)	7 (29)
Transgender	1 (2)	1 (3)	0
Age (years)			
Range	48-67	48-66	48-67
Mean (SD)	55.9 (4.6)	55.5 (4.3)	56.5 (5.1)
Race or ethnicity, n (%)			
Non-Hispanic, White	6 (10)	3 (9)	3 (12)
Non-Hispanic, Black	44 (77)	27 (82)	17 (71)
Hispanic	7 (12)	3 (9)	4 (17)
Marital status[a], n (%)			
No	47 (82)	25 (76)	22 (92)
Yes	10 (18)	8 (24)	2 (8)
Education, n (%)			
Less than high school	18 (32)	13 (39)	5 (21)
High school graduate or GED	19 (33)	6 (18)	13 (54)
More than high school	20 (35)	14 (42)	6 (25)
Homeless in the past 12 months, n (%)			
No	50 (88)	29 (88)	21 (88)
Yes	7 (12)	4 (12)	3 (12)
Employment, n (%)			
Not employed	11 (19)	6 (18)	6 (21)
Employed	13 (23)	4 (12)	9 (38)
Unable to work or disabled	33 (58)	23 (70)	10 (42)
Anxiety[b], n (%)			
None to minimal	29 (51)	15 (46)	14 (58)
Mild	17 (30)	11 (33)	6 (25)
Moderate	7 (12)	4 (12)	3 (12)
Severe	4 (7)	3 (9)	1 (4)
Depression[c], n (%)			
None or minimal	30 (53)	18 (55)	12 (50)
Mild	16 (29)	8 (24)	8 (33)
Moderate	5 (9)	4 (12)	1 (4)
Moderately severe or severe	6 (10)	3 (9)	3 (12)
Alcohol use disorder[d], n (%)			
No	5 (9)	4 (12)	1 (4)
Mild	6 (10)	3 (9)	3 (12)
Moderate	10 (18)	9 (27)	1 (4)
Severe	36 (63)	17 (51)	19 (79)

[a]Married or living with a long-term partner.

[b]Measured by the Generalized anxiety disorder 7-item scale (GAD-7); scores of 5-9=mild, 10-14=moderate, and ≥15=severe.

[c]Measured by the Patient Health Questionnaire-8; scores of 0-4=none or minimal, 5-9=mild, 10-14=moderate, and ≥15=moderately severe or severe.

[d]Measured by diagnostic and statistical manual-V (DSMV) Alcohol Assessment; scores of 0-1=no, 2-3=mild, 4-5=moderate, and ≥6=severe.

Discussion

Previous research on the impact of alcohol on HIV infection has been primarily observational, making it hard to determine whether outcomes associated with alcohol consumption are caused by the alcohol itself. We designed an experimental research study to obtain stronger evidence on whether changes, and specifically, reductions in drinking would correlate with changes in other behavioral or biological processes in the body. The study is unique from other research studies that examined changes in drinking and changes in clinical outcomes. Previous studies examining neurocognitive changes have primarily enrolled persons who were initiating alcohol treatment or included persons without HIV. Other strengths of the study include the simultaneous collection of a range of biological and behavioral data from several time points, including alcohol consumption, cognitive assessments, neuroimaging, Fibroscan liver test, blood biomarkers, and longitudinal changes in gut microbial dysbiosis.

Challenges in the study included recruitment, the complexity of research activity involving several universities and institutional review boards, staff turnover (and delays in replacing staff), participant willingness to wear the ankle biosensor, coordination of study procedures across several settings, and locations for persons who are often without their own transportation. Also, the number of assessments collected at each timepoint led to the decision to collect data over 2 days rather than 1, which limited our ability to enroll more participants. Future research teams should consider the tension between the value of having additional assessments versus the cost savings and convenience of collecting research study data over a single day (rather than spread across 2 days).

The COVID-19 pandemic, starting in early 2020, had a major impact on the study procedures and enrollment. A second clinical research setting was prepared to begin recruitment and data collection in early 2020, but by the time most research activities could be resumed after the COVID-19 pandemic, the study procedures had begun to wind down.

Another limitation of the study is that persons at high risk of alcohol withdrawal were excluded. The research team developed a protocol to enroll drinkers at higher risk of alcohol withdrawal but ultimately decided the risks and complexity outweighed the benefits.

Acknowledgments

We appreciate the contributions of the 30-Day Challenge Research Team: Francisco Aguila, Sandra Neptune, Jessica Orr, Fernando Moradel, Taylor LeCorgne, Christine Austin, Dushyantha Jayaweera, Karina Villalba, Teddy Salan, Margie Roach, Akemi Wijayabahu, Clara Morales, Babette Brumback, Seungjun Ahn, Mark Britton, Anthony Surace, Nadine Mastroleo, Ayla Durst, Tim Souza, Southern HIV & Alcohol Research Consortium (SHARC), SHARC Scientific Advisory Board, SHARC Community Advisory Board, Care Resource, and study participants. We received funding support from grants (U01AA020797, U24 AA022002, U24AA022003, and U01AA026225); Miami (CFAR P30AI073961); Providence or Boston (CFAR P30AI042853, T32 DA017629, and T32 AA025877); University of Florida; and Florida International University.

VLR was affiliated with Southern HIV and Alcohol Research Consortium, University of Florida, Gainesville, FL, United States at the time of the study and is currently affiliated with Edna Bennett Pierce Prevention Research Center, The Pennsylvania State University, University Park, PA, United States

Data Availability

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

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report from the National Institutes of Health.
[PDF File (Adobe PDF File), 177 KB - resprot_v13i1e53684_app1.pdf]

References

1. Alcohol facts and statistics. National Institute on Alcohol Abuse and Alcoholism. 2021. URL: https://www.niaaa.nih.gov/publications/brochures-and-fact-sheets/alcohol-facts-and-statistics [accessed 2024-01-27]
2. Williams EC, Hahn JA, Saitz R, Bryant K, Lira MC, Samet JH. Alcohol use and human immunodeficiency virus (HIV) infection: current knowledge, implications, and future directions. Alcohol Clin Exp Res 2016;40(10):2056-2072 [FREE Full text] [doi: 10.1111/acer.13204] [Medline: 27696523]

3. Edelman EJ, Williams EC, Marshall BDL. Addressing unhealthy alcohol use among people living with HIV: recent advances and research directions. Curr Opin Infect Dis 2018;31(1):1-7. [doi: 10.1097/QCO.0000000000000422] [Medline: 29176446]
4. Kahler CW, Liu T, Cioe PA, Bryant V, Pinkston MM, Kojic EM, et al. Direct and indirect effects of heavy alcohol use on clinical outcomes in a longitudinal study of HIV patients on ART. AIDS Behav 2017;21(7):1825-1835 [FREE Full text] [doi: 10.1007/s10461-016-1474-y] [Medline: 27392417]
5. Rothlind JC, Greenfield TM, Bruce AV, Meyerhoff DJ, Flenniken DL, Lindgren JA, et al. Heavy alcohol consumption in individuals with HIV infection: effects on neuropsychological performance. J Int Neuropsychol Soc 2005;11(1):70-83 [FREE Full text] [doi: 10.1017/S1355617705050095] [Medline: 15686610]
6. Monnig MA, Kahler CW, Lee H, Pantalone DW, Mayer KH, Cohen RA, et al. Effects of smoking and alcohol use on neurocognitive functioning in heavy drinking, HIV-positive men who have sex with men. AIDS Care 2016;28(3):300-305 [FREE Full text] [doi: 10.1080/09540121.2015.1093595] [Medline: 26444260]
7. Cohen RA, Gullett JM, Porges EC, Woods AJ, Lamb DG, Bryant VE, et al. Heavy alcohol use and age effects on HIV-associated neurocognitive function. Alcohol Clin Exp Res 2019;43(1):147-157 [FREE Full text] [doi: 10.1111/acer.13915] [Medline: 30371953]
8. Monnig MA. Immune activation and neuroinflammation in alcohol use and HIV infection: evidence for shared mechanisms. Am J Drug Alcohol Abuse 2017;43(1):7-23 [FREE Full text] [doi: 10.1080/00952990.2016.1211667] [Medline: 27532935]
9. Justice AC, McGinnis KA, Tate JP, Braithwaite RS, Bryant KJ, Cook RL, et al. Risk of mortality and physiologic injury evident with lower alcohol exposure among HIV infected compared with uninfected men. Drug Alcohol Depend 2016;161:95-103 [FREE Full text] [doi: 10.1016/j.drugalcdep.2016.01.017] [Medline: 26861883]
10. Table 15a. Persons living with diagnosed HIV infection, by year and selected characteristics, 2015-2019-United States. Centers for Disease Control and Prevention. 2021. URL: https://www.cdc.gov/hiv/library/reports/hiv-surveillance/vol-32/content/tables.html [accessed 2024-01-27]
11. Rich S, Klann E, Bryant V, Richards V, Wijayabahu A, Bryant K, et al. A review of potential microbiome-gut-brain axis mediated neurocognitive conditions in persons living with HIV. Brain Behav Immun Health 2020;9:100168 [FREE Full text] [doi: 10.1016/j.bbih.2020.100168] [Medline: 34589903]
12. Barnett NP, Celio MA, Tidey JW, Murphy JG, Colby SM, Swift RM. A preliminary randomized controlled trial of contingency management for alcohol use reduction using a transdermal alcohol sensor. Addiction 2017;112(6):1025-1035 [FREE Full text] [doi: 10.1111/add.13767] [Medline: 28107772]
13. Dougherty DM, Lake SL, Hill-Kapturczak N, Liang Y, Karns TE, Mullen J, et al. Using contingency management procedures to reduce at-risk drinking in heavy drinkers. Alcohol Clin Exp Res 2015;39(4):743-751 [FREE Full text] [doi: 10.1111/acer.12687] [Medline: 25833033]
14. Higgins ST, Petry NM. Contingency management. Incentives for sobriety. Alcohol Res Health 1999;23(2):122-127 [FREE Full text] [Medline: 10890806]
15. Barnett NP, Tidey J, Murphy JG, Swift R, Colby SM. Contingency management for alcohol use reduction: a pilot study using a transdermal alcohol sensor. Drug Alcohol Depend 2011;118(2-3):391-399 [FREE Full text] [doi: 10.1016/j.drugalcdep.2011.04.023] [Medline: 21665385]
16. Davis-Martin RE, Alessi SM, Boudreaux ED. Alcohol use disorder in the age of technology: a review of wearable biosensors in alcohol use disorder treatment. Front Psychiatry 2021;12:642813 [FREE Full text] [doi: 10.3389/fpsyt.2021.642813] [Medline: 33828497]
17. Alessi SM, Barnett NP, Petry NM. Experiences with SCRAMx alcohol monitoring technology in 100 alcohol treatment outpatients. Drug Alcohol Depend 2017;178:417-424 [FREE Full text] [doi: 10.1016/j.drugalcdep.2017.05.031] [Medline: 28709081]
18. Dougherty DM, Hill-Kapturczak N, Liang Y, Karns TE, Cates SE, Lake SL, et al. Use of continuous transdermal alcohol monitoring during a contingency management procedure to reduce excessive alcohol use. Drug Alcohol Depend 2014;142:301-306 [FREE Full text] [doi: 10.1016/j.drugalcdep.2014.06.039] [Medline: 25064019]
19. Dougherty DM, Karns TE, Mullen J, Liang Y, Lake SL, Roache JD, et al. Transdermal alcohol concentration data collected during a contingency management program to reduce at-risk drinking. Drug Alcohol Depend 2015;148:77-84 [FREE Full text] [doi: 10.1016/j.drugalcdep.2014.12.021] [Medline: 25582388]
20. Mathias CW, Hill-Kapturczak N, Karns-Wright TE, Mullen J, Roache JD, Fell JC, et al. Translating transdermal alcohol monitoring procedures for contingency management among adults recently arrested for DWI. Addict Behav 2018;83:56-63 [FREE Full text] [doi: 10.1016/j.addbeh.2018.01.033] [Medline: 29397211]
21. Miller WR, Rollnick S. Motivational Interviewing: Helping People Change, 3rd Edition. New York, NY: Guilford Press; 2013.
22. Morton K, Beauchamp M, Prothero A, Joyce L, Saunders L, Spencer-Bowdage S, et al. The effectiveness of motivational interviewing for health behaviour change in primary care settings: a systematic review. Health Psychol Rev 2015;9(2):205-223. [doi: 10.1080/17437199.2014.882006] [Medline: 26209209]
23. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005;53(4):695-699. [doi: 10.1111/j.1532-5415.2005.53221.x] [Medline: 15817019]

24. Pittman B, Gueorguieva R, Krupitsky E, Rudenko AA, Flannery BA, Krystal JH. Multidimensionality of the alcohol withdrawal symptom checklist: a factor analysis of the alcohol withdrawal symptom checklist and CIWA-Ar. Alcohol Clin Exp Res 2007;31(4):612-618. [doi: 10.1111/j.1530-0277.2007.00345.x] [Medline: 17374040]
25. Sobell LC, Sobell MB. Timeline follow-back. In: Litten RZ, Allen JP, editors. Measuring Alcohol Consumption: Psychosocial and Biochemical Methods. Totowa, NJ: Humana Press; 1992:41-72.
26. Ware J, Kosinski M, Keller SD. A 12-item short-form health survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996;34(3):220-233. [doi: 10.1097/00005650-199603000-00003] [Medline: 8628042]
27. Amireault S, Godin G. The Godin-Shephard leisure-time physical activity questionnaire: validity evidence supporting its use for classifying healthy adults into active and insufficiently active categories. Percept Mot Skills 2015;120(2):604-622. [doi: 10.2466/03.27.PMS.120v19x7] [Medline: 25799030]
28. Smola S, Justice AC, Wagner J, Rabeneck L, Weissman S, Rodriguez-Barradas M, VACS 3 Project Team. Veterans Aging Cohort three-site study (VACS 3): overview and description. J Clin Epidemiol 2001;54(Suppl 1):S61-S76. [doi: 10.1016/s0895-4356(01)00448-6] [Medline: 11750212]
29. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28(2):193-213. [doi: 10.1016/0165-1781(89)90047-4] [Medline: 2748771]
30. Cleeland CS, Ryan KM. Pain assessment: global use of the brief pain inventory. Ann Acad Med Singap 1994;23(2):129-138. [Medline: 8080219]
31. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006;166(10):1092-1097 [FREE Full text] [doi: 10.1001/archinte.166.10.1092] [Medline: 16717171]
32. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001;16(9):606-613 [FREE Full text] [doi: 10.1046/j.1525-1497.2001.016009606.x] [Medline: 11556941]
33. Prins A, Bovin MJ, Smolenski DJ, Marx BP, Kimerling R, Jenkins-Guarnieri MA, et al. The Primary Care PTSD screen for DSM-5 (PC-PTSD-5): development and evaluation within a veteran primary care sample. J Gen Intern Med 2016;31(10):1206-1211 [FREE Full text] [doi: 10.1007/s11606-016-3703-5] [Medline: 27170304]
34. Kaufman EA, Xia M, Fosco G, Yaptangco M, Skidmore CR, Crowell SE. The Difficulties in Emotion Regulation Scale Short Form (DERS-SF): validation and replication in adolescent and adult samples. J Psychopathol Behav Assess 2015;38(3):443-455. [doi: 10.1007/s10862-015-9529-3]
35. Pennebaker JW, Susman JR. Disclosure of traumas and psychosomatic processes. Soc Sci Med 1988;26(3):327-332. [doi: 10.1016/0277-9536(88)90397-8] [Medline: 3279521]
36. Stewart AL, Ware JE. Measuring Functioning and Well-Being: The Medical Outcomes Study Approach. Durham, North Carolina: Duke University Press; 1992.
37. Bradley KA, DeBenedetti AF, Volk RJ, Williams EC, Frank D, Kivlahan DR. AUDIT-C as a brief screen for alcohol misuse in primary care. Alcohol Clin Exp Res 2007;31(7):1208-1217. [doi: 10.1111/j.1530-0277.2007.00403.x] [Medline: 17451397]
38. Diagnostic And Statistical Manual Of Mental Disorders, Fifth Edition. Washington, DC: American Psychiatric Association; 2013.
39. Gilson KM, Bryant C, Bei B, Komiti A, Jackson H, Judd F. Validation of the Drinking Motives Questionnaire (DMQ) in older adults. Addict Behav 2013;38(5):2196-2202. [doi: 10.1016/j.addbeh.2013.01.021] [Medline: 23454884]
40. Medical Monitoring Project (MMP). Centers for Disease Control and Prevention. URL: https://www.cdc.gov/hiv/statistics/systems/mmp/resources.html#Questionnaires [accessed 2024-01-27]
41. Kellogg SH, McHugh PF, Bell K, Schluger JH, Schluger RP, LaForge KS, et al. The Kreek-McHugh-Schluger-Kellogg scale: a new, rapid method for quantifying substance abuse and its possible applications. Drug Alcohol Depend 2003;69(2):137-150. [doi: 10.1016/s0376-8716(02)00308-3] [Medline: 12609695]
42. Weinfurt KP, Lin L, Bruner DW, Cyranowski JM, Dombeck CB, Hahn EA, et al. Development and initial validation of the PROMIS(®) sexual function and satisfaction measures version 2.0. J Sex Med 2015;12(9):1961-1974. [doi: 10.1111/jsm.12966] [Medline: 26346418]
43. Weintraub S, Dikmen SS, Heaton RK, Tulsky DS, Zelazo PD, Bauer PJ, et al. Cognition assessment using the NIH toolbox. Neurology 2013;80(11 Suppl 3):S54-S64 [FREE Full text] [doi: 10.1212/WNL.0b013e3182872ded] [Medline: 23479546]
44. Army Individual Test Battery. Manual of Directions and Scoring. Washington, DC: War Department, Adjunct General's Office; 1944.
45. Stroop JR. Studies of interference in serial verbal reactions. J Exp Psychol 1935;18(6):643-662. [doi: 10.1037/h0054651]
46. Benedict RH, Schretlen D, Groninger L, Brandt J. Hopkins verbal learning test—revised: normative data and analysis of inter-form and test-retest reliability. Clin Neuropsychol 1998;12(1):43-55. [doi: 10.1076/clin.12.1.43.1726]
47. Wechsler D. Wechsler Adult Intelligence Scale--Fourth Edition (WAIS-IV). Washington, DC: American Psychological Association; 2012.
48. Cohen RA, Sparling-Cohen YA, O'Donnell BF. The Neuropsychology of Attention. Boston, MA: Springer; 1993.
49. Lezak MD. Neuropsychological Assessment, 3rd Edition. New York: Oxford University Press; 1995.
50. Henry JD, Crawford JR. A meta-analytic review of verbal fluency performance following focal cortical lesions. Neuropsychology 2004;18(2):284-295. [doi: 10.1037/0894-4105.18.2.284] [Medline: 15099151]

51. Monchi O, Petrides M, Petre V, Worsley K, Dagher A. Wisconsin card sorting revisited: distinct neural circuits participating in different stages of the task identified by event-related functional magnetic resonance imaging. J Neurosci 2001;21(19):7733-7741 [FREE Full text] [doi: 10.1523/JNEUROSCI.21-19-07733.2001] [Medline: 11567063]
52. Matthews CG, Klove K. Instruction Manual for the Adult Neuropsychology Test Battery. Madison, WI: University of Wisconsin Medical School; 1964.
53. Mescher M, Merkle H, Kirsch J, Garwood M, Gruetter R. Simultaneous in vivo spectral editing and water suppression. NMR Biomed 1998;11(6):266-272. [doi: 10.1002/(sici)1099-1492(199810)11:6<266::aid-nbm530>3.0.co;2-j] [Medline: 9802468]
54. Lv H, Wang Z, Tong E, Williams LM, Zaharchuk G, Zeineh M, et al. Resting-state functional MRI: everything that nonexperts have always wanted to know. AJNR Am J Neuroradiol 2018;39(8):1390-1399 [FREE Full text] [doi: 10.3174/ajnr.A5527] [Medline: 29348136]
55. Jensen JH, Helpern JA, Ramani A, Lu H, Kaczynski K. Diffusional kurtosis imaging: the quantification of non-gaussian water diffusion by means of magnetic resonance imaging. Magn Reson Med 2005;53(6):1432-1440 [FREE Full text] [doi: 10.1002/mrm.20508] [Medline: 15906300]
56. Maudsley AA, Domenig C, Govind V, Darkazanli A, Studholme C, Arheart K, et al. Mapping of brain metabolite distributions by volumetric proton MR Spectroscopic Imaging (MRSI). Magn Reson Med 2009;61(3):548-559 [FREE Full text] [doi: 10.1002/mrm.21875] [Medline: 19111009]
57. Nath A. Eradication of human immunodeficiency virus from brain reservoirs. J Neurovirol 2015;21(3):227-234 [FREE Full text] [doi: 10.1007/s13365-014-0291-1] [Medline: 25366659]
58. Zahr NM, Pfefferbaum A, Sullivan EV. Perspectives on fronto-fugal circuitry from human imaging of alcohol use disorders. Neuropharmacology 2017;122:189-200 [FREE Full text] [doi: 10.1016/j.neuropharm.2017.01.018] [Medline: 28118989]
59. Adeli E, Zahr NM, Pfefferbaum A, Sullivan EV, Pohl KM. Novel machine learning identifies brain patterns distinguishing diagnostic membership of human immunodeficiency virus, alcoholism, and their comorbidity of individuals. Biol Psychiatry Cogn Neurosci Neuroimaging 2019;4(6):589-599 [FREE Full text] [doi: 10.1016/j.bpsc.2019.02.003] [Medline: 30982583]
60. Brunner E, Stallone D, Juneja M, Bingham S, Marmot M. Dietary assessment in Whitehall II: comparison of 7 d diet diary and food-frequency questionnaire and validity against biomarkers. Br J Nutr 2001;86(3):405-414 [FREE Full text] [doi: 10.1079/bjn2001414] [Medline: 11570993]
61. Villalba K, Cook C, Dévieux JG, Ibanez GE, Oghogho E, Neira C, et al. Facilitators and barriers to a contingency management alcohol intervention involving a transdermal alcohol sensor. Heliyon 2020;6(3):e03612 [FREE Full text] [doi: 10.1016/j.heliyon.2020.e03612] [Medline: 32258468]
62. Barnett NP, Souza T, Glynn TR, Luczak SE, Swift R, Rosen G. The Transdermal Alcohol Sensor Macro (TASMAC): a rapid data processing tool for use with the SCRAMx alcohol sensor. In: 726. Alcoholism: Clinical & Experimental Research. 2015 Presented at: Research Society on Alcohol (RSA) Annual Convention; June 2015; San Antonio, TX p. 39 URL: https://doi.org/10.1111/acer.12741 Available at URL: https://sites.brown.edu/tasmac/
63. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc Ser B Methodol 2018;57(1):289-300. [doi: 10.1111/j.2517-6161.1995.tb02031.x]

Abbreviations

AWSC: Alcohol Withdrawal Symptom Checklist
BVMT-R: Brief Visuospatial Memory Test-Revised
CALCAP: California Computerized Assessment Package
CM: contingency management
FIU: Florida International University
MI: motivational interviewing
MoCA: Montreal Cognitive Assessment
MRI: magnetic resonance imaging
NIAAA: National Institute on Alcohol Abuse and Alcoholism
NIH: National Institutes of Health
SCRAM CAM: Secure Continuous Remote Alcohol Monitor Continuous Alcohol Monitoring
TAC: transdermal alcohol concentration
TASMAC: Transdermal Alcohol Sensor Data Macro
TLFB: 30-Day Drug and Alcohol Timeline Followback
UF: University of Florida
UM: University of Miami
WAIS-IV: Wechsler Adult Intelligence Scale-Fourth Edition

Edited by A Mavragani; submitted 18.10.23; this is a non–peer-reviewed article;accepted 09.11.23; published 02.04.24.

Please cite as:
Cook RL, Richards VL, Gullett JM, Lerner BDG, Zhou Z, Porges EC, Wang Y, Kahler CW, Barnett NP, Li Z, Pallikkuth S, Thomas E, Rodriguez A, Bryant KJ, Ghare S, Barve S, Govind V, Dévieux JG, Cohen RA, The 30-Day Challenge Research Team
Experimentally Induced Reductions in Alcohol Consumption and Brain, Cognitive, and Clinical Outcomes in Older Persons With and Those Without HIV Infection (30-Day Challenge Study): Protocol for a Nonrandomized Clinical Trial
JMIR Res Protoc 2024;13:e53684
URL: https://www.researchprotocols.org/2024/1/e53684
doi:10.2196/53684
PMID:38564243

Protocol

Personalized Management of Fatigue in Individuals With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Long COVID Using a Smart Digital mHealth Solution: Protocol for a Participatory Design Approach

Enrique Dorronzoro-Zubiete[1*], PhD; Jesús Castro-Marrero[2*], PhD; Jorge Ropero[1], PhD; José Luis Sevillano-Ramos[3], PhD; María Dolores Hernández[1], PhD; Ramon Sanmartin Sentañes[2,4], MD, PhD; Jose Alegre-Martin[2,4], MD, PhD; Patricia Launois-Obregón[5,6], MD, PhD; Isabel Martin-Garrido[7], MD, PhD; Asuncion Luque Budia[8], PhD; Juan R Lacalle-Remigio[9], MD, PhD; Luis Béjar Prado[9], PhD; Octavio Rivera Romero[1], PhD

[1]Electronic Technology Department, Universidad de Sevilla, Sevilla, Spain

[2]Research Unit in ME/CFS and Long COVID, Division of Rheumatology, Vall d'Hebron Research Institute, Universitat Autònoma de Barcelona, Barcelona, Spain

[3]Architecture and Technology Department, Universidad de Sevilla, Sevilla, Spain

[4]Division of Rheumatology, Vall d'Hebron University Hospital, Universitat Autònoma de Barcelona, Barcelona, Spain

[5]Physical Medicine and Rehabilitation Department, Vall d'Hebron University Hospital, Barcelona, Spain

[6]Department of Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain

[7]Unidad de Enfermedades Autoinmunes y Minoritarias, Servicio de Medicina Interna, Virgen del Rocio University Hospital, Sevilla, Spain

[8]Salud Mental, Unidad de Gestión Clínica, Virgen del Rocio University Hospital, Sevilla, Spain

[9]Preventive Medicine and Public Health Department, Universidad de Sevilla, Sevilla, Spain

[*]these authors contributed equally

Corresponding Author:
Octavio Rivera Romero, PhD
Electronic Technology Department
Universidad de Sevilla
avda. Reina Mercedes s/n,
ETSII Informática
Sevilla, 41012
Spain
Phone: 34 954554325
Email: orivera@us.es

Abstract

Background: Fatigue is the most common symptom in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and long COVID, impacting patients' quality of life; however, there is currently a lack of evidence-based context-aware tools for fatigue self-management in these populations.

Objective: This study aimed to (1) address fatigue in ME/CFS and long COVID through the development of digital mobile health solutions for self-management, (2) predict perceived fatigue severity using real-time data, and (3) assess the feasibility and potential benefits of personalized digital mobile health solutions.

Methods: The MyFatigue project adopts a patient-centered approach within the participatory health informatics domain. Patient representatives will be actively involved in decision-making processes. This study combines inductive and deductive research approaches, using qualitative studies to generate new knowledge and quantitative methods to test hypotheses regarding the relationship between factors like physical activity, sleep behaviors, and perceived fatigue in ME/CFS and long COVID. Co-design methods will be used to develop a personalized digital solution for fatigue self-management based on the generated knowledge. Finally, a pilot study will evaluate the feasibility, acceptance, and potential benefits of the digital health solution.

Results: The MyFatigue project opened to enrollment in November 2023. Initial results are expected to be published by the end of 2024.

Conclusions: This study protocol holds the potential to expand understanding, create personalized self-management approaches, engage stakeholders, and ultimately improve the well-being of individuals with ME/CFS and long COVID.

International Registered Report Identifier (IRRID): PRR1-10.2196/50157

(JMIR Res Protoc 2024;13:e50157) doi:10.2196/50157

KEYWORDS

acceptability; myalgic encephalomyelitis/chronic fatigue syndrome; long COVID; mHealth; fatigue; physical activity; lifestyle health; personalized self-management; user-centered design

Introduction

Overview

Fatigue is recognized as one of the most common symptoms in individuals with chronic postviral conditions. It is defined as the early onset of tiredness after starting an activity, a feeling of exhaustion or difficulty in carrying out a physical (physical fatigue) or cognitive (cognitive fatigue) task, which is not recovered after a rest [1]. It is relevant to highlight several issues included in this definition. First, fatigue is a consequence of carrying out an activity, also referred to in the scientific literature as "postexertional malaise." Furthermore, patients experience two different types of fatigue—physical and cognitive. Finally, fatigue is essentially a subjective condition, encompassing feelings or difficulties. Thus, it is linked to perceived fatigue, which is defined as the subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities [1]. Myalgic encephalomyelitis, also known as chronic fatigue syndrome (ME/CFS) and post–COVID-19 syndrome or postacute sequelae of SARS-CoV-2 infection (PASC), also known as long COVID, are multisystem postviral conditions where chronic fatigue is present as the most common disabling symptom. ME/CFS is a complex, multisystem, and profoundly debilitating neuroimmune condition. Although individuals with ME/CFS experience several symptoms, fatigue is the most disabling one [1].

Some symptoms associated with the SARS-CoV-2 infection may persist for a significant period. Long COVID or PASC is an umbrella term for the wide range of health consequences that are present 4 or more weeks after SARS-CoV-2 infection. Most cases infected with SARS-CoV-2 are asymptomatic or have mild acute symptoms with low rates of hospitalization and death. However, some of them, including those with mild or asymptomatic infection, develop postacute manifestations following SARS-CoV-2 infection. There are many symptoms presented in PASC, such as sleep difficulties and anxiety or depression [2], with fatigue being the most frequently reported.

The extent of fatigue in patients' lives is huge, affecting their physical, cognitive, and socioeconomic conditions [3]. It affects several aspects of life, including physical and cognitive activity, decreasing adherence to treatments and recommendations, and affecting the ability to function or work. In addition, it is normally misunderstood by the social environment, causing isolation and frustration. Therefore, fatigue strongly affects patients' well-being and significantly reduces their quality of life.

The effective fatigue management of ME/CFS and long COVID would minimize the consequences of the disease, significantly impacting patients' and caregivers' quality of life. The clinical evolution of ME/CFS and long COVID is still unpredictable. Recommendations and strategies should consider the individual's physical and cognitive capabilities and other factors, such as daily perceived fatigue fluctuations, meteorological condition, level of physical activity, caffeine and alcohol consumption, sleep quality, mood, stress, and treatments. Many of those factors present a wide daily variability, and therefore, personalization must be driven by real-time data collected in a patient's real-life setting. An effective personalization strategy may help to increase compliance with management recommendations and strategies.

Digital health allows the implementation of interesting functionalities for the management of long-term conditions, such as tracking activities, remote monitoring of an individual's condition, real-time feedback, just-in-time recommendations, communication, educational content, and reminders. Digital health solutions have proven to be effective in the management of some chronic diseases, such as diabetes and cancer. Therefore, they may be effective as a self-management tool for individuals with ME/CFS or long COVID. Several recent studies have explored the effectiveness of internet-based cognitive behavioral therapies in fatigue management among individuals with ME/CFS [4,5]. Despite the potential benefits of digital health solutions for the self-management of ME/CFS and long COVID, there are no evidence-based, personalized, and context-aware solutions designed specifically for supporting patients with ME/CFS or long COVID in fatigue self-management.

Current Status

Despite the promising benefits of using digital health for the self-management of chronic diseases, there is a lack of studies exploring the specific needs and preferences of individuals with ME/CFS or long COVID haulers regarding digital fatigue self-management. Only 1 study examined how adolescents use the internet to cope with ME/CFS [6]. Moreover, there is a lack of evidence on how digital health may benefit fatigue self-management in this group of patients.

Remote monitoring in real-time is a relevant functionality to personalize fatigue self-management in ME/CFS and long COVID. Several studies that remotely monitor the health conditions of patients with ME/CFS in real-time using mobile health (mHealth) devices have been recently published. Worm-Smeitink et al [5] conducted an ecological momentary assessment (EMA) study aimed to explore the associations

between cognitions, physical and cognitive activity, social behaviors and their effects, as well as fatigue in ME/CFS. King et al [7] used an accelerometer device to objectively measure the physical activity of patients with ME/CFS, intending to classify them into different categories. Palombo et al [8] used a commercial inertial measurement unit to develop a sensor-based method to measure an indicator of ME/CFS disease severity. Josev et al [9] used an actigraphy device to measure the sleep quality of the pediatric ME/CFS population. Russell et al [10] examined the relationship between subjective and actigraphy-defined sleep and next-day fatigue in ME/CFS. However, to our knowledge, there are no studies examining the impact of a combination of contextual factors, physical activity level, sleep quality, and mood on the fatigue severity in ME/CFS and long COVID. Moreover, there are no studies focused on analyzing the similarities and differences in fatigue between ME/CFS and long COVID. Analyzing these contextual data and their relationships with perceived fatigue severity using artificial intelligence (AI) models may enable the definition of successful data-driven personalization strategies for fatigue self-management in ME/CFS and long COVID, leading to an increase in patients' adoption and adherence.

Finally, AI models developed in ME/CFS and long COVID are focused on diagnosis, biomarkers, differentiating from other diseases, prevalence estimation, and association with anxiety or depression symptoms [11,12]. Therefore, there are no AI models to estimate fatigue severity based on contextual and behavioral factors in ME/CFS and long COVID.

Hypothesis

Although the use of digital solutions to self-manage fatigue among people with chronic conditions, such as multiple sclerosis, has been previously studied, the wide range of potential symptoms and their unpredictability and variability in ME/CFS and long COVID define a completely different scenario, posing new challenges to be solved. In addition, the similarities and differences between fatigue in ME/CFS and long COVID are still unknown, and there is a need for new research aimed at discovering them and translating them into actionable recommendations to manage fatigue in long COVID. Defining effective fatigue self-management in ME/CFS and long COVID is crucial to increasing patients' adherence to treatment, reducing mental health problems, and improving individual's well-being and quality of life. The MyFatigue project will progress beyond the state of the art on ME/CFS and long COVID fatigue self-management, providing new insights and actionable recommendations to fill in the gap.

We hypothesize that the use of a personalized and context-aware digital health solution supporting individuals with ME/CFS or long COVID in fatigue self-management increases their self-efficacy, reduces the risk of having mental health problems, and improves their quality of life. We also hypothesize that fatigue in ME/CFS and long COVID presents similar patterns regarding contextual factors.

The MyFatigue project will generate new knowledge on the relevance and relationships of factors impacting perceived fatigue severity in ME/CFS and long COVID, analyzing similarities and differences between both study populations. MyFatigue will also explore the specific needs and preferences of individuals with ME/CFS and long COVID haulers for digital health solutions, supporting fatigue self-management. Based on this knowledge, a personalized and context-aware solution supporting patients in their fatigue self-management will be co-designed, and its acceptance and potential benefits will be assessed.

Aims and Research Questions

The general aim of the MyFatigue project is to contribute to the understanding of fatigue in ME/CFS and long COVID, a modern medical challenge still unresolved, and to find opportunities for designing digital health solutions and supporting self-management to improve individuals' quality of life. The specific aims of this study are as follows:

1. To identify attitudes of patients with ME/CFS and long COVID haulers toward the use of digital health solutions, supporting them in fatigue self-management and their specific needs and preferences
2. To determine the current digital health solutions being used by individuals with ME/CFS and long COVID haulers in their self-management
3. To analyze the relevance of contextual factors and behaviors in the perceived fatigue severity, their daily fluctuations, and their relationships
4. To identify similarities and differences in fatigue symptoms between ME/CFS and long COVID
5. To define patient clusters based on fatigue patterns and to identify relevant factors impacting each cluster
6. To predict the perceived fatigue severity based on real-time data on contextual factors, behaviors, and individuals' conditions collected in real-life settings
7. To determine the feasibility, acceptance, and potential benefits of the use of a personalized and context-aware digital health solution for fatigue self-management in ME/CFS and long COVID

Participants and Methods

Ethical Considerations

Ethical approval will be sought before beginning the recruitment of participants. Written informed consent will be sought from all study participants before the initiation of participant-related study activities, such as the implementation and evaluation of the personalized digital mHealth-solution–based management intervention.

Participant Recruitment and Study Design

Health care institutions, such as Hospital Universitario Virgen del Rocío and Hospital Universitari Vall d'Hebron, are involved in the MyFatigue project. The proposed studies will be conducted in both institutions. Individuals with ME/CFS and long COVID haulers will be invited to participate in these studies. For all the proposed studies, a sample of individuals with ME/CFS and another sample of individuals with long COVID haulers will be recruited in each hospital for each study. In the proposed study, to reach specific aims 3 and 4, a supplementary sample of control healthy individuals, exhibiting

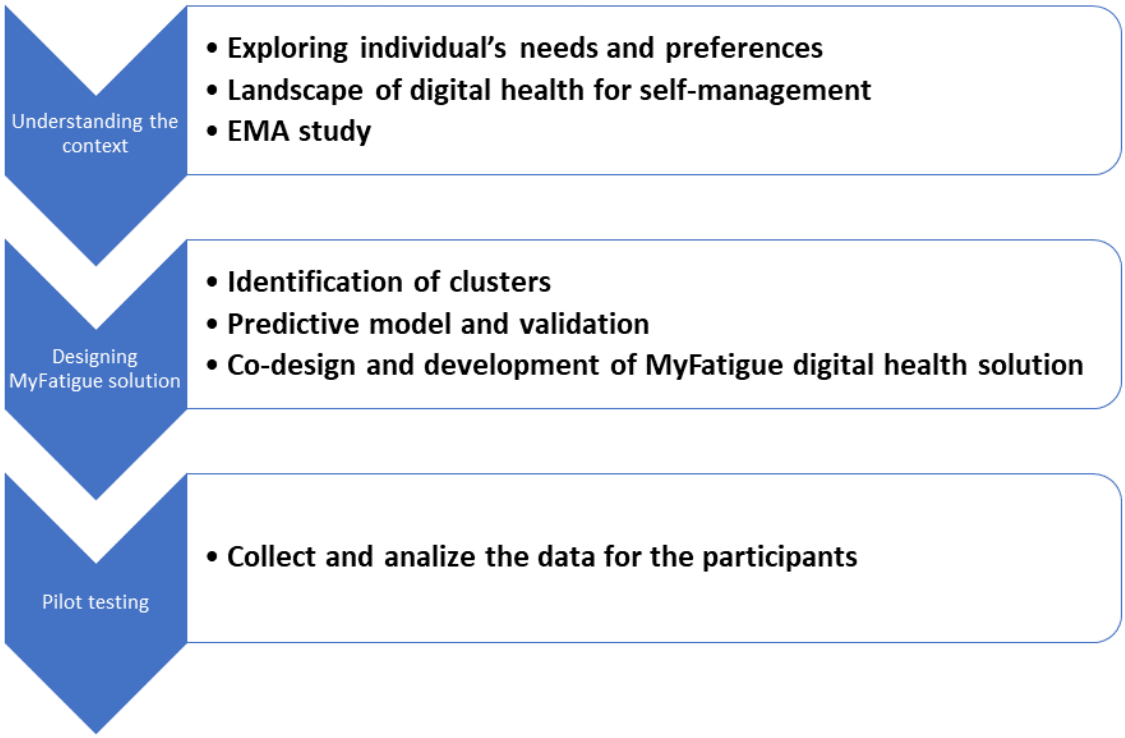
similar sedentary behaviors to those with ME/CFS and long COVID, will be recruited in each site.

Eligibility Criteria

Potential participants should have been diagnosed with ME/CFS (based on the 1994 Fukuda case definition) or long COVID (based on the 2021 World Health Organization clinical case definition), be older than 18 years at the time of recruiting, have none to moderate physical disability, and have communication ability in Spanish. Several factors, such as age and gender, will be considered to ensure a rich sample for analysis. Project objectives, risks, benefits, and their rights as research participants will be explained to potential participants. An information sheet will be provided to the participants, and they will sign an informed consent, indicating that they will be able to withdraw from the study at any time**.**

The work plan and tasks for the MyFatigue project are presented in Figure 1.

Figure 1. MyFatigue work plan. EMA: ecological momentary assessment.



Understanding the Context

Exploring Individuals' Needs and Preferences

A mixed methods study design using qualitative and quantitative methods will be conducted to reach the first objective. Individual semistructured interviews will be carried out with each sample of participants. Once participants sign the informed consent, a face-to-face semistructured interview will be conducted, with a remote interview when an in-person meeting is not possible. An experienced interviewer will lead the interview following the script defined in the protocol. Initially, the defined questions will be inquired during the session. Interesting topics not initially included will be identified and added iteratively to be used during the following sessions. In the same way, irrelevant questions will be removed as the study progresses. All sessions will be recorded, digitally transcribed, and anonymized. Transcripts will be coded, and thematic analysis will be performed in an iterative process. Each participant's comment will be categorized as barriers or facilitators. Further refinement will take place by merging and removing redundant themes until consensus is reached.

Once data analysis ends, the findings will be discussed among all team members participating in the task. A deeper analysis of similarities and differences between findings found in ME/CFS and long COVID will be performed. We will also compare these findings with the findings in the study that is being conducted on multiple sclerosis. Once consensus is reached, we will validate the findings involving some of the participants in the interviews. We will apply a gender perspective in recruitment, data analysis, interpretation of findings, and validation of results.

Landscape of Digital Health for Self-Management

A patient survey will be designed by a group of experts involving health care professionals and computer engineers. The survey will aim to analyze the technological solutions that individuals with ME/CFS and long COVID haulers are currently using to self-manage their conditions, especially fatigue. The questionnaire will include sociodemographic variables, disease-related data, and respondents' general opinions on digital health solutions. It will also include questions about digital literacy and access, the advantages and disadvantages of using technology for fatigue management, perceived barriers in the use of these devices, personal data management, and general functionalities.

Anonymized data will be collected, complying with the current regulations. Web-based questionnaires will be tested on a group of individuals with ME/CFS or long COVID and on professionals to optimize format and wording and to assess their usability before their large-scale administration. Discrepancies among reviewers' comments will be solved by consensus, and a final version of the questionnaire will be developed including the reviewers' suggestions. Participation will be voluntary and anonymous, and duplicate responses will be avoided. Data collected through the questionnaires will be analyzed, and descriptive statistics will be calculated using frequencies and cross-tabulations by key demographic and disease-related variables. Age and gender will be taken into consideration during the analysis. We expect the participation of at least 20 individuals per group (ME/CFS and long COVID).

EMA Study

The proposed quantitative study is based on EMA and continuous data collection using wearable devices (eg, Actigraphy GT3X). The research team has developed a mobile app that enables the remote monitoring of individuals' conditions through a questionnaire. The MyFatigue app will be developed to perform the EMA study. The app will allow participants to self-report fatigue severity during periods when they are not wearing the device required to distinguish low levels of activity from noncompliance, among other factors. The proposed study will begin with one-to-one introductory sessions during which the app and wearable device will be provided. They will be instructed about its use, and their demographic and relevant clinical data will be collected. Finally, participants will complete a set of standard questionnaires to define a baseline. The questionnaires to be filled include the Chalder Fatigue Questionnaire (CFQ), the Modified Fatigue Impact Scale (MFIS-5), the eHealth scale, the Satisfaction with Life Scale (SWLS), The Pittsburgh Sleep Quality Index (PSQI), and the Hospital Anxiety and Depression Scale (HADS). Participants will wear the device and self-report using the app for 14 consecutive days. They will be asked to carry out their regular daytime activities and to keep their usual sleep or wake schedules. The study will be conducted in 4 waves, collecting data in different seasons and avoiding insufficient data due to device failure or losses. We estimate that 120 individuals will participate in each wave. Participants will report the perceived fatigue severity using this app, by responding to a single-item questionnaire. At least, 3 self-reports per day (morning, afternoon, and evening) will be carried out, prompted by the app. Participants will be able to set reminders, postpone them, and silence them, if necessary. Moreover, they can carry out additional self-reports if they feel fatigued. Additionally, the app will collect data on potential factors like temperature, meteorological conditions, mental activity level, and mood.

Physical activity and sleep data will be continuously recorded using an actigraphy device worn on the dominant wrist. The device will be set to record in 1-minute epochs using zero crossing mode. Actigraphy data will be analyzed using a specific software, such as ActiLife. Raw data will be converted to counts, which will be analyzed to identify and calculate different physical activity variables. The intensity and absence of activity will be classified according to Fjeldstad et al [13] and based on the following cut-off points: sedentary (<1.5 metabolic equivalent of task [MET]: 0-199 counts per minute [CPs]); light (1.5-2.99 MET: 200-1952 CPs); moderate (3-5.99 MET: 1953-5724 CPs); hard (6.0-8.99 MET: 5725-9498 CPs); and very hard (>9.0 MET: > 9498 CPs). Other data, such as light conditions, environmental temperature, systolic blood pressure and diastolic blood pressure, heart rate, and heart rate variability could be collected if selected devices and budget allow it.

Descriptive statistics will be calculated, and Pearson correlation analysis will be performed among physical activity, sleep variables, and fatigue severity. Similarities and differences between ME/CFS and long COVID will be identified. Once the study period ends, a new in-person session will be conducted in which participants will return the device and fill out a questionnaire to identify any barriers they found in the use of the digital health solutions used in the EMA study. As a result of this task, a report on the statistical analysis findings will be delivered.

Designing the MyFatigue Digital mHealth Solution

Identification of Clusters

As a first step, we will identify and validate clusters in data collected based on patients who present similar fatigue patterns, considering the contextual data collected. The clusters will be identified using unsupervised learning algorithms and validated with 2 different methodologies. A validation based on a graphical representation will be conducted, and some groups of clusters could be discarded. The remaining groups of clusters will be validated and selected using the following process: first, the research team members with experience in AI will review them and assess their representativeness of the collected data; then, the groups that better represent the collected data and clusters that are easier to understand will be selected by consensus; next, a definition of persona (a representation of a group of patients) for each cluster will be developed; then, a validation through a participatory workshop involving health care professionals of the research team will be conducted.

Predictive Modelling and Validation

To estimate the relationships between perceived fatigue severity and the remaining variables included in the data set and to estimate the fatigue severity, an analysis will be performed using blocks based on the definition of temporal windows. We will develop 2 interpretable models for fatigue severity forecasting: one using decision tree algorithms and the other using autoregressive integrated moving averages. The models will be validated through cross-validation, and their performance will be compared.

Co-Design and Development of the MyFatigue Digital Health Solution

The proposed solution will be developed following user-centered design (UCD), using a co-design workshop that involves patients in the design process. This involvement will present challenges because of the combination of symptoms that patients may present. Cognitive fatigue could pose a great challenge because fatigue severity may increase rapidly when individuals engage in dialogues with multiple participants. We will define a

workshop plan that controls the number of activities to be done, plans frequent breaks, and limits the number of participants in each session. Once the session ends, we will send a questionnaire to participants in which we will ask them to assess the barriers and advantages that they found during the session. Based on UCD, the collected data will be analyzed to identify relevant aspects and challenges in involving individuals with fatigue and other symptoms in the design process and steps to successfully address them. Following our research through a design method based on UCD, we will design and develop a prototype of the MyFatigue digital health solution. This prototype will be evaluated by experts to assess its usability, accessibility, and appropriateness for patients with ME/CFS and long COVID haulers.

Pilot Study

Through an initial in-person session, a member of the research team will provide the required device to participants and support them in the installation and configuration of the MyFatigue digital health solution. The researcher will also instruct participants on how they must process during their participation in the pilot study. A sheet summarizing those instructions and a tutorial on the MyFatigue digital health solution will be provided to participants. The pilot study will last 4 months. User logs for each participant will be saved in the MyFatigue database. After this period a new in-person session will be conducted in which a team member will ask participants to fill in an acceptance questionnaire and several standard questionnaires to assess the level of anxiety or depression, health-related quality of life, and the frequency or severity of fatigue. The acceptance questionnaire will be designed and validated by experts based on the Technology Acceptance Model. The collected data will be analyzed for each group of participants, paying special attention to relevant issues such as age and gender. Similarities and differences between both diseases will be explored.

Results

The MyFatigue project started in September 2022. Intensive administrative tasks alongside technological advancements have been underway, including the development of the web server and mobile app, as well as comprehensive literature review to identify and select appropriate questionnaires and hardware (eg, actigraphy devices) to be used for the project. The project is expected to be concluded in 2025, and initial findings would likely be published by the end of 2025.

Discussion

Expected Outcomes

The MyFatigue project aims to make a significant scientific and technical impact in the field of ME/CFS and long COVID. It seeks to advance the understanding of fatigue by investigating the influence of contextual and behavioral factors on its severity and identifying similarities and differences between ME/CFS and long COVID symptoms. Additionally, the project aims to develop intelligent personalized fatigue self-management methodologies using digital health and patient-reported outcomes, leading to the creation of new personalized management strategies for these conditions.

The project also emphasizes the social and economic impact it intends to generate based on the theory of change, which is a methodology or criterion for planning, participation, adaptive management, and evaluation for promoting social change. By involving people with ME/CFS and long COVID as well as health care professionals in participatory research activities, the project aims to promote mental health and well-being, aligning with the Sustainable Development Goal target 3.4. Through training activities and dissemination efforts, the project aims to increase empowerment and self-efficacy among people with these conditions, potentially reducing the risk of mental health problems.

The MyFatigue project expects to have a positive impact on the quality of life of patients with ME/CFS and long COVID. The project will track impact indicators, such as the number of individuals who experience increased empowerment and self-efficacy, the number of students completing the Massive Open Online Course training, and the number of people who reduce their risk of mental health problems by 20% after participating in the project's activities.

Conclusions

The result of the described study has the potential to advance knowledge, develop personalized management strategies, involve stakeholders, and contribute to improving the well-being of individuals with ME/CFS and long COVID.

Acknowledgments

This study received funding from the Spanish Ministry of Science and Innovation (Knowledge Generation Project Grant PID-2021-125528OB-I00), and it was cofunded by the 2020 European Union's Research and Innovation Funding Program. The authors would like to thank all the Vall d'Hebron Research Institute (VHIR) collaborators and professor Jose Alegre from the Vall d'Hebron University Hospital (Barcelona, Spain) for his contribution to the protocol development. The authors would also like to thank all the study participants as well as the participating health care center professionals for their time in recruiting patients and for sharing their experiences and thoughts. The authors express gratitude to the MyFatigue investigators, who had the ultimate authority in journal selection and the content for publication and provided final approval of the versions for submission and publication.

Data Availability

Data sharing is not applicable to this manuscript, as no data sets were generated or analyzed during the development of this protocol. Once data collection begins, all investigators will have access to anonymized patient-level data.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report from the Spanish Ministry of Science and Innovation (Spanish).
[PDF File (Adobe PDF File), 54 KB - resprot_v13i1e50157_app1.pdf]

Multimedia Appendix 2
Peer-review report from the Spanish Ministry of Science and Innovation (English).
[PDF File (Adobe PDF File), 196 KB - resprot_v13i1e50157_app2.pdf]

References

1. Castro-Marrero J, Zacares M, Almenar-Pérez E, Alegre-Martín J, Oltra E. Complement component C1q as a potential diagnostic tool for myalgic encephalomyelitis/chronic fatigue syndrome subtyping. J Clin Med 2021 Sep 15;10(18):4171 [FREE Full text] [doi: 10.3390/jcm10184171] [Medline: 34575280]
2. Martín-Garrido I, Medrano-Ortega F. [Beyond acute SARS-CoV-2 infection: a new challenge for internal medicine]. Rev Clin Esp 2022 Mar;222(3):176-179 [FREE Full text] [doi: 10.1016/j.rce.2021.09.005] [Medline: 34690357]
3. Estévez-López F, Mudie K, Wang-Steverding X, Bakken IJ, Ivanovs A, Castro-Marrero J, et al. Systematic review of the epidemiological burden of myalgic encephalomyelitis/chronic fatigue syndrome across Europe: current evidence and EUROMENE research recommendations for epidemiology. J Clin Med 2020 May 21;9(5):1557 [FREE Full text] [doi: 10.3390/jcm9051557] [Medline: 32455633]
4. Albers E, Nijhof LN, Berkelbach van der Sprenkel EE, van de Putte EM, Nijhof SL, Knoop H. Effectiveness of internet-based cognitive behavior therapy (fatigue in teenagers on the internet) for adolescents with chronic fatigue syndrome in routine clinical care: observational study. J Med Internet Res 2021 Aug 13;23(8):e24839 [FREE Full text] [doi: 10.2196/24839] [Medline: 34397389]
5. Worm-Smeitink M, van Dam A, van Es S, van der Vaart R, Evers A, Wensing M, et al. Internet-based cognitive behavioral therapy for chronic fatigue syndrome integrated in routine clinical care: implementation study. J Med Internet Res 2019 Oct 10;21(10):e14037 [FREE Full text] [doi: 10.2196/14037] [Medline: 31603428]
6. Brigden A, Barnett J, Parslow RM, Beasant L, Crawley E. Using the internet to cope with chronic fatigue syndrome/myalgic encephalomyelitis in adolescence: a qualitative study. BMJ Paediatr Open 2018 Aug 23;2(1):e000299 [FREE Full text] [doi: 10.1136/bmjpo-2018-000299] [Medline: 30167477]
7. King E, Beynon M, Chalder T, Sharpe M, White P. Patterns of daytime physical activity in patients with chronic fatigue syndrome. J Psychosom Res 2020 Aug;135:110154. [doi: 10.1016/j.jpsychores.2020.110154] [Medline: 32504895]
8. Palombo T, Campos A, Vernon SD, Roundy S. Accurate and objective determination of myalgic encephalomyelitis/chronic fatigue syndrome disease severity with a wearable sensor. J Transl Med 2020 Nov 10;18(1):423 [FREE Full text] [doi: 10.1186/s12967-020-02583-7] [Medline: 33168001]
9. Josev EK, Jackson ML, Bei B, Trinder J, Harvey A, Clarke C, et al. Sleep quality in adolescents with chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). J Clin Sleep Med 2017 Sep 15;13(9):1057-1066 [FREE Full text] [doi: 10.5664/jcsm.6722] [Medline: 28760189]
10. Russell C, Wearden AJ, Fairclough G, Emsley RA, Kyle SD. Subjective but not actigraphy-defined sleep predicts next-day fatigue in chronic fatigue syndrome: a prospective daily diary study. Sleep 2016 Apr 01;39(4):937-944 [FREE Full text] [doi: 10.5665/sleep.5658] [Medline: 26715232]
11. Estiri H, Strasser ZH, Brat GA, Semenov YR, Consortium for Characterization of COVID-19 by EHR (4CE), Patel CJ, et al. Evolving phenotypes of non-hospitalized patients that indicate long COVID. BMC Med 2021 Sep 27;19(1):249 [FREE Full text] [doi: 10.1186/s12916-021-02115-0] [Medline: 34565368]
12. Zhang F, Wu C, Jia C, Gao K, Wang J, Zhao H, et al. Artificial intelligence based discovery of the association between depression and chronic fatigue syndrome. J Affect Disord 2019 May 01;250:380-390. [doi: 10.1016/j.jad.2019.03.011] [Medline: 30877861]
13. Fjeldstad C, Fjeldstad A, Pardo G. Use of accelerometers to measure real-life physical activity in ambulatory individuals with multiple sclerosis: a pilot study. Int J MS Care 2015;17(5):215-220 [FREE Full text] [doi: 10.7224/1537-2073.2014-037] [Medline: 26472942]

Abbreviations

AI: artificial intelligence
CFQ: Chalder Fatigue Questionnaire
CP: count per minute
EMA: ecological momentary assessment
HADS: Hospital Anxiety and Depression Scale
ME/CFS: myalgic encephalomyelitis/chronic fatigue syndrome
MET: metabolic equivalent of task
MFIS-5: Modified Fatigue Impact Scale
mHealth: mobile health
PASC: postacute sequelae of SARS-CoV-2
PSQI: Pittsburgh Sleep Quality Index
SWLS: Satisfaction with Life Scale
UCD: user-centered design

Edited by A Mavragani; submitted 22.06.23; this is a non–peer-reviewed article;accepted 27.07.23; published 12.04.24.

Please cite as:
Dorronzoro-Zubiete E, Castro-Marrero J, Ropero J, Sevillano-Ramos JL, Dolores Hernández M, Sanmartin Sentañes R, Alegre-Martin J, Launois-Obregón P, Martin-Garrido I, Luque Budia A, Lacalle-Remigio JR, Béjar Prado L, Rivera Romero O
Personalized Management of Fatigue in Individuals With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Long COVID Using a Smart Digital mHealth Solution: Protocol for a Participatory Design Approach
JMIR Res Protoc 2024;13:e50157
URL: https://www.researchprotocols.org/2024/1/e50157
doi:10.2196/50157
PMID:38608263

Protocol

Reward Learning as a Potential Mechanism for Improvement in Schizophrenia Spectrum Disorders Following Cognitive Remediation: Protocol for a Clinical, Nonrandomized, Pre-Post Pilot Study

Frances Dark[1,2], MBBS, PhD; Graham Galloway[3,4], PhD, BSc(H); Marcus Gray[3], PGDipPsy, PhD; Matteo Cella[5], MScClinPsych, PhD; Veronica De Monte[1], MClinPsych, PhD; Victoria Gore-Jones[1], BS, BSocSci, MClinPsych; Gabrielle Ritchie[1,2], MClinPsych, PhD

[1]Metro South Addiction and Mental Health Services, Woolloongabba, Australia

[2]Faculty of Medicine, University of Queensland, Brisbane, Australia

[3]Translational Research Institute, Woolloongabba, Australia

[4]Herston Imaging Research Facility, The University of Queensland, Brisbane, Australia

[5]King's College London, London, United Kingdom

Corresponding Author:
Frances Dark, MBBS, PhD
Metro South Addiction and Mental Health Services
Level 2 Woolloongabba Community Health Centre
228 Logan Road
Woolloongabba, 4102
Australia
Phone: 61 0733171080
Email: frances.dark@health.qld.gov.au

Abstract

Background: Cognitive impairment is common with schizophrenia spectrum disorders. Cognitive remediation (CR) is effective in improving global cognition, but not all individuals benefit from this type of intervention. A better understanding of the potential mechanism of action of CR is needed. One proposed mechanism is reward learning (RL), the cognitive processes responsible for adapting behavior following positive or negative feedback. It is proposed that the structure of CR enhances RL and motivation to engage in increasingly challenging tasks, and this is a potential mechanism by which CR improves cognitive functioning in schizophrenia.

Objective: Our primary objective is to examine reward processing in individuals with schizophrenia before and after completing CR and to compare this with a group of matched clinical controls. We will assess whether RL mediates the relationship between CR and improved cognitive function and reduced negative symptoms. Potential differences in social RL and nonsocial RL in individuals with schizophrenia will also be investigated and compared with a healthy matched control group.

Methods: We propose a clinical, nonrandomized, pre-post pilot study comparing the impact of CR on RL and neurocognitive outcomes. The study will use a combination of objective and subjective measures to assess neurocognitive, psychiatric symptoms, and neurophysiological domains. A total of 40 individuals with schizophrenia spectrum disorders (aged 18-35 years) will receive 12 weeks of CR therapy (n=20) or treatment as usual (n=20). Reward processing will be evaluated using a reinforcement learning task with 2 conditions (social reward vs nonsocial reward) at baseline and the 12-week follow-up. Functional magnetic resonance imaging responses will be measured during this task. To validate the reinforcement learning task, RL will also be assessed in 20 healthy controls, matched for age, sex, and premorbid functioning. Mixed-factorial ANOVAs will be conducted to evaluate treatment group differences. For the functional magnetic resonance imaging analysis, computational modeling will allow the estimation of learning parameters at each point in time, during each task condition, for each participant. We will use a variational Bayesian framework to measure how learning occurred during the experimental task and the subprocesses that underlie this learning. Second-level group analyses will examine how learning in patients differs from that observed in control participants and how CR alters learning efficiency and the underlying neural activity.

Results: As of September 2023, this study has enrolled 15 participants in the CR group, 1 participant in the treatment-as-usual group, and 11 participants in the healthy control group. Recruitment is expected to be completed by September 2024. Data analysis is expected to be completed and published in early 2025.

Conclusions: The results of this study will contribute to the knowledge of CR and RL processes in severe mental illness and the understanding of the systems that impact negative symptoms and cognitive impairments within this population.

International Registered Report Identifier (IRRID): DERR1-10.2196/52505

(JMIR Res Protoc 2024;13:e52505) doi:10.2196/52505

KEYWORDS

cognitive remediation; fMRI; functional magnetic resonance imaging; negative symptoms; psychosocial functioning; reward learning

Introduction

Overview

Schizophrenia spectrum disorders (SSDs; eg, schizophrenia, schizoaffective disorder, and schizophreniform disorder) are defined by the presentation of a range of symptoms, including delusions, hallucinations, disorganized thoughts and behaviors, and negative symptoms (ie, reduced motivation and emotional expression) [1]. These disorders are linked to a variety of deficits in cognition, which extend to both neurocognition (eg, attention, memory, and planning) and social cognition (eg, difficulties perceiving and processing emotions) [2]. Both stand-alone and integrated programs have been used to treat these cognitive impairments. Cognitive remediation (CR) therapy has been widely used as an intervention for deficits in global cognition and functional difficulties in schizophrenia and has been shown to be particularly beneficial if rehabilitation is also incorporated into treatment [3,4]. Nevertheless, response to therapy is variable [5], and the impact individual characteristics have on the success of CR is still being investigated. The mechanisms by which CR is effective are yet to be clarified. A core component of CR is strategic learning principles, which ensure tasks are scaffolded based on previous successful achievements and the chances of successful task completion are optimized. There is, therefore, close reinforcement of learning.

One proposed mechanism for the effect of CR is reward learning (RL), which is potentially the pathway to improved cognition and motivational negative symptoms. In schizophrenia, there is impairment in reward anticipation [6,7] and representation [8], leading to poorer decision-making and goal-directed behavior, motivational deficits, and negative symptoms [8-11]. RL is a term used to identify the cognitive processes responsible for adapting behavior following positive or negative feedback. RL is a basic adaptive function of every living organism and provides the possibility to adapt and change in response to internal and environmental demands [12]. This process has been extensively studied in neuroscience and linked to the brain dopamine system. The dopamine hypothesis of schizophrenia is the single most influential theory in our understanding of the neurochemical basis of the disorder [13]. This theory suggests that fundamental dysregulation in this system is responsible for the illness's symptoms. Dysregulation in the dopamine system is also linked to RL abnormalities, which, in turn, are thought to influence cognitive and negative symptoms. A growing body of basic neuroscience literature has identified 2 complementary and interactive neural systems in the dopamine system responsible for predicting outcomes and learning from feedback [14]. The first of these systems, responsible for rapid learning, is mediated by the basal ganglia. This system, referred to as the "fast system," is believed to represent the predicted value of actions and rewards. These predictions bias actions and underlie learning based on positive and negative feedback. The second slower system is based primarily in the prefrontal cortex and allows for more detailed, conscious, and abstract representations of values and rewards. These representations of value are instrumental in allowing individuals to flexibly respond to reward value and adapt to novelty in the environment.

There is consistent evidence that people with SSDs are impaired at making rapid behavioral adjustments in response to feedback and that these impairments are associated with negative and cognitive symptoms [15-17]. Problems using the "fast system" are evident in situations requiring rapid change in responses to environmental changes when a situation previously rewarding begins to be associated with disadvantageous outcomes and oversensitivity to negative feedback and poor sensitivity to positive feedback. In contrast, several studies suggest that the gradual or procedural learning system seems intact in people with schizophrenia [18], but antipsychotic medication dosage, particularly for those with high levels of dopamine 2 receptor blockades, may exert a negative effect on this system.

Social environments are dynamic with constant rapid changes; hence, social situations require rapid behavioral adjustments in response to ever-changing social feedback. People with SSDs have impaired social functioning, and recent studies have shown that they also have impaired social reward processing [19,20]. Social approval induces rewarding feelings and is associated with increased activation in regions and networks associated with reward [21-23]. In those with SSDs, there is reduced activity in common reward brain regions during the experience of social reward [24], suggesting that they may have a reduced experience of the rewarding feeling of positive social attention. Positive social interactions have benefits for mental well-being and give life a sense of meaning [25]. Receiving praise and attention from others improves self-esteem [26] and increases motivation [27]. Although social reward has major impacts on functional outcomes, only recent efforts have explored social reward processing in SSDs. Further behavioral evidence suggests that RL difficulties are more pronounced in learning from positive, rather than negative, feedback [8]. This provides a further link between the effects of impaired RL and negative

symptoms. Learning preferentially from negative outcomes is likely to lead to behavioral avoidance and social withdrawal, and have a negative impact on motivation. This hypothesis is supported by research suggesting that the magnitude of RL impairment, particularly for positive feedback, is associated with negative symptom severity [28].

Despite the significance of RL problems in people with SSDs, there is no therapy targeting this problem. One previous study explored the impact that a course of CR has on RL problems in people with schizophrenia [29]. The results of this study showed that CR could improve sensitivity to positive and negative feedback and that improvement in these parameters was moderated by the severity of negative symptoms. However, this study used a standard CR protocol and may not have achieved the maximum effect on RL problems. Furthermore, the nature of this study did not allow for investigating the retention of RL improvements and, more crucially, how these may impact cognitive and negative symptoms and, more broadly, recovery. RL difficulties in people with SSDs are associated with negative symptoms, and it is plausible that, by reducing RL difficulties, a reduction in negative symptoms could be observed. It is proposed that the structure of CR enhances rewards and motivation to engage in increasingly challenging tasks, and this is a potential mechanism by which CR can achieve functional outcomes in individuals with SSDs.

Aims and Hypotheses

Our primary aim is to investigate reward processing in individuals with SSDs before and after completing a course of CR and to compare this intervention group with a treatment-as-usual (TAU) group of individuals with SSDs. In addition, this study aims to investigate whether RL mediates changes in cognitive function and negative symptoms following CR. We will also examine potential differences in social RL compared with nonsocial RL in individuals with SSDs and the impact of CR on these potential differences in RL domains. Comparison with RL in a healthy adult control group will allow further differentiation of behavioral and neural impairments in SSDs.

Hypothesis 1A

At baseline, participants with SSDs will demonstrate deficits in RL when compared with healthy control volunteers. These differences in learning will be linked to aberrant activity in the dopamine system at a neural level in the prefrontal cortex and subcortical structures such as the basal ganglia, compared with healthy controls.

Hypothesis 1B

At baseline, participants with SSDs will demonstrate greater deficits in social RL when compared with nonsocial RL.

Hypothesis 2

Participants that complete CR will demonstrate improved RL, again reflecting improved neural activity within the prefrontal and basal ganglia regions, when compared with people with SSDs not receiving the intervention.

Hypothesis 3

Reward processing ability will mediate improved cognition following CR in participants receiving the intervention but not in the SSD control group.

Hypothesis 4

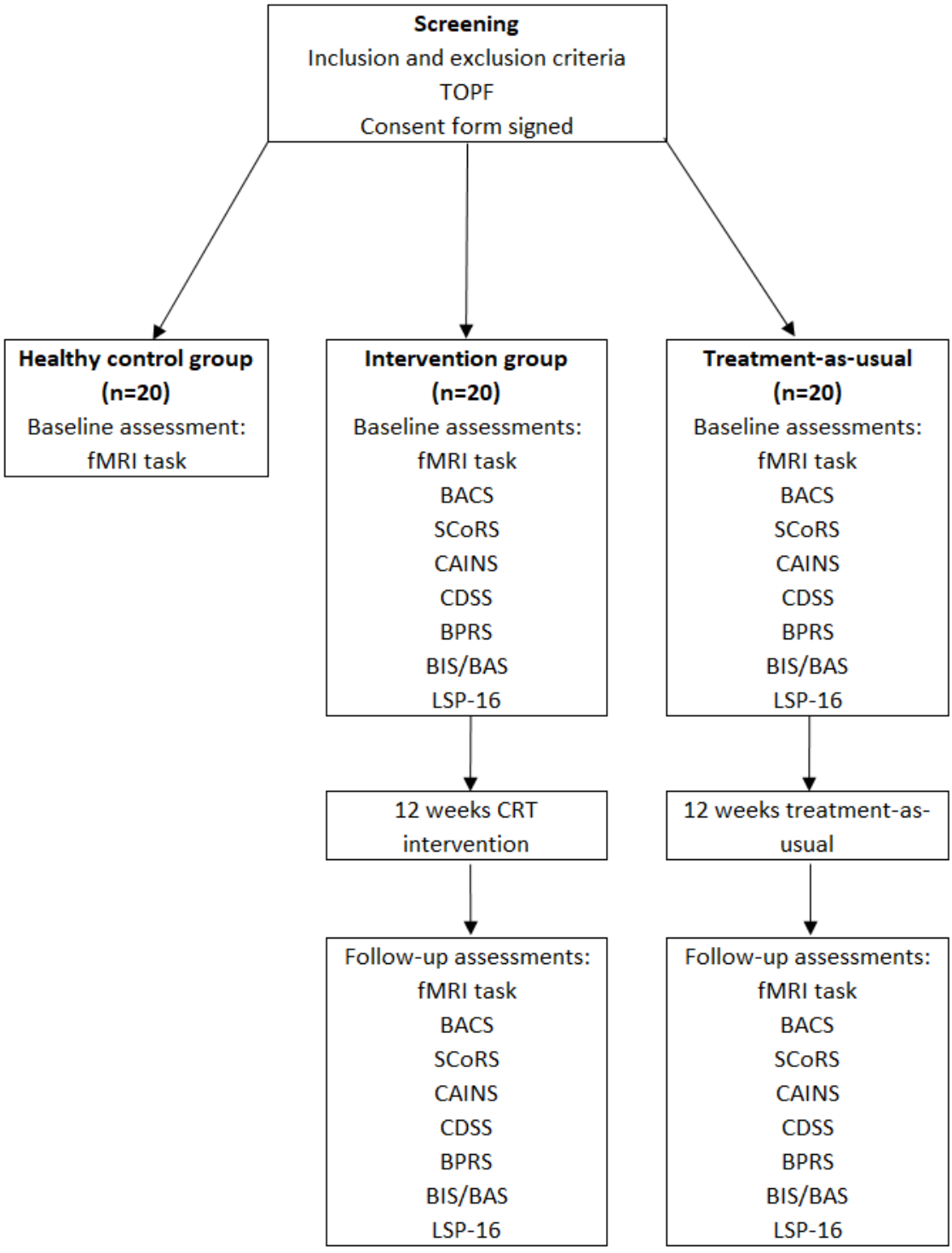
Reward processing will mediate improvements in negative symptoms following CR in participants receiving the intervention but not in the SSD control group.

Methods

Study Design

The study is a nonrandomized clinical pilot trial to investigate whether reward processing pathways are involved in the mechanism of action of cognitive remediation therapy (Computerized Interactive Remediation of Cognition-Training for Schizophrenia [CIRCuiTS]) [30,31]. We will recruit 3 participant groups: 20 participants with SSDs who will complete the CR program (the intervention group), 20 participants with SSDs who will receive TAU, and 20 matched healthy control participants. Figure 1 depicts a schematic of the study design.

Figure 1. The reward learning as a potential mechanism for improvement in schizophrenia spectrum disorders following cognitive remediation pre-post pilot study design. BACS: Brief Assessment of Cognition in Schizophrenia; BIS/BAS: Behavioral Inhibition System and Behavioral Activation System; BPRS: Brief Psychiatric Rating Scale; CAINS: Clinical Assessment Interview for Negative Symptoms; CDSS: Calgary Depression Scale for Schizophrenia; CRT: cognitive remediation therapy; fMRI: functional magnetic resonance imaging; LSP-16: Life Skills Profile; SCoRS: Schizophrenia Cognition Rating Scale; TOPF: Test of Premorbid Functioning.



Participants

A total of 40 participants with a diagnosis of an SSD will be recruited from the Metro South Addiction and Mental Health Service community teams (Brisbane, Australia). Given that this is a pilot study, a power analysis was not conducted [32]. Instead, the sample size was informed by practical factors relating to the project, including the budget, the availability of CR facilitators, and the recruitment and attrition rates from our previous studies. This sample size is also consistent with other research in this area [33].

The inclusion criteria for the intervention and TAU groups and the healthy control group, as well as the exclusion criteria for all groups, have been provided in Textbox 1.

Textbox 1. The inclusion and exclusion criteria.

Inclusion criteria for the intervention and treatment-as-usual (TAU) groups

- Patients of the Metro South Addiction and Mental Health Service
- Aged between 18 and 35 years
- Primary diagnosis of schizophrenia spectrum disorder (SSD)
- English literacy skills of at least grade 4 equivalence
- Absence of neurological disorders or acquired brain injury
- Estimated intelligence quotient >70 on the Test of Premorbid Functioning (TOPF)
- Agree to participate and have the capacity to consent to the study procedures

Inclusion criteria for the healthy control group

- Aged between 18 and 35 years
- No history of diagnosis of SSD
- English literacy skills of at least grade 4 equivalence
- Absence of neurological disorders or acquired brain injury
- Estimated intelligence quotient >70 on the TOPF
- Agree to participate and have the capacity to consent to the study procedures

Exclusion criteria for all groups

- Metallic object in their body (eg, cardiac pacemaker and cochlear implant)
- Pregnant or possibly pregnant (unprotected sex since last menstrual period)
- History of claustrophobia
- Permanent metal dental appliances
- Bodyweight ≥120kg

The researchers will obtain consent from all participants through a participation information and consent form. For participants with SSDs, half (n=20) will complete CR and form the intervention group. Those participants with SSDs (n=20) that are not interested in completing CR will form the patient TAU group and will complete the pre- and postmeasures only. Thus, group allocation will be based on an individual's preference to participate in CR. In addition, matched healthy controls (n=20) will be recruited from the Metro South Addiction and Mental Health community services in the Princess Alexandra Hospital district as well as from the general population. We do not anticipate that it will be difficult to collect these healthy controls, given our already established connections with other researchers and staff within this district. Therefore, we expect to be able to recruit this group through word of mouth and the snowball effect. These health controls will have no history of SSDs. This will provide a benchmark to compare the clinical groups. Hence, the total number of participants for the study is 60.

Intervention

CIRCuiTS is a therapist-supported CR web-based program that focuses on improving cognitive skills, particularly for individuals with psychosis [30,31]. Participants work through different cognitive tasks and exercises, many of which are based on real-life experiences (eg, creating a shopping list or cooking). Previous studies have shown CIRCuiTS leads to improvements in both cognition and functional recovery and is acceptable by participants [34]. Sessions typically last 1 hour, twice a week, for 12 weeks, and task practice is delivered through a computer. CIRCuiTS consists of 40 stages. A total of 20 sessions are considered adequate treatment exposure, and 20 minutes is the minimum time for a "session." In this study, participants in the CR group will have 1 face-to-face meeting with the therapist to orient themselves to the program. These participants will then complete the program either on the web or in person, in a group or individually. Only the intervention group will be able to complete these sessions.

All participants will continue their usual treatment under the supervision of their referring clinical team. This involves pharmacotherapy, monitoring, and case management. They can concurrently attend any psychosocial group that does not focus on improving neurocognition.

Outcomes

Screening Measures

During screening, participants will complete the Test of Premorbid Functioning (TOPF). The TOPF is a test of premorbid intelligence estimated from reading ability and will be used to screen for intellectual impairment [35,36]. It takes

approximately 10 minutes to complete and is composed of a list of 70 words.

Demographic Information

At baseline, demographic and clinical information will be gathered, including sex, age, and date of birth. For the clinical groups, the case management team, primary and secondary diagnoses, mental health status, and list of current medications (name, dose, frequency, and route) will also be recorded.

A battery of validated assessment measures will also be delivered at baseline and follow-up for the clinical groups, as described in the subsequent sections.

Brief Assessment of Cognition in Schizophrenia

The Brief Assessment of Cognition in Schizophrenia (BACS) assesses 5 domains of cognition, with 6 tests taking approximately 30 minutes [37,38]. The 6 tests include list learning (verbal memory), digit sequencing (working memory), token motor task (motor speed), verbal fluency (semantic fluency and letter fluency), Tower of London (reasoning and problem solving), and symbol coding (attention and processing speed). The BACS has high test-retest reliability, is sensitive to the unique cognitive deficits associated with SSDs, and is a routine measure of change in performance over time [37].

Schizophrenia Cognition Rating Scale

The Schizophrenia Cognition Rating Scale (SCoRS) is a 20-item measure of cognitive difficulties in daily activities that is completed by the participant, an informant, and the interviewer at baseline and on completion of the CR program [39]. It has been found that global ratings of cognition are strongly correlated with cognitive performance, functional outcome, and functional capacity. The SCoRS has good interrater reliability [39].

Clinical Assessment Interview for Negative Symptoms

The Clinical Assessment Interview for Negative Symptoms (CAINS) is a measure of anhedonia, avolition, and emotional expression [40] with strong psychometric properties [41]. The CAINS has been found to have good convergent validity with the Brief Negative Symptom Scale [42]. It was developed to better align not only with the negative symptoms but also with constructs emerging from neurobiological research [43].

Calgary Depression Scale for Schizophrenia

The Calgary Depression Scale for Schizophrenia (CDSS) measures symptoms of depression in people with schizophrenia [44]. The scale has 8 structured questions with an additional observational item [45]. The scoring uses a 4-point Likert-type scale (0=absent, 1=mild, 2=moderate, and 3=severe), anchored by descriptors [44]. The summation of scores on all items provides a global score. The scale has good psychometric properties, identifying a major depressive episode at 82% specificity and 85% sensitivity for scores above 6.

Brief Psychiatric Rating Scale

The Brief Psychiatric Rating Scale (BPRS) is a semistructured assessment of 24 symptoms of schizophrenia. The 24-item anchored scale will be used. The anchored version has good psychometric properties [46]. Symptom severity is rated from 1 (not present) to 7 (extremely severe). High scores represent greater symptom severity. Based on a clinical interview, items 1-14 are based on the participants' self-report; observed behavior is also used to rate items 7, 12, and 13. Items 15-24 are rated based on the patient's observed behavior or speech during the interview.

Behavioral Inhibition System and Behavioral Activation System

The Behavioral Inhibition System and Behavioral Activation System (BIS/BAS) is a 24-item self-report measure of behavioral inhibition and activation [46,47]. A total of 13 items reflect the activation system, divided into drive, pleasure-seeking, and sensitivity to reward, and 7 items reflect the inhibition system. There are 4 filler items. Responses are rated on a 4-point Likert-type scale with a range from 1 (very true) to 4 (very false). The BIS/BAS factor structure has been validated in a large Australian community sample [48].

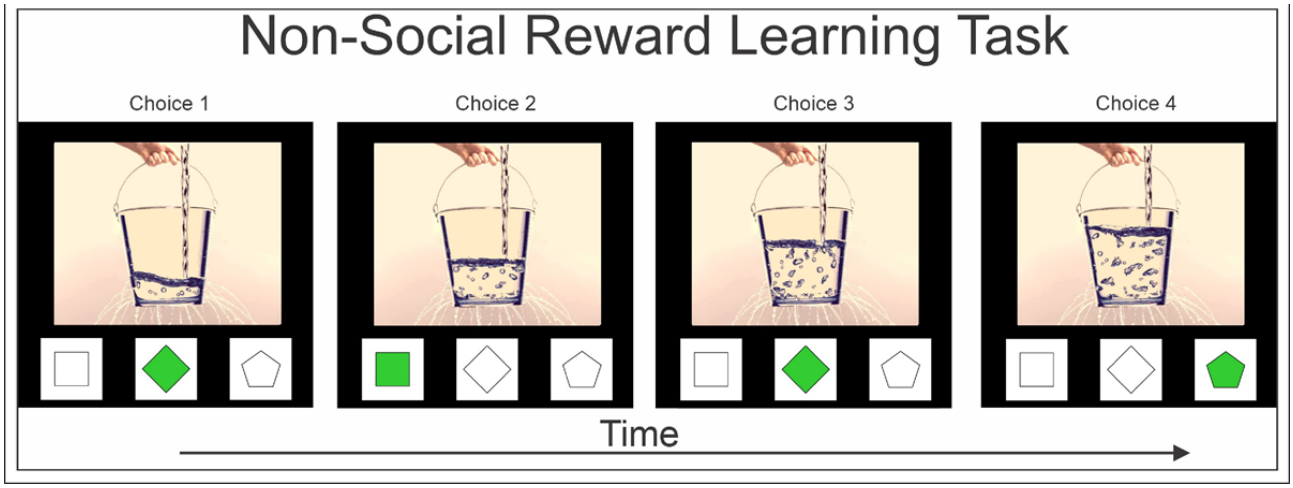
Life Skills Profile

The Life Skills Profile (LSP-16) is a measure of activities of daily living over the previous 3 months with high test-retest and interrater reliability [49]. The 16-item version was specifically developed for use in Australian public mental health services [49-51]. The items are on a 4-point anchored scale. Higher scores indicate a greater disability. A total LSP score is calculated by adding all the individual scores.

Functional Magnetic Resonance Imaging

Participants will complete a computerized experimental learning task with 2 conditions: a social reward condition and a nonsocial reward condition (Figure 2). The task is a simple reinforcement learning design where participants must choose from a small number of potential responses and, over repeated trials, learn about the probable consequences. In our task, participants can choose a response from 3 buttons. Each choice is associated with a probabilistic outcome, generally with 1 winning choice, 1 losing choice, and 1 neutral choice. For example, the task might start with an 80% reward for choice A, a 40% loss for choice B, and no change for choice C. With repeated sampling, people learn to identify responses with the best outcomes and avoid irrelevant or losing responses.

Figure 2. The experimental learning task with the nonsocial reward condition in the pre-post pilot study. Choice 4 represents the best outcome.



During the social learning task, participants view a picture of a neutral face, with rewarded button choices changing the facial expression toward a smile and losing choices changing toward a frowning expression. Alternatively, in the nonsocial learning task, participants view a picture of a bucket half full of water. Rewarded choices further fill the bucket, while losing choices drain the bucket. The task was developed by Dr Marcus Gray for this study and implemented in MATLAB (MathWorks) using the Cogent 2000 toolbox [52]. During the functional magnetic resonance imaging (fMRI) experiment, the task is seen by participants through a tilted mirror attached to the head coil on the magnetic resonance imaging scanner. Responses are made on a commercially available, magnetic resonance-compatible response box [53]. Participants are familiarized with the task and perform 2 blocks of each condition before brain scanning.

During the fMRI, structural and functional magnetic resonance imaging images will also be acquired by a 3T Siemens Magnetom TrioTim (Siemens Healthineers) system using a 12-channel head coil. The sequences acquired and their parameters are as follows: T1-weighted imaging, T2-weighted imaging, fMRI imaging, diffusion-weighted imaging, and susceptibility-weighted imaging.

- T1-weighted imaging: magnetization-prepared 2 rapid acquisition gradient echoes (MP2RAGE) sequence. Time to acquire image=5:02; inversion 1=700 ms; inversion 2=2220 ms; repetition time=4000 ms; echo time=2.96 ms; voxel size=1 mm isotropic; field of vision=230 mm; and 192 slices with full brain coverage.
- T2-weighted imaging: fluid-attenuated inversion recovery sequence. Time to acquire image=2:44; repetition time=9000 ms; echo time=81 ms; inversion time=2500 ms; flip angle=150 degrees; voxel size = 0.72 × 0.72 × 5.2 mm; and 30 slices with full brain coverage.
- fMRI imaging: functional T2*-weighted blood-oxygen-level dependent images are acquired using a multiband, echo-planar sequence across the whole brain (repetition time=0.628 ms; echo time=30 ms; resolution=2.4 mm isotropic; field of view=192 mm; flip angle=52 degrees; and 54 slices with full brain coverage). During fMRI imaging, participants will complete a computerized experimental task. For each task condition, approximately 720 full brain images will be acquired, providing 1440 volumes acquitted in approximately 12 minutes.
- Diffusion-weighted imaging: A neurite orientation dispersion and density imaging sequence with 2 shells and 90 gradient directions (B1=1000 with 30 directions and B2=2500 with 60 directions) with 6 B0 measurements will be acquired in the anterior-posterior phase encoding direction, and an additional 6 B0 measurements will be acquired in the posterior-anterior phase encoding direction. Total acquisition time=7:24; repetition time=4100 ms; echo time=75 ms; voxel size=2mm isotropic; and 68 slices with full brain coverage.
- Susceptibility-weighted imaging: time to acquire image=2:56; repetition time=27 ms; echo time=20 ms; flip angle=15 degrees; voxel size = 0.89 × 0.89 × 2.5 mm; and 64 slices with full brain coverage.

Data Management

The Trial Management Group (TMG) consists of the principal investigator (FD) and associated investigators (GG and MG). All adverse events will be reviewed by the TMG and reported to the ethics committee. The process of recruitment and data management will be overseen by the TMG. The data will be securely entered and stored on the University of Queensland Data Manager repository. This trial may be subject to random auditing by the ethics committee. All protocol amendments will be reported to the ethics committee.

Statistical Analysis

Participants' medication dosages will be converted to olanzapine equivalents [54]. Outcome measures will be analyzed using the SPSS (version 27 or higher; IBM Corp) software package. A series of 2 (group: intervention and patient control) x 2 (time: baseline and postintervention) mixed factorial ANOVAs will be conducted to evaluate the treatment group differences for each of the outcome measures. If the normality assumption is violated, nonparametric analyses will be conducted.

For the fMRI analysis, standard preprocessing of the functionally weighted images will be carried out using the Statistical Parametric Mapping Version 12 [55]. The preprocessing steps follows: slice timing on the functional images, to correct for

differences in slice acquisition times within each volume using the middle slice as reference; realignment (estimate and reslice) on the functional images, to correct for interscan movement within each run (defined as >3 mm translation and >2 degrees rotation); coregistration of the functional and structural images; segmentation of the structural image, with heavy regularization (0.1) recommended for MP2-RAGE sequence; normalization of the resliced images into a standardized, stereotaxic space (according to the Montreal Neurological Institute template); and smoothing of normalized images with a 8 mm full-width-at-half-maximum isotropic Gaussian kernel.

The general linear model approach for event-related designs will be conducted using the Statistical Parametric Mapping Version 8 [55]. For the first-level analysis, task-related changes in the blood-oxygen-level dependent signal will be estimated at each voxel for each participant. Head motion parameters will be included as a regressor to account for participant motion during the experiment. A 1/128 Hz high-pass filter will be used to remove slow signal drifts, and a canonical hemodynamic response function with no derivatives will be selected.

Computational modeling will allow the estimation of learning parameters at each point in time, during each task condition, for each participant. We will use a variational Bayesian framework to compute how the value of each button was estimated based on the behavioral choices made and feedback received. This allows us to measure how learning occurred during the experimental task and the subprocesses that must underlie this learning. Second-level group analyses will examine how learning in patients differs from that observed in control participants and how CR therapy alters learning efficiency and the underlying neural activity. We will correct for multiple comparisons; the voxel-level threshold will be set at $P<.05$ family-wise error corrected.

Ethical Considerations

This trial has been approved by the Metro South Health Human Research and Ethics Committee (HREC/2021/QMS/67093). All protocol modifications and serious adverse events will be reported to the ethics committee. The study will be conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All participation will be based on voluntary, written, and informed consent. Participants with serious mental illness can be challenging to follow up with; thus, the researchers will make multiple attempts to contact each participant at baseline and postintervention. In cases of deterioration in mental state, the intervention will be discontinued, and the participant's treating team will be advised. Participants will be able to withdraw at any point in the study. All data used for analysis will be deidentified.

Results

This trial was registered in August 2018 and commenced recruiting in May 2022. As of September 2023, we have enrolled 11 healthy controls. We have also enrolled 16 individuals with SSDs, 15 into the CR group, and 1 into the TAU group. The projected completion of recruitment is September 2024. The projected final reporting date is September 2025. Results will be disseminated to mental health clinicians, researchers, and key stakeholders through peer-reviewed publications and presentations. In-kind funding is being provided by Metro South Addiction and Mental Health Services and the Translational Research Institute. This study received an Extraordinary Research Grant from the Princess Alexandra Hospital Research Foundation to assist with the purchase of fMRI scans in May 2023.

Discussion

Principal Findings

CR has demonstrated effectiveness in improving neurocognitive functioning in individuals with SSDs; however, the mechanisms that mediate this effect remain unclear. This study describes the unique protocol for a pre-post pilot study that aims to investigate RL as a potential mechanism for improvement following CR. In this study, we predict that at baseline, individuals with schizophrenia will exhibit deficits in RL when compared with healthy controls. Further, we predict that these deficits will be more pronounced in learning tasks that involve social versus nonsocial stimuli. This would support previous research highlighting impaired reward processing in SSDs [8], particularly in social processing [19,20]. Social reward has significant impacts on the functional outcomes of this population, and there are no current interventions that target this problem, emphasizing the importance of this area of research. Moreover, difficulty in responding to feedback has been associated with cognitive function and negative symptoms in SSDs [15-17]. Thus, we propose that by reducing RL problems, we may in turn see a reduction in negative symptoms and an improvement in cognition.

The primary focus of this study is to investigate whether RL is improved after CR in individuals with schizophrenia. Only 1 other study has specially looked at the impact of CR on reward processing in SSDs [29], and results from this research suggest CR may improve response to feedback, moderated by the severity of negative symptoms. We believe CR serves to strengthen the processes involved in rewards and motivation that are needed for participants to persevere with difficult cognitive tasks via reinforcement of learning. Learning more about the way in which CR works is important to be able to maximize the effects of the intervention. Currently, CR is undertaken for around 3 months, with 2-4 sessions per week. Understanding the mechanisms of effect may enable improvements in the programs that enable more efficient delivery of this effective intervention.

Limitations

The lack of blinding of researchers and the nonrandomized assignment of participants to conditions are limitations of the study design. Treatment allocation is based on individuals' preferences to minimize attrition. As the intervention group is self-selecting, arguably, these participants may be better functioning than the patient control group. However, we believe that this will not necessarily be the case. For instance, some higher-functioning participants might select to be in the control group due to time restraints (ie, because of full-time study or work) limiting their ability to complete the CR therapy sessions.

Nevertheless, we aim to recruit comparable participants from the patient control group and intervention group by matching for age, sex, and premorbid function across groups. There will also be some flexibility in the delivery of CR (ie, on the web vs in person and individual vs group), depending on participants' access to the technology to run CR sessions and their preferences. This flexible mode of delivery was aimed at minimizing attrition, which has been an issue identified in the literature, in our work, and because of group therapy shutdowns during the COVID-19 pandemic [56,57].

Conclusions

It is hoped that the results of this study will contribute to the understanding of CR and RL in schizophrenia more generally. Greater knowledge of CR would seek to inform clinicians to develop more targeted interventions and, consequently, reduce negative symptoms and improve functional outcomes in individuals with SSDs. We hope to use this pilot to test the integrity of the protocol and plan for future funding, with the aim of progressing to a larger randomized controlled trial.

Data Availability

The data sets generated or analyzed during this study are not publicly available. Access to research data is restricted and governed by the Queensland Health Government.

Authors' Contributions

FD, MC, GG, MG, VGJ, VDM, and GR contributed to the design of the study. FD and VGJ drafted the original protocol. FD and MC conceptualized the original idea for the study. FD and VDM will run the cognitive remediation (CR) programs. VGJ and GR will conduct the cognitive assessments. MG and GR will support participants during functional magnetic resonance imaging (fMRI). No professional writers will be used. All researchers will have access to the final data set. No generative AI was used in any portion of the manuscript writing.

Conflicts of Interest

FD has received honorariums from Janssen and Lundbeck for the delivery of lectures at clinician education events.

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th Edition. Arlington, VA: American Psychiatric Publishing; 2013.
2. Kharawala S, Hastedt C, Podhorna J, Shukla H, Kappelhoff B, Harvey PD. The relationship between cognition and functioning in schizophrenia: a semi-systematic review. Schizophr Res Cogn 2022 Mar;27:100217 [FREE Full text] [doi: 10.1016/j.scog.2021.100217] [Medline: 34631435]
3. Wykes T, Huddy V, Cellard C, McGurk SR, Czobor P. A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. Am J Psychiatry 2011;168(5):472-485 [FREE Full text] [doi: 10.1176/appi.ajp.2010.10060855] [Medline: 21406461]
4. Dark F, Harris M, Gore-Jones V, Newman E, Whiteford H. Implementing cognitive remediation and social cognitive interaction training into standard psychosis care. BMC Health Serv Res 2018;18(1):458 [FREE Full text] [doi: 10.1186/s12913-018-3240-5] [Medline: 29907105]
5. Reser MP, Slikboer R, Rossell SL. A systematic review of factors that influence the efficacy of cognitive remediation therapy in schizophrenia. Aust N Z J Psychiatry 2019;53(7):624-641 [FREE Full text] [doi: 10.1177/0004867419853348] [Medline: 31177813]
6. Grimm O, Heinz A, Walter H, Kirsch P, Erk S, Haddad L, et al. Striatal response to reward anticipation: evidence for a systems-level intermediate phenotype for schizophrenia. JAMA Psychiatry 2014;71(5):531-539 [FREE Full text] [doi: 10.1001/jamapsychiatry.2014.9] [Medline: 24622944]
7. Subramaniam K, Hooker CI, Biagianti B, Fisher M, Nagarajan S, Vinogradov S. Neural signal during immediate reward anticipation in schizophrenia: relationship to real-world motivation and function. Neuroimage Clin 2015;9:153-163 [FREE Full text] [doi: 10.1016/j.nicl.2015.08.001] [Medline: 26413478]
8. Gold JM, Waltz JA, Prentice KJ, Morris SE, Heerey EA. Reward processing in schizophrenia: a deficit in the representation of value. Schizophr Bull 2008 Sep;34(5):835-847 [FREE Full text] [doi: 10.1093/schbul/sbn068] [Medline: 18591195]
9. Juckel G, Schlagenhauf F, Koslowski M, Wüstenberg T, Villringer A, Knutson B, et al. Dysfunction of ventral striatal reward prediction in schizophrenia. Neuroimage 2006;29(2):409-416. [doi: 10.1016/j.neuroimage.2005.07.051] [Medline: 16139525]
10. Park IH, Chun JW, Park HJ, Koo MS, Park S, Kim SH, et al. Altered cingulo-striatal function underlies reward drive deficits in schizophrenia. Schizophr Res 2015;161(2-3):229-236. [doi: 10.1016/j.schres.2014.11.005] [Medline: 25468177]
11. Billeke P, Aboitiz F. Social cognition in schizophrenia: from social stimuli processing to social engagement. Front Psychiatry 2013;4:4 [FREE Full text] [doi: 10.3389/fpsyt.2013.00004] [Medline: 23444313]

12. Berridge KC. Reward learning: reinforcement, incentives, and expectations. Psychol Learn Motiv 2000;40:223-278. [doi: 10.1016/s0079-7421(00)80022-5]
13. Baumeister AA, Francis JL. Historical development of the dopamine hypothesis of schizophrenia. J Hist Neurosci 2002;11(3):265-277. [doi: 10.1076/jhin.11.3.265.10391] [Medline: 12481477]
14. Schultz W, Dayan P, Montague PR. A neural substrate of prediction and reward. Science 1997;275(5306):1593-1599. [doi: 10.1126/science.275.5306.1593] [Medline: 9054347]
15. Hanssen E, Krabbendam L, Robberegt S, Fett AK. Social and non-social reward learning reduced and related to a familial vulnerability in schizophrenia spectrum disorders. Schizophr Res 2020;215:256-262. [doi: 10.1016/j.schres.2019.10.019] [Medline: 31753593]
16. Waltz JA, Gold JM. Probabilistic reversal learning impairments in schizophrenia: further evidence of orbitofrontal dysfunction. Schizophr Res 2007;93(1-3):296-303 [FREE Full text] [doi: 10.1016/j.schres.2007.03.010] [Medline: 17482797]
17. Waltz JA, Schweitzer JB, Ross TJ, Kurup PK, Salmeron BJ, Rose EJ, et al. Abnormal responses to monetary outcomes in cortex, but not in the basal ganglia, in schizophrenia. Neuropsychopharmacology 2010 Nov;35(12):2427-2439 [FREE Full text] [doi: 10.1038/npp.2010.126] [Medline: 20720534]
18. Schmand B, Kop WJ, Kuipers T, Bosveld J. Implicit learning in psychotic patients. Schizophr Res 1992;7(1):55-64. [doi: 10.1016/0920-9964(92)90074-f] [Medline: 1591197]
19. Catalano LT, Heerey EA, Gold JM. The valuation of social rewards in schizophrenia. J Abnorm Psychol 2018;127(6):602-611 [FREE Full text] [doi: 10.1037/abn0000366] [Medline: 30102066]
20. Robberegt S, Fett AK. M21. Social reward learning deficits in patients with schizophrenia. Schizophr Bull 2017;43(Suppl 1):S219. [doi: 10.1093/schbul/sbx022.020]
21. Spreckelmeyer KN, Krach S, Kohls G, Rademacher L, Irmak A, Konrad K, et al. Anticipation of monetary and social reward differently activates mesolimbic brain structures in men and women. Soc Cogn Affect Neurosci 2009;4(2):158-165 [FREE Full text] [doi: 10.1093/scan/nsn051] [Medline: 19174537]
22. Rademacher L, Krach S, Kohls G, Irmak A, Gründer G, Spreckelmeyer KN. Dissociation of neural networks for anticipation and consumption of monetary and social rewards. Neuroimage 2010;49(4):3276-3285. [doi: 10.1016/j.neuroimage.2009.10.089] [Medline: 19913621]
23. Izuma K, Saito DN, Sadato N. Processing of social and monetary rewards in the human striatum. Neuron 2008 Apr 24;58(2):284-294 [FREE Full text] [doi: 10.1016/j.neuron.2008.03.020] [Medline: 18439412]
24. Lee J, Reavis E. 62.3 Neural correlates of social reward and monetary reward in schizophrenia. Schizophr Bull 2017;43(Suppl 1):S38 [FREE Full text] [doi: 10.1093/schbul/sbx021.100]
25. Uchino BN, Cacioppo JT, Kiecolt-Glaser JK. The relationship between social support and physiological processes: a review with emphasis on underlying mechanisms and implications for health. Psychol Bull 1996;119(3):488-531. [doi: 10.1037/0033-2909.119.3.488] [Medline: 8668748]
26. Hill CA. Affiliation motivation: people who need people ... but in different ways. J Pers Soc Psychol 1987;52(5):1008-1018. [doi: 10.1037//0022-3514.52.5.1008] [Medline: 3585697]
27. Leary MR. Motivational and emotional aspects of the self. Annu Rev Psychol 2007;58:317-344. [doi: 10.1146/annurev.psych.58.110405.085658] [Medline: 16953794]
28. Gold JM, Waltz JA, Matveeva TM, Kasanova Z, Strauss GP, Herbener ES, et al. Negative symptoms and the failure to represent the expected reward value of actions: behavioral and computational modeling evidence. Arch Gen Psychiatry 2012;69(2):129-138 [FREE Full text] [doi: 10.1001/archgenpsychiatry.2011.1269] [Medline: 22310503]
29. Cella M, Bishara AJ, Medin E, Swan S, Reeder C, Wykes T. Identifying cognitive remediation change through computational modelling--effects on reinforcement learning in schizophrenia. Schizophr Bull 2014 Nov;40(6):1422-1432 [FREE Full text] [doi: 10.1093/schbul/sbt152] [Medline: 24214932]
30. Wykes T, Joyce E, Velikonja T, Watson A, Aarons G, Birchwood M, et al. The CIRCuiTS study (Implementation of cognitive remediation in early intervention services): protocol for a randomised controlled trial. Trials 2018;19(1):183 [FREE Full text] [doi: 10.1186/s13063-018-2553-3] [Medline: 29544551]
31. Reeder C, Huddy V, Cella M, Taylor R, Greenwood K, Landau S, et al. A new generation computerised metacognitive cognitive remediation programme for schizophrenia (CIRCuiTS): a randomised controlled trial. Psychol Med 2017;47(15):2720-2730 [FREE Full text] [doi: 10.1017/S0033291717001234] [Medline: 28866988]
32. Pilot studies: common uses and misuses. National Institutes of Health. 2023. URL: https://www.nccih.nih.gov/grants/pilot-studies-common-uses-and-misuses [accessed 2023-12-21]
33. Vita A, Barlati S, Ceraso A, Nibbio G, Ariu C, Deste G, et al. Effectiveness, core elements, and moderators of response of cognitive remediation for schizophrenia: a systematic review and meta-analysis of randomized clinical trials. JAMA Psychiatry 2021;78(8):848-858 [FREE Full text] [doi: 10.1001/jamapsychiatry.2021.0620] [Medline: 33877289]
34. Wykes T, Stringer D, Boadu J, Tinch-Taylor R, Csipke E, Cella M, et al. Cognitive remediation works but how should we provide it? An adaptive randomized controlled trial of delivery methods using a patient nominated recovery outcome in first-episode participants. Schizophr Bull 2023;49(3):614-625 [FREE Full text] [doi: 10.1093/schbul/sbac214] [Medline: 36869733]

35. Advanced clinical solutions for the WAIS-IV and WMS-IV: clinical and interpretive manual. Pearson. San Antonion, Texas: NCS Pearson Inc; 2009. URL: https://www.pearsonassessments.com/store/usassessments/en/Store/Professional-Assessments/Behavior/Autism/Advanced-Clinical-Solutions-for-WAIS-IV-and-WMS-IV/p/100000616.html [accessed 2023-12-21]
36. Wechsler D. Test of Premorbid Functioning. San Antonio, TX: The Psychological Corporation; 2009.
37. Keefe RSE, Goldberg TE, Harvey PD, Gold JM, Poe MP, Coughenour L. The brief assessment of cognition in schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery. Schizophr Res 2004;68(2-3):283-297. [doi: 10.1016/j.schres.2003.09.011] [Medline: 15099610]
38. Keefe RSE, Harvey PD, Goldberg TE, Gold JM, Walker TM, Kennel C, et al. Norms and standardization of the Brief Assessment of Cognition in Schizophrenia (BACS). Schizophr Res 2008;102(1-3):108-115. [doi: 10.1016/j.schres.2008.03.024] [Medline: 18495435]
39. Keefe RSE, Poe M, Walker TM, Kang JW, Harvey PD. The schizophrenia cognition rating scale: an interview-based assessment and its relationship to cognition, real-world functioning, and functional capacity. Am J Psychiatry 2006;163(3):426-432 [FREE Full text] [doi: 10.1176/appi.ajp.163.3.426] [Medline: 16513863]
40. Forbes C, Blanchard JJ, Bennett M, Horan WP, Kring A, Gur R. Initial development and preliminary validation of a new negative symptom measure: the Clinical Assessment Interview for Negative Symptoms (CAINS). Schizophr Res 2010;124(1-3):36-42 [FREE Full text] [doi: 10.1016/j.schres.2010.08.039] [Medline: 20869848]
41. Kring AM, Gur RE, Blanchard JJ, Horan WP, Reise SP. The Clinical Assessment Interview for Negative Symptoms (CAINS): final development and validation. Am J Psychiatry 2013;170(2):165-172 [FREE Full text] [doi: 10.1176/appi.ajp.2012.12010109] [Medline: 23377637]
42. Strauss GP, Gold JM. A psychometric comparison of the clinical assessment interview for negative symptoms and the brief negative symptom scale. Schizophr Bull 2016;42(6):1384-1394 [FREE Full text] [doi: 10.1093/schbul/sbw046] [Medline: 27174556]
43. Barch DM. The CAINS: theoretical and practical advances in the assessment of negative symptoms in schizophrenia. Am J Psychiatry 2013;170(2):133-135 [FREE Full text] [doi: 10.1176/appi.ajp.2012.12101329] [Medline: 23377630]
44. Addington D, Addington J, Maticka-Tyndale E. Assessing depression in schizophrenia: the Calgary Depression Scale. Br J Psychiatry Suppl 1993 Dec(22):39-44. [Medline: 8110442]
45. Kim SW, Kim SJ, Yoon BH, Kim JM, Shin IS, Hwang MY, et al. Diagnostic validity of assessment scales for depression in patients with schizophrenia. Psychiatry Res 2006;144(1):57-63. [doi: 10.1016/j.psychres.2005.10.002] [Medline: 16904189]
46. Hafkenscheid A. Psychometric evaluation of a standardized and expanded brief psychiatric rating scale. Acta Psychiatr Scand 1991;84(3):294-300. [doi: 10.1111/j.1600-0447.1991.tb03147.x] [Medline: 1950632]
47. Carver CS, White TL. Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: the BIS/BAS scales. J Pers Soc Psychol 1994;67(2):319-333. [doi: 10.1037/0022-3514.67.2.319]
48. Jorm AF, Christensen H, Henderson AS, Jacomb PA, Korten AE, Rodgers B. Using the BIS/BAS scales to measure behavioural inhibition and behavioural activation: factor structure, validity and norms in a large community sample. Pers Individ Differ 1998;26(1):49-58. [doi: 10.1016/s0191-8869(98)00143-3]
49. Parker G, Rosen A, Emdur N, Hadzi-Pavlov D. The life skills profile: psychometric properties of a measure assessing function and disability in schizophrenia. Acta Psychiatr Scand 1991;83(2):145-152. [doi: 10.1111/j.1600-0447.1991.tb07381.x] [Medline: 2017913]
50. Rosen A, Trauer T, Hadzi-Pavlovic D, Parker G. Development of a brief form of the Life Skills Profile: the LSP-20. Aust N Z J Psychiatry 2001 Oct;35(5):677-683. [doi: 10.1080/00048670010060518] [Medline: 11551285]
51. Trauer T, Duckmanton RA, Chiu E. The Life Skills Profile: a study of its psychometric properties. Aust N Z J Psychiatry 1995 Sep;29(3):492-499. [doi: 10.3109/00048679509064959] [Medline: 8573054]
52. Wellcome Centre for Human Neuroimaging. London, UK: University College London; 2023. URL: https://www.fil.ion.ucl.ac.uk/ [accessed 2023-12-21]
53. Current Designs. 2023. URL: https://www.curdes.com/ [accessed 2023-12-21]
54. Leucht S, Samara M, Heres S, Davis JM. Dose equivalents for antipsychotic drugs: the DDD method. Schizophr Bull 2016 Jul;42 Suppl 1(Suppl 1):S90-S94 [FREE Full text] [doi: 10.1093/schbul/sbv167] [Medline: 27460622]
55. Friston KJ, Penny W. Posterior probability maps and SPMs. Neuroimage 2003;19(3):1240-1249. [doi: 10.1016/s1053-8119(03)00144-7] [Medline: 12880849]
56. Szymczynska P, Walsh S, Greenberg L, Priebe S. Attrition in trials evaluating complex interventions for schizophrenia: systematic review and meta-analysis. J Psychiatr Res 2017;90:67-77. [doi: 10.1016/j.jpsychires.2017.02.009] [Medline: 28231496]
57. Vita A, Barlati S, Ceraso A, Deste G, Nibbio G, Wykes T. Acceptability of cognitive remediation for schizophrenia: a systematic review and meta-analysis of randomized controlled trials. Psychol Med 2023 Jun;53(8):3661-3671 [FREE Full text] [doi: 10.1017/S0033291722000319] [Medline: 35257646]

Abbreviations

BACS: Brief Assessment of Cognition in Schizophrenia
BIS/BAS: Behavioral Inhibition System and Behavioral Activation System
BPRS: Brief Psychiatric Rating Scale
CAINS: Clinical Assessment Interview for Negative Symptoms
CDSS: Calgary Depression Scale for Schizophrenia
CIRCuiTS: Computerized Interactive Remediation of Cognition-Training for Schizophrenia
CR: cognitive remediation
fMRI: functional magnetic resonance imaging
LSP-16: Life Skills Profile
MP2RAGE: magnetization prepared 2 rapid acquisition gradient echoes
RL: reward learning
ScoRS: Schizophrenia Cognition Rating Scale
SSD: schizophrenia spectrum disorder
TAU: treatment-as-usual
TMG: Trial Management Group
TOPF: Test of Premorbid Functioning

Edited by A Mavragani; submitted 06.09.23; peer-reviewed by PD Harvey, A Hudon, A Lynham; comments to author 05.11.23; revised version received 23.11.23; accepted 04.12.23; published 22.01.24.

Please cite as:
Dark F, Galloway G, Gray M, Cella M, De Monte V, Gore-Jones V, Ritchie G
Reward Learning as a Potential Mechanism for Improvement in Schizophrenia Spectrum Disorders Following Cognitive Remediation: Protocol for a Clinical, Nonrandomized, Pre-Post Pilot Study
JMIR Res Protoc 2024;13:e52505
URL: https://www.researchprotocols.org/2024/1/e52505
doi:10.2196/52505
PMID:38252470

Protocol

Education of Patients With Atrial Fibrillation and Evaluation of the Efficacy of a Mobile Virtual Patient Environment: Protocol for a Multicenter Pseudorandomized Controlled Trial

Panagiotis Antoniou[1], PhD; Eleni Dafli[1], MD, PhD; George Giannakoulas[2], MD, PhD; Gaukhar Igimbayeva[3], MD, PhD; Olga Visternichan[4], MD, PhD; Serhii Kyselov[5], Prof Dr; Ivetta Lykhasenko[6], MD, PhD; Dmytro Lashkul[5], MD, PhD; Ilia Nadareishvili[7], MD, PhD; Sergo Tabagari[7], Prof Dr; Panagiotis D Bamidis[1], PhD

[1]Lab of Medical Physics and Digital Innovation, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece

[2]1st Cardiology Department, AHEPA University General Hospital of Thessaloniki, Thessaloniki, Greece

[3]Orhun Medical Clinic, Almaty, Kazakhstan

[4]Internal Medicine Department, Karaganda Medical University, Karaganda, Kazakhstan

[5]Department of Internal Diseases No.1 and Simulation Medicine, Zaporizhzhia State Medical University, Zaporizhzhia, Ukraine

[6]Department of Propedeutics of Internal Diseases, Radiation Diagnostics and Radiation, Zaporizhzhia State Medical University, Zaporizhzhia, Ukraine

[7]AIETI Medical School, David Tvildiani Medical University, Tbilisi, Georgia

Corresponding Author:
Panagiotis D Bamidis, PhD
Lab of Medical Physics and Digital Innovation
School of Medicine
Aristotle University of Thessaloniki
PO Box 376
Thessaloniki, 541 24
Greece
Phone: 30 6972008122
Email: bamidis@auth.gr

Abstract

Background: Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is a leading cause of mortality and morbidity. Patient knowledge about AF and its management is paramount but often limited. Patients need to be appropriately informed about treatment options, medicinal adherence, and potential consequences of nonadherence, while also understanding treatment goals and expectations from it. Mobile health apps have experienced an explosion both in their availability and acceptance as “soft interventions” for patient engagement and education; however, the prolific nature of such solutions revealed a gap in the evidence base regarding their efficacy and impact. Virtual patients (VPs), interactive computer simulations, have been used as learning activities in modern health care education. VPs demonstrably improved cognitive and behavioral skills; hence, they have been effectively implemented across undergraduate and postgraduate curricula. However, their application in patient education has been rather limited so far.

Objective: This work aims to implement and evaluate the efficacy of a mobile-deployed VP regimen for the education and engagement of patients with AF on crucial topics regarding their condition. A mobile VP app is being developed with the goal of each VP being a simple scenario with a set goal and very specific messages and will be subsequently attempted and evaluated.

Methods: A mobile VP player app is being developed so as to be used for the design of 3 educational scenarios for AF management. A pseudorandomized controlled trial for the efficacy of VPs is planned to be executed at 3 sites in Greece, Ukraine, and Kazakhstan for patients with AF. The Welch *t* test will be used to demonstrate the performance of patients’ evaluation of the VP experience.

Results: Our study is at the development stage. A preliminary study regarding the system’s development and feasibility was initiated in December 2022. The results of our study are expected to be available in 2024 or when the needed sample size is achieved.

Conclusions: This study aims to evaluate and demonstrate the first significant evidence for the value of VP resources in outreach and training endeavors for empowering and patients with AF and fostering healthy habits among them.

International Registered Report Identifier (IRRID): PRR1-10.2196/45946

(JMIR Res Protoc 2024;13:e45946) doi:10.2196/45946

KEYWORDS

atrial fibrillation; virtual patient; scenario based learning; technology enhanced learning; mHealth; mobile health; patient engagement; patient education; cardiac arrhythmia; mortality; mobile application; mobile app; health education; randomized control trial; cardiology; cardiac; heart; Greece; Ukraine; Kazakhstan; clinical decision support systems; CDSS; virtual patient scenario; myocardial infarction; arrhythmia; stroke

Introduction

Impact of Atrial Fibrillation and Non–Vitamin K Oral Anticoagulants and the Role of Integrated Management

Atrial fibrillation (AF) is the most frequent long-term cardiac arrhythmia in adults, presenting a considerable burden on patients, health care systems, societal health, and the global health economy [1]. Because AF is associated with significant morbidity and mortality, numerous research efforts and resources are being directed toward gaining more detailed information about the mechanisms underlying AF, its natural course, and effective treatments, and new evidence is being generated and published on a regular basis [2].

The current estimated prevalence of AF is between 2% and 4% [3], with a 2.3-fold increase projected due to the general population's increased longevity and the intensive search for AF [4]. AF is a well-known risk factor for thrombus development in the left atrium and eventual embolism on the left side. AF raises the risk of stroke by 5 folds, but the risk varies depending on the presence of stroke risk factors or modifiers [2]. Oral anticoagulants (OAC) are the cornerstone of AF treatment. Vitamin K antagonist (VKA) medication (mainly warfarin) lowers the risk of stroke and death by 64% and 26%, respectively, when compared to control or placebo [5]. Non–vitamin K oral OACs (NOACs) have outperformed VKAs in most therapeutic circumstances. NOAC medications do not have the practical constraints of VKAs, such as a small therapeutic window, interactions with food and other treatments, and the need to monitor coagulation levels. In 4 large randomized controlled trials (RCTs) with patients with AF, NOACs were compared to warfarin [6-9]. They were demonstrated to be at least noninferior to VKA therapy for the prevention of stroke or recurrent venous thromboembolism and were associated with a lower risk of bleeding. In a meta-analysis of these RCTs, NOACs were associated with a 19% significant reduction in the risk of stroke or systemic embolism, a 51% reduction in the risk of hemorrhagic stroke, and a similar reduction in the risk of ischemic stroke compared to VKAs. NOACs are also associated with a 10% reduction in all-cause mortality [10].

To provide optimal medical treatment to patients with AF, integrated management necessitates a patient-individualized care route. Treatment choices should be reviewed and a management plan agreed upon with health care experts in this patient-centered approach [11]. Treatment is liable to alter over time as new symptoms, risk factors, disease progression, and novel medicines emerge. To prevent stroke and improve symptoms, it is critical to consider optimizing resource usage. The initial stage in shared decision-making should be to investigate the patients' preferences [12]. The importance of stroke prevention and rhythm control among patients, as well as the corresponding risks of death, stroke, and significant bleeding, should be properly appraised for shared decision-making.

Patients’ awareness of AF and its management is sometimes restricted, especially when first diagnosed, because the majority of treatment decisions must be addressed and made. Furthermore, controlling patients' expectations of treatment goals, as well as ensuring that patients are correctly informed about treatment options, how to better adhere to therapy, and potential repercussions of nonadherence, are critical to increase adherence [2]. Thorough education of physicians on these approaches, as well as correct adherence and active engagement of the patient in the treatment process, are critical to the success of each treatment plan. Soft health interventions for education and empowerment of both clinicians and patients are critical in this environment.

Education and Other Soft Interventions Involving Mobile Health Apps in Cardiology

There has been an explosion of mobile health (mHealth) apps during the previous decade, with an estimated 3.7 billion downloads globally between 2013 and 2017 [13], many of which are intended for AF. A 2020 systematic review revealed around 11,152 articles related to mHealth apps for AF but only included 9 studies with real outcomes about mHealth therapies for AF in its results synthesis [14]. This indicates the prevalence of such solutions, as well as the dearth of data on their efficacy and impact. Only a few apps have been evaluated formally [15-17]. It should be emphasized that there are few apps that are specifically intended for patients. There are numerous informative apps that patients can use; however, a preferred option would be the development of a specific app for the treatment of a given ailment in order to help afflicted individuals in a more appropriate way [18].

Clinical decision support systems that digitize and provide evidence-based recommendations, therapeutic pathways, and algorithms to facilitate individualized, timely, and evidence-based treatment could be a valuable aid in the holistic management of AF. To improve patient-integrated AF management [19], the MobiGuide project [20] and numerous applications have been deployed. The European Society of Cardiology–Characterizing Atrial fibrillation by Translating its Causes into Health Modifiers in the Elderly Consortium partnership offers a smartphone or tablet app for patients with

AF; however, it has yet to be tested prospectively [21]. Contradictory findings highlight the need for more properly designed trials, including evaluation of the intervention's influence on clinical outcomes [22].

As a result, the scope and impact of mHealth apps for AF, as well as the level of patient and health care professional (HCP) engagement and acceptability, are currently unknown. HCP engagement refers to information sharing between the patient and provider, shared responsibilities in decision-making processes, and support of patients' choices and acceptability to a degree to which an intervention is approved by most HCPs. Given both patients and HCPs may easily use these applications, it is critical to understand their scope and content and their acceptability among users, and to investigate the purpose and results of app adoption and usage.

Virtual Patients in Health Care Education

Virtual patients (VPs)—interactive computer-based clinical scenarios for the purpose of medical training, education, or assessment—have been increasingly used as learning activities in current health care education, particularly in teaching decision-making through scenarios [23]. Because VPs can enhance cognitive and behavioral skills, they have been successfully incorporated in undergraduate and postgraduate curricula [24]. With the rising use of VPs, there are opportunities for pedagogical synergies to allow trainees of diverse categories to practice in realistic and safe learning contexts [25]. The key characteristics of VP systems are that they enable repetitive and intentional practice by any student, regardless of time or physical location, and that mistakes are not fatal. These opportunities provided by VPs in current medical education, combined with positive evaluation results from various studies demonstrating that they may improve cognitive and behavioral skills better than traditional methods [24], have resulted in a widespread trend toward VP creation and use among academic institutions [26]. Furthermore, VPs enable the production and usage of more game-based educational content, which provides the student more exploratory flexibility and provides a different area for case-based content in current medical education.

The widespread adoption of these digital technologies, not only in medical student education but also in the health care community in general and in the patient community, has undoubtedly been limited thus far, but it has the potential to educate and psychologically support high-risk patients and vulnerable populations in these new and unprecedented circumstances. Because numerous academic institutions have the VP resources and expertise in their execution, such effective educational content might be simply repurposed in a more patient-centered format and be used more widely by the patient community as an educational aid.

Study Aim and Objectives

In this technological setting, we propose the development of a holistic approach to patient engagement and education based on the fundamentals of AF. The DEEP-RAFT (Doctors' Education, Empowerment of Patients, Regarding Atrial Fibrillation and Venous Thromboembolism) project would generate a suite of educational and informational interventions along an axis created by 2 poles: digital content cocreation and evidence-based educational impact. This effort will be based on a suite of digital teaching resources, in the form of VPs, co-designed by continuous and immediate involvement of health care specialists, health care policy influencers, and patients. This strategy seeks, first and foremost, to develop materials that are more patient-centered and address realistic problems relevant to the health care systems involved in the project. The focus of this effort is on the second topic, evidence-based educational impact, which attempts to demonstrate the educational efficacy and acceptance of the generated resources as they may be used in a diverse but targeted set of education and outreach activities.

In practice, a mobile app for natively deploying VPs on mobile devices is developed, along with a list of relevant VPs. In the following parts, we will provide these concrete and intangible tools and approaches to contextualize the protocol that is described below.

Methods

Study Design

This is a 2-arm, parallel-group pseudorandomized controlled trial that will be performed at 3 sites—Greece, Ukraine, and Kazakhstan—and will include the evaluation of the educational VP interventions. This will be conducted in 2 axes that correspond to the primary outcomes of the study. The first axis aims to determine the efficacy of the educational VP interventions, while the other will involve assessing the acceptance and opinions of the participants about the VP modality for education and information purposes. Correspondingly, the primary outcomes of the study include the efficacy and the acceptance of the VP interventions, and the secondary outcomes include the opinions of the participants about the VP modality for education and information purposes. The aims of the study are summarized in the following research question: are patients with AF better educated about their post–acute phase lifestyle changes and needs by using mobile virtual scenarios compared to conventional patient education methods?

A prepilot arm of the study will be initially conducted in Greece and will consist of hospitalized patients due to AF episodes, all of which should complete a short quiz. From among the patients who complete the quiz, half of the patients will be randomly allocated to the control (normal clinical information) cohort, while the other half will be informed with the help of VP vignettes.

After the prepilot arm, the pseudorandomized controlled trial will be conducted multicentrically. The same process, as in the prepilot arm, will be followed for recruiting the core sample, exploring the efficacy and impact of VPs in educating patients with AF. Since this trial will have been conducted during the COVID-19 pandemic, all national and international health and safety protocols will be followed.

Inclusion and Exclusion Criteria and the Recruitment Process

The inclusion and exclusion criteria are outlined in Textbox 1. The dropout criterion is withdrawing consent during the study period.

In the Greek pilot where randomization of patient cohorts would occur, a simple coin toss algorithm will be used, implemented by Excel's (Microsoft Corp) RANDBETWEEN function. This will allocate patients between the VP education cohort and the control (normal clinical information) cohort. In the Ukraine pilot, a sampling of convenience will allocate most of the participants to the VP cohorts and fewer to the control (normal clinical information) cohort. In the Kazakhstan pilot, all accepted patients will be allocated to the VP intervention cohort. While this decision by the medical team of this center makes impossible the conduct of a distinct local evaluation of impact, we chose to include the sample in the multicentric data processing part of the study. It should be noted that evaluation results will be extracted on a per-site basis only in the Greece and Ukraine arms of the study. In the multisite comparison, the whole sample of intervention patients (including the totality of the Kazakh cohort) will be compared to the totality of the sample of control patients from Greece and Ukraine cohorts.

Patients who meet the requirements for that study will be informed about the study and will be asked if they would like to participate in it. They will then sign the consent form to take part in the study. Patients who may withdraw their consent during the study will be excluded from the analysis.

Textbox 1. Study inclusion and exclusion criteria.

Inclusion criteria:

- Patients with a history of paroxysmal, persistent, or permanent atrial fibrillation
- Access to an internet connection and adequate equipment
- Mastery of the country's first language
- Informed consent provided by the participant

Exclusion criteria:

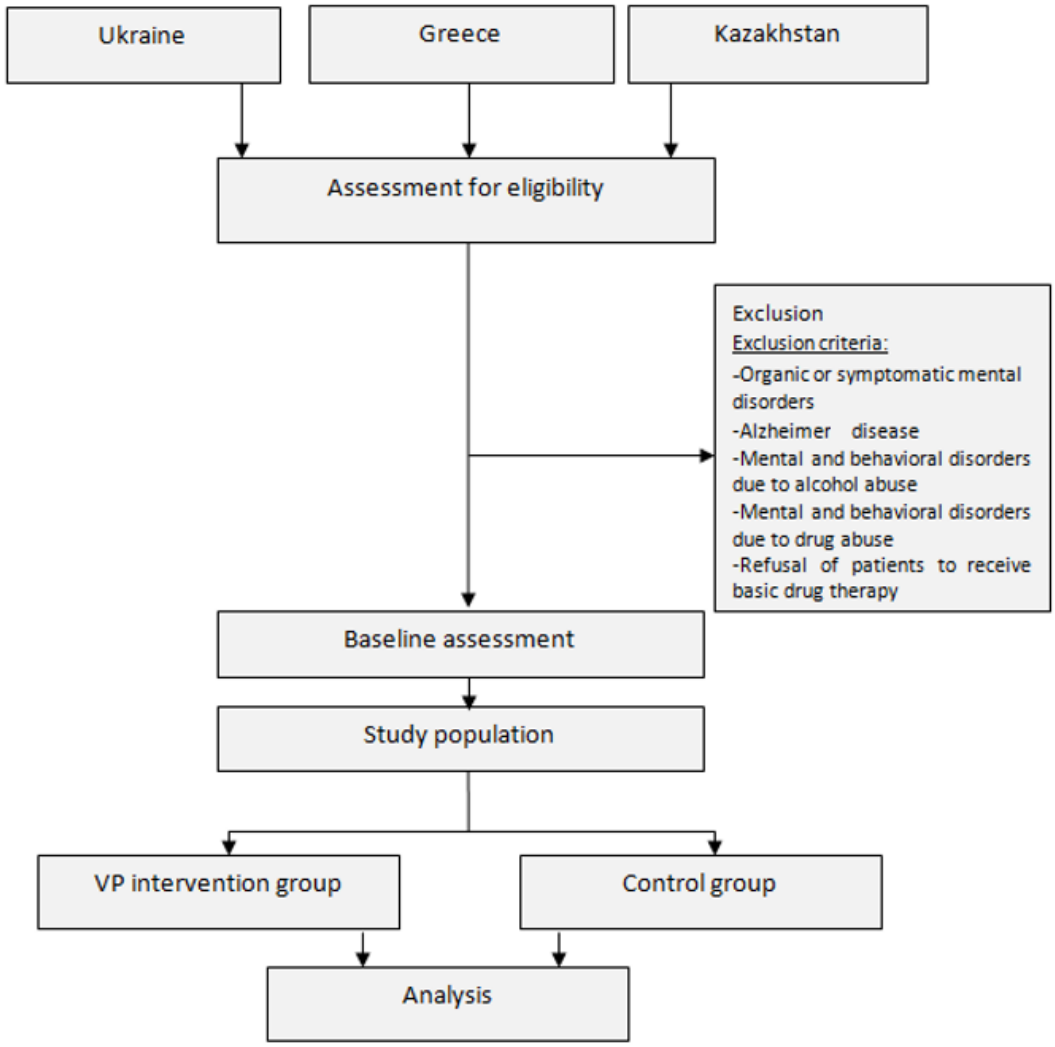
- Organic or symptomatic mental disorders
- Alzheimer disease
- Mental and behavioral disorders due to alcohol abuse
- Mental and behavioral disorders due to drug abuse
- Refusal of patients to receive basic drug therapy

Intervention Cohorts

The full pilot arm of the study will be conducted multinationally in Greece, Ukraine, and Kazakhstan (Figure 1). In Greece, a pool of 700 patients will be reached by phone, and they will participate in the trial from their home. From among the patients contacted remotely, and from those who respond, those who would be eligible will be asked to complete the intervention. From among the patients who choose to complete the quiz, half of them will be randomly allocated to the control (normal clinical information) cohort, while the other half will be informed with the help of VP vignettes. In Ukraine, 160 patients will be reached and will be divided into the control and intervention groups. Finally, at the Kazakhstan center, 190 patients will be contacted.

Given that all recruitment and adherence criteria are followed, sufficient sample sizes for control and intervention groups will be ensured so as to use the Welch *t* test for analysis, which is robust to large sample size inequalities, in order to not exclude any useful data from the generalized multicenter VP cohort.

Figure 1. The flowchart of the full pilot arm of the study. VP: virtual patient.



Blinding (Masking)

Participants and trial personnel will not be blinded after the point of assignment to interventions because of the nature of the interventions and outcomes assessed. Participants will know which group they will belong to because the group-specific intervention will follow immediately after randomization.

The Intervention

The 2 groups that will be compared are as follows.

The VP Cohort

In this cohort, doctors of the research team will contact patients and ask them to participate in the VP vignette case (see *The VPs* section for a detailed description of the virtual scenarios used in the intervention, and the *The Technical Architecture of the Mobile App* section for details of the mobile app that will be used for delivering the intervention). At the end of the case questions, further information will be provided.

The Control (Normal Clinical Information) Cohort

In this cohort, doctors of the research team will contact patients and provide the protocol—this will include dictated information for patients with AF.

The Technical Architecture of the Mobile App

A mobile VP player app has been created, which is capable of tracking the following user data: a detailed log of pathway detection and tracking, time spent in each node of the VPs or mobile VP, tracking of milestones, rate of successful completion of the VPs or mobile VP, and connection to learning outcomes. The player follows a flat development approach and should be available as a progressive web application. A progressive web application is a type of web-based application software that is built using standard web technologies such as HTML, CSS, and JavaScript. It is aimed to be compatible with any platform that supports a standards-compliant browser. The ability to work offline, receive push notifications, and access device hardware will enable the creation of user experiences similar to those found in native applications on desktop and mobile devices. Because a progressive web application is a subset of a web page or website known to be a web application, neither developers nor users should be required to install web applications through digital distribution systems such as the Apple App Store or Google Play.

Technically, communication between the backend and the front end player is accomplished through the use of the JSON application programming interface standard [27], which is an

extremely efficient method of exchanging data over slow networks (eg, mobile phone networks).

The system's appearance and feel are based on Bootstrap, a free and open-source CSS framework for developing responsive, mobile-first front end web applications. It would be optimized for smartphone screens so as to provide a “mobile-first” user experience.

The VPs

Three scenarios will be explored by the participating medical teams. All will be focused on the patients, since these are the target group of the VPs. A tabulated outline of these scenarios is presented in Table 1. The first scenario should be dealing with a chronic case of AF, including guidance for good medication adherence, systematic medical appointments, and correct communication. The second scenario would be about detecting early onset and prevention of paroxysmic AF. The third scenario will deal with a case of AF that involves lifestyle-compounding factors to the disease (smoking, drinking, and unhealthy eating), as well as more heavy complications that are significantly more probable in such cases.

Table 1. Outline of suggested scenarios and educational objectives of virtual patients.

Scenario theme	Educational objectives (after encountering this educational virtual scenario vignette, the patient will be able to…)
Chronic case of AF[a]	• Identify correct medication adherence practices • Identify the correct frequency regimen of doctors’ appointments • Identify correct dietary restrictions
Early-onset and paroxysmic AF	• Identify initial onset of symptoms of AF • Identify timely medical consultation practices • Recognize the correct medicinal adherence procedure for the condition • Identify the correct exercise intensity to manage the condition
AF with lifestyle- compounding factors to the disease (smoking, drinking, and unhealthy eating)	• All educational objectives of “Chronic case of AF” • Identify risks of high-impact complications • Identify best practices for recovering from missed doses of medical treatment

[a]AF: atrial fibrillation.

Iterative brainstorming between the medical experts of all study centers will produce the detailed VP scenarios in the mobile digital platform (for details, refer to the previous section, *The Technical Architecture of the Mobile App*). After an internal review of these scenarios by the multinational expert panel, a selection would be made for the final case to be used. In that context, the team will choose to simply use 1 scenario in the multicenter multinational cohort trials. The most appropriate scenario would have the following characteristics: (1) it should be the most relevant—a significantly larger proportion of patients should be targeted; (2) it should be the most clinically impactful—it is important and useful for patients with AF to be aware of AF complications; and (3) it should be the most educationally important—both patients who fall within the parameters of the described case and those who do not would benefit from information and preventative knowledge of the impact of AF.

An acceptance rate of 75% by medical experts for each criterion for each scenario should be reached to be eligible for recruitment. Moreover, this patient education intervention will be based on techniques from the behavior change technique taxonomy—an international consensus for the reporting of behavior change interventions [28].

After this selection, a process of localization and adaptation to the specifics of each center (Greece, Ukraine, and Kazakhstan) would be conducted.

Evaluation Design

Evaluation Instruments

For educational efficacy, a multiple-choice questionnaire (MCQ) for knowledge retention will be used (Textbox 2). The choice of questions was based on the European Society of Cardiology’s *Guidelines for Management of Atrial Fibrillation* [29]. This instrument will be translated for all participating centers in Greece, Ukraine, and Kazakhstan. The translation and evaluation of the translation will be performed by teams of bilingual experts. The instrument in its original version will be provided to bilingual persons in alternating language order and will be assessed accordingly. Scoring each questionnaire follows a simple process of allocating a numerical score equal to the number of choices in the MCQ to weigh each response for randomly selecting the correct question. For example, a question that has 4 possible responses in the MCQ will be scored 4 points if answered correctly, while a question that has 5 possible answers will be scored with 5 points if correctly answered.

Textbox 2. Questionnaire for knowledge retention on atrial fibrillation (the asterisk indicates the correct answer).

1. Atrial fibrillation:

- Is the most common cardiac arrhythmia
- More often concerns older people, but can occur in any age
- May be related with thyroid disorders
- All of the above*

2. The most common symptom of atrial fibrillation is:

- Chest pain
- Palpitations*
- Dizziness
- Blurry vision

3. How can atrial fibrillation be diagnosed?

- Following an electrocardiogram evaluated by a cardiologist*
- By describing symptoms of the arrhythmia to the doctor
- By checking the indication ‘’arrhythmia’’ of the blood pressure device
- All of the above

4. What is the most important complication a patient with atrial fibrillation not receiving treatment may suffer?

- Fainting spells
- Myocardial infarction
- Lethal arrhythmia
- Ischemic stroke*

5. Treatment with oral anticoagulants always mandates frequent blood tests:

- True
- False*

6. The patient with atrial fibrillation that visits a cardiologist:

- Probably does not need oral anticoagulation to prevent stroke
- Always needs treatment to cure the arrhythmia
- Cardiologist? There is no need to see a doctor
- Might have to be admitted to the hospital at the time of Atrial Fibrillation diagnosis *

7. When the patient with atrial fibrillation is being treated with an oral anticoagulant:

- It is better to receive the reduced dose so as to avoid bleeding
- This is always stopped at 3 months, since the danger for stroke is gradually reduced
- It is fine if he/she occasionally misses a dose
- He/she has to adherently receive the right dose of the drug, as prescribed by his/her treating physician*

8. The newer oral anticoagulants:

- Are at least as safe and effective as warfarin in preventing stroke
- Have to be taken every day on a fixed schedule, so as to be effective
- Do not have important interactions with other drugs or food, in contrast to warfarin
- All of the above*

9. Oral anticoagulants:

- Are not necessary, in case the patient already receives other blood thinning medication, such as aspirin

- Are the most effective treatment in preventing stroke*
- Do not have any significant side effect
- All of the above

10. A patient that is under warfarin:

- Cannot switch to a newer oral anticoagulant if he/she has good anticoagulation control (international normalized ratio within the desired range)
- Can follow an unrestricted diet
- Can get advice from his doctor regarding treatment with a newer anticoagulant, so as there is no need for frequent blood tests*
- Always has good anticoagulation control (INR within the desired range) if he/she receives his medication in a fixed dose

Project Management

All project members will meet remotely every week to work through advances and challenges together and to provide methodological support to remain aligned with the protocol. Researchers will be hired and trained, regulate safety conditions, and oversee the data collection and analysis. The researchers will prepare the data collection tools and perform data collection, and ensure that the materials required are adequate and functional. The senior Greek PI (PDB) will coordinate the overall project.

Ethical Considerations

Ethics approval has been obtained from the Bioethics committee of the Medical School of the Aristotle University of Thessaloniki (178/19-3-2020). This study will be conducted in line with the tenets of the Declaration of Helsinki, and no participant will be randomized unless written informed consent is available for that participant. Participants can withdraw from the trial at any time and will be informed and assured of such right. This study follows the principles of data protection and management described in the European Union's General Data Protection Regulation.

Confidentiality

All personal and collected data will be treated as confidential at all stages of the study and will be stored separately. The electronic data will be saved with metadata in university network drives, which are protected by usernames and passwords. The participant ID list that links the study participants and research data will be disposed of after 15 years. Institutions hold the ownership of registry data.

Results

The trials will start in 2024 and are expected to end later that year or in early 2025 or when the needed sample size is achieved. The initial results are expected by March 2024.

To assess the results from the prepilot evaluation questionnaires, the Welch *t* test will be conducted. Of note, we decided to conduct the Welch *t* test because some of our sample sizes will be heavily unequal between intervention and control groups. The standard Student *t* test is robust to inhomogeneity of variance when sample sizes between cohorts are the same; however, this is not true for largely differing cohort sample sizes. The Welch *t* test does not assume homogeneity of variance and, hence, is robust to widely varying sample sizes [30,31].

Discussion

Expected Findings

The results of this study aim to demonstrate the efficacy of the VP educational modality in transferring knowledge in an impactful way so that it would be useful and retained by the learner. The rationale for this kind of expected efficacy may be attributed to various factors. The impact of information passed through narrative vehicles has been identified early on [32]. Additionally, the initiative that the learner has to guide the narrative through their choices facilitates engagement through 2 avenues: one avenue is the agency that the learner has over their narrative exploration, and the second one, dependent on the first but not identical, is the ability to direct the narrative toward educational needs that the learner may have. These factors are compounded by the immediacy and ease of access that the mobile delivery platform offers, which can create an engaging and user-friendly experience that may amplify the educational impact.

This work will focus on knowledge retention and efficacy and not on perceived changes in quality of life. The impact of AF itself in the quality of life of patients is well documented with a validated questionnaire that has been available since the last decade [33]. A cursory search with the keyword "AFEQT" revealed more than 550 references on Google Scholar, including several reviews (for characteristic examples, see Kotecha et al [34] and Parameswaran et al [35]).

On the other hand, there is a significant body of literature that has identified the perceived impact of impactful patient education in their risks for serious complications and quality of life. AF, when first diagnosed, is an overwhelming situation for the patient, and reliable information is one of the first requirements for alleviating the initial possible shock [36,37]. Furthermore, lack of knowledge leads patients with AF to have significantly skewed perceptions about the importance of their condition and the true risks that stem from this potentially life-threatening, possibly chronic, condition.

Multiple studies have demonstrated that patients do not identify the possibility of stroke as an acute complication of AF; a lot of them cannot even identify their arrhythmias as AF, and they

do not recognize AF as life-threatening even though they receive verbal or printed information about their condition [38,39].

In that context, it is very important to constantly explore information and educational avenues that are impactful and engaging for patients who need reliable and immediately absorbable information. This study aims to demonstrate that in this very important aspect of knowledge retention, the approach of narrative virtual scenarios is one that could provide a distinct impact advantage over the conventional paper-based or verbal information to the patients.

Limitations

The study's core limitation lies with the knowledge retention questionnaire. This is not a validated instrument. While we were aware of a formal validated instrument (the Jessa Atrial fibrillation Knowledge Questionnaire [40]), the knowledge spectrum that it covers is far wider than what our VP vignette may cover. Given that verbal and printed conventional information covers all relevant material, while our VP may cover specific critical topics related to AF, using a wide instrument such as the Jessa Atrial fibrillation Knowledge Questionnaire would run the risk to evaluate knowledge retention gaps that the VP vignette cannot cover. While a counterargument can be made that we are thus narrowing the evaluation scope to the strong points of our VP resource, the concise focus of the VP vignette is itself an argument for implementing it as a more effective educational tool in personalized and focused endeavors for patient empowerment. As a follow through too, we aim to address the second weakness of our study, which is the lack of a qualitative exploration about the acceptance of patients regarding the electronic medium of mobile devices and the modality of VPs in comparison to other existing modalities such as video demonstration or even gamified virtual environments.

Even given these limitations, however, this study can provide evidence for the comparatively better efficacy of the VP modality in mobile media for impactful and effective information for and empowerment of patients with AF. This study would be the first evidence-based step to initiate this process toward better informing and subsequent empowerment of patients with regard to the management of their disease.

Conclusions

This project can generate new knowledge and relevant results for a deployed VP regimen for the education and engagement of patients with AF on crucial topics regarding their condition. A 3-center pseudorandomized controlled trial could add data to the evidence regarding the effects of interventions using VP resources in outreach and training endeavors for empowering patients with AF.

Acknowledgments

This work is partially supported by Pfizer's independent grants for learning and change on Improving the Identification and Management of Patients with Atrial Fibrillation in Order to Reduce Stroke Risk and Venous Thromboembolism in Eastern Europe, project DEEP-RAFT (grant ID 42537945), and the Training and Ubiquitous Outreach, Using Social INnovation and Co-Design of Learning resoUrces and Digital Engagement, project TOUS-INCLUDE (grant ID 63829625).

Conflicts of Interest

GG received fees for lecture travels or research from Bayer, Boehringer Ingelheim, Pfizer, and LeoPharma. The other authors declare no conflicts of interest.

References

1. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, American Heart Association Statistics CommitteeStroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2017 Update: a report from the American Heart Association. Circulation 2017 Mar 07;135(10):e146-e603 [FREE Full text] [doi: 10.1161/CIR.0000000000000485] [Medline: 28122885]
2. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J 2021 Feb 01;42(5):373-498. [doi: 10.1093/eurheartj/ehaa612] [Medline: 32860505]
3. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, American Heart Association Council on EpidemiologyPrevention Statistics CommitteeStroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2019 Update: a report from the American Heart Association. Circulation 2019 Mar 05;139(10):e56-e528 [FREE Full text] [doi: 10.1161/CIR.0000000000000659] [Medline: 30700139]
4. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. Circulation 2014 Feb 25;129(8):837-847 [FREE Full text] [doi: 10.1161/CIRCULATIONAHA.113.005119] [Medline: 24345399]
5. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007 Jun 19;146(12):857-867. [doi: 10.7326/0003-4819-146-12-200706190-00007] [Medline: 17577005]

6. Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M, ARISTOTLE CommitteesInvestigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011 Sep 15;365(11):981-992. [doi: 10.1056/NEJMoa1107039] [Medline: 21870978]
7. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, RE-LY Steering CommitteeInvestigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009 Sep 17;361(12):1139-1151 [FREE Full text] [doi: 10.1056/NEJMoa0905561] [Medline: 19717844]
8. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011 Sep 08;365(10):883-891. [doi: 10.1056/NEJMoa1009638] [Medline: 21830957]
9. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013 Nov 28;369(22):2093-2104 [FREE Full text] [doi: 10.1056/NEJMoa1310907] [Medline: 24251359]
10. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014 Mar 15;383(9921):955-962. [doi: 10.1016/S0140-6736(13)62343-0] [Medline: 24315724]
11. Charles C, Whelan T, Gafni A. What do we mean by partnership in making decisions about treatment? BMJ 1999 Sep 18;319(7212):780-782 [FREE Full text] [doi: 10.1136/bmj.319.7212.780] [Medline: 10488014]
12. Lane DA, Aguinaga L, Blomström-Lundqvist C, Boriani G, Dan G, Hills MT, et al. Cardiac tachyarrhythmias and patient values and preferences for their management: the European Heart Rhythm Association (EHRA) consensus document endorsed by the Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLEACE). Europace 2015 Dec;17(12):1747-1769. [doi: 10.1093/europace/euv233] [Medline: 26108807]
13. van der Velden RM, Hermans AN, Pluymaekers NA, Gawalko M, Vorstermans B, Martens H, et al. Coordination of a remote mHealth infrastructure for atrial fibrillation management during COVID-19 and beyond: TeleCheck-AF. Int J Care Coord 2020 Aug 27;23(2-3):65-70. [doi: 10.1177/2053434520954619]
14. Lane DA, McMahon N, Gibson J, Weldon JC, Farkowski MM, Lenarczyk R, et al. Mobile health applications for managing atrial fibrillation for healthcare professionals and patients: a systematic review. Europace 2020 Aug 27. [doi: 10.1093/europace/euaa269] [Medline: 32853369]
15. Desteghe L, Germeys J, Vijgen J, Koopman P, Dilling-Boer D, Schurmans J, et al. Effectiveness and usability of an online tailored education platform for atrial fibrillation patients undergoing a direct current cardioversion or pulmonary vein isolation. Int J Cardiol 2018 Dec 01;272:123-129. [doi: 10.1016/j.ijcard.2018.07.065] [Medline: 30049498]
16. Desteghe L, Kluts K, Vijgen J, Koopman P, Dilling-Boer D, Schurmans J, et al. The Health Buddies app as a novel tool to improve adherence and knowledge in atrial fibrillation patients: a pilot study. JMIR Mhealth Uhealth 2017 Jul 19;5(7):e98 [FREE Full text] [doi: 10.2196/mhealth.7420] [Medline: 28724512]
17. Guo Y, Chen Y, Lane DA, Liu L, Wang Y, Lip GYH. Mobile health technology for atrial fibrillation management integrating decision support, education, and patient involvement: mAF app trial. Am J Med 2017 Dec;130(12):1388-1396.e6 [FREE Full text] [doi: 10.1016/j.amjmed.2017.07.003] [Medline: 28847546]
18. Martínez-Pérez B, de la Torre-Díez I, López-Coronado M, Herreros-González J. Mobile apps in cardiology: review. JMIR Mhealth Uhealth 2013 Jul 24;1(2):e15 [FREE Full text] [doi: 10.2196/mhealth.2737] [Medline: 25098320]
19. Stephan LS, Dytz Almeida E, Guimaraes RB, Ley AG, Mathias RG, Assis MV, et al. Processes and recommendations for creating mHealth apps for low-income populations. JMIR Mhealth Uhealth 2017 Apr 03;5(4):e41 [FREE Full text] [doi: 10.2196/mhealth.6510] [Medline: 28373155]
20. Parimbelli E, Sacchi L, Budasu R, Napolitano C, Peleg M, Quaglini S. The role of nurses in E-Health: the MobiGuide Project experience. Stud Health Technol Inform 2016;225:153-157. [Medline: 27332181]
21. Kotecha D, Chua WWL, Fabritz L, Hendriks J, Casadei B, Schotten U, European Society of Cardiology (ESC) Atrial Fibrillation Guidelines Taskforce, the CATCH ME consortiumthe European Heart Rhythm Association (EHRA). European Society of Cardiology smartphone and tablet applications for patients with atrial fibrillation and their health care providers. Europace 2018 Feb 01;20(2):225-233 [FREE Full text] [doi: 10.1093/europace/eux299] [Medline: 29040548]
22. Vinereanu D, Lopes RD, Bahit MC, Xavier D, Jiang J, Al-Khalidi HR, IMPACT-AF investigators. A multifaceted intervention to improve treatment with oral anticoagulants in atrial fibrillation (IMPACT-AF): an international, cluster-randomised trial. Lancet 2017 Oct 14;390(10104):1737-1746. [doi: 10.1016/S0140-6736(17)32165-7] [Medline: 28859942]
23. Kononowicz AA, Zary N, Edelbring S, Corral J, Hege I. Virtual patients--what are we talking about? A framework to classify the meanings of the term in healthcare education. BMC Med Educ 2015 Feb 01;15:11 [FREE Full text] [doi: 10.1186/s12909-015-0296-3] [Medline: 25638167]
24. Triola M, Feldman H, Kalet AL, Zabar S, Kachur EK, Gillespie C, et al. A randomized trial of teaching clinical skills using virtual and live standardized patients. J Gen Intern Med 2006 May;21(5):424-429 [FREE Full text] [doi: 10.1111/j.1525-1497.2006.00421.x] [Medline: 16704382]

25. Dafli E, Fountoukidis I, Hatzisevastou-Loukidou C, D Bamidis P. Curricular integration of virtual patients: a unifying perspective of medical teachers and students. BMC Med Educ 2019 Nov 09;19(1):416 [FREE Full text] [doi: 10.1186/s12909-019-1849-7] [Medline: 31706296]
26. EllawayR, CandlerC, GreeneP, SmothersV. An Architectural Model for MedBiquitous Virtual Patients. In: MedBiquitous. 2006 Presented at: MedBiquitous; April 25-27; Baltimore.
27. JSON API. URL: https://jsonapi.org [accessed 2020-11-14]
28. Michie S, Richardson M, Johnston M, Abraham C, Francis J, Hardeman W, et al. The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. Ann Behav Med 2013 Aug;46(1):81-95 [FREE Full text] [doi: 10.1007/s12160-013-9486-6] [Medline: 23512568]
29. 2020 Guidelines for Management of Atrial Fibrillation. European Society of Cardiology. 2020. URL: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Atrial-Fibrillation-Management [accessed 2024-01-16]
30. Delacre M, Lakens D, Leys C. Why psychologists should by default use Welch's t-test instead of Student's t-test. Int Rev Soc Psychol 2017:92-101 [FREE Full text] [doi: 10.5334/irsp.82]
31. Lu ZL, Yuan KH. Welch's t test. In: Encyclopedia of research design. Thousand Oaks, CA: Sage Publications; 2010:1620-1623.
32. Begg M, Macleod H, Dewhurst D, Ellaway R. Virtual Patients: considerations of narrative and gameplay. 2005 Presented at: 4th International Symposium for Information Design; June 2, 2005; Stuttgart, Germany.
33. Spertus J, Dorian P, Bubien R, Lewis S, Godejohn D, Reynolds MR, et al. Development and validation of the Atrial Fibrillation Effect on QualiTy-of-Life (AFEQT) questionnaire in patients with atrial fibrillation. Circ Arrhythm Electrophysiol 2011 Feb;4(1):15-25. [doi: 10.1161/CIRCEP.110.958033] [Medline: 21160035]
34. Kotecha D, Ahmed A, Calvert M, Lencioni M, Terwee CB, Lane DA. Patient-reported outcomes for quality of life assessment in atrial fibrillation: a systematic review of measurement properties. PLoS One 2016 Nov 1;11(11):e0165790 [FREE Full text] [doi: 10.1371/journal.pone.0165790] [Medline: 27802324]
35. Parameswaran R, Al-Kaisey AM, Kalman JM. Catheter ablation for atrial fibrillation: current indications and evolving technologies. Nat Rev Cardiol 2021 Mar;18(3):210-225. [doi: 10.1038/s41569-020-00451-x] [Medline: 33051613]
36. McCabe PJ, Rhudy LM, DeVon HA. Patients' experiences from symptom onset to initial treatment for atrial fibrillation. J Clin Nurs 2015 Mar;24(5-6):786-796. [doi: 10.1111/jocn.12708] [Medline: 25421608]
37. Thrysoee L, Strömberg A, Brandes A, Hendriks JM. Management of newly diagnosed atrial fibrillation in an outpatient clinic setting-patient's perspectives and experiences. J Clin Nurs 2018 Feb;27(3-4):601-611 [FREE Full text] [doi: 10.1111/jocn.13951] [Medline: 28677250]
38. Aliot E, Breithardt G, Brugada J, Camm J, Lip GYH, Vardas PE, Atrial Fibrillation AWareness And Risk Education group, Atrial Fibrillation Association, European Heart Rhythm Association, Stroke Alliance for Europe, World Heart Federation. An international survey of physician and patient understanding, perception, and attitudes to atrial fibrillation and its contribution to cardiovascular disease morbidity and mortality. Europace 2010 May;12(5):626-633 [FREE Full text] [doi: 10.1093/europace/euq109] [Medline: 20421224]
39. Lane DA, Ponsford J, Shelley A, Sirpal A, Lip GY. Patient knowledge and perceptions of atrial fibrillation and anticoagulant therapy: effects of an educational intervention programme. The West Birmingham Atrial Fibrillation Project. Int J Cardiol 2006 Jun 28;110(3):354-358. [doi: 10.1016/j.ijcard.2005.07.031] [Medline: 16253356]
40. Desteghe L, Engelhard L, Vijgen J, Koopman P, Dilling-Boer D, Schurmans J, et al. Effect of reinforced, targeted in-person education using the Jessa Atrial fibrillation Knowledge Questionnaire in patients with atrial fibrillation: A randomized controlled trial. Eur J Cardiovasc Nurs 2019 Mar;18(3):194-203. [doi: 10.1177/1474515118804353] [Medline: 30328701]

Abbreviations

AF: atrial fibrillation
DEEP-RAFT: Doctors' Education, Empowerment of Patients, Regarding Atrial Fibrillation and Venous Thromboembolism
HCP: health care professional
MCQ: multiple-choice questionnaire
mHealth: mobile health
NOAC: non–vitamin K oral coagulant
OAC: oral anticoagulant
RCT: randomized controlled trial
VKA: vitamin K antagonist
VP: virtual patient

Edited by A Mavragani; submitted 30.01.23; peer-reviewed by V Gosselin Boucher, R Rahimi, M Wright; comments to author 11.08.23; revised version received 11.10.23; accepted 27.10.23; published 23.01.24.

Please cite as:
Antoniou P, Dafli E, Giannakoulas G, Igimbayeva G, Visternichan O, Kyselov S, Lykhasenko I, Lashkul D, Nadareishvili I, Tabagari S, Bamidis PD
Education of Patients With Atrial Fibrillation and Evaluation of the Efficacy of a Mobile Virtual Patient Environment: Protocol for a Multicenter Pseudorandomized Controlled Trial
JMIR Res Protoc 2024;13:e45946
URL: https://www.researchprotocols.org/2024/1/e45946
doi:10.2196/45946
PMID:38261376

Protocol

Web-Based Intervention to Act for Weight Loss in Adults With Type 2 Diabetes With Obesity (Chance2Act): Protocol for a Nonrandomized Controlled Trial

Noraini Mohd Saad[1], MBBS, MPH; Mariam Mohamad[1], MD, MCommHlth; Aimi Nadira Mat Ruzlin[1], BSc (Hons), MPH, PhD

Faculty of Medicine, Universiti Teknologi MARA, Sungai Buloh, Selangor, Malaysia

Corresponding Author:
Mariam Mohamad, MD, MCommHlth
Faculty of Medicine
Universiti Teknologi MARA
Sungai Buloh Campus
Jalan Hospital
Sungai Buloh, Selangor, 47000
Malaysia
Phone: 60 361267176
Email: mariammd@uitm.edu.my

Abstract

Background: In adults with type 2 diabetes (T2D), weight loss can improve hemoglobin A_{1c}, blood pressure, and triglycerides, and reduce the frequency of medications needed. Unfortunately, a large proportion of these individuals are not ready to initiate weight efforts, making existing obesity management strategies less effective. Many digital health interventions aim at weight loss, but there is still limited evidence on their effectiveness in changing weight loss behavior, especially in adults with T2D.

Objective: This study aims to develop and validate "Chance2Act," a new web-based intervention, designed specifically to facilitate behavioral change in adults with T2D with obesity who are not ready to act toward weight loss. Then, the effectiveness of the newly developed intervention will be determined from a nonrandomized controlled trial.

Methods: A web-based intervention will be developed based on the Transtheoretical Model targeting adults with T2D with obesity who are not ready to change for weight loss. Phase 1 will involve the development and validation of the web-based health intervention module. In phase 2, a nonrandomized controlled trial will be conducted in 2 government health clinics selected by the investigator. This is an unblinded study with a parallel assignment (ie, intervention vs control [usual care] with an allocation ratio of 1:1). A total of 124 study participants will be recruited, of which 62 participants will receive the Chance2Act intervention in addition to the usual care. The primary outcome is the changes in an individual's readiness from a stage of not being ready to change (precontemplation, contemplation, or preparation stage) to being ready for weight loss (action stage). The secondary outcomes include changes in self-efficacy, decisional balance, family support for weight loss, BMI, waist circumference, and body fat composition.

Results: The phase 1 study will reveal the intervention's validity through the Content Validity Index and Face Validity Index, considering it valid if both indices exceed 0.83. The effectiveness of the intervention will be determined in phase 2, where the differences within and between groups will be analyzed in terms of the improvement of stages of change and all secondary outcomes as defined in the methodology. Data analysis for phase 2 will commence in 2024, with the anticipated publication of results in March 2024.

Conclusions: If proven effective, the result of the study may give valuable insights into the effective behavioral modification strategies for a web-based intervention targeting adults with T2D with obesity but not yet ready to change for weight loss. This intervention may be replicated or adopted in different settings, focusing on behavioral modification support that patients need. This study offers a deeper understanding of the application of behavior change techniques for a more holistic approach to obesity care in T2D.

Trial Registration: ClinicalTrials.gov NCT05736536; https://clinicaltrials.gov/study/NCT05736536

International Registered Report Identifier (IRRID): DERR1-10.2196/48313

(JMIR Res Protoc 2024;13:e48313) doi:10.2196/48313

KEYWORDS

readiness to change; behavior change; diabetes; overweight; weight reduction; eHealth; obesity

Introduction

Obesity has become one of the leading global health concerns over the last century. Numerous studies have proved the complex relationship between obesity and type 2 diabetes (T2D). The majority of patients with T2D are either overweight or obese, thus increasing their long-term risks of developing cardiovascular diseases and diabetes complications [1]. The World Health Organization (WHO) has reported that around 2.8 million people die each year as a result of being overweight or obese [2]. In patients with T2D, weight loss can improve hemoglobin A_{1c}, blood pressure, triglycerides, and health-related quality of life, and reduce the frequency of medications required [3]. A significant reduction of body weight (>10%) can induce diabetes remission even among those with advanced disease and established diabetes complications [4,5].

In Malaysia, the prevalence of obesity among patients with T2D has been increasing each year, whereby 84% of the patients with T2D were recorded to be either overweight or obese in 2019 [6]. Unfortunately, studies have shown that a large proportion of them (59%-79%) are still not ready to act on losing weight [7,8]. Since they do not have the intention of losing weight, they would not be interested in practicing or acting upon the recommendations given by the primary care personnel and thus, are deprived of the benefit of losing weight.

Interventions in behavior modification have been proven as an important component in a successful weight control program, in addition to the dietary and physical activity components. A European guideline has shown that behavioral change can induce 5%-15% weight loss among overweight or obese individuals [9]. Theories on behavior change should be applied when developing any health intervention because it increases the likelihood of being more effective. Among the theories, the Transtheoretical Model (TTM) uniquely describes the behavior change process from not being ready (precontemplation, contemplation, and preparation) to the active stage (action and maintenance). Applying TTM may help researchers in understanding the behavioral issue and help to develop a tailored intervention based on the individualized readiness stage [10]. A systematic review has found that by implementing the stages of change of TTM, there were improvements in physical activity and dietary habits, specifically in terms of exercise duration and frequency, reduction in dietary fat intake, as well as increment in fruits and vegetable consumption [11]. Unfortunately, the current management of T2D does not identify those who are ready or not ready to make changes in their daily life [12]. Clearly, there is a need to help the large proportion of patients who are not ready to change to start taking action for weight loss.

Intervention in behavior modification should address the role of social environment on an individual's readiness to lose weight. Weight loss-related behaviors, specifically healthy diet and physical activity are embedded in the social context, particularly the family context. Therefore, addressing behavior modification embedded in daily family life might be a promising approach to boost family support, thereby facilitating progress. Family support can be received in the form of companionship, emotions, information sharing, and instrumental assistance to facilitate the weight loss journey [13]. Integration with the family support component can lead to a more maintainable behavioral change, a better improvement of diabetes outcomes, as well as help to improve the health of family members [14,15].

Over the decades, web-based health technologies are increasingly used as a delivery mode for health promotion and prevention. The web-based platform will provide a good opportunity to improve the management of patients with T2D with obesity. Implementing web-based health promotion and prevention can widen the opportunity to reach specific target groups, lower the cost of implementation, and improve the health of the population [16]. It may overcome problems such as time constraints, privacy concerns, and the negative perception of being obese. Furthermore, web-based intervention can be delivered within a social system so that all members, for example, of a family can simultaneously and collectively take part in the obesity intervention and share their plans, goals, and progress [17]. To increase the efficiency of the interventions, the intervention can be coupled with tailored feedback and counseling [18]. Unfortunately, there is limited knowledge in the literature on web-based health intervention that has been developed based on the TTM targeting adults with T2D with obesity and integrating the family support component.

The objective of this trial is to develop and validate "Chance2Act," an innovative web-based intervention grounded in the TTM, designed specifically to facilitate behavioral change in overweight or obese adults with T2D who are not ready to take action toward weight loss. Then, the effectiveness of the newly developed digital health intervention will be determined based on a nonrandomized controlled trial.

Methods

Overview

This study will be conducted in two phases, which are (1) phase 1: the development and validation of the Chance2Act intervention module and (2) phase 2: the nonrandomized controlled trial of the Chance2Act intervention.

Phase 1: Content Development and Validation

Phase 1 of the study concerns the development and validation of the health intervention module. To get the initial ideas, framework, and justification for the selection of topics, a literature review and document analysis will be done. The content selection will be based on the key findings from the review of previous studies, the available local and international guidelines, as well as published reports, and available statistical

data. The search sources will involve web-based databases, websites and printed materials (guidelines, pamphlets, posters, factsheets, reports, etc) that incorporate behavior change theories and family support components.

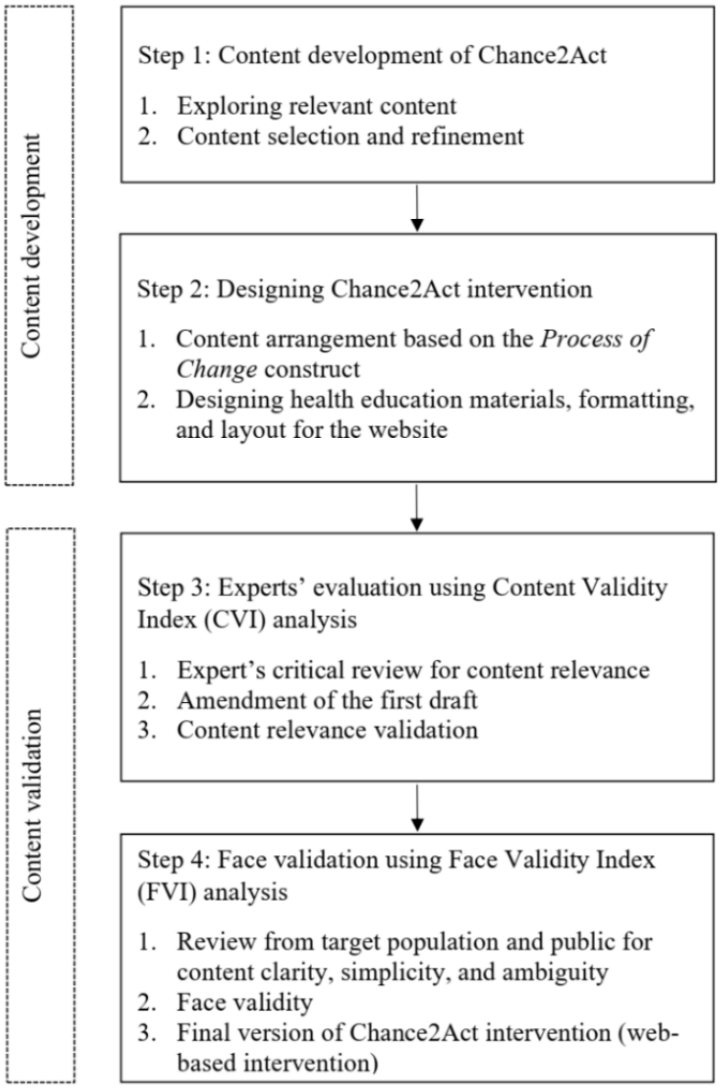
In addition, experts in related fields from different sectors (government, private, and nongovernmental organizations) will be invited for informal interview sessions to share experiences and give input for the new intervention. Further exploration will be conducted through informal interviews with overweight or obese adults with T2D, focusing on the knowledge, awareness, and practice of unhealthy behaviors, challenges, and facilitators for weight loss.

The contents of the health education module will be arranged according to the Process of Change construct of TTM. Then, the contents of the module will be drafted including the texts and graphics, as well as the formatting and layout for the website which acts as the medium of delivery for the health intervention. The local language (Malay language) will be used for the communication. The website will be arranged with consideration of the appropriate sequence. An attractive illustration will be used to ensure participants' engagement and hence complete the entire package of the intervention module.

For the validation of the intervention module, 6 experts from relevant fields related to obesity and diabetes management will be selected to evaluate the newly developed health intervention module. The experts will consist of (1) an epidemiologist of noncommunicable diseases, (2) a health education expert, (3) a family medicine specialist, (4) a dietician, (5) a sports medicine specialist, and (6) a medical officer in-charge of the diabetes program in a health clinic. The Content Validity Index (CVI) will be analyzed to determine the relevance of the intervention content.

A face validation study will be conducted among overweight or obese adults with T2D and the public to determine the clarity, simplicity, and ambiguity of the intervention content. It will be quantified by using the Face Validity Index (FVI). After being proven to be valid to achieve the primary objective, the final version of Chance2Act Health Intervention will be ready to be used in phase 2: the nonrandomized controlled trial. Figure 1 illustrates the study flowchart for phase 1.

Figure 1. Study flowchart for phase 1.



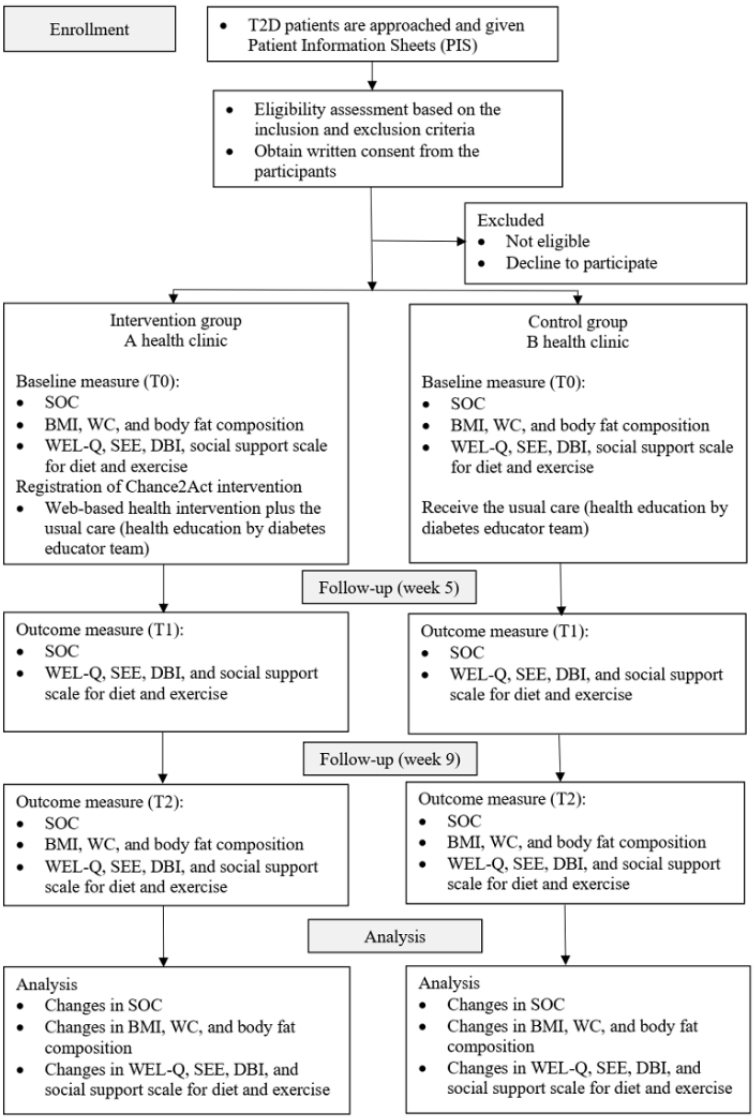
Phase 2: Nonrandomized Controlled Trial

Study Setting

Phase 2 of the study will be conducted as a nonrandomized controlled trial, which is aimed to determine the effectiveness of the Chance2Act intervention. The study is expected to be conducted over 4 to 6 months, at 2 government health clinics in Pahang state, Malaysia. These 2 health clinics will be enrolled by the researcher and are expected to have similarities in terms of the sociodemographic background of the local community. The assignment into either the intervention or control group will be based on the health clinic where the participants are getting their treatment from. One health clinic will be assigned as the intervention arm whereas another clinic as the control arm. The study flowchart for phase 2 is summarized in Figure 2. This is an unblinded study with a parallel assignment (ie, intervention vs control [usual care] with an allocation ratio of 1:1). Blinding is not possible due to the nature of the intervention which is mainly health education.

To avoid contamination, the 2 health clinics will not be selected from neighboring localities. Access to the Chance2Act website will be restricted only to the registered participants and family members from the intervention arm. A username and password will be provided to log in to the website. The participants, family members, and the medical staff at the participating health clinics are not allowed to share any intervention material with a third party.

Figure 2. Study flowchart for phase 2. DBI: Decisional Balance Inventory; SEE: Self-efficacy for Exercise; SOC: Stages of Change; T2D: type 2 diabetes; WC: waist circumference; WEL-Q: Weight-efficacy Lifestyle Questionnaire.



Study Population

The target population is patients with T2D aged 20-60 years old, with a BMI of more or equal to 23 kg/m^2, who are not ready to act for weight loss. Study participants will be selected via purposive sampling method to ensure homogeneity between the 2 arms.

Participants Recruitment

The patients with T2D, who come for a routine appointment at the selected health clinics during the recruitment period will be approached, given the Patient Information Sheet (PIS) about

the study, and invited to participate. If they are willing to participate, they will be screened by the investigators to determine their eligibility based on the inclusion and exclusion criteria. Then, written informed consent will be obtained from those who are eligible. Participants from the intervention arm will be given a username and password to access the Chance2Act intervention, whereas participants from the control arm will continue the existing health education module in the health clinic.

Eligibility Criteria

The patients with T2D aged 20 to 65 years old who fulfill all the following inclusion criteria will be included (1) BMI of more or equal to 23kg/m^2; (2) in the precontemplation, contemplation, or preparation stage of change based on the s-weight questionnaire [19]; (3) able to understand, read, and write in the Malay language; (4) have access to any electronic device with internet service; (5) able to understand information and perform tasks in the digital environment, especially website; and (6) have at least 1 adult family member who is living in the same household.

Patients who fulfill any of the following criteria will be excluded (1) patients who are pregnant; (2) patients with advanced comorbidity and mental conditions that will affect participation and understanding of the study protocol, for example, vision problem, physically unfit to stand up and walk, advanced heart failure or cancer, and schizophrenia; and (3) patients who die or are transferred out to other health clinics during the study period.

Sample Size Calculation

The sample size was calculated using OpenEpi (version 3; Kelsey et al) open-source calculator for cross-sectional, cohort, and randomized control trials. To obtain 95% CI and 80% power of the study (α=.05), the minimum sample size required in each arm is 44 to achieve a 30% proportion difference postintervention [20]. Considering a 40% (n=21 participants) attrition rate, we aim for a total of 65 participants per arm.

Chance2Act Health Intervention

The Chance2Act digital health intervention is a web-based behavior modification program based on the 4 main constructs of the TTM. This model uses the stages of change to integrate the principles and processes of behavior change. The stages of change are influenced by the processes of change (activities people use to progress through stages), decisional balance (an individual's relative weighing of the pros and cons of changing), and self-efficacy (situation-specific confidence that people can cope with without relapsing to their former behavior) [21]. This intervention emphasizes the role of the immediate family members in creating a healthy social environment favoring weight loss. The main components of the intervention will be identified from an extensive review of published studies, health education materials, and gray literature that can boost the readiness to change for weight loss. This is the first version of the study protocol.

Delivery of the Chance2Act Intervention

The Chance2Act intervention will be delivered to the individual participants by the investigators. Participants will be given the Chance2Act website using their login account and password. Access to the website is free of charge. The intervention will comprise 4 main modules and will be delivered in sequence. Each module will take approximately 2 weeks to be completed. The sequence of the intervention was developed based on the Process of Change construct of the TTM [21].

The baseline measurements will be taken before the initiation of the intervention. Follow-up will be done by the investigator after the completion of the first 2 modules, approximately at week 5, and after the completion of the whole package of the intervention, at week 9. In addition, participants can seek help from the investigators to navigate through the functions of the Chance2Act website through the built-in messaging system.

The Chance2Act is a tailored intervention whereby the participants will receive personalized coaching about their weight-related behavioral problems to boost their motivation via the built-in messaging system. The principal investigator will actively monitor the progress of each participant and intervene according to the health education module. Information will be given through text on the website, sets of infographics, animations, and videos. Health quizzes will be conducted to assess the comprehensibility of the module. They will be given printed materials such as weight loss checklists and dietary and exercise weekly plan templates to assist their weight loss journey. Each participant will have at least 1 adult family member to join as part of the intervention modules. The family members will be guided on the ideal way to fully support the participants' efforts for weight loss. They will receive clear information on their role during the weight loss journey.

Participants are expected to finish each module in 2 weeks and give the required feedback and responses at the end of the module accordingly. Follow-up will be done by the investigators. Participants who did not comply with the follow-up requirements will be considered a loss to follow-up. Data analysis will be by the intention-to-treat (ITT). There is no specific concomitant care and intervention that are permitted or prohibited during the trial.

Data Collection

For both arms, the data for phase 2 will be obtained from a set case report form (CRF) which consists of demographic data, self-administered questionnaires, anthropometric measurements, and disease profiles. At week 0 (T0), once consented, anthropometric measurements will be taken by the investigator and clinical data will be obtained from the medical records.

Clear written and verbal instructions will be given on how to answer the questionnaires. Participants will be requested to circle which options suit them the most. Participants will be allowed to answer the questionnaires while waiting their turn for medical consultation. They will be encouraged to seek clarification from investigators at any time, should any queries arise.

Before the initiation of the study, all investigators will be trained regarding the study procedures to minimize variability and bias during the data collection. The study procedures will comply with the Malaysian Guideline for Good Clinical Practice, fourth edition [22].

Study Instruments

For the anthropometric measurement, the height will be taken using a wall mounted stadiometer (SECA 206) and recorded to the nearest 0.1 cm. The body weight and body fat composition (total fat percentage and visceral fat percentage) will be measured using a body fat composition monitor (Omron HBF-222T) with an accuracy of 0.1 kg and 0.1%, respectively. Waist circumference will be measured to the nearest 0.2 cm using nonstretchable measuring tape midway between the lower margin of the 12th rib and the top of the iliac crest, just above the umbilicus in a horizontal plane.

The set of self-administered questionnaires will consist of (1) a Stages of Change (SOC) questionnaire using the S-weight; (2) a Weight-efficacy Lifestyle Questionnaire (WEL-Q); (3) Self-efficacy for Exercise (SEE); (4) a Decisional Balance Inventory (DBI) for weight loss; and (5) social support scale for diet and exercise. Verbal instruction will be given on how to complete the questionnaire. On average, participants will be expected to spend approximately 30 minutes to complete the questionnaires. Once they have finished, they will submit the questionnaires to the investigator to ensure the completeness of the responses given.

The S-weight questionnaire was initially developed in English and Spanish language simultaneously [19,23]. This questionnaire has been translated into Malay language and tested among the adolescent obese population [24]. It consists of a brief series of self-report questions assessing weight loss intentions and current activities. The S-weight has 5 mutually exclusive items each representing the 5 stages of change: precontemplation, contemplation, preparation, action, and maintenance. S-weight has been reported as an efficient tool to assess the readiness to change in weight management by a review [25].

A validated Malay version of WEL-Q will be used to assess dietary self-efficacy for weight loss. It is used to measure an individual's confidence to control eating in specific circumstances. It consists of 20 items representing 5 subscales which are negative emotions, availability, social pressure, physical discomfort, and positive activities. WEL-Q uses a Likert scale ranging from 0 (not confident) to 9 (very confident). The total score of each subscale is ranged between 0 and 36. The higher score shows better control to resist eating. WEL-Q has been tested among the Malaysian population with T2D. It is reported to have a good internal consistency reliability with Cronbach α of .893. Construct validity was measured by the item total correlation of r>0.700 and P<.01, and interitem correlation of r<0.005 and P<.01 [26].

The SEE was originally developed by Bandura and has been modified to suit the Malaysian population. It consists of 18 items measuring an individual's confidence to maintain routine exercises. A 5-point Likert scale is used ranging from 1 (cannot do) to 5 (certain can do). The Malay version of SEE has been tested among Malaysian patients with T2D with a composite reliability (CR) of 0.921 [27].

The DBI was developed in the English language by O'Connell and Velicer in 1988 [28]. It measures an individual's belief of the perceived pros and cons of weight loss. It consists of 20 Likert scale items, 10 items for pro (even-numbered items) and 10 items for cons (odd-numbered items). The scale ranges from 1 (not important at all) to 5 (very important). The total score range is 10 to 50. The Malay version of DBI shows good reliability. For the pro scale reliability was reported as Cronbach α=.902, intraclass correlation (ICC) (95% CI) is 0.88 (0.86-0.90). The con scale Cronbach α=.739 and ICC (95% CI) is 0.72 (0.70-0.78) [24].

The social support scale for diet and exercise was developed in the English language in 1987 [29]. In this study, the social support for diet and exercise will be measured separately and used specifically to measure the perceived social support received from the family members. The social support scale for diet consists of 10 items. Items 1-5 measure the encouragement, whereas items 6-10 measure discouragement received from the family members. The social support scale for exercise behavior consists of 12 items. The measurement uses a Likert scale ranging from 1 (never) to 5 (very often). A higher score implies that the participants have better social support received from their family members to lose weight. These questionnaires have been translated into Malay language and validated. This questionnaire has been proven valid and reliable. The social support for diet has internal consistency reliability of Cronbach α of .61-.91 and test-retest reliability, r of 0.55-0.86 [29]. The social support scale for exercise was reported to be reliable for the Malaysian population. It was reported to have a CR of 0.918, an average variance extracted of 0.560, and an ICC (based on test-retest) of 0.920 [30].

Study Outcome

Outcome measures are categorized into primary and secondary outcomes. These measures will be obtained from both the intervention and control arm at baseline, fifth week, and ninth week after the initiation of the intervention.

The primary outcome will be measured by the changes of the stages of change using the Malay version of the S-weight questionnaire. The secondary outcomes will be measured by (1) a change in dietary self-efficacy will be measured by the WEL-Q, (2) a change in exercise self-efficacy will be measured by the SEE, (3) a change in decisional balance for weight loss will be measured by the DBI, (4) change in family support for diet and exercise will be measured by the social support scale for diet and exercise, (5) change in BMI, (6) change in waist circumference, and (7) change in body fat percentage.

Control Group

The control group will continue to receive the usual care at the health clinic. The usual care includes the health talk and individual or group counseling sessions with the diabetes educators, physiotherapists, dieticians, or medical officers as scheduled by the health clinic. Participants from the control group will be offered to participate in the intervention after the completion of T2 data collection.

Data Management and Statistical Analysis

For phase 1, the data will be entered in Microsoft Excel (Microsoft Office 365) and ready for analysis. The content validity will be assessed by the experts' ratings. The CVI will be assessed based on 2 indices, the Item-level Content Validity Index (I-CVI) and Scale-level Content Validity Index (S-CVI). The criteria that will be assessed are mainly content relevance. The I-CVI will reflect each item or intervention activity relevancy, whereas S-CVI will reflect the overall module relevancy. Then, the face validation will be determined based on the FVI. Similarly, the FVI will be assessed based on 2 indices, the Item-level Face Validity Index (I-FVI) and the Scale-level Face Validity Index (S-FVI). The criteria that will be evaluated are the module clarity, simplicity, and ambiguity. For both CVI and FVI, the results of at least 0.83 will be considered acceptable [31,32].

For phase 2, the data will be entered into IBM SPSS Statistics (version 27; IBM Corp). Each CRF will be given a unique identifier. Screening for missing, redundant data or wrong coding will be done. The investigator will try to contact the participants to complete the missing data via telephone. Then, any remaining missing data will be dealt with an appropriate missing data handling method. For redundant data, only 1 data will be selected. The wrongly coded data will be corrected accordingly based on the CRF. Then, the data will be ready for analysis.

For the descriptive statistics, the normality tests will be used to determine the distribution of the data. The normally distributed will be described by using mean and SD, whereas not normally distributed data will be described by using the median and IQR. The categorical data will be presented by using frequency and percentage.

To determine the homogeneity between the intervention and control group, an independent *t* test and chi-square test will be used to compare the demographic characteristics of the participants. The ITT analysis will be applied to measure the effectiveness of the Chance2Act intervention on the primary and secondary outcomes. The analysis models are within-group differences and between-group differences. The Generalized Estimating Equations (GEE) will be used as statistical analysis. A *P* value of less than .05 is considered statistically significant with 95% CI. Interim analysis will be conducted at T1 which is estimated at week 5. However, only certain outcome measures will be analyzed as predetermined in the phase 2 study flowchart.

Ethical Considerations

This study has been approved by the Medical Research and Ethics Committee, Ministry of Health Malaysia (NMRR ID-22-01073-4YT IIR) and Universiti Teknologi MARA Research Ethics Committee (REC/07/2022PG/MR/157). The ethics committees will be informed in case of any changes to the study protocol. Before participants' enrollment, PIS will be given and explained to all the participants. Written informed consent will be obtained once patients understand the study well. The research assistants will be trained to conduct these procedures. The risk of privacy breaches is minimal. The website will only contain health education material. None of the personal information and medical information will be uploaded on the website. The data for the outcome measures will be stored by the investigator in a password-protected computer and cloud account provided by the Ministry of Health Malaysia (MyGovucUC 2.0 account). The data will be destroyed after 3 years postcompletion of the study. The permission to use the questionnaires has been obtained from the authors with proper citation.

Results

The objective of the phase 1 study is to develop and validate a new web-based intervention (Chance2Act) to facilitate behavioral change for weight loss among adults with T2D with obesity. To confirm the accomplishment of the study objectives, the data gathered from the expert panel's rating and the panel of raters will be analyzed using the CVI and the FVI. The phase 1 study was initiated in October 2022 and is expected to be completed within an 8-month period. Until May 2023, the analysis of the CVI data for the intervention has been finalized and is currently undergoing evaluation by the panel raters for FVI, marking the conclusion of phase 1.

After the validity of the intervention has been confirmed, the effectiveness of the intervention will be determined through a nonrandomized controlled trial. The data collection is expected to have started on June 2023 and to be completed within 4 to 6 months. The analysis will allow us to compare results between the intervention and the control arms, as well as changes within the arm itself in terms of the improvement of the stages of change for weight loss as per the TTM. We also hypothesize that the intervention can result in improvement in self-efficacy, decisional balance, and family support which ultimately may contribute to weight loss. Data analysis for phase 2 will commence in 2024, with anticipated publication of results as early as March 2024. This study was funded in July 2022.

Discussion

Principal Findings

This trial will determine the validity and effectiveness of Chance2Act, a newly developed web-based intervention in changing the behavior of adults with T2D with obesity to initiate weight loss efforts. The validity of the intervention is determined in phase 1 using the CVI and FVI. These tools are widely recognized as quantitative methods to evaluate the content validity of health intervention research [31,32]. In the context of developing interventions, CVI is essential to evaluate whether the elements of the intervention are relevant in relation to the initial objectives or the intended outcomes [33]. Likewise, face validity is crucial to ensure the target users' understanding of each item in the intervention. An intervention that appears relevant, clear, and comprehensible to the participants is more likely to be effective [34]. Integrating both CVI and FVI in the development phase ensures that the intervention is not only theoretically sound but also remains understandable and clear to the target audience.

Then, the results of phase 2 will determine the effectiveness of the intervention in changing the behavior of adults with T2D with obesity toward weight loss. The analysis will focus on the differences of all outcome measures to demonstrate the effects of the intervention both within and across the different groups. If the hypothesis is confirmed, the findings of this study will provide valuable insights into effective strategies for web-based intervention aimed at behavior modification in the context of weight management for adults with T2D.

Strengths and Limitations

To our best knowledge, the Chance2Act intervention is the first web-based intervention that promotes behavior change, specifically designed for adults with T2D with obesity but not yet prepared to start losing weight. Developing an intervention for this population group is crucial, as a significant number (59%-79%) of them are not yet actively making weight loss efforts [7,8]. We hope that this intervention can contribute to better outcomes of obesity care in patients with T2D, thus, potentially leading to the metabolic benefits associated with weight loss.

In terms of the study design, the selection of a nonrandomized controlled trial method is acceptable due to the nature of the intervention given. Since the health interventions are delivered through a website, blinding of the study participants and researcher is not possible. The participants need to be aware of group assignments, thereby they will access the website and be involved in the intervention.

Another potential limitation that may arise during the study is that participants who do manifest interest are limited to patients with T2D with good digital literacy skills only. As a result, the findings of the study may not be applicable to a broader population, especially those with limited digital literacy. Digital literacy of the study participants may influence the conclusions concerning the uptake and attrition rate of the intervention.

Conclusions

To conclude, the potential findings from this study may bring significant implications of the effective strategies for a web-based intervention aimed at adults with T2D with obesity, who are not actively taking action for weight loss. If successful, the newly developed and validated intervention may be replicated or adapted in different settings, addressing the behavior change resistance for weight loss in adults with T2D with obesity. We hope that the Chance2Act intervention will benefit the target group in achieving better diabetes and metabolic control through effective weight loss. These findings may give valuable insights to inform future public health strategies toward a broader approach to obesity management in T2D, emphasizing the importance of behavioral modification in achieving maintainable weight reduction.

Acknowledgments

This study was funded by MyRA research grants of Universiti Teknologi MARA (600-RMC 5/3/GPM 015/2022). All authors declared that they had insufficient or no funding to support open access publication of this manuscript, including from affiliated organizations or institutions, funding agencies, or other organizations. JMIR Publications provided article processing fee support for the publication of this article.

Data Availability

The data sets generated or analyzed during this study are not publicly available in order to comply with the ethical board requirements and participants' confidentiality protection but are available from the corresponding author upon reasonable request, who will then seek necessary permissions from the Director General of Health Malaysia.

Authors' Contributions

NMS conceptualized and designed the study. MM acquired the funding for the study. MM and ANMR review the study critically and revised it for the important intellectual concept.

Conflicts of Interest

None declared.

References

1. Bramante CT, Lee CJ, Gudzune KA. Treatment of obesity in patients with diabetes. Diabetes Spectr 2017 Nov;30(4):237-243 [FREE Full text] [doi: 10.2337/ds17-0030] [Medline: 29151713]
2. World Health Organization newsroom: 6 facts on obesity. World Health Organization. 2021 Jun 9. URL: https://www.who.int/news-room/facts-in-pictures/detail/6-facts-on-obesity [accessed 2023-03-02]
3. Delahanty LM. Weight loss in the prevention and treatment of diabetes. Prev Med 2017 Nov;104:120-123. [doi: 10.1016/j.ypmed.2017.07.022] [Medline: 28757449]
4. Thom G, Messow CM, Leslie WS, Barnes AC, Brosnahan N, McCombie L, et al. Predictors of type 2 diabetes remission in the Diabetes Remission Clinical Trial (DiRECT). Diabetic Medicine 2020 Sep 01;38(8):1-12. [doi: 10.1111/dme.14395] [Medline: 32870520]

5. Dambha‐Miller H, Hounkpatin H, Stuart B, Farmer A. Association between weight change and remission of type 2 diabetes: a retrospective cohort study in primary care. Practical Diabetes 2021 Oct 04;38(5):8-14a [FREE Full text] [doi: 10.1002/pdi.2355]
6. Chandran A, Abdullah MN, Abdul F. National Diabetes Registry Report 2020. Ministry of Health Malaysia. 2021. URL: https://www.moh.gov.my/moh/resources/Penerbitan/Rujukan/NCD/Diabetes/National_Diabetes_Registry_Report_2020.pdf [accessed 2023-01-06]
7. Jalilian H, Pezeshki MZ, Janati A, Najafipour F, Sarbakhsh P, Zarnaq RK. Readiness for weight change and its association with diet knowledge and skills, diet decision making and diet and exercise barriers in patients with type 2 diabetes. Diabetes Metab Syndr 2019;13(5):2889-2895. [doi: 10.1016/j.dsx.2019.07.052] [Medline: 31425953]
8. Holmen H, Wahl A, Torbjørnsen A, Jenum AK, Småstuen MC, Ribu L. Stages of change for physical activity and dietary habits in persons with type 2 diabetes included in a mobile health intervention: the Norwegian study in RENEWING HEALTH. BMJ Open Diabetes Res Care 2016;4(1):e000193 [FREE Full text] [doi: 10.1136/bmjdrc-2016-000193] [Medline: 27239317]
9. Durrer Schutz D, Busetto L, Dicker D, Farpour-Lambert N, Pryke R, Toplak H, et al. European practical and patient-centred guidelines for adult obesity management in primary care. Obes Facts 2019;12(1):40-66. [doi: 10.1159/000496183] [Medline: 30673677]
10. Simpson V. Models and theories to support health behavior intervention and program planning. Health and Human Sciences. 2015. URL: https://extension.purdue.edu/extmedia/hhs/hhs-792-w.pdf [accessed 2023-02-05]
11. Mastellos N, Gunn LH, Felix LM, Car J, Majeed A. Transtheoretical model stages of change for dietary and physical exercise modification in weight loss management for overweight and obese adults. Cochrane Database Syst Rev 2014 Feb 05;2014(2):CD008066 [FREE Full text] [doi: 10.1002/14651858.CD008066.pub3] [Medline: 24500864]
12. Clinical Practice Guidelines: Management of Type 2 Diabetes Mellitus (6th edition). Ministry of Health Malaysia. 2020 Dec. URL: https://www.moh.gov.my/moh/resources/Penerbitan/CPG/Endocrine/CPG_T2DM_6th_Edition_2020_13042021.pdf [accessed 2023-03-06]
13. Wallwork A, Tremblay L. The role of social support in weight loss management for morbidly obese individuals. In: Sockalingam S, Hawa R, editors. Psychiatric Care in Severe Obesity: An Interdisciplinary Guide to Integrated Care. Cham, Switzerland: Springer Nature; 2017:207-219.
14. Martire LM, Helgeson VS. Close relationships and the management of chronic illness: associations and interventions. Am Psychol 2017 Sep;72(6):601-612 [FREE Full text] [doi: 10.1037/amp0000066] [Medline: 28880106]
15. Thirsk LM, Schick-Makaroff K. Family interventions for adults living with type 2 diabetes mellitus: a qualitative meta-synthesis. Patient Educ Couns 2021 Dec;104(12):2890-2899 [FREE Full text] [doi: 10.1016/j.pec.2021.04.037] [Medline: 33992484]
16. Stark AL, Geukes C, Dockweiler C. Digital health promotion and prevention in settings: scoping review. J Med Internet Res 2022 Jan 28;24(1):e21063 [FREE Full text] [doi: 10.2196/21063] [Medline: 35089140]
17. Wunsch K, Eckert T, Fiedler J, Cleven L, Niermann C, Reiterer H, et al. Effects of a collective family-based mobile health intervention called "SMARTFAMILY" on promoting physical activity and healthy eating: protocol for a randomized controlled trial. JMIR Res Protoc 2020 Nov 11;9(11):e20534 [FREE Full text] [doi: 10.2196/20534] [Medline: 33174849]
18. Chen Y, Perez-Cueto FJA, Giboreau A, Mavridis I, Hartwell H. The promotion of eating behaviour change through digital interventions. Int J Environ Res Public Health 2020 Oct 15;17(20):7488. [doi: 10.3390/ijerph17207488] [Medline: 33076239]
19. Andrés A, Saldaña C, Gómez-Benito J. Establishing the stages and processes of change for weight loss by consensus of experts. Obesity (Silver Spring) 2009 Sep;17(9):1717-1723 [FREE Full text] [doi: 10.1038/oby.2009.100] [Medline: 19360014]
20. Sanaeinasab H, Saffari M, Sajedi SH, Sepandi M, Al Shohaib S, Koenig HG. The effect of a psycho-educational intervention on weight management in obese military personnel. Military Psychology 2018 Oct 16;31(1):1-10. [doi: 10.1080/08995605.2018.1522926]
21. Prochaska JO, Redding CA, Evers KE. The transtheoretical model and stages of change. In: Glanz K, Rimer BK, Viswanath K, editors. Health Behavior and Health Education: Theory, Research, and Practice. 4th Edition. San Francisco, CA: Jossey-Bass; 2008:97-121.
22. Ministry of Health Malaysia. Malaysian Guideline for Good Clinical Practice Fourth Edition. Petaling Jaya, Malaysia: National Pharmaceutical Regulatory Agency (NPRA) Ministry of Health Malaysia; 2018.
23. Andrés A, Saldaña C, Beeken RJ. Assessment of processes of change for weight management in a UK sample. Obes Facts 2015;8(1):43-53 [FREE Full text] [doi: 10.1159/000373900] [Medline: 25765163]
24. Johari A, Sutan R. Assessing stages of readiness to lose weight among overweight and obese adolescents using trans-theoretical model. Obes Control Ther 2017;4(1):1-6 [FREE Full text] [doi: 10.15226/2374-8354/4/1/00130]
25. Ceccarini M, Borrello M, Pietrabissa G, Manzoni GM, Castelnuovo G. Assessing motivation and readiness to change for weight management and control: an in-depth evaluation of three sets of instruments. Front Psychol 2015;6:511 [FREE Full text] [doi: 10.3389/fpsyg.2015.00511] [Medline: 26029126]
26. Singh HKG, Mun VLK, Barua A, Ali SZM, Swee WCS. Application and validation of the Weight Efficacy Lifestyle (WEL) questionnaire among type 2 diabetes mellitus patients in Malaysia. Malays J Nutr 2018;24(3):427-440 [FREE Full text]

27. Hidrus A, Kueh YC, Norsa'adah B, Kuan G. Malay version of exercise self-efficacy: a confirmatory analysis among Malaysians with type 2 diabetes mellitus. Int J Environ Res Public Health 2020 Feb 02;17(3):922 [FREE Full text] [doi: 10.3390/ijerph17030922] [Medline: 32024257]
28. O'Connell D, Velicer WF. A decisional balance measure and the stages of change model for weight loss. Int J Addict 1988 Jul;23(7):729-750. [doi: 10.3109/10826088809058836] [Medline: 3192340]
29. Sallis JF, Grossman RM, Pinski RB, Patterson TL, Nader PR. The development of scales to measure social support for diet and exercise behaviors. Prev Med 1987;16(6):825-836. [doi: 10.1016/0091-7435(87)90022-3] [Medline: 3432232]
30. Sabo A, Kueh YC, Arifin WN, Kim Y, Kuan G. The validity and reliability of the Malay version of the social support for exercise and physical environment for physical activity scales. PLoS One 2020;15(9):e0239725 [FREE Full text] [doi: 10.1371/journal.pone.0239725] [Medline: 32986724]
31. Yusoff MSB. ABC of response process validation and face validity index calculation. Educ Med J 2019;11(3):55-61 [FREE Full text] [doi: 10.21315/eimj2019.11.3.6]
32. Yusoff MSB. ABC of content validation and content validity index calculation. Educ Med J 2019;11(2):49-54 [FREE Full text] [doi: 10.21315/eimj2019.11.2.6]
33. Lynn MR. Determination and quantification of content validity. Nurs Res 1986;35(6):382-385. [Medline: 3640358]
34. Holden RR. Face validity. In: Weiner IB, Craighead WE, editors. The Corsini Encyclopedia of Psychology. 4th Edition. New Jersey: John Wiley & Sons, Inc; 2010:1-2.

Abbreviations

CR: composite reliability
CRF: case report form
CVI: Content Validity Index
DBI: Decisional Balance Inventory
FVI: Face Validity Index
GEE: Generalized Estimating Equations
I-CVI: Item-level Content Validity Index
I-FVI: Item-level Face Validity Index
ICC: intraclass correlation
PIS: Patient Information Sheet
S-CVI: Scale-level Content Validity Index
S-FVI: Scale-level Face Validity Index
SEE: Self-efficacy for Exercise
SOC: Stages of Change
TTM: Transtheoretical Model
T2D: type 2 diabetes
UiTM: Universiti Teknologi MARA
WEL-Q: Weight-efficacy Lifestyle Questionnaire
WHO: World Health Organization

Edited by A Mavragani; submitted 02.05.23; peer-reviewed by ZI Azhar, M Gasmi ; comments to author 22.11.23; revised version received 07.12.23; accepted 08.12.23; published 31.01.24.

Please cite as:
Mohd Saad N, Mohamad M, Mat Ruzlin AN
Web-Based Intervention to Act for Weight Loss in Adults With Type 2 Diabetes With Obesity (Chance2Act): Protocol for a Nonrandomized Controlled Trial
JMIR Res Protoc 2024;13:e48313
URL: https://www.researchprotocols.org/2024/1/e48313
doi:10.2196/48313
PMID:38294848

Protocol

Compliance of Type 2 Diabetes Applications to International Guidelines: Protocol for a Quantitative App Assessment

David Rebus[1], BSc; Andrew Iskander[1], BSc; Felicia Deonarine[1], BSc, MSc; Asad Almas[1]; Darren Rattigan[2], BSc, MB, BAO, BCh; Patrick Henn[3], MB, BCh, BAO, MSc, MA; Kayode Philip Fadahunsi[4], MBBS, MPH, MRCGP; John O'Donoghue[3,5], BSc, MSc, PhD

[1]Faculty of Medicine, University College Cork, Cork, Ireland

[2]Department of Medicine, Royal College of Surgeons Ireland, Dublin, Ireland

[3]ASSERT Centre, University College Cork, Cork, Ireland

[4]Department of Primary Care and Public Health, Imperial College London, London, United Kingdom

[5]Malawi eHealth Research Centre, University College Cork, Cork, Ireland

Corresponding Author:
Kayode Philip Fadahunsi, MBBS, MPH, MRCGP
Department of Primary Care and Public Health
Imperial College London
Medical School Building, St Mary's Hospital
Norfolk Place
London, W2 1PG
United Kingdom
Phone: 44 1522 543943
Email: k.fadahunsi14@imperial.ac.uk

Abstract

Background: Diabetes is among the most common chronic conditions people live with across the world. While it can be managed to a substantial degree, it can result in significant complications. As such, easy access to accurate tools to aid diabetes management is useful in minimizing these complications. Mobile apps are highly accessible and widely used, but there is a gap in the literature examining their compliance with medical guidelines.

Objective: The aims of this study are to develop the Analysis of Diabetes Apps (ADA) checklist to evaluate apps' compliance to guidelines set by the International Diabetes Federation (IDF) on the treatment and management of type 2 diabetes; to assess type 2 diabetes apps in the Apple App Store and the Android Google Play Store, and their compliance with international guidelines using the ADA framework; and to compare the novel ADA checklist against both the Mobile App Rating Scale (MARS) tool kit and app ratings for each store.

Methods: We will develop a checklist based on the "IDF Clinical Practice Recommendations for Managing Type 2 Diabetes in Primary Care." Type 2 diabetes apps will be scraped from 6 countries' app stores using web scraping tools. These countries include Australia, Brazil, India, Nigeria, the United States, and the United Kingdom, which were selected based on the largest population of English-speaking people in each continent. The apps will be searched on the web-based scraper using the search terms "blood sugar," "diabetes," "glucose level," "insulin," "sugar level," and "type 2 diabetes." Apps will be excluded if they are paid or are not in English. The apps will be assessed using the ADA checklist to evaluate their compliance to the international diabetes guidelines. Once scored, the results will be analyzed with descriptive statistics. The most popular apps will be further analyzed using the MARS tool kit. The ADA checklist scores will then be compared to both the MARS tool kit score and app ratings for each store.

Results: The ADA checklist developed based on the IDF guidelines focuses on general information, risk factors, diagnosis, pharmacology, lifestyle modification, glycemic recommendations, and medications. The initial stress testing of the protocol resulted in 173 included apps. This will vary in the final search as the app stores are constantly changing.

Conclusions: The protocol presents the development of a checklist to investigate the compliance of type 2 diabetes apps with international guidelines. The checklist will hopefully form the basis of a scoring system for future research on compliance of mobile apps with international guidelines. High standardization of the ADA checklist will make it a robust tool for people with diabetes and their health care providers alike in assessing type 2 diabetes apps in the future.

International Registered Report Identifier (IRRID): PRR1-10.2196/48781

(JMIR Res Protoc 2024;13:e48781) doi:10.2196/48781

KEYWORDS

diabetes; mobile apps; Mobile Apps Rating Scale; mHealth; mobile health; diabetes application; application; chronic condition; monitoring; accuracy; safety; tool; assistance; treatment; management; type 2 diabetes

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic condition that is prevalent worldwide with its prevalence rising in low-, middle-, and high-income countries [1-5]. In the United Kingdom alone, around 4.7 million people were diagnosed with T2DM in 2019 representing about 7% of the population [6,7]. The Centers for Disease Control and Prevention (CDC) reported that 34.2 million people had T2DM in the United States in 2020 [2].

For individuals who are living with T2DM, there are significant risks of complications including cardiovascular and peripheral vascular damage. In the United Kingdom, T2DM causes 20% of strokes [8]. Individuals living with T2DM are 2.5 times more likely to have a myocardial infarction with 25% of patients arriving in a hospital for a stroke, myocardial infarction, or heart failure also having preexisting diabetes [6]. However, the complications also go beyond circulation, and there can be damage to the peripheral nerves as well. Foot ulcers are a common complication of T2DM. These can lead to foot amputations at much higher rates than those without T2DM. This significant change to a person's life can also increase their risk of death, with 40% of people who have had a major amputation dying within 5 years post surgery [6]. Other damages can be caused by the production of advanced glycosylated end products. Retinopathy is a common complication causing blindness. Nephropathy is also a common complication that can lead to kidney failure and death [6].

Diabetes treatment is multifaceted. There are multiple drug therapies as well as tertiary preventive measures that are required to minimize the complications of the disease [9]. Some of these measures including blood sugar monitoring and healthy nutrition are supported through mobile health (mHealth) apps [10]. The use of mHealth apps has shown benefits in the past for T2DM. In 1 paper, there was better control of glycemic indicators [11]. One study showed a reduction in hemoglobin A_{1c} in those who used diabetes apps regularly compared to a control population [12]. Previous research has shown better control of glycemic indicators for individuals who use mHealth applications for the management of their disease compared to those who use other methods [8,10,12-14]. However, more research is required to determine the quality of available apps including the accuracy of the information content.

In the past, mHealth apps for T2DM have been evaluated for their functionality, but not for the quality of the information provided in the apps. mHealth apps are often analyzed through the prism of app review criteria such as the Mobile App Rating Scale (MARS) [15]. In the MARS tool kit, apps are rated based on engagement, functionality, aesthetic information, and subjective opinion. Each of these categories is broken down further into questions whose answers range from inadequate to excellent. While this is good for the analysis of apps across many genres, it does not focus on the quality of specific recommendations on the management of T2DM from the guidelines.

Every country has its own specific guidelines for the management of T2DM. Each varies slightly in recommendations such as the diet preference or the pharmacology. The largest area of variation in guidelines between countries comes in the form of diet and exercise [9]. Each of the countries' guidelines suggests healthy eating, weight loss, as well as moderate exercise. Some countries go into more detailed suggestions for diets for instance in the United States, it is suggested that a weight loss diet of vegetarianism or low carbs is best, whereas in other countries, a Mediterranean diet is recommended. Recommended diets include DASH, Mediterranean, Nordic, or vegetarianism. The DASH diet is comprised of a meal plan with well-balanced meals with lower levels of fat, sugar and sodium in the diet [16]. Similarly, each country recommends at least 150 minutes of moderate exercise a week with variations in the type of recommended exercise. For instance, yoga is recommended in India's guidelines [17]. The differences in the national guidelines can lead to confusion for both users as well as app designers when apps are released in multiple countries [9].

In this review, we will analyze T2DM apps in a selection of countries with the highest population of English speakers in each continent, including Australia, Brazil, the United Kingdom, India, Nigeria, and the United States. As a result, this paper will evaluate the selected apps based on the recommendations of the International Diabetes Federation (IDF), which is a combination of hundreds of the world's national diabetes associations. As a result, the IDF's guidelines form a clear source of recommendations for the management of patients with T2DM across the world. Therefore, we aim to assess the content of selected apps for T2DM based on the IDF's diabetes guidelines [9].

In addition, the result of the content assessment will be compared to the users' rating and the result of another assessment of the same apps using MARS, which is a validated scale. The aim of this comparison is to examine concordance or otherwise between apps' compliance with guidelines, users' ratings, and assessment scores based on validated scales.

Methods

Development of the Analysis of Diabetes Apps Checklist

The checklist (Multimedia Appendix 1) covers key areas of T2DM care. The checklist was developed based on the sections of the "IDF Clinical Practice Recommendations for managing Type 2 Diabetes in Primary Care" [9]. The Analysis of Diabetes Apps (ADA) checklist focuses on general information, risk factors, diagnosis, pharmacologic treatment, lifestyle modification, glycemic recommendations, and medications. The first section focuses on health education. It asks if the app informs the users of the risk factors as listed in the IDF guidelines. The apps gain points depending on what is mentioned. The checklist is useful in that it provides a qualitative manner of ranking apps based on their information content. Information on diabetes diagnosis will also be assessed based on various diagnostic tests and laboratory values used by different systems. Glycemic targets will also be evaluated for accuracy as well as the different units used. Pharmacologic treatment is key for the management of T2DM and will also be evaluated. The final and largest section is the reduction of risk. This includes diet recommendations, exercise strategies, and other lifestyle modifications.

Sources and Search Terms

Both the Google Play Store as well as the Apple App Store will be searched, using a web scraping tool. Google Play Store and Apple Apps Store are the largest app stores on the market for the public. Both stores will be searched across 6 countries including Australia, Brazil, the United Kingdom, India, Nigeria, and the United States, which are countries that have the highest population of English speakers in their respective continents [18-22]. Although English is not the official language of Brazil, it has the highest population of English speakers in South America due to its large population. The inclusion of countries from all continents is intended to achieve a broad geographic coverage, which allows for increased generalizability of the study findings. Limiting the search to only 1 country per continent is aimed to reduce duplication as the same or similar apps are likely to be available across different countries, especially in the same continent.

The search terms to be used are blood sugar, diabetes, glucose level, insulin, sugar level, and type 2 diabetes. These terms were selected after a series of preliminary screenings. The search terms that yielded the most relevant apps were chosen. Each search term will be entered into a web scraping tool to collect apps.

Eligibility Criteria

This review will collect a list of apps that are related to T2DM so that they can be evaluated in terms of their compliance with the recommendations of the IDF. The inclusion criteria for the apps are that (1) the content of the apps is in English; (2) the apps are freely downloadable—that is, no payment is required for downloading or using the apps; (3) apps that focus on the aspects of self-management of T2DM such as diet, physical activity, blood sugar monitoring, and foot care; and (4) apps that are compatible with iOS and Android mobile platforms. Evidence from the literature suggests that T2DM is a condition that is prevalent among people with lower socioeconomic status [23]; hence, fees might limit the use of apps among people with T2DM.

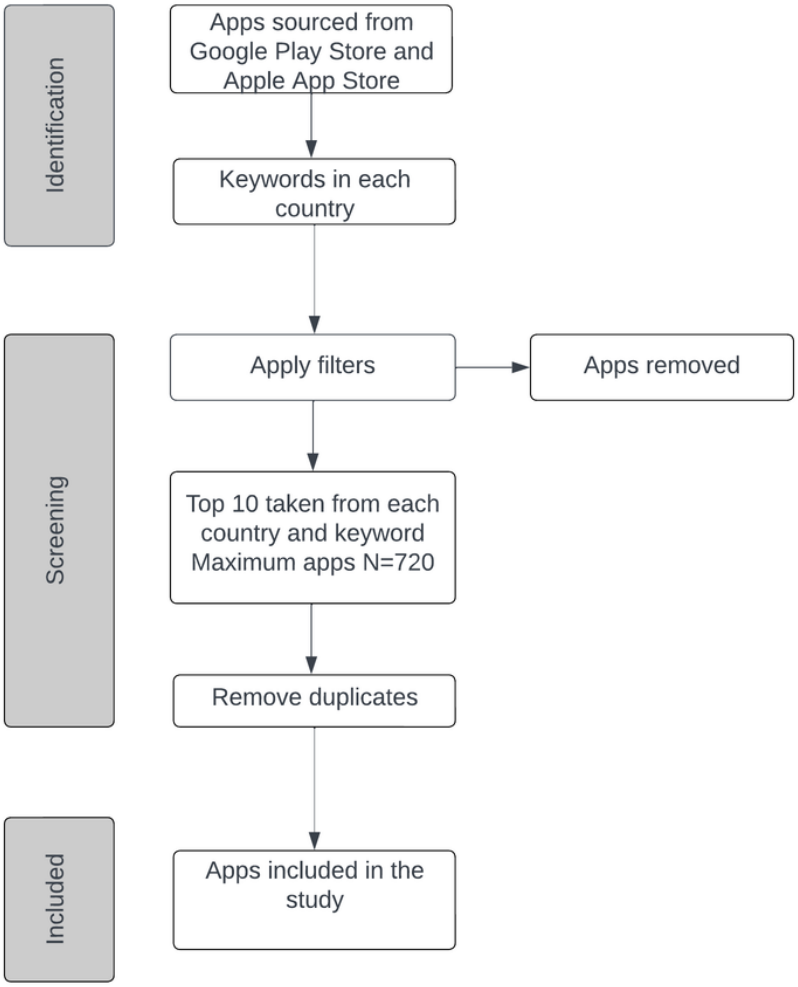
Apps will be excluded based on the following criteria: (1) generic lifestyle apps that are not focused on T2DM; (2) apps requesting fees for download or use; (3) apps in languages other than English; and (4) apps with missing or incorrect information will also be removed as it will be difficult to locate and download them from the app stores. The expected data for each app on the scraping platform include the name of the app, the URL, the title, the star rating score, the last update, the publishing date, the genre, and the number of reviews.

App Selection

The top 30 apps from each keyword search result will be collated due to the limits of the scraping platform. Using the 6 identified search terms for each of the 6 countries will result in 36 different searches and a maximum of 1080 apps. The eligibility criteria relating to cost, language, and compatibility of the apps will be automatically applied using the filters on the scraping platform.

Once the app list is collated, the top 10 apps from each store on each search will be selected with a maximum number of 720 apps. The ranking of apps will be based on the search results with apps higher in the search result being higher on the list. The apps will not be ranked by star rating score or the number of downloads but by whichever method Apple and Google Play sort the apps as this is more representative of what a user would see when searching for a diabetes app [24]. After the compilation of the top apps, duplicates will be removed. A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram showing the proposed scraping method is presented in Figure 1. A similar app scraping methodology has been used in previous assessment studies [25,26].

Figure 1. App selection flowchart.



Apps Evaluation

The included apps will be evaluated within 6 months of first scraping using the novel ADA checklist (Multimedia Appendix 1) developed by the authors from IDF clinical practice recommendations for managing T2DM in primary care [9]. A total of 2 evaluators will independently assess each app based on the checklist. Disagreement will be resolved by discussion between the 2 evaluators [26].

The assessment data will be analyzed by descriptive statistics. As the data from the scoring system are ordinal, they will be compared via frequency distributions, median, and range. This will be used for each of the checklist items to determine whether there are associations or patterns that are visible.

Comparison With Other Rating Systems

Additionally, 12 of the apps will be evaluated using the MARS tool kit. The top app for each country under the keyword diabetes will be selected from both the Google Play Store and the Apple App Store. If there is duplication, the next app on the list will be selected. The results of the app assessment based on MARS will be compared to the results of the app assessment based on the ADA checklist to determine whether there are concordance or correlations. Further comparison will be done to ascertain whether there is a correlation with the star rating of the app stores. We would like to assess whether the score from the ADA checklist has a correlation with scores from MARS and the app stores' star rating. To test for correlation, Spearman rank correlation analysis will be used to compare the ADA checklist's total score to both the MARS total mean score and the app stores' star rating for the 12 selected apps.

Ethical Considerations

No ethics approval is required for this paper as it will not involve animal or human participants and all data to be collected are publicly available.

Results

The ADA checklist (Multimedia Appendix 1) developed based on the IDF guidelines focuses on general information, risk factors, diagnosis, pharmacologic treatment, lifestyle modification, glycemic recommendations, and medications. The initial stress testing of the protocol resulted in 173 included apps. This will vary in the final search as the app stores are constantly changing.

Discussion

Overview

This is the first time, to the best of our knowledge, that an mHealth app assessment checklist is being developed based on

medical guidelines and tested on apps in the mobile app stores. The potential uses of this ADA checklist address a number of issues related to the quality of mHealth apps for T2DM. Primarily, it would provide patients with T2DM and their health care providers with a reliable tool by which they can assess whether diabetes apps provide information based on medical guidelines. The lifestyle changes required as part of diabetes care are extensive and the health consequences of failing to make these changes in a timely and appropriate manner can be severe. Due to the lack of filters in mobile app stores related to compliance with guidelines, it is of the utmost importance that if patients are reliant on apps such as those to be evaluated by this protocol, they are able to avoid those that would mislead them. This new checklist may be useful for further assessment of diabetes apps based on their compliance with medical guidelines. The ADA checklist will allow for more trust and transparency regarding diabetes apps that are currently used, as well as future applications.

Furthermore, it would be of interest to assess if users' star ratings in the app store correlate with app quality based on the novel ADA checklist, as most prospective users might have been relying on user ratings while choosing their apps. Users' star ratings, as a metric, are open to a number of biases that could potentially reduce its correlation to app quality [27,28]. For example, user reviews may be made on the basis of user interface, aesthetics, or the invasiveness and frequency of any advertisements the app displays [27,28]. Previous studies have compared users' star ratings with MARS, an analysis of whether app ratings correlate to compliance with IDF guidelines in this study will further assess the use of users' ratings. On the other hand, comparison with MARS could help to assess whether apps that do well on assessment with a generic mHealth app assessment tool also follow medical guidelines. Irrespective of the results of this comparison between the generic app assessment tool (MARS) and the guidelines-based ADA checklist, both are likely to become complimentary as they focus on different aspects of mHealth apps.

This novel methodology for assessing apps based on medical guidelines can be translated to apps for other conditions such as hypertension, hypercholesterolemia, and atrial fibrillation. While the aspects of the checklist will change between different conditions, the checklist could be used as a baseline framework in future studies, especially with other chronic conditions.

Limitations

The proposed methodology has a number of limitations. First, the app selection process is dependent on the order in which the apps are listed on the search results on both the Google Play Store and the Apple App Store. These algorithms are subject to change at any time without warning, and these changes would likewise be unbeknownst to users. For the purposes of this protocol, this unknown ordering process will influence which apps will be included or excluded in our evaluation, as only the first 30 apps from each set of search results will be included for evaluation, excluding duplicates. This may affect the reproducibility of the results, given the potential for the order of the app listings to change on search results without notification or warning. However, this approach was deemed to be the most objective and unbiased way to select the apps that would be evaluated as these are the apps that are seen first by the users. While analyzing apps based on the number of downloads may be useful, it skews the results of the search to older apps that may not be up to date on guidelines.

Another limitation of this protocol is that only free apps will be evaluated. This is a reasonable exclusion criterion for the purposes of this evaluation, as it would ultimately provide useful information for patients with diabetes in search of a medically accurate and useful app but who are not willing or able to pay for one. However, this also means that the results of this evaluation will not be generalizable across all diabetes apps; it may well be that many purchasable apps, or components of free apps that require in-app purchases, are better than those that would be included in this evaluation based on the criteria described above.

In addition, comparison with the apps' ratings may be problematic. The average score on a 5-star rating system may be skewed by the variability in the number of reviews given. Because we intend to evaluate many apps, there is bound to be a wide range in a number of reviews. As such, apps with few reviews are likely to have less reliable average ratings compared to those with high numbers of reviews. Additionally, this would not at all account for app developers who use methods to inflate their respective app store reviews. Controlling the number of reviews may be a helpful step in reducing the bias this could introduce, though no obvious or reliable method to reduce this bias exists.

Conclusions

There are hundreds of thousands of health-related apps in the app stores. Such apps have been assessed previously from different perspectives, including information quality, reliability, interface, and efficacy. However, there have been no tools to assess apps from a clinical guideline perspective. This methodology developed in this research will demonstrate how to assess the adherence of mHealth apps to clinical guidelines.

Acknowledgments

In this paper, there has been no use of machine learning, artificial intelligence, language models, and similar technology in any of the formation, writing, or analysis of this paper.

Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Conflicts of Interest

None declared.

Multimedia Appendix 1
ADA checklist to be used in protocol.
[PDF File (Adobe PDF File), 50 KB - resprot_v13i1e48781_app1.pdf]

References

1. Lin X, Xu Y, Pan X, Xu J, Ding Y, Sun X, et al. Global, regional, and national burden and trend of diabetes in 195 countries and territories: an analysis from 1990 to 2025. Sci Rep 2020;10(1):14790 [FREE Full text] [doi: 10.1038/s41598-020-71908-9] [Medline: 32901098]
2. National diabetes statistics report, 2020. Centers for Disease Control and Prevention, U.S. Dept of Health and Human Services. 2020. URL: https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf [accessed 2024-01-05]
3. Correr CJ, Coura-Vital W, Frade JCQP, Nascimento RCRM, Nascimento LG, Pinheiro EB, et al. Prevalence of people at risk of developing type 2 diabetes mellitus and the involvement of community pharmacies in a national screening campaign: a pioneer action in Brazil. Diabetol Metab Syndr 2020;12:89 [FREE Full text] [doi: 10.1186/s13098-020-00593-5] [Medline: 33062060]
4. Pradeepa R, Mohan V. Epidemiology of type 2 diabetes in India. Indian J Ophthalmol 2021;69(11):2932-2938 [FREE Full text] [doi: 10.4103/ijo.IJO_1627_21] [Medline: 34708726]
5. Uloko AE, Musa BM, Ramalan MA, Gezawa ID, Puepet FH, Uloko AT, et al. Prevalence and risk factors for diabetes mellitus in Nigeria: a systematic review and meta-analysis. Diabetes Ther 2018;9(3):1307-1316 [FREE Full text] [doi: 10.1007/s13300-018-0441-1] [Medline: 29761289]
6. Whicher CA, O'Neill S, Holt RIG. Diabetes in the UK: 2019. Diabet Med 2020;37(2):242-247 [FREE Full text] [doi: 10.1111/dme.14225] [Medline: 31901175]
7. González ELM, Johansson S, Wallander MA, Rodríguez LAG. Trends in the prevalence and incidence of diabetes in the UK: 1996-2005. J Epidemiol Community Health 2009;63(4):332-336 [FREE Full text] [doi: 10.1136/jech.2008.080382] [Medline: 19240084]
8. National diabetes audit report 2A: complications and mortality royal college of physicians Sentinel Stroke National Audit Programme (SSNAP). NHS Digital. 2016. URL: https://www.strokeaudit.org/results/Clinical-audit/National-Results.aspx [accessed 2024-01-05]
9. Aschner P. New IDF clinical practice recommendations for managing type 2 diabetes in primary care. Diabetes Res Clin Pract 2017;132:169-170 [FREE Full text] [doi: 10.1016/j.diabres.2017.09.002] [Medline: 28962686]
10. Eng DS, Lee JM. The promise and peril of mobile health applications for diabetes and endocrinology. Pediatr Diabetes 2013;14(4):231-238 [FREE Full text] [doi: 10.1111/pedi.12034] [Medline: 23627878]
11. Marcolino MS, Oliveira JAQ, D'Agostino M, Ribeiro AL, Alkmim MBM, Novillo-Ortiz D. The impact of mHealth interventions: systematic review of systematic reviews. JMIR Mhealth Uhealth 2018;6(1):e23 [FREE Full text] [doi: 10.2196/mhealth.8873] [Medline: 29343463]
12. Stevens S, Gallagher S, Andrews T, Ashall-Payne L, Humphreys L, Leigh S. The effectiveness of digital health technologies for patients with diabetes mellitus: a systematic review. Front Clin Diabetes Healthc 2022;3:936752 [FREE Full text] [doi: 10.3389/fcdhc.2022.936752] [Medline: 36992773]
13. Kitsiou S, Paré G, Jaana M, Gerber B. Effectiveness of mHealth interventions for patients with diabetes: an overview of systematic reviews. PLoS One 2017;12(3):e0173160 [FREE Full text] [doi: 10.1371/journal.pone.0173160] [Medline: 28249025]
14. Fiordelli M, Diviani N, Schulz PJ. Mapping mHealth research: a decade of evolution. J Med Internet Res 2013;15(5):e95 [FREE Full text] [doi: 10.2196/jmir.2430] [Medline: 23697600]
15. Chavez S, Fedele D, Guo Y, Bernier A, Smith M, Warnick J, et al. Mobile apps for the management of diabetes. Diabetes Care 2017;40(10):e145-e146 [FREE Full text] [doi: 10.2337/dc17-0853] [Medline: 28774944]
16. Campbell AP. DASH eating plan: an eating pattern for diabetes management. Diabetes Spectr 2017 May;30(2):76-81 [FREE Full text] [doi: 10.2337/ds16-0084] [Medline: 28588372]
17. ICMR guidelines for the management of type 2 diabetes 2018. Indian Council of Medical Research. 2018. URL: https://main.icmr.nic.in/sites/default/files/guidelines/ICMR_GuidelinesType2diabetes2018_0.pdf [accessed 2024-01-05]
18. Hernandez E, Dietrich S. Nearly 68 million people spoke a language other than English at home in 2019. Census.gov. URL: https://www.census.gov/library/stories/2022/12/languages-we-speak-in-united-states.html [accessed 2024-01-05]
19. Census of India 2011 - language ATLAS - India. Office of the Registrar General & Census Commissioner, India (ORGI) - Map Division. 2022. URL: https://censusindia.gov.in/nada/index.php/catalog/42561 [accessed 2024-01-05]

20. White E. 2011 census: quick statistics for England and Wales, March 2011. Census - Office for National Statistics. 2011. URL: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/2011censusquickstatisticsforenglandandwales/2013-01-30 [accessed 2024-01-05]
21. Cultural diversity: census. Australian Bureau of Statistics. 2021. URL: https://www.abs.gov.au/statistics/people/people-and-communities/cultural-diversity-census/2021 [accessed 2024-01-05]
22. Chepkemoi J. What languages are spoken in Nigeria? WorldAtlas. 2019. URL: https://www.worldatlas.com/articles/what-languages-are-spoken-in-nigeria.html [accessed 2024-01-05]
23. Connolly V, Unwin N, Sherriff P, Bilous R, Kelly W. Diabetes prevalence and socioeconomic status: a population based study showing increased prevalence of type 2 diabetes mellitus in deprived areas. J Epidemiol Community Health 2000;54(3):173-177 [FREE Full text] [doi: 10.1136/jech.54.3.173] [Medline: 10746110]
24. Amjad A, Kyle K, Kyunghyun C, Aaron C. Learning distributed representations from reviews for collaborative filtering. Association for Computing Machinery: Association for Computing Machinery; 2015 Presented at: RecSys '15: Ninth ACM Conference on Recommender Systems; September 16-20, 2015; Vienna Austria p. 147-154 URL: https://doi.org/10.1145/2792838.2800192 [doi: 10.1145/2792838.2800192]
25. Anderson K, Burford O, Emmerton L. App chronic disease checklist: protocol to evaluate mobile apps for chronic disease self-management. JMIR Res Protoc 2016;5(4):e204 [FREE Full text] [doi: 10.2196/resprot.6194] [Medline: 27815233]
26. Jimenez G, Lum E, Car J. Examining diabetes management apps recommended from a Google search: content analysis. JMIR Mhealth Uhealth 2019;7(1):e11848 [FREE Full text] [doi: 10.2196/11848] [Medline: 30303485]
27. Genc-Nayebi N, Abran A. A systematic literature review: opinion mining studies from mobile app store user reviews. J Syst Softw 2017;125:207-219 [FREE Full text] [doi: 10.1016/j.jss.2016.11.027]
28. Sällberg H, Wang S, Numminen E. The combinatory role of online ratings and reviews in mobile app downloads: an empirical investigation of gaming and productivity apps from their initial app store launch. J Market Anal 2022;11(3):426-442 [FREE Full text] [doi: 10.1057/s41270-022-00171-w]

Abbreviations

ADA: Analysis of Diabetes Apps
CDC: Centers for Disease Control and Prevention
IDF: International Diabetes Federation
MARS: Mobile App Rating Scale
mHealth: mobile health
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
T2DM: type 2 diabetes mellitus

Edited by A Mavragani; submitted 10.05.23; peer-reviewed by M Kolotylo-Kulkarni, N Buzas; comments to author 03.11.23; revised version received 04.12.23; accepted 02.01.24; published 31.01.24.

Please cite as:
Rebus D, Iskander A, Deonarine F, Almas A, Rattigan D, Henn P, Fadahunsi KP, O'Donoghue J
Compliance of Type 2 Diabetes Applications to International Guidelines: Protocol for a Quantitative App Assessment
JMIR Res Protoc 2024;13:e48781
URL: https://www.researchprotocols.org/2024/1/e48781
doi:10.2196/48781
PMID:38294861

Protocol

Feasibility of a Pediatric Acute Video Consultation Process Among Health Care Professionals in Primary Care in a Rural Setting: Protocol for a Prospective Validation Study

Marta Castillo-Rodenas[1], MD, MSc; Josep Vidal-Alaball[2,3,4], MD, MPH, PhD; Núria Solanas-Bacardit[1], RNC; Clotilde Farràs-Company[5], MD; Aïna Fuster-Casanovas[6], MSc, RPh; Queralt Miró Catalina[3,6], MSc; Francesc López Seguí[7], PhD

[1]Centre d'Atenció Primària Cardona, Gerència Territorial de la Catalunya Central, Institut Català de la Salut, Cardona, Spain

[2]Cap de la Unitat de Suport a la Recerca de la Catalunya Central, Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina, Sant Fruitós de Bages, Spain

[3]Health Promotion in Rural Areas Research Group, Gerència Territorial de la Catalunya Central, Institut Català de la Salut, Sant Fruitós de Bages, Spain

[4]Faculty of Medicine, University of Vic–Central University of Catalonia, Vic, Spain

[5]Direcció del Centre d'Atenció Primària Cardona, Gerència Territorial de la Catalunya Central, Institut Català de la Salut, Cardona, Spain

[6]Unitat de Suport a la Recerca de la Catalunya Central, Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina, Sant Fruitós de Bages, Spain

[7]Chair in ICT and Health, Centre for Health and Social Care Research, University of Vic–Central University of Catalonia, Vic, Spain

Corresponding Author:
Josep Vidal-Alaball, MD, MPH, PhD
Cap de la Unitat de Suport a la Recerca de la Catalunya Central
Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina
Carrer Pica d'Estats, 13-15
Sant Fruitós de Bages, 08272
Spain
Phone: 34 936930040
Email: jvidal.cc.ics@gencat.cat

Related Article:

This is a corrected version. See correction statement: https://www.researchprotocols.org/2024/1/e57937/

Abstract

Background: For years, in Catalonia and in the rest of Spain, there has been a deficit and an unequal geographical distribution of health professionals specializing in pediatrics, especially in rural areas. Among the proposals to improve this situation is the promotion of the use of information and communication technologies (ICT) among users and professionals. Moreover, with the outbreak of COVID-19, the use of telehealth has become an essential tool, with an overall increase in non–face-to-face visits, including in primary care pediatrics. In this context, telemedicine, when used in primary care pediatrics, can be an effective means of improving families' access to medical care. Currently, in Catalonia, telemedicine involving patients and health professionals is used in pediatric primary care through telephone consultation and asynchronous teleconsultation (eConsulta). Video consultation is in practice not used, although it could have different applications.

Objective: The aim of this study is to evaluate the feasibility of a video consultation process with physical examination in acute pediatric pathology in rural areas among primary care professionals. In addition, the level of satisfaction with these remote consultations will be assessed from the perspective of both the users and the health care professionals.

Methods: We will conduct a prospective experimental study to analyze the possibility of using video consultation in pediatric acute care in primary care in central Catalonia (Spain). A minimum of 170 children aged between 0 and 14 years attending the primary care center (PCC) for acute illness for a period of 1 year will be included in the study. Initially, the telemetric visit, including a physical examination, will include a nurse at the patient and family's side and a pediatrician who will participate remotely. Subsequently, the pediatrician will visit the patient in person and the physical examination and diagnosis made during

the remote visit will be compared with the physical examination and diagnosis of the face-to-face visit, which is considered the gold standard.

Results: Recruitment was planned to begin in the second half of 2023 and continue for at least 1 year. It is anticipated to be a good resource for a variety of acute pediatric conditions in primary care. The evaluation will focus on the feasibility of performing live remote visits and comparing their diagnostic accuracy with that of face-to-face visits.

Conclusions: We believe that this study could provide evidence on the feasibility and diagnostic accuracy of video consultation in pediatric acute primary care in a rural setting, as well as on satisfaction with video consultations among both users and professionals. If proven useful in addressing the acute needs of children in a variety of situations, it could become a digital health tool that improves the overall pediatric primary care service in rural areas, for both families and professionals.

International Registered Report Identifier (IRRID): PRR1-10.2196/52946

(JMIR Res Protoc 2024;13:e52946) doi:10.2196/52946

KEYWORDS

primary health care; pediatrics; remote consultation; telemedicine; rural health services; video consultation

Introduction

Over the last years, different demographic, social, and professional factors, such as the growth and depopulation of certain areas, changes in the pattern of use of services, and the lack of professionals with formal training, among others, have made it necessary to reshape pediatrics on a European scale [1]. Specifically in Catalonia (Spain), through the Strategic Plan for the Organization of Pediatric Care in Primary Care and the Health Plan of the Generalitat de Catalunya 2021-2025, several measures have been implemented, such as the development of pediatric territorial teams in some regions [2,3]. There are several difficulties in implementing these changes, particularly the lack of specialized professionals and their heterogeneous distribution, especially in rural areas.

In the human resources map for pediatric care in Catalonia, drawn up in 2018, there were 371 primary care teams with professionals specializing in pediatrics out of more than 400 primary care teams. It is believed that the situation has recently worsened. Of the total number of professionals, 28% worked in a coordinated and integrated manner according to the strategic plan. A survey conducted by the Catalan Society of Pediatrics in 2019 found that around 30% of pediatric positions in primary care were occupied by nonpediatric professionals, who do not need to be certified to provide pediatric care. In addition, the study found that 974 nurses were working in pediatric care without specific training. There are also clear differences in the coverage and availability of professionals between areas [4].

To improve this situation, the Catalan Society of Pediatrics proposes, in addition to increasing human resources and their distribution, the strengthening and optimization of information and communication technologies (ICTs) to facilitate the connection between users and professionals [4].

Likewise, with the emergence of COVID-19, digital health has become a tool commonly used in health care. The pandemic has revolutionized the care model of health systems worldwide and has redirected the system toward telemedicine, with a remarkable increase in remote visits, including in the pediatrics setting [5,6]. It has increased the use of tools such as telephone consultations and eConsulta, a type of asynchronous remote consultation integrated into the Catalan public health system [7-9]. Others, such as video consultation, have been more limited [10]. All of this has led to the question of whether digital tools can improve pediatric care, giving rise to the concept of telepediatrics.

Telepediatrics can be considered a subspecialty of telemedicine and can be defined as the use of ICT to provide health services to children at a distance [11]. In Catalonia, telepediatrics, in the form of telephone consultations and eConsulta, has become an integral part of health care, and in a trend similar to those in other countries, the COVID-19 pandemic has significantly altered the profile of pediatric primary care visit types. As a result, there is now a higher proportion of non–face-to-face visits than ever before [12]. A study indicates that, as of March 2020, in Catalonia, there was a drop of more than 80% in face-to-face pediatric visits compared to the previous year, along with 15 times more remote consultations. Subsequently, while the rate of face-to-face visits began to recover, it has not returned to pre–COVID-19 levels. More than 2 years after the pandemic, non–face-to-face visits continued to account for over 20% of the total [13].

Another type of virtual consultation in the Catalan health care system is the interconsultation, an asynchronous patient-free consultation between different health professionals, usually between primary care and specialized hospital care. It has been incorporated into daily clinical practice and validated by the Ethics Commission of the Barcelona College of Physicians [14]. The main types of this form of consultation are dermatological teleconsultation, teleaudiometry, the teleulcer program, and the tele-eyelid program [15]. Specifically, teledermatology has been established as a standard procedure to connect with the referral service in doubtful cases and before referring a patient face-to-face to specialized dermatologic care [16]. These types of services, moreover, have a positive environmental impact and show significant time savings for users [17].

In addition, at the Catalan Institute of Health (the main service provider of the Catalan health system), a pilot test is being carried out of the “digital briefcase,” which comprises a set of devices and accessories associated with a smartphone or tablet that allow for the provision of a basic level of health care; it aims to improve the capacity to resolve problems of primary care [18]. Some of the devices it incorporates are a blood

pressure monitor with electrocardiographic rhythm, a portable complete electrocardiogram, a digital stethoscope, and a portable ultrasound scanner. It may incorporate other instruments that may be useful depending on the medical specialty.

Despite their potential to enhance communication by enabling visual contact, pediatric video consultations are not commonly used in the public health system [19]. This type of visit briefly emerged during the COVID-19 pandemic, but its current use is anecdotal [13]. It is well established that when video consultations are used by health care professionals, with one physically present alongside the patient, it improves the quality of the care process [20,21].

Video consultation has been applied in follow-up visits in pediatric hospital consultations for chronic illnesses such as diabetes, obesity, and mental health problems, as well as digestive, rheumatic, neurological, and even respiratory illnesses [22,23]. Also, in the hospital setting it has been used as a control after discharge and even to avoid days of hospitalization, with good results in terms of cost reduction and family satisfaction [24,25]. However, there are few studies on video consultation in pediatric primary care [26].

An additional possibility offered by video consultations, besides making a structured anamnesis, could be remotely carrying out physical examinations. This is especially important in cases of pediatric acute pathology, as children at these ages often have difficulties expressing their symptoms. Moreover, in pediatric cases, functional interdependence, that is, the functioning together of a child's organs, can commonly cause an underlying pathology to lead to unclear or ambiguous symptoms. [27]. In response, simple medical devices have been made available for the general population. They are sold in packs and include a digital camera, otoscope, and stethoscope. Good examples of these are the devices sold by the brands TytoCare, approved by the US Food and Drug Administration (FDA), and HIGO, developed by the University of Warsaw [28,29]. These devices are used by caregivers when the child is ill. Clinical data are recorded and sent to the practitioner via a remote application and the practitioner responds with the appropriate diagnosis and treatment. This reduces physical presence in emergency services. Currently, these devices are used in some countries, mainly by private mutual insurance companies [30]. There are also similar devices, such as those of the Firefly brand, aimed at health care professionals [31]. However, in Spain there is little evidence of the use of similar devices in clinical practice. One of the few examples is Kidscare, which offers a telemedicine service aimed at schools [32].

There are several practical reasons to use teleconsultation with physical examination for acute pediatric consultations in a rural context. One is that in rural areas with distant clinics where a pediatrician is not available every day, the pediatric nurse could manage visits with remote support from a pediatrician in another center. Currently, telephone support is already provided in these cases. If this were done through video consultation, the support would be more comprehensive. The second reason is that during vacations or when the pediatrician in charge is on leave, it could be possible in certain cases to see the patient remotely. Finally, a clear benefit would be observed out of hours when a patient needs to be evaluated by a pediatrician.

In this context, the general objective of this protocol is to evaluate a video consultation process with physical examination for acute pediatric pathology in rural areas among primary care professionals. Specifically, the aim is to assess 3 elements: the feasibility of the process, its diagnostic accuracy compared to face-to-face consultation at the same time (considered to be the gold standard), and user and professional satisfaction.

To achieve these specific objectives, the study will analyze the technical and human possibilities of pediatric video consultation, the most appropriate reasons for consultation, the diagnostic accuracy compared to concurrent face-to-face consultation, the difference in duration between the 2 types of visits, the acceptance and satisfaction of patients and professionals using validated questionnaires, and incidents that may occur during virtual visits.

Methods

Study Design

Trial Design

This will be a prospective experimental study of an acute pediatric care process using video consultation with a physical examination among health professionals.

Patients, Scope, and Period of Study

The study will involve children aged 0 to 14 years attending PCC Cardona for acute health problems. The acute pediatric conditions selected for video consultation in this research will be identical to those encountered in regular consultations, including any condition that requires a medical visit. Commonly observed symptoms include fever, cough, runny nose, sore throat, earache, abdominal pain, vomiting, diarrhea, skin lesions, and similar conditions.

The Cardona PCC is part of the health region of central Catalonia. Located in a rural area, Cardona covers a total area of 143 km^2 and serves an assigned population of nearly 5000 people. It comprises 5 family medicine and nursing teams, along with 1 pediatrics and pediatric nursing team, among other services.

Data collection will span at least 1 year to ensure the representation of all seasonal pathologies and was scheduled to commence in the second half of 2023. It is expected that by the end of 2024 all cases will have been collected and the data and conclusions can be analyzed. The results of the study will be published at the end of the project and will be presented in the form of a doctoral thesis.

Inclusion Criteria

The inclusion criteria will be patients aged 0 to 14 years who attend the Cardona PCC for acute conditions and who are authorized to participate by their legal representatives.

Exclusion Criteria

Exclusion criteria will be cases in which the legal representative does not allow participation, check-ups from the Healthy

Childhood Programme, chronic illnesses and follow-up visits, consultations requiring immediate face-to-face medical assessment, and cases where there is a language barrier.

Sample Size Determination

The sample will be for convenience. Considering the main objective of the study (to analyze the diagnostic accuracy of telemedicine compared to concurrent face-to-face consultation), in order to estimate the required sample size, and given the absence of similar studies to predict this accuracy, it will be necessary to include 170 children. This sample size calculation is based on achieving a 95% confidence level, an 8% margin of error, and accounting for a replacement rate of 10%.

Data Collection, Sources of Information, and Intervention

Children aged 0 to 14 years presenting to PCC Cardona with acute conditions will be selected using nonprobability convenience sampling. The procedure will be integrated into the daily pediatric clinical practice to facilitate recruitment. The decision to invite the patient and their family to participate in the study will be based solely on the daily workload of the health care professional (to allow time for both virtual and face-to-face visits).

The patient and their legal representative will be informed verbally and in writing of the purpose of the study and will be given the opportunity to choose whether or not to participate. If they agree, they will be asked to sign the informed consent form.

First, the patient will go to an office with the pediatric nurse and will connect via video call (Microsoft 365 Teams) with their regular pediatrician, who will conduct the anamnesis. Then, the nurse, under the guidance of the pediatrician, will perform the physical examination with approved digital devices, which will include a Firefly digital camera, a video otoscope, and a Littmann CORE digital stethoscope [31,33]. The Firefly camera and video otoscope are FDA-approved and hold certifications for FC, CE, RoSH, and ISO for medical devices. The stethoscope is FDA-approved and complies with Health Insurance Portability and Accountability Act standards [31,33].

To conduct the physical examination, a translated and adapted version of the diagnostic questionnaire for pediatric telemedicine created by Bittmann [34] during the COVID-19 pandemic will be used. The physical examination will be systematic. First, anamnesis will be conducted and the reason for the visit will be recorded. Subsequently, there will be a clinical examination. The final step will be the initiation of treatment.

The case identification data, date and time, age, gender, accompanying person, reason for the visit, and medical history, as well as the results of a physical examination (general appearance, skin, throat, otoscopy, cardiorespiratory auscultation, and other data, if necessary), diagnostic orientation, and duration of the visit will be recorded on the data collection sheet.

To ensure the effectiveness of digital health consultations, both professionals conducting the visit have received training in performing physical examinations using the devices intended for video consultations. Additionally, an incident registration section has been included to identify issues of any type (technical or human).

Afterward, the same pediatrician will again examine the child in person and record the physical examination with the apparatus. The diagnostic orientation and duration of the visit, as well as the concordance between the telemedicine examination and the diagnosis, will be evaluated in comparison to the face-to-face visit (considered the gold standard). In addition, in each case we will record whether the virtual visit was viable (when the anamnesis and physical examination were completed and a diagnosis was reached) and whether there were any incidents.

Validated questionnaires on satisfaction will be given to both the family and health care professionals (nurse or pediatrician) [35,36].

Statistical Analysis

The aforementioned variables will be collected through Microsoft 365 Forms. For data analysis, R (version 4.0.3; R Foundation for Statistical Computing) will be used.

The accuracy of the video consultation diagnosis will be estimated by comparing it to the face-to-face diagnosis. The Pearson chi-square test will be used to analyze the relationship between pairs of categorical variables and the Student *t* test (2-tailed) or Mann-Whitney *U* test will be used to analyze the relationships between pairs of continuous variables. Categorical variables will be described as absolute frequencies and percentages, and continuous variables as mean and SD or median and IQR, depending on the distribution of each variable.

Ethical Considerations

The study protocol, which involves human subjects, was reviewed and approved by the University Institute for Research in Primary Health Care Jordi Gol i Gurina (Barcelona, Spain) ethics committee (22/236-P). Written informed consent will be requested from all parents or legal guardians participating in the study. The original data collection will be conducted with informed consent that includes provision for secondary analysis of the data. The ethics committee has confirmed that the secondary analysis is covered under the initial consent procedure and does not require additional consent forms. Participants in this study will not be compensated.

To protect participant privacy and confidentiality, all study data will be anonymized and deidentified prior to analysis. The video consultation, conducted through the Teams platform, will not be recorded, and no images, sound, or personal data of any patient will be captured. In cases where a photograph is required, for example for teledermatology services, just as in a face-to-face visit, explicit consent will be requested from the patient and their family. Regarding the sounds of cardiorespiratory auscultations that might be recorded for transmission between the nurse and the pediatrician, the audio will not contain any user-identifiable data and will be deleted from the corresponding application at the end of the visit.

In this regard, the fundamental principles of the physician-patient relationship in telemedicine are the same as

in a face-to-face visit. While telemedicine has a distinct impact on the physician-patient relationship framework, adherence to good clinical practice, and ethical and deontological standards, the legal and professional regulations applicable to any medical act must be followed [20]. In the practice of telemedicine during this study, special attention will be given to aspects of identification, trust, prudence, confidentiality, clinical information and communication, informed consent, and clinical judgment, as well as record-keeping of medical history and during treatment, follow-up, and evaluation.

Results

Recruitment was scheduled to begin during the second half of 2023 and is expected to last 1 year and to include 170 patients. Preliminary results will be published by the end of 2024.

The visit via videoconference, with a physical examination of the patient performed by the pediatric nurse and the pediatrician attending remotely, is expected to be feasible and effective for most children with acute illnesses visiting primary care.

We believe that in other cases, such as when children are uncooperative or when the consultation is for specific reasons such as abdominal pain, video consultation may have limitations. In such cases, the reasons for this outcome will be recorded, and a face-to-face visit will always be conducted.

Discussion

Anticipated Findings

This study aims to provide evidence on the feasibility of, diagnostic accuracy of, and satisfaction with video consultation in the primary care pediatric acute care setting in a rural area. One of the traditional recommendations in telemedicine is not to use video consultations when the patient requires a physical examination, as is the case with acute pediatric pathology [21]. In this context, the purpose of this study is to test whether video consultation with a telemetric physical examination can be a viable and effective resource for acute pediatric conditions when there is on-site support from a health care professional. If video consultations are acceptable, they could partially alleviate the effects of the current shortage of pediatricians, particularly in rural areas.

Recommendations in telemedicine emphasize that non–face-to-face consultations should never be used as a way to enhance profitability during the workday or reduce the number of professionals [21]. In this study, these recommendations will not be breached; instead, there will be a redirection of the current approach used by pediatricians in conducting visits for acute conditions. This will ensure that children with acute conditions can be seen by a pediatrician without having to go to other urgent care centers or hospital emergency departments. Professionals must be aware that telemedicine cannot be a substitute for face-to-face examination of the patient when necessary. Therefore, telemedicine should be limited to cases where it is considered feasible. Setting limits on the use of telemedicine for patient care is a matter for the profession and professionals. Professionals must adhere to ethical and professional obligations with the same level of commitment as in face-to-face visits. Consequently, medical care must consistently maintain rigorous standards of both human and technical quality [20,21].

During the pandemic, the use of video consultation has provided an opportunity to understand its functionality and explore the potential it offers as a digital health tool in everyday medical practice. Regarding the potential benefits for pediatricians, just a few years ago it was difficult to imagine a virtual consultation that would involve examining a child, but the boost given to digital tools during the pandemic provides an opportunity to explore new modalities of care that can contribute to an optimization of resources while maintaining the quality of care and patient safety. In this context, it is important to train and raise awareness among professionals in order to determine when a visit can be carried out through a virtual consultation and when it is necessary to do it face to face [20,21]. Moreover, the study highlights the role of the pediatric nurse, who is physically present with the patient and family while the pediatrician guides the anamnesis and physical examination of the child from a distance. We believe involving pediatric nurses in this process will improve the quality of care and increase clinical safety [4].

It is also important to consider the views of health care professionals regarding telemedicine services. A recent study conducted in central Catalonia to evaluate the acceptance of telemedicine services found a positive reception, especially within the nursing community. Almost all participants agreed to continue using telemedicine in the future [37]. In relation to the benefits for health services, some articles have shown that telemedicine in general, and telepediatric health services for children living in rural areas in particular, can reduce the cost and travel time to access these services [38,39]. The use of teleconsultation can reduce the number of displacements, both for users and professionals, contributing to lower costs and time, increased efficiency, reduced pollution, and determining if there is overall greater satisfaction. On the scale of the public health system of Catalonia, studies have demonstrated that some of the digital tools that have been introduced, such as eConsulta, appear to be cost-effective. Others will need to be continually evaluated [40]. In turn, environmental benefits are gained by reducing the emission of atmospheric pollutants [41].

Video consultations can also be useful for health care providers. Health care organizations must develop practical strategies to consolidate the implementation of telemedicine and define new consultation structures to meet this new form of demand [20,21]. However, it should be noted that telemedicine in Spain does not have a specific legal regulation, as is the case in other countries in our context such as France, Sweden, Germany, or Switzerland. In the Spanish legal system and within the European framework, there are rules that are applicable and must be respected equally in both face-to-face and remote consultations [42,43]. Denmark and Israel, pioneers in the implementation of telemedicine, also have no specific legislation on the matter [44]. However, although the laws and regulations governing in-person medicine currently also apply to telemedicine, the development of specific laws and regulations will be essential.

Telemedicine has advantages and limitations in the human, technological, and economic spheres, and these must be understood by all parties involved. Remote consultations performed by health care professionals are medical procedures, and as such they are subject to current legislation based on the General Data Protection Regulation and the doctor-patient confidentiality relationship. For this reason, the use of safe and appropriate technological tools is essential [20].

Limitations

This study has several limitations, primarily the risk of not achieving an accurate diagnosis through the virtual visit compared to the face-to-face visit. This could be due to technical or human causes (eg, if technological devices fail or if the child does not cooperate) or due to care-related factors related to, for example, abdominal pain, which requires careful palpation by an experienced professional to assess a possible acute abdomen. Other possible care demands not accessible at a distance may include eye and genital injuries, some wounds, and serious traumatic injuries. The fact that the video call is made between health care professionals, one of whom is always at the patient's side, will improve the quality of care and reduce the risk of incidents. The presence of an assistant is a well-defined aspect of telemedicine [45,46]. What sets assistants apart is that they are health workers, which means that their role goes beyond merely relaying information; they actively participate in the visit. This collaborative approach is crucial for successful video consultations, where teamwork is essential. In this study, the assistant will be a pediatric nurse who will explain and accompany the families during the remote visit with guidance from the pediatrician. This guidance will include conducting anamnesis and physical examination, as well as providing information, diagnosis, and treatment to both the patient and parents.

Second, there may also be a patient selection bias, since depending on the patient's characteristics (age, accompanying person, reason for consultation), some cases may not be selected if it is assumed that they are not suitable for virtual assistance. For this reason, an attempt will be made to carry out the study without the professionals knowing the characteristics of the patient or the reason for the consultation in advance.

Third, the fact that the same pediatrician performs both the telemetric and then the face-to-face visit may induce confirmation bias. Initially, the study was intended to be multicenter, with the participation of different professionals from different centers, but due to ethics and patient safety, as well as the lack of pediatricians, it was changed to a single-center intervention. Recording the physical examination and the diagnosis made during the virtual visit just prior to the face-to-face visit may mitigate this type of error.

Fourth, another possible limitation is nonacceptance by patients, family members, or the professionals themselves. There may be different reasons for this, including ethical, technological, and human reasons, as well as the risk of losing confidentiality. In this regard, detailed legislative regulation by the competent authorities of medical devices is very important. External validation of these devices must be essential to ensure efficacy and safety in real clinical practice and to be able to define the conditions under which they can be applied. Furthermore, providing adequate training to health care professionals and offering explanations to users is essential. As for the bioethical and patient safety aspects of virtual visits, currently, in Spain, they are comparable to those of face-to-face visits.

Last, other limitations may be the longer duration of virtual visits compared to face-to-face visits and the difficulty of conducting video consultations with families when there is a language barrier.

Conclusion

We believe that this study can have significant future applications and implications, such as providing faster care to families, reducing time and travel for both users and professionals, mitigating the low ratio of pediatricians per population in certain rural areas, reorganizing territorial pediatric care, highlighting the role of the pediatric nurse as a trained professional capable of assessing pediatric needs, and optimizing resources for health service providers.

Acknowledgments

This work has been carried out as part of the Doctoral Program in Medicine and Biomedical Sciences of the Universitat de Vic–Universitat Central de Catalunya. This project is part of the *ajut d'alliberació* (liberation grant) available to the principal researcher: 23a Convocatòria pública per a la realització del Doctorat per part dels professionals sanitaris de l'àmbit de l'Atenció Primària.

Data Availability

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

Authors' Contributions

All authors contributed to the design and content of the study protocol. MC-R is responsible for the coordination of the study. MC-R, JV-A, FLS, AF-C, and QMC were responsible for the design and writing of the initial draft of the manuscript. MC-R, NS-B, and CF-C are responsible for data collection. JV-A, QMC, and AF-C are responsible for data processing and analysis. All authors have read and approved the final version of the manuscript.

Conflicts of Interest

None declared.

References

1. van Esso D, del Torso S, Hadjipanayis A, Biver A, Jaeger-Roman E, Wettergren B, et al. Paediatric primary care in Europe: variation between countries. Arch Dis Child 2010 Oct;95(10):791-795 [FREE Full text] [doi: 10.1136/adc.2009.178459] [Medline: 20403821]
2. Pla Estratègic d'Ordenació de l'Atenció de Pediatria a l'Atenció Primària. Generalitat de Catalunya Departament de Salut. URL: http://tinyurl.com/ctzzpee8 [accessed 2022-09-12]
3. Pla de Salut de Catalunya 2021-2025. Departament de Salut. Generalitat de Catalunya. URL: https://salutweb.gencat.cat/ca/el_departament/pla-salut/ [accessed 2022-09-12]
4. Proposta sobre el model d'Atenció Pediàtrica a l'Atenció Primària a Catalunya. Societat Catalana de Pediatria. URL: http://www.scpediatria.cat/adjunts_mails/prop-model-At-pediatrica-AP_01-06-2022.pdf [accessed 2022-06-19]
5. Vidal-Alaball J, Acosta-Roja R, Pastor Hernández N, Sanchez Luque U, Morrison D, Narejos Pérez S, et al. Telemedicine in the face of the COVID-19 pandemic. Aten Primaria 2020;52(6):418-422 [FREE Full text] [doi: 10.1016/j.aprim.2020.04.003] [Medline: 32402477]
6. Lopez Segui F, Hernandez Guillamet G, Pifarré Arolas H, Marin-Gomez FX, Ruiz Comellas A, Ramirez Morros AM, et al. Characterization and identification of variations in types of primary care visits before and during the COVID-19 pandemic in Catalonia: big data analysis study. J Med Internet Res 2021 Sep 14;23(9):e29622 [FREE Full text] [doi: 10.2196/29622] [Medline: 34313600]
7. Vidal-Alaball J, Camps-Vilà L. [Guidelines for a good and safe telephone service in COVID-19]. Aten Primaria 2021 Apr;53(4):101965 [FREE Full text] [doi: 10.1016/j.aprim.2020.12.006] [Medline: 33530018]
8. Vidal-Alaball J, López Seguí F. Ha llegado para quedarse: beneficios e inconvenientes de la eConsulta. Atención Primaria Práctica 2020 Jan;2(1-2):100043. [doi: 10.1016/j.appr.2020.100043]
9. López Seguí F, Walsh S, Solans O, Adroher Mas C, Ferraro G, García-Altés A, et al. Teleconsultation between patients and health care professionals in the Catalan primary care service: message annotation analysis in a retrospective cross-sectional study. J Med Internet Res 2020 Sep 17;22(9):e19149 [FREE Full text] [doi: 10.2196/19149] [Medline: 32687477]
10. Reingold SM, Hadjipanayis A, van Esso D, Del Torso S, Dornbusch HJ, de Guchtenaere A, et al. COVID-19 era effect on pandemic and post-pandemic pediatric telemedicine use: a survey of the European Academy of Pediatrics Research in Ambulatory Settings Network. Front Pediatr 2021;9:713930 [FREE Full text] [doi: 10.3389/fped.2021.713930] [Medline: 34746051]
11. Sheikhtaheri A, Kermani F. Telemedicine in diagnosis, treatment and management of diseases in children. Stud Health Technol Inform 22018018;248:148-155. [doi: 10.3233/978-1-61499-858-7-148] [Medline: 29726431]
12. Saigí-Rubió F, Vidal-Alaball J, Torrent-Sellens J, Jiménez-Zarco A, López Segui F, Carrasco Hernandez M, et al. Determinants of Catalan public primary care professionals' intention to use digital clinical consultations (eConsulta) in the post-COVID-19 context: optical illusion or permanent transformation? J Med Internet Res 2021 May 31;23(6):e28944 [FREE Full text] [doi: 10.2196/28944] [Medline: 34097638]
13. Castillo RM, Vicente GJ, Fuster CA, Miró CQ, Vidal-Alaball J, López SF. Impact of COVID-19 on the paediatric primary care model in Catalonia: analysis of changes in the number and type of face-to-face and remote visits. JMIR Preprints Preprint posted online on June 14, 2023. [FREE Full text] [doi: 10.2196/preprints.49943]
14. Consideracions deontològiques de les interconsultes sense pacient entre professionals. Nota de la Comissió de Deontologia del COMB. Collegi de Metges de Barcelona. URL: http://tinyurl.com/4m62wkt3 [accessed 2024-01-23]
15. Vidal-Alaball J, Descals Singla E. Abordaje de la telemedicina entre proveedores: ejemplos de uso. Atención Primaria Práctica 2021 Dec;3:100112. [doi: 10.1016/j.appr.2021.100112]
16. Vidal-Alaball J. Evaluating the impact of asynchronous telemedicine in the catalan central region [thesis]. Universitat de Vic-Universitat Central de Catalunya. 2018. URL: https://www.tdx.cat/bitstream/handle/10803/664577/tesdoc_a2018_vidal_alaball_josep_evaluating_impact.pdf?sequence=1&isAllowed=y [accessed 2024-01-24]
17. López Seguí F, Franch Parella J, Gironès García X, Mendioroz Peña J, García Cuyàs F, Adroher Mas C, et al. A cost-minimization analysis of a medical record-based, store and forward and provider-to-provider telemedicine compared to usual care in catalonia: more agile and efficient, especially for users. Int J Environ Res Public Health 2020 Mar 18;17(6):2008 [FREE Full text] [doi: 10.3390/ijerph17062008] [Medline: 32197434]
18. Molina M. El maletín digital de Atención Primaria. Actual Med Fam 2021;17(6):346-351 [FREE Full text]
19. Burke BL, Hall RW, Section on Telehealth Care. Telemedicine: pediatric applications. Pediatrics 2015 Jul;136(1):e293-e308 [FREE Full text] [doi: 10.1542/peds.2015-1517] [Medline: 26122813]
20. Telemedicina. Com i quan utilitzar-la en la pràctica assistencial. Quaderns de la bona praxi. Collegi de Metges de Barcelona. URL: https://www.ccmc.cat/ca/publicacions/qbp [accessed 2024-01-24]
21. Del Barrio J, Sánchez JJ. La salud digital y las nuevas formas de la atención médica. Cordoba, Spain: LID Editorial; 2023:2023-2084.

22. Bellido V, Aguilera E, Ugarte E, Quirós C, Barrio R, González C. Manual de telemedicina y diabetes. Madrid, Spain: Sociedad Española de Diabetes; 2022.
23. García-Pérez A. [Telemedicine in pediatric neurology]. Rev Neurol 2020 Sep 01;71(5):191-196 [FREE Full text] [doi: 10.33588/rn.7105.2020304] [Medline: 32729111]
24. Adroher Mas C, Esposito Català C, Batlle Boada A, Casadevall Llandrich R, Millet Elizalde M, García García JJ, et al. Pediatric tele-home care compared to usual care: cost-minimization analysis. JMIR Pediatr Parent 2022 Jan 20;5(1):e31628 [FREE Full text] [doi: 10.2196/31628] [Medline: 35049513]
25. López Seguí F, Batlle Boada A, García García JJ, López Ulldemolins A, Achotegui Del Arco A, Adroher Mas C, et al. Families' degree of satisfaction with pediatric telehomecare: interventional prospective pilot study in Catalonia. JMIR Pediatr Parent 2020 Mar 26;3(1):e17517 [FREE Full text] [doi: 10.2196/17517] [Medline: 32213471]
26. Bittmann S, Luchter E, Moschuring-Alieva E, Bittmann L, Villalon G. Telemedicine in pediatrics: introduction of an innovative new tool to diagnose and treat children in an ambulatory setting. J Clin Med Res 2021 Nov;13(10-11):515-516 [FREE Full text] [doi: 10.14740/jocmr4614] [Medline: 34925663]
27. Ruiz EA. Pediatría en ciencias de la salud. Granada, Spain: Universidad de Granada; 2013:978-984.
28. TytoCare for Professionals Advanced Telemedicine Solutions. TytoCare. URL: https://www.tytocare.com/ [accessed 2023-07-12]
29. Higo, a small medical device and telemedical solution. HigoSense. URL: https://higosense.com/ [accessed 2023-07-12]
30. Telepediatría para cavernícolas: 2020-2021. Sociedad Valenciana de Pediatría. URL: https://socvalped.com/wp-content/uploads/2021/04/TELEPEDIATRIA-1.pdf [accessed 2024-01-24]
31. Firefly telemedicine. URL: https://fireflyglobal.com/ [accessed 2023-07-12]
32. Kidscare. Kidscare, Telemedicina, Ever Health. URL: https://telepediatria.es/ [accessed 2023-07-12]
33. 3M Littmann Stethoscopes. 3M. URL: https://littmann.3m.com.es/3M/es_ES/p/d/b5005222000/ [accessed 2023-11-11]
34. Bittmann S. Preliminary Results of a Telemedicine Questionnaire in Pediatrics as an Innovative New Tool to Diagnose and Treat Children Virtually in an Ambulatory Setting: Analysis of 400 Pediatric Consultations. J Regen Biol Med 2021;3(6):1-3 [FREE Full text] [doi: 10.37191/MAPSCI-2582-385X-3(6)-098]
35. Telehealth Satisfaction Questionnaire: National First Nations Telehealth Research Project Digital Health Care Research. Agency for Health care Research and Quality. URL: https://digital.ahrq.gov/sites/default/files/docs/survey/telehealthsatisfactionquestionnairecomp.pdf [accessed 2024-01-24]
36. Vidal-Alaball J, Flores Mateo G, Garcia Domingo JL, Marín Gomez X, Sauch Valmaña G, Ruiz-Comellas A, et al. Validation of a short questionnaire to assess healthcare professionals' perceptions of asynchronous telemedicine services: the catalan version of the Health Optimum Telemedicine Acceptance Questionnaire. Int J Environ Res Public Health 2020 Mar 25;17(7):2202 [FREE Full text] [doi: 10.3390/ijerph17072202] [Medline: 32218310]
37. Vidal-Alaball J, López Seguí F, Garcia Domingo JL, Flores Mateo G, Sauch Valmaña G, Ruiz-Comellas A, et al. Primary care professionals' acceptance of medical record-based, store and forward provider-to-provider telemedicine in Catalonia: results of a web-based survey. Int J Environ Res Public Health 2020 Jun 08;17(11):4092 [FREE Full text] [doi: 10.3390/ijerph17114092] [Medline: 32521740]
38. López Seguí F, Vidal-Alaball J, Sagarra Castro M, García-Altés A, García Cuyàs F. General practitioners' perceptions of whether teleconsultations reduce the number of face-to-face visits in the Catalan public primary care system: retrospective cross-sectional study. J Med Internet Res 2020 Mar 16;22(3):e14478 [FREE Full text] [doi: 10.2196/14478] [Medline: 32175914]
39. Gohari S, Keshvardoost S, Sarabi R, Bahaadinbeigy K. Travel avoidance using telepediatric by patients and healthcare providers: a review of the literature. Acta Inform Med 2020 Jun;28(2):124-129 [FREE Full text] [doi: 10.5455/aim.2020.28.124-129] [Medline: 32742065]
40. López SF. Essays on digital health interventions. The digitalization of the Catalan health care system: an opportunity for economic appraisal [thesis]. Universitat Pompeu Fabra. URL: https://www.tdx.cat/bitstream/handle/10803/670055/tfls3.pdf?sequence=7&isAllowed=y [accessed 2024-01-24]
41. Vidal-Alaball J, Franch-Parella J, Lopez Seguí F, Garcia Cuyàs F, Mendioroz Peña J. Impact of a telemedicine program on the reduction in the emission of atmospheric pollutants and journeys by road. Int J Environ Res Public Health 2019 Nov 08;16(22):4366 [FREE Full text] [doi: 10.3390/ijerph16224366] [Medline: 31717386]
42. Ley Orgánica 3/2018, de 5 de diciembre, de Protección de datos personales y garantía de los derechos digitales. Agencia Estatal Boletín Oficial del Estado. URL: https://www.boe.es/boe_catalan/dias/2018/12/06/pdfs/BOE-A-2018-16673-C.pdf [accessed 2023-11-22]
43. Diario Oficial de la Unión Europea L 119/1, de 04 de mayo de 2016; Reglamento (UE) nº 2016/679 del Parlamento Europeo y del Consejo, de 27 de abril de 2016 relativo a la protección de las personas físicas en lo que respecta al tratamiento de datos personales y a la libre circulación de estos datos y por el que se deroga la Directiva 95/46/CE. Agencia Estatal Boletín Oficial del Estado. URL: https://www.boe.es/doue/2016/119/L00001-00088.pdf [accessed 2023-11-22]
44. European Life Sciences Lawyers. Telemedicine legal framework in Europe and Israel. Biolegis. URL: https://biolegis.com/wp-content/uploads/2021/09/EU-Legal-Framework-on-Telemedicine.pdf [accessed 2024-01-24]

45. Rokicki-Parashar J, Phadke A, Brown-Johnson C, Jee O, Sattler A, Torres E, et al. Transforming interprofessional roles during virtual health care: the evolving role of the medical assistant, in relationship to national health profession competency standards. J Prim Care Community Health 2021;12:21501327211004285 [FREE Full text] [doi: 10.1177/21501327211004285] [Medline: 33764223]
46. Pollack S, Skillman S, Mroz T, Frogner B. Medical assistants' telehealth roles and skills in primary care during the COVID-19 pandemic. Center for Health Workforce Studies, University of Washington. URL: https://familymedicine.uw.edu/chws/wp-content/uploads/sites/5/2023/05/MAs-Telehealth-Roles-During-COVID-19-FR-2023-May.pdf [accessed 2024-01-24]

Abbreviations

FDA: US Food and Drug Administration
ICT: information and communication technology
PCC: primary care center

Edited by A Mavragani; submitted 20.09.23; peer-reviewed by Y Chu, H Pilabré; comments to author 05.11.23; revised version received 25.11.23; accepted 04.12.23; published 01.02.24.

Please cite as:
Castillo-Rodenas M, Vidal-Alaball J, Solanas-Bacardit N, Farràs-Company C, Fuster-Casanovas A, Miró Catalina Q, López Seguí F
Feasibility of a Pediatric Acute Video Consultation Process Among Health Care Professionals in Primary Care in a Rural Setting: Protocol for a Prospective Validation Study
JMIR Res Protoc 2024;13:e52946
URL: https://www.researchprotocols.org/2024/1/e52946
doi:10.2196/52946
PMID:38300693

Protocol

Digital Phenotyping for Real-Time Monitoring of Nonsuicidal Self-Injury: Protocol for a Prospective Observational Study

Chan-Young Ahn[1], MA; Jong-Sun Lee[1], PhD

Department of Psychology, Kangwon National University, Chuncheon-si, Republic of Korea

Corresponding Author:
Jong-Sun Lee, PhD
Department of Psychology
Kangwon National University
Kangwondaehak-gil
Chuncheon-si, 24341
Republic of Korea
Phone: 82 0332506853
Email: sunny597@gmail.com

Abstract

Background: Nonsuicidal self-injury (NSSI) is a major global health concern. The limitations of traditional clinical and laboratory-based methodologies are recognized, and there is a pressing need to use novel approaches for the early detection and prevention of NSSI. Unfortunately, there is still a lack of basic knowledge of a descriptive nature on NSSI, including when, how, and why self-injury occurs in everyday life. Digital phenotyping offers the potential to predict and prevent NSSI by assessing objective and ecological measurements at multiple points in time.

Objective: This study aims to identify real-time predictors and explain an individual's dynamic course of NSSI.

Methods: This study will use a hybrid approach, combining elements of prospective observational research with non–face-to-face study methods. This study aims to recruit a cohort of 150 adults aged 20 to 29 years who have self-reported engaging in NSSI on 5 or more days within the past year. Participants will be enrolled in a longitudinal study conducted at 3-month intervals, spanning 3 long-term follow-up phases. The ecological momentary assessment (EMA) technique will be used via a smartphone app. Participants will be prompted to complete a self-injury and suicidality questionnaire and a mood appraisal questionnaire 3 times a day for a duration of 14 days. A wrist-worn wearable device will be used to collect heart rate, step count, and sleep patterns from participants. Dynamic structural equation modeling and machine learning approaches will be used.

Results: Participant recruitment and data collection started in October 2023. Data collection and analysis are expected to be completed by December 2024. The results will be published in a peer-reviewed journal and presented at scientific conferences.

Conclusions: The insights gained from this study will not only shed light on the underlying mechanisms of NSSI but also pave the way for the development of tailored and culturally sensitive treatment options that can effectively address this major mental health concern.

International Registered Report Identifier (IRRID): DERR1-10.2196/53597

(JMIR Res Protoc 2024;13:e53597) doi:10.2196/53597

KEYWORDS

nonsuicidal self-injury; NSSI; digital phenotyping; digital phenotype; wearable device; wearable; wearables; wrist worn; mood; emotion; emotions; heart rate; step; sleep; machine learning; multilevel modeling; ecological momentary assessment; EMA; self-injury; self-harm; psychiatry; psychiatric; mental health; predict; prediction; predictions; predictor; predictors; predictive

Introduction

Nonsuicidal self-injury (NSSI), defined as deliberate self-inflicted bodily harm without suicidal intent [1], is a major global mental health concern. A recent epidemiological study found that the estimated lifetime prevalence of NSSI in adults was 4.86%, with younger age being more associated with NSSI [2]. According to a meta-analysis, the pooled prevalence of NSSI in young adults was 13.4% [3], and epidemiological studies indicate that 1 in 5 young adults engage in NSSI at least once before the age of 25 years [4,5].

Research has shown that NSSI is associated with academic and interpersonal difficulties [6,7], substance dependence [8], rehospitalization [9], and an increased risk for psychiatric disorders [10-14]. Remarkably, NSSI, despite its absence of initial suicidal intent, is a strong predictor of future suicidal thoughts and behaviors, independent of psychiatric disorders [15-18].

A recent scoping review [19] found that most mobile apps designed to intervene in NSSI were effective in reducing the frequency of urges to self-harm. Similarly, a systematic review found preliminary evidence that psychological interventions for self-harm are associated with reductions in self-injurious thoughts and behaviors, with positive treatment effects also found for suicidal ideation [20]. In addition, psychotherapeutic interventions for NSSI have shown efficacy in improving global functioning and reducing NSSI and depressive symptoms [21], with significant improvements in hopelessness and problem-solving [22]. Given the efficacy and effectiveness of interventions for NSSI, it is important to detect people with self-injury behavior early and provide NSSI-specific interventions.

Despite the pressing need for early detection and intervention for NSSI, it is a worrying reality that a majority of people with self-injury behavior do not seek medical care or help, including psychotherapy [2,23-25]. Furthermore, individuals engaging in self-injurious behaviors often face issues of stigma and social undesirability, making it essential to explore non–face-to-face diagnostic and intervention approaches [26-28]. Additionally, retrospective self-reported methods to assess self-injury may be limited by recall bias [29,30], failing to capture the transient nature of self-injurious thoughts, especially in adults, where the frequency and intensity of such thoughts can fluctuate even within a single day [31]. Recognizing that traditional clinical- or laboratory-based methodologies have limitations, there is a pressing need to detect and prevent NSSI at an early stage.

There is an urgent need for rigorous descriptive research, especially observational research to measure change over time and document various aspects of NSSI behavior [32]. Understanding NSSI requires a systematic and meticulous approach to longitudinal and real-time data collection to enable researchers to produce information of a descriptive nature on the occurrence of NSSI. Designating information on NSSI behavior as being of a “descriptive nature” refers to the detail and comprehensiveness of our understanding; for NSSI, this encompasses factors such as its frequency, duration, triggers, and consequences. However, there is still a lack of rigor in understanding when, how, and why self-injury occurs in everyday life [33]. This gap in knowledge largely persists because most NSSI research has relied on cross-sectional designs, which may not capture the dynamic nature of NSSI behavior over time. While there are some longitudinal studies, they often use long observation windows to identify developmental risk factors, providing insights into who is at higher risk of self-injury relative to others over extended periods (ie, at a between-person level) [34]. These methods focus on long-term trends rather than immediate occurrences of NSSI. In other words, these methods may not have the temporal precision to detect imminent risk of self-injury in daily life, occurring within minutes or hours.

Digital phenotyping, as an approach, offers the potential to predict and prevent NSSI in everyday life by assessing an objective and ecological source of measurements at multiple points [35,36]. By leveraging this technology, researchers can collect real-time data on an individual’s self-injury–related markers, such as mood, sleep condition, and physiological responses such as heart rate [37-39]. This comprehensive data set enables a deeper understanding of the complex factors contributing to NSSI behaviors, ultimately facilitating more accurate prediction, early detection, and intervention strategies.

Digital phenotyping techniques, using smartphone and wearable devices, encompass 2 types of data: active and passive. Active data, such as data obtained with ecological momentary assessment (EMA), involve self-reported questionnaires that requires conscious effort from users. Passive data, including heart rate and sleep condition, on the other hand, are collected automatically without any user input. Predicting a high risk of NSSI in daily life can prompt the delivery of early real-time interventions. Despite their potential, few studies have examined individuals’ dynamic NSSI patterns in daily life. This study aims to identify real-time predictors and explain an individual’s dynamic course of NSSI.

This study aims to use cutting-edge digital phenotyping techniques to identify young individuals at risk of NSSI and develop targeted interventions.

Methods

Study Design

This study will use a hybrid approach, combining elements of prospective observational research with non–face-to-face study methods. It will use a digital app to conduct continuous digital phenotype assessments of self-injury and suicide-related conditions, mood, physical activities (eg, walking), and sleep conditions. It will also use a wrist-worn wearable device (Apple Watch) to measure physiological state (eg, heart rate).

Ethical Considerations

The protocol for this study has been approved by the institutional review board of Kangwon National University (KWNUIRB-2023-02-008-001) to ensure compliance with ethical guidelines and research protocols. All participants will be given an informed consent form and will review its contents before making a decision to take part. The consent form will contain information about the purpose of the study, procedures, potential risks of participation, compensation, and privacy guarantees. Each participant will have 3 EMA periods spaced 3 months apart. If the EMA compliance rate is 90% or higher, the reward will be KRW ₩70,000 (equivalent to approximately US $53), if it is 70% or higher, KRW ₩50,000 (approximately US $38), and if it is 50% or higher, KRW ₩30,000 (approximately US $23); the reward will be given in the form of a gift certificate. All collected data will be anonymized and analyzed to ensure individuals cannot be identified. The data will be exclusively used for research purposes and will not serve any other function. Subsequently, data files will be transferred

to an external hard drive and securely stored within the principal investigator's laboratory, secured under lock and key. Access to the data will be restricted to the principal investigator and authorized research staff, with the lab key held solely by the principal investigator.

Participants

This study aims to recruit a cohort of 150 adults aged 20 to 29 years who have self-reported engaging in NSSI on 5 or more days within the past year. Participants to be recruited will own a smartphone and provide signed informed consent. Exclusion criteria for participants are as follows: presenting suicidal ideation and plans at a level requiring immediate intervention, that is, if the participant reports (1) suicidal thoughts with actual intent to attempt suicide or (2) has attempted suicide or taken preparatory actions in the past month; current manifestation of psychotic or manic symptoms or substance use disorders; and currently receiving any other psychotherapy or counseling.

Procedure

Participants will be enrolled in a longitudinal study conducted at 3-month intervals spanning 3 long-term follow-up studies. The procedures shown in Textbox 1 and Figure 1 will be repeated for each study.

Textbox 1. Procedures for this longitudinal study conducted at 3-month intervals spanning 3 long-term follow-up studies.

Recruitment

Potential participants meeting the criteria will be identified through targeted outreach efforts and community engagement. They will be provided with study information and invited to participate.

Informed consent

Participants who express interest in joining the study will be provided with detailed information regarding the study objectives, procedures, potential risks and benefits, and their rights as participants. An electronic version of consent in which participants click "yes" or "no" will be obtained from each participant prior to their inclusion in the study.

Digital app enrollment

After providing consent, participants will be guided through the process of enrolling in the app, named Dear My Mind, specifically developed for this study. This app will facilitate the collection of digital phenotyping data and serve as the primary mode of communication between the researchers and participants.

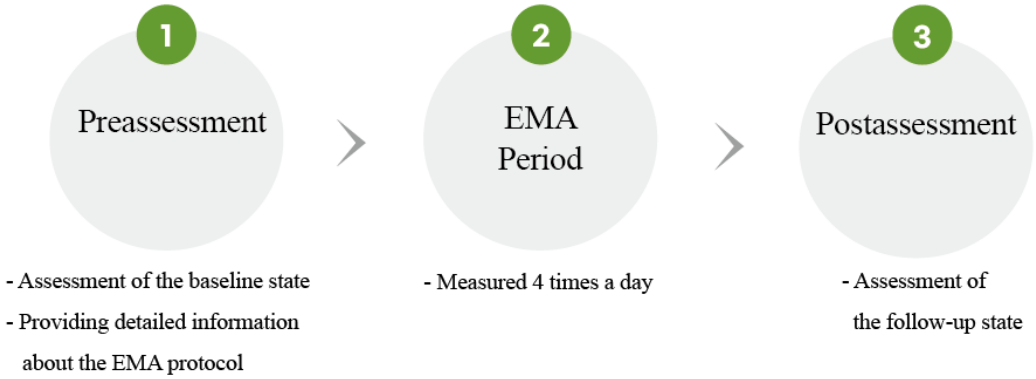
Continuous digital phenotyping assessments

1. Participants will complete a preassessment. The preassessment questionnaire will consist of the following items: the Functional Assessment of Self-Mutilation (FASM) [40] for an in-depth assessment of self-injurious behavior, Columbia Suicide Severity Rating Scale (C-SSRS) [41] to assess suicidality, Patient Health Questionnaire 9-item scale (PHQ-9) [42] to measure depression, Generalized Anxiety Disorder 7-item scale (GAD-7) [43] to measure anxiety, Korean version of the Pittsburgh Sleep Quality Index (PSQI-K) [44] to assess sleep conditions, Primary Care PTSD Screen for DSM-5 (PC-PTSD) [45] to assess posttraumatic stress disorder symptoms, WHO-5 Well-Being Index [46] to measure well-being, Brief Resilience Scale (BRS) [47] to measure levels of resilience, Self-Harm Inventory (SHI) [48] to measure deliberate self-harm, and Personality Assessment Inventory–Borderline Features Scale (PAI-BOR) [49] for the assessment of borderline personality disorder tendencies.
2. Active data will be obtained using ecological momentary assessment. Participants will provide active data regarding their mood, sleep, and self-injury behavior patterns 3 times each day. Additionally, they will be asked to record their mood daily at night time.
3. Passive data will be obtained using a wearable device. All participants will wear a wrist-worn wearable device, specifically an Apple Watch, for 14 days to passively collect data. This will include data related to activity levels, heart rate, and other relevant measures.

Postassessment and debriefing

The same questionnaire used for the preassessment will be administered for the postassessment. As compensation, participants with an overall compliance rate of 50% or more will receive KRW ₩30,000 (approximately US $23), participants with an overall compliance rate of 70% or more will receive KRW ₩50,000 (approximately US $38), and participants with an overall compliance rate of 90% or more will receive KRW ₩70,000 (equivalent to approximately US $53). Compensation will be based on 56 measurements collected over the 14 days.

Figure 1. Study procedure. EMA: ecological momentary assessment.



Measures

Active Assessment

EMA will be conducted via a smartphone app called Dear My Mind (currently under development; Figure 2). The EMA aims to capture real-time data on participants' self-injury and suicidality, as well as mood appraisals. Participants will be prompted to complete the self-injury and suicidality questionnaire and the mood appraisal questionnaire 3 times a day for a duration of 14 days: at noon, in the evening, and at night (Table 1). Each morning, participants will be asked to answer a questionnaire regarding their sleep patterns from the previous night. This questionnaire will provide additional information about participants' sleep conditions to complement the objective sleep measures collected. Furthermore, participants will be asked to complete a mood diary each night (the Mood Diary section below presents detailed information).

Figure 2. Dear My Mind app (under development).

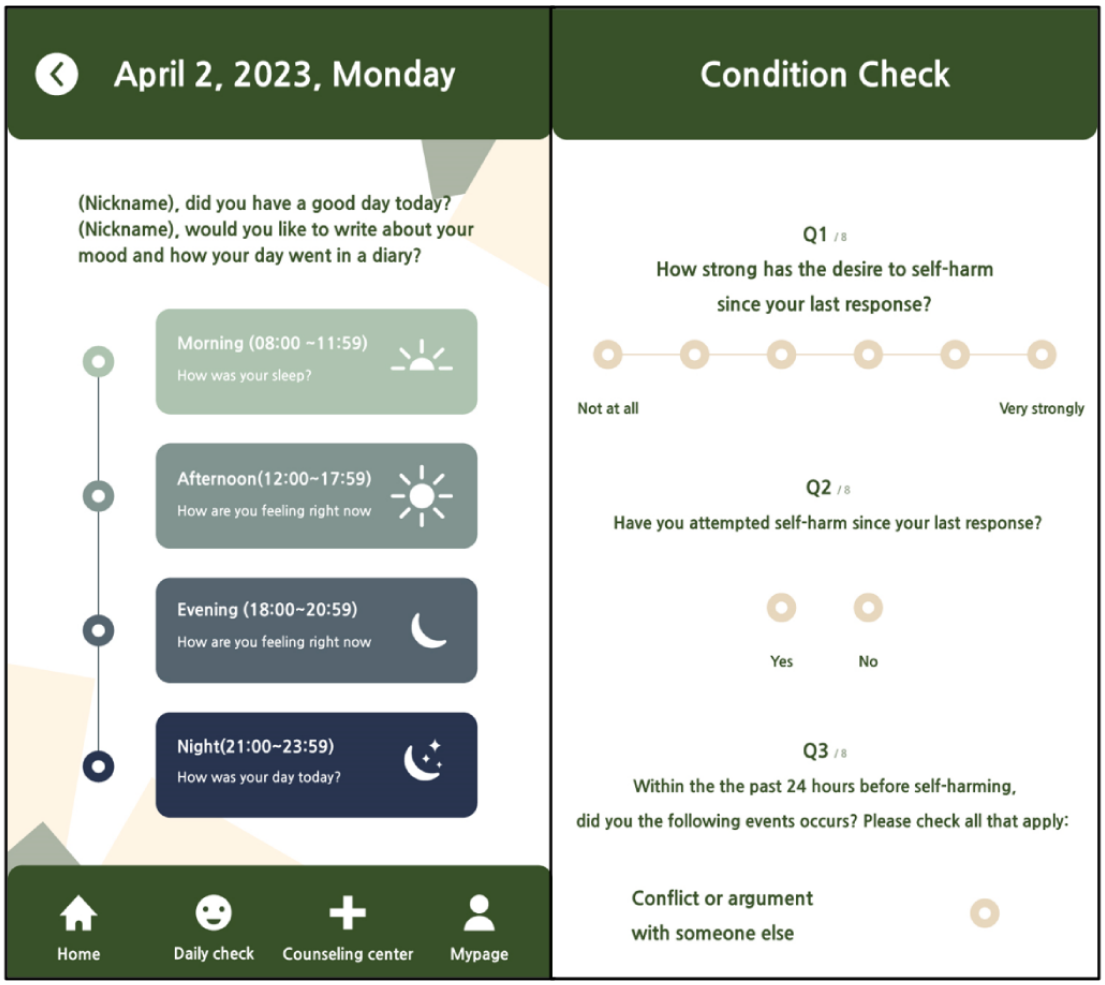


Table 1. Ecological momentary assessment schedule.

	Sleep condition check	Mood condition check	Self-injury and suicidality check	Mood diary
9 AM to 10 AM	✓			
Noon to 1 PM		✓	✓	
6 PM to 7 PM		✓	✓	
9 PM to midnight		✓	✓	✓

Self-Injury and Suicidality Questionnaire

The visual analog scale (VAS) is a rating of the participant's perceived level of "self-injurious & suicidal thoughts and urges." It is constructed on a horizontal line with "not at all" at one end and "very much" at the other (on a 7-point Likert scale). It can quantify a participant's self-injurious and suicidal thoughts and urges and is useful for capturing changes within individuals rather than differences between individuals. In addition, if the participant has attempted self-injury since the last response, a text box prompts the participant to indicate the method of the attempt. There are also additional questions about antecedent events, antecedent emotions that occurred within the 24 hours prior to the self-injury, and experiences immediately following the self-injury. If the participant indicates that they have attempted suicide since their last response, they will be classified

as high risk and the monitoring researcher will contact them immediately to refer them to a local mental health clinic or counseling center for immediate help.

Mood Appraisal Questionnaire

Participants will be instructed to respond to the VAS 3 times a day about the emotions they are experiencing at that moment. The mood VAS will be constructed on a horizontal line with "not at all" at one end and "very much" at the other (on a 9-point Likert scale). Specifically, participants will be asked about their feelings of depression, sadness, anxiety, fear, loneliness, rejection/hurt, anger at self, anger at others, shame, and emptiness.

Mood Diary

Participants will be asked to engage in daily mood diary entries using a free-text box. Each night, participants will be prompted to write about an event they experienced during the day, how it affected their mood, and the strategies they used to resolve it. Participants receive clear instructions regarding the purpose and content of the mood diary entries. A free-text format provides participants the flexibility to express their thoughts and feelings in their own words, allowing for a more nuanced understanding of their mood dynamics. Additionally, we emphasize the importance of consistent and honest reporting to maximize the validity and reliability of the data collected. The purpose of the mood diary is to capture participants' subjective experiences and emotions, as well as their efforts to manage and overcome daily challenges. Participants will be encouraged to be as detailed and specific as possible when describing the event, their emotional response, and their coping strategies. This information will provide valuable insights into the contextual factors that influence participants' mood fluctuations and their adaptive responses. The daily nature of the mood diary entries allows for the examination of day-to-day variations in mood and the exploration of the relationship between specific events and emotional well-being. It provides a comprehensive picture of participants' subjective experiences and contributes to the overall understanding of their digital phenotypes.

Sleep Condition Questionnaire

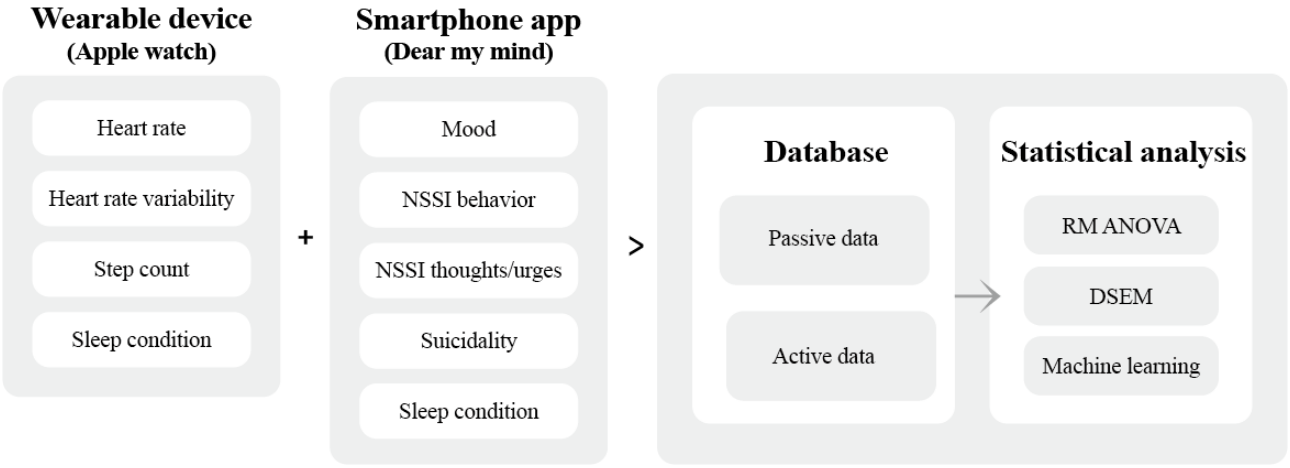
To complement the objective sleep data obtained from the wearable device, participants will also be administered the sleep condition questionnaire to gather subjective sleep measures. This questionnaire includes items related to bedtime and wake time, actual sleep duration, and subjective sleep quality. Participants will be asked to respond to the sleep condition questionnaire once a day, specifically each morning, providing information about their sleep experience during the previous night. By capturing participants' subjective perceptions of their sleep, this questionnaire will help elucidate participants' personal experiences and perceptions of their sleep quality and add a valuable subjective component to the objective sleep data collected. Participants will be encouraged to provide accurate and detailed responses to provide a comprehensive understanding of their sleep patterns and experiences. By combining objective sleep data from the wearable device with participants' subjective reports, this study will gain a more comprehensive and holistic understanding of participants' sleep conditions.

Passive Assessment

The wearable device will be used to collect several types of passive data from participants. Previous studies have shown the psychometric validity of the wearable device in reliably collecting physiological data [50,51]. The types of passive data collected in this study are heart rate, heart rate variability, step count, and sleep patterns. More specifically, the wearable device's photoplethysmography sensor will collect data on an individual's heart rate and heart rate variability [51]. In addition, a combination of sensors, such as the accelerometer, gyroscope, altimeter, and GPS, will be used to count steps. Through a combination of the above sensors, we will also measure sleep patterns such as core sleep, deep sleep, and rapid eye movement (REM) sleep.

To ensure the protection of individual rights and privacy, passive data will only be accessed and used in accordance with Apple's officially authorized data access protocols. Each research participant will be assigned a unique identifier, and their information will be uploaded to the database in a deidentified format. This process safeguards the confidentially of participants' personal information. For the purpose of data collection, participants will be instructed to wear the wearable device on their wrist throughout the day, except during activities such as showering or charging. By leveraging the capabilities of the wearable device, this study aims to capture objective and continuous measurements of participants' physiological variables and activity. These passive data sources will provide valuable insights into participants' daily behaviors and help enhance the understanding of their digital phenotypes. Figure 3 shows an overview of the flow of digital phenotyping.

Figure 3. Flow of digital phenotyping. DSEM: dynamic structural equation modeling; NSSI: nonsuicidal self-injury; RM: repeated measures.



Analytic Plan

This study will use a variety of analytical methods based on the study hypotheses and the characteristics of the data. The analytic methods described below will be used.

Basic Data Analysis

Initially, basic data analysis techniques such as 2-tailed independent *t* tests, linear regression analysis, repeated measures ANOVA, or other appropriate methods will be used to analyze the data and identify any significant changes or associations.

Dynamic Structural Equation Modeling

To examine dynamic changes at the within-individual level, dynamic structural equation modeling (DSEM) will be used. This method allows for the investigation of time-varying relationships and the identification of individual-level patterns of change over time. Specifically, we will examine whether an individual's affective state, physiological state (heart rate, heart rate variability), and sleep state predict NSSI thoughts and behaviors from one observation window to the next. To address these 2-level structured data and to examine the temporal relationships between predictor variables and NSSI thoughts and behavior, multilevel vector autoregressive models were constructed within the framework of DSEM. This approach will enable us to investigate the extent to which time-varying variables at *t*–1 (eg, depressive affect) predict NSSI thoughts and NSSI behavior at *t*.

Machine Learning

To comprehensively analyze participants' digital phenotypes and predict NSSI thoughts and behaviors, sparse logistic regression will be used. Logistic regression predicts the probability of being categorized into 1 of 2 groups when the response variable is binary. This model has the useful property that the estimated coefficients are log odds ratios, but the results are difficult to interpret when the number of variables becomes large. To overcome this problem, sparse logistic regression using the least absolute shrinkage and selection operator (LASSO) can be considered. This model simultaneously conducts feature selection and estimation, allowing for interpretation with a few selected important predictors. To evaluate prediction performance, we will divide the data set into a 30% subset for model estimation and a 70% subset for model training. Additionally, we will perform 5-fold cross validation to avoid overfitting the model. In this process, the full data set will be divided into 5 subsets, with 4 subsets used for training and the remaining subset used as an independent validation set. To solve the problem of imbalance in the training data, the synthetic minority oversampling technique (SMOTE) will be used. SMOTE is an oversampling technique that takes samples from a small number of classes in the data and adds random values to generate new samples to add to the data. This algorithm helps to address the issue of the overfitting problem caused by random oversampling [52].

Other Measures

Measures including accuracy, precision, sensitivity, specificity, and area under the curve will be calculated to explore the prediction performance of sparse logistic regression.

The outcome variables to be entered into the model are NSSI thoughts and behaviors, which will be coded dichotomously (0: absent; 1: present). The predictor variables to be included in the model as interval averages are step count, heart rate, and heart rate variability. These variables will be binned according to the intervals at which the dependent variable, NSSI thoughts and behaviors, will be assessed. The mean value per bin will then be calculated and used as a predictor. For example, as active data collection occurs 4 times, at 9 AM, noon, 6 PM, and 9 PM, the numerous values in the passive data will be divided into 4 bins: 8:00 AM to 11:59 AM, noon to 5:59 PM, 6:00 PM to 8:59 PM, and 9:00 PM to 23:59 PM. For heart rate, values less than 30 or greater than 200 beats per minute (bpm) will be discarded. Heart rate will be calculated as the mean heart rate in bpm, and heart rate variability will be obtained via the SD of the normal-to-normal interval (SDNN), which is the SD of the NN interval and the square root of the variance. Subtracting the mean from each heart rate interval yields the SD of heart rate intervals. Regarding step count, the total step count, average, median, and SD for each period will be calculated. For sleep data, preprocessing will ensure only 1 value per day, representing 1 value per night. Sleep data preprocessing will include the average, median, and SD of core sleep, deep sleep, REM sleep, and total sleeping duration. The ratio of each sleep duration to the total sleep duration will also be calculated as a reference for sleep quality.

Results

Participant recruitment and data collection started in October 2023. Data collection and analysis are expected to be completed by December 2024. The results will be published in a peer-reviewed journal and presented at scientific conferences.

Discussion

The objectives of this study are to identify the factors that can forecast NSSI thoughts and behaviors in real time within an individual's everyday experiences and to explore the dynamic course of NSSI. This study will be the first attempt in Korea to use digital phenotyping for predicting NSSI. In this project, we can quantify the digital phenotypes of NSSI in individuals by measuring daily mood, self-injury and suicidality, sleep state, and physiological data through the Dear My Mind app and a wearable device. By identifying specific digital phenotypes and analyzing within-individual variations over time, this study seeks to categorize NSSI groups that are relevant to Korean culture. Furthermore, the findings of this research are expected to improve the accuracy of NSSI assessment in psychotherapy. By incorporating digital phenotyping, clinicians will have access to objective and real-time data, enabling them to make more informed treatment decisions and personalized interventions based on individual needs. One approach to tailoring interventions is through the integration of digital phenotyping and intervention strategies [53]. For example, by leveraging multimodal digital signals, such as mobile sensing data, in combination with ground truth data like self-reported information using EMA, predictive models of NSSI risk can be developed. These models can be used to create personalized interventions that are specifically tailored to an individual's unique risk factors and patterns of NSSI behavior. By integrating real-time data collection and analysis, these interventions can provide timely and contextually relevant support to individuals at risk for NSSI, potentially enhancing their effectiveness.

One of the major limitations of this study is that it targets individuals who have engaged in NSSI 5 or more days in the past year, yet the brief 14-day monitoring period may not comprehensively capture NSSI behaviors. This can lead to an imbalance in the training data [54] and should be addressed by expanding the observation period and using appropriate methodologies. Despite this limitation, this research will ultimately serve as a crucial foundation for advancing our knowledge of NSSI in the Korean context. The insights gained from this study will not only shed light on the underlying mechanisms of NSSI but also pave the way for the development of tailored and culturally sensitive treatment options that can effectively address this major mental health concern.

Acknowledgments

This work was supported by the Ministry of Education of the Republic of Korea and the National Research Foundation of Korea (NRF-2022S1A5A2A03053627).

Data Availability

The data sets generated and analyzed during this study are not publicly available because this project is currently in progress, but they are available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

References

1. Nock MK, Favazza AR. Nonsuicidal self-injury: definition and classification. In: Nock MK, editor. Understanding Nonsuicidal Self-Injury: Origins, Assessment, and Treatment. Worcester, MA: American Psychological Association; 2009:9-18.
2. Liu RT. The epidemiology of non-suicidal self-injury: lifetime prevalence, sociodemographic and clinical correlates, and treatment use in a nationally representative sample of adults in England. Psychol Med 2023 Jan;53(1):274-282 [FREE Full text] [doi: 10.1017/S003329172100146X] [Medline: 33960286]
3. Swannell SV, Martin GE, Page A, Hasking P, St John NJ. Prevalence of nonsuicidal self-injury in nonclinical samples: systematic review, meta-analysis and meta-regression. Suicide Life Threat Behav 2014 Jun;44(3):273-303. [doi: 10.1111/sltb.12070] [Medline: 24422986]
4. Gandhi A, Luyckx K, Baetens I, Kiekens G, Sleuwaegen E, Berens A, et al. Age of onset of non-suicidal self-injury in Dutch-speaking adolescents and emerging adults: an event history analysis of pooled data. Compr Psychiatry 2018 Jan;80:170-178. [doi: 10.1016/j.comppsych.2017.10.007] [Medline: 29121554]
5. Gillies D, Christou MA, Dixon AC, Featherston OJ, Rapti I, Garcia-Anguita A, et al. Prevalence and characteristics of self-harm in adolescents: meta-analyses of community-based studies 1990-2015. J Am Acad Child Adolesc Psychiatry 2018 Oct;57(10):733-741. [doi: 10.1016/j.jaac.2018.06.018] [Medline: 30274648]
6. Giletta M, Scholte RH, Engels RC, Ciairano S, Prinstein MJ. Adolescent non-suicidal self-injury: a cross-national study of community samples from Italy, the Netherlands and the United States. Psychiatry Res 2012 May 15;197(1-2):66-72 [FREE Full text] [doi: 10.1016/j.psychres.2012.02.009] [Medline: 22436348]

7. Plener PL, Schumacher TS, Munz LM, Groschwitz RC. The longitudinal course of non-suicidal self-injury and deliberate self-harm: a systematic review of the literature. Borderline Personal Disord Emot Dysregul 2015;2:2 [FREE Full text] [doi: 10.1186/s40479-014-0024-3] [Medline: 26401305]
8. Serras A, Saules KK, Cranford JA, Eisenberg D. Self-injury, substance use, and associated risk factors in a multi-campus probability sample of college students. Psychol Addict Behav 2010 Mar;24(1):119-128. [doi: 10.1037/a0017210] [Medline: 20307119]
9. van Alphen NR, Stewart JG, Esposito EC, Pridgen B, Gold J, Auerbach RP. Predictors of rehospitalization for depressed adolescents admitted to acute psychiatric treatment. J Clin Psychiatry 2017 May;78(5):592-598 [FREE Full text] [doi: 10.4088/JCP.15m10326] [Medline: 27529444]
10. Ohlis A, Bjureberg J, Lichtenstein P, D'Onofrio BM, Fruzzetti AE, Cederlöf M, et al. Comparison of suicide risk and other outcomes among boys and girls who self-harm. Eur Child Adolesc Psychiatry 2020 Dec;29(12):1741-1746 [FREE Full text] [doi: 10.1007/s00787-020-01490-y] [Medline: 32056009]
11. Wilkinson PO, Qiu T, Neufeld S, Jones PB, Goodyer IM. Sporadic and recurrent non-suicidal self-injury before age 14 and incident onset of psychiatric disorders by 17 years: prospective cohort study. Br J Psychiatry 2018 Apr;212(4):222-226 [FREE Full text] [doi: 10.1192/bjp.2017.45] [Medline: 29514726]
12. Riley EN, Davis HA, Combs JL, Jordan CE, Smith GT. Nonsuicidal self-injury as a risk factor for purging onset: negatively reinforced behaviours that reduce emotional distress. Eur Eat Disord Rev 2016 Jan;24(1):78-82 [FREE Full text] [doi: 10.1002/erv.2407] [Medline: 26373703]
13. Kiekens G, Claes L. Non-suicidal self-injury and eating disordered behaviors: an update on what we do and do not know. Curr Psychiatry Rep 2020 Oct 10;22(12):68 [FREE Full text] [doi: 10.1007/s11920-020-01191-y] [Medline: 33037934]
14. Goodman M, Tomas IA, Temes CM, Fitzmaurice GM, Aguirre BA, Zanarini MC. Suicide attempts and self-injurious behaviours in adolescent and adult patients with borderline personality disorder. Personal Ment Health 2017 Aug;11(3):157-163 [FREE Full text] [doi: 10.1002/pmh.1375] [Medline: 28544496]
15. Joiner TE, Ribeiro JD, Silva C. Nonsuicidal self-injury, suicidal behavior, and their co-occurrence as viewed through the lens of the interpersonal theory of suicide. Curr Dir Psychol Sci 2012 Oct 01;21(5):342-347. [doi: 10.1177/0963721412454873]
16. Kiekens G, Hasking P, Boyes M, Claes L, Mortier P, Auerbach R, et al. The associations between non-suicidal self-injury and first onset suicidal thoughts and behaviors. J Affect Disord 2018 Oct 15;239:171-179. [doi: 10.1016/j.jad.2018.06.033] [Medline: 30014957]
17. Ribeiro JD, Franklin JC, Fox KR, Bentley KH, Kleiman EM, Chang BP, et al. Self-injurious thoughts and behaviors as risk factors for future suicide ideation, attempts, and death: a meta-analysis of longitudinal studies. Psychol Med 2016 Jan;46(2):225-236 [FREE Full text] [doi: 10.1017/S0033291715001804] [Medline: 26370729]
18. Mortier P, Demyttenaere K, Auerbach R, Cuijpers P, Green J, Kiekens G, et al. First onset of suicidal thoughts and behaviours in college. J Affect Disord 2017 Jan 01;207:291-299 [FREE Full text] [doi: 10.1016/j.jad.2016.09.033] [Medline: 27741465]
19. Huster L. Investigating the effectiveness and design of mobile apps for reducing non-suicidal self-injury: a scoping review [thesis]. University of Twente. URL: http://essay.utwente.nl/96203/ [accessed 2024-01-23]
20. Arshad U, Farhat-Ul-Ain, Gauntlett J, Husain N, Chaudhry N, Taylor PJ. A systematic review of the evidence supporting mobile- and internet-based psychological interventions for self-harm. Suicide Life Threat Behav 2020 Feb;50(1):151-179 [FREE Full text] [doi: 10.1111/sltb.12583] [Medline: 31448847]
21. Pérez Arqueros V, Ibáñez-Beroiz B, Goñi-Sarriés A, Galbete Jiménez A. Efficacy of psychotherapeutic interventions for non-suicidal self-injury in adolescent population: systematic review and meta-analysis. Span J Psychiatry Ment Health 2023;16(2):119-126. [doi: 10.1016/j.rpsm.2022.10.001] [Medline: 37689523]
22. Hawton K, Witt KG, Salisbury TLT, Arensman E, Gunnell D, Hazell P, et al. Psychosocial interventions following self-harm in adults: a systematic review and meta-analysis. Lancet Psychiatry 2016 Aug;3(8):740-750. [doi: 10.1016/S2215-0366(16)30070-0] [Medline: 27422028]
23. Steinhoff A, Ribeaud D, Kupferschmid S, Raible-Destan N, Quednow BB, Hepp U, et al. Self-injury from early adolescence to early adulthood: age-related course, recurrence, and services use in males and females from the community. Eur Child Adolesc Psychiatry 2021 Jun;30(6):937-951 [FREE Full text] [doi: 10.1007/s00787-020-01573-w] [Medline: 32572615]
24. Whitlock J, Muehlenkamp J, Purington A, Eckenrode J, Barreira P, Baral Abrams G, et al. Nonsuicidal self-injury in a college population: general trends and sex differences. J Am Coll Health 2011;59(8):691-698. [doi: 10.1080/07448481.2010.529626] [Medline: 21950249]
25. Macrynikola N, Miranda R, Soffer A. Social connectedness, stressful life events, and self-injurious thoughts and behaviors among young adults. Compr Psychiatry 2018 Jan;80:140-149 [FREE Full text] [doi: 10.1016/j.comppsych.2017.09.008] [Medline: 29091780]
26. Burke TA, Piccirillo ML, Moore-Berg SL, Alloy LB, Heimberg RG. The stigmatization of nonsuicidal self-injury. J Clin Psychol 2019 Mar;75(3):481-498 [FREE Full text] [doi: 10.1002/jclp.22713] [Medline: 30368804]
27. Hasking P, Boyes M. Cutting words: a commentary on language and stigma in the context of nonsuicidal self-injury. J Nerv Ment Dis 2018 Nov;206(11):829-833. [doi: 10.1097/NMD.0000000000000899] [Medline: 30371637]

28. Nock MK. Self-injury. Annu Rev Clin Psychol 2010;6:339-363. [doi: 10.1146/annurev.clinpsy.121208.131258] [Medline: 20192787]
29. Deming CA, Harris JA, Castro-Ramirez F, Glenn JJ, Cha CB, Millner AJ, et al. Inconsistencies in self-reports of suicidal ideation and attempts across assessment methods. Psychol Assess 2021 Mar;33(3):218-229. [doi: 10.1037/pas0000976] [Medline: 33705163]
30. Shiffman S, Stone AA, Hufford MR. Ecological momentary assessment. Annu Rev Clin Psychol 2008;4(1):1-32. [doi: 10.1146/annurev.clinpsy.3.022806.091415] [Medline: 18509902]
31. Kleiman EM, Turner BJ, Fedor S, Beale EE, Huffman JC, Nock MK. Examination of real-time fluctuations in suicidal ideation and its risk factors: Results from two ecological momentary assessment studies. J Abnorm Psychol 2017 Aug;126(6):726-738. [doi: 10.1037/abn0000273] [Medline: 28481571]
32. Millner AJ, Robinaugh DJ, Nock MK. Advancing the understanding of suicide: the need for formal theory and rigorous descriptive research. Trends Cogn Sci 2020 Sep;24(9):704-716 [FREE Full text] [doi: 10.1016/j.tics.2020.06.007] [Medline: 32680678]
33. Kiekens G, Robinson K, Tatnell R, Kirtley OJ. Opening the black box of daily life in nonsuicidal self-injury research: with great opportunity comes great responsibility. JMIR Ment Health 2021 Nov 19;8(11):e30915 [FREE Full text] [doi: 10.2196/30915] [Medline: 34807835]
34. Fox KR, Franklin JC, Ribeiro JD, Kleiman EM, Bentley KH, Nock MK. Meta-analysis of risk factors for nonsuicidal self-injury. Clin Psychol Rev 2015 Dec;42:156-167 [FREE Full text] [doi: 10.1016/j.cpr.2015.09.002] [Medline: 26416295]
35. Jain SH, Powers BW, Hawkins JB, Brownstein JS. The digital phenotype. Nat Biotechnol 2015 May;33(5):462-463. [doi: 10.1038/nbt.3223] [Medline: 25965751]
36. Torous J, Kiang MV, Lorme J, Onnela J. New tools for new research in psychiatry: a scalable and customizable platform to empower data driven smartphone research. JMIR Ment Health 2016 May 05;3(2):e16 [FREE Full text] [doi: 10.2196/mental.5165] [Medline: 27150677]
37. Burke TA, Hamilton JL, Seigel D, Kautz M, Liu RT, Alloy LB, et al. Sleep irregularity and nonsuicidal self-injurious urges and behaviors. Sleep 2022 Jun 13;45(6):zsac084 [FREE Full text] [doi: 10.1093/sleep/zsac084] [Medline: 35397476]
38. Kiekens G, Hasking P, Nock MK, Boyes M, Kirtley O, Bruffaerts R, et al. Fluctuations in affective states and self-efficacy to resist non-suicidal self-injury as real-time predictors of non-suicidal self-injurious thoughts and behaviors. Front Psychiatry 2020;11:214 [FREE Full text] [doi: 10.3389/fpsyt.2020.00214] [Medline: 32265760]
39. Sigrist C, Jakob H, Beeretz CJ, Schmidt SJ, Kaess M, Koenig J. Diurnal variation of cardiac autonomic activity in adolescent non-suicidal self-injury. Eur Arch Psychiatry Clin Neurosci 2023 Mar 05:1-20 [FREE Full text] [doi: 10.1007/s00406-023-01574-1] [Medline: 36871247]
40. Lloyd E. Self-mutilation in a community sample of adolescents [dissertation]. Louisiana State University and Agricultural & Mechanical College. 1997. URL: https://repository.lsu.edu/gradschool_disstheses/6546/ [accessed 2024-01-23]
41. Posner K, Brent D, Lucas C, Gould M, Stanley B, Brown G. Columbia-Suicide Severity Rating Scale (C-SSRS). APA PsycNet. URL: https://psycnet.apa.org/doiLanding?doi=10.1037%2Ft52667-000 [accessed 2024-01-23]
42. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD. JAMA 1999 Nov 10;282(18):1737-1744. [doi: 10.1001/jama.282.18.1737] [Medline: 10568646]
43. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006 May 22;166(10):1092-1097. [doi: 10.1001/archinte.166.10.1092] [Medline: 16717171]
44. Sohn SI, Kim DH, Lee MY, Cho YW. The reliability and validity of the Korean version of the Pittsburgh Sleep Quality Index. Sleep Breath 2012 Sep;16(3):803-812. [doi: 10.1007/s11325-011-0579-9] [Medline: 21901299]
45. Prins A, Bovin MJ, Smolenski DJ, Marx BP, Kimerling R, Jenkins-Guarnieri MA, et al. The Primary Care PTSD Screen for DSM-5 (PC-PTSD-5): development and evaluation within a veteran primary care sample. J Gen Intern Med 2016 Oct;31(10):1206-1211 [FREE Full text] [doi: 10.1007/s11606-016-3703-5] [Medline: 27170304]
46. Staehr-Johansen K. Wellbeing measures in primary health care/the DepCare Project: report on a WHO meeting: Stockholm, Sweden, 12–13 February 1998. World Health Organization. 1998. URL: https://iris.who.int/handle/10665/349766 [accessed 2024-01-30]
47. Smith BW, Dalen J, Wiggins K, Tooley E, Christopher P, Bernard J. The brief resilience scale: assessing the ability to bounce back. Int J Behav Med 2008;15(3):194-200. [doi: 10.1080/10705500802222972] [Medline: 18696313]
48. Sansone RA, Wiederman MW, Sansone LA. The Self-Harm Inventory (SHI): development of a scale for identifying self-destructive behaviors and borderline personality disorder. J Clin Psychol 1998 Nov;54(7):973-983. [doi: 10.1002/(sici)1097-4679(199811)54:7<973::aid-jclp11>3.0.co;2-h] [Medline: 9811134]
49. Morey L. Personality Assessment Inventory. Odessa, FL: Psychological Assessment Resources; 1991.
50. Kunchay S, Abdullah S. WatchOver: using Apple watches to assess and predict substance co-use in young adults. In: Adjunct Proceedings of the 2020 ACM International Joint Conference on Pervasive and Ubiquitous Computing and Proceedings of the 2020 ACM International Symposium on Wearable Computers. 2020 Presented at: UbiComp/ISWC '20; September 12-17, 2020; Virtual event, Mexico. [doi: 10.1145/3410530.3414373]

51. Lui GY, Loughnane D, Polley C, Jayarathna T, Breen PP. The Apple Watch for monitoring mental health-related physiological symptoms: literature review. JMIR Ment Health 2022 Sep 07;9(9):e37354 [FREE Full text] [doi: 10.2196/37354] [Medline: 36069848]
52. Chawla NV, Bowyer KW, Hall LO, Kegelmeyer WP. SMOTE: synthetic minority over-sampling technique. J Artif Intell 2002 Jun 01;16:321-357. [doi: 10.1613/jair.953]
53. Huckvale K, Venkatesh S, Christensen H. Toward clinical digital phenotyping: a timely opportunity to consider purpose, quality, and safety. NPJ Digit Med 2019;2(1):88 [FREE Full text] [doi: 10.1038/s41746-019-0166-1] [Medline: 31508498]
54. Guo Y, Graber A, McBurney RN, Balasubramanian R. Sample size and statistical power considerations in high-dimensionality data settings: a comparative study of classification algorithms. BMC Bioinformatics 2010 Sep 03;11:447 [FREE Full text] [doi: 10.1186/1471-2105-11-447] [Medline: 20815881]

Abbreviations

bpm: beats per minute
DSEM: dynamic structural equation modeling
EMA: LASSO: least absolute shrinkage and selection operator
NSSI: nonsuicidal self-injury
REM: rapid eye movement
SMOTE: synthetic minority oversampling technique
VAS: visual analog scale

Edited by A Mavragani; submitted 11.10.23; peer-reviewed by B Montezano, E Presseller; comments to author 24.11.23; revised version received 29.12.23; accepted 18.01.24; published 08.02.24.

Please cite as:
Ahn CY, Lee JS
Digital Phenotyping for Real-Time Monitoring of Nonsuicidal Self-Injury: Protocol for a Prospective Observational Study
JMIR Res Protoc 2024;13:e53597
URL: https://www.researchprotocols.org/2024/1/e53597
doi:10.2196/53597
PMID:38329791

Protocol

Adapting and Evaluating an AI-Based Chatbot Through Patient and Stakeholder Engagement to Provide Information for Different Health Conditions: Master Protocol for an Adaptive Platform Trial (the MARVIN Chatbots Study)

Yuanchao Ma[1,2,3,4], MSc; Sofiane Achiche[1], PhD; Marie-Pascale Pomey[5,6,7], MD, PhD; Jesseca Paquette[5], MSc; Nesrine Adjtoutah[5,6], MSc; Serge Vicente[2,3,8,9], PhD; Kim Engler[2,3], PhD; MARVIN chatbots Patient Expert Committee[2,10]; Moustafa Laymouna[2,3,8], MD, MSc; David Lessard[2,3,4], PhD; Benoît Lemire[4], MSc; Jamil Asselah[11], MD; Rachel Therrien[5], MSc; Esli Osmanlliu[2,12], MD; Ma'n H Zawati[13], PhD; Yann Joly[13], PhD; Bertrand Lebouché[2,3,4,8], MD, PhD

[1]Department of Biomedical Engineering, Polytechnique Montréal, Montreal, QC, Canada

[2]Centre for Outcomes Research & Evaluation, Research Institute of the McGill University Health Centre, Montreal, QC, Canada

[3]Infectious Diseases and Immunity in Global Health Program, Research Institute of McGill University Health Centre, Montreal, QC, Canada

[4]Chronic Viral Illness Service, Division of Infectious Disease, Department of Medicine, McGill University Health Centre, Montreal, QC, Canada

[5]Research Centre of the University of Montreal Hospital Centre, Montreal, QC, Canada

[6]Department of Health Policy, Management and Evaluation, School of Public Health, University of Montreal, Montreal, QC, Canada

[7]Centre of Excellence on Partnership with Patients and the Public, Montreal, QC, Canada

[8]Department of Family Medicine, Faculty of Medicine and Health Sciences, McGill University, Montreal, QC, Canada

[9]Department of Mathematics and Statistics, University of Montreal, Montreal, QC, Canada

[10]See Acknowledgements

[11]Department of Medicine, Division of Medical Oncology, McGill University Health Centre, Montreal, QC, Canada

[12]Department of Pediatrics, Montreal Children's Hospital, McGill University Health Centre, Montreal, QC, Canada

[13]Centre of Genomics and Policy, McGill University, Montreal, QC, Canada

Corresponding Author:
Bertrand Lebouché, MD, PhD
Chronic Viral Illness Service
Division of Infectious Disease, Department of Medicine
McGill University Health Centre
1001 Decarie Blvd
Montreal, QC, H4A 3J1
Canada
Phone: 1 514 843 2090
Email: bertrand.lebouche@mcgill.ca

Abstract

Background: Artificial intelligence (AI)–based chatbots could help address some of the challenges patients face in acquiring information essential to their self-health management, including unreliable sources and overburdened health care professionals. Research to ensure the proper design, implementation, and uptake of chatbots is imperative. Inclusive digital health research and responsible AI integration into health care require active and sustained patient and stakeholder engagement, yet corresponding activities and guidance are limited for this purpose.

Objective: In response, this manuscript presents a master protocol for the development, testing, and implementation of a chatbot family in partnership with stakeholders. This protocol aims to help efficiently translate an initial chatbot intervention (MARVIN) to multiple health domains and populations.

Methods: The MARVIN chatbots study has an adaptive platform trial design consisting of multiple parallel individual chatbot substudies with four common objectives: (1) co-construct a tailored AI chatbot for a specific health care setting, (2) assess its usability with a small sample of participants, (3) measure implementation outcomes (usability, acceptability, appropriateness,

adoption, and fidelity) within a large sample, and (4) evaluate the impact of patient and stakeholder partnerships on chatbot development. For objective 1, a needs assessment will be conducted within the setting, involving four 2-hour focus groups with 5 participants each. Then, a co-construction design committee will be formed with patient partners, health care professionals, and researchers who will participate in 6 workshops for chatbot development, testing, and improvement. For objective 2, a total of 30 participants will interact with the prototype for 3 weeks and assess its usability through a survey and 3 focus groups. Positive usability outcomes will lead to the initiation of objective 3, whereby the public will be able to access the chatbot for a 12-month real-world implementation study using web-based questionnaires to measure usability, acceptability, and appropriateness for 150 participants and meta-use data to inform adoption and fidelity. After each objective, for objective 4, focus groups will be conducted with the design committee to better understand their perspectives on the engagement process.

Results: From July 2022 to October 2023, this master protocol led to four substudies conducted at the McGill University Health Centre or the Centre hospitalier de l'Université de Montréal (both in Montreal, Quebec, Canada): (1) MARVIN for HIV (large-scale implementation expected in mid-2024), (2) MARVIN-Pharma for community pharmacists providing HIV care (usability study planned for mid-2024), (3) MARVINA for breast cancer, and (4) MARVIN-CHAMP for pediatric infectious conditions (both in preparation, with development to begin in early 2024).

Conclusions: This master protocol offers an approach to chatbot development in partnership with patients and health care professionals that includes a comprehensive assessment of implementation outcomes. It also contributes to best practice recommendations for patient and stakeholder engagement in digital health research.

Trial Registration: ClinicalTrials.gov NCT05789901; https://classic.clinicaltrials.gov/ct2/show/NCT05789901

International Registered Report Identifier (IRRID): PRR1-10.2196/54668

(JMIR Res Protoc 2024;13:e54668) doi:10.2196/54668

KEYWORDS

chatbot; master protocol; adaptive platform trial design; implementation science; telehealth; digital health; Canada; artificial intelligence; conversational agent; self-management; research ethics; patient and stakeholder engagement; co-construction; mobile phone

Introduction

Background

Self-management is key to patient health, and interventions to promote it are being increasingly implemented in the delivery of health care. Effective self-management involves multiple aspects, including problem-solving, decision-making, resource use, patient–health care professional partnership building, and taking action [1,2]. To improve self-management, patients often seek guidance from health care professionals, staff and volunteers from community organizations or peers, and a variety of internet resources [3,4]. However, the availability of these actors and resources can be inconsistent. Moreover, information encountered on the internet varies in quality [5-7]. From reliable but complex scientific articles to opinion blogs or outdated web pages, these sources do not always provide the clearest, most accurate, or most reassuring guidance. The importance of self-management has been further highlighted by the COVID-19 pandemic, which introduced additional barriers to accessing regular follow-up [8] and exposed individuals worldwide to an infodemic [9,10].

In addition to these challenges, frontline professionals are often confronted with complex questions from patients regarding treatment instructions, comorbidity management, side effects, and drug interactions. However, in the context of swiftly evolving knowledge and overwhelming workloads, health care professionals may not have sufficient expertise and time for certain questions [11,12]. Their responses may vary depending on their individual training, proficiency, and clinical experience. Rapidly obtaining accurate and clear health information and relaying it to patients can be a daunting challenge for professionals.

Safe and effective digital health interventions could help address the limitations of existing self-management or care support. A particularly promising avenue is the emergence of artificial intelligence (AI)–based chatbots—software applications that interact with users through simulated human text or voice conversations via smartphones or computers. Often harnessing AI to enable natural language interpretation and assist in decision-making, such tools possess the potential to revolutionize patient self-management and support [13]. They can be applied to diverse platforms to foster mutually beneficial outcomes for health systems and patients, including less time spent in hospitals, outpatient efficiency, and personalized treatment [9].

Successful implementation of an intervention (ie, positive implementation outcomes) is necessary to achieve desired changes in clinical or service outcomes [14]. Multiple studies have investigated the implementation of health-oriented chatbots, including in the areas of mental health support [15-17], problematic substance use treatment [18], cirrhosis patient education [19], and asthma self-management [20]. Nevertheless, such studies have typically focused on feasibility and usability in small-scale prototype implementations [21-23]. Digital health products are often dealt with through an "implement now, clinically validate later" ethos [24], as they encompass a large number of different technologies. Thus, there is no clear consensus on methods for assessing the clinical effectiveness of digital health interventions [24], and data on the impact of chatbot interventions on clinical outcomes are scarce [25]. Large

user samples are necessary to gain more robust insights into chatbot implementation. In-depth studies including other valuable implementation (eg, fidelity, appropriateness, sustainability, and cost-effectiveness) and clinical (eg, safety, effectiveness, and efficacy) outcomes will also be critical for scaling up and long-term adoption of chatbot interventions.

Finally, very little engagement of stakeholders, including patients and health care professionals, has led to poor usability and low adoption of many digital health interventions [26]. In the context of chatbot development, a scoping review investigating patient engagement revealed limited involvement of patients and insufficient reporting of the relevant activities [27]. Among the 16 studies included, only 8 mentioned patient engagement, with just 3 offering adequate details on the methods and approach used. The authors also pointed out that future chatbot development would need to integrate multifaceted means of patient participation and document them thoroughly. Stakeholders should be engaged in defining research objectives and designing interventions tailored to their needs [28]. According to the patient-public partnership continuum proposed by the Montreal model [29], this inclusivity can be extended to "co-construction," where patients and stakeholders are involved throughout the process. Meanwhile, to answer the many questions raised by the use of intelligent machines and ensure that AI develops in harmony with democracy, the responsible integration of AI necessitates a co-construction process [30]. Engaging end users in discussions about the challenges posed by AI and drawing on their lived experiences can reveal key aspects of digital health research that might otherwise be overlooked [31], thus better paving the way for success.

Since 2020, led by YM, SA, and B Lebouché, an innovative chatbot named *Minimal AntiRetroViral INterference* (now named *MARVIN*) has been in development for people with HIV. Through a co-design approach involving patients and stakeholders, MARVIN aims to facilitate antiretroviral therapy self-management. The authors' team subsequently trialed the MARVIN chatbot among people with HIV and validated its usability and acceptability [32]. Given the initial success of MARVIN among people with HIV, we intend to build on this pilot study to increase MARVIN's areas of specialization and continue to develop our algorithms to improve MARVIN's intelligence, thereby expanding its reach and potential benefits to a broader audience.

Aim and Objectives

Grounded in patient and stakeholder engagement strategies and implementation science, this protocol aims to describe the methods and tools necessary to efficiently develop the innovative MARVIN chatbot interventions across multiple health domains and populations and assess their implementation for robust and widespread use. The study's primary objectives are to co-construct versions of MARVIN adapted for different health conditions and target populations (objective 1: development), assess their global usability (usability and acceptability) in a small participant sample context (objective 2: usability), and measure implementation outcomes (usability, acceptability, appropriateness, adoption, and fidelity) in the context of a large sample (objective 3: implementation) through a mixed methods approach in the respective setting of each chatbot. The secondary objective is to evaluate the impact of different stakeholder partnerships established for the aforementioned objectives on the development of the AI health care chatbots (objective 4: partnership evaluation).

Methods

Study Design

This multicenter study follows the CONSORT (Consolidated Standards of Reporting Trials) extension for pilot and feasibility trials [33], CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) [34], and CONSORT-AI (Consolidated Standards of Reporting Trials–Artificial Intelligence) [35] guidelines (Multimedia Appendices 1-3 [33]), as well as the Montréal Declaration for a Responsible Development of Artificial Intelligence [30] regarding the ethical conduct of research involving humans and AI.

The study is presented in the form of a master protocol, defined as a single overarching design developed to evaluate multiple hypotheses with the overall goal of increasing efficiency and establishing uniformity through the standardization of procedures in the development and evaluation of different interventions [36]. This master protocol will encompass multiple parallel individual chatbot projects sharing the MARVIN chatbot technology, subsequently referred to as "substudies." The chatbot of each substudy is considered as a distinct intervention as it will integrate specific features or content tailored to the corresponding health care setting (health condition and target population). The chatbots will be implemented in these different populations without control groups.

To accommodate this, we used an adaptive platform trial design, which combines features of both basket trials (designed to test a single intervention in different populations) and platform trials (designed to test multiple interventions in the context of a single disease) [37]. As defined by the US Food and Drug Administration, an adaptive platform design is appropriate for our trial as it allows for flexibility in managing multiple interventions adapted to different populations while enabling the early removal of ineffective interventions and introduction of new interventions based on interim data [38].

As shown in the example in Figure 1, substudy arms targeting different conditions can be initiated at different time points. The substudies are independent of each other, and their processes are illustrated in Figure 2. Objectives 1 to 3 will be completed in a sequential manner, whereas objective 4 will be assessed throughout the process. A decision will be made on whether to continue with the same chatbot intervention version in objective 3 (implementation) based on the results of objective 2 (usability). In addition, there is no initial fixed duration or sample size for each substudy.

This master protocol outlines the common elements of the individual chatbot substudies in terms of objectives and processes. Concurrently, each substudy will have its own subprotocol describing more specific standardized operational structures; additional inclusion and exclusion criteria;

recruitment and selection methods; and data collection, analysis, and management. All subprotocols will be managed as appendices to this master protocol and will be subject to further review by the research ethics board (REB) when they are ready. In addition, certain criteria of the master protocol may be redefined by the research team based on progress in each substudy and submitted as amendments to the REB for review for subsequent application to all substudies.

Figure 1. Adaptive platform trial design without control group.

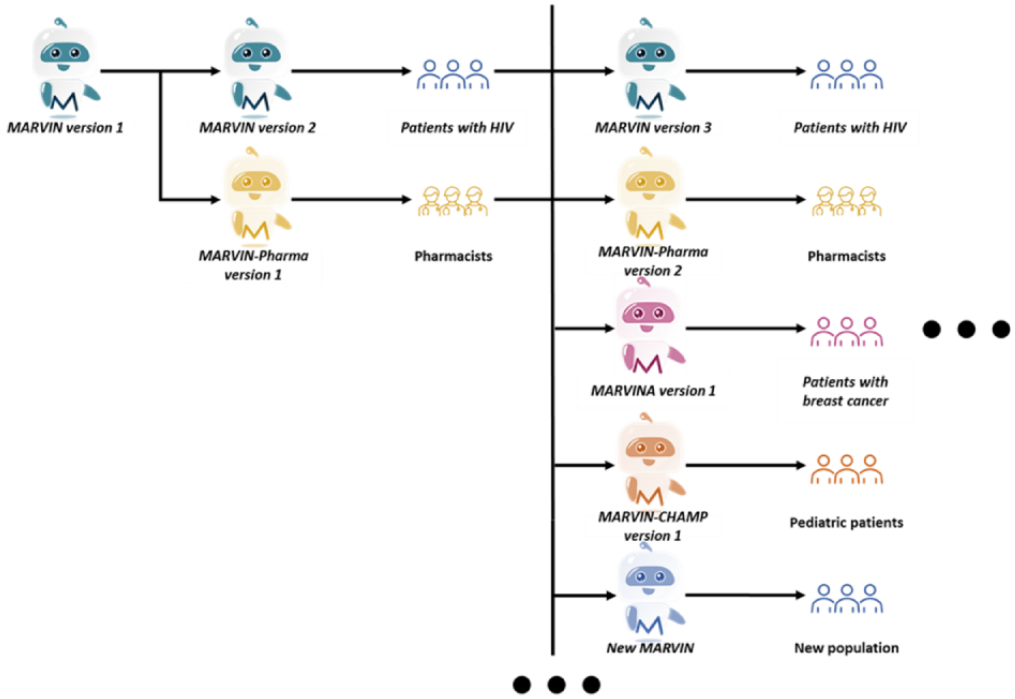
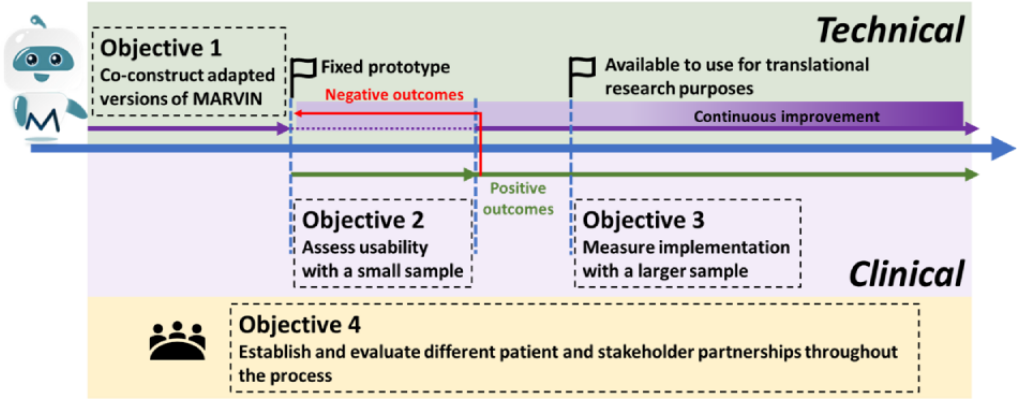


Figure 2. Study steps for each substudy.



Ethical Considerations

This study received approval from the McGill University Health Centre (MUHC) REB on August 9, 2023 (approval MP-37-2023-9333); the Centre hospitalier de l'Université de Montréal REB (approval MEO-37-2024-11732) on October 13, 2023; and the Polytechnique Montréal REB (approval CER-2324-29-D) on October 10, 2023. It is also registered in the ClinicalTrials.gov database (NCT05789901).

Settings and Participants

This study will be conducted at the MUHC and the Centre hospitalier de l'Université de Montréal, both located in Montreal, Quebec, Canada. The study participants include patients and health care professionals, who will be the end users of the chatbots.

Eligibility Criteria

The primary inclusion criteria for participants are as follows: (1) age of ≥18 years; (2) fluency in English or French; (3) ability to understand the requirements of study participation and provide oral and written informed consent before and during the implementation of the study; (4) access to a smartphone, tablet, or computer in a private environment; and (5) access to an internet connection or data plan on their device. Specific to objectives 2 (usability) and 3 (implementation), additional inclusion criteria are (6) acceptance of using or creating a personal Facebook (Meta Platforms) account, (7) acceptance of using a Facebook Messenger-based chatbot, and (8) acceptance of Facebook's privacy and data security policies.

Participants may not take part if they (1) are affected by a cognitive deficit or medical instability that prevents them from

participating in any aspect of the study and (2) self-report being insufficiently able to use the chatbot with the technical support provided. For objectives 2 (usability) and 3 (implementation), the patient partners involved in the co-construction design committee (defined in the following section) will not be able to participate in either phase.

Recruitment and Sample Size Justification

Objectives 1, 2, and 3 will use convenience sampling to recruit participants through different channels, including clinics, patient foundations, community-based organizations, and professional associations [39]. For example, patient participants will be introduced to the study by their health care service provider (eg, physician, nurse, or social and community worker) during their visits. Informational materials such as study flyers and a video (Multimedia Appendix 4) showcasing the MARVIN chatbot will be disseminated via email, newsletters, or a website.

Participants will be required to consent before engaging in each objective. For objectives 1 (development) and 2 (usability), interested individuals can reach out to the study coordinator. Detailed study procedures, eligibility checks, and consent collection will be facilitated by the study coordinator for those expressing interest. Verbal consent may be adopted for participants who continue from objective 1 to objective 2. This will be obtained remotely through teleconference with an impartial witness to ensure compliance with all aspects of free and informed consent. Following the co-construction approach [30], a co-construction design committee consisting of researchers, health care professionals, and volunteer patient partners will be formed starting from objective 1 to carry out the subsequent development. The sample size for objective 1 is 20 participants to ensure saturation for the needs assessment focus groups [40], whereas 30 participants will be recruited to complete the corresponding usability test for objective 2. This sample size is common for pilot studies and satisfies the minimum size recommended in the literature [41,42].

For objective 3 (implementation), an optimized version of the chatbot will be accessible from the web around the clock, 7 days a week, for translational research. As currently the MARVIN chatbots will be only released in Canada, recruitment will be exclusive to the Canadian population, and participants will engage in an electronic consent process through the MARVIN chatbots. Before using the chatbot, individuals will be required to review and accept MARVIN's privacy policy (Multimedia Appendix 5). Subsequently, they will be asked to review an electronic version of the information and consent form and then answer the following verification questions for eligibility criteria 1 to 3 via the chatbot: (1) *Are you at least 18 years old?* (2) *Are you comfortable using English or French while communicating with the chatbot?* (3) *Do you agree to participate in the study as described above?* The remaining criteria (4 to 8) will be met once users connect to the chatbot. Should participants agree to participate, their responses will be securely recorded in a separate encrypted database on the MARVIN cloud servers and synchronized to the electronic enrollment log. If users opt not to participate, no records will be kept. As a Facebook account will be a prerequisite for using the chatbot, no further measures will be taken to detect or prevent the possibility of multiple identities. The target sample size of 30 to 150 participants was obtained based on the usability, acceptability, and appropriateness outcomes, which are considered key outcomes for this objective. The analysis involves a 1-sided Student *t* test (1-tailed) evaluating whether the corresponding average attains a predetermined threshold. A power analysis for a 1-sample *t* test is then performed, with 80% power and a 5% significance level. Within the targeted sample size ($30 \leq n \leq 150$), small to moderate standardized effect sizes ($0.2 \leq \text{Cohen } d \leq 0.5$) are detectable in the total sample with the aforementioned statistical power.

Regarding objective 4 (partnership evaluation), upon completion of each objective, an email invitation will be sent to organize focus groups with stakeholders involved in the chatbot co-construction design committee.

The information and consent forms outline detailed study procedures, anticipated benefits, and potential risks. All template versions are available in Multimedia Appendix 6. Participants may withdraw from the study at any time after providing informed consent. This information will be recorded in the electronic enrollment log, and the related privacy management and protection measures will be detailed later. To protect the participants' personal data and identity, no identifying information will appear in any manuscript or report from this study.

Intervention: Status Quo of the MARVIN Chatbot

Overview

Running on Messenger 24/7 for free [43], MARVIN was created as a bilingual chatbot in both English and French trained to converse with people with HIV on the following self-management aspects: (1) guidance for antiretroviral therapy medication (with regard to time management, dosing, drug interactions, and medication reminders, among other things), (2) antiretroviral therapy management when traveling, and (3) common HIV-related knowledge (eg, symptoms, modes of transmission and prevention, and vaccination recommendations).

The team conducted the first pilot project (MUHC REB 2021-7191) in April 2021 with 28 people with HIV receiving treatment at the MUHC. The study results showed that MARVIN was tailored to patient requirements and was easy to use and approachable but that the chatbot's comprehension had limits [32]. For example, if a patient asked a question that was outside the range of topics in the question bank or was worded differently, the chatbot did not always understand it. Nonetheless, considering the development phase, participants reported being satisfied with MARVIN and mentioned that they intended to use it. Thus, by talking to the on-call chatbot, people with HIV could obtain the information they needed for self-management.

AI Algorithms and Strategies

MARVIN is currently being developed using the Rasa platform (Rasa Technologies Inc), an open-source machine learning framework for automating text- and voice-based virtual assistants [44]. As shown in Figure 3, MARVIN's architecture comprises 3 distinct modules: natural language understanding,

dialogue management, and response selection. Together with a self-built knowledge database, these modules are used to process the message input and generate the message output.

The acceptable input data include natural language in text form as well as some auxiliary expressions commonly used for chatting (eg, emojis such as the thumbs up, smiley face, and sad face). The initial natural language understanding module allows MARVIN to semantically process the input messages through different algorithms such as text preprocessing, entity extraction, and intent classification. The current training data set encompasses a corpus of >3000 questions covering >30 topics. Figure 4 shows an example of text processing. The entity extraction mechanism enables the chatbot to obtain structured information (eg, date, time, and medication name) from the input messages, whereas intent classification helps MARVIN discern the purpose of the information received.

In particular, MARVIN adopts the *FallbackClassifier* algorithm as a fail-safe measure for unprocessable input forms such as images, videos, and sounds. It is also activated when the confidence level of the anticipated intent falls below an established threshold. If the input remains incomprehensible after 2 attempts, the chatbot responds in a uniform manner: "I'm sorry, I can't understand your question right now. Please contact a healthcare professional if you need to." As illustrated in Figure 5, this approach reduces the probability of the chatbot taking incorrect actions when confronted with ambiguity.

The machine learning–driven conversation management determines MARVIN's subsequent actions based on the input message and context in the conversation. A hybrid strategy of the *memoization policy* and *rule policy* was adopted [45]. The *memoization policy* remembers the decision trees from the training data and predicts the next action in conjunction with the derived intention: asking clarifying questions, providing tailored answers, and taking a fallback action. MARVIN can also remember and analyze a certain number of rounds of dialogue to support the prediction. Meanwhile, the *rule policy* handles pieces of conversation that should always follow the fixed behavior defined in the training data (eg, question: *What is ART?* answer: *It means AntiRetroviral Therapies*).

The final response selection module enables MARVIN to select messages predefined by the health care team as output messages. All the data required for processing by the first 3 modules are stored in the knowledge database—after each decision is made in the processing module, MARVIN communicates with the database to compare, extract, or save the data. All data are selected, edited, and validated by the medical team and then processed and added to the database by the development team. Data types include the previously mentioned antiretroviral therapy management–related information, decision trees for different problem scenarios, and predefined answers. An example of response selection from predefined answers in MARVIN is shown in Figure 6.

Figure 3. Operation process of MARVIN.

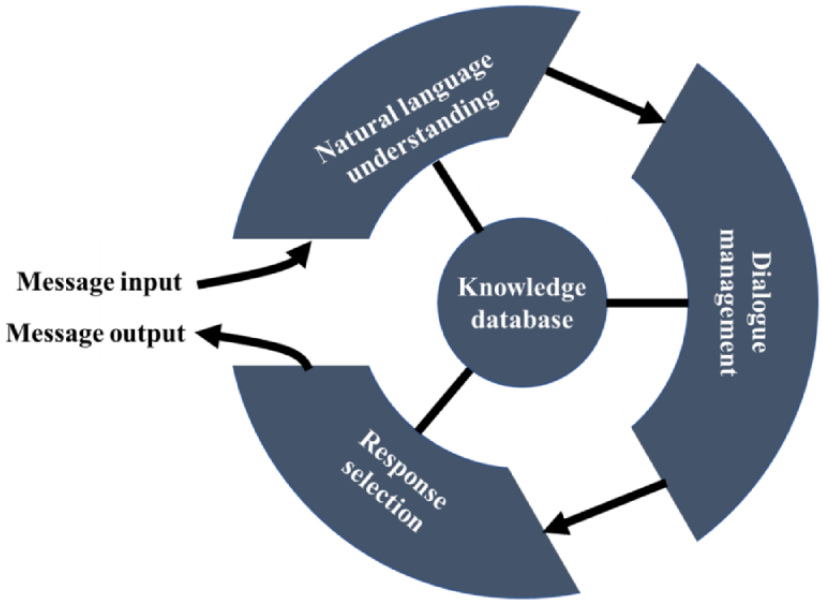


Figure 4. Example of text processing in MARVIN.

Figure 5. Examples of MARVIN handling bad inputs: (A) fallback policy; (B) redirection after 2 failed attempts.

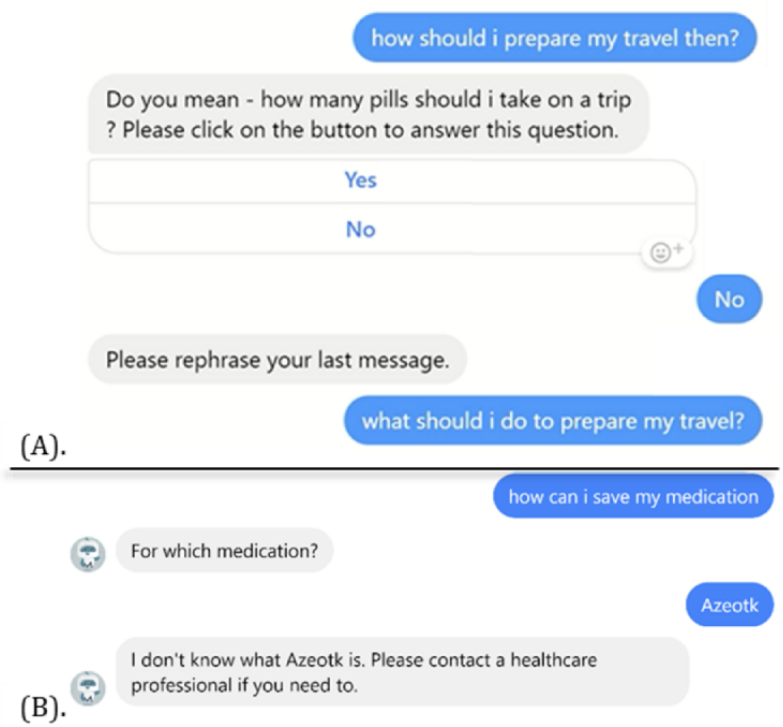
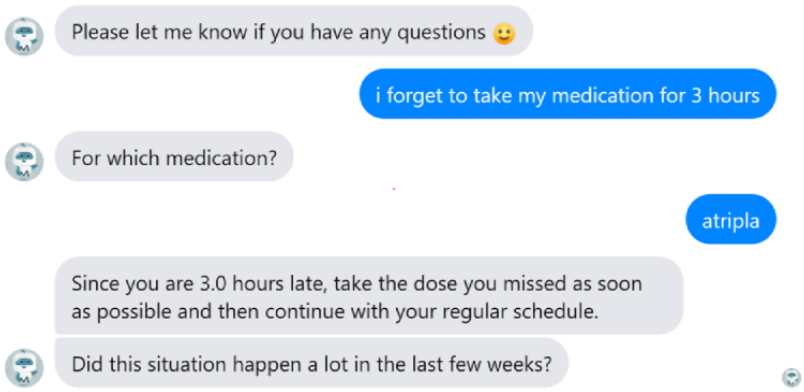


Figure 6. Conversation example with MARVIN.



Content Development and Improvement Process

To train MARVIN to understand different types of questions and provide relevant and accurate answers, we assembled a multidisciplinary team of 2 clinicians (ML and B Lebouché), 2 pharmacists (B Lemire and RT), 4 patients, 2 engineers (YM and SA), and multiple developers. Each group's expertise played a crucial role in chatbot content development and continuous improvement: (1) health care professionals validated the medical accuracy of the answers and information given by the chatbot; (2) together with patient partners, they collaborated to identify common self-care challenges; (3) engineers then assisted in building decision models and preparing chatbot training data based on identified problems; and (4) finally, engineers and patients collaborated on testing and refining the chatbot based on feedback, completing the interdisciplinary cycle. This multidisciplinary team allowed us to ensure the accuracy and quality of the information provided as well as conduct holistic research and ongoing evaluation of the chatbot to promote its long-term usability.

The Interface

Messenger has 1.3 billion monthly active users worldwide exchanging 8 billion messages per day [46]. This indicates a robust familiarity with the Messenger interface among the population, simplifying their grasp of the platform's specifications and interaction capabilities, ultimately favoring the uptake of the MARVIN chatbots. In addition, the versatility of Messenger, compatible across smartphones, tablets, and desktops, reduces the potential risk of participant exclusion because of hardware limitations. Nevertheless, the privacy concerns brought up with Facebook in the past may make people hesitant, which could be one of the potential barriers to the implementation of Messenger for health purposes. Indeed, other user interface options such as a stand-alone mobile app, a web page, or other third-party applications (eg, Telegram or Instagram) are under consideration. As the study proceeds and evolves, relevant changes will be implemented as necessary.

Main Study Process

Overview

Multimedia Appendix 7 illustrates the entire study process.

Objective 1: Co-Construction of the MARVIN Chatbots

Overview

Objective 1 is intended to obtain a stabilized version adapted to the health care context for the subsequent objectives. Similar to the original MARVIN's development, it will follow 3 steps: user needs assessment, knowledge database creation, and continuous improvement of the prototype.

The expected duration of participant involvement in objective 1 is 4 months.

Step 1: Needs Assessment

Four 2-hour focus groups will be organized with 5 participants each led by a trained interviewer. Participants will first be shown a demonstration of the current MARVIN describing the interface, dialogue process, and other instructions for use. Semistructured focus groups will then be conducted to identify use scenarios, topics related to integration, and user expectations and preferences for chatbots.

The co-construction design committee will then be formed and meet every 2 weeks to participate in design tasks. The team may also contact them via email with specific questions.

Step 2: Knowledge Database Creation

A knowledge database will be built based on the results of the needs assessment, which is the core of each new chatbot. This database will include a bank of different questions, plausible answers, and necessary conversation templates. Among the most important components of this knowledge database is a corpus of qualified and trusted answers. The challenge is to generate medically accurate information that is easy to understand and sufficiently colloquial while maintaining professionalism. These data will be collected from different sources and validated by the co-construction design committee for adoption to ensure that the chatbot can respond with appropriate output [29,30]. A total of three 2-hour co-construction workshops will be conducted.

Step 3: Testing, Validation, and Continuous Improvement

The team of engineers will work closely with the co-construction design committee through development workshops to test the prototype's performance, especially its quality and safety. Participants will be invited to converse with the test prototype and complete an assessment. Such an approach will facilitate

the continuous improvement of the prototype and the addition of new features (eg, user interface, questioning methods, and confidentiality measures) as necessary. Thus, each chatbot will evolve in real time during this step. A total of three 2-hour development workshops will be conducted.

It is important to note that, given the nature of software development engineering, steps 2 and 3 will be a continuous cyclic process. The research team will need to continually update the MARVIN chatbots based on feedback from the co-construction design committee on new requirements, improvement ideas, and technology updates.

Quantitative Data Collection and Analysis

During each development workshop, co-construction design committee members will perform a quick descriptive assessment of the tested prototype using the adapted Mobile App Rating Scale for health-related apps [47] (Multimedia Appendix 8).

The scale has 28 items (range 1-5) in 6 sections covering subjects including engagement, functionality, esthetics, information, subjective quality, and health-related quality. Item scores will be averaged to obtain a score for each section and an overall score. It has shown an excellent internal consistency (Cronbach α=.938) and interrater reliability (2-way mixed intraclass correlation coefficient=0.920, 95% CI 0.797-0.987) for the independent overall score ratings of 37 different digital health tools [47]. On the basis of developer recommendations, we will consider a successful prototype for testing to have an average score of at least 4 for the sections on information and health-related quality, as well as an overall average score of 4, as they are identified as key indicators of prototype safety.

Qualitative Data Collection and Analysis

Throughout the study, participants will have the option to take part in either English or French focus groups and workshops. All activities will be moderated by an experienced researcher with an assistant, digitally audio recorded, and manually transcribed verbatim for analysis while removing any nominal information provided to protect the participants' identity. NVivo R1 (QSR International) will be used for qualitative data management.

Participants will also receive transcripts of the sessions in which they participated to ensure the trustworthiness of these data. Therefore, they will have the opportunity to challenge information that is perceived as incorrect. This will also allow them to verify that no information that could potentially identify them was inadvertently retained [48].

A focus group guide will be developed for each substudy considering its specific setting. Focus groups will be analyzed using an inductive thematic analysis approach to gather user recommendations (ie, topics to be addressed, expected conversational style, and desired features). Qualitative workshop data will contribute to thematic analysis in pursuit of objective 4.

Objective 2: Usability Assessment

Overview

Although a usability study among people with HIV has already been conducted [32], usability will be evaluated for other individual chatbot substudies following the same methodology. During this stage, no updates will be made to the chatbots unless (1) the chatbots are not available because of force majeure (eg, host server failure or algorithm dependency update), in which case the team will implement updates to ensure the proper conduct of the study; (2) the results indicate suboptimal usability, in which case we will update the version and repeat the usability study; or (3) new medical information emerges that could benefit participants or prevent harm. Any such event will be documented in detail.

The expected duration of participation for objective 2 is 1 month. At enrollment, 30 participants will be required to complete an initial sociodemographic questionnaire. They will be given a training session and a user guide with instructions on how to access MARVIN via Messenger and the topics of questions they can ask MARVIN. Participants will be enrolled for a 3-week period of interacting with MARVIN by having at least 20 conversations, the topics of which will be specified in each subprotocol. Quantitative data will be collected using a usability survey once their 20 conversations are recorded.

Participants will be free to complete the tasks at any time during this 3-week period. If the chatbot does not receive a message from them within a week of their most recent conversation, it will proactively send a reminder. There will be no active third-party human involvement in the entire testing process between the chatbot and participant user except in the case of user-initiated requests (eg, to solve unexpected bugs).

In week 4, a total of 3 focus groups with 5 randomly selected participants each will be conducted to explore MARVIN's usability in greater depth and in the participants' own words. In total, 3 focus groups can capture at least 80% of the themes, which is sufficient saturation for a usability study [49].

Quantitative Data Collection and Analysis

The initial questionnaire for objective 2 will gather fundamental sociodemographic information (eg, year of birth, preferred language, gender, and ethnic group identity) and digital technology use (Multimedia Appendix 8).

Descriptive statistics will be used to depict the sociodemographic characteristics and digital technology use of the participants. Continuous variables will be reported using measures such as minimum, maximum, mean, and SD. In the case of ordinal and nominal qualitative variables, we will report both counts and proportions.

Global usability will be collected using 2 validated scales: the *shorter version of the Usability Metric for User Experience* (*UMUX-Lite*) [50] and the *Acceptability E-scale* (*AES*) [51] (Multimedia Appendix 8).

Usability is defined in part as "the extent to which a product can be used to be effective, efficient, and provide users' satisfaction within its defined goal" [52]. The UMUX-Lite is a

2-item questionnaire answered on a 7-point Likert scale that is deemed appropriate for use in the evaluation of health technology [53]. The items ask whether the chatbot meets user needs and about perceived ease of use.

Acceptability is related to how agreeable, palatable, or satisfactory an intervention is perceived to be by stakeholders and is also considered part of global usability [14]. The AES contains 6 items rated on different 5-point Likert scales. It is a validated measure of the acceptability and usability of computer-based interventions for health care populations. Items evaluate, for example, how easy and enjoyable the innovation is to use, how helpful it is, and whether the amount of time to engage with it is acceptable.

As continuous outcomes, both usability and acceptability will be summarized using the minimum, maximum, mean, and SD. The sample mean of each global usability outcome will be compared with its recommended usability thresholds—68/100 for the UMUX-Lite score and 24/30 for the AES score—using a Student *t* test. It will test the null hypothesis that the average UMUX-Lite score is ≤68 and that the average AES score is ≤24. A significance level of 5% will be adopted.

Four central subconstructs of the Technology Acceptance Model (TAM) framework will also be assessed as secondary end points via validated instruments to complement the data: (1) perceived ease of use, (2) perceived usefulness, (3) attitude toward use, and (4) behavioral intention to use the chatbots.

Perceived ease of use will be measured using the Single Ease Question [54], which is answered on a 7-point Likert scale.

Drawing on instruments by Chau and Hu [55] and Davis [56], perceived usefulness will be measured on a 7-point Likert scale with 4 items slightly adapted for relevance to chatbots. The final score will be the average of these items.

Attitude toward using chatbots will be measured using the net promoter score (NPS) [57], which is used as a measure of user satisfaction. A single question will be asked on an 11-point Likert scale. To calculate the NPS, 3 groups are created: promoters (score of 9-10), passives (score of 7-8), and detractors (score of 0-6). Subtracting the percentage of detractors from that of promoters provides the NPS (range −100 to 100). Positive scores, and especially those of >50%, are judged positively.

Finally, behavioral intention to use the chatbots will be assessed using a validated 2-item questionnaire [58] rated on a 7-point Likert scale averaged to produce a final score.

Predicted positive associations between subconstructs within the TAM framework will be evaluated using simple linear regressions considering the slope coefficient. Their significance will be tested using a Student *t* test.

All statistical analyses will be conducted using the R software (R Foundation for Statistical Computing) [59].

Qualitative Data Collection and Analysis

Participants' experiences with MARVIN will be explored through a semistructured focus group on the main constructs of the TAM framework (ie, usefulness, ease of use, attitude, and behavioral intention to use), the analysis of which will help further explain the quantitative analysis. A focus group interview guide can be found in Multimedia Appendix 8.

A composite coding matrix based on the TAM and the nonadoption, abandonment, scale-up, spread, and sustainability (NASSS) framework will be favored for deductive content analysis [60]. The NASSS framework [61] was developed to support the implementation and scale-up of technological innovations in health care. It includes seven relevant domains: (1) the illness or condition, (2) the technology, (3) the value proposition, (4) the adopter system, (5) the organization, (6) the wider context, and (7) embedding and adaptation over time. Given that 5 to 7 are more focused on scaling up implementation, objective 2 will likely focus on the first 4 subdomains for analysis to illustrate associated barriers and facilitators of the early phases of implementation. All facilitators and barriers identified will be then subsequently matched to the subconstructs of the TAM, when possible, to understand their impact on global usability.

The content analysis involves 3 phases. In phase 1, preparation, the analyst will attempt to understand the entire data set through immersion in the data. In phase 2, organization, a composite coding matrix will be devised using the NASSS domains and the TAM subconstructs. The data will be coded and categorized using NVivo R1. Finally, in phase 3, reporting, the descriptive content of the categorization will be presented, addressing trustworthiness.

The saved transcripts of users' conversations with the chatbots may also be submitted for content analysis to describe and better understand the nature of chatbot-participant interactions, such as conversation topic trends.

Objective 3: Implementation Assessment

Overview

For this objective, we will further assess the implementation outcomes of the MARVIN chatbots after they are deployed to the general population via Messenger. During this stage, the chatbots will be regularly updated to introduce new features or content, and their impact on implementation will be assessed. If the outcomes are negative, the corresponding version of the chatbot will be submitted for continuous improvement and evaluation.

We anticipate that the participation period will be 12 months and could be adjusted according to the health care context. Participants will receive a link to the same sociodemographic questionnaire as before (ie, via REDCap [Research Electronic Data Capture; Vanderbilt University] or Google Forms) directly through the chatbot at entry into the study (Multimedia Appendix 8). They will then be able to send messages to MARVIN whenever they wish. If the chatbot does not receive a message from the participant within a month of its most recent conversation with them, it will proactively ask the participant the following: "It's been a month since our last conversation. How have you been?" The participant will be able to turn off this inquiry if they so wish.

Every 2 months, participants will receive a link to a questionnaire on implementation outcomes (Appendix 7). The

chatbot will also ask 3 open-ended questions to collect information on the participant's overall experience and suggestions for continuous improvement of the chatbot.

Quantitative Data Collection and Analysis

The implementation outcome questionnaire will assess usability, acceptability, and appropriateness using validated instruments. Fidelity and adoption will be summarized using descriptive statistics on chatbot use metadata.

Usability and acceptability will be measured for objective 3 (implementation) as they will be for objective 2 (usability) using the UMUX-Lite and AES questionnaires as both measures are dynamic and vary with experience. Thus, usability and acceptability ratings may be different for each stage of implementation [14,62].

Appropriateness relates to the relevance or compatibility of the innovation to address a particular issue or problem [14]. The compatibility of an IT innovation is the extent to which it is considered consistent with users' values, needs, and past experiences [63]. The *Compatibility Subscale* is a validated tool that contains 3 items rated on a 7-point Likert scale (range 1-7) to assess how an IT innovation "fits" with the user's work style [64]. An adapted version will be administered to health care professional participants. A minimum average score of 5.5 is set as the threshold for adequate compatibility. For patient participants, the *Intervention Appropriateness Measure* will be used [65]. It contains 4 items scored on a 5-point scale to assess an innovation's suitability for a user. A mean score of at least 4 will indicate the appropriateness of the chatbot intervention for the patient population.

Fidelity is the degree to which the intervention is implemented as intended [14]. On the basis of the fidelity measures of digital health intervention implementation identified by Coorey et al [66], we will analyze the following metadata to comprehensively assess the chatbot fidelity: (1) intervention fidelity (the proportion of participants who continue to use the chatbot after a 1-month period), (2) frequency and duration (the monthly frequency with which participants use the chatbot and the average total duration of using the chatbot), (3) messages delivered (the total number of messages that participants interacted with in the chatbot over the course of the study period as well as the average number per participant), and (4) range of messages received (the frequency distribution of different conversational topics triggered by all participants).

Adoption, or uptake, is "the intention, initial decision, or action to try or employ an innovation or evidence-based practice" [14]. It will be measured using the proportion of monthly new users enrolled to all users in the study. The target will be 5% per month given that the median user growth rate for small-scale software services is 4.4% [67,68].

Statistically, a strategy similar to that of objective 2 will be adopted to describe the data. For usability, acceptability, and appropriateness, a Student *t* test will be used to test the null hypothesis that the average score is inferior or equal to the predetermined thresholds.

Qualitative Data Collection and Analysis

To better understand the implementation outcomes, participants will be invited to answer three open-ended questions: (1) What did you like most about using MARVIN? (2) What did you dislike about using MARVIN? (3) How would you improve MARVIN?

The content analysis of this material using the same coding matrix as in objective 2 will likely include the last 3 subdomains of the NASSS framework given the implementation stage at objective 3. This will help document and detail barriers to and facilitators of using the chatbots and their associated implementation outcomes as well as identify targets for continuous improvement.

As with objective 2 (usability), the saved transcripts of chatbot conversations may also be submitted for content analysis to characterize and better understand the nature of chatbot-participant interactions.

Objective 4: Evaluate the Impact of Different Stakeholder Partnerships

Overview

The reporting of patient and stakeholder engagement roles will follow the revised Guidance for Reporting Involvement of Patients and the Public [69].

Quantitative Data Collection and Analysis

Quantitative data on patient and stakeholder engagement activities, such as the number and length of actual workshops or focus groups conducted; the number of attendees; and the user requirements, design parameters, and improvement recommendations made by stakeholders during the workshops or focus groups, will be reported to illustrate the impact of patient and stakeholder engagement on the adaptation or development of the MARVIN chatbots.

Qualitative Data Collection and Analysis

Upon completion of each objective, focus groups will be conducted with stakeholders involved in the co-construction of the chatbots to identify the participants' perspectives on target users' involvement in research. A focus group guide will be developed for each substudy considering its specific setting. These data will be analyzed thematically along with workshop data from objective 1 to determine how potential end users (patient partners and health care professionals) were integrated into the research team, participated in the work, influenced decision-making, and contributed to chatbot adaptation or development.

Data Management, Confidentiality, and Security

Only data relevant to this study outlined in this protocol will be collected by the research team. A comprehensive overview of the study's data management strategy is presented in Table 1, including the collection of recruitment and study data. For objectives 1 (development), 2 (usability), and 4 (partnership evaluation), participants' basic sociodemographic data and contact information will be recorded. For objective 3 (implementation), only participants' Facebook account names will be gathered alongside their eligibility responses. Participants

will be identified using alphanumeric codes. The link between these codes and the participants' identities will be kept by the research team within a password-protected digital file safeguarded by the MUHC firewall. Access to these records will be exclusive to the research team.

The scope of the study data will include information from the web-based research questionnaire, qualitative data, transcripts of participant conversations with MARVIN, and MARVIN-related metadata. Data required for distinct study objectives through questionnaires will be collected using an appropriate collection tool (eg, Google Forms or REDCap) and subsequently extracted into a password-protected Microsoft Excel (Microsoft Corp) spreadsheet for analysis. Qualitative data, once collected and transcribed, will be password protected and deidentified during analysis. All study data will only be accessible to the research team.

Regarding the technical cybersecurity aspects of the MARVIN chatbots, Figure 7 offers a visual representation of the data flow as participants engage with the chatbots. Throughout the study, participants will send messages to MARVIN chatbots via their personal devices. These messages will be relayed through Messenger's application programming interface to the Amazon Web Services (AWS) cloud server, where the research team deployed the MARVIN service. Response messages from MARVIN chatbots will then be sent back to participants' devices via the Messenger application programming interface. The entire communication process will be encrypted. The research team will be responsible for all of Facebook's MARVIN chatbot accounts and MARVIN servers deployed on the AWS cloud server. Records of chatbot conversations will be stored on an encrypted AWS cloud server. These data will be anonymized by the research team and used exclusively for future model training to enhance chatbot performance for research and quality assurance purposes.

Conversations on Messenger will also be logged and stored on Messenger's server, which is necessary for display on both the participant and chatbot interfaces. The data handling in this context adheres to Facebook's policies [70-72]. If a participant withdraws from the study, the collected study data will be removed as well if the participant so wishes. In particular, in accordance with Messenger's privacy policy, participants will be asked to delete the conversations with MARVIN from their personal accounts, and the research team will delete the conversations from MARVIN's account. Thus, Facebook will stop storing these data as they are no longer required to provide their services and Meta Platforms products.

Note that all platforms involved, including Messenger, Google Forms, and REDCap, comply with the General Data Protection Regulation implemented by the European Union. It is recognized as the highest standard available, especially in terms of AI applications, equivalent to or surpassing the Personal Information Protection and Electronic Documents Act in Canada [73], where MARVIN is deployed. Access to each platform's accounts will be exclusive to the research team and secured through 2-factor authentication.

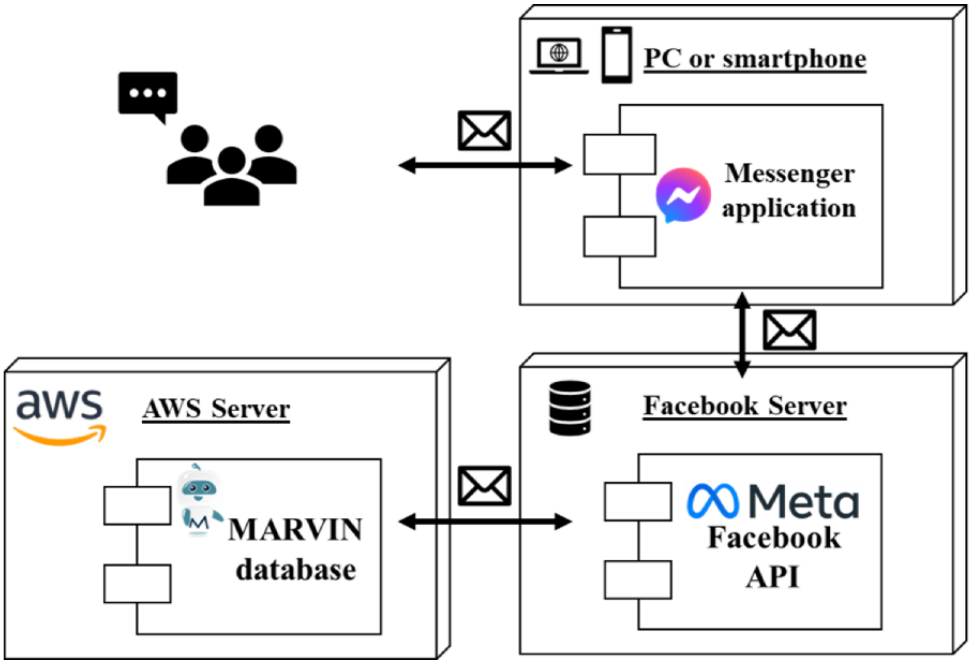
Table 1. Study data management strategy.

	Objective 1	Objective 2	Objective 3	Objective 4
Recruitment data				
Data type	• Basic sociodemographic data and contact information	• Basic sociodemographic data and contact information	• Facebook account name, answers to eligibility questions, and web-based consent records	• Basic sociodemographic data and contact information
Protection method	• Password-protected digital files	• Password-protected digital files	• Encrypted database on Amazon Web Services cloud server and synchronized to password-protected digital files	• Password-protected digital files
Storage location	• MUHC[a] internal storage	• MUHC internal storage	• Amazon Web Services and MUHC internal storage	• MUHC internal storage
Study data				
Data type	• Conversation histories	• Conversation histories • Study questionnaire data • Qualitative data	• Conversation histories • Study questionnaire data	• Qualitative data
Protection method	• Encrypted database on Amazon Web Services cloud server and 2-factor–authenticated Facebook MARVIN account	• Encrypted database on Amazon Web Services cloud server and 2-factor–authenticated Facebook MARVIN account • 2-factor–authenticated Google Forms or REDCap[b] (Vanderbilt University) accounts and password-protected digital files • Password-protected digital files	• Encrypted database on Amazon Web Services cloud server and 2-factor–authenticated Facebook MARVIN account • 2-factor–authenticated Google Forms or REDCap accounts and password-protected digital files	• Password-protected digital files
Storage location	• Amazon Web Services and Facebook	• Amazon Web Services and Facebook • Google Forms or REDCap and MUHC internal storage • MUHC internal storage	• Amazon Web Services and Facebook • Google Forms or REDCap and MUHC internal storage	• MUHC internal storage

[a]MUHC: McGill University Health Centre.

[b]REDCap: Research Electronic Data Capture.

Figure 7. MARVIN chatbot—message data flow diagram. API: application programming interface; AWS: Amazon Web Services.



Governance Board

In view of the current ever shifting regulatory landscape surrounding health care AI applications, a governance board will be formed to help the research team obtain external perspectives; assess the ethical and technological issues that may arise from the MARVIN chatbots; and ensure prudent development, testing, and mitigation of associated risks. The board will also summarize best practices from the substudies to enhance future iterations.

Candidates for the governance board include expert patients as well as experts in the fields of AI, clinical science, ethics, legal affairs, and communications. Invitations will be sent by the research team via email. Annual assemblies will be held for reviewing study progress and exchanging insights. For specific inquiries, members of the governance board will remain reachable by the MARVIN research team via email summons.

Anticipated Risks and Benefits

Participants in this study will not be exposed to direct physical risk while partaking in focus groups or interviews, conversing with chatbots via messaging, or completing web-based surveys as they will not receive any pharmaceutical or invasive medical interventions. Furthermore, the preceding pilot study did not reveal any known risks of participation.

However, potential indirect risks are worth considering. In the case of web-based recruitment and verbal consent acquisition, there is a risk of confidentiality breach. This risk can be exacerbated if participants use a personal email address to communicate with the research team. In response, researchers will only use institutional email addresses for correspondence purposes. Participants will also be advised to protect their pertinent personal electronic data.

When using the web-based chatbot, participants will use their personal Facebook account and may share details of their participation in the study. Vulnerability to security breaches (eg, device loss, inadvertent device exposure, phishing, and malware) may arise concerning participants' Facebook accounts. To mitigate this risk, participants will be explicitly reminded during recruitment to secure relevant personal information. The MARVIN chatbots will similarly provide appropriate reminders in the electronic information and consent forms, such as "I recommend that you do not share study-related information with others unnecessarily."

The time required to complete the questionnaires and participate in interviews or focus groups may be inconvenient and distressing for certain individuals. Others may also be uncomfortable answering specific questions or interacting with the chatbot. In situations in which questions are deemed sensitive, private, or distressing, participants are not obliged to respond. The research team will always be available to discuss participant concerns and refer them to appropriate resources, including teleconsultation with a mental health professional or other support service.

It is possible that the MARVIN chatbots will have difficulty understanding messages from participants during the study. In such instances, the chatbot will indicate that it cannot understand, as described previously in Figure 5, and suggest seeking help from a health care professional. There is also a small chance that the chatbot will provide erroneous advice. As an example, the chatbot might inform a patient who missed a 2-hour dose to stop taking the medication completely and consult a health care professional immediately. To minimize this potential risk, participants will be informed of the limitations of the chatbots during the consent process. In addition, participants will be prompted to report any perceived inaccuracies and their consequences to the research team in a timely manner. Weekly revisions of user chat logs will be conducted by the research team to ensure timely human intervention in the event of errors. The governance board for this study will consistently monitor and discuss these reports.

Finally, any other service-related risks (eg, chatbot or Facebook network service disruptions) will be communicated to each participant in a timely manner and properly documented by the study coordinator.

Participation in the study presents benefits, including early access to chatbot interventions with validated health care information. Participants will also be compensated appropriately upon completion of each study objective [74] in the form of a gift card or, exceptionally, a money transfer.

Results

From July 2022 to October 2023, four substudies were established in conjunction with the completion of this master protocol:

1. The first study is a continuation of the original MARVIN for HIV self-management. This project has secured funding from the Fonds de recherche du Québec – Santé Réseau SIDA/Maladies Infectieuses (AIDS and Infectious Disease Network). A subprotocol targeting objective 3 (implementation) is currently being prepared and scheduled for REB submission in early 2024. Recruitment is scheduled to begin in mid-2024, and the related data analysis will begin in early 2025.
2. The second study is MARVIN-Pharma, a project to promote community pharmacists' knowledge of HIV treatment, with its prototype to be completed by the end of 2023. A related manuscript based on a pharmacist needs assessment is in preparation. A subprotocol for objective 2 (usability) is being developed and is scheduled to be submitted for REB approval in early 2024, and recruitment is scheduled for mid-2024.
3. The third project is to develop the MARVINA chatbot for self-management of patients with breast cancer. This study is supported by funding from the MUHC Cedars Cancer Foundation. The subprotocol was approved by the MUHC REB on September 26, 2023 (approval MP-37-2024-9633). Recruitment for objective 1 (development) is expected to begin in early 2024.
4. The fourth study is to develop MARVIN-CHAMP, an accessible chatbot to assist in the management of pediatric patients with infectious conditions. A funding proposal for this project will be submitted to the Canadian Institutes of Health Research Spring 2024 Project Grant program. A subprotocol for objective 1 (development) is under development and scheduled to be submitted for REB approval in mid–October 2023. Recruitment for objective 1 (development) is expected to start in early 2024.

None of the funding sources had any role in the design of this study and will not be involved in the interpretation of the results or the decision to submit them for publication.

Discussion

Expected Findings

AI technologies have made phenomenal advances, but relevant clinical translation in key areas remains slow. To the best of our knowledge, this is the first known master protocol in digital health dedicated to implementing chatbot interventions across diverse health conditions and clinical settings. Before this, master protocols had been structured primarily for pharmaceutical intervention studies [75]. This master protocol shares key experimental components and operational processes while capitalizing on the similarities of the underlying IT infrastructures already in place. Coupled subsequently with thorough discussion and deliberation among intended users, developers, administrators, and regulators, the efficiency of creating and coordinating multiple studies of the same type has greatly improved. Although the upfront costs and planning time were significant, with this master protocol taking a year to complete from inception to REB approval, it will facilitate the generation of high-quality evidence essential for guiding medical practice. Through centralized management and shared governance, it also reduces development costs, enables broad decision-making, and allows patients to benefit earlier from advanced interventions.

The selected adaptive platform trial format, although designed initially for oncology and infectious disease drug development, has also been identified as being applicable to digital health interventions [76]. Its flexibility is a noteworthy advantage. Digital health interventions are now increasingly being applied to a wide range of conditions. The flexibility of the infrastructure facilitates the addition of substudies or necessary adjustments to each substudy, and health authorities, institutional review boards, and ethics committees will have a clear understanding of what changes are occurring across substudies [77]. Second, design features such as early termination of the trial or re-estimation of the sample size can avoid wasting resources, thus allowing for faster dissemination of research results to the communities that will benefit the most [38].

Patient and stakeholder contributions are integral to shaping this master protocol and associated materials. Their co-constructive engagement allows them to take a leading role in the ongoing digitization of health care and can help mitigate or even address the risks that chatbots face during implementation, such as those tied to trustworthiness, data privacy, and exacerbating inequalities in access to health care. Incorporating patient and stakeholder involvement strategies in developing master protocols, as suggested by Huml et al [78], can make them more successful for patients, providers, and sponsors. Patients and stakeholders will be invited to contribute on an ongoing basis to subsequent chatbot development, reporting of trial results, product marketing, and knowledge translation. Systematically documenting, investigating, and reporting this entire process will be beneficial in providing the scientific community with a clear and replicable model for responsible AI medical research.

Certain limitations need to be recognized. This master protocol focuses solely on the assessment of chatbot implementation outcomes, similar to master protocols typically prepared for pharmaceutical investigations that focus on "early exploratory development phases" [78]. Clinical and service-related outcomes are not included in this master protocol as there is no consensus on their assessment methods. Notably, <25% of AI-based digital health trials include patient-reported outcome measures as end points despite their widespread use in other health care trials

[79]. Therefore, corresponding research efforts are necessary to develop relevant high-quality assessment metrics to foster the development and validation of user-centered chatbots. If the substudy decides to assess their clinical effectiveness, appropriate amendments will be made.

Large language model (LLM) technology is also not considered in this master protocol for the time being. The release of LLMs, represented by GPT-4, has been indeed impressive. Unfortunately, LLM-based chatbots exhibit limitations such as a lack of transparency, sharing of unverified health information, and poor interpretability [80]. These factors threaten the trustworthiness and security of chatbots, which are key to their successful implementation in health care. Although current state-of-the-art LLMs are, of course, embraced to help generate more diverse and personalized responses, trialing these models in clinical settings also remains a challenge owing to the lack of relevant regulatory compliance and the fact that the existing software-as-a-medical-device framework is not suited to such models [81]. Chatbots can be a safe tool to seek information if they are validated and approved by health care professionals and all personal data are properly secured through robust up-to-date privacy and security safeguards [82,83]. In line with this protocol, the team strongly believes in and adheres to a careful content validation and model fine-tuning strategy so as to maximize the accuracy, trustworthiness, and safety of the solutions being delivered for responsible AI innovation.

Finally, another limitation of the protocol is the use of convenience sampling, potentially introducing bias toward individuals more inclined to use digital health technologies. Furthermore, in the web-based direct recruitment process for objective 3 (implementation), all participants will be self-referred, which will make it challenging to assess whether the participants genuinely meet the inclusion criteria. In addition, the self-reported quantitative questionnaire may be susceptible to random participant responses. Outliers in the data will be checked, and appropriate statistical methods will be used to improve the quality of the final data.

Conclusions

Overall, the development and adaptation of the MARVIN chatbots, co-constructed with those directly involved, hold the promise of fostering patient self-management and enhancing health care efficiency. This study shall provide a comprehensive examination of the implementation outcomes of innovative chatbot interventions tailored for patients and health care professionals. Moreover, it will contribute to the formulation of best practice recommendations for the co-constructive engagement of patients and stakeholders in digital health research. If properly applied, this master protocol has the potential to be sustained for years or even decades and allow innovations to be rapidly translated to clinical practice. Advances in methodology combined with the surge in AI will provide deeper evidence to achieve the goal of patient-partnered personalized medicine and, ultimately, help deliver the right interventions for the right patient at the right time.

Acknowledgments

This study secured funding from the Fonds de recherche du Québec – Santé (FRQS) Réseau SIDA-Maladies Infectieuses (AIDS and Infectious Disease Network; project title: *Developing an AI chatbot-based triage solution to support people with HIV*; principal investigators [PIs]: YM, SA, and B Lebouché). This study is also supported by the Canadian Institutes of Health Research Strategy for Patient-Oriented Research Québec Support Unit–Methodological Developments (grant M006; PI: B Lebouché), the Partnerships to Improve HIV Outcomes and Treatments program from ViiV Healthcare (grant 2021-2186-PIHVOT; PI: RT), and the Cedars Cancer Foundation (project title: *Developing MARVINA, an Intelligent Conversational Agent for Breast Cancer Self-Management through Patient Stakeholder Engagement*; PIs: JA and B Lebouché). YM is supported by the Postgraduate Scholarships – Doctoral program; the Optimizing Power Skills in Interdisciplinary, Diverse, and Innovative Academic Networks (OPSIDIAN) program from the Natural Sciences and Engineering Research Council; and a doctoral research award from the Fonds de recherche du Québec – Nature et technologies in partnership with the Unité de soutien au système de santé apprenant Québec. MPP is supported by a Senior Career Award financed by the FRQS (322746 and 322747), the Centre de Recherche du Centre hospitalier de l'Université de Montréal, and the Québec Ministry of Health and Social Services. B Lebouché is supported by 2 career awards—a Senior Salary Award from the FRQS (311200) and the Lettre d'entente 250 from the Quebec Ministry of Health and Social Services for researchers in family medicine—and holds a Canadian Institutes for Health Research Strategy for Patient-Oriented Research Mentorship Chair in Innovative Clinical Trials in HIV. EO is funded as a clinical research scholar–junior 1 (2023-2027) by the FRQS (331771), awarded in partnership with the Unité de soutien au système de santé apprenant Québec. MHZ is supported by a Junior 1 Career Award from the FRQS (309777). The funding sources had no role in the design of this study and were not involved in the interpretation of the results or the decision to submit them for publication. The authors acknowledge the technical support provided by students and interns from Polytechnique Montreal for the development of the MARVIN chatbots and Lévis Thériault for referring the students. The authors also acknowledge Imane Frih, Maria Nait El Haj, and Gavin Tu for the creation of the clinical content. The names of the members of the MARVIN chatbots Patient Expert Committee cannot be provided as they are patients and their names must remain confidential. The authors attest that there was no use of generative artificial intelligence technology in the generation of text, figures, or other informational content of this manuscript.

Data Availability

The data sets generated and analyzed for this study are available from the corresponding author (B Lebouché) upon reasonable request.

Authors' Contributions

In no order of contribution, YM, MPP, JP, NA, SV, KE, and B Lebouché helped conceptualize the study and data collection tools. YM and SA on the software side and ML, B Lemire, RT, B Lebouché, and the MARVIN chatbots Patient Expert Committee on the clinical side collaborated to develop the MARVIN chatbots. YM, JP, and B Lebouché wrote the manuscript. All authors critically reviewed the manuscript and approved the final version.

Conflicts of Interest

B Lebouché has received research support, consulting fees, and speaker fees from ViiV Healthcare, Merck, and Gilead. The authors are developers of the MARVIN chatbot intervention.

Multimedia Appendix 1
CONSORT (Consolidated Standards of Reporting Trials) extension for pilot and feasibility trials checklist.
[PDF File (Adobe PDF File), 93 KB - resprot_v13i1e54668_app1.pdf]

Multimedia Appendix 2
CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) V 1.6.1 checklist.
[PDF File (Adobe PDF File), 1162 KB - resprot_v13i1e54668_app2.pdf]

Multimedia Appendix 3
CONSORT-AI (Consolidated Standards of Reporting Trials–Artificial Intelligence) checklist.
[PDF File (Adobe PDF File), 161 KB - resprot_v13i1e54668_app3.pdf]

Multimedia Appendix 4
Demonstration video—the MARVIN chatbots study.
[MP4 File (MP4 Video), 117965 KB - resprot_v13i1e54668_app4.mp4]

Multimedia Appendix 5
Privacy policy—the MARVIN chatbots study.
[PDF File (Adobe PDF File), 180 KB - resprot_v13i1e54668_app5.pdf]

Multimedia Appendix 6
Information and consent form.
[PDF File (Adobe PDF File), 549 KB - resprot_v13i1e54668_app6.pdf]

Multimedia Appendix 7
Summary of study procedures for participants.
[PDF File (Adobe PDF File), 129 KB - resprot_v13i1e54668_app7.pdf]

Multimedia Appendix 8
Study questionnaires and semistructured interview guide for the usability study.
[PDF File (Adobe PDF File), 227 KB - resprot_v13i1e54668_app8.pdf]

References

1. Lorig KR, Holman HR. Self-management education: history, definition, outcomes, and mechanisms. Ann Behav Med 2003 Aug;26(1):1-7. [doi: 10.1207/S15324796ABM2601_01] [Medline: 12867348]
2. Whitehead L, Seaton P. The effectiveness of self-management mobile phone and tablet apps in long-term condition management: a systematic review. J Med Internet Res 2016 May 16;18(5):e97 [FREE Full text] [doi: 10.2196/jmir.4883] [Medline: 27185295]
3. Wong DK, Cheung MK. Online health information seeking and eHealth literacy among patients attending a primary care clinic in Hong Kong: a cross-sectional survey. J Med Internet Res 2019 Mar 27;21(3):e10831 [FREE Full text] [doi: 10.2196/10831] [Medline: 30916666]

4. Lee HY, Jin SW, Henning-Smith C, Lee J, Lee J. Role of health literacy in health-related information-seeking behavior online: cross-sectional study. J Med Internet Res 2021 Jan 27;23(1):e14088 [FREE Full text] [doi: 10.2196/14088] [Medline: 33502332]
5. Daraz L, Morrow AS, Ponce OJ, Beuschel B, Farah MH, Katabi A, et al. Can Patients trust online health information? A meta-narrative systematic review addressing the quality of health information on the internet. J Gen Intern Med 2019 Sep;34(9):1884-1891 [FREE Full text] [doi: 10.1007/s11606-019-05109-0] [Medline: 31228051]
6. Sun Y, Zhang Y, Gwizdka J, Trace CB. Consumer evaluation of the quality of online health information: systematic literature review of relevant criteria and indicators. J Med Internet Res 2019 May 02;21(5):e12522 [FREE Full text] [doi: 10.2196/12522] [Medline: 31045507]
7. Thoër C, Millerand F, Myles D, Orange V, Gignac O. Enjeux éthiques de la recherche sur les forums Internet portant sur l'utilisation des médicaments à des fins non médicales. Communiquer 2012(7):1-22 [FREE Full text] [doi: 10.4000/communiquer.1085]
8. Miner H, Fatehi A, Ring D, Reichenberg JS. Clinician telemedicine perceptions during the COVID-19 pandemic. Telemed J E Health 2021 May 01;27(5):508-512. [doi: 10.1089/tmj.2020.0295] [Medline: 32946364]
9. Gentili S, Huang V, Mamo J, Cuschieri S. Chronic diseases in 2021. In: Proceedings of the 14th European Public Health Conference. 2022 Presented at: EPH '21; November 10-12, 2021; Virtual Event URL: https://eupha.org/repository/Chronic%20Diseases%20in%202021%20-%20EUPHA%20track%20report.pdf/>
10. Gisondi MA, Barber R, Faust JS, Raja A, Strehlow MC, Westafer LM, et al. A deadly infodemic: social media and the power of COVID-19 misinformation. J Med Internet Res 2022 Feb 01;24(2):e35552 [FREE Full text] [doi: 10.2196/35552] [Medline: 35007204]
11. Dubin RE, Flannery J, Taenzer P, Smith A, Smith K, Fabico R, et al. ECHO Ontario chronic pain and opioid stewardship: providing access and building capacity for primary care providers in underserviced, rural, and remote communities. Stud Health Technol Inform 2015;209:15-22. [Medline: 25980700]
12. Henny KD, Duke CC, Geter A, Gaul Z, Frazier C, Peterson J, et al. HIV-related training and correlates of knowledge, HIV screening and prescribing of nPEP and PrEP among primary care providers in southeast United States, 2017. AIDS Behav 2019 Nov;23(11):2926-2935 [FREE Full text] [doi: 10.1007/s10461-019-02545-1] [Medline: 31172333]
13. Xing Z, Yu F, Qanir YA, Guan T, Walker J, Song L. Intelligent conversational agents in patient self-management: a systematic survey using multi data sources. Stud Health Technol Inform 2019 Aug 21;264:1813-1814. [doi: 10.3233/SHTI190661] [Medline: 31438357]
14. Proctor E, Silmere H, Raghavan R, Hovmand P, Aarons G, Bunger A, et al. Outcomes for implementation research: conceptual distinctions, measurement challenges, and research agenda. Adm Policy Ment Health 2011 Mar;38(2):65-76 [FREE Full text] [doi: 10.1007/s10488-010-0319-7] [Medline: 20957426]
15. Boggiss A, Consedine N, Hopkins S, Silvester C, Jefferies C, Hofman P, et al. Improving the well-being of adolescents with type 1 diabetes during the COVID-19 pandemic: qualitative study exploring acceptability and clinical usability of a self-compassion chatbot. JMIR Diabetes 2023 May 05;8:e40641 [FREE Full text] [doi: 10.2196/40641] [Medline: 36939680]
16. Anmella G, Sanabra M, Primé-Tous M, Segú X, Cavero M, Morilla I, et al. Vickybot, a chatbot for anxiety-depressive symptoms and work-related burnout in primary care and health care professionals: development, feasibility, and potential effectiveness studies. J Med Internet Res 2023 Apr 03;25:e43293 [FREE Full text] [doi: 10.2196/43293] [Medline: 36719325]
17. Klos MC, Escoredo M, Joerin A, Lemos VN, Rauws M, Bunge EL. Artificial intelligence-based chatbot for anxiety and depression in university students: pilot randomized controlled trial. JMIR Form Res 2021 Aug 12;5(8):e20678 [FREE Full text] [doi: 10.2196/20678] [Medline: 34092548]
18. Prochaska JJ, Vogel EA, Chieng A, Kendra M, Baiocchi M, Pajarito S, et al. A therapeutic relational agent for reducing problematic substance use (Woebot): development and usability study. J Med Internet Res 2021 Mar 23;23(3):e24850 [FREE Full text] [doi: 10.2196/24850] [Medline: 33755028]
19. Au J, Falloon C, Ravi A, Ha P, Le S. A beta-prototype chatbot for increasing health literacy of patients with decompensated cirrhosis: usability study. JMIR Hum Factors 2023 Aug 15;10:e42506 [FREE Full text] [doi: 10.2196/42506] [Medline: 37581920]
20. Kadariya D, Venkataramanan R, Yip HY, Kalra M, Thirunarayanan K, Sheth A. kBot: knowledge-enabled personalized chatbot for asthma self-managemen. In: Proceedings of the 2019 IEEE International Conference on Smart Computing. 2019 Presented at: SMARTCOMP '19; June 12-15, 2019; Washington, DC p. 138-143 URL: https://ieeexplore.ieee.org/document/8784055 [doi: 10.1109/smartcomp.2019.00043]
21. Milne-Ives M, de Cock C, Lim E, Shehadeh MH, de Pennington N, Mole G, et al. The effectiveness of artificial intelligence conversational agents in health care: systematic review. J Med Internet Res 2020 Oct 22;22(10):e20346 [FREE Full text] [doi: 10.2196/20346] [Medline: 33090118]
22. Griffin AC, Xing Z, Khairat S, Wang Y, Bailey S, Arguello J, et al. Conversational agents for chronic disease self-management: a systematic review. AMIA Annu Symp Proc 2020;2020:504-513 [FREE Full text] [Medline: 33936424]
23. Xu L, Sanders L, Li K, Chow JC. Chatbot for health care and oncology applications using artificial intelligence and machine learning: systematic review. JMIR Cancer 2021 Nov 29;7(4):e27850 [FREE Full text] [doi: 10.2196/27850] [Medline: 34847056]

24. Shah SS, Gvozdanovic A. Digital health; what do we mean by clinical validation? Expert Rev Med Devices 2021 Dec 12;18(sup1):5-8. [doi: 10.1080/17434440.2021.2012447] [Medline: 34845960]
25. Schachner T, Keller R, V Wangenheim F. Artificial intelligence-based conversational agents for chronic conditions: systematic literature review. J Med Internet Res 2020 Sep 14;22(9):e20701 [FREE Full text] [doi: 10.2196/20701] [Medline: 32924957]
26. Solomon DH, Rudin RS. Digital health technologies: opportunities and challenges in rheumatology. Nat Rev Rheumatol 2020 Sep 24;16(9):525-535. [doi: 10.1038/s41584-020-0461-x] [Medline: 32709998]
27. Sadasivan C, Cruz C, Dolgoy N, Hyde A, Campbell S, McNeely M, et al. Examining patient engagement in chatbot development approaches for healthy lifestyle and mental wellness interventions: scoping review. J Particip Med 2023 May 22;15:e45772 [FREE Full text] [doi: 10.2196/45772] [Medline: 37213199]
28. Kildea J, Battista J, Cabral B, Hendren L, Herrera D, Hijal T, et al. Design and development of a person-centered patient portal using participatory stakeholder co-design. J Med Internet Res 2019 Feb 11;21(2):e11371 [FREE Full text] [doi: 10.2196/11371] [Medline: 30741643]
29. Pomey MP, Flora L, Karazivan P, Dumez V, Lebel P, Vanier MC, et al. Le « Montreal model » : enjeux du partenariat relationnel entre patients et professionnels de la santé. Santé Publique 2015;1:41-50 [FREE Full text] [doi: 10.3917/spub.150.0041]
30. Dilhac MA, Abrassart C, Voarino N. Rapport de la Déclaration de Montréal pour un développement responsable de l'intelligence artificielle. Raisons Politiques 2020;77(1):67-81 [FREE Full text] [doi: 10.3917/rai.077.0067]
31. Gagnon MP, Desmartis M, Lepage-Savary D, Gagnon J, St-Pierre M, Rhainds M, et al. Introducing patients' and the public's perspectives to health technology assessment: a systematic review of international experiences. Int J Technol Assess Health Care 2011 Jan;27(1):31-42. [doi: 10.1017/S0266462310001315] [Medline: 21262085]
32. Ma Y, Tu G, Lessard D, Vicente S, Engler K, Achiche S, et al. An artificial intelligence-based chatbot to promote HIV primary care self-management: a mixed method usability study. Ann Fam Med 2023 Nov;21(Supplement 3):5267 [FREE Full text] [doi: 10.1370/afm.22.s1.5267]
33. Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, PAFS consensus group. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. Pilot Feasibility Stud 2016;2:64 [FREE Full text] [doi: 10.1186/s40814-016-0105-8] [Medline: 27965879]
34. Eysenbach G, CONSORT-EHEALTH Group. CONSORT-EHEALTH: improving and standardizing evaluation reports of web-based and mobile health interventions. J Med Internet Res 2011 Dec 31;13(4):e126 [FREE Full text] [doi: 10.2196/jmir.1923] [Medline: 22209829]
35. Liu X, Cruz Rivera S, Moher D, Calvert MJ, Denniston AK, SPIRIT-AICONSORT-AI Working Group. Reporting guidelines for clinical trial reports for interventions involving artificial intelligence: the CONSORT-AI extension. Nat Med 2020 Sep;26(9):1364-1374 [FREE Full text] [doi: 10.1038/s41591-020-1034-x] [Medline: 32908283]
36. Park JJ, Siden E, Zoratti MJ, Dron L, Harari O, Singer J, et al. Systematic review of basket trials, umbrella trials, and platform trials: a landscape analysis of master protocols. Trials 2019 Sep 18;20(1):572 [FREE Full text] [doi: 10.1186/s13063-019-3664-1] [Medline: 31533793]
37. Woodcock J, LaVange LM. Master protocols to study multiple therapies, multiple diseases, or both. N Engl J Med 2017 Jul 06;377(1):62-70. [doi: 10.1056/NEJMra1510062] [Medline: 28679092]
38. Kaizer AM, Belli HM, Ma Z, Nicklawsky AG, Roberts SC, Wild J, et al. Recent innovations in adaptive trial designs: a review of design opportunities in translational research. J Clin Transl Sci 2023;7(1):e125 [FREE Full text] [doi: 10.1017/cts.2023.537] [Medline: 37313381]
39. Etikan I, Musa SA, Alkassim RS. Comparison of convenience sampling and purposive sampling. Am J Theor Appl Stat 2016;5(1):1. [doi: 10.11648/j.ajtas.20160501.11]
40. Lewis JR. Sample sizes for usability studies: additional considerations. Hum Factors 1994 Jun 23;36(2):368-378. [doi: 10.1177/001872089403600215] [Medline: 8070799]
41. Lewis M, Bromley K, Sutton CJ, McCray G, Myers HL, Lancaster GA. Determining sample size for progression criteria for pragmatic pilot RCTs: the hypothesis test strikes back!. Pilot Feasibility Stud 2021 Feb 03;7(1):40 [FREE Full text] [doi: 10.1186/s40814-021-00770-x] [Medline: 33536076]
42. Lancaster GA, Dodd S, Williamson PR. Design and analysis of pilot studies: recommendations for good practice. J Eval Clin Pract 2004 May;10(2):307-312. [doi: 10.1111/j..2002.384.doc.x] [Medline: 15189396]
43. Ma Y, Achiche S, Lebouché B. Chatbot Marvin Meta page. Meta. URL: https://www.facebook.com/ChatbotMarvin [accessed 2023-10-23]
44. Bocklisch T, Faulkner J, Pawlowski N, Nichol A. Rasa: Open source language understanding and dialogue management. arXiv Preprint posted online Dec 14, 2017 [FREE Full text]
45. Vlasov V, Drissner-Schmid A, Nichol A. Few-shot generalization across dialogue tasks. arXiv Preprint posted online November 28, 2018 [FREE Full text] [doi: 10.48550/arXiv.1811.11707]
46. Smutny P, Schreiberova P. Chatbots for learning: a review of educational chatbots for the Facebook Messenger. Comput Educ 2020 Jul;151:103862 [FREE Full text] [doi: 10.1016/j.compedu.2020.103862]

47. Roberts AE, Davenport TA, Wong T, Moon HW, Hickie IB, LaMonica HM. Evaluating the quality and safety of health-related apps and e-tools: adapting the Mobile App Rating Scale and developing a quality assurance protocol. Internet Interv 2021 Apr;24:100379 [FREE Full text] [doi: 10.1016/j.invent.2021.100379] [Medline: 33777705]
48. Grové C. Co-developing a mental health and wellbeing chatbot with and for young people. Front Psychiatry 2020;11:606041 [FREE Full text] [doi: 10.3389/fpsyt.2020.606041] [Medline: 33597898]
49. Guest G, Namey E, McKenna K. How many focus groups are enough? Building an evidence base for nonprobability sample sizes. Field Methods 2016 Jul 24;29(1):3-22 [FREE Full text] [doi: 10.1177/1525822x16639015]
50. Lewis JR, Utesch BS, Maher DE. UMUX-LITE: when there's no time for the SUS. In: Proceedings of the SIGCHI Conference on Human Factors in Computing Systems. 2013 Presented at: CHI '13; April 27-May 2, 2013; Paris, France p. 2099-2102 URL: https://dl.acm.org/doi/10.1145/2470654.2481287 [doi: 10.1145/2470654.2481287]
51. Tariman JD, Berry DL, Halpenny B, Wolpin S, Schepp K. Validation and testing of the acceptability e-scale for web-based patient-reported outcomes in cancer care. Appl Nurs Res 2011 Feb;24(1):53-58 [FREE Full text] [doi: 10.1016/j.apnr.2009.04.003] [Medline: 20974066]
52. ISO/TS 20282-2(en) usability of consumer products and products for public use- part 2: ummative test method. International Organization for Standardization. 2013. URL: https://www.iso.org/obp/ui/#iso:std:iso:ts:20282:-2:ed-2:v1:en [accessed 2024-01-18]
53. Borsci S, Buckle P, Walne S. Is the LITE version of the usability metric for user experience (UMUX-LITE) a reliable tool to support rapid assessment of new healthcare technology? Appl Ergon 2020 Apr;84:103007. [doi: 10.1016/j.apergo.2019.103007] [Medline: 31785449]
54. Sauro J, Dumas JS. Comparison of three one-question, post-task usability questionnaires. In: Proceedings of the SIGCHI Conference on Human Factors in Computing Systems. 2009 Presented at: CHI '09; April 4-9, 2009; Boston, MA p. 1599-1608 URL: https://dl.acm.org/doi/10.1145/1518701.1518946 [doi: 10.1145/1518701.1518946]
55. Chau PY, Hu PJ. Investigating healthcare professionals' decisions to accept telemedicine technology: an empirical test of competing theories. Inf Manag 2002 Jan;39(4):297-311 [FREE Full text] [doi: 10.1016/s0378-7206(01)00098-2]
56. Davis FD. Perceived usefulness, perceived ease of use, and user acceptance of information technology. MIS Q 1989 Sep;13(3):319 [FREE Full text] [doi: 10.2307/249008]
57. Adams C, Walpola R, Schembri AM, Harrison R. The ultimate question? Evaluating the use of net promoter score in healthcare: a systematic review. Health Expect 2022 Oct 19;25(5):2328-2339 [FREE Full text] [doi: 10.1111/hex.13577] [Medline: 35985676]
58. Venkatesh V, Davis FD. A theoretical extension of the Technology Acceptance Model: four longitudinal field studies. Manage Sci 2000 Feb;46(2):186-204 [FREE Full text] [doi: 10.1287/mnsc.46.2.186.11926]
59. R Core Team. R: a language and environment for statistical computing. R Foundation for Statistical Computing. 2018. URL: https://www.R-project.org/ [accessed 2024-01-12]
60. Braun V, Clarke V. Thematic analysis. In: Cooper H, Coutanche MN, McMullen LM, Panter AT, Rindskopf D, Sher KJ, editors. APA Handbook of Research Methods in Psychology. Washington, DC: American Psychological Association; 2012:57-71.
61. Greenhalgh T, Abimbola S. The NASSS framework - a synthesis of multiple theories of technology implementation. Stud Health Technol Inform 2019 Jul 30;263:193-204. [doi: 10.3233/SHTI190123] [Medline: 31411163]
62. Hornbæk K. Current practice in measuring usability: challenges to usability studies and research. Int J Hum Comput Stud 2006 Feb;64(2):79-102 [FREE Full text] [doi: 10.1016/j.ijhcs.2005.06.002]
63. Engler K, Vicente S, Ma Y, Hijal T, Cox J, Ahmed S, et al. Implementation of an electronic patient-reported measure of barriers to antiretroviral therapy adherence with the Opal patient portal: protocol for a mixed method type 3 hybrid pilot study at a large Montreal HIV clinic. PLoS One 2021;16(12):e0261006 [FREE Full text] [doi: 10.1371/journal.pone.0261006] [Medline: 34969046]
64. Moore GC, Benbasat I. Development of an instrument to measure the perceptions of adopting an information technology innovation. Inf Syst Res 1991 Sep;2(3):192-222 [FREE Full text] [doi: 10.1287/isre.2.3.192]
65. Weiner BJ, Lewis CC, Stanick C, Powell BJ, Dorsey CN, Clary AS, et al. Psychometric assessment of three newly developed implementation outcome measures. Implement Sci 2017 Aug 29;12(1):108 [FREE Full text] [doi: 10.1186/s13012-017-0635-3] [Medline: 28851459]
66. Coorey G, Peiris D, Scaria A, Mulley J, Neubeck L, Hafiz N, et al. An internet-based intervention for cardiovascular disease management integrated with primary care electronic health records: mixed methods evaluation of implementation fidelity and user engagement. J Med Internet Res 2021 Apr 26;23(4):e25333 [FREE Full text] [doi: 10.2196/25333] [Medline: 33900204]
67. Anastaselos T. What is a good SaaS growth rate? ChartMogul. URL: https://chartmogul.com/blog/good-monthly-growth-rate/ [accessed 2023-09-07]
68. Standing out in the crowd: 7 causes of slow or low user growth. Specno. 2023 Feb. URL: https://www.specno.com/blog/low-user-growth#:~:text=Daily%20Active%20Users%20(DAU)%20%E2%80%93,over%2025%25%20is%20excellent!) [accessed 2023-09-07]

69. Staniszewska S, Brett J, Simera I, Seers K, Mockford C, Goodlad S, et al. GRIPP2 reporting checklists: tools to improve reporting of patient and public involvement in research. BMJ 2017 Aug 02;358:j3453 [FREE Full text] [doi: 10.1136/bmj.j3453] [Medline: 28768629]
70. Meta privacy policy. Meta. URL: https://www.facebook.com/privacy/policy/ [accessed 2024-01-12]
71. Meta data security terms. Meta. URL: https://www.facebook.com/legal/terms/data_security_terms [accessed 2024-01-12]
72. Privacy and safety on Messenger. Meta. URL: https://www.facebook.com/help/messenger-app/1064701417063145/?helpref=hc_fnav [accessed 2024-01-12]
73. Merrick R, Ryan S. Data privacy governance in the age of GDPR. Risk Manag 2019;66(3):38-43 [FREE Full text]
74. Geneviève D, Alexandre G, Antoine B, Vincent D. Principes directeurs – Dédommagement financier pour la recherche en partenariat avec les patients et le public. Unité de soutien SRAP du Québec. 2022. URL: https://ceppp.ca/wp-content/uploads/2021/01/USSQ_Principes-directeurs_Dedommagement_vAou%CC%82t2018.pdf [accessed 2024-01-18]
75. Siden EG, Park JJ, Zoratti MJ, Dron L, Harari O, Thorlund K, et al. Reporting of master protocols towards a standardized approach: a systematic review. Contemp Clin Trials Commun 2019 Sep;15:100406 [FREE Full text] [doi: 10.1016/j.conctc.2019.100406] [Medline: 31334382]
76. Subbiah V. The next generation of evidence-based medicine. Nat Med 2023 Jan;29(1):49-58. [doi: 10.1038/s41591-022-02160-z] [Medline: 36646803]
77. Meyer EL, Mesenbrink P, Dunger-Baldauf C, Fülle HJ, Glimm E, Li Y, et al. The evolution of master protocol clinical trial designs: a systematic literature review. Clin Ther 2020 Jul;42(7):1330-1360 [FREE Full text] [doi: 10.1016/j.clinthera.2020.05.010] [Medline: 32622783]
78. Huml RA, Collyar D, Antonijevic Z, Beckman RA, Quek RG, Ye J. Aiding the adoption of master protocols by optimizing patient engagement. Ther Innov Regul Sci 2023 Nov;57(6):1136-1147. [doi: 10.1007/s43441-023-00570-w] [Medline: 37615880]
79. Pearce FJ, Cruz Rivera S, Liu X, Manna E, Denniston AK, Calvert MJ. The role of patient-reported outcome measures in trials of artificial intelligence health technologies: a systematic evaluation of ClinicalTrials.gov records (1997-2022). Lancet Digit Health 2023 Mar;5(3):e160-e167 [FREE Full text] [doi: 10.1016/S2589-7500(22)00249-7] [Medline: 36828608]
80. Thirunavukarasu AJ, Ting DS, Elangovan K, Gutierrez L, Tan TF, Ting DS. Large language models in medicine. Nat Med 2023 Aug;29(8):1930-1940. [doi: 10.1038/s41591-023-02448-8] [Medline: 37460753]
81. Lee P, Goldberg C, Kohane I. The AI Revolution in Medicine: GPT-4 and Beyond. New York, NY: Pearson; 2023.
82. Greene A, Greene CC, Greene C. Artificial intelligence, chatbots, and the future of medicine. Lancet Oncol 2019 Apr;20(4):481-482. [doi: 10.1016/S1470-2045(19)30142-1] [Medline: 30942174]
83. Surani A, Das S. Understanding privacy and security postures of healthcare chatbots. In: Proceedings of the 2022 CHI Conference on Human Factors in Computing Systems. 2022 Presented at: CHI '22; April 29-May 5, 2022; New Orleans, LA p. 1-7 URL: https://cui.acm.org/workshops/CHI2022/pdfs/das_Healthcare_Chatbot_Privacy_and_Security.pdf

Abbreviations

AES: Acceptability E-scale
AI: artificial intelligence
AWS: Amazon Web Services
CONSORT: Consolidated Standards of Reporting Trials
CONSORT-AI: Consolidated Standards of Reporting Trials–Artificial Intelligence
CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
LLM: large language model
MUHC: McGill University Health Centre
NASSS: nonadoption, abandonment, scale-up, spread, and sustainability
NPS: net promoter score
REB: research ethics board
REDCap: Research Electronic Data Capture
TAM: Technology Acceptance Model
UMUX-Lite: shorter version of the Usability Metric for User Experience

Edited by A Mavragani; submitted 18.11.23; peer-reviewed by T Su, A Keogh, L Ursic; comments to author 12.12.23; revised version received 27.12.23; accepted 28.12.23; published 13.02.24.

Please cite as:
Ma Y, Achiche S, Pomey MP, Paquette J, Adjtoutah N, Vicente S, Engler K, MARVIN chatbots Patient Expert Committee, Laymouna M, Lessard D, Lemire B, Asselah J, Therrien R, Osmanlliu E, Zawati MH, Joly Y, Lebouché B
Adapting and Evaluating an AI-Based Chatbot Through Patient and Stakeholder Engagement to Provide Information for Different Health Conditions: Master Protocol for an Adaptive Platform Trial (the MARVIN Chatbots Study)
JMIR Res Protoc 2024;13:e54668
URL: https://www.researchprotocols.org/2024/1/e54668
doi:10.2196/54668
PMID:38349734

Protocol

Development of an App for Symptom Management in Women With Breast Cancer Receiving Maintenance Aromatase Inhibitors: Protocol for a Mixed Methods Feasibility Study

Trine Lund-Jacobsen[1], BSN, MSc; Peter Schwarz[1], MD, DMSc; Gabriella Martino[2], MD, PhD; Helle Pappot[3], MD, DMSc; Karin Piil[3], MHScN, PhD

[1]Department of Endocrinology, Centre for Cancer and Organ Diseases, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

[2]Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy

[3]Department of Oncology, Centre for Cancer and Organ Diseases, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

Corresponding Author:
Trine Lund-Jacobsen, BSN, MSc
Department of Endocrinology, Centre for Cancer and Organ Diseases
Copenhagen University Hospital, Rigshospitalet
Blegdamsvej 9
Copenhagen, 2100
Denmark
Phone: 45 25318056
Email: trine.lund-jacobsen@regionh.dk

Abstract

Background: Patients with postmenopausal nonmetastatic estrogen receptor–positive breast cancer often experience a reduced quality of life after primary treatment. The disease and treatment trajectory consists of surgery followed by chemotherapy or radiation therapy. Upon this, maintenance hormone therapy with an aromatase inhibitor can result in several physical and psychosocial symptoms. Optimal symptom control during maintenance therapy is central to maintaining the patient's quality of life.

Objective: This study aims to (1) develop an electronic symptom management tool for patients with postmenopausal early breast cancer receiving maintenance aromatase inhibitors with an endocrine aspect and (2) assess the feasibility, acceptability, and usability of the pilot version of the Bone@BC app. Furthermore, longitudinally, symptom prevalence and quality of life for patients with postmenopausal nonmetastatic estrogen receptor–positive breast cancer will be explored.

Methods: This study follows a multistage research plan. In stage 1, a systematic literature review to establish an overview of aromatase inhibitor–related symptoms reported by postmenopausal women with nonmetastatic estrogen receptor–positive breast cancer will be completed. In stage 2, a comprehensive overview of symptoms related to aromatase inhibitors (letrozole, exemestane, and anastrozole) will be performed (eg, by reviewing medical leaflets and guidelines). In stage 3, an electronic app with a user-friendly Patient Concern Inventory list to comprise symptoms and concerns will be developed. Last, in stage 4, a convergent mixed methods feasibility study of the pilot version of the Bone@BC app will be conducted. A total of 45 patients with postmenopausal nonmetastatic estrogen receptor–positive breast cancer will use the app daily for symptom identification and respond to 6 serial patient-reported outcome measurements for 12 weeks. Finally, semistructured interviews will be performed. The primary outcome includes consent rate, attrition rate, retention rates, technical issues, and adherence, assessed using preestablished criteria on feasibility and a mixed methods approach for exploring acceptability. A patient advisory board consisting of 5 women with breast cancer is recruited to include their perspectives and experiences in the planning, organization, implementation, and dissemination of the research throughout the project.

Results: At the time of submitting this paper (January 2024), a total of 23 patients have been included in the stage 2 medical audit over the recruitment period of 3 months (November 2022 to February 2023), and 19 patients have been enrolled in stage 2, the semistructured patient interviews.

Conclusions: This protocol describes a study investigating the feasibility, acceptability, and usability of the symptom management tool Bone@BC developed for patients with breast cancer with an endocrine aspect.

Trial Registration: ClinicalTrails.gov NCT05367830; https://clinicaltrials.gov/ct2/show/NCT05367830

International Registered Report Identifier (IRRID): DERR1-10.2196/49549

(JMIR Res Protoc 2024;13:e49549) doi:10.2196/49549

KEYWORDS

acceptability; aromatase inhibitors; breast cancer; cancer; chemotherapy; disease; feasibility; inhibitor; management; mHealth; postmenopausal; psychosocial; QoL; quality of life; radiation therapy; symptom management; symptom; tool; treatment; usability; user-friendliness

Introduction

Breast Cancer

Patients with postmenopausal nonmetastatic estrogen receptor–positive (ER+) breast cancer (BC) in maintenance therapy with an aromatase inhibitor (AI) deal with numerous long-term cancer- and treatment-related side effects (eg, affected bone health). These side effects lead to impaired health-related quality of life (HRQoL) even years after ending primary treatment and during maintenance hormone therapy [1-3].

The Transition

The transition from being closely monitored by specialists to fewer follow-up visits is difficult for the survivors of BC [4]. These difficulties are explained by reduced interaction with and less psychological support from health care professionals (HCPs) [5-8], as well as, in light of the less frequent consultations, the fact that their surroundings begin to consider the survivors of BC to be cured and healthy [9]. Still, patients during this trajectory stage must be capable of reacting sufficiently to the experienced side effects and potential symptoms [9]. Hence, understanding where and how information and support can be sought for these women is crucial [10] to optimize their self-efficacy and self-management [11].

Patient-Reported Outcomes and Mobile Health

Patient-reported outcomes (PROs) are an important element in the person-centered care of patients with cancer [12,13]. Numerous applications have been developed to collect electronic patient-reported outcomes (ePROs) [14-16]. Mobile health (mHealth) apps have the potential to increase patients' self-efficacy, strengthen empowerment, and offer value to patients in their daily lives [17,18]. The growing field of mHealth has been applied to numerous areas, including health promotion, behavior change support, and self-management of cancer diseases. mHealth is a subset of digital health, or eHealth, which also includes health information, telemedicine, and personalized medicine [19]. mHealth can be quickly scaled to reach thousands of people and potentially increase access to health care. mHealth is well-suited to symptom management, as it can provide timely dissemination of health information, encourage patients to acquire information during their communication with clinicians, and guide self-management.

Hypothesis

We hypothesize that patients with postmenopausal nonmetastatic ER+ BC often experience reduced HRQoL after primary treatment due to treatment-related symptoms. Furthermore, transitioning from being closely monitored by HCPs to fewer follow-up visits can indeed be challenging for some patients. The close monitoring provided by HCPs can provide a sense of security and reassurance, and reducing the frequency of visits may therefore lead to feelings of uncertainty or anxiety. To help patients navigate this transition more smoothly, we will develop a symptom management tool in the form of a pilot version of the Bone@BC app. The pilot version of the Bone@BC app has the potential to significantly support patients in several ways, leading to an improved HRQoL and enhanced communication with HCPs. The app can include features that enable patients to monitor their symptoms regularly so that they will be able to act on them if necessary. It is important to note that the effectiveness of the Bone@BC app will depend on its design, functionality, and user experience. Conducting user testing and gathering feedback during the pilot phase will help identify areas for improvement and ensure that the app meets the specific needs of the target group of patients.

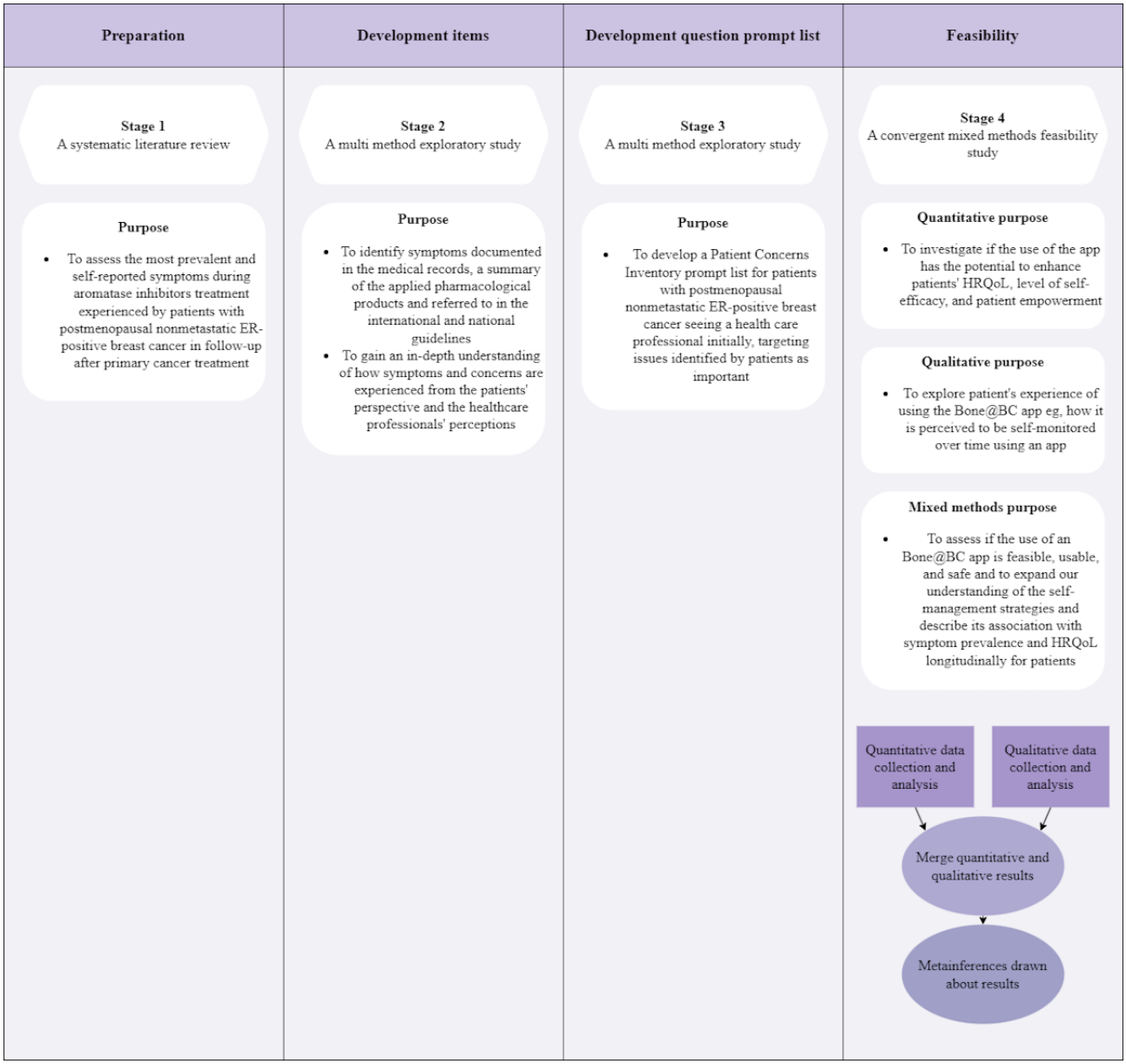
Methods

Study Design

This study follows a multistage feasibility design [20,21] comprising 4 stages (Figure 1 [21]).

As recommended in *Guidelines for Reporting Non-Randomized Pilot and Feasibility Studies* by Lancaster and Thabane [22], the reporting of the study protocol adheres to the CONSORT (Consolidated Standards of Reporting Trials) extension to pilot and feasibility trials.

Figure 1. A multistage feasibility study. Convergent refers to the quantitative and qualitative data set being collected concurrently. Merge mean data will be analyzed separately and then merged according to allowing the research purpose from multiple perspectives. Metainferences refer to quantitative and qualitative results combined in a conclusion. ER: estrogen receptor; HRQoL: health-related quality of life.



Study Setting

This study will be carried out as a single-center study at the endocrinology outpatient clinic at the Copenhagen University Hospital, Rigshospitalet, in Denmark.

Recruitment

The patients will be recruited from the endocrinology outpatient clinic by clinicians at routine consultations. The semistructured interviews will be performed by the principal investigator (TLJ) not being involved in the treatment and care of these patients. Patients will be screened for inclusion criteria during routine appointments. The informed consent can be withdrawn at any time. A screening log will be kept collecting reasons for nonresponses.

Eligibility

The predetermined eligibility criteria are women aged between 50 and 70 years with a diagnosis of postmenopausal nonmetastatic ER+ BC; in maintenance therapy with an AI (letrozole, anastrozole, or exemestane); who are able to understand, read, and speak Danish; have access to a smartphone that can display the app (eg, iOS, iPADOS, or Android); and provide informed consent. Patients will be considered ineligible if they are unable to provide informed consent due to cognitive or linguistic inability, have a physiological or cognitive impairment that would prevent or inhibit the participation in using the app and answering the ePROs, have a previous malignancy, or are in maintenance therapy with tamoxifen.

Patient and Public Involvement

Because patient involvement is essential for this study, to ensure patient-centeredness [23], a patient advisory board consisting of 5 women diagnosed with BC was recruited through an

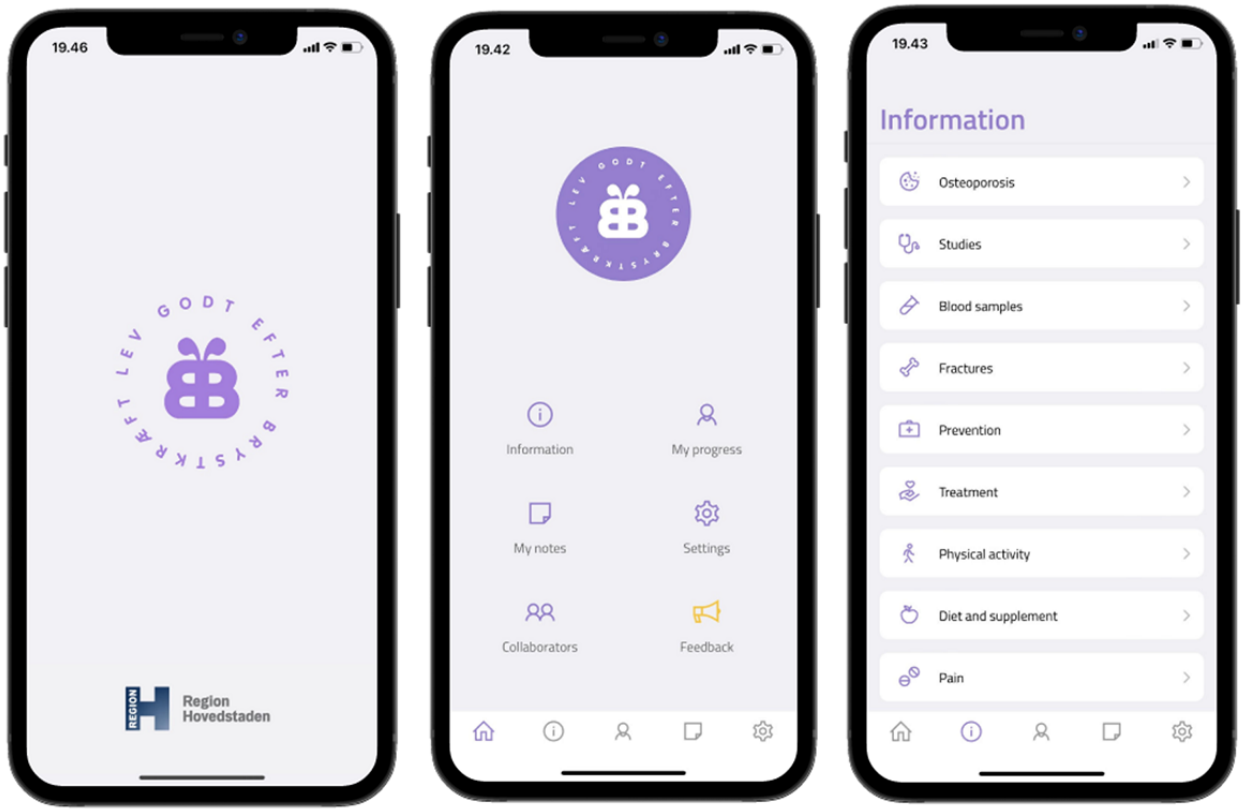
advertisement on the Danish Breast Cancer Organization's website. The primary objective of the patient advisory board is to enhance the researcher's communication and cooperation with patients, thereby ensuring the integration of their perspectives, requirements, experiences, and expectations throughout the various stages of research, including planning, organization, implementation, and dissemination [24,25].

Intervention Description

The Proof-of-Concept Version of the Bone@BC App

Originally, a proof of concept of the Bone@BC app was developed (2015-2018) by a team of clinicians with specialist experience from the Healthy Living After Breast Cancer research group. The proof-of-concept app was published in 2 languages, Danish and English. The proof-of-concept version provides (1) advice on treatment elements (eg, blood samples and prevention); (2) daily questions about daily living; and (3) private notes. However, the proof-of-concept version of the app did not follow a systematic selection of symptoms to include, and no patients were involved in the design or content of the app (Figure 2).

Figure 2. Overview of the proof-of-concept version of the Bone@BC app.



The Pilot Version of the Bone@BC App

The proof-of-concept version of the app yielded several noteworthy patient feedback examples, which are as follows:

- Patients expressed the desire for an app that goes beyond educational purposes and provides support in their daily lives. Specifically, they highlighted the importance of having a tool that helps them remember changes in their symptoms.
- Patients emphasized the need for visual information, such as trends indicating their quality of life based on daily responses to HRQoL assessments.
- Patients expressed the expectation that the app should assist them in identifying relevant topics to discuss with HCPs.
- Some patients did not find the notes module in the app useful.
- Additionally, certain features such as blood samples, daily habits, and dual-energy x-ray absorptiometry scan were deemed unhelpful by patients.

This study seeks to develop a pilot version of the Bone@BC app based on the above feedback from the patients who used the proof-of-concept version of the Bone@BC app. The pilot version of the Bone@BC app will increase patient friendliness by implementing functionalities developed systematically in collaboration with patients and clinicians to solve patients' specific needs using this symptom management tool (Table 1).

Table 1. Overview of components in the proof-of-concept version versus the pilot version.

Components	Proof-of-concept version	Pilot version
Information on treatment-related osteoporosis, blood samples, and physical activity (both text and video) with health care professionals	✓	✓
Training instructions videos		✓
My progress	✓	
My results (eg, blood samples)	✓	
My medication (eg, breast cancer medication)	✓	
Body measures (height and weight)	✓	
Daily habits	✓	
Activity from your mobile phone health tracker		✓
My notes	✓	
Feedback	✓	✓
Patient Concerns Inventory prompt list		✓
Reminder module		✓
Reminder list based on the previous Patient Concerns Inventory prompt list		✓
Intelligent progress of the health-related quality of life measurements		✓
Trends for the health-related quality of life measurements (tendencies algorithm)		✓
Simplified user interface		✓
Danish version	✓	✓
English version	✓	✓

Definition of Symptoms

Our study will use the definition of symptoms from the National Institutes of Health and the National Cancer Institute: "A physical or mental problem that a person experiences that may indicate a disease or condition. Symptoms cannot be seen and do not show up on medical tests. Some examples of symptoms are headache, fatigue, nausea, and pain" [26].

Development of the Pilot Version of the Bone@BC App

To develop the pilot app version, this multistage study consists of 4 stages (Figure 1) where the Bone@BC app will be further developed and then tested in a feasibility study.

Stage 1

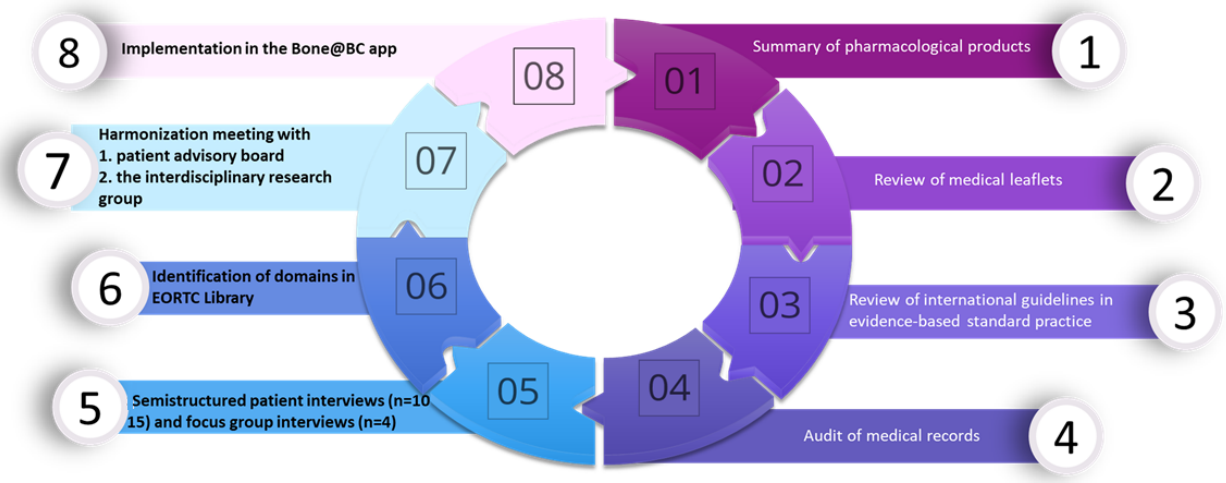
A systematic review will be undertaken to appraise the current literature and provide an overview of AI-related symptoms reported by postmenopausal women with nonmetastatic ER+ BC. The systematic literature review will be reported according to the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis for Protocols) 2015 statement [27]. A comprehensive search will be undertaken on the following databases: PubMed, MEDLINE, CINAHL, Embase, Cochrane, Web of Science, PsycINFO, and Scopus. The Mixed Methods Appraisal Tool version 2018 [28] will be used for assessing the included studies' methodological quality.

Stage 2

Stage 2 will be an explorative multimethod stage relying on patient involvement. Moreover, symptoms and concerns identified by the European Organization for Research and Treatment of Cancer (EORTC) Library Item [29] will be selected to be included in the Bone@BC app.

Multimethod data collection will be carried out to explore the symptoms reported by the patients with postmenopausal nonmetastatic ER+ BC in maintenance therapy with AI (letrozole, anastrozole, and exemestane; Figure 3).

Figure 3. Study assessments in stage 2. EORTC: European Organization for Research and Treatment of Cancer.



1. A summary of pharmacological products at the European Medicines Agency [30] and the Food and Drug Administration [31].
2. Review of medical leaflets at the website Medicine.dk [32].
3. Reviews of international and national guidelines for the standard clinical practice: oncological (American Society of Clinical Oncology [33], European Society for Medical Oncology [34], and Danish Breast Cancer Group [35]) and endocrinological (Endocrine Society [36], European Society of Endocrinology [37], and Danish Endocrinological Society [38]).
4. Medical record audit from patients with postmenopausal nonmetastatic ER+ BC. The inclusion period will be from November 14, 2022, to February 14, 2023. All patients attending routine consultations will be invited to participate. The principal investigator will perform the reviews and exclude patients who do not meet the predetermined inclusion criteria.
5. Semistructured face-to-face patient interviews on symptom experience (n=15-20).
6. The quantitative and qualitative results from steps 1 to 5 will, together with the systematic literature review, provide a comprehensive overview of the symptoms, side effects, and concerns that patients with postmenopausal early BC are dealing with. These symptoms and concerns will be organized into domains for HRQoL measurements to identify related and validated items in the EORTC Library that can be implemented in the pilot version of the Bone@BC app daily questions [29].
7. Finally, a harmonization meeting will be organized, initially involving the patient advisory board, followed by the interdisciplinary research group (the authors). The purpose of this meeting will be to facilitate discussion, collaboration, and consensus among participants regarding the selection of specific items from the EORTC Library [39].

Stage 3: Multimethod Exploratory Study

In this stage, an electronic Patient Concerns Inventory list (PCI) will be adapted from the English version of the PCI developed by Kanatas et al [40] for patients with BC. The adapted PCI will be modified to fit the app. A PCI is a structured list of frequently asked questions and concerns. It is designed to support and encourage patients to acquire information during their communication with HCPs. The development of the electronic PCI relies on the following steps: (1) translation and linguistic validation according to the Professional Society for Health Economics and Outcomes Research [41]; (2) focus group interview with the patient advisory board; (3) development of a minimum variable product (MVP) app only to test the electronic PCI list; (4) the patient advisory board testing the MVP app and evaluating it in a focus group interview; (5) pilot-test patients (n=15) using the MVP app will be interviewed by semistructured face-to-face interviews; and (6) harmonization meeting in the multidisciplinary research team.

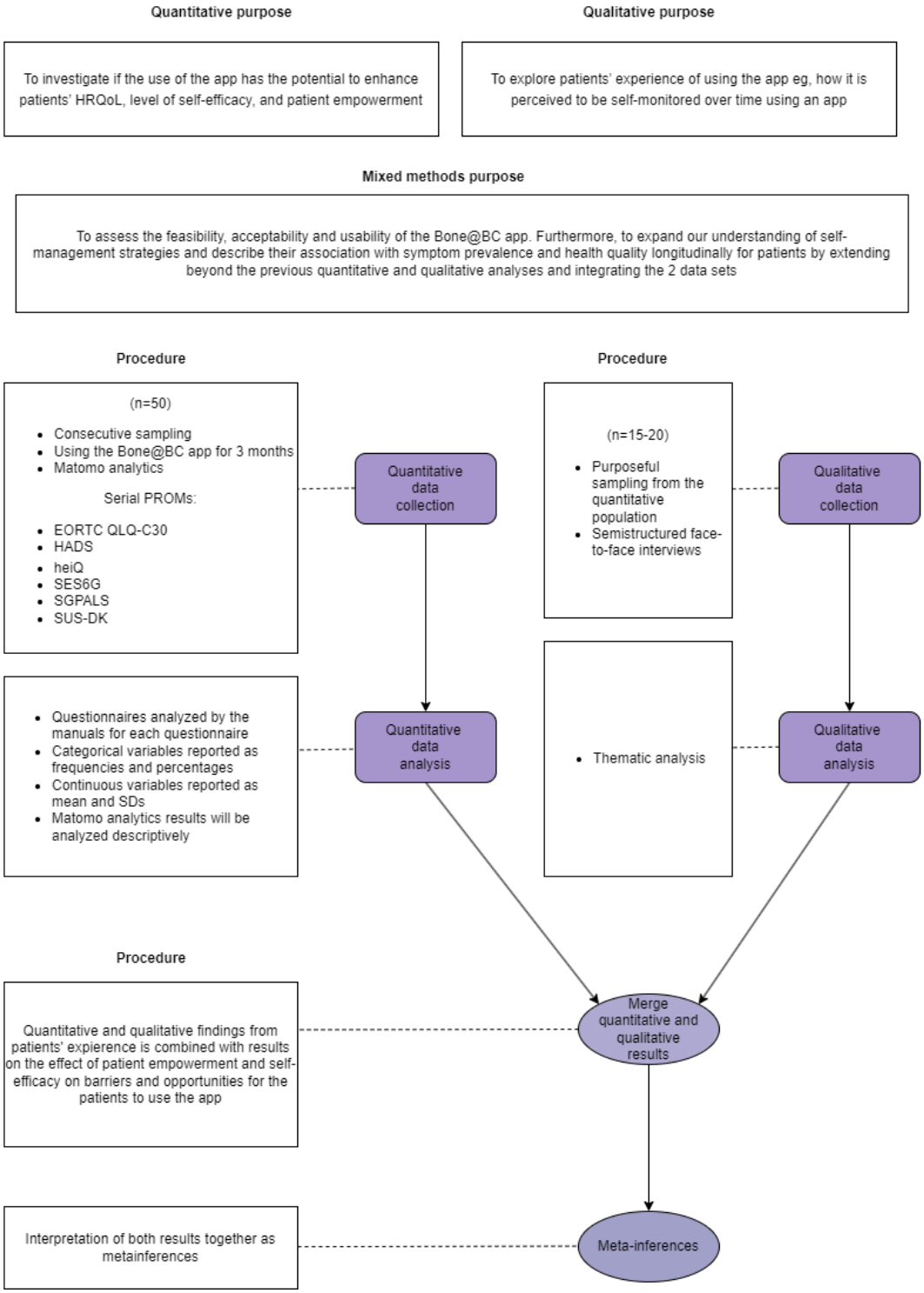
The identified items from the EORTC Library [39] and the PCI will be implemented in the pilot version of the Bone@BC app.

Stage 4

Stage 4 is a convergent, nonrandomized, single-arm mixed methods feasibility study [21] (Figure 4 [20,21,42-49]) investigating the feasibility of the pilot version of the Bone@BC app.

The purpose of this stage will be to explore the patients' perspectives on feasibility, acceptability, and usability while being offered the pilot version of the Bone@BC app, which will be provided to them as a tool for symptom identification over a period of 12 weeks. Moreover, the consent rate, attrition rate, adherence rate, and retention rate will be explored. Furthermore, the potential changes in self-efficacy, HRQoL, and patient empowerment over time will be measured. The findings from the quantitative data (PRO questionnaires and data in the Bone@BC app) and the qualitative data (patient interviews) will be compared and merged. The intent is to obtain a more comprehensive understanding of the feasibility, usability, barriers, and subgroup of patients who may benefit from using the app.

Figure 4. Stage 4: convergent mixed methods feasibility study. Convergent mean that the quantitative and qualitative data sets are collected concurrently, analyzed separately, and then merged accordingly to achieve the research purpose from multiple perspectives. After analysis of each data set, inferences will be drawn. At the end of the study, the metainferences will be drawn and included in the larger interpretation being made in the study's discussion section. Consecutive sampling refers to every participant who meets the criteria of inclusion and is selected until the required sample size is attained [50]. Purposeful sampling refers to the researcher intentionally recruiting participants who have experienced the central phenomenon being explored in the study. Matomo refers to an open-source digital analytics platform (Matomo). EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life C30; HADSA: Hospital Anxiety and Depression Scale; heiQ: Health Education Impact Questionnaire; HRQoL: health-related quality of life; PROM: patient-reported outcome measure; SES6G: Self-Efficacy for Managing Chronic Disease 6-Item Scale; SGPALS: Saltin-Grimby Physical Activity Level Scale; SUS-DK: System Usability Scale–Danish version.



Measures

Feasibility

The feasibility of the study will be assessed by the rate of recruitment and retention over the study duration (12 weeks). The feasibility parameters include adherence rate, acceptability, response rate, representativeness, recruitment rate, technical difficulties, and satisfaction [51].

Acceptability

The acceptability of the pilot version of the Bone@BC app will also be explored by semistructured interviews with a subgroup of the 40-50 invited participants in the study.

Usability

The satisfaction survey will be the System Usability Scale–Danish version (SUS-DK) [42] and will be explored in semistructured patient interviews after the intervention. The System Usability Scale is a 10-item questionnaire with 5 responses ranging from “strongly disagree” to “strongly agree” [42]. The final question allows respondents to provide further comments in an open-ended format. The criteria for being satisfied will be a system usability score of ≥68% [42].

App Use

The open-source web analytic platform Matomo Analytics [43] will be used to investigate user statistics and traffic in the app. In-app user analytics will be collected to track user behavior such as the number of app sessions, length of app sessions, frequency of use, date the app was first opened, the number of pages, time spent on the pages, and bounce rate.

Health-Related Outcomes

Health-related outcomes will be collected at baseline upon registration for the pilot version of the Bone@BC app and then at 3 different time points (Table 2).

Table 2. Study assessments and time points stage 4.

Data Collection (n=50)	Baseline	Week											
		1	2	3	4 (~1 mo)	5	6	7	8 (~2 mo)	9	10	11	12 (~3 mo)
Data for the research database REDCap[a]													
Informed consent	✓												
Demographic data[b]	✓												
EORTC QLQ-C30[c]	✓				✓								✓
SES6G[d]	✓				✓				✓				✓
heiQ[e]	✓												✓
HADS[f]	✓												✓
SGPALS[g]	✓				✓				✓				✓
SUS-DK[h]													✓
Open-source web analytic platform Matomo Analytics 3.0[i]	✓				✓				✓				✓
PRO[j] data through the app													
Electronic patient-reported PRO questionnaires on symptoms Bone@BC (everyday)[k]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Semistructured interviews													✓

[a]REDCap: Research Electronic Data Capture.

[b]Demographic data (eg, marital status, family status, educational level, and occupation).

[c]EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life C30.

[d]SES6G: Self-Efficacy for Managing Chronic Disease 6-Item Scale.

[e]heiQ: Health Education Impact Questionnaire.

[f]HADS: Hospital Anxiety and Depression Scale.

[g]SGPALS: Saltin-Grimby Physical Activity Level Scale.

[h]SUS-DK: System Usability Scale–Danish version.

[i]Open-source web analytic platform Matomo Analytics.

[j]PRO: patient-reported outcome.

[k]Patient-reported outcomes from the app on the questions provided daily on health-related quality of life, late side-effects, symptoms and concerns perspectives, and level of physical activity in the Bone@BC app and question prompt list. Items developed in stage 3 and implemented from the European Organization for Research and Treatment of Quality of Life Item Library in the domains of late side-effects and symptoms management.

The health-related ePROs being assessed before and after the study will be the HRQoL by the 30-item EORTC Quality of Life C30 (QLQ-C30) [44]. The HRQoL domains are divided into multi-item subscales: functional (physical, role, cognitive, emotional, and social), symptom (fatigue, pain, nausea/vomiting, and dyspnea), financial adversity, and global health status [44]. The EORTC-QLQ-C30 has proven to be reliable and valid in a range of patient populations and a variety of treatment settings [52].

Self-efficacy will be measured by the Self-Efficacy for Managing Chronic Disease 6-Item Scale (SES6G) [45]. SES6G is a self-administered questionnaire with 6 items on the patient's perceived self-efficacy on a 10-point Likert scale ranging from "not at all confident" to "totally confident" [45]. Ritter and Lorig [53] conducted 2 new studies and reviewed 8 independent studies to investigate the psychometric properties of the scale. Cronbach α was a minimum of .88 across all studies; minimal floor and ceiling effects were observed; the measure was sensitive to change; and moderate and significant correlations provide convergent validity evidence when measured against selected health indicators [53].

Physical activity will be measured by the Saltin-Grimby Physical Activity Level Scale (SGPALS) [46]. SGPALS is a 4-level scale. The questionnaire measures the level of physical activity as 3 months before the patients were diagnosed with BC and how the level of physical activity is today [46]. The SGPALS is found to be reliable, with a high level of validity and consistency [54].

Anxiety and depressive symptoms will be measured by the Hospital Anxiety and Depression Scale (HADS) [47]. HADS is a validated screening tool and includes 14 questions

addressing anxiety and depressive symptoms with 7 items each in the previous 7 days [47]. In an updated literature review, the HADS was found to be reliable with a Cronbach α between .70 and .90 [55].

Patient empowerment will be measured by the Health Education Impact Questionnaire (heiQ) [48]. heiQ is an outcome and evaluation measure for patient education and self-management interventions for people with chronic conditions. heiQ is a validated screening tool and includes 42 questions with the following 4 options for the answer: "strongly disagree," "disagree, agree," or "completely agree" [48]. The heiQ is a valid, reliable measure of key dimensions of generic health-related empowerment [56].

Statistical Analysis

Preestablished Criteria

Feasibility will be explored by looking at the success threshold, attrition rate, and adherence. The success threshold of ≥60% will be defined as the proportion of informed patients giving consent. The attrition rate will be calculated as the proportion of participants withdrawing from the intervention, leaving no data on outcomes available. The retention rate of ≥85% will be the number of individuals who remained in the study and responded to the daily PRO in 12 weeks. The retention rate and success threshold are based on a recent systematic review of internet-based supportive care for patients with lung disease [57]. Patient adherence will be the proportion of patients completing self-reports for each time point adjusted for withdrawals. The adherence rate is the proportion of patients replying to ≥80% of the daily PRO questions. Adherence to daily completion will be analyzed according to, for example, material status and educational level using the Fisher exact test.

Acceptability will be assessed based on the following predetermined criteria: (1) system usability score ≥68% [42]; (2) patients' experience identified in follow-up interviews; and (3) HRQoL must be at least at the same level before and after the intervention as measured by the EORTC QLQ-C30 [44].

Quantitative Data

The quantitative data will be exported to R software (version 4.1.2; R Foundation for Statistical Computing) [58]. All questionnaires will be scored according to the specific manuals. The analysis of the obtained data will be based on CIs and will focus on exploring the longitudinal changes over time. The daily self-report of symptoms will be analyzed using multiple linear regression after the variables have been checked by diagnostic plots to see if they meet the following 5 main assumptions: (1) linearity, (2) homoskedasticity, (3) independence of errors, (4) normality, and (5) independence of independent variables. Descriptive statistics will be performed to describe the sociographic and clinical characteristics. The categorical variables will be reported as frequencies and percentages. Continuous variables will be tested for normality before we decide to report them as mean and SD or median and IQR. In addition, an open-source digital analysis platform (Matomo) [43] will be used to track traffic and user behavior on the app.

Qualitative Data

The qualitative data will be collected through individual interviews. All interviews will be recorded and transcribed verbatim. The transcripts will be handled systematically in NVivo (QSR International Pty Ltd) [59] to create an audit trail and facilitate transparency [60]. The observational data and interviews will be analyzed based on the 6 steps of thematic analysis outlined by Braun and Clarke [61,62]. Using inductive coding, transcripts will be interpreted, and themes will be generated. Furthermore, researcher triangulation will strengthen the credibility of the results [60].

Power

For the semistructured patient interviews, the sample size will be guided by the notion of information power, according to Malterud et al [50]. Being a feasibility study with predetermined criteria for success, a formal sample size calculation is not necessary [63]. However, sample sizes of 40-50 participants have been recommended for feasibility studies [64]. Thus, 40-50 participants will be recruited for the intervention.

Ethical Considerations

The research will be carried out following the Declaration of Helsinki [65], the General Data Protection Regulation [66], and the Human Research Ethics Committee Denmark [67]. Ethical approval has been obtained from the ethical committee of the Capital Region of Denmark (jr nr 210777457). Data are reviewed and registered in the Capital Region of Denmark (Pactius jr nr P-2022-162). All participants will be required to fill out an informed consent after verbal and written information about the study have been given. A screening logbook will be performed.

The systematic literature review is registered in PROSPERO (ID: DR42021281012). The Bone@BC app is data-reviewed and registered in the Capital Region of Denmark (jr nr 6203, local jr nr RH-2018-38, Pactius jr nr P-2020-520). The Bone@BC app has been approved for the integration of the entered app data with region security requirements and is an official Region Capital of Denmark app. The app uses MITID log-in (national electronic personal ID) and a disclaimer of responsibility. The Bone@BC app is approved by the Danish Breast Cancer Patients Society and the unified Danish eHealth Portal [68]. Licenses are obtained for included patient-reported questionnaires that require a license.

Results

The enrollment for the stage 2 medical audit of patients started in November 2022, and lasted until February 2023; a total of 23 patients have been included. The enrollment for the stage 2 semistructured patient interview is ongoing, and a total of 19 patients have now been enrolled.

The scientific findings derived from the study, regardless of being positive, negative, or inconclusive, will be documented in original manuscripts and submitted for publication in peer-reviewed international journals specializing in the relevant field (with authorship defined by the International Committee of Medical Journal Editors criteria) [69]. The results will

furthermore be disseminated at relevant scientific conferences and professional meetings as oral presentations, as well as in poster forms. The Vancouver recommendations [69] will be followed in all publications based on the study.

Discussion

Principal Findings

This study is, to our knowledge, the first to develop an ePRO platform specific to PRO for patients with postmenopausal nonmetastatic ER+ BC in maintenance therapy with AIs with an endocrinology aspect. Furthermore, to our knowledge, there are no previous studies regarding the development of an electronic app with a user-friendly PCI prompt list. The BELIEVE@BC study will contribute knowledge about how the use of an app for women with BC can be a helpful symptom management tool in their everyday lives. The BELIEVE@BC study will also contribute knowledge about whether the use of an app can be an important communication tool during consultations with HCPs. The use of ePROs offers HCPs an improved understanding of patients' symptoms during the intervals between their hospital visits.

Comparison With Previous Work

Overview

Due to improvements in diagnostics and treatments, the 5-year survival rate for patients with BC is 90% after the initial diagnosis [70]. During treatments, patients typically have consultations weekly and then gradually reduce to annual visits [71]. During this transition from hospital-based care to health self-management, the patients with BC are encouraged to exercise because of accumulating evidence for the efficacy of exercise training in cancer survivorship [6,71] and, in the majority of cases, adherence to endocrine treatments to reduce the risk of BC recurrence [9]. There is accumulating evidence that many patients with BC (and other patients with cancer) find this transition physically and mentally difficult due to reduced interaction with psychological support from HCP [5-8]. Additionally, ongoing late side effects, for example, pain, fatigue, and loss of appetite [9], and less support from surroundings, given that their surroundings consider them to be healthy [9], are important factors. The late side effects may develop months or even years afterward, and the patients with BC are therefore, in their everyday lives, troubled with being alone with their burdens. A systematic review [72] included 42 studies of self-management education for patients with cancer. Hereof, 16 studies concerning BC suggest that self-management interventions may reduce symptoms of fatigue, pain, depression, anxiety, and emotional distress and increase HRQoL [72].

By equipping patients with the necessary skills, confidence, and knowledge to self-manage their health, they gain increased autonomy and control over their well-being. This empowerment fosters healthy behaviors and encourages proactive measures to prevent long-term illnesses. In many cases, individuals are capable of managing minor illnesses on their own, leading to a decreased reliance on professional assistance. This enables HCPs to allocate their resources and attention toward providing care for patients at higher risk, particularly those with coexisting medical conditions or comorbidities. Around 1 in 5 visits to the general practitioners are made for social needs such as isolation, management, low mood, and anxiety [73]. A systematic review from 2019 [18] found that mHealth apps with interventions focusing on BC survivorship showed a positive effect. By promoting weight loss, improving HRQoL, and decreasing stress. They find that future research is needed to explore the impact of mHealth apps on patients with BC undergoing maintenance therapy [18]. The knowledge of the use of mobile apps for monitoring patients with BC during maintenance therapy is still limited.

Timeline

The study will be conducted over a duration of 3 years, encompassing well-defined stages. The planning of the study appears to be realistic and feasible within the specified timeline. Stage 4 is deemed feasible, and the deliverables are realistic given that the Bone@BC app has already been implemented in a proof-of-concept version.

Limitations

One of the limitations of this study is that the EORTC Library was chosen for selecting the ePROs in the app. Despite an overlap of primary treatment symptoms from chemotherapy and maintenance therapy with AI, more specific ePROs measurements could have been included in the app. Furthermore, it is important to note that the app primarily addresses symptoms associated with maintenance therapy. However, it may be worth considering the development of a future app that encompasses symptoms related to both primary and maintenance therapies.

Conclusions

Carefully developed with the involvement of patients and systematically validated, the Bone@BC app may have the potential to be a tool for optimal symptom management for patients with postmenopausal nonmetastatic ER+ BC in maintenance therapy. This protocol outlines the BELIEVE@BC study, which seeks to enhance the care and comprehension of the needs and symptom burden experienced by patients with postmenopausal early BC during maintenance therapy. The patient-friendly version of the Bone@BC app may help to increase patients' self-efficacy. Increased self-efficacy can lead to improved confidence and engagement in their health care decisions and actions.

Acknowledgments

This work will be supported by the Research Fund of Rigshospitalet, Copenhagen University Hospital, Denmark (grant E-23384-04); the Novo Nordisk Foundation, Denmark (grant NNF22OC0080433); and the Minister Erna Hamilton Foundation, Denmark (grant

jr. nr. 06-2019). The study is a part of the Healthy Living After Breast Cancer Research Program, the Models of Cancer Care Research Program, and the PRO-Oncology Research Program.

Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Authors' Contributions

TLJ, PS, HP, and KP were involved in conceptualization. TLJ contributed to the visualization and writing and preparing the original draft. KP, PS, HP, and GM were responsible for supervision. PS and TLJ were involved in project administration and funding acquisition. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

None declared.

References

1. Yu J, Son WS, Lee SB, Chung IY, Son BH, Ahn SH, et al. Uneven recovery patterns of compromised health-related quality of life (EQ-5D-3 L) domains for breast cancer survivors: a comparative study. Health Qual Life Outcomes 2018;16(1):143 [FREE Full text] [doi: 10.1186/s12955-018-0965-0] [Medline: 30029669]
2. Doege D, Thong MSY, Koch-Gallenkamp L, Bertram H, Eberle A, Holleczek B, et al. Health-related quality of life in long-term disease-free breast cancer survivors versus female population controls in Germany. Breast Cancer Res Treat 2019;175(2):499-510. [doi: 10.1007/s10549-019-05188-x] [Medline: 30826935]
3. Schoormans D, Czene K, Hall P, Brandberg Y. The impact of co-morbidity on health-related quality of life in breast cancer survivors and controls. Acta Oncol 2015;54(5):727-734 [FREE Full text] [doi: 10.3109/0284186X.2014.998277] [Medline: 25761088]
4. NCCN guidelines. Breast Cancer. URL: https://www.dropbox.com/s/osirlbe99jqwd93/Breast Cancer NCCN Guidelines.pdf?dl=0 [accessed 2022-08-27]
5. Lawler S, Spathonis K, Masters J, Adams J, Eakin E. Follow-up care after breast cancer treatment: experiences and perceptions of service provision and provider interactions in rural Australian women. Support Care Cancer 2011;19(12):1975-1982. [doi: 10.1007/s00520-010-1041-4] [Medline: 21080202]
6. Midtgaard J, Hammer NM, Andersen C, Larsen A, Bruun DM, Jarden M. Cancer survivors' experience of exercise-based cancer rehabilitation—a meta-synthesis of qualitative research. Acta Oncol 2015;54(5):609-617 [FREE Full text] [doi: 10.3109/0284186X.2014.995777] [Medline: 25751760]
7. Gibson F, Aslett H, Levitt G, Richardson A. Follow up after childhood cancer: a typology of young people's health care need. Clin Eff Nurs 2005;9(3-4):133-146. [doi: 10.1016/j.cein.2006.08.005]
8. Blaauwbroek R, Tuinier W, Meyboom-de Jong B, Kamps WA, Postma A. Shared care by paediatric oncologists and family doctors for long-term follow-up of adult childhood cancer survivors: a pilot study. Lancet Oncol 2008;9(3):232-238 [FREE Full text] [doi: 10.1016/S1470-2045(08)70034-2] [Medline: 18282804]
9. Hershman DL, Shao T, Kushi LH, Buono D, Tsai WY, Fehrenbacher L, et al. Early discontinuation and non-adherence to adjuvant hormonal therapy are associated with increased mortality in women with breast cancer. Breast Cancer Res Treat 2011;126(2):529-537 [FREE Full text] [doi: 10.1007/s10549-010-1132-4] [Medline: 20803066]
10. Foster C, Breckons M, Cotterell P, Barbosa D, Calman L, Corner J, et al. Cancer survivors' self-efficacy to self-manage in the year following primary treatment. J Cancer Surviv 2015;9(1):11-19 [FREE Full text] [doi: 10.1007/s11764-014-0384-0] [Medline: 25028218]
11. Bodenheimer T, Lorig K, Holman H, Grumbach K. Patient self-management of chronic disease in primary care. JAMA 2002;288(19):2469-2475. [doi: 10.1001/jama.288.19.2469] [Medline: 12435261]
12. Basch E, Deal AM, Dueck AC, Scher HI, Kris MG, Hudis C, et al. Overall survival results of a trial assessing patient-reported outcomes for symptom monitoring during routine cancer treatment. JAMA 2017;318(2):197-198 [FREE Full text] [doi: 10.1001/jama.2017.7156] [Medline: 28586821]
13. Basch E, Deal AM, Kris MG, Scher HI, Hudis CA, Sabbatini P, et al. Symptom monitoring with patient-reported outcomes during routine cancer treatment: a randomized controlled trial. J Clin Oncol 2016;34(6):557-565 [FREE Full text] [doi: 10.1200/JCO.2015.63.0830] [Medline: 26644527]
14. Moradian S, Krzyzanowska MK, Maguire R, Morita PP, Kukreti V, Avery J, et al. Usability evaluation of a mobile phone-based system for remote monitoring and management of chemotherapy-related side effects in cancer patients: mixed-methods study. JMIR Cancer 2018;4(2):e10932 [FREE Full text] [doi: 10.2196/10932] [Medline: 30578238]
15. Graetz I, McKillop CN, Stepanski E, Vidal GA, Anderson JN, Schwartzberg LS. Use of a web-based app to improve breast cancer symptom management and adherence for aromatase inhibitors: a randomized controlled feasibility trial. J Cancer Surviv 2018;12(4):431-440 [FREE Full text] [doi: 10.1007/s11764-018-0682-z] [Medline: 29492753]

16. Young-Afat DA, van Gils CH, Bruinvels DJ, van der Pol CC, Witkamp AJ, Sijtsema S, et al. Patients' and health care providers' opinions on a supportive health app during breast cancer treatment: a qualitative evaluation. JMIR Cancer 2016;2(1):e8 [FREE Full text] [doi: 10.2196/cancer.5334] [Medline: 28410170]
17. Groen WG, Kuijpers W, Oldenburg HS, Wouters MW, Aaronson NK, van Harten WH. Empowerment of cancer survivors through information technology: an integrative review. J Med Internet Res 2015;17(11):e270 [FREE Full text] [doi: 10.2196/jmir.4818] [Medline: 26614438]
18. Jongerius C, Russo S, Mazzocco K, Pravettoni G. Research-tested mobile apps for breast cancer care: systematic review. JMIR Mhealth Uhealth 2019;7(2):e10930 [FREE Full text] [doi: 10.2196/10930] [Medline: 30741644]
19. Digital Health Center of Excellence. US Food & Drug Administration. URL: https://www.fda.gov/medical-devices/digital-health-center-excellence [accessed 2023-12-05]
20. Creswell JW, Clark VLP. Designing and Conducting Mixed Methods Research. 3rd Edition. Thousand Oaks, California: Sage; 2018.
21. Creswell JW. A Concise Introduction to Mixed Methods Research. Thousand Oaks, California, United States: SAGE Publications, Inc; 2015.
22. Lancaster GA, Thabane L. Guidelines for reporting non-randomised pilot and feasibility studies. Pilot Feasibility Stud 2019;5:114 [FREE Full text] [doi: 10.1186/s40814-019-0499-1] [Medline: 31608150]
23. Manafo E, Petermann L, Mason-Lai P, Vandall-Walker V. Patient engagement in Canada: a scoping review of the 'how' and 'what' of patient engagement in health research. Health Res Policy Syst 2018;16(1):5 [FREE Full text] [doi: 10.1186/s12961-018-0282-4] [Medline: 29415734]
24. Brett J, Staniszewska S, Mockford C, Herron-Marx S, Hughes J, Tysall C, et al. Mapping the impact of patient and public involvement on health and social care research: a systematic review. Health Expect 2014;17(5):637-650 [FREE Full text] [doi: 10.1111/j.1369-7625.2012.00795.x] [Medline: 22809132]
25. Bombard Y, Baker GR, Orlando E, Fancott C, Bhatia P, Casalino S, et al. Engaging patients to improve quality of care: a systematic review. Implement Sci 2018;13(1):98 [FREE Full text] [doi: 10.1186/s13012-018-0784-z] [Medline: 30045735]
26. Definition of symptom—NCI dictionary of cancer terms—NCI. National Cancer Institute. URL: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/symptom [accessed 2023-02-08]
27. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4(1):1 [FREE Full text] [doi: 10.1186/2046-4053-4-1] [Medline: 25554246]
28. Hong QN, Pluye P, Fabregues S, Bartlett G, Boardman F, Cargo M, et al. Mixed methods appraisal tool (MMAT), version 2018 user guide. EdTech Hub. URL: https://docs.edtechhub.org/lib/VGEQX2AW [accessed 2023-12-28]
29. EORTC Item Library. URL: https://www.eortc.be/itemlibrary/ [accessed 2021-01-07]
30. Medicines. European Medicines Agency. URL: https://www.ema.europa.eu/en/medicines [accessed 2023-03-16]
31. US Food and Drug Administration. URL: https://www.fda.gov/ [accessed 2023-03-16]
32. pro.medicin.dk—information om medicin. Medicin.dk. URL: https://pro.medicin.dk/ [accessed 2023-03-16]
33. ASCO—American Society of Clinical Oncology. URL: https://www.asco.org/ [accessed 2023-03-16]
34. European society for medical oncology. ESMO—Good Science Better Medicine Best Practice. URL: https://www.esmo.org/ [accessed 2023-03-16]
35. DBCG—Danish Breast Cancer Group. URL: https://www.dbcg.dk/ [accessed 2023-03-16]
36. Endocrine Society. URL: https://www.endocrine.org/ [accessed 2023-03-16]
37. European Society of Endocrinology. URL: https://www.ese-hormones.org/ [accessed 2023-03-16]
38. Dansk Endokrinologisk Selskab. URL: https://endocrinology.dk/ [accessed 2023-03-16]
39. Item library—EORTC—quality of life? EORTC—Quality of Life. URL: https://qol.eortc.org/item-library/ [accessed 2023-03-16]
40. Kanatas A, Lowe D, Velikova G, Roe B, Horgan K, Shaw RJ, et al. Issues patients would like to discuss at their review consultation in breast cancer clinics--a cross-sectional survey. Tumori 2014;100(5):568-579. [doi: 10.1700/1660.18184] [Medline: 25343554]
41. Wild D, Grove A, Martin M, Eremenco S, McElroy S, Verjee-Lorenz A, et al. Principles of good practice for the translation and cultural adaptation process for patient-reported outcomes (PRO) measures: report of the ISPOR Task Force for translation and cultural adaptation. Value Health 2005;8(2):94-104 [FREE Full text] [doi: 10.1111/j.1524-4733.2005.04054.x] [Medline: 15804318]
42. Hvidt JCS, Christensen LF, Sibbersen C, Helweg-Jørgensen S, Hansen JP, Lichtenstein MB. Translation and validation of the system usability scale in a danish mental health setting using digital technologies in treatment interventions. Int J Hum-Comput Interact 2019;36(8):709-716. [doi: 10.1080/10447318.2019.1680922]
43. Matomo Analytics. URL: https://matomo.org/ [accessed 2022-08-04]
44. Fayers P, Bottomley A, EORTC Quality of Life Group, Quality of Life Unit. Quality of life research within the EORTC-the EORTC QLQ-C30. European Organisation for Research and Treatment of Cancer. Eur J Cancer 2002;38(Suppl 4):S125-S133. [doi: 10.1016/s0959-8049(01)00448-8] [Medline: 11858978]

45. Lorig KR, Sobel DS, Ritter PL, Laurent D, Hobbs M. Self-efficacy for managing chronic disease 6-item scale. Eff Clin Pract 2001:256-262 [FREE Full text]
46. Grimby G, Börjesson M, Jonsdottir IH, Schnohr P, Thelle DS, Saltin B. The "Saltin-Grimby Physical Activity Level Scale" and its application to health research. Scand J Med Sci Sports 2015;25(Suppl 4):119-125 [FREE Full text] [doi: 10.1111/sms.12611] [Medline: 26589125]
47. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand 1983;67(6):361-370. [doi: 10.1111/j.1600-0447.1983.tb09716.x] [Medline: 6880820]
48. Osborne RH, Elsworth GR, Whitfield K. The Health Education Impact Questionnaire (heiQ): an outcomes and evaluation measure for patient education and self-management interventions for people with chronic conditions. Patient Educ Couns 2007;66(2):192-201. [doi: 10.1016/j.pec.2006.12.002] [Medline: 17320338]
49. Polit DF, Beck CT. Sampling in qualitative research. In: Nursing Research: Generating and Assessing Evidence for Nursing Practice. Philadelphia: Wolters Kluwer; 2021:497-509.
50. Malterud K, Siersma VD, Guassora AD. Sample size in qualitative interview studies: guided by information power. Qual Health Res 2016;26(13):1753-1760. [doi: 10.1177/1049732315617444] [Medline: 26613970]
51. Bowen DJ, Kreuter M, Spring B, Cofta-Woerpel L, Linnan L, Weiner D, et al. How we design feasibility studies. Am J Prev Med 2009;36(5):452-457 [FREE Full text] [doi: 10.1016/j.amepre.2009.02.002] [Medline: 19362699]
52. Cocks K, Wells JR, Johnson C, Schmidt H, Koller M, Oerlemans S, et al. Content validity of the EORTC Quality of Life Questionnaire QLQ-C30 for use in cancer. Eur J Cancer 2023;178:128-138 [FREE Full text] [doi: 10.1016/j.ejca.2022.10.026] [Medline: 36436330]
53. Ritter PL, Lorig K. The English and Spanish self-efficacy to manage chronic disease scale measures were validated using multiple studies. J Clin Epidemiol 2014;67(11):1265-1273. [doi: 10.1016/j.jclinepi.2014.06.009] [Medline: 25091546]
54. Flosadottir V, Roos EM, Ageberg E. Translation, cross-cultural adaptation, and validation of the Activity Rating Scale for disorders of the knee. Orthop J Sports Med 2017;5(9):2325967117729361 [FREE Full text] [doi: 10.1177/2325967117729361] [Medline: 28979920]
55. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. an updated literature review. J Psychosom Res 2002;52(2):69-77. [doi: 10.1016/s0022-3999(01)00296-3] [Medline: 11832252]
56. Maunsell E, Lauzier S, Brunet J, Pelletier S, Osborne RH, Campbell HS. Health-related empowerment in cancer: validity of scales from the Health Education Impact Questionnaire. Cancer 2014;120(20):3228-3236 [FREE Full text] [doi: 10.1002/cncr.28847] [Medline: 24988944]
57. Curry J, Patterson M, Greenley S, Pearson M, Forbes CC. Feasibility, acceptability, and efficacy of online supportive care for individuals living with and beyond lung cancer: a systematic review. Support Care Cancer 2021;29(11):6995-7011 [FREE Full text] [doi: 10.1007/s00520-021-06274-x] [Medline: 34008080]
58. R: The R Project for Statistical Computing. URL: https://www.r-project.org/ [accessed 2023-01-29]
59. Lumivero. URL: https://lumivero.com/ [accessed 2023-03-16]
60. Shenton AK. Strategies for ensuring trustworthiness in qualitative research projects. Educ Inf 2004;22(2):63-75. [doi: 10.3233/efi-2004-22201]
61. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol 2006;3(2):77-101. [doi: 10.1191/1478088706qp063oa]
62. Braun V, Clarke V. Reflecting on reflexive thematic analysis. Qual Res Sport Exerc Health 2019;11(4):589-597. [doi: 10.1080/2159676x.2019.1628806]
63. Thabane L, Lancaster G. A guide to the reporting of protocols of pilot and feasibility trials. Pilot Feasibility Stud 2019;5:37 [FREE Full text] [doi: 10.1186/s40814-019-0423-8] [Medline: 30858987]
64. Justify sample size for a feasibility study. RDS London. URL: https://www.rds-london.nihr.ac.uk/resources/justify-sample-size-for-a-feasibility-study/ [accessed 2023-03-14]
65. World Medical Association. World Medical Association declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013;310(20):2191-2194 [FREE Full text] [doi: 10.1001/jama.2013.281053] [Medline: 24141714]
66. Regulation (EU) 2016/679 of the European Parliament and of the council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing directive 95/46/EC. Official Journal of the European Union. 2016. URL: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32016R0679 [accessed 2023-12-28]
67. National Committee on Health Research Ethics. URL: https://en.nvk.dk/ [accessed 2022-03-29]
68. sundhed.dk. URL: https://www.sundhed.dk/ [accessed 2024-01-08]
69. Defining the role of authors and contributors. ICMJE. URL: https://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html [accessed 2023-03-16]
70. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global Cancer Statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68(6):394-424 [FREE Full text] [doi: 10.3322/caac.21492] [Medline: 30207593]

71. Khatcheressian JL, Wolff AC, Smith TJ, Grunfeld E, Muss HB, Vogel VG, et al. American Society of Clinical Oncology 2006 update of the breast cancer follow-up and management guidelines in the adjuvant setting. J Clin Oncol 2006;24(31):5091-5097 [FREE Full text] [doi: 10.1200/JCO.2006.08.8575] [Medline: 17033037]
72. Howell D, Harth T, Brown J, Bennett C, Boyko S. Self-management education interventions for patients with cancer: a systematic review. Support Care Cancer 2017;25(4):1323-1355. [doi: 10.1007/s00520-016-3500-z] [Medline: 28058570]
73. Integrated care in action—self-care and prevention. NHS England. URL: https://www.england.nhs.uk/publication/integrated-care-in-action-self-care-and-prevention/ [accessed 2021-05-20]

Abbreviations

AI: aromatase inhibitor
BC: breast cancer
CONSORT: Consolidated Standards of Reporting Trials
EORTC: European Organization for Research and Treatment of Cancer
EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life C30
ePRO: electronic patient-reported outcome
ER+: estrogen receptor–positive
HADS: Hospital Anxiety and Depression Scale
HCP: health care professional
heiQ: Health Education Impact Questionnaire
HRQoL: health-related quality of life
mHealth: mobile health
MVP: minimum variable product
PCI: Patient Concerns Inventory list
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis for Protocols
PRO: patient-reported outcome
SES6G: Self-Efficacy for Managing Chronic Disease 6-Item Scale
SGPALS: Saltin-Grimby Physical Activity Level Scale
SUS-DK: System Usability Scale–Danish version

Edited by A Mavragani; submitted 01.06.23; peer-reviewed by R Knoerl, Y Yang; comments to author 04.12.23; revised version received 06.12.23; accepted 11.12.23; published 15.02.24.

Please cite as:
Lund-Jacobsen T, Schwarz P, Martino G, Pappot H, Piil K
Development of an App for Symptom Management in Women With Breast Cancer Receiving Maintenance Aromatase Inhibitors: Protocol for a Mixed Methods Feasibility Study
JMIR Res Protoc 2024;13:e49549
URL: https://www.researchprotocols.org/2024/1/e49549
doi:10.2196/49549
PMID:38358787

Protocol

A Virtual Hospital Model of Care for Low Back Pain, Back@Home: Protocol for a Hybrid Effectiveness-Implementation Type-I Study

Alla Melman[1*], BAppSci, MSc; Min Jiat Teng[1,2*], BAppSci, MHSM; Danielle M Coombs[1*], BAppSci, PhD; Qiang Li[3*], MSc; Laurent Billot[3*], MSc, MRes; Thomas Lung[3,4*], MSc, PhD; Eileen Rogan[5*], MBBS, MHSM, PhD; Mona Marabani[5*], MBBS; Owen Hutchings[2*], MBBS; Chris G Maher[1*], BAppSci, DMedSc, PhD; Gustavo C Machado[1*], BPhty, PhD

[1]Sydney Musculoskeletal Health, The University of Sydney and Sydney Local Health District, Camperdown, Australia

[2]RPA Virtual Hospital, Sydney Local Health District, Sydney, Australia

[3]The George Institute for Global Health, University of New South Wales, Sydney, Australia

[4]School of Public Health, Faculty of Medicine and Health, The University of Sydney, Sydney, Australia

[5]Department of Medicine, Canterbury Hospital, Sydney Local Health District, Sydney, Australia

[*]all authors contributed equally

Corresponding Author:
Alla Melman, BAppSci, MSc
Sydney Musculoskeletal Health
The University of Sydney and Sydney Local Health District
Level 10N, King George V Building, Royal Prince Alfred Hospital
Missenden Road
Camperdown, 2050
Australia
Phone: 61 286276263
Email: alla.melman@sydney.edu.au

Abstract

Background: Low back pain (LBP) was the fifth most common reason for an emergency department (ED) visit in 2020-2021 in Australia, with >145,000 presentations. A total of one-third of these patients were subsequently admitted to the hospital. The admitted patient care accounts for half of the total health care expenditure on LBP in Australia.

Objective: The primary aim of the Back@Home study is to assess the effectiveness of a virtual hospital model of care to reduce the length of admission in people presenting to ED with musculoskeletal LBP. A secondary aim is to evaluate the acceptability and feasibility of the virtual hospital and our implementation strategy. We will also investigate rates of traditional hospital admission from the ED, representations and readmissions to the traditional hospital, demonstrate noninferiority of patient-reported outcomes, and assess cost-effectiveness of the new model.

Methods: This is a hybrid effectiveness-implementation type-I study. To evaluate effectiveness, we plan to conduct an interrupted time-series study at 3 metropolitan hospitals in Sydney, New South Wales, Australia. Eligible patients will include those aged 16 years or older with a primary diagnosis of musculoskeletal LBP presenting to the ED. The implementation strategy includes clinician education using multimedia resources, staff champions, and an "audit and feedback" process. The implementation of "Back@Home" will be evaluated over 12 months and compared to a 48-month preimplementation period using monthly time-series trends in the average length of hospital stay as the primary outcome. We will construct a plot of the observed and expected lines of trend based on the preimplementation period. Linear segmented regression will identify changes in the level and slope of fitted lines, indicating immediate effects of the intervention, as well as effects over time. The data will be fully anonymized, with informed consent collected for patient-reported outcomes.

Results: As of December 6, 2023, a total of 108 patients have been cared for through Back@Home. A total of 6 patients have completed semistructured interviews regarding their experience of virtual hospital care for nonserious back pain. All outcomes will be evaluated at 6 months (August 2023) and 12 months post implementation (February 2024).

Conclusions: This study will serve to inform ongoing care delivery and implementation strategies of a novel model of care. If found to be effective, it may be adopted by other health districts, adapting the model to their unique local contexts.

International Registered Report Identifier (IRRID): PRR1-10.2196/50146

(JMIR Res Protoc 2024;13:e50146) doi:10.2196/50146

KEYWORDS

length of stay; back pain; musculoskeletal pain; telemedicine; hospital-based home care; mobile phone; home care; virtual care; remote care; virtual hospital; pain; telehealth; eHealth; musculoskeletal; implementation; model of care; back; cost; economic; readmission; hospital stay

Introduction

Background

Low back pain (LBP) was the fifth most common reason for an emergency department (ED) visit in 2020-2021 in Australia, with more than 145,000 presentations [1]. One-third of these patients were subsequently admitted to hospital. The current annual admission rates for spinal conditions are high in Australia, at 465 per 100,000 population, compared to 219 in the United Kingdom, 197 in the Netherlands, and 142 in Canada [2]. Admission rates following LBP presentations to ED are higher in Australia [3,4] than have been reported in the United States [5]. The potential contributors to high admission rates are differences in case mix [6], patient expectations of hospital admission when experiencing high levels of distress [7], and lack of alternative pathways for prompt pain management. These hospitalizations pose a significant burden on the health care system. In Australia, for example, admitted patient care of LBP lasts an average of 9 days and costs Aus $15,000 (US $10,000) per admission [8].

Most patients admitted to the hospital with a primary LBP diagnosis do not have a serious underlying condition and there is evidence that admissions carry the risk of harm. Our recent medical record review of 1982 admissions found that 57% of inpatients with provisionally diagnosed musculoskeletal LBP in ED were discharged with this same diagnosis [9]. Bed rest, as typically occurs with traditional hospital admission, is not recommended in LBP guidelines [10] as it can delay recovery. A recent study showed that 23% of LBP admissions had opioid-related complications and other serious events such as falls in hospital (4%) and hospital-acquired infections (1.4%) [11]. These patients could be diverted to more cost-effective and safer alternate clinical pathways.

Virtual hospitals have been proposed as a potential clinical pathway for people with LBP [12], to facilitate early discharge. Interviews with people admitted for acute LBP have identified that returning home as soon as possible is a key patient priority; however, patients fear a lack of support if discharged home [13]. There is also evidence from other conditions that virtual hospitals are cost-effective. Systematic reviews of “early supported discharge” have been shown to safely reduce the length of the hospital stay in adults with a range of medical conditions [14]. A recent US trial of virtual hospital admission for mixed acute medical conditions showed 38% lower costs for virtual hospital patients compared to traditional admissions, and reduced use of laboratory tests, imaging, and consultations [15]. The virtual hospital cohort had higher levels of patient satisfaction and lower rates of adverse events [15].

We currently lack alternatives to traditional hospital admission for patients with musculoskeletal LBP who present to Australian EDs and require acute clinical care. A virtual hospital has been implemented in Sydney Local Health District, Australia for COVID-19–positive patients and other patient cohorts [16], caring for over 16,000 patients to date [17]. In the virtual hospital, clinicians use technologies for remote patient monitoring and management [12]. Monitoring via daily clinician contact is designed to reduce representation to the ED while providing clinical support and pain management until the patient is able to link in with and attend outpatient services. Given the higher rates of potentially serious pathology in this cohort (compared to primary care), it is also a form of safety netting, allowing prompt escalation if required. Physical activity monitoring is designed to substitute regular reminders to mobilize as would be delivered on a traditional ward and encourage patients to slowly upgrade physical activity. A virtual hospital service, however, is yet to be formally evaluated in patients with musculoskeletal LBP.

Alongside the diagnostic challenge of LBP, is the difficulty of discharging patients home when safe mobility is not yet achieved. Some patients may still require short-term traditional hospital admission to allow for effective analgesia to facilitate mobility. Hence, in this study, we will evaluate the effectiveness of an early-supported discharge virtual hospital model of care, with traditional hospital length of stay as the primary outcome.

Aims

The main aims of the Back@Home study are to assess the effectiveness of a virtual hospital model of care for LBP on health service outcomes (eg, length of admission), patient-reported outcomes (eg, satisfaction with care), and costs. The secondary aims are to evaluate the acceptability and appropriateness of the virtual hospital model of care for LBP, as well as the feasibility and fidelity of our multifaceted implementation strategy.

Methods

Study Design

This is a hybrid effectiveness-implementation type-I study [18]. This study design will allow us to assess the effectiveness of a new virtual hospital model of care for LBP on health services outcomes while assessing the feasibility and acceptability of the new model and our multifaceted implementation strategy, as described by Curran et al [18]. We have used the guidance for conducting implementation trials by Pearson et al [19] and Proctor et al [20] to design this study.

Setting

This study will be conducted at 3 public hospitals in Sydney, New South Wales, Australia. The hospitals have a combined 169,000 ED attendances per year, with 650,000 total “bed days” available annually, averaging 1530 inpatients per day [21].

Population

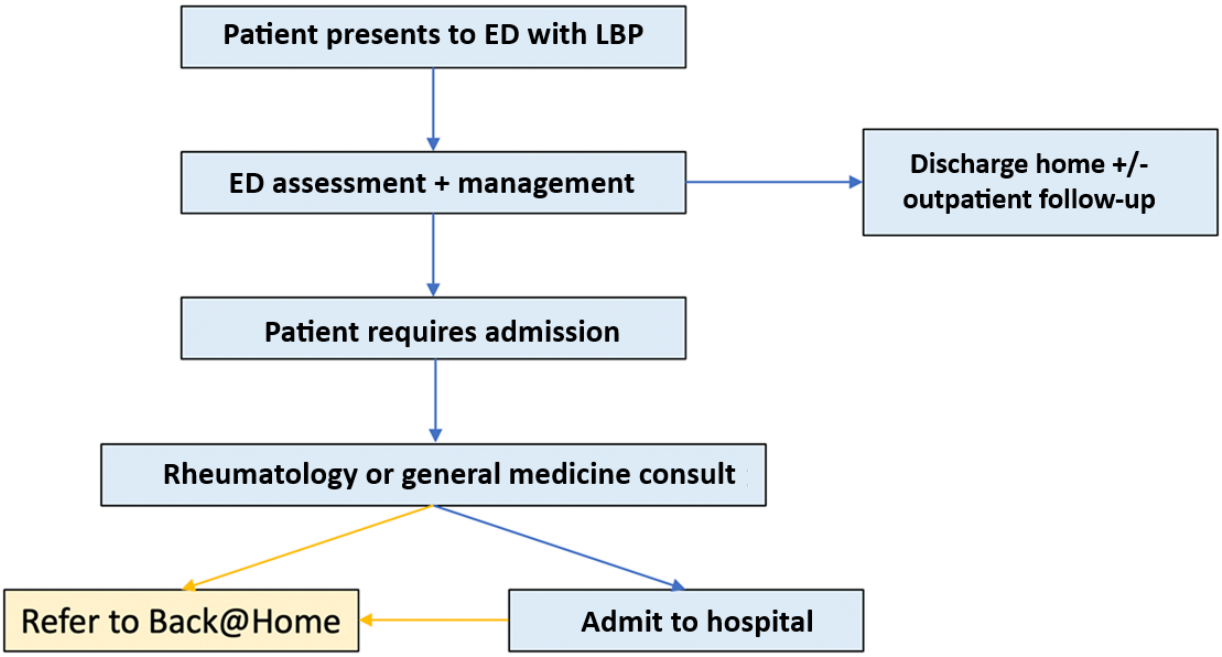
To identify the study population, Systematized Nomenclature of Medicine Clinical Terms-Australian (SNOMED-CT-AU) diagnosis codes will be used to select patients in the ED aged 16 years and older with a primary discharge diagnosis related to musculoskeletal LBP. Those with an ED diagnosis code of a "serious" LBP condition (eg, vertebral fracture, spinal abscess, and cauda equina syndrome) will be excluded. We will then use inpatient discharge diagnosis codes (*International Classification of Diseases, Tenth Revision, Australian Modification* [*ICD-10 AM*]) to classify the LBP admissions as "serious" or "musculoskeletal" (ie, nonspecific LBP and lumbosacral radicular pain). Only data from admissions where inpatient discharge diagnosis codes are musculoskeletal LBP admissions will be evaluated.

Patients who presented to the ED with a primary diagnosis related to musculoskeletal LBP and were discharged without admission into a short stay or inpatient unit will be included in the data analysis to determine rates of hospital admission.

Intervention

Patients with LBP requiring admission in ED short stay or inpatient units will be assessed by senior ED staff. Eligible patients will be referred to the "Back@Home" virtual LBP service by the ED medical officer, in consultation with local rheumatology or general medicine admitting teams. The eligibility criteria for the virtual hospital are people aged 16 years and older diagnosed with musculoskeletal LBP, with or without radicular pain, requiring a higher level of clinical support above standard discharge home (see Figure 1).

Figure 1. Virtual low back pain service workflows. ED: Emergency Department; LBP: low back pain.



Back@Home, a service run by Royal Prince Alfred Hospital (RPA) Virtual Hospital, will provide virtual "Hospital in the Home" care, including home visits, video calls, and remote monitoring. Eligible patients already admitted to the inpatient ward will also be referred to "Back@Home" to facilitate earlier discharge. Patients will be remotely monitored from home, and have 24/7 access to hospital-based clinicians through a "virtual" care center. An escalation pathway will be available if a patient's condition deteriorates at home, and traditional admission, expedited imaging, or intervention is deemed necessary.

Medical care will be provided by virtual hospital physicians and nurses, with consultations from rheumatology specialists provided as required. All patients will be virtually assessed and treated by a physiotherapist, with additional assessments provided by occupational therapists, psychologists, and social workers as required.

Videoconferencing calls will be used to collect clinical observations and provide care. If required, patients will receive home visits from a physiotherapist [17]. The need for home visits will be decided by the multidisciplinary team (physician, nurse, and physiotherapist) during daily clinical reviews, in response to patient needs. If a patient appears to not be coping well at home and is at risk of ED representation, a home visit will be scheduled.

Remote monitoring of physical activity, such as step count, will be enabled via an activity tracker. The wearable device used (Garmin Vivovit 4) is a validated method of recording sleep cycles and sedentary and active time in community settings [22,23]. Patients will be able to report activity measures to their virtual physiotherapist during daily video calls, assisting in goal setting and behavioral health coaching.

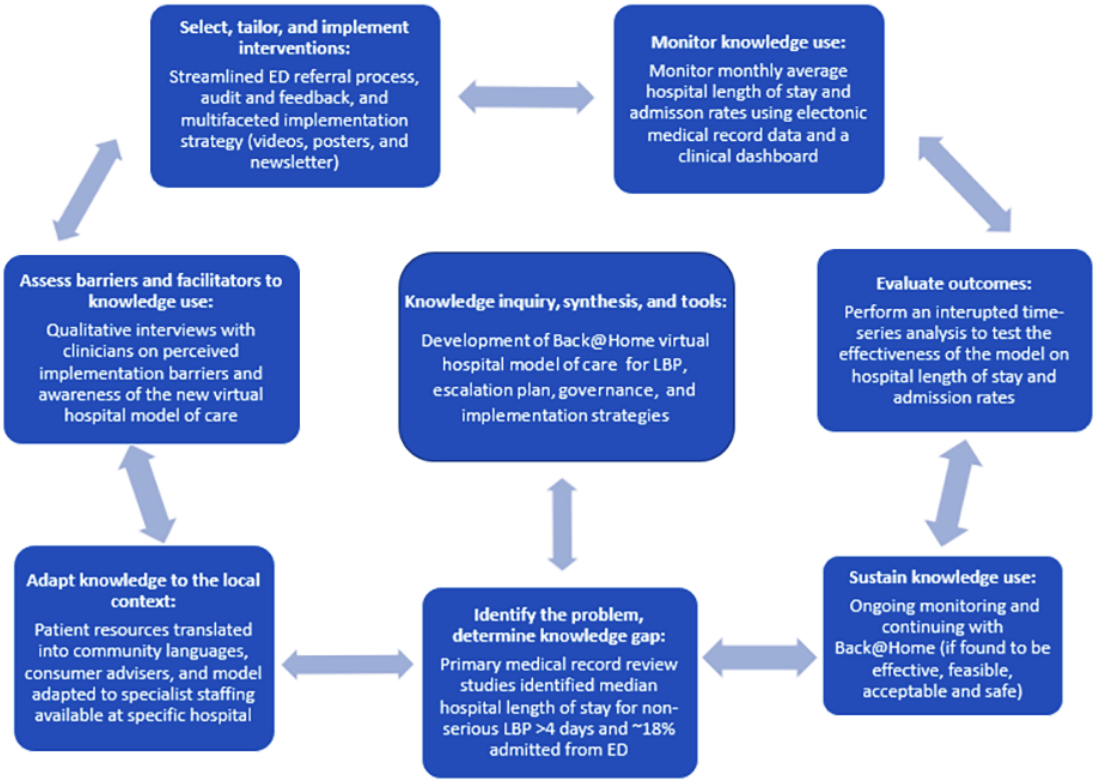
Care will be provided through a variety of technologies as appropriate. SMS, telephone calls, videoconferencing calls (Zoom; Zoom Video Communications), patient information sheets emailed directly to patients, as well as access to the "Physitrack" smartphone app for the provision of health information content and exercise programs.

Traditionally admitted patients will receive usual clinical care, with a referral for physiotherapy mobility assessment if required, as per standard ward protocols. They will be eligible for referral to Back@Home to facilitate early supported discharge, if appropriate.

Implementation Strategy

The implementation strategy will last for 3 months at each site. The "Knowledge to Action Framework" [24] (see Figure 2) was used to guide a research program to develop and evaluate the implementation of Back@Home. The framework structure includes identifying a clinical problem, and then developing evidence-based potential solutions while adapting these to the local context, evaluating the solution, and monitoring outcomes.

Figure 2. Knowledge to action framework. ED: Emergency Department; LBP: low back pain.



Semistructured interviews with hospital clinicians regarding perceived barriers and facilitators to implementation have informed the current design of the model of care [7]. Based on clinicians' input, the Back@Home model of care will incorporate the loan of internet-enabled devices, health care interpreters, and written resources translated into community languages to facilitate more equitable access to care for marginalized groups. Feedback was provided by the Director of Aboriginal Health and the Aboriginal Cultural Support Team. Consultation on the model was also provided by ED medical officers, rheumatology, general medicine, and allied health departments, as well as nurse practitioners and social workers.

We will explore additional local barriers to implementation, design, and implement strategies to address these barriers, and monitor clinical practice and clinician behavior change. The evaluation will determine the effectiveness of the model of care, and if found effective, we will develop strategies to maintain health care system changes (see Figure 1).

To increase the uptake of the Back@Home model of care, we plan to use several implementation strategies that have been previously shown to be effective in changing professional behavior. First, staff training will be delivered by Back@Home investigators (MJT, ER, MM, and OH) at scheduled staff education sessions attended by physiotherapists, nurses, registrars, trainees, and consultants in ED and general medicine. Sessions will last 15 minutes and be delivered before implementation and at 1 and 3 months post implementation. Training will describe the process of referral to virtual care, deliver updates on implementation progress, and provide a forum to raise concerns or questions. Second, key local opinion leaders [25], in the form of "staff champions" will be provided with training. These staff will remind all clinical staff about Back@Home as an option for patients with musculoskeletal LBP requiring admission and will be identified by wearing a badge with the Back@Home logo. The ED primary care physiotherapist will play a key role in championing the Back@Home model of care. Third, a summary card containing admission criteria and contact details for the virtual hospital will be provided to relevant staff, which can be attached to staff lanyards for easy access (if permitted). This printed material will be used to reinforce the content of educational sessions [26,27]. Fourth, a monthly email update will be sent to ED, general medicine, and rheumatology staff regarding the length of hospital stay and rates of admission to traditional hospitals. Audit and feedback strategies have been shown to be effective in influencing health professionals' behavior [28], and in

supporting back pain model of care implementation strategies [29].

Evaluation

Health Service Outcomes

The health service outcomes include (1) monthly mean length of hospital stay (ED short stay units and inpatient units) in those admitted as a traditional inpatient following an ED presentation for musculoskeletal LBP (primary outcome; Table 1); (2) monthly proportion of ED musculoskeletal LBP presentations that result in traditional hospital admissions (ED short stay or inpatient units); (3) monthly proportion of admitted patients representing to traditional hospital, including representations to the ED within 48 hours since discharge and readmissions to an inpatient unit within 28 days; and (4) mean and total hospital health care costs per month, for patients admitted to traditional and virtual hospitals.

Table 1. Evaluation plan.

Outcome dimension	Outcome	Outcome definition	Data source	Data collection and analysis period
Service	(1) Length of hospital stay; (2) inpatient admission; (3) rerepresentations; and (4) readmissions to inpatient units	(1) Monthly mean length of hospital stay (ED[a] short stay units and inpatient units) in those admitted as traditional inpatients following an ED presentation for musculoskeletal LBP[b]; (2) monthly proportion of ED musculoskeletal LBP presentations that result in traditional hospital admissions (ED short stay or inpatient units); (3) monthly proportion of admitted patients representing to a traditional hospital, including representations to the ED within 48 hours since discharge; and (4) monthly proportion of admitted patients who are readmissions to an inpatient unit within 28 days.	1-4: eMR[c]	Baseline: 2016 January to 2023 February; T1[d]: 2023 August; T2[e]: 2024 February
Implementation	(1) Acceptability; (2) appropriateness; (3) feasibility; and (4) fidelity	(1-3) acceptability, appropriateness, and feasibility of the Back@Home "Model of Care" and implementation strategies (posters, staff training, videos, and newsletter); and (4) fidelity of the delivery of implementation strategies as planned.	(1-3) Semistructured interviews with clinicians and patients; (4) logbook of implementation delivery	T1: 2023 August
Patient	(1) Pain intensity; (2) physical function; (3) satisfaction with care; and (4) adverse events	(1) Numeric rating pain scale (0-10); (2) PROMIS[f] Physical Function-6a; (3) global satisfaction with care for traditional and virtual admissions (0-10 points) and patient-reported experience measures as routinely collected by the virtual hospital (26-item survey); and (4) proportion of patients experiencing any AE[g]; frequency of AEs for virtual admissions	(1-3) Patient survey; (4) eMR	Collected at 2 and 4 weeks post ED presentation or during admission (adverse events), analyzed at T1 and T2
Process	(1) Diagnostic tests ordered; (2) pain medicines used; (3) video and phone calls; (4) home visits received; (5) Physitrack app use; and (6) Physitrack and activity tracker usefulness	(1) Proportion of virtually admitted patients receiving diagnostic tests; (2) proportion of virtually admitted patients prescribed specific medicines; (3) number and frequency of video consultations with virtual hospital clinical staff; (4) number and frequency of clinician home visits; (5) usage rates of the Physitrack app by patients (log-ins, viewing, and marked completion of exercise program); and (6) patient-reported experience measures questions 7 and 9 (5-point scale).	(1-4) eMR; (5) Physitrack app; and (6) Patient-Reported Experience Measure survey	Collected during virtual admission, analyzed at T1 and T2
Health economic	Hospital admission costs	Cost of delivering virtual care compared to inpatient care for nonserious low back pain.	eMR and finance reporting systems	Collected during admission and analyzed at T1 and T2

[a]ED: Emergency Department.

[b]LBP: low back pain.

[c]eMR: electronic medical record.

[d]T1: 6 months post implementation.

[e]T2: 12 months post implementation.

[f]PROMIS: Patient-Reported Outcomes Measurement Information System.

[g]AE: adverse event.

Implementation Outcomes

Implementation outcomes discussed in clinician and patient interviews will include (1) acceptability, appropriateness, and feasibility of the model of care to clinicians and the health service evaluated at 6 months using semistructured interviews [30] and (2) fidelity to planned implementation at 6 months using a logbook of implementation.

Patient-Reported Outcomes

Patient-reported outcomes will be collected at 2 and 4 weeks following hospital admission from patients admitted to traditional and virtual hospitals. Outcomes include average pain intensity in the past week (Numeric Rating Scale, range 0-10), Patient-Reported Outcomes Measurement Information System (PROMIS) Short Form—Physical Function 6b (range 6-30), and global rating of satisfaction with care (range 0-10).

Process Measures (Virtual Hospital Admissions Only)

First, the proportion of virtually admitted patients receiving diagnostic tests, by type: laboratory tests; lumbar imaging tests: plain radiography (x-ray), computerized tomography scan, magnetic resonance imaging; and per month.

Second, the proportion of virtually admitted patients prescribed specific medicines, per month. Pain medicines will be classified according to the Anatomical Therapeutic Chemical (ATC) classification systems. The drug dosage regimens will also be collected for the following groups of medicines: simple analgesics (ie, paracetamol); nonsteroidal anti-inflammatory drugs; weak opioids (eg, tramadol and codeine); strong opioids (eg, oxycodone and morphine); muscle relaxants; benzodiazepines; antiepileptics; antidepressants; and corticosteroids.

Third, the usage rates of the Physitrack app by patients (log-ins, viewing, and marked completion of exercise program). Fourth, the number and frequency of video consultations with virtual hospital clinical staff. Fifth, the number and frequency of face-to-face consultations (home visits) with staff. Sixth, the number and frequency of escalations of care (patient transferred to hospital), and adverse events. Seventh, the patient-reported experience measures as routinely collected by the virtual hospital, with additional questions relevant to Back@Home patients (26-item survey).

Data Collection

Health Service Outcomes

We will extract primary and secondary health care use data from electronic medical records. Data extracted will include patient demographics (eg, age, gender, and postcode), ED presentation and inpatient admission or discharge date, length of ED and admission stay, discharge primary and secondary Systematized Nomenclature of Medicine (SNOMED)/*ICD-10* codes, diagnostic tests used (eg, laboratory tests and imaging), pain medicines received, specialist and allied health consultations, and health care costs. Hospital-acquired complications or adverse events will be identified via Classification of Hospital Acquired Diagnoses (CHADx) codes present in *ICD-10 AM* data [30]. Patient medical record number, encounter or visit identifier will be replaced by study ID as part of the data extraction process, resulting in deidentified data.

Implementation Outcomes

Semistructured interviews will be conducted with key clinical staff and hospital managers at the implementation site, as well as those involved in delivering virtual care. Purposeful sampling will aim for input from physiotherapists, nurses, ED medical officers, and rheumatologists. Patients who have experienced Back@Home virtual care will also be asked to participate (approved by Sydney Local Health District X21-0094 and 2021/ETH00591).

The fidelity of training-related implementation delivery will be assessed via a logbook of staff training, noting the number of sessions delivered, session delivery mode, and number of attendees.

Patient-Reported Outcomes

Patients with musculoskeletal LBP as the primary reason for admission (to traditional or virtual hospitals) will be eligible to complete the patient-reported outcome survey. Before implementation, we will use electronic medical records to identify a cohort that would have likely been eligible for virtual admission if it were available. This will include traditionally admitted patients with a Waterlow Mobility Score of 0-3 (not bed-bound) on admission, with a diagnosis of musculoskeletal LBP. All virtually admitted patients with LBP will be eligible. Automated text message invitations will be sent to eligible patients (via REDCap [Research Electronic Data Capture; Vanderbilt University] and Twilio) containing a link to an web-based survey, at 2 and 4 weeks following the ED presentation. One reminder message will be sent to nonresponders, and patients who do not respond to the text message will be followed up with a telephone call and offered the opportunity to ask any questions regarding participation or complete the survey by telephone. This process will be used to maximize the response rate of the surveys and has been proven to be feasible [31].

Statistical Analysis Plan

Health Service Outcomes

Time-series trends during a retrospective 48-month period before the implementation of the new model of care will be compared with trends during a 12-month postimplementation period. Preliminary analysis will be conducted at 6 months post implementation. We will display the length of admissions as monthly averages and construct a plot of the observed and expected lines of the trend based on the preimplementation period. Linear segmented regression will identify changes in the level and slope of fitted lines. The standard interrupted time series model that will be used is

In this equation, Y_t is the outcome variable (eg, length of admission) measured at each equally spaced time point t (monthly). β_0 represents the intercept or starting level of the outcome variable and β_1, the slope or trajectory of the outcome variable until the introduction of the intervention. T_t represents the month of the initial ED presentation with T_0 representing the first month (2017 January). β_2 represents the change in the level of the outcome that occurs in the period immediately following the introduction of the intervention (compared with what would have happened in the absence of the intervention). β_3 represents the difference between preintervention and postintervention slopes of the outcome. Thus, we look for

significant differences in β_2 to indicate an immediate treatment effect, and in β_3 to indicate a treatment effect over time.

Data will be analyzed using SAS software (version 9.4; SAS Institute). Descriptive statistics will be used for patient demographics and clinical characteristics. Categorical variables will be described with frequencies (%) and continuous variables will be described with means and SDs.

To account for fluctuations in preimplementation hospital admissions due to COVID-19 pandemic–related restrictions, a time series analysis will account for these time periods. Restricted periods will be considered as February 1 to June 30, 2020; June 1 to December 1, 2021; and January 1 to May 1, 2022.

Patient-Reported Outcomes

Patient-reported secondary outcomes will include pain, physical function, and satisfaction with care at 2 and 4 weeks following admission. Group sample sizes of 100 eligible patients admitted to traditional hospital wards and 100 patients admitted to RPA Virtual Hospital, will be required to achieve 80% power to detect a noninferiority 1-point difference in patient-reported outcomes for satisfaction with care (0-10 continuous scale) between groups using a 1-sided, 2-sample equal-variance *t* test. The margin of noninferiority will be –1. The actual difference between the means will be assumed to be 0. The significance level (α) of the test will be set at .025. The data will be drawn from populations with an SD of 2.5 in both groups.

Ethical Considerations

This investigation will be conducted in full compliance with the Declaration of Helsinki. Ethics approval has been granted by the Ethics Review Committee of Royal Prince Alfred Hospital (protocol X21-0278 and 2021/ETH10967). A waiver of consent has been approved for routinely collected data sourced from electronic medical records. Study data will be fully deidentified, to protect patient, clinician privacy, and confidentiality. Informed consent will be collected for all patient-reported outcomes. No compensation will be offered for participation.

Patient and Public Involvement

The virtual hospital model of care was developed with the assistance of semistructured interviews with clinicians from several disciplines across 3 metropolitan hospitals. Clinicians from the departments of physiotherapy, rheumatology, and emergency medicine participated in a co-design process with researchers and administrators at RPA Virtual Hospital at Sydney Local Health District.

Economic Evaluation Plan

An economic evaluation will be undertaken from the health system perspective. Costs associated with implementing Back@Home virtual care and patients' health service use will be measured, using a combination of electronic medical records and financial trial records. Intervention-related costs include the development of training materials and salaried time of staff attending training workshops, changes in workload for staff delivering virtual care and costs related to information technology support and maintenance of the virtual network. Health service costs will be measured using Independent Health and Aged Care Pricing Authority national weighted activity units for admitted inpatient hospital and ED presentations; prescription and over-the-counter medications using the Pharmaceutical Benefits Scheme and pharmacy prices. All costs will be reported in Australian dollars. Where necessary, costs will be converted to 2023 prices using the health consumer price index published by the Australian Bureau of Statistics. Costs and effects will be discounted where appropriate.

We plan to conduct a cost-effectiveness analysis alongside this time series analysis with data from the intervention site. Similar to the time series model for health service outcomes, a generalized linear model with a gamma distribution and logarithmic link function will be used for the segmented regression analysis of health care costs. An incremental cost-effectiveness ratio will be calculated for the health services outcomes: length of stay and hospital admissions. This will be presented as incremental costs per bed day avoided and incremental cost per hospital admission avoided. Nonparametric bootstrapping with 5000 replications will be used to estimate the 95% CIs around the incremental cost and effect pairs for both health services outcomes. These will be presented on an incremental cost-effectiveness plane. We also plan to explore the cost-effectiveness using the patient outcomes from this study. If the patient outcomes analysis shows noninferiority as hypothesized, we will perform a cost-minimization analysis by comparing the cost between the control and intervention phases.

Results

We will collect data from January 1, 2017, to September 30, 2024, and a 60-month period within this time frame will be used in the analysis, determined by the implementation schedule for the new model of care. Back@Home participant data will be collected from February 2023, following roll out of the service. For primary and secondary health service outcomes, we expect to collect data from approximately 12,500 patients with musculoskeletal LBP attending the 3 study EDs over a 5-year period, via the electronic medical record system. Interim process evaluation and implementation outcomes are expected to be published in early 2024, and the final study results are expected to be published in 2025. As of December 6, 2023, a total of 108 patients have been cared for through Back@Home. A total of 6 patients have completed semistructured interviews regarding their experience of virtual hospital care for nonserious back pain. All outcomes will be evaluated at 6 months (2023 August) and 12 months post implementation (2024 February).

Discussion

This study will investigate the implementation of a novel model of care for nonserious back pain, delivered through a virtual hospital. Process evaluation will be used to inform further iterations of the service, guided by the Knowledge To Action framework [24]. We anticipate that the feasibility of implementing Back@Home will be demonstrated, along with the acceptability of the model of care to clinicians and patients and cost-effectiveness. Additionally, we hypothesize that

patient-reported outcomes (pain and satisfaction with care) will be noninferior to traditional hospital admission. Interpretation of the patient-reported outcomes may be limited by response rate and strategies have been planned to optimize the response rate.

The interrupted time-series design has been commonly used to evaluate the impact of new patient pathways on admission rates, length of stay, and ED representation [32-34] for a variety of health conditions. We hypothesize that following the introduction of Back@Home, hospital length of stay, and admission rates for LBP will be reduced, compared to preimplementation measures. If proven to be safe, acceptable, effective, and cost-effective, virtual care for nonserious back pain could be expanded to other health districts in New South Wales, and potentially other states. Implementation in other jurisdictions would depend on staffing and technological resources to deliver virtual care.

Acknowledgments

This study has received a Hospitals Contribution Fund (HCF) Research Grant: Optimizing outcomes for patients with back pain by preventing hospital admission (Aus $315,000 [US $207,500]), HCF Health Services Research Grant, HCF Research Foundation. We would like to thank the Back@Home collaborators (Bethan Richards, Ananthila Anandacoomarasamy, Kirsten McCaffery, Miranda Shaw, Cassandra Dearing, Ian Harris, Rachelle Buchbinder, Chris Needs, James Edwards, Narcyz Ghinea, Michael Dinh, Dane Chalkley, and Rachael Dodd) for their assistance with the project planning and governance.

Data Availability

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

Authors' Contributions

AM, CGM, and GCM conceived the research evaluation. AM drafted the protocol with guidance from GCM, DMC, and CGM. MJT, DMC, OH, MM, and ER are involved in developing and implementing the model of care. QL and LB contributed to the statistical analysis plan. All authors revised and reviewed the final protocol paper.

Conflicts of Interest

MJT is a physiotherapist at RPA Virtual Hospital.

References

1. Emergency department care. Australian Institute of Health and Welfare (AIHW). 2021. URL: https://www.aihw.gov.au/reports-data/myhospitals/sectors/emergency-department-care [accessed 2024-01-17]
2. Healthcare utilisation: hospital average length of stay by diagnostic categories. Organisation for Economic Co-operation and Development. 2018. URL: https://stats.oecd.org/index.aspx?queryid=30165 [accessed 2024-01-17]
3. Buchbinder R, Underwood M, Hartvigsen J, Maher CG. The Lancet series call to action to reduce low value care for low back pain: an update. Pain 2020;161 Suppl 1(1):S57-S64 [FREE Full text] [doi: 10.1097/j.pain.0000000000001869] [Medline: 33090740]
4. Buchbinder R, van Tulder M, Öberg B, Costa LM, Woolf A, Schoene M, et al. Low back pain: a call for action. Lancet 2018;391(10137):2384-2388 [FREE Full text] [doi: 10.1016/S0140-6736(18)30488-4] [Medline: 29573871]
5. Waterman BR, Belmont PJ, Schoenfeld AJ. Low back pain in the United States: incidence and risk factors for presentation in the emergency setting. Spine J 2012;12(1):63-70. [doi: 10.1016/j.spinee.2011.09.002] [Medline: 21978519]
6. Melman A, Lord HJ, Coombs D, Zadro J, Maher CG, Machado GC. Global prevalence of hospital admissions for low back pain: a systematic review with meta-analysis. BMJ Open 2023;13(4):e069517 [FREE Full text] [doi: 10.1136/bmjopen-2022-069517] [Medline: 37085316]
7. Melman A, Vella SP, Dodd RH, Coombs DM, Richards B, Rogan E, et al. Clinicians' perspective on implementing virtual hospital care for low back pain: qualitative study. JMIR Rehabil Assist Technol 2023;10:e47227 [FREE Full text] [doi: 10.2196/47227] [Medline: 37988140]
8. Coombs DM, Machado GC, Richards B, Wilson R, Chan J, Storey H, et al. Healthcare costs due to low back pain in the emergency department and inpatient setting in Sydney, Australia. Lancet Reg Health West Pac 2021;7:100089 [FREE Full text] [doi: 10.1016/j.lanwpc.2020.100089] [Medline: 34327417]
9. Melman A, Maher CG, Needs C, Machado GC. Many people admitted to hospital with a provisional diagnosis of nonserious back pain are subsequently found to have serious pathology as the underlying cause. Clin Rheumatol 2022;41(6):1867-1871 [FREE Full text] [doi: 10.1007/s10067-022-06054-w] [Medline: 35015190]
10. Oliveira CB, Maher CG, Pinto RZ, Traeger AC, Lin CC, Chenot J, et al. Clinical practice guidelines for the management of non-specific low back pain in primary care: an updated overview. Eur Spine J 2018;27(11):2791-2803 [FREE Full text] [doi: 10.1007/s00586-018-5673-2] [Medline: 29971708]

11. Kyi L, Kandane-Rathnayake R, Morand E, Roberts LJ. Outcomes of patients admitted to hospital medical units with back pain. Intern Med J 2019;49(3):316-322. [doi: 10.1111/imj.14075] [Medline: 30091257]
12. Melman A, Maher CG, Machado GC. Virtual hospitals: why we need them, how they work and what might come next. J Physiother 2021;67(3):156-157 [FREE Full text] [doi: 10.1016/j.jphys.2021.06.018] [Medline: 34148815]
13. El-Haddad C, Damodaran A, McNeil HP, Hu W. The experience of patients admitted to hospital with acute low back pain: a qualitative study. Int J Rheum Dis 2018;21(4):796-803. [doi: 10.1111/1756-185X.12870] [Medline: 27125577]
14. Gonçalves-Bradley DC, Iliffe S, Doll HA, Broad J, Gladman J, Langhorne P, et al. Early discharge hospital at home. Cochrane Database Syst Rev 2017;6(6):CD000356 [FREE Full text] [doi: 10.1002/14651858.CD000356.pub4] [Medline: 28651296]
15. Levine DM, Ouchi K, Blanchfield B, Saenz A, Burke K, Paz M, et al. Hospital-level care at home for acutely ill adults. Ann Intern Med 2019;172(2):77-85. [doi: 10.7326/m19-0600]
16. Hutchings OR, Dearing C, Jagers D, Shaw MJ, Raffan F, Jones A, et al. Virtual health care for community management of patients with COVID-19 in Australia: observational cohort study. J Med Internet Res 2021;23(3):e21064 [FREE Full text] [doi: 10.2196/21064] [Medline: 33687341]
17. Hutchings OD, Dearing C, Jagers D, Shaw MJ, Raffan F, Jones A, et al. Virtual health care for community management of patients with COVID-19 in Australia: observational cohort study. J Med Internet Res 2021;23(3):e21064 [FREE Full text] [doi: 10.2196/21064] [Medline: 33687341]
18. Curran GM, Bauer M, Mittman B, Pyne JM, Stetler C. Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact. Med Care 2012;50(3):217-226 [FREE Full text] [doi: 10.1097/MLR.0b013e3182408812] [Medline: 22310560]
19. Pearson N, Naylor PJ, Ashe MC, Fernandez M, Yoong SL, Wolfenden L. Guidance for conducting feasibility and pilot studies for implementation trials. Pilot Feasibility Stud 2020;6(1):167 [FREE Full text] [doi: 10.1186/s40814-020-00634-w] [Medline: 33292770]
20. Proctor E, Silmere H, Raghavan R, Hovmand P, Aarons G, Bunger A, et al. Outcomes for implementation research: conceptual distinctions, measurement challenges, and research agenda. Adm Policy Ment Health 2011;38(2):65-76 [FREE Full text] [doi: 10.1007/s10488-010-0319-7] [Medline: 20957426]
21. Year in review 2019-20. Sydney Local Health District. 2020. URL: https://www.slhd.nsw.gov.au/pdfs/YIR_19-20.pdf [accessed 2024-01-17]
22. Šimůnek A, Dygrýn J, Gába A, Jakubec L, Stelzer J, Chmelík F. Validity of Garmin Vivofit and polar loop for measuring daily step counts in free-living conditions in adults. Acta Gymnica 2016;46(3):129-135 [FREE Full text] [doi: 10.5507/ag.2016.014]
23. Kamišalić A, Fister I, Turkanović M, Karakatič S. Sensors and functionalities of non-invasive wrist-wearable devices: a review. Sensors (Basel) 2018;18(6):1714 [FREE Full text] [doi: 10.3390/s18061714] [Medline: 29799504]
24. Graham ID, Logan J, Harrison MB, Straus SE, Tetroe J, Caswell W, et al. Lost in knowledge translation: time for a map? J Contin Educ Health Prof 2006;26(1):13-24. [doi: 10.1002/chp.47] [Medline: 16557505]
25. Flodgren G, O'Brien MA, Parmelli E, Grimshaw JM. Local opinion leaders: effects on professional practice and healthcare outcomes. Cochrane Database Syst Rev 2019;6(6):CD000125 [FREE Full text] [doi: 10.1002/14651858.CD000125.pub5] [Medline: 31232458]
26. Giguère A, Zomahoun HTV, Carmichael PH, Uwizeye CB, Légaré F, Grimshaw JM, et al. Printed educational materials: effects on professional practice and healthcare outcomes. Cochrane Database Syst Rev 2020;8(8):CD004398 [FREE Full text] [doi: 10.1002/14651858.CD004398.pub4] [Medline: 32748975]
27. Forsetlund L, Bjørndal A, Rashidian A, Jamtvedt G, O'Brien MA, Wolf F, et al. Continuing education meetings and workshops: effects on professional practice and health care outcomes. Cochrane Database Syst Rev 2009;2009(2):CD003030 [FREE Full text] [doi: 10.1002/14651858.CD003030.pub2] [Medline: 19370580]
28. Ivers N, Jamtvedt G, Flottorp S, Young JM, Odgaard-Jensen J, French SD, et al. Audit and feedback: effects on professional practice and healthcare outcomes. Cochrane Database Syst Rev 2012(6):CD000259. [doi: 10.1002/14651858.CD000259.pub3] [Medline: 22696318]
29. Coombs DM, Machado GC, Richards B, Needs C, Buchbinder R, Harris IA, et al. Effectiveness of a multifaceted intervention to improve emergency department care of low back pain: a stepped-wedge, cluster-randomised trial. BMJ Qual Saf 2021;30(10):825-835. [doi: 10.1136/bmjqs-2020-012337] [Medline: 33692191]
30. Jackson TJ, Michel JL, Roberts RF, Jorm CM, Wakefield JG. A classification of hospital-acquired diagnoses for use with routine hospital data. Med J Aust 2009;191(10):544-548. [doi: 10.5694/j.1326-5377.2009.tb03307.x] [Medline: 19912086]
31. Amorim AB, Coombs D, Richards B, Maher CG, Machado GC. Text messaging and survey system to recruit patients with low back pain and collect outcomes in the emergency department: observational study. JMIR Mhealth Uhealth 2021;9(3):e22732 [FREE Full text] [doi: 10.2196/22732] [Medline: 33661125]
32. Elwenspoek MM, Jones T, Dodd JW. Effects of an integrated respiratory service on chronic obstructive pulmonary disease hospital admissions in England: an interrupted time series analysis. J Health Serv Res Policy 2021;26(4):242-250. [doi: 10.1177/1355819620974054] [Medline: 33225763]

33. Wammes JD, Bakx P, Wouterse B, Buurman BM, Murphy TE, MacNeil Vroomen JL. Acute hospital use in older adults following the 2015 Dutch reform of long-term care: an interrupted time series analysis. Lancet Healthy Longev 2023;4(6):e257-e264 [FREE Full text] [doi: 10.1016/s2666-7568(23)00064-8]
34. Grimley RS, Collyer T, Dewey HM, Andrew N, Cadilhac DA. Stroke and emergency department re-presentation after outpatient TIA management: an interrupted time series study. J Stroke Cerebrovasc Dis 2023;32(1):106900. [doi: 10.1016/j.jstrokecerebrovasdis.2022.106900] [Medline: 36427470]

Abbreviations

ATC: Anatomical Therapeutic Chemical
CHADx: Classification of Hospital Acquired Diagnoses
ED: emergency department
ICD-10 AM: International Classification of Diseases, Tenth Revision, Australian Modification
LBP: low back pain
PROMIS: Patient-Reported Outcomes Measurement Information System
REDCap: Research Electronic Data Capture
RPA: Royal Prince Alfred Hospital
SNOMED: Systematized Nomenclature of Medicine
SNOMED-CT-AU: Systematized Nomenclature of Medicine Clinical Terms-Australian

Edited by A Mavragani; submitted 20.06.23; peer-reviewed by V Brahmbhatt, H Xiang, M Tegern; comments to author 04.12.23; revised version received 12.12.23; accepted 13.12.23; published 22.02.24.

Please cite as:
Melman A, Teng MJ, Coombs DM, Li Q, Billot L, Lung T, Rogan E, Marabani M, Hutchings O, Maher CG, Machado GC
A Virtual Hospital Model of Care for Low Back Pain, Back@Home: Protocol for a Hybrid Effectiveness-Implementation Type-I Study
JMIR Res Protoc 2024;13:e50146
URL: https://www.researchprotocols.org/2024/1/e50146
doi:10.2196/50146
PMID:38386370

Protocol

Investigating Digital Patient-Reported Outcome Measures in Patient-Centered Diabetes Specialist Outpatient Care (DigiDiaS): Protocol for a Multimethod Prospective Observational Study

Astrid Torbjørnsen[1], RN, MSc, PhD; Ingeborg Spildo[1*], MSc; Maria Aadland Mollestad[1*], MSc; Annesofie Lunde Jensen[2,3], RN, MSc, PhD; Tone Singstad[4], RN, MSc; Nina Mickelson Weldingh[5], MSc; Pål Joranger[1], PhD; Lis Ribu[6], RN, MSc, Prof Dr; Heidi Holmen[1,7], RN, MSc, PhD

[1]Department of Nursing and Health Promotion, Faculty of Health Sciences, Oslo Metropolitan University – OsloMet, Oslo, Norway

[2]Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

[3]SDCA-Steno Diabetes Centre, Aarhus, Aarhus University Hospital, Aarhus, Denmark

[4]Division of Medicine, Akershus University Hospital, Akershus, Norway

[5]Division of Research and Innovation, Department of Research Support Service, Akershus University Hospital, Akershus, Norway

[6]The Centre for Senior Citizen Staff, Oslo Metropolitan University – OsloMet, Oslo, Norway

[7]The Intervention Centre, Oslo University Hospital, Oslo, Norway

[*]these authors contributed equally

Corresponding Author:
Astrid Torbjørnsen, RN, MSc, PhD
Department of Nursing and Health Promotion
Faculty of Health Sciences
Oslo Metropolitan University – OsloMet
Postboks 4, St. Olavs plass
Oslo, 0130
Norway
Phone: 47 67236199
Email: astridto@oslomet.no

Abstract

Background: Living with type 1 diabetes is challenging, and to support self-management, repeated consultations in specialist outpatient care are often required. The emergence of new digital solutions has revolutionized how health care services can be patient centered, providing unprecedented opportunities for flexible, high-quality care. However, there is a lack of studies exploring how the use of digital patient-reported outcome measures (PROMs) for flexible specialist care affects diabetes self-management. To provide new knowledge on the relevance of using PROMs in standard care, we have designed a multimethod prospective study.

Objective: The overall aim of this protocol is to describe our prospective multimethod observational study designed to investigate digital PROMs in a routine specialist outpatient setting for flexible patient-centered diabetes care (DigiDiaS).

Methods: This protocol outlines the design of a multimethod prospective observational cohort study that includes data from electronic health records, self-reported questionnaires, clinical consultation field observations, and individual in-depth interviews with patients and diabetes health care personnel. All patients with type 1 diabetes at a designated outpatient clinic were invited to participate and use the digital PROM implemented in clinical care. Both users and nonusers of the digital PROM were eligible for the prospective study, allowing for a comparison of the two groups. Data were collected at baseline and after 12 months, including self-management as the primary outcome assessed using the Patient Activation Measure, along with the secondary outcomes of digital health literacy, quality of life, health economy, and clinical variables such as glycated hemoglobin.

Results: The digital solution was implemented for routine clinical care in the department in November 2021, and data collection for the prospective study started in October 2022. As of September 6, 2023, 84.6% (186/220) of patients among those in the digital PROM and 15.5% (34/220) of patients among the nonusers have consented to participate. We expect the study to have enough participants by the autumn of 2023. With 1 year of follow-up, the results are expected by spring 2025.

Conclusions: In conclusion, a multimethod prospective observational cohort study can offer valuable insights into the relevance, effectiveness, and acceptability of digital tools using PROMs in diabetes specialist care. Such knowledge is crucial for achieving broad and successful implementation and use of these tools in a large diabetes outpatient clinic.

International Registered Report Identifier (IRRID): DERR1-10.2196/52766

(JMIR Res Protoc 2024;13:e52766) doi:10.2196/52766

KEYWORDS

patient-reported outcome measures; PROMs; diabetes mellitus; DM; type 1; patient acceptance of health care; telemedicine; mobile apps; mobile phone

Introduction

Background

Living with type 1 diabetes can impact one's daily life [1]. Self-management is required to reduce late complications, but it can be exhausting and stressful [2], and the burden of living with type 1 diabetes often impacts a person's mental health [3,4]. However, there is a significant variation in the needs and concerns of people with type 1 diabetes and varying perceptions of the diabetes burden. To improve patient-centered diabetes care, targeting unique needs and perspectives in both clinical care and research is necessary [5].

A recent systematic review has provided evidence for the effect of an integrated care model in diabetes care on essential patient outcomes [6], which is in line with clinical recommendations [7]. Thus, the increased involvement of patients is warranted. One way of increasing the involvement and bringing the voice of the patients forward is through "patient-reported outcomes" (PROs), that is, patients' responses to outcomes relevant to their condition [8]. Therefore, PRO measures (PROMs) are the measures used to assess PROs systematically.

PROMs in diabetes care can improve patient-centered care by collecting information directly from patients to obtain a complete picture of the patient's health status. Health care providers could better understand their patients' needs and concerns and tailor care to meet these individual needs [8,9]. However, it has been challenging to select the tools for PRO measurement to ensure that they are valid and responsive to changes in patient health status [10]. In addition, the clinical value of the PROMs has not been established, and the adaptation of standardized PROMs used in research might not be straightforward because the measures are usually lengthy and time-consuming to answer for the patient and to interpret for the clinician. The use of PROMs in previous research has varied widely in terms of using one or several PROMs, using disease-specific or generic PROMs, and determining at what times or under which conditions the measures are used [11]. The use of PROMs in diabetes care has become increasingly multidimensional, focusing on a range of patient outcomes and highlighting the need for a broader multidisciplinary and shared effort in clinical practice [12].

Digital development has affected the use of digital PROMs in the last decades, offering easier and more timely access to patient reports and an easier and more timely way of evaluating patient reports for health care personnel [13,14]. Digital PROMs have been successfully implemented in various services [15], including diabetes [16,17]. Despite the many benefits of digital PROMs, the reasons for the lack of use among patients remain, including a lack of motivation, technical barriers, emotional distress, and a reduced ability to participate in a digital PROM [18].

To ensure the patients' participation in digital PROMs as intended by the health services, research on the patients' perspectives is essential to providing a more complete understanding of health care needs and preferences. Patients' acceptance of digital support is crucial and can affect their engagement and adherence [19]. Furthermore, patient perception, acceptability, and engagement in designing and implementing digital health intervention evaluations remain crucial [20]. By understanding and addressing the concerns and barriers to digital solutions faced by patients who may be uncomfortable or unable to engage in digital support, we can promote more equitable access to health care services. Similarly, measuring technology acceptability after use—rather than predicted use—might provide valuable insights into users' perceptions and experiences of technology, helping to identify areas for improvement [21].

An increasing number of patients are in need of care, with limited resources and staff to ensure their needs, which holds true in diabetes care [22]. Thus, implementing digital PROMs to support self-management in line with patient-centered care might alleviate the burden on both patients and services [23]. However, further research is needed to fully understand the interactions in these new services among the patient, the clinicians, and the digital solution to understand the effects and implications on the users.

Aims

The overall aim of this protocol is to describe our prospective multimethod observational study designed to investigate digital PROMs in a routine specialist outpatient setting for flexible patient-centered diabetes care. Specifically, the DigiDiaS will (1) quantitatively investigate and describe the characteristics of patients with type 1 diabetes participating in a digital PROM in comparison with patients in traditional follow-up and evaluate the effect of participating in digital PROMs on clinical outcomes, self-management, diabetes distress, quality of life, and health care utilization and (2) qualitatively, through observations and qualitative interviews, assess patients' acceptability of consultations prepared and supported by digital and flexible services using PROMs.

Methods

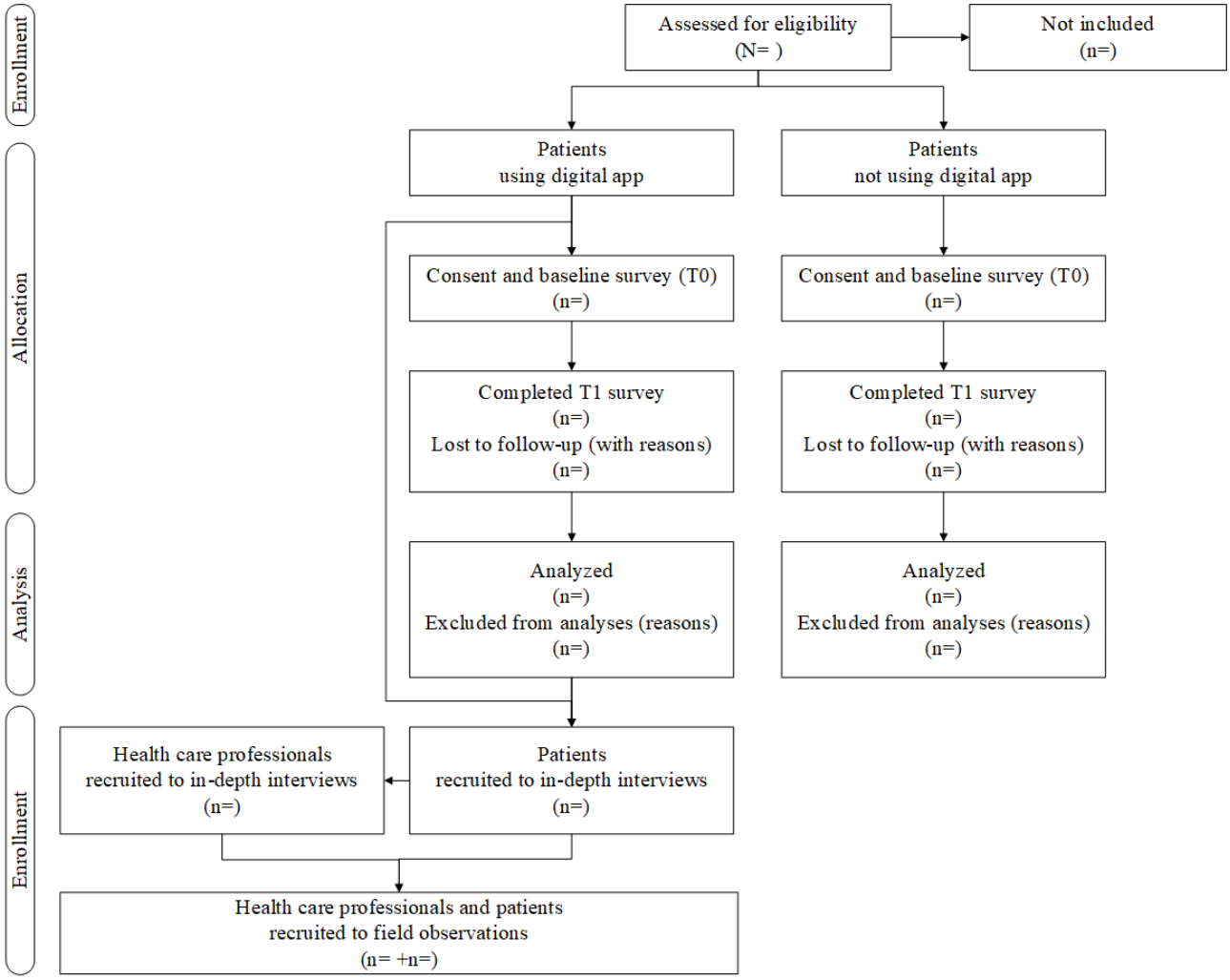
Study Design

This protocol describes a prospective, multimethod observational cohort study to investigate the relevance and effects of digital and flexible services using PROMs. The PROM in the planned trial is based on DiabetesFlex, which was developed and implemented in Danish health care services for type 1 diabetes [16,17,24], and it has been adapted to a Norwegian digital context in preparation for this study [25]. Consenting participants will be enrolled for 12 months, with assessments at baseline (T0) and 12 months (T1), with additional data from electronic health records, field observations of clinical video, or in-person consultations, along with individual in-depth interviews with the patients and diabetes health care personnel (Figure 1). Field observations and in-depth interviews among the patients participating in the digital PROMs will be conducted at any given time for those not participating in the survey and after completing T1 for those consenting to the survey study to avoid contamination of the survey and interview data.

This study is a collaboration between Akershus University Hospital and Oslo Metropolitan University—OsloMet and will be conducted at the Endocrinological Outpatient Clinic at Akershus University Hospital.

This protocol is reported in line with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidance [26]. The reporting of the proposed study and participation in digital tools and PROMs in clinical practice will be guided by better reporting of interventions: template for intervention description and replication (TIDieR) [27] and the PRO reporting guide [28].

Figure 1. Study flow.



Overview of the Implemented Service

A Digital and Flexible Service

All patients at the clinic will be offered to engage with digital and flexible services in addition to standard care. If they are interested, the digital service will be available through a mobile app on their private smartphone and will contain functions for self-monitoring, chat, video consultations, and PROMs before or between consultations. The digital PROMs implemented in this study have been described in detail elsewhere [25]. Standard care at the outpatient clinic includes a once-a-year consultation with an endocrinologist, a diabetes specialist nurse, or both. In the given situations, patients have ≥1 added consultation a year [29]. The clinic offers video-based and physical face-to-face consultations based on the patient's preferences and needs for care through solutions approved by the hospital.

Digital Platform: Dignio Connected Care

Although the study does not focus on evaluating the functionality of a specific digital solution, the clinical implementation of elements from DiabetesFlex will be carried out through the digital platform Dignio Connected Care [30]. The MyDignio and DignioPrevent interfaces are presented in Multimedia Appendices 1 and 2. The patient app MyDignio allows patients to store health data and communicate with health care personnel at the clinic through self-monitoring, answering PROM questionnaires sent between consultations, communicating through a message system (chat), or engaging in video consultations with their health care personnel [31]. The health care personnel software DignioPrevent offers a flexible way of reviewing patent-reported data, using the traffic light principle to guide and prioritize which patients need attention. Dignio Connected Care allows patients to reflect on self-care and needs, take preventive actions, and prepare for consultations, both for patients to give responses of their prioritizing of needs and for the health care personnel to obtain an overview of the complexity, personalize the care, and offer the right level of expertise at the right time [25,32]. The platform facilitates a more informed dialogue between patients and health care personnel based on experience and knowledge [33]. It has also been suggested to make specialist health care more fluid and accessible to patients [34].

Information and Training

The patients will receive information regarding the digital service in consultation, regardless of this research project. If they consent to engage in the digital service, more detailed information on the MyDignio app will be provided by the diabetes specialist nurse. An invitation to download MyDignio will be sent to the patient's smartphone in consultation, and if they wish and have their national ID with them, they can download MyDignio immediately. The patient interface is easy and intuitive, and extensive training should not be required for most patients.

As the patient interface, the health care personnel site DignioPrevent has been developed to be simple and intuitive. The diabetes specialist nurses have been trained in using the Dignio Connected Care personnel interface DignioPrevent, by personnel from the information and communications technology unit at the university hospital, in addition to a close collaboration with personnel from Dignio Connected Care. Similarly, diabetes health care personnel will receive training in the video consultation systems used in the clinic.

Participants

Patient Participants

Patients with type 1 diabetes at the Endocrinological Outpatient Clinic at Akershus University Hospital who meet the inclusion criteria are eligible for enrollment. The inclusion criteria include age ≥18 years, a type 1 diabetes diagnosis, and the ability to read Norwegian. Both users and nonusers of the MyDignio platform are eligible. The exclusion criteria are type 2 diabetes, gestational diabetes, or any cognitive impairment inflicting their ability to participate in the research project. Patients with type 1 diabetes are not eligible if they are pregnant at the time of recruitment, and they will be excluded from follow-up if they become pregnant during the 12 months because of an expected change in response caused by the pregnancy and not digital care. They will still be able to participate in the flexible digital care model.

Health Care Personnel Participants

In the outpatient clinic, health secretaries, diabetes specialist nurses, and physicians will be involved in the digital platform. The health secretaries send the PROM in the app to the patients along with their scheduled appointments. If the patients wish to change their scheduled appointment, the health secretaries can arrange this, but they do not handle any medical questions, assessments of PRO responses, or other messages in the system. The diabetes specialist nurses are responsible for all questions from the patients and PRO responses, including the need for a consultation, new tasks in the system, and any need for information. The physicians handle the PRO response for the yearly control in the system and otherwise consult and guide the diabetes specialist nurses if needed. Except for the yearly physician consultation, the diabetes specialist nurses are responsible for all consultations with patients with type 1 diabetes at the clinic. Thus, both diabetes specialist nurses and physicians are eligible for participation in field observations of their consultations with patients in the digital service and for in-depth interviews.

Procedures

Eligible patients will be identified and given brief information at the outpatient clinic by health care professional staff. If the patients are interested, they will be contacted by a researcher (IS or MAM). If they consent to participate after receiving oral and written information, their written consent will be secured either through Nettskjema digital consent or through a paper-based consent form. Immediately after their consent, the patients can choose whether they will fill out the baseline questionnaire digitally through Nettskjema, paper-based in the mail at home with a free return envelope, or through a telephone interview with a researcher (IS or MAM). For consenting participants not responding to or returning the baseline questionnaire or the 1-year follow-up, an automatic email reminder will be sent, followed by a phone call reminder and a SMS text message reminder if they still do not reply. The digital consents and the digital questionnaire data will be securely stored in the Service for Sensitive Data at the University in Oslo. Paper-based consent forms and questionnaires will be securely locked in a safe for storage, and the paper-based questionnaires will be manually entered into SPSS (IBM Corp). Data from the patients' medical records will be extracted by a researcher (IS), and 10% of the extractions will be controlled by a second researcher (MAM) to ensure valid and reliable data extraction.

Health care personnel will be recruited for 2 purposes: in-depth interviews and observations of consultations with patients engaged in the digital PROM. The personnel will be recruited from the department, and written informed consent will be secured using the same procedures as those for the patients.

Study Outcomes

Overview

The primary outcome in this study is the change in self-management, as measured through the Patient Activation Measure (PAM) questionnaire after 1 year, which will then be compared between the users and the nonusers of the digital PROM. The secondary outcomes include glycated hemoglobin (HbA_{1c}), quality of life, health literacy, acceptability, health economics, and the use of health service resources. Quantitative data will be collected through patients' self-reports and the extraction of clinical variables from patients' medical records. In addition, data on the patients' use of MyDignio will be extracted, including how many clinical PROMs they completed during the study period. Self-reported and clinical variables will be collected among all consenting participants, regardless of their participation in the digital solution. The standardized self-reported outcome measures are presented in Table 1.

Table 1. Standardized self-reported outcome measures.

Domain and questionnaire and item, scale, and interpretation	Time point	
	T0	T1
Self-management		
PAM-13[a]		
• 13 items • 4-point Likert scale ranging from “strongly disagree” to “strongly agree” and “nonapplicable” • Higher scores indicate higher patient activation • A total of 4 activation levels in progressing difficulty: (1) belief that their role is important (0-47; items 1-2); (2) confidence and knowledge to act (47.1-55.1; items 3-8); (3) taking action (55.2-72.4; items 9-11); (4) staying on course under stress (72.5-100; items 12-13) • Domains: Knowledge, beliefs, confidence, and skills related to self-managing health and improving outcomes	✓	✓
Diabetes distress		
PAID[b]		
• 20 items • 5-point Likert scale ranging from 0 (“not a problem”) to 4 (“serious problem”) • The sum score multiplied by 1.25 gives a total score ranging from 0 to 100. • A higher score reflects greater emotional distress. A score of ≥40 indicates severe emotional distress.	✓	✓
Quality of life		
WHO-5[c]		
• 5 items (statements) • 6-point Likert scale ranging from 0 (“at no time”) to 5 (“all of the time”) • Total raw score ranging from 0 to 25 is multiplied by 4 (total score), where 0 represents worst imaginable well-being and 100 represents best imaginable well-being.	✓	✓
EQ-5D-5L		
• 5 dimensions: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression • Each dimension has 5 levels, from “no problems” (level 1) to “extreme problems” (level 5)	✓	✓
Digital health literacy		
HLS19-DHC-NO[d]		
• 10 items • 4-point Likert scale from 1 (“very hard”) to 4 (“very easy”) with added “I don’t know” • Higher scores reflect higher digital health literacy.		✓
HLS-Q12[e]		
• 12 items • 4-point Likert scale from 1 (“very hard”) to 4 (“very easy”) with added “I don’t know” • Higher scores reflect higher digital health literacy.		✓
Patient acceptability		
SUTAQ[f]		
• 22 items • 6-point Likert scale ranging from 1 to 6, reflecting more or less agreement with the statements. • High values reflect a high degree of agreement, except for 2 categories: *privacy and discomfort and care personnel concerns.*		✓
Perceived benefit		
• Enhanced care—beliefs about how health technology enhances care from health care personnel • Increased accessibility—beliefs on how health technology increases access to care		✓
Privacy and discomfort		
• Concerns about the impact of the kit on the person and the safety of the information monitored		✓

Domain and questionnaire and item, scale, and interpretation	Time point	
	T0	T1
Care personnel concerns		
• Beliefs about personnel skills and continuity of care		✓
Kit as substitution		
• Beliefs about health technology as an alternative to standard care		✓
Satisfaction		
• Beliefs of acceptance and satisfaction with health technology used in health care services		✓

[a]PAM: Patient Activation Measure.

[b]PAID: Problem Areas in Diabetes.

[c]WHO-5: World Health Organization-5.

[d]HLS19-DHC-NO: Health Literacy Survey-19 Digital Health Care in Norwegian.

[e]HLS-Q12: Health Literacy Survey Questionnaire-12 item.

[f]SUTAQ: Service User Technology Acceptability Questionnaire.

Self-Management

To evaluate self-management, we propose the PAM short version (PAM-13) for assessing self-management through patient activation in 4 domains: knowledge, beliefs, confidence, and skills for managing one's health [35]. The PAM-13 is suitable for the evaluation of health programs, which will enable patients to take responsibility for their own health; it contains 13 items, with scoring ranging from strongly disagree to strongly agree. The total PAM score can be divided into 4 levels: level 1 ("not believing activation is important") and level 2 ("a lack of knowledge and confidence to take action") indicate lower patient activations and level 3 ("beginning to take action") and level 4 "taking action" indicate higher patient activation. The PAM-13 was developed by Hibbard et al [35,36] for working with people with and without chronic conditions, and the initial validation showed strong psychometric properties. The PAM has previously been used among people with diabetes, albeit mostly type 2 diabetes [37], and has been translated into Norwegian and validated in a previous study [38].

Diabetes Distress

To evaluate diabetes distress, the Problem Areas in Diabetes-20 scale is used. This is an emotional distress scale for measuring diabetes-related concepts, such as depression, social support, health beliefs, and coping style; the scale aims to identify high risk for negative effects on self-management and emotional burnout because of diabetes [39]. The Problem Areas in Diabetes-20 contains 20 items, with a 4-point Likert scale ranging from no problem to a serious problem. It has been translated into Norwegian and validated in a previous study [40].

Quality of Life

Quality of life will be assessed using the 5-item World Health Organization Well-Being Index, which is a measure of current mental well-being and overall quality of life over the individual's past 2 weeks [41]. It contains 5 statements, with responses on a 6-point Likert scale that ranges from "no time" to "all of the time." The questionnaire has been validated and applied across various study fields [41] and is available and widely used in Norwegian.

To assess quality of life with added relevance to the health economic analyses, the EQ-5D-5L, including the EQ visual analogue scale, will be used. EQ-5D includes questions about mobility, self-care, usual activities, pain, discomfort, anxiety, and depression on a 4-level scale that ranges from "no problem" to "unable to/extreme problems." The EQ-5D visual analogue scale allows patients to rate their own overall current health. EQ-5D is a standardized generic instrument that is suitable for use in economic evaluations in health care. It was previously translated to Norwegian with population norms established [42], and it is widely applied on a global scale [43,44].

Digital and Health Literacy

Digital health literacy will be evaluated using the generic Health Literacy Survey-19 Digital Health Care in Norwegian (HLS19-DHC-NO). It measures the skills in using electronic tools to follow-up on one's own health and disease, as well as the competence to use digital home-based follow-up. This scale contains 10 items that are scored on a 4-point Likert scale from very hard to very easy, in addition to an "I don't know" category. It has recently been translated and applied to a Norwegian population survey [45] and is currently under validation.

The 12-Item Short-Form Health Literacy Survey Questionnaire is a generic measure of the ability to make informed health choices through 4 domains: access, understand, appraise, and apply health information. This scale contains 12 items, which are scored on a 4-point Likert scale that ranges from "very hard" to "very easy," in addition to an "I don't know" category. The 12-Item Short-Form Health Literacy Survey Questionnaire has been validated among the general Norwegian population [46].

Patient Acceptability of Digital Care

To assess the patients' satisfaction and acceptability with participating in digital care, we will use the Service User Technology Acceptability Questionnaire, which has 22 items

[21]. The Service User Technology Acceptability Questionnaire measures the acceptance of mobile health technology and can also be used to identify the characteristics of participants with low acceptance of technology. The responses are given on a 6-point Likert scale, ranging from strongly agree to strongly disagree. It has been translated into Norwegian and validated in a previous study [47].

Sociodemographic and Clinical Variables

Sociodemographic variables will be extracted from the patient records, whereas clinical variables will comprise self-reported data and data extracted from the patients' medical records (Table 2).

Table 2. Sociodemographic and clinical variables.

Variables, scale, and interpretation	Time point	
	T0	T1
Sociodemographic variables		
Age		
• Years	✓	
Sex		
• Female or male	✓	
Education		
• Not completed primary school (10 years) • Primary upper secondary school • Vocational school • College or university (≤4 years) • College or university (>4 years) • Unknown	✓	
Employment status		
• Employed 100% • Student • Unemployed (disability benefits or retired or other) • Part-time employment (≤25%, 26%-50%, 51%-75%, 76%-99%)	✓	✓
Cohabitation status		
• Living alone yes or no	✓	
Ethnicity		
• European • Asian • African • Unknown	✓	
Tobacco habits		
• Current user • Previous user	✓	✓
Clinical variables		
Diabetes duration		
• Years	✓	
HbA_{1c} [a]		
• Mmol/mol	✓	✓
Time in the range		
• The last 14 days • Time below range <3.9 mmol/L • Time in range of 3.9-10 mmol/L • Time above range >10 mmol/L	✓	✓
Diabetes complications		
• Number of diabetes late complications; • Albuminuria, treated with dialysis, transplanted kidney, retinopathy, neuropathy, stroke, arterial vascular surgery, amputation, and diabetic foot ulcers	✓	
Equipment		
• Pump, CGM[b] sensor, pump and pen	✓	✓

Variables, scale, and interpretation	Time point	
	T0	T1
DKA[c]		
• Never • Once • Several times • Unknown	✓	✓
Hypoglycemia in need of help		
• Never • Once • Several times • Unknown	✓	✓
Symptomatic hypoglycemia		
• Number of incidents, 0-90 past 30 days	✓	✓
Height		
• cm	✓	
Weight		
• kg	✓	✓
Lipid status		
• LDL[d]-cholesterol, mmol/L	✓	✓
Blood pressure		
• Systolic and diastolic mm Hg	✓	✓
Comorbidity		
CCI[e]		
• Myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular accident or transient ischemic attack, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease, hemiplegia, chronic kidney disease, solid tumor, leukemia, lymphoma, and AIDS	✓	

[a]HbA_{1c}: glycated hemoglobin.

[b]CGM: continuous glucose monitoring system.

[c]DKA: diabetic ketoacidosis.

[d]LDL: low-density lipoprotein.

[e]CCI: Charlson Comorbidity Index.

Utilization of Health Care Resources

Data regarding the utilization of health care resources will be collected, including the type of health care services provided, frequency of utilization, participation, and any engagement in digital services. The variables are presented in Table 3.

Table 3. Utilization of digital solutions and health care resources.

Variables, scale, and interpretation	Time point	
	T0	T1
Health care use		
Consultation type		
• Physical, video, or telephone		✓
Attendance		
• Number of on-attendance and number of late cancelations		✓
Health care profession		
• Number of consultations with a physician, a nurse, and a nutritionist		✓
GP[a] visits		
• Number of GP consultations		✓
Absence from work		
• Days of absence		✓
Patient involvement		
Patient involvement and shared decision-making		
• 6 items reflecting decision-making, communication, and interaction • 5-point Likert scale from 1, “absolutely not” to 5, “to a very high degree,” with an added “I don’t know” • Higher scores reflect a higher feeling of involvement	✓	✓
Digital user data		
Participation in the digital outpatient care		
• Yes or no, including start date	✓	✓
PROMs[b] completed		
• Type of measures and frequency, number		✓
Messaging services		
• Frequency of use and number		✓
Use of other mobile health apps		
• 2 items reflecting use and frequency • Including open-ended responses	✓	✓

[a]GP: general practitioner.

[b]PROM: patient-reported outcome measure.

The items reflecting patient involvement [48] and patient role [49] have been previously adapted from their original form and used in the DiabetesFlex study [16,17]. For this project, the items adapted in the DiabetesFlex study have been translated from Danish by the project team into Norwegian and then back-translated by a bilingual Danish researcher not affiliated with the project. The translation was then reviewed by ALJ, AT, and IS, and small adjustments were made before a translation consensus was reached.

Health Economy

To estimate the cost-effectiveness of the digital care model, we will conduct a cost-utility analysis based on decision-analytic modeling [50,51]. Those using the digital PROMs will be compared with those continuing with the standard follow-up. Health benefits will be measured using the EQ-5D-5L at baseline and at 12 months. Data for health care resource use will be collected using survey data on general practitioner visits, visits to nurses and other health care professionals, and absences from planned consultations and hospital admissions (Table 3). The time used for training will be based on experiences from implementing the digital care model. Microsimulations will be used to estimate the cost of traveling and other patient expenses. The unit costs will be based on the Norwegian reimbursement systems, the marked prices, and the literature. The results will be reported as incremental cost-effectiveness ratios with

credibility intervals and cost-effectiveness acceptability curves. We use probabilistic sensitivity analysis to estimate the uncertainty caused by parameter uncertainty and use deterministic sensitivity analysis to assess the effect of changes in resource use, unit cost, and assumptions [52].

Qualitative Outcomes

The qualitative outcomes of this proposed project include in-depth interviews with patients with diabetes and diabetes health care personnel and observations of consultations between diabetes health care personnel and patients participating in the digital care model. The semistructured in-depth interviews will aim to explore patients' acceptability of digital communication and how patients and diabetes health care personnel utilize the technology. The same patients will be observed and interviewed after obtaining their written informed consent. The interview guide for patients and health care professionals can be found in Multimedia Appendices 3 and 4, respectively.

Sample Size

The proposed study will evaluate the relevance and effects of digital services in practice without participants being randomly drawn to a control group and, therefore, excluded from the possibility of using technological solutions in clinical follow-up. Therefore, we can assume that there is a difference between patients who choose to engage in digital care and those who choose traditional health care services. It is impossible to foresee or decide how many patients will participate through the digital PROM, but we expect more patients in the group of users of the digital service. To statistically identify the similarities and differences between the groups, we consider a 10% alteration in PAM-13 to be clinically significant, such as a change of ≥4 points. To identify a clinically relevant change to this extent, a minimum of 32 participants is required in each group. To account for potential dropouts, we will continue the recruitment of participants until we have included the required number of at least 35 participants in the control group. Consenting patients will be compared based on their chosen group, that is, engaged or not engaged in digital care. If they choose to continue with standard care at the clinic, they will contribute data for comparison purposes after providing their consent. Recruitment will continue for an estimated year, or until nearly all patients in the clinic have been offered the digital solution.

We will use purposive sampling for the qualitative interviews and the observations [53] when recruiting patients and health care personnel for the qualitative study. Approximately 25 patients participating in the digital care model are regarded as sufficient. Patient participants will be included based on purposeful sampling to gain variations in age, gender, and HbA_{1c} levels. Thus, the number of patients included will depend on the findings of a constant comparative analysis. The sample size for diabetes health care personnel depends on the consenting number of health care personnel from the outpatient clinic under study.

Analysis

Statistical Analysis

The baseline (T0) and follow-up (T1) variables will be descriptively presented, whereas continuous variables will be analyzed using the median and range if the data are skewed and the mean and SD for normally distributed data. Categorical data will be presented as counts and percentages. The mean change will be estimated by subtracting the baseline scores from the follow-up scores. Any differences in mean changes in short- and long-term variables will be modeled using an ANOVA. To adjust for possible confounders, logistic regression models will include age, gender, and education. We will assess the number of patients tested for eligibility, declined to participate, lost to follow-up, and included in the analysis.

Qualitative Analysis

In the qualitative analysis, we will use interpretive description as a methodology [53-55]. Interpretive description aims to generate a practical understanding of the importance of applied disciplines within their context [53]. The interpretive description analysis will be performed in parallel with the data collection. All data from the transcribed interviews and field notes from the participant observation will be included in the analysis. Interpretive description analysis is an inductive, open, and exploratory approach that includes a constant comparative analysis. Hence, it builds from specific data toward a broader generalization. This analysis will lead to the identification of final themes describing patients' acceptability of digital communication and how patients and diabetes health care personnel use the technology [53]. The NVivo software is used for data management, coding, and analysis [56]. The initial coding phase will be broad-based inductive coding into categories, followed by fine-tuned coding and interpretation of the data.

User Involvement

In this study, health care personnel will participate alongside patients and stakeholders to adapt the DiabetesFlex to a Norwegian context, resulting in a set of PROM items that may be highly relevant to the patients. On the basis of their answers, health care personnel can triage their patients to offer suitable treatment when needed through a traffic light model. User involvement regarding the project's development has been described elsewhere [25]. In addition, a reference group for the project will be established, containing individuals with type 1 diabetes, diabetes specialist nurses, endocrinologists, management, and researchers.

Ethical Considerations

The Data Protection Office approved the study at Akershus University Hospital (2022_125). Patients at the outpatient clinic will be screened for eligibility for the study by health professionals, and all patients meeting the inclusion criteria will be offered the digital PROM. Therefore, a randomized controlled trial is impossible, and the proposed study has no control group. However, those declining to engage in digital tools will act as a comparative group in the analysis. All participants will provide their written informed consent before the study starts. All data will be securely stored in Services for Sensitive Data. Data

shared in the MyDignio app will be encrypted and stored according to legislation on the privacy and secure storage of sensitive health information. The Data Protection Office performed a comprehensive risk assessment analysis of the technology upon initiation, and the research team completed a risk assessment analysis of the risks related to the conduct of the research before the start of the study. SIKT—the Norwegian Agency for Shared Services in Education and Research—will be notified per the Norwegian protocol to assess project data protection and information security.

To ensure data safety, patients must use their national ID to identify themselves, either through BankID or MinID, both to provide their digital consent and self-report on the digital questionnaires of the research evaluation and to log in when using MyDignio.

Results

The study received funding in March and October 2022 from Oslo Metropolitan University–OsloMet internal funding. The digital solution was implemented in clinical care at the department in November 2021, and the first participant was enrolled in the research project with a completed T0 on October 27, 2022. As of September 6, 2023, a total of 220 patients have been enrolled in the project, of which 84.5% (n=186) are digital users and 15.5% (n=34) are nonusers in the comparative group. The data collection is projected to end during 2024.

Discussion

Overview

We anticipate that this study will generate knowledge on the relevance and effects of participation in digital PROMs for communication and self-management and about the characteristics of users compared with nonusers of the digital PROM. Evaluating the use of digital follow-up might facilitate the need for further development of the tools based on actual clinical use. Finally, investigating the communication between patients and their health care personnel will increase the understanding of how technology impacts consultation.

Significance of the Study

Although diabetes care has faced considerable improvements in medical equipment facilitation and glycemic control, there is a need for more patient-centered and flexible care using recent developments in digital PROMs in routine care [11,12]. To do so, the possibilities of flexible digital care using PROMs in clinical care must be investigated. The study described in this protocol aims to provide knowledge regarding the characteristics of patients with type 1 diabetes engaged in a digital PROM, their effect on participating in digital PROMs, the patients' acceptability of consultations prepared and supported by digital and flexible services using PROs, and how these services affect health care personnel.

Although previous research from Norway provides valuable insights into the use of PROMs in clinical diabetes consultations through the DiaPROM study, their findings highlight the need for further investigation into implementation challenges and patient acceptability [57]. In the Danish DiabetesFlex study, PROMs in the diabetes outpatient clinic had a positive impact on patients' management of their diabetes and their responsibility for care plans. Compared with standard care, using PROM in flexible visits improved diabetes-related well-being and decreased face-to-face visits while maintaining safe diabetes management [16,24]. Using a PROM, patients were encouraged to reflect on their diabetes management; this led to a more tailored and individualized treatment approach and made the consultations more flexible, allowing for a broader dialogue between patients and health care providers [24]. Similarly, diabetes care support is crucial when living with diabetes [58]. Using PROMs in diabetes specialist care can improve communication, enhance patient engagement in their care, and improve patient outcomes. Nonetheless, it remains necessary to explore the acceptability of the use of digital PROMs to prevent inequality in health for patients who do not engage in digital health care and, as such, do not receive the intended care [18], while also identifying the barriers preventing these patients from accessing care and exploring alternative ways of delivering health care services and support. This study will investigate the effects and acceptability of a digital PROM, emphasize the potential benefits and barriers by further exploring the impact of using a PROM in a diabetes outpatient clinic, and, as such, add knowledge to existing evidence.

Limitations

In evaluating the implementation of digital tools and PROMs, a randomized controlled trial could be considered the gold standard to minimize confounding variables and provide stronger evidence. In this case, to design a control group, we would have to withhold the tools from patients in the clinic, which could be considered unfair clinical practice in the clinic. We could have chosen to have a control group at another hospital. However, practices in endocrinology outpatient clinics are changing, making it difficult to find a hospital department administering the usual care. Therefore, this study has been planned as an observational quasi-experimental design, with its limitations being potential confounding variables and bias. This is a novel study, and we plan to include numerous participants with a long follow-up period. We will minimize bias and confounding by including patients engaged in digital PROMs and patients choosing traditional care, controlling for known confounders, and using appropriate statistical methods to analyze data in collaboration with a statistician.

A potential limitation, according to the qualitative part of the study, is related to the conduct of the observations of consultations with patients and being interviewed about their practice, with a potential risk for reactivity of social desirability bias. Diabetes health care personnel might modify their behavior while being observed to conform to expectations about performance. Similarly, they could provide responses in the interviews that they believe are socially acceptable, rather than giving honest and accurate answers. It will be important for the researchers to establish trust and ensure that the responses are kept confidential and not used to evaluate performance.

Conclusions

There is a need for elaborate knowledge on patient participation in digital tools using PROMs in diabetes specialist care. A multimethod prospective observational cohort study can provide valuable insights into the effectiveness and acceptability of PROM digital tools, aiming for a broad measurement of their full-scale implementation in a large diabetes outpatient clinic.

Acknowledgments

The authors sincerely acknowledge all the participating patients. The authors want to give their utmost appreciation to all the diabetes specialist nurses participating in this study's development and patient follow-up. This work has received funding from Akershus University Hospital and Oslo Metropolitan University.

Authors' Contributions

AT, TS, NMW, ALJ, LR, and HH substantially contributed to the development of this study protocol. AT drafted the manuscript in collaboration and through discussions with HH on the adaptation and tailoring of the intervention. TS, NMW, IS, MAM, PJ, LR, and ALJ commented on and revised versions of the draft, and all authors approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Screenshot of the MyDignio interface.
[DOCX File , 95 KB - resprot_v13i1e52766_app1.docx]

Multimedia Appendix 2
Screenshot of the DignioPrevent interface.
[DOCX File , 54 KB - resprot_v13i1e52766_app2.docx]

Multimedia Appendix 3
Interview guide—patients.
[DOCX File , 34 KB - resprot_v13i1e52766_app3.docx]

Multimedia Appendix 4
Interview guide—health care professionals.
[DOCX File , 30 KB - resprot_v13i1e52766_app4.docx]

References

1. Speight J, Holmes-Truscott E, Hendrieckx C, Skovlund S, Cooke D. Assessing the impact of diabetes on quality of life: what have the past 25 years taught us? Diabet Med 2020 Mar;37(3):483-492. [doi: 10.1111/dme.14196] [Medline: 31797443]
2. Martyn-Nemeth P, Schwarz Farabi S, Mihailescu D, Nemeth J, Quinn L. Fear of hypoglycemia in adults with type 1 diabetes: impact of therapeutic advances and strategies for prevention - a review. J Diabetes Complications 2016;30(1):167-177. [doi: 10.1016/j.jdiacomp.2015.09.003] [Medline: 26439754]
3. Chireh B, Li M, D'Arcy C. Diabetes increases the risk of depression: a systematic review, meta-analysis and estimates of population attributable fractions based on prospective studies. Prev Med Rep 2019 Jun;14:100822 [FREE Full text] [doi: 10.1016/j.pmedr.2019.100822] [Medline: 30815337]
4. Nouwen A, Adriaanse MC, van Dam K, Iversen MM, Viechtbauer W, Peyrot M, European Depression in Diabetes (EDID) Research Consortium. Longitudinal associations between depression and diabetes complications: a systematic review and meta-analysis. Diabet Med 2019 Dec;36(12):1562-1572. [doi: 10.1111/dme.14054] [Medline: 31215077]
5. Bour C, Ahne A, Aguayo G, Fischer A, Marcic D, Kayser P, et al. Global diabetes burden: analysis of regional differences to improve diabetes care. BMJ Open Diabetes Res Care 2022 Oct;10(5):e003040 [FREE Full text] [doi: 10.1136/bmjdrc-2022-003040] [Medline: 36307139]
6. Zarora R, Immanuel J, Chivese T, MacMillan F, Simmons D. Effectiveness of integrated diabetes care interventions involving diabetes specialists working in primary and community care settings: a systematic review and meta-analysis. Int J Integr Care 2022 May;22(2):11 [FREE Full text] [doi: 10.5334/ijic.6025] [Medline: 35634254]
7. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D. Improving care and promoting health in populations: standards of care in diabetes? Diabetes Care 2022;46(Supplement_1):S10-S18. [doi: 10.2337/dc23-s001]

8. Santana MJ, Haverman L, Absolom K, Takeuchi E, Feeny D, Grootenhuis M, et al. Training clinicians in how to use patient-reported outcome measures in routine clinical practice. Qual Life Res 2015 Jul;24(7):1707-1718 [FREE Full text] [doi: 10.1007/s11136-014-0903-5] [Medline: 25589231]
9. Greenhalgh J, Gooding K, Gibbons E, Dalkin S, Wright J, Valderas J, et al. How do patient reported outcome measures (PROMs) support clinician-patient communication and patient care? A realist synthesis. J Patient Rep Outcomes 2018 Dec;2:42 [FREE Full text] [doi: 10.1186/s41687-018-0061-6] [Medline: 30294712]
10. Churruca K, Pomare C, Ellis LA, Long JC, Henderson SB, Murphy LE, et al. Patient-reported outcome measures (PROMs): a review of generic and condition-specific measures and a discussion of trends and issues. Health Expect 2021 Aug;24(4):1015-1024 [FREE Full text] [doi: 10.1111/hex.13254] [Medline: 33949755]
11. Bandurska E. The voice of patients really matters: using patient-reported outcomes and experiences measures to assess effectiveness of home-based integrated care-a scoping review of practice. Healthcare (Basel) 2022 Dec 28;11(1):98 [FREE Full text] [doi: 10.3390/healthcare11010098] [Medline: 36611558]
12. Skovlund SE, Lichtenberg TH, Hessler D, Ejskjaer N. Can the routine use of patient-reported outcome measures improve the delivery of person-centered diabetes care? A review of recent developments and a case study. Curr Diab Rep 2019 Aug 16;19(9):84. [doi: 10.1007/s11892-019-1190-x] [Medline: 31420754]
13. Meirte J, Hellemans N, Anthonissen M, Denteneer L, Maertens K, Moortgat P, et al. Benefits and disadvantages of electronic patient-reported outcome measures: systematic review. JMIR Perioper Med 2020 Apr 03;3(1):e15588 [FREE Full text] [doi: 10.2196/15588] [Medline: 33393920]
14. Glenwright BG, Simmich J, Cottrell M, O'Leary SP, Sullivan C, Pole JD, et al. Facilitators and barriers to implementing electronic patient-reported outcome and experience measures in a health care setting: a systematic review. J Patient Rep Outcomes 2023 Feb 14;7(1):13 [FREE Full text] [doi: 10.1186/s41687-023-00554-2] [Medline: 36786914]
15. Schougaard LM, Larsen LP, Jessen A, Sidenius P, Dorflinger L, de Thurah A, et al. AmbuFlex: tele-patient-reported outcomes (telePRO) as the basis for follow-up in chronic and malignant diseases. Qual Life Res 2016 Mar;25(3):525-534 [FREE Full text] [doi: 10.1007/s11136-015-1207-0] [Medline: 26790427]
16. Laurberg T, Schougaard LM, Hjollund NH, Lomborg KE, Hansen TK, Jensen AL. Randomized controlled study to evaluate the impact of flexible patient-controlled visits in people with type 1 diabetes: the DiabetesFlex trial. Diabet Med 2022 May;39(5):e14791. [doi: 10.1111/dme.14791] [Medline: 35028992]
17. Jensen A, Lomborg K, Hjollund NH, Schougaard LV, Olesen LB, Laurberg T, et al. DiabetesFlex™ – the effect of PRO-based telehealth and user involvement in care management of patients with type 1 diabetes: Trial protocol for a non-inferiority randomised controlled study. Med Res Arch 2020;8(7):1-16 [FREE Full text] [doi: 10.18103/mra.v8i7.2145]
18. Nielsen AS, Kidholm K, Kayser L. Patients' reasons for non-use of digital patient-reported outcome concepts: a scoping review. Health Informatics J 2020 Dec 30;26(4):2811-2833 [FREE Full text] [doi: 10.1177/1460458220942649] [Medline: 32731773]
19. Kidholm K, Jensen LK, Kjølhede T, Nielsen E, Horup MB. Validity of the model for assessment of telemedicine: a Delphi study. J Telemed Telecare 2018 Feb;24(2):118-125. [doi: 10.1177/1357633X16686553] [Medline: 28024442]
20. Kidholm K, Clemensen J, Caffery LJ, Smith AC. The model for assessment of telemedicine (MAST): a scoping review of empirical studies. J Telemed Telecare 2017 Oct;23(9):803-813. [doi: 10.1177/1357633X17721815] [Medline: 28758525]
21. Hirani SP, Rixon L, Beynon M, Cartwright M, Cleanthous S, Selva A, et al. Quantifying beliefs regarding telehealth: development of the whole systems demonstrator service user technology acceptability questionnaire. J Telemed Telecare 2017 May;23(4):460-469. [doi: 10.1177/1357633X16649531] [Medline: 27224997]
22. Gregory GA, Robinson TI, Linklater SE, Wang F, Colagiuri S, de Beaufort C, International Diabetes Federation Diabetes Atlas Type 1 Diabetes in Adults Special Interest Group, et al. Global incidence, prevalence, and mortality of type 1 diabetes in 2021 with projection to 2040: a modelling study. Lancet Diabetes Endocrinol 2022 Oct;10(10):741-760. [doi: 10.1016/S2213-8587(22)00218-2] [Medline: 36113507]
23. Aiyegbusi OL, Hughes SE, Peipert JD, Schougaard LM, Wilson R, Calvert MJ. Reducing the pressures of outpatient care: the potential role of patient-reported outcomes. J R Soc Med 2023 Feb 09;116(2):44-64 [FREE Full text] [doi: 10.1177/01410768231152222] [Medline: 36758615]
24. Jensen AL, Schougaard LM, Laurberg T, Hansen TK, Lomborg K. Flexible patient-reported outcome-based telehealth follow-up for type 1 diabetes: a qualitative study. Scand J Caring Sci 2023 Sep;37(3):662-676. [doi: 10.1111/scs.13154] [Medline: 36775917]
25. Holmen H, Singstad T, Ribu L, Jensen AL, Weldingh NM, Torbjørnsen A. Adapting a patient-reported outcome measure to digital outpatient specialist health care services for type 1 diabetes: user involvement study. JMIR Hum Factors 2022 Nov 15;9(4):e38678 [FREE Full text] [doi: 10.2196/38678] [Medline: 36378513]
26. Chan AW, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ 2013 Jan 08;346:e7586 [FREE Full text] [doi: 10.1136/bmj.e7586] [Medline: 23303884]
27. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ 2014 Mar 07;348:g1687 [FREE Full text] [doi: 10.1136/bmj.g1687] [Medline: 24609605]

28. Calvert M, Kyte D, Mercieca-Bebber R, Slade A, Chan AW, King MT, the SPIRIT-PRO Group, et al. Guidelines for inclusion of patient-reported outcomes in clinical trial protocols: the SPIRIT-PRO extension. JAMA 2018 Feb 06;319(5):483-494 [FREE Full text] [doi: 10.1001/jama.2017.21903] [Medline: 29411037]
29. Nasjonal faglig retningslinje for diabetes. Helsedirektoratet. 2016. URL: https://www.helsedirektoratet.no/tema/diabetes [accessed 2024-01-18]
30. Dignio connected care. Dignio. URL: https://dignio.com/uk/page/connected-care/ [accessed 2024-01-18]
31. Grisot M, Moltubakk KA, Hagen L, Aanestad M. Supporting patient self-carexamining nurses' practices in a remote care setting. In: Moen A, Ugon A, Karlsson D, Klein GO, editors. Building Continents of Knowledge in Oceans of Data: The Future of Co-Created eHealth. Amsterdam, The Netherlands: IOS Press; 2018:601-605.
32. Grisot M, Moltubakk Kempton A, Hagen L, Aanestad M. Data-work for personalized care: examining nurses' practices in remote monitoring of chronic patients. Health Informatics J 2019 Sep;25(3):608-616 [FREE Full text] [doi: 10.1177/1460458219833110] [Medline: 30880551]
33. Hansen LA, Almqvist F, Ørjasæter NO, Kistorp KM. Velferdsteknologi i sentrum (VIS) - evaluering av velferdsteknologi fra et tjenestedesignperspektiv. Tidsskrift Omsorgsforskning 2017 Sep 06;3(2):144-152 [FREE Full text] [doi: 10.18261/issn.2387-5984-2017-02-12]
34. Advancing the technology enhanced living service (TEL). Stockport Metropolitan Borough Council. URL: https://www.innovationagencyexchange.org.uk/sites/default/files/TEL%20external.pdf [accessed 2024-01-18]
35. Hibbard JH, Stockard J, Mahoney ER, Tusler M. Development of the Patient Activation Measure (PAM): conceptualizing and measuring activation in patients and consumers. Health Serv Res 2004 Aug;39(4 Pt 1):1005-1026 [FREE Full text] [doi: 10.1111/j.1475-6773.2004.00269.x] [Medline: 15230939]
36. Hibbard JH, Mahoney ER, Stockard J, Tusler M. Development and testing of a short form of the patient activation measure. Health Serv Res 2005 Dec;40(6 Pt 1):1918-1930 [FREE Full text] [doi: 10.1111/j.1475-6773.2005.00438.x] [Medline: 16336556]
37. Rademakers J, Maindal HT, Steinsbekk A, Gensichen J, Brenk-Franz K, Hendriks M. Patient activation in Europe: an international comparison of psychometric properties and patients' scores on the short form Patient Activation Measure (PAM-13). BMC Health Serv Res 2016 Oct 12;16(1):570 [FREE Full text] [doi: 10.1186/s12913-016-1828-1] [Medline: 27729079]
38. Steinsbekk A. Måling av effekt av pasientopplæring Measurement of the Effectiveness of Patient Education. Tidsskr Nor Legeforen 2008;20:2316-2318 [FREE Full text] [Medline: 19096487]
39. Polonsky WH, Anderson BJ, Lohrer PA, Welch G, Jacobson AM, Aponte JE, et al. Assessment of diabetes-related distress. Diabetes Care 1995 Jun;18(6):754-760. [doi: 10.2337/diacare.18.6.754] [Medline: 7555499]
40. Graue M, Haugstvedt A, Wentzel-Larsen T, Iversen MM, Karlsen B, Rokne B. Diabetes-related emotional distress in adults: reliability and validity of the Norwegian versions of the Problem Areas in Diabetes Scale (PAID) and the Diabetes Distress Scale (DDS). Int J Nurs Stud 2012 Feb;49(2):174-182. [doi: 10.1016/j.ijnurstu.2011.08.007] [Medline: 21924422]
41. Topp CW, Østergaard SD, Søndergaard S, Bech P. The WHO-5 Well-Being Index: a systematic review of the literature. Psychother Psychosom 2015;84(3):167-176 [FREE Full text] [doi: 10.1159/000376585] [Medline: 25831962]
42. Garratt AM, Hansen TM, Augestad LA, Rand K, Stavem K. Norwegian population norms for the EQ-5D-5L: results from a general population survey. Qual Life Res 2022 Feb;31(2):517-526 [FREE Full text] [doi: 10.1007/s11136-021-02938-7] [Medline: 34272631]
43. Devlin NJ, Brooks R. EQ-5D and the EuroQol group: past, present and future. Appl Health Econ Health Policy 2017 Apr;15(2):127-137 [FREE Full text] [doi: 10.1007/s40258-017-0310-5] [Medline: 28194657]
44. Smith-Palmer J, Bae JP, Boye KS, Norrbacka K, Hunt B, Valentine WJ. Evaluating health-related quality of life in type 1 diabetes: a systematic literature review of utilities for adults with type 1 diabetes. Clinicoecon Outcomes Res 2016;8:559-571 [FREE Full text] [doi: 10.2147/CEOR.S114699] [Medline: 27785079]
45. Le C, Finbråten HS, Pettersen KS, Joranger P, Guttersrud Ø. Befolkningens helsekompetanse, del I. The International Health Literacy Population Survey 2019–2021 (HLS19) – et samarbeidsprosjekt med nettverket M-POHL tilknyttet WHO-EHII. Rapport IS-2959. ResearchGate. 2021. URL: http://tinyurl.com/3bpazxw9 [accessed 2024-01-18]
46. Finbråten HS, Wilde-Larsson B, Nordström G, Pettersen KS, Trollvik A, Guttersrud Ø. Establishing the HLS-Q12 short version of the European health literacy survey questionnaire: latent trait analyses applying Rasch modelling and confirmatory factor analysis. BMC Health Serv Res 2018 Jun 28;18(1):506 [FREE Full text] [doi: 10.1186/s12913-018-3275-7] [Medline: 29954382]
47. Torbjørnsen A, Småstuen MC, Jenum AK, Årsand E, Ribu L. The service user technology acceptability questionnaire: psychometric evaluation of the Norwegian version. JMIR Hum Factors 2018 Dec 21;5(4):e10255 [FREE Full text] [doi: 10.2196/10255] [Medline: 30578191]
48. Hørlück JT, Sevelsted J, Riiskjær E. Udvælgelse af inddragelsesspørgsmål til patienter: validitet, reliabilitet og accept. DEFAKTUM, Region Midtjylland. 2017. URL: https://www.defactum.dk/siteassets/sider/kvalitetsudvikling/indikatorer-for-patientinddragelse/delrapport-3--regionsvalidering_vigtighed_relevans.pdf [accessed 2024-02-02]
49. De Las Cuevas C, Peñate W. Validity of the Control Preferences Scale in patients with emotional disorders. Patient Prefer Adherence 2016;10:2351-2356 [FREE Full text] [doi: 10.2147/PPA.S122377] [Medline: 27895470]

50. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the Economic Evaluation of Health Care Programmes. Oxford, UK: Oxford University Press; 2015.
51. Hunink MM, Weinstein MC, Wittenberg E, Drummond MF, Pliskin JS, Wong JB. Decision Making in Health and Medicine: Integrating Evidence and Values. Cambridge, MA: Cambridge University Press; 2014.
52. Briggs A, Sculpher M, Claxton K. Decision Modelling for Health Economic Evaluatio. Oxford, UK: Oxford University Press; 2006.
53. Thorne S. Interpretive Description: Qualitative Research for Applied Practice. New York, NY: Routledge; 2016.
54. Thorne S. Applied interpretive approaches. In: Leavy P, editor. The Oxford Handbook of Qualitative Research. 2nd edition. Oxford, UK: Oxford University Press; 2014.
55. Handberg C, Jensen AL. Interpretive Description: En Anvendelsesorienteret Forskningsmetodologi. Aarhus, Denmark: Aarhus Universitetsforlag; 2021.
56. Jackson K, Bazeley P. Qualitative Data Analysis with NVivo. Thousand Oaks, CA: Sage Publications; 2019.
57. Hernar I, Graue M, Richards DA, Strandberg RB, Nilsen RM, Rekdal M, et al. Use of patient-reported outcome measures (PROMs) in clinical diabetes consultations: the DiaPROM randomised controlled pilot trial. BMJ Open 2021 Apr 14;11(4):e042353 [FREE Full text] [doi: 10.1136/bmjopen-2020-042353] [Medline: 33853796]
58. Svedbo Engström M, Leksell J, Johansson UB, Gudbjörnsdottir S. What is important for you? A qualitative interview study of living with diabetes and experiences of diabetes care to establish a basis for a tailored patient-reported outcome measure for the Swedish national diabetes register. BMJ Open 2016 Mar 24;6(3):e010249 [FREE Full text] [doi: 10.1136/bmjopen-2015-010249] [Medline: 27013595]

Abbreviations

HbA_{1c}: glycated hemoglobin
HLS19-DHC-NO: Health Literacy Survey-19 Digital Health Care in Norwegian
PAM: Patient Activation Measure
PRO: patient-reported outcome
PROM: patient-reported outcome measure
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

Edited by A Mavragani; submitted 14.09.23; peer-reviewed by B Detournay, C Jimeno; comments to author 02.12.23; revised version received 22.12.23; accepted 11.01.24; published 05.03.24.

Please cite as:
Torbjørnsen A, Spildo I, Mollestad MA, Jensen AL, Singstad T, Weldingh NM, Joranger P, Ribu L, Holmen H
Investigating Digital Patient-Reported Outcome Measures in Patient-Centered Diabetes Specialist Outpatient Care (DigiDiaS): Protocol for a Multimethod Prospective Observational Study
JMIR Res Protoc 2024;13:e52766
URL: https://www.researchprotocols.org/2024/1/e52766
doi:10.2196/52766
PMID:38441955

Protocol

Effectiveness of Chinese Herbal Medicine as a Complementary Treatment for Neutropenia Prevention and Immunity Modulation During Chemotherapy in Patients With Breast Cancer: Protocol for a Real-World Pragmatic Clinical Trial

Kai-Hung Wang[1*], PhD; Hsuan-Shu Shen[2,3,4*], MD; Sung-Chao Chu[5,6], MD, PhD; Tso-Fu Wang[5,6], MD; Ching-Wei Lin[2,3], MD; Wei-Han Huang[5,6,7], MD; Yi-Feng Wu[5,6], MD; Ching-Chun Ho[8], MD; Cheng-Yoong Pang[1,9], PhD; Chi-Cheng Li[5,6,10], MD

[1]Department of Medical Research, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan
[2]Department of Chinese Medicine, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan
[3]School of Post-Baccalaureate Chinese Medicine, Tzu Chi University, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan
[4]Sports Medicine Center, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan
[5]Department of Hematology and Oncology, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan
[6]School of Medicine, Tzu Chi University, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan
[7]Department of Clinical Pathology, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan
[8]Department of Surgery, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan
[9]Institute of Medical Sciences, Tzu Chi University, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan
[10]Center of Stem Cell and Precision Medicine, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan
[*]these authors contributed equally

Corresponding Author:
Chi-Cheng Li, MD
Center of Stem Cell and Precision Medicine
Hualien Tzu Chi Hospital
Buddhist Tzu Chi Medical Foundation
Xie-Li Building, 4th Floor
No. 707, Section 3, Chung-Yang Road
Hualien, 970
Taiwan
Phone: 886 03 8561825 ext 18661
Fax: 886 038573710
Email: kevinlcc1234@gmail.com

Abstract

Background: In recent years, advancements in cancer treatment have enabled cancer cell inhibition, leading to improved patient outcomes. However, the side effects of chemotherapy, especially leukopenia, impact patients' ability to tolerate their treatments and affect their quality of life. Traditional Chinese medicine is thought to provide complementary cancer treatment to improve the quality of life and prolong survival time among patients with cancer.

Objective: This study aims to evaluate the effectiveness of Chinese herbal medicine (CHM) as a complementary treatment for neutropenia prevention and immunity modulation during chemotherapy in patients with breast cancer.

Methods: We will conduct a real-world pragmatic clinical trial to evaluate the effectiveness of CHM as a supplementary therapy to prevent neutropenia in patients with breast cancer undergoing chemotherapy. Patients will be classified into CHM or non-CHM groups based on whether they received CHM during chemotherapy. Using generalized estimating equations or repeated measures ANOVA, we will assess differences in white blood cell counts, absolute neutrophil counts, immune cells, and programmed cell death protein 1 (PD-1) expression levels between the 2 groups.

Results: This study was approved by the research ethics committee of Hualien Tzu Chi Hospital (IRB 110-168-A). The enrollment process began in September 2021 and will stop in December 2024. A total of 140 patients will be recruited. Data cleaning and analysis are expected to finish in the middle of 2025.

Conclusions: Traditional Chinese medicine is the most commonly used complementary medicine, and it has been reported to significantly alleviate chemotherapy-related side effects. This study's findings may contribute to developing effective interventions targeting chemotherapy-related neutropenia among patients with breast cancer in clinical practice.

Trial Registration: International Traditional Medicine Clinical Trial Registry ITMCTR2023000054; https://tinyurl.com/yc353hes

International Registered Report Identifier (IRRID): DERR1-10.2196/55662

(JMIR Res Protoc 2024;13:e55662) doi:10.2196/55662

KEYWORDS

complementary treatment for cancer; neutropenia; real-world study; bedside to bench study; immune cell profile; programmed cell death protein 1; PD-1; breast cancer; breast; cancer; oncology; Chinese medicine; herb; herbs; herbal; complementary; immunity; immunology; immunomodulation; immunological; neutrophil; chemotherapy; blood cell; blood cells

Introduction

Chemotherapy-induced neutropenia (CIN) is a common complication and represents the most severe hematological toxicity associated with cancer chemotherapy. This condition has several complications, including severe infections, aggressive hospital management, life-threatening morbidity, and mortality [1]. Briefly, CIN is generally characterized by a decreased absolute neutrophil count (ANC) of <2000 cells/mm^3 in the peripheral blood and is classified into 4 grades according to the National Cancer Institute Common Toxicity Criteria. The classifications of CIN severity are as follows: (1) grade 1 with an ANC of 1500-2000 cells/mm^3, (2) grade 2 with an ANC of 1000-1500 cells/mm^3, (3) grade 3 with an ANC of 500-1000 cells/mm^3, and (4) grade 4 with an ANC <500 cells/mm^3. The current standard treatment for CIN is the use of granulocyte colony-stimulating factor (G-CSF) to attenuate white blood cell (WBC) count and ANC [2]. The use of prophylactic G-CSF also improves patients' quality of life (QoL) [3].

Breast cancer, particularly triple-negative breast cancer (TNBC), encompasses a heterogeneous group of cancer cells, and its treatment remains challenging. In patients with neoadjuvant chemotherapy (NAC)–treated TNBC with residual disease, higher stromal tumor–infiltrating lymphocytes (sTILs) in the resected tumor conferred an improved prognosis [4]. Moreover, higher pre-NAC sTILs and elevated pre-NAC expression of cytotoxic T-cell markers and cytokines are associated with better pathological complete response and overall survival rates [5]. sTILs, with a published cutoff of 30%, are the most widely studied marker of antitumor immunity. Besides, these sTILs could be used to predict improved response to NAC and better prognosis in the context of residual disease of patients lacking pathologic complete response. However, the mechanisms underlying the immunomodulatory effects of chemotherapy on sTILs and the influence of chemotherapy on the tumor-immune microenvironment are poorly understood.

NAC alters both tumor-infiltrating and peripheral immune cells in patients with breast cancer. The reduced levels of signal transducer and activator of transcription 1 (STAT1), activator protein-1 transcription factor subunit (Jun), and nuclear factor kappa B (NF-κB) in B cells, cytotoxic T cells, and natural killer (NK) cells, respectively, from the pretreatment stage to the mid- and posttreatment stages indicated that NAC could inhibit the activation, proliferation, and differentiation of these cells. Moreover, B cell signatures detected using single-cell RNA sequencing are significantly associated with improved survival in patients with breast cancer [6]. However, a significant decrease in the fraction of B cells and C-X-C chemokine receptor type 4, which are involved in maintaining B cell population and function, was reported during and after NAC in peripheral blood mononuclear cells (PBMCs). A previous study also demonstrated that decreased neutrophil levels correlated with a poor response to NAC [7]. High levels of systemic cluster of differentiation 8 (CD8+) cytotoxic T cells are associated with improved survival in patients with metastatic breast cancer [8]. Furthermore, the expression of cytotoxic genes in PBMCs, as opposed to tumor-immune microenvironment, may be invasive biomarkers of persistent micrometastatic disease, ultimately leading to recurrence [9]. Accordingly, lower neutrophil density in patients with breast cancer is associated with metastasis or poor prognosis.

In addition, the percentages of CD3+CD4+CD25+CD127-FoxP3+ regulatory T cells, intermediate monocytes (CD14++CD16+), and HLA-DR-CD11b+CD33+CD15+ myeloid-derived suppressor cells were reported to be significantly higher in the PBMCs of patients with breast cancer. After a single round of NAC, the intensity of CD56 expression in NK cells was significantly increased, as was the percentage of activating receptors NKp44, NKp30, and 2B4 and inhibitory receptors leukocyte-associated immunoglobulin-like receptor (LAIR) and NKG2A. The activity, rather than the proportion of NK cells, is affected [10].

In addition to conventional therapy, an increasing number of patients with breast cancer are seeking Chinese herbal medicine (CHM), as indicated by web-based surveys exploring the perspectives of patients with breast cancer concerning complementary and alternative medicine. CHM has been reported as one of the most common complementary treatments for patients with breast cancer, associated with a possible reduction in the risk of complications, including alopecia [11], neuropathy [12], and fatigue [13], as well as with an

improvement in the overall QoL [14]. Moreover, the results based on claims data suggest that using CHM in combination with conventional therapy may improve the overall survival rate by 45% [15]. However, whether CHM as a complementary therapy can alleviate myelosuppression and neutropenia remains controversial. Previous studies have demonstrated that *shenqi fuzheng* injection [16] and *xihuang* pill or capsule [17] could regulate immunity and reduce tumor markers. Nevertheless, other placebo-controlled randomized controlled trials have stated that using CHM as a complementary therapy did not prevent myelosuppression in patients with breast cancer treated with adjuvant chemotherapy [18].

Understanding how NAC reshapes antitumor immunity, both in the tumor and peripheral compartments, is essential; however, the immunomodulatory effects of NAC are still unclear. The Chinese herbs frequently used in cancer treatment, including *huang qi*, *dang gui*, *huang qin*, *bai zhu*, and *nuzhenzi* (Table 1), could regulate immunity, but how they affect immune cell profiles is mainly unknown. Given that some CHM has been suggested to have immune regulatory effects, we hypothesized that CHM, as a supplementary therapy during chemotherapy, could lower the risk of neutropenia in patients with breast cancer. Accordingly, we are conducting a real-world pragmatic clinical trial to evaluate the effectiveness of CHM as a complementary treatment for neutropenia prevention and immune modulation during chemotherapy in patients with breast cancer.

Table 1. Candidate Chinese herbal medicines in this study.

Pharmaceutical Latin	Chinese name	Applications or effects	Possible side effects
Astragalus membranaceus	*Huang qi*	Enhance immune system, heart function, and blood sugar control	Rash, itching, runny nose, nausea, and diarrhea
Angelica sinensis	*Dang gui*	Heart diseases, menopausal and menstrual symptoms, high blood pressure, and inflammation	Fatigue, allergic reactions, and should not be prescribed to pregnant women and children
Scutellaria baicalensis Georgi	*Huang qin*	Diarrhea, insomnia, dysentery, high blood pressure, hemorrhaging, respiratory infections, and inflammation	Gastric discomfort, nausea and vomiting, and diuresis
Atractylodes macrocephala	*Bai zhu*	Antiulcer, enhance immunity, and antioxidant	Decrease blood pressure and hypoglycemia
Fructus ligustri lucidi	*Nuzhenzi*	Optic neuritis, leukopenia, chronic hepatitis, hyperlipidemia, coronary heart disease, and hypertension	Dizziness and diarrhea

Methods

Participant Recruitment

Participants are being recruited from the Hualien Tzu Chi Hospital. Recruitment began on September 12, 2021, and is expected to continue until December 2024. We expect to complete the study in the middle of 2024.

Ethical Considerations

This study was approved by the research ethics committee of Hualien Tzu Chi Hospital (IRB 110-168-A), and informed consent will be collected from all study participants. The information of patients will be deidentified, and each visit will be compensated for US $16. This study was registered on the International Traditional Medicine Clinical Trial Registry website (ITMCTR2023000054).

Sample Size Estimation

The sample size calculation was based on the mean and SD of the amount of CD4+ between control and treatment groups based on the published literature [19]. By setting the effect size as 0.5, the sample size of each group was estimated as 64 to achieve a power of 0.80 at a significance level of .05 using G*Power software (version 3.1; Heinrich-Heine-Universität Düsseldorf). After accounting for an anticipated dropout rate of 10%, the final sample size was determined to be 70 in each group.

Inclusion Criteria

Patients aged 20 years and older, with a histologically confirmed diagnosis of breast cancer before the initiation of chemotherapy, are considered eligible for this study.

Exclusion Criteria

Patients who will not be able to complete the chemotherapy and follow-up procedures based on oncologists' experience before grouping, those who receive other medication, and those with an Eastern Cooperative Oncology Group score of 3-4 will be excluded from the study.

Study Design

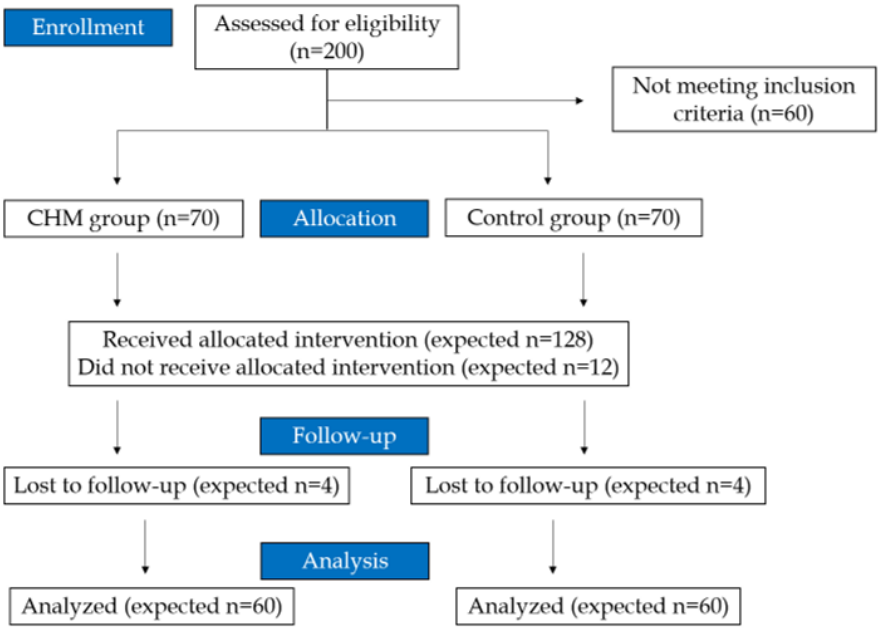
This study is a real-world pragmatic clinical trial conducted at the Hualien Tzu Chi Hospital in Taiwan. Patients with breast cancer scheduled to receive chemotherapy for their cancer treatment will be recruited as per the flowchart shown in Figure 1. Patients willing to receive CHM during chemotherapy are allocated to the CHM group, whereas those in the non-CHM group will not receive CHM.

To evaluate the effectiveness of CHM, the number of WBCs, the ANC, and the use of G-CSF in patients will be measured. The following questionnaires in Taiwanese will be used: (1) the Brief Fatigue Inventory—Taiwanese Version, (2) the World Health Organization Quality of Life-BREF, (3) the National Cancer Institute-Common Terminology Criteria for Adverse Events & Patient Reported Outcomes, and (4) the body

constitution questionnaire. In addition, blood samples will be collected and analyzed for immune profiles and programmed cell death protein 1 (PD-1) expression. Generally, visit 1 represents the first collection of questionnaires and blood samples before the first chemotherapy session. Following the chemotherapy regimen, the first 4 rounds of chemotherapy will be performed every 3 weeks with 3 visits (visits 2-4). Subsequently, 12 rounds of chemotherapy will be performed once per week with another 4 visits (visits 5-8, 3 weeks per visit). Patients will be followed up within 1 month of undergoing chemotherapy. Patients in the CHM group will receive complementary CHM treatment after the first chemotherapy session.

The clinical data will be extracted from the medical history system. The questionnaires will be coded and transformed into numerical values (eg, 5=very satisfied or none, 4=satisfied or light, 3=no change or intermediate, 2=unsatisfied or severe, and 1=very unsatisfied or none) to facilitate statistical analysis. Immune profiles will be analyzed using flow cytometry. The data monitoring committee, clinical trial center of Hualien Tzu Chi Hospital, is independent from the funder and competing interests. The SPIRIT (Standard Protocol Items: Recommendation for Interventional Trials) 2013 checklist is provided in Multimedia Appendix 1 [20].

Figure 1. Flowchart of the study design from enrollment to analysis. CHM: Chinese herbal medicine.



Chemotherapy and CHM Administration Protocol

Upon the diagnosis of breast cancer in a patient, a clinical nurse manages the case. The questionnaire and blood collection before chemotherapy are represented by visit 1 (red arrow in Figure 2). The first 4 rounds of chemotherapy will be performed every 3 weeks, and visits 2-4 will be located in the second, third, and fifth rounds, respectively, 1 day before chemotherapy treatment.

The following 12 rounds of chemotherapy will be performed every week, and visits 5-8 will be located in the first, fourth, seventh, and tenth rounds, respectively, 1 day before chemotherapy treatment. The patients will be followed up within 1 month after chemotherapy (Figure 2 and Table 2). Patients receiving CHM 3 times per day started the first round of chemotherapy.

Figure 2. Chemotherapy, Chinese herbal medicine intervention, and data collection procedures. The questionnaire and blood collection before chemotherapy represent V1 (red arrow). The first 4 rounds of chemotherapy will be performed every 3 weeks (V2 to V4), 1 day before chemotherapy treatment. The subsequent 12 rounds of chemotherapy will be performed every week (V5 to V8), 1 day before chemotherapy treatment. The patients will be followed up (FU) after chemotherapy within 1 month. V: visit.

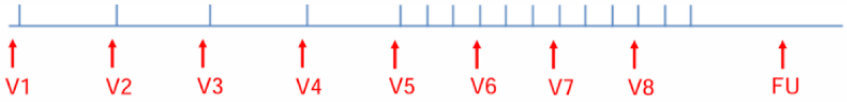


Table 2. Recommended content for the schedule according to the SPIRIT (Standard Protocol Items: Recommendation for Interventional Trials) 2013 guidelines.

Time point	Enrollment	Allocation	Treatment								Follow-up
	Week 1	Week 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	
Enrollment											
Eligibility screen	✓										
Informed consent	✓										
Allocation		✓									
Intervention											
Control group			✓	✓	✓	✓	✓	✓	✓	✓	
CHM[a] group			✓	✓	✓	✓	✓	✓	✓	✓	
Assessment											
ANC[b] or WBC[c]			✓	✓	✓	✓	✓	✓	✓	✓	
Frequency of G-CSF[d] injection			✓	✓	✓	✓	✓	✓	✓	✓	
Questionnaire			✓	✓	✓	✓	✓	✓	✓	✓	
Immune cell profile			✓	✓	✓	✓	✓	✓	✓	✓	
Adverse events			✓	✓	✓	✓	✓	✓	✓	✓	

[a]CHM: Chinese herbal medicine.

[b]ANC: absolute neutrophil count.

[c]WBC: white blood cell.

[d]G-CSF: granulocyte colony-stimulating factor.

Primary Outcome

The primary outcome used in this study is the number of immune cells, including CD4+ and CD8+ T cells (under CD45+ and CD3+ population), CD56+ NK cells (under CD45+ population), CD19+ B cells (under CD45+ population), CD14+ monocytes (under CD45+ population), and CD11c dendritic cells (under CD45+ population), as well as PD-1 expression levels in these cells. For NK cells, the expression of NKG2D will be also confirmed. The analytic panels used are listed in Table 3.

Table 3. Antibodies used for flow cytometry analysis[a].

Cells or conjugate	FITC[b]	PE[c]	APC[d]	APC-Cy7[e]	PE-Cy7[f]
T cells	CD45[g]	CD4	CD8	CD3	PD-1[h]
B and NK[i] cells	CD45	NKG2D	CD56	CD19	PD-1
Monocytes or DCs[j]	CD45	CD14	CD11c	—[k]	PD-1

[a]CD45 (304006), CD4 (317410), CD8 (301014), CD3 (344818), and CD19 (302218) were purchased from Biolegend. PD-1 (25-9969-42), CD56 (17-0567-42), NKG2D (12-5878-42), CD14 (12-0149-42), and CD11c (17-0114-82) were purchased from eBioscience.

[b]FITC: fluorescein isothiocyanate.

[c]PE: phycoerythrin.

[d]APC: allophycocyanin.

[e]APC-Cy7: allophycocyanin-cyanine 7.

[f]PE-Cy7: phycoerythrin-cyanine 7.

[g]CD: cluster of differentiation.

[h]PD-1: programmed cell death protein 1.

[i]NK: natural killer.

[j]DC: dendritic cell.

[k]Not available.

Secondary Outcome

Secondary outcomes include the number of WBCs, the ANC, evaluation of the Brief Fatigue Inventory—Taiwanese Version, World Health Organization Quality of Life-BREF, National Cancer Institute-Common Terminology Criteria for Adverse Events & Patient Reported Outcomes, body constitution questionnaire, and frequency of G-CSF inoculation.

Safety Assessments

All adverse events (AEs) will be recorded throughout the study. In cases where AEs are caused by chemotherapy or CHM intervention, prompt measures will be taken to address those AEs. If needed, participants will be withdrawn from the study. Continuous monitoring of the participant's blood, liver, and kidney functions, body weight, and vital signs will be performed throughout the study. The possible side effects associated with CHM are listed in Table 1.

Flow Cytometry Analysis

Peripheral blood (10 mL) will be collected in ethylenediaminetetraacetic acid–coated tubes and processed within 24 hours of collection. Whole blood (100 µL) will be mixed directly with the fluorescence-conjugated antibodies, including CD45, CD3, CD4, CD8, CD19, CD56, NKG2D, CD14, CD11c, and PD-1 (Table 3), protected from the light, and incubated for 20 minutes at 4 ˚C. Blood cells will be washed twice with 2 mL staining buffer (phosphate buffered saline+2% fetal bovine serum), centrifuged at 300×g for 5 minutes at room temperature, and further incubated with Red Blood Cell Lysis Buffer (Thermo Fisher Scientific) for lysing the erythrocytes for 10 minutes at room temperature. This step may repeat until the red blood cell is completely lyzed. The cells will be further fixed in 2% paraformaldehyde for 10 minutes at room temperature. Subsequently, the cells will be subjected to 2 additional washes with 2 mL staining buffer and centrifuged 300×g for 5 minutes at room temperature. Then, the cells will be preserved at 4 ˚C and analyzed using flow cytometry (Lyric, BD) within 3 days.

Statistical Analysis

All statistical analyses will be performed using the SPSS software (version 13.0; IBM Corp) or SAS software (version 9.4; SAS Institute Inc). Continuous variables will be reported as mean and SD, whereas categorical variables will be reported as frequencies and percentages. The Shapiro-Wilk test will be used to analyze the normality of baseline characteristics and outcome variables. The Mann-Whitney *U* test will be used to compare nonnormally distributed continuous data, and the 2-tailed *t* test will be used to compare normally distributed continuous data. The chi-square test will be used to compare categorical data between the groups. Both primary and secondary outcomes involve repeated measurement data. The Friedman test and repeated measures ANOVA will be used to compare the differences between every visit in each group in nonparametric and parametric data, respectively. In addition, we will use generalized estimating equations or repeated measures ANOVA to compare the differences between the 2 groups. We will evaluate the risks of each clinical characteristic by the multivariate logistic regression analysis and adjust the age and other factors or characteristics that may have bias in the analysis. We set $P<.05$ as a significant difference. All data will be recorded in a case report form.

Results

This study was approved by the research ethics committee of Hualien Tzu Chi Hospital (IRB 110-168-A). The enrollment process began in September 2021 and will stop in December 2024. A total of 140 patients will be recruited. Data cleaning and analysis are expected to finish in the middle of 2025.

Discussion

Advantages and Disadvantages of Selected CHM

Traditional Chinese medicine is the most commonly used drug in Taiwan and shows significant potential in alleviating side effects related to anticancer treatments, such as chemotherapy. Even with sourcing from traditional Chinese medicine pharmaceutical factories in Taiwan certified under the Good Manufacturing Practices guidelines, our rigorous approach involves continuous toxicity monitoring throughout the study to minimize AEs.

Astragalus polysaccharide (APs), a bioactive extract of *Astragalus membranaceus*, has many biological activities, including anti-inflammatory, antioxidant, and immunoregulatory properties [21,22]. APs may modulate immunity by activating the toll-like receptor 4 (TLR4)–mediated myeloid differentiation primary response 88 (MyD88)–dependent signaling pathway [22] and induce apoptosis in human hepatocellular carcinoma cells by decreasing the expression of Notch1 [23]. Furthermore, APs inhibit TNBC cell invasion and proliferation and induce apoptosis through the PIK3CG/AKT/BCL2 pathway [24]. APs could activate macrophages to release nitric oxide and tumor necrosis factor alpha, directly blocking breast cancer cell growth [25]. *A membranaceus* extract has also been reported to inhibit breast cancer cell proliferation via the PI3K/AKT/mTOR signaling pathway [26].

Polysaccharides of *Angelica sinensis (Oliv) Diels* promote apoptosis in breast cancer cells via cyclic adenosine monophosphate response–binding protein (CREB)–regulated caspase-3 activation [27]. In a population-based case-control study in Taiwan, the use of *A sinensis* showed a significant protective effect on breast cancer (adjusted odds ratio 0.95, 95% CI 0.93-0.98) [28].

Baicalin, a flavonoid compound isolated from the roots of *Scutellaria lateriflora*Georgi, enhanced the chemosensitivity of breast cancer cells to doxorubicin via the upregulation of oxidative stress–mediated mitochondria-dependent apoptosis [29] and inhibited the metastasis and epithelial-to-mesenchymal transition of highly aggressive breast cancer cells by targeting β-catenin signaling [30].

Atractylenolide-I, a major bioactive component from *Atractylodes macrocephala*, suppressed tumorigenesis of breast cancer by inhibiting TLR4-mediated NF-κB signaling pathway [31] and sensitized TNBC cells to paclitaxel by blocking connective tissue growth factor expression [32].

Fructus ligustri lucidi could enhance chemosensitivity and induce apoptosis via Tbx3 suppression in human colorectal carcinoma cells [33]. Besides, it has been reported to induce apoptosis in glioma cells in vitro and in vivo through the regulation of the AKT/mTOR pathway [34]. In addition, it induces senescence and apoptosis in hepatocellular carcinoma cells by upregulating p21 [35].

While these CHMs have mostly exhibited antitumor effects, their effects on immune cells have not been fully elucidated. Hence, we aimed to investigate the effects of these CHMs as a complementary treatment on neutropenia, a common chemotherapy side effect known to damage qi and aggravate its depletion. Notably, these CHMs not only regulate qi but also modulate immune cells and their functions. Thus, this study may provide additional insights into therapeutic strategies for breast cancer, including immunotherapy.

Strengths and Limitations

The strength of this study lies in its pragmatic trial design conducted in a clinical setting. Compared with randomized controlled trials, this study design has higher generalizability and provides evidence of its effectiveness in daily practice. This study has some limitations that may have affected the results. First, the internal validity was compromised. A pragmatic clinical trial design could achieve greater generalizability of the effectiveness of CHM as a complementary treatment. To improve internal validity, the statistician analyzing the data was blinded to the group assignment and adjusted for all confounding variables during data analysis. Second, there was a lack of important clinical characteristics, such as dietary and exercise habits. Although dietary intake and moderate-intensity aerobic exercise are crucial for patients with cancer during chemotherapy [36], we could not control daily diet and exercise intensity in this real-world clinical trial. In our clinical setting, oncology nurses educate all participants about the importance of healthy dietary intake and exercise habits during chemotherapy. Third, due to financial considerations, the observation time was not long enough to detect the change in the lymphocyte levels after completing chemotherapy, and further long-term and large-scale studies are needed to evaluate the variation in the number of WBCs and the ANC during the recovery phase after chemotherapy.

Conclusions

In conclusion, we have proposed an open-label, single-center, pragmatic clinical trial and a real-world study to evaluate the effectiveness and safety of CHMs for treating CIN in patients with breast cancer. Using this study platform, we will analyze the effects of CHM on the regulation of QoL by evaluating the complications of chemotherapy and immune cell profiles. The findings of this study may contribute to developing an effective intervention for chemotherapy-related neutropenia in patients with breast cancer in clinical practice.

Acknowledgments

The authors thank the clinical nurse, Yu-Li Lin, for case management and questionnaires and the research assistant, Yin-Mei Chen, for the analysis of the immune cell profile. The authors also thank Yu-Hsien Chiang and Editage for the English editing of the paper. This study is funded by the National Research Institute of Chinese Medicine, Ministry of Health and Welfare, Taiwan (MOHW110-NRICM-M-124-122005 and MOHW111-NRICM-M-124-122005), and the Buddhist Tzu Chi Medical Foundation (TCMF-CM2-111-09).

Authors' Contributions

HSS, SCC, TFW, CYP, and CCL conceptualized and designed the study. KHW, HSS, and SCC were involved in data analysis. KHW and HSS drafted the paper. HSS, CWL, SCC, TFW, WHH, and YFW were involved in the selection and enrollment of participants. All authors finally approved the paper. CCL was responsible for the integrity of the work.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendation for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 119 KB - resprot_v13i1e55662_app1.pdf]

References

1. Partridge AH, Burstein HJ, Winer EP. Side effects of chemotherapy and combined chemohormonal therapy in women with early-stage breast cancer. J Natl Cancer Inst Monogr 2001(30):135-142 [FREE Full text] [doi: 10.1093/oxfordjournals.jncimonographs.a003451] [Medline: 11773307]
2. Kuderer NM, Dale DC, Crawford J, Lyman GH. Impact of primary prophylaxis with granulocyte colony-stimulating factor on febrile neutropenia and mortality in adult cancer patients receiving chemotherapy: a systematic review. J Clin Oncol 2007;25(21):3158-3167. [doi: 10.1200/JCO.2006.08.8823] [Medline: 17634496]
3. Padilla G, Ropka ME. Quality of life and chemotherapy-induced neutropenia. Cancer Nurs 2005;28(3):167-171. [doi: 10.1097/00002820-200505000-00001] [Medline: 15915058]

4. Luen SJ, Salgado R, Dieci MV, Vingiani A, Curigliano G, Gould RE, et al. Prognostic implications of residual disease tumor-infiltrating lymphocytes and residual cancer burden in triple-negative breast cancer patients after neoadjuvant chemotherapy. Ann Oncol 2019;30(2):236-242 [FREE Full text] [doi: 10.1093/annonc/mdy547] [Medline: 30590484]
5. Li X, Warren S, Pelekanou V, Wali V, Cesano A, Liu M, et al. Immune profiling of pre- and post-treatment breast cancer tissues from the SWOG S0800 neoadjuvant trial. J Immunother Cancer 2019;7(1):88 [FREE Full text] [doi: 10.1186/s40425-019-0563-7] [Medline: 30967156]
6. Hu Q, Hong Y, Qi P, Lu G, Mai X, Xu S, et al. Atlas of breast cancer infiltrated B-lymphocytes revealed by paired single-cell RNA-sequencing and antigen receptor profiling. Nat Commun 2021;12(1):2186 [FREE Full text] [doi: 10.1038/s41467-021-22300-2] [Medline: 33846305]
7. Zhou H, Li G, Yin J, Wang T, Hu H, Li T, et al. Neoadjuvant chemotherapy alters peripheral and tumour-infiltrating immune cells in breast cancer revealed by single-cell RNA sequencing. Clin Transl Med 2021;11(12):e621 [FREE Full text] [doi: 10.1002/ctm2.621] [Medline: 34919339]
8. Larsson AMJ, Nordström O, Johansson A, Rydén L, Leandersson K, Bergenfelz C. Peripheral blood mononuclear cell populations correlate with outcome in patients with metastatic breast cancer. Cells 2022;11(10):1639 [FREE Full text] [doi: 10.3390/cells11101639] [Medline: 35626676]
9. Axelrod ML, Nixon MJ, Gonzalez-Ericsson PI, Bergman RE, Pilkinton MA, McDonnell WJ, et al. Changes in peripheral and local tumor immunity after neoadjuvant chemotherapy reshape clinical outcomes in patients with breast cancer. Clin Cancer Res 2020;26(21):5668-5681 [FREE Full text] [doi: 10.1158/1078-0432.CCR-19-3685] [Medline: 32826327]
10. Foulds GA, Vadakekolathu J, Abdel-Fatah TMA, Nagarajan D, Reeder S, Johnson C, et al. Immune-phenotyping and transcriptomic profiling of peripheral blood mononuclear cells from patients with breast cancer: identification of a 3 gene signature which predicts relapse of triple negative breast cancer. Front Immunol 2018;9:2028 [FREE Full text] [doi: 10.3389/fimmu.2018.02028] [Medline: 30254632]
11. Yu F, Li Y, Zou J, Jiang L, Wang C, Tang Y, et al. The Chinese herb Xiaoaiping protects against breast cancer chemotherapy-induced alopecia and other side effects: a randomized controlled trial. J Int Med Res 2019;47(6):2607-2614 [FREE Full text] [doi: 10.1177/0300060519842781] [Medline: 31099281]
12. Abe H, Kawai Y, Mori T, Tomida K, Kubota Y, Umeda T, et al. The Kampo medicine Goshajinkigan prevents neuropathy in breast cancer patients treated with docetaxel. Asian Pac J Cancer Prev 2013;14(11):6351-6356 [FREE Full text] [doi: 10.7314/apjcp.2013.14.11.6351] [Medline: 24377531]
13. Deng SM, Chiu AF, Wu SC, Huang YC, Huang SC, Chen SY, et al. Association between cancer-related fatigue and traditional Chinese medicine body constitution in female patients with breast cancer. J Tradit Complement Med 2021;11(1):62-67 [FREE Full text] [doi: 10.1016/j.jtcme.2020.08.005] [Medline: 33511063]
14. Liew AC, Peh KK, Tan BS, Zhao W, Tangiisuran B. Evaluation of chemotherapy-induced toxicity and health-related quality of life amongst early-stage breast cancer patients receiving Chinese herbal medicine in Malaysia. Support Care Cancer 2019;27(12):4515-4524. [doi: 10.1007/s00520-019-04724-1] [Medline: 30911917]
15. Lee YW, Chen TL, Shih YRV, Tsai CL, Chang CC, Liang HH, et al. Adjunctive traditional Chinese medicine therapy improves survival in patients with advanced breast cancer: a population-based study. Cancer 2014;120(9):1338-1344 [FREE Full text] [doi: 10.1002/cncr.28579] [Medline: 24496917]
16. Zhang H, Chen T, Shan L. ShenQi FuZheng injection as an adjunctive treatment to chemotherapy in breast cancer patients: a meta-analysis. Pharm Biol 2019;57(1):612-624 [FREE Full text] [doi: 10.1080/13880209.2019.1660383] [Medline: 31522596]
17. Ge A, Yang K, Deng X, Zhao D, Ge J, Liu L. The efficacy and safety of Xihuang Pill/capsule in adjuvant treatment of breast cancer: a systematic review and meta-analysis of 26 randomized controlled trials. J Ethnopharmacol 2022;295:115357 [FREE Full text] [doi: 10.1016/j.jep.2022.115357] [Medline: 35545184]
18. Hong J, Chen X, Huang J, Li C, Zhong L, Chen L, et al. Danggui Buxue Decoction, a classical formula of traditional Chinese medicine, fails to prevent myelosuppression in breast cancer patients treated with adjuvant chemotherapy: a prospective study. Integr Cancer Ther 2017;16(3):406-413 [FREE Full text] [doi: 10.1177/1534735416675952] [Medline: 28818031]
19. Xiong Y, Zhu Y, Xu X. Effects of Huaier Granule combined with TAC chemotherapy on immunologic function and prognosis in triple negative breast cancer patients after operation. Int J Surgery 2015;12:608-611 [FREE Full text]
20. Chan AW, Tetzlaff JM, Altman DG, Dickersin K, Moher D. SPIRIT 2013: new guidance for content of clinical trial protocols. Lancet 2013;381(9861):91-92. [doi: 10.1016/S0140-6736(12)62160-6] [Medline: 23305999]
21. Pu X, Ma X, Liu L, Ren J, Li H, Li X, et al. Structural characterization and antioxidant activity in vitro of polysaccharides from angelica and astragalus. Carbohydr Polym 2016;137:154-164. [doi: 10.1016/j.carbpol.2015.10.053] [Medline: 26686116]
22. Zhou L, Liu Z, Wang Z, Yu S, Long T, Zhou X, et al. Astragalus polysaccharides exerts immunomodulatory effects via TLR4-mediated MyD88-dependent signaling pathway in vitro and in vivo. Sci Rep 2017;7:44822 [FREE Full text] [doi: 10.1038/srep44822] [Medline: 28303957]

23. Huang WH, Liao WR, Sun RX. Astragalus polysaccharide induces the apoptosis of human hepatocellular carcinoma cells by decreasing the expression of Notch1. Int J Mol Med 2016;38(2):551-557 [FREE Full text] [doi: 10.3892/ijmm.2016.2632] [Medline: 27279598]
24. Liu C, Wang K, Zhuang J, Gao C, Li H, Liu L, et al. The modulatory properties of Astragalus membranaceus treatment on triple-negative breast cancer: an integrated pharmacological method. Front Pharmacol 2019;10:1171 [FREE Full text] [doi: 10.3389/fphar.2019.01171] [Medline: 31680955]
25. Li W, Song K, Wang S, Zhang C, Zhuang M, Wang Y, et al. Anti-tumor potential of astragalus polysaccharides on breast cancer cell line mediated by macrophage activation. Mater Sci Eng C Mater Biol Appl 2019;98:685-695 [FREE Full text] [doi: 10.1016/j.msec.2019.01.025] [Medline: 30813073]
26. Zhou R, Chen H, Chen J, Chen X, Wen Y, Xu L. Extract from Astragalus membranaceus inhibit breast cancer cells proliferation via PI3K/AKT/mTOR signaling pathway. BMC Complement Altern Med 2018;18(1):83 [FREE Full text] [doi: 10.1186/s12906-018-2148-2] [Medline: 29523109]
27. Zhou WJ, Wang S, Hu Z, Zhou ZY, Song CJ. Angelica sinensis polysaccharides promotes apoptosis in human breast cancer cells via CREB-regulated caspase-3 activation. Biochem Biophys Res Commun 2015;467(3):562-569. [doi: 10.1016/j.bbrc.2015.09.145] [Medline: 26431878]
28. Chen JY, Wang YH, Hidajah AC, Li CY. A population-based case-control study on the association of exposure Angelica sinensis with risk of breast cancer. J Tradit Complement Med 2020;10(5):454-459 [FREE Full text] [doi: 10.1016/j.jtcme.2019.10.003] [Medline: 32953561]
29. Lin MY, Cheng WT, Cheng HC, Chou WC, Chen HI, Ou HC, et al. Baicalin enhances chemosensitivity to doxorubicin in breast cancer cells via upregulation of oxidative stress-mediated mitochondria-dependent apoptosis. Antioxidants (Basel) 2021;10(10):1506 [FREE Full text] [doi: 10.3390/antiox10101506] [Medline: 34679641]
30. Zhou T, Zhang A, Kuang G, Gong X, Jiang R, Lin D, et al. Baicalin inhibits the metastasis of highly aggressive breast cancer cells by reversing epithelial-to-mesenchymal transition by targeting β-catenin signaling. Oncol Rep 2017;38(6):3599-3607 [FREE Full text] [doi: 10.3892/or.2017.6011] [Medline: 29039569]
31. Long F, Lin H, Zhang X, Zhang J, Xiao H, Wang T. Atractylenolide-I suppresses tumorigenesis of breast cancer by inhibiting toll-like receptor 4-mediated nuclear factor-κb signaling pathway. Front Pharmacol 2020;11:598939 [FREE Full text] [doi: 10.3389/fphar.2020.598939] [Medline: 33363472]
32. Wang M, Li XZ, Zhang MX, Ye QY, Chen YX, Chang X. Atractylenolide-I sensitizes triple-negative breast cancer cells to paclitaxel by blocking CTGF expression and fibroblast activation. Front Oncol 2021;11:738534 [FREE Full text] [doi: 10.3389/fonc.2021.738534] [Medline: 34692516]
33. Zhang JF, He ML, Dong Q, Xie WD, Chen YC, Lin MCM, et al. Aqueous extracts of Fructus Ligustri Lucidi enhance the sensitivity of human colorectal carcinoma DLD-1 cells to doxorubicin-induced apoptosis via Tbx3 suppression. Integr Cancer Ther 2011;10(1):85-91 [FREE Full text] [doi: 10.1177/1534735410373921] [Medline: 20702496]
34. Jeong JC, Kim JW, Kwon CH, Kim TH, Kim YK. Fructus ligustri lucidi extracts induce human glioma cell death through regulation of Akt/mTOR pathway in vitro and reduce glioma tumor growth in U87MG xenograft mouse model. Phytother Res 2011;25(3):429-434. [doi: 10.1002/ptr.3265] [Medline: 20737659]
35. Hu B, Du Q, Deng S, An HM, Pan CF, Shen KP, et al. Ligustrum lucidum Ait. fruit extract induces apoptosis and cell senescence in human hepatocellular carcinoma cells through upregulation of p21. Oncol Rep 2014;32(3):1037-1042 [FREE Full text] [doi: 10.3892/or.2014.3312] [Medline: 25017491]
36. Mohamady HM, Elsisi HF, Aneis YM. Impact of moderate intensity aerobic exercise on chemotherapy-induced anemia in elderly women with breast cancer: a randomized controlled clinical trial. J Adv Res 2017;8(1):7-12 [FREE Full text] [doi: 10.1016/j.jare.2016.10.005] [Medline: 27872759]

Abbreviations

AE: adverse event
ANC: absolute neutrophil count
AP: Astragalus polysaccharide
CD8: cluster of differentiation 8
CHM: Chinese herbal medicine
CIN: chemotherapy-induced neutropenia
CREB: cyclic adenosine monophosphate response–binding protein
G-CSF: granulocyte colony-stimulating factor
LAIR: leukocyte-associated immunoglobulin-like receptor
MyD88: myeloid differentiation primary response 88
NAC: neoadjuvant chemotherapy
NF-κB: nuclear factor kappa B
NK: natural killer
PBMC: peripheral blood mononuclear cell

PD-1: programmed cell death protein 1
QoL: quality of life
SPIRIT: Standard Protocol Items: Recommendation for Interventional Trials
STAT1: signal transducer and activator of transcription 1
sTIL: stromal tumor–infiltrating lymphocyte
TLR4: toll-like receptor 4
TNBC: triple-negative breast cancer
WBC: white blood cell

Edited by A Mavragani; submitted 20.12.23; peer-reviewed by Y Ji, K Zhang; comments to author 05.01.24; revised version received 25.01.24; accepted 01.02.24; published 11.03.24.

Please cite as:
Wang KH, Shen HS, Chu SC, Wang TF, Lin CW, Huang WH, Wu YF, Ho CC, Pang CY, Li CC
Effectiveness of Chinese Herbal Medicine as a Complementary Treatment for Neutropenia Prevention and Immunity Modulation During Chemotherapy in Patients With Breast Cancer: Protocol for a Real-World Pragmatic Clinical Trial
JMIR Res Protoc 2024;13:e55662
URL: https://www.researchprotocols.org/2024/1/e55662
doi:10.2196/55662
PMID:38466979

Protocol

Navigating Social Cognitive Impairments in Schizophrenia Spectrum Disorders: Protocol for a Pilot Pre-Post Quasi-Experimental Study for Remote Avatar-Assisted Cognitive Remediation Therapy

Elisabeth Thibaudeau[1,2], PhD; Elodie Peyroux[3], PhD; Nicolas Franck[3,4], MD, PhD; Hannah Carling[1,2], BA; Martin Lepage[1,2], PhD

[1]Department of Psychiatry, McGill University, Montreal, QC, Canada

[2]Douglas Research Center, Montreal, QC, Canada

[3]Centre Hospitalier Le Vinatier, Lyon, France

[4]Université Claude-Bernard-Lyon-I, Lyon, France

Corresponding Author:
Elisabeth Thibaudeau, PhD
Douglas Research Center
6875 Boulevard LaSalle
Montreal, QC, H4H 1R3
Canada
Phone: 1 514 761 6131 ext 4393
Email: elisabeth.thibaudeau@mail.mcgill.ca

Abstract

Background: Social cognitive impairments are prevalent in schizophrenia spectrum disorder (SSD) and have detrimental effects on functioning. Cognitive remediation (CR) has shown its efficacy in improving social cognitive impairments, although the transfer of these skills to daily life and the personalization of these interventions remain challenging. RC2S (*Remédiation Cognitive de la Cognition Sociale dans la Schizophrénie*; Cognitive remediation of social cognition in Schizophrenia) is a French CR that combines the learning of strategies and practice using paper-and-pencil exercises and digital relational simulations. This French program was designed as an in-person intervention.

Objective: This project aims to culturally adapt the RC2S program, in French-Canadian and North American English and to assess the feasibility, acceptability, safety, and implementation of a remote version in people with SSD. An exploratory objective is to assess the preliminary effect of remote RC2S on goal attainment, social cognition, and psychosocial outcomes.

Methods: We will use a pre-post quasi-experimental design. First, the translation and cultural adaptation in North American English and French-Canadian of RC2S is presented. Then, 20 participants aged ≥18 years with a diagnosis of SSD, presenting with a subjective or an objective impairment in social cognition, will be included to receive RC2S. In addition, 5 therapists will be included as research participants to assess their perspective on RC2S. Participants with SSD will undergo a baseline remote assessment of their social cognition, clinical symptoms, and functioning. They will then start remote RC2S for 24 biweekly individual 1-hour sessions with a therapist. Following the case formulation and goal setting, participants will complete personalized paper-and-pencil exercises to develop strategies and integrative digital relational simulations, during which they will help an avatar navigate through a variety of social contexts and relationships. The last 2 sessions are dedicated to the transfer to daily life. All participants will complete in-session questionnaires assessing therapeutic alliance, motivation, acceptability, feasibility, and implementation. Following RC2S, the participants with SSD will repeat the same assessment as the baseline. Descriptive statistics will be used to summarize the data about acceptability, feasibility, safety, and implementation. To assess the preliminary effect of RC2S, an intention-to-treat approach will be used with linear mixed models for repeated measures with fixed effects of time.

Results: So far, 45% (9/20) of participants with SSD (mean age 37.9, SD 9.3 years) have completed the project. They received a mean of 20.5 out of 24 (SD 3.5) sessions of RC2S. A total of 5 therapists also completed the project.

Conclusions: Improving social cognitive impairments is an important target in SSD to promote functional recovery. Using digital technologies to address these impairments and deliver the intervention is a promising approach to increase the ecological validity of CR and access to the intervention.

Trial Registration: ClinicalTrials.gov NCT05017532; https://classic.clinicaltrials.gov/ct2/show/NCT05017532

International Registered Report Identifier (IRRID): DERR1-10.2196/54251

(JMIR Res Protoc 2024;13:e54251) doi:10.2196/54251

KEYWORDS

social cognition; schizophrenia spectrum disorder; psychosis; cognitive remediation therapy; social cognitive training; digital relational simulation; cultural adaptation; feasibility; acceptability; mobile phone

Introduction

Background

Social cognitive impairments are among the most important barriers to functional recovery in people with schizophrenia spectrum disorder (SSD) [1,2]. Significant relationships have been highlighted between social cognition and personal recovery [3] as well as between different areas of functioning, including social functioning, productive activities, and instrumental activities of daily living [1,2]. Thus, social cognitive impairments are a relevant treatment target to support recovery in people with SSD.

Social cognition refers to the mental processes underlying social interactions, including the abilities involved in perceiving and interpreting social information to guide social interactions [4,5]. The experts of the Social Cognition Psychometric Evaluation initiative have selected the most relevant social cognitive domains in schizophrenia, including emotion processing (ie, perceiving and using emotions), social perception (ie, decoding and interpreting social cues in others, including social context processing and social knowledge), theory of mind (ie, the ability to represent the mental states of others including the inference of intentions, dispositions, or beliefs), and attributional style and bias (ie, the way in which individuals explain the causes or make sense of social events or interactions) [6]. Social cognitive impairments are highly prevalent in people with SSD [7,8] and have been observed in all phases of the illness [7,9,10]. A recent meta-analysis assessing the performance in each of the 4 main domains of social cognition in people with SSD, compared with healthy controls, revealed decreased performance in emotion processing (medium to large effect size), social perception (large effect size), theory of mind (large effect size), and attributional bias (small to medium effect size) [8].

Cognitive remediation (CR) therapy is an evidence-based intervention that has shown benefits for social cognitive impairments in people with SSD [11,12]. CR has been defined by a consortium of experts as a "behavioral training intervention targeting cognitive deficits (attention, memory, executive function, social cognition, or metacognition), using scientific principles of learning, with the ultimate goal of improving functional outcomes. Its effectiveness is enhanced when provided in a context (formal or informal) that provides support and opportunity for extending to everyday functioning" (Cognitive Remediation Experts Working Group, 2010 [13]). CR for social cognition falls under the umbrella term of social cognitive training that includes targeted programs to train specific domains of social cognition (eg, [14,15]), broad-based interventions targeting multiple domains (eg, [16-18]), and interventions combining the training of neurocognition (eg, attention) and social cognition (eg, [19,20]) [21,22]. These programs include strategy learning as well as the practice of these strategies through various social stimuli, such as pictures, videos, or role-playing.

Several meta-analyses have assessed the effect of social cognitive training [12,21,22], revealing their effectiveness in most social cognitive domains. In 2020, Nijman et al [22] published a network meta-analysis comparing targeted and broad-based interventions with or without training in neurocognition, active control interventions, and treatment as usual. The results suggest that broad-based interventions targeting multiple domains and focusing solely on social cognition (ie, without the training of neurocognitive functions) yielded the most consistent effect on most social cognitive domains, including emotion recognition (medium effect size), social perception (large effect size), and theory of mind (medium effect size), in addition to benefits on social functioning. No significant effect was observed for attributional bias. In 2022, Yeo et al [12] also performed a network meta-analysis with supplementary references and included only social cognitive training with or without minimal training in neurocognition. The results suggest medium effect sizes for social perception and theory of mind, and a medium to large effect size for emotion recognition. No significant effect was observed for attributional bias, in addition to a small and nonsignificant effect on functioning.

Altogether, these results suggest a significant effect of social cognitive training on most social cognitive domains in people with SSD, while also highlighting that the effect on functioning remains limited and influenced by the methodology of the studies. The results of a recent systematic review [23] focusing on the methodological quality and intervention modalities of social cognitive interventions for people with SSD have concluded the need to improve skill transfer during social cognitive training to everyday functioning. This review also highlights the importance of investigating the service user's perspective and personal goals in treatment to address their needs and priorities.

Thus, the results of these recent systematic reviews and meta-analyses suggest the potential benefit of using a social cognitive training program with a broad-based approach (ie,

targeting multiple domains of social cognition), tailored to the person's needs, and focusing on transferring skills to functioning. Previous social cognitive training programs present with several strengths and have shown their efficacy to improve different domains of social cognition, particularly lower-level domains such as emotion recognition and social perception. However, as proposed by Peyroux and Franck [24], most programs currently use relatively basic deductive reasoning and associations and focus on only one domain of social cognition at a time, which is not representative of everyday social interactions that involve multiple domains of social cognition simultaneously. Using a program that emulates complex and multimodal real-life interactions, in addition to learning strategies to improve each domain of social cognition, might generalize learning to higher-order processes such as theory of mind or attributional bias. Furthermore, group interventions might not always be appropriate; an individualized and personalized approach using ecological digital relational simulations could help people with SSD practice these new skills in a safe environment with a therapist.

The program *Remédiation Cognitive de la Cognition Sociale dans la Schizophrénie* (RC2S; Cognitive remediation of social cognition in Schizophrenia) is a French personalized social cognitive training targeting the 4 main domains of social cognition in SSD [6]. This program uses a practice and strategy learning approach to target the person's specific social cognitive deficits while also building on social cognitive domains that are preserved or less affected. RC2S includes paper-and-pencil sessions dedicated to learning strategies to improve the different social cognitive domains as well as integrative computerized ecological sessions to further practice these skills by interacting with an avatar in different social contexts and relationships through digital relational simulations [25]. A total of 2 case studies and a randomized controlled trial (manuscript in preparation) conducted in France with people with SSD have provided preliminary evidence of the acceptability, feasibility, and efficacy of RC2S with the report of significant improvements in social cognitive and functional impairments [24,26]. Although these preliminary results are encouraging, social stimuli and social behaviors can be interpreted differently and are influenced by the culture of the geographic regions in which they are assessed [8,27]. Thus, it is necessary to adapt social cognitive training programs to the language, expressions, and context of the culture in which they are used and to assess their effects in these different settings. This is particularly true for social cognitive training programs using digital relational simulations that include both verbal and nonverbal cues.

In addition, there is also a need to develop social cognitive interventions that are accessible to many people with SSD. The COVID-19 pandemic has highlighted the important vulnerability of health care delivery for people with SSD and the need to adapt evidence-based interventions such as CR to increase access to mental health care services. Remote interventions have rapidly developed in recent years, and these interventions address important factors that are known to limit access to psychiatric care for people with SSD, such as territorial disparities in the provision of health care services, geographic distance, or symptoms such as avolition or social withdrawal. Furthermore, for people with SSD within their process of recovery, it can also be a challenge to combine work, school, or other engagements with multiple visits to the clinic to receive CR. Delivering care remotely could also decrease the stigma and the self-stigma associated with visiting a hospital or a clinic to receive mental health care.

Objectives

This project aims to culturally adapt (ie, language, expression, and geographic context) the French program RC2S in North American English and French-Canadian. As RC2S was initially developed as an in-person intervention, we also aim to assess the feasibility, acceptability, safety, and implementation of the remote French-Canadian and North American English versions of RC2S in people with SSD. An additional exploratory objective is to assess the preliminary effect of remote RC2S on goal attainment, social cognition, and other psychosocial variables (eg, functioning and positive and negative symptoms). The data from this preliminary study will provide information for a future efficacy study of remote RC2S (randomized controlled trial).

Methods

Ethical Considerations

This project was approved by the Ethics Committee of the Montreal West Island Integrated University Health and Social Services Centre (#2022-333, IUSMD-21-34) on August 17, 2021.

Cultural Adaptation of RC2S

From August 2021 to December 2021, our team adapted and translated the RC2S program into North American English and French-Canadian. For the North American English version, the translation was performed by a professional agency and further revised by the bilingual members of our team. For the French-Canadian version, all scenarios were revised to adapt expressions and turns of phrase. The names of places and characters were also revised in both versions to culturally adapt to the scenarios. All audio files were then recorded by professional actors, and the realization was performed using the studio SFX based in Quebec City, Quebec, Canada. Our team then applied North American English and French-Canadian audio files to the computerized scenarios and videos in collaboration with the company Happy Neuron.

Study Design

This study is a pre-post quasi-experimental design. Quantitative measures will be used to assess the preliminary effect of RC2S on primary and secondary outcomes. To assess the feasibility, acceptability, and implementation of RC2S, homemade questionnaires including both quantitative variables and open-ended questions will be used.

Recruitment

A total of 2 categories of participants will be recruited for this study: participants with SSD and participants delivering the intervention (therapists).

Participants With SSD

We aim at recruiting 20 participants with SSD. For these participants, the inclusion criteria will be as follows: (1) a diagnosis of schizophrenia or a related psychotic disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; (2) being followed and treated by a clinician at the Douglas Mental Health University Hospital; (3) being aged ≥18 years; (4) having either a self-report or an objective impairment (≤1 SD) in at least 1 social cognition domain (ie, emotion recognition, theory of mind, attributional bias, or social perception); (5) being considered symptomatically stable and capable of using the web-based platforms, as judged by their primary clinicians (ie, psychiatrist, case manager, or psychologist); (6) having access to the internet and to a private space (a room where the participant can be alone); and (7) being able to nominate an emergency contact as the study is conducted remotely. For this group, the exclusion criteria will be as follows: (1) evidence of an organic cause for cognitive difficulties (eg, neurological disease and history of brain trauma), (2) history of intellectual disability or autism spectrum disorder, (3) being hospitalized at the time of recruitment, and (4) inability to speak or read French or English.

Participants with SSD will be recruited through convenience sampling at the Douglas Mental Health University Institute. Participants will be recruited from (1) direct reference of the treating psychologist at the Centre d'Intervention Psychologique Personnalisé pour la Psychose (Ci3P; a clinic dedicated to psychological treatments for psychotic disorders), (2) directly from the individual's case manager following a clinic visit by the research coordinator to explain the research project, or (3) from our list of participants who were recruited in previous studies and gave their consent to be recontacted for future studies. A research assistant will call the participant to explain the research project, including the inclusion criteria, the assessment and treatment procedures, and the consent form. During this first contact, the research assistant will also assess access to the digital technology required for this project (eg, a smartphone, a tablet, or a computer).

Therapists

We aim at recruiting 5 therapists who will be included if they have a master's or doctoral degree in psychology, neuropsychology, or any relevant field or relevant clinical experience. They will be excluded if they are unable to speak or read French or English. The therapists will be recruited among the professionals offering services at the Douglas Mental Health Institute as well as research assistants in the Comprehensive Research into Schizophrenia and Other Psychopathologies laboratory. Participation in the project will be optional for those offering RC2S. Once they agree to act as therapists for this intervention and complete their training, they will be offered to participate in the research project. If they are interested, a research assistant will contact them by phone or a secure videoconferencing platform to complete a short screening and present the consent form. If they agree to participate, a short sociodemographic questionnaire will be administered. If they refuse to participate, the therapists will still be allowed to offer the intervention.

Procedure

Participants With SSD

The assessments will be conducted remotely via a secure videoconference platform by a trained research assistant physically present at the Douglas Research Center. A baseline will first be conducted during which the participants will read and sign the consent form and will be invited to ask any questions they may have. If they choose to participate, they will be invited to complete the remote assessment, which will last for approximately 2 hours. To continue with the intervention, the participant will have to present with a self-reported or an objective impairment in at least one of the main domains of social cognition, which will be determined by the baseline assessment. If a participant does not present with such a complaint or an impairment, financial compensation for the assessment will be provided, and it will be possible for the participant to be contacted for other psychosocial and cognitive interventions offered at the Ci3P.

For participants presenting with at least 1 social cognitive complaint or impairment following the baseline assessment, the intervention with RC2S will begin for 12 weeks. The intervention will be conducted remotely by trained therapists using a secure videoconference platform. In-session questionnaires will be administered to participants to assess their motivation toward treatment, their perception of the therapeutic alliance, their acceptability of the program, and its implementation. A posttest assessment will be conducted directly after 12 weeks of treatment.

Therapist

The therapists will be contacted by phone or videoconference to administer a short screening questionnaire and to present the informed consent form. If they are eligible and interested in participating, a short sociodemographic questionnaire will be administered. In addition, the in-session questionnaires will be completed at the same time as the participants with SSD. These questionnaires will assess their perception of the therapeutic alliance, the program, and the motivation of their client toward treatment.

Measures

For participants with SSD, the primary outcomes will consist of (1) therapy goal attainment (ie, assessing if the participants have not reached, reached partially, or reached completely their initial CR goals in daily life) and (2) the 4 main domains of social cognition (emotion recognition, social knowledge, theory of mind, and attributional bias) in addition to the functional impact of social cognitive impairments. The secondary outcomes will include measures of symptoms (positive and negative symptoms, depression, and social anxiety), functioning, recovery, and cognitive biases. In addition, complementary outcomes pertaining to different aspects of RC2S (eg, program interface, cultural adaptation, and ease of use) and remote delivery will be assessed through in-session questionnaires. These will include motivation toward the treatment, perception of therapeutic alliance, suicide risk, engagement toward treatment, feeling of immersion in the digital relational simulations, and aspects related to implementation (eg, attitudes

toward the intervention such as its usefulness, the probability of using it, and the perception about one's ability to use the intervention).

For therapists, in-session questionnaires will be administered to assess their perception of their client's motivation toward treatment, therapeutic alliance, and their perspective and satisfaction toward RC2S. The details regarding the different measures and time of administration for both categories of participants are presented in Table 1.

Table 1. List of measures included in the study.

Name of the measure and domain assessed	Time point
Participants receiving RC2S[a]	
Primary outcomes	
Goal Attainment Scale [28]	
Therapy goals attainment	Sessions 1 and 24
Penn Emotion Recognition Task [29]	
Emotion recognition	Baseline, posttest
Social knowledge test [30]	
Social knowledge	Baseline, posttest
Combined Stories Test [30]	
Theory of mind	Baseline, posttest
Internal, Personal and Situational Attributions Questionnaire [31]	
Attributional style	Baseline, posttest
Secondary outcomes	
Davos Assessment of Cognitive Biases Scale [32]	
Cognitive biases	Baseline, posttest
6-item Positive and Negative Syndrome Scale [33]	
Positive and negative symptoms	Baseline, posttest
Social Interaction Anxiety Scale [34]	
Social anxiety	Baseline, posttest
Patient Health Questionnaire [35]	
Depressive symptoms	Baseline, posttest
First Episode Social Functioning Scale [36]	
Functioning	Baseline, posttest
Questionnaire about the process of recovery [37]	
Recovery	Baseline, posttest
Échelle de répercussions fonctionnelles des troubles de la Cognition Sociale [38]	
Functional impacts of social cognitive impairments	Sessions 1 and 24
Other outcomes	
Ask Suicide-Screening Questionnaire [39]	
Suicide risk	Session 1
MUSIC Model of Motivation Inventory, Cognitive Training version [40]	
Motivation toward RC2S	Sessions 5, 11, and 23
Working Alliance Inventory-Short form [41]	
Therapeutic alliance in RC2S	Sessions 5, 11, and 23
e-Therapy Attitudes and Process Questionnaire [42]	
Engagement in e-interventions	Session 24
RC2S+ Acceptability, Usability, Safety, Impact, and Satisfaction Questionnaire	
Implementation of RC2S	Session 24
Igroup Presence Questionnaire [43]	
Feeling of immersion in RC2S	Session 24
Therapists	
MUSIC Model of Motivation Inventory, Cognitive Training version for clinicians [40]	

Name of the measure and domain assessed	Time point
Perceived client's motivation toward RC2S	Sessions 5, 11, and 23
Working Alliance Inventory-Short form—therapist [41]	
Therapeutic alliance	Sessions 5, 11, and 23
Questionnaire on therapists' perspective	
Perspective and satisfaction of the therapist regarding RC2S	Session 24

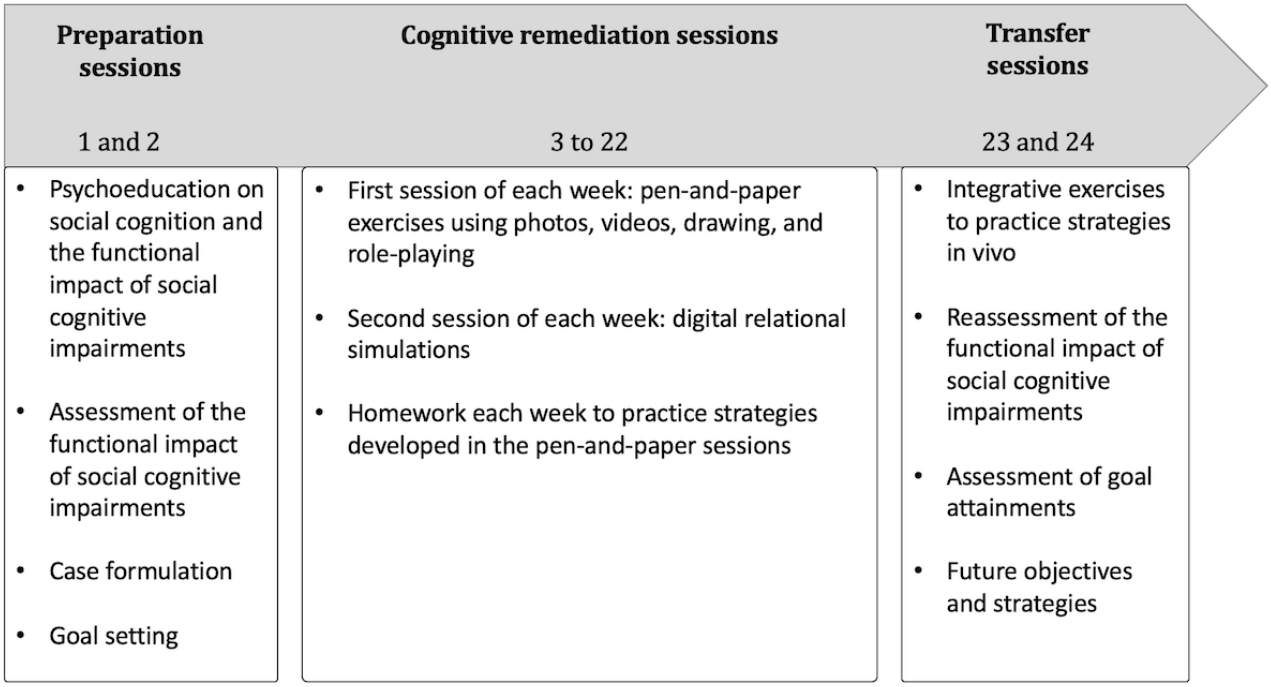
[a]RC2S: Remédiation Cognitive de la Cognition Sociale dans la Schizophrénie.

In addition to measures administered with both categories of participants, objective indicators of feasibility will be collected, including the safety of the study (comprising whether there are any adverse events reported), the number of participants who have completed therapy (at least 50% of the treatment completed), reasons for dropping out, duration of sessions, and the number of missed sessions and reasons.

Intervention: RC2S

RC2S is an individualized computerized CR composed of 24 biweekly individual sessions of 1 hour with a therapist. The intervention is divided into 3 parts, as presented in Figure 1 and described in the subsequent section. RC2S provides a standardized approach regarding the material, duration, frequency, delivery of intervention, and CR principles and strategies, while also offering a personalized approach as a function of the person's profile.

Figure 1. Description of RC2S (Remédiation Cognitive de la Cognition Sociale dans la Schizophrénie) sessions.



During the first 2 sessions of therapy, a case formulation is elaborated to identify the strengths, weaknesses, and CR goals. Psychoeducation about social cognition and the impact of social cognitive impairments on functioning is presented. To complement the objective assessment of social cognition performed at baseline, the functional impacts of social cognitive impairments are assessed with the Échelle de répercussions fonctionnelles des troubles de la Cognition Sociale (ERF-CS; *Scale for the assessment of functional impacts of social cognitive deficits*) [38]. This semistructured interview explores the presence and impact of various social cognitive impairments in daily life. The interview also assesses how much the participant is bothered by these impairments. The results from the ERF-CS provide a detailed perspective on how social cognitive impairments disrupt the participant's life. Furthermore, given the psychometric limitations of most available social cognitive tasks, particularly regarding the ecological aspect of these tasks, the ERF-CS provides in-depth and concrete information to build a case formulation and support the client while creating treatment objectives. In this project, treatment objectives will be developed with the Goal Attainment Scale (GAS) [28], a flexible scale that allows the elaboration of personalized objectives before starting treatment, with a reassessment at the end of therapy. The GAS is rated on a scale from −2 to +2. A score of 0 indicates that the participant has reached their initial goal. Scores of +1 or +2 are obtained if the participant has exceeded or greatly exceeded their initial goal. Scores of −1 and −2 are obtained if the participant did not completely reach their objective. When the objectives are set, an operational definition is established for each level of rating.

Weeks 2 to 11 of RC2S are dedicated to CR. During the first session of each week, stimuli such as photography, videos, and role-plays are used to teach strategies for social cognitive impairments, first for basic (eg, emotion recognition) and then for complex (eg, theory of mind) social cognitive processes. The number of paper-and-pencil sessions dedicated to each social cognitive domain, the exercises used to work on these domains, and the intensity of difficulty used are tailored based on the participant's objective and subjective social cognitive impairments, as well as the treatment objectives. Evidence-based strategies used in CR are applied in RC2S (eg, repeated practice, scaffolding, verbalization, errorless learning, and information reduction).

During the second session of each week, digital relational simulations are used. During each simulation, the participant assists a character named Tom in different social scenarios presenting various types of relationships and interactions (eg, Tom is having an altercation with his boss or Tom initiates a conversation with an acquaintance). Depending on each participant's individual difficulties, the order of presentation of the different scenarios is adapted to respect an increase in difficulty each week. For each scenario, the participant must read a short vignette introducing the simulation and answer the different questions on the *wheel of questions* (Figure 2A). The participant gathers information through the wheel of questions, including who will be involved in the simulation, where and when it is happening, what will be happening in the situation, why, and how. This initial analysis allows the participant to differentiate between what is a known fact in the situation and what is unknown, thus supporting the interpretations and choices that they will make during the simulation. Once the wheel has been completed, the participant begins the digital relational simulation. Each scenario is based on an algorithm of various propositions of behavioral patterns, and the scenario evolves based on the answer of the participant at each interaction. To assist Tom in navigating the different social scenes, the participant can choose among 3 types of behavior (ie, passive, aggressive, or assertive) based on social skills training and self-affirmation programs [24] (refer to Figure 2B for an example). The simulations are multimodal and integrative sessions that allow working on several social cognitive domains simultaneously including analyzing social context (social perception), emotions through verbal and nonverbal cues (emotion recognition), and understanding the mental states of Tom and his interlocutor (theory of mind) as well as their reactions (attributional style). For each interaction, the participant is encouraged to use the strategies learned during the paper-and-pencil sessions to perceive and interpret the different social cues and to verbalize these strategies. After the simulation, the participants' choices are decomposed to focus on specific social cues. It is also possible to run the simulation again to experience another behavioral approach to the scene; this allows the participant to experience how different social approaches can lead to different outcomes for both Tom and his interlocutor.

Figure 2. Digital relational simulations in RC2S (Remédiation Cognitive de la Cognition Sociale dans la Schizophrénie): (A) The wheel of questions presented before each simulation; (B) An example of a digital relational simulation with an avatar.

In addition to the 2 therapy sessions, each week, the participant is also assigned a home activity related to the objectives of CR to practice strategies learned in sessions and to support bridging in everyday life.

Week 12 (sessions 23 and 24) is dedicated not only to the transfer of acquired skills to daily life via role-play or activities in the community but also to a final assessment of the progress that was made. These last 2 sessions are thus also dedicated to assessing the current situation of the participants regarding their perception of the functional impacts of social cognitive impairments and their objectives. During these sessions, the ERF-CS will be administered again to assess the progression regarding the functional impacts of social cognitive impairments from the beginning of the therapy. Furthermore, goal attainment will be assessed again with the GAS to determine if the participant reached their goals partially or completely. This will also allow a discussion on how the participant can continue working on goals that are partially reached and set new goals to work on in the future.

Statistical Analysis

Power

On the basis of previous psychosocial intervention studies with a similar population at our recruitment site, we expect an attrition rate of 20% for the participants with SSD [44,45]. Thus, for a targeted sample of 20 participants, the inclusion of a maximum of 4 additional participants should be expected, leading to 24 participants with SSD. This sample size will allow us to determine potential barriers for remote RC2S, improve the protocol and the adapted versions, determine the preliminary effects of the treatment, and obtain sufficient data to compute effect sizes for statistical power analyses in a future efficacy study. Although no stratification for gender and language will be applied, we aim, as much as possible, to recruit 10 English speakers and 10 French speakers, and we aim to have a proportion of men and women that is consistent with what is observed clinically.

As for the therapists, we aim to recruit 5 participants to obtain a variety of perspectives.

Data Analysis

To assess the acceptability, feasibility, safety, and implementation of remote North American English and French-Canadian versions of RC2S, descriptive statistics will be used to summarize the objective indicators and the quantitative answers from the questionnaires (eg, number of missed sessions). Open-ended questions in the RC2S+ Acceptability, Usability, Safety, Impact, and Satisfaction Questionnaire and the Questionnaire on therapists' perspective will be classified into categories associated with the implementation of remote psychosocial interventions [46,47]. These analyses will notably determine if the participants with SSD and the therapists perceive the remote administration of the culturally adapted versions of RC2S as feasible and acceptable. We will assess the engagement of participants (eg, motivation, number of sessions completed, and number of completers), the perception of the usefulness of the intervention by both participants with SSD and therapists, and the overall satisfaction with the intervention and the delivery mode. This information is necessary to determine if the remote administration of the culturally adapted versions of RC2S is feasible and acceptable before planning an efficacy trial. These results will also provide information to determine if some modifications to the protocol are necessary.

For the objective regarding the preliminary effect of RC2S on primary and secondary outcomes, we will use an intention-to-treat approach, including the data of all participants who entered the study. Effect sizes will be calculated by subtracting scores at baseline from posttest scores and dividing them by the SD of baseline scores for both primary and secondary outcomes. Linear mixed models for repeated measures will be used to assess the effect of RC2S on both primary and secondary outcomes, with fixed effects of time. Gender, language, and the severity of social cognitive impairments will be used as covariates. Although *P* values will be calculated, we will be mostly interested in the effect sizes to guide power analyses for a future efficacy trial.

For other outcomes, including the in-session questionnaires, descriptive statistics will be used to summarize the data for both groups of participants. Motivation toward treatment and perception of therapeutic alliance will be correlated with primary and secondary outcomes, as well as with the objective indicators of feasibility and acceptability.

Results

Recruitment and data collection for the project started in January 2022, and the study is expected to be completed by August 2024. To date, 9 participants with SSD (3/9, 33% women and 6/9, 67% men) have completed the project (mean age 37.9, SD 9.3 years; mean years of education 12.6, SD 1.9 years). All participants completed the baseline and posttest assessments. They received a mean of 20.5 of 24 (SD 3.5) sessions of therapy, with a mean of 1.3 (SD 1.8) missed sessions. The reasons for missing sessions were related to the participant's health status (eg, being too tired or sick), schedule conflicts (eg, work or a medical appointment), or forgetting about the scheduled session.

We also recruited 5 women therapists who were doctoral-level students in psychology and neuropsychology (4/5, 80%) or a licensed neuropsychologist (1/5, 20%).

Discussion

Overview

This study will first provide necessary information regarding the translation and adaptation of RC2S in North American English and French-Canadian. Participants with SSD, therapists, and the members of the research team will be able to test the program to identify any typo or error that might be present in these initial versions of the program. This will be important to correct any issues for a future efficacy trial.

This project will also provide initial information regarding the feasibility and acceptability of remote administration of these new versions of RC2S. Thus, this study will provide the first insights into the positive impacts and challenges of delivering this intervention remotely, which has never been done before. We hope that we will be able to address most of these challenges in a future efficacy trial. Furthermore, the results from this project will provide information regarding the implementation of RC2S in clinical settings. This information is central to documentation in any intervention study, given the significant research-to-practice gap [48] limiting the implementation of interventions developed in the context of research in clinical settings.

Finally, this study will provide preliminary information regarding the effect of the intervention on different outcomes. This type of pilot study is essential to gathering data to guide a future efficacy trial. Among other advantages, the results of this study will provide the data to calculate the effect sizes necessary to determine the required sample size in a future randomized controlled trial assessing the efficacy of RC2S.

Dissemination of Results

The ClinicalTrials.gov page for this project will be updated with the results. We also plan on presenting the results of this project

at local and international conferences and submitting them to a scientific journal in the fields of SSD and cognition. We also plan to disseminate these results to clinical teams and people with SSD through conferences to help recognize the presence and impacts of social cognitive impairments and the type of intervention that exists to support these difficulties. We also hope that this project will provide initial insight into the implementation of this intervention to facilitate its inclusion in clinical care.

Limitations

The first limitation of this study is the absence of a control group. We chose this quasi-experimental design because the main objective of this study is to adapt RC2S in North American English and French-Canadian and to assess the acceptability, feasibility, safety, and implementation of administering this intervention remotely. Although an exploratory objective is to assess the preliminary effect on different outcomes, we do not aim to establish the efficacy of this intervention. Even though we believe that a control group is not necessary to achieve these objectives, we recognize that the absence of a control group can limit our interpretations regarding the preliminary effects of the intervention.

The second limitation is the potential imbalance between gender and language among the participants. Our final sample might have an unequal proportion of women and men, as well as English- and French-speaking participants. On the basis of our previous studies with the same population and the same site of recruitment, we believe it will be possible to have a good representation of both genders and languages, with a ratio of 60% to 40% of people receiving their services in French or English at the Ci3P clinic and a ratio of 50% to 50% of women and men interested in participating in psychosocial interventions at the clinic. These variables will also be considered in our statistical analyses.

Conclusions

This is the first study to assess the acceptability, feasibility, safety, implementation, and preliminary effects of the new and remote North American English and French-Canadian versions of RC2S. Improving social cognitive impairment is an important target for SSD to promote functional recovery. Using digital technology to address these symptoms but also to deliver the interventions is a promising approach to increasing the ecological validity of CR and increasing access to the intervention.

Acknowledgments

The authors want to thank Karyne Anselmo for coordinating the different parts of this project. The authors also want to thank Jesse Rae and Vanessa McGorry for their help with the translation and adaptation of the English version and for the assessment of the participants. None of the sponsors listed are involved in the design of the study, the data collection, or the publication of the results.

Data Availability

The data sets analyzed in this study are available from the corresponding author on reasonable request.

Authors' Contributions

ET was responsible, in collaboration with others, for the design of the study, the adaptation and translation of the program, for offering therapy to the participants, as well as the training and supervision of the therapists, and for writing this manuscript. She will also be responsible for the statistical analyses and for leading the future publications associated with this project.
ML was responsible, in collaboration with ET, for the design of the study and the writing of the manuscript. He will also be involved in the future publications associated with this project.
EP and NF both created the original French version of RC2S. They agreed to collaborate on the adaptation of their program in North American English and French-Canadian languages. EP trained ET to deliver the intervention and train therapists for the project. EP and NF were both available to answer any questions regarding the program and its delivery, and they revised the current manuscript. They will be involved in the future publications associated with this project.
HC helped with the revision of the manuscript and performed the formatting and linguistic revision. She also helped as a research assistant with the translation and adaptation of the North American English version and the assessment of the participants.

Conflicts of Interest

This project is carried out in collaboration with the company Happy Neuron, which owns the rights to the RC2S program. The RC2S program was originally developed in the French language, in France. This research project involves French-Canadian adaptation as well as North American English translation of the program, which has been conducted in collaboration with the company. However, no raw data from this project are shared with the company, and the company is not involved in the planning or administration of this project. The research team will receive profits from the sale of the French-Canadian and North American English licenses to reimburse the costs of translating and adapting the 2 licenses. Once this reimbursement is made, the research team will not receive any profits associated with the sales. Through this collaboration, the research team has free access to the RC2S license. This research was undertaken thanks in part to funding from the Canada First Research Excellence Fund awarded

through the Healthy Brains, Healthy Lives initiative at McGill University. ET receives postdoctoral fellowship funding from the Canadian Institutes of Health Research (#171198). ML is supported by a James McGill Professorship from McGill University.

References

1. Thibaudeau E, Cellard C, Turcotte M, Achim AM. Functional impairments and theory of mind deficits in schizophrenia: a meta-analysis of the associations. Schizophr Bull 2021 Apr 29;47(3):695-711 [FREE Full text] [doi: 10.1093/schbul/sbaa182] [Medline: 33433606]
2. Halverson TF, Orleans-Pobee M, Merritt C, Sheeran P, Fett AK, Penn DL. Pathways to functional outcomes in schizophrenia spectrum disorders: meta-analysis of social cognitive and neurocognitive predictors. Neurosci Biobehav Rev 2019 Oct;105:212-219. [doi: 10.1016/j.neubiorev.2019.07.020] [Medline: 31415864]
3. Kern RS, Glynn SM, Horan WP, Marder SR. Psychosocial treatments to promote functional recovery in schizophrenia. Schizophr Bull 2009 Mar;35(2):347-361 [FREE Full text] [doi: 10.1093/schbul/sbn177] [Medline: 19176470]
4. Green MF, Horan WP, Lee J. Social cognition in schizophrenia. Nat Rev Neurosci 2015 Oct;16(10):620-631. [doi: 10.1038/nrn4005] [Medline: 26373471]
5. Pinkham AE. Social cognition in schizophrenia. J Clin Psychiatry 2014;75 Suppl 2:14-19. [doi: 10.4088/JCP.13065su1.04] [Medline: 24919166]
6. Pinkham AE, Penn DL, Green MF, Buck B, Healey K, Harvey PD. The social cognition psychometric evaluation study: results of the expert survey and RAND panel. Schizophr Bull 2014 Jul;40(4):813-823 [FREE Full text] [doi: 10.1093/schbul/sbt081] [Medline: 23728248]
7. Savla GN, Vella L, Armstrong CC, Penn DL, Twamley EW. Deficits in domains of social cognition in schizophrenia: a meta-analysis of the empirical evidence. Schizophr Bull 2013 Sep;39(5):979-992 [FREE Full text] [doi: 10.1093/schbul/sbs080] [Medline: 22949733]
8. Weinreb S, Li F, Kurtz MM. A meta-analysis of social cognitive deficits in schizophrenia: does world region matter? Schizophr Res 2022 May;243:206-213. [doi: 10.1016/j.schres.2022.04.002] [Medline: 35429775]
9. van Donkersgoed RJ, Wunderink L, Nieboer R, Aleman A, Pijnenborg GH. Social cognition in individuals at ultra-high risk for psychosis: a meta-analysis. PLoS One 2015;10(10):e0141075 [FREE Full text] [doi: 10.1371/journal.pone.0141075] [Medline: 26510175]
10. Healey KM, Bartholomeusz CF, Penn DL. Deficits in social cognition in first episode psychosis: a review of the literature. Clin Psychol Rev 2016 Dec;50:108-137. [doi: 10.1016/j.cpr.2016.10.001] [Medline: 27771557]
11. Kurtz MM, Gagen E, Rocha NB, Machado S, Penn DL. Comprehensive treatments for social cognitive deficits in schizophrenia: a critical review and effect-size analysis of controlled studies. Clin Psychol Rev 2016 Feb;43:80-89. [doi: 10.1016/j.cpr.2015.09.003] [Medline: 26437567]
12. Yeo H, Yoon S, Lee J, Kurtz MM, Choi K. A meta-analysis of the effects of social-cognitive training in schizophrenia: the role of treatment characteristics and study quality. Br J Clin Psychol 2022 Mar;61(1):37-57. [doi: 10.1111/bjc.12320] [Medline: 34291465]
13. Bowie CR, Bell MD, Fiszdon JM, Johannesen JK, Lindenmayer JP, McGurk SR, et al. Cognitive remediation for schizophrenia: an expert working group white paper on core techniques. Schizophr Res 2020 Jan;215:49-53. [doi: 10.1016/j.schres.2019.10.047] [Medline: 31699627]
14. Wölwer W, Frommann N, Halfmann S, Piaszek A, Streit M, Gaebel W. Remediation of impairments in facial affect recognition in schizophrenia: efficacy and specificity of a new training program. Schizophr Res 2005 Dec 15;80(2-3):295-303. [doi: 10.1016/j.schres.2005.07.018] [Medline: 16125367]
15. Passerieux C, Bazin N, Roux P, Hardy-Bayle MC. Le programme ToMRemed: remédiation des troubles de la théorie de l'esprit. In: Franck N, editor. Cognition Sociale et Schizophrénie: Outils D'évaluation et de Remédiation. Île-de-France, France: Elsevier Masson; 2014:123-144.
16. Penn DL, Roberts DL, Combs D, Sterne A. Best practices: the development of the social cognition and interaction training program for schizophrenia spectrum disorders. Psychiatr Serv 2007 Apr;58(4):449-451. [doi: 10.1176/ps.2007.58.4.449] [Medline: 17412842]
17. Horan WP, Kern RS, Shokat-Fadai K, Sergi MJ, Wynn JK, Green MF. Social cognitive skills training in schizophrenia: an initial efficacy study of stabilized outpatients. Schizophr Res 2009 Jan;107(1):47-54 [FREE Full text] [doi: 10.1016/j.schres.2008.09.006] [Medline: 18930378]
18. Roberts DL, Combs DR, Willoughby M, Mintz J, Gibson C, Rupp B, et al. A randomized, controlled trial of Social Cognition and Interaction Training (SCIT) for outpatients with schizophrenia spectrum disorders. Br J Clin Psychol 2014 Sep;53(3):281-298. [doi: 10.1111/bjc.12044] [Medline: 24417608]
19. Hogarty GE, Flesher S, Ulrich R, Carter M, Greenwald D, Pogue-Geile M, et al. Cognitive enhancement therapy for schizophrenia: effects of a 2-year randomized trial on cognition and behavior. Arch Gen Psychiatry 2004 Sep 01;61(9):866-876. [doi: 10.1001/archpsyc.61.9.866] [Medline: 15351765]
20. Roder V, Mueller DR, Mueser KT, Brenner HD. Integrated psychological therapy (IPT) for schizophrenia: is it effective? Schizophr Bull 2006 Oct 18;32(Suppl 1):S81-S93 [FREE Full text] [doi: 10.1093/schbul/sbl021] [Medline: 16916888]

21. Kurtz MM, Richardson CL. Social cognitive training for schizophrenia: a meta-analytic investigation of controlled research. Schizophr Bull 2012 Sep;38(5):1092-1104 [FREE Full text] [doi: 10.1093/schbul/sbr036] [Medline: 21525166]
22. Nijman SA, Veling W, van der Stouwe EC, Pijnenborg GH. Social cognition training for people with a psychotic disorder: a network meta-analysis. Schizophr Bull 2020 Sep 21;46(5):1086-1103 [FREE Full text] [doi: 10.1093/schbul/sbaa023] [Medline: 32162658]
23. Grant N, Lawrence M, Preti A, Wykes T, Cella M. Social cognition interventions for people with schizophrenia: a systematic review focussing on methodological quality and intervention modality. Clin Psychol Rev 2017 Aug;56:55-64 [FREE Full text] [doi: 10.1016/j.cpr.2017.06.001] [Medline: 28688282]
24. Peyroux E, Franck N. RC2S: a cognitive remediation program to improve social cognition in schizophrenia and related disorders. Front Hum Neurosci 2014 Jun 13;8:400 [FREE Full text] [doi: 10.3389/fnhum.2014.00400] [Medline: 24982627]
25. Gainsford K, Fitzgibbon B, Fitzgerald PB, Hoy KE. Transforming treatments for schizophrenia: virtual reality, brain stimulation and social cognition. Psychiatry Res 2020 Jun;288:112974. [doi: 10.1016/j.psychres.2020.112974] [Medline: 32353694]
26. Peyroux E, Franck N. Improving social cognition in people with schizophrenia with RC2S: two single-case studies. Front Psychiatry 2016 Apr 25;7:66 [FREE Full text] [doi: 10.3389/fpsyt.2016.00066] [Medline: 27199776]
27. Hajdúk M, Achim AM, Brunet-Gouet E, Mehta UM, Pinkham AE. How to move forward in social cognition research? Put it into an international perspective. Schizophr Res 2020 Jan;215:463-464 [FREE Full text] [doi: 10.1016/j.schres.2019.10.001] [Medline: 31615739]
28. Turner-Stokes L. Goal attainment scaling (GAS) in rehabilitation: a practical guide. Clin Rehabil 2009 Apr 29;23(4):362-370. [doi: 10.1177/0269215508101742] [Medline: 19179355]
29. Kohler CG, Turner TH, Bilker WB, Brensinger CM, Siegel SJ, Kanes SJ, et al. Facial emotion recognition in schizophrenia: intensity effects and error pattern. Am J Psychiatry 2003 Oct;160(10):1768-1774. [doi: 10.1176/appi.ajp.160.10.1768] [Medline: 14514489]
30. Achim AM, Ouellet R, Roy MA, Jackson PL. Mentalizing in first-episode psychosis. Psychiatry Res 2012 Apr 30;196(2-3):207-213. [doi: 10.1016/j.psychres.2011.10.011] [Medline: 22377576]
31. Kinderman P, Bentall RP. A new measure of causal locus: the internal, personal and situational attributions questionnaire. Pers Indiv Differ 1996 Feb;20(2):261-264. [doi: 10.1016/0191-8869(95)00186-7]
32. van der Gaag M, Schütz C, Ten Napel A, Landa Y, Delespaul P, Bak M, et al. Development of the Davos assessment of cognitive biases scale (DACOBS). Schizophr Res 2013 Mar;144(1-3):63-71. [doi: 10.1016/j.schres.2012.12.010] [Medline: 23332365]
33. Østergaard SD, Lemming OM, Mors O, Correll CU, Bech P. PANSS-6: a brief rating scale for the measurement of severity in schizophrenia. Acta Psychiatr Scand 2016 Jun 12;133(6):436-444. [doi: 10.1111/acps.12526] [Medline: 26558537]
34. Mattick RP, Clarke JC. Development and validation of measures of social phobia scrutiny fear and social interaction anxiety. Behav Res Ther 1998 Apr;36(4):455-470. [doi: 10.1016/s0005-7967(97)10031-6] [Medline: 9670605]
35. Kroenke K, Strine TW, Spitzer RL, Williams JB, Berry JT, Mokdad AH. The PHQ-8 as a measure of current depression in the general population. J Affect Disord 2009 Apr;114(1-3):163-173. [doi: 10.1016/j.jad.2008.06.026] [Medline: 18752852]
36. Lecomte T, Corbière M, Ehmann T, Addington J, Abdel-Baki A, Macewan B. Development and preliminary validation of the First Episode Social Functioning Scale for early psychosis. Psychiatry Res 2014 May 30;216(3):412-417. [doi: 10.1016/j.psychres.2014.01.044] [Medline: 24613006]
37. Neil ST, Kilbride M, Pitt L, Nothard S, Welford M, Sellwood W, et al. The questionnaire about the process of recovery (QPR): a measurement tool developed in collaboration with service users. Psychosis 2009 Aug;1(2):145-155. [doi: 10.1080/17522430902913450]
38. Gaudelus B, Peyroux E, Colson S, Franck N. L'évaluation des répercussions fonctionnelles des altérations de la cognition sociale favorise-t-elle l'engagement dans les soins des personnes ayant des troubles psychotiques ? Ann Med Psychol 2018 Jan;176(1):94-99. [doi: 10.1016/j.amp.2017.11.003]
39. Horowitz LM, Bridge JA, Teach SJ, Ballard E, Klima J, Rosenstein DL, et al. Ask Suicide-Screening Questions (ASQ): a brief instrument for the pediatric emergency department. Arch Pediatr Adolesc Med 2012 Dec 01;166(12):1170-1176 [FREE Full text] [doi: 10.1001/archpediatrics.2012.1276] [Medline: 23027429]
40. Parkes KA, Jones BD, Wilkins JL. Assessing music students' motivation using the MUSIC model of academic motivation inventory. Update Appl Res Music Educ 2015 Dec 04;35(3):16-22. [doi: 10.1177/8755123315620835]
41. Horvath AO, Greenberg LS. Development and validation of the Working Alliance Inventory. J Counsel Psychol 1989;36(2):223-233. [doi: 10.1037//0022-0167.36.2.223]
42. Clough BA, Eigeland JA, Madden IR, Rowland D, Casey LM. Development of the eTAP: a brief measure of attitudes and process in e-interventions for mental health. Internet Interv 2019 Dec;18:100256 [FREE Full text] [doi: 10.1016/j.invent.2019.100256] [Medline: 31890610]
43. Schubert T, Friedmann F, Regenbrecht H. The experience of presence: factor analytic insights. Presence (Camb) 2001 Jun;10(3):266-281. [doi: 10.1162/105474601300343603]

44. Montreuil TC, Malla AK, Joober R, Bélanger C, Myhr G, Lepage M. Manualized group cognitive-behavioral therapy for social anxiety in at-risk mental state and first episode psychosis: a pilot study of feasibility and outcomes. Int J Group Psychother 2016 Jan 19;66(2):225-245. [doi: 10.1080/00207284.2015.1106190]
45. Benoit A, Harvey PO, Bherer L, Lepage M. Does the beck cognitive insight scale predict response to cognitive remediation in schizophrenia? Schizophr Res Treatment 2016;2016:6371856 [FREE Full text] [doi: 10.1155/2016/6371856] [Medline: 27516906]
46. Bell IH, Lim MH, Thomas N. Chapter 27 - the therapeutic use of digital technologies in psychosis. In: Badcock JC, Paulik G, editors. A Clinical Introduction to Psychosis: Foundations for Clinical Psychologists and Neuropsychologists. Cambridge, MA: Academic Press; 2020.
47. Borghouts J, Eikey E, Mark G, De Leon C, Schueller SM, Schneider M, et al. Barriers to and facilitators of user engagement with digital mental health interventions: systematic review. J Med Internet Res 2021 Mar 24;23(3):e24387 [FREE Full text] [doi: 10.2196/24387] [Medline: 33759801]
48. Stirman SW, Gutner CA, Langdon K, Graham JR. Bridging the gap between research and practice in mental health service settings: an overview of developments in implementation theory and research. Behav Ther 2016 Nov;47(6):920-936. [doi: 10.1016/j.beth.2015.12.001] [Medline: 27993341]

Abbreviations

Ci3P: Centre d'Intervention Psychologique Personnalisé pour la Psychose
CR: cognitive remediation
ERF-CS: Échelle de répercussions fonctionnelles des troubles de la Cognition Sociale
GAS: Goal Attainment Scale
RC2S: Remédiation Cognitive de la Cognition Sociale dans la Schizophrénie
SSD: schizophrenia spectrum disorder

Edited by A Mavragani; submitted 02.11.23; peer-reviewed by E Deja, P Harvey; comments to author 24.12.23; revised version received 06.01.24; accepted 09.01.24; published 13.03.24.

Please cite as:
Thibaudeau E, Peyroux E, Franck N, Carling H, Lepage M
Navigating Social Cognitive Impairments in Schizophrenia Spectrum Disorders: Protocol for a Pilot Pre-Post Quasi-Experimental Study for Remote Avatar-Assisted Cognitive Remediation Therapy
JMIR Res Protoc 2024;13:e54251
URL: https://www.researchprotocols.org/2024/1/e54251
doi:10.2196/54251
PMID:38477975

Protocol

Implementing and Evaluating a National Integrated Digital Registry and Clinical Decision Support System in Early Intervention in Psychosis Services (Early Psychosis Informatics Into Care): Co-Designed Protocol

Siân Lowri Griffiths[1], PhD; Graham K Murray[2,3], MBBS, MD, PhD; Yanakan Logeswaran[4], MSc; John Ainsworth[5,6], PhD; Sophie M Allan[7,8], ClinPsyD; Niyah Campbell[1], MSc; Richard J Drake[5,9], MBChB, MRCPsych, PhD; Mohammad Zia Ul Haq Katshu[10,11], MBBS, DPM, MRCPsych, PhD; Matthew Machin[5], BEng; Megan A Pope[1], MSc; Sarah A Sullivan[12,13], CPsychol, PhD; Justin Waring[14], PhD; Tumelo Bogatsu[1], MSc; Julie Kane[15], MSc; Tyler Weetman[15], MSc; Sonia Johnson[4,16], BM BCh, MSc, DM; James B Kirkbride[4], PhD; Rachel Upthegrove[1,15], MBBS, PhD

[1]Institute for Mental Health, University of Birmingham, Birmingham, United Kingdom

[2]Department of Psychiatry, University of Cambridge, Cambridge, United Kingdom

[3]CAMEO, Cambridgeshire and Peterborough NHS Foundation Trust, Cambridge, United Kingdom

[4]Division of Psychiatry, University College London, London, United Kingdom

[5]The University of Manchester, Manchester, United Kingdom

[6]NIHR Manchester Biomedical Research Centre, Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, United Kingdom

[7]Department of Clinical Psychology and Psychotherapies, Medical School, University of East Anglia, Norwich, United Kingdom

[8]School of Health Sciences, University of East Anglia, Norwich, United Kingdom

[9]Greater Manchester Mental Health NHS Foundation Trust, Manchester, United Kingdom

[10]Institute of Mental Health, School of Medicine, University of Nottingham, Nottingham, United Kingdom

[11]Nottinghamshire Healthcare NHS Foundation Trust, Nottingham, United Kingdom

[12]Centre for Academic Mental Health, University of Bristol, Bristol, United Kingdom

[13]Biomedical Research Centre, University of Bristol, Bristol, United Kingdom

[14]School of Social Policy, University of Birmingham, Birmingham, United Kingdom

[15]Birmingham Women's and Children's NHS Foundation Trust, Birmingham, United Kingdom

[16]Camden and Islington NHS Foundation Trust, London, United Kingdom

Corresponding Author:
Rachel Upthegrove, MBBS, PhD
Institute for Mental Health
University of Birmingham
Wolfson Centre
52 Pritchatts Road
Birmingham, B15 2TT
United Kingdom
Phone: 44 01214146241
Email: r.upthegrove@bham.ac.uk

Abstract

Background: Early intervention in psychosis (EIP) services are nationally mandated in England to provide multidisciplinary care to people experiencing first-episode psychosis, which disproportionately affects deprived and ethnic minority youth. Quality of service provision varies by region, and people from historically underserved populations have unequal access. In other disease areas, including stroke and dementia, national digital registries coupled with clinical decision support systems (CDSSs) have revolutionized the delivery of equitable, evidence-based interventions to transform patient outcomes and reduce population-level disparities in care. Given psychosis is ranked the third most burdensome mental health condition by the World Health Organization, it is essential that we achieve the same parity of health improvements.

Objective: This paper reports the protocol for the program development phase of this study, in which we aimed to co-design and produce an evidence-based, stakeholder-informed framework for the building, implementation, piloting, and evaluation of a national integrated digital registry and CDSS for psychosis, known as EPICare (Early Psychosis Informatics into Care).

Methods: We conducted 3 concurrent work packages, with reciprocal knowledge exchange between each. In work package 1, using a participatory co-design framework, key stakeholders (clinicians, academics, policy makers, and patient and public contributors) engaged in 4 workshops to review, refine, and identify a core set of essential and desirable measures and features of the EPICare registry and CDSS. Using a modified Delphi approach, we then developed a consensus of data priorities. In work package 2, we collaborated with National Health Service (NHS) informatics teams to identify relevant data currently captured in electronic health records, understand data retrieval methods, and design the software architecture and data model to inform future implementation. In work package 3, observations of stakeholder workshops and individual interviews with representative stakeholders (n=10) were subject to interpretative qualitative analysis, guided by normalization process theory, to identify factors likely to influence the adoption and implementation of EPICare into routine practice.

Results: Stage 1 of the EPICare study took place between December 2021 and September 2022. The next steps include stage 2 building, piloting, implementation, and evaluation of EPICare in 5 demonstrator NHS Trusts serving underserved and diverse populations with substantial need for EIP care in England. If successful, this will be followed by stage 3, in which we will seek NHS adoption of EPICare for rollout to all EIP services in England.

Conclusions: By establishing a multistakeholder network and engaging them in an iterative co-design process, we have identified essential and desirable elements of the EPICare registry and CDSS; proactively identified and minimized potential challenges and barriers to uptake and implementation; and addressed key questions related to informatics architecture, infrastructure, governance, and integration in diverse NHS Trusts, enabling us to proceed with the building, piloting, implementation, and evaluation of EPICare.

International Registered Report Identifier (IRRID): DERR1-10.2196/50177

(JMIR Res Protoc 2024;13:e50177) doi:10.2196/50177

KEYWORDS

Early Intervention in Psychosis; digital registry; clinical decision support system; participatory co-design; participatory; co-design; registry; psychosis; mental health; psychiatry; decision support; study protocol

Introduction

Background

Psychotic disorders, including schizophrenia, are among the most disabling illnesses worldwide and are often accompanied by enormous personal, family, societal, and caregiver burden [1]. Rates of psychosis are unequally distributed throughout the population, with the highest rates found in historically underserved communities, younger populations, and those from minority ethnic backgrounds [2-5]. For example, within the United Kingdom, people from Black ethnic backgrounds (African, Caribbean, and British) are between 3 and 5 times more likely to experience a first episode of psychosis than White British individuals, and there is evidence that the rates are also approximately twice as high for people from Pakistan, Bangladesh, and mixed ethnic backgrounds in England [2,6]. Further, the need for treatment delivered by early intervention in psychosis (EIP) services in England has been identified as highest in several historically underserved regions of England, and in related major conurbations, such as Birmingham, Greater Manchester, Bradford, and parts of inner-city London [6]. This need for EIP care is closely aligned to populations exposed to greater structural disadvantage including multiple deprivation and social fragmentation [6].

EIP is an internationally adopted model of care based largely on social inclusion, service user and caregiver engagement, and relapse prevention. In England, EIP services are nationally commissioned to provide evidence-based, multidisciplinary care according to eight National Institute for Health and Care Excellence (NICE)–based national standards for people experiencing first-episode psychosis: (1) maximum waiting time of 14 days from initial referral to commencement of treatment; (2) offer of cognitive behavioral therapy for psychosis; (3) take-up of family interventions; (4) offer of clozapine after poor response to at least 2 other antipsychotic medications; (5) take-up of supported employment and education programs; (6) annual physical health assessments; (7) offer of interventions relevant to physical health (for example, smoking cessation, exercise, or substance use programs); and (8) take-up or referral to caregiver-focused education and support programs [7]. Each care standard is evidence-based, often from randomized controlled trials. Each standard has demonstrated improvement in patient outcomes, including remission of symptoms, readmission, recovery, premature mortality, and important social and vocational outcomes [8,9]. Importantly, EIP care is cost-effective relative to other forms of care and management for people with psychosis, and EIP services are highly valued by service users [10,11].

Despite evidence-based standardized targets, only 30%-40% of people experiencing psychotic disorders make a full recovery [12], with evidence of large variation in care [13-16]. Longer-term outcomes are equally poor, with increased rates of physical illnesses [17] and life expectancy reduced by around 15 years compared with people who do not go on to develop severe mental illness [18]. This suggests that much work is needed to understand which elements of EIP services are

working, for whom, and whether they lead to better long-term outcomes [16].

Variation in outcomes may be related to regional or individual disparities in the care offered and received during EIP, particularly in historically underserved communities where the need is greatest, but where there may be insufficient resources to offer standardized care tailored to the needs of local populations. For example, recent data indicate that people with psychosis from Black African and Caribbean backgrounds were 15%-30% less likely to receive the equivalent level of cognitive behavioral therapy for their condition compared to White British people [19]. Cross-sectional survey data from England and Wales has highlighted further inequalities in care, with Black service users being around 44% less likely to be offered clozapine [19], the only existing medication for treatment-resistant schizophrenia [13]. There is also evidence for disparities in outcomes post-EIP, with deprivation related to higher rates of relapse and the need for continuing care in secondary mental health services [20]. Black and Asian racial minoritized groups are also more likely to continue in secondary mental health care 2 years following EIP discharge [21].

Despite this, data currently being routinely collected via a patient's electronic health record does not provide accessible, longitudinal, and nationally representative data to determine the magnitude, causes, or consequences of inequitable access to EIP care in England. Relatedly, routine data collected by EIP services in England does not include measures of symptomatic recovery, usually the primary outcome for understanding what treatments work for whom, thus preventing us from developing a national understanding of the clinical effectiveness of treatments in the real world. In turn, neither does it provide a mechanism for immediately improving clinical practice by feeding back real-time actionable insights that would allow treatments to be targeted and tailored to individual patient needs. For example, while all EIP providers send data on broad levels of service use into National Health Service (NHS) Digital's Mental Health Services Data Set, the data set is less suited to ascertain accurate estimates of the incidence of psychotic disorders in England, because current methods of data collection do not differentiate between people engaging in EIP treatment for their first-ever episode of psychosis and those who may have existing psychosis, but are engaging in treatment in a new EIP service for the first time. Further, Mental Health Services Data Set data do not record whether those engaging with EIP treatment later fulfill diagnostic criteria for psychotic disorder. The Mental Health Services Data Set also does not allow us to understand what treatments are delivered to whom and when, nor their impact on patient recovery and other downstream outcomes. Furthermore, the pioneering National Clinical Audit of Psychosis [22], which has assessed service fidelity annually since 2017, is a retrospective, cross-sectional manual audit of up to 100 patients with first-episode psychosis in each EIP team in England [22]. Although plans exist to revise the data collection methodology, the current practice reduces data quality, delays service improvement, and diverts finite EIP resources away from frontline care. There are also no plans for the audit to provide real-time feedback of data to clinical teams. These issues could be eliminated by the provision of a prospectively collected national digital psychosis registry, able to supply actionable insights in real time to patients, clinical teams, service managers, and policy makers via an embedded clinical decision support system (CDSS).

We propose to revolutionize the use of electronic health record data to improve national, local, and individual clinical decision-making and promote better patient and public health outcomes for people experiencing first-episode psychosis, by carefully developing and demonstrating the effectiveness of a prospectively collected digital registry and CDSS in England, capable of being implemented nationally. This would provide standardized information to understand the treated burden of psychosis in the NHS; ensure equitable, responsive, local resource allocation; support reliable, quick, and efficient identification and targeting of any local, regional, or group-based disparities in access to care; improve patient pathways through care and downstream outcomes, including recovery; and finally, enhance understanding of the relationship between interventions provided and outcomes, as well as the relationship between clinical and social characteristics and outcomes.

The potential for further record linkage to other health and social domains also offers the prospect of integrating prospectively collected data from other routine sources including primary care, the Office for National Statistics mortality, the Office for National Statistics Census, the National Pupil Database, and Hospital Episode Statistics. This would provide a deeply phenotyped, longitudinal database for clinical and policy decision-making. It would also support gold-standard research in clinical psychiatry, experimental medicine, and observational epidemiology, to identify, understand, and address the causes and consequences of disparities in health and patient treatment, as well as improve downstream outcomes for people experiencing psychosis.

Digital registries have been deployed successfully in the United Kingdom for other disease areas such as stroke, cancer, cystic fibrosis, and dementia [23-28]. For example, in the United Kingdom, a national stroke registry has transformed patient care and outcomes, with early recognition of different patterns of stroke presentation, focused treatment on previously untreated risk factors, and targeted interventions for improving cognitive impairment [27]. In cancer care, tailored interventions based on risk profiles have extended the lives of thousands of people [28]. Yet there are no contemporary examples of digital registries for any secondary care-treated mental health condition listed in the Health Research Classification System mental health category, nor within the international literature, and no specific CDSS for any mental health condition. Integration of a patient-centered digital registry and CDSS for psychosis could be equally transformative and give parity of esteem to one of the most common and disabling sets of mental health disorders—psychosis—where there is already a well-developed national infrastructure of EIP services.

To achieve this paradigmatic change in mental health care, our aim is to develop, evaluate, and establish a national psychosis registry and CDSS, known as EPICare (Early Psychosis Informatics into Care) in 3 stages. Stage 1—establish a multidisciplinary and multisector stakeholder network to

co-design, derisk, and define the framework and protocols required to build and implement EPICare as a successful national registry and CDSS. Stage 2—build, pilot, implement, and evaluate the ability of the EPICare platform to improve patient care, enhance service delivery, reduce disparities in care, and demonstrate cost-effectiveness in 5 demonstrator NHS Trusts, serving underserved and diverse populations with substantial need for EIP care in England. Stage 3—subject to successful implementation and evaluation, seek NHS adoption of EPICare for rollout to all EIP services in England.

Aims and Objectives

In this paper, we report the protocol for the program development phase of our activity (stage 1), in which we aimed to co-design and produce a framework and protocols for onward building, implementation, piloting, and evaluation of a national integrated, patient-centered digital registry and CDSS for psychosis.

To meet this aim, we specifically addressed the following objectives: (1) establish a network with strong patient and public involvement and engagement (PPIE) and other essential stakeholders to identify essential and desirable elements and minimize unforeseen challenges (work package 1), (2) address key questions on informatics architecture, infrastructure, governance, and integration plans to facilitate onward development and testing of EPICare in diverse NHS Trusts (work package 2), and (3) identify implementation factors from the outset to ensure they are considered in designing, implementing, and maintaining the future deployment of EPICare in a measurable way (work package 3).

Methods

Study Design

We conducted 3 concurrent work packages over 12 months, with reciprocal knowledge exchange between work packages, coordinated via fortnightly program management group meetings. Figure 1 provides a schematic of work packages. The program management group contained a lived experience facilitator, lived experience member, clinicians working in early psychosis, and academic members from epidemiology, NHS health informatics, data, and implementation science.

Figure 1. EPICare program development phase study design. CDSS: clinical decision support system; EPICare: Early Psychosis Informatics into Care; PPIE: patient and public involvement and engagement.

Work Package 1: Stakeholder Co-Design of the EPICare Registry and CDSS

A participatory co-design framework previously established for informatics in mental health [29] was used to engage a diverse network of stakeholders, including clinicians, academics, policy makers, and PPIE members, in a series of 4 co-design workshops. Due to the COVID-19 pandemic, the workshops were convened online. While this enhanced the scope for collaboration between centers in the study, there were also potential drawbacks of this approach, which included PPIE members needing to have access to and know-how of technology. Second, hosting face-to-face meetings on neutral ground in an approachable format may have helped to remove traditional power structures. The workshops were in a facilitator-led, semistructured format, including presentations, whole-group discussions, and themed breakout activities (card-sort tasks and small group discussion) with both mixed (random allocation) and streamed group (by broad stakeholder type) sessions on a per-task basis. Essential materials were circulated to stakeholders in advance of each meeting. We also convened additional online preparatory sessions for PPIE

stakeholders, led by our PPIE coordinator, to aid understanding and participation in the main workshops. Registry and CDSS goals were examined by stakeholders, who reviewed, refined, and identified a core set of essential and desirable measures that should be collected in the integrated EPICare registry and CDSS, across 4 domains: sociodemographic measures, treatment measures, patient-reported outcome measures, and clinician-reported outcome measures.

To facilitate this process, stakeholders were provided with a list of data already recorded in electronic health records in EIP services, in addition to information on data relevant to the 8 nationally mandated NICE standards for EIP care [30] and key outcome measures (Health of the Nation Outcomes Scales [HoNOS] on functioning; quality of life and treatment satisfaction [DIALOG]; and patient-reported recovery [QPR]). This was supplemented with a minimal set of other initial measures recognized as potentially relevant by the program management group based on expert knowledge, prior to the first workshop. Examples included symptom ratings, duration of untreated psychosis, and genotyping, among others. In workshops 1 and 2, stakeholders were asked to review, refine, prioritize, and suggest additions or subtractions from this list, with other data that may not currently be routinely collected, but considered by stakeholders to be essential or desirable. The group also explored what barriers to implementation and uptake may be encountered in EPICare (eg, data security and ownership, time for completion, and digitizing of routine data currently collected on paper). Similarly, in workshop 3, stakeholders identified the essential and desirable features of a CDSS to provide timely actionable insights for patients and clinicians, including potential clinician prompts to complete health assessments aligned to NICE standards for EIP care.

After these 3 initial workshops, we synthesized all information gathered via a modified Delphi approach involving all stakeholders and members of the research team, to develop a consensus of data priorities (what, when, and by whom). We shared this with the members of work package 2 to understand technical and governance barriers to implementation to further refine our framework to identify a set of "must have" and "could have" data elements. Finally, in workshop 4, we presented our proposed framework to stakeholders, sought further feedback, and outlined our plans for stage 2 of EPICare development. From our initial stakeholder network, we sought to retain a representative group of stakeholders for our stage 2 activity, who will continue to guide the pilot, testing, and evaluation throughout the project.

Work Package 2: Informatics Architecture, Infrastructure, and Integration—Framework, Protocol, and Tool Kit

Work package 2 aimed to reduce technical and governance challenges in the future full build of EPICare by addressing key questions and unknowns. Based on prior experience and knowledge, the area of biggest technical risk for EPICare is the retrieval of data from electronic health records and the standardization of this into a common data model, while ensuring compliance with information governance and ethical standards. Previous work by the group involved auditing all EIP services that are part of the National Institute for Health Research (NIHR) Mental Health Translational Research Collaboration in Early Psychosis (MHTRC-Early Psychosis), to inform understanding of the existing infrastructure, capacity, capabilities, and limitations around designing and developing the EPICare platform for potential national implementation. This initial scoping work has highlighted several different electronic health records in use as well as different ways of capturing and storing relevant data in each of the trusts.

To build on this knowledge, health informatics specialists within the research team contacted and liaised with 5 NHS Trusts, including Greater Manchester Mental Health NHS Foundation Trust, Birmingham Women's and Children's NHS Foundation Trust, Cambridgeshire and Peterborough NHS Foundation Trust, Nottinghamshire Healthcare NHS Foundation Trust, and Camden and Islington NHS Foundation Trust. Information technology team leads and proposed demonstrator sites were identified, gathering information to further understand what electronic health record system is used by each trust; what relevant data are currently captured in the electronic health record (key foci: 8 NICE standards for first-episode psychosis treatment); how that data can be retrieved, such as via application programming interface or through regular exports; how the data can, and should be secured during retrieval, complying to the highest information governance standards; and the data formats used for each type of data.

Once this information was captured from all trusts, it was then used alongside the information gathered from the stakeholders in work package 1 to develop and document key requirements for the EPICare system; software architecture for the registry and CDSS; data model design including standardization of data items into a common format; security threat model including planned treatments for identified threats; proposed infrastructure to include an appropriate hosting solution, such as a secure cloud environment; and an integration plan for retrieval of data from each trust's electronic health record.

This was drafted into an overall framework document and set of technical infrastructure and information governance protocols and tool kits to inform the future build, pilot, implementation, and evaluation of the EPICare platform. With all of this in place, the technical and governance challenges for the main program grant for applied research application should be significantly reduced.

Work Package 3: Implementation Evaluation Framework

Working in parallel and in collaboration with the members of work packages 1 and 2, the purpose of this work package was to establish the preliminary implementation framework for the subsequent testing and rollout of EPICare. Founded on the idea that implementation research should be integrated throughout all stages of innovation development rather than at "end-stage," this involved understanding the distinct and interconnected implementation issues within the stages of problem definition; iterative evidence-building, intervention conceptualization, development, and testing; and subsequent rollout, experimentation, and embedding in different service settings. With particular reference to EPICare, this involved

understanding how the earlier stages of stakeholder engagement contributed to intervention development and, at the same time, how stakeholders perceived challenges to future adoption and use. With regards to PPIE stakeholders (work package 1), this involved understanding views about (1) current challenges in EIP care; (2) how clinical registries and CDSS might influence care and service improvement; (3) expectations about how interventions might be used in standard practice; and (4) participants' experiences of the co-design process. We also studied the early stage activities of the health informatics team (work package 2) to understand the explicit and tacit design assumptions; the contingencies presented by current technological parameters; the influence of prevailing governance arrangements; and importantly, to understand and evidence the interaction between the relative influence of multiple stakeholders in the co-design process. This evidence will be brought together with existing implementation science frameworks, such as normalization process theory (NPT) [31], in conjunction with complementary insights drawn from science and technology studies [32,33].

NPT helps understand how service innovations are implemented, embedded, and normalized within organizations, to the point where new practices are no longer regarded as new. It is different from other implementation models because it focuses on the specific "work" undertaken by social actors to implement innovations into everyday practice while taking into consideration the interplay between actions, contexts, and objects. NPT has 4 linked constructs, "coherence," or the work of making sense of an innovation; "cognitive participation," or the work involved when engaging with an innovation; "collective action," or the combined work of integrating new practices into existing skills, relationships, and contexts; and "reflexive monitoring," or the work of continually appraising and adapting to the introduction of new practices. It has been widely used to explain the factors that shape the implementation of complex interventions [31].

Field researchers directly observed all 4 stakeholder co-design workshops and considered the influence of multiple social, cultural, and organizational factors on the co-design process. They also observed a selection of key design meetings held between the technologists, NHS Trust partners, and other stakeholder groups to map and describe the iterative development of EPICare. Each researcher recorded their observations following an agreed semistructured guide which were then aggregated for analysis.

To clarify the observational data, qualitative semistructured interviews guided by the constructs from NPT were then conducted with all stakeholder groups to understand the factors likely to influence the subsequent implementation of EPICare. An initial set of questions and topics derived from the study objectives were used to systematically code interview transcripts and develop themes. This was piloted on 4 transcripts by 2 researchers, before agreeing to a revised set of codes, followed by further coding of remaining transcripts. Interviews focused on the different cognitive-cultural perspectives of each stakeholder group, their experiences of participating in the co-design process, and their perceptions about their influence on the co-design, together with their recommendations for subsequent development and testing.

Study Participants

Participants were recruited between November and December 2021. We recruited 40 participants across all stakeholder workshops (work package 1). This included at least 10 people with lived experience of psychosis, and ideally, lived experience of early intervention, to form the PPIE stakeholder group. PPIE members were recruited from the Birmingham University Youth Advisory Group, Cambridgeshire and Peterborough Foundation Trust, Bristol Lived Experience Advisory Panel, and PPIE networks at University College London, including those associated with the NIHR Mental Health Policy Research Unit. As an acknowledgment of the time and effort involved in taking part in the study, PPIE participants were reimbursed in line with the Involve payment policy [34], which equates to £25 (US $33.19 at the time of the study) per hour of participation.

The remaining 30 participants were recruited from the breadth of multidisciplinary care in EIP services (psychiatrists, psychologists, occupational therapists, social workers, and nurses), in addition to stakeholders from the charitable sector, NHS England, policy makers, and other academics, for facilitated group meetings. The clinical collaborators were recruited from NHS Trusts serving diverse and underserved areas with a combined population of approximately 3.4 million people (corresponding to 9.1% of the English population eligible for EIP services): Birmingham Women's and Children's Trust, Manchester Health and Care NHS Foundation Trust, Camden and Islington NHS Foundation Trust, Avon and Wiltshire Mental Health Partnership Trust, and Cambridgeshire and Peterborough Foundation Trust. Attendance at the stakeholder group meetings was taken as consent for this process and no individual written consent was required from stakeholders (including PPIE).

All stakeholders were also invited to participate in individual qualitative interviews in work package 3 to ensure that we selected a representative subset of each stakeholder group from our work package 1 stakeholder meetings. Written informed consent was obtained and interviewees were given a unique participant identification number, which was used throughout the transcription of interviews to ensure anonymity.

Given the online group format of the stakeholder workshops, individual participants attending these workshops were identifiable to each other and to the authors. However, the identities of participants who consented to an individual qualitative interview were known only to the interviewer, and as noted above, interviewees were assigned a unique participant identification number to ensure their anonymity during the transcription of their interviews.

Ethical Considerations

The EPICare study was reviewed and granted full ethical approval by the Health Research Authority on November 8, 2021 (306234). Attendance at the stakeholder group meetings in work package 1 was taken as consent for this process and no individual written consent was required from stakeholders, including PPIE contributors. Written informed consent was

obtained from all stakeholders who participated in individual qualitative interviews as part of work package 3.

Given the online group format of the stakeholder workshops, participants attending these workshops were identifiable to each other and to the authors. However, the identities of participants who consented to an individual qualitative interview were known only to the interviewer, and interviewees were assigned a unique participant identification number to preserve the anonymity of their interview transcripts. PPIE contributors were reimbursed £25 (US $33.19 at the time of the study) per hour for their participation in the study, in line with the Involve payment policy [34].

Results

Work Package 1: Stakeholder Co-Design of the EPICare Registry and CDSS

In work package 1, we established a network with representation from PPIE and other essential stakeholder groups (clinicians, academics, and policy makers) and engaged stakeholders in a series of 4 workshops, using a modified Delphi approach to identify essential and desirable elements of the EPICare registry and CDSS and to develop a consensus of data priorities. The 4 co-design workshops took place in December 2021, February 2022, May 2022, and September 2022, respectively.

Work Package 2: Informatics Architecture, Infrastructure, and Integration—Framework, Protocol, and Tool Kit

Work package 2 occurred in parallel with work packages 1 and 3, between December 2021 and September 2022. In this work package, we collaborated with NHS informatics teams to address key questions about informatics architecture, infrastructure, governance, and integration plans to facilitate onward development and testing of EPICare in diverse NHS Trusts.

Work Package 3: Implementation Evaluation Framework

Work package 3 also took place between December 2021 and September 2022. In this work package, we conducted individual qualitative interviews with representative stakeholders and took notes during observation of the stakeholder workshops to identify implementation factors from the outset and ensure they are considered in designing, implementing, and maintaining the future deployment of EPICare in a measurable way. All interviews were recorded and transcribed. For quality control, transcript summaries were shared with participants and feedback was elicited as to their veracity. Observation notes of the stakeholder workshops and transcripts of the individual interviews were subject to interpretative qualitative analysis, guided by the NPT implementation science framework. Preliminary data analysis of observation notes involved producing short descriptive summaries of field observations, for the purpose of summarizing and sharing data with the study team. NVivo software (Lumivero) was used to organize the qualitative observational and transcribed interview data. An iterative coding process was followed with data being subject to systematic close reading and coding. Through sharing and deliberating preliminary codes and interpretations with the wider study team and through the processes of constant comparison, secondary inductive, and interpretative themes were developed. At this stage, the constructs of NPT were used to further analyze and explain the study findings. Through discussion and disputation with PPIE, clinicians, and the project team, inferences were made about how the implementation science framework should be further refined.

Stage 1 of the EPICare study is now complete and we are currently preparing a paper detailing our findings from work package 3 activities (ie, field observations of the stakeholder workshops and qualitative interviews). Data collected and decisions made in the stage 1 program development phase of the project will directly inform the stage 2 building, piloting, implementation, and evaluation of the EPICare platform and CDSS in 5 demonstrator NHS Trusts serving underserved and diverse populations with substantial need for EIP care in England. If successful, this will be followed by stage 3, in which we will seek NHS adoption of EPICare for rollout to all EIP services in England.

Discussion

In this program development phase (stage 1), we co-designed a framework and protocols for the onward building, implementation, piloting, and evaluation of the EPICare registry and CDSS. We achieved this by adopting a participatory design with input from diverse relevant stakeholders, including lived experience experts and clinical, academic, technologist, and organizational stakeholders. By engaging multiple stakeholders in an iterative co-design process, using qualitative methods to capture and synthesize rich data representing a variety of perspectives, we have met our work package 1 objectives of establishing a network with representation from PPIE and other essential stakeholder groups to collaboratively identify essential and desirable elements of the EPICare platform and CDSS. In addition, we have addressed key questions related to informatics architecture, infrastructure, governance, and integration in diverse NHS Trusts (in line with our work package 2 objectives), and in doing so, have identified and minimized potential challenges and barriers to uptake and implementation (thereby meeting our work package 3 objectives).

We are now ready to build, implement, and evaluate a national patient-centered digital registry and CDSS for psychosis (EPICare) to improve national, local, and individual clinical decision-making and promote improved outcomes for people experiencing first-episode psychosis. While similar efforts to leverage routinely collected data in EIP services are currently underway in other parts of the world; for instance, in Canada [35] and Australia [36]; the EPICare registry and CDSS potentially represent a paradigmatic shift, as they would be the first national patient-centered digital registry and integrated CDSS for psychosis, one of the most common and disabling mental health disorders disproportionately affecting deprived and disadvantaged youth. By combining routine, standardized, prospective data collection via a national digital registry with real-time actionable insights delivered to patients, clinical teams, service managers, and policy makers via an embedded CDSS,

the overall aim of EPICare is to improve patient care, enhance service delivery, reduce disparities in care, and further our understanding of the relationship between the interventions offered to, and received by, young people receiving EIP care and outcomes. Insights provided by the EPICare registry will also enable more equitable, responsive resource allocation and more rapid, reliable identification of local, regional, or group-based disparities in access to care and treatment outcomes and will support clinical and policy decision-making and research on various aspects of early psychosis. The registry may also improve access to much-needed stratified trials (eg, for clozapine and neurostimulation) and facilitate the development of novel treatments.

While we have achieved all of the objectives set out for the first phase of this study, it is worth noting that adoption and integration of all the desirable elements identified by stakeholders may not be feasible or pragmatic for the initial build of the EPICare platform and CDSS. This will be tested in our next stage, as noted above.

A national psychosis digital registry—leveraging routine data to provide real-time actionable insights—will be vital to improving real-world outcomes, identifying and preventing inequalities in care, and ensuring that individuals receive the most appropriate treatments at the right time to promote recovery and maximize life chances.

Acknowledgments

Early Psychosis Informatics into Care (EPICare) is fully funded by the National Institute for Health Research (NIHR) Programme Development Grants (PDG) Mental Health Call 2021 (grant NIHR203669). Birmingham Women's and Children's National Health Service (NHS) Foundation Trust agreed to act as sponsor for this study. This research is supported by the NIHR Oxford Health Biomedical Research Centre, the NIHR University College London Hospitals (UCLH) Biomedical Research Centre, the NIHR Cambridge Biomedical Research Centre (NIHR203312), and the NIHR Applied Research Collaboration East of England. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Authors' Contributions

RU and JBK are joint project leads and hold joint senior authorship. SLG drafted the paper with further input from RU and JBK. SJ, GKM, MAP, NC, JW, JA, RJD, MM, SMA, TW, JBK, YL, TB, and SAS also contributed to the study as well as provided comments on the paper. All authors approved the final version.

Conflicts of Interest

GKM has received consultancy fees from ieso. RU reports speaker fees from Sunovion, Springer Healthcare, Otsuka, and Vitaris outside the submitted work and holds unpaid officership with the British Association for Pharmacology—Honorary General Secretary 2021-2024 and is deputy editor of the British Journal of Psychiatry. JA is funded by the NIHR Manchester Biomedical Research Centre. The views expressed in this publication are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health.

References

1. an der Heiden W, Häfner H. The epidemiology of onset and course of schizophrenia. Eur Arch Psychiatry Clin Neurosci 2000;250(6):292-303. [doi: 10.1007/s004060070004] [Medline: 11153964]
2. Kirkbride JB, Errazuriz A, Croudace TJ, Morgan C, Jackson D, Boydell J, et al. Incidence of schizophrenia and other psychoses in England, 1950-2009: a systematic review and meta-analyses. PLoS One 2012;7(3):e31660 [FREE Full text] [doi: 10.1371/journal.pone.0031660] [Medline: 22457710]
3. Jongsma HE, Turner C, Kirkbride JB, Jones PB. International incidence of psychotic disorders, 2002-17: a systematic review and meta-analysis. Lancet Public Health 2019 May;4(5):e229-e244 [FREE Full text] [doi: 10.1016/S2468-2667(19)30056-8] [Medline: 31054641]
4. March D, Hatch SL, Morgan C, Kirkbride JB, Bresnahan M, Fearon P, et al. Psychosis and place. Epidemiol Rev 2008;30:84-100 [FREE Full text] [doi: 10.1093/epirev/mxn006] [Medline: 18669521]
5. O'Donoghue B, Roche E, Lane A. Neighbourhood level social deprivation and the risk of psychotic disorders: a systematic review. Soc Psychiatry Psychiatr Epidemiol 2016 Jul;51(7):941-950. [doi: 10.1007/s00127-016-1233-4] [Medline: 27178430]
6. McDonald K, Ding T, Ker H, Dliwayo TR, Osborn DPJ, Wohland P, et al. Using epidemiological evidence to forecast population need for early treatment programmes in mental health: a generalisable Bayesian prediction methodology applied to and validated for first-episode psychosis in England. Br J Psychiatry 2021 Jul;219(1):383-391 [FREE Full text] [doi: 10.1192/bjp.2021.18] [Medline: 34475575]

7. QS80: psychosis and schizophrenia in adults. National Institute for Health and Care Excellence. 2015. URL: https://wels.open.ac.uk/research-project/caren/node/2782 [accessed 2024-02-24]
8. Bird V, Premkumar P, Kendall T, Whittington C, Mitchell J, Kuipers E. Early intervention services, cognitive-behavioural therapy and family intervention in early psychosis: systematic review. Br J Psychiatry 2010 Nov;197(5):350-356 [FREE Full text] [doi: 10.1192/bjp.bp.109.074526] [Medline: 21037211]
9. Anderson KK, Norman R, MacDougall A, Edwards J, Palaniyappan L, Lau C, et al. Effectiveness of early psychosis intervention: comparison of service users and nonusers in population-based health administrative data. Am J Psychiatry 2018 May 01;175(5):443-452. [doi: 10.1176/appi.ajp.2017.17050480] [Medline: 29495897]
10. McCrone P, Craig TKJ, Power P, Garety PA. Cost-effectiveness of an early intervention service for people with psychosis. Br J Psychiatry 2010 May;196(5):377-382. [doi: 10.1192/bjp.bp.109.065896] [Medline: 20435964]
11. Lester H, Marshall M, Jones P, Fowler D, Amos T, Khan N, et al. Views of young people in early intervention services for first-episode psychosis in England. Psychiatr Serv 2011 Aug;62(8):882-887. [doi: 10.1176/ps.62.8.pss6208_0882] [Medline: 21807826]
12. Lally J, Ajnakina O, Stubbs B, Cullinane M, Murphy KC, Gaughran F, et al. Remission and recovery from first-episode psychosis in adults: systematic review and meta-analysis of long-term outcome studies. Br J Psychiatry 2017 Dec;211(6):350-358. [doi: 10.1192/bjp.bp.117.201475] [Medline: 28982659]
13. Stokes I, Griffiths SL, Jones R, Everard L, Jones PB, Fowler D, et al. Prevalence of treatment resistance and clozapine use in early intervention services. BJPsych Open 2020 Sep 17;6(5):e107 [FREE Full text] [doi: 10.1192/bjo.2020.89] [Medline: 32938513]
14. Rammou A, Fisher HL, Johnson S, Major B, Rahaman N, Chamberlain-Kent N, et al. Negative symptoms in first-episode psychosis: clinical correlates and 1-year follow-up outcomes in London Early Intervention Services. Early Interv Psychiatry 2019 Jun;13(3):443-452. [doi: 10.1111/eip.12502] [Medline: 29148264]
15. Marwaha S, Thompson A, Upthegrove R, Broome MR. Fifteen years on - early intervention for a new generation. Br J Psychiatry 2016 Sep;209(3):186-188. [doi: 10.1192/bjp.bp.115.170035] [Medline: 27587758]
16. Griffiths SL, Lalousis PA, Wood SJ, Upthegrove R. Heterogeneity in treatment outcomes and incomplete recovery in first episode psychosis: does one size fit all? Transl Psychiatry 2022 Nov 17;12(1):485 [FREE Full text] [doi: 10.1038/s41398-022-02256-7] [Medline: 36396628]
17. Firth J, Siddiqi N, Koyanagi A, Siskind D, Rosenbaum S, Galletly C, et al. The Lancet Psychiatry Commission: a blueprint for protecting physical health in people with mental illness. Lancet Psychiatry 2019;6(8):675-712. [doi: 10.1016/S2215-0366(19)30132-4] [Medline: 31324560]
18. Hjorthøj C, Stürup AE, McGrath JJ, Nordentoft M. Years of potential life lost and life expectancy in schizophrenia: a systematic review and meta-analysis. Lancet Psychiatry 2017 Apr;4(4):295-301. [doi: 10.1016/S2215-0366(17)30078-0] [Medline: 28237639]
19. Morris RM, Sellwood W, Edge D, Colling C, Stewart R, Cupitt C, et al. Ethnicity and impact on the receipt of cognitive-behavioural therapy in people with psychosis or bipolar disorder: an English cohort study. BMJ Open 2020 Dec 15;10(12):e034913 [FREE Full text] [doi: 10.1136/bmjopen-2019-034913] [Medline: 33323425]
20. Puntis S, Oke J, Lennox B. Discharge pathways and relapse following treatment from early intervention in psychosis services. BJPsych Open 2018 Sep;4(5):368-374 [FREE Full text] [doi: 10.1192/bjo.2018.50] [Medline: 30202598]
21. Griffiths SL, Bogatsu T, Longhi M, Butler E, Alexander B, Bandawar M, et al. Five-year illness trajectories across racial groups in the UK following a first episode psychosis. Soc Psychiatry Psychiatr Epidemiol 2023 Apr;58(4):569-579 [FREE Full text] [doi: 10.1007/s00127-023-02428-w] [Medline: 36717434]
22. National clinical audit in psychosis audit. Healthcare Quality Improvement Partnership. 2021. URL: https://www.hqip.org.uk/a-z-of-nca/national-clinical-audit-of-psychosis/ [accessed 2024-02-24]
23. Heuschmann PU, Grieve AP, Toschke AM, Rudd AG, Wolfe CDA. Ethnic group disparities in 10-year trends in stroke incidence and vascular risk factors: the South London Stroke Register (SLSR). Stroke 2008 Aug;39(8):2204-2210. [doi: 10.1161/STROKEAHA.107.507285] [Medline: 18535279]
24. Kelsey EA, Njeru JW, Chaudhry R, Fischer KM, Schroeder DR, Croghan IT. Understanding user acceptance of clinical decision support systems to promote increased cancer screening rates in a primary care practice. J Prim Care Community Health 2020;11:2150132720958832 [FREE Full text] [doi: 10.1177/2150132720958832] [Medline: 33016170]
25. Taylor-Robinson D, Archangelidi O, Carr SB, Cosgriff R, Gunn E, Keogh RH, CF-EpinNet collaboration. Data resource profile: the UK Cystic Fibrosis Registry. Int J Epidemiol 2018 Feb 01;47(1):9-10e [FREE Full text] [doi: 10.1093/ije/dyx196] [Medline: 29040601]
26. Stephan BCM, Siervo M, Brayne C. How can population-based studies best be utilized to reduce the global impact of dementia? Recommendations for researchers, funders, and policymakers. Alzheimers Dement 2020 Oct;16(10):1448-1456. [doi: 10.1002/alz.12127] [Medline: 32573915]
27. Langhorne P, Taylor G, Murray G, Dennis M, Anderson C, Bautz-Holter E, et al. Early supported discharge services for stroke patients: a meta-analysis of individual patients' data. Lancet 2005;365(9458):501-506. [doi: 10.1016/S0140-6736(05)17868-4] [Medline: 15705460]

28. Mazo C, Kearns C, Mooney C, Gallagher WM. Clinical decision support systems in breast cancer: a systematic review. Cancers (Basel) 2020 Feb 06;12(2):369 [FREE Full text] [doi: 10.3390/cancers12020369] [Medline: 32041094]
29. Ospina-Pinillos L, Davenport T, Mendoza Diaz A, Navarro-Mancilla A, Scott EM, Hickie IB. Using participatory design methodologies to co-design and culturally adapt the Spanish version of the mental health eClinic: qualitative study. J Med Internet Res 2019 Aug 02;21(8):e14127 [FREE Full text] [doi: 10.2196/14127] [Medline: 31376271]
30. National Institute for Health and Care Excellence (NICE). Psychosis and Schizophrenia in Adults: Treatment and Management. London, UK: Royal College of Psychiatrists; 2014.
31. Murray E, Treweek S, Pope C, MacFarlane A, Ballini L, Dowrick C, et al. Normalisation process theory: a framework for developing, evaluating and implementing complex interventions. BMC Med 2010 Oct 20;8:63 [FREE Full text] [doi: 10.1186/1741-7015-8-63] [Medline: 20961442]
32. Robertson A, Cresswell K, Takian A, Petrakaki D, Crowe S, Cornford T, et al. Implementation and adoption of nationwide electronic health records in secondary care in England: qualitative analysis of interim results from a prospective national evaluation. BMJ 2010 Sep 01;341:c4564 [FREE Full text] [doi: 10.1136/bmj.c4564] [Medline: 20813822]
33. Ainsworth J, Harper R. The PsyGrid experience: using web services in the study of schizophrenia. IJHISI 2008;2(2):365-386. [doi: 10.4018/978-1-60566-050-9.ch030]
34. Involve. URL: https://www.involve.org.uk/ [accessed 2024-02-24]
35. Ferrari M, Iyer S, LeBlanc A, Roy MA, Abdel-Baki A. A rapid-learning health system to support implementation of early intervention services for psychosis in Quebec, Canada: protocol. JMIR Res Protoc 2022 Jul 19;11(7):e37346 [FREE Full text] [doi: 10.2196/37346] [Medline: 35852849]
36. Thompson A, Fitzsimons J, Killackey E, Ahern S, Amminger P, Alvarez-Jimenez M, et al. The Australian Early Psychosis Collaborative Consortium (AEPCC): improving clinical care in early psychosis. Australas Psychiatry 2023 Jun;31(3):306-308. [doi: 10.1177/10398562231174691] [Medline: 37171091]

Abbreviations

CDSS: clinical decision support system
EIP: early intervention in psychosis
EPICare: Early Psychosis Informatics into Care
HoNOS: Health of the Nation Outcomes Scales
MHTRC-Early Psychosis: Mental Health Translational Research Collaboration in Early Psychosis
NHS: National Health Service
NICE: National Institute for Health and Care Excellence
NIHR: National Institute for Health Research
NPT: normalization process theory
PPIE: patient and public involvement and engagement
QPR: The Questionnaire about the Process of Recovery

Edited by A Mavragani; submitted 23.06.23; peer-reviewed by S Sabarguna, K Uludag; comments to author 02.10.23; revised version received 21.01.24; accepted 21.02.24; published 19.03.24.

Please cite as:
Griffiths SL, Murray GK, Logeswaran Y, Ainsworth J, Allan SM, Campbell N, Drake RJ, Katshu MZUH, Machin M, Pope MA, Sullivan SA, Waring J, Bogatsu T, Kane J, Weetman T, Johnson S, Kirkbride JB, Upthegrove R
Implementing and Evaluating a National Integrated Digital Registry and Clinical Decision Support System in Early Intervention in Psychosis Services (Early Psychosis Informatics Into Care): Co-Designed Protocol
JMIR Res Protoc 2024;13:e50177
URL: https://www.researchprotocols.org/2024/1/e50177
doi:10.2196/50177
PMID:38502175

Protocol

Examining Parent Mood, Feeding Context, and Feeding Goals as Predictors of Feeding Practices Used by Parents of Preschool Children With Avid Eating Behavior: Protocol for an Ecological Momentary Assessment Study

Katie Edwards[1], PhD; Helen Croker[2], PhD; Claire Farrow[1], PhD; Emma Haycraft[3], PhD; Moritz Herle[4], PhD; Clare Llewellyn[5], PhD; Abigail Pickard[1], PhD; Jacqueline Blissett[1], PhD

[1]School of Psychology and Institute of Health and Neurodevelopment, Aston University, Birmingham, United Kingdom

[2]World Cancer Research Fund International, London, United Kingdom

[3]School of Sport, Exercise and Health Sciences, Loughborough University, Loughborough, United Kingdom

[4]Social, Genetic & Developmental Psychiatry Centre, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, United Kingdom

[5]Research Department of Behavioural Science and Health, Institute of Epidemiology and Health Care, University College London, London, United Kingdom

Corresponding Author:
Katie Edwards, PhD
School of Psychology and Institute of Health and Neurodevelopment
Aston University
Aston Triangle
Birmingham, B4 7ET
United Kingdom
Phone: 44 121 204 3784
Email: k.edwards4@aston.ac.uk

Abstract

Background: An avid eating behavior profile is characterized by a greater interest in food and a tendency to overeat in response to negative emotions. Parents use specific strategies to manage feeding interactions with children with avid eating behavior. While momentary and contextual factors, such as parental mood, have been found to influence parental feeding practices, there is a lack of research examining parents' daily experiences of feeding children with avid eating behavior. Examining this is important because parental feeding practices are key levers in tailored interventions to support children's healthy eating behavior.

Objective: We aim to describe the ecological momentary assessment methods and procedures used in the APPETItE (Appetite in Preschoolers: Producing Evidence for Tailoring Interventions Effectively) project, which aims to examine how variation in parental mood, feeding goals, and the context of eating occasions affect the parental feeding practices used to manage feeding interactions with children with an avid eating behavior profile.

Methods: Participants are primary caregivers from the APPETItE cohort who have a preschool-age child (aged 3-5 years) with an avid eating behavior profile. Caregivers complete a 10-day ecological momentary assessment period using signal- and event-contingent surveys to examine (1) mood and stress, (2) parental feeding goals, and (3) contextual factors as predictors of parental feeding practices.

Results: Recruitment and data collection began in October 2023 and is expected to be completed by spring 2024. The data have a 3-level structure: repeated measurements (level 1) nested within days (level 2) nested within an individual (level 3). Thus, lag-dependent models will be conducted to test the main hypotheses.

Conclusions: The findings from this study will provide an understanding of caregivers' daily experiences of feeding preschool children with avid eating behavior, who are at greater risk for the development of obesity. Understanding the predictors of feeding practices at the moment they occur, and across various contexts, will inform the development of tailored resources to support caregivers in managing children's avid eating behavior.

International Registered Report Identifier (IRRID): DERR1-10.2196/55193

(JMIR Res Protoc 2024;13:e55193) doi:10.2196/55193

KEYWORDS

ecological momentary assessment; avid eating; children's eating behavior; parental feeding practices; feeding behaviour; parent; children; eating behaviour; obesity; environmental factors; observational study; feeding; United Kingdom

Introduction

Individuals differ in their susceptibility to obesity due to complex interactions between genetic and environmental factors that contribute to the development of eating behavior [1]. One population who are at greater risk of developing obesity is children with more avid appetites. Avid eating behavior is characterized by higher enjoyment of food, greater responsiveness to food cues, a tendency to overeat in response to negative emotions, faster eating, less sensitivity to satiety cues, and lower levels of food fussiness [2,3]. We have established that around 1 in 5 children aged 3-5 years in the United Kingdom show an avid eating behavior profile [3]. The findings from prospective research have shown that avid eating behaviors are positively associated with children's adiposity [4]. Thus, children with avid eating behavior may be at greater risk of developing obesity. Given the immediate and long-term negative health consequences associated with childhood obesity [5], it is vital to identify strategies across time and contexts to support the development of healthy eating behavior for children with avid eating behavior profiles.

One powerful and modifiable influence on the development of children's eating behavior is the feeding practices used by parents or caregivers which directly influence what, when, and how much food children consume [6,7]. We have demonstrated that parents of children aged 3-5 years with an avid eating behavior profile use more restriction of food and greater use of food for emotion regulation than those children without avid eating behavior [3]. However, this analysis, like much research examining parental feeding practices, has relied on static, self-report measures that do not capture the intraindividual variability in parent feeding behavior across time and context. Further, 1 methodology that has been used more recently to capture variations in factors that influence feeding behavior is ecological momentary assessment (EMA). Research using EMA has extended our understanding of parent-child feeding interactions, demonstrating that parental feeding practices differ across time and contexts (eg, the type of eating occasion) [8,9]. This suggests that the use of specific parental feeding practices is situation-dependent and highlights the complexity of parent-child feeding relationships. While the use of momentary parental feeding practices remains to be examined in children with avid eating behavior, findings from qualitative research suggest that parental feeding practices used to manage children's avid eating behavior also vary by context, such as the type and location of the eating occasion [2]. For example, parents of children with an avid eating behavior profile reported greater use of controlling feeding practices at snack times, compared to mealtimes. Therefore, since feeding practices to manage children's avid eating behavior appear situation-dependent, research using momentary observation (eg, EMA) is needed to examine the effect of contextual factors on feeding interactions with children with avid eating behavior.

Other key influences on parental feeding practices include parental mood and stress [10]. EMA research has demonstrated that fluctuations in parental mood and stress throughout the day influence the subsequent use of parental feeding practices. For example, higher maternal stress and depressed mood earlier in the day have been found to predict feeding practices (eg, greater pressure to eat), and the type of food served in the evening (eg, fewer homemade meals) [11-13]. Furthermore, qualitative research has shown that parents use specific feeding strategies to manage challenging feeding interactions with children with avid eating behavior [2]. For example, parents described using indulgent feeding strategies, such as emotional feeding and food as a reward, when parenting energy is low. Given this, it is possible that momentary changes in parental mood and stress could influence the use of subsequent feeding practices with children with avid eating behavior. This remains to be examined but is critical for the development of effective support targeting feeding practices of parents of children with avid eating behavior. If mood and stress are key predictors of the use of less adaptive strategies, our intervention must provide support tailored for the management of those experiences.

Parental feeding goals have also been shown to influence feeding interactions [14]. Parental feeding goals may predict feeding practices, for example, parents may use greater restriction of less healthy foods when their feeding goal is health-related. Previous research has specifically focused on mealtime feeding goals [14], however, it is also important to investigate parental feeding goals during snack times, to determine whether feeding goals vary by time and context. Examining this is particularly important because parents of children with avid eating behavior have described their children as frequently requesting snacks [2]. Additionally, it is possible that parental mood throughout the day could influence subsequent feeding goals. For example, parents might aim to avoid stress and conflict at an evening meal after experiencing high stress throughout the day. However, whether fluctuations in parental mood throughout the day influence subsequent feeding goals remains to be examined.

In summary, EMA research has extended our understanding of parent-child feeding interactions, demonstrating that parental feeding practices are situation-dependent and are influenced by momentary factors, such as context and parental mood [8,11-13]. Feeding children with avid eating behavior is challenging [2], however, there is a lack of research examining parents' daily experiences. Thus, examining feeding interactions as they occur in real time and contexts using EMA will provide insight into the parents' experiences of feeding their child with avid eating behavior. Hence, this protocol aims to provide a detailed overview of the EMA methods and procedures used in the APPETItE (Appetite in Preschoolers: Producing Evidence for Tailoring Interventions Effectively) project. This study aims to

examine how variation in parental mood, feeding goals, and the context of eating occasions affects the parental feeding practices used to manage feeding interactions with children with an avid eating behavior profile.

Methods

Study Design and Participants

This observational study is part of a larger program of research (APPETItE project) which examines feeding and eating in preschool children with avid eating behavior, to inform future intervention design and efficacy. The APPETItE project has identified an avid eating behavior profile in preschool children using latent profile analysis [3]. Primary caregivers (N=200) of a child aged 3-5 years who was identified as having an avid eating behavior profile in this initial study [3] are invited to participate in this EMA study. Given the novelty of this research, a reliable power calculation could not be conducted. Thus, based on previous research [11] we aimed to invite 200 parents to participate to account for attrition and to provide sufficient data to examine within- and between-subject effects. Eligibility criteria include English-speaking primary caregivers from the United Kingdom who are responsible for feeding their child for more than half the time when their child is at home. Caregivers whose child is autistic, has severe learning disabilities, or a chronic illness that directly influences their dietary requirements and eating habits are not eligible to participate.

Ethical Considerations

Ethical approval was provided by the Aston University Health and Life Sciences Research Ethics Committee (HLS21003). All participants are asked to provide informed consent.

Recruitment

Eligible primary caregivers are invited to participate by email. After registering their interest to participate, caregivers receive an email including details of how to download the mobile app, and how to complete the baseline questionnaire. Following completion of the baseline questionnaire, caregivers receive an email including details about how to complete the survey period, along with an information video and leaflet. If caregivers experience any technical difficulties, have any questions, or want to go through this study's procedures, they can contact the research team by email or arrange a video call.

Data Collection Procedures

Overview

Caregivers complete a baseline questionnaire, 10 days of EMA, and an end-of-study questionnaire. Participation in this study is remote; surveys are administered through a mobile smartphone app, which is downloaded directly to caregivers' personal smartphones. Caregivers who do not own a smartphone can request one from the research team to use for this study's period. This study, including a list of all the items used, was preregistered on the Open Science Framework [15].

Baseline Questionnaire

The baseline questionnaire gathers information about caregivers' food security and general mood (anxiety, depression, stress, and well-being). Caregivers are also asked to provide their home postcode as a measure of Index of Multiple Deprivation. The Index of Multiple Deprivation decile scores are calculated by ranking residential areas in England into 10 equal groups, with scores ranging from 1 (indicating the most deprived 10% of residential areas) to 10 (indicating the least deprived 20%-30% of residential areas) [16]. Caregivers' food security is measured using the Short Form of the Household Food Security Scale [17]. Responses are summed and categorized as 0-1 = high or marginal food security, 2-4 = low food security, and 5-6 = very low food security.

Additionally, caregivers are asked to complete 3 questionnaires to assess their general mood. The Hospital Anxiety and Depression Scale [18] measures caregivers' anxiety (7 items, eg, "I feel tense or wound up") and depression (7 items, eg, "I still enjoy the things I used to enjoy"). Responses are on a 4-point Likert scale from 0 (eg, "not at all") to 3 (eg, "most of the time"). The Hospital Anxiety and Depression Scale has been found to have good reliability and validity [19]. The Perceived Stress Scale [20] measures caregivers' baseline stress across 10 items (eg, "in the last month, how often have you felt nervous and stressed?"), with scores from 0 ("never") to 4 ("very often"). The Perceived Stress Scale is a valid and reliable measure [21]. Finally, the World Health Organization Well-Being Index [22] assesses caregivers' well-being across 5 items (eg, "I have felt calm and relaxed"), with scores from 0 ("at no time") to 5 ("all of the time"). The World Health Organization Well-Being Index has been found to have good reliability and validity [22].

Caregivers also provide information about how much time they usually spend with their child on a weekday and weekend, upcoming periods where their typical eating routine is altered (eg, holidays and feasting or fasting for religious reasons), or periods where they are not with their child (eg, shared custody). This information is gathered so that the EMA period can be adjusted to suit participants (eg, delaying the start date of the EMA period).

Ten-Day EMA Period

Overview

Caregivers complete 10 days of EMA surveys. While 7 complete days are required for this study, caregivers are asked to complete 10 consecutive days of EMA to allow flexibility for some incomplete days (eg, a sensitization period) [23]. The EMA period examines parents' mood, feeding goals, feeding practices, and contextual factors using three sampling schemes: (1) signal-contingent surveys (morning and mood surveys), (2) event-contingent surveys (food surveys), and (3) end-of-day surveys (Table 1). Surveys take less than 5 minutes for caregivers to complete.

Table 1. Primary variables and covariates assessed during the 10-day EMA[a] period.

Survey (delivery) and variables	Example item
Mood survey (notification)	
Feeding goals[b]	To give my child food that is nutritious
Mood	I feel annoyed
Stress	I feel tense
Context	Who am I with?
Food survey (self-initiated)	
Feeding practices	Did you have to make sure your child did not eat too much food?
Feeding goals	I didn't want to give in to my child, even if this caused an argument
Context	Where did your child ask for food?
End-of-day survey (notification)	
Mood	How stressful was your day?
Feeding practices	Today, how often did you have to limit your child's eating of snack foods?
Children's eating behavior	How satisfied are you with how your child ate today?

[a]EMA: ecological momentary assessment.

[b]Examined at the morning survey only.

Signal-Contingent Surveys

Each day, caregivers are sent four signal-contingent surveys at semirandom times within one of four 120-minute blocks: 7 AM to 9 AM (morning survey); 10 AM to noon; 1 PM to 3 PM; and 4 PM to 6 PM. Each block is separated by 60 minutes, to avoid overlap between surveys. To accommodate different routines, the notification window for morning surveys can be adjusted between 5 AM and 9 AM. When a survey is ready to complete, caregivers receive a notification on their phone. A reminder notification is sent 15 minutes after the initial notification, if the survey has not been completed, to ensure that responses are momentary [24]. From the first notification, caregivers have 60 minutes to complete notification surveys before the link expires.

Signal-contingent surveys examine caregivers' mood (positive and negative affect), stress, and the context in which the survey is completed. Items measuring positive and negative affect are adapted from the Positive and Negative Affect Schedule [25] and have been used extensively in EMA research [26]. Items measuring parents' stress are adapted from the Perceived Stress Scale [20] for use in EMA research [23,27]. All responses are made on a 5-point Likert scale from 1 ("not at all") to 5 ("extremely"). Surveys also examine the context in which caregivers complete the survey, using questions adapted from the PsyMate (Department of Psychiatry and Psychology at Maastricht University) standard assessment protocol [28]. To determine whether feeding goals vary throughout the day, morning surveys examine parental feeding goals. Questions are adapted from the Family Mealtime Goals Questionnaire [14] to assess caregivers' health-related goals and stress and conflict avoidance goals. Feeding goals are not examined in other mood surveys.

Event-Contingent Surveys

Event-contingent (food) surveys are self-initiated by caregivers each time their child asks for or consumes food when their caregiver is present. For example, eating occasions when children are at preschool will not be reported. Caregivers have previously reported that children with avid eating behavior frequently ask for food [2], thus, caregivers are asked to report each time their child requests food, even if their child is not given food (eg, not allowing children a snack before dinner). Food surveys involve (1) "food consumed" surveys and (2) "food request" surveys. While the same broad domains are assessed, questions are adapted to suit the type of feeding situation. For example, "food consumed" surveys ask caregivers about their goals for the eating occasion ("what was your aim for this meal or snack time?"), whereas "food request" surveys ask caregivers about their goal for saying no ("what was your aim for saying no to your child when they asked for food?"). Caregivers are directed to complete a "food consumed" survey if they report that their child has eaten or to complete a "food request survey" if they report their child asked them for food but has not eaten.

Food surveys examine parental feeding practices across several domains: structure-related, autonomy support, coercive control, and indulgent feeding practices. Indulgent feeding practices are only measured in "food consumed" surveys because questions relate to occasions where children consume food. Questions are adapted from the Real-Time Parent Feeding Practices measurement tool [29]. Food surveys also examine parental feeding goals, including health-related goals, and stress and conflict avoidance goals. Questions are adapted from The Family Mealtime Goals Questionnaire [14] to suit the EMA format. For example, responses were changed from a 5-point Likert scale to "yes" or "no." A "not applicable" option was also included for questions about parental feeding practices. When assessing parents' main feeding goal, the "other" response option

can be selected for parents to specify their own feeding goal. Questions examining the context of eating occasions and requests for food are adapted from the EMA component of the Family Matters study [23].

Completing event-based surveys relies on self-initiation by caregivers, thus, there may be occasions when caregivers forget to report children's food requests or consumption. To ensure these feeding interactions are captured, each EMA survey ends with the option to report an occasion where children have asked for, or consumed food, that caregivers have not previously reported, as done in other EMA research [23,30].

End-of-Day Surveys

Each day, caregivers are asked to complete an end-of-day survey to provide a summary of how their day has been. Caregivers receive a semirandom notification between 8 PM and 10 PM when the end-of-day survey is ready to complete. Caregivers can adjust the survey window between 7 PM and midnight, to suit their evening routines. A reminder notification is administered 15 minutes after the first notification if caregivers have not yet completed the survey. End-of-day surveys are available for 60 minutes after the initial notification, before expiring.

End-of-day surveys include general questions about parental mood and feeding practices, the amount of time parents spent with their child, children's eating behavior, and a feasibility question [23]. Questions also assess the number of meals and snacks children consumed and requested throughout the day, to help determine parents' compliance with completing food surveys.

Feasibility and Usability

After the 10-day EMA period, caregivers complete a short questionnaire to assess the feasibility and usability of completing the EMA period. Questions are adapted from the PsyMate standardized protocol [31]. Examining the feasibility and usability of completing EMA research is important in this sample since feeding interactions with children with avid eating behavior can be challenging [2].

Incentives

Caregivers receive a £100 (approximately US $126) shopping voucher if at least 8 days of surveys are complete. Based on previous research [29], the criteria for 1 complete day of EMA includes the completion of 2 signal-initiated (random) surveys and 1 event (food) survey. This accommodates for a variation in routines (eg, families where the child consumes most of their food in childcare settings), but also provides sufficient data to analyze within-day effects. All caregivers who complete 10 days of EMA are entered into a prize draw to win an additional £100 (approximately US $126) shopping voucher. If participants withdraw prematurely from this study, their time is reimbursed on a pro rata basis of £10 (approximately US $12.60) per complete day. The digital shopping vouchers are emailed to participants after taking part.

Pilot Study

Study procedures were piloted with 25 primary caregivers of children aged 3-6 years with high food approach tendencies, to determine the feasibility and usability of this study's processes. All caregivers provided feedback about their participation in this study which informed researchers of the adjustments needed (eg, increasing the time surveys are available) and technical difficulties.

Results

Overview

Recruitment and collection of data began in October 2023. At the time of this paper's submission, data collection is ongoing and is anticipated until spring 2024. This study hypothesizes that parental mood, feeding goals, and the context of eating occasions (eg, meal setting) will predict the feeding practices that parents use to manage children's avid eating behavior. Specifically, analyses will test the following hypotheses: (1) higher momentary stress, negative affect, and goals of reducing mealtime chaos will predict use of coercive and instrumental feeding practices at the subsequent eating occasion; (2) parental feeding goals will change throughout the day in response to parental mood, feeding goals, and mealtime context; (3) momentary mood and context will be associated with parental feeding goals; (4) parents will be more likely to report coercive and instrumental feeding practices when in public and when they report the atmosphere as tense or stressful; and (5) parental low mood, high stress, increased requests for food will predict changes in feeding goals.

Statistical Analysis Plan

SPSS (IBM Corp) will be used for data cleaning and descriptive analyses, and R (R Foundation for Statistical Computing) will be used for main analyses. Skewness and kurtosis will be evaluated before data analysis, with relevant transformations administered if data violate the assumptions of the model. The data have a 3-level structure: repeated measurements (level 1) nested within days (level 2) and nested within an individual (level 3). Thus, lag-dependent models will be used to test our main hypotheses. More details of the analytic plan are on the Open Science Framework [15].

Discussion

Principal Findings

This will be the first study to examine how fluctuations in parental mood, feeding goals, and the context of eating occasions affect the parental feeding practices used with children with avid eating behavior. Determining momentary and contextual factors that influence parental feeding behavior is essential for better understanding caregivers' daily feeding experiences. This is particularly important for caregivers of children with avid eating behavior since eating occasions have been reported as frequent and challenging [2].

However, experiencing frequent and challenging feeding occasions could negatively impact caregivers' engagement with EMA. For example, caregivers would need to complete many food surveys, making this study more burdensome. In addition, time constraints have been reported to impact feeding decisions [32]; thus, caregivers of preschool children who are time-poor

may struggle to engage with the EMA period. Hence, this study will provide an important understanding of the feasibility of conducting EMA research with a diverse sample of caregivers of preschool children with challenging eating behavior.

Strengths and Limitations

This use study uses a novel methodology to gather a large amount of data about parental behavior across multiple time points and contexts. This novel approach will further our understanding of parental feeding practices, which has been predominantly based on static self-report measures, by capturing the intraindividual variability in feeding behavior across time and context. However, this study has several limitations. First, the use of a mobile app in this study relies on participants having good technological literacy, which may exclude participants from underrepresented communities. To improve the accessibility of this study, researchers from the APPETItE team can be contacted by email, web-based video chat, or phone to discuss and troubleshoot issues. Second, the limited number of items used in this study may not fully reflect parents' experiences. However, given the large number of surveys, each survey must be short enough to reduce participant burden, while gathering sufficient information about parent behavior. Finally, the 10-day survey period may be particularly intensive for parents of preschool children with avid eating behavior given the expected frequent requests for food. This could potentially result in high attrition and data loss, and limit the findings to parents with the resources to complete multiple surveys. Given this, and the novelty of EMA research in this area, it is important to examine the feasibility of using this methodology with parents who may be experiencing feeding challenges with their child.

Conclusion

Overall, this novel study will provide momentary evidence about caregivers' daily experiences of feeding preschool children with avid eating behavior. The findings will contribute to the APPETItE project which aims to produce tailored guidelines to help parents nurture the development of children's healthy eating behavior, particularly for children who are at greater risk for the development of obesity.

Acknowledgments

This research was supported by the Economic and Social Research Council (ES/V014153/1). The funding organization had no role in the design and conduct of this study's collection, management, preparation, review, or approval.

Data Availability

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

Authors' Contributions

All authors were involved in the conceptualization and methodology of this study, and the writing (review and editing) of this paper. KE was responsible for writing the original draft. JB, HC, CF, MH, CL, and EH worked on the funding acquisition.

Conflicts of Interest

None declared.

References

1. Llewellyn C, Wardle J. Behavioral susceptibility to obesity: gene-environment interplay in the development of weight. Physiol Behav 2015;152(Pt B):494-501. [doi: 10.1016/j.physbeh.2015.07.006] [Medline: 26166156]
2. Edwards KL, Blissett J, Croker H, Farrow C, Herle M, Kininmonth A, et al. Examining parents' experiences and challenges of feeding preschool children with avid eating behaviour. Appetite Under review.
3. Pickard A, Croker H, Edwards K, Farrow C, Haycraft E, Herle M, et al. Identifying an avid eating profile in childhood: associations with temperament, feeding practices and food insecurity. Appetite 2023;191:107050 [FREE Full text] [doi: 10.1016/j.appet.2023.107050] [Medline: 37793473]
4. Kininmonth A, Smith A, Carnell S, Steinsbekk S, Fildes A, Llewellyn C. The association between childhood adiposity and appetite assessed using the child eating behavior questionnaire and baby eating behavior questionnaire: a systematic review and meta-analysis. Obes Rev 2021;22(5):e13169 [FREE Full text] [doi: 10.1111/obr.13169] [Medline: 33554425]
5. Lister NB, Baur LA, Felix JF, Hill AJ, Marcus C, Reinehr T, et al. Child and adolescent obesity. Nat Rev Dis Primers 2023;9(1):24 [FREE Full text] [doi: 10.1038/s41572-023-00435-4] [Medline: 37202378]
6. Savage JS, Fisher JO, Birch LL. Parental influence on eating behavior: conception to adolescence. J Law Med Ethics 2007;35(1):22-34 [FREE Full text] [doi: 10.1111/j.1748-720X.2007.00111.x] [Medline: 17341215]
7. Scaglioni S, De Cosmi V, Ciappolino V, Parazzini F, Brambilla P, Agostoni C. Factors influencing children's eating behaviours. Nutrients 2018;10(6):706 [FREE Full text] [doi: 10.3390/nu10060706] [Medline: 29857549]
8. Berge JM, Tate A, Trofholz A, Loth K, Miner M, Crow S, et al. Examining variability in parent feeding practices within a low-income, racially/ethnically diverse, and immigrant population using ecological momentary assessment. Appetite 2018;127:110-118 [FREE Full text] [doi: 10.1016/j.appet.2018.04.006] [Medline: 29684414]

9. Loth KA, Huang Z, Wolfson J, Neumark-Sztainer D, Fisher J, Fulkerson JA, et al. Leveraging ecological momentary assessment to understand variability in food parenting practices within a low-income racially/ethnically diverse sample of parents of preschoolers. Appetite 2023;188:106635. [doi: 10.1016/j.appet.2023.106635] [Medline: 37321277]
10. Almaatani D, Zurbau A, Khoshnevisan F, Bandsma RHJ, Khan TA, Sievenpiper JL, et al. The association between parents' stress and parental feeding practices and feeding styles: systematic review and meta-analysis of observational studies. Matern Child Nutr 2023;19(1):e13448 [FREE Full text] [doi: 10.1111/mcn.13448] [Medline: 36284502]
11. Berge JM, Tate A, Trofholz A, Fertig AR, Miner M, Crow S, et al. Momentary parental stress and food-related parenting practices. Pediatrics 2017;140(6):e20172295 [FREE Full text] [doi: 10.1542/peds.2017-2295] [Medline: 29167378]
12. Berge JM, Fertig AR, Trofholz A, Neumark-Sztainer D, Rogers E, Loth K. Associations between parental stress, parent feeding practices, and child eating behaviors within the context of food insecurity. Prev Med Rep 2020;19:101146 [FREE Full text] [doi: 10.1016/j.pmedr.2020.101146] [Medline: 32642403]
13. Berge JM, Fertig AR, Trofholz A, de Brito JN. Real-time predictors of food parenting practices and child eating behaviors in racially/ethnically diverse families. Int J Behav Nutr Phys Act 2023;20(1):86 [FREE Full text] [doi: 10.1186/s12966-023-01476-4] [Medline: 37434195]
14. Snuggs S, Houston-Price C, Harvey K. Development of a parental feeding goal measure: The Family Mealtime Goals Questionnaire. Front Psychol 2019;10:455 [FREE Full text] [doi: 10.3389/fpsyg.2019.00455] [Medline: 30914992]
15. APPETItE - Ecological Momentary Analysis Public registration Updates. OSF Registries. URL: https://osf.io/n48yv [accessed 2024-02-16]
16. Monthly populations by Index of Multiple Deprivation (IMD) decile, England: January 2019 to August 2022. Office for National Statistics. URL: https://tinyurl.com/4rrw62sa [accessed 2022-11-29]
17. Blumberg SJ, Bialostosky K, Hamilton WL, Briefel RR. The effectiveness of a short form of the household food security scale. Am J Public Health 1999;89(8):1231-1234. [doi: 10.2105/ajph.89.8.1231] [Medline: 10432912]
18. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67(6):361-370. [doi: 10.1111/j.1600-0447.1983.tb09716.x] [Medline: 6880820]
19. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the hospital anxiety and depression scale. An updated literature review. J Psychosom Res 2002;52(2):69-77. [doi: 10.1016/s0022-3999(01)00296-3] [Medline: 11832252]
20. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav 1983;24(4):385-396. [doi: 10.2307/2136404]
21. Lee EH. Review of the psychometric evidence of the perceived stress scale. Asian Nurs Res (Korean Soc Nurs Sci) 2012;6(4):121-127 [FREE Full text] [doi: 10.1016/j.anr.2012.08.004] [Medline: 25031113]
22. Topp CW, Østergaard SD, Søndergaard S, Bech P. The WHO-5 well-being index: a systematic review of the literature. Psychother Psychosom 2015;84(3):167-176 [FREE Full text] [doi: 10.1159/000376585] [Medline: 25831962]
23. Trofholz A, Tate A, Janowiec M, Fertig A, Loth K, de Brito JN, et al. Ecological momentary assessment of weight-related behaviors in the home environment of children from low-income and racially and ethnically diverse households: development and usability study. JMIR Res Protoc 2021;10(12):e30525 [FREE Full text] [doi: 10.2196/30525] [Medline: 34855612]
24. Degroote L, DeSmet A, De Bourdeaudhuij I, Van Dyck D, Crombez G. Content validity and methodological considerations in ecological momentary assessment studies on physical activity and sedentary behaviour: a systematic review. Int J Behav Nutr Phys Act 2020;17(1):35 [FREE Full text] [doi: 10.1186/s12966-020-00932-9] [Medline: 32151251]
25. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. J Pers Soc Psychol 1988;54(6):1063-1070. [doi: 10.1037//0022-3514.54.6.1063] [Medline: 3397865]
26. Kirtley O, Hiekkaranta AP, Kunkels YK, Eisele G, Schoefs S, Kemme N, et al. The Experience Sampling Method (ESM) item repository. OSFHOME. URL: https://osf.io/kg376/ [accessed 2023-11-29]
27. Vaessen T, van Nierop M, Reininghaus U, Myin-Germeys I. Stress assessment using experience sampling: convergent validity and clinical relevance. Stress self-assessment questionnaires: choice, appl, limits 2015:21-35 [FREE Full text] [doi: 10.1007/978-3-031-27349-0_7]
28. Verhagen SJW, Hasmi L, Drukker M, van Os J, Delespaul PAEG. Use of the experience sampling method in the context of clinical trials. Evid Based Ment Health 2016;19(3):86-89 [FREE Full text] [doi: 10.1136/ebmental-2016-102418] [Medline: 27443678]
29. Loth KA, Ji Z, Wolfson J, Berge JM, Neumark-Sztainer D, Fisher JO. COVID-19 pandemic shifts in food-related parenting practices within an ethnically/racially and socioeconomically diverse sample of families of preschool-aged children. Appetite 2022;168:105714 [FREE Full text] [doi: 10.1016/j.appet.2021.105714] [Medline: 34619241]
30. Mason TB, Smith KE, Crosby RD, Dvorak R, Engel SG, Crow S, et al. Self-discrepancy as a predictor of eating disorder symptoms: findings from two ecological momentary assessment studies of adults with binge eating. Cogn Ther Res 2022;46(3):580-589. [doi: 10.1007/s10608-021-10279-5]
31. Bartels SL, van Knippenberg RJM, Malinowsky C, Verhey FRJ, de Vugt ME. Smartphone-based experience sampling in people with mild cognitive impairment: feasibility and usability study. JMIR Aging 2020;3(2):e19852 [FREE Full text] [doi: 10.2196/19852] [Medline: 33064084]
32. Rylatt L, Cartwright T. Parental feeding behaviour and motivations regarding pre-school age children: a thematic synthesis of qualitative studies. Appetite 2016;99:285-297. [doi: 10.1016/j.appet.2015.12.017] [Medline: 26719102]

Abbreviations

APPETItE: Appetite in Preschoolers: Producing Evidence for Tailoring Interventions Effectively
EMA: ecological momentary assessment

Edited by A Mavragani; submitted 05.12.23; peer-reviewed by H Zeidler, ME Laforest; comments to author 06.02.24; revised version received 12.02.24; accepted 13.02.24; published 19.03.24.

Please cite as:
Edwards K, Croker H, Farrow C, Haycraft E, Herle M, Llewellyn C, Pickard A, Blissett J
Examining Parent Mood, Feeding Context, and Feeding Goals as Predictors of Feeding Practices Used by Parents of Preschool Children With Avid Eating Behavior: Protocol for an Ecological Momentary Assessment Study
JMIR Res Protoc 2024;13:e55193
URL: https://www.researchprotocols.org/2024/1/e55193
doi:10.2196/55193
PMID:38502178

Protocol

Evaluation of the Gonadotoxicity of Cancer Therapies to Improve Counseling of Patients About Fertility and Fertility Preservation Measures: Protocol for a Retrospective Systematic Data Analysis and a Prospective Cohort Study

Michael von Wolff[1], MD; Ariane Germeyer[2], MD; Bettina Böttcher[3], MD; Isotta Martha Magaton[1], MD; Irene Marcu[1], PhD; Janna Pape[1], MD; Nicole Sänger[4], MD; Verena Nordhoff[5], PhD; Marie Roumet[6], PhD; Susanna Weidlinger[1], MD

[1]Division of Gynaecological Endocrinology and Reproductive Medicine, University Women's Hospital, Bern, Switzerland

[2]Department of Gynaecological Endocrinology and Fertility Disorders, University Women's Hospital, Heidelberg, Germany

[3]Department of Gynaecological Endocrinology and Reproductive Medicine, Medical University of Innsbruck, Innsbruck, Austria

[4]Department of Gynaecological Endocrinology and Reproductive Medicine, University Women's Hospital, Bonn, Germany

[5]Centre of Reproductive Medicine and Andrology, Department of Clinical and Surgical Andrology, University of Münster, Münster, Germany

[6]Clinical Trial Unit, University of Bern, Bern, Switzerland

Corresponding Author:
Michael von Wolff, MD
Division of Gynaecological Endocrinology and Reproductive Medicine
University Women's Hospital
Friedbuehlstrasse 19
Bern, 3010
Switzerland
Phone: 41 317321303
Email: Michael.vonWolff@insel.ch

Abstract

Background: Cytotoxic treatments such as chemo- and radiotherapy and immune therapies are required in cancer diseases. These therapies have the potential to cure patients but may also have an impact on gonadal function and, therefore, on fertility. Consequently, fertility preservation treatments such as freezing of gametes and gonadal tissue might be required. However, as detailed data about the necessity to perform fertility preservation treatment are very limited, this study was designed to fill this data gap.

Objective: Primary objective of this study is to analyze the impact of cancer therapies and chemotherapies on the ovarian reserve and sperm quality. Secondary objectives are to analyze the (1) impact of cancer therapies and chemotherapies on other fertility parameters and (2) probability of undergoing fertility preservation treatments in relation to specific cancer diseases and treatment protocols and the probability to use the frozen gametes and gonadal tissue to achieve pregnancies.

Methods: First, previously published studies on the gonadotoxicity of chemo- and radiotherapies among patients with cancer will be systematically analyzed. Second, a prospective cohort study set up by approximately 70 centers in Germany, Switzerland, and Austria will collect the following data: ovarian function by analyzing anti-Müllerian hormone (AMH) concentrations and testicular function by analyzing sperm parameters and total testosterone immediately before and around 1 year after gonadotoxic therapies (short-term fertility). A follow-up of these fertility parameters, including history of conceptions, will be performed 5 and 10 years after gonadotoxic therapies (long-term fertility). Additionally, the proportion of patients undergoing fertility-preserving procedures, their satisfaction with these procedures, and the amount of gametes and gonadal tissue and the children achieved by using the frozen material will be analyzed. Third, the data will be merged to create the internet-based data platform FertiTOX. The platform will be structured in accordance with the *ICD* (*International Classification of Diseases*) classification of cancer diseases and will be easily be accessible using a specific App.

Results: Several funding bodies have funded this study. Ten systematic reviews are in progress and the first one has been accepted for publication. All Swiss and many German and Austrian ethics committees have provided their approval for the

prospective cohort study. The study registry has been set up, and a study website has been created. In total, 50 infertility centers have already been prepared for data collection, which started on December 1, 2023.

Conclusions: The study can be expected to bridge the data gap regarding the gonadotoxicity of cancer therapies to better counsel patients about their infertility risk and their need to undergo fertility preservation procedures. Initial data are expected to be uploaded on the FertiTOX platform in 2026.

Trial Registration: ClinicalTrials.gov NCT05885048; https://clinicaltrials.gov/study/NCT05885048

International Registered Report Identifier (IRRID): DERR1-10.2196/51145

(JMIR Res Protoc 2024;13:e51145) doi:10.2196/51145

KEYWORDS

fertility; fertility preservation; cancer; gonadotoxicity; FertiPROTEKT; FertiTOX; data analysis; cohort study; internet; platform; internet-based; data

Introduction

Background

After reaching milestones in fertility preservation such as freezing of sperm and testicular tissue—and more recently, the first birth after transplantation of cryopreserved ovarian tissue [1], the introduction of luteal-phase random-start gonadotropin stimulation [2], and vitrification of oocytes [3]—fertility preservation treatments have been introduced in most countries, and fertility preservation has been accepted and defined as an important element to be considered before cancer treatments (Figure 1).

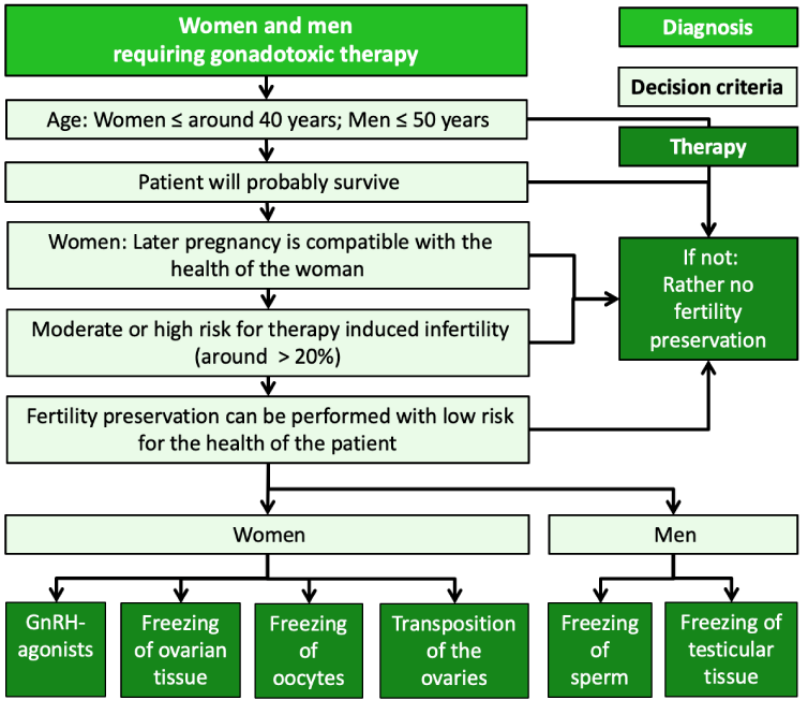
Medically, this has been evidenced by several national and international guidelines stating that fertility preservation counseling is required before administering gonadotoxic therapies [4-11], and this has been politically been shown as many countries have introduced reimbursement or coverage of fertility preservation treatments.

However, data about the gonadotoxicity of the numerous cancer treatment regimens are mostly very limited. Additionally, a recent study in mice has revealed that immune therapies such as checkpoint inhibitors have substantial impact on the ovarian reserve [12], but human data are not yet available.

Accordingly, indications for or against fertility-preserving therapies are not well defined with either the risk of overtreating patients or imposing unnecessary medical risks and burdens to the patients and, therefore, unnecessarily postponing the gonadotoxic therapies. However, the risk of undertreating patients with respective therapies imposes the risk of infertility, which can have a substantial impact on their quality of life after the onset of cancer [13].

Meanwhile, effective methods are available to reliably quantify the gonadotoxicity of cancer therapies. In women, ovarian function can be evaluated by analyzing anti-Müllerian hormone (AMH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol (E2) concentrations, and in men, testicular function is evaluated by analyzing sperm counts and total testosterone, FSH, and LH concentrations.

Figure 1. Algorithm for indicating fertility preserving therapies in women and men.



Even though these functional parameters exist, prospective and systematic short- and long-term data regarding the impact of specific cancer therapies on fertility based on these parameters are limited. It can be assumed that this is due to a lack of effective fertility preservation network structures in most countries. However, in Switzerland, Germany, and Austria, network structures that permit a systematic and continuous large-scale data analysis have been established.

Data should be made available as an easily accessible internet-based platform that is merged with already published data on the gonadotoxicity of cancer therapies and other relevant data such as the 5-year survival rates of the cancer diseases. The data platform will support physicians and other experts as well as patients in counseling about fertility risks imposed by cancer treatments and the necessity to undergo fertility-preserving measures.

We, therefore, designed a study to collect data on the gonadotoxicity of cancer therapies by systematically analyzing already published data and by setting up an international multicenter prospective cohort study to collect data on the gonadotoxicity of chemotherapies, radiotherapies, and immune therapies among men and women and to upload summarized data on an internet-based data platform.

Objectives

The primary objective is to determine whether cancer therapies and specific chemotherapy protocols reduce AMH concentrations in women and sperm quality in men.

Secondary objectives are to analyze the impact of cancer therapies and chemotherapies on other fertility parameters such as the probability of undergoing fertility-preserving treatments in relation to the type of cancer disease and specific treatment protocols, the number of children, the future wish to have children, and age. Further objectives are to assess satisfaction with the decision to have undergone fertility-preserving procedures, the proportion of women and men who use their frozen gametes to achieve a pregnancy, the effect of different gonadotoxic therapies on long-term fertility, and the quality of life after the administration of cancer therapies.

Methods

Study Design

The study consists of 2 parts: first, a series of systematic reviews; second, an international multicenter prospective exploratory observational cohort study of fertility-related parameters with a long-term follow-up of the fertility of patients with cancer in university and nonuniversity public hospitals and private infertility centers in Germany, Switzerland, and Austria. All data will be uploaded on an internet-based data platform.

First Part: Retrospective Systematic Data Analysis

A series of systematic reviews will be performed in Switzerland, one of which will be performed in Germany. The reviews encompass diseases for which a sufficient number of studies has been published to perform a systematic review and which are relevant regarding fertility and fertility-preserving issues. The following reviews were initiated in 2023 and 2024 or are expected to be published in 2024 and 2025. They are registered in PROSPERO:

- A systematic review of the gonadotoxicity of Osteoscarcoma and Ewing´s sarcoma chemotherapies in postpubertal females and males: CRD42023331654, accepted for publication (*Journal of Adolescent and Young Adult Oncology*).
- Effects of chemotherapy and radiation in male genital organ tumors on ovarian and testicular function and fertility: CRD42023384057, submitted for publication in 2024.
- Effects of chemotherapy and radiation in mesothelial and soft tissue cancer on ovarian and testicular function and fertility: CRD42023385402, to be submitted for publication in 2024.
- Effects of chemotherapy, radiation and immunotherapy in breast cancer on ovarian and testicular function and fertility: CRD42023384042, to be submitted for publication in 2024.
- Effects of bone marrow transplantation in hematological cancers on ovarian and testicular function and fertility: CRD42023486928, to be submitted for publication in 2024.
- Effects of chemotherapy and radiation in eye, brain and central nervous system cancer on ovarian and testicular function and fertility: CRD42023385408, to be submitted for publication in 2024.
- Effects of chemotherapy and radiation in Hodgkin lymphoma on ovarian and testicular function and fertility: CRD42023384052, to be submitted for publication in 2025.
- Effects of chemotherapy and radiation in Non-Hodgkin lymphoma on ovarian and testicular function and fertility: CRD42024511940, to be submitted for publication in 2025.
- Effects of chemotherapy and radiation in colorectal cancer on ovarian and testicular function and fertility: CRD42024511944, to be submitted for publication in 2025.
- Effects of chemotherapy and radiation in leukemia on ovarian and testicular function and fertility: CRD42024511946, to be submitted for publication in 2025.

Second Part: Prospective Cohort Study

The cohort study will collect data on the ovarian reserve and sperm from patients undergoing gonadotoxic therapies. Data collection was initiated on December 1, 2023, and will be continued at least for 5 years to analyze short-term fertility. Long-term fertility data will be collected until at least 2036. An initial version of the FertiTOX internet-based platform is expected to be set up in 2026. The trial is registered in ClinicalTrials.gov (NCT05885048).

Inclusion Criteria

Each center that counsels patients with cancer about fertility issues and can also provide fertility-associated parameters may participate. A prerequisite requirement is that each center has received ethical approval for the study. Even though the study is intended to mainly include FertiPROTEKT network centers [14] and FERTISAVE [15] networks in Germany, Switzerland, and Austria, any other center worldwide can participate if the inclusion criteria are fulfilled.

Women and men aged 14-50 years (18-50 years in Germany due to national regulations) undergoing cancer therapies using

chemotherapy, radiotherapy, or immune therapy (Figure 1) will be included.

Recruitment and Informed Consent Procedure

Patients are recruited by reproductive physicians who are associated with the participating infertility centers. Approximately 70 centers (44 in Germany, 21 in Switzerland, and 6 in Austria) will participate in the study and will collect data (see Multimedia Appendix 1).

Patients who need gonadotoxic therapies will be counseled before the onset of the respective therapies. During counseling, patients are screened for their eligibility to be included in the study.

Furthermore, patients will be provided counseling forms to provide informed consent before the onset of gonadotoxic therapy to collect specific basic data and data on gonadal function from patients with cancer. Data will also be collected 12-15 months and 5 and 10 years after the end of gonadotoxic therapy.

The study participants will be informed that they will be contacted by the fertility center or a defined coworker of the study by telephone, email, or post to collect the respective data after the administration of gonadotoxic therapy.

Study Registry

Data will be collected using the REDCap (Research Electronic Data Capture) software, a secure web application for building databases [16]. The REDCap registry has been set up and optimized by the study consortium with the support of the Clinical Trials Unit in Bern, REDCap technicians, and statisticians. The contents of the study registry (consultation before and 12-15 months after the end of the gonadotoxic therapy) are shown in the paper version of the registry (Multimedia Appendices 2-5). The participating centers will add the data to the registry without adding any definite identifiers such as name and date of birth. The participating centers can only see their patients. Patients can be traced with an individual code that is safeguarded by the centers. Only very few authorized persons will be provided access to all data in order to assess the data quality and to remind the centers to invite the patients for follow-up consultations.

End Points

The primary end points are the AMH concentration in women and sperm count before and after gonadotoxic treatments. End points will be assessed before and 12-15 months after the end of the gonadotoxic treatments (patients with melanoma receiving adjuvant checkpoint inhibitor treatment will be evaluated every 3 months).

Secondary end points are FSH, LH, and E2 concentrations in women and total testosterone, FSH, and LH concentrations, total sperm count, and sperm motility in men. Further secondary outcome parameters are the number of patients who freeze gametes and gonadal tissue and satisfaction with the decision to have undergone fertility-preserving measures.

Long-term end points to be determined 5 and 10 years after the end of the gonadotoxic therapy are the abovementioned hormone and sperm parameters as well as the number of patients who become pregnant after gonadotoxic therapies spontaneously or after the use of frozen gametes and gonadal tissue.

Sample Size Calculation

A power calculation was performed to determine whether the expected number of patients is sufficient to detect an effect of cancer treatment on fertility with a reasonable power.

The calculation was performed for the primary outcome (ie, sperm count for men and AMH concentration for women) for men and women separately. Calculations were performed within each cancer entity and for each specific treatment protocol separately with a paired *t* test using Stata (release 17.0; StataCorp).

We set the effect size so that a relative risk of 50% was not missed. For the sperm count, where the mean value in healthy men is 64 million (SD 47 million) [17], this would correspond to an effect size of 0.67. For AMH concentration in women, where means and SDs can be assumed to be equal [18], it would correspond to an effect size of 0.5. The intraindividual correlation was set to 0.5 [17,18]. To account for multiple testing (analysis will be performed with 43 treatment groups for men and women separately), the Šidák correction was used, and the significance level was adjusted to 0.0006 (2-sided).

Table 1 shows that a sufficient power of >80% will be reached for most treatments. If the number of cases was twice as high and the intrapatient correlation coefficient was 0.7, a power of >80% would be reached for all treatment levels. As the study is expected to be extended, a sufficient number of patients can be expected in order to reach this goal.

Table 1. Expected number of cases and resulting power reached per specific treatment (treatment protocols) in the most common *ICD (International Classification of Diseases)* cancer groups [19].

ICD cancer group	Cases, n[a]	Specific treatments (treatment protocols), n	Effect size (females/ males)[b]	Power (females/ males)[b], %/%
Breast	2000	6	0.5/—[c]	100/—
Hodgkin lymphoma	1000	2	0.5/0.68	100/100
Bone and articular cartilage	400	3	0.5/0.68	98.6/100
Female genital organs	350	3	0.5/—	96.5/—
Male genital organs	2000	4	—/0.68	—/100
Digestive organs	200	7	0.5/0.68	14.3/41.4
Mesothelial and soft tissue	200	3	0.5/0.68	67.2/96.7
Eye, brain, and central nervous system	300	2	0.5/0.68	99.5/100
Non-Hodgkin lymphoma	300	8	0.5/0.68	26.2/64.4
Leukemia	200	5	0.5/0.68	30.6/70.8

[a]The estimation of the number of cases is based on the number of patients previously counseled and documented in the FertiPROTEKT and FERTISAVE registries.

[b]Power is calculated for each treatment protocol for men and women separately. The number of patients per protocol is calculated as the number of cases divided by the number of treatment protocols. The sex ratio is assumed to be 1:1, except for cancer of the breast and genital organs.

[c]Not available.

Data Analysis

The impact of cancer therapies and chemotherapies on the primary outcomes will be assessed for each *ICD* cancer group [19] and for each specific treatment regimen separately by comparing values measured before and after the gonadotoxic therapy using paired *t* tests. *P* values will be adjusted for multiple testing using the false discovery rate controlling procedure.

Consequences on other fertility parameters measured before and 12-15 months after the end of gonadotoxic therapy (ie, AMH, FSH, LH, and E2 concentrations in women and total testosterone, FSH, and LH concentrations and total sperm count, sperm concentration and motility in men) will be assessed using the same methodology, but without false discovery rate adjustment. Long-term consequences will be investigated later by comparing values measured before and 5 and 10 years after the gonadotoxic therapy. However, due to the long period until the final analysis, statistics might be adapted in relation to future development of cancer and fertility-preserving therapies.

As age was identified to potentially modify the effect of gonadotoxic therapy on female fertility, we will additionally conduct stratified analyses and document the impact of gonadotoxic therapy in the different female age groups.

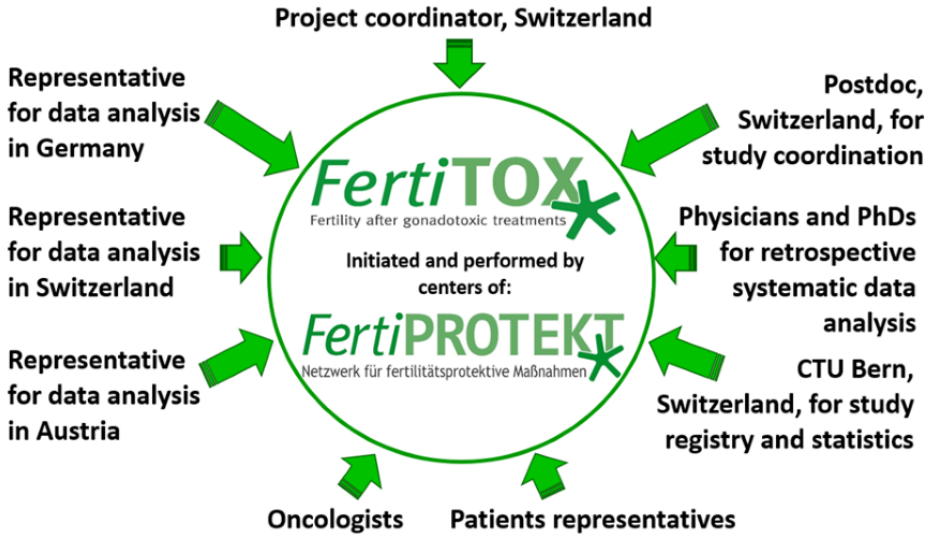
Finally, the effects of different cancers, treatment protocols, age, and the presence of the patients' children before cancer therapy on primary and secondary fertility outcomes will be analyzed using linear mixed effect models.

The frequency of patients undergoing fertility-preserving treatments, namely freezing of ovarian tissue, oocytes and embryos, testicular tissue, and sperm will be calculated for each *ICD* cancer group and for each specific treatment protocol separately and additionally presented with the associated 95% Wilson CI. Potential effects of the patients' characteristics on the abovementioned binary outcomes will be analyzed using logistic regression analysis.

Consortium of Experts Involved in the Study

The study is supervised by several experts in Germany, Switzerland, and Austria (Figure 2). Each country provides the logistics, manpower, and experts to collect and control data collection and analysis. Interpretation of data will be supported by oncologists. Data are added to a REDCap study registry, which is provided by the Clinical Trial Unit in Bern, Switzerland, which is also responsible for statistical analysis. The data platform will be programmed by an IT company, and data presentation will be optimized by the involved experts and by the patients' representatives. The data platform, called "FertiTOX," will be part of the network "FertiPROTEKT."

Figure 2. The consortium of experts who control the project.



The FertiTOX Platform

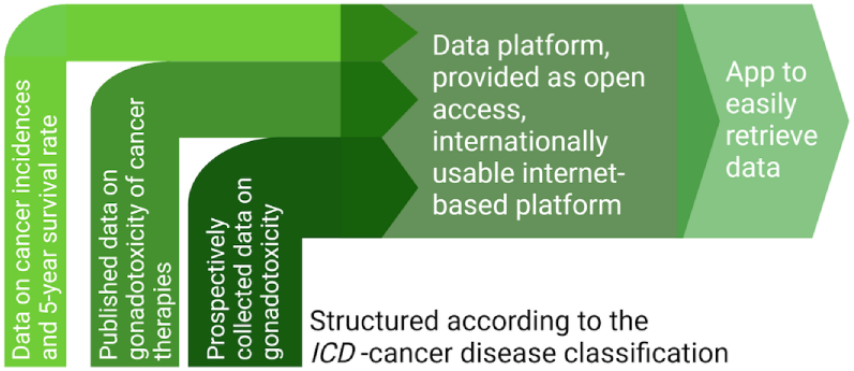
The FertiTOX platform is an internet-based information platform that will be accessible to everybody and will be structured on the basis of the *ICD* cancer disease groups (Figure 3). The brand name FertiTOX has been registered and the domains will be used. A study website [20] has been set up.

Data of women and men will be presented on the FertiTOX platform in 3 hierarchies:

- First hierarchy: presentation of data regarding incidences and 5-year survival according to the *ICD*-classified cancer disease.
- Second hierarchy: presentation of already published data regarding gonadotoxicity and fertility preservation issues regarding specific *ICD*-classified diseases.
- Third hierarchy: presentation of prospective short-term and long-term data on the ovarian reserve and sperm quality before and after gonadotoxic therapies in accordance with *ICD*-classified diseases.

Once the internet-based platform is successfully established, a platform-specific app will be developed to allow easy retrieval of data.

Figure 3. The internet-based platform FertiTOX that will be used to distribute the data. *ICD: International Classification of Diseases.*



Dissemination

Data about the progress of the study will be disseminated through a study website [20]. The findings will be propagated through journal articles, conference presentations, and the FertiTOX platform.

Ethical Considerations

Ethical approval has been granted by the relevant ethics committees. In Switzerland, all 7 cantonal ethical committees have provided consent for all 21 participating centers. In Germany, the ethics committee in Heidelberg and in Austria, the committee in Innsbruck were chosen as the national leading ethical committees. Based on the ethical votes approved by these 2 committees, all other participating centers in Germany and Austria submitted an ethics application to their ethical committee.

Written consent was obtained from the participants. The participants have been informed about the processing of data and their rights. The participants also provided written consent for anonymized data to be transferred to other registries for further analysis if the other registries have the same high security standards as the REDCap registry. The data are collected in a REDCap study registry that complies with several data security and confidentiality conditions. Specific identifiers are not added to the registry; only the year of birth is added. The data are stored in Bern, Switzerland.

The participating centers can only access the patient's data that they have added to the registry. The patients can be identified with an individual code generated by the REDCap system, which is locked in a safe place by the investigator of the participating center. Traceability of the data is ensured by these identification codes. Patients provide permission to be followed up. Patients are only contacted by the center or by authorized personnel employed by the principal investigator or the national representatives of the study. Statistical analysis will be based on anonymized data.

No compensation will be offered to the patients (potential users of the internet-based platform) for participating in the study.

Results

As of February 18, 2024, the following has been accomplished.

The first systematic review analyzing the impact of cancer therapies on bone tumors has been accepted for publication (in the *Journal of Adolescent and Young Adult Oncology*). Nine more systematic reviews have been initiated, encompassing the impact of cancer therapies on fertility in testicular cancer; soft tissue cancer; breast cancer; eye, brain, or central nervous system cancer; Hodgkin lymphoma; non-Hodgkin lymphoma; rectal or sigmoid cancer; leukemia; and on bone marrow transplantation.

The prospective cohort study has been prepared. All Swiss ethics committees and the leading ethics committees in Germany and in Austria have provided their approval. In total, 70 infertility centers (Multimedia Appendix 1) have started to be prepared for data collection. The study registry has been set up and activated, and a study website [20] has been created.

Funding for the study has been obtained from several funding bodies, which were not involved in the study's conceptualization, analysis, and data dissemination.

Recruitment of the patients started on December 1, 2023, and initial data are expected to be uploaded on the FertiTOX platform in 2026.

Discussion

Anticipated Findings

The first systematic reviews we have already carried out have revealed that data on the impact of gonadotoxic therapies on fertility are quite comprehensive in some diseases such as breast and testicular cancers and Hodgkin lymphoma. For these diseases, a meta-analysis will also be carried out to analyze the overall effect of oncological therapies on fertility. Furthermore, for these diseases, the gonadotoxic effect of specific chemotherapy protocols on fertility will also be assessed. For the other diseases, data are very poor, and outcome parameters will probably need to be limited to a rather vague outcome parameter defined as "suspected infertility." Long-term fertility data based on the ovarian reserve and sperm parameters and on spontaneous conceptions and conceptions using cryopreserved gametes or gonadal tissues are very poor or nonexistent in all kinds of cancers.

This finding supports the necessity to perform the large prospective cohort studies, as described in this paper. This cohort study has already successfully been set up and data collection was initiated on December 1, 2023.

Robust data on the gonadotoxicity of different treatment regimens, mainly in cancer therapies, is the last major deficit in fertility preservation. All other requirements have been established in many countries, such as fertility preservation procedures and specialized centers to counsel patients and to perform these procedures. Furthermore, many oncologists have been sensitized to address the fertility risk of cancer therapies and the possibility to perform fertility preservation procedures.

However, comprehensive data about the specific gonadotoxicity of different treatment regimens required to counsel patients and to decide if fertility preservation measures should be recommended or not are still missing.

Previous studies have addressed fertility issues in patients with cancer and the impact of cancer therapies on fertility, but these studies are mostly based on spontaneous pregnancies following cancer therapies or are based on data such as the onset of puberty, cycle regularity, and low sperm counts. Studies based on pre- and postchemotherapy levels of AMH and sperm counts are very limited and are mainly limited to female patients with breast cancer [21-24].

To bridge this data gap, we designed a study to analyze published data and data that will be collected in at least 3 countries by centers belonging to the FertiPROTEKT network. The data will be analyzed und disseminated via the FertiFOX web-based platform to provide patients, researchers, and clinicians access to the analysis, which will be graphically illustrated. By including patients' representatives in the data analysis, we will ensure that the data are presented in a manner that is also understandable to patients. The data will not only be presented as a single curve presenting the means and showing odds ratios and CIs, which presents the average impact of therapies on gonadal function, but also show individual variations by presenting a set of curves.

The study has been designed to follow up on patients for at least 10 years. Such a long follow-up will enable us to evaluate how many patients have undergone fertility-preserving procedures but unfortunately did not survive. Furthermore, we will be able to estimate how many patients conceived spontaneously or by using the frozen gametes and gonadal tissue. Such an analysis is essential to evaluate the long-term efficacy of fertility preservation counseling and treatment. We are aware that some patients might be lost to follow-up. However, as the number of included patients is expected to be very high, it can be assumed that the amount of data will still be sufficiently high.

Limitations

A limitation of this study is that data are mainly collected in Germany, Switzerland, and Austria. Accordingly, data will not be available for other treatment regimens performed elsewhere. However, as other countries are also invited to participate in this study, this limitation could possibly be reduced. Another limitation is that children will not be evaluated primarily because the study is based on AMH values and sperm parameters, which

can hardly be interpreted in (AMH concentration) or cannot be collected from (sperm parameters) children.

The last limiting factor is that new therapies are evolving very fast and that new combination therapies combining conventional chemotherapy agents and immune therapies will be developed, which will increase the complexity of our data analysis. However, it is expected that this limitation can at least in part be compensated by the prospective design of the study, which will include a higher number of new therapies. Furthermore, the impact of checkpoint inhibitors, which have been shown to be gonadotoxic in female mice, will be analyzed separately in women with melanoma undergoing adjuvant therapy with checkpoint inhibitors. These results can be used to better estimate the gonadotoxicity of combination therapies involving checkpoint inhibitors.

Conclusions

In conclusion, the study can be expected to bridge the data gap regarding the gonadotoxicity of several therapies and gonadotoxic treatment regimens to better counsel patients regarding their infertility risk and their need to undergo fertility-preserving procedures.

Acknowledgments

We would like to thank all the participating centers for their support in preparing this study and collecting the data. This study is funded by several funding bodies such as the Swiss Cancer League (grant KLS-5650-08-2022: CHF 349.000,-) and pharmaceutical companies such as IBSA Institut Biochimique SA, Theramex Switzerland GmbH, and Ferring AG, Switzerland. These pharmaceutical companies are not involved in any issues regarding the study's conceptualization, the analysis, and the dissemination of data. A grant application has been submitted to the German Cancer Aid "Deutsche Krebshilfe."

Data Availability

Participants have provided written consent that the data can also be analyzed by others if sufficient data safety can be confirmed. Accordingly, data can be considered by the study consortium to be transferred to others if sufficient data safety has been proven.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Centers participating the prospective cohort study (in alphabetical order).
[DOCX File , 23 KB - resprot_v13i1e51145_app1.docx]

Multimedia Appendix 2
REDCap registry: Documentation in females before gonadotoxic therapy.
[PDF File (Adobe PDF File), 1440 KB - resprot_v13i1e51145_app2.pdf]

Multimedia Appendix 3
REDCap registry: Documentation in males before gonadotoxic therapy.
[PDF File (Adobe PDF File), 1362 KB - resprot_v13i1e51145_app3.pdf]

Multimedia Appendix 4
REDCap registry: Documentation in females 12-15 months after the end of gonadotoxic therapy.
[PDF File (Adobe PDF File), 1499 KB - resprot_v13i1e51145_app4.pdf]

Multimedia Appendix 5
REDCap registry: Documentation in males 12-15 months after the end of gonadotoxic therapy.
[PDF File (Adobe PDF File), 1485 KB - resprot_v13i1e51145_app5.pdf]

References

1. Donnez J, Dolmans MM, Demylle D, Jadoul P, Pirard C, Squifflet J, et al. Livebirth after orthotopic transplantation of cryopreserved ovarian tissue. Lancet 2004;364(9443):1405-1410. [doi: 10.1016/S0140-6736(04)17222-X] [Medline: 15488215]
2. Cobo A, Meseguer M, Remohí J, Pellicer A. Use of cryo-banked oocytes in an ovum donation programme: a prospective, randomized, controlled, clinical trial. Hum Reprod 2010 Sep;25(9):2239-2246. [doi: 10.1093/humrep/deq146] [Medline: 20591872]

3. von Wolff M, Thaler CJ, Frambach T, Zeeb C, Lawrenz B, Popovici RM, et al. Ovarian stimulation to cryopreserve fertilized oocytes in cancer patients can be started in the luteal phase. Fertil Steril 2009 Oct;92(4):1360-1365 [FREE Full text] [doi: 10.1016/j.fertnstert.2008.08.011] [Medline: 18930226]
4. Oktay K, Harvey BE, Partridge AH, Quinn GP, Reinecke J, Taylor HS, et al. Fertility preservation in patients with cancer: ASCO Clinical Practice Guideline Update. J Clin Oncol 2018 Jul 01;36(19):1994-2001. [doi: 10.1200/JCO.2018.78.1914] [Medline: 29620997]
5. Fertilitätsprotektion bei onkologischen Erkrankungen. 2022. URL: https://www.awmf.org/uploads/tx_szleitlinien/015-082l_S2k_Fertilitaetserhaltung-bei-onkologischen-Therapien_2017-12-verlaengert.pdf [accessed 2023-04-23]
6. Practice Committee of the American Society for Reproductive Medicine. Electronic address: asrm@asrm.org. Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion. Fertil Steril 2019 Dec;112(6):1022-1033 [FREE Full text] [doi: 10.1016/j.fertnstert.2019.09.013] [Medline: 31843073]
7. ESHRE Guideline Group on Female Fertility Preservation, Anderson R, Amant F, Braat D, D'Angelo A, Chuva de Sousa Lopes SM, et al. ESHRE guideline: female fertility preservation. Hum Reprod Open 2020;2020(4):hoaa052 [FREE Full text] [doi: 10.1093/hropen/hoaa052] [Medline: 33225079]
8. Suzuki N. Clinical practice guidelines for fertility preservation in pediatric, adolescent, and young adults with cancer. Int J Clin Oncol 2019 Jan 26;24(1):20-27. [doi: 10.1007/s10147-018-1269-4] [Medline: 29582194]
9. Harada M, Kimura F, Takai Y, Nakajima T, Ushijima K, Kobayashi H, et al. Japan Society of Clinical Oncology Clinical Practice Guidelines 2017 for fertility preservation in childhood, adolescent, and young adult cancer patients: part 1. Int J Clin Oncol 2022 Feb;27(2):265-280 [FREE Full text] [doi: 10.1007/s10147-021-02081-w] [Medline: 34973107]
10. Mulder RL, Font-Gonzalez A, Green DM, Loeffen EAH, Hudson MM, Loonen J, et al. Fertility preservation for male patients with childhood, adolescent, and young adult cancer: recommendations from the PanCareLIFE Consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group. Lancet Oncol 2021 Feb;22(2):e57-e67. [doi: 10.1016/s1470-2045(20)30582-9]
11. Mulder RL, Font-Gonzalez A, Hudson MM, van Santen HM, Loeffen EAH, Burns KC, et al. Fertility preservation for female patients with childhood, adolescent, and young adult cancer: recommendations from the PanCareLIFE Consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group. Lancet Oncol 2021 Feb;22(2):e45-e56. [doi: 10.1016/s1470-2045(20)30594-5]
12. Winship AL, Alesi LR, Sant S, Stringer JM, Cantavenera A, Hegarty T, et al. Checkpoint inhibitor immunotherapy diminishes oocyte number and quality in mice. Nat Cancer 2022 Aug 25;3(8):1-13. [doi: 10.1038/s43018-022-00413-x] [Medline: 36008687]
13. Ussher JM, Perz J. Infertility-related distress following cancer for women and men: a mixed method study. Psychooncology 2019 Mar;28(3):607-614. [doi: 10.1002/pon.4990] [Medline: 30659694]
14. FertiPROTEKT. URL: https://fertiprotekt.com/ [accessed 2024-02-06]
15. SGRM. URL: https://www.sgrm.org/de/kommissionen/fertisave-main-de [accessed 2024-02-06]
16. REDCap. URL: https://www.project-redcap.org/ [accessed 2024-02-06]
17. Cooper TG, Noonan E, von Eckardstein S, Auger J, Baker HWG, Behre HM, et al. World Health Organization reference values for human semen characteristics. Hum Reprod Update 2010;16(3):231-245. [doi: 10.1093/humupd/dmp048] [Medline: 19934213]
18. Segawa T, Omi K, Watanabe Y, Sone Y, Handa M, Kuroda M, et al. Age-specific values of Access anti-Müllerian hormone immunoassay carried out on Japanese patients with infertility: a retrospective large-scale study. BMC Womens Health 2019 Apr 25;19(1):57 [FREE Full text] [doi: 10.1186/s12905-019-0752-z] [Medline: 31023297]
19. Zentrum für Krebsregisterdaten. URL: https://www.krebsdaten.de/Krebs/DE/Home/homepage_node.html [accessed 2024-02-07]
20. FertiTOX. URL: http://www.fertitox.com [accessed 2024-02-06]
21. Dezellus A, Barriere P, Campone M, Lemanski C, Vanlemmens L, Mignot L, et al. Prospective evaluation of serum anti-Müllerian hormone dynamics in 250 women of reproductive age treated with chemotherapy for breast cancer. Eur J Cancer 2017 Jul;79:72-80. [doi: 10.1016/j.ejca.2017.03.035] [Medline: 28463758]
22. Perdrix A, Saint-Ghislain M, Degremont M, David M, Khaznadar Z, Loeb A, et al. Influence of adjuvant chemotherapy on anti-Müllerian hormone in women below 35 years treated for early breast cancer. Reprod Biomed Online 2017 Oct;35(4):468-474. [doi: 10.1016/j.rbmo.2017.06.005] [Medline: 28652099]
23. Trapp E, Steidl J, Rack B, Kupka M, Andergassen U, Jückstock J, et al. Anti-Müllerian hormone (AMH) levels in premenopausal breast cancer patients treated with taxane-based adjuvant chemotherapy - A translational research project of the SUCCESS A study. Breast 2017 Oct;35:130-135. [doi: 10.1016/j.breast.2017.07.007] [Medline: 28732324]
24. Zhou B, Kwan B, Desai MJ, Nalawade V, Ruddy KJ, Nathan PC, et al. Long-term antimüllerian hormone patterns differ by cancer treatment exposures in young breast cancer survivors. Fertil Steril 2022 May;117(5):1047-1056 [FREE Full text] [doi: 10.1016/j.fertnstert.2022.01.016] [Medline: 35216831]

Abbreviations

AMH: anti-Müllerian hormone
E2: estradiol
FSH: follicle-stimulating hormone
***ICD*:** *International Classification of Diseases*
LH: luteinizing hormone
REDCap: Research Electronic Data Capture

Edited by A Mavragani; submitted 23.07.23; peer-reviewed by K Gupta, M Gasmi , R Mitchell; comments to author 03.11.23; revised version received 03.12.23; accepted 29.12.23; published 20.03.24.

Please cite as:
von Wolff M, Germeyer A, Böttcher B, Magaton IM, Marcu I, Pape J, Sänger N, Nordhoff V, Roumet M, Weidlinger S
Evaluation of the Gonadotoxicity of Cancer Therapies to Improve Counseling of Patients About Fertility and Fertility Preservation Measures: Protocol for a Retrospective Systematic Data Analysis and a Prospective Cohort Study
JMIR Res Protoc 2024;13:e51145
URL: https://www.researchprotocols.org/2024/1/e51145
doi:10.2196/51145
PMID:38506900

Protocol

Using a Rapid Learning Health System for Stratified Care in Emerging Adult Mental Health Services: Protocol for the Implementation of Patient-Reported Outcome Measures

Gina Dimitropoulos[1,2], MSW, PhD; David Lindenbach[1], PhD; Melissa Potestio[3], PhD; Tom Mogan[3], MSW; Amanda Richardson[3], MCP; Alida Anderson[1], BSc; Madison Heintz[1], MSW; Karen Moskovic[3], BN; Jason Gondziola[3], MBA; Jessica Bradley[3], MN; Haley M LaMonica[4], PhD; Frank Iorfino[4], PhD; Ian Hickie[4], PhD; Scott B Patten[1,5], MD, PhD; Paul D Arnold[1], MD, PhD

[1]Mathison Centre for Mental Health & Education, University of Calgary, Calgary, AB, Canada

[2]Faculty of Social Work, University of Calgary, Calgary, AB, Canada

[3]Alberta Health Services, Edmonton, AB, Canada

[4]Brain and Mind Centre, The University of Sydney, Sydney, Australia

[5]Department of Community Health Sciences, University of Calgary, Calgary, AB, Canada

Corresponding Author:
Gina Dimitropoulos, MSW, PhD
Mathison Centre for Mental Health & Education
University of Calgary
3280 Hospital Drive NW
Calgary, AB, T2N 4Z6
Canada
Phone: 1 403 210 6464
Email: gdimit@ucalgary.ca

Abstract

Background: Mental illness among emerging adults is often difficult to ameliorate due to fluctuating symptoms and heterogeneity. Recently, innovative approaches have been developed to improve mental health care for emerging adults, including (1) implementing patient-reported outcome measures (PROMs) to assess illness severity and inform stratified care to assign emerging adults to a treatment modality commensurate with their level of impairment and (2) implementing a rapid learning health system in which data are continuously collected and analyzed to generate new insights, which are then translated to clinical practice, including collaboration among clients, health care providers, and researchers to co-design and coevaluate assessment and treatment strategies.

Objective: The aim of the study is to determine the feasibility and acceptability of implementing a rapid learning health system to enable a measurement-based, stratified care treatment strategy for emerging adults.

Methods: This study takes place at a specialty clinic serving emerging adults (age 16-24 years) in Calgary, Canada, and involves extensive collaboration among researchers, providers, and youth. The study design includes six phases: (1) developing a transdiagnostic platform for PROMs, (2) designing an initial stratified care model, (3) combining the implementation of PROMs with stratified care, (4) evaluating outcomes and disseminating results, (5) modification of stratified care based on data derived from PROMs, and (6) spread and scale to new sites. Qualitative and quantitative feedback will be collected from health care providers and youth throughout the implementation process. These data will be analyzed at regular intervals and used to modify the way future services are delivered. The RE-AIM (Reach, Effectiveness, Adoption, Implementation, and Maintenance) framework is used to organize and evaluate implementation according to 3 key objectives: improving treatment selection, reducing average wait time and treatment duration, and increasing the value of services.

Results: This project was funded through a program grant running from 2021 to 2026. Ethics approval for this study was received in February 2023. Presently, we have developed a system of PROMs and organized clinical services into strata of care. We will soon begin using PROMs to assign clients to a stratum of care and using feedback from youth and clinicians to understand how to improve experiences and outcomes.

Conclusions: This study has key implications for researchers and clinicians looking to understand how to customize emerging adult mental health services to improve the quality of care and satisfaction with care. This study has significant implications for mental health care systems as part of a movement toward value-based health care.

International Registered Report Identifier (IRRID): PRR1-10.2196/51667

(JMIR Res Protoc 2024;13:e51667) doi:10.2196/51667

KEYWORDS

learning health system; stratified care; patient-reported outcome measures; mental health; emerging adults; protocol papers; pragmatic clinical trials; e-mental health; RE-AIM; Reach, Effectiveness, Adoption, Implementation, and Maintenance; implementation science; adult; health system; stratified care; treatment; implementation; acceptability; measurement-based care

Introduction

Background

Most mental disorders emerge before the age of 25 years, resulting in a considerable burden of disease across the life span [1,2]. Emerging adulthood (age 16-24 years) represents a unique stage in life [3], characterized by low mental health service use and high treatment attrition rates [4,5]. Emerging adults are also burdened by perceptions of stigma and embarrassment surrounding help-seeking behaviors, which is further worsened by the lack of mental health literacy in this population [6,7].

Transdiagnostic Stratification of Mental Illness

Symptoms of mental illness in emerging adults are often evolving and do not always fit neatly into diagnostic categories created for older adults [8]. Rapid changes in symptoms make it difficult to conduct accurate diagnostic assessments and select appropriate treatments, especially when there are significant delays between first contact with a health care provider and the beginning of treatment [9].

Adopting a transdiagnostic approach to mental illness in young adults may improve assessment and treatment [10-12]. Transdiagnostic assessments focus on identifying the severity of mental illness and symptom domains, which cut across conventional diagnoses rather than diagnosing a discrete disorder [8,11]. Likewise, transdiagnostic treatments use shared principles of evidence-based therapies to help clients manage a range of symptoms [13].

Another emerging method to improve youth mental health treatment is through an approach whereby standardized patient-reported outcome measures (PROMs) of mental health are used to monitor treatment progress. A growing body of literature is showing how adopting PROMs in mental health care settings improves clinical outcomes, improves communication between patients and providers, and reduces treatment attrition, although the evidence supporting integrating PROMs into clinical decision-making is stronger among older adults relative to young people [14-18]. To date, mental health providers have been slow to embrace the routine use of PROMs even though many acknowledge the potential benefits [19].

Pairing the implementation of PROMs with a transdiagnostic approach facilitates the use of "stratified care." Stratified and stepped care represent 2 different models of care with differing approaches to selecting the most appropriate interventions for patients. With "stepped care," all patients begin with lower-intensity treatments and change to higher-intensity treatments if they do not respond [20]. In contrast, stratified care patients with more severe illness (and associated functional impairment) will receive appropriately more intensive treatment from the outset [20,21]. Recent randomized clinical trials of depression and anxiety indicate that the stratified care approach resulted in better clinical outcomes than stepped care or standard care [22,23].

Rapid Learning Health Systems

The implementation of a stratified care model in clinical settings is complicated by the fact that it is difficult for individual clinics to understand how to assign clients to strata and how to select which services should be available in each stratum. One potential way to implement stratified care in a routine clinical setting is through the adoption of a rapid learning health system (RLHS). The RLHS was first proposed by Etheredge [24] and involves the use of health records to determine the best treatment options in a personalized care environment based on the specific needs of each presenting patient. By comparing a patient's health records to individuals in similar medical situations, health practitioners unlock new capabilities to compare treatment effectiveness, adopt best practices, assess results, and provide feedback from their unique case [25]. Furthermore, as evidence is formulated through information supplied by typical health care patients rather than clinical trial participants selected based on highly specific criteria, the RLHS may not face issues of generalizability that are typically associated with randomized clinical trials [24]. As such, this lends credence to the use of the RLHS in biomedical practice, where clients are heterogenous, time and resource constraints are common, and treatment planning needs to evolve dynamically to fit the situation.

An RLHS has been shown to improve the quality, efficiency, and cost-effectiveness of health care delivery across a range of patients, medical conditions, and settings [26]. For example, in cancer care, Abernethy et al [27] showed that an RLHS provided detailed data on the patient's experience and rapid analysis of feedback to support subsequent care and allowed for continuous monitoring of outcomes to support patient safety, quality of care, and rapport with health practitioners. Although the RLHS has primarily been used in physical health care [26], there has been recent interest in using RLHS methods to treat mental disorders. Several commentaries have been published providing advice on implementing an RLHS in mental health, behavioral health, and substance use [28-30]. Likewise, several recent protocol papers describe ongoing work using an RLHS to

improve treatments for epilepsy [31], autism [32], and early intervention for psychosis [33].

An RLHS is an inherently collaborative process that involves coproduction and joint evaluation of new models of care by patients, family members, providers, researchers, and decision makers [29]. Thus, the RLHS may also be beneficial for bridging the gap between research and practice [25]. To facilitate the uptake and use of an RLHS, implementation science methods can be used to guide and document the process [30,31,33].

Using Implementation Science to Promote New Models of Care

One of the most widely used implementation science frameworks is the RE-AIM (Reach, Effectiveness, Adoption, Implementation, and Maintenance) model [34]. RE-AIM evolved from a need to evaluate health care interventions when conducted under complex situations typically found in a health care setting. Outcomes for each dimension provide researchers and policy makers insight as to the use of an intervention for a certain population and setting. *Reach* is defined by the number, or proportion, of willing participants undergoing the intervention. *Effectiveness* examines the impact of the intervention on individual outcomes. *Adoption* refers to the proportion of organizations that agree to take part in the intervention. *Implementation* is the extent to which a program is adapted, modified, or used as intended within an organization. Finally, *Maintenance* considers the sustainability of the intervention at an individual and organizational level.

Several studies have used the RE-AIM framework to describe and enhance the implementation of PROMs in mental health care. For example, Mascayano et al [35] paired RE-AIM with measurement-based care to evaluate the implementation of early intervention for psychosis program and identified key areas for improvement such as lack of access in rural areas, lack of qualified staff, and an unsustainable funding model. Several teams have also used RE-AIM to facilitate the uptake of PROMs in primary care clinics to screen adolescent and adult patients for potential mental health issues [36,37]. Finally, a protocol paper by Ferrari et al [33] described using RE-AIM to evaluate the impacts of an RLHS designed to improve early intervention for psychosis.

This protocol will use the RE-AIM framework to evaluate the implementation of standardized PROMs delivered using a digital platform and an RLHS as a way to allocate clients to stratified care in an effort to improve mental health outcomes in a specialty clinic for young adults (age 16-24 years). True to the goals of an RLHS, this project entails a collaboration among youth, family members, health care providers, and researchers to co-design a patient-centered system of care that collects data in real time to identify how to continuously improve both processes and outcomes.

Methods

Clinical Setting

This study will take place in a clinic that provides specialized mental health services within a large publicly funded provincial health care organization (Alberta Health Services) to emerging adults in Calgary, Alberta, Canada. Emerging adults (age 16-24 years) referred to the clinic are accepted based on whether they require level 3 care (High Intensity Community Based Services) on the Level of Care Utilization System developed by the American Association of Community Psychiatrists [38]. The clinic requires a referral, which may come from a health care provider or self-referral through telephone helplines. The clinic primarily provides psychotherapy (although psychiatric assessment and medication are also available) so clients need to be motivated to engage in treatment and demonstrate sufficient cognitive capacity to benefit from psychotherapy.

Ethical Considerations

This study was approved by the Conjoint Health Research Ethics Board at the University of Calgary (REB21-0616). Potential participants will be recruited through referral by staff within the clinic. Participants will sign a consent form, which includes study information, procedures, length, potential risks and benefits, confidentiality measures, and information about choosing not to participate or withdrawing from the study with no penalty and no impact on the standard of medical care they receive. Participants receive an electronic gift card as an incentive for participating in this study (CAD $40 [approximately US $30] for completing each assessment). Participant data collected in this study are stored on the Research Electronic Data Capture (REDCap; Vanderbilt University) platform and backed up on the University of Calgary's secure data storage servers. Data are also stored within the Innowell (Innowell Pty Ltd) platform, which is legally an Alberta Health Services–held repository of patient data that uses encryption to protect data. Data access is limited to clinicians, individual participants, and the research team.

Key Objectives

The objectives of the study are as follows:

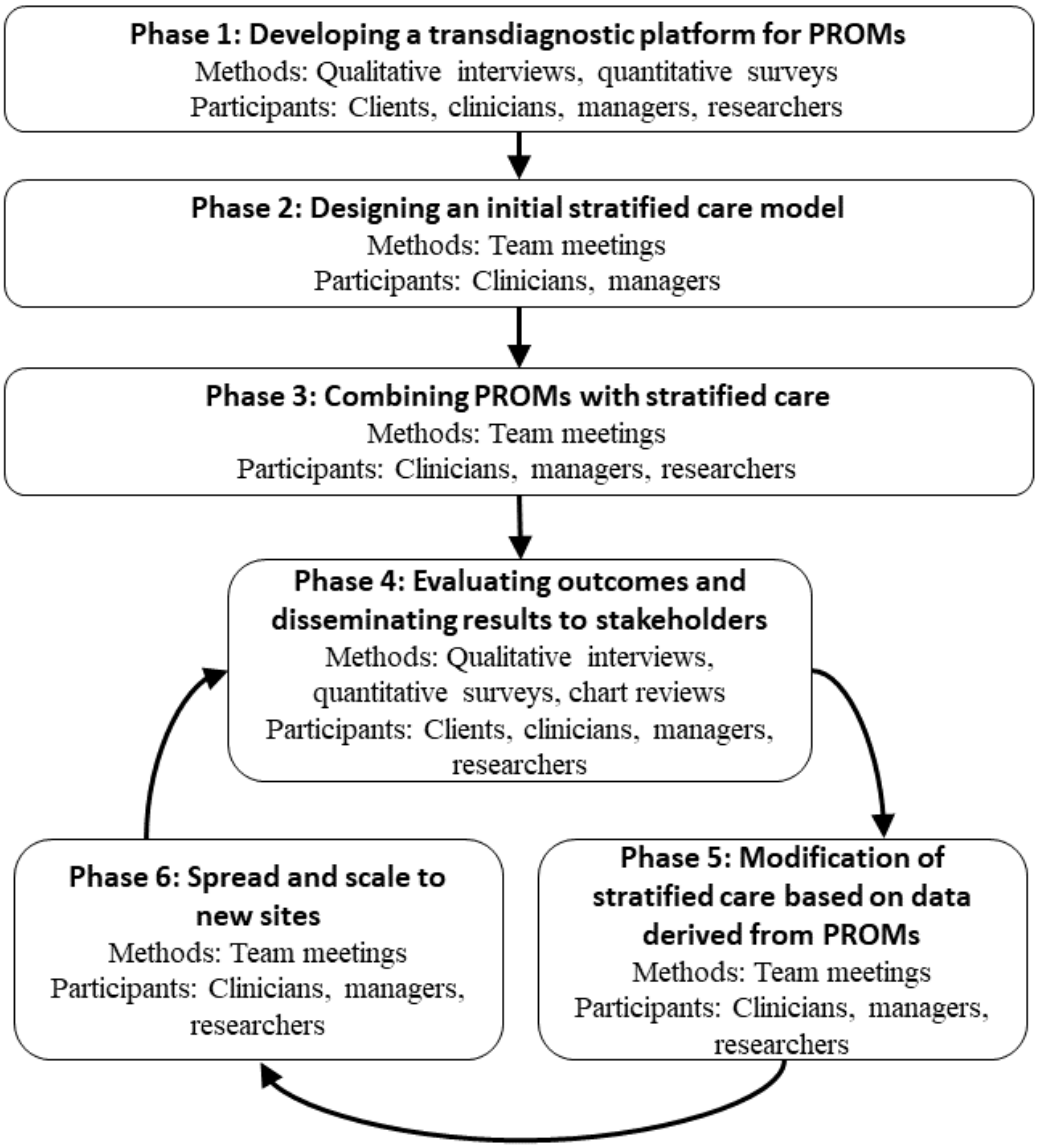
1. Improve treatment selection: Through the use of stratified care, the clinic is seeking to provide the right intensity of service the first time, resulting in better alignment between client needs and services offered.
2. Reduce average wait time (prior to service) and treatment duration (once in service): If the clinic can increase the precision of services by providing higher-intensity services for higher-need clients and lower-intensity services for lower-need clients, the increased efficiency has the potential to reduce wait times and treatment duration.
3. Increase the value of services: The clinic also seeks to understand the value of services provided to increase cost-effectiveness. By tracking client outcomes associated with each treatment, the clinic can identify which services provide the greatest return on investment.
4. Understand barriers and facilitators to implementing standardized PROMs delivered using a digital platform and to stratified care: Knowledge gained about the barriers and facilitators will rapidly be applied to improve organizational, clinical, and youth-related factors to improve care in the clinic.

Study Design and Phases

Overview

The study phases and their relation to an RLHS model are outlined in Figure 1.

Figure 1. Phases in the development and evaluation of a rapid learning health system using PROMs and stratified care. PROM: patient-reported outcome measure.



Phase 1: Developing a Transdiagnostic Platform for PROMs

We set out to select a platform of PROMs, delivered digitally, that would be useful for clinicians in categorizing the severity of mental illness and would be brief and respond to patient-oriented concerns. The goal was to identify a platform that would allow for the simple sharing of information among the relevant stakeholders (clients, clinicians, and researchers) while being compliant with local privacy laws for the storage and distribution of health information. Perhaps most critically, the platform needed to have high acceptability for youth so that they would be willing to complete the instruments.

We decided to implement Innowell [39], which uses freely available, validated instruments that are part of a curated set of instruments that are embedded in a proprietary web-based platform that was primarily developed by Australian academics with support from the Australian government [39-41]. Raw scores on instruments are converted into categories with clinical interpretations (Figure 2). For example, responses to the Overall Anxiety Severity and Impairment Scale [42] are automatically categorized as “minimal,” “mild,” “moderate,” or “high.” The Innowell platform also allows clients to access resources to work on a specific domain (eg, depressed mood), either by referring them to external resources (typically websites, mobile apps, or phone lines) or allowing them to flag to their provider that they want to address a specific domain.

Clients will complete the Innowell instruments at a minimum of baseline, 6 months, and 12 months (Table 1). If a client is discharged or transferred before 12 months, we will ask them to complete one final assessment at discharge or transfer. Clients can also repeat 1 or more Innowell instruments at any time to gauge treatment progress. All fixed time points except baseline also include a custom instrument to provide feedback on the

Innowell system, which includes measures of satisfaction, clinical use, and ease of use. To minimize attrition between time points, we will include the following in the protocol: (1) research coordinator following up with patients to complete measures and sending up to 3 email or text reminders, (2) sharing results with patients including visual graphs so they can see their progress, and (3) providing a small honorarium (in the form of a gift card) for completing measures.

Several additional measures will be collected using the REDCap platform since Innowell does not allow for instrument customization. After each therapy session, clients will be sent an SMS text message (via REDCap) asking them to complete 2 brief 4-item instruments: the Outcome Rating Scale, which measures overall well-being, and the Session Rating Scale, which measures satisfaction with a therapy session [43,44]. At baseline, 6 months, and 12 months, clinicians will be sent an email asking them to provide feedback on the use of PROMs in the Innowell platform and stratified care using the measures listed in Table 2.

Figure 2. Dashboard for Innowell software used in patient-reported outcome measures among emerging adults to assess disease severity.

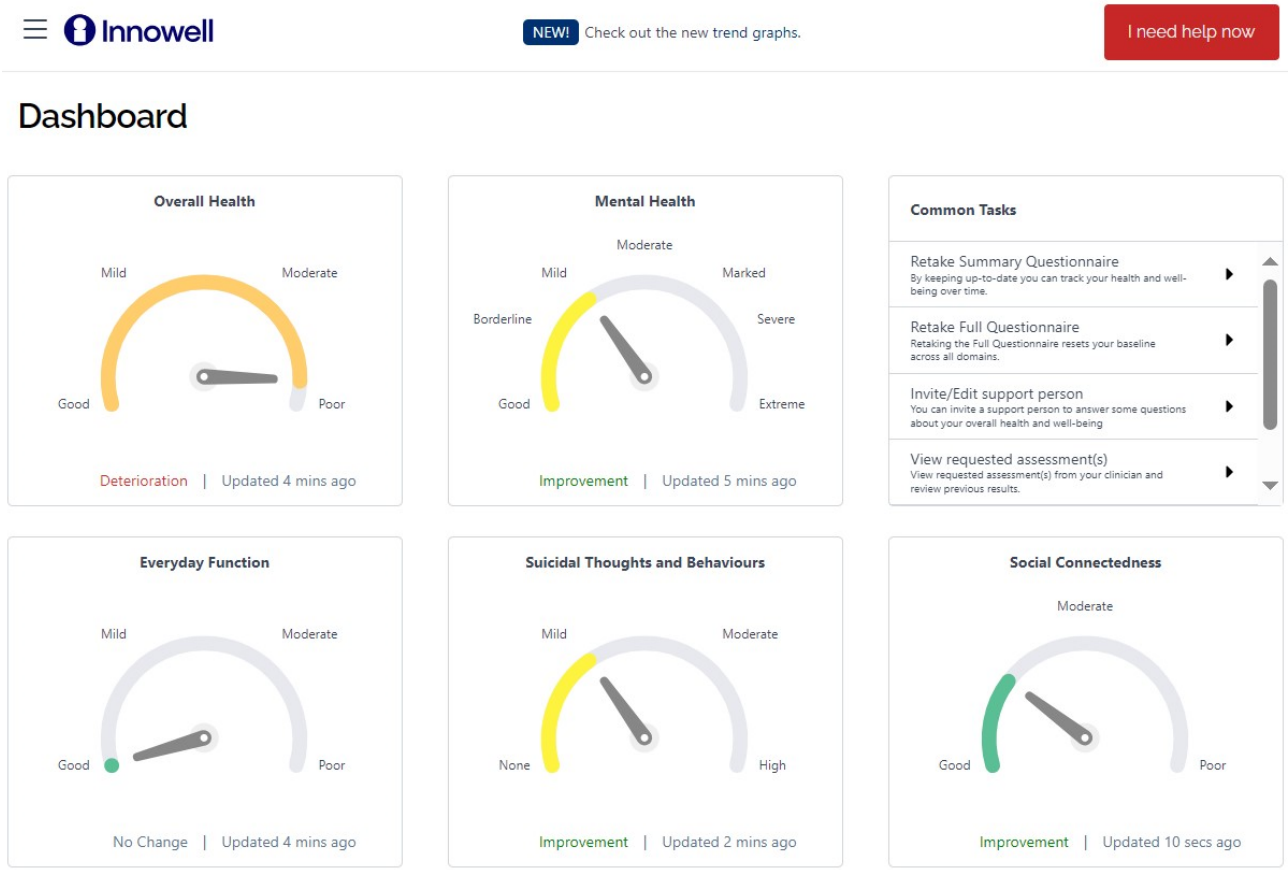


Table 1. Standardized measures collected from clients. All instruments are administered at baseline, 6 months, and 12 months using the Innowell platform, except for the Outcome Rating Scale and Session Rating Scale, which are collected after each treatment session using the Research Electronic Data Capture (REDCap) platform.

Instruments	Domains
Kessler Psychological Distress Scale	Psychological distress
Overall Anxiety Severity and Impairment Scale	Anxiety
Quick Inventory of Depressive Symptomology	Depressed mood
Prodromal Questionnaire	Psychosis-like experiences
Altman Self-Rating Mania Scale	Mania-like experiences
Primary Care PTSD[a] Screen for DSM-5[b]	Posttraumatic stress
Eating Disorder Examination	Eating behaviors and body image
Suicidal Ideation Attributes Scale; Columbia Suicide Severity Rating Scale	Suicidal thoughts and behaviors
Brief Non-Suicidal Self-Injury Assessment Tool	Self-harm
Alcohol, Smoking and Substance Involvement Screening Test; AUDIT[c] Alcohol Consumption Questions	Alcohol, tobacco, and cannabis use
OECD[d] Youth not in Education or Employment; WHO[e] Disability Assessment Schedule; Work and Social Adjustment Scale	Social and occupational function
Schuster's Social Support Scale	Social connectedness
Pittsburgh Sleep Quality Index; Munich Chronotype Questionnaire	Sleep-wake cycle
Child and Youth Resilience Measure—Revised	Resilience
Multigroup Ethnic Identity Measure	Cultural connectedness
Spiritual Health and Life-Orientation Measure	Spirituality
Inventory of Complicated Grief	Grief and loss
Height, weight, and waist circumference; International Physical Activity Questionnaire	Physical health
Outcome Rating Scale	Overall well-being
Session Rating Scale	Treatment session satisfaction

[a]PTSD: posttraumatic stress disorder.

[b]DSM-5: *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*.

[c]AUDIT: Alcohol Use Disorders Identification Test.

[d]OECD: Organization for Economic Co-operation and Development.

[e]WHO: World Health Organization.

Table 2. Standardized measures collected from clinicians to assess feasibility and satisfaction with the use of patient-reported outcome measures. All instruments are administered at baseline, 6 months, and 12 months using the Research Electronic Data Capture (REDCap) platform.

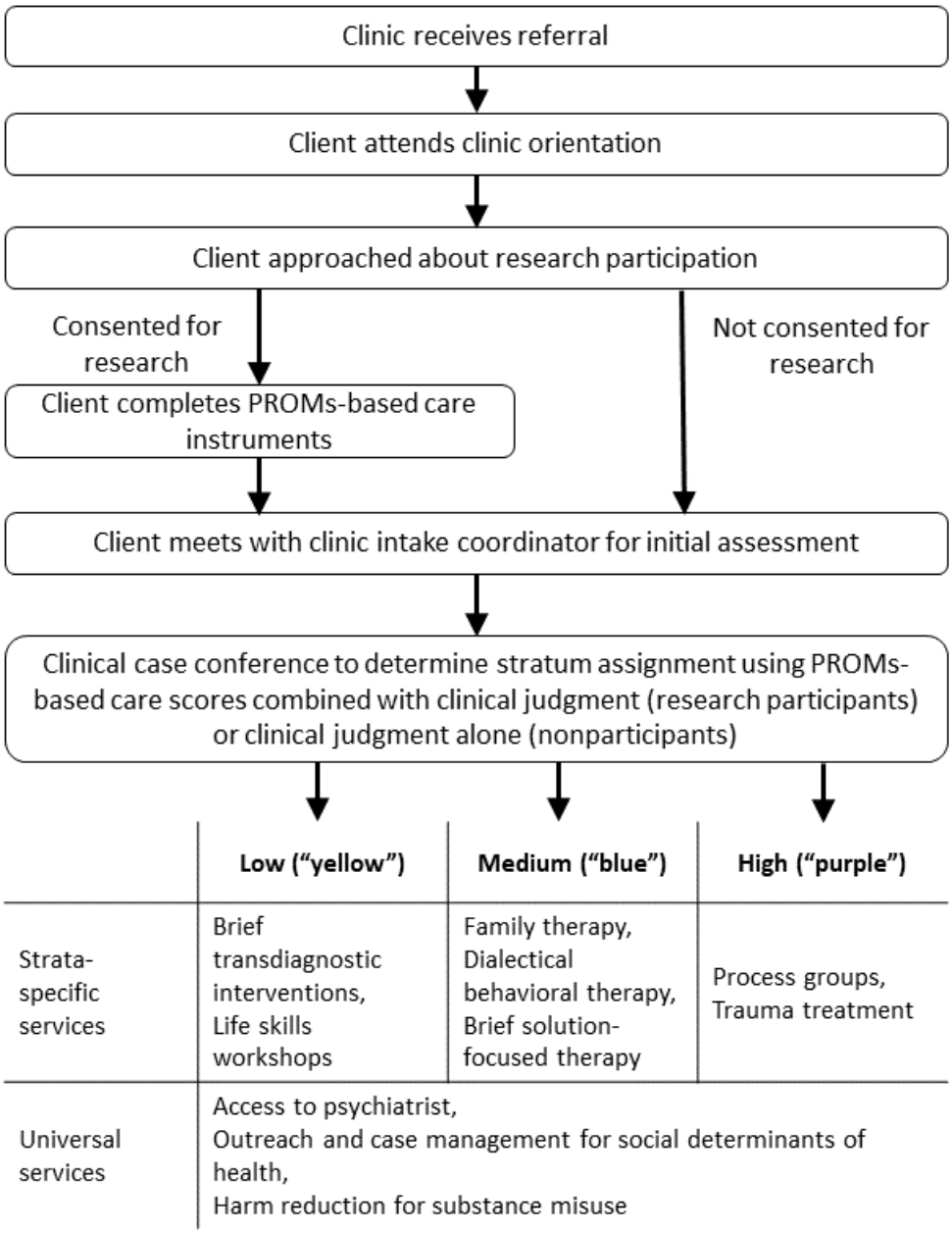
Instruments	Domains
Attitudes Toward Standardized Assessment Scale	Opinion on psychometric instruments
Evidence-Based Practice Attitudes Scale	Opinion on using evidence-based interventions
Monitoring and Feedback Attitudes Scale	Opinion on routine progress monitoring
Brief Individual Readiness for Change Scale	Capacity to implement change in clinical practice
Implementation Leadership Scale	Capacity to implement evidence-based practice
Factors Associated with Referrals and Holding	Stratified care decision-making

Phase 2: Designing an Initial Stratified Care Model

Prior to the implementation of an RLHS, standard care at the study clinic was to have clients work with their assigned clinician to select appropriate treatments from among the available options at the clinic. Coincident with the implementation of an RLHS, the clinic made an operational decision to move to a stratified care model, whereby new clients would be appropriately matched to different intensities of care. The optimal timing for PROMs was identified within the clinical workflow: specifically, after a client had received their orientation to the clinic, but before they were assigned to a primary clinician. Managers and clinicians at the study site engaged in multiple rounds of discussion, feedback, and

revisions to organize both existing and new services into different strata of care. The initial model includes 3 strata of care (low, medium, and high, which are known in the clinic as "yellow," "blue," and "purple," respectively). Some services are only available to clients in each stratum, while other services are available to all clients regardless of stratum (Figure 3).

Figure 3. Clinical and research flow diagram showing progression from emerging adult patient intake into clinical strata using PROMs. PROM: patient-reported outcome measure.



Phase 3: Combining Implementation of PROMs With Stratified Care

After selecting and implementing a digital platform for the delivery of PROMs and a stratified care model, the next phase was to identify how to use the platform to guide stratification within the study clinic. This involves engaging in rapid learning cycles as the Innowell system was created with a population-wide focus, but the study site serves a much narrower population of emerging adults with moderate to severe mental health concerns. Further, given the clinic-specific stratified care model implemented, further learning cycles were required to determine how to use the results from the selected platform to assign a stratum of care. To accomplish this, at the study site, new clients who consent are onboarded to the Innowell platform and asked to complete all 20 domains available on the platform. In the last 9 months, we introduced the Innowell platform and successfully onboarded 56 clients. Uptake has increased during this time, and at the time of writing, we were onboarding an average of 9 emerging adults per month. Managers and clinicians participate in weekly case conferences where individual clients' results, referral information, and case history are presented and discussed. Consensus-based decision-making is used to determine the initial client stratum. A researcher will be present during each case conference to capture notes regarding the decision-making process including the key

findings used to determine stratum and level of agreement among team members.

As per the stratified model of care, clients will meet with their clinician every 3 months to review treatment progress including current results from readministering all 20 domains. Treatment reviews will be used to determine if clients should be moved to a different stratum of care, transferred to another program, or discharged from the health system. After each clinical stratification treatment review, clients will complete a custom form to provide their feedback on the treatment review and clinical stratification process. We will also conduct a detailed chart review to understand the impact of implementing standardized PROMs and stratified care on the services clients use at the study clinic as well as their use of wider health system resources. This chart review will also include clients who did not consent to research if a waiver of consent can be obtained.

Phase 4: Evaluating Outcomes and Disseminating Results to Stakeholders

An exploratory mixed methods approach will be used to evaluate implementation outcomes. Initially, feedback from qualitative interviews will be prioritized since qualitative interviews yield rich data and allow flexibility to probe deeply on specific issues. The first 20 clients to use the digital platform to inform their stratification of care will be approached for qualitative interviews. We will ask clients about their satisfaction with the PROMs and stratified care systems, what factors they felt influenced the stratification decision, the extent to which they agreed with the stratification decision, as well as probe for barriers and facilitators to the use of PROMs and stratified care.

Once 100 clients have been enrolled in the study for at least 3 months (meaning they have received their initial clinical stratification and at least one treatment review), we will begin to use quantitative data to evaluate outcomes of the stratified care process. Based on current rates of onboarding described earlier, we estimate that we will reach this target sample size in approximately 1 year. We will examine the stratum a client is assigned to and map the trajectory of symptoms and satisfaction with clinical services (see instruments in Table 3). Statistical regression models will be developed to describe symptom change over time and determine whether symptom trajectory (eg, slope of regression model) is modified by stratum of care when controlling for other variables (eg, demographics and social determinants of health).

Clients and their clinicians will have access to the data provided by the client to inform future treatment decisions. The research team will present their interim analysis of the results to the clinical team at team meetings at least once every 3 months. One year after recruitment begins, the research team will conduct focus groups and interviews with clinicians and managers at the study site to understand their satisfaction with PROMs and stratified care, barriers and facilitators to the use of PROMs and stratified care, and the factors that influence their decisions about clinical stratification.

Table 3. Data collection using RE-AIM (Reach, Effectiveness, Adoption, Implementation, and Maintenance) framework.

RE-AIM category and data source	Items
Reach (individual)	
Clients	The proportion of clients who participate in a research study, complete quantitative surveys, take part in qualitative interviews, and use extra support resources in Innowell platform
Clinicians	The proportion of clinicians who complete training on using PROMs[a], participate in a research study, complete quantitative surveys, and take part in qualitative interviews
Managers	The proportion of managers who complete training on using PROMs, participate in a research study, and take part in qualitative interviews
Effectiveness (individual)	
Admin data (health region)	The proportion of clients who (for psychiatric reasons) visit urgent care center, who visit emergency department, and who are hospitalized
Admin data (clinic)	Change over time in the proportion of clients assigned to each stratum of care, the proportion of clients who drop out of treatment, length of waitlist, time spent in the program, cost of services used, number of sessions used, type of services accessed, and number and timing of strata changes
Clients	Change over time in answers to quantitative surveys, reasons for dropping out of research or treatment, confidence managing mental health services, satisfaction with mental health services and care coordination, satisfaction with the use of PROMs and stratified care, individual barriers and facilitators to the use of PROMs and stratified care, and agreement with clinician and data derived from PROMs regarding stratified of care assignment
Clinicians	Change over time in answers to quantitative surveys, satisfaction with the use of PROMs and stratified care, individual barriers and facilitators to the use of PROMs and stratified care, and agreement with client and data derived from PROMs regarding stratum of care assignment
Managers	Change over time in satisfaction with the use of PROMs and stratified care and individual barriers and facilitators to the use of PROMs and stratified care
Adoption (organizational)	
Clinics, clients, clinicians, managers	The proportion of clinics that adopt PROMs and stratified care and stakeholders within clinics (clients, clinicians, and managers) who take part in the implementation of PROMs and stratified care
Implementation (organizational)	
Clinics, clients, clinicians, managers	Organizational barriers and facilitators to the implementation of PROMs and stratified care and changes to the use of PROMs and stratified care relative to the intended use
Maintenance (individual and organizational)	
Clinicians, managers, executive leaders	Commitment to continuing using PROMs and stratified care beyond the study period and spread and scale of PROMs and stratified care

[a]PROM: patient-reported outcome measure.

Phase 5: Modification of Stratified Care Based on Data Derived From PROMs

Initially, the clinical team will make rapid changes to both the services offered within each stratum of care and the way dashboards displaying data from PROMs are interpreted and used to match clients into a stratum of care. This pilot phase will be used to ensure managers and clinicians can use early learnings to make effective and efficient changes. Once the management and clinical team report that early learnings have plateaued, planned for 3 months into implementation, the team will use the researcher's summary analysis of case notes from each case conference to create a decision tree to assign patients to appropriate clinical interventions using the stratified care model developed by the clinical team. As an added step before acting upon the decision tree, every 3 months the research and clinical team will meet to examine the data that have been generated and try to understand how they can adapt the decision tree to increase the precision of using data derived from PROMs to assign a client to a stratum of care. The clinical services available in each stratum will also be re-evaluated.

Phase 6: Spread and Scale to New Sites

Initially, this research will be conducted at a single clinic to maximize feasibility and allow for careful evaluation of the use of the stratified care model and its integration with the digital PROM platform.

Data Analysis

We will use the RE-AIM framework to design and organize the data collection system (Table 3). The *Reach* dimension captures individual outcomes and includes the proportion of stakeholders who take part in the research, complete quantitative and qualitative assessments, and use the additional care options, apps, and e-tools on the Innowell platform. The *Effectiveness* domain also examines individual outcomes and measures changes over time in key outcomes related to mental health

(among youth clients), satisfaction with PROMs and stratified care (among clients and clinicians), as well as the use of health care resources (from administrative data). *Adoption* and *Implementation* measure organizational outcomes and so will be more important in later phases of the research when examining how many clinics adopt PROMs and stratified care as well as what are the barriers and facilitators to adoption. *Maintenance* has the longest timescale among RE-AIM dimensions, and it will be used to measure the sustainability of implementation of PROMs and stratified care over time at an organizational and individual level.

This study will begin at the same time as the clinic is implementing stratified care for all clients. For clients who consent to research, PROM results will be used to help inform stratified care, whereas nonresearch participants will be stratified based on clinical judgment alone. The impact of stratified care and implementing PROMs will be inferred from longitudinal changes in client and clinic data, although we cannot control for the impact of other variables changing over time. We will seek a waiver of consent to compare research participants to nonresearch participants, which will provide more direct insights into the impact of using PROMs to inform a stratified care model of mental health service delivery. Analysis will be guided by the three key objectives.

1. Improving treatment selection: We will examine changes over time in symptoms for clients at the study clinic. To the extent that implementation of PROMs is leading to continuous improvements in treatment selection as part of an RLHS, we would expect that participants enrolled at the beginning of the study will show slower improvements in their mental health relative to clients enrolled later in the study (as measured by instruments in Table 1). Additionally, if a waiver of consent can be obtained to compare research participants to nonresearch participants, we expect that research participants will show greater improvements in mental health than nonresearch participants when controlling for clinic intake date.
2. Reducing average wait time (prior to service) and treatment duration (once in service): We will examine clinic administrative data to understand whether the implementation of PROMs and stratified care leads to reductions in wait time and treatment duration. If we can obtain a waiver of consent, we will examine whether research participants (completing PROMs using the Innowell platform) spend less time in treatment than those who opt out of research (and do not complete PROMs using the Innowell platform).
3. Increasing the value of services: Clinic administrative data will be used to understand the cost of providing care to each client. When combined with data derived from PROMs, this will provide information about the degree of symptom improvement associated with each type of service. If we can obtain a waiver of consent, we will be able to determine whether the average cost of providing care to a client changes when informed by PROMs. The clinic also seeks to understand the value of services provided to increase cost-effectiveness. By tracking client outcomes associated with each treatment, we can identify which services provide the greatest return on investment.

Results

This project is funded by the Alberta Children's Hospital Foundation as one part of a program grant (the "Framework for Research in Emerging Adults") that is funded from 2021 to 2026. Ethics approval for this study was received in February 2023. Presently, we have developed a system of PROMs and organized clinical services into strata of care. We will soon begin using PROMs to assign clients to a stratum of care and using feedback from youth and clinicians to understand how to improve experiences and outcomes.

Discussion

Principal Findings

This protocol paper describes how we will evaluate the implementation of an RLHS to improve service delivery within a stratified model of care. The study clinic is looking for ways to target the right service to the right client at the right time, in line with current movements toward a precision mental health care system [20]. However, standard care at the study clinic has historically been similar to mental health care in most areas of the world, in that, treatment progress is not systematically tracked using objective measures for most clients [19]. Thus, even if the clinic implemented stratified care as a means to tailor services to client needs, the clinic would have no way of knowing if the stratified care model resulted in improved outcomes. Therefore, the clinic needed to develop a platform for PROMs to monitor outcomes to understand the impact of their new stratified care model. Using PROMs to inform stratified care is challenging since there are no existing guidelines to help clinicians understand how scores on different standardized measures translate into treatment recommendations. Therefore, the clinic will need to use an RLHS framework to guide the use of PROMs in informing stratified care decision-making. Initially, stratification using data derived from PROMs (in combination with clinical judgment) may not be superior to stratification using clinical judgment alone. However, as data are collected on how stratification and treatment selection impact the trajectory of a client's symptoms, the goal is to iteratively improve the ability to stratify clients and select the best treatment plan.

This project has broad implications for mental health care systems as part of a movement toward value-based health care, which is grounded in the notion that compensation for health care services should be based on the amount of benefit to patients rather than the expense incurred by providers and the system [45]. By tracking the relationship between health services and health outcomes, organizations that pay for health care (eg, governments and insurance companies) can obtain an enhanced understanding of which services provide the greatest value for patients at the lowest financial cost [45]. Implementing value-based health care requires a digital platform, patient-centered outcome measurements, tools to support clinical decision-making, and the means to allow for continuous improvement based on data fed into the digital platform [45,46].

An RLHS, such as the one we are implementing and evaluating, leverages these same key components [47] and therefore represents a potentially important first step toward achieving the goal of a value-based health care system [48].

This research will provide practical guidance to help other research and clinical teams collaborate to implement an RLHS as part of the transition toward value-based health care. The engagement of multiple stakeholders early in the design process allowed us to identify the key outcomes that are fundamental toward creating a value-based health care system. Testing out multiple strategies should allow us to identify a system that patients and providers would be willing to use consistently enough to understand which services are having the biggest impact on patient outcomes. Once additional data are generated, we will be able to report on strategies that clinicians use to identify the treatment that is predicted to provide the most value to patients. However, this research protocol focuses on the systematic evaluation of individual outcomes, which is only one component of a value-based mental health care system. At a population level, value-based mental health care also requires additional system-level quality measures including evaluation of structure (eg, number and availability of mental health specialists) and process (eg, number of sessions of psychotherapy) [48].

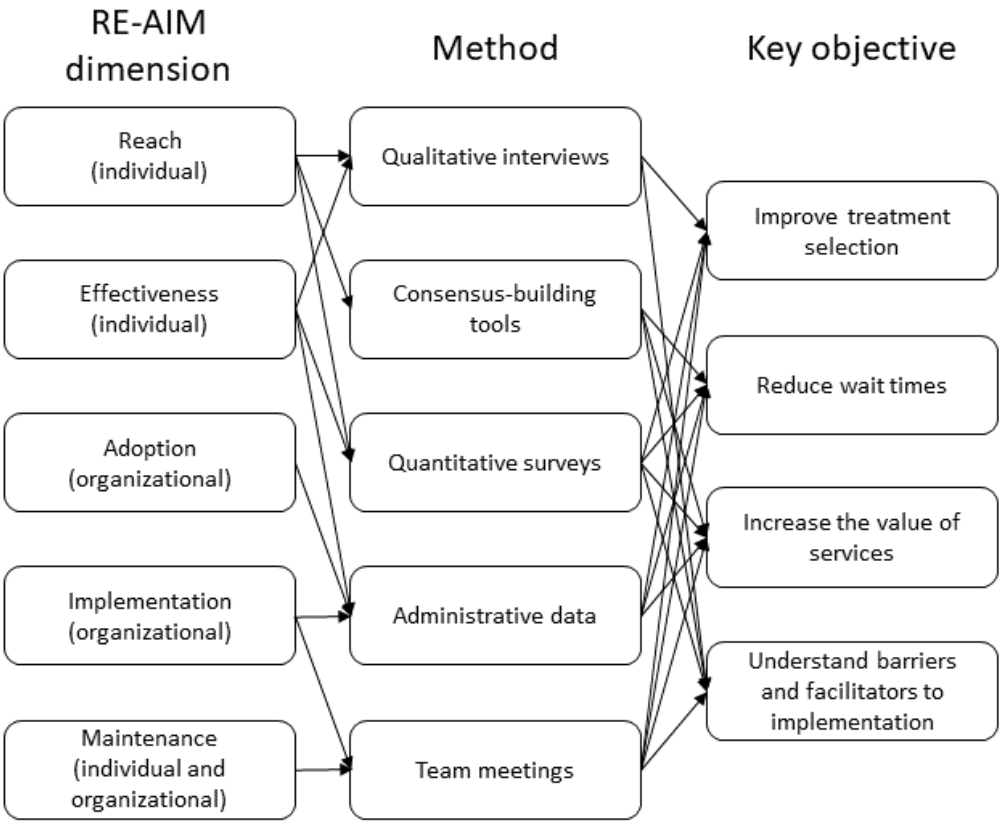
Potential Challenges and Limitations

A major uncertainty is the extent to which clinicians will be willing to embrace the use of standardized PROMs to inform decisions about stratified care. Most mental health providers do not use standardized measures and instead rely on their own clinical judgment to determine the best course of care [19]. It will take some time before enough data are collected to allow for past client outcome data to meaningfully inform decisions about future client stratification. The status quo exerts a powerful effect on organizations, and it is common for new mental health initiatives to be abandoned after a few years, especially if there are problems with staff turnover or funding [49,50]. To mitigate these issues, our team spent 3 years building collaborative relationships among researchers, clinic management, and staff through working together on smaller projects, such as a feasibility study of brief transdiagnostic psychotherapy [12]. We are also embedding qualitative and quantitative measures of clinician satisfaction and decision-making throughout the process to identify how we can support clinicians to implement standardized PROMs and stratified care. Another limitation of this protocol is that the decision tree will have limited generalizability to clinics with different patient populations and referral criteria. In the future, we plan to include additional sites to evaluate the approach in other clinical settings serving emerging adults with mental health concerns. Finally, there is the potential bias toward those who contribute the most data [51]. Specifically, emerging adults who consent to completing PROMs and participating in research may not fully represent all patients referred to the clinic. We will evaluate this potential source of bias by analyzing differences between clients who consent to research and those who do based on demographic and clinical variables (eg, diagnoses) available in administrative data.

Conclusions

This project aims to implement and evaluate an RLHS and enable a data-driven, stratified care approach to improving emerging adult mental health services. The RE-AIM framework is being used to organize and evaluate the implementation according to the key objectives (Figure 4). The goal of this work is to move away from a “one size fits all” approach to youth mental health services and toward one that customizes the modality and intensity of treatment based on client symptoms and preferences. Now that the initial system has been designed, the immediate next steps are to collect and analyze the outcome data to make iterative improvements in stratification. This study will provide valuable insights for clinicians and researchers who are seeking to use mental health data to improve the allocation and delivery of health care resources in real-world settings.

Figure 4. Relationship among RE-AIM framework, research methods, and key objectives. RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance.



Acknowledgments

The authors thank Courtney Habina and Diana Pricop for project coordination. The authors also thank Judith Heidbuurt and Patti Beres for providing insights into clinical care for emerging adults.

Data Availability

The data sets generated during this study are not publicly available because they contain potentially identifiable health care data but are available from the corresponding author on reasonable request.

Conflicts of Interest

IH is the codirector of health and policy at the Brain and Mind Centre at the University of Sydney. The Brain and Mind Centre operates early intervention youth services at Camperdown under contract to headspace. IH is the chief scientific advisor to, and a 5% equity shareholder in, Innowell Pty Ltd. Innowell was formed by the University of Sydney (45% equity) and PwC (Australia; 45% equity) to deliver the Aus $30 million (US $21.63 million) Australian government–funded Project Synergy (2017-2020; a 3-year program for the transformation of mental health services) and to lead the transformation of mental health services internationally through the use of innovative technologies. PDA receives support from the Alberta Innovates Translational Health Chair in Child and Youth Mental Health. HML is a section editor at JMIR Aging, but this does not afford HML preferential treatment in the peer review or publication process. The other authors have no financial relationships or other ties to disclose.

References

1. Erskine HE, Moffitt TE, Copeland WE, Costello EJ, Ferrari AJ, Patton G, et al. A heavy burden on young minds: the global burden of mental and substance use disorders in children and youth. Psychol Med 2015;45(7):1551-1563 [FREE Full text] [doi: 10.1017/S0033291714002888] [Medline: 25534496]
2. Patton GC, Sawyer SM, Santelli JS, Ross DA, Afifi R, Allen NB, et al. Our future: a Lancet commission on adolescent health and wellbeing. Lancet 2016;387(10036):2423-2478 [FREE Full text] [doi: 10.1016/S0140-6736(16)00579-1] [Medline: 27174304]
3. Hochberg ZE, Konner M. Emerging adulthood, a pre-adult life-history stage. Front Endocrinol (Lausanne) 2019;10:918 [FREE Full text] [doi: 10.3389/fendo.2019.00918] [Medline: 31993019]

4. Cadigan JM, Lee CM, Larimer ME. Young adult mental health: a prospective examination of service utilization, perceived unmet service needs, attitudes, and barriers to service use. Prev Sci 2019;20(3):366-376 [FREE Full text] [doi: 10.1007/s11121-018-0875-8] [Medline: 29411197]
5. MacDonald K, Fainman-Adelman N, Anderson KK, Iyer SN. Pathways to mental health services for young people: a systematic review. Soc Psychiatry Psychiatr Epidemiol 2018;53(10):1005-1038 [FREE Full text] [doi: 10.1007/s00127-018-1578-y] [Medline: 30136192]
6. Kaushik A, Kostaki E, Kyriakopoulos M. The stigma of mental illness in children and adolescents: a systematic review. Psychiatry Res 2016;243:469-494. [doi: 10.1016/j.psychres.2016.04.042] [Medline: 27517643]
7. Gulliver A, Griffiths KM, Christensen H. Perceived barriers and facilitators to mental health help-seeking in young people: a systematic review. BMC Psychiatry 2010;10:113 [FREE Full text] [doi: 10.1186/1471-244X-10-113] [Medline: 21192795]
8. Shah JL, Scott J, McGorry PD, Cross SPM, Keshavan MS, Nelson B, et al. Transdiagnostic clinical staging in youth mental health: a first international consensus statement. World Psychiatry 2020;19(2):233-242 [FREE Full text] [doi: 10.1002/wps.20745] [Medline: 32394576]
9. Malla A, Iyer S, McGorry P, Cannon M, Coughlan H, Singh S, et al. From early intervention in psychosis to youth mental health reform: a review of the evolution and transformation of mental health services for young people. Soc Psychiatry Psychiatr Epidemiol 2016;51(3):319-326. [doi: 10.1007/s00127-015-1165-4] [Medline: 26687237]
10. Jeppesen P, Wolf RT, Nielsen SM, Christensen R, Plessen KJ, Bilenberg N, et al. Effectiveness of transdiagnostic cognitive-behavioral psychotherapy compared with management as usual for youth with common mental health problems: a randomized clinical trial. JAMA Psychiatry 2021;78(3):250-260 [FREE Full text] [doi: 10.1001/jamapsychiatry.2020.4045] [Medline: 33355633]
11. Iorfino F, Cheng VWS, Cross SP, Yee HF, Davenport TA, Scott EM, et al. Right care, first time: developing a theory-based automated protocol to help clinically stage young people based on severity and persistence of mental illness. Front Public Health 2021;9:621862 [FREE Full text] [doi: 10.3389/fpubh.2021.621862] [Medline: 34513775]
12. Dimitropoulos G, Lindenbach D, Rowbotham M, Devoe DJ, Richardson A, Mogan T, et al. Feasibility and acceptability of a brief, online transdiagnostic psychotherapy for young adults. J Can Acad Child Adolesc Psychiatry 2023;32(2):111-125 [FREE Full text]
13. Sauer-Zavala S, Gutner CA, Farchione TJ, Boettcher HT, Bullis JR, Barlow DH. Current definitions of "transdiagnostic" in treatment development: a search for consensus. Behav Ther 2017;48(1):128-138. [doi: 10.1016/j.beth.2016.09.004] [Medline: 28077216]
14. Parikh A, Fristad MA, Axelson D, Krishna R. Evidence base for measurement-based care in child and adolescent psychiatry. Child Adolesc Psychiatr Clin N Am 2020;29(4):587-599. [doi: 10.1016/j.chc.2020.06.001] [Medline: 32891364]
15. Hickie IB, Scott EM, Cross SP, Iorfino F, Davenport TA, Guastella AJ, et al. Right care, first time: a highly personalised and measurement-based care model to manage youth mental health. Med J Aust 2019;211(Suppl 9):S3-S46 [FREE Full text] [doi: 10.5694/mja2.50383] [Medline: 31679171]
16. Resnick SG, Oehlert ME, Hoff RA, Kearney LK. Measurement-based care and psychological assessment: using measurement to enhance psychological treatment. Psychol Serv 2020;17(3):233-237 [FREE Full text] [doi: 10.1037/ser0000491] [Medline: 32881578]
17. Zhu M, Hong RH, Yang T, Yang X, Wang X, Liu J, et al. The efficacy of measurement-based care for depressive disorders: systematic review and meta-analysis of randomized controlled trials. J Clin Psychiatry 2021;82(5):21r14034 [FREE Full text] [doi: 10.4088/JCP.21r14034] [Medline: 34587377]
18. Lewis CC, Boyd M, Puspitasari A, Navarro E, Howard J, Kassab H, et al. Implementing measurement-based care in behavioral health: a review. JAMA Psychiatry 2019;76(3):324-335 [FREE Full text] [doi: 10.1001/jamapsychiatry.2018.3329] [Medline: 30566197]
19. Jensen-Doss A, Haimes EMB, Smith AM, Lyon AR, Lewis CC, Stanick CF, et al. Monitoring treatment progress and providing feedback is viewed favorably but rarely used in practice. Adm Policy Ment Health 2018;45(1):48-61 [FREE Full text] [doi: 10.1007/s10488-016-0763-0] [Medline: 27631610]
20. Delgadillo J, Lutz W. A development pathway towards precision mental health care. JAMA Psychiatry 2020;77(9):889-890. [doi: 10.1001/jamapsychiatry.2020.1048] [Medline: 32459326]
21. Foster NE, Hill JC, O'Sullivan P, Hancock M. Stratified models of care. Best Pract Res Clin Rheumatol 2013;27(5):649-661. [doi: 10.1016/j.berh.2013.10.005] [Medline: 24315146]
22. Delgadillo J, Ali S, Fleck K, Agnew C, Southgate A, Parkhouse L, et al. Stratified care vs stepped care for depression: a cluster randomized clinical trial. JAMA Psychiatry 2022;79(2):101-108 [FREE Full text] [doi: 10.1001/jamapsychiatry.2021.3539] [Medline: 34878526]
23. Fletcher S, Spittal MJ, Chondros P, Palmer VJ, Chatterton ML, Densley K, et al. Clinical efficacy of a decision support tool (Link-me) to guide intensity of mental health care in primary practice: a pragmatic stratified randomised controlled trial. Lancet Psychiatry 2021;8(3):202-214. [doi: 10.1016/S2215-0366(20)30517-4] [Medline: 33571453]
24. Etheredge LM. A rapid-learning health system. Health Aff (Millwood) 2007;26(2):w107-w118. [doi: 10.1377/hlthaff.26.2.w107] [Medline: 17259191]

25. Etheredge LM. Rapid learning: a breakthrough agenda. Health Aff (Millwood) 2014;33(7):1155-1162. [doi: 10.1377/hlthaff.2014.0043] [Medline: 25006141]
26. Platt JE, Raj M, Wienroth M. An analysis of the learning health system in its first decade in practice: scoping review. J Med Internet Res 2020;22(3):e17026 [FREE Full text] [doi: 10.2196/17026] [Medline: 32191214]
27. Abernethy AP, Etheredge LM, Ganz PA, Wallace P, German RR, Neti C, et al. Rapid-learning system for cancer care. J Clin Oncol 2010;28(27):4268-4274 [FREE Full text] [doi: 10.1200/JCO.2010.28.5478] [Medline: 20585094]
28. Galvin HK, Petersen C, Subbian V, Solomonides A. Patients as agents in behavioral health research and service provision: recommendations to support the learning health system. Appl Clin Inform 2019;10(5):841-848 [FREE Full text] [doi: 10.1055/s-0039-1700536] [Medline: 31694055]
29. Gremyr A, Malm U, Lundin L, Andersson AC. A learning health system for people with severe mental illness: a promise for continuous learning, patient coproduction and more effective care. Digital Psychiatry 2019;2(1):8-13 [FREE Full text] [doi: 10.1080/2575517X.2019.1622397]
30. Kilbourne AM, Evans E, Atkins D. Learning health systems: driving real-world impact in mental health and substance use disorder research. FASEB Bioadv 2021;3(8):626-638 [FREE Full text] [doi: 10.1096/fba.2020-00124] [Medline: 34377958]
31. Feofanova EV, Zhang GQ, Lhatoo S, Metcalf GA, Boerwinkle E, Venner E. The Implementation Science for Genomic Health Translation (INSIGHT) study in epilepsy: protocol for a learning health care system. JMIR Res Protoc 2021;10(3):e25576 [FREE Full text] [doi: 10.2196/25576] [Medline: 33769305]
32. Murray DS, Anixt JS, Coury DL, Kuhlthau KA, Seide J, Kelly A, et al. Transforming an Autism pediatric research network into a learning health system: lessons learned. Pediatr Qual Saf 2019;4(2):e152 [FREE Full text] [doi: 10.1097/pq9.0000000000000152] [Medline: 31321366]
33. Ferrari M, Iyer S, LeBlanc A, Roy MA, Abdel-Baki A. A rapid-learning health system to support implementation of early intervention services for psychosis in Quebec, Canada: protocol. JMIR Res Protoc 2022;11(7):e37346 [FREE Full text] [doi: 10.2196/37346] [Medline: 35852849]
34. Glasgow RE, Vogt TM, Boles SM. Evaluating the public health impact of health promotion interventions: the RE-AIM framework. Am J Public Health 1999;89(9):1322-1327 [FREE Full text] [doi: 10.2105/ajph.89.9.1322] [Medline: 10474547]
35. Mascayano F, Nossel I, Bello I, Smith T, Ngo H, Piscitelli S, et al. Understanding the implementation of coordinated specialty care for early psychosis in New York state: a guide using the RE-AIM framework. Early Interv Psychiatry 2019;13(3):715-719 [FREE Full text] [doi: 10.1111/eip.12782] [Medline: 30672144]
36. Trivedi MH, Jha MK, Kahalnik F, Pipes R, Levinson S, Lawson T, et al. VitalSign6: a Primary Care First (PCP-First) model for universal screening and measurement-based care for depression. Pharmaceuticals (Basel) 2019;12(2):71 [FREE Full text] [doi: 10.3390/ph12020071] [Medline: 31091770]
37. Wray LO, Ritchie MJ, Oslin DW, Beehler GP. Enhancing implementation of measurement-based mental health care in primary care: a mixed-methods randomized effectiveness evaluation of implementation facilitation. BMC Health Serv Res 2018;18(1):753 [FREE Full text] [doi: 10.1186/s12913-018-3493-z] [Medline: 30285718]
38. LOCUS: Level of Care Utilization System for Psychiatric and Addiction Services. American Association for Community Psychiatry (AACP). URL: https://www.communitypsychiatry.org/keystone-programs/locus [accessed 2023-08-07]
39. Iorfino F, Cross SP, Davenport T, Carpenter JS, Scott E, Shiran S, et al. A digital platform designed for youth mental health services to deliver personalized and measurement-based care. Front Psychiatry 2019;10:595 [FREE Full text] [doi: 10.3389/fpsyt.2019.00595] [Medline: 31507465]
40. Rowe SC, Davenport TA, Easton MA, Jackson TA, Melsness J, Ottavio A, et al. Co-designing the InnoWell platform to deliver the right mental health care first time to regional youth. Aust J Rural Health 2020;28(2):190-194. [doi: 10.1111/ajr.12617] [Medline: 32281183]
41. Davenport TA, LaMonica HM, Whittle L, English A, Iorfino F, Cross S, et al. Validation of the InnoWell platform: protocol for a clinical trial. JMIR Res Protoc 2019;8(5):e13955 [FREE Full text] [doi: 10.2196/13955] [Medline: 31152524]
42. Campbell-Sills L, Norman SB, Craske MG, Sullivan G, Lang AJ, Chavira DA, et al. Validation of a brief measure of anxiety-related severity and impairment: the Overall Anxiety Severity and Impairment Scale (OASIS). J Affect Disord 2009;112(1-3):92-101 [FREE Full text] [doi: 10.1016/j.jad.2008.03.014] [Medline: 18486238]
43. Miller SD, Duncan BL, Brown J. The outcome rating scale: a preliminary study of the reliability, validity, and feasibility of a brief visual analog measure. J Brief Ther 2003;2(2):91-100 [FREE Full text]
44. Duncan BL, Miller SD, Sparks JA, Claud DA, Reynolds LR, Brown J, et al. The Session Rating Scale: preliminary psychometric properties of a "working" alliance measure. J Brief Ther 2003;3(1):3-12 [FREE Full text]
45. Larsson S, Clawson J, Howard R. Value-based health care at an inflection point: a global agenda for the next decade. NEJM Catalyst 2023;4(1):1-22 [FREE Full text] [doi: 10.1056/CAT.22.0332]
46. Baumhauer JF, Bozic KJ. Value-based healthcare: patient-reported outcomes in clinical decision making. Clin Orthop Relat Res 2016;474(6):1375-1378 [FREE Full text] [doi: 10.1007/s11999-016-4813-4] [Medline: 27052020]
47. Menear M, Blanchette MA, Demers-Payette O, Roy D. A framework for value-creating learning health systems. Health Res Policy Syst 2019;17(1):79 [FREE Full text] [doi: 10.1186/s12961-019-0477-3] [Medline: 31399114]

48. Kilbourne AM, Beck K, Spaeth-Rublee B, Ramanuj P, O'Brien RW, Tomoyasu N, et al. Measuring and improving the quality of mental health care: a global perspective. World Psychiatry 2018;17(1):30-38 [FREE Full text] [doi: 10.1002/wps.20482] [Medline: 29352529]
49. Damschroder LJ, Aron DC, Keith RE, Kirsh SR, Alexander JA, Lowery JC. Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. Implement Sci 2009;4:50 [FREE Full text] [doi: 10.1186/1748-5908-4-50] [Medline: 19664226]
50. King JC, Hibbs R, Saville CWN, Swales MA. The survivability of dialectical behaviour therapy programmes: a mixed methods analysis of barriers and facilitators to implementation within UK healthcare settings. BMC Psychiatry 2018;18(1):302 [FREE Full text] [doi: 10.1186/s12888-018-1876-7] [Medline: 30231865]
51. Wiens J, Saria S, Sendak M, Ghassemi M, Liu VX, Doshi-Velez F, et al. Do no harm: a roadmap for responsible machine learning for health care. Nat Med 2019;25(9):1337-1340. [doi: 10.1038/s41591-019-0548-6] [Medline: 31427808]

Abbreviations

PROM: patient-reported outcome measure
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance
REDCap: Research Electronic Data Capture
RLHS: rapid learning health system

Edited by A Mavragani; submitted 12.08.23; peer-reviewed by A AL-Asadi, D Adler; comments to author 02.12.23; revised version received 13.01.24; accepted 09.02.24; published 20.03.24.

Please cite as:
Dimitropoulos G, Lindenbach D, Potestio M, Mogan T, Richardson A, Anderson A, Heintz M, Moskovic K, Gondziola J, Bradley J, LaMonica HM, Iorfino F, Hickie I, Patten SB, Arnold PD
Using a Rapid Learning Health System for Stratified Care in Emerging Adult Mental Health Services: Protocol for the Implementation of Patient-Reported Outcome Measures
JMIR Res Protoc 2024;13:e51667
URL: https://www.researchprotocols.org/2024/1/e51667
doi:10.2196/51667
PMID:38506921

Protocol

Remote Evaluation of Sleep and Circadian Rhythms in Older Adults With Mild Cognitive Impairment and Dementia: Protocol for a Feasibility and Acceptability Mixed Methods Study

Victoria Grace Gabb[1,2], BSc (Hons), MSc; Jonathan Blackman[1,2], BSc (Hons), BMBS; Hamish Duncan Morrison[1,2], BMedSci (Hons), MBChB; Bijetri Biswas[1], BSc (Hons), MSc; Haoxuan Li[1,2,3,4], BSc (Hons), MBBS; Nicholas Turner[1], BSc, MSc, PhD; Georgina M Russell[1], BSc, BM, BCh; Rosemary Greenwood[1,5], BSc, MSc; Amy Jolly[6,7], BSc, MSc, PhD; William Trender[6], BS, MRes; Adam Hampshire[6], PhD; Alan Whone[1,2], MBCHB, PhD; Elizabeth Coulthard[1,2], BA, MBBS, PhD

[1]Bristol Medical School, University of Bristol, Bristol, United Kingdom

[2]Neurology Department, Bristol Brain Centre, North Bristol NHS Trust, Bristol, United Kingdom

[3]King's College Hospital, King's College Hospital NHS Foundation Trust, London, United Kingdom

[4]Bristol Royal Infirmary, University Hospitals Bristol and Weston NHS Foundation Trust, Bristol, United Kingdom

[5]Research & Innovation, University Hospitals Bristol and Weston NHS Foundation Trust, Bristol, United Kingdom

[6]Department of Brain Sciences, Faculty of Medicine, Imperial College London, London, United Kingdom

[7]UCL Queen Square Institute of Neurology, Faculty of Brain Sciences, University College London, London, United Kingdom

Corresponding Author:
Victoria Grace Gabb, BSc (Hons), MSc
Bristol Medical School
University of Bristol
Bristol Brain Centre, Elgar House
Southmead Road
Bristol, BS10 5NB
United Kingdom
Phone: 44 117 456 0700
Email: victoria.gabb@bristol.ac.uk

Abstract

Background: Sleep disturbances are a potentially modifiable risk factor for neurodegenerative dementia secondary to Alzheimer disease (AD) and Lewy body disease (LBD). Therefore, we need to identify the best methods to study sleep in this population.

Objective: This study will assess the feasibility and acceptability of various wearable devices, smart devices, and remote study tasks in sleep and cognition research for people with AD and LBD.

Methods: We will deliver a feasibility and acceptability study alongside a prospective observational cohort study assessing sleep and cognition longitudinally in the home environment. Adults aged older than 50 years who were diagnosed with mild to moderate dementia or mild cognitive impairment (MCI) due to probable AD or LBD and age-matched controls will be eligible. Exclusion criteria include lack of capacity to consent to research, other causes of MCI or dementia, and clinically significant sleep disorders. Participants will complete a cognitive assessment and questionnaires with a researcher and receive training and instructions for at-home study tasks across 8 weeks. At-home study tasks include remote sleep assessments using wearable devices (electroencephalography headband and actigraphy watch), app-based sleep diaries, online cognitive assessments, and saliva samples for melatonin- and cortisol-derived circadian markers. Feasibility outcomes will be assessed relating to recruitment and retention, data completeness, data quality, and support required. Feedback on acceptability and usability will be collected throughout the study period and end-of-study interviews will be analyzed using thematic analysis.

Results: Recruitment started in February 2022. Data collection is ongoing, with final data expected in February 2024 and data analysis and publication of findings scheduled for the summer of 2024.

Conclusions: This study will allow us to assess if remote testing using smart devices and wearable technology is a viable alternative to traditional sleep measurements, such as polysomnography and questionnaires, in older adults with and without MCI or dementia due to AD or LBD. Understanding participant experience and the barriers and facilitators to technology use for

research purposes and remote research in this population will assist with the development of, recruitment to, and retention within future research projects studying sleep and cognition outside of the clinic or laboratory.

International Registered Report Identifier (IRRID): DERR1-10.2196/52652

(JMIR Res Protoc 2024;13:e52652) doi:10.2196/52652

KEYWORDS

feasibility; sleep; mild cognitive impairment; dementia; Lewy body disease; Alzheimer disease; Parkinson; wearable devices; research; mobile phone; electroencephalography; accelerometery; mobile applications; application; app; cognitive; cognitive impairment; sleeping; sleep disturbance; risk factor; Alzheimer; wearable; wearables; acceptability; smart device

Introduction

Background

Dementia is the leading cause of death in the United Kingdom [1]. While the search continues for disease-modifying therapies, key research priorities include preventing, identifying, and reducing dementia risk and improving symptom burden and quality of life for patients with dementia and those who care for them [2]. With increasing evidence to support poor sleep as an important risk factor for dementia [3-5], sleep may offer an untapped opportunity in both reducing dementia incidence and improving quality of life for those with or at risk of developing dementia.

Sleep and Dementia

Sleep is essential for optimal brain function and health [3]. Disrupted sleep and circadian rhythms are considered among the most debilitating symptoms in dementia, and increasing evidence suggests that sleep disturbances are a consequence of and contribute toward neurodegeneration underlying dementia including Alzheimer disease (AD) and Lewy body disease (LBD) [3,6].

Changes to sleep such as shorter total sleep time, more nocturnal awakenings, less time spent in deep slow-wave and rapid eye movement (REM) sleep, and a slight shift to earlier circadian rhythms are commonly observed as we age [7,8]. Most of these changes appear to stabilize around the seventh decade of life in healthy older adults [9]. In AD, sleep and circadian disturbances are more robust and severe than the changes seen in normal aging [10,11]. Some people with AD also experience a phenomenon known as “sundowning” (worsening of neuropsychiatric symptoms in the late afternoon or evening), which is thought to be in part caused by disturbances in circadian rhythms [12,13]. LBD is more typically associated with worse subjective sleep quality, REM sleep behavior disorder, sleep-related movement disorders such as restless legs syndrome, and higher levels of daytime sleepiness [5] compared to other dementias.

Sleep as a Modifiable Risk Factor for Dementia

Individuals with sleep disorders (such as insomnia), sleep-disordered breathing, sleep-related movement disorders, circadian rhythm disorders, and poor quality or insufficient sleep are more likely to develop dementia later in life [14].

Mechanistically, chronic sleep deprivation and fragmentation are associated with various neurodegenerative processes including neuroinflammation [15], amyloid deposition [16,17], autophagy [15], tau phosphorylation [18], and hippocampal atrophy [19,20]. Sleep and circadian disturbances can precede cognitive and functional impairment, appearing in cognitively unimpaired older adults with AD biomarkers such as decreased cerebrospinal fluid amyloid-beta 42 and in mild cognitive impairment (MCI), and correlate with severity of cognitive impairment in AD [21-23]. Sleep disturbances also appear early in the disease course for LBD, particularly REM sleep behavior disorder [24,25]. Profiling sleep may offer noninvasive biomarkers for earlier diagnosis and staging, as well as targets for intervention to improve prognosis.

Improving Quality of Life and Symptom Burden for People With Dementia

Sleep disturbances impact daily functioning, socialization, emotional well-being, and cognitive function in patients [26] and have a profound impact on caregivers [27]. Identifying targets for sleep interventions, whether tailored to an individual’s sleep profile or general advice given alongside dementia diagnosis or care, could help improve the quality of life for both persons with dementia and their caregivers. A single night of sleep deprivation disrupts cognitive performance [28], increases AD-related pathology such as amyloid burden [29], and reduces waste clearance in the brain [30], and improving sleep through treating sleep-disordered breathing has been associated with improvements in both neuropsychological assessments and blood biomarkers relating to AD in people with MCI [31]. Therefore, improving sleep could also benefit those with already established dementia and MCI, in addition to reducing incidence.

Further research is warranted to identify the most important sleep metrics and different sleep profiles in older adults with and without cognitive impairment to help identify targets for intervention [32].

Measuring Sleep in Individuals With, or at Risk of, Dementia

Technological advancements in “wearables” (such as smartwatches and electroencephalography (EEG) headsets), “nearables” (such as a mattress or room sensors), and smartphones offer the unprecedented ability for tracking sleep at home for both consumers and researchers—to varying degrees of accuracy and accessibility [33,34]. The use of wearable technology is not new to sleep medicine or research; the current gold standard for sleep medicine is polysomnography (PSG) conducted under laboratory conditions, and wrist-worn actigraphy has been used for decades alongside paper-based sleep diaries to monitor rest and activity patterns typically over days or a couple of weeks [35]. However, most studies to date

assessing sleep in individuals with MCI and early dementia have used questionnaires, with fewer studies adopting objective sleep technologies that could complement them such as actigraphy and EEG [32,36].

Alongside technological advancements, improved digital literacy and accessibility in older adults in recent years offer great promise for sleep research. A 2020 survey identified that 94.6% of 55-64 year olds, 85.5% of 65-74 year olds, and 54% of those aged 75 years and older had used the internet in the last 3 months [37]. Leveraging technology and remote assessments offers several potential benefits above PSG under laboratory conditions. PSG is often used across 1 or 2 nights, potentially leaving results vulnerable to the well-established "first-night effect," which describes how sleep is quantitatively and qualitatively different during the first compared to subsequent night recordings. This has been observed to affect REM and non-REM sleep, awakenings, total sleep time, and subjective sleep quality [38]. PSG also limits mobility during the night. Conducting research in the home setting is more likely to capture naturalistic sleep as participants can largely continue their usual sleep-wake routines. Remote assessments enable longitudinal assessment, which may uncover natural night-to-night sleep variations. Newer sleep technologies enable the collection of both objective (via wearables and nearables) and subjective (via smartphone apps) sleep data that are considered the best practice to accurately capture sleep quality in older adults [39]. Subjective and objective sleep data may produce complementary or conflicting results [22] and allow multiple aspects of sleep (architecture vs experience) to be captured, enabling comprehensive profiling of sleep. Circadian and infradian rhythms may also be more accurately captured over a longer assessment period than is practical in a laboratory or outpatient setting, using actigraphy and repeated saliva samples that participants complete themselves. Finally, since participants do not need to attend sleep clinics, remote and technology-supported research may improve accessibility to research studies for those with less access to transport, reduce participant and study partner burden, and be more affordable, allowing for larger sample sizes.

However, before large-scale clinical trials and observational studies invest in and adopt technology- and home-based sleep measurements for dementia research, it is important to determine whether research conducted in this way is feasible and acceptable to older adults with and without cognitive impairment or dementia. People living with MCI and dementia experience changes in their communication or thinking, which may influence their experience of remote research, or they may have difficulty remembering to complete or understanding tasks without in-person support from a researcher; however, remote research may offer significant benefits including overcoming logistical issues typically faced in research and thus increase participation while reducing study burden [40]. The few studies that have addressed the feasibility of home-based sleep research and wearable technologies have often collected basic short-term feasibility data across only a few nights [41,42] and have typically required participants to be supported by a caregiver or care home staff [43,44]. Research is needed to see if community-dwelling participants with MCI and early dementia tolerate remote sleep and memory testing across an extended period of weeks or months (as would be expected in a clinical trial setting) and if they themselves can complete the study tasks. Caregivers or partners can provide important contributions to sleep and dementia research [45,46] but they often report poor quality sleep and high burden [47,48], and requiring a study partner may be a barrier to enrollment in research [49]. Independent (or minimally supported) involvement in research in milder stages of cognitive impairment may also positively acknowledge someone's cognitive ability to engage in autonomous decision-making regarding their health [50].

Improving how we measure sleep and cognition in this population can deepen our understanding of the link between sleep and brain health, advice around sleep we give to patients, and improve monitoring in future interventional studies.

Objectives

We will test the feasibility and acceptability of remote, in-home sleep and cognitive testing in a cohort of older adults with MCI or mild to moderate dementia due to AD or LBD and older adults without cognitive impairment. We hypothesize that using technology (wearable devices and smart devices) and remote study tasks will be well-tolerated by all study participants. Firstly, we will apply mixed methods to evaluate the feasibility and acceptability of remote study tasks based on the recruitment and retention of study participants, participant adherence to remote study tasks, data quality and completeness, and qualitative feedback on study tasks from participants. Secondly, we will explore whether sociodemographic or clinical variables explain any of the variability in feasibility and acceptability outcomes (whether someone is supported with tasks at home, cognitive impairment at baseline, and psychological variables at baseline such as apathy and anxiety). Thirdly, we will compare agreement on core sleep outcome measures (such as total sleep time, sleep efficiency, nocturnal awakenings, and sleep quality) across different measures. Finally, we will explore key themes in feedback from participants to identify strengths, limitations, and guidance for future sleep and remote-based research.

It is envisaged that these outcomes will be used to inform future research methodologies for both observational and interventional sleep research in older adults with and without dementia.

Methods

Study Design

This is a mixed methods study assessing the feasibility and acceptability of a novel combination of remote technology-supported sleep and cognitive assessments in older adults with and without cognitive impairment and dementia. The feasibility study is embedded within a prospective, longitudinal, and observational cohort study called the Remote Evaluation of Sleep to Enhance Understanding of Early Dementia (RESTED) study. Participants will complete baseline assessments and undergo remote sleep and cognitive assessments for a main study period of 8 weeks and a follow-up cognitive assessment at 6 months. Feasibility and acceptability will be assessed through the analysis of quantitative and qualitative

data collected throughout the study and during the end-of-study interviews. Qualitative data will help to contextualize and enhance quantitative outcomes to deliver a more comprehensive analysis of the feasibility and acceptability [51].

Setting

The study will be conducted at the Bristol Brain Centre, Southmead Hospital, within the North Bristol NHS (National Health Service) Trust and is sponsored by the University of Bristol. Baseline and follow-up assessments will be conducted at Southmead Hospital, remotely via phone or video call, or at the participant's home. Participants will be asked to complete study activities from home, with visits from a researcher where needed, to deliver or collect study materials or provide support with study activities. Participants will be asked to complete a follow-up cognitive assessment at 6 months.

Participants and Sample Size

Participants will be eligible if they are 50 years of age and older at consent, have full capacity to consent and are willing to adhere to study procedures, have Wi-Fi at home, and meet the criteria to fall into 1 of the 3 study arms: AD group, LBD group, and the control group.

For the AD group, participants will require a clinical diagnosis of MCI due to probable AD or mild AD dementia obtained from medical records. This may include participants with mixed dementia where AD is considered a significant component of clinical presentation.

For the LBD group, participants will require a clinical diagnosis of established or prodromal Parkinson disease dementia, dementia with Lewy bodies, MCI due to Parkinson disease, or MCI due to LBD obtained from medical records. This may include participants with mixed dementia where LBD is considered a significant component to clinical presentation.

For the control group, participants will confirm that they have no known cognitive impairment or neurodegenerative condition. Efforts will be made to match the AD and LBD cohorts on age and sex.

For all groups, participants with a clinically significant untreated sleep disorder predating or unrelated to a dementia diagnosis (such as narcolepsy or untreated sleep apnea), a severe medical or psychiatric comorbidity that may substantially impact sleep (such as refractory epilepsy), or a diagnosis of dementia other than AD or LBD will be excluded from the study.

Study participants will be recruited from cognitive and movement disorders clinics at the North Bristol NHS Trust, volunteer databases, and Join Dementia Research. The study is expected to be open to recruitment between February 2022 and June 2023 with a recruitment target of 75 participants (n=25 in each group). Prospective participants will be introduced to the study via a telephone call from the research team or during a meeting with their clinical team and provided with a digital or paper copy of the participant information sheet. Those who are interested in taking part will be invited to a screening visit for further discussion and, if agreeable, to provide consent. The participants will be asked if they would like to attend with a friend or relative, but we will not recruit formal study partners.

Following consent, participants will undergo a Montreal Cognitive Assessment (MoCA). Those scoring <11/30 will be withdrawn from the study as this would indicate more advanced cognitive impairment, unless in the opinion of the principal investigator that there is a mitigating factor impacting performance on the MoCA (such as prominent speech disorder), in which case they will be eligible to continue in the study.

Outcome Measures

Brief Overview of the RESTED Study

Participants in the RESTED study will be asked to undergo screening and baseline assessments, including the MoCA, medical and clinical observations, questionnaires on sleep (Pittsburgh Sleep Quality Index [52], including responses from a cohabitant if available at the assessment, Epworth Sleepiness Scale [53], STOP (Snoring Tiredness Observed Pressure)-Bang Questionnaire [54], REM Sleep Behavior Disorder Single-Question Screen [55], Ultra-Short Version of the Munich ChronoType Questionnaire [56]), anxiety (Generalized Anxiety Disorder—7-item scale [57]), depression (Patient Health Questionnaire depression scale—8 [58]), and apathy (Apathy Evaluation Scale [59]). Participants will be asked to undergo blood biomarker testing for potential biomarkers of AD (amyloid beta 40 and 42, phosphorylated tau 181), neuroinflammation (glial fibrillary acidic protein), and neurodegeneration (neurofilament light chain) and overnight pulse oximetry using the Nonin 3150 WristOx$_2$ to screen for obstructive sleep apnea (OSA), except where a diagnosis of OSA has already been given or assessment has been completed within 6 months of recruitment to the study. The main study period will involve 8 weeks of remote study tasks, such as sleep diaries (Consensus Sleep Diary—Main [60] with a bespoke additional question on comparison of the previous night to typical sleep), wrist-based actigraphy (Axivity AX3), and regular online cognitive tests (choice reaction time, digit span, and self-ordered search via Cognitron). Throughout the main study period, participants are supported by researchers via MyDignio, a patient-facing mobile platform designed specifically for delivering remote health care, using task reminders and checklists. During 1 of the 8 weeks, participants will undergo an "intensive week" consisting of daily browser-based cognitive testing, wearing a Dreem 2 EEG headband during sleep, saliva samples for dim light melatonin onset (evening) and cortisol awakening response analyses (morning), and verbal memory recall and recognition tasks via a video link with a researcher. Participants will also be asked to provide feedback on their experiences throughout the study. A subsample of participants will be invited to take part in an end-of-study interview. Finally, participants will be invited to a 6-month follow-up MoCA.

Feasibility Outcomes

The feasibility and acceptability outcomes will be predominantly based on data relating to recruitment and retention, the remote study tasks (Table 1), and participant feedback. The core outcomes of the study are outlined in Figure 1.

Table 1. Summary of data collection methods and frequency of remote home-based study tasks for the Remote Evaluation of Sleep to Enhance Understanding of Early Dementia study.

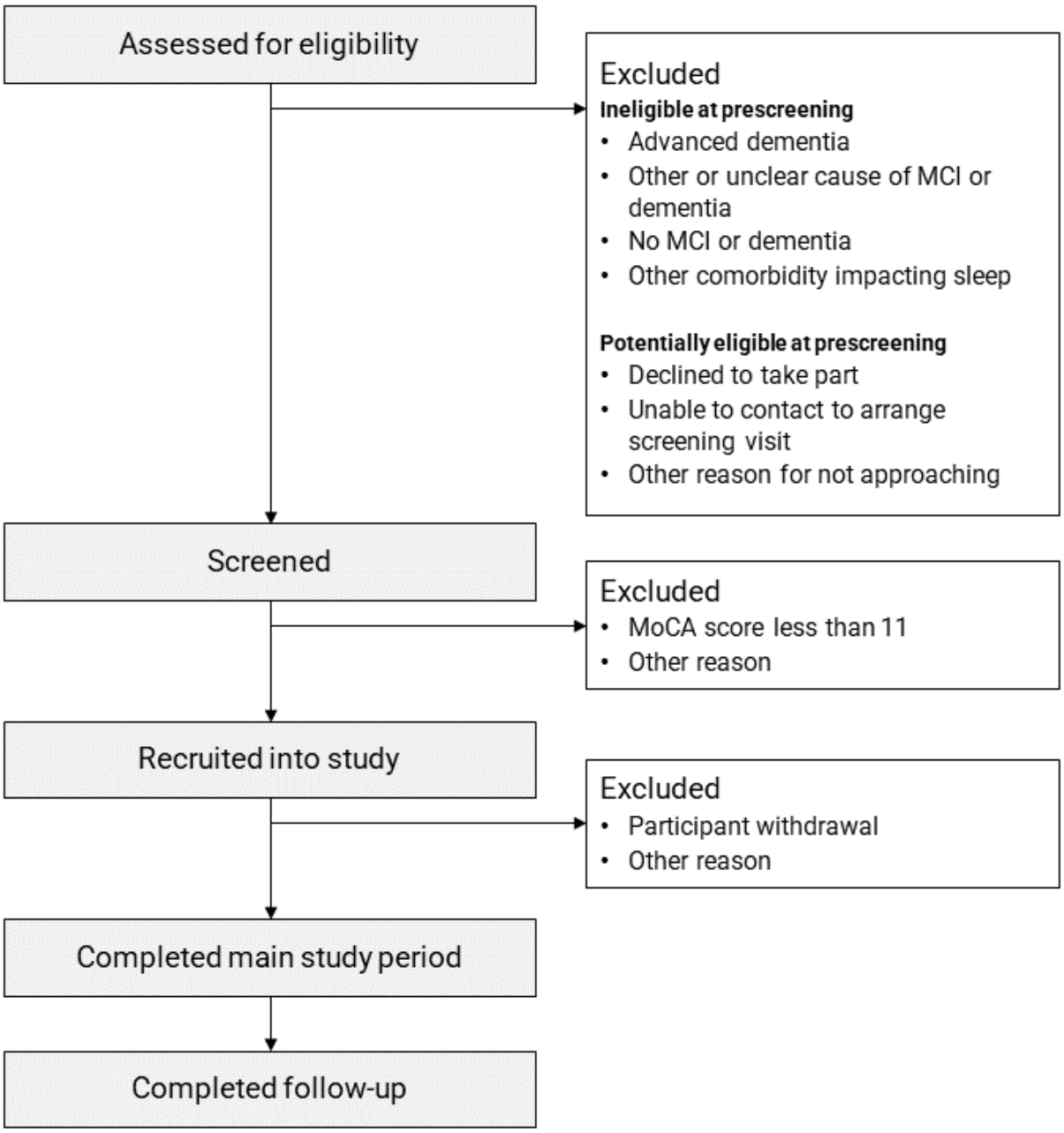
Remote study task	Method of data collection	Frequency of data collection	Duration of data collection
Sleep diary	App-based, via MyDignio	Daily	8 weeks
Actigraphy	Wrist-based actigraphy	Continuous	8 weeks
Remote browser-based cognitive tasks	Participants' own device, via Cognitron website	Twice per week, then daily during intensive week	8 weeks
Recall and recognition tasks with a researcher	Videoconferencing software	Four brief tasks to complete across 4 separate days (<5 minutes each)	1 week (intensive week only)
Overnight electroencephalography (EEG)	Dreem EEG headband	Every night	1 week (intensive week only)
Saliva samples for cortisol awakening response	Saliva swabs	Three swabs (0, 30, and 60 minutes after awakening)	1 morning (intensive week only)
Saliva samples for dim light melatonin assay	Passive drool samples	Seven samples hourly starting from 5 hours before usual bedtime	1 evening (intensive week only)
Overnight pulse oximetry for sleep apnea screening	Pulse oximeter	Overnight	2 nights

Figure 1. Conceptual map of feasibility and acceptability outcomes for the remote evaluation of sleep to enhance understanding of early dementia study. The core outcomes will be recruitment and retention, data quality, resources required, and participant experience.

Recruitment and Retention Rates

Recruitment and retention to the study will be described and presented in a flowchart following Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Figure 2). Key recruitment and retention outcomes will include the proportion of eligible patients who consent to take part in the study and the proportion of patients who withdraw from the study after consent. Reasons for ineligibility and nonparticipation at each stage (prescreening, screening, main study period, and follow-up), as well as barriers and facilitators to recruitment, will be summarized. Sample characteristics will be presented in tables.

Figure 2. A template flowchart of participant flow through the RESTED study, based on STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines. This flowchart will document participant recruitment and retention at each stage of the study. MCI: mild cognitive impairment; MoCA: Montreal Cognitive Assessment; RESTED: Remote Evaluation of Sleep to Enhance Understanding of Early Dementia.



Data Quality, Participant Adherence, and Data Completeness

The participants will be provided written and verbal guidance and reminders on how and when to complete each of the study tasks. Descriptive statistics on adherence and data completeness for each remote study task will be summarized (eg, the number of nights the EEG headband was worn and the number of completed sleep diaries). Reasons for incompleteness (eg, participant nonadherence and technical problems) and methods used to encourage or improve data completion (eg, reminders to complete tasks) will be described.

We will also assess the extent to which data appear to be valid and of sufficient quality for analysis of core sleep metrics (eg, for EEG data, this will include individual EEG channels and overall record quality metrics).

Where multiple sleep metrics are measured on a single night (eg, total sleep time via actigraphy, sleep diary, and EEG), an agreement between different measurement tools will be calculated (eg, Bland-Altman plot comparing sleep diary-adjusted actigraphy to EEG).

Resources

We will assess the amount of support and resources (eg, in-person visits, email, app-based, and telephone support) required from the research team to complete remote study tasks. Though the study will not require a study partner, we will also record whether participants perceive that they have access to support from outside of the study team (eg, family member, caregiver, or friend), whether this support is used, and what support is provided (eg, technical support and reminders).

Barriers, Facilitators, and Participant Feedback

We will review participant feedback expressed before, during, and at the end-of-study interviews to identify barriers and facilitators in (1) participating in remote sleep and cognitive research in general and (2) study-specific remote tasks.

The end-of-study interviews were designed and guided by the Capability Opportunity Motivation-Behavior (COM-B) system model of behavior, which suggests that capability, opportunity, and motivation interact with behavior in a system [61]. The interviews will probe the capacity to engage in the study activities (capability), habits and decision-making around study involvement (motivation), external factors that influenced behavior, and completion of the study tasks (opportunity). Interview transcripts will be coded and organized into themes using NVivo (version 20; Lumivero; or newer) software. We will use an inductive approach to thematic analysis and aim to identify semantic and latent themes [62,63].

Where appropriate and scientifically sound, we will incorporate feedback on acceptability and feasibility to improve the study design. Changes to the study design due to feasibility or acceptability or based on feedback from prospective or enrolled participants will be documented.

Subgroup Analyses

We will compare acceptability and feasibility outcomes between study arms (AD, LBD, or controls) and conduct exploratory analyses to determine whether subjective sleep quality support from a relative or friend or baseline apathy and anxiety predict overall adherence to study tasks.

Ethical Considerations

This study has been approved by the Health Research Authority (Yorkshire and the Humber—Bradford Leeds Research Ethics Committee, reference 21/YH/0177) and carries minimal risk to participants. The study will be conducted in accordance with Good Clinical Practice and the Helsinki Declaration to protect the rights and welfare of all participants. All data will be kept securely and handled in accordance with the General Data Protection Regulation (EU 2016/679). Capacity to consent to the research study will be assessed and participants will be required to provide full written informed consent prior to participation in any study activities. The participants will be reminded of their right to withdraw at any point, without providing a reason, and without this affecting their health care. Participants will be offered cash reimbursement for travel or postage expenses incurred during the study. The participants will be assigned a study ID at consent to allow pseudonymization of participant data, with personal information stored separately and securely from deidentified data. The final paper and any data shared will contain no information that allows for the identification of individual participants.

Results will be presented at scientific meetings and conferences and published in peer-reviewed journals. Summaries will be provided to participants where they have indicated consent to be contacted about results from the study.

Results

The study opened to recruitment in February 2022. Participant recruitment is scheduled to be completed in 2023. Data collection is anticipated to continue until February 2024, with analysis beginning in 2023 and continuing into 2024.

Results will be reported in line with guidance from the STROBE checklist [64] and the CONSORT 2010 extension [65] for pilot and feasibility trials [66].

Discussion

Principal Findings

Sleep is a fundamental component of health, and sleep disturbances are commonly observed in people living with MCI and dementia. Insufficient or poor sleep may represent both a risk factor and a symptom of these conditions, but more work is needed to confirm the relationship between sleep and MCI or dementia. Improvements to the way we measure sleep, such as measuring sleep in someone's natural home environment and using technologies to supplement data collected from sleep questionnaires may help us to better understand the sleep profile in these conditions compared to normal aging, identify targets for intervention, and monitor disease progression [32,67]. However, we first need to understand whether it is possible to collect good-quality sleep and cognitive data from people living with MCI and dementia in their own homes. Accordingly, this paper proposes a study to investigate the feasibility and acceptability of remote sleep and memory data collection using study tasks designed to be completed at home by people living with MCI or dementia. The study aims to assess whether people with MCI or dementia are willing to engage in sleep studies using technology and home-based study tasks, describe participant experience, and evaluate the study tasks based on retrieving complete and analyzable data. The findings from this study will guide future research design in sleep and memory.

Limitations

The eligibility criteria for the study require participants to have an internet connection and be willing to use technology for the duration of the study. Understanding the feasibility and acceptability of technology-supported remote research is the purpose of the study; however, this inherently may introduce bias into the study. For example, it is possible this may mean those who are unfamiliar or uncomfortable with technology may not take part, or those who are particularly interested in technology may find the study more acceptable or feasible. If recruitment, retention rates, or feedback from patients who would otherwise be eligible but were unable or unwilling to take part because of limited access to or ability to use the

internet or a smart device, we may offer an adapted version of the study and will record whether this influences recruitment rate and other relevant outcomes.

Subjective measures used in the study may be prone to recall bias and may be difficult for individuals with cognitive impairment to answer accurately. While participants themselves will need to provide answers to questions during the study, they can be supported by a family member, friend, or caregiver where needed and requested by the participant. Subjective measures will also be complemented by objective measures which are not prone to recall bias.

The longitudinal and remote nature of the study may result in a greater proportion of missing data compared to sleep research studies conducted in a laboratory setting. As a study enrolling persons with MCI and dementia, it is also expected that participants may have difficulty remembering to complete study tasks. Reasonable efforts will be taken to encourage adherence and data completion throughout the study period, particularly in the intensive week (eg, schedules and digital reminders via SMS text messaging or email). Automated scheduled reminders and task lists will be supplemented with ad hoc contacts from the research team directly (eg, contacting to ascertain reasons behind consecutive days of missing data).

Conclusions

Technological advancements and improved digital literacy offer the opportunity to research sleep longitudinally and in the home environment. However, further research is needed to understand whether these developments may benefit MCI and dementia study design. This protocol outlines a mixed methods study that examines the feasibility and acceptability of remote sleep and cognitive testing in a cohort of older adults specifically those with MCI or dementia due to probable AD or LBD. Outputs from the study will inform the approach to studying sleep in people with MCI or dementia in this population, contributing toward global efforts to identify and better understand potentially modifiable risk factors in these conditions.

Acknowledgments

With thanks to the Respiratory Physiology department at North Bristol National Health Service (NHS) Trust, the research teams at Cognitron and Dreem, Ewa G Truchanowicz and Phil Reay in the Dignio team, and our Patient and Public Involvement contributors. We would also like to thank all individuals who took part in the research, including the participants and those who supported them.

Data Availability

Data sets generated during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

VGG contributed to the study authorship, protocol authorship, study management, study design, participant recruitment, participant consent, and data collection. JB and HDM contributed to the protocol authorship, study design, sub principal investigators, participant recruitment, participant consent, data collection, and study review. EC contributed to the project conception, study design, principal investigator, and study review. BB contributed to the study design, data collection, and study review. HL contributed to the participant recruitment, participant consent, and data collection. NT contributed to the data analysis methodology. AJ, WT, and AH performed the cognitive task formulation. AW, GMR, and RG contributed to the study design.

Conflicts of Interest

AH is owner and director of Future Cognition Ltd and H2 Cognitive Designs, which provide custom cognitive assessment software and digital research and healthcare services. WT is employed by H2 Cognitive Designs LTD, owners and developers of the Cognitron software

References

1. Leading causes of death, UK: 2001 to 2018. Office for National Statistics. 2020. URL: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/causesofdeath/articles/leadingcausesofdeathuk/2001to2018#:~:text=From%202001%20to%202018%2C%20suicide,deaths%20for%20this%20age%20group [accessed 2024-02-15]
2. Shah H, Albanese E, Duggan C, Rudan I, Langa KM, Carrillo MC, et al. Research priorities to reduce the global burden of dementia by 2025. Lancet Neurol 2016;15(12):1285-1294. [doi: 10.1016/S1474-4422(16)30235-6] [Medline: 27751558]
3. Lewis LD. The interconnected causes and consequences of sleep in the brain. Science 2021;374(6567):564-568 [FREE Full text] [doi: 10.1126/science.abi8375] [Medline: 34709917]
4. Sabia S, Fayosse A, Dumurgier J, van Hees VT, Paquet C, Sommerlad A, et al. Association of sleep duration in middle and old age with incidence of dementia. Nat Commun 2021;12(1):2289 [FREE Full text] [doi: 10.1038/s41467-021-22354-2] [Medline: 33879784]
5. Elder GJ, Lazar AS, Alfonso-Miller P, Taylor JP. Sleep disturbances in Lewy body dementia: a systematic review. Int J Geriatr Psychiatry 2022;37(10):1-22 [FREE Full text] [doi: 10.1002/gps.5814] [Medline: 36168299]

6. Fifel K, Videnovic A. Circadian and sleep dysfunctions in neurodegenerative disorders-an update. Front Neurosci 2020;14:627330 [FREE Full text] [doi: 10.3389/fnins.2020.627330] [Medline: 33536872]
7. Lavoie CJ, Zeidler MR, Martin JL. Sleep and aging. Sleep Sci Pract 2018;2(1):3 [FREE Full text] [doi: 10.1186/s41606-018-0021-3]
8. Bliwise DL. Sleep in normal aging and dementia. Sleep 1993;16(1):40-81 [FREE Full text] [doi: 10.1093/sleep/16.1.40] [Medline: 8456235]
9. Ohayon MM, Carskadon MA, Guilleminault C, Vitiello MV. Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. Sleep 2004;27(7):1255-1273 [FREE Full text] [doi: 10.1093/sleep/27.7.1255] [Medline: 15586779]
10. Romanella SM, Roe D, Tatti E, Cappon D, Paciorek R, Testani E, et al. The sleep side of aging and Alzheimer's disease. Sleep Med 2021;77:209-225 [FREE Full text] [doi: 10.1016/j.sleep.2020.05.029] [Medline: 32912799]
11. Cordone S, de Gennaro L. Insights from human sleep research on neural mechanisms of Alzheimer's disease. Neural Regen Res 2020;15(7):1251-1252 [FREE Full text] [doi: 10.4103/1673-5374.272579] [Medline: 31960807]
12. Volicer L, Harper DG, Manning BC, Goldstein R, Satlin A. Sundowning and circadian rhythms in Alzheimer's disease. Am J Psychiatry 2001;158(5):704-711 [FREE Full text] [doi: 10.1176/appi.ajp.158.5.704] [Medline: 11329390]
13. Khachiyants N, Trinkle D, Son SJ, Kim KY. Sundown syndrome in persons with dementia: an update. Psychiatry Investig 2011;8(4):275-287 [FREE Full text] [doi: 10.4306/pi.2011.8.4.275] [Medline: 22216036]
14. Damsgaard L, Janbek J, Laursen TM, Erlangsen A, Spira AP, Waldemar G. Hospital-diagnosed sleep disorders and incident dementia: a nationwide observational cohort study. Eur J Neurol 2022;29(12):3528-3536 [FREE Full text] [doi: 10.1111/ene.15517] [Medline: 35916072]
15. Xie Y, Ba L, Wang M, Deng SY, Chen SM, Huang LF, et al. Chronic sleep fragmentation shares similar pathogenesis with neurodegenerative diseases: endosome-autophagosome-lysosome pathway dysfunction and microglia-mediated neuroinflammation. CNS Neurosci Ther 2020;26(2):215-227 [FREE Full text] [doi: 10.1111/cns.13218] [Medline: 31549780]
16. Mander BA, Marks SM, Vogel JW, Rao V, Lu B, Saletin JM, et al. β-amyloid disrupts human NREM slow waves and related hippocampus-dependent memory consolidation. Nat Neurosci 2015;18(7):1051-1057 [FREE Full text] [doi: 10.1038/nn.4035] [Medline: 26030850]
17. Cordone S, Annarumma L, Rossini PM, de Gennaro L. Sleep and ß-amyloid deposition in Alzheimer disease: insights on mechanisms and possible innovative treatments. Front Pharmacol 2019;10:695 [FREE Full text] [doi: 10.3389/fphar.2019.00695] [Medline: 31281257]
18. Barthélemy NR, Liu H, Lu W, Kotzbauer PT, Bateman RJ, Lucey BP. Sleep deprivation affects tau phosphorylation in human cerebrospinal fluid. Ann Neurol 2020;87(5):700-709 [FREE Full text] [doi: 10.1002/ana.25702] [Medline: 32057125]
19. Fjell AM, Sørensen Ø, Amlien IK, Bartrés-Faz D, Bros DM, Buchmann N, et al. Self-reported sleep relates to hippocampal atrophy across the adult lifespan: results from the Lifebrain consortium. Sleep 2020;43(5):zsz280 [FREE Full text] [doi: 10.1093/sleep/zsz280] [Medline: 31738420]
20. Noh HJ, Joo EY, Kim ST, Yoon SM, Koo DL, Kim D, et al. The relationship between hippocampal volume and cognition in patients with chronic primary insomnia. J Clin Neurol 2012;8(2):130-138 [FREE Full text] [doi: 10.3988/jcn.2012.8.2.130] [Medline: 22787497]
21. Naismith SL, Mowszowski L. Sleep disturbance in mild cognitive impairment: a systematic review of recent findings. Curr Opin Psychiatry 2018;31(2):153-159. [doi: 10.1097/YCO.0000000000000397] [Medline: 29256922]
22. Palmer K, Mitolo M, Burgio F, Meneghello F, Venneri A. Sleep disturbance in mild cognitive impairment and association with cognitive functioning. a case-control study. Front Aging Neurosci 2018;10:360 [FREE Full text] [doi: 10.3389/fnagi.2018.00360] [Medline: 30473661]
23. Zhang Y, Ren R, Yang L, Zhang H, Shi Y, Okhravi HR, et al. Sleep in Alzheimer's disease: a systematic review and meta-analysis of polysomnographic findings. Transl Psychiatry 2022;12(1):136 [FREE Full text] [doi: 10.1038/s41398-022-01897-y] [Medline: 35365609]
24. Schenck CH, Boeve BF, Mahowald MW. Delayed emergence of a parkinsonian disorder or dementia in 81% of older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder: a 16-year update on a previously reported series. Sleep Med 2013;14(8):744-748. [doi: 10.1016/j.sleep.2012.10.009] [Medline: 23347909]
25. Fei M, Wang F, Wu H, Liu S, Gan J, Ji Y. Characteristics of initial symptoms in patients with dementia with Lewy body disease. Front Neurol 2022;13:1024995 [FREE Full text] [doi: 10.3389/fneur.2022.1024995] [Medline: 36313495]
26. Petrovsky DV, McPhillips MV, Li J, Brody A, Caffeé L, Hodgson NA. Sleep disruption and quality of life in persons with dementia: a state-of-the-art review. Geriatr Nurs 2018;39(6):640-645 [FREE Full text] [doi: 10.1016/j.gerinurse.2018.04.014] [Medline: 29803606]
27. McCurry SM, Logsdon RG, Teri L, Gibbons LE, Kukull WA, Bowen JD, et al. Characteristics of sleep disturbance in community-dwelling Alzheimer's disease patients. J Geriatr Psychiatry Neurol 1999;12(2):53-59. [doi: 10.1177/089198879901200203] [Medline: 10483925]
28. Holding BC, Ingre M, Petrovic P, Sundelin T, Axelsson J. Quantifying cognitive impairment after sleep deprivation at different times of day: a proof of concept using ultra-short smartphone-based tests. Front Behav Neurosci 2021;15:666146 [FREE Full text] [doi: 10.3389/fnbeh.2021.666146] [Medline: 33927603]

29. Shokri-Kojori E, Wang GJ, Wiers CE, Demiral SB, Guo M, Kim SW, et al. β-Amyloid accumulation in the human brain after one night of sleep deprivation. Proc Natl Acad Sci U S A 2018;115(17):4483-4488 [FREE Full text] [doi: 10.1073/pnas.1721694115] [Medline: 29632177]
30. Eide PK, Vinje V, Pripp AH, Mardal KA, Ringstad G. Sleep deprivation impairs molecular clearance from the human brain. Brain 2021;144(3):863-874 [FREE Full text] [doi: 10.1093/brain/awaa443] [Medline: 33829232]
31. Huang H, Li M, Zhang M, Qiu J, Cheng H, Mou X, et al. Sleep quality improvement enhances neuropsychological recovery and reduces blood Aß42/40 ratio in patients with mild-moderate cognitive impairment. Medicina (Kaunas) 2021;57(12):1366 [FREE Full text] [doi: 10.3390/medicina57121366] [Medline: 34946311]
32. Blackman J, Morrison HD, Lloyd K, Gimson A, Banerjee LV, Green S, et al. The past, present, and future of sleep measurement in mild cognitive impairment and early dementia-towards a core outcome set: a scoping review. Sleep 2022;45(7):zsac077 [FREE Full text] [doi: 10.1093/sleep/zsac077] [Medline: 35373837]
33. de Zambotti M, Cellini N, Goldstone A, Colrain IM, Baker FC. Wearable sleep technology in clinical and research settings. Med Sci Sports Exerc 2019;51(7):1538-1557 [FREE Full text] [doi: 10.1249/MSS.0000000000001947] [Medline: 30789439]
34. Bianchi MT. Sleep devices: wearables and nearables, informational and interventional, consumer and clinical. Metabolism 2018;84:99-108. [doi: 10.1016/j.metabol.2017.10.008] [Medline: 29080814]
35. Marino M, Li Y, Rueschman MN, Winkelman JW, Ellenbogen JM, Solet JM, et al. Measuring sleep: accuracy, sensitivity, and specificity of wrist actigraphy compared to polysomnography. Sleep 2013;36(11):1747-1755 [FREE Full text] [doi: 10.5665/sleep.3142] [Medline: 24179309]
36. van de Water ATM, Holmes A, Hurley DA. Objective measurements of sleep for non-laboratory settings as alternatives to polysomnography–a systematic review. J Sleep Res 2011;20(1 Pt 2):183-200. [doi: 10.1111/j.1365-2869.2009.00814.x] [Medline: 20374444]
37. Internet users, UK: 2020. Office for National Statistics. 2020. URL: https://www.ons.gov.uk/businessindustryandtrade/itandinternetindustry/bulletins/internetusers/2020 [accessed 2024-02-15]
38. Le Bon O, Arpi S. Effect of the first sleep night in polysomnography: classification by variable sensitivity and factorial analysis of differences between nights. Rev Neurol (Paris) 2003;159(Suppl 11):6S42-6S47. [Medline: 14646799]
39. Landry GJ, Best JR, Liu-Ambrose T. Measuring sleep quality in older adults: a comparison using subjective and objective methods. Front Aging Neurosci 2015;7:166 [FREE Full text] [doi: 10.3389/fnagi.2015.00166] [Medline: 26441633]
40. Maddali HT, Dixon E, Pradhan A, Lazar A. Supporting remote participation when designing with people with dementia. CSCW 20 Companion (2020) 2020;2020:335-340 [FREE Full text] [doi: 10.1145/3406865.3418316] [Medline: 35098257]
41. Kent BA, Casciola AA, Carlucci SK, Chen M, Stager S, Mirian MS, et al. Home EEG sleep assessment shows reduced slow-wave sleep in mild-moderate Alzheimer's disease. Alzheimers Dement (N Y) 2022;8(1):e12347 [FREE Full text] [doi: 10.1002/trc2.12347] [Medline: 35992215]
42. van den Berg JF, van Rooij FJA, Vos H, Tulen JHM, Hofman A, Miedema HME, et al. Disagreement between subjective and actigraphic measures of sleep duration in a population-based study of elderly persons. J Sleep Res 2008;17(3):295-302. [doi: 10.1111/j.1365-2869.2008.00638.x] [Medline: 18321246]
43. Pavlickova H, Russell AE, Lightman S, McCabe R. Feasibility of salivary cortisol collection in patients and companions attending dementia diagnostic meetings in memory clinics. BMC Res Notes 2021;14(1):30 [FREE Full text] [doi: 10.1186/s13104-021-05446-6] [Medline: 33478564]
44. Jones C, Moyle W. A feasibility study of Dreampad™ on sleep, wandering and agitated behaviors in people living with dementia. Geriatr Nurs 2020;41(6):782-789. [doi: 10.1016/j.gerinurse.2020.04.014] [Medline: 32522427]
45. Black BS, Taylor H, Rabins PV, Karlawish J. Researchers' perspectives on the role of study partners in dementia research. Int Psychogeriatr 2014;26(10):1649-1657 [FREE Full text] [doi: 10.1017/S1041610214001203] [Medline: 24990196]
46. Denny A, Bartley K, Edwards S, Webbe F, LoGalbo A. AD8 patient-informant discrepancy predicts insight and cognitive impairment in Alzheimer's disease. Geriatr Nurs 2021;42(1):262-267. [doi: 10.1016/j.gerinurse.2020.08.009] [Medline: 32891442]
47. Song MJ, Kim JH. Family caregivers of people with dementia have poor sleep quality: a nationwide population-based study. Int J Environ Res Public Health 2021;18(24):13079 [FREE Full text] [doi: 10.3390/ijerph182413079] [Medline: 34948685]
48. Osakwe ZT, Senteio C, Bubu OM, Obioha C, Turner AD, Thawani S, et al. Sleep disturbance and strain among caregivers of persons living with dementia. Front Aging Neurosci 2021;13:734382 [FREE Full text] [doi: 10.3389/fnagi.2021.734382] [Medline: 35185513]
49. Grill JD, Zhou Y, Elashoff D, Karlawish J. Disclosure of amyloid status is not a barrier to recruitment in preclinical Alzheimer's disease clinical trials. Neurobiol Aging 2016;39:147-153 [FREE Full text] [doi: 10.1016/j.neurobiolaging.2015.11.007] [Medline: 26923411]
50. Bosco A, Schneider J, Coleston-Shields DM, Jawahar K, Higgs P, Orrell M. Agency in dementia care: systematic review and meta-ethnography. Int Psychogeriatr 2019;31(5):627-642. [doi: 10.1017/S1041610218001801] [Medline: 30520403]
51. Doyle L, Brady AM, Byrne G. An overview of mixed methods research—revisited. J Res Nurs 2016;21(8):623-635. [doi: 10.1177/1744987116674257]

52. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28(2):193-213. [doi: 10.1016/0165-1781(89)90047-4] [Medline: 2748771]
53. Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. Sleep 1991;14(6):540-545 [FREE Full text] [doi: 10.1093/sleep/14.6.540] [Medline: 1798888]
54. Chung F, Abdullah HR, Liao P. STOP-bang questionnaire: a practical approach to screen for obstructive sleep apnea. Chest 2016;149(3):631-638 [FREE Full text] [doi: 10.1378/chest.15-0903] [Medline: 26378880]
55. Postuma RB, Arnulf I, Hogl B, Iranzo A, Miyamoto T, Dauvilliers Y, et al. A single-question screen for rapid eye movement sleep behavior disorder: a multicenter validation study. Mov Disord 2012;27(7):913-916 [FREE Full text] [doi: 10.1002/mds.25037] [Medline: 22729987]
56. Ghotbi N, Pilz LK, Winnebeck EC, Vetter C, Zerbini G, Lenssen D, et al. The µMCTQ: an ultra-short version of the Munich ChronoType Questionnaire. J Biol Rhythms 2020;35(1):98-110 [FREE Full text] [doi: 10.1177/0748730419886986] [Medline: 31791166]
57. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006;166(10):1092-1097 [FREE Full text] [doi: 10.1001/archinte.166.10.1092] [Medline: 16717171]
58. Kroenke K, Strine TW, Spitzer RL, Williams JBW, Berry JT, Mokdad AH. The PHQ-8 as a measure of current depression in the general population. J Affect Disord 2009;114(1-3):163-173. [doi: 10.1016/j.jad.2008.06.026] [Medline: 18752852]
59. Marin RS, Biedrzycki RC, Firinciogullari S. Reliability and validity of the apathy evaluation scale. Psychiatry Res 1991;38(2):143-162. [doi: 10.1016/0165-1781(91)90040-v] [Medline: 1754629]
60. Carney CE, Buysse DJ, Ancoli-Israel S, Edinger JD, Krystal AD, Lichstein KL, et al. The consensus sleep diary: standardizing prospective sleep self-monitoring. Sleep 2012;35(2):287-302 [FREE Full text] [doi: 10.5665/sleep.1642] [Medline: 22294820]
61. Michie S, van Stralen MM, West R. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. Implement Sci 2011;6:42 [FREE Full text] [doi: 10.1186/1748-5908-6-42] [Medline: 21513547]
62. Proudfoot K. Inductive/deductive hybrid thematic analysis in mixed methods research. J Mix Methods Res 2022;17(3):308-326 [FREE Full text] [doi: 10.1177/15586898221126816]
63. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol 2006;3(2):77-101. [doi: 10.1191/1478088706qp063oa]
64. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol 2008;61(4):344-349 [FREE Full text] [doi: 10.1016/j.jclinepi.2007.11.008] [Medline: 18313558]
65. Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ 2016;355:i5239 [FREE Full text] [doi: 10.1136/bmj.i5239] [Medline: 27777223]
66. Lancaster GA, Thabane L. Guidelines for reporting non-randomised pilot and feasibility studies. Pilot Feasibility Stud 2019;5:114 [FREE Full text] [doi: 10.1186/s40814-019-0499-1] [Medline: 31608150]
67. Blackman J, Butters A, Oliver C, Coulthard E. Sleep measurement in mild cognitive impairment and early dementia: is it time for a rethink? Sleep 2023;46(11):zsad185. [doi: 10.1093/sleep/zsad185] [Medline: 37467353]

Abbreviations

AD: Alzheimer disease
COM-B: Capability Opportunity Motivation-Behavior
CONSORT: Consolidated Standards of Reporting Trials
EEG: electroencephalography
LBD: Lewy body disease
MCI: mild cognitive impairment
MoCA: Montreal Cognitive Assessment
NHS: National Health Service
OSA: obstructive sleep apnea
PSG: polysomnography
REM: rapid eye movement
RESTED: Remote Evaluation of Sleep to Enhance Understanding of Early Dementia
STOP: Snoring Tiredness Observed Pressure
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

Edited by A Mavragani; submitted 19.09.23; peer-reviewed by O Grau-Rivera, TAR Sure; comments to author 01.02.24; revised version received 12.02.24; accepted 13.02.24; published 22.03.24.

Please cite as:
Gabb VG, Blackman J, Morrison HD, Biswas B, Li H, Turner N, Russell GM, Greenwood R, Jolly A, Trender W, Hampshire A, Whone A, Coulthard E
Remote Evaluation of Sleep and Circadian Rhythms in Older Adults With Mild Cognitive Impairment and Dementia: Protocol for a Feasibility and Acceptability Mixed Methods Study
JMIR Res Protoc 2024;13:e52652
URL: https://www.researchprotocols.org/2024/1/e52652
doi:10.2196/52652
PMID:38517469

Protocol

Benchmarking Mental Health Status Using Passive Sensor Data: Protocol for a Prospective Observational Study

Robyn E Kilshaw[1], MS; Abigail Boggins[1], BA; Olivia Everett[1]; Emma Butner[1], BS; Feea R Leifker[1], MPH, PhD; Brian R W Baucom[1], PhD

Department of Psychology, University of Utah, Salt Lake City, UT, United States

Corresponding Author:
Robyn E Kilshaw, MS
Department of Psychology
University of Utah
380 S 1530 E BEH S 502
Salt Lake City, UT, 84112
United States
Phone: 1 (801) 581 6124
Fax: 1 (801) 581 5841
Email: robyn.kilshaw@psych.utah.edu

Abstract

Background: Computational psychiatry has the potential to advance the diagnosis, mechanistic understanding, and treatment of mental health conditions. Promising results from clinical samples have led to calls to extend these methods to mental health risk assessment in the general public; however, data typically used with clinical samples are neither available nor scalable for research in the general population. Digital phenotyping addresses this by capitalizing on the multimodal and widely available data created by sensors embedded in personal digital devices (eg, smartphones) and is a promising approach to extending computational psychiatry methods to improve mental health risk assessment in the general population.

Objective: Building on recommendations from existing computational psychiatry and digital phenotyping work, we aim to create the first computational psychiatry data set that is tailored to studying mental health risk in the general population; includes multimodal, sensor-based behavioral features; and is designed to be widely shared across academia, industry, and government using gold standard methods for privacy, confidentiality, and data integrity.

Methods: We are using a stratified, random sampling design with 2 crossed factors (difficulties with emotion regulation and perceived life stress) to recruit a sample of 400 community-dwelling adults balanced across high- and low-risk for episodic mental health conditions. Participants first complete self-report questionnaires assessing current and lifetime psychiatric and medical diagnoses and treatment, and current psychosocial functioning. Participants then complete a 7-day in situ data collection phase that includes providing daily audio recordings, passive sensor data collected from smartphones, self-reports of daily mood and significant events, and a verbal description of the significant daily events during a nightly phone call. Participants complete the same baseline questionnaires 6 and 12 months after this phase. Self-report questionnaires will be scored using standard methods. Raw audio and passive sensor data will be processed to create a suite of daily summary features (eg, time spent at home).

Results: Data collection began in June 2022 and is expected to conclude by July 2024. To date, 310 participants have consented to the study; 149 have completed the baseline questionnaire and 7-day intensive data collection phase; and 61 and 31 have completed the 6- and 12-month follow-up questionnaires, respectively. Once completed, the proposed data set will be made available to academic researchers, industry, and the government using a stepped approach to maximize data privacy.

Conclusions: This data set is designed as a complementary approach to current computational psychiatry and digital phenotyping research, with the goal of advancing mental health risk assessment within the general population. This data set aims to support the field's move away from siloed research laboratories collecting proprietary data and toward interdisciplinary collaborations that incorporate clinical, technical, and quantitative expertise at all stages of the research process.

International Registered Report Identifier (IRRID): DERR1-10.2196/53857

(JMIR Res Protoc 2024;13:e53857) doi:10.2196/53857

KEYWORDS

audio data; computational psychiatry; data repository; digital phenotyping; machine learning; passive sensor data

Introduction

Background

Modern mental health care is the product of a tremendous volume of basic and applied research. Until recently, the majority of this research has relied on methods and practices (eg, randomized controlled trials [1]) that require large amounts of human labor to recruit participants (eg, through in-person recruitment at clinics or calls to members of research registries) and collect the necessary data (eg, through clinical interviews, performance-based tasks, or manual extraction from eHealth records). These methods and practices also tend to generate siloed data sets that are difficult to share beyond the original study team (see [2] for a review). Though existing research using these methods and practices has produced very valuable findings and greatly improved treatment options for individuals coping with mental health challenges, the pace of development is slow [3], and recent estimates suggest that only 40% to 50% of Americans who need mental health care receive treatment [4]. Novel approaches to mental health research are needed to address these challenges, and recent advances in computational analysis and digital technology have the potential to do just that (see [5-7] for reviews).

Computational psychiatry is an approach that includes both theory- and data-driven applications of mathematical modeling with the goal of advancing the diagnosis, mechanistic understanding, and treatment of mental health conditions [8-10]. For example, on the theory-driven side, reinforcement-learning models applied to functional magnetic resonance imaging data have helped predict posttreatment outcomes (ie, abstinence vs relapse) in patients with alcohol dependence [11], and Bayesian models of cognitive task performance have improved our understanding of how the ability to flexibly update previous beliefs differs between diagnoses (see [12] for a review). Similarly, data-driven studies using machine learning models with high-dimensional data (eg, electroencephalogram and magnetic resonance imaging data) have been able to accurately distinguish patients with schizophrenia from controls [13,14] and have also identified multivariate "biomarkers" that have helped improve pharmacological treatment-response prediction in patients with depression [15-17].

Enthusiasm about this body of work has led to numerous calls to extend these methods to mental health risk assessment in the general public [18-20]. However, one of the largest barriers to doing so is that many of the data sources used in computational psychiatry research with clinical samples (eg, brain imagery data and standardized task performance data) are not available for community-dwelling individuals in the general population. As a result, researchers are increasingly leveraging the near ubiquity of personal digital devices (PDDs) [21] (eg, smartphones and smartwatches) as a more scalable and accessible means of collecting high-dimensional behavioral, contextual, and even physiological data streams from individuals [22,23]. Research of this type represents a subset of the broader computational psychiatry field commonly referred to as digital phenotyping.

Digital phenotyping refers to using quantitative methods with PDD data—particularly passive sensor data (eg, GPS, accelerometry, call and text logs, and app usage)—to identify behavioral phenotypes or "digital biomarkers" relevant to mental health [24-26]. Thus far, digital phenotyping research has primarily focused on using computational methods such as machine learning models for detecting, monitoring, and predicting changes in symptom severity as well as predicting or improving treatment response in clinical samples (for reviews, see [27-29]). For example, machine learning algorithms applied to passive sensor data have been able to successfully identify depressive and manic episodes in individuals with bipolar disorder [30,31] and predict psychotic relapses in patients with schizophrenia [32]. Furthermore, digital biomarkers derived from PDD data have demonstrated reasonable accuracy for predicting treatment response to transcranial magnetic stimulation in patients with depression [33]. Finally, a growing body of research demonstrates that passive sensor data from PDDs can also be used to identify common risk factors for mental health conditions (eg, stress, depressed mood, and anxiety) in clinical [34] and student samples [35].

This nascent body of research provides an empirical and methodological foundation for extending digital phenotyping to identify markers of mental health risk in the general population. While, to the best of our knowledge, no studies have done this using a prospective study design with community-dwelling adults, existing computational psychiatry and digital phenotyping research, along with guidance from leading advocates in these fields, provides a strong set of recommendations for generating a data set that is well-suited to this objective. These recommendations include: (1) using a transdiagnostic and dynamic understanding of mental health to guide study design and data collection [20,36]; (2) incorporating the data requirements of cutting-edge computational methods into data collection methods [37,38]; and (3) using careful consent procedures and data curation methods to ensure that data can be safely and ethically shared with researchers across academia, industry, and government so as to harness the expertise of diverse professionals working toward improving mental health [39].

Objectives

On the National Institute of Mental Health Data Archive [40], there currently exists a small number of shareable computational psychiatry data sets that include longitudinal PDD data from community-dwelling participants [41,42], while other such data sets are in the process of being created [43,44]. Nevertheless, all of these data sets comprise participants who either meet specific diagnostic criteria (eg, trauma exposure [42], diagnosis with a serious mental illness [43], and binge drinking [44]) or developmental characteristics (eg, school-attending adolescents) and are best suited for identifying digital biomarkers of mental health risk in clearly defined subsamples of the population.

Therefore, as a complement to this existing work, we aim to create the first computational psychiatry data set that is tailored to studying mental health risk in the adult general population, includes PDD sensor-based behavioral features, and is designed to be widely shared across academia, industry, and government using gold standard guidelines for privacy, confidentiality, and data integrity.

To maximize the relevance and use of this data set for researchers from a wide array of disciplines, we will use the guidelines listed above to ensure our proposed data set is optimized for both mental health and computational considerations. On the mental health side, our proposed data set will be informed by state-of-the-art etiological and phenomenological models of mental health and mental health disorders. On the computational side, our proposed methods are designed to generate a high-dimensional, multimodal, and multirate feature set with maximum variability across levels of measurement and analysis, a balanced classification design, and minimal missing data [22,38]. These considerations will therefore support the primary objective of this project, which is to create a data set that, through its design and accessibility, has the potential to advance mental health risk assessment in the general population using digital phenotyping methods. Although we do not have specific hypotheses or analytic plans guiding the creation of this data set, we believe that in combination with computational methods, the data we collect could be used to investigate research questions such as the following: can PDD sensor-based features predict the likelihood of a future mental health event (eg, receiving a psychiatric diagnosis or treatment) at rates significantly above chance? and does incorporating information about preexisting vulnerability factors (eg, difficulties with emotion regulation and past mental health conditions) improve the accuracy of these predictions?

Methods

Participants

We are recruiting 400 individuals at varying levels of risk for a lifetime incidence of experiencing an episodic mental health disorder (eg, depression, anxiety, and adjustment disorder). To achieve this goal, we are using a stratified, random sampling design with 2 crossed factors: (1) difficulties with emotion regulation [45], a transdiagnostic risk factor for a wide range of mental health conditions [46], and (2) perceived overall life stress during the past 30 days [47]. These 2 factors are assessed during screening, and eligible individuals will be included in the sample such that 40% to 60% of participants report higher than average difficulties regulating strong emotions and 40% to 60% report currently experiencing significant life stress. This sampling design and the choice of these 2 factors were guided by the diathesis-stress model of psychopathology, which suggests that many episodic (ie, non-neurodevelopmental [48]) psychological disorders are the result of an interaction between preexisting vulnerabilities—in this case, difficulties with emotion regulation—and stress due to life experiences [49]. Participants must also meet the following eligibility criteria: be 18 years of age or older, currently living in Utah, have a smartphone with an active cellular data plan and an Apple or Android operating system, be able to speak and read English fluently, and receive their health care through either the University of Utah Health (UHealth) or Intermountain Health Care (IMHC) systems.

Individuals who report suicidal ideation in the past 3 months or any history of a suicide attempt, active mania, or psychosis (ie, severe mental health problems potentially requiring hospitalization during their participation) during screening are ineligible to participate. Initially, individuals who reported current symptoms of a substance use disorder (eg, daily binge drinking) and were not engaged in substance use treatment were also ineligible for participation; however, we received additional funding after beginning the study that allowed us to increase the study staffing so that we could remove this exclusion criterion. This change to the exclusion criteria occurred approximately 6 months into recruitment, after 180 participants—almost half of our target sample size of 400—had provided consent. Finally, individuals with a history of conviction for a violent crime; a history of child abuse or neglect perpetration substantiated by child protective services; and, for individuals in committed relationships, recent physical intimate partner violence are also excluded for potential ethical reasons. Specifically, licensed mental health providers and physicians are legally required to report instances of each of these final criteria to authorities in most states in the United States, and this duty is not waived by a certificate of confidentiality. The presence of these events would therefore render the data set unshareable for most purposes.

Procedures

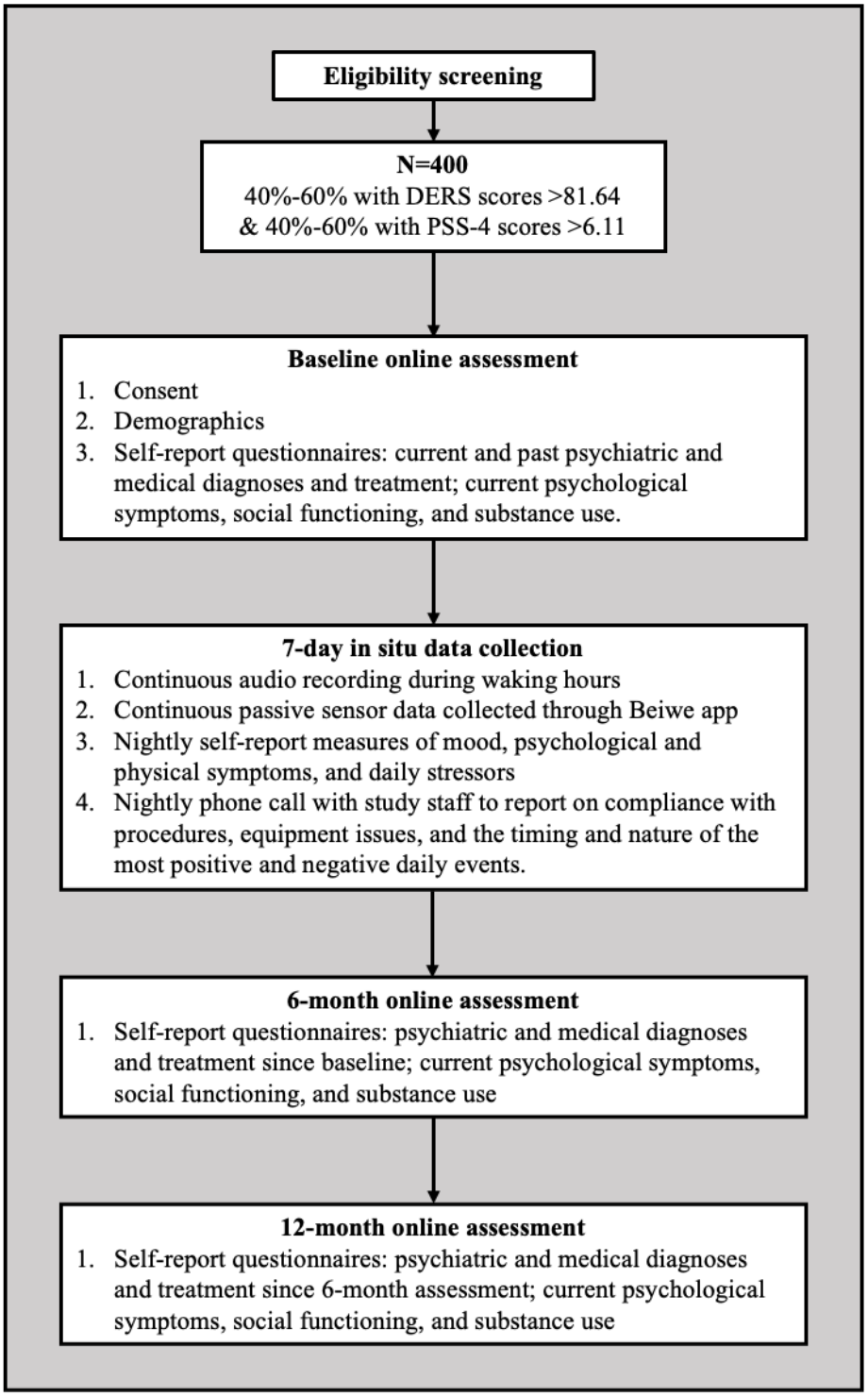
Participants are recruited using web-based advertising through the University of Utah websites, social media websites, and listserves, as well as paper fliers posted throughout the Salt Lake City area. Interested participants complete a web-based screening survey to determine eligibility. Eligible participants are then forwarded to an electronic consent form, and consenting participants complete another web-based battery of questionnaires to assess current and lifetime psychiatric and medical diagnosis and treatment, current psychological symptoms and social functioning, and demographic variables. Participants who complete this baseline battery are compensated US $25 and are scheduled for a videoconference call during which study staff instructs them on how to use the study equipment (ie, audio recorder) that is mailed to them.

Following this call, participants begin a continuous 7-day period of intensive data collection that includes wearing the audio recorder during waking hours, providing raw sensor data collected through a smartphone app (Beiwe [50]), completing a brief survey to assess mood and important events at the end of each day, and responding to a brief phone call from study staff every evening. During this phone call, study staff assess compliance with study procedures, ask participants to describe the most positive and negative events from that day, and inquire whether there is any period of the recording from that day that they wish to delete. Providing participants the opportunity to review the contents of their recordings is necessary to meet ethical standards for long-term, ambulatory data collection [51]. After returning the audio recorder, participants are compensated

US $10 and US $4.28 for every day that they provided raw sensor (PDD) data and audio recording, respectively.

Participants also complete web-based questionnaires 6 and 12 months after the 7-day intensive data collection phase to reassess current psychological symptoms and social functioning, as well as psychiatric and medical diagnosis and treatment during the intervening time; they are compensated US $20 for the completion of each of these questionnaires. See Figure 1 for the complete procedure flow diagram. All of these procedures are described in more depth below.

Figure 1. Procedures flowchart. DERS: Difficulties with Emotion Regulation Scale; PSS-4: Perceived Stress Scale-4.



Data Privacy and Confidentiality

To maximize data privacy and security, data from all sources are encoded and can only be matched using a key maintained in a password-protected file only accessible to approved study personnel. Study data collected from the Beiwe app are encrypted in transit and at rest, and no identifiable data are stored on participants' devices. For complete details on all the security features of the Beiwe research platform, see [52]. Audio files are saved to a microSD card and returned with the recorders through registered mail. All digital data, both in raw and processed formats, are stored in a Health Insurance Portability and Accountability Act (HIPAA)–compliant protected environment maintained by the University of Utah Center for High-Performance Computing.

Data Sources

Self-Report Questionnaires

Participants are given the option to skip any self-report questionnaire item. See [53] for full versions of all publicly available standardized measures as well as any nonstandardized questionnaires included in this study (ie, demographics questionnaire, clinical history questionnaire, and daily events questionnaire).

Difficulties With Emotion Regulation Scale

The Difficulties with Emotion Regulation Scale (DERS) [45] is a well validated and widely used measure of subjective emotion regulation ability [54]. A total of 36 items are responded to on a 5-point Likert scale (from 1="almost never [0%-10%]" to 5="almost always [91%-100%]"; range of scores 36-180), such that higher total scores indicate greater difficulty regulating in the context of strong emotions. Overall, 6 subscale scores can also be generated, capturing individuals' lack of emotional awareness, lack of emotional clarity, nonacceptance of emotions, limited access to emotional regulation strategies, and difficulties engaging in goal-directed behavior or inhibiting impulsive responses in the context of strong emotions. The DERS is administered as part of the screening survey and is only presented to individuals who have already met all other inclusion and exclusion criteria. The mean total DERS score from a community sample [55] is used to classify participants as having high (ie, total score >81.64) versus low (ie, total score ≤81.64) difficulties with emotion regulation for enrollment purposes.

Perceived Stress Scale-4

The Perceived Stress Scale-4 (PSS-4) [47] is a 4-item short form of the widely used Perceived Stress Scale, which measures individuals' subjective level of life stress during the previous month. The PSS-4 displays acceptable psychometric properties in nonclinical populations [47,56] and is used to assess how unpredictable and overwhelming individuals currently find their lives. Items are responded to on a 5-point scale anchored by 0 (never) and 4 (very often), and higher total scores indicate greater perceived stress (range of scores 0-16). The PSS-4 is only presented to eligible participants as part of the screening survey. The mean total score from a validation sample of community participants [56] is used to identify participants experiencing high (ie, total score >6.11) versus low (ie, total score ≤6.11) life stress for enrollment purposes.

Demographics Questionnaire

As part of the baseline battery, participants are asked to report on a number of demographic factors, including age, biological sex, gender, sexuality, relationship status, race, ethnicity, spoken languages, religion, education history, and current employment and income.

Clinical History Questionnaire

Participants are asked to provide information about their current and past physical and mental health, including smoking status; history of a major medical event (eg, cancer, diabetes, or stroke); current and past psychiatric diagnoses; current and past use of psychiatric medication; or other mental health treatment, including when and what service or medication was used. This questionnaire was created for this study and is included in the baseline battery as well as the 6- and 12-month follow-up questionnaires as a way of assessing any significant physical or mental health changes during the study period.

Depression, Anxiety, and Stress Scale-21

The Depression, Anxiety, and Stress Scale-21 (DASS-21) [57] is a 21-item questionnaire designed to measure depression, anxiety, and tension or stress during the past week. It is a short form of the widely used and well-validated original DASS-42 [58]. Individuals respond to items on a 4-point Likert scale from 0 (did not apply to me at all) to 3 (applied to me very much or most of the time), and 3 subscale scores are produced corresponding with the 3 negative emotional states. The DASS-21 is administered at baseline as well as at the 6- and 12-month time points.

Tobacco, Alcohol, Prescription Medications, and Other Substance Tool

The Tobacco, Alcohol, Prescription Medications, and Other Substance (TAPS) [59] tool is a 2-part measure of substance use. In the first part, individuals respond to 4 items assessing how frequently (ranging from "never" to "daily or almost daily") they have used tobacco, alcohol, illicit drugs, or prescription drugs for nonmedical reasons in the past year. Any individual who screens positive in part 1 (ie, responds with anything other than "never") then completes part 2, which consists of a brief assessment of use-related behaviors during the past 3 months. Scores from part 2 can be used to generate 3 levels of risk for each substance endorsed (ie, no use in the past 3 months, problem use, and higher risk). The TAPS tool has demonstrated adequate psychometric properties as a screening measure for high-risk substance use behaviors in adult primary care patients [59]. We are including a measure of substance use in our data set because this is a well-established, transdiagnostic behavioral marker of risk, and in combination with our affective marker of risk (ie, difficulty regulating emotions), it will improve the precision of risk estimation [60]. This measure is administered at baseline as well as at the 6- and 12-month time points.

Life Functioning Questionnaire

The Life Functioning Questionnaire (LFQ) [61] is a 2-part questionnaire designed to assess individuals' subjective difficulty functioning in 4 domains of life (leisure time with friends, leisure time with family, duties at work or school, and

duties at home) during the past month. In part 1 of the LFQ, individuals indicate the degree of problems (from 1 [no problems] to 4 [severe problems]) they have experienced within each domain in terms of the amount of time spent on related activities, amount of conflict experienced, level of enjoyment, and self-assessed performance (for work and home duties only). For duties in the work or school domain, individuals are also asked to indicate the number of days they were absent as well as the factors that contributed to their absence (eg, mental or physical health symptoms and interpersonal difficulties). Part 2 asks additional questions about individuals' work situation during the previous month, previous full-time work, and reasons for leaving, as well as their living and financial status in the past 6 months. The LFQ was originally designed to assess functional capacity in psychiatric patients and has demonstrated adequate psychometric properties with adult inpatients seeking treatment for mood disorders [61]. In this study, the LFQ is administered at baseline and at the 6- and 12-month time points.

Brief Symptom Inventory-18

The Brief Symptom Inventory-18 (BSI-18) [62] is an 18-item measure that assesses the level of distress a person has experienced in the past day due to various psychological (eg, feelings of worthlessness) and physical (eg, pains in the heart or chest) symptoms. Questions are responded to on a 5-point scale from 0 (not at all) to 4 (extremely) and can be summed to produce 3 subscale scores (depression, anxiety, and somatization) as well as a global severity index that measures overall psychological distress. The BSI-18 has been validated and normed with community samples and is acceptable to use repeatedly as a measure of symptom change [63]. The BSI-18 is administered nightly during the 7-day intensive data collection phase of this study.

Daily Positive and Negative Mood Questionnaire

Aspects of participants' daily mood are assessed using a version of the Positive and Negative Affect Schedule [64] described by Smyth et al [65]. Participants rate their current level of 4 positive and 5 negative mood adjectives on a 7-point scale anchored by 0 (not at all) and 6 (extremely). Items are summed to produce positive and negative mood subscales that demonstrated acceptable psychometric properties in a previous sample of community participants [65]. This measure is administered nightly during the 7-day intensive data collection phase of this study.

Daily Events Questionnaire

The Daily Events Questionnaire asks individuals to select from a list of common daily stressors (eg, a lot of work at school or work or a financial problem) and people (eg, a friend or spouse) to assess if any troublesome events happened to them since they woke up that morning, as well as if they experienced any tension or arguments with anyone. Individuals can select as many options as apply and have the option to describe any "other" event or relationship not listed. For each selected event, individuals are then asked to indicate approximately when this event occurred and how distressed they felt during the event, from 1 (not at all) to 10 (very much). Similarly, for each person that a participant indicates they had an argument with, they are asked to provide approximately when the argument began and ended, as well as how distressed they felt and how satisfied they felt with the outcome of the event (using the same 10-point response scale). This measure has been used previously to successfully identify the approximate timing of various distressing events throughout the day [66]. In this study, it is administered nightly during the 7-day intensive data collection phase of this study.

Daily Call With Study Staff

Study staff calls participants each evening near the end of the day (ie, between 6 PM and 8 PM) to inquire about compliance with study procedures, problems with study equipment, and the nature and timing of participants' most positive and negative events of the day. A transcript of the semistructured interview questions used during these phone calls is available on our Open Science Foundation site [53].

Audio Data

In situ audio is continuously recorded while participants are awake at 24-bit/48 kHz using omnidirectional Lavalier microphones connected to miniature field recorders. Recordings are segmented into smaller, 15-minute-long files to optimize data transfer and increase data processing efficiency.

We have carefully considered legal and ethical issues in proposing these in situ recordings. Audio recordings are governed by wiretapping laws, which vary from state to state. Utah is a single-party consent state, meaning that as long as a study participant consents to be recorded, other individuals captured on those recordings do not need to additionally consent. However, the ethical principles of beneficence, nonmaleficence, autonomy, and justice require that other individuals who may be recorded need to be aware of that possibility and given the opportunity to not be recorded. For these reasons, participants are instructed to wear a badge that states that they are participating in a study that records audio during daily life and will be allowed to pause the recording whenever an individual they come into contact with requests that they do so, or the participant wishes or is required to do so by policy or law [51]. We have used these methods in previous work, and they typically generate 10 to 14 hours of audio per day.

Passive Sensor Data

Raw smartphone sensor data are collected using Beiwe, a cross-platform digital phenotyping app created by Onnela and colleagues [25,50]. The Beiwe platform collects raw data generated by smartphone sensors, including, but not limited to, GPS and accelerometry, Wi-Fi connectivity, Bluetooth device scans, phone and screen status, and phone call and SMS text message event logs linked to onboard device contacts. The specific data collected for a participant is determined by the sensors on their smartphone and the policies of the smartphone manufacturer [52].

Medical Records

The state of Utah maintains the Utah Population Database (UPDB) and All Payer Claims Database, which are standardized (ie, use the Systemized Nomenclature of Medicine–Clinical Terms), digital archives of medical encounters in the UHealth

and IMHC systems, and insurance claims filed in the state, respectively. These databases are generated for research purposes and will be used to verify and augment participant reports. These databases represent a highly unique and valuable opportunity because it is well documented that retrospective reports of psychiatric history incorrectly fail to identify ~25% to 40% of true positives relative to medical records [67]. Relevant records from these databases will be linked to other participant data. UPDB policy dictates that these records will not be shareable, and individuals or entities wishing to access them will have to seek permission directly from the database administrators.

Planned Data Processing

Raw item responses as well as relevant total and subscale scores from the self-report questionnaires will be created using standard scoring protocols and included for all self-report measures in the final data set. In addition to raw DERS scores, age- and gender-adjusted *t*-scores computed using the methods in [55] will be included in the final data set. Annotations of participants' most positive and negative daily events will also be available in the data set. To create these, study staff will use the information provided by participants during the daily phone calls to annotate details about their most positive and negative event for each day, including the beginning and end time of the event, and the type (eg, interaction with another person or financial problem) and nature of the event (eg, positive vs negative). Study staff will additionally annotate speaker IDs (eg, participant and female 1), emotional expressions, and communication behaviors (eg, arguing or cooperating) using information from the corresponding recorded audio.

Audio recordings will be processed to generate gold-standard acoustic feature sets used in behavioral signal processing [68] and affective computing [69] research using the openSMILE toolkit [70]. These methods produce 88 acoustic variables that represent frequency-, energy-, and spectral-related aspects of speech and ambient noise. Acoustic variables will be generated over the smallest window of time possible for each variable and downsampled to produce a summary score for each acoustic variable for each 1 second of the recording.

Raw PDD sensor data will be processed using Forest [71], a freely available library for analyzing Beiwe data developed by the creators of Beiwe. Similar to the acoustic variables described above, Forest produces summary variables for each sensor type that quantify a wide range of behavioral and contextual information. For example, outputs of GPS data include time spent at home, total distance traveled, physical circadian rhythm, and the type (eg, shop, restaurant, and place of worship) and duration of locations visited. The location type is generated using information from the open-source platform OpenStreetMap [72] and is particularly valuable for the current data set as it will allow for the creation of a library of geographically referenced place tags that index risky (eg, amenity=bar; amenity=tobacco retailer) and protective (eg, amenity=library; amenity=gym) locations and will increase the potential information value of the database by providing additional context for the passive sensor data streams collected. Another example of the summary features available from Forest includes outputs of call and text logs, the total number of calls received, the total number of unique callers, and the total duration of calls received. Additional details about all summary variables are available on the Forest GitHub page [71]. Summary variables will be generated for each day and included in our final data set.

Ethical Considerations

All study procedures were approved by the University of Utah Institutional Review Board (00149365). Eligible participants are given the opportunity to review all study procedures, including planned data-sharing processes, and are provided with contact information for the study's principal investigator to answer any additional questions before signing the consent form on the internet. Several measures are in place to protect the privacy and confidentiality of participants' data (see *Data Privacy and Confidentiality* and *Results* sections for additional details). These include using a secure and password-protected database for storing all study data, only sharing deidentified and nonsensitive data publicly, and requiring a more stringent data use agreement and relevant ethics approval to be provided by individuals requesting access to identifiable data sources (eg, raw audio data). All participants are offered US $165 as compensation for completing all study procedures.

Results

Data collection for this project began in June 2022 and is expected to conclude by July 2024. To date, 310 participants have consented to the study; 149 have completed the baseline questionnaire and 7-day intensive data collection phase; and 61 (ie, 85% of eligible participants) and 31 (ie, 91% of eligible participants) have completed the 6- and 12-month follow-up questionnaires, respectively.

Once completed, the proposed data set will be made available consistent with the findable, accessible, interoperable, and reusable guidelines for data management and stewardship [73]. We will publish a description of the data set in a general science outlet with a broad readership to increase awareness of it among a broad audience. We will also index the data set on recommended data banks, such as the Open Science Foundation and Science Data Bank [74] to increase its findability.

We will use a stepped approach to making the data set accessible to academic researchers, industry, and government. Deidentified, nonsensitive data (eg, raw item and scale scores from self-report measures, summary features from acoustic and passive sensor data, and annotations of daily events) will be publicly available for download directly from data repositories after completion of a brief data use agreement but without contact with the study team. Identifiable and other sensitive data (eg, raw audio recordings and raw passive sensor data) will only be made available for download from a University of Utah server after researchers have provided evidence of the necessary approvals from their institutional review board or comparable entity, completed a more stringent data use agreement, and have communicated with a member of the study team. Data will be made available to academic and government researchers at no cost and licensed to commercial entities.

Discussion

Contributions

Computational psychiatry and digital phenotyping have the potential to make significant contributions to mental health research and treatment development. Digital phenotyping studies have already demonstrated that by applying machine learning techniques to PDD data, it may be possible to predict upcoming mental health events (eg, manic episodes and hospitalization) in clinical samples [32] and detect mental health risk factors (eg, increasing stress and depressed mood) in students [35]. These findings are paving the way for a future where digital markers of increased risk could be used to trigger just-in-time interventions that connect individuals with their mental health care team when they need support most and before their symptoms worsen [75]. Similarly, ongoing computational psychiatry work aims to improve mental health treatment by using machine learning to identify the precise cognitive and neurobiological mechanisms underlying psychiatric disorders and their symptoms [76]. These findings may then be used to gain a better understanding of which treatments work best for which patients at what time.

Whereas much of this existing work focuses on predicting and treating mental health symptoms in individuals who meet certain diagnostic criteria or have received treatment for a psychiatric diagnosis, we are proposing a data set that is designed to advance the field's ability to identify community-dwelling members of the adult general population at risk for a future mental health event. This is a complementary approach to current computational psychiatry and digital phenotyping research and has the potential to improve mental health risk assessment within the general population. The proposed data set possesses several strengths that make it well suited for this goal. First, in response to numerous calls for more theory-driven digital phenotyping studies [20], both the sample we are recruiting and the data we are collecting are guided by a well-established, transdiagnostic model of psychopathology development—the diathesis-stress model [49]. Second, instead of focusing on stable individual differences or 1-time measures of risk, the proposed data set will include multimodal data collected across multiple time scales and levels of analysis. By including digital traces of behavior that can be linked to both time and context, the proposed data set will therefore allow for the identification of features that better capture the dynamic nature of mental health risk [36,37]. Third, by using the Beiwe platform to collect raw PDD data, future analyses will not be limited by inconsistencies in the algorithms used to derive summary statistics or features from different devices [22]. Similarly, including raw PDD data in this data set means that not only is it designed to support current computational techniques, but it will continue to be relevant for future quantitative developments. Finally, the shareable nature of this data set will encourage interdisciplinary collaboration and ideally maximize the rate, rigor, and accuracy of the predictive machine learning models that are developed from it.

Limitations

Although the proposed data set possesses many strengths, there are also some limitations to acknowledge. First, the types of digital data included in this data set are limited to what is available through the Beiwe platform [52]. Although it is possible that other passive data streams (eg, app usage log) may carry digital traces of participants' behaviors that are informative for mental health prediction, our decision to use only what is available from Beiwe was guided by the desire to prioritize participant privacy and the shareability of the data set, which are 2 features supported by the design and maintenance of Beiwe. Second, some of the data sources captured by Beiwe are not consistent across Apple and Android devices due to variability in the sensors installed on different devices and the policies of different smartphone manufacturers (eg, call and SMS text message logs are only available on Android devices [52]). This may limit some of the analyses that can be performed and features that can be developed if certain data sources are only available from a small subset of the total sample. Third, our decision to exclude participants with suicidal thoughts and behaviors or other persistent and severe mental health conditions (ie, active mania or psychosis) means that the predictive models arising from this data set will not be optimized for identifying an increase in risk for the mental health events associated with these conditions (eg, inpatient hospitalization). However, such events are less likely in the general population and are not the primary outcome of interest for the proposed data set.

Conclusions

Computational psychiatry and digital phenotyping have been lauded as pillars of the next great revolution in mental health care [7,8,39]. The past 2 decades have seen a dramatic increase in the number of mental health studies using these methodologies with PDD data. Furthermore, rapid developments in digital technology and quantitative analysis suggest that the potential benefits of PDD data and computational techniques for mental health research and treatment development are only going to continue to expand. In order to achieve these benefits, it will be important for the field to move away from siloed research laboratories collecting proprietary data and toward interdisciplinary collaborations that use clinical, technical, and quantitative expertise to produce widely applicable and shareable data sets.

Acknowledgments

REK conceptualized and designed the study, led data collection, and drafted the manuscript. AB, OE, and EB assisted with data collection and provided feedback and edits for the manuscript. FRL provided clinical oversight for the study and feedback and edits for the manuscript. BRWB conceptualized and designed the study and provided feedback and edits on the manuscript.

REK was supported, in part, by funding from the Social Sciences and Humanities Research Council of Canada.

Data Availability

Upon completion of this study, the data sets generated and analyzed during this study will be available in a widely accessible data repository.

Conflicts of Interest

None declared.

References

1. Bickman L. Improving mental health services: a 50-year journey from randomized experiments to artificial intelligence and precision mental health. Adm Policy Ment Health 2020;47(5):795-843 [FREE Full text] [doi: 10.1007/s10488-020-01065-8] [Medline: 32715427]
2. Tackett JL, Brandes CM, King KM, Markon KE. Psychology's replication crisis and clinical psychological science. Annu Rev Clin Psychol 2019;15:579-604 [FREE Full text] [doi: 10.1146/annurev-clinpsy-050718-095710] [Medline: 30673512]
3. Morris ZS, Wooding S, Grant J. The answer is 17 years, what is the question: understanding time lags in translational research. J R Soc Med 2011;104(12):510-520 [FREE Full text] [doi: 10.1258/jrsm.2011.110180] [Medline: 22179294]
4. Reinert M, Fritze D, Nguyen T. The state of mental health in America 2022. Mental Health America. Alexandria VA; 2021. URL: https://archive.hshsl.umaryland.edu/handle/10713/17070 [accessed 2024-02-28]
5. Bucci S, Schwannauer M, Berry N. The digital revolution and its impact on mental health care. Psychol Psychother 2019;92(2):277-297. [doi: 10.1111/papt.12222] [Medline: 30924316]
6. Montag C, Sindermann C, Baumeister H. Digital phenotyping in psychological and medical sciences: a reflection about necessary prerequisites to reduce harm and increase benefits. Curr Opin Psychol 2020;36:19-24. [doi: 10.1016/j.copsyc.2020.03.013] [Medline: 32361334]
7. Insel TR. Digital phenotyping: technology for a new science of behavior. JAMA 2017;318(13):1215-1216. [doi: 10.1001/jama.2017.11295] [Medline: 28973224]
8. Huys QJM, Maia TV, Frank MJ. Computational psychiatry as a bridge from neuroscience to clinical applications. Nat Neurosci 2016;19(3):404-413 [FREE Full text] [doi: 10.1038/nn.4238] [Medline: 26906507]
9. Maia TV. Introduction to the series on computational psychiatry. Clin Psychol Sci 2015;3(3):374-377. [doi: 10.1177/2167702614567350]
10. Stephan KE, Mathys C. Computational approaches to psychiatry. Curr Opin Neurobiol 2014;25:85-92. [doi: 10.1016/j.conb.2013.12.007] [Medline: 24709605]
11. Garbusow M, Schad DJ, Sebold M, Friedel E, Bernhardt N, Koch SP, et al. Pavlovian-to-instrumental transfer effects in the nucleus accumbens relate to relapse in alcohol dependence. Addict Biol 2016;21(3):719-731. [doi: 10.1111/adb.12243] [Medline: 25828702]
12. Huys QJM, Browning M, Paulus MP, Frank MJ. Advances in the computational understanding of mental illness. Neuropsychopharmacology 2021;46(1):3-19 [FREE Full text] [doi: 10.1038/s41386-020-0746-4] [Medline: 32620005]
13. Silva RF, Castro E, Gupta CN, Cetin M, Arbabshirani M, Potluru VK, et al. The tenth annual MLSP competition: schizophrenia classification challenge. 2014 Presented at: 2014 IEEE International Workshop on Machine Learning for Signal Processing (MLSP); September 21-24, 2014; Reims, France. [doi: 10.1109/mlsp.2014.6958889]
14. Solin A, Särkkä S. The 10th annual MLSP competition: first place. 2014 Presented at: 2014 IEEE International Workshop on Machine Learning for Signal Processing (MLSP); September 21-24, 2014; Reims, France. [doi: 10.1109/mlsp.2014.6958886]
15. Khodayari-Rostamabad A, Reilly JP, Hasey GM, de Bruin H, Maccrimmon DJ. A machine learning approach using EEG data to predict response to SSRI treatment for major depressive disorder. Clin Neurophysiol 2013;124(10):1975-1985. [doi: 10.1016/j.clinph.2013.04.010] [Medline: 23684127]
16. Etkin A, Patenaude B, Song YJC, Usherwood T, Rekshan W, Schatzberg AF, et al. A cognitive-emotional biomarker for predicting remission with antidepressant medications: a report from the iSPOT-D trial. Neuropsychopharmacology 2015;40(6):1332-1342 [FREE Full text] [doi: 10.1038/npp.2014.333] [Medline: 25547711]
17. Korgaonkar MS, Rekshan W, Gordon E, Rush AJ, Williams LM, Blasey C, et al. Magnetic resonance imaging measures of brain structure to predict antidepressant treatment outcome in major depressive disorder. EBioMedicine 2015;2(1):37-45 [FREE Full text] [doi: 10.1016/j.ebiom.2014.12.002] [Medline: 26137532]
18. Baumgartner R. Precision medicine and digital phenotyping: digital medicine's way from more data to better health. Big Data Soc 2021;8(2):205395172110664 [FREE Full text] [doi: 10.1177/20539517211066452]
19. Onnela JP, Rauch SL. Harnessing smartphone-based digital phenotyping to enhance behavioral and mental health. Neuropsychopharmacology 2016;41(7):1691-1696 [FREE Full text] [doi: 10.1038/npp.2016.7] [Medline: 26818126]
20. Davidson BI. The crossroads of digital phenotyping. Gen Hosp Psychiatry 2022;74:126-132. [doi: 10.1016/j.genhosppsych.2020.11.009] [Medline: 33653612]
21. Perrin A. Mobile technology and home broadband 2021. Pew Research Center. 2021. URL: https://www.pewresearch.org/internet/2021/06/03/mobile-technology-and-home-broadband-2021/ [accessed 2024-01-22]

22. Onnela JP. Opportunities and challenges in the collection and analysis of digital phenotyping data. Neuropsychopharmacology 2021;46(1):45-54 [FREE Full text] [doi: 10.1038/s41386-020-0771-3] [Medline: 32679583]
23. Mohr DC, Zhang M, Schueller SM. Personal sensing: understanding mental health using ubiquitous sensors and machine learning. Annu Rev Clin Psychol 2017;13:23-47 [FREE Full text] [doi: 10.1146/annurev-clinpsy-032816-044949] [Medline: 28375728]
24. Dagum P, Montag C. Ethical considerations of digital phenotyping from the perspective of a healthcare practitioner. In: Montag C, Baumeister H, editors. Digital Phenotyping and Mobile Sensing: New Developments in Psychoinformatics. Cham: Springer Nature; 2019:13-29.
25. Torous J, Kiang MV, Lorme J, Onnela JP. New tools for new research in psychiatry: a scalable and customizable platform to empower data driven smartphone research. JMIR Ment Health 2016;3(2):e16 [FREE Full text] [doi: 10.2196/mental.5165] [Medline: 27150677]
26. Birk RH, Samuel G. Can digital data diagnose mental health problems? a sociological exploration of 'digital phenotyping'. Sociol Health Illn 2020;42(8):1873-1887 [FREE Full text] [doi: 10.1111/1467-9566.13175] [Medline: 32914445]
27. Huckvale K, Venkatesh S, Christensen H. Toward clinical digital phenotyping: a timely opportunity to consider purpose, quality, and safety. NPJ Digit Med 2019;2:88 [FREE Full text] [doi: 10.1038/s41746-019-0166-1] [Medline: 31508498]
28. Dlima SD, Shevade S, Menezes SR, Ganju A. Digital phenotyping in health using machine learning approaches: scoping review. JMIR Bioinform Biotech 2022;3(1):e39618 [FREE Full text] [doi: 10.2196/39618]
29. Moura I, Teles A, Viana D, Marques J, Coutinho L, Silva F. Digital phenotyping of mental health using multimodal sensing of multiple situations of interest: a systematic literature review. J Biomed Inform 2023;138:104278 [FREE Full text] [doi: 10.1016/j.jbi.2022.104278] [Medline: 36586498]
30. Gershon A, Ram N, Johnson SL, Harvey AG, Zeitzer JM. Daily actigraphy profiles distinguish depressive and interepisode states in bipolar disorder. Clin Psychol Sci 2016;4(4):641-650 [FREE Full text] [doi: 10.1177/2167702615604613] [Medline: 27642544]
31. Saeb S, Zhang M, Karr CJ, Schueller SM, Corden ME, Kording KP, et al. Mobile phone sensor correlates of depressive symptom severity in daily-life behavior: an exploratory study. J Med Internet Res 2015;17(7):e175 [FREE Full text] [doi: 10.2196/jmir.4273] [Medline: 26180009]
32. Barnett I, Torous J, Staples P, Sandoval L, Keshavan M, Onnela JP. Relapse prediction in schizophrenia through digital phenotyping: a pilot study. Neuropsychopharmacology 2018;43(8):1660-1666 [FREE Full text] [doi: 10.1038/s41386-018-0030-z] [Medline: 29511333]
33. Kelkar RS, Currey D, Nagendra S, Mehta UM, Sreeraj VS, Torous J, et al. Utility of smartphone-based digital phenotyping biomarkers in assessing treatment response to transcranial magnetic stimulation in depression: proof-of-concept study. JMIR Form Res 2023;7:e40197 [FREE Full text] [doi: 10.2196/40197] [Medline: 37656496]
34. Jacobson NC, Chung YJ. Passive sensing of prediction of moment-to-moment depressed mood among undergraduates with clinical levels of depression sample using smartphones. Sensors (Basel) 2020;20(12):3572 [FREE Full text] [doi: 10.3390/s20123572] [Medline: 32599801]
35. Wang W, Nepal S, Huckins JF, Hernandez L, Vojdanovski V, Mack D, et al. First-gen lens: assessing mental health of first-generation students across their first year at college using mobile sensing. Proc ACM Interact Mob Wearable Ubiquitous Technol 2022;6(2):95 [FREE Full text] [doi: 10.1145/3543194] [Medline: 36561350]
36. Hitchcock PF, Fried EI, Frank MJ. Computational psychiatry needs time and context. Annu Rev Psychol 2022;73:243-270 [FREE Full text] [doi: 10.1146/annurev-psych-021621-124910] [Medline: 34579545]
37. Cohen AS, Cox CR, Masucci MD, Le TP, Cowan T, Coghill LM, et al. Digital phenotyping using multimodal data. Curr Behav Neurosci Rep 2020;7(4):212-220. [doi: 10.1007/s40473-020-00215-4]
38. Rutledge RB, Chekroud AM, Huys QJ. Machine learning and big data in psychiatry: toward clinical applications. Curr Opin Neurobiol 2019;55:152-159. [doi: 10.1016/j.conb.2019.02.006] [Medline: 30999271]
39. Browning M, Carter CS, Chatham C, Den Ouden H, Gillan CM, Baker JT, et al. Realizing the clinical potential of computational psychiatry: report from the Banbury Center meeting, february 2019. Biol Psychiatry 2020;88(2):e5-e10. [doi: 10.1016/j.biopsych.2019.12.026] [Medline: 32113656]
40. NDA data repositories. NIMH Data Archive. URL: https://nda.nih.gov/nda/about-us [accessed 2024-02-07]
41. Garavan H, Bartsch H, Conway K, Decastro A, Goldstein RZ, Heeringa S, et al. Recruiting the ABCD sample: design considerations and procedures. Dev Cogn Neurosci 2018;32:16-22 [FREE Full text] [doi: 10.1016/j.dcn.2018.04.004] [Medline: 29703560]
42. McLean SA, Ressler K, Koenen KC, Neylan T, Germine L, Jovanovic T, et al. The AURORA study: a longitudinal, multimodal library of brain biology and function after traumatic stress exposure. Mol Psychiatry 2020;25(2):283-296 [FREE Full text] [doi: 10.1038/s41380-019-0581-3] [Medline: 31745239]
43. Granholm E. Context-aware mobile intervention for social recovery in serious mental illness. NIMH Data Archive. URL: https://nda.nih.gov/edit_collection.html?id=4216 [accessed 2024-02-07]
44. Chung T. Smartphone sensors to detect shifts toward healthy behavior during alcohol treatment. NIMH Data Archive. URL: https://nda.nih.gov/edit_collection.html?id=4661 [accessed 2024-02-07]

45. Gratz KL, Roemer L. Multidimensional assessment of emotion regulation and dysregulation: development, factor structure, and initial validation of the difficulties in emotion regulation scale. J Psychopathol Behav Assess 2008;30(4):315-315 [FREE Full text] [doi: 10.1007/s10862-008-9102-4]
46. Aldao A, Gee DG, De Los Reyes A, Seager I. Emotion regulation as a transdiagnostic factor in the development of internalizing and externalizing psychopathology: current and future directions. Dev Psychopathol 2016;28(4pt1):927-946. [doi: 10.1017/S0954579416000638] [Medline: 27739387]
47. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav 1983;24(4):385-396. [Medline: 6668417]
48. Neurodevelopmental disorders. In: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, Text Revision (DSM-5-TR). Washington, DC: American Psychiatric Association; 2022.
49. Chaplin TM, Cole PM. The role of emotion regulation in the development of psychopathology. In: Hankin BL, Abela JRZ, editors. Development of Psychopathology: A Vulnerability-Stress Perspective. Thousand Oaks, CA: SAGE Publications, Inc; 2005.
50. Onnela JP, Dixon C, Griffin K, Jaenicke T, Minowada L, Esterkin S, et al. Beiwe: a data collection platform for high-throughput digital phenotyping. J Open Source Softw 2021;6(68):3417 [FREE Full text] [doi: 10.21105/joss.03417]
51. Mehl MR, Robbins M. Naturalistic observation sampling: the electronically activated recorder. In: Handbook of Research Methods for Studying Daily Life. New York, NY: Guilford Press; 2012:176-192.
52. Onnela Lab Contributors. Beiwe documentation. GitHub. URL: https://github.com/onnela-lab/beiwe/wiki [accessed 2023-08-16]
53. Kilshaw RE, Baucom BRW. Benchmarking mental health status using passive sensor data. Open Science Foundation. URL: https://osf.io/sb8yw [accessed 2024-01-26]
54. Hallion LS, Steinman SA, Tolin DF, Diefenbach GJ. Psychometric properties of the Difficulties in Emotion Regulation Scale (DERS) and its short forms in adults with emotional disorders. Front Psychol 2018;9:539 [FREE Full text] [doi: 10.3389/fpsyg.2018.00539] [Medline: 29725312]
55. Giromini L, Ales F, de Campora G, Zennaro A, Pignolo C. Developing age and gender adjusted normative reference values for the Difficulties in Emotion Regulation Scale (DERS). J Psychopathol Behav Assess 2017;39(4):705-714. [doi: 10.1007/s10862-017-9611-0]
56. Warttig SL, Forshaw MJ, South J, White AK. New, normative, english-sample data for the short form Perceived Stress Scale (PSS-4). J Health Psychol 2013;18(12):1617-1628. [doi: 10.1177/1359105313508346] [Medline: 24155195]
57. Henry JD, Crawford JR. The short-form version of the Depression Anxiety Stress Scales (DASS-21): construct validity and normative data in a large non-clinical sample. Br J Clin Psychol 2005;44(Pt 2):227-239. [doi: 10.1348/014466505X29657] [Medline: 16004657]
58. Lovibond SH, Lovibond PF. Manual for the Depression Anxiety Stress Scales, 2nd Edition. Sydney: Psychology Foundation of Australia; 1996.
59. McNeely J, Wu LT, Subramaniam G, Sharma G, Cathers LA, Svikis D, et al. Performance of the Tobacco, Alcohol, Prescription medication, and other Substance use (TAPS) tool for substance use screening in primary care patients. Ann Intern Med 2016;165(10):690-699 [FREE Full text] [doi: 10.7326/M16-0317] [Medline: 27595276]
60. Eaton NR, Rodriguez-Seijas C, Carragher N, Krueger RF. Transdiagnostic factors of psychopathology and substance use disorders: a review. Soc Psychiatry Psychiatr Epidemiol 2015;50(2):171-182. [doi: 10.1007/s00127-014-1001-2] [Medline: 25563838]
61. Altshuler L, Mintz J, Leight K. The Life Functioning Questionnaire (LFQ): a brief, gender-neutral scale assessing functional outcome. Psychiatry Res 2002;112(2):161-182. [doi: 10.1016/s0165-1781(02)00180-4] [Medline: 12429362]
62. Derogatis LR. BSI 18, Brief Symptom Inventory 18: Administration, Scoring and Procedures Manual. Minneapolis, MN: NCS Pearson, Inc; 2001.
63. Derogatis L, Fitzpatrick M. The SCL-90-R, the Brief Symptom Inventory (BSI), and the BSI-18. In: Maruish ME, editor. The Use of Psychological Testing for Treatment Planning and Outcomes Assessment: Volume 3, 3rd Edition. Mahwah, N.J: Lawrence Erlbaum Associates; 2004:1-41.
64. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. J Pers Soc Psychol 1988;54(6):1063-1070. [doi: 10.1037//0022-3514.54.6.1063] [Medline: 3397865]
65. Smyth JM, Zawadzki MJ, Santuzzi AM, Filipkowski KB. Examining the effects of perceived social support on momentary mood and symptom reports in asthma and arthritis patients. Psychol Health 2014;29(7):813-831. [doi: 10.1080/08870446.2014.889139] [Medline: 24568534]
66. Baucom BRW, Baucom KJW, Hogan JN, Crenshaw AO, Bourne SV, Crowell SE, et al. Cardiovascular reactivity during marital conflict in laboratory and naturalistic settings: differential associations with relationship and individual functioning across contexts. Fam Process 2018;57(3):662-678. [doi: 10.1111/famp.12353] [Medline: 29577270]
67. Vieira LS, Nguyen B, Nutley SK, Bertolace L, Ordway A, Simpson H, et al. Self-reporting of psychiatric illness in an online patient registry is a good indicator of the existence of psychiatric illness. J Psychiatr Res 2022;151:34-41 [FREE Full text] [doi: 10.1016/j.jpsychires.2022.03.022] [Medline: 35436704]

68. Narayanan S, Georgiou PG. Behavioral signal processing: deriving human behavioral informatics from speech and language: computational techniques are presented to analyze and model expressed and perceived human behavior-variedly characterized as typical, atypical, distressed, and disordered-from speech and language cues and their applications in health, commerce, education, and beyond. Proc IEEE Inst Electr Electron Eng 2013;101(5):1203-1233 [FREE Full text] [doi: 10.1109/JPROC.2012.2236291] [Medline: 24039277]
69. Eyben F, Scherer KR, Schuller BW, Sundberg J, Andre E, Busso C, et al. The Geneva Minimalistic Acoustic Parameter Set (GeMAPS) for voice research and affective computing. IEEE Trans Affective Comput 2016;7(2):190-202 [FREE Full text] [doi: 10.1109/taffc.2015.2457417]
70. Eyben F, Schuller B. openSMILE:): the Munich open-source large-scale multimedia feature extractor. ACM SIGMultimedia Rec 2015;6(4):4-13. [doi: 10.1145/2729095.2729097]
71. Onnela Lab Contributors. Forest. URL: https://forest.beiwe.org/en/latest/ [accessed 2023-08-16]
72. OpenStreetMap Contributors. Planet OSM. URL: https://planet.openstreetmap.org/ [accessed 2023-08-16]
73. Wilkinson MD, Dumontier M, Aalbersberg IJ, Appleton G, Axton M, Baak A, et al. The FAIR guiding principles for scientific data management and stewardship. Sci Data 2016;3:160018 [FREE Full text] [doi: 10.1038/sdata.2016.18] [Medline: 26978244]
74. Data repository guidance. Nature. URL: https://www.nature.com/sdata/policies/repositories [accessed 2022-05-25]
75. Marsch LA. Opportunities and needs in digital phenotyping. Neuropsychopharmacology 2018;43(8):1637-1638 [FREE Full text] [doi: 10.1038/s41386-018-0051-7] [Medline: 29703995]
76. Gueguen MCM, Schweitzer EM, Konova AB. Computational theory-driven studies of reinforcement learning and decision-making in addiction: what have we learned? Curr Opin Behav Sci 2021;38:40-48 [FREE Full text] [doi: 10.1016/j.cobeha.2020.08.007] [Medline: 34423103]

Abbreviations

BSI-18: Brief Symptom Inventory-18
DASS-21: Depression, Anxiety, and Stress Scale-21
DERS: Difficulties with Emotion Regulation Scale
HIPAA: Health Insurance Portability and Accountability Act
IMHC: Intermountain Health Care
LFQ: Life Functioning Questionnaire
PDD: personal digital device
PSS-4: Perceived Stress Scale-4
TAPS: Tobacco, Alcohol, Prescription medications, and Other Substance
UHealth: University of Utah Health
UPDB: Utah Population Database

Edited by A Mavragani; submitted 21.10.23; peer-reviewed by B Montezano, A Hudon; comments to author 02.12.23; revised version received 27.01.24; accepted 22.02.24; published 27.03.24.

Please cite as:
Kilshaw RE, Boggins A, Everett O, Butner E, Leifker FR, Baucom BRW
Benchmarking Mental Health Status Using Passive Sensor Data: Protocol for a Prospective Observational Study
JMIR Res Protoc 2024;13:e53857
URL: https://www.researchprotocols.org/2024/1/e53857
doi:10.2196/53857
PMID:38536220

Protocol

A Global Health Survey of People Who Vape but Never Smoked: Protocol for the VERITAS (Vaping Effects: Real-World International Surveillance) Study

Jeffrey Zamora Goicoechea[1,2,3], BA; Allison Boughner[4,5], AA; Juan José Cirion Lee[6], LLM; Aman Mahajan, PGD; Kurt Yeo[7,8], HS; Maris Sproga, MA, EMBA; Tasmin Patel[9], BTECH, MBA; Claudio Saitta[10], HS; Christopher Russell[11], PhD; Michael Coughlan[10], MA; Pasquale Caponnetto[12,13], PhD, PsyD; Riccardo Polosa[13,14], MD, PhD

[1]International Network of Nicotine Consumer Organisations, Vejle, Denmark
[2]Asociación de Reducción de Daños del Tabaquismo, Bogota, Colombia
[3]Asociacio´n de usuarios de vaporizadores y me´todos de reduccio´n de dan˜os por tabaquismo de Costa Rica, San José, Costa Rica
[4]American Vapor Manufacturers, Prescott, AZ, United States
[5]South Carolina Vapor Association, Charleston, SC, United States
[6]México y el Mundo Vapeando, Mexico City, Mexico
[7]Vaping Saved My Life, Benoni, Gauteng, South Africa
[8]World Vapers Alliance, Miami, FL, United States
[9]Confidosoft Ltd, Leatherhead, London, United Kingdom
[10]ECLAT Srl, University of Catania, Catania, Italy
[11]Russell Burnett Research and Consultancy Ltd, Glasgow, United Kingdom
[12]Section of Psychology, Department of Science of Education, University of Catania, Catania, Italy
[13]Center of Excellence for the Acceleration of Harm Reduction, University of Catania, Catana, Italy
[14]Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy

Corresponding Author:
Riccardo Polosa, MD, PhD
Center of Excellence for the Acceleration of Harm Reduction
University of Catania
Via Santa Sofia 89
Catana, 95123
Italy
Phone: 39 0954781124
Email: polosa@unict.it

Abstract

Background: There is only limited information about the health effects of regular vaping. Research on the health status of people who used to smoke faces the challenge that previous smoking may have caused unknown health effects. Only studies of people who vape but have never smoked combustible cigarettes can enable the detection of harms attributable to vaping. Large prospective studies of well-characterized electronic cigarette users with and without a history of combustible cigarette smoking are warranted to establish the long-term effects of regular vaping on respiratory health.

Objective: We will conduct a global cross-sectional survey of individuals from 6 world regions. Respiratory symptoms will be assessed using a validated questionnaire—the Respiratory Symptom Experience Scale (RSES). Current vapers who are nonusers of other tobacco or nicotine products will be compared with matched controls who are nonusers of vapes and other tobacco or nicotine products.

Methods: This will be a multicountry, cross-sectional internet-based survey of 750 adults aged ≥18 years who satisfy the criteria for inclusion in either a cohort of people who exclusively vape and who are nonusers of other tobacco or nicotine products (“vapers cohort”; target N=500) or a cohort of nonvapers who are also nonusers of other tobacco or nicotine products (“controls cohort”; target N=250). The primary end point of the study is the RSES score. RSES scores of people in the “vapers cohort” will be compared with those of people in the “controls cohort.” Additionally, the study will collect data to characterize patterns of vaping product use among the vapers cohort. Data collection will include information about the age initiation of using vape products,

reasons for starting and continuing the use of vape products, specific types of products used, flavors and nicotine strengths of recently used products, as well as the frequency and intensity of product use in the past 30 days.

Results: Participant recruitment started in April 2023, and enrollment was completed by November 2023 with 748 participants. Results will be reported in 2024.

Conclusions: This will be the first study providing key insights into respiratory health effects associated with using electronic cigarettes in people who vape with no established use of combustible cigarettes or other tobacco or nicotine products.

International Registered Report Identifier (IRRID): DERR1-10.2196/54236

(JMIR Res Protoc 2024;13:e54236) doi:10.2196/54236

KEYWORDS

electronic cigarette; health effects; respiratory symptoms; survey; real-world use study; e-cigarette; e-cigarettes; smoke; smoker; smokers; smoking; vape; vaping; respiratory; pulmonary; cross-sectional; questionnaire; questionnaires; survey; surveys

Introduction

Electronic cigarettes (ECs) are battery-powered electronic devices that vaporize a water-soluble nicotine solution for inhalation. They do not create smoke or use combustion to operate. These consumer products have been rapidly gaining ground on combustible cigarettes (CCs) among smokers because of their potential for harm reduction from cigarette smoke and smoking cessation [1-3], their competitive price [4,5], and because of allowing people who smoke to continue having a "smoking experience without smoking" [6-8].

Considerable controversy persists surrounding the use of these products, particularly concerning potential misuse by nonsmoking youths and their potential negative impact on respiratory health [9-11]. Many studies examining nicotine vaping face challenges in data analysis due to participants having a history of CC smoking. This history might contribute to some of the adverse effects reported in prior studies, as highlighted in recent papers [12-14].

Under normal operational conditions (without overheating or dry burning coils), ECs present a significant reduction in exposure to harmful constituents compared to CCs [15-17]. No discernible negative health effects solely attributed to EC use (commonly known as "vaping") have been conclusively established [18-20]. Analytical chemistry and toxicology studies of vaporized chemicals suggest no imminent health risks, although concerns persist about potential long-term respiratory implications [21-23]. Hence, further investigation into the prolonged health impact of persistent vaping is warranted.

The respiratory system is the most likely site for any potentially harmful effects of constituents in EC aerosol emissions. Only a few clinical studies have investigated the impact of regular vaping. No deterioration in lung function, airway responses, and respiratory symptoms were observed in a 1-year prospective randomized controlled trial of "healthy" people who smoked and were invited to quit or reduce their cigarette consumption by switching to ECs [24,25]. Specifically, FEF25-75% (a sensitive measure of obstruction in the more peripheral airways) [24], nitric oxide (a noninvasive biomarker of airway inflammation in airway disease as well as in studies of environmental and occupational exposure) [25], and carbon monoxide (an exposure unique to smoking, among tobacco product uses, causing airway inflammation and cardiovascular disease) in the exhaled breath returned to normal limits [25]. Similar results were observed for those who continued to use ECs versus those who quit using them. In addition, restoration of lung defense has been shown in smokers who had switched to exclusive use of ECs; they exhibited mucociliary clearance efficiency similar to that of a never-smoker and a former smoker [26]. Overall, these preliminary studies do not appear to suggest negative respiratory health outcomes in people who smoke and have switched to ECs.

Researching individuals who switch from CC smoking to ECs and then quit presents challenges in understanding their health outcomes. Studying the health of former smokers is complicated due to unknown health effects caused by previous smoking. Precise information about their smoking history—duration, quantity, and puffing behavior—alongside a large sample size is necessary to accurately control for these effects. Recent work by Sargent et al [13] underscores the importance of appropriately accounting for smoking history. They used data from the PATH (Population Assessment of Tobacco and Health) study and, by adjusting for the cumulative amount of CCs smoked (pack-years), demonstrated how using more refined analytical approaches revealed a previously significant association as nonsignificant. This highlights the substantial residual confounding present when using basic binary measures instead of more comprehensive assessments.

Therefore, only studies of people who vape but have never smoked CCs or have only a limited smoking history (ie, those who have smoked fewer than 100 CCs in their lifetime) can enable the detection of harms attributable to EC use. Without studies of people who use ECs with no established smoking history, it will be impossible to distinguish the harms of vaping from neither vaping nor smoking. Concluding that vaping poses less risk than smoking is easy [11,15-20,27-29]. Quantifying the absolute health risks of vaping independent of smoking requires cleaner data.

In a small study of daily EC users who had never smoked, no noticeable changes in blood pressure, heart rate, lung function, respiratory symptoms, exhaled breath nitric oxide, exhaled carbon monoxide, and high-resolution computed tomography of the lungs from baseline were observed over an average 3.5-year observation period [30]. Daily exposure to EC aerosol emissions caused no significant changes in any of the health outcomes investigated, including measures of lung function and

lung inflammation. Moreover, no significant structural abnormalities were identified in the high-resolution computed tomography of the lungs, and no respiratory symptoms were consistently reported. Some of the strengths of this study included prospective rather than retrospective data collection from study participants; the detailed vaping history and precise characterization of the study participants; as well as the use of a panel of different clinical, functional, and inflammatory measures during the study.

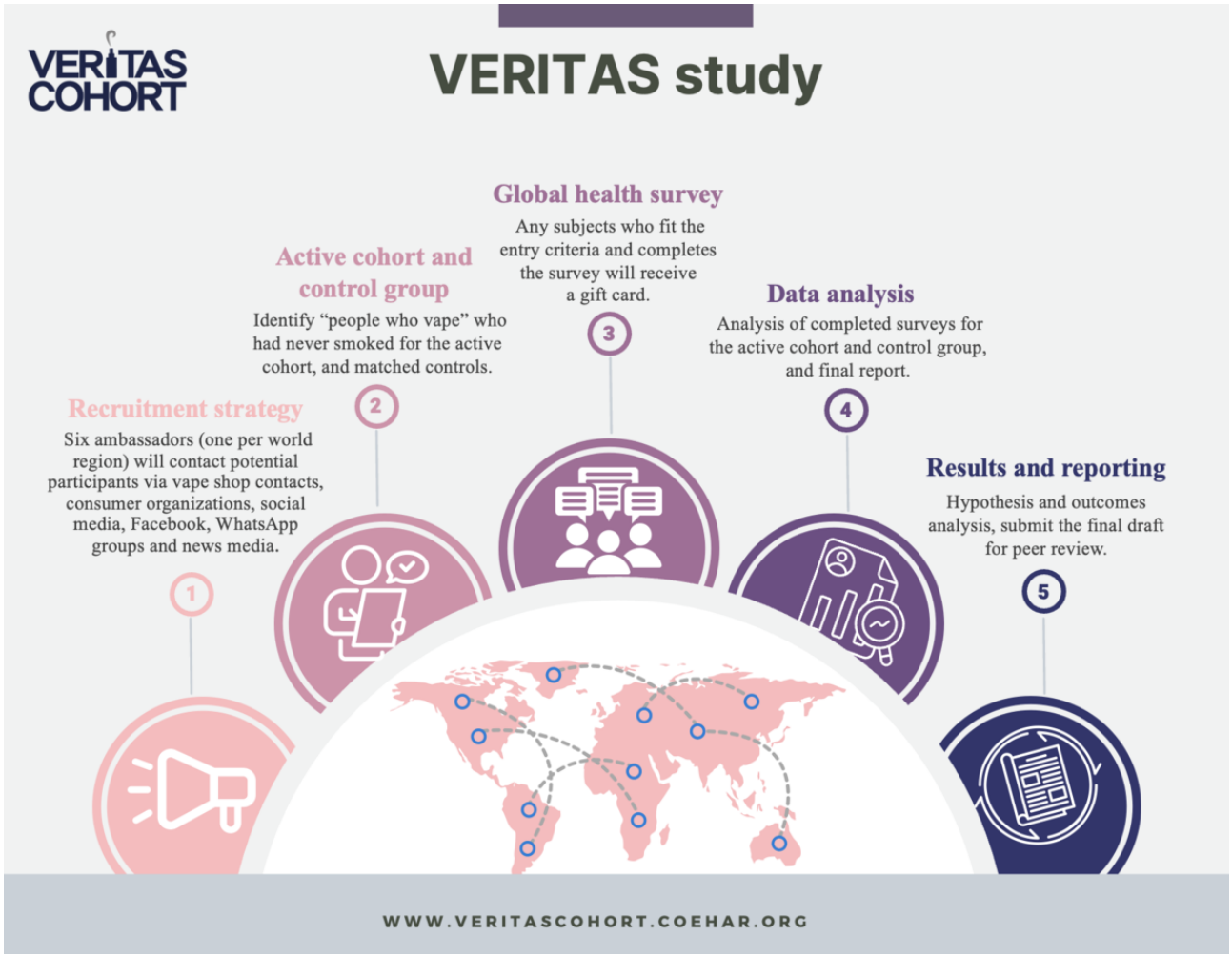
Large prospective studies of well-characterized EC users with and without a history of CC smoking are warranted to establish the long-term effects of regular vaping on respiratory health. We will conduct a global cross-sectional survey of individuals from 6 world regions. Respiratory symptoms reported by a cohort of individuals who vape with no established history of CC smoking or other tobacco or nicotine product use will be compared against those reported by a cohort of matched controls with no established history of vaping, smoking, or use of any other tobacco products.

The primary aim of this study is to test the hypothesis that chronic exposure to EC aerosols does not cause an increase in respiratory symptoms among people who vape with no established cigarette smoking or other tobacco and nicotine product use history. The secondary aims are to determine the feasibility of assembling a large cohort of individuals who vape with no other established tobacco or nicotine product use history to evaluate such effects for future studies and to characterize patterns of vaping product use behavior among this unique cohort.

Methods

An overview of the study is illustrated in Figure 1.

Figure 1. Study design. The infographic illustrates the different stages of the study.



Study Design

This will be a multicountry, cross-sectional, internet-based survey study. Individuals expressing an interest in participating in the study will be directed toward a website [31] with further information and will be screened using a brief questionnaire to assess their eligibility (Multimedia Appendix 1). All screening information gathered for contacts who are not potential recruits (ie, screen failures) will be discarded. Before conducting the survey, potential participants will be rescreened via telephone or email to confirm eligibility, to make sure they have an adequate understanding of the study, and to determine what language is required for the survey. Participants in the cohort will then be subjected to a web-based or mobile-based survey [32] using standard secure web-based survey tools, with central data collection. After completing the survey, participants will receive an email explaining how to redeem an Amazon or

Take-A-Lot gift card code for an equivalent value of US $30, as appreciation for participating in the study.

Ethics Approval

The study protocol has been reviewed and approved by the Ethic Review Board of Dipartimento di Scienze della Formazione Sezione di Psicologia at the University of Catania on November 25, 2020 (Ref 104/20).

Population

This study plans to recruit approximately 750 individuals globally, who satisfy the criteria for inclusion in either a cohort of "people who vape and who are nonusers of other tobacco or nicotine products" ("vapers cohort"; target N=500) or a cohort of "nonvapers who are also nonusers of other tobacco or nicotine products ("controls cohort"; target N=250), as defined in the following sections.

Recruitment

Carefully selected recruiters, the VERITAS (Vaping Effects: Real-World International Surveillance) ambassadors (AB, JJCL, AM, KY, and MS), will make sure to identify and screen individuals for the VERITAS Cohort Study. The VERITAS ambassadors will pursue recruitment through social media channels, WhatsApp groups, Google email groups, posters in vape shops and universities, recommendations from other participants, and recommendations from local vape shop owners in each of the 6 geopolitical world regions (ie, Africa and Middle East, North America, Latin and South America, Asia-Pacific, Western Europe, and Eastern Europe). Ambassadors will instruct vape shop owners to ask their regular clients about their smoking history and EC use patterns to identify potential participants. The reference or control group will comprise adults who never used any tobacco or nicotine products. Control group participants will be recruited primarily among vaping individuals' circles of friends and acquaintances. They will be matched for age and sex to the extent possible. In the event of shortfalls from this recruiting pathway, the Veritas Ambassadors will recruit further controls.

VERITAS ambassadors will be acting as the main point of contact for study participants and will be coordinated by a project leader (JZG). A document detailing the ambassadors' roles can be found on the VERITAS Cohort website [33].

Eligibility Criteria

Eligibility to participate in this study will be assessed by a self-complete screener questionnaire administered immediately after participants provide informed consent to participate.

Inclusion Criteria

Eligibility for participation in the study is determined by the following criteria. All individuals who wish to participate must be aged ≥18 years and provide informed consent to participate in the study.

The vapers cohort should meet the following inclusion criteria:

1. Use at least 1 of 3 types of EC or vape—disposables, rechargeable with replaceable prefilled pods or cartridges, or rechargeable and refillable with e-liquid.
2. Have never smoked a CC *or* have smoked a CC *but* have not smoked more than 100 CCs in their lifetime [34] *and* have not smoked a CC in the past 3 months.
3. Has never used, *or* has never used more than once a week, any of 9 other tobacco or nicotine products listed below:
   - Traditional cigars
   - Cigarillos or filtered cigars
   - Smoked tobacco in a hookah
   - Smoked tobacco in a pipe
   - Smokeless tobacco (including dip, spit, moist snuff, pouches, and chewing tobacco)
   - Snus pouches
   - Dissolvable tobacco
   - Heated tobacco products (eg, iQOS, Glo, and Pulze)
   - Tobacco-free nicotine pouches

The controls cohort should meet the following inclusion criteria:

1. Have never used, or have never used more than once a week, any of the 3 types of EC or vaping products listed above.
2. Same as the vapers cohort's inclusion criterion 2.
3. Same as the vapers cohort's inclusion criterion 3.

Exclusion Criteria

Individuals who do not satisfy the criteria for inclusion in either the vapers cohort or the controls cohort will be excluded.

Study Procedures

All study procedures, from recruitment and obtaining consent to eligibility checks, questionnaires, data collection, and participant compensation, will be carried out exclusively online. The VERITAS web-based survey software (custom-based) will serve as the primary platform for data collection and displaying the Informed Consent Form. This software is intended not only to optimize the presentation of materials for study participants but also to facilitate data submission across various devices, such as laptops, smartphones, and tablets, while being compatible with all web browsers, including Chrome, Safari, Firefox, and Internet Explorer. By adopting this approach, study participants will have the freedom to engage in the research at their convenience, within the privacy of their choosing, and using their preferred device. As a result, participants will be empowered to take part in the study on their terms, in a comfortable setting, and at a time that suits them best.

Web-Based Survey Questionnaires

After prescreening by the ambassadors, eligible individuals who consent to participate will be directed to the study website [32], where they will be subject to a 2-step verification process. When participants reach the survey platform, they will click "Don't have an account? Register"; participants will register their email addresses. Following registration, participants will receive a "Welcome email" and a link to re-enter the survey platform, where they will be asked for their phone number to receive a confirmation code via SMS. After confirming their email addresses, they will start filling out the survey, which will consist of sociodemographic data, medical history, as well as tobacco and nicotine product use behavior. Details about the VERITAS survey document can be shared upon specific request

to the corresponding author. The information collected via the web-based questionnaire will help to characterize or describe the unique cohort. Individuals will then be included in the vapers cohort or the controls cohort or they will be excluded based on their responses to questions about their past and current use of cigarettes, EC or vapes, and other tobacco and nicotine-containing products.

Individuals in the vapers cohort will then be asked questions about their historical and current patterns of use of 3 types of vaping products (ie, disposable vaping products, rechargeable prefilled pod vaping products, and rechargeable refillable vaping products). For each vaping product category, data will be collected on 12 outcomes, as applicable: (1) age of first use; (2) age of initiation, when started to vape more than once a week; (3) the number of product units used in their lifetime; (4) the number of product use days in the past 30 days; (5) length of time (eg, years or months) of vaping more than once a week; (6) nicotine content of products used; (7) flavor categories vaped more than once a week; (8) number of flavors vaped more than once a week; (9) name of favorite flavor used in the past 30 days; (10) number of product units used in the past 30 days; (11) reasons for initiating product use (free-text response); and (12) reasons for current product use (free-text response). The VERITAS survey document can be shared upon specific request to the corresponding author.

All participants will then complete the Respiratory Symptom Experience Scale (RSES), a validated scale that asks participants to rate the frequency with which they experienced 5 respiratory symptoms in the past 30 days [35]. The 5 symptoms rated are as follows: (1) morning cough with phlegm or mucous, (2) coughing frequently throughout the day, (3) shortness of breath that makes it difficult to do normal daily activities, (4) becoming easily winded during normal daily activities, and (5) wheezing or whistling in the chest at times when not exercising or doing other physically strenuous daily activities. Rating for each symptom is made on a 5-point scale, where 1=Never (0 out of the last 30 days); 2=Rarely (1-5 days); 3=Occasionally (6-15 days); 4=Most days (16-29 days); 5=Every day (all 30 out of the last 30 days). A mean RSES score will be calculated by averaging the 5-item scores. The RSES can be found in the Multimedia Appendix 1.

Lastly, questions will assess participants' sex, country of residence, employment status, highest educational attainment, height, and weight.

If necessary, surveys will be translated into the local language by the ambassador for countries where not all participants are fluent in English. Data will be collected on whether the participant completed the survey in English, Spanish (translation available on the platform), or their local language (in case it is determined that some questions of interest had some important difference in nuance when translated).

Study End Points

The primary end point of the study is the RSES score [35]. The objective of the study is to compare the RSES scores between people who vape with no established CC smoking history (ie, the "vapers cohort") and people who have never vaped nor smoked (ie, the "controls cohort").

Additionally, the study will collect data to carefully characterize people who vape with no established CC smoking history in the "vapers cohort." Data collection will include information about the age of initiation of using vaping products, reasons for starting and continuing use of vaping products, specific types of products used, flavors and nicotine strengths of recently used vaping products, as well as the frequency and intensity of product use in the past 30 days.

Statistical Analyses and Reporting

The primary objective of the study is to retrospectively estimate the effect of current, regular use of vaping products on respiratory symptom experience in the past 30 days, measured in this study by the mean score (0 to 5) on the 5-item RSES [35]. Details of sample size calculation and power analysis to detect differences in respiratory symptoms (ie, the RSES scores) between the "vapers cohort" and the "controls cohort" are included in Multimedia Appendix 1. In brief, with 75 participants per group, a study should be adequately powered to detect a difference of 0.57, the proposed minimal important difference, with a power of 98%. However, to detect a more conservative difference of 0.40, a study with 75 individuals per group would still have a power of 89%. The target study population will consist of approximately 500 exposed individuals and 250 matched controls–approximately 83 people who vape per each of the 6 world regions. If the initial recruitment falls short of the goal, or in the case of substantial early loss to follow-up, rolling enrollment will be considered to make up the deficit.

Data analysis of the RSES scores will be both descriptive and inferential in nature. The RSES scores and the demographic characteristics of the vapers cohort and the controls cohort will be descriptively summarized. We will test the null hypothesis that the RSES scores will not significantly differ between the vapers cohort and the controls cohort when adjusted for demographic differences. This hypothesis will be tested through a one-way between-subjects Analysis of Covariance in which the mean RSES score will be entered as the dependent variable, "Cohort" will be entered as the between-subjects independent variable, and 4 demographic variables—age, sex, education, and employment status—will be entered as covariates. Inferential and descriptive statistics will be reported for the Cohort variable adjusted for the effects of the covariates. *P* values <.05 will be considered statistically significant.

The secondary objective of this study is to characterize the use of different vaping products by the vapers cohort. Data analysis of this objective will be purely descriptive in nature. Descriptive summary statistics will be reported for all questionnaire measures of vapers' use of vaping products within each of the 3 product categories—disposable vapes, rechargeable prefilled pod vapes, and rechargeable refillable vapes. Data on the following variables will be descriptively summarized for the subsets of participants within the vapers cohort who are current users of each product category, as follows: number of current users, age of first use, age of first regular use, number of products used in a lifetime, number of product use days in the

past 30 days, time of regular product use, the nicotine concentration of products used typically, type of e-liquid flavors used in the past 30 days, number of e-liquid flavors used regularly in the past 30 days, and number of products used in the past 30 days.

Descriptive summary statistics for continuous variables will include the number of participants in the population of interest (N), the number of participants in the population of interest with nonmissing data on the variable or measure (n), as well as appropriate measures of central tendency (eg, mean and median) and dispersion (eg, SD, SE, range, and IQR) for the observed data. Descriptive statistics reported for categorical variables or measures will include the total number of participants in each subject group who provided nonmissing responses, the proportion of each subject group who selected each categorical response option, and when appropriate, 95% CIs around the proportion of participants who selected each categorical response option.

Additional data analyses may be conducted where data on variables or measures are filtered or stratified by other independent variables of interest. If undertaken, the reporting of descriptive summary statistics for each variable or measure filtered and stratified by additional independent variables of interest will closely resemble the reporting of the planned analyses described above. All data analyses will be conducted using the IBM SPSS (version 27 or higher; IBM Corp) statistical software. Data tables not presented in primary reports or in the manuscript will be presented in supplementary files.

Results

Participant recruitment started in April 2023, and enrollment was completed by November 2023 with 748 participants. Results will be reported in 2024.

Discussion

Research into the respiratory health effects of regular vaping is limited [11,36,37]. Previous research investigating the health status of individuals who used to smoke faces challenges due to unknown health effects caused by prior smoking. Consequently, studies involving individuals who solely vape with no established smoking history are essential to identify potential harms attributed to vaping. A small prospective study of daily EC users who never smoked CCs demonstrated no significant alterations in lung function, inflammation, or structural abnormalities observed in lung scans [30]. Moreover, consistent respiratory symptoms were not reported in this study [30]. However, large longitudinal studies focusing on well-characterized EC users, with and without a history of CC smoking, are necessary to establish the long-term effects of regular vaping on respiratory health.

This proposed study aims to be the first investigation exploring the association between respiratory health effects and the use of ECs in a large group of individuals who exclusively vape, with no established CC smoking history. Additionally, the research will delve into potential confounding factors that could influence any association identified between vaping and respiratory symptoms.

Several noteworthy features distinguish this study. First, by enlisting participants globally, it intends to capture diverse experiences and behaviors related to EC use across different countries and regions. Second, the study's focus on respiratory symptoms and in-depth characterization of vaping product use in a real-world context enhances its generalizability. Third, the study sample has been adequately powered to detect minimum clinically important differences in respiratory symptoms between exclusive vapers and those who neither vape nor smoke. Finally, the study implements a stringent 2-step verification process to deter potential abuse by unauthorized users attempting to exploit the possibility of receiving a gift card and uses manual analysis to identify and verify legitimate participants.

Although this study promises important insights into respiratory symptoms and vaping behaviors among a culturally diverse group of adults who exclusively vape, it should be considered within the context of several limitations. First, its cross-sectional design limits the ability to draw conclusions about the causal relationship between vaping and respiratory symptoms. Longitudinal studies will be crucial to discern the prospective effects of vaping behavior on respiratory health. Second, the study's reliance on nonprobability sampling methods may introduce a self-selection bias, impacting the generalizability of the findings to the broader population of exclusive vapers. However, given the rarity of this population subgroup, these methods were deemed the most practical approach to gathering a sufficient sample. Third, relying on a single respiratory health assessment (ie, RSES) based on self-report might introduce biases and inaccuracies. Participants might hesitate to disclose certain information or be influenced by social desirability bias, potentially affecting the data quality. Lastly, variations in survey interpretation due to linguistic, cultural, or regulatory differences across countries could lead to diverse responses, impacting the consistency and accuracy of the data collected for the research question.

The results obtained from the VERITAS study may offer crucial insights into the impact of vaping on health outcomes, providing a foundation for implementing essential public health measures. These findings can be effectively used within public health sectors and policies to address health concerns related to vaping, establishing necessary preventive measures to safeguard vulnerable populations. Moreover, the study methodology stands as a valuable reference for forthcoming research. Building such unique cohorts could serve as a pivotal resource for future studies, enabling the thorough examination of safety concerns and the quantification of potential risks or harm associated with vaping.

Acknowledgments

AM and MS are independent Tobacco Harm Reduction activists. This investigator-initiated research is sponsored by ECLAT Srl, a spin-off of the University of Catania, through a grant from the Foundation for a Smoke-Free World, a US nonprofit 501(c)(3) private foundation. ECLAT Srl is a research-based company that delivers solutions to global health problems with particular emphasis on harm minimization and technological innovation.

The contents, selection, and presentation of facts, as well as any opinions expressed herein, are the sole responsibility of the authors and under no circumstances shall be regarded as reflecting the positions of the funders.

Conflicts of Interest

JZG is the President of the Asociación de Usuarios de Vaporizadores y Métodos de Reducción de Daños por Tabaquismo de Costa Rica (ASOVAPE Costa Rica), a consumer organization in favor of harm reduction; president of Asociación de Reducción de Daños del Tabaquismo Iberoamérica (ARDT Iberoamérica), an alliance of consumer organizations in Latin America, Spain, and Portugal in favor of harm reduction; director of social media and audiovisual producer of the International Network of Nicotine Consumer Organisations (INNCO), a global coalition of consumer organizations in favor of harm reduction; and a recipient of a scholarship from Knowledge-Action-Change.
TP serves as the director for Confidosoft Ltd, a company specializing in creating tailored software and crafting sophisticated solutions for various research projects. In addition to offering application development services, the company has secured funding for software development and maintains a collaboration agreement with ECLAT Srl.
CS is the owner of Seo Ergo Web, a company that specializes in web design, web security, and digital system administration.
CR acts as codirector of Russell Burnett Research and Consultancy Ltd, which has received research funding or consultancy fees from Cheerain HK Ltd, McKinney Regulatory Science Advisors LLC, Los Angeles Clinical Trials LLC, Health Diplomats, Centre for Substance Use Research Ltd, whatIF? Consulting Ltd, British American Tobacco, Rogue Holdings LLC, Japan Tobacco International, NJOY LLC, SkyX Group Inc, and ECLAT Srl to conduct or consult on perception and behavioral research of noncombustible tobacco and nicotine products.
JJCL is the president of Mexico y el Mundo Vapeando ONG, recipient of a scholarship from Knowledge-Action-Change (a program funded with an unrestricted grant from the Foundation for a Smoke-Free World, Inc. (FSFW), a US nonprofit 501 (c) (3) private foundation).
MS is the cofounder of the Smoke Free Baltic and Smoke Free Latvia non-profit organizations, recipient of a scholarship from Knowledge Action Centre (a program funded with an unrestricted grant from the Foundation for a Smoke-Free World, Inc. (FSFW), a US nonprofit 501 (c) (3) private foundation).
RP is a full-tenured professor of Internal Medicine at the University of Catania (Italy) and medical director of the Institute for Internal Medicine and Clinical Immunology at the same University. He has received grants from U-BIOPRED and AIR-PROM; Integral Rheumatology & Immunology Specialists Network (IRIS); Foundation for a Smoke-Free World; Pfizer; GlaxoSmithKline; CV Therapeutics; NeuroSearch A/S; Sandoz, Merk Sharp & Dohme; Boehringer Ingelheim; Novartis; Arbi Group Srl; Duska Therapeutics; Forest Laboratories; Ministero dell Universita' e della Ricerca (MUR) Bando PNRR 3277/2021 (CUP E63C22000900006) and 341/2022 (CUP E63C22002080006), funded by NextGenerationEU of the European Union (EU); and the ministerial grant PON REACT-EU 2021 GREEN- Bando 3411/2021 by Ministero dell Universita' e della Ricerca (MUR)—PNRR EU Community. He is the founder of the Center for Tobacco Prevention and Treatment (CPCT) at the University of Catania and of the Center of Excellence for the Acceleration of Harm Reduction at the same university. He receives consultancy fees from Pfizer, Boehringer Ingelheim, Duska Therapeutics, Forest Laboratories, CV Therapeutics, Sermo Inc, GRG Health, Clarivate Analytics, Guidepoint Expert Network, and GLG Group. He receives textbook royalties from Elsevier. He is also involved in a patent application for ECLAT Srl. He is a pro bono scientific advisor for Lega Italiana Anti Fumo (LIAF) and the International Network of Nicotine Consumers Organizations (INNCO), and he is chair of the European Technical Committee for Standardization on "Requirements and test methods for emissions of electronic cigarettes" (CEN/TC 437; WG4).
KY is the cofounder of the Consumer Advocacy movement Vaping Saved My Life, a consultant for the Vapour Products Association of South Africa, a member of the Advisory Board for the World Vapers Alliance, and a recipient of the Tobacco Harm Reduction Scholarship Programme from Knowledge Action Change. Knowledge Action Change receives funding from the Foundation for a Smoke-Free World.
Other authors declare no conflicts of interest.

Multimedia Appendix 1
Cohort study questionnaire.
[DOCX File , 237 KB - resprot_v13i1e54236_app1.docx]

References

1. O'Leary R, Polosa R. Tobacco harm reduction in the 21st century. DAT 2020 Jul 13;20(3):219-234 [FREE Full text] [doi: 10.1108/dat-02-2020-0007]

2. Lindson N, Theodoulou A, Ordóñez-Mena JM, Fanshawe TR, Sutton AJ, Livingstone-Banks J, et al. Pharmacological and electronic cigarette interventions for smoking cessation in adults: component network meta-analyses. Cochrane Database Syst Rev 2023 Sep 12;9(9):CD015226 [FREE Full text] [doi: 10.1002/14651858.CD015226.pub2] [Medline: 37696529]
3. Fagerström K. Can alternative nicotine products put the final nail in the smoking coffin? Harm Reduct J 2022 Dec 01;19(1):131 [FREE Full text] [doi: 10.1186/s12954-022-00722-5] [Medline: 36456941]
4. Wagoner KG, Cornacchione J, Wiseman KD, Teal R, Moracco KE, Sutfin EL. E-cigarettes, hookah pens and vapes: adolescent and young adult perceptions of electronic nicotine delivery systems. Nicotine Tob Res 2016 Oct;18(10):2006-2012 [FREE Full text] [doi: 10.1093/ntr/ntw095] [Medline: 27029821]
5. Patel D, Davis KC, Cox S, Bradfield B, King BA, Shafer P, et al. Reasons for current e-cigarette use among U.S. adults. Prev Med 2016 Dec;93:14-20 [FREE Full text] [doi: 10.1016/j.ypmed.2016.09.011] [Medline: 27612572]
6. Caponnetto P, Maglia M, Polosa R. Commentary on Dawkins et al. (2015): electronic cigarettes - from smoking cessation to smoking sensation and back. Addiction 2015 Apr 15;110(4):678-679. [doi: 10.1111/add.12854] [Medline: 25771692]
7. Etter J. Throat hit in users of the electronic cigarette: an exploratory study. Psychol Addict Behav 2016 Feb;30(1):93-100 [FREE Full text] [doi: 10.1037/adb0000137] [Medline: 26653150]
8. DiPiazza J, Caponnetto P, Askin G, Christos P, Maglia MLP, Gautam R, et al. Sensory experiences and cues among e-cigarette users. Harm Reduct J 2020 Oct 15;17(1):75 [FREE Full text] [doi: 10.1186/s12954-020-00420-0] [Medline: 33059666]
9. Polosa R, Casale TB, Tashkin DP. A close look at vaping in adolescents and young adults in the United States. J Allergy Clin Immunol Pract 2022 Nov;10(11):2831-2842 [FREE Full text] [doi: 10.1016/j.jaip.2022.06.005] [Medline: 35718259]
10. Gotts JE, Jordt S, McConnell R, Tarran R. What are the respiratory effects of e-cigarettes? BMJ 2019 Sep 30;366:l5275 [FREE Full text] [doi: 10.1136/bmj.l5275] [Medline: 31570493]
11. Polosa R, O'Leary R, Tashkin D, Emma R, Caruso M. The effect of e-cigarette aerosol emissions on respiratory health: a narrative review. Expert Rev Respir Med 2019 Sep 02;13(9):899-915. [doi: 10.1080/17476348.2019.1649146] [Medline: 31375047]
12. Hajat C, Stein E, Selya A. Polosa R; CoEHAR study group. Analysis of common methodological flaws in the highest cited e-cigarette epidemiology research. Intern Emerg Med 2022 Apr 17;17(3):887-909. [doi: 10.32388/izgwnj.2]
13. Sargent J, Halenar M, Edwards K, Woloshin S, Schwartz L, Emond J, et al. Tobacco use and respiratory symptoms among adults: findings from the longitudinal population assessment of Tobacco and Health (PATH) Study 2014-2016. Nicotine Tob Res 2022 Oct 17;24(10):1607-1618 [FREE Full text] [doi: 10.1093/ntr/ntac080] [Medline: 35366322]
14. Polosa R, Farsalinos K. A tale of flawed e-cigarette research undetected by defective peer review process. Intern Emerg Med 2023 Jun 08;18(4):973-975 [FREE Full text] [doi: 10.1007/s11739-022-03163-x] [Medline: 36480082]
15. Daynard R. Public health consequences of e-cigarettes: a consensus study report of the national academies of sciences, engineering, and medicine. J Public Health Pol 2018 Jul 5;39(3):379-381. [doi: 10.1057/s41271-018-0132-1]
16. Caruso M, Emma R, Distefano A, Rust S, Poulas K, Zadjali F, et al. Electronic nicotine delivery systems exhibit reduced bronchial epithelial cells toxicity compared to cigarette: the Replica Project. Sci Rep 2021 Dec 17;11(1):24182 [FREE Full text] [doi: 10.1038/s41598-021-03310-y] [Medline: 34921164]
17. Emma R, Fuochi V, Distefano A, Partsinevelos K, Rust S, Zadjali F, et al. Li Volti G; Replica Project Group. Cytotoxicity, mutagenicity and genotoxicity of electronic cigarettes emission aerosols compared to cigarette smoke: the REPLICA project. Sci Rep 2023 Oct 30;13(1):17859. [doi: 10.1101/2022.10.28.514205]
18. Hajat C, Stein E, Shantikumar S, Niaura R, Ferrara P, Polosa R. A scoping review of studies on the health impact of electronic nicotine delivery systems. Intern Emerg Med 2022 Jan 12;17(1):241-268 [FREE Full text] [doi: 10.1007/s11739-021-02835-4] [Medline: 34637075]
19. Qureshi MA, Vernooij RWM, La Rosa GRM, Polosa R, O'Leary R. Respiratory health effects of e-cigarette substitution for tobacco cigarettes: a systematic review. Harm Reduct J 2023 Oct 04;20(1):143 [FREE Full text] [doi: 10.1186/s12954-023-00877-9] [Medline: 37794458]
20. La Rosa G, Vernooij R, Qureshi M, Polosa R, O'Leary R. Clinical testing of the cardiovascular effects of e-cigarette substitution for smoking: a living systematic review. Intern Emerg Med 2023 Apr 07;18(3):917-928 [FREE Full text] [doi: 10.1007/s11739-022-03161-z] [Medline: 36609804]
21. Cohen JE, Krishnan-Sarin S, Eissenberg T, Gould TJ, Berman ML, Bhatnagar A, et al. Balancing risks and benefits of e-cigarettes in the real world. Am J Public Health 2022 Feb;112(2):e1-e2. [doi: 10.2105/ajph.2021.306607]
22. Balfour DJK, Benowitz NL, Colby SM, Hatsukami DK, Lando HA, Leischow SJ, et al. Balancing consideration of the risks and benefits of e-cigarettes. Am J Public Health 2021 Sep;111(9):1661-1672. [doi: 10.2105/ajph.2021.306416]
23. Travis N, Knoll M, Cadham CJ, Cook S, Warner KE, Fleischer NL, et al. Health effects of electronic cigarettes: an umbrella review and methodological considerations. Int J Environ Res Public Health 2022 Jul 25;19(15):9054 [FREE Full text] [doi: 10.3390/ijerph19159054] [Medline: 35897421]
24. Cibella F, Campagna D, Caponnetto P, Amaradio MD, Caruso M, Russo C, et al. Lung function and respiratory symptoms in a randomized smoking cessation trial of electronic cigarettes. Clin Sci (Lond) 2016 Nov 01;130(21):1929-1937. [doi: 10.1042/CS20160268] [Medline: 27543458]

25. Campagna D, Cibella F, Caponnetto P, Amaradio MD, Caruso M, Morjaria JB, et al. Changes in breathomics from a 1-year randomized smoking cessation trial of electronic cigarettes. Eur J Clin Invest 2016 Aug 08;46(8):698-706. [doi: 10.1111/eci.12651] [Medline: 27322745]
26. Polosa R, Emma R, Cibella F, Caruso M, Conte G, Benfatto F, et al. Impact of exclusive e-cigarettes and heated tobacco products use on muco-ciliary clearance. Ther Adv Chronic Dis 2021 Aug 12;12:20406223211035267 [FREE Full text] [doi: 10.1177/20406223211035267] [Medline: 34422253]
27. Nutt DJ, Phillips LD, Balfour D, Curran HV, Dockrell M, Foulds J, et al. Estimating the harms of nicotine-containing products using the MCDA approach. Eur Addict Res 2014 Apr 3;20(5):218-225 [FREE Full text] [doi: 10.1159/000360220] [Medline: 24714502]
28. Nicotine without smoke: tobacco harm reduction. Royal College of Physicians. 2016 Apr 28. URL: https://www.rcplondon.ac.uk/projects/outputs/nicotine-without-smoke-tobacco-harm-reduction-0 [accessed 2024-02-20]
29. McNeill A, Brose L, Calder R, Bauld L. Evidence review of e-cigarettes and heated tobacco products 2018. A report commissioned by Public Health England. Public Health England. 2018 Feb 01. URL: https://assets.publishing.service.gov.uk/media/5a981c6740f0b67aa27253cc/Evidence_review_of_e-cigarettes_and_heated_tobacco_products_2018.pdf [accessed 2024-03-14]
30. Polosa R, Cibella F, Caponnetto P, Maglia M, Prosperini U, Russo C, et al. Health impact of e-cigarettes: a prospective 3.5-year study of regular daily users who have never smoked. Sci Rep 2017 Nov 17;7(1):13825 [FREE Full text] [doi: 10.1038/s41598-017-14043-2] [Medline: 29150612]
31. The Veritas cohort study. VERITAS Cohort. URL: https://veritascohort.coehar.org/ [accessed 2024-03-14]
32. Veritas cohort online survey. VERITAS Cohort. URL: https://veritasbe.coehar.org/auth [accessed 2024-01-14]
33. Job description – VERITAS project ambassador. Veritas Cohort. URL: https://veritascohort.coehar.org/wp-content/uploads/2023/08/Ambassador-Job-Description.pdf [accessed 2024-03-14]
34. Centers for Disease Control and Prevention (CDC). State-specific secondhand smoke exposure and current cigarette smoking among adults - United States, 2008. MMWR Morb Mortal Wkly Rep 2009 Nov 13;58(44):1232-1235 [FREE Full text] [Medline: 19910910]
35. Shiffman S, McCaffrey SA, Hannon MJ, Goldenson NI, Black RA. A new questionnaire to assess respiratory symptoms (The Respiratory Symptom Experience Scale): quantitative psychometric assessment and validation study. JMIR Form Res 2023 Apr 14;7:e44036. [doi: 10.2196/44036] [Medline: 37058347]
36. Morjaria JB, Campagna D, Caci G, O'Leary R, Polosa R. Health impact of e-cigarettes and heated tobacco products in chronic obstructive pulmonary disease: current and emerging evidence. Expert Rev Respir Med 2022 Jan 22;16(11-12):1213-1226. [doi: 10.1080/17476348.2023.2167716] [Medline: 36638185]
37. Mendelsohn CP, Morjaria JB, Polosa R. Respiratory harms from vaping: questions for debate and discussion. Respirology 2022 Jan 08;27(1):93-95 [FREE Full text] [doi: 10.1111/resp.14183] [Medline: 34878211]

Abbreviations

CC: combustible cigarette
EC: electronic cigarette
PATH: Population Assessment of Tobacco and Health
RSES: Respiratory Symptom Experience Scale
VERITAS: Vaping Effects: Real-World International Surveillance

Edited by A Mavragani; submitted 02.11.23; peer-reviewed by A Selya; comments to author 01.12.23; revised version received 19.12.23; accepted 31.01.24; published 28.03.24.

Please cite as:
Zamora Goicoechea J, Boughner A, Cirion Lee JJ, Mahajan A, Yeo K, Sproga M, Patel T, Saitta C, Russell C, Coughlan M, Caponnetto P, Polosa R
A Global Health Survey of People Who Vape but Never Smoked: Protocol for the VERITAS (Vaping Effects: Real-World International Surveillance) Study
JMIR Res Protoc 2024;13:e54236
URL: https://www.researchprotocols.org/2024/1/e54236
doi:10.2196/54236
PMID:38546715

Protocol

Design of a Remote Multiparametric Tool to Assess Mental Well-Being and Distress in Young People (mHealth Methods in Mental Health Research Project): Protocol for an Observational Study

Thais Castro Ribeiro[1,2], PhD; Esther García Pagès[1,2], MSc; Laura Ballester[3,4], PhD; Gemma Vilagut[3,4], PhD; Helena García Mieres[3,4], PhD; Víctor Suárez Aragonès[5], MSc; Franco Amigo[3,4], MSc; Raquel Bailón[1,6], PhD; Philippe Mortier[3,4], PhD; Víctor Pérez Sola[7,8,9,10], PhD; Antoni Serrano-Blanco[3,11], PhD; Jordi Alonso[3,4,10], PhD; Jordi Aguiló[1,2], PhD

[1]CIBER de Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN), Instituto de Salud Carlos III, Madrid, Spain
[2]Departament of Microelectronics and Electronic Systems, Autonomous University of Barcelona, Bellaterra, Spain
[3]CIBER de Epidemiología y Salud Pública (CIBERESP), Instituto de Salud Carlos III, Madrid, Spain
[4]Health Services Research Group, Hospital del Mar Research Institute, Barcelona, Spain
[5]Department of Clinical Psychology and Psychobiology, University of Barcelona, Barcelona, Spain
[6]Aragón Institute of Engineering Research (I3A), University of Zaragoza, Zaragoza, Spain
[7]CIBER en Salud Mental (CIBERSAM), Instituto de Salud Carlos III, Madrid, Spain
[8]Institute of Neuropsychiatry and Addictions (INAD), Parc de Salut Mar (PSMAR), Barcelona, Spain
[9]Neurosciences Research Group, Hospital del Mar Research Institute, Barcelona, Spain
[10]Department of Medicine and Life Sciences, Universitat Pompeu Fabra, Barcelona, Spain
[11]Institut de Recerca Sant Joan de Déu, Parc Sanitari Sant Joan de Déu, Barcelona, Spain

Corresponding Author:
Thais Castro Ribeiro, PhD
CIBER de Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN)
Instituto de Salud Carlos III
Calle Monforte de Lemos, 3-5, Pabellón 11
Madrid, 28029
Spain
Phone: 34 935868430
Email: thais.castro@uab.cat

Abstract

Background: Mental health conditions have become a substantial cause of disability worldwide, resulting in economic burden and strain on the public health system. Incorporating cognitive and physiological biomarkers using noninvasive sensors combined with self-reported questionnaires can provide a more accurate characterization of the individual's well-being. Biomarkers such as heart rate variability or those extracted from the electrodermal activity signal are commonly considered as indices of autonomic nervous system functioning, providing objective indicators of stress response. A model combining a set of these biomarkers can constitute a comprehensive tool to remotely assess mental well-being and distress.

Objective: This study aims to design and validate a remote multiparametric tool, including physiological and cognitive variables, to objectively assess mental well-being and distress.

Methods: This ongoing observational study pursues to enroll 60 young participants (aged 18-34 years) in 3 groups, including participants with high mental well-being, participants with mild to moderate psychological distress, and participants diagnosed with depression or anxiety disorder. The inclusion and exclusion criteria are being evaluated through a web-based questionnaire, and for those with a mental health condition, the criteria are identified by psychologists. The assessment consists of collecting mental health self-reported measures and physiological data during a baseline state, the Stroop Color and Word Test as a stress-inducing stage, and a final recovery period. Several variables related to heart rate variability, pulse arrival time, breathing, electrodermal activity, and peripheral temperature are collected using medical and wearable devices. A second assessment is

carried out after 1 month. The assessment tool will be developed using self-reported questionnaires assessing well-being (short version of Warwick-Edinburgh Mental Well-being Scale), anxiety (Generalized Anxiety Disorder-7), and depression (Patient Health Questionnaire-9) as the reference. We will perform correlation and principal component analysis to reduce the number of variables, followed by the calculation of multiple regression models. Test-retest reliability, known-group validity, and predictive validity will be assessed.

Results: Participant recruitment is being carried out on a university campus and in mental health services. Recruitment commenced in October 2022 and is expected to be completed by June 2024. As of July 2023, we have recruited 41 participants. Most participants correspond to the group with mild to moderate psychological distress (n=20, 49%), followed by the high mental well-being group (n=13, 32%) and those diagnosed with a mental health condition (n=8, 20%). Data preprocessing is currently ongoing, and publication of the first results is expected by September 2024.

Conclusions: This study will establish an initial framework for a comprehensive mental health assessment tool, taking measurements from sophisticated devices, with the goal of progressing toward a remotely accessible and objectively measured approach that maintains an acceptable level of accuracy in clinical practice and epidemiological studies.

Trial Registration: OSF Registries N3GCH; https://doi.org/10.17605/OSF.IO/N3GCH

International Registered Report Identifier (IRRID): DERR1-10.2196/51298

(JMIR Res Protoc 2024;13:e51298) doi:10.2196/51298

KEYWORDS

mental health; mental well-being; mobile health; mHealth; remote monitoring; physiological variables; experimental protocol; depression; anxiety

Introduction

Background

Mental health conditions are one of the leading causes of disability worldwide and are estimated to reduce life expectancy by 10 years [1]. For instance, depressive disorders were considered the eighth cause of disability in Spain in 2000, rising to fifth in 2019 [2]. Depression, anxiety, and stress-related disorders impose a major economic impact and burden on the public health system. To date, the prevalence of depression in the Spanish population is close to 5%, and the annual cost is estimated at €6145 (US $6648) million [3].

Young people and university students are populations of particular interest. Approximately 75% of mental health conditions have an early onset before the age of 24 years, and several risk factors (including genetic, early life adversity, family, community, and environmental factors) are involved in the development and course of these conditions [4]. Moreover, the recent COVID-19 pandemic has aggravated this situation [5]. Several systematic reviews and meta-analyses have indicated a high prevalence of mental health conditions among young people, with a pooled prevalence for depression of 31% to 33.6%, anxiety of 28% to 39%, sleep problems of 40%, and suicidal ideation of 12.3% [6-8], in line with the results of longitudinal studies suggesting a possible worsening of mental health in this population in recent years [9]. There is a need for early identification and prevention of mental health conditions, which includes the design and implementation of mental health promotion activities that lead to an increase in emotional well-being [10].

In recent decades, interest in mental health research has been steadily increasing, recognizing it a crucial aspect of overall health, rather than simply the absence of related conditions [11]. According to the World Health Organization [12], mental health is characterized by individuals' ability to effectively manage typical stressful situations, develop their potential and skills, and contribute productively to both themselves and the community. This comprises an adequate stress response and recovery as well as maintaining cognitive abilities such as attentional level and proper time of response. Stress reactivity is this capacity to respond to a stressor. It is a disposition that underlies individual differences in response to stressors and is assumed to be a vulnerability factor for the development of mental health conditions [13]. In this context, monitoring physiological response during a stress-inducing task could yield different reactivity patterns, offering valuable insights to differentiate between mental well-being and distress.

In clinical practice, self-reported questionnaires are commonly used to assess the severity of mental health symptoms, quality of life, and mental well-being. Nevertheless, several studies have reported limitations of these tests related to memory biases and distortions in retrospective recall [14,15]. To expand such assessments, including physiological biomarkers information will improve the characterization of endophenotypes (research domain criteria) [16]. Owing to technological advances, small sensors can measure physiological data for behavioral health, interventions, and outcomes (digital phenotyping) [17,18]. Given the significance of stress reactions as complex phenomena encompassing psychological, cognitive, and physiological reactions involving the autonomic nervous system (ANS) and the neuroendocrine system, which, in turn, can affect other bodily systems, exploring these dynamics could enhance our comprehension of mental distress. Hence, physiological data monitoring including a stress-eliciting task may have an important role in early detection and intervention in mental health care. Heart rate variability (HRV), pulse arrival time (PAT), breathing parameters, electrodermal activity (EDA), and skin temperature (ST) are physiological variables broadly used to study the stress response and gather information about ANS functioning [19-24].

To progress in this field, the use of wearables in mental health research shows promise, offering increased accuracy in data collection and reduced participant burden. Wearable devices allow researchers to passively monitor individuals in real time and gather data outside of traditional laboratory settings, that is, along with everyday life situations, providing a more holistic understanding of mental health status [25,26]. Currently, many studies on stress detection are conducted in controlled environments because accuracy decreases when conducted in real-time environments [27]. In addition, different instruments to measure perceived stress are used, which hinders the comparability of results [28], or a small number of signals are usually collected [29-31]. However, previous studies have shown optimistic results for further advancement in the field for the objective assessment of mental health status and stress. A study analyzing data from 510 participants wearing a Fitbit device during a 2-year follow-up [32] showed a correlation between decreased resting heart rate variation during the day and the severity of depression, whereas the mean heart rate at night was higher in participants with more severe depressive symptoms. In line with these results, a decreased autonomic reactivity measured through dynamic changes in photoplethysmography (PPG) waveform morphology was associated with a higher degree of depression in the study by Kontaxis et al [33]. Sano et al [30] conducted an observational study among university students using wearable sensors that collected EDA and ST, and using psychometric questionnaires as reference, they found an accuracy of 78% and 87% to classify into high or low stress groups and high or low mental health groups, respectively. Similarly, Sano et al [34] found an accuracy of 90% in classifying stress and mental health groups. From a literature review [27], it was observed that heart rate and EDA are the most regularly used sensory signals, offering the most promising results and high accuracy for detecting stress.

Effective prevention interventions require strategies to identify early risk groups according to risk factors through the development of predictive models. In addition, from a mental health promotion perspective, effectively assessing mental well-being would help identify the right time to intervene, evaluate the efficacy of the therapy applied, empower the citizens, offer stress-reducing programs, and prevent negative consequences. Here, we present the development and evaluation of a novel multiparametric tool to improve mental health assessments and to facilitate the evaluation of risk and protective factors as well as the effectiveness of promotion and prevention interventions.

Objectives

This study aims to design and validate a remote multiparametric tool, including several physiological and cognitive variables, to objectively assess mental well-being as well as mental distress (ie, symptoms of depression and anxiety) among young people for epidemiologic and clinical studies.

The specific objectives of this study are (1) to develop an assessment tool for mental well-being and distress based on the most relevant physiological and cognitive variables; (2) to validate the assessment tool using self-reported measures and evaluate the tool reliability and accuracy; and (3) to develop and establish a protocol to automate the measurement process, ensuring that it can be reproduced in large populations.

Methods

Study Design and Setting

This is a multicenter observational study of the mHealth Methods in Mental Health Research (M&M) project, currently ongoing, being conducted by the Autonomous University of Barcelona (UAB) and Parc de Salut Mar (PSMAR).

Three different mental health states will be studied: (1) high mental well-being, (2) presenting mild to moderate psychological distress, and (3) depressive or anxiety disorder (diagnosed by a mental health professional). For the high mental well-being and the mild to moderate psychological distress groups, a web-based mental health questionnaire is being distributed among UAB students for screening and analyzed to determine the participant's eligibility. Participants who meet the selection criteria are consecutively included. For the mental health condition group, the patients are being referred from the Institute of Neuropsychiatry and Addictions-PSMAR, the Hospital Sant Joan de Déu, and the Psychology and Speech Therapy Service of the UAB. The assessments are planned at 2 time points and are being conducted at the site of recruitment (UAB, Institute of Neuropsychiatry and Addictions-PSMAR, or Hospital Sant Joan de Déu). The second assessment takes place after 1 month of the first assessment.

Participants and Eligibility Criteria

The 3 abovementioned participant groups are being recruited according to the inclusion and exclusion criteria described in detail in Table 1. To ensure a homogeneous sample in terms of age, participants aged between 18 and 34 years are being recruited in all 3 groups.

Table 1. Inclusion and exclusion criteria for the 3 groups of the participants being recruited in the multicenter observational study (mHealth Methods in Mental Health Research project).

Groups	Inclusion criteria	Exclusion criteria	Site of recruitment
High mental well-being	• No history of emotional distress for at least a year • PHQ-4[a] score: <3 and SWEMWBS[b] score: ≥30	• Cognitive impairment or damage, including presence or history of head trauma, dementia, or intellectual disability (IQ ≤80) • History of schizophrenia or other psychotic spectrum disorders • Problems understanding Spanish or Catalan	University campus (UAB[c])
Mild to moderate psychological distress	• Recent history of mental health issues • PHQ-4 score: 3-8 or SWEMWBS score: 20-29	• Cognitive impairment or damage, including presence or history of head trauma, dementia, or intellectual disability (IQ ≤80) • History of schizophrenia or other psychotic spectrum disorders • Problems understanding Spanish or Catalan	University campus (UAB)
Mental health condition	• Diagnosed with current depression or anxiety by a mental health professional	• Cognitive impairment or damage, including presence or history of head trauma, dementia, or intellectual disability (IQ ≤80) • History of schizophrenia or other psychotic spectrum disorders • Problems understanding Spanish or Catalan • The symptomatology has an organic origin or is owing to the physiological effects of a substance • Presence of acute suicidal ideation • Being medicated	Mental health services (INAD-PSMAR[d] or HSJD[e])

[a]PHQ-4: Patient Health Questionnaire-4.

[b]SWEMWBS: short version of Warwick-Edinburgh Mental Well-being Scale.

[c]UAB: Autonomous University of Barcelona.

[d]INAD-PSMAR: Institute of Neuropsychiatry and Addictions-Parc de Salut Mar.

[e]HSJD: Hospital Sant Joan de Déu.

For the high mental well-being and mild to moderate psychological distress groups, inclusion criteria are assessed for eligibility through a web-based questionnaire that contains questions about mental health history (eg, "Have you ever experienced any mental health issue?"). The Patient Health Questionnaire (PHQ; PHQ-4) [35] is used to screen for anxiety and depression symptoms, and the short version of Warwick-Edinburgh Mental Well-being Scale (SWEMWBS) [36,37] is used to evaluate mental well-being. The cutoff points to be considered as high mental well-being are based on data from a representative sample of young adults of Catalonia from the Catalonia Health Survey conducted in 2016 [38], in which a median score of 30 points in SWEMWBS was found. Individuals with SWEMWBS well-being score ≥30 and PHQ-4 <3 points are classified in the high well-being group. Individuals with SWEMWBS score between 20 and 29 points or a PHQ-4 score between 3 and 8 are classified into the mild to moderate psychological distress group.

Recruitment

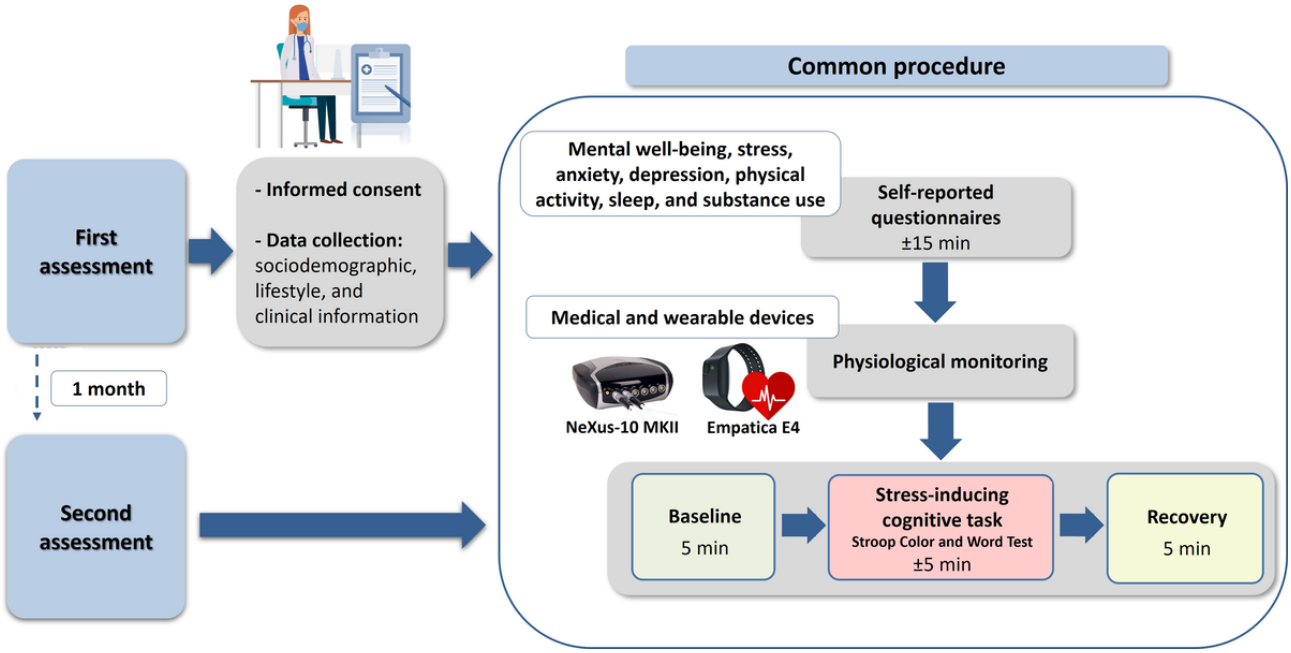
The primary recruitment pathway for nonpatients is the dissemination of the study through institutional mail or social media and the placement of posters in public areas of UAB. The information includes a link or QR code to answer a web-based questionnaire. To facilitate the recruitment of the mild to moderate psychological distress group, the Psychology and Speech Therapy Service of the UAB is collaborating by inviting students who attended the service to participate in this study. In both cases, once the responsible researcher confirms the eligibility criteria, the participant is contacted to schedule the first assessment.

For the mental health condition group, the patients who meet the criteria are identified at the consultation with the psychologist or psychiatrist, who briefly informs them about the study and suggests participation. The research assistant contacts the interested patients by phone and makes an appointment for the first assessment. Written informed consent is provided by all participants before starting the first assessment interview.

Study Procedure

All participants who agree to participate are asked to abstain from tobacco, alcohol, caffeine, or any other beverage or stimulating substance for 2 hours before the study. Figure 1 shows the complete schematic of the experimental procedure.

Figure 1. The study experimental procedure outline for the first and second (conducted after 1 month) assessments includes recruitment, obtaining informed consent, and data collection. A research assistant performs the same procedure for both assessments in this observational study (mHealth Methods in Mental Health Research [M&M] project).



At the first assessment, the participants are fully informed about the study procedure and are requested to sign the informed consent form. This visit includes an ad hoc interview conducted by a qualified examiner to collect individuals' sociodemographic, modifiable lifestyle factors, health-related variables, and clinical data through the management software Qualtrics (Silver Lake). Subsequently, a psychological assessment is carried out. The participants respond to 7 self-reported questionnaires using the same software. These questionnaires aim to estimate the current mental well-being, stress perception, symptoms of anxiety and depression, physical activity, sleep quality, and substance use. All these measures are described in the *Study Variables* section.

The physiological assessment consists of recording different stress-related physiological signals using (1) the medical-graded device NeXus-10 MKII (Mind Media BV) and (2) the wearable E4 Empatica wristband (Empatica Inc). PPG, EDA, and ST will be the physiological signals recorded simultaneously by both devices. The electrocardiogram (ECG) and respiration can only be measured using a medical-graded device. This device is used to obtain a more accurate measure for preliminary analysis and, thereafter, validate the predictive model with the wearable device.

The wristband is placed on the nondominant wrist and the PPG (middle finger), EDA (middle phalanges of the second and fourth digits), and ST (fingertip of the fifth finger) sensors are placed on the nondominant hand to avoid excessive movement artifacts. An adjustable elastic band is placed over the abdomen to measure the respiration signal. For lead 1 of the ECG signal, electrodes are positioned below the right collarbone and below the left rib cage, whereas for lead 2, electrodes are positioned on the fifth intercostal space along the midaxillary line on the left side and symmetrically on the right side. The reference electrode is placed on the left collarbone.

This part of the procedure lasts approximately 15 minutes and is divided into three different stages: (1) baseline (green block in Figure 1): participant in a resting state, sitting comfortably with eyes open; (2) cognitive task (red block in Figure 1): corresponds to the stress-inducing stage, when the individual is submitted to a cognitive task, the Stroop Test [39]; and (3) recovery (yellow block in Figure 1): when the individual's physiological responses are expected to return to the baseline levels. All physiological signals and variables of interest will be detailed in the *Physiological Variables* section.

A second assessment is then scheduled 1 month apart and includes the same psychological and physiological assessments. This follow-up session is intended to allow test-retest reliability and account for random errors that could occur in a single session.

Study Variables

Outcome Measures

The following outcome measures are used:

1. Depression: It is evaluated using the PHQ-9 [40,41]. It is a Likert-type scale used to screen the severity of depressive symptoms according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. All 9 items are rated from 0 (not at all) to 3 (nearly every day). Total scores can range from 0 to 27, with higher scores indicating more severe depression. Furthermore, 5, 10, 15, and 20 represent the cutoff points for mild, moderate, moderately severe, and severe depression, respectively [42].
2. Anxiety: The Generalized Anxiety Disorder-7 [43,44] is an instrument for screening the presence of symptoms of anxiety as listed in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. It is a 1-dimensional scale with scores for all 7 items ranging from 0 (not at all) to 3 (nearly every day). The total score was categorized

into 4 severity groups according to the original authors: minimal (0-4), mild (5-9), moderate (10-14), and severe (>15).

3. Mental well-being: The SWEMWBS [36,37] is an instrument used to assess mental well-being. This unidimensional scale comprises 7 items ranging from 1 (none of the time) to 5 (all of the time). The higher the total score, the greater the perception of well-being.

Covariates

Sociodemographic variables include age, gender, nationality, marital status, living status, educational level, and occupation.

Current physical and mental health conditions, previous mental health treatments, medication, and suicidal thoughts and behaviors are evaluated through items in the ad hoc interview. Perceived stress is evaluated using the 10-item Perceived Stress Scale [45,46]. It is a 5-point Likert scale with questions about the frequency of feelings and thoughts during the last month, with each item ranging from 0 (never) to 4 (very often). Higher scores indicate higher levels of perceived stress. To assess substance use problems, the CAGE-Adapted to Include Drugs [47] scale is used. It is an adaptation of the original CAGE questionnaire [48] for conjointly screening for alcohol and drug problems based on lifetime. The scale contains 4 yes or no questions, and a higher score indicates substance use problems.

Modifiable lifestyle variables are assessed using an ad hoc interview, including coffee consumption, cigarette smoking, alcohol and drug consumption, and BMI. Physical activity is measured using the short form of the International Physical Activity Questionnaire [49,50]. This questionnaire comprises 7 open-ended questions about individuals' 7-day recall of physical activity. According to the total energy expenditure in metabolic equivalent of task (ie, 1 metabolic equivalent of task is the energy cost of sitting quietly) in minutes per week, the physical activity level is determined as low or inactive, moderate, or high.

Sleep is evaluated using the Medical Outcomes Study Sleep Scale [51,52]. This questionnaire contains 12 items about a 4-week recall, divided into 8 subscales (sleep adequacy, optimal sleep, quantity of sleep, awakening shortness of breath or with headache, snoring, sleep disturbance, somnolence, and global index of sleep interference). In general, higher scores indicate greater sleep problems. The quantity of sleep score is the patient-reported number of hours of sleep per night, and optimal sleep is scored as 1 (7 or 8 h of sleep per night) or 0 (any different response).

The comfort level is evaluated by asking participants if they are currently experiencing higher stress than usual and identifying its potential causes.

Stress-Inducing Cognitive Task

The Spanish version of the standard Stroop Color and Word Test (SCWT) is applied (originally [53] and Spanish version [39]) as a cognitive stress-inducing task. This test is extensively used to assess cognitive inhibition and processing speed. Furthermore, it has also been shown to be a reliable method to induce mental stress in experimental settings [54]. The individuals are required to read the 3-color cards as fast as possible in a fixed time of 45 seconds each. The stimuli presented on the first 2 cards are congruent, that is, read names of colors or name different colors. In contrast, the last card represents the incongruent stimuli, that is, name the color of the ink instead of reading the color.

Three direct scores are derived by tallying the correct responses for each condition: (1) *W* (word) represents the number of colors read on the first card (where colors are written in black ink), (2) *C* (color) represents the number of elements identified on the card of colors (where name colors are represented with strings of XXXXs), and (3) *CW* (color word) represents the number of items correctly identified on the third card (where colors are printed in an ink that does not correspond to the color name, requiring participants to say the colors of the ink). Two other scores will be calculated from these: (1) predicted *CW* (*PCW*): ($W \times C / W + C$) and (2) interference: ($CW - PCW$). A higher score indicates a greater ability to inhibit interference.

Direct scores are then converted to *T* scores, with a preset mean of 50 and SD of 10, so that they can be more easily compared in similar age ranges (in this study, young adults aged between 18 and 44 years). The limits considered normal are between 35 and 65 *T* points in any of the scores (for details, refer the study by Golden [39]).

Physiological Variables

Overview

We are following a methodology already used and validated as stress assessment for healthy students and principal caregivers [20,55]; the electrophysiological raw signals recorded with NeXus-10 MKII (ie, ECG, PPG, EDA, respiration, and ST) are analyzed using BioSigBrowser [56] in MATLAB software (The MathWorks Inc); and several groups of variables are extracted, as described in Table 2. A literature review was conducted to select the most relevant variables for assessing stress response and mental health. A summary of the findings can be found in Multimedia Appendix 1 [19-24,57-65].

Table 2. Description of the variables that will be extracted from raw electrophysiological signals monitored with the medical device NeXus-10 MKII.

Group of variables	Electrophysiological signal	Physiological variables	Description
HRV[a] or PRV[b]	ECG[c] or PPG[d]	HR[e,f] (bpm)[g]	Mean HR
HRV or PRV	ECG or PPG	IBI[f] (ms)[h]	Mean IBI
HRV or PRV	ECG or PPG	pNN50[f] (%)	Percentage of adjacent normal beats intervals differing from each other by >50 ms
HRV or PRV	ECG or PPG	SDNN[f] (ms)	SD of normal beats intervals
HRV or PRV	ECG or PPG	RMSSD[f] (ms)	Root mean square of successive differences between normal beats
HRV or PRV	ECG or PPG	SDSD[f] (ms)	SD of differences between adjacent R-R peaks intervals
HRV or PRV	ECG or PPG	VLF[i] (s^{-2})	Absolute power of the VLF band (0.003-0.04 Hz)
HRV or PRV	ECG or PPG	LF[f,j] (s^{-2})	Absolute power of the LF band (0.04-0.15 Hz)
HRV or PRV	ECG or PPG	HF[f] (s^{-2})[k]	Absolute power of the HF band (0.15-0.4 Hz)
HRV or PRV	ECG or PPG	LF/HF ratio[f]	Ratio of LF to HF power
HRV or PRV	ECG or PPG	HFn[f] (nu)	Relative power of the HF band normalized
PAT[l]	ECG and PPG	PAT (ms)	Mean PAT, the time between the beat detected by ECG and the pulse by PPG
PAT	ECG and PPG	stdPAT (ms)	SD of PAT
Breathing	Respiration	RR[m] (Hz)	Mean RR
Breathing	Respiration	Pk (%)	Peak of respiratory power spectra
EDA[n]	EDA	Tonic[f] (µS)	Average value of the tonic component, that is, slowly changing skin conductance level, also known as SCL[o]
EDA	EDA	Phasic[f] (µS)	Average value of the phasic component, that is, fast-changing responses typically associated with short-term events, also known as SCR[p]
EDA	EDA	aucPhasic[f] (µS·s)	Area under the curve of the phasic component, which is related to SCR
EDA	EDA	EDASymp[f] (µS)	Electrodermal response in the power spectrum (0.045-0.25 Hz)
Peripheral temperature	ST[q]	TFinger[f] (°C)	Mean finger temperature
Peripheral temperature	ST	TGradient[f] (°C)	Mean gradient of finger temperature
Peripheral temperature	ST	TPower[f] ($°C^2$)	Mean power of finger temperature

[a]HRV: heart rate variability.
[b]PRV: pulse rate variability.
[c]ECG: electrocardiogram.
[d]PPG: photoplethysmography.
[e]HR: heart rate.
[f]These will also be extracted from the recordings of the Empatica E4 wearable device.
[g]bpm: beats per minute.
[h]IBI: interbeat interval.
[i]VLF: very low frequency
[j]LF: low frequency.
[k]HF: high frequency.
[l]PAT: pulse arrival time.
[m]RR: respiratory rate.
[n]EDA: electrodermal activity.
[o]SCL: skin conductance level.

[p]SCR: skin conductance response.

[q]ST: skin temperature.

The raw signals recorded with the Empatica E4 wearable device (ie, EDA, PPG, and ST) will be also analyzed in MATLAB (The MathWorks Inc) using a similar procedure, given the different format files. The variables intended to be explored in this case are indicated in the footnotes in Table 2. Furthermore, the stress reactivity, that is, the difference between the stress-inducing cognitive task stage and the baseline stage (stress−baseline), and the stress recovery, that is, the difference between the stress and the posterior recovery stage (stress−recovery), will also be computed for each variable to determine the most relevant set of variables to be considered to design the final model.

Physiological Data Processing

For processing the ECG signal, beat detection is performed through a discrete wavelet transform [66]. Afterward, the existence of ectopic beats or false QRS detections will be verified and corrected using the algorithm reported by Mateo and Laguna [67] before the computation of the interbeat interval series. Segments of up to 3 interpolated or corrected beats are accepted and assumed to be normal. Following this, the HRV parameters are calculated by a time-domain analysis and a frequency-domain analysis by Fourier transform of the heart rate signal.

PPG signal is preprocessed using a low-pass finite impulse response (FIR) filter with a cutoff frequency of 35 Hz (order 50) and then a high-pass FIR filter with a cutoff frequency of 0.3 Hz (order 5000). PPG artifacts are suppressed using a Hjorth parameter–based PPG artifact detector described by Gil et al [68]. Pulses are detected from the PPG signal on those time slots without artifacts using an algorithm based on the study by Lázaro et al [69]. The same ECG parameters are also extracted in PPG, in this case, referred to as pulse rate variability. Subsequently, the mean time difference between the R peak in the ECG signal and the point of 50% increase, corresponding to the pulse detected on the finger by the PPG signal, is considered as the PAT, and its SD (SD of PAT) is also calculated.

The respiration wave is filtered with an FIR passband filter with cutoff frequencies of 0.03 and 0.9 Hz. The respiratory rate is estimated as the frequency to which the maximum peak of the power density spectrum corresponds, estimated using a fast Fourier transform [70]. When the peak is >65%, then respiratory rate is considered valid.

The EDA signal is visually inspected to remove motion artifacts and linearly interpolated. First, a time-domain analysis is performed using a convex optimization model, called cvxEDA [57], to calculate the tonic and phasic components. The second procedure is a frequency-domain analysis, proposed to assess sympathetic tone through a parameter named EDASymp, described in the study by Posada-Quintero et al [71].

Finally, for the ST signal, a visual inspection is carried out to look for possible large artifacts. These segments are discarded before proceeding with the calculation of the parameters.

Statistical Analysis Plan

An initial descriptive analysis will be conducted for all study variables, for the overall sample and stratified by study group. The quantitative variables will be summarized, assuming normal distribution (Shapiro-Wilk normality test), using the mean and SD. The qualitative variables will be summarized using the relative and absolute frequencies. Physiological variables that present a skewed distribution will be logarithmically transformed.

A parametric test (Pearson correlation) or nonparametric test (Spearman correlation) will be, accordingly, applied as a descriptive measure of the association between quantitative variables.

To develop a useful tool for assessing mental distress and well-being, the initial step of the statistical analysis plan will involve variables reduction using two methods: (1) a correlation analysis to prioritize the most relevant variables for the prediction of the primary outcome measures and (2) a principal component analysis to find the directions of maximum variance in the data and reduce collinearity. Subsequently, the generated components that account for at least 85% (51/60) of the sample's variability will be included. From these components, 2 separate analyses will be conducted. First, a generalized linear model will be fitted to predict the values of each primary outcome measure. Second, a model will be developed to differentiate the 3 groups identified in the study, each representing a different level of mental health. The models will be fitted using standardized variables and performing k-fold cross-validation to quantify the model's performance using R^2 for the linear regression model and area under the curve for the classification models. Known-group validity will be assessed by comparing the mean scores of the tool among the preestablished groups at baseline: diagnosed with current depression or anxiety, symptoms of mental distress, and high mental well-being. The predefined hypothesis that higher model scores are predicted for individuals with higher well-being will be evaluated using the Jonckheere-Terpstra test, and Cohen effect sizes will be computed for each category as compared with the lowest category (mental health condition), considering small (0.2), moderate (0.5), and large (0.8) effect sizes [72].

The model test-retest reliability will be assessed with a 2-way random effect intraclass correlation coefficient (ICC), taking repeated evaluations of the same *unchanged* individuals, to assess the extent to which measures remain stable. A *change* will be considered a clinically relevant change in the outcome scores, ie, ≥4 points for the Generalized Anxiety Disorder-7, ≥5 points for PHQ-9, or ≥3 points for SWEMWBS) [73-75].

The significance level will be set at α=.05. Statistical analysis will be performed using SAS (version 9.4; SAS Institute).

Sample Size

As a proof-of-concept study, we plan to include 20 individuals per group (a total of 60 individuals×2 evaluations). For the assessment of known-groups validity of the developed tool,

with this sample size of 20 individuals per group, and a type I error rate α=.05 on a 1-sided *t* test, we will have power of 0.80 to detect a difference between 2 groups corresponding to an effect size of 0.8. For a moderate effect size of 0.5, the power will decrease to 0.47 [17].

Concerning the assessment of test-retest reliability of the tool, assuming a 15% (9/60) loss in follow-up or nonstable participants from baseline participants, an ICC of 0.6 under the null hypothesis, and a type I error rate of α=.05, a sample size of 51 participants with 2 observations per participant achieves a power of 0.90 to detect a hypothetical ICC value of 0.8 under the alternative hypothesis [17].

Ethical Considerations

This study protocol was approved by the research ethics committees of both institutions (2021/10163 for PSMAR and 5912 for UAB). This study is in line with the principles established by national and international regulations, including the Declaration of Helsinki and the Code of Ethics. Ethics approval has been obtained in Barcelona from the independent PSMAR Clinical Research Ethics Committee and the Research Ethics Committee of the UAB. Informed consent is requested from all participants before their inclusion in the study. Participants are explained that they can withdraw from the study at any time without giving a reason and that they can request to delete all the data collected from them.

All personal data will be handled following Regulation (European Union) 2016/679 of the European Parliament and the Council on the protection of natural persons concerning the processing of personal data and on the free movement of such data and the National Organic Law 3/2018, of December 5, on Personal Data Protection and the Guarantee of Digital Rights. Physiological and psychometric data will be pseudoanonymized to guarantee privacy in data analysis and will be stored in a research database following the General Data Protection Regulation of the European Union.

Participants receive a €10 (US $11) gift card for enrolling in the study, and participants receive another gift card of the same value if they complete the second assessment.

Results

The project was granted in February 2022 and the approval from ethical committees was obtained between April and May 2022. Participant recruitment started in October 2022 and is expected to continue through June 2024. Different recruitment strategies are implemented, including advertising campaigns and invitation letters at the university and recruitment of patients by psychologists.

As of July 2023, a total of 41 participants completed the first and second assessments. The sample corresponds mainly to the group with mild to moderate psychological distress (n=20, 49%), followed by the group with high mental well-being (n=13, 32%) and, finally, those diagnosed with an anxiety disorder (n=8, 20%). At this point, preprocessing and quality checks of the data are ongoing, and the statistical analysis will subsequently begin. The first results are expected to be published in September 2024.

Discussion

Overview

There is a growing interest in remotely assessing mental health through changes in the ANS functioning and its association with mental health and well-being [26]. There is significant evidence to support the notion that changes in the ANS can be inferred from changes in physiological variables, such as HRV, EDA response, and peripheral temperature [58,76,77]. However, there is a challenge in designing a robust predictive model that allows this assessment to be easy and objective to be systematically used in epidemiology and clinical settings. To fill this gap, it is important to carefully measure electrophysiological signals considering the updated standards of measurement (eg, [78]), following a structure of 3-time point experimental design: considering a basal condition, during a stress-inducing task to investigate the stress reactivity, and a recovery stage. This study is applying a similar methodology used in previous research that reached good reliability in its predictive models [20,79]. However, in this novel approach, individuals with a clinically diagnosed mental health condition are being enrolled, which may allow for a better distinction between different profiles of mental health through the stress reactivity pattern and cognitive performance.

The SCWT is a well-known neuropsychological test reported as a reliable moderate mental stressor, provoking significant physiological changes such as reduced HRV and increased EDA and blood pressure [59,80,81]. Furthermore, it is a useful tool for evaluating cognitive processes and has the advantage of not generating a significant learning effect [82]. Cognitive inhibition is compromised in multiple mental health conditions; for example, individuals with anxiety disorders tend to have longer reaction times and higher error rates on the SCWT, particularly in the incongruent condition, which suggests difficulties with selective attention and response inhibition [83]. Thus, although the impaired performance of the task may be indicative of an underlying neurological disorder, a good result performance may add another layer of confidence in evaluating mental well-being.

There is a lot of research committed to investigating biomarkers and stress reactivity in patients diagnosed with depression and anxiety disorders [15,84]. The evidence supports differences in physiological behavior in patients with depression and anxiety compared with healthy individuals. Considering this, the decision to include 3 groups with different mental health states will facilitate the detection of patterns that could discriminate them more accurately. The age range selected is justified by the typical early age of onset of mental health conditions and the need for assertive responses to prevent a poor prognosis. Moreover, the recruitment is planned to be carried out in part at a university, considering that university students have been reported as a susceptible population with a higher risk to manifest mental health symptoms [85], which enables us to recruit the mild to moderate psychological distress group effortlessly. To minimize interindividual variation in

physiological measures and the influence of external factors, we propose 2 different sessions with the same participants, which will also increase the statistical power [78].

Mobile health (mHealth), which includes physical devices, sensors, software, and other technologies, has been proposed to improve clinical care as it enables data collection, symptom monitoring, and provision of interventions [29]. In this sense, it could be a valuable resource to reach both regular patients and those who do not receive adequate care [12]. Specifically, the use of wearables provides a new and unobtrusive way to monitor physiological biomarkers and gather continuous information about individuals' daily lives and clinical symptoms for both clinical and research purposes. These devices with multiple embedded sensors can be useful in following up patients and remotely assessing their mental well-being through robust models that combine a set of relevant biomarkers [31].

Nevertheless, to ensure that autonomous nervous system biomarkers are effectively used for objectively measuring mental well-being in health services, it is necessary to undertake substantial work in identifying the most useful biomarkers and comprehending the possible obstacles and enablers of widespread adoption. To advance in this direction, this study intends to carry out a preliminary model validation by enrolling a preselected sample with different states of mental well-being in a laboratory-controlled condition; subsequently, we plan to explore its application in larger populations and in a real-life context.

To summarize, our study aims to design a comprehensive multiparametric model combining physiological and cognitive variables to assess the mental well-being among young people. The self-reported questionnaires currently used in clinical settings will be used as a reference to select the best model fit. This novel approach proposes shifting the paradigm to assessing mental well-being rather than measuring the severity of symptoms or a mental health condition. We believe that this change may allow health professionals to properly recommend prevention strategies and increase the possibility of intervening before the diagnosis of a mental health condition. To effectively develop a model that can be easily calculated by a wearable device, we first take a measurement of a standard medical device to ensure the best quality of physiological signal and then establish the final predictive tool.

Conclusions

This study represents the primary phase in developing a comprehensive mental well-being assessment tool. Our goal is to progress toward remote measurements with acceptable accuracy, using sophisticated devices as a benchmark for comparison. Developing a robust predictive model will facilitate objective assessment that can be systematically used in epidemiological and clinical settings. Further research is required to explore the full potential of this technology in mental health research and clinical practice.

Acknowledgments

This study is receiving funding from the Centro de Investigación Biomédica en Red (CIBER) de Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN, Instituto de Salud Carlos III [ISCIII], Madrid, Spain) and the CIBER de Epidemiología y Salud Pública (CIBERESP, ISCIII, Madrid, Spain) for CIBERESP-BBN Collaboration Projects and the Departament de Recerca i Universitats of the Generalitat de Catalunya (AGAUR 2021 SGR 00624). This work is also partially funded by Ministerio de Ciencia e Innovación and European Social Fund, Spain (TED2021-131106B-I00), and the European Social Fund (European Union). PM received funding from the ISCIII-FSE (Fondo Social Europeo; Miguel Servet grant CP21/00078). RB received funding from the BSICoS (Biomedical Signal Interpretation and Computational Simulation) group (T39 23R) by the Aragon Government.

Data Availability

The data sets generated during this study will be deposited in the Open Science Framework public repository.

Authors' Contributions

TCR, EGP, and J Aguiló drafted the first version of this manuscript. LB, J Alonso, and GV provided critical revision of further drafts of the manuscript. J Alonso, J Aguiló, TCR, EGP, HGM, GV, and FA made substantial contributions to the conception and design of the study protocol. RB and PM contributed to the scientific knowledge of the project. VPS and ASB contributed to patients' referral. TCR, EGP, and VSA were involved with the clinical interviews and psychophysiological assessments. J Alonso and J Aguiló are the principal investigator and coinvestigator of the study, respectively. All authors reviewed the latest version of the paper draft, provided comments, and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Summary of the literature review of the physiological variables assessed in the M&M mHealth Methods in Mental Health Research (M&M) Project

[DOCX File , 23 KB - resprot_v13i1e51298_app1.docx]

References

1. Walker ER, McGee RE, Druss BG. Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis. JAMA Psychiatry 2015 Apr;72(4):334-341 [FREE Full text] [doi: 10.1001/jamapsychiatry.2014.2502] [Medline: 25671328]
2. Global health estimates. World Health Organization. 2019. URL: https://www.who.int/data/global-health-estimates [accessed 2023-07-11]
3. Vieta E, Alonso J, Pérez-Sola V, Roca M, Hernando T, Sicras-Mainar A, et al. Epidemiology and costs of depressive disorder in Spain: the EPICO study. Eur Neuropsychopharmacol 2021 Sep;50:93-103 [FREE Full text] [doi: 10.1016/j.euroneuro.2021.04.022] [Medline: 34058711]
4. Fusar-Poli P. Integrated mental health services for the developmental period (0 to 25 years): a critical review of the evidence. Front Psychiatry 2019 Jun 7;10:355 [FREE Full text] [doi: 10.3389/fpsyt.2019.00355] [Medline: 31231250]
5. de Sousa GM, Tavares VD, de Meiroz Grilo ML, Coelho ML, de Lima-Araújo GL, Schuch FB, et al. Mental health in COVID-19 pandemic: a meta-review of prevalence meta-analyses. Front Psychol 2021 Sep 21;12:703838 [FREE Full text] [doi: 10.3389/fpsyg.2021.703838] [Medline: 34621212]
6. Dragioti E, Li H, Tsitsas G, Lee KH, Choi J, Kim J, et al. A large-scale meta-analytic atlas of mental health problems prevalence during the COVID-19 early pandemic. J Med Virol 2022 May;94(5):1935-1949 [FREE Full text] [doi: 10.1002/jmv.27549] [Medline: 34958144]
7. Li W, Zhao Z, Chen D, Peng Y, Lu Z. Prevalence and associated factors of depression and anxiety symptoms among college students: a systematic review and meta-analysis. J Child Psychol Psychiatry 2022 Nov;63(11):1222-1230. [doi: 10.1111/jcpp.13606] [Medline: 35297041]
8. Farooq S, Tunmore J, Wajid Ali M, Ayub M. Suicide, self-harm and suicidal ideation during COVID-19: a systematic review. Psychiatry Res 2021 Dec;306:114228 [FREE Full text] [doi: 10.1016/j.psychres.2021.114228] [Medline: 34670162]
9. Lipson SK, Zhou S, Abelson S, Heinze J, Jirsa M, Morigney J, et al. Trends in college student mental health and help-seeking by race/ethnicity: findings from the national healthy minds study, 2013-2021. J Affect Disord 2022 Jun 01;306:138-147 [FREE Full text] [doi: 10.1016/j.jad.2022.03.038] [Medline: 35307411]
10. Solmi M, Radua J, Olivola M, Croce E, Soardo L, Salazar de Pablo G, et al. Age at onset of mental disorders worldwide: large-scale meta-analysis of 192 epidemiological studies. Mol Psychiatry 2022 Jan;27(1):281-295 [FREE Full text] [doi: 10.1038/s41380-021-01161-7] [Medline: 34079068]
11. World Health Organization. The World health report : 2001 : mental health : new understanding, new hope. World Health Organization. 2001. URL: https://iris.who.int/handle/10665/42390 [accessed 2021-11-15]
12. Promoting mental health: concepts, emerging evidence, practice. World Health Organization. 2005 Jan 01. URL: https://www.who.int/publications/i/item/9241562943 [accessed 2021-11-15]
13. Kiecolt-Glaser JK, Renna ME, Shrout MR, Madison AA. Stress reactivity: what pushes us higher, faster, and longer - and why it matters. Curr Dir Psychol Sci 2020 Oct 01;29(5):492-498 [FREE Full text] [doi: 10.1177/0963721420949521] [Medline: 33758478]
14. Rodrigues S, Kaiseler M, Queirós C. Psychophysiological assessment of stress under ecological settings. Eur Psychol 2015 Jul;20(3):204-226. [doi: 10.1027/1016-9040/a000222]
15. Ahmed T, Qassem M, Kyriacou PA. Physiological monitoring of stress and major depression: a review of the current monitoring techniques and considerations for the future. Biomed Signal Process Control 2022 May;75:103591. [doi: 10.1016/j.bspc.2022.103591]
16. Cuthbert BN. Research domain criteria (RDoC): progress and potential. Curr Dir Psychol Sci 2022 Apr;31(2):107-114 [FREE Full text] [doi: 10.1177/09637214211051363] [Medline: 35692384]
17. Visintainer PF. SAMPICC: stata module to compute sample size for an intra-class correlation (ICC). Boston College Department of Economics. 2008. URL: https://ideas.repec.org/c/boc/bocode/s456978.html [accessed 2023-12-14]
18. Insel TR. Digital phenotyping: technology for a new science of behavior. JAMA 2017 Oct 03;318(13):1215-1216. [doi: 10.1001/jama.2017.11295] [Medline: 28973224]
19. Kim HG, Cheon EJ, Bai DS, Lee YH, Koo BH. Stress and heart rate variability: a meta-analysis and review of the literature. Psychiatry Investig 2018 Mar;15(3):235-245 [FREE Full text] [doi: 10.30773/pi.2017.08.17] [Medline: 29486547]
20. García Pagès E, Arza A, Lazaro J, Puig C, Castro T, Ottaviano M, et al. Psychosomatic response to acute emotional stress in healthy students. Front Physiol 2023 Jan 9;13:960118 [FREE Full text] [doi: 10.3389/fphys.2022.960118] [Medline: 36699693]
21. Tipton MJ, Harper A, Paton JF, Costello JT. The human ventilatory response to stress: rate or depth? J Physiol 2017 Sep 01;595(17):5729-5752 [FREE Full text] [doi: 10.1113/JP274596] [Medline: 28650070]
22. Ghiasi S, Greco A, Barbieri R, Scilingo EP, Valenza G. Assessing autonomic function from electrodermal activity and heart rate variability during cold-pressor test and emotional challenge. Sci Rep 2020 Mar 25;10(1):5406 [FREE Full text] [doi: 10.1038/s41598-020-62225-2] [Medline: 32214158]

23. Vinkers CH, Penning R, Hellhammer J, Verster JC, Klaessens JH, Olivier B, et al. The effect of stress on core and peripheral body temperature in humans. Stress 2013 Sep;16(5):520-530. [doi: 10.3109/10253890.2013.807243] [Medline: 23790072]
24. Pisanski K, Kobylarek A, Jakubowska L, Nowak J, Walter A, Błaszczyński K, et al. Multimodal stress detection: testing for covariation in vocal, hormonal and physiological responses to trier social stress test. Horm Behav 2018 Nov;106:52-61. [doi: 10.1016/j.yhbeh.2018.08.014] [Medline: 30189213]
25. Matcham F, Leightley D, Siddi S, Lamers F, White KM, Annas P, et al. Remote Assessment of Disease and Relapse in Major Depressive Disorder (RADAR-MDD): recruitment, retention, and data availability in a longitudinal remote measurement study. BMC Psychiatry 2022 Feb 21;22(1):136 [FREE Full text] [doi: 10.1186/s12888-022-03753-1] [Medline: 35189842]
26. W Adams Z, McClure EA, Gray KM, Danielson CK, Treiber FA, Ruggiero KJ. Mobile devices for the remote acquisition of physiological and behavioral biomarkers in psychiatric clinical research. J Psychiatr Res 2017 Feb;85:1-14 [FREE Full text] [doi: 10.1016/j.jpsychires.2016.10.019] [Medline: 27814455]
27. Gedam S, Paul S. A review on mental stress detection using wearable sensors and machine learning techniques. IEEE Access 2021 Jun 02;9:84045-84066. [doi: 10.1109/access.2021.3085502]
28. Klimek A, Mannheim I, Schouten G, Wouters EJ, Peeters MW. Wearables measuring electrodermal activity to assess perceived stress in care: a scoping review. Acta Neuropsychiatr 2023 Mar 24:1-11. [doi: 10.1017/neu.2023.19] [Medline: 36960675]
29. Gaskin J, Jenkins J, Meservy T, Steffen J, Payne K. Using wearable devices for non-invasive, inexpensive physiological data collection. In: Proceedings of the 50th Hawaii International Conference on System Sciences. 2017 Presented at: HICSS 2017; January 4-7, 2017; Hilton Waikoloa Village, Hawaii. [doi: 10.24251/HICSS.2017.072]
30. Sano A, Taylor S, McHill AW, Phillips AJ, Barger LK, Klerman E, et al. Identifying objective physiological markers and modifiable behaviors for self-reported stress and mental health status using wearable sensors and mobile phones: observational study. J Med Internet Res 2018 Jun 08;20(6):e210 [FREE Full text] [doi: 10.2196/jmir.9410] [Medline: 29884610]
31. Shanmugasundaram G, Yazhini S, Hemapratha E, Nithya S. A comprehensive review on stress detection techniques. In: Proceedings of the 2019 IEEE International Conference on System, Computation, Automation and Networking (ICSCAN). 2019 Presented at: ICSCAN 2019; March 29-30, 2019; Pondicherry, India. [doi: 10.1109/icscan.2019.8878795]
32. Siddi S, Bailon R, Giné-Vázquez I, Matcham F, Lamers F, Kontaxis S, PAB members, et al. The usability of daytime and night-time heart rate dynamics as digital biomarkers of depression severity. Psychol Med 2023 Jun;53(8):3249-3260. [doi: 10.1017/S0033291723001034] [Medline: 37184076]
33. Kontaxis S, Gil E, Marozas V, Lazaro J, Garcia E, Posadas-de Miguel M, et al. Photoplethysmographic waveform analysis for autonomic reactivity assessment in depression. IEEE Trans Biomed Eng 2021 Apr;68(4):1273-1281. [doi: 10.1109/tbme.2020.3025908]
34. Sano A, Phillips AJ, Yu AZ, McHill AW, Taylor S, Jaques N, et al. Recognizing academic performance, sleep quality, stress level, and mental health using personality traits, wearable sensors and mobile phones. In: Proceedings of the 2015 IEEE 12th International Conference on Wearable and Implantable Body Sensor Networks (BSN). 2015 Presented at: BSN 2015; June 9-12, 2015; Cambridge, MA. [doi: 10.1109/bsn.2015.7299420]
35. Kroenke K, Spitzer RL, Williams JB, Löwe B. An ultra-brief screening scale for anxiety and depression: the PHQ-4. Psychosomatics 2009;50(6):613-621. [doi: 10.1176/appi.psy.50.6.613] [Medline: 19996233]
36. Stewart-Brown S, Tennant A, Tennant R, Platt S, Parkinson J, Weich S. Internal construct validity of the Warwick-Edinburgh Mental Well-being Scale (WEMWBS): a Rasch analysis using data from the Scottish Health Education Population Survey. Health Qual Life Outcomes 2009 Feb 19;7:15 [FREE Full text] [doi: 10.1186/1477-7525-7-15] [Medline: 19228398]
37. López MA, Gabilondo A, Codony M, García-Forero C, Vilagut G, Castellví P, et al. Adaptation into Spanish of the Warwick-Edinburgh Mental Well-being Scale (WEMWBS) and preliminary validation in a student sample. Qual Life Res 2013 Jun;22(5):1099-1104. [doi: 10.1007/s11136-012-0238-z] [Medline: 22836376]
38. Medina A, Schiaffino A. Enquesta de salut de Catalunya, 2016. Direcció General de Planificació en Salut. 2017. URL: https://hdl.handle.net/11351/3205 [accessed 2023-07-23]
39. Golden CJ. Stroop. Test de Colores y Palabras – Edición Revisada (B. Ruiz-Fernández, T. Luque y F. Sánchez-Sánchez, adaptadores). TEA Ediciones. Madrid: TEA Ediciones; 2020. URL: https://web.teaediciones.com/Ejemplos/STROOP-extracto-Web.pdf [accessed 2023-04-27]
40. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary care evaluation of mental disorders. Patient health questionnaire. JAMA 1999 Nov 10;282(18):1737-1744. [doi: 10.1001/jama.282.18.1737] [Medline: 10568646]
41. Diez-Quevedo C, Rangil T, Sanchez-Planell L, Kroenke K, Spitzer RL. Validation and utility of the patient health questionnaire in diagnosing mental disorders in 1003 general hospital Spanish inpatients. Psychosom Med 2001;63(4):679-686. [doi: 10.1097/00006842-200107000-00021] [Medline: 11485122]
42. Levis B, Benedetti A, Thombs BD, DEPRESsion Screening Data (DEPRESSD) Collaboration. Accuracy of Patient Health Questionnaire-9 (PHQ-9) for screening to detect major depression: individual participant data meta-analysis. BMJ 2019 Apr 09;365:l1476 [FREE Full text] [doi: 10.1136/bmj.l1476] [Medline: 30967483]

43. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006 May 22;166(10):1092-1097. [doi: 10.1001/archinte.166.10.1092] [Medline: 16717171]
44. García-Campayo J, Zamorano E, Ruiz MA, Pardo A, Pérez-Páramo M, López-Gómez V, et al. Cultural adaptation into Spanish of the Generalized Anxiety Disorder-7 (GAD-7) scale as a screening tool. Health Qual Life Outcomes 2010 Jan 20;8:8 [FREE Full text] [doi: 10.1186/1477-7525-8-8] [Medline: 20089179]
45. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav 1983 Dec;24(4):385-396. [doi: 10.2307/2136404]
46. Remor E. Psychometric properties of a European Spanish version of the Perceived Stress Scale (PSS). Span J Psychol 2006 May;9(1):86-93 [FREE Full text] [doi: 10.1017/s1138741600006004] [Medline: 16673626]
47. Brown RL, Rounds LA. Conjoint screening questionnaires for alcohol and other drug abuse: criterion validity in a primary care practice. Wis Med J 1995;94(3):135-140. [Medline: 7778330]
48. Ewing JA. Detecting alcoholism: the CAGE Questionnaire. JAMA 1984 Oct 12;252(14):1905-1907. [doi: 10.1001/jama.1984.03350140051025]
49. Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, et al. International Physical Activity Questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 2003 Aug;35(8):1381-1395. [doi: 10.1249/01.MSS.0000078924.61453.FB] [Medline: 12900694]
50. Román Viñas B, Ribas Barba L, Ngo J, Serra Majem L. Validity of the International Physical Activity Questionnaire in the Catalan population (Spain) [Article in Spanish]. Gac Sanit 2013;27(3):254-257 [FREE Full text] [doi: 10.1016/j.gaceta.2012.05.013] [Medline: 23103093]
51. Stewart AL, Ware JE. Measuring Functioning and Well-being: The Medical Outcomes Study Approach. Durham, NC: Duke University Press; 1992.
52. Rejas J, Ribera MV, Ruiz M, Masrramón X. Psychometric properties of the MOS (Medical Outcomes Study) sleep scale in patients with neuropathic pain. Eur J Pain 2007 Apr;11(3):329-340. [doi: 10.1016/j.ejpain.2006.05.002] [Medline: 16765622]
53. Stroop JR. Studies of interference in serial verbal reactions. J Exp Psychol 1935;18(6):643-662. [doi: 10.1037/h0054651]
54. Hamid FA, Saad MN, Malik AS. Characterization stress reactions to Stroop Color-Word Test using spectral analysis. Mater Today Proc 2019;16(4):1949-1958. [doi: 10.1016/j.matpr.2019.06.073]
55. Aguiló Mir S, García Pagès E, López Barbeito B, Ribeiro TC, Garzón-Rey JM, Aguiló Llobet J. Design and validation of an electrophysiological based tool to assess chronic stress. case study: burnout syndrome in caregivers. Stress 2021 Jul;24(4):384-393. [doi: 10.1080/10253890.2020.1807512] [Medline: 32865469]
56. Bolea J, Almeida R, Laguna P, Sornmo L, Martinez JP. BioSigBrowser, biosignal processing interface. In: Proceedings of the 2009 9th International Conference on Information Technology and Applications in Biomedicine. 2009 Presented at: ITAB 2009; November 4-7, 2009; Larnaka, Cyprus. [doi: 10.1109/itab.2009.5394301]
57. Greco A, Valenza G, Lanata A, Scilingo E, Citi L. cvxEDA: a convex optimization approach to electrodermal activity processing. IEEE Trans Biomed Eng 2016 Apr;63(4):797-804. [doi: 10.1109/tbme.2015.2474131]
58. Pham T, Lau ZJ, Chen SH, Makowski D. Heart rate variability in psychology: a review of HRV indices and an analysis tutorial. Sensors (Basel) 2021 Jun 09;21(12):3998 [FREE Full text] [doi: 10.3390/s21123998] [Medline: 34207927]
59. Nardelli M, Greco A, Sebastiani L, Scilingo EP. ComEDA: a new tool for stress assessment based on electrodermal activity. Comput Biol Med 2022 Nov;150:106144 [FREE Full text] [doi: 10.1016/j.compbiomed.2022.106144] [Medline: 36215850]
60. Finnegan E, Davidson S, Harford M, Jorge J, Watkinson P, Young D, et al. Pulse arrival time as a surrogate of blood pressure. Sci Rep 2021 Nov 23;11(1):22767 [FREE Full text] [doi: 10.1038/s41598-021-01358-4] [Medline: 34815419]
61. Celka P, Charlton PH, Farukh B, Chowienczyk P, Alastruey J. Influence of mental stress on the pulse wave features of photoplethysmograms. Healthc Technol Lett 2019 Nov 26;7(1):7-12 [FREE Full text] [doi: 10.1049/htl.2019.0001] [Medline: 32190335]
62. Castro Ribeiro T, Sobregrau Sangrà P, García Pagès E, Badiella L, López-Barbeito B, Aguiló S, et al. Assessing effectiveness of heart rate variability biofeedback to mitigate mental health symptoms: a pilot study. Front Physiol 2023 May 10;14:1147260 [FREE Full text] [doi: 10.3389/fphys.2023.1147260] [Medline: 37234414]
63. Leyro TM, Versella MV, Yang MJ, Brinkman HR, Hoyt DL, Lehrer P. Respiratory therapy for the treatment of anxiety: meta-analytic review and regression. Clin Psychol Rev 2021 Mar;84:101980 [FREE Full text] [doi: 10.1016/j.cpr.2021.101980] [Medline: 33540222]
64. Hernando A, Lazaro J, Gil E, Arza A, Garzon JM, Lopez-Anton R, et al. Inclusion of respiratory frequency information in heart rate variability analysis for stress assessment. IEEE J Biomed Health Inform 2016 Jul;20(4):1016-1025 [FREE Full text] [doi: 10.1109/jbhi.2016.2553578]
65. Gioia F, Callara AL, Bruderer T, Ripszam M, Di Francesco F, Scilingo EP, et al. Potential physiological stress biomarkers in human sweat. In: Proceedings of the 2022 IEEE International Symposium on Medical Measurements and Applications (MeMeA). 2022 Presented at: MeMeA 2022; June 22-24, 2022; Messina, Italy. [doi: 10.1109/MeMeA54994.2022.9856534]
66. Martinez JP, Almeida R, Olmos S, Rocha AP, Laguna P. A wavelet-based ECG delineator: evaluation on standard databases. IEEE Trans Biomed Eng 2004 Apr;51(4):570-581. [doi: 10.1109/tbme.2003.821031]

67. Mateo J, Laguna P. Analysis of heart rate variability in the presence of ectopic beats using the heart timing signal. IEEE Trans Biomed Eng 2003 Mar;50(3):334-343. [doi: 10.1109/tbme.2003.808831]
68. Gil E, Mendez M, Vergara JM, Cerutti S, Bianchi AM, Laguna P. Discrimination of sleep-apnea-related decreases in the amplitude fluctuations of PPG signal in children by HRV analysis. IEEE Trans Biomed Eng 2009 Apr;56(4):1005-1014. [doi: 10.1109/tbme.2008.2009340]
69. Lazaro J, Gil E, Vergara JM, Laguna P. Pulse rate variability analysis for discrimination of sleep-apnea-related decreases in the amplitude fluctuations of pulse photoplethysmographic signal in children. IEEE J Biomed Health Inform 2014 Jan;18(1):240-246. [doi: 10.1109/jbhi.2013.2267096]
70. Lázaro J, Alcaine A, Romero D, Gil E, Laguna P, Pueyo E, et al. Electrocardiogram derived respiratory rate from QRS slopes and R-wave angle. Ann Biomed Eng 2014 Oct;42(10):2072-2083. [doi: 10.1007/s10439-014-1073-x] [Medline: 25118665]
71. Posada-Quintero HF, Florian JP, Orjuela-Cañón AD, Aljama-Corrales T, Charleston-Villalobos S, Chon KH. Power spectral density analysis of electrodermal activity for sympathetic function assessment. Ann Biomed Eng 2016 Oct;44(10):3124-3135. [doi: 10.1007/s10439-016-1606-6] [Medline: 27059225]
72. Cohen J. Statistical Power Analysis for the Behavioral Sciences. Cambridge, MA: Academic Press; 1969.
73. Löwe B, Unützer J, Callahan CM, Perkins AJ, Kroenke K. Monitoring depression treatment outcomes with the Patient Health Questionnaire-9. Med Care 2004 Dec;42(12):1194-1201. [doi: 10.1097/00005650-200412000-00006] [Medline: 15550799]
74. Shah N, Cader M, Andrews WP, Wijesekera D, Stewart-Brown SL. Responsiveness of the Short Warwick Edinburgh Mental Well-Being Scale (SWEMWBS): evaluation a clinical sample. Health Qual Life Outcomes 2018 Dec 22;16(1):239 [FREE Full text] [doi: 10.1186/s12955-018-1060-2] [Medline: 30577856]
75. Toussaint A, Hüsing P, Gumz A, Wingenfeld K, Härter M, Schramm E, et al. Sensitivity to change and minimal clinically important difference of the 7-item Generalized Anxiety Disorder Questionnaire (GAD-7). J Affect Disord 2020 Mar 15;265:395-401. [doi: 10.1016/j.jad.2020.01.032] [Medline: 32090765]
76. Amin R, Faghih RT. Physiological characterization of electrodermal activity enables scalable near real-time autonomic nervous system activation inference. PLoS Comput Biol 2022 Jul 28;18(7):e1010275 [FREE Full text] [doi: 10.1371/journal.pcbi.1010275] [Medline: 35900988]
77. Arza A, Garzón-Rey JM, Lázaro J, Gil E, Lopez-Anton R, de la Camara C, et al. Measuring acute stress response through physiological signals: towards a quantitative assessment of stress. Med Biol Eng Comput 2019 Jan;57(1):271-287. [doi: 10.1007/s11517-018-1879-z] [Medline: 30094756]
78. Laborde S, Mosley E, Thayer JF. Heart rate variability and cardiac vagal tone in psychophysiological research - recommendations for experiment planning, data analysis, and data reporting. Front Psychol 2017 Feb 20;8:213 [FREE Full text] [doi: 10.3389/fpsyg.2017.00213] [Medline: 28265249]
79. Garzón-Rey JM. Psychosomatic approach to stress measurement. Universitat Autònoma de Barcelona. 2017. URL: https://hdl.handle.net/10803/458661 [accessed 2020-09-17]
80. Satish P, Muralikrishnan K, Balasubramanian K, Shanmugapriya. Heart rate variability changes during Stroop Color and Word Test among genders. Indian J Physiol Pharmacol 2015;59(1):9-15. [Medline: 26571978]
81. Boutcher YN, Boutcher SH. Cardiovascular response to Stroop: effect of verbal response and task difficulty. Biol Psychol 2006 Oct;73(3):235-241. [doi: 10.1016/j.biopsycho.2006.04.005] [Medline: 16730405]
82. MacLeod CM. Half a century of research on the Stroop effect: an integrative review. Psychol Bull 1991;109(2):163-203. [doi: 10.1037//0033-2909.109.2.163]
83. Berggren N, Derakshan N. Inhibitory deficits in trait anxiety: increased stimulus-based or response-based interference? Psychon Bull Rev 2014 Oct;21(5):1339-1345. [doi: 10.3758/s13423-014-0611-8] [Medline: 24610066]
84. Koch C, Wilhelm M, Salzmann S, Rief W, Euteneuer F. A meta-analysis of heart rate variability in major depression. Psychol Med 2019 Sep;49(12):1948-1957. [doi: 10.1017/S0033291719001351] [Medline: 31239003]
85. Hernández-Torrano D, Ibrayeva L, Sparks J, Lim N, Clementi A, Almukhambetova A, et al. Mental health and well-being of university students: a bibliometric mapping of the literature. Front Psychol 2020 Jun 9;11:1226 [FREE Full text] [doi: 10.3389/fpsyg.2020.01226] [Medline: 32581976]

Abbreviations

ANS: autonomic nervous system
ECG: electrocardiogram
EDA: electrodermal activity
FIR: finite impulse response
HRV: heart rate variability
ICC: intraclass correlation coefficient
M&M: mHealth Methods in Mental Health Research
mHealth: mobile health

PAT: pulse arrival time
PHQ: Patient Health Questionnaire
PPG: photoplethysmography
PSMAR: Parc de Salut Mar
SCWT: Stroop Color and Word Test
ST: skin temperature
SWEMWBS: short version of Warwick-Edinburgh Mental Well-being Scale
UAB: Autonomous University of Barcelona

Edited by A Mavragani; submitted 27.07.23; peer-reviewed by V Sideropoulos; comments to author 09.11.23; revised version received 22.12.23; accepted 11.01.24; published 29.03.24.

Please cite as:
Castro Ribeiro T, García Pagès E, Ballester L, Vilagut G, García Mieres H, Suárez Aragonès V, Amigo F, Bailón R, Mortier P, Pérez Sola V, Serrano-Blanco A, Alonso J, Aguiló J
Design of a Remote Multiparametric Tool to Assess Mental Well-Being and Distress in Young People (mHealth Methods in Mental Health Research Project): Protocol for an Observational Study
JMIR Res Protoc 2024;13:e51298
URL: https://www.researchprotocols.org/2024/1/e51298
doi:10.2196/51298
PMID:38551647

Protocol

National Tunisian Study of Cardiac Implantable Electronic Devices: Design and Protocol for a Nationwide Multicenter Prospective Observational Study

Sonia Chabrak[1], MD; Abdeddayem Haggui[2], MD; Emna Allouche[3], MD; Sana Ouali[4], MD; Afef Ben Halima[5], MD; Slim Kacem[6], MD; Salma Krichen[7], MD; Sonia Marrakchi[8], MD; Wafa Fehri[9], MD; Mohamed Sami Mourali[4], MD; Zeineb Jabbari[4], MD; Manel Ben Halima[10], MD; Elyes Neffati[11], MD; Aymen Heraiech[11], MD; Mehdi Slim[11], MD; Salem Kachboura[10], MD; Habib Gamra[12], MD; Majed Hassine[12], MD; Sondes Kraiem[13], MD; Sofien Kammoun[13], MD; Leila Bezdah[3], MD; Gouider Jridi[14], MD; Hatem Bouraoui[14], MD; Samir Kammoun[15], MD; Rania Hammami[15,16], MD; Rafik Chettaoui[1], MD; Youssef Ben Ameur[17], MD; Fares Azaiez[17], MD; Rami Tlili[17], MD; Kais Battikh[18], MD; Hedi Ben Slima[19], MD; Rim Chrigui[1], MD; Samia Fazaa[1], MD; Islem Sanaa[20], MD; Yassine Ellouz[1], MD; Mohamed Mosrati[21], MD; Sami Milouchi[16,22], MD; Soumaya Jarmouni[1], MD; Wacef Ayadi[7], MD; Malek Akrout[7], MD; Rabie Razgallah[23], MD; Wissal Neffati[23], MD; Meriem Drissa[16,17], MD; Selma Charfeddine[15,16], MD; Salem Abdessalem[16], MD; Leila Abid[15], MD; Lilia Zakhama[24], MD

[1]Pasteur Clinic, General and Cardiovascular Clinic of Tunis, Tunis, Tunisia
[2]Military Hospital, Faculty of Medicine of Tunis, University of Tunis, Tunis, Tunisia
[3]Cardiology Department, Faculty of Medicine of Tunis, Charles Nicole Hospital, University of Tunis, Tunis, Tunisia
[4]Cardiology Department, Faculty of Medicine of Tunis, La Rabta Hospital, University of Tunis, Tunis, Tunisia
[5]Abderrahmen Mami Hospital, Faculty of Medicine of Tunis, University of Tunis, Tunis, Tunisia
[6]Essalem Center, Sousse, Tunisia
[7]Bassetine Clinic, Sfax, Tunisia
[8]Cardiology Department, Versailles Cardiology Center, Paris, France
[9]Cardiology Department, Faculty of Medicine of Tunis, Military Hospital, University of Tunis, Tunis, Tunisia
[10]Cardiology Department, Faculty of Medicine of Tunis, Abderrahmen Mami Hospital, University of Tunis, Tunis, Tunisia
[11]Cardiology Department, Faculty of Medicine of Sousse, Sahloul Hospital, University of Sousse, Sousse, Tunisia
[12]Cardiology A Department, Fattouma Bourguiba Hospital, Monastir, Tunisia
[13]Cardiology Department, Faculty of Medicine of Tunis, Habib Thameur Hospital, University of Tunis, Tunis, Tunisia
[14]Cardiology Department, Faculty of Medicine of Sousse, Farhat Hached Hospital, University of Sousse, Sousse, Tunisia
[15]Cardiology Department, Faculty of Medicine of Sfax, Hedi Chaker Hospital, University of Sfax, Sfax, Tunisia
[16]Tunisian Society of Cardiology and Cardiovascular Surgery, Tunis, Tunisia
[17]Cardiology Department, Faculty of Medicine of Tunis, Mongi Slim Hospital, University of Tunis, Tunis, Tunisia
[18]Berges du Lac Clinic, Medenine, Tunisia
[19]Cardiology Department, Faculty of Medicine of Tunis, Menzel Bourguiba Hospital, University of Tunis, Bizerte, Tunisia
[20]General & Cardiovascular Clinic, Tunis, Tunisia
[21]Carthage International Medical Center, Monastir, Tunisia
[22]Cardiology Department, Habib Bourguiba Hospital, University of Sfax, Medenine, Tunisia
[23]DACIMA Consulting, Tunis, Tunisia
[24]Cardiology Department, Hospital of the Interior Force Security, University of Tunis, Tunis, Tunisia

Corresponding Author:
Sonia Chabrak, MD
Pasteur Clinic
General and Cardiovascular Clinic of Tunis
Elkhadhra avenue, X 2 Pathway
Tunis, 1003
Tunisia
Phone: 216 22 889 349
Email: chabraksonia04@gmail.com

Abstract

Background: In Tunisia, the number of cardiac implantable electronic devices (CIEDs) is increasing, owing to the increase in patient life expectancy and expanding indications. Despite their life-saving potential and a significant reduction in population morbidity and mortality, their increased numbers have been associated with the development of multiple early and late complications related to vascular access, pockets, leads, or patient characteristics.

Objective: The study aims to identify the rate, type, and predictors of complications occurring within the first year after CIED implantation. It also aims to describe the demographic and epidemiological characteristics of a nationwide sample of patients with CIED in Tunisia. Additionally, the study will evaluate the extent to which Tunisian electrophysiologists follow international guidelines for cardiac pacing and sudden cardiac death prevention.

Methods: The Tunisian National Study of Cardiac Implantable Electronic Devices (NATURE-CIED) is a national, multicenter, prospectively monitored study that includes consecutive patients who underwent primary CIED implantation, generator replacement, and upgrade procedure. Patients were enrolled between January 18, 2021, and February 18, 2022, at all Tunisian public and private CIED implantation centers that agreed to participate in the study. All enrolled patients entered a 1-year follow-up period, with 4 consecutive visits at 1, 3, 6, and 12 months after CIED implantation. The collected data are recorded electronically on the clinical suite platform (DACIMA Clinical Suite).

Results: The study started on January 18, 2021, and concluded on February 18, 2023. In total, 27 cardiologists actively participated in data collection. Over this period, 1500 patients were enrolled in the study consecutively. The mean age of the patients was 70.1 (SD 15.2) years, with a sex ratio of 1:15. Nine hundred (60%) patients were from the public sector, while 600 (40%) patients were from the private sector. A total of 1298 (86.3%) patients received a conventional pacemaker and 75 (5%) patients received a biventricular pacemaker (CRT-P). Implantable cardioverter defibrillators were implanted in 127 (8.5%) patients. Of these patients, 45 (3%) underwent CRT-D implantation.

Conclusions: This study will establish the most extensive contemporary longitudinal cohort of patients undergoing CIED implantation in Tunisia, presenting a significant opportunity for real-world clinical epidemiology. It will address a crucial gap in the management of patients during the perioperative phase and follow-up, enabling the identification of individuals at particularly high risk of complications for optimal care.

Trial Registration: ClinicalTrials.gov NCT05361759; https://classic.clinicaltrials.gov/ct2/show/NCT05361759

International Registered Report Identifier (IRRID): RR1-10.2196/47525

(JMIR Res Protoc 2024;13:e47525) doi:10.2196/47525

KEYWORDS

Tunisia; study; pacemaker; implantable cardioverter defibrillator; cardiac resynchronization therapy; design; complication

Introduction

Background

Cardiac implantable electronic devices (CIEDs), including permanent pacemakers (PMs), implantable cardioverter defibrillators (ICDs), and cardiac resynchronization therapy devices with or without defibrillators (CRT-Ds or CRT-Ps), are standard therapy for bradyarrhythmia, tachyarrhythmia, and systolic heart failure [1,2]. Their use has increased over the last decade [3,4]. However, CIED implantation comes with a considerable burden of complications, leading to elevated patient morbidity, health care costs, and mortality [5-8]. The most recent consensus on device implantation and replacement by the European Heart Rhythm Association [9] has been significantly influenced by the invaluable contributions of various international registries. One of the most prominent among them is the “Replace” registry [10], which has played a pivotal role in advancing our understanding of this crucial aspect of cardiac care.

A comprehensive understanding of post-CIED implantation complications and their predictive factors is essential for patient management when considering CIED implantation. Therefore, a survey of patients undergoing CIED implantation in Tunisia is crucial to identify specific CIED complications due to the demographic and epidemiological specificities of the patients, as well as the conditions of the local health care system.

Study Aims

This study aims to assess the incidence, characteristics, and predictors of complications arising in the initial 12 months following the implantation of CIEDs, describe the demographic and epidemiological profiles of a national cohort of consecutive patients with CIED, and provide insights into the level of compliance exhibited by Tunisian electrophysiologists with international guidelines pertaining to cardiac pacing and the prevention of sudden cardiac death.

Methods

Study Design and Patients’ Enrollment

NATURE-CIED (National Study of Cardiac Implantable Electronic Devices) is a nationwide, multicenter, prospective observational study with a 1-year follow-up period. The study’s steering committee extended invitations to all electrophysiologists, interventional cardiologists, and

cardiovascular surgeons with experience in CIED implantation, regardless of whether they are practicing in the Tunisian public or private sectors, to participate in the study.

Patients' enrollment occurred between January 18, 2021, and February 18, 2022, at all Tunisian public and private CIED implantation centers that agreed to participate in the study. Eligibility screening was conducted during hospitalization.

The study population consisted of consecutive patients undergoing primary CIED (conventional PMs, ICDs, and cardiac resynchronization: CRT-P–CRT-D) implantation, generator replacement, and upgrade procedure. To be enrolled, eligible patients have to provide written informed consent. All enrolled patients entered a 1-year follow-up period with 4 consecutive visits at 1, 3, 6, and 12 months after the CIED implantation. Exclusion criteria are nonconsenting patients and those operated exclusively for lead dysfunction.

Data Sources

A steering board with 2 main investigators pre-established a specific case report form (CRF) for each type of CIED. Baseline data included patient demographics, ethnic specificity, medical history, cardiovascular history, cardiovascular risk factors, the CIED implantation indication, vital signs, laboratory measurements, electrocardiographic and echocardiographic findings, details of medical management, and results of eventual invasive and noninvasive investigations prior to CIED implantation (echocardiography, Holter monitoring, treadmill exercise stress test, and electrophysiological study).

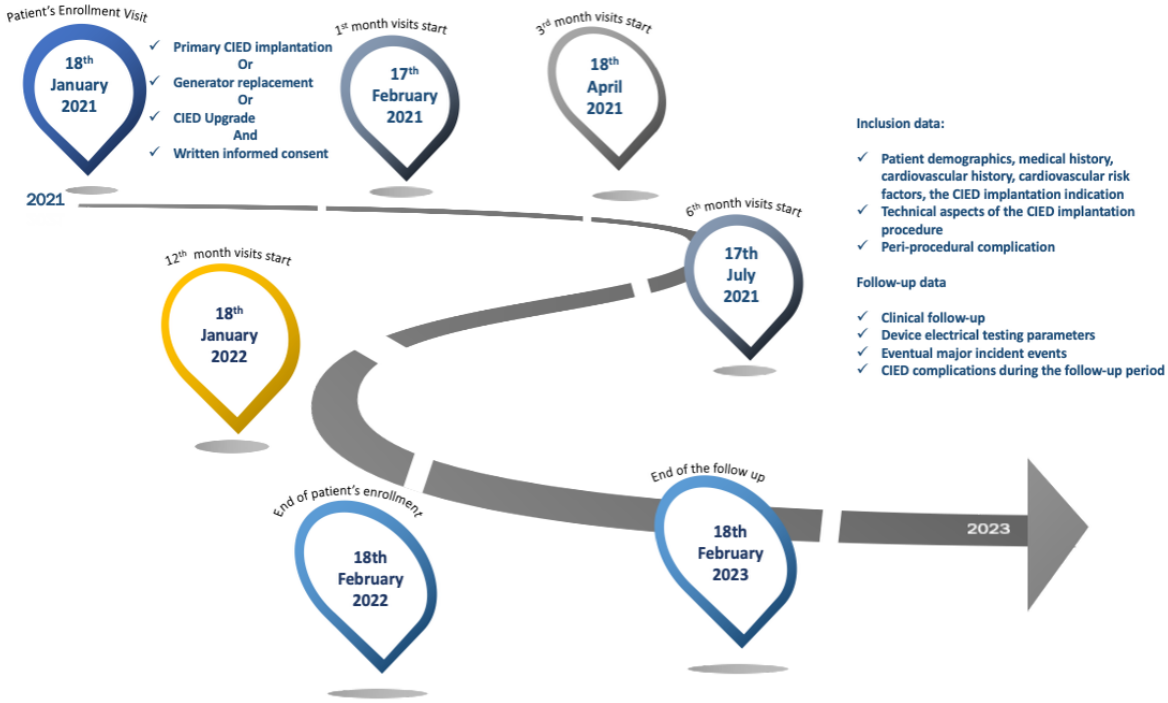
The form also includes data regarding the technical aspects of the CIED implantation procedure and the occurrence of any periprocedural complications. Finally, the form specifies data on the clinical follow-up and device electrical testing parameters, as well as the eventual major incident events and CIED complications during the follow-up period. Investigators (electrophysiologists and interventional cardiologists) who agreed to participate in the study were asked to complete the pre-established form (CRF) for each type of implanted device at the enrollment visit and each scheduled visit.

Collected data were electronically recorded on a clinical suite platform (DACIMA software), which complies with international standards including US FDA 21 CRF part 11 (Food and Drug Administration 21 Code of Federal Regulations Part 11), US HIPAA (Health Insurance Portability and Accountability Act) and ICH (International Conference on Harmonisation), and Medical Dictionary for Regulatory Activities. The main investigators and the DACIMA consulting team periodically validated recorded data. The clinical suite platform generates alerts and requests in case of inconsistencies and missing data. Throughout the planned duration of the study, the steering board supervises the inclusion of patients, checks the data sources, and prepares the study's statistical analysis plan.

Timeline

Patient enrollment and data collection began on January 18, 2021, and continued until February 18, 2022. Follow-up continued until all patients had 1-year data. The end of the study was therefore scheduled for February 18, 2023 (Figure 1).

Figure 1. The Timeline of the Nature CIED study.



If patients missed a scheduled follow-up visit, they or their relatives were contacted by phone to assess any adverse event and to reschedule a follow-up appointment.

Outcomes

The main objective of this observational study is to assess the incidence, characteristics, and predictors of major and minor

complications arising in the initial 12 months following the implantation of CIEDs.

The complications were characterized as major when life-threatening or requiring surgical reintervention for correction, and minor when suitable for treatment on an outpatient basis, involving device reprogramming, or requiring exclusive clinical observation [11]. Major complications include implantation failure, lead-related reinterventions, tamponade or myocardial perforation, pneumothorax requiring drainage, hematoma requiring evacuation, wound or pocket infection, systemic infections or endocarditis, Twiddler syndrome, and procedure-related deaths. Minor complications include pacing threshold increase, phrenic nerve stimulation, heart failure or left ventricular ejection fraction decrease, pericardial effusion, and conservatively treated hematoma and pneumothorax.

Ethical Considerations

The study was performed according to the ethical principles for medical research involving human subjects specified in the Declaration of Helsinki and the ICH Good Clinical Practices. Ethics approval was obtained from the human research ethics committees at Abderrahmen Mami Hospital in Tunis (04/2021). Written informed consent was obtained from all the patients who participated in the study. The protocol of NATURE-CIED was approved by the Tunisian Society of Cardiology and Cardiovascular Surgery. The NATURE-CIED study was submitted to ClinicalTrials.gov (NCT05361759).

Statistical Analysis

The DACIMA Clinical Suite platform enables the collection of web-based data and their extraction in SAS (SAS Institute) or SPSS (IBM Corp) format. The statistical analysis is exploratory, involving the calculation of 95% CI. The data will be described for the whole analyzed population. Continuous variables will be described by mean and SD or median and IQR. Categorical variables will be described by the size and frequency of every modality. Mean comparison will be performed by analysis of variance or by nonparametric tests if the hypothesis of normality is rejected.

The normality of continuous variables will be verified with the Shapiro-Wilk test. The statistical tests are bilateral with a 95% CI. A chi-square test will be performed for categorical variables. Yates correction or the Fisher exact test will be used if the conditions of validity for the chi-square test are not met.

A multivariate analysis will be performed with each complication as a dependent factor. The independent variables will be age, gender, ethnic specificity, BMI, CIED type, procedure type, procedure priority, implantation center (private and public), and CIED implanting operator whether he is an electrophysiologist or not (interventional cardiologist or cardiac surgeon).

Univariate logistic regression will be carried out with a 10% output threshold. The final model will be performed with the parameters selected by the backward stepwise method of Wald. The selected variables in the final model will be tested at the 5% threshold. The interaction between selected parameters is tested at the 10% threshold. The intermediate analyses will be carried out after formulating the statistical analysis plan.

Expected Implications

NATURE-CIED is the first national and North African study that will (1) provide validated data on short- and medium-term complications and their predictors, which will allow us to individualize high-risk patients for optimal care, (2) identify the epidemiologic and demographic characteristics of Tunisian patients undergoing CIED implantation, and (3) clarify the contemporary CIED indications in Tunisia and their compliance with international guidelines.

Results

In total, 27 investigators, comprising 14 from the public sector and 13 from the private sector, volunteered to take part in the study. It is worth noting that some of the investigators were involved in both the public and private sectors. A total of 1500 consecutive patients were enrolled for a 12-month follow-up period following CIED implantation. Sixty percent (n=900) of the patients were from the public sector, while 40% (n=600) were from the private sector. The patients' mean age was 70.1 (SD 15.2) years, with a sex ratio of 1:15. A total of 1298 (86.3%) patients received a conventional PM and 75 (5%) patients received a biventricular pacemaker (CRT-P). ICDs were implanted in 127 (8.5%) patients. Of these patients, 45 (3%) underwent CRT-D implantation. The detailed analyses of this study are currently under investigation and will be published elsewhere in the near future.

Discussion

Summary

To the best of our knowledge, NATURE-CIED is the first National study of CIEDs in North Africa to provide the combination of large numbers of patients and devices and diverse implanting physicians. Twenty-seven cardiologists (electrophysiologists and interventional cardiologists) enrolled 1500 patients who underwent CIED implantation.

According to the second report from the Pan African Society of Cardiology working group on cardiac arrhythmias and pacing [12], Tunisia had the highest implant rates, with 164.3 PMs per million inhabitants and 2.16 PM implantation practitioners per million inhabitants in 2018, which makes it rank in the second position after Mauritius [12].

However, there is still a gap concerning patients' demographics, CIED indications, and conformity to recent European Society of Cardiology guidelines [2] and CIED-related complications [12-14].

Both patient-related and procedure-related predictors of complications may identify patients with a particularly high risk of complications [15]. Previously reported incidences of complications after CIED implantation varied widely because of differences in the definitions of complications and length of follow-up [15-18]. Several previous studies in the 2000s reported that complication rates for PM were 4%-10% [13,17-19] and 3%-10% for ICDs and CTRDs [6,20]; however, an analysis of

US Medicare states that data in 2014 showed much lower complication rates [21].

In 2010, the "Replace" registry, comprising data from a substantial cohort of 1744 patients who underwent device replacement procedures, yielded pivotal insights into predictive factors for complications [10]. This comprehensive analysis has, in turn, informed the development of practical and evidence-based procedural recommendations. By identifying the key determinants of complications, the registry has empowered health care professionals to more effectively anticipate and mitigate risks, ultimately leading to improved patient outcomes.

Therefore, the NATURE CIED study aims to offer detailed and comprehensive data on the predictors of CIED complications during the perioperative and 1-year follow-up period, which are derived from real-world data in Tunisia. The information generated by this study will prove valuable in the development of a national peri-implantation management protocol and the assessment of overall health care costs [11,12,14,22].

Study Limitations

This study presents some limitations that must be considered in the interpretation of the results. This study is voluntary for both investigators and patients, and there is no routine audit to monitor the proportion of enrolled patients by participating electrophysiologists or cardiologists. This currently limits our ability to examine exact implant rates and to examine equity of access to PM therapy across the country. Some patients were lost to follow-up.

We identified all complications documented in patients during hospitalization and follow-up. We believe that this approach is the most accurate and comprehensive way to detect complications. In addition, this study was not designed to assess the effects of each investigator's experience level and the volume of procedures performed individually. Therefore, the electrophysiologists' or interventional cardiologists' positions on their learning curve may influence the rate of complications mainly in teaching hospitals.

Conclusions

NATURE-CIED study will fill an important gap in the management of patients undergoing CIED implantation both perioperatively and during follow-up and will identify patients at particularly high risk of complications for optimal management.

In Tunisia, this study will yield the largest contemporary longitudinal cohort of patients undergoing CIED implantation and will provide real-world data regarding heart rhythm diseases' epidemiology and management with insights into the degree of adherence to international guidelines.

Acknowledgments

NATURE-CIED was financed by the Tunisian Society of Cardiology and Cardiovascular Surgery.

Conflicts of Interest

None declared.

References

1. Priori SG, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, ESC Scientific Document Group. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Eur Heart J 2015 Nov 01;36(41):2793-2867. [doi: 10.1093/eurheartj/ehv316] [Medline: 26320108]
2. Glikson M, Nielsen JC, Kronborg MB, Michowitz Y, Auricchio A, Barbash IM, ESC Scientific Document Group. 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. Eur Heart J 2021 Sep 14;42(35):3427-3520. [doi: 10.1093/eurheartj/ehab364] [Medline: 34455430]
3. Zecchin M, Torre M, Carrani E, Sampaolo L, Ciminello E, Ortis B, et al. Seventeen-year trend (2001-2017) in pacemaker and implantable cardioverter-defibrillator utilization based on hospital discharge database data: an analysis by age groups. Eur J Intern Med 2021 Feb;84:38-45 [FREE Full text] [doi: 10.1016/j.ejim.2020.09.003] [Medline: 32933841]
4. Raatikainen MJP, Arnar DO, Merkely B, Nielsen JC, Hindricks G, Heidbuchel H, et al. A decade of information on the use of cardiac implantable electronic devices and interventional electrophysiological procedures in the European Society of Cardiology Countries: 2017 report from the European Heart Rhythm Association. Europace 2017 Aug 01;19(suppl_2):ii1-ii90. [doi: 10.1093/europace/eux258] [Medline: 28903470]
5. Diemberger I, Lorenzetti S, Vitolo M, Boriani G. Infective endocarditis in patients with cardiac implantable electronic devices: impact of comorbidities on outcome. Eur J Intern Med 2019 Aug;66:e9-e10. [doi: 10.1016/j.ejim.2019.06.015] [Medline: 31280907]
6. Reynolds MR, Cohen DJ, Kugelmass AD, Brown PP, Becker ER, Culler SD, et al. The frequency and incremental cost of major complications among Medicare beneficiaries receiving implantable cardioverter-defibrillators. J Am Coll Cardiol 2006 Jun 20;47(12):2493-2497 [FREE Full text] [doi: 10.1016/j.jacc.2006.02.049] [Medline: 16781379]

7. Sohail MR, Henrikson CA, Braid-Forbes MJ, Forbes KF, Lerner DJ. Mortality and cost associated with cardiovascular implantable electronic device infections. Arch Intern Med 2011 Nov 14;171(20):1821-1828. [doi: 10.1001/archinternmed.2011.441] [Medline: 21911623]
8. Sgreccia D, Vitolo M, Valenti AC, Manicardi M, Boriani G. Burden of disease and costs of infections associated with cardiac implantable electronic devices. Expert Rev Pharmacoecon Outcomes Res 2022 Jan;22(1):7-16. [doi: 10.1080/14737167.2021.1980386] [Medline: 34517745]
9. Burri H, Starck C, Auricchio A, Biffi M, Burri M, D'Avila A, Reviewers:, et al. EHRA expert consensus statement and practical guide on optimal implantation technique for conventional pacemakers and implantable cardioverter-defibrillators: endorsed by the Heart Rhythm Society (HRS), the Asia Pacific Heart Rhythm Society (APHRS), and the Latin-American Heart Rhythm Society (LAHRS). Europace 2021 Jul 18;23(7):983-1008. [doi: 10.1093/europace/euaa367] [Medline: 33878762]
10. Poole JE, Gleva MJ, Mela T, Chung MK, Uslan DZ, Borge R, REPLACE Registry Investigators. Complication rates associated with pacemaker or implantable cardioverter-defibrillator generator replacements and upgrade procedures: results from the REPLACE registry. Circulation 2010 Oct 19;122(16):1553-1561. [doi: 10.1161/CIRCULATIONAHA.110.976076] [Medline: 20921437]
11. Silva K, Albertini C, Crevelari ES, Carvalho E, Fiorelli AI, Martinelli M, et al. Complications after surgical procedures in patients with cardiac implantable electronic devices: results of a prospective registry. Arq Bras Cardiol 2016 Sep;107(3):245-256 [FREE Full text] [doi: 10.5935/abc.20160129] [Medline: 27579544]
12. Bonny A, Ngantcha M, Yuyun MF, Karaye KM, Scholtz W, Suliman A, et al. Cardiac arrhythmia services in Africa from 2011 to 2018: the second report from the Pan African Society of Cardiology working group on cardiac arrhythmias and pacing. Europace 2020 Mar 01;22(3):420-433. [doi: 10.1093/europace/euz354] [Medline: 31989158]
13. Boriani G, Proietti M, Bertini M, Diemberger I, Palmisano P, Baccarini S, On Behalf Of Ri-Aiac Registry Investigators. Incidence and predictors of infections and all-cause death in patients with cardiac implantable electronic devices: the Italian Nationwide RI-AIAC Registry. J Pers Med 2022 Jan 11;12(1):1-16 [FREE Full text] [doi: 10.3390/jpm12010091] [Medline: 35055406]
14. Tobin K, Stewart J, Westveer D, Frumin H. Acute complications of permanent pacemaker implantation: their financial implication and relation to volume and operator experience. Am J Cardiol 2000 Mar 15;85(6):774-776, A9. [doi: 10.1016/s0002-9149(99)00861-9] [Medline: 12000060]
15. Kirkfeldt RE, Johansen JB, Nohr EA, Jørgensen OD, Nielsen JC. Complications after cardiac implantable electronic device implantations: an analysis of a complete, nationwide cohort in Denmark. Eur Heart J 2014 May;35(18):1186-1194 [FREE Full text] [doi: 10.1093/eurheartj/eht511] [Medline: 24347317]
16. van Eck JWM, van Hemel NM, Zuithof P, van Asseldonk JPM, Voskuil T, Grobbee D, et al. Incidence and predictors of in-hospital events after first implantation of pacemakers. Europace 2007 Oct;9(10):884-889. [doi: 10.1093/europace/eum113] [Medline: 17556376]
17. Lin YS, Hung SP, Chen PR, Yang CH, Wo HT, Chang PC, et al. Risk factors influencing complications of cardiac implantable electronic device implantation: infection, pneumothorax and heart perforation: a nationwide population-based cohort study. Medicine (Baltimore) 2014 Dec;93(27):e213 [FREE Full text] [doi: 10.1097/MD.0000000000000213] [Medline: 25501080]
18. Johansen JB, Jørgensen OD, Møller M, Arnsbo P, Mortensen PT, Nielsen JS. Infection after pacemaker implantation: infection rates and risk factors associated with infection in a population-based cohort study of 46299 consecutive patients. Eur Heart J 2011 Apr;32(8):991-988 [FREE Full text] [doi: 10.1093/eurheartj/ehq497] [Medline: 21252172]
19. Eberhardt F, Bode F, Bonnemeier H, Boguschewski F, Schlei M, Peters W, et al. Long term complications in single and dual chamber pacing are influenced by surgical experience and patient morbidity. Heart 2005 Apr;91(4):500-506 [FREE Full text] [doi: 10.1136/hrt.2003.025411] [Medline: 15772212]
20. Freeman JV, Wang Y, Curtis JP, Heidenreich PA, Hlatky MA. Physician procedure volume and complications of cardioverter-defibrillator implantation. Circulation 2012 Jan 03;125(1):57-64. [doi: 10.1161/CIRCULATIONAHA.111.046995] [Medline: 22095828]
21. Prutkin JM, Reynolds MR, Bao H, Curtis JP, Al-Khatib SM, Aggarwal S, et al. Rates of and factors associated with infection in 200 909 Medicare implantable cardioverter-defibrillator implants: results from the National Cardiovascular Data Registry. Circulation 2014 Sep 23;130(13):1037-1043. [doi: 10.1161/CIRCULATIONAHA.114.009081] [Medline: 25081281]
22. Larsen PD, Kerr AJ, Hood M, Harding SA, Hooks D, Heaven D, ANZACS-QI investigators. Pacemaker use in New Zealand - data from the New Zealand Implanted Cardiac Device Registry (ANZACS-QI 15). Heart Lung Circ 2017 Mar;26(3):235-239. [doi: 10.1016/j.hlc.2016.06.1206] [Medline: 27475261]

Abbreviations

CIED: cardiac implantable electronic device
CRF: case report form
CRT-D: cardiac resynchronization therapy defibrillator
CRT-P: cardiac resynchronization therapy pacemaker

HIPAA: Health Insurance Portability and Accountability Act
ICD: implantable cardioverter defibrillator
ICH: International Conference on Harmonisation
NATURE-CIED: National Study of Cardiac Implantable Electronic Devices
PM: pacemaker

Edited by A Mavragani; submitted 24.03.23; peer-reviewed by H Ross, E Mekhael; comments to author 13.10.23; revised version received 29.10.23; accepted 31.10.23; published 08.04.24.

Please cite as:
Chabrak S, Haggui A, Allouche E, Ouali S, Ben Halima A, Kacem S, Krichen S, Marrakchi S, Fehri W, Mourali MS, Jabbari Z, Ben Halima M, Neffati E, Heraiech A, Slim M, Kachboura S, Gamra H, Hassine M, Kraiem S, Kammoun S, Bezdah L, Jridi G, Bouraoui H, Kammoun S, Hammami R, Chettaoui R, Ben Ameur Y, Azaiez F, Tlili R, Battikh K, Ben Slima H, Chrigui R, Fazaa S, Sanaa I, Ellouz Y, Mosrati M, Milouchi S, Jarmouni S, Ayadi W, Akrout M, Razgallah R, Neffati W, Drissa M, Charfeddine S, Abdessalem S, Abid L, Zakhama L
National Tunisian Study of Cardiac Implantable Electronic Devices: Design and Protocol for a Nationwide Multicenter Prospective Observational Study
JMIR Res Protoc 2024;13:e47525
URL: https://www.researchprotocols.org/2024/1/e47525
doi:10.2196/47525
PMID:38588529

Protocol

Preference-Based Implementation of Video Consultations in Urban and Rural Regions in Outpatient Care in Germany: Protocol for a Mixed Methods Study

Lara Kleinschmidt[1], MSc; Anke Walendzik[1], Dr; Jürgen Wasem[1], Prof Dr; Klemens Höfer[1], MA; Beatrice Nauendorf[2], MSc; Matthias Brittner[3], MA; Paul Brandenburg[4], MA; André Aeustergerling[5], MA; Udo Schneider[6], PD Dr; Anja Wadeck[6], MA; Stephanie Sehlen[7], Dr; Sebastian Liersch[7], Dr; Katharina Schwarze[8], MA; Carsten Schwenke[9], Dr PH; Theresa Hüer[1], MA

[1]Institute for Health Care Management and Research, University of Duisburg-Essen, Essen, Germany
[2]Kassenärztliche Vereinigung Berlin, Berlin, Germany
[3]Kassenärztliche Vereinigung Westfalen-Lippe, Dortmund, Germany
[4]Kassenärztliche Vereinigung Schleswig-Holstein, Bad Segeberg, Germany
[5]Kassenärztliche Vereinigung Mecklenburg-Vorpommern, Schwerin, Germany
[6]Techniker Krankenkasse, Hamburg, Germany
[7]AOK Nordost, Potsdam, Germany
[8]AOK NordWest, Dortmund, Germany
[9]SCO:SSiS, Minden, Germany

Corresponding Author:
Lara Kleinschmidt, MSc
Institute for Health Care Management and Research
University of Duisburg-Essen
Thea-Leymann-Straße 9
Essen, 45127
Germany
Phone: 49 201 18 3377
Email: lara.kleinschmidt@medman.uni-due.de

Abstract

Background: Particularly in rural regions, factors such as lower physician density and long travel distances complicate adequate outpatient care. However, urban regions can also be affected by deficits in care, for example, long waiting times. One model of care intending to improve the situation is the implementation of video consultations. The study protocol presents the methodology of the research project titled “Preference-based implementation of the video consultation in urban and rural regions” funded by the German Federal Joint Committee (funding number 01VSF20011).

Objective: This study aims to identify existing barriers to the use of video consultation and the preferences of insured individuals and physicians as well as psychotherapists in order to optimize its design and thus increase acceptance and use of video consultations in urban and rural regions.

Methods: Built on a mixed methods approach, this study first assesses the status quo of video consultation use through claims data analysis and carries out a systematic literature review on barriers and promoting factors for the use of video consultations. Based on this preliminary work, focus groups are conducted in order to prepare surveys with insureds as well as physicians and psychotherapists in the second study phase. The central element of the survey is the implementation of discrete choice experiments to elicit relevant preferences of (potential) user groups and service providers. The summarized findings are discussed in a stakeholder workshop and translated into health policy recommendations.

Results: The methodological approach used in this study is the focus of this paper. The study is still ongoing and will continue until March 2024. The first study phase has already been completed, in which preliminary work has been done on potential applications and hurdles for the use of video consultations. Currently, the survey is being conducted and analyses are being prepared.

Conclusions: This study is intended to develop a targeted strategy for health policy makers based on actual preferences and perceived obstacles to the use of video consultations. The results of this study will contribute to further user-oriented development of the implementation of video consultations in German statutory health insurance. Furthermore, the iterative and mixed methods approach used in this study protocol is also suitable for a variety of other research projects.

International Registered Report Identifier (IRRID): DERR1-10.2196/50932

(JMIR Res Protoc 2024;13:e50932) doi:10.2196/50932

KEYWORDS

study protocol; video consultation; preference elicitation; discrete choice experiment; implementation; telemedicine; teleconsultation; e-consultation; outpatient; rural area; remote; preferences; strategy

Introduction

Particularly in rural regions, factors such as lower physician density and long travel distances complicate adequate outpatient care [1]. However, urban regions can also be affected by deficits in care, for example, due to long waiting times [2]. One model of care that could improve the situation is the implementation of video consultations in outpatient care, meaning online contact in real time with video transmission between physician or psychotherapist and patient. In addition to questioning about symptoms and medical history (anamnesis), signs of illness can be examined, and—possibly—a diagnosis can be made. Particularly in the case of long journeys, for follow-up appointments (for example after minor surgeries), or for the provision of repeated prescriptions, video consultations can be a useful tool and the insured individual does not have to visit the doctor’s office for every appointment. In the field of psychotherapy, therapeutic or certain diagnostic sessions can also take place in the form of video consultations [3].

Several studies provide preliminary clinical evidence of the benefits of telemedicine in certain patient populations, such as the chronically ill or patients living in nursing homes. A project in a predominantly rural region in Germany demonstrated the effectiveness of video consultations for nursing home residents. In particular, routine appointments, such as follow-up treatments, could be carried out efficiently remotely. Advantages for all parties involved were demonstrated through improved access to general practitioners (GPs) and specialists, a reduction in hospital admissions, and the elimination of stressful journeys and time-consuming home visits [4]. For people with mental disorders such as depression, telemedicine has proven to be a promising tool to enhance quality of life and access to treatment [5-7]. In addition, high patient satisfaction rates with video consultations could be shown in the field of orthopedics [8,9].

Since the health care system in Germany is predominately based on a social insurance system, in which 88.3% of the German population is insured [10], the project focuses on the statutory health insurance (SHI) system. In the German SHI, since April 2017, video consultations could initially only be provided by a few specialist groups and only for selected indications and follow-up appointments. In the second quarter of 2019, these restrictions were mostly abolished and the assessment of the appropriateness of a diagnosis or treatment via video consultation was placed in the decision-making responsibility of the physician [3,11]. During the COVID-19 pandemic, there were numerous (primarily temporary) adjustments in the regulations for their provision. Video consultations are part of the SHI benefits catalog. The remuneration of video consultations in outpatient medical care in the German SHI system is not fee-for-service based, but predominantly part of age-differentiated quarterly flat rates, which cover the entire medical care of a patient (not just video consultations) by the attending physician during this period. In addition, there are supplementary payments that compensate for the additional technical effort and the digital authentication of an unknown patient in video consultations [3].

However, since 2017 and up to the beginning of the COVID-19 pandemic, video consultations have hardly played a role in outpatient medical care in Germany [11]. Many physicians feared an estrangement of the physician-patient relationship and that as a consequence this would result in the physician's inability to meet the patients' needs. In addition, some assume that the reduced sensory perception on the screen and the lack of a holistic perspective could lead more easily to treatment errors or misdiagnoses. Concerns are also expressed about data protection and data security [12]. A study by Noweski et al [13] also showed that personal contact with the doctor is given high priority by the insured individual and that the insured individual only accepts digital doctor-patient consultations as an alternative in part or under specific conditions.

Thus, the central prerequisite for the creation of acceptance—related to the willingness to offer video consultations, but also to the willingness to make use of them—is the consideration of the preferences and perceived barriers of those involved. For this reason, this study addresses the question of how video consultations should be designed to improve situations of outpatient medical care while taking into account the preferences of the insured individual and physicians as well as psychotherapists. Weinhold and Gurtner [14] showed that patient satisfaction in primary care in rural regions depends on different factors than in urban regions. In order to be able to develop targeted strategies, a comparative preference assessment between rural and urban regions is carried out.

This study aims to address the following research questions:

- How often and for which treatment occasions are video consultations used in outpatient medical care in the SHI system in Germany? What are the characteristics of the user groups in rural and urban areas (use of video consultations in standard care)?

- What findings can be drawn from national and international studies on the implementation of video consultation with regard to best practices so far?
- Under what conditions (expectations of form and content, inhibiting and promoting factors) do insured individuals accept the digitalization of their medical consultations?
- Which application options do physicians and psychotherapists prefer?
- How do the preferences differ among GPs, psychotherapists, and other specialist groups?
- How do the preferences of insured individuals and the physicians as well as psychotherapists differ between urban and rural regions?
- Which kind of implementation of video consultations should be pursued in rural and urban regions?
- Where are the hurdles that need to be overcome?
- Is there a need for regulatory adaptations?

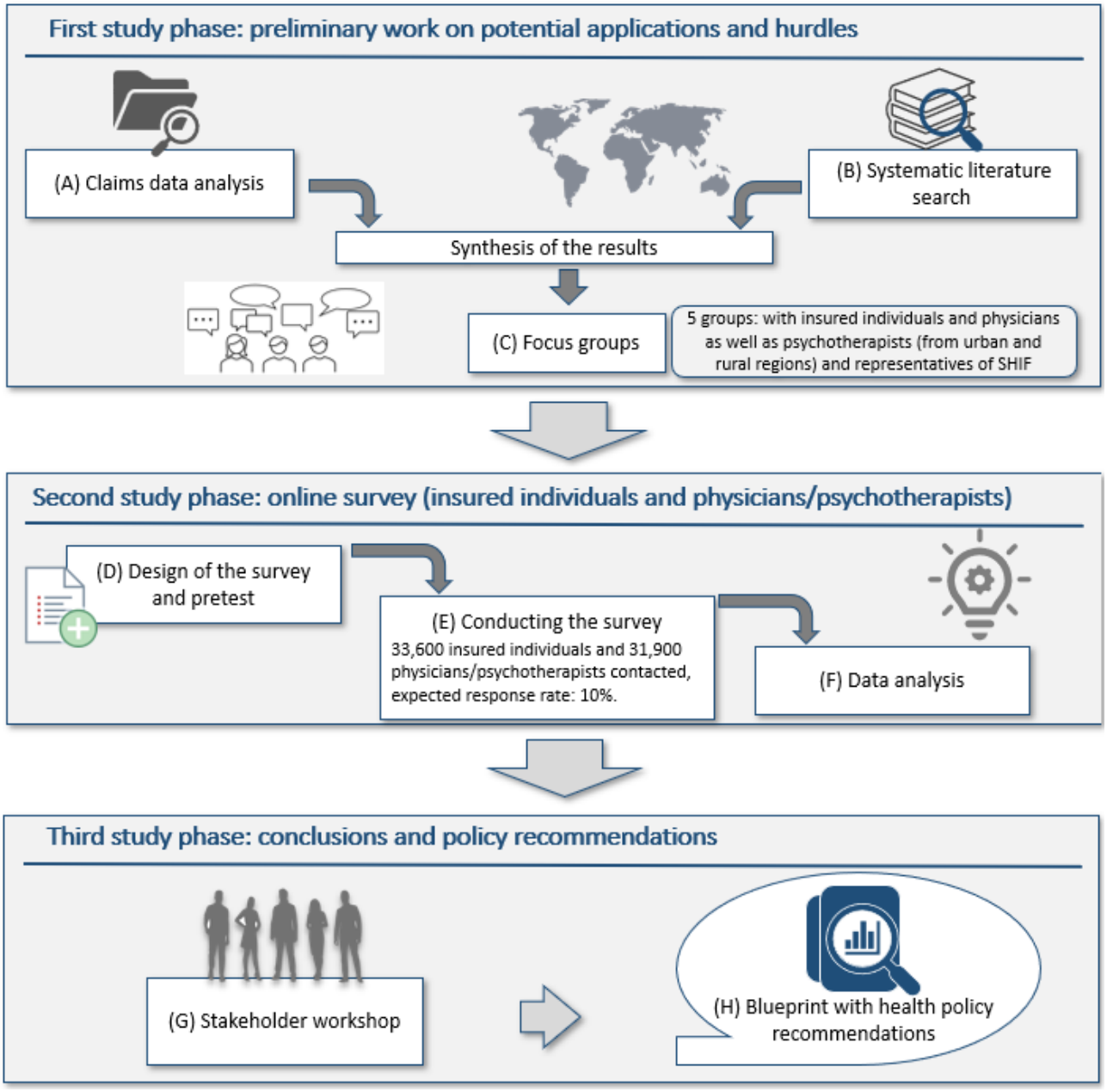
So far, there are no research results on the use of video consultations that consider users (patients) and providers (physicians/psychotherapists) on the one hand and compare preferences between urban and rural regions on the other hand. To elicit these preferences, this study uses the particularly suitable method of discrete choice experiments (DCE), which, in contrast to other instruments of preference elicitation, allow for an intuitive decision-making process by evaluating alternatives as a bundle of their characteristics. A DCE also offers the advantage of a realistic assessment situation, which avoids the problem of compositional methods, which is that respondents tend to rate all attributes as very important [15].

Methods

Study Design

In order to develop a strategy for the preference-based implementation of video consultations in rural and urban regions, this study uses a mixed methods approach with a particular focus on DCE. The following Figure 1 shows the course of the study. The duration of the study is 3 years, beginning in April 2021 and continuing prospectively until March 2024.

Figure 1. Study design and course of the study from April 2021 to March 2024. SHIF: statutory health insurance fund.



In the first study phase, the status quo of the use of video consultations is examined by a claims data analysis (A). At the same time, a systematic literature review (B) on possible barriers and promoting factors on the use and provision of video consultation is conducted. Then, preliminary findings are discussed in focus groups (C) in order to prepare the following surveys with DCE. In the second phase of the study, surveys including DCE are designed (D), conducted (E), and analyzed (F) to elicit preferences for the design of video consultation of insured individuals on the one hand and physicians as well as psychotherapists on the other hand, comparing rural and urban regions. In the third study phase, all results are combined and discussed in a stakeholder workshop (G) and policy recommendations (H) are developed.

Claims Data Analysis (A)

In work package A, claims data are analyzed focusing on patterns of the use of video consultations as well as the characteristics of their user groups in rural and urban regions (status quo).

To depict both, the perspective of insured and service providers, claims data from 3 statutory health insurance funds (SHIF) and 4 regional associations of statutory health insurance physicians (ASHIP) are used from the period April 2017 to the end of 2020.

Data for insured individuals and physicians, as well as psychotherapists in 4 German regions (“Westfalen-Lippe,” “Mecklenburg-Vorpommern,” “Schleswig-Holstein,” and “Berlin”), are analyzed. These regions are chosen because they include both rural and urban districts. The classification as a rural or urban district is carried out using the interactive web app “INKAR: Indicators and Maps of Spatial and Urban Development” offered by the Federal Institute for Research on Building, Urban Affairs, and Spatial Development. Among other things, the settlement structure of the district is considered

as a combination of the population density and the settlement area share [16].

After a preliminary analysis of the data by the SHIF and ASHIP according to a consented evaluation concept, only aggregated data are sent to the University of Duisburg-Essen for further analysis. There, the data are combined and further evaluated according to the research question.

Aggregated data of approximately 6 million insured living in 1 of the 4 selected regions are analyzed. In addition to data on the use of video consultation, patient data on sociodemographic characteristics and diagnostic records are included. To depict the perspective of service providers, data from 31,900 physicians and psychotherapists are analyzed. Information on specialist groups (eg, GPs, psychotherapists, and other specialist groups) and sociodemographic characteristics of users compared with nonusers are collected. Furthermore, the influence of the place of residence or practice location on the use of video consultation is examined.

Descriptive analyses, differentiated according to subgroups (insured: age group, gender, employment situation, and type of region; physicians/psychotherapists: specialist group, age group, gender, type of operation and employment, and type of region) are conducted. Since the data are not provided at the individual level, the analysis of the aggregated data is performed using Excel (version 16.0; Microsoft Corp).

Systematic Literature Review (B)

A systematic literature review including national and international studies on the application settings of video consultation as well as possible hurdles in their implementation is conducted in parallel with the claims data analysis. Best practice models and, if applicable, existing empirical results (especially with regard to the acceptance of users) are to be analyzed. The systematic review is conducted in accordance with PRISMA (Preferred Reporting for Systematic Reviews and Meta-Analyses) guidelines [17]. Literature research is performed in PubMed and Embase. The search strategy is developed using the PICO scheme [18]. Relevant search, MeSH (Medical Subject Headings) or Emtree, terms are assigned to each category and linked with Boolean operators. The search is limited to publications from 2011 onward and to articles written in English and German. The study selection is divided into the steps of title, abstract, and full-text screening. To ensure an objective approach, literature screening, as well as extraction, is carried out by 2 researchers independently of each other. Studies are included according to the following criteria: the study deals with the implementation of video consultation in the form of video-based consultation via web in real time between the patient and the medical or psychotherapeutic service provider in outpatient care, and the study focuses on useful fields of application and promoting/inhibiting factors. Since a very high heterogeneity of the results is assumed, a qualitative information synthesis of the results of the included studies on possible implementation factors, encouraging features, and barriers is performed using the program MAXQDA (VERBI).

Focus Groups (C)

At the end of the first phase, 5 focus group discussions with relevant stakeholders on potential applications of video consultation and barriers to its use are conducted. The interim results of the claims data analysis and the systematic literature review are reviewed in order to achieve a well-grounded basis for the development of the interview guidelines for the focus groups.

Due to the uncertainties associated with the coronavirus pandemic regarding the possibility of face-to-face meetings, all focus groups are conducted online. In 2015, Abrams et al [19] demonstrated that focus groups in an audio-visual format can achieve a similar richness of data as physical face-to-face focus groups, distinguishing them from purely written text-based forms.

Relevant stakeholders include representatives of insured individuals, physicians as well as psychotherapists, and the SHIF perspective. In order to adequately take into account the differences between urban and rural areas, for each region type 2 focus groups are conducted for both the perspective of insured individuals and that of the service providers in order to include content relevant to urban and rural regions.

The recruitment of physicians and psychotherapists is carried out by the participating ASHIP, and interested insured persons are recruited by a cooperating self-help association. Participants of the payer perspective are recruited by the participating SHIF themselves. The composition of the focus groups with insured individuals should take into account characteristics such as age group, gender, presence of a chronic disease, and video consultation users/nonusers. For the focus groups with physicians and psychotherapists, relevant characteristics are age group, gender, and specialist group. The focus groups are led by a team of moderators, as described by Krueger and Casey [20], and take approximately 60 minutes per stakeholder group. The basis for the focus groups are semistructured interview guides that are derived from the content-related preliminary work of the systematic literature research. The course of the focus groups is video-recorded and transcribed afterward. On this basis, a qualitative content analysis according to Mayring [21] is carried out using the software for qualitative data analysis MAXQDA (VERBI).

Design of the Surveys Including Discrete Choice Experiments (D-F)

Preferences play an increasingly important role in health care decision-making [22]. However, the complexity of health-related decisions poses a challenge due to the multitude of alternatives available. In such circumstances, the DCE method has been widely used for preference elicitation in health care [23]. DCEs are based on Random Utility Theory, a theory of human preference behavior that assumes respondents behave in a manner that maximizes their utility. Therefore, econometric models based on Random Utility Theory can be used to analyze data from DCE surveys. It is assumed that services or goods can be valued on the basis of the characteristics (called attributes) that determine them [24]. DCEs usually consist of a number of choice sets that represent hypothetical options as

alternatives. Each choice set is composed of a set of attributes and each attribute is described by values (called levels). By asking respondents to choose between the choice alternatives, preferences are determined. The respondents' choices are then used to derive the importance of the attributes and levels in terms of overall utility [25]. DCEs support the design of health programs and the prediction of demand and acceptability [23].

Based on the preliminary work, namely literature searches and focus groups, the survey and the DCEs are constructed. The DCEs are designed to elicit preferences for the design of video consultations of insured persons as well as physicians and psychotherapists. Relevant attributes and their levels are therefore determined in the first study phase. Following, choice alternatives are modeled using SAS (version 9.4; SAS Institute Inc).

The choice set (which covers multiple choice alternatives) should take into account design recommendations by Huber and Zwerina [26]. Generally, choice sets should not contain any stimuli for which 1 option is clearly advantageous and therefore does not require weighing. According to The Professional Society for Health Economics and Outcomes Research—ISPOR—recommendation on conjoint analyses, the maximum number of pairwise comparisons (tasks) that each respondent should answer should be between 8 and 16 [27]. In order to limit the number of stimuli per respondent, it is possible to use optimal designs in which, based on certain quality criteria, an appropriate subset (fractional design) is selected from the set of theoretically possible stimuli (full-factorial design) and thus a minimum number of pairwise comparisons is required [28]. Additionally, if the number of calculated tasks exceeds ISPOR recommendations, the questionnaire could be split into 2 or more blocks as response efficiency could decrease otherwise [27].

The DCE is embedded in a survey which is structured into three sections: (1) possible barriers and promoting factors for the use of video consultations, (2) preference survey using DCE, and (3) sociodemographic information. Additionally, for the insured individuals, health-related information is requested and for the physicians or psychotherapists, information on the medical profession are asked in the third section.

Prior to the distribution of the questionnaires, they are subjected to a pretest and revised accordingly. The methods of think-aloud and probing are used to determine comprehensibility, manageability, completeness, and the time required for completion [29].

To determine the sample size, the rule of thumb according to Reed and Orme [30] is applied. Under the further assumptions of generating multiple questionnaire versions with different blocks, an estimated 10% response rate, and in order to enable differentiated statements about subgroups, around 33,000 insured persons have to be contacted. Applying the previously described rule of thumb, possible blocking, 10% response rate, and possible subgroup analysis for the survey of physicians and psychotherapists 31,900 individuals are contacted. The final sample size depends on the results of claims data analysis and systematic literature review in order to form relevant subgroups.

The surveys are carried out with randomly selected insured persons—under the application of defined inclusion and exclusion criteria—by the participating SHIF and with all physicians as well as psychotherapists of the ASHIP who are allowed to provide video consultations in principle.

Inclusion criteria for the survey of insured individuals contain (1) insurance by 1 of the 3 participating SHIF, (2) 18 years or older, and (3) place of residence in 1 of the 4 selected regions as done in claims data analysis (A). Insured persons under legal guardianship, with a high need for nursing care ("Pflegegrad 4" and higher), nursing home residents, patients in palliative care, patients diagnosed with dementia, and insured persons whose data may not be used for research are excluded.

The participating SHIF and ASHIP contact their insured and members by means of a short letter, which includes further information on the study, the survey itself for paper-participation as well as an invitation to participate web-based via QR code.

The survey starts in November 2022 and ends at the end of March 2023. If necessary, a reminder is used to increase the response rate.

The survey is analyzed in terms of possible barriers and preferences. Econometric analysis follows the ISPOR guidance for DCEs [31]. Descriptive procedures as well as logistic regression analyses are carried out. The target variable of the DCE is the subjects' choice decision for 1 of 2 stimuli. Depending on the model, the attributes or their characteristics as well as sociodemographic and health-related characteristics of the test persons are included as explanatory variables. A mixed logit model is estimated. A hierarchical Bayesian model is used for the main analysis.

Workshop With Stakeholders (G) and Health Policy Recommendations (H)

Finally, a stakeholder workshop (G) is performed to combine all findings of prior sections and summarize results. Participants include 1 representative each from the participating associations of SHI-accredited physicians, the participating SHIF and the participating cooperation partners of the self-help associations, patient representatives, the German Association of Medical Specialists, and the Professional Association of German Internists. Participants are asked to sign a declaration of consent. The workshop is held in person with an estimated duration of 6 hours and is led by a team of moderators from the University of Duisburg-Essen.

Finally, the results of the workshop are implemented in a blueprint with health policy recommendations (H).

Ethical Considerations

The study received ethical approval from the Ethics Committee of the Medical Faculty of the University of Duisburg-Essen on September 27, 2022 (reference: 21-10283-BO). For the purpose of claims data analysis, the University of Duisburg-Essen only has access to aggregated data. There is no possibility of participant identification. The data collected in the focus groups is considered pseudonymized, with only statements needed in connection with the project being stored. The list of participants is deleted after the focus groups have been conducted and the

audio recordings are deleted after transcription. For the participation in focus groups participants are compensated with 50 Euro (US $49.98) for insured individuals and 120 Euro (US $119.952) for physicians as well as psychotherapists. To take part in the surveys or the workshop, participants are asked to sign a declaration of consent.

Results

As the study runs until March 2024, the methodological approach used in this study is the focus of this paper. The claims data analysis (A) demonstrates that video consultation has had almost no relevance in outpatient care in the German health care system from 2017 to 2019. This changes significantly with the beginning of the COVID-19 pandemic. Displaying the initial situation gives insights into areas of application and user groups which are published separately. Furthermore, the analysis is a necessary basis for further work.

The systematic research (B) on possible applications of video consultation and possible hurdles as well as promoting factors also aims to identify possible attributes and their levels for the DCE. Challenging aspects of the video consultation have been identified. In-depth descriptions of hurdles and promoting factors on the use of video consultation are published separately.

Focus groups (C) complement the systematic literature research to discuss the relevance of the attributes identified, as well as the levels and their scaling, which supported developing additions or modifications if necessary. They have been conducted with insured persons as well as with physicians and psychotherapists from rural and urban regions. This was supplemented by a focus group with representatives of SHIF.

The conception of the surveys (D) to collect preferences for the design of video consultations by insured individuals as well as by physicians and psychotherapists has been completed. Extensive pretests have been conducted. In addition, the questionnaires have been implemented on the web-based survey platform Question Pro for the additional option of digital participation, so that the recruitment of survey participants could begin in the fourth quarter of 2022 and was completed in March 2023 (E). The data are analyzed since April 2023 (E).

Discussion

Video consultation is a promising tool in medical and psychotherapeutic care, as shown by its increasing use with the onset of the COVID-19 pandemic in claims data analysis (A) and more generally in light of advancing digitalization [32]. The study is directly designed for practical use to further develop the potential of video consultation in Germany. To the authors' knowledge, a comprehensive approach to analyzing the use and provision of video consultations from the providers' perspective on the one hand and the perspective of insured individuals on the other hand in 1 study has not been conducted to date in Germany. The results of this study will specifically address the conditions (expectations of form and content, inhibiting and promoting factors) under which the insured individual accepts the digitalization of their medical consultations and which application possibilities of video consultation are accepted by medical and psychotherapeutic service providers (differentiated by specialist groups). This is accomplished by taking into account possible barriers and considering the differences between rural and urban regions in order to be able to apply the defined recommendations in a targeted manner. Recommendations for legal and sublegal adjustments are then derived from this.

However, as this study addresses the German SHI, the legal framework might differ elsewhere; thus, our results may not be completely applicable to other countries. The subject of this study is video consultation and does not include telephone care or other types of telemedicine, which limits the perspective of this research.

Regardless of the topic addressed by this study (video consultations in outpatient medical care in Germany), the iterative and mixed methods approach used in this study protocol is also suitable for a variety of other research projects. The use of a systematic literature review as a first step to examine settings for video consultation and possible barriers ensures a systematic inclusion of the current state of the art while also taking into account the quality of the literature. The explorative elicitation of initial information on the basis of qualitative methods (in this case focus groups, which can also be supplemented or replaced by expert interviews) in the first study phase as a solid basis for the second study phase, in which the exploratively collected theses are to be examined quantitatively, is suitable for a wide range of inquiries in health services research. Furthermore, as urban and rural settings are explored, the study in general contributes to a better understanding of urban and rural differences in preferences in the provision of digital care. This can help policy makers in finding suitable solutions for both the rural and the urban population.

Acknowledgments

This study was entirely funded by the Innovation Fund of the German Federal Joint Committee (funding number 01VSF20011). The Funder did not influence the design of the study; the collection, analysis, and interpretation of data; or the writing process of this manuscript.

Furthermore, support by the Open Access Publication Fund of the University of Duisburg-Essen for Publication is acknowledged.

Data Availability

The data sets generated or analyzed during this study are not publicly available due to data protection reasons.

Authors' Contributions

All authors contributed to the study organization and conception of the surveys. LK and TH were the major contributors to writing this manuscript. All authors contributed to the manuscript in different stages and also read and approved the final version.

Conflicts of Interest

None declared

References

1. Neumeier S. Haus- und Facharzterreichbarkeit in Deutschland: Regionalisierte Betrachtung auf Basis einer GIS-Erreichbarkeitsanalyse. Forum Wohnen Stadtentwicklung 2018;1:39-44 [FREE Full text]
2. Werbeck A, Wübker A, Ziebarth NR. Cream skimming by health care providers and inequality in health care access: evidence from a randomized field experiment. J Econ Behav Organ 2021;188:1325-1350 [FREE Full text] [doi: 10.1016/j.jebo.2021.05.028]
3. Bericht des Bewertungsausschusses und des ergänzenden Bewertungsausschusses zur telemedizinischen Leistungserbringung im Einheitlichen Bewertungsmaßstab. (BT-Drucksache 20/4982). Deutscher Bundestag. 2022. URL: https://dserver.bundestag.de/btd/20/049/2004982.pdf [accessed 2023-04-05]
4. Zentrum für Telematik und Telemedizin. 1.000 Videosprechstunden in Pflegeheimen. Zentrum für Telematik und Telemedizin. 2018. URL: https://www.ztg-nrw.de/2018/02/1-000-videosprechstunden-in-pflegeheimen/ [accessed 2020-03-03]
5. Shih YH, Wang JY, Chou PH, Lin KH. The effects of treatment via telemedicine interventions for patients with depression on depressive symptoms and quality of life: a systematic review and meta-ranalysis. Ann Med 2023;55(1):1092-1101 [FREE Full text] [doi: 10.1080/07853890.2023.2187078] [Medline: 36920229]
6. Berryhill MB, Halli-Tierney A, Culmer N, Williams N, Betancourt A, King M, et al. Videoconferencing psychological therapy and anxiety: a systematic review. Fam Pract 2019;36(1):53-63 [FREE Full text] [doi: 10.1093/fampra/cmy072] [Medline: 30188992]
7. Milosevic I, Cameron DH, Milanovic M, McCabe RE, Rowa K. Face-to-face versus video teleconference group cognitive behavioural therapy for anxiety and related disorders: a preliminary comparison. Can J Psychiatry 2022;67(5):391-402 [FREE Full text] [doi: 10.1177/07067437211027319] [Medline: 34159838]
8. Buvik A, Bugge E, Knutsen G, Småbrekke A, Wilsgaard T. Patient reported outcomes with remote orthopaedic consultations by telemedicine: a randomised controlled trial. J Telemed Telecare 2019;25(8):451-459 [FREE Full text] [doi: 10.1177/1357633X18783921] [Medline: 29973130]
9. Haider Z, Aweid B, Subramanian P, Iranpour F. Telemedicine in orthopaedics during COVID-19 and beyond: a systematic review. J Telemed Telecare 2022;28(6):391-403 [FREE Full text] [doi: 10.1177/1357633X20938241] [Medline: 32762270]
10. GKV Spitzenverband. Amtliche Statistik KM1 zum 1. Dezember 2021. GKV Spitzenverband. 2023. URL: https://www.gkv-spitzenverband.de/service/zahlen_und_grafiken/zahlen_und_grafiken.jsp [accessed 2023-05-25]
11. Bericht des Bewertungsausschusses zur Überprüfung des Einheitlichen Bewertungsausschusses auf die Möglichkeit zur ambulanten telemedizinischen Leistungserbringung. (BT-Drucksache 19/6020). Deutscher Bundestag. 2018. URL: http://dip21.bundestag.de/dip21/btd/19/060/1906020.pdf [accessed 2024-02-22]
12. Hartmannbund. Das Fernbehandlungsverbot vor dem aus?! Überfällig oder Tabubruch? - Kommentare zum Nein Votum. Hartmannbund. 2018. URL: https://www.hartmannbund.de/wp-content/uploads/2019/08/Kommentare_zum_Nein-Votum.pdf [accessed 2020-03-05]
13. Noweski M, Altin S, Walendzik A, Wasem J. Versichertenpräferenzen in der ambulanten Versorgung in Westfalen-Lippe. Gesundheits- und Sozialpolitik 2019;73(6):14-19. [doi: 10.5771/1611-5821-2019-6-14]
14. Weinhold I, Gurtner S. Rural - urban differences in determinants of patient satisfaction with primary care. Soc Sci Med 2018;212:76-85 [FREE Full text] [doi: 10.1016/j.socscimed.2018.06.019] [Medline: 30025382]
15. Himme A. Conjoint-analysen. In: Albers S, Klapper D, Konradt U, Walter A, Wolf J, editors. Methodik der Empirischen Forschung. 3. Auflage. Wiesbaden: Gabler Verlag; 2009:283-298.
16. Bundesinstitut für Bau-, Stadt- und Raumforschung. INKAR - Indikatoren und Karten zur Raum- und Stadtentwicklung. Bundesinstitut für Bau-, Stadt- und Raumforschung. 2020. URL: https://www.inkar.de/ [accessed 2020-11-19]
17. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:71 [FREE Full text] [doi: 10.1136/bmj.n71] [Medline: 33782057]
18. Schardt C, Adams MB, Owens T, Keitz S, Fontelo P. Utilization of the PICO framework to improve searching PubMed for clinical questions. BMC Med Inform Decis Mak 2007;7:16 [FREE Full text] [doi: 10.1186/1472-6947-7-16] [Medline: 17573961]
19. Abrams KM, Wang Z, Song YJ, Galindo-Gonzalez S. Data richness trade-offs between face-to-face, online audiovisual, and online text-only focus groups. Soc Sci Comput Rev 2014;33(1):80-96 [FREE Full text] [doi: 10.1177/0894439313519733]
20. Krueger R, Casey MA. Focus Groups : A Practical Guide for Applied Research: 4th Edition. Los Angeles: SAGE; 2009.
21. Mayring P. Qualitative Inhaltsanalyse: Grundlagen und Techniken: 12 Edition. Weinheim: Beltz; 2015.

22. Utens CMA, Dirksen CD, van der Weijden T, Joore MA. How to integrate research evidence on patient preferences in pharmaceutical coverage decisions and clinical practice guidelines: a qualitative study among Dutch stakeholders. Health Policy 2016;120(1):120-128 [FREE Full text] [doi: 10.1016/j.healthpol.2015.10.005] [Medline: 26563630]
23. Mühlbacher AC, Bethge S, Tockhorn A. Präferenzmessung im Gesundheitswesen: Grundlagen von Discrete-Choice-Experimenten. Gesundheitsökonomie Qualitätsmanagement 2013;18(4):159-172 [FREE Full text] [doi: 10.1055/s-0032-1330500]
24. Clark MD, Determann D, Petrou S, Moro D, de Bekker-Grob EW. Discrete choice experiments in health economics: a review of the literature. Pharmacoeconomics 2014;32(9):883-902 [FREE Full text] [doi: 10.1007/s40273-014-0170-x] [Medline: 25005924]
25. Lancsar E, Louviere J. Conducting discrete choice experiments to inform healthcare decision making: a user's guide. Pharmacoeconomics 2008;26(8):661-677 [FREE Full text] [doi: 10.2165/00019053-200826080-00004] [Medline: 18620460]
26. Huber J, Zwerina K. The importance of utility balance in efficient choice designs. J Mark Res 2018;33(3):307-317 [FREE Full text] [doi: 10.1177/002224379603300305]
27. Johnson FR, Lancsar E, Marshall D, Kilambi V, Mühlbacher A, Regier DA, et al. Constructing experimental designs for discrete-choice experiments: report of the ISPOR conjoint analysis experimental design good research practices task force. Value Health 2013;16(1):3-13 [FREE Full text] [doi: 10.1016/j.jval.2012.08.2223] [Medline: 23337210]
28. Bridges JFP, Kinter ET, Kidane L, Heinzen RR, McCormick C. Things are looking up since we started listening to patients: trends in the application of conjoint analysis in health 1982-2007. Patient 2008;1(4):273-282. [doi: 10.2165/01312067-200801040-00009] [Medline: 22272995]
29. Häder M. Empirische Sozialforschung: Eine Einführung: 1st Edition. Wiesbaden: VS Verlag für Sozialwissenschaften; 2006.
30. Reed JF, Orme BK. Sample size issues for conjoint analysis. In: Orme BK, editor. Getting Started with Conjoint Analysis: Strategies for Product Design and Pricing Research. 2 Edition. Madison, WI: Research Publishers; 2010:57-66.
31. Hauber AB, González JM, Groothuis-Oudshoorn CGM, Prior T, Marshall DA, Cunningham C, et al. Statistical methods for the analysis of discrete choice experiments: a report of the ISPOR conjoint analysis good research practices task force. Value Health 2016;19(4):300-315 [FREE Full text] [doi: 10.1016/j.jval.2016.04.004] [Medline: 27325321]
32. Meier R, Holderried M, Kraus TM. Digitalisierung der Arzt-Patienten-Kommunikation. In: Pfannstiel MA, Da-Cruz P, Rasche C, editors. Entrepreneurship im Gesundheitswesen III. Wiesbaden: Springer Gabler; 2018:63-75.

Abbreviations

ASHIP: associations of statutory health insurance physicians
DCE: discrete choice experiment
GP: general practitioner
MeSH: Medical Subject Headings
PRISMA: Preferred Reporting for Systematic Reviews and Meta-Analyses
SHI: statutory health insurance
SHIF: statutory health insurance fund

Edited by A Mavragani; submitted 17.07.23; peer-reviewed by J Hensel, J Wherton; comments to author 20.10.23; revised version received 07.11.23; accepted 29.11.23; published 11.04.24.

Please cite as:
Kleinschmidt L, Walendzik A, Wasem J, Höfer K, Nauendorf B, Brittner M, Brandenburg P, Aeustergerling A, Schneider U, Wadeck A, Sehlen S, Liersch S, Schwarze K, Schwenke C, Hüer T
Preference-Based Implementation of Video Consultations in Urban and Rural Regions in Outpatient Care in Germany: Protocol for a Mixed Methods Study
JMIR Res Protoc 2024;13:e50932
URL: https://www.researchprotocols.org/2024/1/e50932
doi:10.2196/50932
PMID:38602749

Protocol

Participation in Advance Care Planning Among Medically At-Risk Rural Veterans: Protocol for a Personalized Engagement Model

Tammy Walkner[1,2*], PhD; Daniel W Karr[1,2], BS; Sarah Murray[1,2*], MPH; Amanda Heeren[3,4*], MSW, LISW; Maresi Berry-Stoelzle[1,5*], PhD, MD

[1]Veterans Rural Health Resource Center, Iowa City VA Health Care System, Iowa City, IA, United States

[2]Center for Access & Delivery Research and Evaluation (CADRE), Iowa City VA Health Care System, Iowa City, IA, United States

[3]Iowa City VA Health Care System, Iowa City, IA, United States

[4]Department of Psychiatry, Carver College of Medicine, Unviersity of Iowa, Iowa City, IA, United States

[5]Vaughan Institute, Tippie College of Business, University of Iowa, Iowa City, IA, United States

[*]these authors contributed equally

Corresponding Author:
Maresi Berry-Stoelzle, PhD, MD
Veterans Rural Health Resource Center
Iowa City VA Health Care System
601 Highway 6 West
Iowa City, IA, 52246
United States
Phone: 1 319 338 0581
Email: maresi.berry-stoelzle@va.gov

Abstract

Background: Many of the challenges in advanced care planning (ACP) conversations are linked to the waxing and waning progress of serious illnesses. Conversations with patients about future medical care decisions by a surrogate decision maker have historically been left until late in the patient's disease trajectory. These conversations often happen at a time when the patient is already very ill. The challenge in effective early ACP and serious illness conversations is to create a situation where patients appreciate the link between current and future medical care. Setting the stage to make these conversations more accessible includes using telehealth to have conversations at the patient's place of choice. The personalization used includes addressing the current medical and social needs of the patient and ensuring that expressed needs are addressed as much as possible. Engaging patients in these conversations allows the documentation of patient preferences in the electronic health record (EHR), providing guidelines for future medical care.

Objective: The objective of our telehealth serious illness care conversations program was to successfully recruit patients who lacked up-to-date documentation of ACP in their EHR. Once these patients were identified, we engaged in meaningful, structured conversations to address the veterans' current needs and concerns. We developed a recruitment protocol that increased the uptake of rural veterans' participation in serious illness care conversations and subsequent EHR documentation.

Methods: The recruitment protocol outlined herein used administrative data to determine those patients who have not completed or updated formal ACP documentation in the EHR and who are at above-average risk for death in the next 3-5 years. The key features of the telehealth serious illness care conversations recruitment protocol involve tailoring the recruitment approach to address current patient concerns while emphasizing future medical decision-making.

Results: As of September 2022, 196 veterans had completed this intervention. The recruitment method ensures that the timing of the intervention is patient driven, allowing for veterans to engage in ACP at a time and place convenient for them and their identified support persons.

Conclusions: The recruitment protocol has been successful in actively involving patients in ACP conversations, leading to an uptick in completed formal documentation of ACP preferences within the EHR for this specific population. This documentation is then available to the medical team to guide future medical care.

International Registered Report Identifier (IRRID): RR1-10.2196/55080

(JMIR Res Protoc 2024;13:e55080) doi:10.2196/55080

KEYWORDS

advance care planning; chronic disease; end-of-life care; health care decision; medical decision-making; recruiting; shared medical decision-making

Introduction

Overview

Advance care planning (ACP) involves dialogues between patients and their health care providers regarding the patient's values and health care preferences [1-3]. These discussions provide a foundation for health care providers and surrogate decision makers to make informed decisions in situations where the individual is unable to do so. Veterans Health Administration (VHA) offers ACP as a named health care benefit for enrolled veterans [4]. Advance directives (ADs) are documents outlining instructions for future medical care and go into effect only if an individual is not capable of making medical decisions or communicating their wishes [3]. Not all ACP sessions result in the completion of an AD, nor is completing an AD always the goal of specific ACP discussions [1,2]. This project focuses on increasing ACP participation and documentation among VHA enrolled veterans.

ACP is a key factor in end-of-life care, yet it is an underused intervention [5]. Among US veterans, it is estimated that 7.1 million of the 9.6 million veterans who are enrolled in VHA do not have ACP preferences documented in their medical records [1,6,7]. Work on AD discussions by Matthieu and colleagues [1] shows only 5.2% of all VHA beneficiaries had a documented ACP discussion in 2020.

Research suggests older adults may not be informed about the ACP process and may assume that physicians initiate conversations about advanced illness or end-of-life care [5,8]. Additionally, some older adults might lack adequate health literacy to understand the contents of end-of-life care conversations or the risks related to treatments they may receive throughout the illness trajectory [9-12]. Communication about end-of-life preferences may also be difficult if the health care provider or the patient is reluctant to initiate discussion or the provider lacks sufficient time to engage in the conversation [1,9,13,14]. Yet there are benefits to ACP, such as reducing uncertainty when a patient is unable to communicate their wishes, receiving care that is more congruent with personal preferences, and including care that is more consistent with the spiritual cultural needs of patients and their families [14-17]. Additionally, for specific high-risk populations, the presence of an advanced care plan before hospital admission has been shown to decrease intensive care unit length of stay [8,18,19].

VHA supports multiple approaches to facilitate ACP conversations between patients, surrogate decision makers, and providers, including, but not limited to, the serious illness care conversation (SICC), the goals of care conversations, and the Life-Sustaining Treatment Decisions Initiative [4,20]. The National Center for Ethics in Health Care is at the forefront of making ACP information available to veterans and the Veterans Administration's (VA) clinical and nonclinical workforce. National Center for Ethics in Health Care has been central to providing guidelines and training to support ACP practices within VHA. Enterprise-wide initiatives, such as advance care planning through group visits, are additional offerings at various VA sites that are successfully increasing access to ACP [1,21]. VHA has been promoting life-sustaining treatment (LST) as the AD of choice for VHA; however, the limitation of LSTs to VA health systems restricts the transferability of the veteran's wishes to community-based hospitals and providers. LSTs are ADs that are only valid in VA health facilities and are not widely accepted outside of VHA. Despite known benefits and resources for providers and veterans for engaging in ACP, documentation of ACP discussions in veterans' electronic health records (EHRs) remains low [1].

Challenges of ACP in a Rural Veteran Population

Rural veterans living with serious illness, compared to their urban peers, have increased barriers to ACP within VHA and community health care systems [15,22,23]. Serious illness has been defined as a "health condition that carries a high risk of mortality and either negatively impacts a person's daily function or quality of life or excessively strains their caregivers" [24]. Veterans who rely on VHA for care are often sicker, tend to live in rural areas, and face significant travel challenges regarding broad geographic distance and seasonal weather impacting travel safety [22,23]. While the VA Mission Act of 2018 has increased access to medical care for rural veterans [25], formalizing ACP processes still lags for rural veterans [1,26]. Access to medical care is a concern for many rural veterans, and with fewer care options, there are fewer opportunities to talk about serious illness and advance care planning [15,27]. Urban-dwelling veterans often face similar challenges, so any improvements to access through these interventions have the potential to benefit all veterans.

Many rural veterans use both VA and community-based health care [28,29], indicating a need for ACP that is translatable to both VA and community-obtained health care. As such, this intervention seeks to promote ACP and offers support to veterans wishing to complete whichever formal AD documentation format is best suited for their unique health care needs. For veterans, whose primary care location is VA, LST offers a nuanced format for documenting future care decisions. For those, whose primary site of care is outside VA, the state-based AD, such as the durable power of attorney form, should be filled out.

SICC acknowledge that the disease is unlikely to resolve, and managing symptoms and medical crises is an ongoing challenge for patients and their support team [2-4,30]. While SICCs are widely applicable, they are an underutilized structure for conversations between a provider and a patient who is focusing on living with a serious illness [9,31]. The telehealth serious illness care conversation (tSICC) adapts many of the tenets of SICC for a telehealth intervention while utilizing VA clinical standards designed for ACP [32]. These frameworks have been adjusted to suit conversations with veterans in their homes who are not expected to be in a current medical crisis [4,32]. The

provider talks with the patient about their values and priorities for health care, as well as how those might change in the context of advancing illness with or without an acute medical crisis. The goal is more than simply discussing resuscitation status; but rather, it is to develop a personalized plan for medical care as the patient's illness progresses. While SICC acts as an entry into the ACP process, these types of conversations often happen too late in a person's medical trajectory [16,31]. Early engagement allows for relational decision-making for veterans and their families [33], accommodating the more complex information about the variable clinical trajectory of older and more seriously ill veterans.

Personalized approaches have been shown to promote engagement in the ACP process [5,34]. Our project tailored the recruitment strategies for rural veterans, recognizing they have more barriers to receiving end-of-life health care, including limited access to hospice and palliative care services [15]. This manuscript outlines a recruitment protocol for rural, seriously ill veterans into a quality improvement (QI) project at a veteran healthcare system in the Midwestern United States.

To optimize integration of veteran-specific values, this QI project used community-based participatory research (CBPR) practices [35-37]. According to National Institutes of Health, CBPR involves researchers and community members to combine "knowledge with action to improve health outcomes and eliminate health disparities" [38]. To accomplish our goal of developing a veteran-centric approach to engaging in ACP, we established a team that included veterans and veterans' proxy decision makers (through a Veteran Engagement Panel [VEP]), an advocacy expert, social workers, licensed VA medical providers, and veteran service officers. The VEP was convened specifically to provide guidance for the pilot, accompanying the project from institutional review board (IRB) approval through the development of the intervention and analysis of preliminary results. The VEP was integral to the development of veteran-facing materials, including flyers and other recruitment materials, as well as the development of metrics reflecting veteran priorities. Panel members shared their insights on how to personalize all aspects of the study to support the goal of making the process relatable to the veteran population.

A Telehealth-Based, Multimodal, and Veteran-Centric Intervention

Improving access and decreasing barriers were driving forces in our QI project: develop and disseminate a veteran-centric clinical protocol for ACP through tSICC. Telehealth visits expand access for patients who face barriers to receiving medical care [39-41]. However, technology issues limit the use of telehealth as an equitable or appropriate care mechanism [39]. While VHA has been using telehealth for many years, rural veterans' limited access to high-quality broadband service can be a barrier to telehealth services [42,43]. Evidence has suggested veterans with a serious illness were satisfied with telehealth encounters, as these types of appointments improved their access to care and diminished the need for travel [39].

Information About the tSICC Pilot

Our project targets at-risk veterans with no ADs or out-of-date AD documentation in veterans' EHRs. Our team obtained funding through VHA Office of Rural Health for a QI project within VHA; we are a rural-serving Midwest VA medical center. We present here a systematic description of a stakeholder informed, multimodal recruitment strategy for a clinical intervention for ACP.

Setting for the Development of the Engagement Strategy

Our QI project sought to determine the appropriate timing and setting for a tSICC within a veteran's clinical trajectory. We had a driving slogan: "the right care, for the right veteran, at the right time." The steps chosen for recruitment were consistent with local IRB guidelines, local and national VA practices, and were influenced by veteran feedback [32]. To our knowledge, there is no specific literature outlining the development of a veteran-centric recruitment model for telehealth-based ACP.

Objective

This manuscript describes a recruitment protocol for engaging veterans who have not been reached through existing opportunities to participate in a tSICC and ACP within VHA.

Methods

Study Context

This paper reports on the methodology of an initial pilot study that is part of a larger clinical work-flow QI project to increase veteran engagement in and documentation of ACP within VHA. Our team is developing a telehealth-based approach to an existing clinical intervention, the SICC, with a focus on allowing the veteran and their chosen support persons to participate in ACP on their own timeline and in a setting that is convenient and comfortable for them. This is especially important for rural veterans who may face a significant travel burden to access care at VHA. Veterans and their families often accommodate this burden by cramming many of their medical appointments into one day. However, reducing the travel burden can lead to a busy, medically-focused schedule and increased fatigue. The lack of time during clinical visits is a barrier for interventions like SICC that promote ACP [31,39,44]. By removing this clinical intervention from an already taxing day and creating a space for this important conversation to occur outside of stressful clinical visit days, we hypothesized that veterans would be better able to participate in ACP. Consequently, as this discussion is documented in the EHR and veterans are guided on how to have future ACP conversations, there is a prospect for increased efficacy in future discussions of ACP among veteran participants and their VHA medical providers and social workers.

Engaging participants in research or QI studies can be difficult, especially if participants are seriously ill or the study is focused on a sensitive issue such as ACP. Further study of clinical interventions can help identify better strategies for recruitment and participation in research focused on ACP and palliative care [44,45]. Studies have shown that using multiple strategies in the recruiting phase may help increase participation related to

ACP [46-48]. Chau and colleagues [46] demonstrated that mailing information along with making phone calls to participants is an effective method for increasing their willingness to engage in the ACP process. For this QI project, an assortment of methods were used to recruit participants to the ACP process.

Study Design

The tSICC intervention was implemented in a medium-sized VA health care system in a Midwestern city in the central United States with a regional metropolitan population of 171,000. VHA EHR system was used for population-based identification of medically at-risk veterans. The pilot cohort was recruited from July 2021 to October 2021 using a project-developed risk metric that identifies and categorizes by risk level those who might experience a serious health episode in the next 5 years. Veterans were identified as not having an AD or other VHA-based ACP documentation in their EHR within the last 2 years. Veterans were receiving care through VHA but may also be supplementing it with community-based care. The recruitment goal was for 200 veterans to participate in the intervention.

While the intervention was planned as a telehealth intervention, recruitment was initially done during a clinical appointment starting in April 2021. The project team quickly identified that in-clinic recruitment was difficult due to existing workflows that did not easily integrate the recruitment process. This experience is noted in the literature, with previous works [33,40] showing that having ACP conversations as part of the clinical workflow is challenging and does not engage populations that may have significant comorbidities and more pressing medical concerns. In October 2021, the study team transitioned to an entirely remote, multimodal recruitment process.

Applying CBPR principles to further enhance veteran-centricity, veteran participants were invited to take part in a concise survey of their experience in both the recruitment process and the intervention. Evaluation questions from the CollaboRATE survey, based on core elements of shared decision-making [49], were used in a postintervention call to assess if participants felt informed about the purpose of the intervention and if they felt they were part of the decision-making process [50]. The collaboRATE questions have been delivered through multiple modalities (eg, paper, digital tablet, and social media) [50,51], which makes this short survey a viable option for individualized projects such as our QI pilot. Feedback from these questions was an important element in adapting the pilot study to veteran-identified concerns and wishes.

Study Protocol

The required steps of local IRB and VA offices at the time of this intervention development were mail notification before placing up to 3 unsolicited phone calls and leaving up to 1 unsolicited voicemail. The parameter aligns with evidence that 3 phone calls promote engagement and minimize fatigue [34]. In addition to institutional guidelines, the recruitment strategy was shaped by our work with the VEP, which identified 3 concepts that became guideposts for the recruitment strategy: personalization, continuity of information, and the benefit of participating in ACP now. See Figure 1 below for an overview of the major steps in our pilot project. Figure 2 offers a more detailed view of our process.

Figure 1. Overview of the quality improvement recruitment process. ACP: advanced care planning.

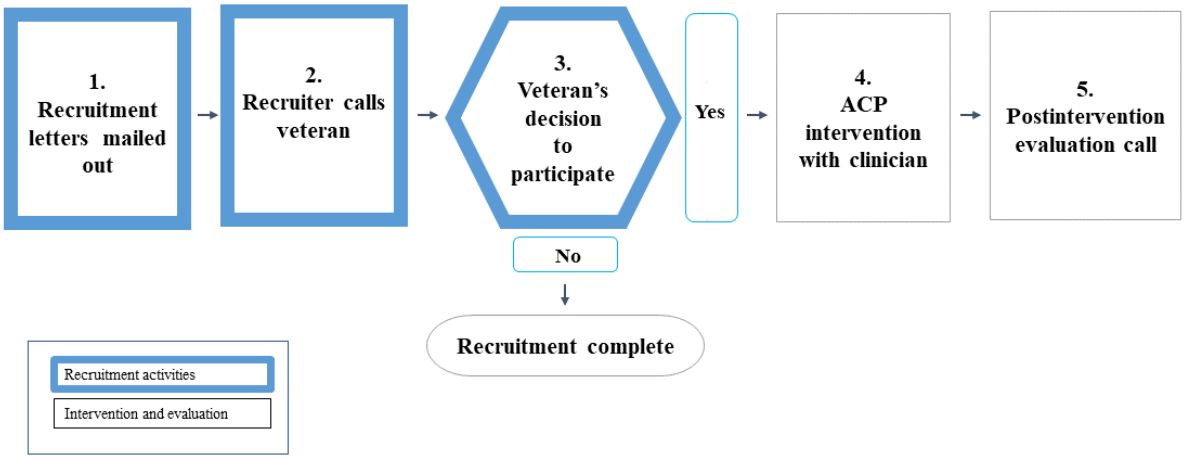
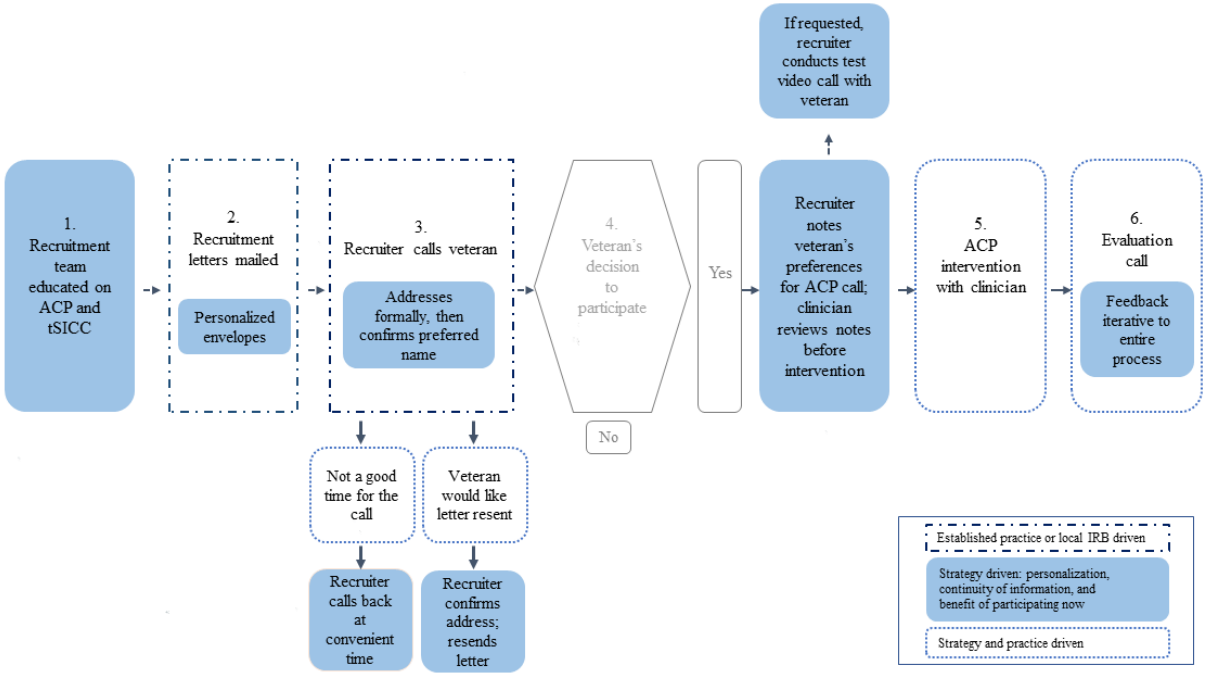


Figure 2. A detailed view of the personalized recruiting process. ACP: advanced care planning; IRB: institutional review board; tSICC: telehealth serious illness care conversations.



To personalize the mailing phase of recruitment, special attention was given to the items being sent to the veteran. Large manilla envelopes were hand-addressed in blue ink to appear unique among other pieces of mail and later be referenced by color and size during recruitment phone calls.

Several strategies were available during phone recruitment to personalize the experience for the veteran. The recruiter, trained on the components of ACP, reviewed the veteran's medical record before the call to ensure familiarity with the veteran's preferred name and correct address, identify any recent major medical events, and obtain the name of the veteran's emergency contact or next of kin (inviting the veteran to include them in the tSICC if they wished). During the call, attention was paid to the veteran's health literacy and comfort with technology. The recruiter estimated the veteran's understanding of the project and if the veteran might need technical assistance (ie, in preparing for video chat) to participate in the telehealth intervention. When needed, further explanation was provided, or plans were made to provide technical assistance before the intervention.

Continuity of information can be challenging in any large health care system, and veterans may feel that information is not shared among members of the health care team. This was reported as a negative experience by the VEP and indicated decreased confidence in both competency and compassion from their care team. To address that concern, the recruitment team used a formal hand-off to ensure that concerns and topics raised by the veteran during the recruitment call were passed on to the next team member. During recruitment, veterans were informed that they would have an opportunity to talk with a VA medical provider about their general concerns related to ACP. Concerns shared during the recruitment phone call would be relayed to the provider and could be discussed further during the telehealth visit.

The final concept proffered by the VEP regarded the benefit of this ACP intervention and said that every interaction with the veteran should be of potential benefit. Early in the disease process, veterans are active decision makers, and tSICCs are grounded in patient autonomy. The tSICC protocol offers ACP at the veteran's convenience rather than during a busy clinic schedule or a time of medical crisis, creating time and space for veterans to ask for help with medical decision-making. In line with the project's objective to enhance veteran comprehension of ACP and the support available from VA, veterans were informed that the health care provider involved in this intervention could assist them in translating their values, goals, and wishes into future treatment decisions, all of which would be recorded in their VA EHR. This included how completing an AD can be a significant step in gaining agency in their future medical decision-making.

How the Principle of Tailoring Follows Through Subsequent Steps

Veterans successfully recruited for the project participated in the tSICC intervention and a postintervention follow-up call. During the intervention, the VA provider was sure to ask about topics important to the veteran and their family that may have been identified during the recruiting phone call. The VA provider then documented the ACP conversation in the veteran's EHR. As needed, appropriate referrals were made to VA providers, and relevant resources were shared with the veteran.

Following the intervention, veterans were invited to participate in the evaluation of the recruitment and intervention protocols. To assess the appropriateness, timeliness, and usefulness of the intervention, there was a 3-item questionnaire as well as a query of their opinion about the intervention and any suggestions they may have for improving the process. An iterative process was used to incorporate input from veterans that shaped continued recruitment procedures. The concluding phone call also provided

a chance to address any inquiries regarding ACP or the tSICC and to ensure the completion of any previous tasks.

Analysis of Project-Generated Engagement Data

Data collection on recruitment focused on monitoring the number of attempts, the results of these attempts, and veteran-reported satisfaction with the recruitment process. The structure of the phone call outcomes gave insight into the challenges of reaching veterans at home (Textbox 1).

Textbox 1. The possible outcomes for telephone recruiting.

Outcomes of phone calls

- Message left
- Did not leave message
- Telephone problem
- Wrong number or disconnected
- Deceased
- Call back requested
- Declined
- Asked for more information
- Resend letter
- Agreed to participate
- Refused to participate

If the recruiter got a message "No longer in service," "Busy signal," or "Unable to leave a message," it was not logged as first contact; those were simple telephone problems or technical issues. Some cellular services provide a message if the call cannot be completed as dialed. If the issue was telephone company-related and not customer-related, it was not considered a contact.

Ethical Considerations

This project was determined as quality improvement nonhuman participants research by the University of Iowa IRB for January 2020 (#201911479), March 2020 (#202002148), and April 2021 (#202102175). We did not require a waiver or informed consent as this intervention was nonhuman subject research. All study data for this QI project has been deidentified, and no personal information has been reported in this paper. There was no compensation since this project was nonhuman subject research.

Results

This project seeks to understand how VHA can deliver ACP that supports "the right care, for the right veteran, at the right time." Here we report the results of the feedback received from veterans in the development of the recruitment process and its integration into our ongoing recruitment for this multiyear project. VEP and intervention participants provided the insight that 3 concepts should be at the forefront of our approach: personalization, continuity of information, and a benefit to the veteran now.

Personalization occurred at all levels of the recruitment protocol. Our team aimed to have mailed materials "stand out" against mail that could otherwise be perceived as junk by using larger envelopes and hand-addressing them. We also customized recruitment discussions (and subsequent intervention discussions) to align with the veteran's ACP experiences to date. Further, project team members recognized and addressed the individual needs of the veteran as identified in the EHR and from previous interactions with the project team. By not repeating already shared information, veterans, and staff saved time. This allowed conversations to move to solutions for veterans' concerns and building next steps for planning more efficiently.

Immediate benefits to veterans from the intervention included: provider documentation of veterans' values and personal health goals to be used as guidance to future proxy decision makers; updating incorrect or incomplete next-of-kin information stored in the EHR; and assistance in the completion of AD to be entered into the EHR. Further, increasing a veteran's understanding of ACP and how VHA can help the veteran with future medical decision-making was a vital component of the clinical intervention and, as such, was integrated into every contact, starting at recruitment. To facilitate this, our recruiter was knowledgeable of ACP principles and the tSICC intervention and had the necessary resources to explain the project and the background verbally in electronic and paper form.

The impact of the recruitment strategy was that of the 343 veterans successfully reached during recruitment by phone, 199 agreed to participate, and 196 completed the intervention. From this group, 146 completed the post call evaluation. Veteran satisfaction with the intervention is reported in Table 1. Notably, 50% (98/196) of veterans who completed the intervention then requested to have AD forms mailed to them for completion. When asked whether the timing of the tSICC was appropriate and timely for them, 66.4% (97/146) of respondents agreed it was.

Table 1. Veterans' satisfaction with a telehealth Serious Illness Care Conversation intervention (N=146).

Veteran agreement with elements of satisfaction	Value, n (%)
Provider understood patient's values	
Rural[a]	86 (76.1)
Urban[a]	23 (65.7)
Total	109 (74.7)
Provider includes what matters most	
Rural[a]	83 (73.4)
Urban[a]	22 (66.7)
Total	105 (71.9)
Appropriate timing of conversation	
Rural[a]	75 (66.3)
Urban[a]	22 (66.7)
Total	97 (66.4)

[a]Rural-Urban Commuting Area Codes guidelines were used to determine rural or urban status [52].

The intervention and related data collection for the ongoing QI project are expected to be completed in the fiscal year 2024. The results of that data are forthcoming.

Discussion

The results of this QI project support the hypothesis that veterans are more likely to engage in ACP if the conversation is timely, not perceived as burdensome, and addresses veterans' current medical and related concerns [5,14,41]. The recruitment method outlined herein offers personalized strategies to engage veterans in ACP outside of a clinical setting that were informed and evaluated by veterans.

The QI team adapted VA trainings on advance care and serious illness conversations to be used in a short, home telehealth setting and focused on identifying a process to engage veterans in a way that fits their unique needs. The digital divide was identified as a significant barrier for rural veterans [42-44]. Our findings are consistent with previous results, which show that offering lower tech communication options as well as support for connectivity in the form of personalized assistance lowered systemic barriers to access [43,46].

Data reported in the literature and gathered from our dedicated VEP underscores the importance of the veteran's perception that their unique needs and perspectives are important to the ACP process [39]. This both serves to build rapport and to tailor subsequent information offered in the course of the intervention about ACP. Particular focus was on how engaging in ACP now can help inform their current medical decision-making as well as the benefit of formal documentation of ACP within the veteran's EHR [9,14].

A notable limitation of this study is that while we documented increases in ACP behaviors across the sample, we did not capture uniform, preintervention data that may have provided insight into the unique barriers and facilitators that influence an individual's engagement in ACP. Another limitation is the study's small size, at 1 Midwest VA medical center. This important limitation will require further study before any generalization, ideally as a multisite pilot.

The recruitment strategies used over the course of this QI project support veterans in accessing and understanding ACP by addressing both common and unique barriers to engaging in ACP. Furthermore, this project demonstrates that telehealth is a viable mechanism to provide meaningful and satisfactory recruitment of veterans into the ACP process. Overall, we show that personalization in recruitment allows veterans to see that their needs are being met by VHA services. Demonstrating sensitivity to current veteran needs can increase access to the delivery of ACP. This approach is clinically feasible as a telehealth intervention. We demonstrate that a telehealth protocol with personalization and continuity of communication increases the engagement of veterans in clinical interventions about sensitive issues such as ACP and SICC. Engaging veterans in these conversations and documenting the results in the EHR is the first important step in ensuring veteran-centric care in times of medical crisis.

Acknowledgments

This material is based upon work supported (or supported in part) by the Department of Veterans Affairs, Veterans Health Administration, Office of Rural Health, and Veterans Rural Health Resource Center-Iowa City (Project 03522 and Project 03861).

Part of MBS's time was covered by the Veterans Rural Health Resource Center—Iowa City (Project 03522 and Project 03861). The authors are grateful to Andrea Holcombe, PhD, for providing statistical consultation and Keith Swetz, MD, for providing feedback on a draft of this paper.

The views expressed in this paper are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the US government.

Conflicts of Interest

None declared.

References

1. Matthieu MM, Ounpraseuth ST, Williams JS, Hu B, Adkins DA, Taylor LD, et al. "Advancing" advance care planning to veterans in the Veterans Health Administration. Mil Med 2023 Mar 20;188(3-4):786-791. [doi: 10.1093/milmed/usac196] [Medline: 35801841]
2. Health care ethics resources for veterans, patients, and families. US Dept of Veterans Affairs. 2023. URL: https://www.ethics.va.gov/for_veterans.asp [accessed 2023-03-26]
3. Advance care planning: advance directives for health care. National Institutes of Health. URL: https://www.nia.nih.gov/health/advance-care-planning/advance-care-planning-advance-directives-health-care [accessed 2024-01-14]
4. Advance care planning and management of advance directives. Department of Veterans Affairs, Veterans Health Administration. 2013. URL: https://www.ethics.va.gov/docs/policy/VHA_Handbook_1004_02_Advance_Care_Planning.pdf [accessed 2024-01-11]
5. Fried TR, Redding CA, Robbins ML, Paiva AL, O'Leary JR, Iannone L. Development of Personalized Health Messages to Promote Engagement in Advance Care Planning. J Am Geriatr Soc 2016 Feb;64(2):359-364 [FREE Full text] [doi: 10.1111/jgs.13934] [Medline: 26804791]
6. Rao JK, Anderson LA, Lin FC, Laux JP. Completion of advance directives among U.S. consumers. Am J Prev Med 2014 Jan;46(1):65-70 [FREE Full text] [doi: 10.1016/j.amepre.2013.09.008] [Medline: 24355673]
7. About the department. US Department of Veterans Affairs. URL: https://department.va.gov/about/#:~:text=Veterans%20Health%20Care,million%20enrolled%20Veterans%20each%20year [accessed 2024-01-17]
8. Tripken JL, Elrod C, Bills S. Factors Influencing Advance Care Planning Among Older Adults in Two Socioeconomically Diverse Living Communities. Am J Hosp Palliat Care 2018 Jan;35(1):69-74. [doi: 10.1177/1049909116679140] [Medline: 27852819]
9. Bernacki RE, Block SD, American College of Physicians High Value Care Task Force. Communication about serious illness care goals: a review and synthesis of best practices. JAMA Intern Med 2014 Dec;174(12):1994-2003. [doi: 10.1001/jamainternmed.2014.5271] [Medline: 25330167]
10. Ladin K, Buttafarro K, Hahn E, Koch-Weser S, Weiner DE. "End-of-Life Care? I'm not Going to Worry About That Yet." Health literacy gaps and end-of-life planning among elderly dialysis patients. Gerontologist 2018 Mar 19;58(2):290-299 [FREE Full text] [doi: 10.1093/geront/gnw267] [Medline: 28329829]
11. Melhado L, Bushy A. Exploring uncertainty in advance care planning in African Americans: does low health literacy influence decision making preference at end of life. Am J Hosp Palliat Care 2011 Nov;28(7):495-500. [doi: 10.1177/1049909110398005] [Medline: 21398263]
12. Nouri SS, Barnes DE, Volow AM, McMahan RD, Kushel M, Jin C, et al. Health Literacy Matters More Than Experience for Advance Care Planning Knowledge Among Older Adults. J Am Geriatr Soc 2019 Oct;67(10):2151-2156 [FREE Full text] [doi: 10.1111/jgs.16129] [Medline: 31424575]
13. Rose BL, Leung S, Gustin J, Childers J. Initiating advance care planning in primary care: a model for success. J Palliat Med 2019 Apr;22(4):427-431. [doi: 10.1089/jpm.2018.0380] [Medline: 30481086]
14. You JJ, Downar J, Fowler RA, Lamontagne F, Ma IWY, Jayaraman D, Canadian Researchers at the End of Life Network. Barriers to goals of care discussions with seriously ill hospitalized patients and their families: a multicenter survey of clinicians. JAMA Intern Med 2015 Apr;175(4):549-556 [FREE Full text] [doi: 10.1001/jamainternmed.2014.7732] [Medline: 25642797]
15. Del Rosario C, Kutney-Lee A, Sochalski J, Ersek M. Does quality of end-of-life care differ by urban-rural location? A comparison of processes and family evaluations of care in the VA. J Rural Health 2019 Sep;35(4):528-539 [FREE Full text] [doi: 10.1111/jrh.12351] [Medline: 30742330]
16. Lakin JR, Koritsanszky LA, Cunningham R, Maloney FL, Neal BJ, Paladino J, et al. A systematic intervention to improve serious illness communication in primary care. Health Aff (Millwood) 2017 Jul 01;36(7):1258-1264. [doi: 10.1377/hlthaff.2017.0219] [Medline: 28679813]
17. Lu H, Trancik E, Bailey FA, Ritchie C, Rosenfeld K, Shreve S, et al. Families' perceptions of end-of-life care in Veterans Affairs versus non-Veterans Affairs facilities. J Palliat Med 2010 Aug;13(8):991-996. [doi: 10.1089/jpm.2010.0044] [Medline: 20649437]

18. Kupensky D, Hileman BM, Emerick ES, Chance EA. Palliative Medicine Consultation Reduces Length of Stay, Improves Symptom Management, and Clarifies Advance Directives in the Geriatric Trauma Population. J Trauma Nurs 2015;22(5):261-265 [FREE Full text] [doi: 10.1097/JTN.0000000000000151] [Medline: 26352657]
19. Lee JS, Khan AD, Dorlac WC, Dunn J, McIntyre RC, Wright FL, et al. The patient's voice matters: the impact of advance directives on elderly trauma patients. J Trauma Acute Care Surg 2022 Feb 01;92(2):339-346. [doi: 10.1097/TA.0000000000003400] [Medline: 34538829]
20. VA National Center for Ethics in Health Care: life-sustaining treatment decisions: eliciting, documenting, and honoring patients' values, goals, and preferences. VA National Center for Ethics in Health Care. URL: https://www.ethics.va.gov/docs/policy/VHA_Handbook_1004_03_LST.pdf [accessed 2024-01-12]
21. Enterprise-wide initiatives. U.S. Department of Veterans Affairs, Office of Rural Health. URL: https://www.ruralhealth.va.gov/providers/Enterprise_Wide_Initiatives.asp [accessed 2024-02-13]
22. Farmer CM, Hosek SD, Adamson DM. Balancing demand and supply for veterans' health care: a summary of three RAND assessments conducted under the Veterans Choice Act. Rand Health Q 2016 Jun 20;6(1):12 [FREE Full text] [Medline: 28083440]
23. Schooley BL, Horan TA, Lee PW, West PA. Rural veteran access to healthcare services: investigating the role of information and communication technologies in overcoming spatial barriers. Perspect Health Inf Manag 2010 Apr 01;7(Spring):1f [FREE Full text] [Medline: 20697468]
24. Kelley AS, Bollens-Lund E. Identifying the Population with Serious Illness: The "Denominator" Challenge. J Palliat Med 2018 Mar;21(S2):S7-S16 [FREE Full text] [doi: 10.1089/jpm.2017.0548] [Medline: 29125784]
25. Sullivan E, Zahnd WE, Zhu JM, Kenzie E, Patzel M, Davis M. Mapping rural and urban veterans' spatial access to primary care following the MISSION Act. J Gen Intern Med 2022 Sep;37(12):2941-2947 [FREE Full text] [doi: 10.1007/s11606-021-07229-y] [Medline: 34981345]
26. Irvin S, McGowan M, Zavala A. Advance care planning and advance directives completion of elderly patients at a rural health clinic on a regional medical campus. J Reg Med Campuses 2020 Aug 14;3(2). [doi: 10.24926/jrmc.v3i2.2221]
27. Tasseff TL, Tavernier SS, Neill KS, Watkins PR. Exploring perceptions of palliative care among rural dwelling veterans. Online J Rural Nurs Health Care 2019;19(1):159-178 [FREE Full text] [doi: 10.14574/ojrnhc.v19i1.528]
28. West AN, Charlton ME. Insured veterans' use of VA and non-VA health care in a rural state. J Rural Health 2016 Sep;32(4):387-396. [doi: 10.1111/jrh.12196] [Medline: 27481190]
29. Coughlin SS, Young L. A review of dual health care system use by veterans with cardiometabolic disease. J Hosp Manag Health Policy 2018 Aug;2:39 [FREE Full text] [doi: 10.21037/jhmhp.2018.07.05] [Medline: 30198018]
30. Serious illness conversation guide. Ariadne Labs. 2015. URL: https://www.ariadnelabs.org/wp-content/uploads/2023/05/Serious-Illness-Conversation-Guide.2023-05-18.pdf [accessed 2024-02-13]
31. Ouchi K, George N, Schuur JD, Aaronson EL, Lindvall C, Bernstein E, et al. Goals-of-Care Conversations for Older Adults With Serious Illness in the Emergency Department: Challenges and Opportunities. Ann Emerg Med 2019 Aug;74(2):276-284 [FREE Full text] [doi: 10.1016/j.annemergmed.2019.01.003] [Medline: 30770207]
32. Goals of care conversation skills training for clinicians. Veterans Affairs Healthcare. 2019. URL: https://www.ethics.va.gov/GoCC.asp [accessed 2024-02-13]
33. Combes S, Gillett K, Norton C, Nicholson CJ. The importance of living well now and relationships: a qualitative study of the barriers and enablers to engaging frail elders with advance care planning. Palliat Med 2021 Jun;35(6):1137-1147 [FREE Full text] [doi: 10.1177/02692163211013260] [Medline: 33934669]
34. Gerger H, van Dijk-de Vries A, Moser A, Jochem I, Veenstra M, Perry M, et al. Adjusting advance care planning to older people's needs: results from focus groups and interviews. BMC Health Serv Res 2024 Jan 10;24(1):51 [FREE Full text] [doi: 10.1186/s12913-023-10491-x] [Medline: 38200528]
35. DeVoe ER, Ross AM, Paris R. Build it together and they will come: the case for community-based participatory research with military populations. Adv Soc Work 2012;13(1):149-165.
36. Riffin C, Kenien C, Ghesquiere A, Dorime A, Villanueva C, Gardner D, et al. Community-based participatory research: understanding a promising approach to addressing knowledge gaps in palliative care. Ann Palliat Med 2016 Jul;5(3):218-224 [FREE Full text] [doi: 10.21037/apm.2016.05.03] [Medline: 27481321]
37. Holkup PA, Tripp-Reimer T, Salois EM, Weinert C. Community-based participatory research: an approach to intervention research with a Native American community. ANS Adv Nurs Sci 2004;27(3):162-175 [FREE Full text] [doi: 10.1097/00012272-200407000-00002] [Medline: 15455579]
38. Community-Based Participatory Research Program. National Institutes of Health. 2018. URL: https://www.nimhd.nih.gov/programs/extramural/community-based-participatory.html [accessed 2024-02-13]
39. Gordon HS, Solanki P, Bokhour BG, Gopal RK. "I'm Not Feeling Like I'm Part of the Conversation" Patients' Perspectives on Communicating in Clinical Video Telehealth Visits. J Gen Intern Med 2020 Jun;35(6):1751-1758 [FREE Full text] [doi: 10.1007/s11606-020-05673-w] [Medline: 32016705]
40. Seecof OM, Allanoff M, Liantonio J, Parks S. Lessons Learned From a Pilot Project on Telemedicine Advance Care Planning in an Urban Geriatric Primary Care Office. Am J Hosp Palliat Care 2022 Jun;39(6):701-704. [doi: 10.1177/10499091211036978] [Medline: 34350802]

41. Soliman AA, Akgün KM, Coffee J, Kapo J, Morrison LJ, Hopkinson E, et al. Quality of telehealth-delivered inpatient palliative care during the early COVID-19 pandemic. J Pain Symptom Manage 2023 Jan;65(1):6-15 [FREE Full text] [doi: 10.1016/j.jpainsymman.2022.09.014] [Medline: 36206949]
42. Ko JS, El-Toukhy S, Quintero SM, Wilkerson MJ, Nápoles AM, Stewart AL, et al. Disparities in telehealth access, not willingness to use services, likely explain rural telehealth disparities. J Rural Health 2023 Jun;39(3):617-624. [doi: 10.1111/jrh.12759] [Medline: 37042413]
43. Cortelyou-Ward K, Atkins DN, Noblin A, Rotarius T, White P, Carey C. Navigating the Digital Divide: Barriers to Telehealth in Rural Areas. J Health Care Poor Underserved 2020;31(4):1546-1556. [doi: 10.1353/hpu.2020.0116] [Medline: 33416736]
44. Chatland LE, Harvey C, Kelly K, Paradine S, Bhagat M, Hudson BF. Research participation in palliative medicine-benefits and barriers for patients and families: rapid review and thematic synthesis. BMJ Support Palliat Care 2023 Mar;13(1):35-44 [FREE Full text] [doi: 10.1136/bmjspcare-2021-003093] [Medline: 34404745]
45. LeBlanc TW, Wheeler JL, Abernethy AP. Research in end-of-life settings: an ethical inquiry. J Pain Palliat Care Pharmacother 2010 Sep;24(3):244-250. [doi: 10.3109/15360288.2010.493579] [Medline: 20718645]
46. Chau AJ, Sudore RL, Hays RD, Tseng CH, Walling AM, Rahimi M, et al. Telephone Outreach Enhances Recruitment of Underrepresented Seriously Ill Patients for an Advance Care Planning Pragmatic Trial. J Gen Intern Med 2023 Jun;38(8):1848-1853 [FREE Full text] [doi: 10.1007/s11606-022-08000-7] [Medline: 36717432]
47. Schmidt ME, Daly JM, Xu Y, Levy BT. Improving Iowa Research Network Patient recruitment for an advance care planning study. J Prim Care Community Health 2021;12:21501327211009699 [FREE Full text] [doi: 10.1177/21501327211009699] [Medline: 33840295]
48. Stewart RR, Dimmock AEF, Green MJ, Van Scoy LJ, Schubart JR, Yang C, et al. An analysis of recruitment efficiency for an end-of-life advance care planning randomized controlled trial. Am J Hosp Palliat Care 2019;36(1):50-54 [FREE Full text] [doi: 10.1177/1049909118785158] [Medline: 29976075]
49. Elwyn G, Barr PJ, Grande SW, Thompson R, Walsh T, Ozanne EM. Developing CollaboRATE: a fast and frugal patient-reported measure of shared decision making in clinical encounters. Patient Educ Couns 2013;93(1):102-107 [FREE Full text] [doi: 10.1016/j.pec.2013.05.009] [Medline: 23768763]
50. Forcino RC, Barr PJ, O'Malley AJ, Arend R, Castaldo MG, Ozanne EM, et al. Using CollaboRATE, a brief patient-reported measure of shared decision making: results from three clinical settings in the United States. Health Expect 2018 Feb;21(1):82-89 [FREE Full text] [doi: 10.1111/hex.12588] [Medline: 28678426]
51. Barr PJ, Forcino RC, Thompson R, Ozanne EM, Arend R, Castaldo MG, et al. Evaluating CollaboRATE in a clinical setting: analysis of mode effects on scores, response rates and costs of data collection. BMJ Open 2017 Mar 24;7(3):e014681 [FREE Full text] [doi: 10.1136/bmjopen-2016-014681] [Medline: 28341691]
52. Rural-urban commuting area codes. U.S. Department of Agriculture. URL: https://www.ers.usda.gov/data-products/rural-urban-commuting-area-codes/documentation/ [accessed 2024-02-13]

Abbreviations

ACP: advanced care planning
AD: advance directive
CBPR: community-based participatory research
EHR: electronic health record
IRB: institutional review board
LST: life-sustaining treatment
QI: quality improvement
SICC: serious illness care conversations
tSICC: telehealth serious illness care conversations
VA: Veterans Administration
VEP: Veteran Engagement Panel
VHA: Veterans Health Administration

Edited by A Mavragani; submitted 01.12.23; peer-reviewed by C Stults, R Gopal, M Ersek; comments to author 24.12.23; revised version received 26.01.24; accepted 31.01.24; published 12.04.24.

Please cite as:
Walkner T, Karr DW, Murray S, Heeren A, Berry-Stoelzle M
Participation in Advance Care Planning Among Medically At-Risk Rural Veterans: Protocol for a Personalized Engagement Model
JMIR Res Protoc 2024;13:e55080
URL: https://www.researchprotocols.org/2024/1/e55080
doi:10.2196/55080
PMID:38608267

Protocol

Fostering Digital Life Skills Through Social Media With Adolescents in 6 German States: Protocol for an Accessibility Study According to the RE-AIM Framework

Elizabeth Zimmermann[1*], MSc; Samuel Tomczyk[1*], Dr Phil, Jun prof

Institute for Health Psychology, Department of Psychology, University of Greifswald, Greifswald, Germany

[*]all authors contributed equally

Corresponding Author:
Elizabeth Zimmermann, MSc
Institute for Health Psychology
Department of Psychology
University of Greifswald
Robert-Blum-Str 13
Greifswald, 17489
Germany
Phone: 49 3834420 ext 3807
Email: elizabeth.zimmermann@uni-greifswald.de

Abstract

Background: Social media is essential in the lives of adolescents, with 97% of US teenagers engaging daily. While it facilitates communication, learning, and identity development, it also poses risks like harmful content exposure and psychological distress, particularly for adolescents in their critical developmental stage. Teaching digital life skills innovatively counters these risks, adapting traditional competencies such as decision-making, problem-solving, creative and critical thinking, communication, interpersonal skills, self-awareness, empathy, and emotional and stress management to digital challenges.

Objective: This study evaluates the accessibility of the "leduin" program, a novel intervention designed to impart digital life skills through Instagram. The program aims to leverage social media's educational potential, focusing on effective strategies to engage adolescents. Emphasizing accessibility is crucial, as it determines the program's overall impact.

Methods: The leduin program, developed through intervention mapping, applies behavior change techniques via social media for 9th and 10th graders. It is a 14-week spaced learning curriculum with daily sessions <5 minutes. Emphasizing the "reach" aspect of the reach, effectiveness, adoption, implementation, and maintenance (RE-AIM) model, the recruitment targets diverse educational settings across 6 German states, aiming for inclusivity. Recruitment will involve schools, youth centers, and therapeutic facilities. The study seeks at least 128 participants, a calculated minimum to detect medium-sized effects in the quasi-experimental design and explore varying engagement levels and program responses. Data collection includes preintervention, postintervention, and 6-month follow-up surveys, using multilevel regression, latent growth models, and qualitative analysis to extensively assess reach and gain first insights on effectiveness, acceptance, implementation, and maintenance. The study aims to reveal key factors influencing program participation and interaction; a detailed analysis of engagement patterns will reveal the effectiveness of the recruitment strategies and barriers to participation. Additionally, initial indications of the program's impact on life skills, social media–related skills, health status, risk behaviors, and academic performance will be analyzed.

Results: Recruitment was planned from May 2023 until the beginning of the leduin program in October 2023. As of March 2024, we have recruited 283 participants.

Conclusions: The leduin program stands as an innovative and essential initiative in adolescent health promotion, harnessing the power of social media to teach important digital life skills. This study highlights the critical role of accessibility in the success of social media interventions. Effective adolescent engagement strategies are imperative, as they dictate the overall impact of such interventions. The insights gained from this study will be instrumental in shaping future programs, laying groundwork for a subsequent, more comprehensive cluster-randomized controlled trial. The study's design acknowledges the limitations of the current quasi-experimental approach, including the anticipated sample size and the absence of a control group, and aims to provide a foundational understanding for future research in this field.

Trial Registration: Deutsches Register Klinischer Studien DRKS00032308; https://drks.de/search/de/trial/DRKS00032308

International Registered Report Identifier (IRRID): PRR1-10.2196/51085

(JMIR Res Protoc 2024;13:e51085) doi:10.2196/51085

KEYWORDS

adolescents; social media; prevention; life skills; RE-AIM-framework; mixed-methods; digital life; accessibility; innovative; utilization; teaching skill; empower; digital skill; life skill; German; digitalized; adolescent; adolescent health; study protocol; validity; innovation; leduin-program

Introduction

Background

Social media, a staple in the lives of 97% of US teenagers [1], facilitates communication, learning, and identity development for adolescents [2-5]. However, the functions and the lack of censorship on these platforms can lead to risks such as addiction, psychological distress, and exposure to harmful content [6-8]. Given the ongoing developmental stage of adolescents [9], they frequently lack the essential social-emotional and cognitive skills required for functional and constructive engagement with social media [10]. These challenges underscore the importance of building social media literacy, a crucial skill that enables adolescents to navigate digital content critically and responsibly [11]. Enhancing media literacy involves teaching adolescents to understand and manage the psychological impacts of digital interactions, including the development of self-regulation and critical thinking skills [12-14].

The widespread use of social media also offers a unique opportunity for preventive health interventions. As a cost-effective platform with a broad reach [3,15-17], social media can play a pivotal role in promoting mental and physical health [18-22]. Its accessibility makes it particularly valuable for reaching socially disadvantaged adolescents, who may engage more frequently with digital platforms, often in dysfunctional ways [23-26]. Thus, social media emerges as a critical tool in enhancing equity in health promotion.

While recognizing the potential of social media in adolescent health promotion, the limited evidence base highlights the need for careful consideration of practical, methodological, and ethical implications [22,27-30]. Current studies focus on engaging content and tailored interventions for diverse needs [20,29,31,32] but often lack a comprehensive, evidence-based approach that integrates psychological mechanisms and behavioral change techniques [30]. This gap extends to the challenge of effectively recruiting adolescents, especially for programs addressing sensitive health issues [33,34]. Recruitment complexities arise from stigma and the need to align with adolescents' varied interests and obtain parental consent [35-37]. Addressing these challenges necessitates multifaceted strategies: empathetic engagement; using diverse channels; and clearly communicating the benefits while ensuring trust, confidentiality, and cultural sensitivity [38,39]. These methods emphasize the need for a supportive and safe environment, messages that resonate with adolescents, and the involvement of the broader community in the recruitment process for prevention programs.

Digital Life Skills in the Age of Social Media

Modern prevention strategies must encompass the growing convergence of analog and digital life, acknowledging the diverse challenges in both realms. In this context, promoting life skills emerges as a valuable and effective approach, contributing significantly to overall well-being, academic success, and the reduction of risk behaviors and chronic diseases [40-44].

Life skills, as defined by the World Health Organization [45], include decision-making, problem-solving, creative and critical thinking, communication and interpersonal skills, self-awareness, empathy, and managing emotions and stress. Traditional programs, despite their benefits, face challenges such as high costs and limited accessibility [46,47]. The digital era offers new avenues through e-learning and apps to effectively impart these skills while addressing issues such as substance abuse [48-53] but also necessitates developing digital skills to tackle digital challenges [11,12,54].

Development of a Digital Life Skills Program (Leduin)

Overview

Consequently, we have developed the "leduin" program, using the social media platform Instagram to teach digital life skills in a low-threshold and interactive manner, seamlessly integrated into everyday life. In doing so, we followed the intervention mapping methodology [55], which directs the conceptualization, development, and implementation of health promotion programs. The leduin program is a digital intervention specifically designed to empower adolescents in the 9th and 10th grades with crucial digital life skills to navigate challenges presented by social media and everyday life. The following steps were undertaken to develop the leduin program (E Zimmermann and S Tomczyk, unpublished data, 2024).

Logic Model Development

The development of the leduin program began with a comprehensive logic model, addressing the complexities of adolescent life in the context of social media. This model focuses on developing digital life skills that enhance health, reduce risk behaviors, and improve school performance, particularly targeting 9th and 10th graders. This timing is strategic as life skills are especially beneficial and more effectively imparted during such transitional periods in a student's life [56]. The model was informed by focus groups with 67 adolescents aged 14 to 17 years and heterogeneous educational backgrounds.

Psychological Mechanisms Identification

The second step involved identifying psychological mechanisms vital for behavioral change and digital life skills development.

The leduin program integrates (1) personal variables such as attitudes and self-efficacy, based on social cognitive theory and the theory of planned behavior [57-59]; (2) environmental factors including social norms and support [60,61]; and (3) information processing mechanisms to optimize message impact [62]. Additionally, it focuses on (4) activating resources to support the development of digital life skills [63].

Developing Methodological Framework and Intervention Design

For the third step, we crafted a methodological framework using the behavior change taxonomy [64], tailored to social media context. Influenced by research on social media [65], behavior change techniques in health programs [66], and user preferences [67], we chose Instagram for its interactivity and popularity [3,68]. The program integrates behavior change techniques within Instagram, encompassing (1) content sharing through posts and stories for information dissemination, (2) interactive features such as quizzes for behavioral regulation, (3) material and social incentives to enhance engagement, and (4) social processes such as polling and commenting to encourage participation. These components collectively support habit formation, problem-solving, and identity development related to behavior change (see Table 1 for detailed mechanisms and associated features), with the selection process also being guided by adolescent focus group feedback.

Table 1. Mechanisms, exemplary behavior change techniques, and associated exemplary social media features within the social media–based life skills program (leduin).

Mechanism	Exemplary behavior change techniques	Exemplary social media features
Content sharing	• Information about (1) health consequences (5.1) • Information about (2) social and environmental consequences (5.3) • Information about (3) emotional consequences (5.6) • Pros and cons (9.2) • Salience of consequences (5.2) • Instruction on how to perform the behavior (4.1) • Verbal persuasion about capability (15.1) • Credible source (9.1)	• Content sharing methods: posts, tweets, and stories using text, image, and video
Behavioral regulation	• Self-monitoring of behavior (2.3) • Self-monitoring of outcomes of behavior (2.4) • Discrepancy between current behavior and goal (1.6)	• Interactive elements like quizzes, sliders (similar to Likert-scale), templates, and question stickers
Incentives	• Material incentive (behavior; 10.1) • Social reward (10.4)	• Raffles and prizes • Likes, comments, and direct messages
Social processes	• Social comparison (6.2) • Social support (unspecified; 3.1) • Restructuring the social environment (12.2)	• Sliders, polls, and direct messages • Direct messages, likes, and group chats • Community and account recommendations
Processes initiated	• Habit formation (8.3) • Problem-solving (1.2) • Goal setting (behavior; 1.1) • Identity associated with changed behavior (4.1)	• Push notifications

Program and Module Structuring

In the fourth step of the intervention mapping approach, the leduin program's structure and modules were developed. It resulted in a 14-week program that encompasses modules on individual, social, and health skills, detailed in Textbox 1. Each module introduces, specifies, applies concepts to risk situations and relates them to everyday life, aligning with World Health Organization life skills education guidelines [69]. Modules cover areas such as emotional and stress management, communication skills, and digital safety. Content is delivered through Instagram stories and feeds using short videos, images, quizzes, and surveys to foster active learning. Additionally, the program incorporates weekly self-care and stress management activities and interactive challenges with prizes to boost engagement. An accompanying analog workbook with journaling activities complements the digital content. This dual approach ensures comprehensive life skills training, emphasizing concise, daily content to promote spaced learning [70], contrasting with traditional massed learning methods.

Textbox 1. Contents of the 14 modules of the 14-week social media–based life skills program (leduin) divided into individual, social, and health skills.

Individual skills (modules 1-4):

- Strengths, goals, emotions, and stress

Social skills (modules 5-8):

- Communication, needs, boundaries, identity, and peer pressure

Health skills (modules 9-12):

- Risks, addictions, digital violence, and information

Cross-module:

- Self-care, stress reduction, problem-solving, and self-reflection
- Modules 0 and 13 contain introduction and conclusion

Pilot Study of the Leduin Program

In a pilot study, we assessed the feasibility, acceptance, and engagement of the leduin program, implementing it with 101 students of 9th and 10th-grade in high schools and secondary schools in North Rhine-Westphalia and Lower Saxony, Germany, from November 2022 to February 2023 (E Zimmermann and S Tomczyk, unpublished data, 2024). A total of 13 interviews with participating adolescents aged 14 to 17 years and 6 interviews with their teachers were conducted to evaluate acceptance and initial effectiveness. These qualitative findings indicate that the social media–based prevention program was successfully conducted, well-received by participants, and executed with high commitment. Participants reported positive subjective learning outcomes in social media use, self-care, and stress reduction and perceived the leduin program as personally beneficial and enriching. Although the program yielded favorable results, its accessibility presented a substantial hurdle in the recruitment phase. We conducted informational sessions in schools and a youth center to educate adolescents about the program, enabling them to make informed choices about participating in their leisure time. However, the participation rates varied significantly among schools, with certain classes showing high engagement, while others had minimal involvement. This variation underscores the importance of developing effective strategies to engage adolescents in social media–based prevention programs. Consequently, in the fifth step of the intervention mapping approach as the subject of this study, our focus is to examine and enhance accessibility to guarantee effective program execution.

Methods

Overview

The objectives of the accessibility study for the leduin program, grounded in the reach, effectiveness, adoption, implementation, and maintenance (RE-AIM) framework [71], primarily focus on evaluating the first dimension of the framework—"reach"—to identify effective strategies for engaging adolescents in digital life skills interventions on social media. This includes reaching a diverse demographic of 9th and 10th graders, encouraging participation, and ensuring sustained engagement. While also considering the remaining RE-AIM aspects—effectiveness, adoption, implementation, and maintenance—the study mainly seeks to understand the characteristics and engagement levels of participating adolescents and to identify what drives active or low engagement. This understanding is critical for refining recruitment strategies and enhancing the impact of social media–based health interventions for youth.

Reach

The focal point of our study is to encompass a broad and representative demographic of 9th- and 10th-grade adolescents. To achieve this, we are targeting a diverse population from various school types, including grammar schools, comprehensive schools, secondary schools, and independent schools. Moreover, recognizing the importance of reaching adolescents undergoing high stress, recruitment efforts are also extended to youth centers and therapeutic facilities. We will explore the characteristics of adolescents who have consented to participate. Based on insights from the pilot study, we anticipate varying levels of engagement among the participants: some may actively engage with the program's social media content, while others may have minimal to no interaction although initially interested. This variance allows for a quasi-experimental design, using engagement levels (ranging from none to high) as the basis for group assignment. Such a design is capable of highlighting differences between these engagement groups, and we will explore the predictors that are associated with active engagement or no or low engagement. We will also conduct a qualitative process evaluation to explore the facilitators and barriers encountered during recruitment. This will involve the recruitment team documenting feedback about the program and information event, as well as the reasons participants choose to join or decline participation. This documentation will be captured both in written form and verbally.

Effectiveness

The program's effectiveness will be evaluated by its impact on life skills, social media–related skills, health status, risk behaviors, and school performance. Using the quasi-experimental design, we aim to test the hypothesis that enhancing digital life skills through the intervention leads to improved social media skills and reduced risk behaviors. To detect medium-sized effects, a power analysis indicates the need

for 128 adolescent participants (power=0.8, α=.05), aligning with existing evidence of medium effect sizes in digital interventions (d=0.30 to 0.76) [72]. This evaluation will provide crucial data for potential effectiveness, shaping the direction of future trials.

Adoption

The study will evaluate the proportion of schools, youth centers, and therapists willing to participate, providing insights into broader program acceptance and feasibility.

Implementation

We will examine the effectiveness of data collection and participant engagement on Instagram, which is critical for understanding how the program can be successfully implemented in a larger trial.

Maintenance

A 6-month follow-up will gauge the long-term impact of the intervention on intended outcomes and evaluate interaction and retention rates. These data are crucial for understanding the sustainability of the program's effects.

The operationalization of these dimensions is summarized in Table 2. The trial will be conducted in a single-group design.

Table 2. Overview of the questionnaires used with a single-group design to assess primary and secondary outcomes in preintervention, postintervention, and 6-month follow-up surveys.

Outcome and construct	Questionnaire	Reliability
Primary outcomes		
Life skills		
Decision-making or goal setting	Subscale "goal setting" of the Life Skills Ability Scale (LSAS) [73]	α=.89
Problem-solving	Subscale "problem solving" of the Life Skills Ability Scale (LSAS) [73]	α=.85
Creative and critical thinking	Self-generated items to test knowledge based on the developed program content	—[a]
Communication	Subscale "communication" of the Life Skills Ability Scale (LSAS) [73]	α=.78
Interpersonal skills and empathy		
—	Questionnaire on resources in childhood and adolescence (FRKJ 8-16) [74]	α=.68-.89
—	Subscale "Social skills" of the Life Skills Ability Scale (LSAS) [73]	α=.82
Self-confidence and self-efficacy	Questionnaire on resources in childhood and adolescence (FRKJ 8-16) [74]	α=.68-.89
Dealing with emotions	Emotion regulation questionnaire [75]	α=.74-.76
Dealing with stress		α=.69-.88
—	Stress- and Coping-Inventory (SCI)	—
—	Subscales "Physical symptoms" + "Coping strategies" [76]	—
Social media–related skills		
Cyberbullying	European Cyberbullying Intervention Project Questionnaire (ECIPQ) [77]	α=.96
Media-based empathy		α=.80
—	Media-Based Empathy (MBE)	—
—	Subscale "Cognitive Media Empathy with Real Persons" [78]	—
Social media use		
—	Social media use time	—
—	Social media disorder scale-short form [79]	α=.81
—	Bergen social media addiction scale [80]	r_{tt}=.82
Smartphone use	Smartphone addiction scale [81]	α=.85
Secondary outcomes		
Risk behavior		
Substance use		
—	Alcohol Use Disorder Identification Test (AUDIT) [82]	α=.80
—	Cigarettes and cannabis - questions from the HBSC study [83]	—
Health status		
Subjective state of health	Subjective state of health [84,85]	—
Well-being	World Health Organization-5 well-being-index [86]	α=.92
Life satisfaction		
—	German version of the Satisfaction with Life Scale (SWLS) [87,88]	α=.87
—	Short scale for the assessment of general life satisfaction (L-1) [89]	r_{tt}=.67
Mental health: anxiety and depression	Hopkins Symptom Checklist-25 (HSCL-25) [90]	α=.94
School performance	School grades (German, English, and Math), grade point average, and change	—
Covariants		
General		
Acceptance and feasibility of the program		—

Outcome and construct	Questionnaire	Reliability
—	Self-generated items based on the Training Evaluation Inventory (TEI) [91]	—
—	Net-Promoter-Score	—
Sociodemographic variables		
—	Gender, age, migration background, socioeconomic status: family affluence scale [92,93]	r_{tt}=.90
—	Subjective Socioeconomic Status scale (SSS-Scale) [94]	α=.70

[a]Not applicable.

Recruitment

This accessibility study will recruit participants via schools, youth centers, and therapeutic facilities across Germany. Adolescents from various school types (grammar, secondary, comprehensive, and independent) and socioeconomic backgrounds are targeted. Recruitment spans several federal states (Berlin, Mecklenburg-Western Pomerania, North Rhine-Westphalia, Saxony, Lower Saxony, and Thuringia), chosen for representativeness and synchronized holidays, encompassing both rural and urban areas. State school participation requires ethical approval and ministry or school board consent. Schools, youth centers, and therapeutic facilities are randomly selected within these states.

Recruitment will begin once approvals are obtained, with invitations issued in waves based on response rates. Teachers, youth workers, and therapists initially agreed to participate (Multimedia Appendix 1). Adolescents are then recruited through digital information events, which aim to build motivation to participate through highlighting the relevance of the programs' content for their life stage (Multimedia Appendix 2). In addition to research findings on that, key adolescent concerns were identified in the pilot study. The use of Instagram minimizes participation effort and the recruitment in schools fosters group dynamics. Further, the program incentivizes engagement with rewards and ensures anonymity and confidentiality, creating a safe space for discussing sensible and at the same time interesting topics. Finally, together with their parents, adolescents agree to participate in the study.

To join the study, participants need an Instagram account, must be proficient in German, and must be aged 14-17 years. The recruitment goal includes 2 classes from grammar schools, 3 classes from secondary schools, and 1 class from an independent school per state, plus 20 adolescents from youth centers and therapeutic institutions in each state, accommodating additional participants if interested.

As we are taking an innovative approach, it is not clear how complete the recruitment will be. The sample size depends on adolescents who voluntarily want to participate. Since adolescents work on the program in their free time, it can be assumed that fewer will participate than in compulsory programs conducted in school. Recruitment will start in May 2023 and end as soon as the target criteria are met or the program starts in September.

Data Collection

In this study, both qualitative and quantitative data are gathered to explore the RE-AIM framework's dimensions, involving (1) documentation by the recruitment team and (2) personal-level outcomes via questionnaires. Figure 1 illustrates the study design with the recruitment phase and points of assessment.

To assess RE-AIM's aspects of reach, acceptance, and implementation, data will be collected on the number of schools, youth centers, and therapeutic facilities contacted per state; their response rates; information events held; and consents after the event. The recruitment team will also document institutions' responses.

Personal level characteristics outcomes, measuring reach, effectiveness, and maintenance, are gathered through web-based questionnaires in a preintervention, postintervention, and follow-up design. Participants and institutions receive unique codes for tracking. The institutional link aims for support through teachers or youth workers and therapists and thus comprehensive data collection by conducting the entire study, including data collection, within 1 school year. Schools optionally receive supplementary teaching materials for the leduin program content.

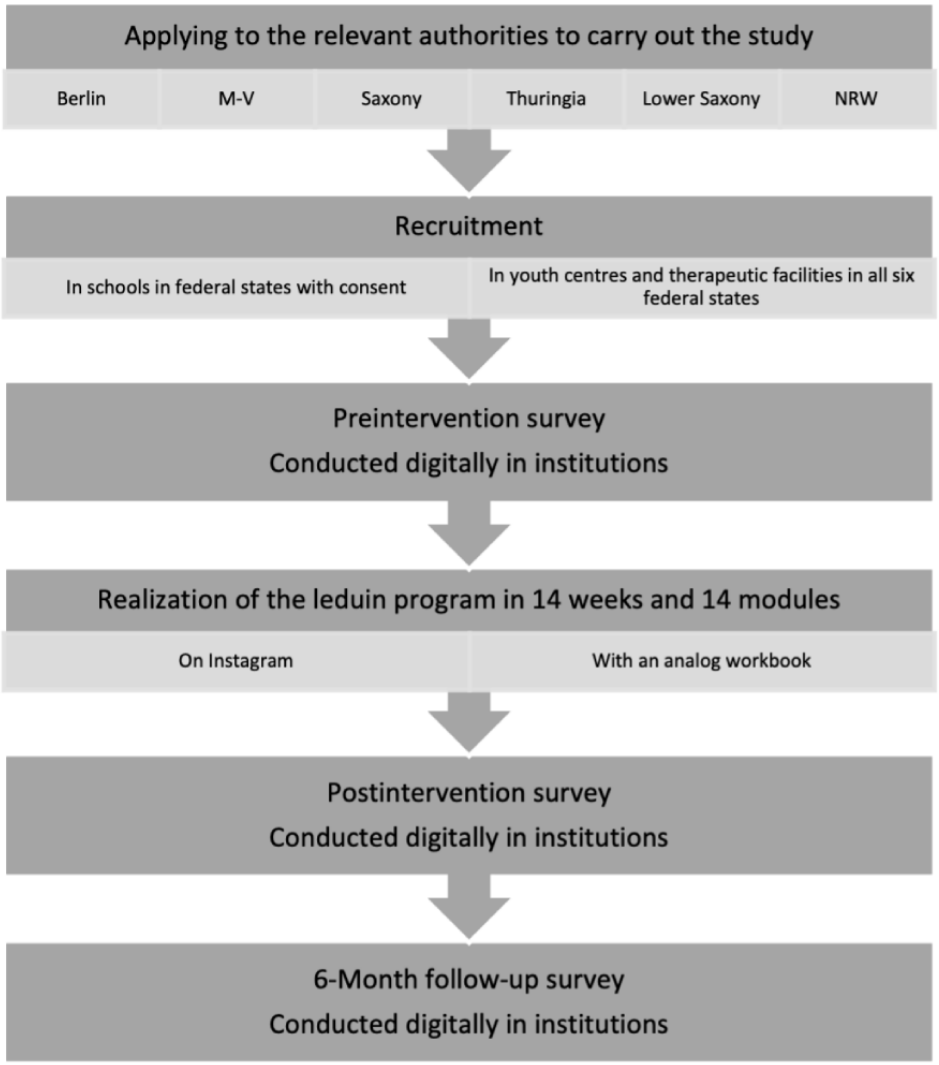
The following constructs are collected by means of questionnaires: primary outcomes (life skills [decision-making or goal setting, problem-solving, creative and critical thinking, communication, interpersonal skills and empathy, self-confidence and self-efficacy, managing emotions, and managing stress], and social media–related skills [media-based empathy, cyberbullying, smartphone, and addictive or disordered social media use]); secondary outcomes (health status [well-being, subjective health and mental health, and life satisfaction], risk behavior [substance use], and school performance); and covariants (acceptance and feasibility of the program and sociodemographic variables). Table 2 lists the survey instruments used to measure the constructs just described, including reliability.

For the web-based data collection of the participants' personal data, we use the SoSci Survey platform with which we have an order data processing agreement for the leduin study that has been reviewed by the data protection officer of the University of Greifswald. This ensures the technical and organizational measures required for data security. The provider SoSci Survey works with SSL encryption (HTTPS) of the data when filling out the questionnaire and when retrieving the collected data. A secure SSL configuration (Qualys SSL Labs) secures the transmission of the data. The servers of the University of

Greifswald are used to store the data. The data are secured by daily backup and are usually stored for 90 days (3 months).

The initial data collection in the pilot study proved successful due to teacher involvement. However, transferring responsibility for the subsequent data collection to the adolescents led to significant gaps in the data. To address this in the accessibility study, we will prioritize early emphasis on the importance of data collection and ensure consistent supervision of the adolescents to mitigate missing data issues.

Figure 1. Flowchart illustrating recruitment process, single-group design (1 intervention group), and points of assessment (preintervention, postintervention, and 6-month follow-up surveys). M-V: Mecklenburg-Western Pomerania; NRW: North Rhine-Westphalia.



Data Management

Participation in the study is voluntary, with participants receiving detailed information about the procedure and providing informed consent according to the Declaration of Helsinki. This consent can be withdrawn anytime without justification or repercussions. Pseudonymized data can be deleted until fully anonymized, a detail made clear in the study information.

The data are stored on password-protected servers at the University of Greifswald, secured by daily backups. Access is restricted to authorized scientific personnel for qualitative and quantitative analysis. Project management and data processing staff at the university ensure data plausibility, completeness, and accuracy. After collection, data are quickly anonymized.

Data management adheres to the German Psychological Society's recommendations, focusing on quality assurance, knowledge optimization, and maximizing cost-benefit ratios. Cleaned, anonymized primary data, along with associated syntax commands, will be openly accessible in line with open science principles, a fact communicated to participants in the study information.

Data Analysis

Statistical Methods

Quantitative analyses will vary according to the different dimensions of the RE-AIM framework [71]. The software R Studio (Posit) and SPSS (IBM Corp) will be used [95]. Multilevel logistic regressions will be conducted to evaluate the dimensions of reach, acceptance, and implementation. Here, the extent to which the following variables influence institutions' initial interest in the program, individuals' initial willingness to participate in the program, completeness of data, and individual engagement within the program is examined: socioeconomic status, gender, age, mode of recruitment (school,

youth center, and therapeutic facility), school type, performance, well-being, life satisfaction, and mental health. The initial interest of institutions in the program is operationalized by the proportion of institutions (schools, youth centers, and therapeutic institutions) that participated in an information session. The initial willingness of individuals to participate in the program is assessed by the percentage of students who decide to participate in the program after an information session. The completeness of data is examined by the percentage of data in the preintervention, postintervention, and follow-up surveys, and individual engagement is measured by the participants' self-assessment.

For quantitative analyses of the dimensions of reach, effectiveness, and sustainability, mixed-effect multilevel regression analysis with institutions (school, youth center, and therapeutic facility), classes, and individuals as evaluation levels and 3 measurement points (preintervention, postintervention, and follow-up) will be carried out. The multilevel structure will be assumed if the actual design effect resulting from the intraclass correlation is >2 [96]. The influence of covariants such as gender, age, and socioeconomic status will be controlled. In addition, the individual courses in the outcome variables, as described before, will be examined by using latent growth models across the 3 time points. Logistic regressions will be conducted to investigate the impact of the program on participants' addictive or disordered social media use by comparing pre- and postintervention data.

Qualitative analyses of the recruitment process will be executed by conducting a qualitative content analysis [97] using the software MAXQDA (VERBI Software). This should provide information on the barriers to participation in the program and also identify the facilitators.

Table 3 summarizes the different dimensions of the RE-AIM framework, their operationalization, and corresponding statistical methods.

Table 3. Dimensions of the reach, effectiveness, adoption, implementation, and maintenance (RE-AIM) framework, operationalization, and statistical methods to evaluate a social media–based life skills program (leduin).

Dimension	Operationalization	Statistical method

Reach	• Dependent variables
	  • Initial interest
	  • Institutional level: number of institutions (schools, youth centers, and therapeutic facilities) contacted per federal state and positive responses
	  • Individual level: proportion of adolescents who agree to participate
	  • Qualitative process information of facilitators and carriers
	• Independent variables from questionnaires
	  • Socioeconomic status, gender, age, mode of recruitment (school, youth center, and therapeutic facility), school type, well-being, life satisfaction, and mental health
		• Multilevel logistic regressions
		• Qualitative content analysis

Effectiveness	• Primary outcomes: Life skills and social media–related skills • Secondary outcomes: mental health, well-being, risk behavior, school performance	• Mixed-effect multilevel regression analysis with institutions (school, youth center, and therapeutic facility), classes, and individuals as evaluation levels and 3 measurement points (preintervention, postintervention, and follow-up) • Latent growth models • Logistic regressions

Acceptance	• Dependent variables
	  • Willingness to participate:
	  • Number of information events
	  • Number of consents
	  • Individual engagement
	• Independent variables from questionnaires
	  • Socioeconomic status, gender, age, mode of recruitment (school, youth center, and therapeutic facility), school type, well-being, life satisfaction, and mental health
	  • Qualitative process information of facilitators and carriers
		• Multilevel logistic regressions
		• Qualitative content analysis

Implementation	• Dependent variables
	  • Completeness of data collection in the different institutions
	  • Participation of adolescents in the program on Instagram (active and passive)
	• Independent variables from questionnaires
	  • Socioeconomic status, gender, age, mode of recruitment (school, youth center, and therapeutic facility), school type, well-being, life satisfaction, and mental health
		• Multilevel logistic regressions

Maintenance	• Primary outcomes: life skills and social media–related skills • Secondary outcomes: mental health, well-being, risk behavior, school performance • Participation of adolescents in the program on Instagram (active and passive)	• Mixed-effect multilevel regression analysis with institutions (school, youth center, and therapeutic facility), classes, and individuals as evaluation levels and 3 measurement points (preintervention, postintervention, follow-up) • Latent growth models • Logistic regressions

Monitoring

Since the leduin study is not a clinical study, it is not expected that the participants will experience any harm. Therefore, the use of a data monitoring committee is waived. However, communication within the program will be monitored by an internal monitoring team in accordance with netiquette [98]. Violations of netiquette will be commented on and discussed within the program, and if necessary, the authors will be excluded from the program if there is no improvement. If harm is unexpectedly caused to a participant during the program, the program will be interrupted if there are indications that the harm may have been caused by the program. After review, the program will either be revised or continued.

Ethical Considerations

The leduin study has been positively assessed by the ethics committee of the Greifswald University Medical School (BB

190/22). Approval for the study has also been sought from the relevant education authorities and ministries for state schools in Germany. The data protection regulations have been developed with the data protection officer of the University of Greifswald and a register of processing activities is available. If important protocol modifications are made, this will be communicated to the responsible ethics committee, the school authorities and ministries, the data protection officer, and the study participants.

Participating adolescents and their parents consent to their participation in the study. Consent is given on the basis of the study information and information events.

Dissemination Policy

Trial results will be communicated to participants, schools, prevention professionals, and authorities via publication and in edited form in a brochure and on the project website, further through publications, conference contributions at academic conferences, and practitioners' congresses (eg, Digitallabor and Medienschule).

Results

Recruitment for the study was planned from May 2023 until the beginning of the leduin program in October 2023. As of March 2024, a total of 283 participants agreed to participate in the study.

Discussion

Overview

Social media offers effective ways of reaching a broad audience and can be used to address risk behavior and skill development [3,15,22]. To this aim, life skills can be a holistic approach. Despite the prevalence of digital training, few are evidence-based and access to the target audience remains challenging [27,29,30,33]. Moreover, existing life skills training often fails to address digital challenges. Further, the potential of using existing social media to reach adolescents has not been exploited. Our program is designed to improve digital life skills using Instagram, a platform that aligns with adolescents' habits and offers interactive features suitable for e-learning. The program addresses both the benefits and the risks associated with social media use. Our upcoming study aims to assess the accessibility of this innovative approach, leveraging existing social media to develop digital life skills, with future plans to evaluate its effectiveness.

In a pilot study, the leduin program was tested with 101 students in 9th and 10th grade across schools in North Rhine-Westphalia and Lower Saxony, Germany (E Zimmermann and S Tomczyk, unpublished data, 2024). The study, conducted from November 2022 to February 2023, involved interviews with 14- to 17-year-old participants and their teachers to evaluate the program's acceptance and initial effectiveness. Results showed positive reception and commitment, with participants reporting beneficial learning outcomes in social media use, self-care, and stress reduction. However, our pilot study highlighted substantial challenges in reaching the target group. While some classes were very interested in participating, others showed minimal involvement. This disparity suggests that simply making the program available is not sufficient. Effective strategies are needed to actively engage adolescents, ensuring they are both aware of and interested in participating. The leduin program is crafted to subtly enhance life skills through everyday activities with minimal effort over an extended period with spaced learning, aligning with effective learning and skill acquisition theories [69,70]. While social media proves effective in health interventions [22,30], participation depends on the individual's choice. Accordingly, adolescents might not fully appreciate the personal benefits of such engagement in their developmental stage [9]. To address this, we aim to reach adolescents through institutions already engaged in preventative work. However, since the intervention occurs during leisure time, even with its low barriers, consistent participation cannot be assured. Additionally, there is a possibility of waning intrinsic motivation over time.

The objectives of the accessibility study focus on identifying effective methods to engage adolescents in a digital life skills program on social media. It aims to encourage participation and sustain engagement to improve digital life skills. The study uses the RE-AIM model to guide its design, primarily focusing on the dimension "reach". Accordingly, key aspects include reaching a representative adolescent sample, examining the characteristics of consenting participants, and analyzing the variance in engagement levels. We thus aim to assess the accessibility of a social media intervention amidst heightened stress levels in schools and among adolescents post–COVID-19 pandemic, as indicated by our pilot study. Despite the critical need for prevention work, overall accessibility may be significantly constrained due to resource limitations, independent of the program's specifics.

The study further aims to identify relevant aspects of the other dimensions of the RE-AIM framework (effectiveness, acceptance, implementation, and maintenance) and thus examines the program's effects on life skills and social media–related skills, along with health, risk behavior, and school performance. It assesses program acceptance among schools, youth centers, and therapeutic facilities; the effectiveness of data collection, participant interaction, and retention rates on Instagram; and the long-term impact of the intervention. While this approach may yield valuable information, further studies must follow to fully evaluate the aspects of the comprehensive RE-AIM model.

Limitations

The limitations of the described approach include potential sampling bias, as engagement levels and the willingness of schools and youth centers to participate may not represent the broader adolescent population. Schools and youth centers facing significant challenges could be unable to participate in the study due to capacity constraints. This stress could be related to having a particularly burdened student body, affecting representativeness. Moreover, while directly recruiting adolescents for a social media intervention via social media platforms might initially appear to be an effective strategy, it presents substantial challenges in the context of a scientific

study. The primary issue lies in the difficulty of reliably verifying adolescents' identities and securing parental consent in an online environment. Additionally, while data collection itself is not intended to be conducted through social media, motivating adolescents to consistently participate in data collection becomes challenging without a supervised setting. This lack of direct oversight and engagement can significantly impact the reliability and consistency of data collection. Therefore, this approach is considered unfeasible for maintaining the rigorous standards required for scientific research.

The quasi-experimental design, while useful, might not fully account for confounding variables influencing engagement and outcomes. We are launching the leduin program with a digital information event, aiming for cost-effectiveness and wide reach among adolescents from diverse regions. This event serves to arouse interest. However, it is essential to thoroughly explain the scientific study's framework accompanying the program for informed consent. While this detailed explanation may dampen interest, it is a necessary step to ensure ethical compliance and informed participation. Consequently, we will only be able to examine the characteristics of adolescents who initially agreed to participate in the study and take part in the follow-up survey. This will limit representativeness. Since we are also dependent on the voluntary participation of the participants, dropouts are to be expected, both in the program itself and in the surveys.

Additionally, relying on social media platforms, Instagram could limit reach to adolescents not actively using or engaging with this platform. The follow-up period of 6 months, although significant, may not be sufficient to fully assess the long-term sustainability of the intervention's effects. Further, our sample size for evaluating the effectiveness of the intervention is calibrated for detecting medium-sized effects, which, while possible, are not guaranteed.

Conclusions

Our aim is to deepen our understanding in this field by identifying effective access strategies for social media interventions. Accessibility is crucial, acting as the "eye of the needle" for such interventions. Even the most effective programs cannot achieve their intended impact if they fail to reach and be accepted by the target group. By successfully navigating this pivotal aspect, we can ensure that our interventions are both accessible and effective, maximizing their potential benefits. We recognize the dual role of social media in interventions. On the one hand, these platforms offer valuable tools for reaching and engaging our target audience. On the other, it is imperative to acknowledge and address the inherent risks associated with social media use. Neglecting these risks could lead to unintended negative consequences, following a "dark-logic-model" where interventions might inadvertently cause harm. Thus, our focus is not only on leveraging social media for positive outcomes but also on mitigating its potential adverse effects to ensure a safe and effective intervention environment.

Acknowledgments

The authors thank the University of Greifswald and the Heinrich-Böll-Foundation for supporting our research. The funding institutions do not have ultimate authority over the study design, collection, management, analysis, and interpretation of data, nor the writing of the report, or the decision to submit the report for publication. The authors acknowledge the use of ChatGPT 4.0 (OpenAI, 2024) [99], in the revision of our initial manuscript. This artificial intelligence tool aided in summarizing, abbreviating, and enhancing the text, thereby contributing to our productivity. Despite this assistance, the ultimate responsibility for the content and integrity of the manuscript lies with the authors.

Authors' Contributions

EZ was involved in conceptualization, as well as writing the original draft and reviewing and editing. ST contributed to the conceptualization and participated in reviewing and editing the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Study information and declaration of consent for the leduin study for caregivers.
[PDF File (Adobe PDF File), 252 KB - resprot_v13i1e51085_app1.pdf]

Multimedia Appendix 2
Study information and declaration of consent for the leduin study for adolescents.
[PDF File (Adobe PDF File), 251 KB - resprot_v13i1e51085_app2.pdf]

References

1. Vogels EA, Gelles-Watnick R, Massarat N. Teens, social media and technology 2022. Pew Research Center. 2022. URL: https://www.pewresearch.org/internet/2022/08/10/teens-social-media-and-technology-2022/ [accessed 2023-04-05]

2. Livingstone SM, Hasebrink U, Haddon L. Comparing Children's Online Opportunities and Risks Across Europe: Cross-national Comparisons for EU Kids Online, 2nd Edition. New York: Springer; 2009.
3. Moorhead SA, Hazlett DE, Harrison L, Carroll JK, Irwin A, Hoving C. A new dimension of health care: systematic review of the uses, benefits, and limitations of social media for health communication. J Med Internet Res 2013;15(4):e85 [FREE Full text] [doi: 10.2196/jmir.1933] [Medline: 23615206]
4. Peralta L, Rowling L, Samdal O, Hipkins R, Dudley D. Conceptualising a new approach to adolescent health literacy. Health Educ J 2017;76(7):787-801. [doi: 10.1177/0017896917714812]
5. Subrahmanyam K, Smahel D. Digital Youth: The Role of Media in Development. New York: Springer; 2011.
6. Dunlop S, Freeman B, Jones SC. Marketing to youth in the digital age: the promotion of unhealthy products and health promoting behaviours on social media. Media Commun 2016;4(3):35-49 [FREE Full text] [doi: 10.17645/mac.v4i3.522]
7. Alimoradi Z, Lotfi A, Lin CY, Griffiths MD, Pakpour AH. Estimation of behavioral addiction prevalence during COVID-19 pandemic: a systematic review and meta-analysis. Curr Addict Rep 2022;9(4):486-517 [FREE Full text] [doi: 10.1007/s40429-022-00435-6] [Medline: 36118286]
8. Allcott H, Braghieri L, Eichmeyer S, Gentzkow M. The welfare effects of social media. Am Econ Rev 2020;110(3):629-676 [FREE Full text] [doi: 10.1257/aer.20190658]
9. Crone EA, Konijn EA. Media use and brain development during adolescence. Nat Commun 2018;9(1):588 [FREE Full text] [doi: 10.1038/s41467-018-03126-x] [Medline: 29467362]
10. Digital skills gap. Initiative D21. 2021. URL: https://initiatived21.de/d21skillsgap/ [accessed 2024-03-21]
11. Festl R. Social media literacy and adolescent social online behavior in Germany. J Child Media 2020;15(2):249-271. [doi: 10.1080/17482798.2020.1770110]
12. Polanco-Levicán K, Salvo-Garrido S. Understanding social media literacy: a systematic review of the concept and its competences. Int J Environ Res Public Health 2022;19(14):8807 [FREE Full text] [doi: 10.3390/ijerph19148807] [Medline: 35886657]
13. Abi-Jaoude E, Naylor KT, Pignatiello A. Smartphones, social media use and youth mental health. CMAJ 2020;192(6):E136-E141 [FREE Full text] [doi: 10.1503/cmaj.190434] [Medline: 32041697]
14. Beyens I, Frison E, Eggermont S. “I don’t want to miss a thing”: adolescents’ fear of missing out and its relationship to adolescents’ social needs, Facebook use, and Facebook related stress. Comput Human Behav 2016;64:1-8. [doi: 10.1016/j.chb.2016.05.083]
15. Wiederhold BK, Miller I, Wiederhold MD. Augmenting behavioral healthcare: mobilizing services with virtual reality and augmented reality. In: Rivas H, Wac K, editors. Digital Health. Cham: Springer; 2018:123-137.
16. Jimison H, Gorman P, Woods S, Nygren P, Walker M, Norris S, et al. Barriers and drivers of health information technology use for the elderly, chronically ill, and underserved. Evid Rep Technol Assess (Full Rep) 2008(175):1-1422. [Medline: 19408968]
17. Williams G, Hamm MP, Shulhan J, Vandermeer B, Hartling L. Social media interventions for diet and exercise behaviours: a systematic review and meta-analysis of randomised controlled trials. BMJ Open 2014;4(2):e003926 [FREE Full text] [doi: 10.1136/bmjopen-2013-003926] [Medline: 24525388]
18. Guse K, Levine D, Martins S, Lira A, Gaarde J, Westmorland W, et al. Interventions using new digital media to improve adolescent sexual health: a systematic review. J Adolesc Health 2012;51(6):535-543. [doi: 10.1016/j.jadohealth.2012.03.014] [Medline: 23174462]
19. Laranjo L, Arguel A, Neves AL, Gallagher AM, Kaplan R, Mortimer N, et al. The influence of social networking sites on health behavior change: a systematic review and meta-analysis. J Am Med Inform Assoc 2015;22(1):243-256 [FREE Full text] [doi: 10.1136/amiajnl-2014-002841] [Medline: 25005606]
20. Thomas VL, Chavez M, Browne EN, Minnis AM. Instagram as a tool for study engagement and community building among adolescents: a social media pilot study. Digit Health 2020;6:2055207620904548 [FREE Full text] [doi: 10.1177/2055207620904548] [Medline: 32215216]
21. Yonker LM, Zan S, Scirica CV, Jethwani K, Kinane TB. "Friending" teens: systematic review of social media in adolescent and young adult health care. J Med Internet Res 2015;17(1):e4 [FREE Full text] [doi: 10.2196/jmir.3692] [Medline: 25560751]
22. Kruzan KP, Williams KDA, Meyerhoff J, Yoo DW, O'Dwyer LC, De Choudhury M, et al. Social media-based interventions for adolescent and young adult mental health: a scoping review. Internet Interv 2022;30:100578 [FREE Full text] [doi: 10.1016/j.invent.2022.100578] [Medline: 36204674]
23. Mediensucht 2020—Gaming Und Social Media in Zeiten von Corona. DAK-Längsschnittstudie: Befragung von Kindern, Jugendlichen (12-17 Jahre) Und Deren Eltern. DAK Forschung. 2020. URL: https://www.dak.de/dak/gesundheit/dak-studie-gaming-social-media-und-corona-2295548.html#/ [accessed 2024-03-21]
24. Chung S, Lee J, Lee HK. Personal factors, internet characteristics, and environmental factors contributing to adolescent internet addiction: a public health perspective. Int J Environ Res Public Health 2019;16(23):4635 [FREE Full text] [doi: 10.3390/ijerph16234635] [Medline: 31766527]

25. He ZH, Li MD, Ma XY, Liu CJ. Family socioeconomic status and social media addiction in female college students: the mediating role of impulsiveness and inhibitory control. J Genet Psychol 2021;182(1):60-74. [doi: 10.1080/00221325.2020.1853027] [Medline: 33292090]
26. Karaer Y, Akdemir D. Parenting styles, perceived social support and emotion regulation in adolescents with internet addiction. Compr Psychiatry 2019;92:22-27 [FREE Full text] [doi: 10.1016/j.comppsych.2019.03.003] [Medline: 31003724]
27. Orben A. Teenagers, screens and social media: a narrative review of reviews and key studies. Soc Psychiatry Psychiatr Epidemiol 2020;55(4):407-414 [FREE Full text] [doi: 10.1007/s00127-019-01825-4] [Medline: 31925481]
28. Schønning V, Hjetland GJ, Aarø LE, Skogen JC. Social media use and mental health and well-being among adolescents—a scoping review. Front Psychol 2020;11:1949 [FREE Full text] [doi: 10.3389/fpsyg.2020.01949] [Medline: 32922333]
29. Plaisime M, Robertson-James C, Mejia L, Núñez A, Wolf J, Reels S. Social media and teens: a needs assessment exploring the potential role of social media in promoting health. Soc Med Soc 2020;6(1):1-11 [FREE Full text] [doi: 10.1177/2056305119886025]
30. Lehtimaki S, Martic J, Wahl B, Foster KT, Schwalbe N. Evidence on digital mental health interventions for adolescents and young people: systematic overview. JMIR Ment Health 2021;8(4):e25847 [FREE Full text] [doi: 10.2196/25847] [Medline: 33913817]
31. Bopp T, Stellefson M. Practical and ethical considerations for schools using social media to promote physical literacy in youth. Int J Environ Res Public Health 2020;17(4):1225 [FREE Full text] [doi: 10.3390/ijerph17041225] [Medline: 32074968]
32. Gudka M, Gardiner KLK, Lomas T. Towards a framework for flourishing through social media: a systematic review of 118 research studies. J Posit Psychol 2021;18(1):86-105 [FREE Full text] [doi: 10.1080/17439760.2021.1991447]
33. Klaic M, Kapp S, Hudson P, Chapman W, Denehy L, Story D, et al. Implementability of healthcare interventions: an overview of reviews and development of a conceptual framework. Implement Sci 2022;17(1):10 [FREE Full text] [doi: 10.1186/s13012-021-01171-7] [Medline: 35086538]
34. Sekhon M, Cartwright M, Francis JJ. Acceptability of healthcare interventions: an overview of reviews and development of a theoretical framework. BMC Health Serv Res 2017;17(1):88 [FREE Full text] [doi: 10.1186/s12913-017-2031-8] [Medline: 28126032]
35. Kapungu CT, Nappi CM, Thakral C, Miller SA, Devlin C, McBride C, et al. Recruiting and retaining high-risk adolescents into family-based HIV prevention intervention research. J Child Fam Stud 2011;21(4):578-588. [doi: 10.1007/s10826-011-9510-z]
36. Vogel A, Comtesse H, Rosner R. Challenges in recruiting and retaining adolescents with abuse-related posttraumatic stress disorder: lessons learned from a randomized controlled trial. Child Adolesc Psychiatry Ment Health 2020;14:14 [FREE Full text] [doi: 10.1186/s13034-020-00320-y] [Medline: 32322300]
37. Smokowski P, Corona R, Bacallao M, Fortson BL, Marshall KJ, Yaros A. Addressing barriers to recruitment and retention in the implementation of parenting programs: lessons learned for effective program delivery in rural and urban areas. J Child Fam Stud 2018;27(9):2925-2942 [FREE Full text] [doi: 10.1007/s10826-018-1139-8] [Medline: 30100698]
38. Kilicel D, De Crescenzo F, Pontrelli G, Armando M. Participant recruitment issues in child and adolescent psychiatry clinical trials with a focus on prevention programs: a meta-analytic review of the literature. J Clin Med 2023;12(6):2307 [FREE Full text] [doi: 10.3390/jcm12062307] [Medline: 36983307]
39. Powell TW, Willis K, Smith B, Lewis Q, Offiong A. "Don't close the door on them": recruiting and retaining vulnerable Black adolescents in prevention research. J Community Psychol 2021;49(5):994-1009 [FREE Full text] [doi: 10.1002/jcop.22584] [Medline: 33937999]
40. Botvin GJ. Prevention of adolescent substance abuse through the development of personal and social competence. NIDA Res Monogr 1983;47:115-140. [Medline: 6419112]
41. Weichold K, Blumenthal A. Long-term effects of the life skills program IPSY on substance use: results of a 4.5-year longitudinal study. Prev Sci 2016;17(1):13-23. [doi: 10.1007/s11121-015-0576-5] [Medline: 26202801]
42. Ciarrochi J, Scott G, Deane FP, Heaven PCL. Relations between social and emotional competence and mental health: a construct validation study. Pers Individ Dif 2003;35(8):1947-1963. [doi: 10.1016/s0191-8869(03)00043-6]
43. Kimber B, Sandell R, Bremberg S. Social and emotional training in Swedish classrooms for the promotion of mental health: results from an effectiveness study in Sweden. Health Promot Int 2008;23(2):134-143 [FREE Full text] [doi: 10.1093/heapro/dam046] [Medline: 18211887]
44. Norris SL, Engelgau MM, Narayan KM. Effectiveness of self-management training in type 2 diabetes: a systematic review of randomized controlled trials. Diabetes Care 2001;24(3):561-587 [FREE Full text] [doi: 10.2337/diacare.24.3.561] [Medline: 11289485]
45. WHO. Partners in life skills education—conclusions from a United Nations inter-agency meeting. Department of Mental Health World Health Organization Geneva. 1999. URL: https://pdf4pro.com/view/partners-in-life-skills-education-who-world-287ba2.html [accessed 2024-03-21]
46. Bittlingmayer U, Hurrelmann K. Präventionsstrategien für sozial Benachteiligte. In: Kirch W, Badura B, editors. Prävention. Berlin, Heidelberg: Springer; 2006.

47. Storck C, Dupreé T, Bölcskei PL. Erreicht schulische gesundheitsförderung kinder aus sozial benachteiligten gruppen? verbreitung und umsetzung des programms klasse2000. Präv Gesundheitsf 2008;3(2):95-102. [doi: 10.1007/s11553-008-0102-8]
48. Lubans DR, Smith JJ, Peralta LR, Plotnikoff RC, Okely AD, Salmon J, et al. A school-based intervention incorporating smartphone technology to improve health-related fitness among adolescents: rationale and study protocol for the NEAT and ATLAS 2.0 cluster randomised controlled trial and dissemination study. BMJ Open 2016;6(6):e010448 [FREE Full text] [doi: 10.1136/bmjopen-2015-010448] [Medline: 27354070]
49. Castro RP, Haug S, Wenger A, Schaub MP. Longer-term efficacy of a digital life-skills training for substance use prevention. Am J Prev Med 2022;63(6):944-953 [FREE Full text] [doi: 10.1016/j.amepre.2022.06.017] [Medline: 35985899]
50. Haug S, Castro RP, Meyer C, Filler A, Kowatsch T, Schaub MP. A mobile phone-based life skills training program for substance use prevention among adolescents: pre-post study on the acceptance and potential effectiveness of the program, Ready4life. JMIR Mhealth Uhealth 2017;5(10):e143 [FREE Full text] [doi: 10.2196/mhealth.8474] [Medline: 28978498]
51. Champion KE, Newton NC, Spring B, Wafford QE, Parmenter BJ, Teesson M. A systematic review of school-based eHealth interventions targeting alcohol use, smoking, physical inactivity, diet, sedentary behaviour and sleep among adolescents: a review protocol. Syst Rev 2017;6(1):246 [FREE Full text] [doi: 10.1186/s13643-017-0645-x] [Medline: 29208040]
52. Champion KE, Gardner LA, McGowan C, Chapman C, Thornton L, Parmenter B, et al. A web-based intervention to prevent multiple chronic disease risk factors among adolescents: co-design and user testing of the Health4Life school-based program. JMIR Form Res 2020;4(7):e19485 [FREE Full text] [doi: 10.2196/19485] [Medline: 32720898]
53. Lampert C. [Gesundheitsangebote für Kinder und Jugendliche im App-Format]. health programs for children and adolescents in an app format. Präv Gesundheitsf 2018;13(4):280-284. [doi: 10.1007/s11553-018-0665-y]
54. Aufenanger S. Norbert Groeben/Bettina Hurrelmann (Hrsg.): Medienkompetenz. voraussetzungen, dimensionen, funktionen. Pub 4x 2002 Dec 1;47(4):478-478 [FREE Full text] [doi: 10.1007/s11616-002-0153-3]
55. Bartholomew L, Parcel GS, Kok G, Gottlieb N. Planning Health Promotion Programs: An Intervention Mapping Approach. Hoboken, NJ: Jossey-Bass; 2006.
56. Durlak JA, Weissberg RP, Pachan M. A meta-analysis of after-school programs that seek to promote personal and social skills in children and adolescents. Am J Community Psychol 2010;45(3-4):294-309. [doi: 10.1007/s10464-010-9300-6] [Medline: 20300825]
57. Bandura A. Social Foundations of Thought and Action: A Social Cognitive Theory. Englewood Cliffs, NJ: Prentice-Hall; 1986:23-28.
58. Ajzen I. The theory of planned behavior. Organ Behav Hum Decis Process 1991;50(2):179-211. [doi: 10.1016/0749-5978(91)90020-t]
59. Fishbein M, Ajzen I. Predicting and Changing Behavior: The Reasoned Action Approach. New York: Psychology Press; 2010.
60. Bandura A. Social Learning Theory. Englewood Cliffs, NJ: Prentice Hall; 1977.
61. Bandura A, Ross D, Ross SA. Transmission of aggression through imitation of aggressive models. J Abnorm Soc Psychol 1961;63(3):575-582. [doi: 10.1037/h0045925]
62. Petty RE, Wegener DT, Fabrigar LR. Attitudes and attitude change. Annu Rev Psychol 1997;48:609-647. [doi: 10.1146/annurev.psych.48.1.609] [Medline: 9046570]
63. Grawe K. Psychologische Therapie. Göttingen: Hogrefe, Verlag für Psychologie; 1998.
64. Michie S, Richardson M, Johnston M, Abraham C, Francis J, Hardeman W, et al. The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. Ann Behav Med 2013;46(1):81-95 [FREE Full text] [doi: 10.1007/s12160-013-9486-6] [Medline: 23512568]
65. Elaheebocus SMRA, Weal M, Morrison L, Yardley L. Peer-based social media features in behavior change interventions: systematic review. J Med Internet Res 2018;20(2):e20 [FREE Full text] [doi: 10.2196/jmir.8342] [Medline: 29472174]
66. Simeon R, Dewidar O, Trawin J, Duench S, Manson H, Pardo JP, et al. Behavior change techniques included in reports of social media interventions for promoting health behaviors in adults: content analysis within a systematic review. J Med Internet Res 2020;22(6):e16002 [FREE Full text] [doi: 10.2196/16002] [Medline: 32525482]
67. Yardley L, Choudhury T, Patrick K, Michie S. Current issues and future directions for research into digital behavior change interventions. Am J Prev Med 2016;51(5):814-815. [doi: 10.1016/j.amepre.2016.07.019] [Medline: 27745680]
68. Boulos MNK, Giustini DM, Wheeler S. Instagram and WhatsApp in health and healthcare: an overview. Future Internet 2016;8(3):37 [FREE Full text] [doi: 10.3390/fi8030037]
69. Programme on mental health: life skills in schools. World Health Organization. 1994. URL: https://apps.who.int/iris/handle/10665/63552 [accessed 2024-03-21]
70. Smolen P, Zhang Y, Byrne JH. The right time to learn: mechanisms and optimization of spaced learning. Nat Rev Neurosci 2016;17(2):77-88 [FREE Full text] [doi: 10.1038/nrn.2015.18] [Medline: 26806627]
71. Glasgow RE, Vogt TM, Boles SM. Evaluating the public health impact of health promotion interventions: the RE-AIM framework. Am J Public Health 1999;89(9):1322-1327 [FREE Full text] [doi: 10.2105/ajph.89.9.1322] [Medline: 10474547]
72. Zhou X, Edirippulige S, Bai X, Bambling M. Are online mental health interventions for youth effective? a systematic review. J Telemed Telecare 2021;27(10):638-666 [FREE Full text] [doi: 10.1177/1357633X211047285] [Medline: 34726992]

73. Cronin L, Allen J, Ellison P, Marchant D, Levy A, Harwood C. Development and initial validation of the life skills ability scale for higher education students. Stud High Educ 2019;46(6):1011-1024. [doi: 10.1080/03075079.2019.1672641]
74. Petermann F. Fragebogen zu ressourcen im kindes- und jugendalter (FRKJ 8–16). [resource questionnaire on childhood and adolescence (FRKJ 8-16)]. Zeitschrift für Psychiatrie Psychologie und Psychotherapie 2017;65(1):61-62. [doi: 10.1024/1661-4747/a000302]
75. Abler B, Kessler H. Emotion Regulation Questionnaire – Eine deutschsprachige Fassung des ERQ von Gross und John. Diagnostica 2009 Jul;55(3):144-152. [doi: 10.1026/0012-1924.55.3.144]
76. Satow L. Stress- und Coping-Inventar (SCI): Test- und Skalendokumentation. URL: https://www.drsatow.de/tests/stress-und-coping-inventar/SCI-Testdokumentation.pdf [accessed 2023-07-13]
77. Del Rey R, Casas JA, Ortega-Ruiz R, Schultze-Krumbholz A, Scheithauer H, Smith P, et al. Structural validation and cross-cultural robustness of the European cyberbullying intervention project questionnaire. Comput Human Behav 2015;50:141-147. [doi: 10.1016/j.chb.2015.03.065]
78. Happ C, Pfetsch J. Medienbasierte empathie (MBE): entwicklung eines instruments zur erfassung empathischer reaktionen bei mediennutzung. Diagnostica 2016;62(2):110-125. [doi: 10.1026/0012-1924/a000152]
79. van den Eijnden RJJM, Lemmens JS, Valkenburg PM. The social media disorder scale: validity and psychometric properties. Comput Human Behav 2016;61:478-487 [FREE Full text] [doi: 10.1016/j.chb.2016.03.038]
80. Andreassen CS, Torsheim T, Brunborg GS, Pallesen S. Development of a Facebook addiction scale. Psychol Rep 2012;110(2):501-517. [doi: 10.2466/02.09.18.PR0.110.2.501-517] [Medline: 22662404]
81. Haug S, Castro RP, Kwon M, Filler A, Kowatsch T, Schaub MP. Smartphone use and smartphone addiction among young people in Switzerland. J Behav Addict 2015;4(4):299-307 [FREE Full text] [doi: 10.1556/2006.4.2015.037] [Medline: 26690625]
82. Dybek I, Bischof G, Grothues J, Reinhardt S, Meyer C, Hapke U, et al. The reliability and validity of the Alcohol Use Disorders Identification Test (AUDIT) in a German general practice population sample. J Stud Alcohol 2006;67(3):473-481. [doi: 10.15288/jsa.2006.67.473] [Medline: 16608159]
83. Felder-Puig R, Teutsch F, Ramelow D, Maier G. Gesundheit und Gesundheitsverhalten von österreichischen Schülerinnen und Schülern. Vienna: Bundesministerium für Arbeit, Soziales, Gesundheit und Konsumentenschutz (BMASGK); 2018. URL: https://www.sozialministerium.at/dam/jcr:0f4973f8-dc8b-4227-9e64-c76cec64b343/2018%20HBSC-Bericht%20mit%20Alternativtexten_final.pdf [accessed 2024-03-21]
84. Boardman JD. Self-rated health among U.S. adolescents. J Adolesc Health 2006;38(4):401-408 [FREE Full text] [doi: 10.1016/j.jadohealth.2005.01.006] [Medline: 16549301]
85. Breidablik HJ, Meland E, Lydersen S. Self-rated health in adolescence: a multifactorial composite. Scand J Public Health 2008;36(1):12-20. [doi: 10.1177/1403494807085306] [Medline: 18426780]
86. Brähler E, Mühlan H, Albani C, Schmidt S. Teststatistische prüfung und normierung der deutschen versionen des EUROHIS-QOL lebensqualität-index und des WHO-5 wohlbefindens-index. Diagnostica 2007;53(2):83-96. [doi: 10.1026/0012-1924.53.2.83]
87. Diener E, Emmons RA, Larsen RJ, Griffin S. The satisfaction with life scale. J Pers Assess 1985;49(1):71-75. [doi: 10.1207/s15327752jpa4901_13] [Medline: 16367493]
88. Glaesmer H, Grande G, Braehler E, Roth M. The German version of the Satisfaction With Life Scale (SWLS). Eur J Psychol Assess 2011;27(2):127-132. [doi: 10.1027/1015-5759/a000058]
89. Beierlein C, Kovaleva A, László Z, Kemper CJ, Rammstedt B. Kurzskala zur Erfassung der Allgemeinen Lebenszufriedenheit (L-1). Zusammenstellung sozialwissenschaftlicher Items und Skalen (ZIS). 2015. URL: https://tinyurl.com/ycwcwau5 [accessed 2024-03-21]
90. Poinstingl H, Herzberg PY, Brähler E. Psychometrische untersuchung der Hopkins Symptom Checklist (HSCL-25) mit dem partial credit model. 2011 Presented at: 10. Tagung der Fachgruppe Methoden and Evaluation; September 21-23, 2011; Bamberg. [doi: 10.13140/RG.2.2.29748.60802]
91. Ritzmann S, Hagemann V, Kluge A. Training Evaluations Inventar [Verfahrensdokumentation, Inventar deutsch und englisch]. 2020. URL: https://doi.org/10.23668/psycharchives.4493 [accessed 2024-03-21]
92. Hartley JEK, Levin K, Currie C. A new version of the HBSC family affluence scale—FAS III: Scottish qualitative findings from the international FAS development study. Child Indic Res 2016;9:233-245 [FREE Full text] [doi: 10.1007/s12187-015-9325-3] [Medline: 26925177]
93. Torsheim T, Cavallo F, Levin KA, Schnohr C, Mazur J, Niclasen B, et al. Psychometric validation of the revised family affluence scale: a latent variable approach. Child Indic Res 2016;9:771-784 [FREE Full text] [doi: 10.1007/s12187-015-9339-x] [Medline: 27489572]
94. Hoebel J, Müters S, Kuntz B, Lange C, Lampert T. Messung des subjektiven sozialen Status in der gesundheitsforschung mit einer deutschen version der MacArthur scale. [measuring subjective social status in health research with a German version of the MacArthur scale]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2015;58(7):749-757 [FREE Full text] [doi: 10.1007/s00103-015-2166-x] [Medline: 25986532]
95. Allaire JJ. RStudio: integrated development environment for R. J Wildl Manage 2015;78(8):1 [FREE Full text]

96. Muthen BO, Satorra A. Complex sample data in structural equation modeling. Sociol Methodol 1995;25(1995):267. [doi: 10.2307/271070]
97. Mayring P, Fenzl T. Qualitative inhaltsanalyse. In: Baur N, Blasius J, editors. Handbuch Methoden Der Empirischen Sozialforschung. Wiesbaden: Springer Fachmedien Wiesbaden; 2019:633-648.
98. Shea V. Netiquette. Albion Books. 1994. URL: http://www.albion.com/netiquette/book/index.html [accessed 2023-07-13]
99. ChatGPT 4.0. OpenAI. URL: https://openai.com/gpt-4 [accessed 2024-04-05]

Abbreviations

RE-AIM: reach, effectiveness, adoption, implementation, and maintenance

Edited by A Mavragani; submitted 20.07.23; peer-reviewed by S Haug, T Baranowski; comments to author 02.01.24; revised version received 23.01.24; accepted 22.02.24; published 17.04.24.

Please cite as:
Zimmermann E, Tomczyk S
Fostering Digital Life Skills Through Social Media With Adolescents in 6 German States: Protocol for an Accessibility Study According to the RE-AIM Framework
JMIR Res Protoc 2024;13:e51085
URL: https://www.researchprotocols.org/2024/1/e51085
doi:10.2196/51085
PMID:38631035

Protocol

Toward Telemonitoring in Immune-Mediated Inflammatory Diseases: Protocol for a Mixed Attention Model Study

Marta Novella-Navarro[1*], MD; Jose M Iniesta-Chamorro[2*], MSc; Diego Benavent[3], MD; Javier Bachiller-Corral[4], MD; Enrique Calvo-Aranda[5], MD, PhD; Helena Borrell[6], MD; Laura Berbel-Arcobé[3], MD; Victoria Navarro-Compan[1], MD, PhD; Xabier Michelena[6], MD, PhD; Leticia Lojo-Oliveira[5], MD; Jaime Arroyo-Palomo[4], MD; Mariana Diaz-Almiron[7], PhD; Verónica García García[4], MD; Irene Monjo-Henry[1], MD; Claudia María Gómez González[5], MD; Enrique J Gomez[2,8], PhD, Prof Dr; Alejandro Balsa[1], MD, PhD; Chamaida Plasencia-Rodríguez[1], MD, PhD

[1]Rheumatology Department, Hospital Universitario La Paz, Madrid, Spain

[2]Biomedical Engineering and Telemedicine Centre, Center for Biomedical Technology, Escuela Tecnica Superior de Ingenieros de Telecomunicacion, Universidad Politecnica de Madrid, Madrid, Spain

[3]Rheumatolgy Department, Hospital Universitari Bellvitge, Barcelona, Spain

[4]Rheumatology Department, Hospital Universitario Ramon y Cajal, Madrid, Spain

[5]Rheumatology Department, Hospital Universitario Infanta Leonor, Madrid, Spain

[6]Hospital Universitari Vall D´Hebron, Barcelona, Spain

[7]Biostatistics Hospital Universitario La Paz, Madrid, Spain

[8]Centro De Investigación Biomédica En Red De Bioingeniería, Biomateriales Y Nanomedicina, Madrid, Spain

[*]these authors contributed equally

Corresponding Author:
Marta Novella-Navarro, MD
Rheumatology Department
Hospital Universitario La Paz
Paseo de la Castellana 261
Madrid, 28046
Spain
Phone: 34 9172777108
Email: mnovellanavarro@gmail.com

Abstract

Background: Rheumatic and musculoskeletal diseases (RMDs) are chronic diseases that may alternate between asymptomatic periods and flares. These conditions require complex treatments and close monitoring by rheumatologists to mitigate their effects and improve the patient's quality of life. Often, delays in outpatient consultations or the patient's difficulties in keeping appointments make such close follow-up challenging. For this reason, it is very important to have open communication between patients and health professionals. In this context, implementing telemonitoring in the field of rheumatology has great potential, as it can facilitate the close monitoring of patients with RMDs. The use of these tools helps patients self-manage certain aspects of their disease. This could result in fewer visits to emergency departments and consultations, as well as enable better therapeutic compliance and identification of issues that would otherwise go unnoticed.

Objective: The main objective of this study is to evaluate the implementation of a hybrid care model called the mixed attention model (MAM) in clinical practice and determine whether its implementation improves clinical outcomes compared to conventional follow-up.

Methods: This is a multicenter prospective observational study involving 360 patients with rheumatoid arthritis (RA) and spondylarthritis (SpA) from 5 Spanish hospitals. The patients will be followed up by the MAM protocol, which is a care model that incorporates a digital tool consisting of a mobile app that patients can use at home and professionals can review asynchronously to detect incidents and follow patients' clinical evolution between face-to-face visits. Another group of patients, whose follow-up will be conducted in accordance with a traditional face-to-face care model, will be assessed as the control group. Sociodemographic characteristics, treatments, laboratory parameters, assessment of tender and swollen joints, visual analog scale for pain, and electronic patient-reported outcome (ePRO) reports will be collected for all participants. In the MAM group, these items will be self-assessed via both the mobile app and during face-to-face visits with the rheumatologist, who will do the same for patients

included in the traditional care model. The patients will be able to report any incidence related to their disease or treatment through the mobile app.

Results: Participant recruitment began in March 2024 and will continue until December 2024. The follow-up period will be extended by 12 months for all patients. Data collection and analysis are scheduled for completion in December 2025.

Conclusions: This paper aims to provide a detailed description of the development and implementation of a digital solution, specifically an MAM. The goal is to achieve significant economic and psychosocial impact within our health care system by enhancing control over RMDs.

Trial Registration: ClinicalTrials.gov NCT06273306; https://clinicaltrials.gov/ct2/show/NCT06273306

International Registered Report Identifier (IRRID): PRR1-10.2196/55829

(JMIR Res Protoc 2024;13:e55829) doi:10.2196/55829

KEYWORDS

digital health; mHealth, telemonitoring, rheumatic musculoskeletal diseases; digital resources, mixed attention model; rheumatic disease; musculoskeletal diseases; chronic diseases; pain; inflammation; antirheumatic drugs; telemonitoring; rheumatology; hybrid care model; care model; MAM; implementation; clinical outcome

Introduction

Background

Rheumatic and musculoskeletal diseases (RMDs) are a heterogeneous group of chronic diseases that mainly affect the joints, bones, muscles, tendons, and ligaments, but they can also affect other organs and systems. The growing significance of these diseases stems from their prevalence and their profound impact on the patient's quality of life. Some examples of RMD are rheumatoid arthritis (RA), with a global prevalence estimated at 0.46% (95% CI 0.39-0.54), and spondyloarthritis (SpA), with a prevalence between 0.2% and 1.6% [1,2].

These diseases are characterized by symptoms including pain or inflammation that may flare up, requiring professional evaluation and treatment modifications. Because these flares may negatively impact a patient's quality of life, it is essential to identify them and act as early as possible. For this reason, closely monitoring the disease and its treatment is important. Sometimes, this follow-up can be hampered by the enormous burden of care and consultation time limitations typical of outpatient settings, as well as by the patients' difficulty in keeping appointments due, in many cases, to work-related reasons or displacements [3]. In addition, the complexity of the treatments administered can lead to doubts regarding dosage and potential contraindications or adverse effects [4-7]. For all these reasons, it is important to maintain open communication channels between patients and professionals to keep everyone informed of incidents in the evolution of the disease and treatment. Telemedicine and digital health thus present a novel opportunity for the clinical management of chronic patients. In this context, implementing telemonitoring in the field of rheumatology has great potential, as it can enable the close monitoring of patients with RMDs [8].

Telemedicine has seen widespread implementation in recent years, not only in rheumatology (as we want to highlight in this protocol) but also in other areas of health care (eg, emergency departments, intensive care units, pharmacies, primary care, etc) [9]. This approach to patient care is endorsed by the World Health Organization (WHO) [10], as increasing scientific evidence shows that it can be a very important channel in patient-physician communication, improving clinical care and aiding in therapeutic decision-making. In fact, it has gained more strength following the COVID pandemic, a time when face-to-face visits to hospitals or health centers were restricted, especially for patients who were more susceptible due to their clinical history [11,12]. Moreover, recently published literature on telemedicine in the context of rheumatology care suggests that telemedicine may be an effective mode of care delivery for diagnosing and managing rheumatic diseases. However, despite these promising results, more studies are still needed to evaluate the effectiveness of this new approach [13,14].

Telemedicine does not necessarily substitute the traditional care model but rather complements it. Both telemedicine and traditional care have their own advantages, and the most effective approach often involves integrating these models to provide comprehensive and patient-centered health care. Telemedicine can complement traditional care by offering additional options for delivering health care services. It provides a means for remote consultations, monitoring, and follow-up care, especially in situations where physical presence is not mandatory. However, for some cases, traditional care models with in-person consultations, diagnostic tests, and procedures may be more appropriate. Therefore, adopting hybrid models that combine in-person and telemedicine services may optimize the strengths of both models and provide a more flexible and adaptive health care system [15,16].

Considering the increasing relevance of telemedicine and the need to continue to provide further evidence, the objectives of this study are outlined in the following section.

Objectives

The main objective is to evaluate the implementation of a conceptual framework for a hybrid care model called the mixed attention model (MAM) for use in clinical practice.

The secondary objectives are as follows: (1) to identify features associated with adherence to follow-up through the MAM; (2) to evaluate the technological acceptance of the digital solutions included in the MAM; (3) to assess the agreement between patient-reported join assessments and clinician-based join assessments; (4) to evaluate whether the implementation of the

MAM improves clinical outcomes compared to conventional follow-up; and (5) to assess patients´ health literacy using a digital interface.

Methods

Study Context

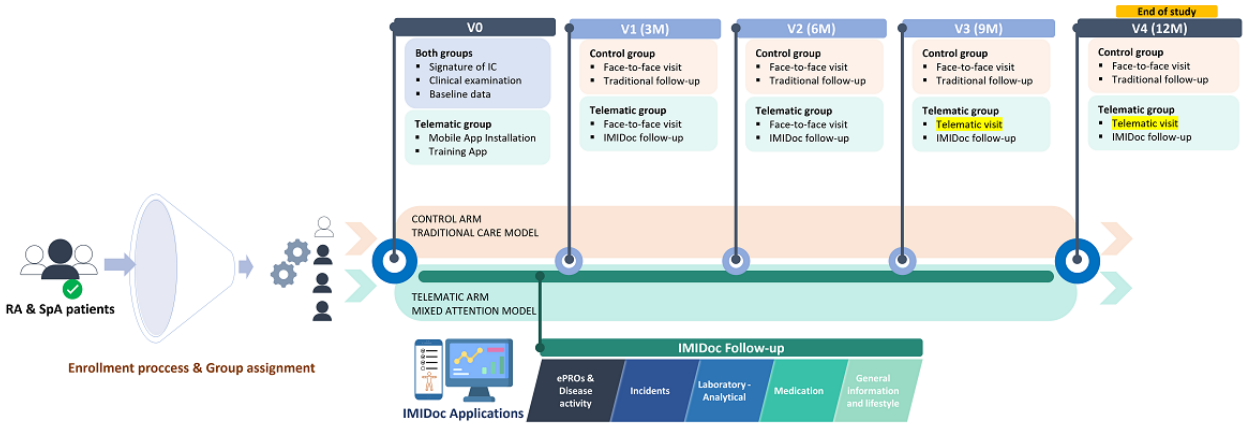
Using this framework, we conducted a previous pilot study (Digireuma study) [17] on the needs of patients with RMDs to develop a treatment strategy combining face-to-face visits with telematics follow-up through a mobile health (mHealth) tool. This tool allowed for the monitoring of disease activity, functionality, and overall patient health using electronic patient-reported outcomes (ePROs). Moreover, patients could also report incidents such as flares between their outpatient visits. This pilot study essentially sought to identify unmet needs in the follow-up and treatment of patients with RMDs and redefine the functionalities and features of future versions of this digital tool. During a 3-month follow-up period, patients had the opportunity to complete disease-specific ePROs at a prespecified frequency, as well as flare-ups and medication changes at any time. The number of interactions and alerts was assessed. The usability of the mobile solution was measured using the Net Promoter Score (NPS). Following the MAM development, there were 46 patients, 22 with RA (48%) and 24 (52%) with SpA). There were a total of 4019 interactions in the RA group and 3160 in the SpA group. A total of 15 patients generated a total of 26 alerts, of which the majority were managed remotely. In terms of patient satisfaction, 65% of respondents were considered to have approved the mobile solution, resulting in an NPS of 57 and an overall rating of 4.3 out of 5 stars, so we conclude that the use of the digital health solution is feasible in clinical practice to monitor ePROs for RA and SpA. Therefore, these results highlighted the next steps in implementing this telemonitoring method in a multicenter setting.

Accordingly, with the results and feedback obtained from previous experience, we detail the design of a clinical study wherein we will evaluate a new version of our digital health solution for monitoring and treating patients with RA and SpA.

MAM Explanation

All patients with RMDs treated with biological or targeted disease-modifying antirheumatic drugs (b/ts-DMARDs) are followed up in the immune-mediated disease (IMID) unit. This is a structured care unit comprising a multidisciplinary team of rheumatologists and specialized nurses. All care actions are protocolized, and face-to-face IMID unit visits of patients with RMDS under b/ts-DMARDs are recorded in a database. Based on the objectives described, a theoretical protocol was drawn up on how to implement a mixed model combining face-to-face visits with telematic follow-up. The MAM protocol [17] is a care model that incorporates a digital mobile app that patients can use at home and professionals can review asynchronously to detect incidents and monitor clinical evolution between face-to-face visits (Figure 1 depicts a flowchart escribing the participant inclusion in the study and subsequent steps). This protocol considers the role of each of the professionals in the unit, how face-to-face and telematic follow-up is carried out, and how to act according to the response to prescribed treatment.

Figure 1. Flowchart describing the inclusion in the study and the different steps according to the timetable established for the face-to-face and digital visits. ePRO: electronic patient-reported outcome; IC: informed consent; RA: rheumatoid arthritis; SpA: spondyloarthritis.

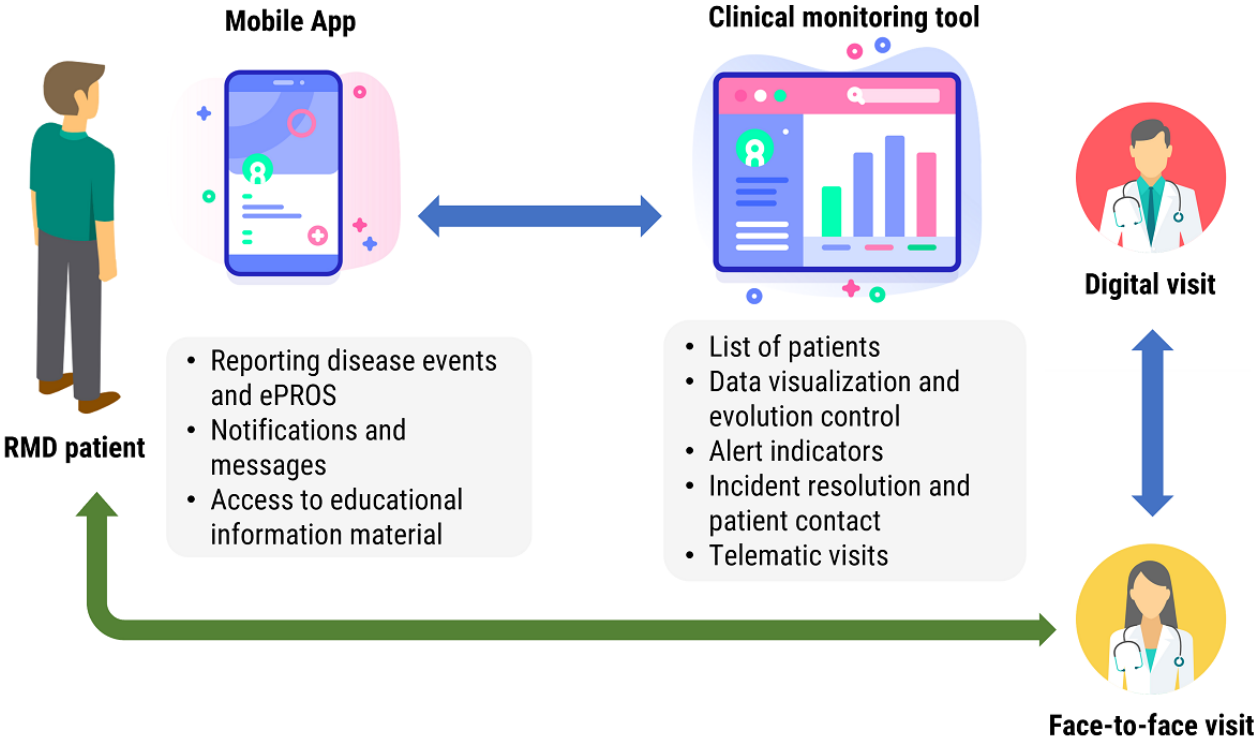


Development of the Digital Health Solution

A survey of health professionals and patients was carried out with the aim of identifying their needs and preferences regarding digital health as applied to rheumatology. Questions queried patients' familiarity with telemonitoring tools and mobile apps, the ease with which they could contact their rheumatologists, and their preferences and suggestions about the features that a digital solution should include. As for the professionals, they responded to a survey on the use of telemonitoring tools in clinical practice, training in the subject, and restrictions that hinder a wider implementation of telemedicine.

Combining this information and following a team-based approach, the IMIDoc digital health tool was then designed and developed (Figure 2 shows the digital solution outline). Throughout the process, clinical, technical, and biomedical researchers and patient teams participated in a collaborative and interdisciplinary manner. IMIDoc is based on the MAM.

Figure 2. Digital health solution outline. ePRO: electronic patient-reported outcome; RMD: rheumatic and musculoskeletal disease.



The IMIDoc technical platform consists of a mobile app for patients with RA and SpA, a web tool for clinicians, and the back-end infrastructure for data processing and storage. The IMIDoc platform has its own infrastructure to function independently of the hospital information system. Its back-end implementation is deployed in the cloud with a service-based technology approach that provides support to the IMIDoc mobile app and clinical tool.

The IMIDoc mobile app has been developed for both Android and iOS platforms and will be available through Google Play and the Apple Store, respectively. This implementation ensures that the app is easily accessible to a wide population of patients and accommodates various smart device preferences. On the other hand, the clinical tool is a web-based application accessible via a link in any standard web browser.

Patients with RA and SpA can record disease-related events and incidents, as well as ePROs, and they can receive messages from rheumatologists and automatic notifications regarding pending tasks and educational content. Likewise, rheumatologists can access the information recorded by patients through a web application. This enables clinicians to monitor and track the disease and contact patients to address any issues remotely.

Study Design

Overview

This is a multicenter prospective observational study involving 360 patients with RA and SpA from 5 Spanish Hospitals: Hospital Universitario La Paz (HULP), Hospital Universitario Vall d´Hebron (HUVH), Hospital Universitario Bellvitge (HUB), Hospital Universitario Infanta Leonor (HUIL), and Hospital Universitario Ramón y Cajal (HURyC).

Participants

A total of 360 patients will be enrolled in the clinical study, comprising the group receiving MAM intervention and the control group, following the traditional care model matched by age and sex (Table 1). The inclusion criteria for patients in the MAM group are as follows: (1) adult patients >18 years; (2) patients with RA or SpA under treatment with b/tsDMARDs followed in the complex therapy unit (CTU); and (3) patients with an available smartphone. The exclusion criterion includes patients with conditions that hinder or prevent the use of a mobile app (eg, blindness, developmental delay, dementia, and digital illiteracy).

Table 1. Patients at each hospital treated with the MAM[a] or a traditional care model.

Hospital	Patients in the MAM (n=280), n		Patients in the traditional care model (n=80), n	
	RA[b]	SpA[c]	RA	SpA
HULP[d]	40	40	10	10
HURyC[e]	30	30	10	10
HUVH[f]	30	30	10	10
HUIL[g]	20	20	5	5
HUB[h]	20	20	5	5

[a]MAM: mixed attention model.

[b]RA: rheumatoid arthritis.

[c]SpA: spondylarthritis.

[d]HULP: Hospital Universitario La Paz.

[e]HURyC: Hospital Universitario Ramón y Cajal.

[f]HUVH: Hospital Universitario Vall.

[g]HUIL: Hospital Universitario Infanta Leonor.

[h]HUB: Hospital Universitario Bellvitge.

All patients from outpatient consultations treated with b/tsDMARDs for at least 6 months will be invited to participate in the study. Those who have been invited but have declined will be registered, and then if they accept, will be enrolled in the study. The control group will be formed by patients with the same treatments and similar sociodemographic and clinical characteristics.

Due to the exploratory nature of the trial and the fact that the objectives will be measured with different end points, no formal sample size calculation was performed. Based on previous studies in rheumatology comparing clinical parameters using telemonitoring versus conventional monitoring, the number of patients included varied in a wide range (from 44 to 294 patients) [18-20]. The primary end point considered in our study in terms of a 20% reduction in face-to-face visits has not been previously studied, and there is no data in the literature to support the inclusion of a specific number of patients. Therefore, using a crude calculation, we estimated a sample size of 300 patients to be sufficient, considering an infinite population, a confidence level of 95%, a precision of 3%, and an assumption of 15% loss to follow-up. Furthermore, other important aspects to consider in telemonitoring projects with digital health tools are usability and feasibility. Recent studies, similar in objectives to the one proposed here, have included between 40 and 120 patients to evaluate the usability and feasibility of telemedicine applications and systems in RMDs [21]. As for the usability evaluation of the clinical tool discussed in this paper, the study is designed as a multicenter initiative, anticipating the participation of at least 10 health care professionals or digital clinicians. Considering the factors mentioned earlier and the expertise of these users within the field, we contend that this participant count is sufficient for the intended evaluation.

Data Collection and Statistical Analysis

Data Sources

The application of MAM, via the use of IMIDoc incorporates 2 primary sources of information.

First, demographic, laboratory, clinical, and treatment characteristics will be extracted from electronic clinical records during the initial visit.

Second, ePROs recorded by patients participating in the IMIDoc users' arm through the application, as well as those documented by health care personnel during telematic and face-to-face visits through the web application, will be stored in the system's database in a pseudoanonymized and encrypted format.

Access to this data will be restricted exclusively to members of the research team. Data security will be supervised by the data protection officer. All actions performed on the platform will be traceable to the authorized personnel with access to the platform. User authentication tied to role-based security protocols will allow for the effective management of varying access privileges among members of the research team.

Data Collection and Schedule for Digital and Face-to-Face Visits

Overview

To facilitate understanding, variables are divided into general variables, face-to-face variables, and digital variables (Table 2). General variables correspond to background information captured during baseline visits. Face-to-face variables are captured during in-person visits and are registered in the electronic health record.

Table 2. Variables reported in both face-to-face and digital visits.

Dimensions and variables	AR[a]	SpA[b]	Frequency
ePROs[c] and disease activity			
PGA[d], VAS[e], TJC[f], SJC[g]	✓	✓	Every 15 days
Enthesis		✓	Every 15 days
DAS28[h], HAQ[i]	✓		Monthly
ASAS-HI[j], ASDAS[k], BASDAI[l]		✓	Monthly
Incidents			
Flares, infections, medication problems, and others	✓	✓	By occurrence
Laboratory and analytical variables			
CRP[m] and ESR[n]	✓	✓	Monthly
Medication			
Medication list and reminders	✓	✓	On demand
CQR[o]	✓	✓	Monthly
General information about the disease and lifestyle	✓	✓	Every 7 days

[a]RA: rheumatoid arthritis.
[b]SpA: spondylarthritis.
[c]ePRO: electronic patient-reported outcome.
[d]PGA: Patient Global Assessment.
[e]VAS: visual analog scale.
[f]TJC: tender joint count.
[g]SJC: swollen joint count.
[h]DAS28: Disease Activity Score 28.
[i]HAQ: Health Assessment Questionnaire.
[j]ASAS-HI: Assessment of Spondyloarthritis International Society Health Index.
[k]ASDAS: Ankylosing Spondylitis Disease Activity Score.
[l]BASDAI: Bath Ankylosing Spondylitis Disease Activity Index.
[m]CRP: C-reactive protein.
[n]ESR: erythrocyte sedimentation rate.
[o]CQR: Compliance Questionnaire for Rheumatology.

General Variables

General variables are those that correspond to clinical records documenting background or baseline information. The following will be collected during baseline visits: demographic variables (sex, age, and BMI); smoking habit; date of diagnosis; serological status for RA, such as rheumatoid factor (RF) anticitrullinated peptide antibodies (ACPA), and histocompatibility antigen (HLA)-B27 for SpA; and treatment information, including start date of current b/tsDMARDs and concomitant therapies such as prednisone, conventional disease-modifying antirheumatic drugs (csDMARDs), and previous treatments.

Face-to-Face Variables

Clinical activity and functional capacity will be evaluated according to specific indexes and questionnaires compiled in clinical practice.

For patients with RA, these include the tender joint count (TJC) and swollen joint count (SJC), Disease Activity Score 28 (DAS28), Simplified Disease Activity Score (SDAI), and Health Assessment Questionnaire (HAQ).

For patients with SpA, these include TJC and SJC, Ankylosing Spondylitis Disease Activity Score (ASDAS), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), and Assessment of Spondyloarthritis International Society Health Index (ASAS-HI).

Results from laboratory parameters, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are routinely determined in routine clinical practice at each patient visit.

Digital Variables and ePROS

For RA patients, the variables include self-assessed tender joint count (sTJC), self-assessed swollen joint count (sSJC), and SDAI. DAS28 will be calculated and managed as patient-derived DAS28 (PtDAS28) and HAQ. Finally, in patients with SpA, the variables include sTJC, sSJC, BASDAI, BASFI, and ASAS-HI.

Health care resource utilization will be documented, including the number of outpatient consultations, emergency visits, drug switches, and nursing and consultant calls. Questions for assessing patient status and treatment tolerance will be recorded. These will include questions such as, “Are you feeling well with the current treatment regimen?” “Have you had symptoms similar to previous outbreaks of your disease?” “If yes, how many outbreaks have you had during the last month?” “Have you experienced any symptoms that you attribute to tolerance problems with the current treatment?” “If yes, please indicate which symptom and to which treatment you attribute it.” “Have you had any recent fever or infections?” “Have you engaged in any physical activity equivalent to walking for 30 min at least 3 times during the past week?”

To assess the usability of the IMIDoc, questionnaires will collect information regarding willingness, such as the NPS, which evaluates how participants recommend the IMIDo, and follow-up with other patients using the MAM. The System Usability Scale (SUS), consisting of a 10-item questionnaire answered on a scale from 1 to 5 (strongly disagree to strongly agree), will also be used to assess the IMIDoc.

All patients who sign the informed consent form for this project will be invited to participate in a mixed clinical follow-up combining traditional face-to-face visits and home monitoring. The patients will be provided with access to a mobile app that can be downloaded free of charge and that was specially designed in consultation with and under supervision by rheumatologists. The patients will have access to complete questionnaires addressing disease activity, disability, and other domains such as ePROs (Figures 1 and 2). Face-to-face visits will be scheduled at baseline and 6 and 12 months, both for patients included in MAM and for those under the traditional care model.

Support Resources for Patients

Explanatory material will be provided at the scheduled routine medical visit for all patients included. This explanatory material includes the information required to download the digital solution, the content, and recommendations regarding the frequency with which patients should fill out the questionnaires. Once the patient agrees to be part of the MAM, they will receive a phone call from the digitally partnered clinician to ensure understanding of all the material, clarify doubts, and resolve any issues.

Clinical activity, functional capacity, and overall health will be evaluated according to specific indexes and questionnaires included in IMIDoc, with a predefined frequency for each instrument (alternate assessments of pooled instruments every 15 days, implying a weekly assessment). Reminders with predefined frequencies for each variable will be sent to guarantee their fulfillment.

A messaging and alert system will be available whereby patients can notify their physician of any incidents.

Additionally, the IMIDoc educational material will be provided to patients in a short text format containing information of interest regarding their disease, the different treatments available, and explanatory videos recorded by collaborating rheumatologists.

Workshops and Tasks for Collaborators

The established collaboration between HULP, HUVH, HUB, HUIL, and HRyC will also act as a facilitator for the development of this study. In fact, web-based meetings have already been held between researchers from all centers to evaluate the resources and the viability of implementing this project. Prior to starting patient recruitment, a web-based meeting will be held with the entire research team to discuss the best way to identify patients and carefully review the methodology that will be followed in the participating centers. Thus, all the information provided to patients will be shared and agreed upon by the centers. Moreover, reminders will be sent to the people responsible for and involved in each project task. In this regard, the clinician in charge of the telematic (digital clinicians) and clinical (onsite clinicians) for each center will be assigned. The incidents recorded in the tool will be periodically reviewed on a web interface by a physician whose clinical work is partly dedicated to this purpose (digital clinician). This professional or another professional from the CTU or biologic clinic (onsite clinician) will contact the patient by telephone to resolve the reported incident. The incident may be resolved completely remotely, or a face-to-face visit may be arranged to address the problem.

Assessment of Primary and Secondary End Points:

The primary end point will be an at least 20% reduction in face-to-face visits compared to visits carried out in the previous year. This reduction in face-to-face visits will be driven by the number of incidents that can be resolved telematically, the number of total interactions, and the number of ePROS that patients complete during the follow-up period that allows us to assess adherence and telematic monitoring.

The secondary end points will be assessed by tracking the number of accesses and time per access to the digital solution per patient to assess adherence. Agreements between the patients' self-assessment and clinician assessment will be assessed to compare face-to-face visits at 6-month intervals with the closest assessment in the digital solution. We will also measure the proportion of patients in remission or low disease activity according to the activity index every 6 months. Usability and satisfaction perceived by patients will be assessed by the SUS NPS.

Data Analysis

A descriptive analysis of the demographic and clinical variables will be performed. The results will be expressed as the mean and SD or median and IQR for continuous variables and absolute numbers and relative frequencies for categorical variables. The frequency data will be compared using a chi-square or Fisher exact test depending on the distribution of the variables. Comparisons for unpaired continuous data will be assessed using a Mann-Whitney U test or *t* test depending on the variable distribution. Comparisons of paired continuous data will be conducted using the paired *t* test or Wilcoxon test, depending on data distribution. $P<.05$ will be considered statistically significant. Univariate analysis will be carried out using the

most relevant demographic and clinical variables (ie, age, sex, concomitant methotrexate, baseline activity score measured by DAS28 or BASDAI, disease duration, and smoking habit). In the multivariate analysis, only the variables with a $P<0.1$ in the univariate analysis will be included. Interactions and collinearity will be evaluated. The last phase of the study will consist of exploring the construction of a predictive model from the follow-up data using the MAM. For this purpose, artificial intelligence tools and techniques such as machine learning will be utilized. R-Cran (version 3.5.1; R Project for Statistical Computing))software will be used for the statistical analysis.

Ethical Considerations

This study will be conducted in accordance with the Declaration of Helsinki and the General Data Protection Regulation (GDPR) of the European Union. The protocol has been approved by the local Ethics Committees of HULP (PI-4519), HUB, HUIL, HRyC, and HUVH. This protocol was submitted to a public call for applications and obtained funding for the development of a solution and implementation of the MAM in clinical practice. Informed consent will be obtained from all participants prior to study onset. This study will have a protected and anonymized database, wherein data will be stored at baseline and throughout follow-up. All patient data will be collected and handled confidentially in a protected database located on an encrypted server owned by the digital health company in compliance with the European GDPR of May 25, 2018.

Results

Recruitment began in March 2024 through initial contacts with patients at the IMID unit, and it will continue until December 2024. The follow-up period will be extended for 12 months for all patients. Data collection and analysis are scheduled for completion in December 2025. The main contribution of this protocol paper is a detailed description of the development of a digital solution to improve and implement an MAM in the field of RMDs.

Discussion

We have designed a clinical study to evaluate the MAM in clinical practice using the IMIDoc digital health tool. We developed this tool in collaboration with clinicians, biomedical engineers, and patients using a participatory or team-based approach. We believe that close collaboration between health care professionals and patients is essential for developing mHealth solutions tailored to patients' needs.

Digital health solutions or tools based on the use of mHealth technologies can empower patients by supporting self-management skills and providing information on health status and symptom management [8,17,22]. The application of health information technologies and wearable monitoring is widespread in other fields of medicine, such as brain health, HIV, and cancer [23-25]. In addition, mHealth supports the follow-up of symptoms that rheumatologists might miss during time-limited visits, thereby helping reduce the mismatch between issues important to patients versus those important to clinicians [26]. Piga et al [27] published a systematic review of tools for remote monitoring and treatment that included studies of patients with rheumatoid arthritis, systemic sclerosis, fibromyalgia, and osteoarthritis. Their study showed that feasibility and patient satisfaction rates were high or very high depending on the type of intervention and that the efficacy of these interventions was at least similar to that of standard care. Thus, it was shown that telemedicine could assist both rheumatologists in monitoring treatment and patients in participating in their treatment. However, according to the same study, the tools developed were generally unidirectional, serving either the clinician in disease assessment and treatment monitoring or the patient as an educational or disease support tool.

In this context, 2 systematic reviews have shown that there is scant evidence concerning instruments and their use for following up patients with RA [28,29]. Although several projects, such as My Joint Pain or RAHelp [30-32], have shown that telemedicine can provide a new opportunity for managing patients with chronic illness, further research is still needed, as implementation in clinical practice remains very limited [18]. Some new tools have recently been designed ranging from rheumatology referral support [33] to symptom capture [34]; however, the evidence on app use in IMIDs lags far behind that of other fields in terms of treatment adherence [35] or disease symptom improvement [36].

Both the development and implementation of mHealth technologies present several challenges and risks. In this regard, our project meets relevant Sustainable Development Goals adopted by the United Nations. First, our project addresses the goal of “good health and well-being” in the interest of promoting better patient care. Since this project focuses on chronic inflammatory diseases, good disease control can empower patients to reduce their functional disability, resulting in less impact on the quality of life. All this is only possible with a personalized follow-up approach, enabling clinicians to anticipate disease damage. The ability to access more detailed information on patient evolution and adherence problems or adverse effects can ameliorate the repercussions of erroneous therapeutic decisions [37,38].

Overall, this project aims to have both an economic and psychosocial impact on our health care system. On the one hand, the use of these tools can help educate patients about their disease, providing instructions on self-management for certain disease aspects. This can result in fewer visits to the emergency department, fewer consultations, and better therapeutic compliance. On the other hand, the availability of ever-greater amounts of data will make it possible to identify challenges or issues that would otherwise go unnoticed, thus avoiding incorrect strategies. New disease management strategies aimed at more appropriate resource use, based on clinical practice data, are needed.

Acknowledgments

The authors would like to thank the patients for their willingness and collaboration in participating in this project, as well as all colleagues involved in clinical care. The authors also thank the Spanish Foundation of Rheumatology for providing medical writing/editorial assistance during the preparation of the manuscript (FERTB2022). This work was supported by: Fondo para la Investigación Sanitaria, Instituto de Salud Carlos III (PI22/00777).

Authors' Contributions

MNN and JMIC wrote the first version of the manuscript and share the first authorship. MNN, CPR, JMIC, and DB contributed to the design and conceptualization of the manuscript. All the authors have participated in the preparation of this article, reviewed it, and made extensive comments and valuable contributions.

Conflicts of Interest

MNN reports grants from UCB Pharma, Lilly, Galapagos, and Janssen outside the submitted work. DBN reports grants from Lilly, Janssen, UCB Pharma, MSD, Galapagos, and Novartis. ECA reports grants from Menarini, Grünenthal, Asac Pharma, MSD, Lilly, Pfizer, Roche, Astra-Zeneca, and Galapagos. HB reports grants from Lilly, Abbvie, Galapagos, Bristol Myers Squibb (BMS), Nordic Pharma, and UCB Pharma. LBA reports grants from Novartis, Lilly, Janssen, MSD, Theramex, and Abbvie. VNC reports grants from Abbvie, Lilly, Fresenius Kabi, Janssen, MSD, Novartis, Pfizer, and UCB Pharma. IMH reports grants from Roche, Novartis, UCB, and Gedeon Richter outside the submitted work. CP-R reports grants from AbbVie, Pfizer, Novartis, Lilly, and Roche outside the submitted work. AB reports grants from AbbVie, Amgen, Pfizer, Galapagos, Novartis, Gilead, BMS, Nordic, Sanofi, Sandoz, Lilly, UCB, and Roche outside the submitted work. The rest of the authors have no conflicts of interest to declare.

References

1. Almutairi K, Nossent J, Preen D, Keen H, Inderjeeth C. The global prevalence of rheumatoid arthritis: a meta-analysis based on a systematic review. Rheumatol Int 2021 May 11;41(5):863-877. [doi: 10.1007/s00296-020-04731-0] [Medline: 33175207]
2. Woolf A, Erwin J, March L. The need to address the burden of musculoskeletal conditions. Best Pract Res Clin Rheumatol Internet 2012 Apr;2:186-224 [FREE Full text] [doi: 10.1016/j.berh.2012.03.005] [Medline: 22794094]
3. Woolf A, Pfleger B. Burden of major musculoskeletal conditions. Bull World Health Organ 2003;81(9):646-656. [Medline: 14710506]
4. Taylor PC, Ancuta C, Nagy O, de la Vega MC, Gordeev A, Janková R, et al. Treatment satisfaction, patient preferences, and the impact of suboptimal disease control in a large international rheumatoid arthritis cohort: SENSE study. PPA 2021 Feb;Volume 15:359-373. [doi: 10.2147/ppa.s289692]
5. Magrey M, Bozyczko M, Wolin D, Mordin M, McLeod L, Davenport E, et al. A pilot study to assess the feasibility of a web-based survey to examine patient-reported symptoms and satisfaction in patients with ankylosing spondylitis receiving secukinumab. Drugs Real World Outcomes 2019 Jun 3;6(2):83-91 [FREE Full text] [doi: 10.1007/s40801-019-0154-4] [Medline: 31054047]
6. Nowell WB, Gavigan K, Hunter T, Bolce RJ, Lisse JR, Himelein C, et al. Patient perspectives on biologics for axial spondyloarthritis in a cross-sectional study in a predominantly female population: treatment satisfaction, wear-off between doses, and use of supplemental medication. Rheumatol Ther 2022 Apr 27;9(2):509-520 [FREE Full text] [doi: 10.1007/s40744-021-00417-6] [Medline: 34958453]
7. Schäfer M, Albrecht K, Kekow J, Rockwitz K, Liebhaber A, Zink A, et al. Factors associated with treatment satisfaction in patients with rheumatoid arthritis: data from the biological register RABBIT. RMD Open 2020 Oct 13;6(3):e001290 [FREE Full text] [doi: 10.1136/rmdopen-2020-001290] [Medline: 33051270]
8. Matcham F, Hotopf M, Galloway J. Mobile apps, wearables and the future of technology in rheumatic disease care. Rheumatology (Oxford) 2019 Jul 01;58(7):1126-1127. [doi: 10.1093/rheumatology/key391] [Medline: 30535022]
9. Avouac J, Marotte H, Balsa A, Chebbah M, Clanche SL, Verhagen LA, et al. Teleconsultation in rheumatology: A literature review and opinion paper. Semin Arthritis Rheum 2023 Dec;63:152271. [doi: 10.1016/j.semarthrit.2023.152271] [Medline: 37813005]
10. World Health Organization. WHO/CONRAD technical consultation on nonoxynol-9, World Health Organization, Geneva, 9-10 October 2001: summary report. Reprod Health Matters 2002 Nov;10(20):175-181. [doi: 10.1016/s0968-8080(02)00085-x] [Medline: 12569895]
11. Mortezavi M, Lokineni S, Garg M, Chen YL, Ramsey A. Rheumatology patient satisfaction with telemedicine during the COVID-19 pandemic in the United States. J Patient Exp 2021 Apr 23;8:23743735211008825 [FREE Full text] [doi: 10.1177/23743735211008825] [Medline: 34179440]
12. Nash P. Telemedicine and rheumatology. Joint Bone Spine 2022 Nov;89(6):105439 [FREE Full text] [doi: 10.1016/j.jbspin.2022.105439] [Medline: 35933086]

13. Lockwood MM, Wallwork RS, Lima K, Dua AB, Seo P, Bolster MB. Telemedicine in adult rheumatology: in practice and in training. Arthritis Care Res (Hoboken) 2022 Aug 03;74(8):1227-1233. [doi: 10.1002/acr.24569] [Medline: 33555127]
14. Jackson LE, Edgil TA, Hill B, Owensby JK, Smith CH, Singh JA, et al. Telemedicine in rheumatology care: A systematic review. Semin Arthritis Rheum 2022 Oct;56:152045. [doi: 10.1016/j.semarthrit.2022.152045] [Medline: 35843158]
15. Müskens WD, Rongen-van Dartel SAA, Vogel C, Huis A, Adang EMM, van Riel PLCM. Telemedicine in the management of rheumatoid arthritis: maintaining disease control with less health-care utilization. Rheumatol Adv Pract 2021;5(1):rkaa079 [FREE Full text] [doi: 10.1093/rap/rkaa079] [Medline: 33688619]
16. Sloan M, Lever E, Harwood R, Gordon C, Wincup C, Blane M, et al. Telemedicine in rheumatology: a mixed methods study exploring acceptability, preferences and experiences among patients and clinicians. Rheumatology (Oxford) 2022 May 30;61(6):2262-2274 [FREE Full text] [doi: 10.1093/rheumatology/keab796] [Medline: 34698822]
17. Benavent D, Fernández-Luque L, Núñez-Benjumea FJ, Navarro-Compán V, Sanz-Jardón M, Novella-Navarro M, et al. Monitoring chronic inflammatory musculoskeletal diseases mixing virtual and face-to-face assessments-Results of the digireuma study. PLOS Digit Health 2022 Dec 7;1(12):e0000157 [FREE Full text] [doi: 10.1371/journal.pdig.0000157] [Medline: 36812651]
18. Salaffi F, Carotti M, Ciapetti A, Di Carlo M, Gasparini S, Farah S, et al. Effectiveness of a telemonitoring intensive strategy in early rheumatoid arthritis: comparison with the conventional management approach. BMC Musculoskelet Disord 2016 Apr 02;17(1):146 [FREE Full text] [doi: 10.1186/s12891-016-1002-2] [Medline: 27038788]
19. de Thurah A, Stengaard-Pedersen K, Axelsen M, Fredberg U, Schougaard LMV, Hjollund NHI, et al. Tele-health followup strategy for tight control of disease activity in rheumatoid arthritis: results of a randomized controlled trial. Arthritis Care Res (Hoboken) 2018 Mar 23;70(3):353-360. [doi: 10.1002/acr.23280] [Medline: 28511288]
20. Pers Y, Valsecchi V, Mura T, Aouinti S, Filippi N, Marouen S, et al. A randomized prospective open-label controlled trial comparing the performance of a connected monitoring interface versus physical routine monitoring in patients with rheumatoid arthritis. Rheumatology (Oxford) 2021 Apr 06;60(4):1659-1668. [doi: 10.1093/rheumatology/keaa462] [Medline: 33020846]
21. Mucke J, Knitza J, Muehlensiepen F, Grahammer M, Stenzel R, Simon D, et al. TELERA-asynchronous telemedicine for patients with rheumatoid arthritis: study protocol for a prospective, multi-center, randomized controlled trial. Front Med (Lausanne) 2021 Dec 13;8:791715 [FREE Full text] [doi: 10.3389/fmed.2021.791715] [Medline: 34966765]
22. Shelton J, Casey S, Puhl N, Buckingham J, Yacyshyn E. Electronic patient-reported outcome measures using mobile health technology in rheumatology: A scoping review. PLoS One 2021 Jul 22;16(7):e0253615 [FREE Full text] [doi: 10.1371/journal.pone.0253615] [Medline: 34292955]
23. Moreno-Blanco D, Solana-Sánchez J, Sánchez-González P, Oropesa I, Cáceres C, Cattaneo G, et al. Technologies for monitoring lifestyle habits related to brain health: a systematic review. Sensors (Basel) 2019 Sep 26;19(19):4183 [FREE Full text] [doi: 10.3390/s19194183] [Medline: 31561599]
24. Gárate FJ, Chausa P, Whetham J, Jones C, García F, Cáceres C, On Behalf Of The EmERGE Consortium. EmERGE mHealth platform: implementation and technical evaluation of a digital supported pathway of care for medically stable HIV. Int J Environ Res Public Health 2021 Mar 18;18(6):3156 [FREE Full text] [doi: 10.3390/ijerph18063156] [Medline: 33803821]
25. Iniesta-Chamorro J. The mHealth ALIBIRD platform: supporting cancer patient treatment and follow-up. 2023 Presented at: 2023 International Symposium on Computer Based Medical Systems (CBMS); June 22-24; L'Aquila, Italy p. 149-152. [doi: 10.1109/cbms58004.2023.00207]
26. Main CJ, Buchbinder R, Porcheret M, Foster N. Addressing patient beliefs and expectations in the consultation. Best Pract Res Clin Rheumatol 2010 Apr;24(2):219-225 [FREE Full text] [doi: 10.1016/j.berh.2009.12.013] [Medline: 20227643]
27. Piga M, Cangemi I, Mathieu A, Cauli A. Telemedicine for patients with rheumatic diseases: systematic review and proposal for research agenda. Semin Arthritis Rheum 2017 Aug;47(1):121-128 [FREE Full text] [doi: 10.1016/j.semarthrit.2017.03.014] [Medline: 28420491]
28. Luo D, Wang P, Lu F, Elias J, Sparks JA, Lee YC. Mobile apps for individuals with rheumatoid arthritis. J Clin Rheumatol 2019;25(3):133-141. [doi: 10.1097/RHU.0000000000000800]
29. Grainger R, Townsley H, White B, Langlotz T, Taylor WJ. Apps for people with rheumatoid arthritis to monitor their disease activity: a review of apps for best practice and quality. JMIR Mhealth Uhealth 2017 Feb 21;5(2):e7 [FREE Full text] [doi: 10.2196/mhealth.6956] [Medline: 28223263]
30. Umapathy H, Bennell K, Dickson C, Dobson F, Fransen M, Jones G, et al. The web-based osteoarthritis management resource my joint pain improves quality of care: a quasi-experimental study. J Med Internet Res 2015 Jul 07;17(7):e167 [FREE Full text] [doi: 10.2196/jmir.4376] [Medline: 26154022]
31. Nishiguchi S, Ito H, Yamada M, Yoshitomi H, Furu M, Ito T, et al. Self-assessment tool of disease activity of rheumatoid arthritis by using a smartphone application. Telemed J E Health 2014 Mar;20(3):235-240 [FREE Full text] [doi: 10.1089/tmj.2013.0162] [Medline: 24404820]
32. Shigaki CL, Smarr KL, Siva C, Ge B, Musser D, Johnson R. RAHelp: an online intervention for individuals with rheumatoid arthritis. Arthritis Care Res (Hoboken) 2013 Oct;65(10):1573-1581 [FREE Full text] [doi: 10.1002/acr.22042] [Medline: 23666599]

33. Urruticoechea-Arana A, León-Vázquez F, Giner-Ruiz V, Andréu-Sánchez JL, Olivé-Marqués A, Freire-González M, et al. Development of an application for mobile phones (App) based on the collaboration between the Spanish Society of Rheumatology and Spanish Society of Family Medicine for the referral of systemic autoimmune diseases from primary care to rheumatology. Reumatología Clínica (English Edition) 2020 Sep;16(5):373-377. [doi: 10.1016/j.reumae.2019.09.001]
34. Powley L, McIlroy G, Simons G, Raza K. Are online symptoms checkers useful for patients with inflammatory arthritis? BMC Musculoskelet Disord 2016 Aug;17(1):362 [FREE Full text] [doi: 10.1186/s12891-016-1189-2] [Medline: 27553253]
35. Kang H, Park H. A mobile app for hypertension management based on clinical practice guidelines: development and deployment. JMIR Mhealth Uhealth 2016 Feb;4(1):e12 [FREE Full text] [doi: 10.2196/mhealth.4966] [Medline: 26839283]
36. Yang J, Weng L, Chen Z, Cai H, Lin X, Hu Z, et al. Development and testing of a mobile app for pain management among cancer patients discharged from hospital treatment: randomized controlled trial. JMIR Mhealth Uhealth 2019 May 29;7(5):e12542 [FREE Full text] [doi: 10.2196/12542] [Medline: 31144672]
37. Najm A, Nikiphorou E, Kostine M, Richez C, Pauling JD, Finckh A, et al. EULAR points to consider for the development, evaluation and implementation of mobile health applications aiding self-management in people living with rheumatic and musculoskeletal diseases. RMD Open 2019 Sep 13;5(2):e001014 [FREE Full text] [doi: 10.1136/rmdopen-2019-001014] [Medline: 31565245]
38. Najm A, Lempp H, Gossec L, Berenbaum F, Nikiphorou E. Needs, experiences, and views of people with rheumatic and musculoskeletal diseases on self-management mobile health apps: mixed methods study. JMIR Mhealth Uhealth 2020 Apr 20;8(4):e14351 [FREE Full text] [doi: 10.2196/14351] [Medline: 32310151]

Abbreviations

ACPA: anticitrullinated peptide antibodies
ASAS: Assessment of Spondyloarthritis International Society
ASAS-HI: Assessment of Spondyloarthritis International Society Health Index
ASDAS: Ankylosing Spondylitis Disease Activity Score
b/ts-DMARD: biologic or targeted synthetic disease-modifying antirheumatic drug
BASDAI: Bath Ankylosing Spondylitis Disease Activity Index
BASFI: Bath Ankylosing Spondylitis Functional Index
CRP: C-reactive protein
csDMARD: conventional disease-modifying antirheumatic drug
CTU: complex therapy unit
DAS28: Disease Activity Score 28
ePRO: electronic patient-reported outcome
ESR: erythrocyte sedimentation rate
GDPR: General Data Protection Regulation
HAQ: Health Assessment Questionnaire
HLA: histocompatibility antigen
HUB: Hospital Universitario Bellvitge
HUIL: Hospital Universitario Infanta Leonor
HULP: Hospital Universitario La Paz
HURyC: Hospital Universitario Ramón y Cajal
HUVH: Hospital Universitario Vall d´Hebron
IMID: immune-mediated disease
MAM: mixed attention model
mHealth: mobile health
NPS: Net Promoter Score
PtDAS28: patient-derived Disease Activity Score 28
RA: rheumatoid arthritis
RF: rheumatoid factor
RMD: rheumatic and musculoskeletal disease
SDAI: Simplified Disease Activity Index
SJC: swollen joint count
SpA: spondylarthritis
sSJC: self-assessed swollen joint count
sTJC: self-assessed tender joint count
SUS: System Usability Scale
TJC: tender joint count

Edited by A Mavragani; submitted 26.12.23; peer-reviewed by A Saraux, C Baxter; comments to author 20.02.24; revised version received 11.03.24; accepted 14.03.24; published 22.04.24.

Please cite as:
Novella-Navarro M, Iniesta-Chamorro JM, Benavent D, Bachiller-Corral J, Calvo-Aranda E, Borrell H, Berbel-Arcobé L, Navarro-Compan V, Michelena X, Lojo-Oliveira L, Arroyo-Palomo J, Diaz-Almiron M, García García V, Monjo-Henry I, Gómez González CM, Gomez EJ, Balsa A, Plasencia-Rodríguez C
Toward Telemonitoring in Immune-Mediated Inflammatory Diseases: Protocol for a Mixed Attention Model Study
JMIR Res Protoc 2024;13:e55829
URL: https://www.researchprotocols.org/2024/1/e55829
doi:10.2196/55829
PMID:38501508

Protocol

Digital Remote Monitoring Using an mHealth Solution for Survivors of Cancer: Protocol for a Pilot Observational Study

Pasquale F Innominato[1,2,3], MD, PhD; Jamie H Macdonald[4], PhD; Wendy Saxton[5], BA, RGN; Laura Longshaw[5], BSc; Rachel Granger[4], PhD; Iman Naja[6], PhD; Carlo Allocca[7], PhD; Ruth Edwards[8], BSc, MSc; Solah Rasheed[8], PhD; Frans Folkvord[9,10], PhD; Jordi de Batlle[11], PhD; Rohit Ail[7], PhD; Enrico Motta[6], PhD; Catherine Bale[1], MD; Claire Fuller[1], MBBCh; Anna P Mullard[1], MBBCh; Christian P Subbe[12,13], MD; Dawn Griffiths[1], ANP; Nicholas I Wreglesworth[1,13], MBBS; Leandro Pecchia[14,15], PhD; Giuseppe Fico[16], PhD; Alessio Antonini[6], PhD

[1]Oncology Department, Ysbyty Gwynedd, Betsi Cadwaladr University Health Board, Bangor, United Kingdom
[2]Warwick Medical School & Cancer Research Centre, University of Warwick, Coventry, United Kingdom
[3]Chronotherapy, Cancers and Transplantation Research Unit, Faculty of Medicine, Université Paris-Saclay, Villejuif, France
[4]Institute for Applied Human Physiology, School of Psychology and Sports Science, Bangor University, Bangor, United Kingdom
[5]Research and Development Department, Ysbyty Gwynedd, Betsi Cadwaladr University Health Board, Bangor, United Kingdom
[6]Knowledge Media Institute, The Open University, Milton Keynes, United Kingdom
[7]Health Innovation, Samsung, Staines, United Kingdom
[8]Dietetics Department, Ysbyty Gwynedd, Betsi Cadwaladr University Health Board, Bangor, United Kingdom
[9]PredictBy, Barcelona, Spain
[10]Tilburg School of Humanities and Digital Sciences, Tilburg University, Tilburg, Netherlands
[11]Institut de Recerca Biomèdica de Lleida, Lleida, Spain
[12]Acute and Critical Care Medicine, Ysbyty Gwynedd, Betsi Cadwaladr University Health Board, Bangor, United Kingdom
[13]School of Medical Sciences, Bangor University, Bangor, United Kingdom
[14]School of Engineering, University of Warwick, Coventry, United Kingdom
[15]Facoltà Dipartimentale di Ingegneria, Università Campus Bio-Medico di Roma, Rome, Italy
[16]Life Supporting Technologies, Escuela Técnica Superior de Ingenieros de Telecomunicaciones, Universidad Politécnica de Madrid, Madrid, Spain

Corresponding Author:
Alessio Antonini, PhD
Knowledge Media Institute
The Open University
Level 4, Room 4
Berrill Building, Walton Hall
Milton Keynes, MK7 6AA
United Kingdom
Phone: 44 1908 654356
Email: alessio.antonini@open.ac.uk

Abstract

Background: Healthy lifestyle interventions have a positive impact on multiple disease trajectories, including cancer-related outcomes. Specifically, appropriate habitual physical activity, adequate sleep, and a regular wholesome diet are of paramount importance for the wellness and supportive care of survivors of cancer. Mobile health (mHealth) apps have the potential to support novel tailored lifestyle interventions.

Objective: This observational pilot study aims to assess the feasibility of mHealth multidimensional longitudinal monitoring in survivors of cancer. The primary objective is to test the compliance (user engagement) with the monitoring solution. Secondary objectives include recording clinically relevant subjective and objective measures collected through the digital solution.

Methods: This is a monocentric pilot study taking place in Bangor, Wales, United Kingdom. We plan to enroll up to 100 adult survivors of cancer not receiving toxic anticancer treatment, who will provide self-reported behavioral data recorded via a dedicated app and validated questionnaires and objective data automatically collected by a paired smartwatch over 16 weeks. The participants will continue with their normal routine surveillance care for their cancer. The primary end point is feasibility (eg, mHealth

monitoring acceptability). Composite secondary end points include clinically relevant patient-reported outcome measures (eg, the Edmonton Symptom Assessment System score) and objective physiological measures (eg, step counts). This trial received a favorable ethical review in May 2023 (Integrated Research Application System 301068).

Results: This study is part of an array of pilots within a European Union funded project, entitled "GATEKEEPER," conducted at different sites across Europe and covering various chronic diseases. Study accrual is anticipated to commence in January 2024 and continue until June 2024. It is hypothesized that mHealth monitoring will be feasible in survivors of cancer; specifically, at least 50% (50/100) of the participants will engage with the app at least once a week in 8 of the 16 study weeks.

Conclusions: In a population with potentially complex clinical needs, this pilot study will test the feasibility of multidimensional remote monitoring of patient-reported outcomes and physiological parameters. Satisfactory compliance with the use of the app and smartwatch, whether confirmed or infirmed through this study, will be propaedeutic to the development of innovative mHealth interventions in survivors of cancer.

International Registered Report Identifier (IRRID): PRR1-10.2196/52957

(JMIR Res Protoc 2024;13:e52957) doi:10.2196/52957

KEYWORDS

cancer; survivorship; artificial intelligence; remote monitoring; mobile health; mHealth; digital health; circadian; actigraphy; mobile phone

Introduction

Background

Cancer survivorship begins with the diagnosis and continues throughout the whole life span of the person [1]. Owing to repeated advances in anticancer and supportive treatments, survivors of cancer represent an ever-growing population [2]. Indeed, accelerated by the recent COVID-19 pandemic, alternative models of care for survivors of cancer are being proposed to meet the growing demands, driven by patient-specific issues and local health care resource constraints [3]. Survivors of cancer could be still receiving anticancer treatment, or they may have already completed treatment, albeit only temporarily. In the former case, acute toxicities from anticancer treatment might be the most relevant and bothersome, whereas in the latter case, delayed and long-lasting toxicities and a plethora of physical, emotional, social, practical, and informational issues become the most critical unmet care needs for their well-being [4].

Healthy lifestyle interventions have a positive impact on cancer-related outcomes, such as overall survival, tolerance to treatment, and health-related quality of life (HRQoL), as well as other metabolic and degenerative diseases [5]. Specifically, appropriate habitual physical activity, adequate sleep, and a regular wholesome diet are of paramount importance for the wellness of survivors of cancer [1] and are considered fundamental pillars of supportive care in survivors of cancer [6]. Thus, the promotion of interventions for healthier habitual nutritional, sleep, and physical activity behaviors is broadly recommended [7]. Nevertheless, there are motivational, practical, and informational barriers to the wide adoption of modifiable healthy lifestyle behaviors in survivors of cancer [8-10].

As a class of ubiquitous technologies, mobile health (mHealth) apps have the potential to support lifestyle interventions. The combination of wearables and smartphone sensors allows scalable and practically implementable study of human behavior and physiology [11]. Automatic collection of personal health data can be complemented by self-reported assessments delivered through mHealth apps, allowing real-time monitoring of patient-reported outcomes. Such a combination of mHealth data with electronic medical records and electronic health records also opens the possibility of a new breed of artificial intelligence (AI) apps, with the potential to facilitate early detection of new conditions, identify worsening of symptoms, and provide novel delivery methods for lifestyle interventions.

Objectives

The European Union's (EU's) Horizon 2020 GATEKEEPER (GK) project is a flagship innovation action aimed at implementing this vision and delivering the future EU data and AI infrastructure for health care solutions [12]. GK has several goals, ranging from the technical software architecture and cross-countries' and cross-organizations' information security and data policy to the evaluation of data-driven services and AI-based interventions. GK's key innovation is combining health medical records with medical sensors and non–medical data from mHealth apps, wearables, and smart devices. The intuition is that apps and devices would bring critical contextual and behavioral information that, combined with medical data and knowledge, would lead to a breakthrough in AI for health care. For instance, ongoing investigations within the GK project involve the development of risk prediction algorithms for mental health and cognitive impairment and digital coaching to mitigate loneliness-related risks [13]. These breakthroughs are the result of this new approach and the data sets collected as part of the project.

In this regard, GK includes a multicentric large-scale pilot across 8 EU and 3 Asian countries for a total of 11 Reference Pilot Sites. The large-scale pilot aims to develop and test a novel approach to the evaluation of digital innovation in health care. The proposed approach can be described as an integrative analysis of cost-benefits, combining the local evaluation of the wide range of approaches and solutions at the reference sites with 10 main health care themes [13]. Pilots within the GK project evaluate, monitor, or treat the most prevalent, chronic, noncommunicable conditions according to the World Health

Organization, including cardiovascular, metabolic, and respiratory diseases, whereas this pilot study focuses on cancer [14].

Specifically, the proposed study is 1 of the 3 UK Reference Pilot Sites and falls under the Reference Use Cases on *co-morbidity and polymedication*. In preparation for the proposed study, a new mHealth solution for survivors of cancer was co-designed. This solution was initially tested in a small-scale study focused on the use of a wearable mHealth app before further expansion within the context of GK [13].

In the proposed study, behavioral data (nutritional intake, physical activity, and sleep) will be obtained through self-reporting (recorded via an app) and automatic collection (by a wearable smartwatch). The data will then be used for remote monitoring of cancer symptoms, automatic assessments of biometric data, and integration with health medical records. Thus, the aim of this study is to assess the feasibility of mHealth monitoring in survivors of cancer. It is hypothesized that mHealth monitoring will be feasible in survivors of cancer; specifically, at least 50% (50/100) of the participants will engage with the GK app at least once a week in 8 of the 16 study weeks.

Methods

Ethical Considerations

The study protocol has been approved by the National Health Services (NHS) Research Ethics Committee (Integrated Research Application System ID: 301068; Research Ethics Committee reference: 22//SC/0323) and therefore by the Health Research Authority and Health and Care Research Wales.

Informed consent describes both the primary and secondary uses of data. Concerning secondary uses, participants are informed about the full anonymization of their data with the aim of creating a resource for the study of predictors of symptom worsening, cancer relapse, and hospitalization events. The informed consent form is provided both in English and Welsh.

The study approval included a comprehensive data protection impact assessment and a data management plan concerning data flow, processing, and sharing. In summary, participants will be given a study code and an anonymous user account for the use of the wearable device and study app. The study will only use biometric data generated through commercially available systems—Samsung Health (SH) app and Samsung Galaxy Watch. The mHealth solution decouples and anonymizes data from their data vault on patients' phones before transfer and processing. Only the hospital staff will have access to the identity or personal information of patients, and no other researchers involved will be able to access the registry of patient identifiers.

Participants will be gifted with the wearable device (smartwatch) and replacement Android phone (provided to iOS users). Furthermore, a form of compensation is the training in the use of these widely available technologies as well as the opportunity to learn more about how digital coaching and digital health technologies make use of personal data. Finally, the study will provide participants with the opportunity to reflect on the role of self-management and potential support available to them.

Study Setting

This study is the result of a co-design approach involving the Betsi Cadwaldr University Health Board Cancer Services; specialists on nutrition, sleep, and physical activity; technology providers; AI researchers; experts on clinical research and evaluation; acute medicine physicians; and patients with cancer. Over a period of 2 years, weekly meetings between main investigators and technical partners, focus groups with patients with cancer, and a cocreation group involving all stakeholders generated a patient-facing app, a clinician facing dashboard, AI algorithms, communication and training materials, and specialist outcome assessments, which led to an mHealth solution that could be pragmatically implemented alongside current routine care for survivors of cancer, as provided by the public health care system, NHS Wales.

The study design is also the result of learning from other GK Reference Pilot Sites. In this regard, we propose a feasibility design with a duration of 16 weeks, which will be conducted at a single institution, the Oncology Service of Ysbyty Gwynedd Hospital, Bangor, Wales, United Kingdom.

Eligibility Criteria

To be enrolled in the study, all participants must meet all the following requirements: (1) diagnosis of any solid malignancy, at any stage; (2) completion of treatment (including surgery, radiotherapy, and any type of systemic anticancer treatment); (3) clinical, biochemical, and radiological confirmation of controlled disease (no evidence of residual disease or nonprogressive disease); (4) scheduled for either a therapeutic break (from systemic anticancer treatment) or having completed the planned multimodal treatment; (5) scheduled for active surveillance plan within the oncology service; (6) male or female patients aged at least 18 years; and (7) scored World Health Organization performance status 0 to 2 [15].

Patients will be excluded from participating in the study if they meet any of the following criteria: (1) not possessing a SIM card, (2) no internet access through Wi-Fi or unwilling to use mobile data allowance on a daily basis, (3) inability to understand and follow the instructions autonomously, (4) uncontrolled severe comorbidities (eg, cardiovascular, metabolic, neurological, and respiratory), (5) lack of capacity, (6) inability to understand English, (7) still undergoing systemic anticancer treatment (apart from bone-targeted agents, hormonal treatment against breast or prostate cancers, or maintenance monoclonal antibody monotherapy), (8) poor general condition (performance status>2), and (9) inability to sign informed consent.

We decided to focus on survivors of cancer who were not receiving anticancer treatment to minimize the potential impact of treatment-induced fatigue or anorexia. On the basis of previous discussion with patients with cancer, it was felt that this population was the most suitable to test our mHealth solution in the first place, which can be adapted in future studies to the needs of patients on active disease-modifying treatment.

Digital Health Care Technology

SH App and Samsung Galaxy Watch

The SH app, coupled with Samsung Galaxy Watch, can track a number of parameters, including (1) food and water intake (including calorie tracking), (2) sleep patterns, (3) blood oxygen saturation levels, (4) body composition, (5) body weight, (6) calorie intake, (7) heart rate, (8) blood pressure, and (9) habitual physical activity (step counts and minutes of moderate and physical activity completed per day).

The SH app uses biometrics obtained by the connected wearable device, the smartphone itself, and self-reporting to record variables such as accelerometry, heart rate, time, distance traveled, and speed. Data are then used for activity tracking by matching the signature characteristics of a wide range of exercises (such as walking, hiking, or swimming) to calculate step counts, the number of minutes of moderate and vigorous physical activity completed, and the number of calories expended. The SH app supports tracking of food intake during the day. For instance, users can record meals and snacks as well as fluid and caffeine intake. Macronutrients (proteins, carbohydrates, and fats) and micronutrients (vitamins and minerals) can be calculated. The SH app also implements sleep analysis, sleep duration tracking, and sleep stages to provide insights about the quantity and quality of sleep.

GK App

The GK app is an mHealth solution that will be installed on a personal smartphone and paired with the SH app. Patients will use it to periodically fill self-assessment questionnaires and view data visualization analytics.

Web Portals and Tablets

To complement the data collected by the SH app, Samsung Galaxy watch, and GK app, the patients will fill in questionnaires. These questionnaires will be completed by patients using a tablet, and paper forms will be provided in cases where a tablet is not available. The questionnaires will cover data describing HRQoL, symptoms, sleep, and patient feedback on care. Patients will also use an web-based survey platform (Qualtrics) to fill in questionnaires about habitual physical activity, any structured exercise completed, and patient activation.

Recruitment Program

Participants will be identified from oncology services at Ysbyty Gwynedd Hospital, Betsi Cadwaladr University Health Board, by reviewing the outpatient clinic lists of each participating oncologist, advanced nurse practitioner, and clinical pharmacist on a daily basis. For potentially eligible patients, the appropriateness of proposing participation in this trial will be decided by the lead oncologist. At the end of the clinical consultation, if deemed appropriate, the clinician will introduce the study and provide the information leaflet, and a date in the future will be set for the volunteer to meet a member of the clinical research team to answer all the possible queries and to confirm sign-up for participation. If and when a participant agrees to proceed with the study, they will be asked to sign the consent form and will receive the smartwatch (and a smartphone, if required). The clinical research team member will help with the setup of the apps and smartwatch pairing and will provide a technical overview of both as well as the troubleshooting and contact information. Baseline questionnaires will be completed on a dedicated tablet or paper as per the recommended procedures with a standard approach to collect these patient-generated data with the supervision of the clinical research nurse or officer [16]. The same approach will be used to collect end-of-study questionnaires data. The expected recruitment period is January 2024 to June 2024, with the maximum duration of data collection for each participant set to up to 16 weeks. We anticipate being able to recruit about 5 patients per week over a 24-week period to reach our target.

Contingency Plans for Potential Recruitment Risks

For this monocentric pilot, we have built on previous experience within the oncology department with digital monitoring studies [17-19], and the estimated recruitment has been discussed at length between clinicians and research team members. A risk assessment analysis has been performed, and no transfer, avoidance, or prevention of the risk of poor recruitment has been identified. To mitigate the risk of lower than expected acceptance from the patients, we have trained the involved clinician to present the study to their patients, who were potentially eligible for participation, rather than simply referring them to the research team for study explanation. To mitigate the risk of poor engagement from the clinicians themselves, we have already involved them since the beginning of the study, and we have planned meetings between the delivery research team and clinicians after multidisciplinary team meetings to remind them of the study objectives and inclusion criteria. We have also printed a leaflet containing the main study features for each relevant outpatient clinic. Finally, we decided to accept the risk of slow recruitment as, within the GK project, we have no further studies pending upon the results of this study.

Study Procedures

Following the provision of written informed consent, the following measures will be obtained and recorded in the case report form (CRFs) at baseline and at the end of the study (16 weeks):

- Height (only measured at study entry)
- Body mass
- BMI
- Waist circumference
- Hip circumference
- Medical history
- Concurrent conditions
- Concomitant medications
- WHO performance status [15]
- Cancer type and stage
- Harms—adverse events.

We will record and report “unexpected” serious adverse events resulting in death, life-threatening complications, hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, congenital abnormality or birth defect, and other “important medical events” that are considered serious if they jeopardize the participant or require

an intervention to prevent 1 of the abovementioned consequences.

The following adverse events are considered to be "expected": anxiety related to the monitoring of symptoms, diet, and exercise; distress related to the regular use of digital well-being technology; cutaneous allergic reactions to the smartwatch; and visual strain with the light-emitting smartphone screen.

The study uses the following questionnaires:

- EQ-5D-5L: Participants' HRQoL will be measured using the EQ-5D-5L questionnaire [20]. EQ-5D-5L is a widely used tool for assessing the domains of mobility, self-care, usual activities, pain or discomfort, and anxiety or depression as well as recording patients' self-rated health on a visual analog scale.
- Multidimensional Fatigue Inventory Short Form: Multidimensional Fatigue Inventory Short Form [21] will be used to assess fatigue. This is a validated short form of the more in-depth Multidimensional Fatigue Inventory questionnaire [22] and uses 10 simple questions to assess physical, emotional, and cognitive fatigue [21].
- Satisfaction, Alertness, Timing, Efficiency and Duration (SATED): The SATED questionnaire [23] will be used to assess subjective sleep. SATED is a simple questionnaire to determine the degree of sleep fulfillment and to measure the dimensions of sleep health based on 5 simple questions [24]. It has been used in >150 peer-reviewed papers and studies.
- Patient Assessment of Chronic Illness Care: Patient Assessment of Chronic Illness Care questionnaire [25] will be used to assess experience with care. It is recommended for research and quality improvement and has been successfully deployed in digital oncology studies [26].
- Edmonton Symptom Assessment System (ESAS; digital form completed daily through the GK app): The global symptom burden will be assessed through ESAS [27]. ESAS has a recall time of 24 hours and is adapted to daily completion [28]. Daily total symptom distress scores (ESAS physical score+emotional score+well-being) [29] will be computed, and their temporal trajectories will be compared using general linear and random mixed effects models for longitudinal data [30].
- Global Physical Activity Questionnaire: Habitual physical activity will be assessed using the Global Physical Activity Questionnaire short form [31] and four unvalidated questions: (1) minutes of moderate physical activity completed per week, (2) minutes of vigorous physical activity completed per week, (3) number of sessions of strength training completed per week, and (4) number of sessions of balance training completed per week.
- Patient Activation Measure–13: Patient activation, an individual's knowledge, skills, and confidence integral to managing their own health and health care, will be assessed using the Patient Activation Measure–13 [32].

Table 1 lists the timeline and type of data collected throughout the study period.

Participants will then be presented with the mHealth solution: the GK app on a personal smartphone and a smartwatch paired with the SH app. The participant will be trained to use the apps and watch. The GK app features a set of interactive questionnaires to collect the baseline and periodic self-assessment data. Furthermore, the GK app provides timely reminders about the need to complete the self-assessments and data visualization analytics. Finally, the GK app collects and anonymizes data from the smartwatch and SH app for daily data collection on a dedicated remote server. The smartwatch adopted can be configured and used in different ways; each patient will be able to set up complementary apps offering extra functionalities such as the stress level analysis and to identify the preferred patterns of use. Overall, the data generated by the smartwatch will be collected and aggregated on a daily basis, including heart rate, sleep and physical activity patterns, and calories and food intake. The sampling of data will be dependent on the user settings and contingencies, such as charging at night or battery level. Throughout the 16-week study period, the smartwatch will continuously and unobtrusively record habitual physical activity, sleep patterns, energy expenditure, step counts, and oxygen saturation through its biosensors (Figure 1). For example, the amount of moderate and vigorous physical activity completed per week will be obtained automatically through the study using heart rate data recorded by the wearable smartwatch. Specifically, the maximal heart rate will first be predicted using the following formula: maximal heart rate = 207 − (0.7 × age) [33].

Table 1. Data collected at each time point of the study.

	Baseline: day 0	Day 1-14	Daily from baseline	Thrice weekly (alternate days)	Weekly	End of the study (4 months +7 or −7 days)
Eligibility	✓					
Informed consent	✓					
Demographics	✓					
Height, weight, BMI, and waist circumference	✓[a]					✓
WHO[b] performance status	✓					
Medical history or concomitant conditions and medications	✓					✓
Cancer type and stage	✓					
ED-5D-5L	✓[a]					✓
MFI[c]-10	✓[a]					✓
SATED[d]	✓[a]					✓
PACIC[e]	✓[a]					✓
PAM 13[f]	✓[a]					
Issue of smartwatch and Android device if required	✓[a]					
Food diary				✓		
Weight					✓	
Physical activity appointment including cardiorespiratory fitness and muscular strength		✓				
GPAQ[g]		✓				✓
Habitual physical activity assessment		✓				
Minutes of activity done by patient including strength and balance					✓	
Borg's CR100 rating of perceived exertion scale					✓	
ESAS[h]			✓			✓
Continuous smartwatch data collection	✓[i]	✓	✓			
Usability questionnaire						✓
Adverse event assessment	✓[i]	✓	✓	✓	✓	✓
Collection of UKONS[j]	✓[i]	✓	✓	✓	✓	✓

[a]Conducted in person at baseline assessment visit.

[b]WHO: World Health Organization.

[c]MFI-10: Multidimensional Fatigue Inventory Short Form.

[d]SATED: Satisfaction, Alertness, Timing, Efficiency and Duration.

[e]PACIC: Patient Assessment of Chronic Illness Care.

[f]PAM-13: Patient Activation Measure–13.

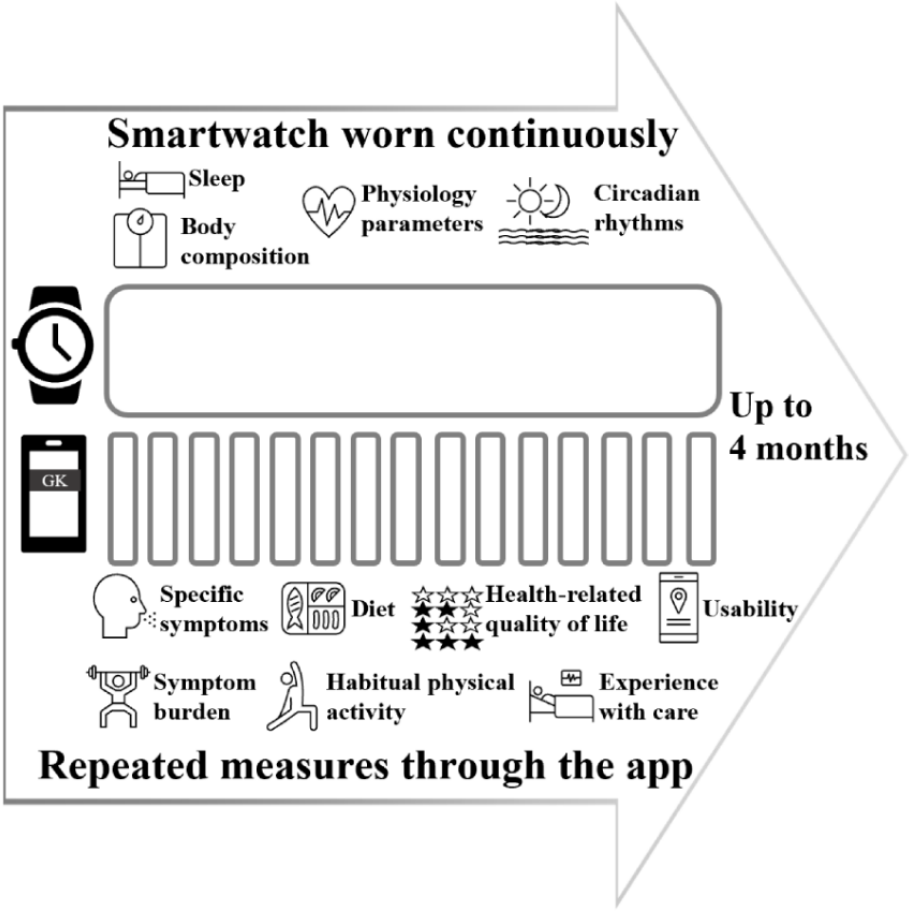
[g]GPAQ: Global Physical Activity Questionnaire.

[h]ESAS: Edmonton Symptom Assessment System.

[i]To be collected from informed consent onward.

[j]UKONS: United Kingdom Oncology Nursing Society.

Figure 1. Study schematic of the trial design (longitudinal and observational) with features of the patient-generated data collected through the smartwatch (objective and mostly continuous) and app (subjective and repeated measures or snapshots).



If a patient obtains a higher than predicted maximal heart rate during exercise, the actual maximal heart rate will replace the predicted maximal heart rate. The resting heart rate will then be recorded automatically by the watch. Heart rate zones will then be used to identify habitual physical activity intensity: very light (<30% heart rate reserve [HRR]), light (30%-39% HRR), moderate (40%-59% HRR), vigorous (60%-89% HRR), and near maximal to maximal (≥90% HRR) [34].

Energy expenditure during structured exercise will be estimated from the power output calculated from the mode of exercise, distance completed, and floors climbed. Other measurements such as body fat percentage, oxygen saturation, and blood pressure will be obtained using the standard features available within the smartwatch and smartphone.

The smartwatch will also prompt the participant to complete the ESAS questionnaire on a daily basis and to self-report the amount of habitual physical activity using the 4 abovementioned unvalidated questions on a weekly basis.

The SH app uses the Samsung Galaxy Watch to monitor sleep patterns, track sleep movements, and generate a sleep score. Additionally, the SH app provides daily goals and coaching programs based on sleep data to help improve sleep habits. Sleep analysis uses Samsung proprietary algorithms currently available through the public release of the SH app.

The SH app also allows the self-logging of the type and timing of meals and snacks. It is possible to set a daily target for caloric intake. After inputting details of the food type and quantity from a menu of common meals, the SH app provides a real-time view of the current calorie count for the day and a summary of the nutritional intake to determine if one is within the recommended levels. Moreover, it provides access to an overall dietary report over the span of a week.

Contact From the Research Team

To ensure compliance with the trial, a telephone call by a member of the research team to all participants will be arranged at week 1 and then, if required, every 4 weeks until the end of the trial data collection period. The nature of these calls is to resolve any problems or concerns. The frequency of calls will be arranged and adapted by the research team members on an individual basis according to each participant's needs and wishes. On the basis of prior experience with digital monitoring in patients with cancer [19], we believe that offering a regular opportunity to speak to someone who can help reassures participants, reduces anxiety, and in turn facilitates more accurate and consistent data collection.

Concomitant Care Permitted During the Trial

During the study period, each participant will receive the indicated surveillance and routine care in accordance with their needs and clinical condition. Thus, any form of intervention for the underlying cancer or any intercurrent issue will be allowed (and recorded). Similarly, any type of diagnostic investigation, workup, or health care provider encounter will be permitted.

To maximize participants' safety, multiple measures have been put into place.

We will provide technical support and contact information for any inquiries, along with an escalation plan for clinical needs. This support includes online assistance, drop-in clinics, and remote technical support during office hours. Patients will be directed for any medical concerns to contact the Acute Oncology Hotline: 24/7 availability of the Acute Oncology Hotline support, to which participants have been accustomed during the on-treatment period in Alaw (oncology department in Ysbyty Gwynedd, Bangor, United Kingdom). The occurrence of any unplanned health care encounter (with general practitioner, district nurse, practitioner nurse, specialist nurse, dietician, physiotherapist, psychologist, occupational therapist, clinical pharmacist, or any hospital specialist) will be recorded with a weekly question through the GK app. Finally, members of the research team will be given access to a web-based portal, where they can log in and access patient data. Although data will not be checked with regard to patient clinical condition (the portal is designed to check only if data have been collected or not), for safety reasons, if when checking for data availability, the research team will notice any symptom with a severity score of ≥7 (on a 10-point scale) or any other potentially serious medical issue, the lead clinician or the consultant oncologist of the week (available 24/7) will be informed, and they will decide accordingly whether it is sensible to contact the participant to inquire about their complaint and select the most appropriate action.

Primary Outcome

The main outcome of this trial is to assess the feasibility of mHealth monitoring in survivors of cancer not receiving toxic anticancer treatment. A priori criteria based on a traffic light system will be used to determine whether mHealth monitoring is unfeasible and future trials should be halted (red), whether changes to the study design or mHealth intervention are required before future trials are initiated (amber), or whether mHealth monitoring is considered feasible, and progress to future trials can occur without modification of the study design or intervention (green) [35]. The traffic light system will be applied at the end of the 16-week study period following collection of the last follow-up assessment from the last participant (on an intention-to-treat basis) to the following feasibility outcomes: eligibility (no set criteria but number of patients screened and eligible will be recorded); recruitment rate (green: n =>75, amber: n =≥50, and red: n=<50); acceptability of randomization and assessment procedure (no set criteria but the characteristics [and the proportion by group] of participants withdrawing post randomization will be captured); mHealth acceptability (green: ≥50/100, ≥50% of participants engage with the app at least once a week on at least 12 weeks out of the 16-week study, amber: ≥50/100, ≥50% of participants engage with the app at least once a week on at least 8 weeks out of the 16-week study, and red: <50/100, <50% of participants engage with the GK app at least once a week on at least 8 weeks out of the 16-week study); attrition rate (green: 20/100, <20% dropout rate, amber: ≤40/100, ≤40% dropout rate, and red: <40/100, >40% dropout rate); and missing data (green: <20/100, <20% of data missing, amber: ≤40/100, ≤40% of data missing, and red: >40/100, >40% of data missing). Engagement with the GK app is defined as logging on and completing at least 1 of the scheduled measures (ESAS, food intake, or habitual physical activity).

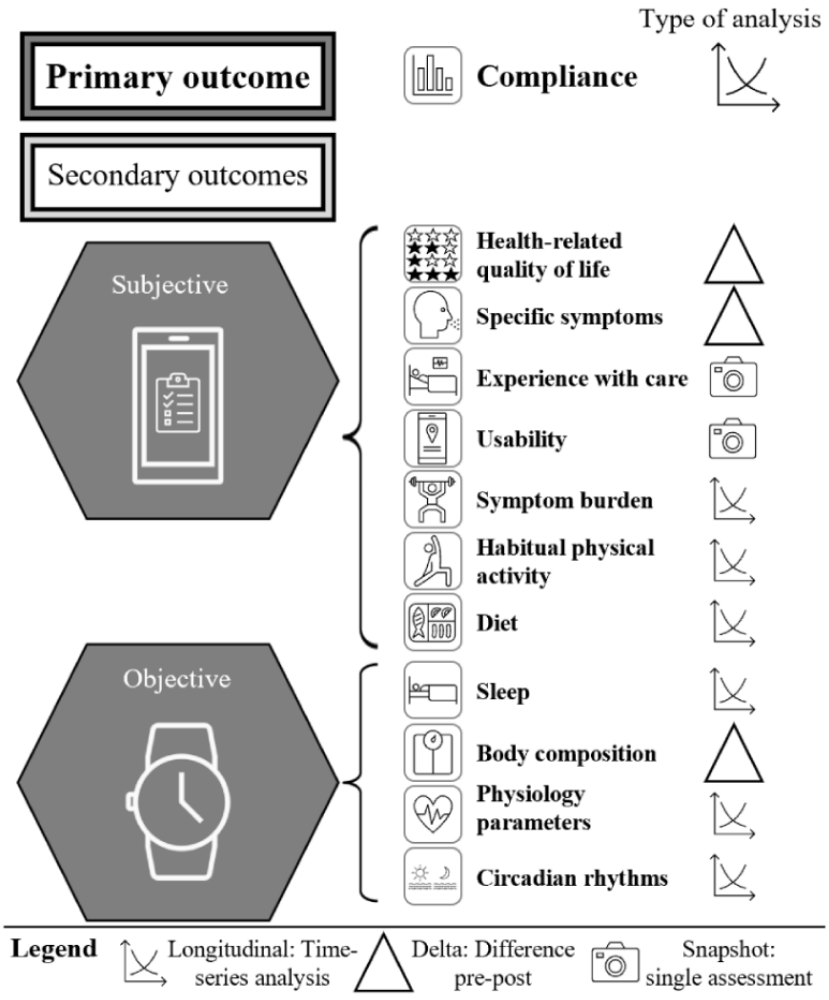
Secondary Outcomes

All other measures (as described in the *Study Procedures* section and in Figure 2) are secondary outcomes. They will be obtained to explore the direction and effect size of any changes as a groundwork for the development of future trials with meaningful end points, if appropriate. HRQoL will be further used in cost-effectiveness analyses. Within GK, cost-effectiveness is being conducted with the Monitoring and Assessment Framework for the European Innovation Partnership on Active and Healthy Ageing (MAFEIP) tool [36] to support evidence-based decision-making processes for all institutions and users in the health care sector. The main objective of the MAFEIP tool is to estimate the outcomes of a large variety of social and technological innovations by providing an early assessment of the likelihood that interventions will achieve their anticipated impact. In addition, MAFEIP also helps identify the drivers of a technology's effectiveness or efficiency to guide further design, development, or evaluation. To conduct the cost-effectiveness assessment, all costs will be included in a comprehensive impact assessment (eg, hospitalizations, emergency department admissions, and procedures). The costs for treatment as usual will be collected from historical evidence to complement the comparison.

The patterns over 24 hours of accelerometry and heart rate measurements collected *continuously* (epochs defined through user settings ranging from hourly to continuously during workouts) through the smartwatch will be analyzed to retrieve relevant circadian (ie, of approximately 1 day) physiology parameters through cosinor, nonparametric, and hidden Markov model methods [37-40]. The circadian biorhythms parameters that will be retrieved integrate the endogenous body clock [41], physical activity, and sleep cycles [42]. Circadian rest-activity rhythm has shown relevance in oncology with regard to the well-being and overall survival of patients with cancer [43-45].

At 2 and 4 months, participants will also be asked to complete a usability questionnaire to obtain a System Usability Score [46] and a Net Promoter Score [47]. In addition, patients will be invited to attend a participant focus group. The focus group question guide will include two aspects: (1) experience of using the app and smartwatch during the previous 16 weeks and (2) a beta version of a future iteration of the app will be presented to the patients, and potential acceptability of the new features of this beta version will be explored.

Figure 2. Summary of the pilot primary and secondary outcomes, which are categorized as subjective (from questionnaires) and objective (measured or from the smartwatch).



Exploratory Outcomes

The exploratory end points include the assessment of the precision (sensitivity and specificity) of AI-generated prediction of events based on the longitudinal patient-generated data sets. Specifically, events of interest will be severe symptoms requiring a call to the Acute Oncology Service (ranked amber and red on the United Kingdom Oncology Nursing Society triage tool [48]) or relapse (recurrence or progression) of cancer. Machine learning techniques applied to longitudinal datasets will be used, based on our previous experience [49].

Data Management

Data in this study are multidimensional and will be collected via a range of sources including paper-based CRFs, paper-based and electronic questionnaires (completed via the GK app), and biometric data obtained from the smartwatches. All anonymized data collected by the NHS research team via paper-based methods will be transferred into a secure digital database, in a locked room, and on a password-protected desktop computer, whose access will be logged and monitored and limited to the research team members involved in the study.

Raw accelerations and heart rate data collected through the smartwatch will be periodically and seamlessly downloaded and sent to the GK app onto the paired smartphone. Afterward, once a day, these data will be automatically and securely uploaded onto the GK repository server through the internet in an anonymized fashion, where they will be kept for further time-series analyses, as previously described.

Confidentiality and Data Protection Considerations

The sponsor (Betsi Cadwaladr University Health Board) has undertaken a full data protection impact assessment. To protect the confidentiality of participant data, paper-based CRFs and questionnaires will be linked to the participant via a trial identification number and stored in a separate location in the Investigator Site File containing the original consent forms. All paper-based documents will be stored in a locked cabinet in a restricted access office area. Participants will not be required to provide any personal information (such as name and date of birth) to register or use the GK app; instead, they will use the provided study account. The GK app will pull and anonymize data from the SH app, excluding contact details and other information that could be used to reidentify participants. The key linking the participant with the data set will only be held by the NHS research team and never be shared with other organizations.

Trial Management and Risk Assessment

The sponsor has undertaken a risk assessment in line with the sponsor's standard operating procedures, and the overall trial has been assessed as moderate risk, principally in relation to the multidimensional monitoring. The trial conduct and progress will be monitored by a trial management group including independent experts and patients to provide advice and support. A trial risk-adapted monitoring plan has been developed to check the research procedures; evaluate overall safety; and assess protocol compliance, data accuracy, and completeness.

Statistical Considerations

The study's primary outcome is feasibility, which, by design, is assessed by multiple outcomes (as described above). Arguably, the most important of these is patient engagement with the mHealth solution, and we have defined the solution as feasible if at least 50% (50/100) of the participants engage with the app at least once a week in 8 of the 16 study weeks. If we recruit 100 eligible participants, we will be able to estimate an engagement rate of 50% (n=50) with a 95% CI of +10% or −10%, whereby the width of the CI (in percentage) was calculated as follows:

$$1.96\times\sqrt{(p\times(1-p)/n)} \quad \textbf{(1)}$$

where p is the percentage (50%) and n is the intended sample size (100). For this feasibility study, we considered this CI appropriate for estimating drop-off rates in future studies. Finally, we considered this sample size suitable for the preplanned exploratory subgroup analyses.

The main analysis of the primary outcome (compliance) will be performed on an intention-to-treat basis. Similarly, the secondary outcomes will be evaluated on an intention-to-treat basis. However, for the secondary outcomes, preplanned subgroup and sensitivity analyses will also be conducted. They will include (1) subgroups with at least 75% (75/100) of available patient-generated data (from the app and the smartwatch combined) to exclude unengaged participants and focus on the most committed participants, (2) subgroups defined by the performance status and presence or absence of evidence of neoplastic disease, and (3) subgroups defined by sex and median age. For the primary outcome, no form of inference will be performed on the missing data, as they provide the main outcome of the study. For secondary analyses, neither mean imputation nor the last observation carried forward will be used [50]. However, based on the proportion of missing data, exploratory analyses including low-rank approximation–based imputation [51] could be performed to ensure that the observed effect sizes remain of the same order of magnitude with this approach as well.

Results

As of January 8, 2024, we are performing the last preparatory steps before enrollment, such as finalizing letters for GPs and internal communication to the oncology department staff about the study, its finalities, and referral criteria.

We anticipate enrolling the 100th patient by the end of June 2024. Thus, the last patient's last visit is expected in late November 2024. We foresee an additional month to complete the data collection and solve the pending queries. Data analyses will then be performed once all data have been collected, and the database will be frozen. Primary and secondary outcomes will be prioritized over the exploratory and sensitivity analyses. The overall evaluation of the study will be presented as part of the results of the GK large-scale pilot to the EU Commission and via the project web portal.

The main outcomes will be submitted for publication to an appropriate peer-reviewed scientific journal and, if opportune, to a scientific meeting in the domains of oncology, digital health, behavioral medicine, and sport and exercise science. Additional reports of specific findings elaborated more in depth will be considered for submission for scientific publication or presentation, according to the pertinence of the results obtained and their clinical and scientific relevance.

Discussion

Study Goals and Expected Findings

This study aims to determine the feasibility of self-monitoring of symptoms, biometrics, and behavior using an mHealth solution. If feasible, the efficacy of the mHealth solution will be addressed in subsequent studies. Ultimately, this study has two synergic objectives: (1) The first concerns the improvement of the quality of life and expectancy of independent active life. (2) The second concerns the cost-benefit to health care systems facing an increasing number of older adults and an increase in life expectancy, which is not compensated by a comparable increase in budget and staff. Regarding the first concern, in the case of patients with chronic conditions, this expectation should be considered in the context of the detrimental effects of long-term treatments and stress and anxiety related to the monitoring period. Regarding the second concern, the ultimate goal of the mHealth solution is to lower the likelihood of hospitalization, the worsening of patients' conditions, and the resulting complexity of life-long treatments. In this regard, the mHealth solution we propose to evaluate here for acceptance and compliance aims to ultimately lower the risks of worsening and adverse events via a combination of (1) early prediction leading to early intervention, and (2) prevention through behavioral intervention focused on the wide-spread adoption of good healthy lifestyle practices.

Technology is a key enabler in achieving these synergistic objectives. On the one hand, devices and apps lower the cost of monitoring while improving the variety, granularity, and frequency of data. For instance, apps exploit patients' hardware, freeing up time during appointments to be used to discuss patients' well-being. In the context of cancer survivorship and unmet care needs, the use of digital tools to try to overcome some of the barriers to the adoption of a healthy diet, sleep, and exercise behaviors is particularly relevant from the clinical, scientific, and health economics standpoints.

Thus, this observational pilot study has been tailored to provide feasibility evidence in view of future interventional studies aimed at specifically addressing some of the unmet needs of survivors of cancer. The personalized promotion of healthy

habits, including diet, sleep, and physical activity, as pillars of supportive care in survivors of cancer combined with the monitoring of signs and symptoms is expected to improve (or at least sustain) HRQoL. Moreover, given its relatively inexpensive implementation and the potential for benefits, we expect such an intervention to be cost-effective.

With this objective in mind, we have selected multiple secondary end points, all relevant for gaining insight into (1) the effect size of the clinical impact of the mHealth solution on symptom burden, HRQoL, and perceived care; (2) the temporal patterns of physical activity, diet, and sleep in survivors of cancer; and (3) the usability of such digital solutions. In our opinion, collecting these dense, multidimensional, longitudinal patient-generated data is paramount for the development of new forms of tailored behavioral interventions. Indeed, initial evidence in oncology is being produced, testing integrative behavioral approaches to improve cancer-associated and treatment-induced symptoms [5,52-58].

Along with these observational outcomes, patient safety remains paramount in our pilot and in all future interventions [59,60]. Therefore, besides the patient-prompted 24/7 acute oncology helpline, we have also put in place a safety net by which the clinical research team will have access to the web-based dashboard summarizing all the ESAS scores and the smartwatch objective data, with the possibility of escalation to the leading oncologist in case of severe symptoms or profoundly abnormal vital data. Moreover, as part of the exploratory analyses, we plan to use AI to investigate whether adverse events (unplanned health care provider encounter, emergency admission, or severe symptoms) could be reliably predicted between 3 and 5 days in advance from the temporal patterns of the collected objective and subjective patient-generated data [61-64]. Finally, we plan to use the same AI-enabled predictive approach to explore the accuracy of predicting cancer relapse at least 3 weeks before formal clinical suspicion. However, we expect relatively few such events during the study period.

Strengths and Limitations

The main limitations of this study include the choice of a very heterogeneous population of survivors of cancer, at very different stages of the clinical trajectory of their disease, as well as marked diversity in terms of prognosis. This was a deliberate choice for our first pilot, influenced by recruitment time constraints exacerbated by the disruption in research delivery caused by the COVID-19 pandemic. Associated with this is the monocentric nature of the study, a limitation in terms of potential generalizability but a compelled choice for an initial testing of the digital solution in a pilot feasibility trial.

We also acknowledge that the behavioral medicine approach deployed in this study has been derived mainly from published evidence [65,66] and minimally from in-house expertise. Thus, we have consciously selected to simplify our behavioral change approach, for example, avoiding ecological momentary assessments [67] or interpersonal social rhythm interventions [68].

We also accept that technology faces some barriers to adoption. From digital literacy to internet access, a large segment of the older adult population does not have or does not wish to use digital technology. Although this is likely a temporary challenge, characteristic of a demographic transition, it provides the need or opportunity to design noninvasive solutions that blend within our activities and habits. In the case of patients with chronic conditions, this type of design can be seen as part of the effort in mitigating the long-term effects of having to manage their conditions and treatments on their mental health and well-being.

Despite these limitations, we believe that this pilot study is both timely and relevant. Digital monitoring in oncology is becoming increasingly widespread and often integrates both patient-reported outcomes and data from a wearable biosensor [69-73]. We focus here on survivors of cancer after treatment, a population in which gaps in research have been identified [73]. Integrating in the future, an interventional approach of tailored coaching for behavioral change alongside the longitudinal multidimensional digital telemonitoring, we trust this pilot can provide unique and novel insight into the clinical relevance of predictive, preventive, personalized and participatory (P4) medicine in survivors of cancer [74]. Thus, we anticipate that if feasibility is demonstrated with this pilot study, we will test a novel form of AI-enabled digital behavioral intervention in a future dedicated randomized study. Such a future intervention could include (1) an initial dietary, sleep, and physical activity consultation; (2) behavioral monitoring recorded via a smartphone app and wearable smartwatch; (3) monitoring of symptoms and health medical records; (4) integration of data to allow delivery of AI-generated, personalized digital coaching on nutritional and physical activity behaviors; and (5) development of risk prediction algorithms to allow early identification and management of cancer-related symptoms, hospitalization events, and cancer relapse.

Conclusions

As part of the GK large-scale pilot, this study (its design, anonymized data, results, and technologies) will be made available to other selected health care organizations. These organizations, such as regional health care agencies and hospitals, will assess and evaluate the proposed approach with the aim of transferring the lessons learned from the study and, ideally, readapting and adopting this approach to their context, resources, and constraints. These activities are part of a specific *twinning* work strand that is open to both GK Reference Pilot Sites and third-party health care organizations interested in practices exchange and in being early adopters of new AI solutions.

This study is one of the many being developed within the scope of the GK project, all of which share the underlying aim of improving the quality of life of the aging population and people living with chronic conditions. However, this is 1 of the only 2 GK studies focused on cancer, with a study in Cyprus focusing on palliative care for the end of life [13]. As such, this is the only pilot in the GK large-scale pilot that addresses the challenges of long-term monitoring of cancer symptoms. Although its uniqueness is limited only to the GK projects, this study provides essential input to understand how a fairly common technological setting (a mobile app and wearable) can be adapted to this scenario and be potentially used at scale for

lifelong monitoring of survivors of cancer. This type of study generates an unprecedented quantity of multidimensional and longitudinal datapoints. It provides an opportunity but also a new set of risks. Indeed, part of the GK project activities concern the legal, policy, and practical arrangements necessary to move, share, combine, and reuse patient data. This is a significant challenge that can be addressed through this type of study, which is also aimed at identifying hidden barriers. Furthermore, this new setting presents both a challenge and an opportunity to redefine the relationship between patients and caregivers. It raises questions about the optimal use of data to promote dialogue and enhance understanding of the recovery journey after discharge, such as from a cancer support service.

Acknowledgments

This project has received funding from the European Union's Horizon 2020 Research and Innovation Program (grant 85722). JdB acknowledges receiving financial support from Instituto de Salud Carlos III (Miguel Servet 2019: CP19/00108), cofunded by the European Social Fund "Investing in your future." PFI and NIW acknowledge receiving financial support from Cancer Research Wales (DOESC-01).

Data Availability

The data sets generated and analyzed during this study will be made available in the Open Research Online repository of the Open University.

Authors' Contributions

PFI, JHM, WS, LL, LP, and AA contributed to the conception of the study. PFI, JHM, WS, IN, CA, RE, SR, and AA contributed to the design. PFI, JHM, WS, LL, RG, IN, CA, FF, JdB, and AA drafted the paper as the first authors. PFI and AA were responsible for funding acquisition and CPS helped in funding support. All authors performed contributed to critical review.
All coauthors gave their final approval for submission and agreed to be accountable for all aspects of this study.

Conflicts of Interest

CA and RA are employed by Health Innovation, Samsung, Communications House, United Kingdom, and as part of their paid employment, they have helped develop the digital health solution used in this study. No patent applications (pending or actual), including individual applications or those belonging to the institution to which the authors are affiliated, have been submitted regarding the digital health solution. All other authors declare no other conflicts of interest.

References

1. Shapiro CL. Cancer survivorship. N Engl J Med 2018 Dec 20;379(25):2438-2450. [doi: 10.1056/NEJMra1712502] [Medline: 30575480]
2. Miller KD, Nogueira L, Devasia T, Mariotto AB, Yabroff KR, Jemal A, et al. Cancer treatment and survivorship statistics, 2022. CA Cancer J Clin 2022 Sep 23;72(5):409-436 [FREE Full text] [doi: 10.3322/caac.21731] [Medline: 35736631]
3. Jefford M, Howell D, Li Q, Lisy K, Maher J, Alfano CM, et al. Improved models of care for cancer survivors. Lancet 2022 Apr 16;399(10334):1551-1560 [FREE Full text] [doi: 10.1016/S0140-6736(22)00306-3] [Medline: 35430022]
4. Schmidt ME, Goldschmidt S, Hermann S, Steindorf K. Late effects, long-term problems and unmet needs of cancer survivors. Int J Cancer 2022 Oct 15;151(8):1280-1290 [FREE Full text] [doi: 10.1002/ijc.34152] [Medline: 35657637]
5. Rock CL, Thomson CA, Sullivan KR, Howe CL, Kushi LH, Caan BJ, et al. American Cancer Society nutrition and physical activity guideline for cancer survivors. CA Cancer J Clin 2022 May;72(3):230-262 [FREE Full text] [doi: 10.3322/caac.21719] [Medline: 35294043]
6. Ligibel JA, Bohlke K, May AM, Clinton SK, Demark-Wahnefried W, Gilchrist SC, et al. Exercise, diet, and weight management during cancer treatment: ASCO guideline. J Clin Oncol 2022 Aug 01;40(22):2491-2507. [doi: 10.1200/JCO.22.00687] [Medline: 35576506]
7. Doyle C, Kushi LH, Byers T, Courneya KS, Demark-Wahnefried W, Grant B, 2006 Nutrition, Physical Activity and Cancer Survivorship Advisory Committee, American Cancer Society. Nutrition and physical activity during and after cancer treatment: an American Cancer Society guide for informed choices. CA Cancer J Clin 2006;56(6):323-353 [FREE Full text] [doi: 10.3322/canjclin.56.6.323] [Medline: 17135691]
8. Hoedjes M, Nijman I, Hinnen C. Psychosocial determinants of lifestyle change after a cancer diagnosis: a systematic review of the literature. Cancers (Basel) 2022 Apr 16;14(8):2026 [FREE Full text] [doi: 10.3390/cancers14082026] [Medline: 35454932]
9. Demark-Wahnefried W, Morey MC, Sloane R, Snyder DC, Cohen HJ. Promoting healthy lifestyles in older cancer survivors to improve health and preserve function. J Am Geriatr Soc 2009 Nov;57 Suppl 2(Suppl 2):S262-S264 [FREE Full text] [doi: 10.1111/j.1532-5415.2009.02507.x] [Medline: 20122025]

10. Wu YP, Yi J, McClellan J, Kim J, Tian T, Grahmann B, et al. Barriers and facilitators of healthy diet and exercise among adolescent and young adult cancer survivors: implications for behavioral interventions. J Adolesc Young Adult Oncol 2015 Dec;4(4):184-191 [FREE Full text] [doi: 10.1089/jayao.2015.0028] [Medline: 26697268]
11. Cola G, Vecchio A. Wearable systems for e-health and wellbeing. Pers Ubiquit Comput 2017 Jul 4;22(2):225 [FREE Full text] [doi: 10.1007/s00779-017-1041-1]
12. Gatekeeper project. Gatekeeper. URL: https://www.gatekeeper-project.eu/ [accessed 2023-06-27]
13. de Batlle J, Benítez ID, Moncusí-Moix A, Androutsos O, Angles Barbastro R, Antonini A, GATEKEEPER project. GATEKEEPER's strategy for the multinational large-scale piloting of an eHealth platform: tutorial on how to identify relevant settings and use cases. J Med Internet Res 2023 Jun 28;25:e42187 [FREE Full text] [doi: 10.2196/42187] [Medline: 37379060]
14. Boele F, Harley C, Pini S, Kenyon L, Daffu-O'Reilly A, Velikova G. Cancer as a chronic illness: support needs and experiences. BMJ Support Palliat Care (Forthcoming) 2019 Sep 19. [doi: 10.1136/bmjspcare-2019-001882] [Medline: 31537579]
15. Kos M, Pijnappel EN, Buffart LM, Balvers BR, Kampshoff CS, Wilmink JW, et al. The association between wearable activity monitor metrics and performance status in oncology: a systematic review. Support Care Cancer 2021 Nov 12;29(11):7085-7099 [FREE Full text] [doi: 10.1007/s00520-021-06234-5] [Medline: 34117567]
16. Efficace F, Innominato PF, Bjarnason G, Coens C, Humblet Y, Tumolo S, Chronotherapy Group of the European Organisation for ResearchTreatment of Cancer. Validation of patient's self-reported social functioning as an independent prognostic factor for survival in metastatic colorectal cancer patients: results of an international study by the Chronotherapy Group of the European Organisation for Research and Treatment of Cancer. J Clin Oncol 2008 Apr 20;26(12):2020-2026. [doi: 10.1200/JCO.2007.12.3117] [Medline: 18421055]
17. Komarzynski S, Wreglesworth NI, Griffiths D, Pecchia L, Subbe CP, Hughes SF, et al. Embracing change: learnings from implementing multidimensional digital remote monitoring in oncology patients at a district general hospital during the COVID-19 pandemic. JCO Clin Cancer Inform 2021 Feb;5:216-220 [FREE Full text] [doi: 10.1200/CCI.20.00136] [Medline: 33606562]
18. Jones HV, Smith H, Cooksley T, Jones P, Woolley T, Gwyn Murdoch D, et al. Checklists for complications during systemic cancer treatment shared by patients, friends, and health care professionals: prospective interventional cohort study. JMIR Mhealth Uhealth 2020 Sep 25;8(9):e19225 [FREE Full text] [doi: 10.2196/19225] [Medline: 32975526]
19. Lévi F, Komarzynski S, Huang Q, Young T, Ang Y, Fuller C, et al. Tele-monitoring of cancer patients' rhythms during daily life identifies actionable determinants of circadian and sleep disruption. Cancers (Basel) 2020 Jul 17;12(7):1938 [FREE Full text] [doi: 10.3390/cancers12071938] [Medline: 32708950]
20. Feng YS, Kohlmann T, Janssen MF, Buchholz I. Psychometric properties of the EQ-5D-5L: a systematic review of the literature. Qual Life Res 2021 Mar;30(3):647-673 [FREE Full text] [doi: 10.1007/s11136-020-02688-y] [Medline: 33284428]
21. Baussard L, Carayol M, Porro B, Baguet F, Cousson-Gelie F. Fatigue in cancer patients: development and validation of a short form of the Multidimensional Fatigue Inventory (MFI-10). Eur J Oncol Nurs 2018 Oct;36:62-67. [doi: 10.1016/j.ejon.2018.07.005] [Medline: 30322511]
22. Smets EM, Garssen B, Bonke B, De Haes JC. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosom Res 1995 Apr;39(3):315-325. [doi: 10.1016/0022-3999(94)00125-o] [Medline: 7636775]
23. Benítez I, Roure N, Pinilla L, Sapiña-Beltran E, Buysse DJ, Barbé F, et al. Validation of the Satisfaction, Alertness, Timing, Efficiency and Duration (SATED) questionnaire for sleep health measurement. Ann Am Thorac Soc 2020 Mar;17(3):338-343. [doi: 10.1513/AnnalsATS.201908-628OC] [Medline: 31899656]
24. Buysse DJ. Sleep health: can we define it? Does it matter? Sleep 2014 Jan 01;37(1):9-17 [FREE Full text] [doi: 10.5665/sleep.3298] [Medline: 24470692]
25. Glasgow RE, Wagner EH, Schaefer J, Mahoney LD, Reid RJ, Greene SM. Development and validation of the Patient Assessment of Chronic Illness Care (PACIC). Med Care 2005 May;43(5):436-444. [doi: 10.1097/01.mlr.0000160375.47920.8c] [Medline: 15838407]
26. Mir O, Ferrua M, Fourcade A, Mathivon D, Duflot-Boukobza A, Dumont S, et al. Digital remote monitoring plus usual care versus usual care in patients treated with oral anticancer agents: the randomized phase 3 CAPRI trial. Nat Med 2022 Jun 25;28(6):1224-1231. [doi: 10.1038/s41591-022-01788-1] [Medline: 35469070]
27. Bruera E, Kuehn N, Miller MJ, Selmser P, Macmillan K. The Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients. J Palliat Care 1991;7(2):6-9. [Medline: 1714502]
28. Hui D, Bruera E. The Edmonton symptom assessment system 25 years later: past, present, and future developments. J Pain Symptom Manage 2017 Mar;53(3):630-643 [FREE Full text] [doi: 10.1016/j.jpainsymman.2016.10.370] [Medline: 28042071]
29. Zimmermann C, Burman D, Bandukwala S, Seccareccia D, Kaya E, Bryson J, et al. Nurse and physician inter-rater agreement of three performance status measures in palliative care outpatients. Support Care Cancer 2010 May 23;18(5):609-616. [doi: 10.1007/s00520-009-0700-9] [Medline: 19629537]

30. Cnaan A, Laird NM, Slasor P. Using the general linear mixed model to analyse unbalanced repeated measures and longitudinal data. Stat Med 1997 Oct 30;16(20):2349-2380. [doi: 10.1002/(sici)1097-0258(19971030)16:20<2349::aid-sim667>3.0.co;2-e] [Medline: 9351170]
31. WHO noncommunicable diseases surveillance. World Health Organization. URL: https://www.who.int/teams/noncommunicable-diseases/surveillance/systems-tools/physical-activity-surveillance [accessed 2022-10-21]
32. Health-patient activation measure (PAM). Insignia. URL: https://www.insigniahealth.com/pam [accessed 2023-06-27]
33. Gellish RL, Goslin BR, Olson RE, McDonald A, Russi GD, Moudgil VK. Longitudinal modeling of the relationship between age and maximal heart rate. Med Sci Sports Exerc 2007 May;39(5):822-829. [doi: 10.1097/mss.0b013e31803349c6] [Medline: 17468581]
34. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee I, American College of Sports Medicine. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc 2011 Jul;43(7):1334-1359. [doi: 10.1249/MSS.0b013e318213fefb] [Medline: 21694556]
35. Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, PAFS consensus group. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. Pilot Feasibility Stud 2016 Oct 21;2(1):64 [FREE Full text] [doi: 10.1186/s40814-016-0105-8] [Medline: 27965879]
36. Birov S, Lavin C, Stroetmann V, Vilar R, Lupiáñez-Villanueva F. MAFEIP user guide. Version 2. MAFEIP. 2017. URL: https://tool.mafeip.eu/assets/files/MAFEIP_User_Guide_v2_Website.pdf [accessed 2023-08-05]
37. Cornelissen G. Applications of cosinor rhythmometry in pharmacology. J Pharmacokinet Pharmacodyn 2021 Jun 23;48(3):339-359. [doi: 10.1007/s10928-021-09748-x] [Medline: 33755872]
38. Gonçalves BS, Cavalcanti PR, Tavares GR, Campos TF, Araujo JF. Nonparametric methods in actigraphy: An update. Sleep Sci 2014 Sep;7(3):158-164 [FREE Full text] [doi: 10.1016/j.slsci.2014.09.013] [Medline: 26483921]
39. Huang Q, Cohen D, Komarzynski S, Li XM, Innominato P, Lévi F, et al. Hidden Markov models for monitoring circadian rhythmicity in telemetric activity data. J R Soc Interface 2018 Feb;15(139):20170885 [FREE Full text] [doi: 10.1098/rsif.2017.0885] [Medline: 29436510]
40. Bowman C, Huang Y, Walch OJ, Fang Y, Frank E, Tyler J, et al. A method for characterizing daily physiology from widely used wearables. Cell Rep Methods 2021 Aug 23;1(4):100058 [FREE Full text] [doi: 10.1016/j.crmeth.2021.100058] [Medline: 34568865]
41. Allada R, Bass J. Circadian mechanisms in medicine. N Engl J Med 2021 Feb 11;384(6):550-561. [doi: 10.1056/nejmra1802337]
42. Healy KL, Morris AR, Liu AC. Circadian synchrony: sleep, nutrition, and physical activity. Front Netw Physiol 2021 Oct 12;1:732243 [FREE Full text] [doi: 10.3389/fnetp.2021.732243] [Medline: 35156088]
43. Innominato PF, Komarzynski S, Palesh OG, Dallmann R, Bjarnason GA, Giacchetti S, et al. Circadian rest-activity rhythm as an objective biomarker of patient-reported outcomes in patients with advanced cancer. Cancer Med 2018 Sep;7(9):4396-4405 [FREE Full text] [doi: 10.1002/cam4.1711] [Medline: 30088335]
44. Lévi F, Dugué PA, Innominato P, Karaboué A, Dispersyn G, Parganiha A, ARTBC Chronotherapy Group. Wrist actimetry circadian rhythm as a robust predictor of colorectal cancer patients survival. Chronobiol Int 2014 Oct;31(8):891-900. [doi: 10.3109/07420528.2014.924523] [Medline: 24927369]
45. Milanti A, Chan DN, Li C, So WK. Actigraphy-measured rest-activity circadian rhythm disruption in patients with advanced cancer: a scoping review. Support Care Cancer 2021 Dec 17;29(12):7145-7169. [doi: 10.1007/s00520-021-06317-3] [Medline: 34142279]
46. Brooke J. SUS - a quick and dirty usability scale. Agency for Health Research and Quality. URL: https://digital.ahrq.gov/sites/default/files/docs/survey/systemusabilityscale%2528sus%2529_comp%255B1%255D.pdf [accessed 2023-09-06]
47. Reichheld FF. The one number you need to grow. Harv Bus Rev 2003 Dec;81(12):46-54. [Medline: 14712543]
48. Oncology/Haematology 24-hour triage: rapid assessment and access toolkit. UKONS. URL: https://www.ukons.org/site/assets/files/1134/oncology_haematology_24_hour_triage.pdf [accessed 2023-09-05]
49. Innominato PF, Komarzynski S, Mohammad-Djafari A, Arbaud A, Ulusakarya A, Bouchahda M, et al. Clinical relevance of the first domomedicine platform securing multidrug chronotherapy delivery in metastatic cancer patients at home: the inCASA European project. J Med Internet Res 2016 Nov 25;18(11):e305 [FREE Full text] [doi: 10.2196/jmir.6303] [Medline: 27888171]
50. Blankers M, Koeter MW, Schippers GM. Missing data approaches in eHealth research: simulation study and a tutorial for nonmathematically inclined researchers. J Med Internet Res 2010 Dec 19;12(5):e54 [FREE Full text] [doi: 10.2196/jmir.1448] [Medline: 21169167]
51. Kim KH, Kim KJ. Missing-data handling methods for lifelogs-based wellness index estimation: comparative analysis with panel data. JMIR Med Inform 2020 Dec 17;8(12):e20597 [FREE Full text] [doi: 10.2196/20597] [Medline: 33331831]
52. Christensen JF, Simonsen C, Hojman P. Exercise training in cancer control and treatment. Compr Physiol 2018 Dec 13;9(1):165-205. [doi: 10.1002/cphy.c180016] [Medline: 30549018]
53. Amidi A, Wu LM. Circadian disruption and cancer- and treatment-related symptoms. Front Oncol 2022 Oct 28;12:1009064 [FREE Full text] [doi: 10.3389/fonc.2022.1009064] [Medline: 36387255]

54. Palesh O, Solomon N, Hofmeister E, Jo B, Shen H, Cassidy-Eagle E, et al. A novel approach to management of sleep-associated problems in patients with breast cancer (MOSAIC) during chemotherapy : a pilot study. Sleep 2020 Oct 13;43(10):zsaa070 [FREE Full text] [doi: 10.1093/sleep/zsaa070] [Medline: 32274500]
55. Maccora J, Bean HR, Diggens J, Ftanou M, Alexander M, Lu Q, et al. Mechanisms of cognitive behavioral therapy and light therapy for cancer-related insomnia: a randomized clinical trial during chemotherapy for breast cancer. Behav Sleep Med 2023 May 17;21(3):227-241. [doi: 10.1080/15402002.2022.2075364] [Medline: 35580165]
56. Kronish IM, Cheung YK, Julian J, Parsons F, Lee J, Yoon S, et al. Clinical usefulness of bright white light therapy for depressive symptoms in cancer survivors: results from a series of personalized (N-of-1) trials. Healthcare (Basel) 2019 Dec 30;8(1):10 [FREE Full text] [doi: 10.3390/healthcare8010010] [Medline: 31905890]
57. Bean HR, Diggens J, Ftanou M, Alexander M, Stafford L, Bei B, et al. Light enhanced cognitive behavioral therapy for insomnia and fatigue during chemotherapy for breast cancer: a randomized controlled trial. Sleep 2022 Mar 14;45(3):zsab246. [doi: 10.1093/sleep/zsab246] [Medline: 34618907]
58. Maccora J, Garland SN, Ftanou M, Day D, White M, Lopez VA, et al. The Sleep, Cancer and Rest (SleepCaRe) trial: rationale and design of a randomized, controlled trial of cognitive behavioral and bright light therapy for insomnia and fatigue in women with breast cancer receiving chemotherapy. Contemp Clin Trials 2022 Sep;120:106877. [doi: 10.1016/j.cct.2022.106877] [Medline: 35961468]
59. Subbe C, Hughes DA, Lewis S, Holmes EA, Kalkman C, So R, et al. Value of improving patient safety: health economic considerations for rapid response systems-a rapid review of the literature and expert round table. BMJ Open 2023 Apr 17;13(4):e065819 [FREE Full text] [doi: 10.1136/bmjopen-2022-065819] [Medline: 37068893]
60. Subbe CP, Bramley R. Digital NEWS? How to amplify the benefits of NEWS in a digital healthcare system. Clin Med (Lond) 2022 Nov;22(6):534-538 [FREE Full text] [doi: 10.7861/clinmed.2022-0349] [Medline: 36427893]
61. Hong JC, Niedzwiecki D, Palta M, Tenenbaum JD. Predicting emergency visits and hospital admissions during radiation and chemoradiation: an internally validated pretreatment machine learning algorithm. JCO Clin Cancer Inform 2018 Dec;2:1-11 [FREE Full text] [doi: 10.1200/CCI.18.00037] [Medline: 30652595]
62. Daly B, Gorenshteyn D, Nicholas KJ, Zervoudakis A, Sokolowski S, Perry CE, et al. Building a clinically relevant risk model: predicting risk of a potentially preventable acute care visit for patients starting antineoplastic treatment. JCO Clin Cancer Inform 2020 Mar;4:275-289 [FREE Full text] [doi: 10.1200/CCI.19.00104] [Medline: 32213093]
63. Csik VP, Li M, Binder AF, Handley NR. Development of an oncology acute care risk prediction model. JCO Clin Cancer Inform 2021 Mar;5:266-271 [FREE Full text] [doi: 10.1200/CCI.20.00146] [Medline: 33720762]
64. Peterson DJ, Ostberg NP, Blayney DW, Brooks JD, Hernandez-Boussard T. Machine learning applied to electronic health records: identification of chemotherapy patients at high risk for preventable emergency department visits and hospital admissions. JCO Clin Cancer Inform 2021 Oct;5:1106-1126 [FREE Full text] [doi: 10.1200/CCI.21.00116] [Medline: 34752139]
65. Voorheis P, Zhao A, Kuluski K, Pham Q, Scott T, Sztur P, et al. Integrating behavioral science and design thinking to develop mobile health interventions: systematic scoping review. JMIR Mhealth Uhealth 2022 Mar 16;10(3):e35799 [FREE Full text] [doi: 10.2196/35799] [Medline: 35293871]
66. Wolever RQ, Simmons LA, Sforzo GA, Dill D, Kaye M, Bechard EM, et al. A systematic review of the literature on health and wellness coaching: defining a key behavioral intervention in healthcare. Glob Adv Health Med 2013 Jul;2(4):38-57 [FREE Full text] [doi: 10.7453/gahmj.2013.042] [Medline: 24416684]
67. Stinson L, Liu Y, Dallery J. Ecological momentary assessment: a systematic review of validity research. Perspect Behav Sci 2022 Jun 06;45(2):469-493 [FREE Full text] [doi: 10.1007/s40614-022-00339-w] [Medline: 35719870]
68. Frank E, Swartz HA, Boland E. Interpersonal and social rhythm therapy: an intervention addressing rhythm dysregulation in bipolar disorder. Dialogues Clin Neurosci 2022 Apr 01;9(3):325-332. [doi: 10.31887/dcns.2007.9.3/efrank]
69. Garg S, Williams NL, Ip A, Dicker AP. Clinical integration of digital solutions in health care: an overview of the current landscape of digital technologies in cancer care. JCO Clin Cancer Inform 2018 Dec;2:1-9 [FREE Full text] [doi: 10.1200/CCI.17.00159] [Medline: 30652580]
70. Beauchamp UL, Pappot H, Holländer-Mieritz C. The use of wearables in clinical trials during cancer treatment: systematic review. JMIR Mhealth Uhealth 2020 Nov 11;8(11):e22006 [FREE Full text] [doi: 10.2196/22006] [Medline: 33174852]
71. Low CA. Harnessing consumer smartphone and wearable sensors for clinical cancer research. NPJ Digit Med 2020;3:140 [FREE Full text] [doi: 10.1038/s41746-020-00351-x] [Medline: 33134557]
72. Dzimitrowicz HE, Blakely LJ, Jones LW, LeBlanc TW. Bridging new technology into clinical practice with mobile apps, electronic patient-reported outcomes, and wearables. Am Soc Clin Oncol Educ Book 2022 Apr;42:1-6 [FREE Full text] [doi: 10.1200/EDBK_350550] [Medline: 35522912]
73. Liao Y, Thompson C, Peterson S, Mandrola J, Beg MS. The future of wearable technologies and remote monitoring in health care. Am Soc Clin Oncol Educ Book 2019 Jan;39:115-121 [FREE Full text] [doi: 10.1200/EDBK_238919] [Medline: 31099626]
74. Flores M, Glusman G, Brogaard K, Price ND, Hood L. P4 medicine: how systems medicine will transform the healthcare sector and society. Per Med 2013;10(6):565-576 [FREE Full text] [doi: 10.2217/pme.13.57] [Medline: 25342952]

Abbreviations

AI: artificial intelligence
CRF: case report form
ESAS: Edmonton Symptom Assessment System
EU: European Union
GK: GATEKEEPER
HRQoL: health-related quality of life
HRR: heart rate reserve
MAFEIP: Monitoring and Assessment Framework for the European Innovation Partnership on Active and Healthy Ageing
mHealth: mobile health
NHS: National Health Services
SATED: Satisfaction, Alertness, Timing, Efficiency and Duration
SH: Samsung Health

Edited by A Mavragani; submitted 21.09.23; peer-reviewed by K Le Du, J Piera Jiménez, M Peyroteo; comments to author 05.11.23; revised version received 16.01.24; accepted 05.02.24; published 30.04.24.

Please cite as:
Innominato PF, Macdonald JH, Saxton W, Longshaw L, Granger R, Naja I, Allocca C, Edwards R, Rasheed S, Folkvord F, de Batlle J, Ail R, Motta E, Bale C, Fuller C, Mullard AP, Subbe CP, Griffiths D, Wreglesworth NI, Pecchia L, Fico G, Antonini A
Digital Remote Monitoring Using an mHealth Solution for Survivors of Cancer: Protocol for a Pilot Observational Study
JMIR Res Protoc 2024;13:e52957
URL: https://www.researchprotocols.org/2024/1/e52957
doi:10.2196/52957
PMID:38687985

Protocol

KIJANI App to Promote Physical Activity in Children and Adolescents: Protocol for a Mixed Method Evaluation

Laura Willinger[1], PhD; Birgit Böhm[1], PhD; Florian Schweizer[2], MSc; Lara Marie Reimer[2,3], PhD; Stephan Jonas[3], Prof Dr; Daniel A Scheller[4], MSc; Renate Oberhoffer-Fritz[1], MD; Jan Müller[1], Prof Dr

[1]Chair of Preventive Pediatrics, Technical University of Munich, Munich, Germany

[2]Department of Informatics, Technical University of Munich, Munich, Germany

[3]Department of Digital Medicine, University Hospital Bonn, Bonn, Germany

[4]Associate Professorship of Didactics in Sport and Health, Technical University of Munich, Munich, Germany

Corresponding Author:
Laura Willinger, PhD
Chair of Preventive Pediatrics
Technical University of Munich
Georg-Brauchle-Ring 60/62
80992 München
Munich
Germany
Phone: 49 28924900
Email: laura.willinger@tum.de

Abstract

Background: The prevalence of physical inactivity among children and adolescents is alarmingly high despite the well-documented and comprehensive benefits of regular physical activity (PA). Therefore, PA promotion should start early in childhood and adolescence. Although reducing recreational screen time in children and adolescents is an urgent concern, digital approaches have the potential to make activity promotion attractive and age appropriate for the target group. KIJANI is a mobile app approach to promote PA in children and adolescents via gamification and augmented reality.

Objective: This study protocol aims to describe the KIJANI intervention in detail, as well as the evaluation approach.

Methods: KIJANI is based on the concept that virtual coins can be earned through PA, for example, in the form of a collected step count. With these coins, in turn, blocks can be bought, which can be used to create virtual buildings and integrate them into the player's real-world environment via augmented reality. PA of users is detected via accelerometers integrated into the smartphones. KIJANI can be played at predefined play locations that were comprehensively identified as safe, child-friendly, and attractive for PA by the target group in a partner project. The evaluation process will be divided into 2 different stages. The phase-I evaluation will be a mixed methods approach with one-on-one semistructured interviews and questionnaires to evaluate the user experience and receive feedback from the target group. After the implementation of results and feedback from the target group, the phase-II evaluation will proceed in the form of a 2-arm randomized controlled trial, in which the effectiveness of KIJANI will be assessed via objectively measured PA as well as questionnaires.

Results: The study received ethical approval from the ethical board of the Technical University of Munich. Participants for the phase-I evaluation are currently being recruited.

Conclusions: The study will help to determine the efficacy, applicability, and user experience of a gamified activity promotion application in children and adolescents. Overall, digital health approaches provide easy and wide reachability at low cost and are age appropriate and attractive for the target group of adolescents. Strategies have to be developed to apply digital health approaches in the best possible way for activity promotion.

International Registered Report Identifier (IRRID): DERR1-10.2196/55156

(JMIR Res Protoc 2024;13:e55156) doi:10.2196/55156

KEYWORDS

physical activity; health promotion; digital health; gamification; childhood; adolescence; adolescents; adolescent; children; augmented reality; KIJANI intervention; KIJANI; intervention; user experience

Introduction

Physical inactivity has emerged as a worldwide pandemic, constituting the fourth leading cause of mortality worldwide [1]. A study involving 1.6 million healthy adolescents aged 11 to 17 years revealed that a staggering 81% of healthy youth are not sufficiently physically active [2]. The situation has been further exacerbated by the emergence of the COVID-19 pandemic and its associated restrictions that have further increased physical inactivity among adolescents. According to current analyses, activity levels among healthy youth decreased by 20% during the COVID-19 pandemic [3]. The prevalence of physical inactivity among children and adolescents is alarmingly high despite the well-documented and comprehensive benefits of regular physical activity (PA) including improvements in physical fitness, cardiometabolic health, bone health, cognitive performance, and mental health, among other benefits [4].

Adolescence marks a critical transitional phase during which health habits such as an active lifestyle and future health behaviors are established and manifest [5]. This implies the presence of a tracking effect of PA, whereby the more active a person is during childhood and adolescence, the more likely they are to remain active in adulthood [6,7]. Therefore, PA promotion starting from childhood and adolescence is of immense importance.

Although reducing recreational screen time in children and adolescents is an urgent concern and is strongly recommended by the World Health Organization, the potential of digital technology to make prevention and health promotion attractive and age appropriate for adolescents needs to be recognized [4]. Adolescents are power users of technology, and digital approaches allow them to reach adolescents in their personal environment. To promote PA in the particularly important phase of adolescence, we have developed a digital intervention approach called “KIJANI” that provides new opportunities for promoting and supporting PA. Specifically by targeting children and adolescents, the interdisciplinary project aims to motivate the target group through an app with a game-based concept and augmented reality to engage in PA, especially outdoors [8]. Various studies have demonstrated that gamification in health applications positively influences the behavior of the target audience [8-10] and enables children and adolescents to achieve recommended activity goals in a playful context [11]. Based on a review exploring the potential of augmented reality games for children and adolescents, the fusion of virtual and real-world elements offers promising opportunities to enhance PA and social interaction [12]. Augmented reality integrated into exergames has shown particular appeal among children [13], possibly due to their innate inclination toward play, making children an ideal target audience for gamified activity promotion [9].

This paper describes the KIJANI intervention in detail as well as the study protocol for its evaluation.

Methods

KIJANI Intervention

The name KIJANI is Swahili and translates to “green.” It stands as a German abbreviation for “Children & Youth: active, nature-conscious, innovative!” KIJANI is a smartphone app explicitly developed for children and adolescents to increase PA through a gamified approach. The basic game concept is that virtual coins can be “earned” through PA, for example, in the form of a collected step count. These coins can in turn be used to “buy” blocks, which can be used to create virtual buildings and integrate them into the player’s real-world environment via augmented reality, see Figure 1. Using challenge-achievement-reward loops as provided via the coin reward system in KIJANI was shown to increase the desire to play in previous research [14]. PA of users is detected via accelerometers integrated into smartphones and is linked to the KIJANI app on a technical basis.

Earning coins is based on a fitness challenge in the app, for example, consisting of 10,000 steps per day. The achievement of the main goal as well as intermediate goals are rewarded with coins. The main goal of 10,000 steps is rewarded with 50 coins, and intermediate goals, for example, 5000 steps, are rewarded with 20 coins. The blocks differ in price, for example, grass and brick cost 2 coins, water and bookshelf cost 5 coins, and the most expensive is glass and gold with 10 coins. Some blocks such as dirt and stone are free and unlimited to ensure enjoyment for the users. A progress bar in the app shows the individual progress over the course of the day, encouraging participants to reach the daily goal.

KIJANI is designed to be played both alone and with friends in a group. To play together with friends, requests must be sent and confirmed. Then KIJANI can be played together in a group and buildings can be created together. Players can individually specify who can visit, build, and administrate buildings, which ensures that no uninvited players can participate and therefore is another safety issue in KIJANI. In addition, the individual activity behavior can be compared with friends in a ranking list, which is another incentive for PA, see Figure 2. The ranking is also available for nonfriends, as there is a setting to show all players.

Figure 1. An overview of screens in the KIJANI app: KIJANI home screen (left), KIJANI shop to buy blocks (middle), and KIJANI game in augmented reality (right).

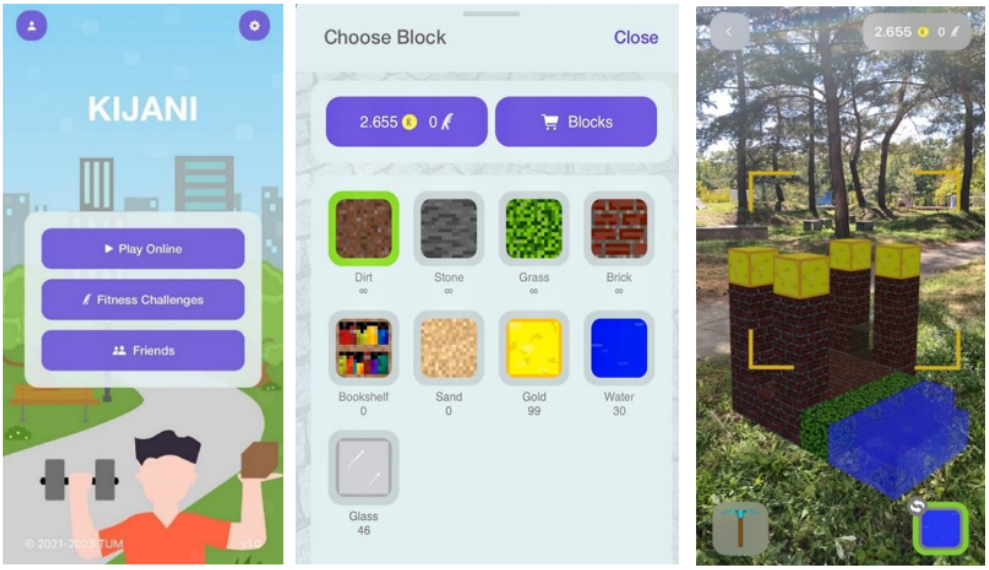
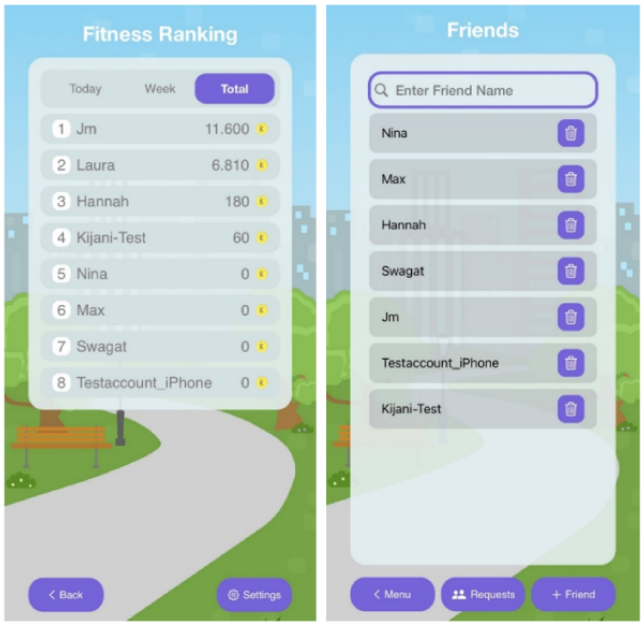


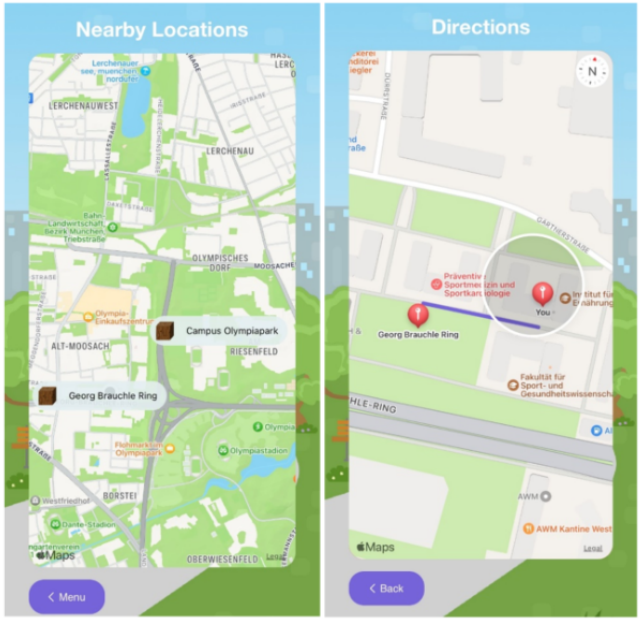
Figure 2. The features of the KIJANI app to connect with friends: friends ranking (left) and friends list (right).



KIJANI was developed in cooperation with the research project "WALKI-MUC – Evaluation of physical activity opportunities and walkability perceived by children and youth in Munich," conducted by the Associate Professorship of Didactics in Sport and Health at the Technical University of Munich. In WALKI-MUC, children and adolescents aged 6 to 17 years (n=93) identified walkable places in Munich (places within walking distance from their homes) that they considered supportive of PA. The participants provided qualitative descriptions of these PA-friendly places through participatory methods such as photovoice, walking interviews, and mapping exercises while researchers tracked the walked routes and GPS locations. Focus group discussions and the one-on-one sharing of the individual significance of these places in interviews provided insights into factors contributing to safety and attractiveness (eg, accessibility and presence of people) at the locations, as perceived by the children and adolescents. The descriptions and locations of these identified PA-friendly places of WALKI-MUC are incorporated into the KIJANI app. KIJANI can only be played in these comprehensively defined, child-friendly locations, ensuring that KIJANI can only be used in a safe and appealing environment for the target group. There is a location search feature implemented in the KIJANI app to find the play locations in the close environment. In addition, the route to the locations is displayed on the map (see Figure 3). This not only encourages users to be active but also supports a healthy lifestyle as extra steps can be accumulated.

At these play locations, a server is created in which KIJANI is played. Multiple servers can be created at 1 play location so that different buildings with different friends can be created at 1 play location. If players want to play in groups, friends have to be invited to the server to ensure that the players are in a safe play environment where no one else can intrude.

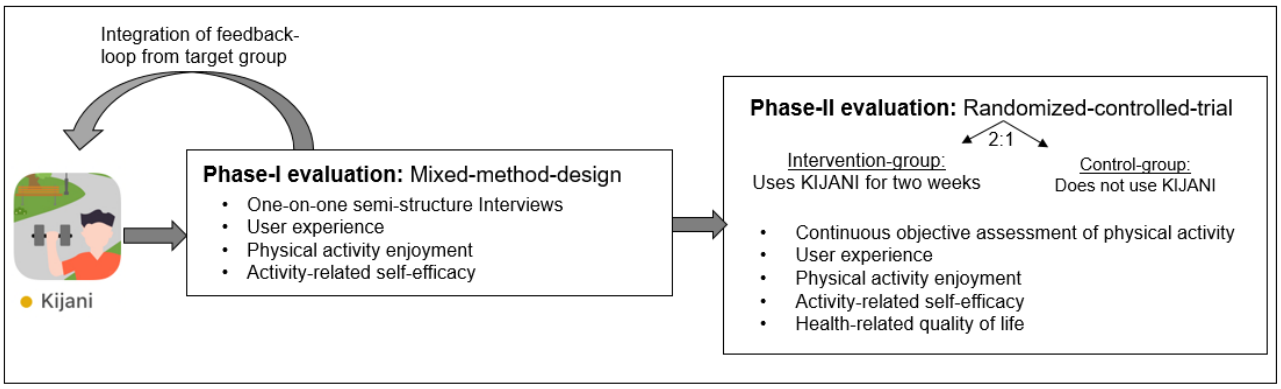
Figure 3. The WALKI-MUC map with play locations (left) and the navigation to play locations (right).



Evaluation Design

It is planned to evaluate the KIJANI app in a 2-phase approach as displayed in Figure 4. The phase-I evaluation will be a mixed methods design, in which the target group evaluates the user experience of the KIJANI app. The phase-II evaluation will be a 2-arm randomized controlled trial (RCT), in which the intervention group (IG) will use the KIJANI app, while the control group (CG) will not use the KIJANI app. Within this second evaluation stage, the effectiveness of KIJANI will be assessed via objectively assessed PA as well as standardized questionnaires.

Figure 4. The evaluation procedure with the phase-I and phase-II evaluations and feedback loop.



Ethical Considerations

The study protocol has already been approved by the ethical board of the Technical University of Munich (project 2023-185-S-NP). All children and their guardians will provide written informed consent.

For the described evaluation study of KIJANI, a development version of the app is used and distributed through TestFlight. Participants are required to log into the app using pseudonyms to safeguard their data privacy. Throughout app use, step count and GPS location are shared and digitally stored in a firebase. Personal data is processed in accordance with the provisions of the current data protection laws pursuant to Art. 12 (1) BayDSG. Prior to the official release of KIJANI, all necessary international regulations will be considered.

Participants and Enrollment

Children and adolescents at the age of 10-16 years will be included in this study. Children with walking impairments and cognitive impairments that hinder their ability to understand the task will be excluded from the study.

Phase-I Evaluation

Overview

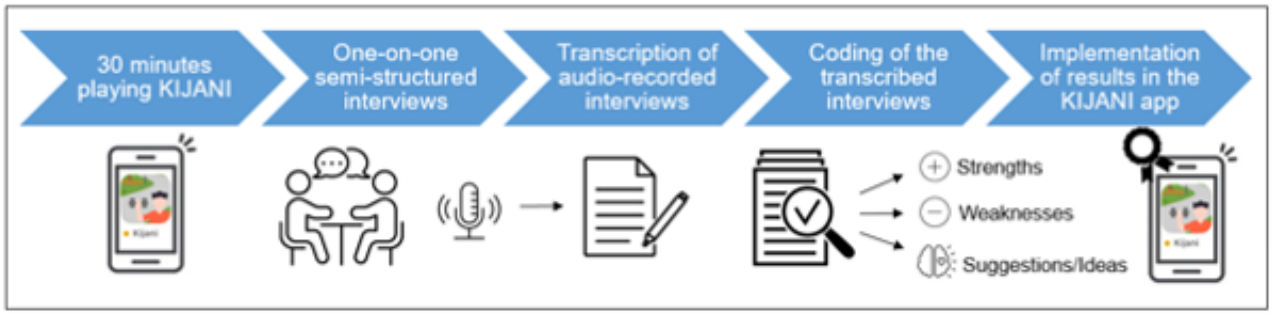
The primary outcome of the phase-I evaluation is the individual evaluation and feedback on KIJANI by the target population. Study participants will use the KIJANI app for 25 minutes in a group of 3 participants at a KIJANI play location under the supervision of the researcher. For this evaluation design, participants will have enough coins available as the main focus is on the user experience with KIJANI. Researchers ensure that all participants of a group have sufficient time and experience

with the app allowing them to give informed feedback at a later stage. Afterward, the app will be evaluated qualitatively with each participant in one-on-one semistructured interviews as well as quantitatively with standardized questionnaires on user experience, PA enjoyment, as well as activity-related self-efficacy.

Qualitative Evaluation

In one-on-one semistructured interviews, participants will report on their opinions and experiences with KIJANI. For this purpose, a previously generated interview guide, including mainly open - ended questions, will be used. The interview guide includes warm-up questions to establish a good relationship with the participants and to inquire about their attitudes toward smartphone use, digital games, as well as PA. The main part of the interview is related to the participants' opinions on the KIJANI app, including questions about what participants liked and what they would improve in the app. At the end of the interview, participants will have another opportunity to express further comments and ideas. All interviews will be conducted in person, audio recorded, and then transcribed verbatim. Interviewers will not be familiar with the participants prior to study initiation. The interviews will be evaluated by the respective interviewer. For evaluation purposes, categories will be generated guided by a systematic reduction process during data analysis. Text sequences will be classified into suitable categories, and thereby codes will be generated inductively. Possible uncertainties concerning the coding scheme will be discussed by the researchers and homogeneously adjusted. Data collection will proceed until data saturation has been achieved. Data will be considered saturated when recurring codes are observed across various interviews, accompanied by a decreased emergence of new codes during analysis (inductive thematic saturation). The qualitative evaluation process is displayed in Figure 5.

Figure 5. The procedure of the qualitative evaluation process of KIJANI.



User Experience

In addition, the user experience with the KIJANI app is evaluated with a user experience questionnaire [15]. User experience thereby summarizes different aspects that are important for the subjective evaluation of a product: usability aspects, joy of use, as well as aesthetic design. The user experience questionnaire consists of 26 bipolar terms (pairs of opposites, eg, annoying and enjoyable), which are evaluated over 7 levels. The items consist of the following 6 domains: effectiveness, transparency, predictability, stimulation, originality, and attractiveness. The questionnaire shows high reliability and construct validity [16].

PA Enjoyment

PA enjoyment is evaluated using the short version of the PA Enjoyment Scale (PACES-S). The PACES-S is a measurement tool commonly used in intervention research to measure enjoyment of PA, as it is closely associated with adherence and compliance to PA guidelines [17]. The German version of the PACES is reliable and valid for use in children and adolescents [18]. The short version of the questionnaire consists of 4 items with 5 scales (eg, PA brings me joy). It shows comparable measurement properties to the long version of the PACES and is therefore used in this study [19].

Activity-Related Self-Efficacy

Perceived self-efficacy in the context of PA is measured using the German version of the PA Self-Efficacy Scale. The scale consists of 8 items, each of which is answered on a 5-point Likert scale ranging from 1 ("do not agree at all") to 5 ("fully agree"). The self-efficacy scale for PA measures activity-related self-efficacy with 6 items and activity-related social support from family and friends via the remaining 2 items. The reliability and validity of the German version were shown in a study with 454 schoolchildren [20].

Phase-II Evaluation

Overview

After the implementation of the results of the first evaluation phase, the second evaluation in the form of an RCT will be conducted. The IG will use the KIJANI app in their everyday life over a period of 2 weeks, while the CG sticks to their normal everyday life without using the KIJANI app. Randomization will be 2:1 into IG and CG, with the randomization process clustered by age and gender to ensure equal distribution in the groups. The phase-II evaluation sample size was calculated with G*power (2-sided α of 0.05, power 0.9). A sample of 62 participants is planned for this study. Of these, 41 participants will be assigned to the IG and 21 participants will be assigned to the CG. After completion of the study, the CG will also have the opportunity to use the KIJANI app.

The primary outcome of the phase-II evaluation is the everyday PA of the children and adolescents. PA is objectively recorded in the form of daily step count via accelerometers integrated into the smartphone over the entire study period in IG and CG.

Through the KIJANI intervention, we hope to increase the PA of children and adolescents by 10%.

Secondary end points are health-related quality of life, activity-related self-efficacy, PA enjoyment, as well as the user experience with the app. The last 3 will be investigated as described above in the phase-I evaluation. Secondary end points will be assessed before and after the intervention period.

Health-Related Quality of Life

Health-related quality of life is self-assessed by the Kinder Lebensqualitätsfragebogen (KINDL) questionnaire. The KINDL is a generic instrument for assessing health-related quality of life in children and adolescents. For study participants younger than 14 years, the KINDL child version is used, and for study participants 14 years and older, the KINDL adolescent version is used. The KINDL is a short, methodologically tested, and flexible measurement instrument consisting of 24 questions on the 6 domains of body/physis, feelings/psychology, self-assessment, family, friends, and school [21].

Statistical Methods

The data analysis will involve both descriptive and analytical analyses. Initially, descriptive analysis will focus on the sociodemographic characteristics of the study population. Normal distribution of the data will be tested with the Shapiro-Wilk test. In terms of dropouts, intention-to-treat analysis will be performed using multiple imputations, to be able to calculate with a complete data set. To capture the longitudinal development of the activity level throughout the study period, a linear mixed model will be used to compare the change of the PA behavior over time between IG and CG. To investigate differences between the groups in activity-related self-efficacy, health-related quality of life, and PA enjoyment, these will be compared with 2-tailed *t* test or Mann-Whitney *U* test as appropriate depending on the distribution of the data. All analyses will be performed with RStudio (version 4.1.2; RStudio Team), with the level of significance set to 2-sided *P* values <.05 for all tests. RStudio was used for its tailored integration with the R programming language, providing an efficient and organized environment for reproducible data analysis, visualization, and documentation in our scientific study.

Results

Once the phase-I evaluation is completed, the outcomes will be discussed with the app development team and adjustments will be incorporated in KIJANI through this feedback loop. Data collection for the phase-I evaluation started in August 2023 and recruitment is currently still ongoing.

Discussion

Principal Findings

KIJANI is a mobile game explicitly developed for PA promotion in children and adolescents with a special focus on creativity as well as PA in the outdoor setting. The objective of the KIJANI intervention is to increase everyday PA in adolescents through a digital intervention approach using gamification and augmented reality. This study protocol describes the KIJANI intervention in detail, as well as the evaluation approach.

Even though activity promotion is highly indicated in adolescents, this young target group is difficult to reach, and adherence to intervention approaches, especially over the long term, is mostly rather low [22].

Several previous studies have assessed the effectiveness of mobile health approaches to increase PA in healthy adolescents. A systematic review on the effects of mobile health to increase PA concluded that mobile devices and apps may be an effective strategy for promoting PA in adolescents as they have high technology use. However, overall, there is only a small number of studies; a lack of RCTs; and a high risk of bias in this research sector, mostly including self-reported measures with the risk for recall as well as report bias [23]. Another systematic review on the quality and features of apps to improve PA, sedentary behavior, and diet also reported that generally, very few apps are available that specifically target children and adolescents and app quality was only moderate [24]. Overall, there is a need for high-quality app-based activity promotion approaches especially in children and adolescents.

Some previous studies have assessed the effects of digital gamification approaches on activity promotion. A meta-analysis revealed that the popular mobile augmented reality game “Pokémon Go” was associated with a significant increase in the users’ daily step count. In the game, participants are required to travel to different locations to capture virtual characters. Even though the game was not primarily designed to promote PA, it has reached masses of users and has shown to have the potential to influence their health behavior at least in the short term [25]. Long-term results are rare, but it seems that the novelty effect tends to wear off with time, and after 3 months, 80% of players stopped using the app [26].

Direito et al [27] assessed the effect of 2 smartphone apps, 1 immersive and 1 nonimmersive app, on cardiorespiratory fitness and PA levels in healthy young people. Both apps consisted of 8-week training programs, whereby in the immersive app the training program was embedded with a story where the user has to collect supplies and protect a town from zombies. After 8 weeks, they were not able to report any intervention effect compared with a CG in both apps. Adherence to app use was a major concern during their investigation [27].

Garde et al [28] evaluated another smartphone app called “MobileKids Monster Manor,” in which behavioral psychology, positive peer pressure, and rewards are used with a monster character theme to increase PA in healthy adolescents. In a school-based environment, this intervention increased PA over a short-term period [28].

Limitations

Several limitations should be considered when discussing this study protocol. In the phase-I evaluation, one-on-one interviews carry the risk of social desirability bias, where participants may provide responses perceived as socially acceptable rather than expressing their true opinions or behaviors. The phase-II evaluation carries the risk of the Hawthorn effect, which implies the awareness of being observed and studied that impacts

people's behavior. Based on this effect, PA levels might be higher than normal throughout the measurement period of 2 weeks.

Conclusions

Overall, digital health approaches provide easy and wide reachability at low cost and are age appropriate and attractive for the target group of adolescents. Strategies have to be developed to apply digital health approaches in the best possible way for activity promotion. The study will help to determine the efficacy, applicability, and user experience of a gamified activity promotion application in children and adolescents.

Acknowledgments

This study was funded by an unrestricted grant from the Bavarian State Ministry for Health and Care (StMGP) as part of the initiative "Gesund.Leben.Bayern."

Data Availability

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

Authors' Contributions

JM, BB, DAS, and LW were all involved in the development of the study protocol. LW prepared the initial draft of the manuscript. FS, LMR, and SJ developed the KIJANI app. ROF and JM gave important input for revising and improving the quality of the manuscript. All authors have read and approved the final version of the manuscript.

Conflicts of Interest

None declared.

References

1. Kohl HW, Craig CL, Lambert EV, Inoue S, Alkandari JR, Leetongin G, et al. The pandemic of physical inactivity: global action for public health. Lancet 2012;380(9838):294-305 [FREE Full text] [doi: 10.1016/S0140-6736(12)60898-8] [Medline: 22818941]
2. Guthold R, Stevens GA, Riley LM, Bull FC. Global trends in insufficient physical activity among adolescents: a pooled analysis of 298 population-based surveys with 1·6 million participants. Lancet Child Adolesc Health 2020;4(1):23-35 [FREE Full text] [doi: 10.1016/S2352-4642(19)30323-2] [Medline: 31761562]
3. Neville RD, Lakes KD, Hopkins WG, Tarantino G, Draper CE, Beck R, et al. Global changes in child and adolescent physical activity during the COVID-19 pandemic: a systematic review and meta-analysis. JAMA Pediatr 2022;176(9):886-894 [FREE Full text] [doi: 10.1001/jamapediatrics.2022.2313] [Medline: 35816330]
4. WHO Guidelines on Physical Activity and Sedentary Behaviour: Web Annex Evidence Profiles. Geneva: World Health Organization; 2020.
5. Sawyer SM, Afifi RA, Bearinger LH, Blakemore SJ, Dick B, Ezeh AC, et al. Adolescence: a foundation for future health. Lancet 2012;379(9826):1630-1640. [doi: 10.1016/S0140-6736(12)60072-5] [Medline: 22538178]
6. Hallal PC, Wells JCK, Reichert FF, Anselmi L, Victora CG. Early determinants of physical activity in adolescence: prospective birth cohort study. BMJ 2006;332(7548):1002-1007 [FREE Full text] [doi: 10.1136/bmj.38776.434560.7C] [Medline: 16601016]
7. Telama R, Yang X, Viikari J, Välimäki I, Wanne O, Raitakari O. Physical activity from childhood to adulthood: a 21-year tracking study. Am J Prev Med 2005;28(3):267-273. [doi: 10.1016/j.amepre.2004.12.003] [Medline: 15766614]
8. Deterding S, Dixon D, Khaled R, Nacke L. From game design elements to gamefulness: defining "gamification". 2011 Presented at: MindTrek '11: Proceedings of the 15th International Academic MindTrek Conference: Envisioning Future Media Environments; September 28-30, 2011; Tampere, Finland. [doi: 10.1145/2181037.2181040]
9. Pereira P, Duarte E, Rebelo F, Noriega P. A review of gamification for health-related contexts. In: Marcus A, editor. Design, User Experience, and Usability User Experience Design for Diverse Interaction Platforms and Environments: Third International Conference, DUXU 2014, Held as Part of HCI International 2014, Heraklion, Crete, Greece, June 22-27, 2014, Proceedings, Part II 3. Cham: Springer; 2014.
10. Sardi L, Idri A, Fernández-Alemán JL. A systematic review of gamification in e-health. J Biomed Inform 2017;71:31-48 [FREE Full text] [doi: 10.1016/j.jbi.2017.05.011] [Medline: 28536062]
11. Perron RM, Graham CA, Feldman JR, Moffett RA, Hall EE. Do exergames allow children to achieve physical activity intensity commensurate with national guidelines? Int J Exerc Sci 2011;4(4):257-264 [FREE Full text] [Medline: 27182367]
12. Das P, Zhu M, McLaughlin L, Bilgrami Z, Milanaik RL. Augmented reality video games: new possibilities and implications for children and adolescents. Multimodal Technol Interact 2017;1(2):8 [FREE Full text] [doi: 10.3390/mti1020008]

13. Laine TH, Suk HJ. Designing mobile augmented reality exergames. Games Cult 2016;11(5):548-580. [doi: 10.1177/1555412015572006]
14. Zichermann G, Cunningham C. Gamification by Design: Implementing Game Mechanics in Web and Mobile Apps. Sebastopol, CA: O'Reilly Media; 2011.
15. Laugwitz B, Held T, Schrepp M. Construction and evaluation of a user experience questionnaire. In: Holzinger A, editor. HCI and Usability for Education and Work: 4th Symposium of the Workgroup Human-Computer Interaction and Usability Engineering of the Austrian Computer Society, USAB 2008, Graz, Austria, November 20-21, 2008, Proceedings. Cham: Springer; 2008.
16. Hinderks A, Schrepp M, Rauschenberger M, Olschner S, Thomaschewski J. Konstruktion eines fragebogens für jugendliche personen zur messung der user experience. Tagungsband UP12. 2012. URL: https://dl.gi.de/server/api/core/bitstreams/d7e53c5f-0e9c-4b32-92c0-7d1d3ed45711/content [accessed 2024-03-22]
17. Jekauc D, Nigg C, Nigg CR, Reichert M, Krell-Roesch J, Oriwol D, et al. Measurement properties of the German version of the Physical Activity Enjoyment Scale for adults. PLoS One 2020;15(11):e0242069 [FREE Full text] [doi: 10.1371/journal.pone.0242069] [Medline: 33206685]
18. Jekauc D, Voelkle M, Wagner MO, Mewes N, Woll A. Reliability, validity, and measurement invariance of the German version of the Physical Activity Enjoyment Scale. J Pediatr Psychol 2013;38(1):104-115 [FREE Full text] [doi: 10.1093/jpepsy/jss088] [Medline: 22946084]
19. Chen C, Weyland S, Fritsch J, Woll A, Niessner C, Burchartz A, et al. A short version of the Physical Activity Enjoyment Scale: development and psychometric properties. Int J Environ Res Public Health 2021;18(21):11035 [FREE Full text] [doi: 10.3390/ijerph182111035] [Medline: 34769552]
20. Bachner J, Sturm DJ, Haug S, Demetriou Y. Multi-level validation of the German Physical Activity Self-Efficacy Scale in a sample of female sixth-graders. BMC Public Health 2020;20(1):979 [FREE Full text] [doi: 10.1186/s12889-020-09096-4] [Medline: 32571271]
21. Ravens-Sieberer U, Bullinger M. Assessing health-related quality of life in chronically ill children with the German KINDL: first psychometric and content analytical results. Qual Life Res 1998;7(5):399-407. [doi: 10.1023/a:1008853819715] [Medline: 9691720]
22. van Sluijs EMF, McMinn AM, Griffin SJ. Effectiveness of interventions to promote physical activity in children and adolescents: systematic review of controlled trials. BMJ 2007;335(7622):703 [FREE Full text] [doi: 10.1136/bmj.39320.843947.BE] [Medline: 17884863]
23. Böhm B, Karwiese SD, Böhm H, Oberhoffer R. Effects of mobile health including wearable activity trackers to increase physical activity outcomes among healthy children and adolescents: systematic review. JMIR Mhealth Uhealth 2019;7(4):e8298 [FREE Full text] [doi: 10.2196/mhealth.8298] [Medline: 31038460]
24. Schoeppe S, Alley S, Rebar AL, Hayman M, Bray NA, Van Lippevelde W, et al. Apps to improve diet, physical activity and sedentary behaviour in children and adolescents: a review of quality, features and behaviour change techniques. Int J Behav Nutr Phys Act 2017;14(1):83 [FREE Full text] [doi: 10.1186/s12966-017-0538-3] [Medline: 28646889]
25. Khamzina M, Parab KV, An R, Bullard T, Grigsby-Toussaint DS. Impact of Pokémon Go on physical activity: a systematic review and meta-analysis. Am J Prev Med 2020;58(2):270-282. [doi: 10.1016/j.amepre.2019.09.005] [Medline: 31836333]
26. Broom DR, Flint SW. Gotta catch 'em all: impact of Pokémon Go on physical activity, sitting time, and perceptions of physical activity and health at baseline and three-month follow-up. Games Health J 2018;7(6):401-408. [doi: 10.1089/g4h.2018.0002] [Medline: 30044136]
27. Direito A, Jiang Y, Whittaker R, Maddison R. Apps for improving fitness and increasing physical activity among young people: the AIMFIT pragmatic randomized controlled trial. J Med Internet Res 2015;17(8):e210 [FREE Full text] [doi: 10.2196/jmir.4568] [Medline: 26316499]
28. Garde A, Umedaly A, Abulnaga SM, Junker A, Chanoine JP, Johnson M, et al. Evaluation of a novel mobile exergame in a school-based environment. Cyberpsychol Behav Soc Netw 2016;19(3):186-192. [doi: 10.1089/cyber.2015.0281] [Medline: 26882222]

Abbreviations

CG: control group
IG: intervention group
KINDL: Kinder Lebensqualitätsfragebogen
PA: physical activity
PACES: Physical Activity Enjoyment Scale
PACES-S: short version of the Physical Activity Enjoyment Scale
RCT: randomized controlled trial

Edited by A Mavragani; submitted 04.12.23; peer-reviewed by Y Wang, TAR Sure; comments to author 01.02.24; revised version received 12.02.24; accepted 14.02.24; published 03.05.24.

Please cite as:
Willinger L, Böhm B, Schweizer F, Reimer LM, Jonas S, Scheller DA, Oberhoffer-Fritz R, Müller J
KIJANI App to Promote Physical Activity in Children and Adolescents: Protocol for a Mixed Method Evaluation
JMIR Res Protoc 2024;13:e55156
URL: https://www.researchprotocols.org/2024/1/e55156
doi:10.2196/55156
PMID:38700911

Protocol

A Factorial Randomized Controlled Trial to Optimize User Engagement With a Chatbot-Led Parenting Intervention: Protocol for the ParentText Optimisation Trial

Maria Da Graca Ambrosio[1], MPH, MD; Jamie M Lachman[1,2,3], DPhil, MSci; Paula Zinzer[1], MS, MA; Hlengiwe Gwebu[4], PhD; Seema Vyas[1], PhD; Inge Vallance[1], PhD; Francisco Calderon[1], MPhil; Frances Gardner[1], Prof Dr; Laurie Markle[2], MA; David Stern[5], PhD; Chiara Facciola[5], PhD; Anne Schley[6], MS; Nompumelelo Danisa[7], BA; Kanyisile Brukwe[7], MS; GJ Melendez-Torres[8], PhD

[1]University of Oxford, Oxford, United Kingdom
[2]Parenting for Lifelong Health, Oxford, United Kingdom
[3]University of Cape Town, Cape Town, South Africa
[4]University of Fort Hare, Eastern Cape, South Africa
[5]Innovations in Development, Education and the Mathematical Sciences International, Reading, United Kingdom
[6]mothers2mothers, Mpumalanga, South Africa
[7]Clowns Without Borders, Cape Town, South Africa
[8]University of Exeter, Exeter, United Kingdom

Corresponding Author:
Maria Da Graca Ambrosio, MPH, MD
University of Oxford
Barnett House, 32-37 Wellington Square
Oxford, OX1 2ER
United Kingdom
Phone: 44 (0)1865270325
Email: maria.ambrosio@wolfson.ox.ac.uk

Abstract

Background: Violence against children (VAC) is a serious public health concern with long-lasting adverse effects. Evidence-based parenting programs are one effective means to prevent VAC; however, these interventions are not scalable in their typical in-person group format, especially in low- and middle-income countries where the need is greatest. While digital delivery, including via chatbots, offers a scalable and cost-effective means to scale up parenting programs within these settings, it is crucial to understand the key pillars of user engagement to ensure their effective implementation.

Objective: This study aims to investigate the most effective and cost-effective combination of external components to optimize user engagement with ParentText, an open-source chatbot-led parenting intervention to prevent VAC in Mpumalanga, South Africa.

Methods: This study will use a mixed methods design incorporating a 2 × 2 factorial cluster-randomized controlled trial and qualitative interviews. Parents of adolescent girls (32 clusters, 120 participants [60 parents and 60 girls aged 10 to 17 years] per cluster; N=3840 total participants) will be recruited from the Ehlanzeni and Nkangala districts of Mpumalanga. Clusters will be randomly assigned to receive 1 of the 4 engagement packages that include ParentText alone or combined with in-person sessions and a facilitated WhatsApp support group. Quantitative data collected will include pretest-posttest parent- and adolescent-reported surveys, facilitator-reported implementation data, and digitally tracked engagement data. Qualitative data will be collected from parents and facilitators through in-person or over-the-phone individual semistructured interviews and used to expand the interpretation and understanding of the quantitative findings.

Results: Recruitment and data collection started in August 2023 and were finalized in November 2023. The total number of participants enrolled in the study is 1009, with 744 caregivers having completed onboarding to the chatbot-led intervention. Female participants represent 92.96% (938/1009) of the sample population, whereas male participants represent 7.03% (71/1009). The average participant age is 43 (SD 9) years.

Conclusions: The ParentText Optimisation Trial is the first study to rigorously test engagement with a chatbot-led parenting intervention in a low- or middle-income country. The results of this study will inform the final selection of external delivery components to support engagement with ParentText in preparation for further evaluation in a randomized controlled trial in 2024.

Trial Registration: Open Science Framework (OSF); https://doi.org/10.17605/OSF.IO/WFXNE

International Registered Report Identifier (IRRID): DERR1-10.2196/52145

(JMIR Res Protoc 2024;13:e52145) doi:10.2196/52145

KEYWORDS

parenting intervention; chatbot-led public health intervention; engagement; implementation science; mobile phone

Introduction

Background and Rationale

The detrimental consequences of physical and emotional violence against children (VAC) have been associated with multiple lifelong health disorders [1-3]. VAC negatively affects children's physical (ie, atypical structural development of the brain and altered functioning of the endocrine system) and cognitive (ie, harsh corporal punishment in children increases the risk of alcohol and substance abuse in adulthood and affects cognitive processes such as reasoning and attention) development [1,4]. Children exposed to violence also have an increased risk of experiencing and perpetrating domestic violence in adulthood [5]. VAC has also been associated with inequalities in academic achievements for boys and girls, with children exposed to physical and sexual violence being 13% less likely to complete high school [6].

While VAC is a global public health concern, rates are higher in low- and middle-income countries (LMICs) such as South Africa [7]. In a study with 3515 South African children, the prevalence of lifetime physical and emotional abuse was 56% and 35%, respectively [8,9]. Child sexual abuse is also widespread in the country, with a nationally representative cross-sectional survey reporting that 14.6% of girls and 10% of boys had experienced this form of abuse [10]. The economic costs of VAC in South Africa are significant. In the fiscal year 2015-2016, an estimated 4.3% of the country's gross domestic product was lost to VAC [11]. In addition, the expenditure on childcare and protection attributable to VAC was estimated to be 1.6 billion South African rands (US $124 million) [11].

Inequitable gender norms, such as societal acceptance of male aggression toward women and children, further impede adolescent girls' healthy development and education in South Africa [12]. In addition, adolescent girls are a recognized vulnerable group and susceptible to increased risk of sexually transmitted infections, including HIV, and violence, risks that stem from sexist social principles (ie, adolescent girls tend to be sexualized because of their physical development changes) and structural constraints (eg, poverty, socioeconomic inequality, and high levels of alcohol abuse and crime within communities) [12,13]. In 2018, approximately 16% of adolescent girls aged 15 to 17 years reported that they had experienced sexual abuse perpetrated mainly by a known male adult [10]. In addition, 21% of girls aged 15 to 21 years indicated that their first sexual experience was either coerced or forced [14].

While legislative development efforts have been made to address VAC in South Africa, entrenched social norms condoning physical and emotional abuse toward children are hard to change [15]. Research has demonstrated that a healthy growing environment positively affects children's early brain development, providing the foundations for developing long-term cognitive abilities such as language and reading [4]. Previous research has linked parental engagement in early childhood with better language development and literacy outcomes in children [16,17]. Open access, evidence-based parenting interventions such as the Parenting for Lifelong Health (PLH) suite of programs offer a prime opportunity to address such norms both within the family and at the broader societal level and create a safer environment for children. These interventions, typically delivered as in-person, group-based programs, have been effectively implemented worldwide to increase responsive and positive parenting [18]. However, in low-resource settings, factors such as employment, transportation, and childcare costs represent a significant financial and accessibility barrier to in-person parenting programs for many participants [19-21].

Prospects for Implementing Chatbot-Led Public Health Interventions

In recent years, digital interventions have been used as a delivery mechanism to address the structural barriers to accessing in-person parenting programs [22,23]. For example, PLH has recently developed digital adaptations of their in-person programs in response to restrictions placed on in-person parenting programs during the COVID-19 pandemic and challenges reported by implementing partners in delivering programs at scale in low-resource settings in sub-Saharan Africa. One such PLH adaptation is ParentText, an internet-based self-guided chatbot sent via instant messaging platforms such as WhatsApp and Telegram [24]. Text-based chatbots delivered through instant messaging platforms are being widely explored in the digitalization of public health programs, including parenting interventions. The Oxford Dictionary defines a chatbot as "a computer programme that can hold a conversation with a person, usually over the internet" [25]. They are also referred to as conversational software applications designed to interact in humanlike in-text or text-to-speech conversations with human users [26]. There is evidence suggesting that chatbots have been successfully applied to support health promotion interventions focused on improving mental well-being [27], reducing alcohol consumption [28], and supporting weight loss [29,30].

In 2022, according to World Bank estimates, 70% of South Africa's population had internet access, and there were 162 mobile phone subscriptions per 100 people [31]. This level of digital coverage makes internet-based interventions such as chatbots a promising delivery channel for parenting programs in the country. Several chatbot-led public health interventions have already been successfully implemented in South Africa. MomConnect, a chatbot that provides pre- and postnatal health information to pregnant women and new mothers to improve their health and that of their babies, has been operating in the country since 2014. By 2016, the chatbot, an initiative of the South African National Department of Health, had reached over half a million users [32]. In 2020, HealthConnect was launched to provide COVID-19–related health information to the general population, and it was estimated that the platform had reached tens of millions of users [33]. Another successful chatbot-led intervention is ChattyCuz, a gamified interactive chatbot targeted at young women to support them in maintaining healthy dating relationships and preventing intimate partner violence (IPV). In a randomized controlled trial with 19,643 young women, researchers reported 59% retention in the intervention [34]. Participants reported improved gender beliefs and reduced rates of IPV because of their interaction with ChattyCuz [34].

Despite the promise of chatbot interventions, the engagement rate of users enrolled in digital parenting interventions and public health interventions more broadly remains low [35-37]. Several factors that affect human-chatbot interaction, such as user trust, satisfaction, and external structures (eg, difficult access to smartphones and the internet and low levels of digital literacy), may undermine their effective implementation [38]. To date, research has primarily focused on investigating the effectiveness of chatbot-led public health interventions on changing behavior and health outcomes [38,39]. However, few digital public health interventions have investigated the factors underlying participant engagement [38,39]. Engagement can be conceptualized as "the extent (e.g., duration of interaction, frequency of contact and depth or variety of content used) of usage" and as "a subjective experience characterised by attention, interest and affect" [40]. Previous research has suggested 4 distinguishable attributes inherent to engagement: point of engagement (ie, initiation stage), period of sustained engagement (ie, maintenance stage), disengagement (ie, period of interruption), and re-engagement [41]. Even though understanding how each of these stages occurs is of extreme relevance to designing the most optimal digital health interventions, this study will focus on the second stage. The rationale behind this decision stems from previous research reporting higher dropout rates after 2 weeks of enrollment in digital health interventions [29,42,43]. In addition, there is a paucity of research focused on investigating how users remain engaged with parenting chatbots [44].

High engagement rates are presented in the literature as an average open-app ratio of 17.71 and 12.14 times over a 2-week period [29,42]. Another complication is that high rates of participant dropout challenge this research, and the determinants of attrition are uncertain as previous studies have lacked statistical power to analyze engagement [27,38]. Another critical factor in user dropout in human-chatbot interaction is the interaction breakdown due to the chatbot's inability to understand users' input, which may arouse negative emotional responses in users [45-47].

Cultural determinants are another potential factor affecting user enrollment and engagement with digital public health interventions. Cultural determinants of health refer to factors related to perceptions, relationships, and cultural identity that interact with society and influence an individual's good health and well-being [48]. Once identified, efforts can be made to promote positive cultural aspects supporting user engagement with chatbot-led public health interventions. In a Kenyan study, intent to use mobile health (mHealth) was associated with the degree to which individuals perceived that their peers had a favorable opinion about their use of mHealth [49]. In Pakistan, participants' perceptions of how easy it was to use an mHealth intervention and their positive attitude toward digital health interventions were associated with their intent to use them [50]. This finding highlights the need for increased user participation in the design process of digitally supported interventions [51] and competent cross-cultural delivery of digital parenting programs. There is also a need to strengthen the evidence base to optimize chatbot-led parenting interventions in LMICs. Such research should (1) assess the financial and implementation constraints to institutionalize them across stakeholders efficiently, (2) develop a culturally sensitive approach in their implementation to ensure effectiveness in terms of the acceptability and satisfaction of users, and (3) evaluate their effectual impact in increasing positive parenting behavior and reducing VAC.

Objectives

Overview

The ParentText Optimisation Trial aims to optimize user engagement through a chatbot-led parenting intervention delivered to parents (ie, any adult responsible for the care and well-being of a child regardless of biological relationship) and their adolescent girls aged 10 to 17 years in South Africa. It will test the relative effectiveness and cost-effectiveness of two intervention components designed to support user engagement with the ParentText chatbot: (1) remotely facilitated WhatsApp support groups delivered to participating parents and (2) in-person sessions delivered to parents and their adolescent girls. In addition, this study will investigate the effectiveness of selected intervention component levels on adolescent and parent behavioral, mental health, and educational outcomes.

Primary Objectives

The primary objectives are as follows:

1. To examine the effectiveness and cost-effectiveness of selected component levels on the primary engagement outcome of the total number of modules completed in ParentText.
2. To examine the effectiveness and cost-effectiveness of selected component levels on secondary engagement outcomes in terms of the percentage of modules and goals completed, the rate of self-reported completion of home practice activities based on the self-reported intention to

do home practice activities, and the total number of overall interactions of participants with the chatbot.

Secondary Objectives

The secondary objectives are as follows:

1. To examine the effectiveness and cost-effectiveness of intervention component levels on parent and adolescent behavioral, mental health, and educational outcomes assessed at baseline and 6 weeks after the baseline.
2. To identify the cultural determinants (perceived ease of use, perceived usefulness, hedonic motivation, habit, price value, and social influence) that significantly contribute to improved behavioral intentions of parents to engage with ParentText.
3. To identify how behavioral intention significantly contributes to improved primary and secondary engagement outcomes.
4. To identify participants' baseline characteristics and cultural determinants that predict primary and secondary engagement outcomes of parents with ParentText.
5. To explore the role of baseline characteristics as potential moderators of the effectiveness of the intervention components on primary and secondary engagement outcomes.
6. To identify participants' characteristics that moderate the effect of behavioral intention on primary and secondary engagement outcomes.
7. To explore the role of baseline characteristics as potential moderators of the effectiveness and cost-effectiveness of intervention components on parent and adolescent behavioral, mental health, and educational outcomes assessed at baseline and 6 weeks after the baseline.
8. To qualitatively explore parents' perceptions of challenges in engaging with ParentText and their perception of the most feasible and acceptable components and component levels for its implementation in South Africa.
9. To identify the incremental cost of adding each of the component levels in the ParentText implementation package.
10. To select the most effective and cost-effective combination of components and component levels to be tested further in a randomized controlled trial in 2024.

Trial Design

Overview

This study design was derived from the multiphase optimization strategy framework developed by Collins [52], which consists of 3 stages: preparation, optimization, and evaluation. In the multiphase optimization strategy, intervention optimization is the process of evaluating and identifying from a set of intervention components the combination with the most effective and scalable design that can be obtained subject to existing constraints such as limited financial and human resources [49]. The preparation phase of this study took place between October 2022 and February 2023. It comprised a formative evaluation with stakeholders from government and nongovernmental organizations (NGOs) in South Africa. The findings of this phase informed the selection of the intervention components for inclusion in this trial.

The ParentText Optimisation Trial will be conducted from August 21, 2023, to November 10, 2023, in Mpumalanga, South Africa. It will use a 2 × 2 cluster-randomized experimental design to investigate the effectiveness and cost-effectiveness of two components delivered externally from the ParentText chatbot: (1) in-person sessions with parents and adolescent girls (1 or 4 sessions) and (2) facilitated WhatsApp support groups with parents (yes or no). All caregivers and adolescent girls will be onboarded to ParentText in the in-person session (the first session for those assigned to receive 4 in-person sessions). The 2 × 2 factorial trial will include four experimental conditions (Table 1):

1. Condition 1: ParentText chatbot and 1 in-person session (onboarding to ParentText) with parents and adolescent girls
2. Condition 2: ParentText chatbot, 1 in-person session (onboarding to ParentText) with parents and adolescent girls, and facilitated WhatsApp groups for parents
3. Condition 3: ParentText chatbot and 4 in-person sessions (with the first session focused on onboarding to ParentText) with parents and adolescent girls
4. Condition 4: ParentText chatbot, 4 in-person sessions (with the first session focused on onboarding to ParentText) with parents and adolescent girls, and facilitated WhatsApp groups for parents

The study will randomly assign 32 clusters split equally (n=8 clusters) across the 4 different treatment conditions. A total of 1920 parents and their adolescent girls aged 10 to 17 years (approximately 60 parents and 60 adolescent girls per cluster) will be recruited to participate in the study. Each cluster will be randomly assigned a dedicated community-based facilitator to deliver the in-person and WhatsApp support group sessions. The study will adopt a between-cluster assignment to prevent contamination across experimental conditions.

Table 1. Experimental conditions for a 2 × 2 factorial trial (n=32 clusters, n=60 parent-adolescent dyads, and N=3840 participants).

Condition	Clusters[a] (n=32), n (%)	ParentText (always on)[b]	In person (1 session vs 4 sessions)[c]	WhatsApp groups (yes vs no)[d]
1	8 (25)	On	1	No
2	8 (25)	On	1	Yes
3	8 (25)	On	4	No
4	8 (25)	On	4	Yes

[a]*Cluster* refers to parent and adolescent groups linked to a designated facilitator.

[b]*Always on* refers to the provision of the chatbot without any external support.

[c]Parents and adolescent girls will receive either 1 or 4 in-person sessions.

[d]Parents will either receive (yes) or not receive (no) facilitated WhatsApp groups.

Primary Hypotheses

The primary hypotheses are as follows:

1. Facilitated WhatsApp support groups (yes or no): we hypothesize that parents receiving the ParentText delivery package combined with web-based support via WhatsApp groups will have higher engagement rates than those receiving the ParentText delivery package without facilitated support via WhatsApp groups.
2. In-person sessions (1 or 4 sessions): we hypothesize that parents receiving the ParentText delivery package combined with 4 in-person sessions will have higher engagement rates than those receiving the ParentText delivery package with 1 in-person session.
3. Incremental cost-effectiveness: we hypothesize that, while the inclusion of facilitated WhatsApp groups will be more cost-effective than not including facilitated WhatsApp groups based on the incremental cost advantage, the higher dosage of in-person sessions will not be a cost-effective component.

Secondary Hypotheses

The secondary hypotheses are as follows:

1. Behavior outcomes: we hypothesize that the most intensive combination of component levels will have the greatest effect on parent and adolescent behavioral, mental health, and education outcomes.
2. Cultural determinants: we hypothesize that cultural determinants (perceived ease of use, perceived usefulness, hedonic motivation, habit, price value, and social influence) will be associated with more favorable intentions to engage with ParentText.
3. Behavioral intention: we hypothesize that more favorable intentions to engage with ParentText will lead to higher primary and secondary engagement rates.

The positive directionality of the effects of the 2 intervention components on engagement outcomes will be preferred in this study due to evidence of the positive impact of engagement boosters in parenting interventions [53,54]. No hypotheses will be made a priori for potential moderators of effectiveness or cost-effectiveness.

Methods

Study Setting

The ParentText Optimisation Trial is nested within a larger project implemented by mothers2mothers (m2m), a South African NGO, as part of their Children and Adolescents Are My Priority (CHAMP) program funded by the US Agency for International Development and the President's Emergency Plan for AIDS Relief. The study will be conducted across 2 districts in Mpumalanga Province—Ehlanzeni (mostly rural zones) and Nkangala (rural and periurban zones)—where CHAMP was implementing the orphaned and vulnerable children program or Determined, Resilient, Empowered, AIDS-free, Mentored, and Safe (DREAMS) family-strengthening interventions to approximately 28,500 adolescent women and girls (aged between 10 and 17 years) and their caregivers in 2023. The primary home languages spoken by participants include English, isiZulu, and siSwati. The CHAMP program delivers a portfolio of age-specific, needs-based interventions aimed at reducing HIV and AIDS incidence among orphaned and vulnerable children, adolescents, and their families in communities across the province. A key component of CHAMP includes evidence-based interventions to decrease family violence and improve health and social outcomes for orphaned and vulnerable children and adolescents, such as the PLH program.

Eligibility Criteria

Participants recruited for this trial will be parents, adolescent girls, and implementing facilitators.

Eligible clusters are communities with at least 60 households with a resident adolescent girl aged between 10 and 17 years and assigned to an m2m CHAMP implementer. Each implementer will be responsible for 60 households.

Eligible parents are those (1) aged ≥18 years and who are English, isiZulu, or siSwati speakers; (2) currently caring for an adolescent girl aged between 10 and 17 years; (3) living in the same household with the adolescent girl for a minimum of 4 nights a month over the previous 3 months; (4) having access to a mobile phone compatible with WhatsApp; (5) willing to enroll in the ParentText chatbot and receive messages via WhatsApp; and (6) who provide written informed consent to participate in the full study.

Eligible adolescents are (1) female teenagers aged between 10 and 17 years who (2) have a parent enrolled in the trial and (3) have provided written informed assent to enroll in the full study.

Eligible facilitators are (1) m2m CHAMP implementers in Mpumalanga aged ≥18 years who (2) have completed a workshop training for program delivery before the trial; (3) have a mobile phone compatible with WhatsApp and access to the internet or a data bundle; (4) speak English, isiZulu, or siSwati; and (5) have provided written informed consent to participate in the trial.

Parents with a severe learning disability or those exhibiting acute mental health disorders will be excluded due to their limited capacity to provide informed consent. Parents whose child refuses to participate in the study will not be excluded to prevent threats to internal validity. Children who have healthier relationships with their parents could be more interested in participating in the study; thus, this could lead to selection bias.

Informed Consent

Trained m2m program facilitators will collect informed consent from adults and informed assent from adolescents before the baseline at local schools in communities where the study is taking place (Multimedia Appendices 1 and 2). Informed consent and assent forms will include clear descriptions of the intervention, study objectives, use and protection measures for participant data, and participant rights to refuse to respond to survey questions or withdraw at any point from the study. Adolescents' participation will be conditional on their parents providing consent. Adults and adolescents who agree to participate in the intervention will be invited to sign a paper-based informed consent form to indicate their consent. Participants will also receive a hard copy of information sheets, which include contact details of the local research team and ethics board.

Additional Consent Provisions for Collection and Use of Participant Data

Parents and adolescents will be required to have provided informed consent to participate in the CHAMP project before recruitment to the study.

Interventions

Intervention Description

The core parenting intervention component will be ParentText, a chatbot that delivers personalized and gamified scheduled and on-demand messages through text, audio, and visual media based on development stages for parents of children aged 0 to 23 months, 2 to 9 years, and 10 to 17 years. Previous research has reported the acceptability and feasibility of ParentText in LMICs. A qualitative formative research study in Jamaica reported an average participant (ie, parents) engagement length of 14 days throughout the 37 days of the intervention [43]. The version of the program targeting those aged 10 to 17 years will be used in this study in alignment with the age group of adolescent girls targeted by the CHAMP program. ParentText was originally developed by the UK-based charities PLH and Innovations in Development, Education, and the Mathematical Sciences (IDEMS) International in collaboration with the United Nations Children's Fund (UNICEF); the Universities of Oxford and Cape Town; and Clowns Without Borders South Africa (CWBSA), one of the local partners, to ensure linguistic, cultural, and contextual relevance. The main program content was derived from the PLH for Parents and Teens program, a 14-session in-person intervention developed and tested in a cluster-randomized controlled trial in South Africa [55]. Additional content was included to support adolescent mental health (UNICEF's Helping Adolescents Thrive program [56]), adolescent educational outcomes (the LEGO Foundation's learning through play resources [57]), and gender-based violence prevention (No Means No Worldwide). All content was translated into isiZulu and siSwati and reviewed by parenting experts who were fluent in the 2 languages.

ParentText messages are grouped into nine positive parenting goals: (1) *improve my relationship with my teen*; (2) *understand teen development*; (3) *support my teen's education*; (4) *create structure for my teen*; (5) *improve my family's finances*; (6) *care for my teen's well-being*; (7) *manage my teen's behavior*; (8) *keep my teen safe*; and (9) *have a healthy relationship with my partner*, the latter only delivered to parents who have indicated that they are in a partnered relationship. Each goal is supported by learning modules (37 in total) designed to build parent interpersonal skills through comics, videos, and text illustrating key parenting tips. ParentText also includes internal components to support user engagement, such as gamification (eg, earning badges toward goals), personalization (eg, male and female videos), and activities (eg, quizzes). Participants can select the order of goals based on their preferences after completion of the first goal (*improve my relationship with my teen*).

The goal *improve my relationship with my teen* "improve my relationship with my teen" (Table 2) will provide content on how to spend one-on-one time with the teenager and techniques to praise the adolescent and talk about feelings. For the goal "understand teen development," parents will complete modules related to understanding teenage mental, social, and physical changes. The goal "support my teen's education" will deliver content related to creating a fun and positive environment to support the teenager's academic learning process. Parents will learn skills to create a routine for teenagers and establish rules for the goal "creating a structure for my teen." The goal "improve my family's finances" will equip parents with budgeting skills through lessons related to savings and expenses. The goal "show kindness to your teen" will deliver content related to identifying and managing stress signs and techniques for supporting adolescents. For the goal "keep my teen safe," parents will receive content related to building skills to manage teenagers' misbehavior and help keep their adolescents safe in the community and relationships. Finally, parents who report being in a relationship will receive additional content on how to be supportive, solve conflicts in a relationship, and share responsibilities. The number of assigned modules will vary based on the age of the child and the number of goals but will be up to a total of 37, or 32 for nonpartnered parents.

Participants will be enrolled in the intervention for 6 weeks. Participants who enroll in the hybrid format of the program will also participate in 6 weekly WhatsApp live support sessions and 3 biweekly sessions of the in-person program subject to the

study components available to their cluster. Parents will participate in the intervention by interacting with ParentText and completing each of the 37 modules and 9 goals sequentially. All goals and modules will be available to parents from the moment they enroll in the parenting chatbot. The goal "Have a Healthy Relationship with my Partner" will only be available for parents who reported being in a relationship. The order in which parents choose to access the goals will not be relevant because the goals were not developed to be interdependent. Adolescents will not interact with the chatbot but will experience the program through voluntary participation in the home practice activities of their parents.

The implementation will follow a group-based format that includes 3 joint parent-and-teenager sessions on (1) emotional check-in and mindfulness-based exercises to reduce stress, (2) feedback activity on participants' experience with ParentText, (3) core lesson supported by illustrations, (4) collaborative discussion problem-solving, and (5) practice of skills at home. Participants will be trained on skills such as family budgeting, widening circles of support, and keeping safe in the community and in relationships. WhatsApp live chat group sessions will only include text messages. The session will include (1) a welcome and check-in message sent by the m2m facilitator, (2) sharing success (parents will be encouraged to share a positive experience when trying one of the ParentText skills with their teenagers), (3) fun activity that parents will be encouraged to replicate after with their teenagers (eg, a dance move), (4) sharing challenges (challenges faced by parents when trying a new skill with their child), and (5) collaborative discussion problem-solving.

Table 2. Intervention modules—ParentText content.

Goal	Number of modules	Justification
Improve my relationship with my teenager	3	A stronger parent-child relationship is associated with lower levels of conflict and violence in families [58].
Understand teenager development	3	Parents who understand the development of an adolescent's sexual and reproductive health are better equipped to create a safe and supportive environment for them. Parental monitoring, communication, and support are vital in sexual violence and VAC[a] prevention [59].
Support my teenager's education	5	Research suggests that parents who are involved in their adolescents' education help provide a positive school environment by promoting the love for learning [60].
Create structure for my teenager	4	Rulemaking can decrease disputes between parents and their children. When parents set rules, they can protect their children from harmful acts or behaviors that may result in abuse by other adults [61].
Manage my teenager's behavior	4	Managing adolescents' behavior prevents later involvement in risky behavior, such as substance use, violence, later delinquency, and conduct problems [62].
Care for my teenager's well-being	4	Listening actively helps adolescents feel heard, understood, less alone, and calmer. In contrast, if parents do not listen to and support their adolescents properly, this can leave them feeling defensive, frustrated, alone, or hurt [63].
Keep my teenager safe	4	Adolescents are at a higher risk of becoming victims of crime than any other age group [64].
Have a healthy relationship with my partner	5	Fatherhood programs that encourage fathers to be more engaged in caregiving and parenting show hopeful findings in terms of reducing VAC and IPV[b] [65].
Improve my family's finances	4	According to the family stress model, financial problems increase parents' stress and depression, which in turn increases harsh parenting practices and child maltreatment [66].

[a]VAC: violence against children.

[b]IPV: intimate partner violence.

Tested Intervention Components

Intervention Component 1: In-Person Sessions

This trial will examine whether varying frequency of in-person human support significantly affects user engagement with the chatbot. In-person parenting programs come with the costs of training facilitators and commonly present limited community resources and infrastructure for their delivery [21]. Of the variants of human support selected for this trial, the in-person component requires a greater allocation of resources. Nevertheless, there is great value in understanding how much of the in-person component is necessary to bolster engagement in chatbot-led public health interventions. Proponents of remote support tools argue that including social networking as a tool to support participants is associated with greater engagement rates [67,68]. In supported digital interventions, participants receive technical and clinical troubleshooting assistance to bolster engagement [69]. Previous studies have reported that the frequency with which participants interacted with a counselor or clinician coach predicted their adherence to digital health interventions [67,70].

This study will compare the differential effects of delivering either 1 or 4 in-person group-based sessions to parents and their adolescents (maximum of 60 families per group). Each session will be delivered by an m2m CHAMP lead facilitator and a cofacilitator and last approximately 2 hours.

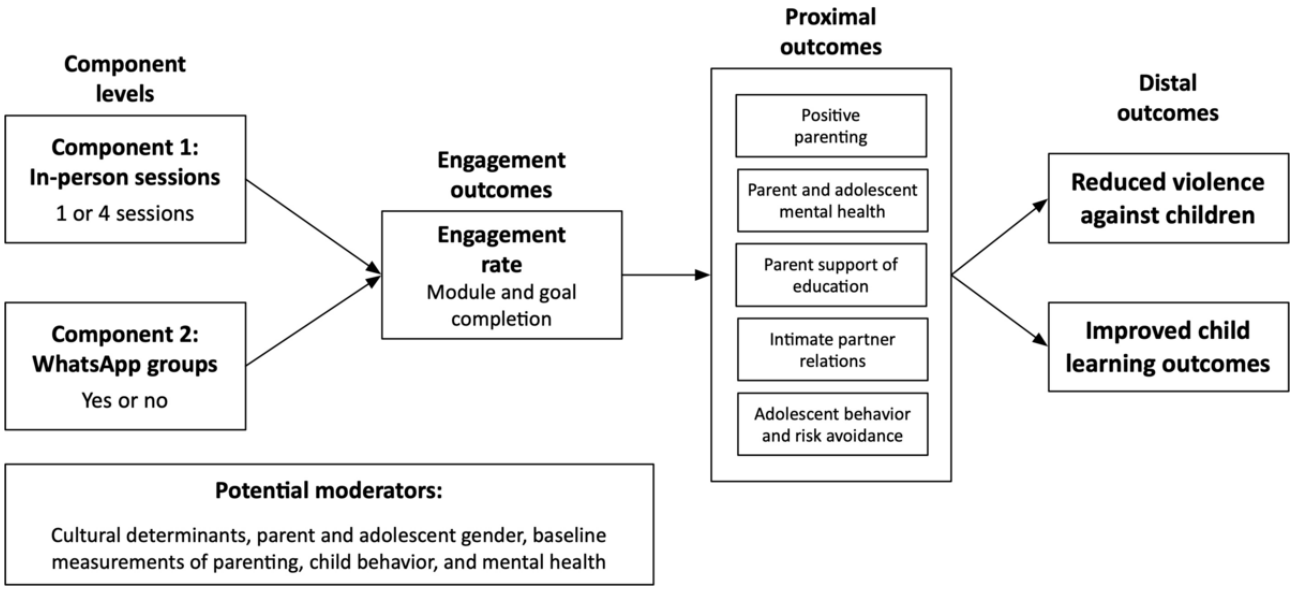
Intervention Component 2: Facilitated WhatsApp Support Groups

This study will also test the impact of facilitated WhatsApp support groups on user engagement in the ParentText chatbot intervention. Self-guided interventions present greater scope for scalability due to the low allocation of financial and human resources required. However, low engagement rates risk their sustainability over time. Although including engagement boosters is a common practice in parenting programs to increase parent engagement [53,54], their effectiveness in increasing engagement has been challenged in previous studies. Day and Sanders [71] found that parents benefited from phone support when completing the Triple P Online self-guided parenting program. Parents in the practitioner-supported condition engaged more with the program, completing more modules and reporting greater program satisfaction [71]. However, Epstein et al [72] found that providing opportunities for parents to interact via Facebook groups while participating in a self-directed family intervention did not increase engagement or improve parenting practices.

In this study, 6 one-hour WhatsApp support groups will be delivered to participating parents (maximum of 60 participants) by a trained m2m CHAMP facilitator. The facilitator will lead and monitor discussions and respond to any questions parents raise about technical troubleshooting and the content of the chatbot. At the end of the fifth WhatsApp group session, participants will be asked to select 2 peer leaders who will assume the responsibility of moderating the group after the sixth session.

As shown in Figure 1, the study components will contribute to increased engagement rates (eg, the number of modules and home practice activities completed within the parenting chatbot) among participants. Higher engagement rates will lead to more positive parenting practices and parent-teenager relationships, resulting in improved mental health and education outcomes for teenagers. Engagement with the chatbot will also contribute to improved intimate partner relationships and lead to positive mental health outcomes for parents. The sustainment of proximal outcomes will lead to a healthier environment within the household and contribute to reduced VAC and improved child learning outcomes.

Figure 1. ParentText Optimisation Trial conceptual model.



Training of Facilitators

m2m staff will be trained as program facilitators by certified trainers from CWBSA, a South African NGO with vast expertise in leading PLH program training. Training will occur over 2 days lasting a total of 12 hours. In total, 4 separate intervention manuals were developed to create a standardized delivery of the sessions based on condition allocation (ParentText+onboarding; ParentText+onboarding+WhatsApp support group; ParentText+onboarding+WhatsApp support group+3 in-person sessions; ParentText+onboarding+3 in-person sessions).

Criteria for Discontinuing or Modifying Allocated Interventions

Adult and adolescent participants will have the right to decline any assessment or participation at any time during the study. Participants can opt out of receiving ParentText messages at any point by typing "EXIT" or simply by not responding to the messages. The decision to withdraw from the study will not affect a participant's entitlement to other services or result in any penalty. Data collected through paper-based surveys and in-built assessments will be retained unless participants request otherwise.

Strategies to Improve Adherence to the Intervention

Internet bundles (50 ZAR [approximately US $2.60] per person) will also be provided to support engagement with ParentText regardless of intervention condition allocation. Additional data bundles will also be provided to those allocated to participate in WhatsApp support groups.

Relevant Concomitant Care Permitted or Prohibited During the Trial

Participants will not be prevented from receiving other care or services during the trial period.

Provisions for Posttrial Care

Safeguarding procedures will be used to mitigate risks to participants. There is a possibility of participants disclosing violent practices toward their children, their partners, or themselves. The informed consent form indicates that some information regarding harmful behaviors will be disclosed without the participant's consent if they pose a danger or harm to themselves or their family members. Participants at risk will be referred to local child welfare, health organizations, and other social services. Building on UNICEF's safeguarding guidelines, ParentText has been designed to recognize high-risk keywords such as "trouble," "SOS," "ill," "anxiety," and "fire" in free-text fields. Participants can also type "HELP" to receive troubleshooting messages. The chatbot will respond to participants' disclosure of dangerous situations automatically in an empathetic and empowering manner. It will also provide referral contacts localized in Mpumalanga to offer support to participants who are in danger of being harmed. All supporting services available for participants were identified by m2m and implementing teams following a meticulous mapping of local governmental and nongovernmental support systems. Finally, if respondents or their families are determined to have experienced significant harm because of participating in the study (ie, severe abuse, suicidality, IPV, or other potential psychological or physical injuries), we will cease further activities until these issues can be addressed adequately.

Outcomes

Primary and secondary engagement outcomes will be collected through the course of the program implementation from August 21, 2023, to September 8, 2023.

Primary Outcomes: Engagement

The primary outcome related to user engagement is defined as the overall number of modules completed within the ParentText chatbot.

Secondary Outcomes

Engagement Outcomes

Secondary engagement outcomes will include the percentage of modules and goals completed. We will also examine the rate of self-reported completion of home practice activities based on the self-reported intention to do home practice activities. In total, 3 home practice activities will involve actual interaction with the chatbot, which will allow for testing whether users lie about completing home activities when prompted. Additional engagement outcomes will include the number of days users interact with the chatbot, number of triggered safeguarding messages, number of active and passive dropout from the chatbot, number of times users use the menu and option functions, number of times users access learning through play activities and type of activity (ie, calm, active, quick, or group), type of media selected for engagement (ie, text, audio, or video), and goal selected by users after completion of the first goal. For participants in all clusters, we will compute sum scores for each engagement outcome measure for the complete study period. High engagement rates will be defined as values standing at the highest quartile of the averaged engagement score, medium engagement rates will be defined as values at the second or third quartile, and low engagement rates will be defined as values at the lowest quartile.

Adult and Child Behavior Outcomes

Data collection of parent- and adolescent-reported mental health and behavior outcomes will occur at 2 time points: baseline and postintervention. Outcome measurements will be standardized to capture the occurrence of practices and behaviors over the "past month (last 30 days)."

1. *Child maltreatment (adult and adolescent report)* will be assessed using a subset of items from the physical abuse (2 items) and emotional abuse (2 items) subscales of the International Society for the Prevention of Child Abuse and Neglect Child Abuse Screening Tool–Trial Version [73].
2. *Positive parenting (adult and adolescent report)* will be assessed using a subset of items from the positive involvement (3 items), positive parenting (3 items), and parental supervision (3 items) subscales of the Alabama Parenting Questionnaire [74].
3. *Parent support of education (adult and adolescent report)* will be measured using 4 items assessing how often the parent engages the adolescent in behaviors that support learning [75].
4. *Mental health distress (adult and adolescent report)* will be measured using the 4-item Patient Health Questionnaire, which screens for anxiety and depression symptoms [76].
5. *Parenting stress (adult report only)* will be measured using the parental stressors subscale (6 items) of the Parental Stress Scale [77].
6. *Economic strengthening (adult report only)* will be measured using 1 item from the Financial Self-Efficacy Scale [78].
7. *Parent-child communication (adult report only)* will be measured using items adapted from the Parent-Child Communication Scale used in the Fast Track intervention study [79].
8. *Learning through play (adult report only)* will be assessed using a subset of items from the Alabama Parenting Questionnaire, the Parent-Child Communication Scale, and the items on parent support of education [74,75,80]. The selected scales will overarch the learning through play characteristics evidenced in the literature [57,81]. Parents will report the frequency of parent-child engagement [78].
9. *Intimate partner relationships (adult report only)* will be investigated by assessing gender-equitable behavior. Gender-equitable behavior will be measured using items adapted from the core questionnaire in the World Health Organization multicountry study on domestic violence [82] and from questionnaires used in previous violence prevention studies [83,84].
10. *Risk avoidance (adolescent report only)* will be assessed using 4 locally derived items on risk.
11. *Adolescent involvement in decision-making (adolescent report only)* will be assessed to investigate to what extent

adolescents' voices are heard within families regarding decisions affecting their lives. A total of 3 items adapted from questionnaires used in previous research on parent-child engagement in decision-making will be used to assess adolescent involvement in decisions related to their education, daily activities, and money expenditure in the household [85].

12. *Attitude toward punishment (adult and adolescent report)* will be assessed using a single item from the UNICEF Multiple Indicator Cluster Surveys 5 child discipline module [86].

ParentText also includes 1-item questions on parenting stress, parent-teenager interaction and communication, parental monitoring, teenage behavior, and intimate partner relationships that are embedded within the chatbot. These will be assessed both before and 1 week after the completion of each ParentText goal (total: 9 items).

Cultural Determinants of Engagement Outcomes

This study will investigate the cultural determinants associated with user engagement with ParentText through a parent-reported survey administered immediately after the in-person onboarding session. We will use the technology acceptance model 1 scale (16 items) to assess the following constructs: perceptions (ie, knowledge, attitudes, values, and beliefs affecting parents' motivation for engaging with ParentText), enablers (ie, structural factors within society motivating parents' engagement with ParentText, such as access to the internet), and nurturers (ie, the extent to which parents' beliefs and attitudes are influenced and nurtured by their family, friends, and peers) [87]. Hedonic motivation (the perceived enjoyment of using the technology), habit (the extent to which an individual believes the use of a technology to be automatic), price value, and social influence were also included as additional variables to the technology acceptance model 1 due to their potential influence on the relationship between intention to use and engagement [88,89].

Moderators and Covariates

Sociodemographic characteristics (adult and adolescent report) such as age, gender, literacy, disability, and family structure will be assessed at baseline to describe the sample population and investigate whether the intervention and components have differential effects across these subgroups.

Study assessments are summarized in Table 3.

Table 3. Summary of study measures.

	Measurement instrument	Study period			
		Baseline	Onboarding	Intervention	Posttest
Primary engagement outcome					
Number of modules completed	—[a]			✓	
Secondary engagement outcomes				✓	
Percentage of goals and modules completed	—			✓	
Rate of self–home practice activity completion	—			✓	
Total number of interactions	—			✓	
Number of days of interaction	—			✓	
Behavior outcomes					
Child maltreatment	ISPCAN[b] Child Abuse Screening Tool–Trial Version (4 items)	✓			✓
Positive parenting	Alabama Parenting Questionnaire (9 items)	✓			✓
Parent support of education	4 items	✓			✓
Mental health distress	Patient Health Questionnaire (4 items)	✓			✓
Parenting stress	Parental Stress Scale (6 items)	✓			✓
Economic strengthening	Financial Self-Efficacy Scale (1 item)	✓			✓
Parent-child communication	Parent-Child Communication Scale (5 items)	✓			✓
Intimate partner relationships	WHO[c] multi-country study on domestic violence (4 items)	✓			✓
Risk avoidance	6 items	✓			✓
Adolescent involvement in decision-making	3 items	✓			✓
Attitude toward punishment	Multiple Indicator Cluster Surveys (1 item)	✓			✓
Moderators and covariates					
Cultural determinants of engagement	Technology acceptance model 1 (16 items)		✓		
Sociodemographic characteristics and family structure	For example, age, gender, literacy, and disability	✓			
Cost outcomes					
Intervention costs	Staff time and expenditures related to the preparation and delivery of specific intervention components		✓	✓	✓
Qualitative interviews and focus groups	—				✓

[a]The outcome indicated was not collected at the referred time point.

[b]ISPCAN: International Society for the Prevention of Child Abuse and Neglect.

[c]WHO: World Health Organization.

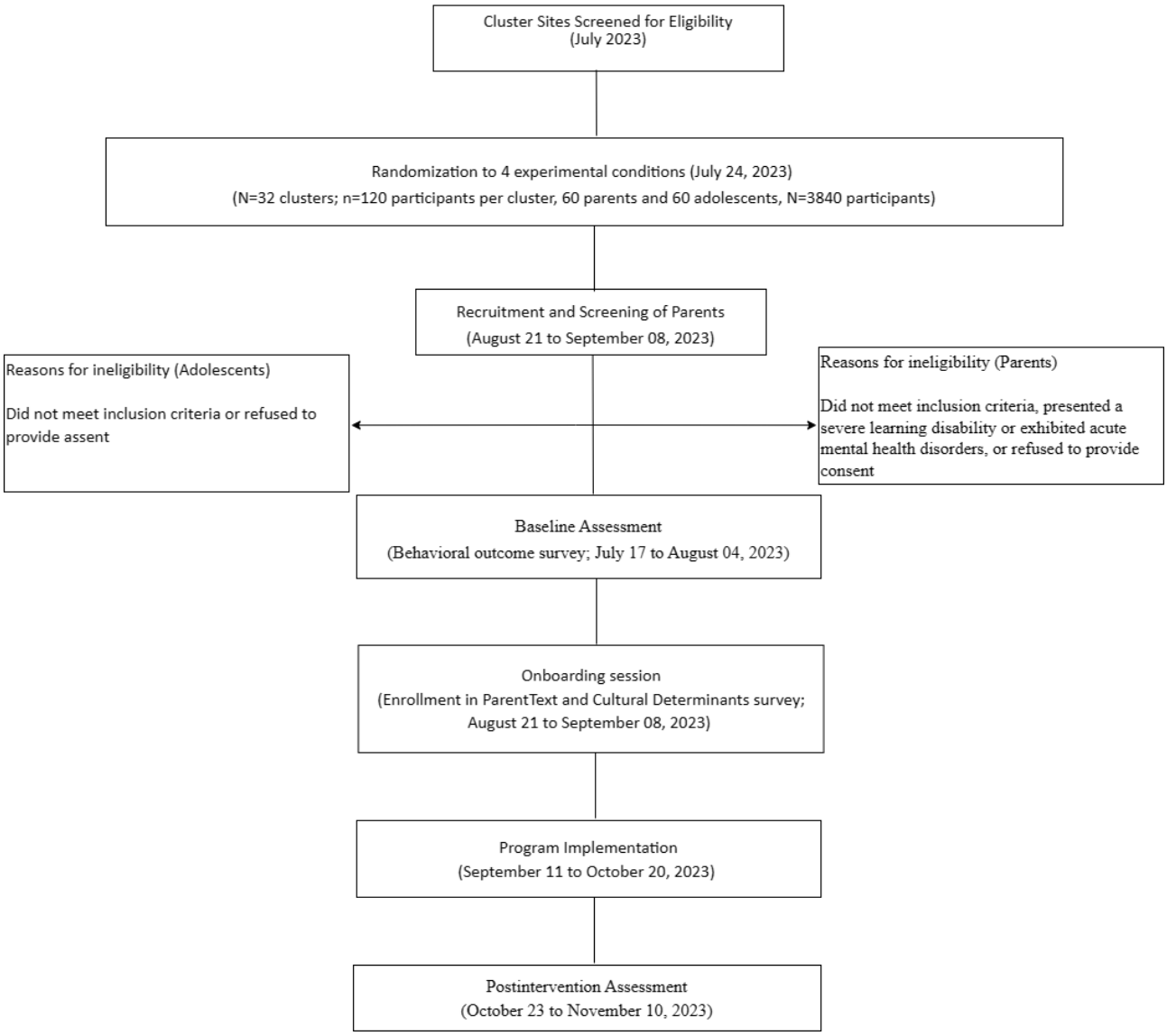
Qualitative Assessment

Qualitative interviews with parents will investigate their overall experiences with the chatbot-led intervention, including the enrollment and interaction process. Questions will probe participants' perceptions regarding the acceptability, usefulness, and cultural relevance of the chatbot, WhatsApp groups, and in-person sessions. Interviews will also explore the perceived impact of the intervention on parenting and family relationships.

Participant Timeline

The participant timeline is summarized in Figure 2. Sampling will be purposive and integrated into m2m CHAMP's current recruitment strategy for the DREAMS project component. Recruitment will proceed until 60 parent-adolescent dyads per cluster are enrolled. Adult and adolescent participants will then be invited to an in-person session that will include (1) informed consent, (2) baseline assessment, (3) onboarding session, and (4) intention to use and cultural determinant survey (August 21, 2023, to September 8, 2023). Parents who complete the baseline assessment will receive a WhatsApp link to connect with ParentText and receive guidance on how to interact with the chatbot. The onboarding session will also include end-to-end testing to ensure that the chatbot functions correctly. Participants will be invited to interact with the chatbot for 5 minutes simulating a real-world interaction. They will then be asked to complete a paper-based assessment to collect their behavioral intention to use ParentText and cultural determinants. Depending on their assignment condition, parents will also be invited to join a facilitated WhatsApp support group or attend additional in-person sessions with their adolescent girls. The ParentText messages will be sent daily to parents via WhatsApp regardless of assignment condition. Data collectors will conduct posttest assessments approximately 6 weeks after the baseline (October 8-27, 2023). Follow-up assessments beyond the postintervention end point will not be conducted.

Figure 2. Study flow diagram.



Sample Size

The study has a fixed sample size by design with 32 clusters of equal size and equal treatment allocation across intervention arms. Sensitivity power analysis was conducted to estimate the minimum detectable effect size of the selected components on engagement and on behavior outcomes. Assuming a 2-sided test at the 10% level of significance varying the power (0.9 and 0.8) and the intracluster coefficient (0.02, 0.05, and 0.10), the minimum detectable effect ranges between a mean difference of 0.168 and 0.298 (80% power) and between a mean difference of 0.197 and 0.351 (90% power).

Recruitment

Recruitment of participants will be based on purposive sampling relying entirely on 32 m2m CHAMP implementers and previous

enrollment in the CHAMP program. CHAMP implementers will screen parents and their children to verify their eligibility for the trial. If required, recruitment will include peer-to-peer referrals in the community through respondent-driven sampling. Recruitment will proceed until 60 parent-adolescent dyads per cluster are enrolled. Participants will then be invited for a baseline assessment with trained data collectors where they will provide full written consent and complete the baseline assessment.

Assignment of Interventions: Allocation

Sequence Generation

This study will adopt a cluster randomization procedure with allocation stratified by district using a parallel design. Cluster randomization will be stratified by facilitators and occur before the baseline assessments (12 clusters from Nkangala and 20 from Ehlanzeni). Random allocation will be conducted by the off-site research team in the United Kingdom using the Excel (Microsoft Corp) function "=Rand()." The in-country research team will assign clusters to 1 of the 4 experimental conditions (32 total clusters, 120 participants per cluster; 60 parents and 60 adolescent girls; N=3840 total participants). Using a 2 × 2 factorial design, this trial will randomly assign clusters so that parents receive the following engagement packages:

1. Engagement package 1: ParentText plus onboarding session for parents and adolescents led by an m2m facilitator
2. Engagement package 2: ParentText plus onboarding session for parents and adolescents and 6 moderated WhatsApp group sessions for parents only led by an m2m facilitator
3. Engagement package 3: ParentText plus onboarding session plus 3 in-person sessions for parents and adolescents and 6 moderated WhatsApp group sessions for parents only led by an m2m facilitator
4. Engagement package 4: ParentText plus onboarding session and 3 in-person sessions for parents and adolescents led by an m2m facilitator

Concealment Mechanism

Participants within a specific cluster and treatment condition will not be aware of the allocation of other clusters due to the geographical distance between clusters and lack of communication across groups.

Implementation

Participants will be recruited in blocks of 32 clusters linked by m2m. Households will be randomly selected from the assigned communities, and recruitment will proceed until 60 households are recruited in each block of 32 clusters.

Assignment of Interventions: Blinding

Who Will Be Blinded

Due to the nature of the intervention, CHAMP facilitators, research assistants, and participants will be aware of condition allocation (based on cluster assignment). The range of conditions and allocation status of other enrolled clusters will be concealed from participants to reduce the risk of contamination. Trial statisticians conducting analyses on postintervention effects will be blinded to the assignment condition of clusters.

Procedure for Unblinding if Needed

This is not applicable for this study.

Data Collection and Management

Plans for Assessment and Collection of Outcomes

This study will include quantitative and qualitative procedures for data collection. Data collected will consist of pretest-posttest parent and adolescent behavior questionnaires, parent cultural determinants of engagement, digitally tracked engagement data, and facilitator process data. All data will be collected using paper-and-pen forms. Individual semistructured interviews will be conducted to further explore participants' engagement with ParentText and observed behavior outcomes.

Quantitative Data Collection

Baseline and Postintervention Surveys

Parent and adolescent behavior outcome surveys will be administered at baseline and the postintervention time point. Data collection will occur at the household level or at a meeting venue at the designated DREAMS schools. Data collectors will be 32 CHAMP implementers fluent in written English, isiZulu, or siSwati trained in ParentText delivery and study procedures such as interview techniques, research ethics, safety protocol, data management and security, informed consent, and adverse event report procedures. CWBSA and local researchers will conduct training and supervision of data collection. All measures, interview guides, workshop modules, and ParentText content will be translated from English into isiZulu and siSwati. Considering potential low literacy levels among some participants, data collection staff will read out the survey questions and response options, and participants will follow along. Facilitators will capture all data collected via Open Data Kit–based surveys (Get ODK Inc).

Cultural Determinants of Engagement Surveys

Cultural determinant outcome surveys will be collected at the ParentText onboarding session.

Chatbot Engagement Data

ParentText engagement data will be tracked digitally by the software developers, IDEMS International.

Engagement on Human Support Components

Facilitators will record in-person attendance and WhatsApp group discussion participation of parents enrolled in the cluster to which they were assigned.

Cost Data

Financial and economic costs associated with the resource inputs required to deliver the intervention and the intervention components will be considered in this study. Financial costs are defined as actual expenditures incurred on resource inputs, and economic costs are defined as the market value of all donated and subsidized resource inputs. Intervention costs include facilitator costs such as those associated with their training to deliver ParentText (captured as their time spent attending training sessions) and with preparing and delivering specific intervention components. Physical space used to deliver in-person sessions, as well as expenditures related to travel and

supplies (such as internet data and cell phones), will be audited and valued. Local researchers and coordinators will collect resource use data *inreal time* (ie, alongside the full study trial) via the completion of weekly Open Data Kit–based surveys. Costs related to the development of ParentText and content adaptation and translation will be included as a capital start-up cost. Because the cost analyses will be conducted from the provider perspective, costs incurred by participants (travel expenditure and opportunity costs) will be excluded. While the implementing organization's program monitoring and evaluation costs will be included in cost estimates, broader research activity costs will be excluded.

Qualitative Data Collection

A subsample of parents will be purposively selected and invited via phone for in-person or over-the-phone individual semistructured interviews. Purposive selection will be based on gender and those with low, medium, and high levels of engagement (approximately 5 male and 5 female parents from different age groups). Engagement levels will be operationalized based on quartiles (ie, low engagement=lowest quartile; medium engagement=second and third quartile; high engagement=highest quartile). The subsample size will depend on the heterogeneity and availability of participants. To ensure that the interviews are standardized, interviewers will follow an interview guide developed by the research team. The interviews will be conducted by a trained qualitative researcher with the support of an interpreter. In addition, focus group discussions will be conducted with the implementing partner, m2m, to understand the challenges and opportunities during implementation.

Plans to Promote Participant Retention and Complete Follow-Up

To promote retention in the chatbot, participants will receive badges for each module completed, a trophy for each goal, and a certificate of completion at the end of the program. Participants attending the in-person sessions will be provided with refreshments at each session and receive a certificate of acknowledgment at the end of the fourth session.

Data Management

This study will implement the following data management measures to ensure confidentiality, security, and safety. Per the US Agency for International Development implementation guidance, raw baseline and postintervention data collected will be captured to the Community-Based Intervention Monitoring System database, a South African community-based intervention monitoring system. Zoë-Life, a global training and consulting firm, will assist m2m with the deidentification of the data before they are transferred to the University of Oxford central server via an application programming interface. A Community-Based Intervention Monitoring System or system-generated ID will be assigned to uniquely identify each participant. ParentText engagement data will be automatically stored through end-to-end encryption to an IDEMS International server. During the data merging process, participants will be assigned a unique study code. The data on the University of Oxford central server will be managed by the University of Oxford Global Parenting Initiative data management team with technical support from the University of Oxford Department of Social Policy and Intervention IT team. Hard copies (eg, paper-and-pen questionnaires and participant attendance records of WhatsApp group and in-person sessions) will be stored in locked fireproof storage spaces and be permanently destroyed after being uploaded to a secure web-based data repository managed by the University of Oxford. Consent forms will be retained for at least 3 years after the study is published in compliance with the funders' requirements.

Confidentiality

Anonymized baseline and postintervention data sets will be stored in a password-protected server at the University of Oxford. Access will be controlled and only granted to members of the study team or partnered institutions that aided in the research project. Audio recordings of interviews and focus group discussions will be transcribed verbatim and stored in password-protected devices and will then be securely uploaded and backed up at the University of Oxford server. Once uploaded to the server, audio files will be deleted from the recording devices. After anonymizing and verifying the transcripts, audio recordings will be permanently deleted from data repositories. All Excel and Word (Microsoft Corp) files will be named following a standardized protocol, including the download date, to ease version control. Deidentified interview transcripts and data sets will only be shared by the Global Parenting Initiative data manager by granting access to specific files through the OneDrive for Business at the University of Oxford. Deidentified data sets will be stored securely for perpetuity and use per UK Data Archive guidance [90]. Raw baseline and postintervention data collected will be owned by the m2m South Africa office. Participants' data will be stored by m2m in compliance with the South African Protection of Personal Information Act. IDEMS International will own the raw data collected through ParentText.

Plans for Collection, Laboratory Evaluation, and Storage of Biological Specimens for Genetic or Molecular Analysis in This Trial or Future Use

This is not applicable for this study as no biological specimens for genetic or molecular analysis will be collected.

Data Analysis

Statistical Methods for Primary and Secondary Outcomes

This study will examine the main effects of each component level on user engagement and behavior outcomes**.**

Engagement Outcomes

Baseline differences between groups will be described using proportions, means, and SDs. The main effect of each intervention component and interaction effects between components on primary and secondary engagement outcomes will be estimated using multilevel models (including mixed models if outcomes are continuous, Poisson models if outcomes are counts or count distributed, and logistic models if outcomes are binary). Separate models will be tested using effect coding [91,92]. Each model will specify 3 levels to account for the longitudinal and clustered nature of the data—repeated measures are nested within individuals, which are, in turn, nested within

clusters. Level 1 will include a term for categorical time (pre- and posttest time points) and for the interaction between time and intervention status, level 2 will include terms for individual sociodemographics such as age (parent and adolescent) and gender (parent) and other individual-level covariates centered at the sample mean, and level 3 will include terms for the intervention components and the stratifying factor. Robust SEs will also be estimated to adjust for clustering. This study will report the direction and magnitude of β, incidence risk ratios, and odds ratios at a significance level of $P<.10$ with 90% CIs. Two-tailed tests will be conducted across all analyses.

Behavioral, Mental Health, and Educational Outcomes

The main effect of each intervention component and interaction effects between components on behavioral, mental health, and educational secondary outcomes will be estimated using the same multilevel models and specifying the same levels and structures as with the engagement outcomes. Within-group analyses will also be conducted to examine pretest-posttest differences across the sample accounting for clustering in analyses.

Analysis of Qualitative Data

Qualitative data will be analyzed using NVivo (QSR International) and Word through framework analysis [93]. Qualitative data analysis will be performed simultaneously with quantitative analysis to assess whether qualitative themes generalize to the entire population and expand the understanding of quantitative results. The analysis will include 5 stages: familiarization, identification of themes, indexing, charting and summarization, and interpretation and mapping. Researchers will begin by familiarizing themselves with the transcripts and identifying emerging themes. A code will then be assigned to each theme and subtheme at the indexing stage. After themes are indexed, they will be charted and summarized. Finally, interpretation and mapping will be used to understand the findings more deeply.

Cost-Effectiveness Analysis

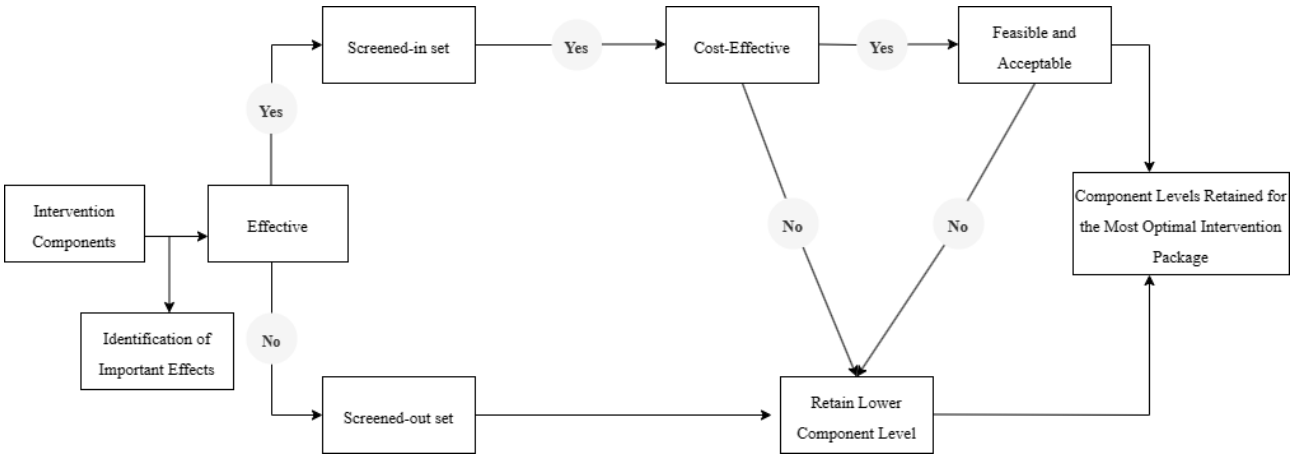
This study will evaluate the efficiency and affordability that results from the expansion or contraction of the ParentText delivery package from the provider's perspective. Program implementation costs and outcome data will be recorded and analyzed in Excel. The total costs of the intervention (setup and operating costs) for each intervention component and the average cost per participant enrolled (unit cost) will be estimated. The trial's primary outcome relates to levels of user engagement (ie, the overall number of modules completed by participants), and this will be used to understand the cost-effectiveness of the intervention components that will maximize user engagement with ParentText. The estimated cost-to-engagement ratio for each of the intervention components will be calculated and compared to assess the incremental cost-effectiveness of each component. All costs will be adjusted to 2023 US dollars using the Consumer Price Index.

Analytical Strategy for Selecting the Most Optimal Intervention Package

We will use the decision-making framework presented by Collins [52] to select the most effective, cost-effective, and feasible components and component levels for inclusion in the optimized intervention before testing in a randomized controlled trial. As shown in Figure 3, the most optimal intervention package will be the one presenting higher effectiveness while considering resource and feasibility constraints. First, the main effects of each component on primary engagement outcomes will be identified and averaged across the other intervention components. Second, intervention components will be divided into a screened-in and screened-out set based on their positive effectiveness on participants' engagement with ParentText. Intervention components with negative or no effect will be included in the screened-out set, and the lower level of that component will not be considered further. Third, intervention components in the screened-in set (ie, those showing positive effects and cost-effectiveness) will be considered for further evaluation. Results from qualitative interviews and focus group discussions conducted with the implementing partner will be used to further understand the feasibility, acceptability, effectiveness, and cost-effectiveness of the retained component levels and draw conclusions to develop the final optimized ParentText delivery package.

The posterior expected value approach will be included in the decision-making process to increase the robustness of our results. In previous research, the posterior expected value approach has modestly outperformed the component screening approach in accuracy, sensitivity, and specificity [94]. Estimates of the posterior expected value for each intervention component will be obtained using Markov chain Monte Carlo methods. We will prefer intervention components with higher Markov chain Monte Carlo posterior distribution of mean outcomes.

Figure 3. Analytical strategy for selecting the most optimal intervention package for evaluation in a subsequent randomized controlled trial.



Interim Analyses

No interim analyses will be conducted.

Methods for Additional Analyses

Exploratory analysis will examine the effect of cultural determinants on parents' behavioral intention to use ParentText. Pearson correlations will be used to determine the relationship between cultural determinants (perceived ease of use, perceived usefulness, hedonic motivation, habit, price value, and social influence) and behavioral intention toward ParentText use. Multiple regression analysis will be used to investigate the strength of the association between cultural determinants and behavioral intention and between behavioral intention and primary and secondary engagement outcomes. Predictive models will be used to investigate how behavioral intention predicts parents' primary and secondary engagement outcomes.

Moderation Analyses

In addition, the study will use regression analysis and multilevel regression models to investigate the following: (1) which adult baseline characteristics moderate the effect of the intervention components on primary and secondary engagement outcomes and (2) which adult baseline characteristics moderate the effect of the intervention components on parent and adolescent behavioral, mental health, and educational outcomes.

Methods in Analysis to Handle Protocol Nonadherence and Any Statistical Methods to Handle Missing Data

Quantitative data analysis will be conducted on an intention-to-treat basis. Missingness will be inspected before analysis and addressed via multiple imputation techniques. Multiple imputation by chained equations will be favored to estimate item-level missing data when response patterns allow for estimation. Multiple imputation by chained equations allows more complex models involving moderations and multiple levels of mixed modeling to be accounted for.

Plans to Give Access to the Full Protocol, Participant-Level Data, and Statistical Code

This research protocol and all components of this research, including but not limited to publications, fully anonymized data sets, data analysis plans, and code, will be available to the public at the Open Science Framework on an access-upon-request basis.

Oversight and Monitoring

Composition of the Coordinating Center and Trial Steering Committee

A Trial Steering Committee (TSC) has been assembled and includes international experts with vast experience in experimental and implementation research and VAC prevention. The TSC will meet twice a year and at key study implementation time points (eg, after final data analyses) to ensure that the study is being conducted with rigor and respond to any arising issues associated with participant safety and study conduct.

Composition of the Data Monitoring Committee and its Role and Reporting Structure

The research team, including the principal investigators, research assistants and coordinators, and data managers, will monitor the full life cycle of data management, such as baseline and posttest collection, curation, storage, and analysis. Data quality checks will be conducted by creating a survey monitoring checklist to track errors (eg, wrong name in participant ID list, duplicated data entries, noneligible participants, and survey answers submitted incorrectly).

Adverse Event Reporting and Harms

Safeguarding strategies for each stage of this trial were created based on the universal principles of research ethics, respect, beneficence, and justice. The local research team will be trained on the safety protocol developed for this study. The local partner, m2m, also has a child safeguarding policy complying with the South African child welfare and protection legislation [95]. The policy includes guidelines for reporting suspected child abuse and exploitation. All m2m employers, partners, and other representatives have a duty to respond immediately (within 24 hours) to any allegations of child abuse and exploitation. They are trained to minimize risks and prevent harm to children.

Participants will be informed that ParentText is an entirely self-guided chatbot. However, building on UNICEF's safeguarding guidelines, ParentText has been designed to recognize high-risk keywords such as "trouble," "SOS," "ill," "anxiety," and "fire" in free-text fields. The chatbot will respond to participants' disclosure of dangerous situations automatically

in an empathetic and empowering manner. It will also provide referral contacts localized in Mpumalanga to offer support to participants who are subject to being harmed. There is a possibility of participants' disclosure of violent practices toward their children, their partners, or themselves. The informed consent form indicates that some information regarding harmful behaviors will be disclosed without the participant's consent if they pose a danger or harm to themselves or their family members. Weekly supervision meetings with all qualitative project staff members will discuss issues that arise concerning harm to research participants and children. Finally, if we determine that respondents or their families have experienced significant harm because of participating in the study (ie, severe abuse, suicidality, IPV, or other potential psychological or physical injuries), we will cease further activities until these issues can be addressed adequately.

Frequency and Plans for Auditing Trial Conduct

Given that the intervention is being led by an external partner, trial conduct audits will be mainly processed by m2m. Deem it necessary, before any necessary actions or modifications affecting the implementation course of this intervention, m2m will communicate and seek advice from the TSC.

Plans for Communicating Important Protocol Amendments to Relevant Parties (eg, Trial Participants and Ethics Committees)

Any significant modifications to this protocol version 1.0 (August 7, 2023), including changes to objectives; design; recruitment; and data collection, storage, and analysis, will require a formal amendment. Modifications will be submitted for consideration and approval to the TSC and approved by the respective institutional research ethics committees. Minor administrative modifications not affecting the methodology described in this manuscript will be documented and reported to the TSC and ethics committees.

Ethical Considerations

Ethics approval for this study was granted by the University of Cape Town Centre for Social Science Research Ethics Committee (reference: CSSR 2023/05), the University of Oxford Social Sciences and Humanities Interdivisional Research Ethics Committee (reference: R88177/RE001), and the Mpumalanga Department of Health and Department of Social Development (reference: R69569/RE003). Before the baseline assessments, participants will be asked to provide written informed consent by trained assessors under the supervision of the local research team. Participants assigned to facilitated WhatsApp groups will receive data bundles of 50 ZAR (approximately US $2.60) per person and a certificate of completion at the end of the sixth session. Study retention will be promoted by providing each parent and adolescent with 60 ZAR (approximately US $3.21) per person at each assessment point. Participants will be informed of any potential risks related to their participation in the trial and have the ability withdraw from the study without affecting any entitlement to other services or result in any penalty system. Deidentification of the data will be conducted before analysis and storage.

Results

Overview

The results of this study will be disseminated through publications in peer-reviewed journals, webinars, and conferences in South Africa and worldwide. Authorship of publications emerging from this study will adopt the recommended guidelines of the International Committee of Medical Journal Editors [96]. Brief reports containing relevant information and recommendations will also be created for stakeholders within NGOs, public health, and social care services in South Africa. Researchers will also provide verbal reports to local participants through local community meetings to help disseminate findings. Participant-identifiable details will be omitted in all research dissemination processes. The dissemination approach will provide the opportunity for early-career researchers and South African partners involved in this study to publish and present findings.

Trial Status

Recruitment for the ParentText Optimisation Trial will begin on August 21, 2023, and is anticipated to continue until September 8, 2023. Baseline data collection will start on August 21, 2023, and is expected to be completed by September 8, 2023. This is the protocol version [1] of August 22, 2023.

Discussion

Expected Findings

Chatbot-led public health interventions offer a promising opportunity to scale up parenting programs in LMICs. However, it is crucial to understand the key pillars of user engagement to ensure their effective implementation. The ParentText Optimisation Trial is the first study to rigorously test engagement with a chatbot-led parenting intervention in an LMIC. This study brings a novel perspective to the research field of digital health interventions as it investigates the impact of engagement boosters associated with human support and the role of cultural determinants of health in designing a chatbot-led public health intervention. Moreover, the results that emerge from this trial will provide recommendations to enhance the development and delivery of interventions tailored for populations in LMICs. The identification of a context requiring lower resources and presenting higher acceptability and feasibility will enable the scale-up of digital public health interventions and support governments in improving populations' health and addressing health inequalities.

Acknowledgments

The authors are grateful to mothers2mothers South Africa for the superb support provided by their Children and Adolescents Are My Priority program team led by Clever Mubuyayi, Dlalisile Lekhuleni, and Boitumelo Buthelezi in preparation for data collection

and intervention delivery. Similarly, the authors extend their appreciation for their partners Zoë-Life South Africa, Dewald Heath, Nokuthula Heath, and Nompumelelo Mathonsi for facilitating the data management process in this study. They would also like to thank their Trial Steering Committee for their ongoing guidance. Finally, they thank their funders for making this study possible. This study is part of the Global Parenting Initiative, which is funded by the LEGO Foundation, Oak Foundation, World Childhood Foundation (16191), The Human Safety Net, and the UK Research and Innovation Global Challenges Research Fund (ES/S008101/1). Funding for the implementation of the ParentText Optimisation Trial was provided by the United States Agency for International Development (72067418CA00026). The sponsor and funders did not influence any stage of the study design and will not be involved in any stage of the study execution, data analysis, and dissemination of the results.

Data Availability

No data sets or analysis were generated during the development of this manuscript as the research trial is still in the initial stage and no data have been collected at this point.

Authors' Contributions

JML and HG are the principal investigators of the study. MGA led the conceptualization and writing of this protocol. All authors contributed to the conceptualization, development, and writing of this manuscript. MGA, JML, FG, PZ, FC, GJMT, IV, and SV provided critical input in the selection of the quantitative measures in this study. HG led the development of the qualitative measures. SV, GJMT, and JML proposed power simulation and contributed to the proposed research design and statistical analysis. PZ, DS, CF, and LM developed the content for the chatbot. KB and ND contributed to the development of the cultural adaptation of the intervention. All authors provided critical feedback on the manuscript and approved the final version. Authorship in this study will follow the International Committee of Medical Journal Editors guidelines.

Conflicts of Interest

ParentText, the primary intervention in this study, was developed and implemented by members of the research team. JML is the chief executive officer of the Parenting for Lifelong Health (PLH) charity. The intellectual property of the intervention is licensed by the PLH charity under a Creative Commons Attribution 4.0 International license (CC BY 4.0). MGA, JML, FG, FC, IV, SV, HS, PZ, LM, and GJMT currently work on other studies by PLH, and the University of Oxford receives research grants to support this work. The investigators will not benefit from any financial gains from implementing and disseminating this intervention. ND and KB work for Clowns Without Borders South Africa, a South African–based nonprofit organization responsible for providing capacity training and technical support on the delivery of PLH programs in Africa.

Multimedia Appendix 1
Qualitative information sheet and consent forms for interviews.
[DOCX File , 359 KB - resprot_v13i1e52145_app1.docx]

Multimedia Appendix 2
Quantitative information sheets and consent for participation in surveys.
[DOCX File , 89 KB - resprot_v13i1e52145_app2.docx]

References

1. Cuartas J, Weissman DG, Sheridan MA, Lengua L, McLaughlin KA. Corporal punishment and elevated neural response to threat in children. Child Dev 2021 May 09;92(3):821-832 [FREE Full text] [doi: 10.1111/cdev.13565] [Medline: 33835477]
2. Bugental DB, Martorell GA, Barraza V. The hormonal costs of subtle forms of infant maltreatment. Horm Behav 2003 Jan;43(1):237-244. [doi: 10.1016/s0018-506x(02)00008-9] [Medline: 12614655]
3. Sheu YS, Polcari A, Anderson CM, Teicher MH. Harsh corporal punishment is associated with increased T2 relaxation time in dopamine-rich regions. Neuroimage 2010 Nov 01;53(2):412-419 [FREE Full text] [doi: 10.1016/j.neuroimage.2010.06.043] [Medline: 20600981]
4. Ozernov-Palchik O, Norton ES, Wang Y, Beach SD, Zuk J, Wolf M, et al. The relationship between socioeconomic status and white matter microstructure in pre-reading children: a longitudinal investigation. Hum Brain Mapp 2019 Feb 15;40(3):741-754 [FREE Full text] [doi: 10.1002/hbm.24407] [Medline: 30276914]
5. Gershoff ET, Grogan-Kaylor A. Spanking and child outcomes: old controversies and new meta-analyses. J Fam Psychol 2016 Jun;30(4):453-469 [FREE Full text] [doi: 10.1037/fam0000191] [Medline: 27055181]
6. Fry D, Fang X, Elliott S, Casey T, Zheng X, Li J, et al. The relationships between violence in childhood and educational outcomes: a global systematic review and meta-analysis. Child Abuse Negl 2018 Jan;75:6-28 [FREE Full text] [doi: 10.1016/j.chiabu.2017.06.021] [Medline: 28711191]

7. Global status report on preventing violence against children 2020. World Health Organization. URL: https://www.who.int/teams/social-determinants-of-health/violence-prevention/global-status-report-on-violence-against-children-2020 [accessed 2023-05-04]
8. Artz L, Ward CL, Leoschut L, Kassanjee R, Burton P. The prevalence of child sexual abuse in South Africa: the Optimus Study South Africa. S Afr Med J 2018 Oct 02;108(10):791-792. [doi: 10.7196/samj.2018.v108i10.13533]
9. Meinck F, Cluver LD, Boyes ME, Loening-Voysey H. Physical, emotional and sexual adolescent abuse victimisation in South Africa: prevalence, incidence, perpetrators and locations. J Epidemiol Community Health 2016 Sep;70(9):910-916 [FREE Full text] [doi: 10.1136/jech-2015-205860] [Medline: 26962202]
10. Ward CL, Artz L, Leoschut L, Kassanjee R, Burton P. Sexual violence against children in South Africa: a nationally representative cross-sectional study of prevalence and correlates. Lancet Glob Health 2018 Apr;6(4):e460-e468 [FREE Full text] [doi: 10.1016/S2214-109X(18)30060-3] [Medline: 29530424]
11. Fang X, Zheng X, Fry DA, Ganz G, Casey T, Hsiao C, et al. The economic burden of violence against children in South Africa. Int J Environ Res Public Health 2017 Nov 22;14(11):1431 [FREE Full text] [doi: 10.3390/ijerph14111431] [Medline: 29165332]
12. Ngidi ND. "I feel scared of being a girl": adolescent girls' conversations about heteropatriarchal sexual violence in South African townships. Geoforum 2022 Aug;134:40-47 [FREE Full text] [doi: 10.1016/j.geoforum.2022.06.003]
13. Richter LM, Mathews S, Kagura J, Nonterah E. A longitudinal perspective on violence in the lives of South African children from the Birth to Twenty Plus cohort study in Johannesburg-Soweto. S Afr Med J 2018 Feb 27;108(3):181-186 [FREE Full text] [doi: 10.7196/SAMJ.2018.v108i3.12661] [Medline: 30004360]
14. Appollis TM, Jonas K, Beauclair R, Lombard C, Duby Z, Cheyip M, et al. Early sexual debut and the effects on well-being among South African adolescent girls and young women aged 15 to 24 years. Int J Sex Health 2021 Mar 09;34(2):242-253 [FREE Full text] [doi: 10.1080/19317611.2021.1979162] [Medline: 36092761]
15. Ward CL, Makusha T, Bray R. Parenting, poverty and young people in South Africa: what are the connections? In: South African Child Gauge. Cape Town, South Africa: Children's Institute, University of Cape Town; 2015:69-74.
16. Jeynes WH. The relationship between parental involvement and urban secondary school student academic achievement. Urban Educ 2016 Aug 19;42(1):82-110. [doi: 10.1177/0042085906293818]
17. Varghese C, Wachen J. The determinants of father involvement and connections to children's literacy and language outcomes: review of the literature. Marriage Fam Rev 2015 Oct 07;52(4):331-359. [doi: 10.1080/01494929.2015.1099587]
18. Richter LM, Daelmans B, Lombardi J, Heymann J, Boo FL, Behrman JR, et al. Investing in the foundation of sustainable development: pathways to scale up for early childhood development. The Lancet 2017 Jan;389(10064):103-118. [doi: 10.1016/s0140-6736(16)31698-1]
19. Ward CL, Wessels IM, Lachman JM, Hutchings J, Cluver LD, Kassanjee R, et al. Parenting for Lifelong Health for Young Children: a randomized controlled trial of a parenting program in South Africa to prevent harsh parenting and child conduct problems. J Child Psychol Psychiatry 2020 Apr 19;61(4):503-512 [FREE Full text] [doi: 10.1111/jcpp.13129] [Medline: 31535371]
20. Williams ME, Foran HM, Hutchings J, Frantz I, Taut D, Lachman JM, et al. Exploring factors associated with parent engagement in a parenting program in southeastern Europe. J Child Fam Stud 2022 Aug 25;31(11):3097-3112. [doi: 10.1007/s10826-022-02411-0]
21. Lachman JM, Kelly J, Cluver L, Ward CL, Hutchings J, Gardner F. Process evaluation of a parenting program for low-income families in South Africa. Res Soc Work Pract 2016 Apr 28;28(2):188-202. [doi: 10.1177/1049731516645665]
22. David OA. The Rational Parenting Coach app: REThink parenting! A mobile parenting program for offering evidence-based personalized support in the prevention of child externalizing and internalizing disorders. J Evid Based Psychother 2019;19(2):97-108. [doi: 10.24193/jebp.2019.2.15]
23. Feil EG, Sprengelmeyer PG, Leve C. A randomized study of a mobile behavioral parent training application. Telemed J E Health 2018 Jun;24(6):457-463 [FREE Full text] [doi: 10.1089/tmj.2017.0137] [Medline: 29232180]
24. Cluver L, Lachman JM, Sherr L, Wessels I, Krug E, Rakotomalala S, et al. Parenting in a time of COVID-19. Lancet 2020 Apr 11;395(10231):e64 [FREE Full text] [doi: 10.1016/S0140-6736(20)30736-4] [Medline: 32220657]
25. chatbot. Oxford Learner's Dictionaries. URL: https://www.oxfordlearnersdictionaries.com/definition/english/chatbot#:~:text=%2F%CB%88t%CA%83%C3%A6tb%C9%91%CB%90t%2F,step%20in%20and%20take%20over [accessed 2023-03-10]
26. Wilson L, Marasoiu M. The development and use of chatbots in public health: scoping review. JMIR Hum Factors 2022 Oct 05;9(4):e35882 [FREE Full text] [doi: 10.2196/35882] [Medline: 36197708]
27. Gardiner PM, McCue KD, Negash LM, Cheng T, White LF, Yinusa-Nyahkoon L, et al. Engaging women with an embodied conversational agent to deliver mindfulness and lifestyle recommendations: a feasibility randomized control trial. Patient Educ Couns 2017 Sep;100(9):1720-1729 [FREE Full text] [doi: 10.1016/j.pec.2017.04.015] [Medline: 28495391]
28. Ogilvie L, Prescott J, Carson J. The use of chatbots as supportive agents for people seeking help with substance use disorder: a systematic review. Eur Addict Res 2022 Aug 30;28(6):405-418 [FREE Full text] [doi: 10.1159/000525959] [Medline: 36041418]
29. Ly KH, Ly AM, Andersson G. A fully automated conversational agent for promoting mental well-being: a pilot RCT using mixed methods. Internet Interv 2017 Dec;10:39-46 [FREE Full text] [doi: 10.1016/j.invent.2017.10.002] [Medline: 30135751]

30. Gabarron E, Larbi D, Denecke K, Årsand E. What do we know about the use of chatbots for public health? Stud Health Technol Inform 2020 Jun 16;270:796-800. [doi: 10.3233/SHTI200270] [Medline: 32570492]
31. Mobile cellular subscriptions (per 100 people) - South Africa. The World Bank. URL: https://data.worldbank.org/indicator/IT.CEL.SETS.P2?locations=ZA [accessed 2023-05-15]
32. Seebregts C, Tanna G, Fogwill T, Barron P, Benjamin P. MomConnect: an exemplar implementation of the Health Normative Standards Framework in South Africa. S Afr Health Rev 2016:125-136 [FREE Full text]
33. HealthConnect in South Africa: a chatbot tool for pandemic response. Exemplars. URL: https://www.exemplars.health/emerging-topics/epidemic-preparedness-and-response/digital-health-tools/healthconnect-in-south-africa [accessed 2023-05-15]
34. De Filippo A, Bellatin P, Tietz N, Grant E, Whitefield A, Nkopane P, et al. Effects of digital chatbot on gender attitudes and exposure to intimate partner violence among young women in South Africa. PLOS Digit Health 2023 Oct;2(10):e0000358 [FREE Full text] [doi: 10.1371/journal.pdig.0000358] [Medline: 37844088]
35. Eysenbach G. The law of attrition. J Med Internet Res 2005 Mar 31;7(1):e11 [FREE Full text] [doi: 10.2196/jmir.7.1.e11] [Medline: 15829473]
36. Titov N, Dear BF, Johnston L, Lorian C, Zou J, Wootton B, et al. Improving adherence and clinical outcomes in self-guided internet treatment for anxiety and depression: randomised controlled trial. PLoS One 2013;8(7):e62873 [FREE Full text] [doi: 10.1371/journal.pone.0062873] [Medline: 23843932]
37. van Kessel R, Roman-Urrestarazu A, Anderson M, Kyriopoulos I, Field S, Monti G, et al. Mapping factors that affect the uptake of digital therapeutics within health systems: scoping review. J Med Internet Res 2023 Jul 25;25:e48000 [FREE Full text] [doi: 10.2196/48000] [Medline: 37490322]
38. Rapp A, Curti L, Boldi A. The human side of human-chatbot interaction: a systematic literature review of ten years of research on text-based chatbots. Int J Hum Comput Stud 2021 Jul;151:102630 [FREE Full text] [doi: 10.1016/j.ijhcs.2021.102630]
39. Vaidyam AN, Linggonegoro D, Torous J. Changes to the psychiatric chatbot landscape: a systematic review of conversational agents in serious mental illness. Can J Psychiatry 2021 Apr 16;66(4):339-348 [FREE Full text] [doi: 10.1177/0706743720966429] [Medline: 33063526]
40. Perski O, Blandford A, West R, Michie S. Conceptualising engagement with digital behaviour change interventions: a systematic review using principles from critical interpretive synthesis. Transl Behav Med 2017 Jun;7(2):254-267 [FREE Full text] [doi: 10.1007/s13142-016-0453-1] [Medline: 27966189]
41. O'Brien HL, Toms EG. What is user engagement? A conceptual framework for defining user engagement with technology. J Am Soc Inf Sci 2008 Feb 28;59(6):938-955. [doi: 10.1002/asi.20801]
42. Fitzpatrick KK, Darcy A, Vierhile M. Delivering cognitive behavior therapy to young adults with symptoms of depression and anxiety using a fully automated conversational agent (Woebot): a randomized controlled trial. JMIR Ment Health 2017 Jun 06;4(2):e19 [FREE Full text] [doi: 10.2196/mental.7785] [Medline: 28588005]
43. Schafer M, Lachman JM, Gardner F, Zinser P, Calderon F, Han Q, et al. Integrating intimate partner violence prevention content into a digital parenting chatbot intervention during COVID-19: intervention development and remote data collection. BMC Public Health 2023 Sep 04;23(1):1708 [FREE Full text] [doi: 10.1186/s12889-023-16649-w] [Medline: 37667352]
44. Klapow MC, Rosenblatt A, Lachman J, Gardner F. The implementation feasibility and acceptability of using a digital conversational agent (chatbot) for delivering parenting interventions: systematic review. JMIR Preprints Preprint posted online January 16, 2024 [FREE Full text] [doi: 10.2196/preprints.55726]
45. Akhtar M, Neidhardt J, Werthner H. The potential of chatbots: analysis of chatbot conversations. In: Proceedings of the IEEE 21st Conference on Business Informatics (CBI). 2019 Presented at: CBI 2019; July 15-17, 2019; Moscow, Russia. [doi: 10.1109/CBI.2019.00052]
46. Ashktorab Z, Jain M, Liao QV, Weisz JD. Resilient chatbots: repair strategy preferences for conversational breakdowns. In: Proceedings of the 2019 CHI Conference on Human Factors in Computing Systems. 2019 Presented at: CHI '19; May 4-9, 2019; Glasgow, UK. [doi: 10.1145/3290605.3300484]
47. Tärning B, Silvervarg A. “I didn’t understand, I´m really not very smart”—how design of a digital tutee’s self-efficacy affects conversation and student behavior in a digital math game. Educ Sci 2019 Jul 24;9(3):197. [doi: 10.3390/educsci9030197]
48. Fernandez JC. Determinantes culturais da saúde: uma abordagem para a promoção de equidade. Saude Soc 2014;23(1):167-179. [doi: 10.1590/S0104-12902014000100013]
49. Kiongo FN. A framework for mobile health adoption in developing countries-case study Kenya. University of Nairobi. 2014. URL: http://erepository.uonbi.ac.ke/handle/11295/74353 [accessed 2023-03-23]
50. Alsswey A, Naufal Bin Umar I, Bervell B. Investigating the acceptance of mobile health application user interface cultural-based design to assist Arab elderly users. Int J Adv Comput Sci Appl 2018;9(8). [doi: 10.14569/IJACSA.2018.090819]
51. Meister S, Burmann A, Deiters W. Digital health innovation engineering: enabling digital transformation in healthcare: introduction of an overall tracking and tracing at the super hospital Aarhus Denmark. In: Urbach N, Röglinger M, editors. Digitalization Cases. Cham, Switzerland: Springer; 2019.

52. Collins LM. Conceptual introduction to the multiphase optimization strategy (MOST). In: Optimization of Behavioral, Biobehavioral, and Biomedical Interventions. Cham, Switzerland: Springer; Feb 09, 2018.
53. Axford N, Lehtonen M, Kaoukji D, Tobin K, Berry V. Engaging parents in parenting programs: lessons from research and practice. Child Youth Serv Rev 2012 Oct;34(10):2061-2071 [FREE Full text] [doi: 10.1016/j.childyouth.2012.06.011]
54. Koerting J, Smith E, Knowles MM, Latter S, Elsey H, McCann DC, et al. Barriers to, and facilitators of, parenting programmes for childhood behaviour problems: a qualitative synthesis of studies of parents' and professionals' perceptions. Eur Child Adolesc Psychiatry 2013 Nov;22(11):653-670 [FREE Full text] [doi: 10.1007/s00787-013-0401-2] [Medline: 23564207]
55. Cluver LD, Meinck F, Steinert JI, Shenderovich Y, Doubt J, Herrero Romero R, et al. Parenting for Lifelong Health: a pragmatic cluster randomised controlled trial of a non-commercialised parenting programme for adolescents and their families in South Africa. BMJ Glob Health 2018 Jan 31;3(1):e000539 [FREE Full text] [doi: 10.1136/bmjgh-2017-000539] [Medline: 29564157]
56. Helping adolescents thrive toolkit: strategies to promote and protect adolescent mental health and reduce self-harm and other risk behaviours: executive summary. World Health Organization and United Nations Children's Fund. 2021. URL: https://iris.who.int/handle/10665/341344 [accessed 2023-06-10]
57. Zosh JM, Hopkins EJ, Jensen H, Liu C, Neale D, Hirsh-Pasek K, et al. Learning through play: a review of the evidence. The LEGO Foundation. 2017. URL: https://www.researchgate.net/publication/325171106_Learning_through_play_a_review_of_the_evidence [accessed 2023-05-22]
58. Durrant JE. Positive discipline in everyday parenting (PDEP). In: Ending the Physical Punishment of Children: A Guide for Clinicians and Practitioners. Washington, DC: American Psychological Association; 2020.
59. Grossman JM, Tracy AJ, Charmaraman L, Ceder I, Erkut S. Protective effects of middle school comprehensive sex education with family involvement. J Sch Health 2014 Nov;84(11):739-747. [doi: 10.1111/josh.12199] [Medline: 25274174]
60. Park N, Peterson C. Character strengths: research and practice. J Coll Character 2009;10(4). [doi: 10.2202/1940-1639.1042]
61. Youn S. Parental influence and teens' attitude toward online privacy protection. J Consum Aff 2008 Aug 28;42(3):362-388 [FREE Full text] [doi: 10.1111/j.1745-6606.2008.00113.x]
62. Ralph A, Sanders MR. The "Teen Triple P" Positive Parenting Program: A Preliminary Evaluation. Canberra, Australia: Australian Institute of Criminology; 2004.
63. Finkelstein DM, Kubzansky LD, Capitman J, Goodman E. Socioeconomic differences in adolescent stress: the role of psychological resources. J Adolesc Health 2007 Feb;40(2):127-134 [FREE Full text] [doi: 10.1016/j.jadohealth.2006.10.006] [Medline: 17259052]
64. Injuries among children and teens. Centers for Disease Control and Prevention. URL: https://www.cdc.gov/injury/features/child-injury/index.html [accessed 2023-05-07]
65. Siu GE, Wight D, Seeley J, Namutebi C, Sekiwunga R, Zalwango F, et al. Men's involvement in a parenting programme to reduce child maltreatment and gender-based violence: formative evaluation in Uganda. Eur J Dev Res 2017 Nov;29:1017-1037. [doi: 10.1057/s41287-017-0103-6]
66. Newland RP, Crnic KA, Cox MJ, Mills-Koonce WR, Family Life Project Key Investigators. The family model stress and maternal psychological symptoms: mediated pathways from economic hardship to parenting. J Fam Psychol 2013 Feb;27(1):96-105 [FREE Full text] [doi: 10.1037/a0031112] [Medline: 23421837]
67. Schubart JR, Stuckey HL, Ganeshamoorthy A, Sciamanna CN. Chronic health conditions and internet behavioral interventions: a review of factors to enhance user engagement. Comput Inform Nurs 2011 Feb;29(2):81-92 [FREE Full text] [doi: 10.1097/NCN.0b013e3182065eed] [Medline: 21164337]
68. Brouwer W, Kroeze W, Crutzen R, de Nooijer J, de Vries NK, Brug J, et al. Which intervention characteristics are related to more exposure to internet-delivered healthy lifestyle promotion interventions? A systematic review. J Med Internet Res 2011 Jan 06;13(1):e2 [FREE Full text] [doi: 10.2196/jmir.1639] [Medline: 21212045]
69. Rogers J, Gladstone T, Van Voorhees B, Bunge EL. The role of human support on engagement in an online depression prevention program for youth. Soc Sci 2021 Jul 27;10(8):285. [doi: 10.3390/socsci10080285]
70. Kelders SM, Kok RN, Ossebaard HC, Van Gemert-Pijnen JE. Persuasive system design does matter: a systematic review of adherence to web-based interventions. J Med Internet Res 2012 Nov 14;14(6):e152 [FREE Full text] [doi: 10.2196/jmir.2104] [Medline: 23151820]
71. Day JJ, Sanders MR. Do parents benefit from help when completing a self-guided parenting program online? A randomized controlled trial comparing triple p online with and without telephone support. Behav Ther 2018 Nov;49(6):1020-1038. [doi: 10.1016/j.beth.2018.03.002]
72. Epstein M, Oesterle S, Haggerty KP. Effectiveness of Facebook groups to boost participation in a parenting intervention. Prev Sci 2019 Aug;20(6):894-903 [FREE Full text] [doi: 10.1007/s11121-019-01018-0] [Medline: 31124023]
73. Meinck F, Boyes ME, Cluver L, Ward CL, Schmidt P, DeStone S, et al. Adaptation and psychometric properties of the ISPCAN Child Abuse Screening Tool for use in trials (ICAST-Trial) among South African adolescents and their primary caregivers. Child Abuse Negl 2018 Aug;82:45-58 [FREE Full text] [doi: 10.1016/j.chiabu.2018.05.022] [Medline: 29860107]
74. Essau CA, Sasagawa S, Frick PJ. Psychometric properties of the Alabama parenting questionnaire. J Child Fam Stud 2006 May 18;15:595-614. [doi: 10.1007/s10826-006-9036-y]

75. Ceballo R, Maurizi LK, Suarez GA, Aretakis MT. Gift and sacrifice: parental involvement in Latino adolescents' education. Cultur Divers Ethnic Minor Psychol 2014 Jan;20(1):116-127. [doi: 10.1037/a0033472] [Medline: 23834259]
76. Kroenke K, Spitzer RL, Williams JB, Löwe B. An ultra-brief screening scale for anxiety and depression: the PHQ-4. Psychosomatics 2009;50(6):613-621. [doi: 10.1176/appi.psy.50.6.613] [Medline: 19996233]
77. Berry JO, Jones WH. The parental stress scale: initial psychometric evidence. J Soc Pers Relatsh 1995;12(3):463-472. [doi: 10.1177/0265407595123009]
78. Nguyen HT. Development and validation of a women's financial self-efficacy scale. J Financ Couns Plan 2019 Jun;30(1):142-154. [doi: 10.1891/1052-3073.30.1.142]
79. McCarty CM, Doyle SR. Parent-child communication (parent) (Fast track project technical report). Fast Track Project. 2001. URL: http://www.fasttrackproject.org [accessed 2023-05-18]
80. Orm S, Haukeland YB, Vatne T, Fjermestad K. Measuring family communication in pediatric nursing: psychometric properties of the parent-child communication scale - child report (PCCS-CR). J Pediatr Nurs 2022;62:78-83 [FREE Full text] [doi: 10.1016/j.pedn.2021.10.022] [Medline: 34799202]
81. Hirsh-Pasek K, Adamson LB, Bakeman R, Owen MT, Golinkoff RM, Pace A, et al. The contribution of early communication quality to low-income children's language success. Psychol Sci 2015 Jul 05;26(7):1071-1083. [doi: 10.1177/0956797615581493] [Medline: 26048887]
82. WHO multi-country study on women's health and domestic violence against women: summary report. World Health Organization. 2005 Feb 9. URL: https://www.who.int/publications/i/item/9241593512 [accessed 2023-12-15]
83. Doyle K, Levtov RG, Barker G, Bastian GG, Bingenheimer JB, Kazimbaya S, et al. Gender-transformative Bandebereho couples' intervention to promote male engagement in reproductive and maternal health and violence prevention in Rwanda: Findings from a randomized controlled trial. PLoS One 2018;13(4):e0192756 [FREE Full text] [doi: 10.1371/journal.pone.0192756] [Medline: 29617375]
84. Abramsky T, Kapinga I, Mshana G, Lees S, Hansen CH, Hashim R, et al. Couples data from north-western Tanzania: Insights from a survey of male partners of women enrolled in the MAISHA cluster randomized trial of an intimate partner violence prevention intervention. PLoS One 2020;15(10):e0240112 [FREE Full text] [doi: 10.1371/journal.pone.0240112] [Medline: 33006997]
85. Xiao L, Bechara A, Palmer PH, Trinidad DR, Wei Y, Jia Y, et al. Parent-Child Engagement in Decision Making and the Development of Adolescent Affective Decision Capacity and Binge Drinking. Pers Individ Dif 2011 Aug 01;51(3):285-292 [FREE Full text] [doi: 10.1016/j.paid.2010.04.023] [Medline: 21804682]
86. MICS7 Tools. United Nations International Children's Emergency Fund. URL: https://mics.unicef.org/tools [accessed 2023-05-08]
87. Iwelunmor J, Newsome V, Airhihenbuwa CO. Framing the impact of culture on health: a systematic review of the PEN-3 cultural model and its application in public health research and interventions. Ethn Health 2014 Feb;19(1):20-46 [FREE Full text] [doi: 10.1080/13557858.2013.857768] [Medline: 24266638]
88. Rondan-Cataluña FJ, Arenas-Gaitán J, Ramírez-Correa PE. A comparison of the different versions of popular technology acceptance models: a non-linear perspective. Kybernetes 2015;44(5):788-805. [doi: 10.1108/K-09-2014-0184]
89. Nikolopoulou K, Gialamas V, Lavidas K. Habit, hedonic motivation, performance expectancy and technological pedagogical knowledge affect teachers' intention to use mobile internet. Computers and Education Open 2021 Dec;2:100041 [FREE Full text] [doi: 10.1016/j.caeo.2021.100041]
90. The importance of managing and sharing data. UK Data Service. URL: https://ukdataservice.ac.uk/learning-hub/research-data-management/#document-your-data [accessed 2023-06-01]
91. Kugler KC, Dziak JJ, Trail J. Coding and interpretation of effects in analysis of data from a factorial experiment. In: Collins L, Kugler K, editors. Optimization of Behavioral, Biobehavioral, and Biomedical Interventions. Cham, Switzerland: Springer; 2018.
92. Nahum-Shani I, Dziak JJ, Collins LM. Multilevel factorial designs with experiment-induced clustering. Psychol Methods 2018 Sep;23(3):458-479 [FREE Full text] [doi: 10.1037/met0000128] [Medline: 28383950]
93. Gale NK, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. BMC Med Res Methodol 2013 Sep 18;13:117 [FREE Full text] [doi: 10.1186/1471-2288-13-117] [Medline: 24047204]
94. Strayhorn JC, Collins LM, Vanness DJ. A posterior expected value approach to decision-making in the multiphase optimization strategy for intervention science. Psychol Methods 2023 Apr 13. [doi: 10.1037/met0000569] [Medline: 37053415]
95. Child safeguarding policy. mothers2mothers. URL: https://m2m.org/wp-content/uploads/2020/02/IntlOp_01_v01_2017-Child-Safeguarding-Policy_Version-3.pdf [accessed 2023-05-20]
96. Up-dated ICMJE recommendations. International Committee of Medical Journal Editors. URL: https://www.icmje.org/news-and-editorials/new_journal_dec2021.html [accessed 2023-08-20]

Abbreviations

CHAMP: Children and Adolescents Are My Priority
CWBSA: Clowns Without Borders South Africa
DREAMS: Determined, Resilient, Empowered, AIDS-free, Mentored, and Safe
IDEMS: Innovations in Development, Education, and the Mathematical Sciences
IPV: intimate partner violence
LMIC: low- and middle-income country
m2m: mothers2mothers
mHealth: mobile health
NGO: nongovernmental organization
PLH: Parenting for Lifelong Health
TSC: Trial Steering Committee
UNICEF: United Nations Children's Fund
VAC: violence against children

Edited by A Mavragani; submitted 24.08.23; peer-reviewed by K Guastafarro, E Eboreime, T Su; comments to author 22.02.24; revised version received 12.03.24; accepted 15.03.24; published 03.05.24.

Please cite as:
Ambrosio MDG, Lachman JM, Zinzer P, Gwebu H, Vyas S, Vallance I, Calderon F, Gardner F, Markle L, Stern D, Facciola C, Schley A, Danisa N, Brukwe K, Melendez-Torres GJ
A Factorial Randomized Controlled Trial to Optimize User Engagement With a Chatbot-Led Parenting Intervention: Protocol for the ParentText Optimisation Trial
JMIR Res Protoc 2024;13:e52145
URL: https://www.researchprotocols.org/2024/1/e52145
doi:10.2196/52145
PMID:38700935

Protocol

Digital Interventions to Understand and Mitigate Stress Response: Protocol for Process and Content Evaluation of a Cohort Study

Josh Martin[1], BSc; Alice Rueda[1], PhD; Gyu Hee Lee[1], BSc; Vanessa K Tassone[1], BA; Haley Park[1], BSc, MSc; Martin Ivanov[2], BSc; Benjamin C Darnell[3,4], PhD; Lindsay Beavers[5,6], BSc, MPT; Douglas M Campbell[5,7,8,9], MD, MSc; Binh Nguyen[2], BEng; Andrei Torres[10], BArch, MEng; Hyejung Jung[11], MSc; Wendy Lou[11], PhD; Anthony Nazarov[12], PhD; Andrea Ashbaugh[13], PhD; Bill Kapralos[10], PhD; Brett Litz[3,4], PhD; Rakesh Jetly[14], MD; Adam Dubrowski[10], PhD; Gillian Strudwick[15,16,17], PhD; Sridhar Krishnan[2], PhD; Venkat Bhat[1,18], MD, MSc

[1]Interventional Psychiatry Program, St Michael's Hospital, Unity Health Toronto, Toronto, ON, Canada
[2]Department of Electrical, Computer, and Biomedical Engineering, Toronto Metropolitan University, Toronto, ON, Canada
[3]Massachusetts Veterans Epidemiology Research and Information Center, VA Boston Healthcare System, Boston, MA, United States
[4]Department of Psychiatry, Boston University Chobanian and Avedisian School of Medicine, Boston, MA, United States
[5]Allan Waters Family Simulation Program, Unity Health Toronto, Toronto, ON, Canada
[6]Department of Physical Therapy, University of Toronto, Toronto, ON, Canada
[7]Neonatal Intensive Care Unit, St Michael's Hospital, Unity Health Toronto, Toronto, ON, Canada
[8]Li Ka Shing Knowledge Institute, St Michael's Hospital, Unity Health Toronto, Toronto, ON, Canada
[9]Department of Pediatrics, Faculty of Medicine, University of Toronto, Toronto, ON, Canada
[10]maxSIMhealth Group, Ontario Tech University, Oshawa, ON, Canada
[11]Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada
[12]MacDonald Franklin OSI Research Centre, Lawson Health Research Institute, London, ON, Canada
[13]School of Psychology, University of Ottawa, Ottawa, ON, Canada
[14]Institute of Mental Health Research, University of Ottawa, Ottawa, ON, Canada
[15]Centre For Addiction & Mental Health, Toronto, ON, Canada
[16]Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada
[17]Arthur Labatt Family School of Nursing, Western University, London, ON, Canada
[18]Department of Psychiatry, University of Toronto, Toronto, ON, Canada

Corresponding Author:
Venkat Bhat, MD, MSc
Interventional Psychiatry Program
St Michael's Hospital
Unity Health Toronto
193 Yonge Street
Suite 6-013
Toronto, ON, M5B 1M4
Canada
Phone: 1 416 360 4000 ext 76404
Email: venkat.bhat@utoronto.ca

Abstract

Background: Staffing and resource shortages, especially during the COVID-19 pandemic, have increased stress levels among health care workers. Many health care workers have reported feeling unable to maintain the quality of care expected within their profession, which, at times, may lead to moral distress and moral injury. Currently, interventions for moral distress and moral injury are limited.

Objective: This study has the following aims: (1) to characterize and reduce stress and moral distress related to decision-making in morally complex situations using a virtual reality (VR) scenario and a didactic intervention; (2) to identify features contributing to mental health outcomes using wearable, physiological, and self-reported questionnaire data; and (3) to create a personal digital phenotype profile that characterizes stress and moral distress at the individual level.

Methods: This will be a single cohort, pre- and posttest study of 100 nursing professionals in Ontario, Canada. Participants will undergo a VR simulation that requires them to make morally complex decisions related to patient care, which will be administered before and after an educational video on techniques to mitigate distress. During the VR session, participants will complete questionnaires measuring their distress and moral distress, and physiological data (electrocardiogram, electrodermal activity, plethysmography, and respiration) will be collected to assess their stress response. In a subsequent 12-week follow-up period, participants will complete regular assessments measuring clinical outcomes, including distress, moral distress, anxiety, depression, and loneliness. A wearable device will also be used to collect continuous data for 2 weeks before, throughout, and for 12 weeks after the VR session. A pre-post comparison will be conducted to analyze the effects of the VR intervention, and machine learning will be used to create a personal digital phenotype profile for each participant using the physiological, wearable, and self-reported data. Finally, thematic analysis of post-VR debriefing sessions and exit interviews will examine reoccurring codes and overarching themes expressed across participants' experiences.

Results: The study was funded in 2022 and received research ethics board approval in April 2023. The study is ongoing.

Conclusions: It is expected that the VR scenario will elicit stress and moral distress. Additionally, the didactic intervention is anticipated to improve understanding of and decrease feelings of stress and moral distress. Models of digital phenotypes developed and integrated with wearables could allow for the prediction of risk and the assessment of treatment responses in individuals experiencing moral distress in real-time and naturalistic contexts. This paradigm could also be used in other populations prone to moral distress and injury, such as military and public safety personnel.

Trial Registration: ClinicalTrials.gov NCT05923398; https://clinicaltrials.gov/study/NCT05923398

International Registered Report Identifier (IRRID): DERR1-10.2196/54180

(JMIR Res Protoc 2024;13:e54180) doi:10.2196/54180

KEYWORDS

web-based platform; stress; distress; moral distress; wearable; oura ring; virtual reality; VR; COVID-19; nursing; digital health implementation

Introduction

Background

Work-related stress is a major issue encountered by health care workers (HCWs), as they face a variety of stressors due to the nature of their work, which often involves high-pressure situations and contact with pain and death [1]. The COVID-19 pandemic caused numerous difficulties for many individuals, with HCWs bearing unprecedented professional and personal demands due to challenges such as resource and staffing shortages. Nurses were affected most significantly, reporting the highest levels of burnout, emotional exhaustion, and psychological distress among all HCWs [2]. As COVID-19 cases decreased, levels of emotional exhaustion and psychological distress also decreased but continued to remain higher than the levels reported before the pandemic [2]. Prolonged elevated levels of stress can lead to anxiety, depression, and chronic diseases such as hypertension [3]. Work-related stress can also lead to burnout, a major contributor to nursing shortages faced by health care systems across the globe [4]. In a recent survey, 62% of Canadian nurses said they were considering leaving nursing altogether, citing stressors such as increased workload, staffing shortages, and frequent overtime [5]. Importantly, excessive stress can also impact the quality of care; increased stress is associated with increased medical errors [6] and decreased caring behaviors [7].

Continued unrelenting personal and work-related challenges have, at times, resulted in individuals compromising their beliefs and values to make difficult decisions, which may have life-or-death consequences [8-12]. Clinicians have reported acting in ways that are contrary to their moral values, integrity, and professional commitments, particularly during the initial phases of the COVID-19 pandemic [13,14]. Moral suffering can ensue when a clinician's moral foundation has been threatened or violated because of witnessing, participating in, or precipitating decisions or actions that degrade their integrity [15].

Moral suffering encompasses the related but distinct concepts of moral distress and moral injury. Moral distress was first described within the nursing context by Jameton [16] as "...when one knows the right thing to do, but institutional constraints make it nearly impossible to pursue the right course of action." For example, commonly cited sources of moral distress in nursing include inadequate staffing, inadequate pain relief for patients, and prolongation of life support when they believe it is not in the best interest of the patient [17]. First defined within the military and veteran context, moral injury was said to be the maladaptive biopsychosocial and spiritual outcome of a betrayal of moral character, typically by an individual holding authority [18]. Since this original definition was suggested, literature within the military context has expanded the definition to include maladaptive outcomes following perpetration, witnessing, and being the victim of acts that violate one's moral values [19]. Importantly, moral suffering is thought to exist on a continuum, with moral injury representing a more extreme outcome; repeated instances of moral distress can ultimately lead to moral injury, which is characterized by impaired function and longer-term psychological harm [20]. Also of relevance is the concept of potentially morally injurious events, which have been described in nursing as situations in which professionals find it impossible to carry out the usual standards of care [21].

Limited information exists on treating and preventing moral injury and moral distress, especially in a health care context. While moral injury may have overlapping symptoms with posttraumatic stress disorder (PTSD), treatments used for PTSD have generally been found to be less effective for the treatment of moral injury [22]. Effective treatments for moral injury are likely required to tap into integrity that is degraded, as strengthening an individual's moral compass has been shown to be an effective way to promote healing [23]. Additionally, psychoeducation on ethics [24] and moral distress [25], support seeking [20], and engagement in critical self-reflection [26] have been suggested as potential interventions for moral distress.

Given that it is infeasible and unethical to subject HCWs to real-life events that evoke moral suffering, virtual reality (VR) represents a promising tool for studying this topic. Exposure to VR scenarios is more ethical, as it is unlikely to cause severe distress but has nonetheless been shown to elicit real psychophysiological responses [27,28]. Moreover, VR allows for the creation of customizable environments and real-time data capture of physiological responses in a controlled setting. VR has previously shown success in the assessment and treatment of a variety of mental health disorders, including anxiety-related disorders, schizophrenia, substance use disorders, and eating disorders [28]. In the assessment of mental health disorders, VR can be used to present potentially triggering scenarios during which physiological measurements are made. For example, several studies have used VR to simulate combat situations while measuring markers of stress in those with PTSD [29-31]. Moreover, the ability of VR to simulate reality in a low-stakes environment renders it useful for exposure therapy. Indeed, a meta-analysis of studies that used VR exposure therapy (VRET) found that VRET was effective in treating a variety of anxiety and related disorders, including PTSD, and did not differ in effectiveness from in vivo exposure therapy [32]. Given the similarities previously outlined between moral injury and PTSD, and the variety of anxiety-related conditions that have been shown to be responsive to VRET, VR may be a promising tool for the treatment of stress and moral suffering.

In phase 1 of this project, we examined the feasibility of using our digital suite (VR and app-based monitoring of participants' physical activity and subjective states) in 15 HCWs to understand stress and moral distress. This work was published as a protocol paper [33], a machine learning model used to predict moral distress [34], and a summary of our results [35]. Based on the feasibility demonstrated in phase 1, we are completing phase 2 with several key changes. First, the study will be conducted with a larger sample of 100 nursing professionals to evaluate the preliminary efficacy of our digital suite in mitigating and understanding both stress in general and moral distress in particular. Additionally, using feedback from phase 1, we developed a new VR simulation and educational video, as described by Sivanathan et al [36]. We aimed to create a more immersive environment to increase perspective-taking and heighten moral awareness, closing the dissonance in moral judgment between hypothetical scenarios and real-life situations. Also new in this study, we will use a wearable device [37] to longitudinally monitor participants' physiological states. Combining this with longitudinal monitoring of participants' subjective states with a web-based platform, we will use a novel machine learning approach [38] to predict stress and moral distress on an individual level. Furthermore, based on poor engagement in phase 1 [35], we have created a new strategy for encouraging participant compliance. Both phases 1 and 2 of the study are funded by the Canadian Department of National Defence.

Objectives

In the current trial, nursing professionals (registered nurses and registered practical nurses) in the province of Ontario will be recruited. During the experimental visit, participants will use our digital intervention suite, composed of (1) a VR moral decision-making simulation and educational video, to examine the acute effects of the simulated moral dilemmas. For at least 2 weeks before and 12 weeks after the intervention, participants will complete questionnaires through (2) a web-based platform and (3) use a wearable device to longitudinally monitor the effects of the VR session.

In conducting this trial, we have the following aims: aim 1—we will use a VR simulation to characterize and reduce stress and moral distress related to difficult decision-making in complex moral situations faced by nursing professionals; aim 2—we will use a web-based platform to measure stress, moral distress, and other mental health symptoms, as well as a commercial wearable device to collect physiological data (this will be done to understand and examine the contribution of active, ie, subjective experiences as reported through self-report assessments, and passive, ie, physiological measurements collected without conscious participant input, data in predicting stress and moral distress); aim 3—we will create a personal digital phenotype profile (pDPP) based on the physiological data (ie, electrocardiogram, electrodermal activity (EDA), plethysmography, and respiration) collected during exposure to a hypothetical moral dilemma in a virtual environment, as well as the wearable and web-based data, to help understand its impact on stress and moral distress at the individual level.

Methods

Participants

A total of 100 nursing professionals from Ontario will be recruited to determine the preliminary efficacy of our digital intervention suite. Eligible participants must (1) be a registered practical nurse or a registered nurse currently employed at an Ontario health care institution and (2) be an owner of a smartphone. Exclusion criteria include (1) history of seizures except febrile seizures (as seizures are listed as an unlikely but possible symptom of using the VR headset [39]); (2) use of electronic medical devices (due to the risk of interference with physiological data collection); (3) score of ≥15 on the 7-item Generalized Anxiety Disorder-7 (GAD-7) [40] scale, an indication of severe anxiety; and (4) score of ≥20 on the 9-item Patient Health Questionnaire (PHQ-9) [41], an indication of severe depression.

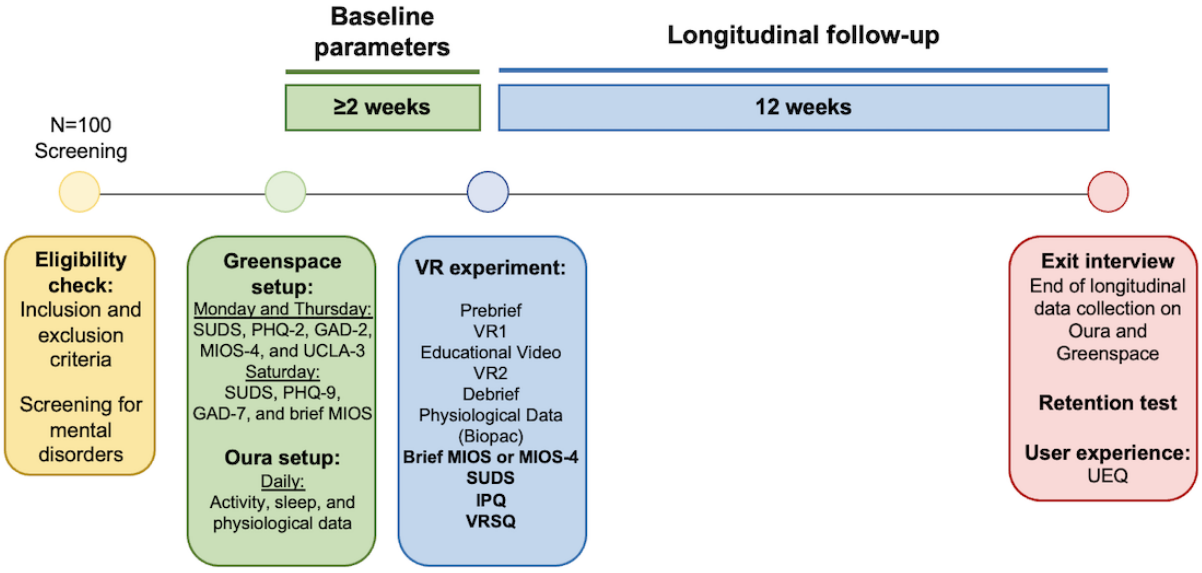
Participants will be recruited through (1) social media advertisements, (2) flyers posted at St. Michael's Hospital, and (3) email notices sent through various listservs (eg, the Canadian

Nursing Informatics Association and the Nursing Research Interest Group). Interested participants will contact the study coordinator, who will send potential participants an informed consent form, a demographic form, and the PHQ-9 and GAD-7 scales. The coordinator will also confirm the individuals' employment and lack of seizure history and electronic medical devices. If the eligibility criteria (as defined above) are met and the participant consents, they will be scheduled for a baseline visit at the interventional psychiatry program.

Trial Design

The trial will take place at St. Michael's Hospital, Unity Health Toronto, Ontario, and will be composed of 3 main phases: baseline, VR simulation, and follow-up, which are visualized in Figure 1. The baseline period will last for a minimum of 2 weeks, during which participants will use the wearable every day and complete scales on a commercial web-based data collection platform, according to the schedule outlined in Figure 1. Following this, participants will engage in a VR simulation that requires complex moral decision-making. The simulation will be followed by an educational video on stress response, and then participants will repeat the simulation to provide them with the opportunity to apply the stress management strategies from the video. At the conclusion of the VR session, participants will engage in a semistructured debrief interview. Physiological signals will be collected through the entirety of the VR session and the debrief. The wearable and web-based platform will continue to be used by participants in the follow-up period, which will take place approximately 12 weeks following the VR session. As described in "Engagement Strategy" section, research team members will be actively involved during this follow-up period to encourage compliance and assess engagement. A semistructured exit interview will take place at the conclusion of participation.

Figure 1. Phase 2 study schema. Brief MIOS: (clinical version) MIOS-4; GAD-2/7: Generalized Anxiety Disorder-2/7 item scale; IPQ: Igroup Presence Questionnaire; MIOS-4: Moral Injury Outcomes Scale; PHQ-2/9: Patient Health Questionnaire-2/9 item scale; SUDS: Subjective Units of Distress Scale; UCLA-3: UCLA 3-item loneliness scale; UEQ: User Experience Questionnaire; VR1: Virtual Reality Simulation Run 1; VR2: Virtual Reality Simulation Run 2; VRSQ: Virtual Reality Sickness Questionnaire Scale.



Data Storage

Eligible participants who are screened will be assigned a unique 7-digit ID. All identifiable information will be handled in one password-encrypted master linking file on the Unity Health Toronto server. The master linking file will contain identifiable information corresponding to the assigned participant's unique ID. Deidentified information will be stored on 2 password-protected (through advanced encryption standard encryption) external hard drives located in a locked office at a Unity Health Toronto research site. Participant information will be deidentified on the wearable app and the web-based platform through the use of a unique ID and dummy emails. Data from each of these sources will be downloaded in a weekly data pull, and data from VR sessions will be transferred daily onto the external hard drives.

VR Session

Design of VR Simulation

Details on the development of the simulation are described elsewhere [36]. Briefly, the content of the VR simulation was developed by a panel of subject-matter experts using a modified Delphi methodology [42]. The script was then created in an iterative manner, with versions reviewed and adjustments made on a regular basis until a final version was approved.

The VR simulation places a novice nurse (the research participant) in a high-stakes scenario within a general ward unit. Faced with a code-blue situation, the participant must make a critical decision between attending to one of 2 patients: one experiencing ventricular fibrillation and the other in cardiac arrest. Compounding the urgency, the general ward unit is devoid of additional medical staff and lacks emergency crash carts. On the second run-through of the VR simulation,

participants are automatically directed to care for the same patient they chose during their initial experience. The design, software, and hardware are identical to phase 1 (reported in the protocol paper [33]).

At several points during the VR simulation, participants will be asked to respond to the situation by selecting a response from a list of options (Figure 2). Participants will be instructed before the VR simulation to select the responses that best represent their internal feelings, even if they are not reflective of what they would say in a professional setting. The research team will record all responses.

Participants will view the educational video (Multimedia Appendix 1) following the first simulation. The video was designed using a similar iterative feedback method and provides psychoeducation on stress and moral distress, as well as strategies to mitigate their effects. Specifically, we will teach unburdening techniques [43], self-compassion [44], and grounding tools (ie, diaphragmatic breathing [45]).

Figure 2. User interface displaying an example of a participant response.

VR Data Collection

A visual overview of the data collection process during the VR simulation is shown in Figure 3.

A total of 4 scales and one short-form scale will be used to collect self-reported data during the session. The Moral Injury Outcome Scale (MIOS) [46] is used to assess an individual's reaction to a potentially morally injurious event and is indexed to the most morally distressing experience of their life that currently distresses them. While the VR simulation is intended to simulate moral distress, the MIOS is designed to assess moral injury and, as such, is used as a proxy of our intended measure. This study will use the clinical version of the brief MIOS (Multimedia Appendix 2), which consists of 14 questions that assess an individual's thoughts and feelings in response to a distressing event and eight items that assess how the event has impacted their daily life. The scale was adapted for nursing professionals by the research team in collaboration with the creator of the scale. Additionally, we will use a shortened version, termed the MIOS-4 (Multimedia Appendix 2), which contains the 4 items from the MIOS with the largest variance. The purpose of the MIOS during the VR session is 2-fold: first, it is used to characterize preexisting moral injury symptoms in participants. Second, the content of the scale is leveraged to assess acute reactions to the simulated moral dilemma.

The Subjective Units of Distress Scale (SUDS) [47] measures the level of distress an individual is experiencing at the moment. Individuals rate their current level of anxiety or discomfort on a scale of 0 to 100, in intervals of 10. The purpose of administering this scale is to obtain a general measure of acute distress elicited by exposure to a moral dilemma.

The Igroup Presence Questionnaire Scale [48] measures an individual's sense of presence and reality during the VR session. This scale is used to assess the VR quality and user experience.

The Virtual Reality Sickness Questionnaire [49] assesses common side effects after VR exposure. This scale will be used to assess the safety and tolerability of the VR simulation.

Physiological data will be collected throughout the duration of the VR session, from the beginning of baseline until the end of the debriefing. Data collection will be done using a Biopac MP160 (Biopac Systems Inc) system, as described in phase 1 [33]. The following 4 physiological signals will be collected as indicators of stress: EDA, electrocardiogram, respiratory impedance (RI), and photoplethysmography. EDA is a measure of the change in conductivity of the skin, which occurs due to changes in the activity of sweat glands. Since sweat gland

activity is mediated by activation of the sympathetic nervous system, EDA provides a measure of sympathetic activity and, thus, arousal [50]. An electrocardiogram measures the electrical activity of the heart. Relevant features extracted from the electrocardiogram signal will include heart rate, which increases with arousal, and heart rate variability (HRV), a signal that reflects the activity of the autonomic nervous system and can be used as an indicator of stress [51]. RI, which is defined as the mechanical load of ventilation, will be used to measure the respiratory rate, which also increases with arousal [52]. Lastly, photoplethysmography uses infrared light to measure changes in blood volume. Similar to HRV, peripheral blood flow is mediated by the autonomic nervous system and, thus, is an indicator of acute mental stress [53]. Representative tracings of these signals are shown in Figure 4.

Figure 3. Design of the virtual reality (VR) experimental session. All scales during the VR session will be completed in the immersive virtual environment. Brief MIOS: (clinical version) MIOS-4; IPQ: Igroup Presence Questionnaire; MIOS-4: Moral Injury Outcomes Scale; SUDS: Subjective Units of Distress Scale; VR1: Virtual Reality Simulation Run 1; VR2: Virtual Reality Simulation Run 2; VRSQ: Virtual Reality Sickness Questionnaire Scale.

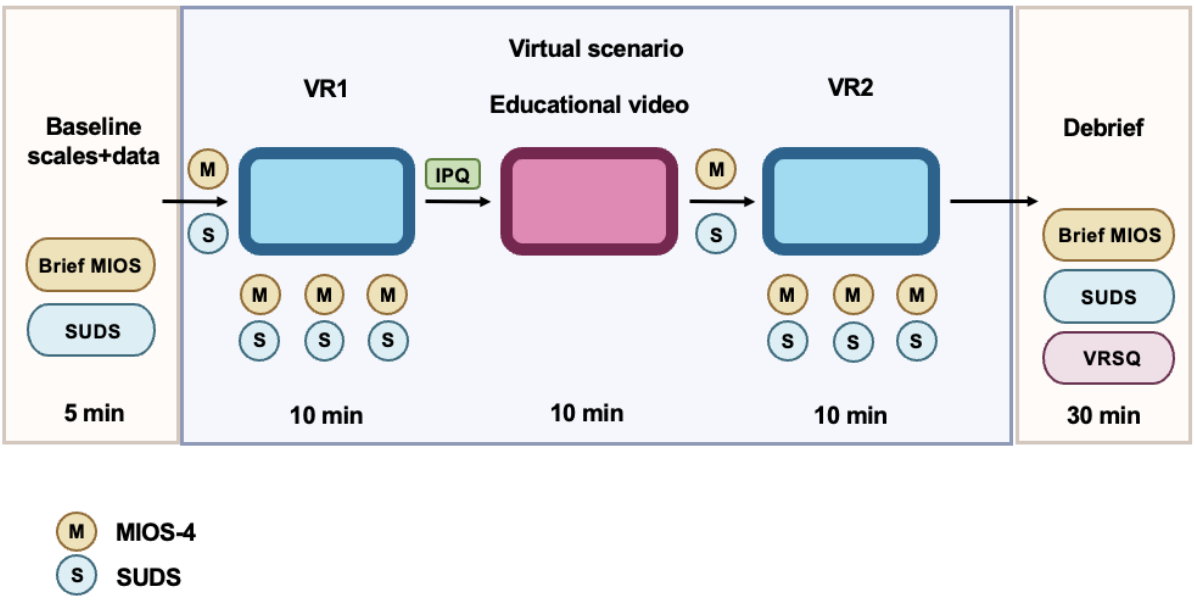
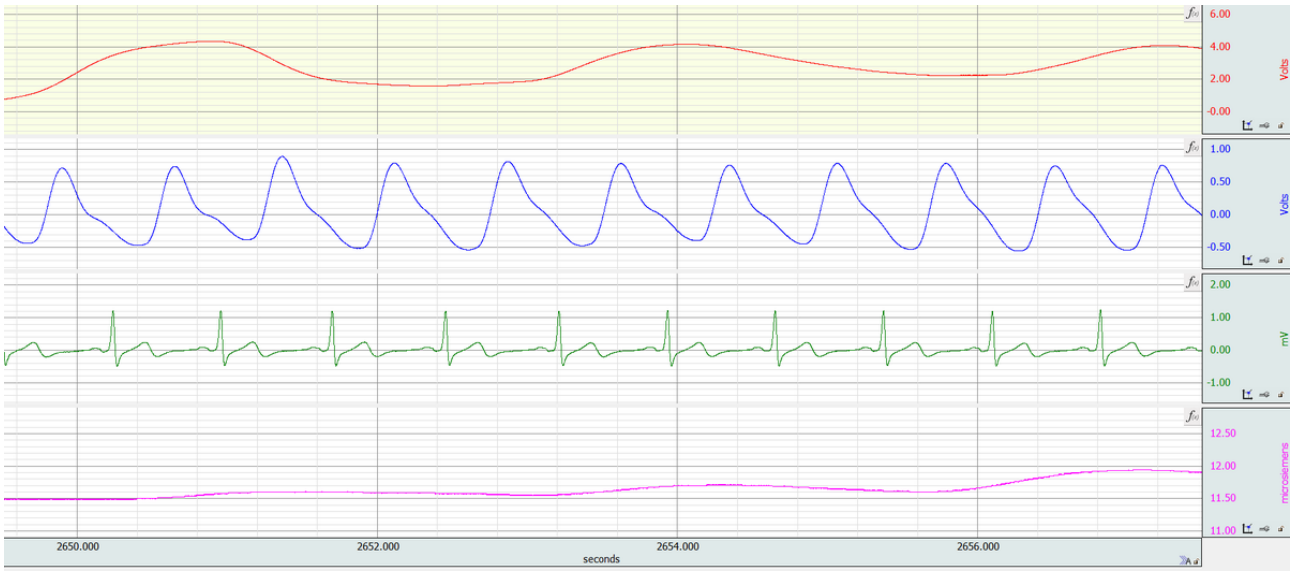


Figure 4. Physiological data collected during the virtual reality (VR) session and debrief. The image shows representative tracings of (from top to bottom): respiratory impedance (RI), photoplethysmography, electrocardiogram, and electrodermal activity (EDA) signals.



Wearable

Passive data will be collected using an Oura Ring (Oura Health Oy), a commercially available wearable device [37]. The ring can be worn on the finger with minimal interference to collect a variety of physiological signals, including heart rate, workout heart rate, respiratory rate, HRV, daily activity, activity score, body temperature (delta), blood oxygen saturation, recovery score, sleep efficiency, and sleep score. The device will be worn for a minimum of 2 weeks before the VR session to ensure appropriate baseline data collection and will be worn continuously for 12 weeks post-VR. Participants will be asked

to open the app daily to allow their data to be uploaded, and they can use the app to monitor their personal data.

Web-Based Platform

We will use the web-based platform developed by Greenspace Mental Health (Greenspace) to collect active data during the trial [54]. This platform facilitates the continuous measurement of mental health symptoms and well-being through the regular administration of standardized assessments. Participants will complete these assessments for the duration of their enrollment in the trial, including the baseline period leading up to the VR session and the 12-week follow-up thereafter.

Additional Scales

In addition to the brief MIOS or MIOS-4 and the SUDS, the scales in the following sections will be included on the web-based platform.

GAD Scale

The GAD Scale [40] is a measure that assesses the level of anxiety a person has experienced over the last 2 weeks. The scale consists of 7 items, with each item scoring on a Likert scale of 0 to 3. The total score ranges from 0 to 21, with higher scores indicating greater anxiety. The GAD-2 only includes items 1 and 2 of the GAD-7 and has a total score that ranges from 0 to 6.

PHQ Scale

The PHQ [41] is a self-report questionnaire assessing symptoms of depression over the last 2 weeks. The PHQ-9 scale consists of 9 items, with each item scoring on a 4-point Likert scale from 0 (not at all) to 3 (nearly every day). The total score ranges from 0 to 27, with higher scores indicating more severe symptoms of depression. The PHQ-2 includes only the first 2 items of the PHQ-9 and has a total score range of 0 to 6.

UCLA 3-item Loneliness Scale

The UCLA 3-item Loneliness Scale (UCLA-3) [55] is a self-report questionnaire assessing subjective feelings of loneliness and social isolation. This scale consists of three items, with each item scoring from 1 (hardly ever) to 3 (often). The total score ranges from 3 to 9, with higher scores indicating more severe symptoms of loneliness.

Scales will be administered 3 times per week, according to the schedule shown in Table 1.

Table 1. Scale administration schedule.

Day	Scale
Monday	• SUDS[a] • GAD-2[b] • PHQ-2[c] • MIOS-4[d] • UCLA-3[e]
Thursday	• SUDS • GAD-2 • PHQ-2 • MIOS-4 • UCLA-3
Saturday	• SUDS • GAD-7[f] • PHQ-9[g] • Brief MIOS[h]

[a]SUDS: Subjective Units of Distress Scale.

[b]GAD-2: Generalized Anxiety Disorder-2.

[c]PHQ-2: Patient Health Questionnaire-2.

[d]MIOS-4: Moral Injury Outcome Scale-4.

[e]UCLA-3: UCLA 3-item Loneliness Scale.

[f]GAD-7: Generalized Anxiety Disorder-7.

[g]PHQ-9: Patient Health Questionnaire-9.

[h]Brief MIOS: Brief Moral Injury Outcome Scale.

Engagement Strategy

We will use several new strategies to maximize participant engagement. First, we will send daily SMS text messages reminding participants to use their wearable and to open the wearable app. The text messages will also include a reminder on Mondays, Thursdays, and Saturdays to complete the questionnaires. Second, we will send emails reminding participants on Mondays, Thursdays, and Saturdays to complete the questionnaires. Third, we will actively monitor which participants are missing data and contact those who are on a weekly basis. Different actions will be taken depending on the amount of missing data, which are outlined in Table 2.

Lastly, we will establish a compensation system to further encourage compliance. For every 2-week period following their VR session, participants will be compensated CAD $30 (US $21.93) if they did not go a single day without any missing active or passive data. Participants will be given this honorarium upon completing the study. Participants will also be given CAD $80 (US $58.48) for completing the screening visit, CAD $80 for the VR visit, and CAD $30 for the exit interview (see Exit Interview section).

Table 2. Engagement action according to the amount of missing questionnaire and wearable data received.

Severity level	Amount of missing data	Engagement action
Minor	Missing at least one day of questionnaires or one day of wearable data in a week.	Call participant and ask them to contact the research team if they are having technical difficulties.
Medium	Missing one or 2 days of questionnaires, 2 weeks in a row; 2 questionnaires in one week; or wearable data 3 days a week, 2 weeks in a row.	Call and text participants, ask them to contact the research team regarding their missing data regardless of whether there are no technical difficulties. Repeat contact daily until response is established.
Major	Missing questionnaire 3 days in a week; wearable 4 days or more in a week; or at least 3 days of wearable data in addition to one day of questionnaires per week.	Call and text participants, ask them to contact the research team regarding their missing data regardless of whether there are no technical difficulties. Repeat contact daily until response is established.

Debrief

The debrief, which will take place immediately after the VR session, will be composed of a semistructured interview, open-ended feedback, and 3 Likert-rated statements (an interview guide is included in Multimedia Appendix 3). The semistructured interview will ask participants to reflect on and explore emotions elicited by the VR simulation and will test participants' retention of the material from the educational video. Open-ended feedback and Likert-rated statements will explore participants' impressions of the VR simulation and how it could be improved and made more realistic.

Exit Interview

At the end of the 12-week follow-up period, participants will complete a semistructured exit interview regarding their experience in the study, including perceptions of the utility and relevance of the educational video and barriers to the use of digital platforms (an interview guide is included in Multimedia Appendix 4). Included in this interview will be a retention test on the concepts and strategies discussed in the educational video. After the interview, the participant will complete the User Experience Questionnaire for the wearable and web-based platform. The User Experience Questionnaire is a widely used questionnaire for measuring impressions of the user experience of interactive products [56,57].

Quantitative Data Analysis

Sample Size

This project aims to demonstrate the preliminary utility of multimodal digital platforms to understand and mitigate general stress and moral distress. Sample size calculations were estimated based on the results of a post hoc analysis of a pilot study [33].

We calculated sample sizes for a 2-tailed paired *t* test to compare the means of the prescore and postscore of MIOS using the POWER procedure in SAS (version 9.4; SAS Institute). Parameters for the sample size calculation were estimated from a pilot study, as the SD of each score was 9.86 and the correlation of pre- and postscores was 0.75. A sample size of 55 pairs (55 patients) was estimated with a 2-sided α of 5% and a power of 90%. We set the effect size (mean difference between prescore and postscore) to detect at 3.13. Therefore, assuming a conservative dropout rate of 30%, the proposed sample size of 100 patients will still provide 70 pairs, which is sufficient to achieve >90% power based on the parameter assumptions.

Statistical Analysis

R (R Core Team) and SAS will be used to conduct statistical analysis. General participant characteristics and demographics will be listed in a baseline characteristics table. Continuous variables will be presented with the mean and SD when normally distributed, or with the median and IQR for skewed data. Dichotomous and categorical variables will be presented with frequency and percentage.

For the brief MIOS and other scales from the VR session (eg, MIOS-4 and SUDS), the prescore, postscore, and their differences will be summarized using descriptive statistics such as mean (SD) and median (IQR). For each scale, the prescore and the postscore will be compared using 2-tailed paired *t* tests. Similar analyses will be performed for the scales in the web-based platform (eg, GAD-7, GAD-2, PHQ-9, PHQ-2, and UCLA-3). The normality of all scale data will be assessed using a Shapiro-Wilk test to validate the use of the 2-tailed paired *t* test, which assumes normality. If the normality test indicates a significant deviation from a normal distribution, the Wilcoxon signed rank test, a nonparametric test for paired data, will be used. Results will be considered significant with a P value ≤ 0.05.

Personal Digital Phenotype Profile

With the active and passive data collected throughout this study, we will perform digital phenotyping as outlined in aim 3 to further understand and quantify the experience of stress and moral distress in a naturalistic setting (details on the methodology are described by Nguyen et al [34]). Digital phenotyping is defined as the "moment-by-moment quantification of the individual-level human phenotype in situ using data from smartphones and other personal digital devices" [58]. This approach can be used to effectively represent longitudinal data and may present an opportunity for tailored monitoring of treatment response and relapse prediction in individuals with mental disorders [59]. Additionally, digital

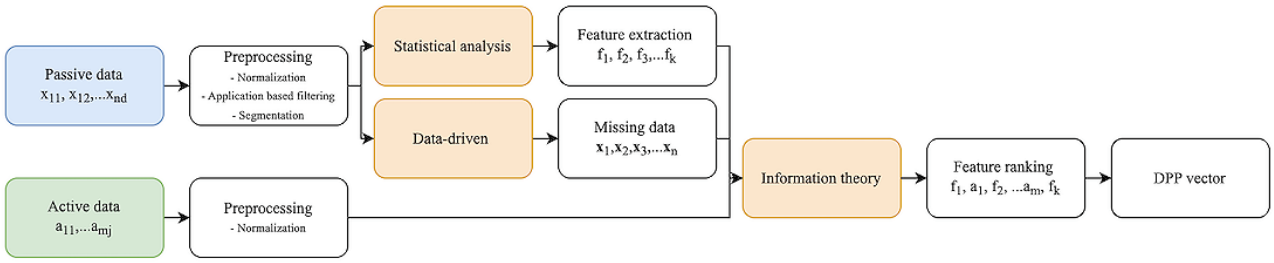
phenotyping allows for the monitoring of patients in natural contexts and in real time [59].

Once the digital phenotype profile (DPP) representation has been created, we additionally enhance this definition by proposing the term personal DPP (pDPP) as a personalized version of the DPP, where we collect longitudinal data to design digital biomarkers to monitor the changes in physical and behavioral health of an individual participant. The pDPP will be used to provide insight into a person's affective state using an individual's physiological data, even without any active data.

The process of digital phenotyping involves building a machine learning model using the active and passive data collected from each participant. An individual model is built for each person by incorporating their physiological data together with their self-reported affective states collected from questionnaires. In the long run, such models could allow for insights into nurses' mental well-being in a nonintrusive way that can improve mental health care and responses to stress.

Our goal is to perform a systematic investigation of the DPP with an emphasis on robustness for long-term utility. We envision the DPP to be represented as a multidimensional vector composed of passive and active data, where each profile is unique to one another. To do so, we propose a statistics, information theory, and data-driven (SID) pipeline to develop the foundation of the DPP as described by Nguyen et al [38]. The proposed novel SID pipeline is shown in Figure 5.

Figure 5. A block diagram representation of the proposed statistics, information theory, and data-driven (SID) pipeline (adapted from Nguyen et al [38], with permission from the Institute of Electrical and Electronics Engineers [IEEE]). DPP: digital phenotype profile.



The DPP will be created through the use of the SID and will be a representation for each individual user. Once the DPP is created, we will enhance the analysis by proposing the pDPP, where we develop individual models for each participant by incorporating their physiological data together with their self-reported affective states collected from questionnaires. The pDPP will be used for long-term utility, where we monitor the changes in physical and behavioral health of an individual participant.

MATLAB (Cleve Moler) and Python (Python Software Foundation) language will be used for signal processing and machine learning. The physiological signals will be collected in raw format during the VR intervention and will be further sent to preprocessing, feature extraction, and machine learning techniques for data analysis. Preprocessing techniques involve filtering and cleaning the signal. Techniques such as low-pass, high-pass, and notch filters will be used to remove noise, and the resulting filtered signal will be submitted to the extraction of relevant features. Feature extraction will involve extracting attributes of the signal to be better represented. Both handcrafted features and deep learning features will be extracted. Techniques for feature extraction include handcrafted features and automatic deep learning features. Handcrafted features will involve statistical values extracted from the signal, whereas automatic deep learning features will be extracted through deep learning models. Since deep learning models will be used, the features may be abstract and better represent the data in a higher dimension. Lastly, machine learning techniques will be used for the final data analytics. Trends, classifications, and relationships will be determined using different machine learning techniques. Implementations of preprocessing, feature extraction, and machine learning will be conducted in MATLAB and Python.

Preprocessing, feature extraction, and machine learning techniques will be applied to the data collected during the VR intervention to identify data patterns and develop prediction models for stress and moral distress. Similarly, active data from the web-based platform and passive data from the wearable device will be analyzed using data-driven techniques to monitor participants' activity and mental well-being in naturalistic environments and develop prediction models for stress and moral distress.

Qualitative Analysis

Audio recordings from the post-VR debrief and exit interviews will be transcribed using a 3-stage approach. First, each audio file will be transcribed (audio to text) using an automated pipeline. Each transcript will then be reviewed for accuracy and adapted to simple transcription conventions that preserve conversational prosody and deidentify personally identifying information [60].

Thematic analysis will be used to extract recurring codes and overarching themes elicited during the post-VR debrief session and exit interview [61,62]. In particular, the post-VR debrief analysis will focus on themes arising from the emotional experiences elicited by the VR simulation, decisions made in the VR simulation, and feedback on how participants thought the scenario could be improved. The exit interview analyses will focus on themes emerging from participants' recollection and impressions of the VR simulation, the perceived usefulness of the techniques presented in the educational video, and experiences with the wearable and web-based platform.

Ethical Considerations

This study was approved by the St. Michael's Hospital Research Ethics Board (22-279) in April 2023 before any participants were recruited.

Results

This project was funded by Innovation for Defence Excellence and Security: Competitive Projects, Department of Defence, Canada in January 2022. The first participant was enrolled in May 2023. As of September 2023, all 100 participants had completed screening, and 99 had completed their VR session (1 dropout). The data collection was completed in December 2023.

Discussion

Potential Benefits

Participants may benefit from psychoeducation related to stress, moral distress, and techniques to address those experiences. Participants may also experience some degree of relief from moral distress throughout this study from the educational video, and the opportunity to better understand their mental and physical health through self-monitoring built into the web-based and wearable platforms. Further, participation in this study can benefit nursing professionals as a whole, contributing to the understanding and prevention of stress and moral distress in health care professions.

Potential Risks

There are no serious risks associated with participation in this study. Participants may experience side effects associated with VR, such as nausea and dizziness, in which case the experiment will be paused. These symptoms are typically transient in nature and are expected to pass within hours after VR exposure. Participants will be asked about the occurrence of such symptoms during their VR session through the Virtual Reality Sickness Questionnaire scale. There is always a risk of data leaks when using digital platforms. However, data shared with third parties (ie, Greenspace and Oura) will be shared under a dummy email. As such, third-party platforms will have no identifiable information about participants. Data stored at St Michael's Hospital, Unity Health Toronto will be stored on encrypted and password-protected drives. It is possible that exposure to a simulated distressing event may provoke negative feelings in participants, which warrants professional assistance. The study psychiatrist will be on call should such a situation arise. Finally, all adverse events will be recorded in an adverse event log maintained by study staff.

Limitations

There are several limitations to this study. One drawback is the potentially limited ability of the VR simulation to mimic a real-life moral dilemma, which would lead to a less ecologically valid understanding of moral distress. Previous research using VR simulations has demonstrated the elicitation of genuine subjective experiences, including fear, anxiety, and paranoia, as well as objective psychophysiological responses such as changes in heart rate and skin conductance [27,28]. However, the VR simulation in phase 1 of this study induced limited changes in MIOS and Perceived Stress Scale scores [63], albeit in a small sample. Another limitation is the lack of a control group. Given that all 100 participants will be subjected to the VR simulation twice with the educational video played in between, we will not be able to discern whether changes in responses between the first and second instances of the VR simulation are caused by the educational video itself or other factors such as simulation repetition. That being said, evaluation of the efficacy of the educational video in reducing acute symptoms of stress is not the primary aim of this study.

Future Directions

The proposed project could allow for the development of evidence-based methods for the prevention and treatment of stress, moral distress, and moral injury. This will allow for a conceptual integration of perspectives from ethics, nursing, philosophy, psychology, mental health, and social science through concept mapping and examination under a rigorous data analytical framework of biostatistics and machine learning.

There is a promising potential for digital platforms to aid in the real-time identification of factors that mediate the potential for long-term psychological trauma and impairment associated with ethical conflicts. However, this will require significant modifications to the application of existing digital technologies and seamless integration across modalities. Integration with wearables and examination in virtual environments represent the next wave of digital innovation to understand patterns of physiological response and the development of machine learning training models, which would assist in predicting and responding to risks associated with moral distress.

This project is built upon the original proof-of-concept study, where a process and content evaluation of the technology platform, VR environment, and remote interventions will be undertaken by each participant over approximately 3 months. This will set the stage for more definitive studies to develop the potential of these technologies to predict and prevent moral distress. This project has the potential to develop innovative paradigms, which can be further examined in other occupational contexts prone to moral distress or injury (eg, military populations).

Acknowledgments

The team would like to thank contributions from Valentina Zuluaga Cuartas, Josheil Boparai, Nancy Zhou, Alexandra Ouellette-Zuk, Fatemeh Gholamali Nezhad, Robyn Mauro, Danielle Shin, Christine Bucago, Julia So Young Kim, Lily Le, Susan Murphy, and Sarah Ling.

Conflicts of Interest

JM, AR, HP, VKT, GHL, MI, BCD, LB, DMC, BN, AT, HJ, WL, AN, AA, BK, BL, RJ, AD, GS, and SK declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. VB is supported by an Academic Scholar Award from the Department of Psychiatry, University of Toronto, and has received research support from the Canadian Institutes of Health Research, Brain & Behavior Foundation, Ministry of Health Innovation Funds, Royal College of Physicians and Surgeons of Canada, Department of Defence (Canada), New Frontiers Research Fund, American Foundation for Suicide Prevention, University of Toronto Connaught Funds, University of Toronto EMH Seed Fund, and investigator-initiated trials from Roche Canada, Eisai Canada, Novartis, Associated Medical Services Inc Healthcare, and the National Research Council of Canada.

Multimedia Appendix 1
Educational video on stress and moral distress.
[MP4 File (MP4 Video), 190396 KB - resprot_v13i1e54180_app1.mp4]

Multimedia Appendix 2
Moral Injury Outcome Scale (MIOS) versions used in this study.
[DOCX File , 14 KB - resprot_v13i1e54180_app2.docx]

Multimedia Appendix 3
Post-VR debrief interview guide.
[DOCX File , 14 KB - resprot_v13i1e54180_app3.docx]

Multimedia Appendix 4
Exit interview guide.
[DOCX File , 12 KB - resprot_v13i1e54180_app4.docx]

References

1. Vera M, Lorente L. Nurses' performance: the importance of personal resources for coping with stressors. Issues Ment Health Nurs 2023;44(9):844-853. [doi: 10.1080/01612840.2023.2239908] [Medline: 37643368]
2. Maunder RG, Heeney ND, Hunter JJ, Strudwick G, Jeffs LP, Ginty L, et al. Trends in burnout and psychological distress in hospital staff over 12 months of the COVID-19 pandemic: a prospective longitudinal survey. J Occup Med Toxicol 2022;17(1):11 [FREE Full text] [doi: 10.1186/s12995-022-00352-4] [Medline: 35614505]
3. Ruotsalainen J, Serra C, Marine A, Verbeek J. Systematic review of interventions for reducing occupational stress in health care workers. Scand J Work Environ Health 2008;34(3):169-178 [FREE Full text] [doi: 10.5271/sjweh.1240] [Medline: 18728906]
4. Kurtzman ET, Ghazal LV, Girouard S, Ma C, Martin B, McGee BT, et al. Nursing workforce challenges in the postpandemic world. J Nurs Regul 2022;13(2):49-60 [FREE Full text] [doi: 10.1016/S2155-8256(22)00061-8] [Medline: 35880143]
5. The state of nursing in Ontario: a 2023 review. Registered Practical Nurses Association of Ontario. 2023. URL: https://www.werpn.com/wp-content/uploads/2022/08/WeRPN_The-State-of-Nursing-in-Ontario-A-2022-Review-Report.pdf [accessed 2024-03-29]
6. Park YM, Kim SY. Impacts of job stress and cognitive failure on patient safety incidents among hospital nurses. Saf Health Work 2013;4(4):210-215 [FREE Full text] [doi: 10.1016/j.shaw.2013.10.003] [Medline: 24422177]
7. Babapour AR, Gahassab-Mozaffari N, Fathnezhad-Kazemi A. Nurses' job stress and its impact on quality of life and caring behaviors: a cross-sectional study. BMC Nurs 2022;21(1):75 [FREE Full text] [doi: 10.1186/s12912-022-00852-y] [Medline: 35361204]
8. Šmigelskas K, Digrytė-Šertvytienė L, Argustaitė-Zailskienė G, Griciūtė A, Urbonaitė G, Banienė I, et al. Wellbeing and stress coping among healthcare and pharmacy workers: experiences during the first COVID-19 lockdown in Lithuania. Healthcare (Basel) 2022;10(5):787 [FREE Full text] [doi: 10.3390/healthcare10050787] [Medline: 35627925]
9. Benfante A, Di Tella M, Romeo A, Castelli L. Traumatic stress in healthcare workers during COVID-19 pandemic: a review of the immediate impact. Front Psychol 2020;11:569935 [FREE Full text] [doi: 10.3389/fpsyg.2020.569935] [Medline: 33192854]
10. Dutheil F, Mondillon L, Navel V. PTSD as the second tsunami of the SARS-Cov-2 pandemic. Psychol Med 2021;51(10):1773-1774 [FREE Full text] [doi: 10.1017/S0033291720001336] [Medline: 32326997]
11. Gavin B, Hayden J, Adamis D, McNicholas F. Caring for the psychological well-being of healthcare professionals in the COVID-19 pandemic crisis. Ir Med J 2020;113(4):51. [Medline: 32268045]

12. Kisely S, Warren N, McMahon L, Dalais C, Henry I, Siskind D. Occurrence, prevention, and management of the psychological effects of emerging virus outbreaks on healthcare workers: rapid review and meta-analysis. BMJ 2020;369:m1642 [FREE Full text] [doi: 10.1136/bmj.m1642] [Medline: 32371466]
13. Asken MJ. Now it is moral injury: the COVID-19 pandemic and moral distress. Medical Economics. 2020. URL: https://www.medicaleconomics.com/view/now-it-moral-injury-covid-19-pandemic-and-moral-distress [accessed 2024-03-29]
14. Travers M. COVID-19 poses a major quandary for the field of moral psychology. Forbes. URL: https://www.forbes.com/sites/traversmark/2020/04/15/covid-19-poses-a-major-quandary-for-the-field-of-moral-psychology/?sh=5946e22a6612 [accessed 2024-03-29]
15. Holtz H, Heinze K, Rushton C. Interprofessionals' definitions of moral resilience. J Clin Nurs 2018;27(3-4):e488-e494. [doi: 10.1111/jocn.13989] [Medline: 28771909]
16. Jameton A. Nursing Practice: the Ethical Issues. Englewood Cliffs, NJ: Prentice-Hall; 1984.
17. Corley MC. Nurse moral distress: a proposed theory and research agenda. Nurs Ethics 2002;9(6):636-650. [doi: 10.1191/0969733002ne557oa] [Medline: 12450000]
18. Zanker G. Achilles in Vietnam: combat trauma and the undoing of character (review). Philos Lit 1995;19(2):376-377. [doi: 10.1353/phl.1995.0087]
19. Litz BT, Stein N, Delaney E, Lebowitz L, Nash WP, Silva C, et al. Moral injury and moral repair in war veterans: a preliminary model and intervention strategy. Clin Psychol Rev 2009;29(8):695-706. [doi: 10.1016/j.cpr.2009.07.003] [Medline: 19683376]
20. Moral distress and moral injury: recognising and tackling it for UK doctors. British Medical Association. 2021. URL: https://www.bma.org.uk/media/4209/bma-moral-distress-injury-survey-report-june-2021.pdf# [accessed 2024-03-29]
21. Epstein EG, Whitehead PB, Prompahakul C, Thacker LR, Hamric AB. Enhancing understanding of moral distress: the measure of moral distress for health care professionals. AJOB Empir Bioeth 2019;10(2):113-124. [doi: 10.1080/23294515.2019.1586008] [Medline: 31002584]
22. Steinmetz SE, Gray MJ. Treatment for distress associated with accurate appraisals of self-blame for moral transgressions. Curr Psychiatry Rev 2015;11(3):207-219. [doi: 10.2174/1573400511666150629105709]
23. Southwick SM, Charney DS. The science of resilience: implications for the prevention and treatment of depression. Science 2012;338(6103):79-82. [doi: 10.1126/science.1222942] [Medline: 23042887]
24. Burston AS, Tuckett AG. Moral distress in nursing: contributing factors, outcomes and interventions. Nurs Ethics 2013;20(3):312-324. [doi: 10.1177/0969733012462049] [Medline: 23275458]
25. Denham F, Varese F, Hurley M, Allsopp K. Exploring experiences of moral injury and distress among health care workers during the COVID-19 pandemic. Psychol Psychother 2023;96(4):833-848 [FREE Full text] [doi: 10.1111/papt.12471] [Medline: 37203424]
26. Rice EM, Rady MY, Hamrick A, Verheijde JL, Pendergast DK. Determinants of moral distress in medical and surgical nurses at an adult acute tertiary care hospital. J Nurs Manag 2008;16(3):360-373. [doi: 10.1111/j.1365-2834.2007.00798.x] [Medline: 18324996]
27. Bell IH, Nicholas J, Alvarez-Jimenez M, Thompson A, Valmaggia L. Virtual reality as a clinical tool in mental health research and practice? Dialogues Clin Neurosci 2020;22(2):169-177 [FREE Full text] [doi: 10.31887/DCNS.2020.22.2/lvalmaggia] [Medline: 32699517]
28. Freeman D, Reeve S, Robinson A, Ehlers A, Clark D, Spanlang B, et al. Virtual reality in the assessment, understanding, and treatment of mental health disorders. Psychol Med 2017;47(14):2393-2400 [FREE Full text] [doi: 10.1017/S003329171700040X] [Medline: 28325167]
29. Ridout SJ, Spofford CM, van't Wout-Frank M, Philip NS, Unger WS, Carpenter LL, et al. Heart rate variability responses to a standardized virtual reality exposure in veterans with PTSD. Curr Treat Options Psych 2017;4(3):271-280. [doi: 10.1007/s40501-017-0118-9]
30. van 't Wout M, Spofford CM, Unger WS, Sevin EB, Shea MT. Skin conductance reactivity to standardized virtual reality combat scenes in Veterans with PTSD. Appl Psychophysiol Biofeedback 2017;42(3):209-221. [doi: 10.1007/s10484-017-9366-0] [Medline: 28646388]
31. Malta LS, Giosan C, Szkodny LE, Altemus MM, Rizzo AA, Silbersweig DA, et al. Development of a virtual reality laboratory stressor. Virtual Real 2020;25(2):293-302. [doi: 10.1007/s10055-020-00455-5]
32. Carl E, Stein AT, Levihn-Coon A, Pogue JR, Rothbaum B, Emmelkamp P, et al. Virtual reality exposure therapy for anxiety and related disorders: a meta-analysis of randomized controlled trials. J Anxiety Disord 2019;61:27-36. [doi: 10.1016/j.janxdis.2018.08.003] [Medline: 30287083]
33. Nguyen B, Torres A, Sim W, Kenny D, Campbell DM, Beavers L, et al. Digital interventions to reduce distress among health care providers at the frontline: protocol for a feasibility trial. JMIR Res Protoc 2022;11(2):e32240 [FREE Full text] [doi: 10.2196/32240] [Medline: 34871178]
34. Nguyen B, Torres A, Espinola CW, Sim W, Kenny D, Campbell DM, et al. Development of a data-driven digital phenotype profile of distress experience of healthcare workers during COVID-19 pandemic. Comput Methods Programs Biomed 2023;240:107645 [FREE Full text] [doi: 10.1016/j.cmpb.2023.107645] [Medline: 37352806]

35. Espinola CW, Nguyen B, Torres A, Sim W, Rueda A, Beavers L, et al. Digital interventions for stress among frontline health care workers: results from a pilot feasibility cohort trial. JMIR Serious Games 2024;12:e42813 [FREE Full text] [doi: 10.2196/42813] [Medline: 38194247]
36. Sivanathan M, Espinola CW, Quevedo AU, Kapralos B, Krishnan S, Bhat V, et al. Development of content for a virtual reality simulation to understand and mitigate moral distress in healthcare workers. Cureus 2022;14(11):e31240 [FREE Full text] [doi: 10.7759/cureus.31240] [Medline: 36505119]
37. Accurate health information accessible to everyone. Oura Ring. URL: https://ouraring.com/product/rings/heritage/silver [accessed 2024-03-29]
38. Nguyen B, Nigro M, Rueda A, Bhat V, Krishnan S. Digital phenotype representation by statistical, information theory, data-driven approach with digital health data. 2023 Presented at: ICASSP 2023—2023 IEEE International Conference on Acoustics, Speech and Signal Processing (ICASSP); June 04-10, 2023; Rhodes, Greece p. 1-5. [doi: 10.1109/icassp49357.2023.10095849]
39. Meta quest 2: health and safety information. Meta Platforms Technologies. URL: https://www.meta.com/ca/legal/quest/health-and-safety-warnings/ [accessed 2024-03-29]
40. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006;166(10):1092-1097 [FREE Full text] [doi: 10.1001/archinte.166.10.1092] [Medline: 16717171]
41. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001;16(9):606-613 [FREE Full text] [doi: 10.1046/j.1525-1497.2001.016009606.x] [Medline: 11556941]
42. Hsu CC, Sandford BA. The Delphi technique: making sense of consensus. University of Massachusetts Amherst 2007;12(1):10. [doi: 10.7275/PDZ9-TH90]
43. Gillman L, Adams J, Kovac R, Kilcullen A, House A, Doyle C. Strategies to promote coping and resilience in oncology and palliative care nurses caring for adult patients with malignancy: a comprehensive systematic review. JBI Database System Rev Implement Rep 2015;13(5):131-204. [doi: 10.11124/jbisrir-2015-1898] [Medline: 26455609]
44. Hagerman LA, Manankil-Rankin L, Schwind JK. Self-compassion in undergraduate nursing: an integrative review. Int J Nurs Educ Scholarsh 2020;17(1):20200021. [doi: 10.1515/ijnes-2020-0021] [Medline: 33151177]
45. Balban MY, Neri E, Kogon MM, Weed L, Nouriani B, Jo B, et al. Brief structured respiration practices enhance mood and reduce physiological arousal. Cell Rep Med 2023;4(1):100895 [FREE Full text] [doi: 10.1016/j.xcrm.2022.100895] [Medline: 36630953]
46. Litz BT, Plouffe RA, Nazarov A, Murphy D, Phelps A, Coady A, et al. Defining and assessing the syndrome of moral injury: initial findings of the moral injury outcome scale consortium. Front Psychiatry 2022;13:923928 [FREE Full text] [doi: 10.3389/fpsyt.2022.923928] [Medline: 35873252]
47. Tanner BA. Validity of global physical and emotional SUDS. Appl Psychophysiol Biofeedback 2012;37(1):31-34. [doi: 10.1007/s10484-011-9174-x] [Medline: 22038278]
48. Igroup presence questionnaire (IPQ) overview. igroup.org. URL: http://www.igroup.org/pq/ipq/index.php [accessed 2023-06-26]
49. Kim HK, Park J, Choi Y, Choe M. Virtual Reality Sickness Questionnaire (VRSQ): motion sickness measurement index in a virtual reality environment. Appl Ergon 2018;69:66-73. [doi: 10.1016/j.apergo.2017.12.016] [Medline: 29477332]
50. Zangróniz R, Martínez-Rodrigo A, Pastor JM, López MT, Fernández-Caballero A. Electrodermal activity sensor for classification of calm/distress condition. Sensors (Basel) 2017;17(10):2324 [FREE Full text] [doi: 10.3390/s17102324] [Medline: 29023403]
51. Kim HG, Cheon EJ, Bai DS, Lee YH, Koo BH. Stress and heart rate variability: a meta-analysis and review of the literature. Psychiatry Investig 2018;15(3):235-245 [FREE Full text] [doi: 10.30773/pi.2017.08.17] [Medline: 29486547]
52. Roscoe AH. Assessing pilot workload. Why measure heart rate, HRV and respiration? Biol Psychol 1992;34(2-3):259-287. [doi: 10.1016/0301-0511(92)90018-p] [Medline: 1467396]
53. Minakuchi E, Ohnishi E, Ohnishi J, Sakamoto S, Hori M, Motomura M, et al. Evaluation of mental stress by physiological indices derived from finger plethysmography. J Physiol Anthropol 2013;32(1):17 [FREE Full text] [doi: 10.1186/1880-6805-32-17] [Medline: 24119254]
54. Measurement-based care solutions. Greenspace Mental Health. 2022. URL: https://greenspacehealth.com/en-ca/ [accessed 2023-06-26]
55. Hughes ME, Waite LJ, Hawkley LC, Cacioppo JT. A short scale for measuring loneliness in large surveys: results from two population-based studies. Res Aging 2004;26(6):655-672 [FREE Full text] [doi: 10.1177/0164027504268574] [Medline: 18504506]
56. Schrepp M, Hinderks A, Thomaschewski J. Design and evaluation of a short version of the User Experience Questionnaire (UEQ-S). Int J Interact Multimed Artif Intell 2017;4(6):103-108 [FREE Full text] [doi: 10.9781/ijimai.2017.09.001]
57. Schrepp M, Hinderks A, Thomaschewski J. Applying the User Experience Questionnaire (UEQ) in different evaluation scenarios. In: Marcus A, editor. Design, User Experience, and Usability: Theories, Methods, and Tools for Designing the User Experience: Third International Conference, DUXU 2014, Held as Part of the HCI International 2014, Heraklion, Crete, Greece, June 22-27, 2014, Proceedings, Part I, LNCS 8517. Cham, Switzerland: Springer International Publishing; 2014:383-392.

58. Torous J, Kiang MV, Lorme J, Onnela JP. New tools for new research in psychiatry: a scalable and customizable platform to empower data driven smartphone research. JMIR Ment Health 2016;3(2):e16 [FREE Full text] [doi: 10.2196/mental.5165] [Medline: 27150677]
59. Torous J, Myrick KJ, Rauseo-Ricupero N, Firth J. Digital mental health and COVID-19: using technology today to accelerate the curve on access and quality tomorrow. JMIR Ment Health 2020;7(3):e18848 [FREE Full text] [doi: 10.2196/18848] [Medline: 32213476]
60. Thorsten D, Thorsten P, Christian S. Manual (on) Transcription: Transcription Conventions, Software Guides and Practical Hints for Qualitative Researchers, 3rd English Edition. Marburg: Dr. Dresing et Pehl GmbH; 2015.
61. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol 2006;3(2):77-101. [doi: 10.1191/1478088706qp063oa]
62. Virginia B, Victoria C. Thematic Analysis: A Practical Guide. London: SAGE Publications Ltd; 2021.
63. Espinola CW, Nguyen B, Torres A, Sim W, Rueda A, Beavers L, et al. Digital interventions for stress among frontline health care workers: results from a pilot feasibility cohort trial. JMIR Serious Games 2024;12:e42813 [FREE Full text] [doi: 10.2196/42813] [Medline: 38194247]

Abbreviations

DPP: digital phenotype profile
EDA: electrodermal activity
GAD-7: Generalized Anxiety Disorder-7
HCW: health care worker
HRV: heart rate variability
MIOS: Moral Injury Outcome Scale
pDPP: personal digital phenotype profile
PHQ-9: Patient Health Questionnaire-9
PTSD: posttraumatic stress disorder
SID: statistics, information theory, and data-driven
SUDS: Subjective Units of Distress Scale
UCLA-3: UCLA 3-item Loneliness Scale
VR: virtual reality
VRET: VR exposure therapy

Edited by A Mavragani; submitted 01.12.23; peer-reviewed by S Al Mukhtar, M Cummins; comments to author 20.02.24; revised version received 04.03.24; accepted 06.03.24; published 06.05.24.

Please cite as:
Martin J, Rueda A, Lee GH, Tassone VK, Park H, Ivanov M, Darnell BC, Beavers L, Campbell DM, Nguyen B, Torres A, Jung H, Lou W, Nazarov A, Ashbaugh A, Kapralos B, Litz B, Jetly R, Dubrowski A, Strudwick G, Krishnan S, Bhat V
Digital Interventions to Understand and Mitigate Stress Response: Protocol for Process and Content Evaluation of a Cohort Study
JMIR Res Protoc 2024;13:e54180
URL: https://www.researchprotocols.org/2024/1/e54180
doi:10.2196/54180
PMID:38709554

Protocol

Measuring Physical Functioning Using Wearable Sensors in Parkinson Disease and Chronic Obstructive Pulmonary Disease (the Accuracy of Digital Assessment of Performance Trial Study): Protocol for a Prospective Observational Study

Debbie de Graaf[1], MSc; Nienke M de Vries[1], PhD; Tessa van de Zande[1], MSc; Janneke J P Schimmel[1], MSc; Sooyoon Shin[2], PhD; Nathan Kowahl[2], MSc; Poulami Barman[2], MSc; Ritu Kapur[1,2], PhD; William J Marks Jr[2], MD, MS; Alex van 't Hul[3], PhD; Bastiaan Bloem[1], MD, PhD

[1]Radboud University Medical Center, Donders Institute for Brain, Cognition and Behavior, Department of Neurology, Center of Expertise for Parkinson & Movement Disorders, Nijmegen, Netherlands

[2]Verily Life Sciences, South San Fransisco, CA, United States

[3]Radboud University Medical Center, Radboud Institute for Health Sciences, Department of Respiratory Diseases, Nijmegen, Netherlands

Corresponding Author:
Debbie de Graaf, MSc
Radboud University Medical Center
Donders Institute for Brain, Cognition and Behavior
Department of Neurology, Center of Expertise for Parkinson & Movement Disorders
Reinier Postlaan 4
Nijmegen, 6525 GC
Netherlands
Phone: 31 243613450
Email: debbie.degraaf@radboudumc.nl

Abstract

Background: Physical capacity and physical activity are important aspects of physical functioning and quality of life in people with a chronic disease such as Parkinson disease (PD) or chronic obstructive pulmonary disease (COPD). Both physical capacity and physical activity are currently measured in the clinic using standardized questionnaires and tests, such as the 6-minute walk test (6MWT) and the Timed Up and Go test (TUG). However, relying only on in-clinic tests is suboptimal since they offer limited information on how a person functions in daily life and how functioning fluctuates throughout the day. Wearable sensor technology may offer a solution that enables us to better understand true physical functioning in daily life.

Objective: We aim to study whether device-assisted versions of 6MWT and TUG, such that the tests can be performed independently at home using a smartwatch, is a valid and reliable way to measure the performance compared to a supervised, in-clinic test.

Methods: This is a decentralized, prospective, observational study including 100 people with PD and 100 with COPD. The inclusion criteria are broad: age ≥18 years, able to walk independently, and no co-occurrence of PD and COPD. Participants are followed for 15 weeks with 4 in-clinic visits, once every 5 weeks. Outcomes include several walking tests, cognitive tests, and disease-specific questionnaires accompanied by data collection using wearable devices (the Verily Study Watch and Modus StepWatch). Additionally, during the last 10 weeks of this study, participants will follow an aerobic exercise training program aiming to increase physical capacity, creating the opportunity to study the responsiveness of the remote 6MWT.

Results: In total, 89 people with PD and 65 people with COPD were included in this study. Data analysis will start in April 2024.

Conclusions: The results of this study will provide information on the measurement properties of the device-assisted 6MWT and TUG in the clinic and at home. When reliable and valid, this can contribute to a better understanding of a person's physical capacity in real life, which makes it possible to personalize treatment options.

Trial Registration: ClinicalTrials.gov NCT05756075; https://clinicaltrials.gov/study/NCT05756075

International Registered Report Identifier (IRRID): DERR1-10.2196/55452

(JMIR Res Protoc 2024;13:e55452) doi:10.2196/55452

KEYWORDS

Parkinson disease; COPD; chronic obstructive pulmonary disease; physical activity; physical capacity; wearable devices; walking; exercise; locomotion; home-based; wearable; wearables; wearable sensor; dementia; smartwatch; StepWatch; treatment

Introduction

Physical functioning is an important aspect of daily living. It represents a broad concept defined as one's ability to carry out activities that require physical actions, ranging from activities of daily living to more complex activities that require a combination of skills within a social context. It is also known to be a powerful factor in the prevention and treatment of several health conditions in older adults [1-5]. Physical functioning is an independent predictor of functional independence, disability, morbidity, and mortality in healthy older people [4,5]. It is also relevant in a wide spectrum of people with chronic diseases [6-9], which makes it an important aspect to measure. Physical functioning requires multiple factors, including physical capacity and physical activity [1]. Physical capacity can be defined as what a person can do in a standardized environment, where physical activity is what a person truly does in daily life [10,11]. Today, physical capacity is measured in clinical settings using advanced tests like maximal oxygen uptake or walking tests such as the 6-minute walk test (6MWT) [1]. Validated questionnaires are generally used to obtain self-reported levels of physical activity in real-life situations [12,13].

Relying only on in-clinic standardized tests is suboptimal for several reasons. First, in-clinic tests give limited information on how a person is functioning in daily life. For example, people with Parkinson disease (PD) experience the so-called *kinesia paradoxa* in which they function unexpectedly well under stressful circumstances, which a clinic visit is for most [14]. Other symptoms such as tremors are typically worse during in-clinic assessments [15]. This problem is compounded by the fact that many people with PD take extra medication before their consultation hoping to make a good impression. Some even practice the clinical tests while sitting in the waiting room. Second, episodic visits are not well suited to detect the complex and evolving fluctuations in daily functioning [6,9,16]. Moreover, the brief in-clinic evaluations cannot reliably capture the common and disabling fluctuations in response to Parkinson medication [17]. Finally, measuring physical activity with a questionnaire is highly unreliable because of its retrospective and subjective nature [13].

With the advent of innovative technologies such as smartwatches, both aspects of physical functioning have become measurable in a person's free-living environment [18-22]. Wearable technology may thus offer an attractive solution to overcome the aforementioned limitations of in-clinic testing [23]. This would be especially helpful for the evaluation of people with chronic conditions like PD or chronic obstructive pulmonary disease (COPD) because the symptoms of both diseases fluctuate within a single day per medication intake or environmental factors [17,24]. Deploying wearable sensors enables monitoring of daily physical functioning over a prolonged period, without relying on the person's in-clinic performance or memory. Remote assessments of physical activity may also lower the barrier for people to check their performance regularly, and also lower the burden to do so for caregivers and researchers [25]. Wearable technology can also better evaluate the effectiveness of treatments, thus enabling a more personalized treatment. Today, measuring physical activity at home using wearable devices has become mainstream and is feasible [12,26,27]. More recently, also measuring physical capacity using wearables has been shown to be feasible but the clinimetric properties have been investigated to a very limited extent as yet [8,28-31].

Here, we propose a protocol to study a wrist-worn device that can measure physical activity and physical capacity passively and remotely while performing assessments at home. The measurement properties of this device regarding physical activity are good but have been obtained in a healthy population [32,33]. We will extend these results and focus on the measurement properties of measuring physical capacity using the 6MWT in people with PD and COPD.

Our primary aim is to study the measurement properties of a device-assisted 6MWT performed at home compared to in-clinic assessments. Our secondary aim is to study the clinimetric properties of the device-assisted Timed Up and Go test (TUG) at home compared to in-clinic assessments.

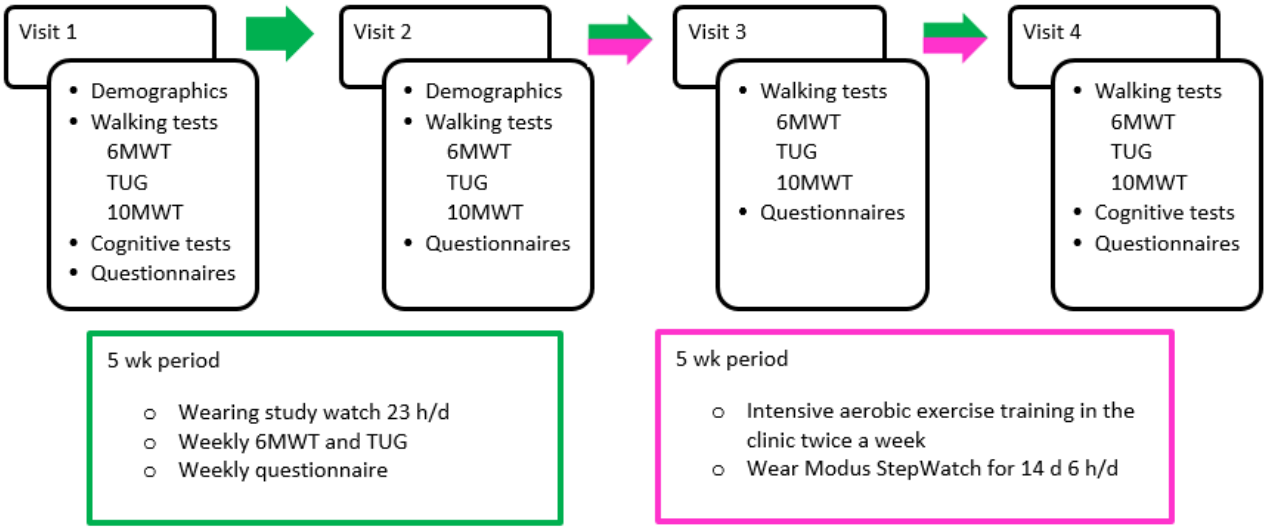
Methods

Study Design

This is a decentralized, prospective, observational study with a 15-week follow-up involving participants with PD and COPD (Figure 1). This study will be coordinated by the Radboudumc and will be executed in 25 physiotherapy practices throughout the Netherlands. The physiotherapists will perform the in-clinic assessments. Participants will visit their local physiotherapy practice 4 times, once every 5 weeks, for in-clinic assessments of walking capacity, cognitive functioning, daily functioning, and specific disease symptoms. Data collection during each visit will take approximately 2 hours. During the in-clinic assessments, participants will wear 2 different wearable sensor devices; the Verily Study Watch on 1 wrist and the Modus StepWatch on the ankle. Participants will be instructed to wear the devices on the same side throughout this study. Moreover, during the course of this study, participants will wear the Verily Study Watch at home for 23 hours a day. Additionally, participants will perform 2 walk tests at home every week. Between visit 2 and visit 4, participants will participate in supervised, in-clinic, high-intensity exercise training according to the current physiotherapy guidelines [34,35]. During this training period, participants will wear the Modus StepWatch at home for 2 weeks. This will provide data to validate real-life walking measures from this study's watch against the StepWatch. Throughout this study, a dedicated helpdesk will

proactively assist participants, address problems and questions, and solve issues regarding this study and the devices. The Accuracy of Digital Assessment of Performance Trial (ADAPT) study is registered at ClinicalTrials.gov (NCT05756075).

Figure 1. Study overview. 6MWT: 6-minute walk test; 10MWT: 10-meter walk test; TUG: Timed Up and Go test.



Study Population

We aim to enroll 200 participants, 100 with PD and 100 with COPD between December 2021 and July 2023. Participants are eligible for this study if they meet the following inclusion criteria:

PD or COPD diagnosed by a neurologist or pulmonologist, respectively; aged 18 years or older; able to read and understand Dutch; willing, competent, and able to comply with all aspects of the protocol, including follow-up schedule; willing and able to complete patient-reported outcomes via the internet; able to walk without the use of an assistive device; Hoehn and Yahr stage 1 or 2 (PD-specific); and COPD with perceived limited exercise capacity, irrespective of airway obstruction severity (COPD-specific).

Potential participants will be excluded if they have a high fall risk (for PD) or cardiovascular risk profile (for COPD) impacting the safety of performing the walk tests at home without supervision, as judged by the general practitioner. Patients with other comorbidities are explicitly not excluded from participation. Other exclusion criteria include a co-occurrence of PD and COPD, the inability to make an arm swing at all or if a patient is in a situation that prevents arm swing completely (eg, use of rollator), pregnancy, cognitive impairment as judged by the physiotherapist, participating in another investigational study, participating in a supervised high-intensity aerobic exercise program, or nickel allergy as components of the Verily Study Watch contain trace amounts of this metal.

Recruitment and Enrollment

In each physiotherapy practice, 2 physiotherapists will participate, 1 specializing in COPD and 1 specializing in PD affiliated with the Dutch nationwide ParkinsonNet infrastructure [36]. The physiotherapists will be trained extensively and certified in performing all assessments of this study's protocol to facilitate standardization between the participating practices. Up-to-date standard operating procedures will be shared with every practice as a reference and will be reviewed by the Radboudumc research team regularly. Further, the Radboudumc research team will guide and coach the physiotherapists to support adherence to this study's protocol.

Physiotherapists will identify potentially eligible patients who are already known in their practice because of a former treatment episode or patients newly referred by the general practitioner or medical specialist and provide them with the information letter. If a patient shows interest in this study, a researcher from the Radboudumc will contact them providing additional information, address any questions, and check eligibility. When willing and eligible to participate, participants will be directed to Verily's proprietary web-based system "Baseline Platform" where they are invited to create an account and digitally sign the screening consent form. Once the account is created, the physiotherapist will contact the participant's treating physician to confirm the diagnosis and will ask about potential contraindications to participation in this study (ie, history of falling or cardiovascular risk). If the treating physician expresses no objections, the first appointment will be scheduled.

At the first visit, the physiotherapist will check eligibility again whereafter this study's informed consent form will be signed on paper by both the participant and physiotherapist, who will perform the assessments. A copy will be provided to the participant. Participants who withdraw their participation during this study will be excluded from follow-up, but the data obtained will be kept in the central database and will be used for data analysis.

Devices

Verily Study Watch

Throughout this study, participants with PD will wear the Verily Study Watch on the wrist of the least affected side while participants with COPD will wear the watch on the wrist of the nondominant side.

Participants will be asked to wear the Verily Study Watch preferably for 24 hours a day, except during daily charging and during wet activities (eg, showering or swimming). During the baseline visit, the physiotherapist will clarify the importance of the wear time with the participant and will explain and demonstrate the use of the Verily Study Watch. A paper-based manual plus an instructional video will be available for participants with instructions for the Verily Study Watch.

The Verily Study Watch is exclusively for investigational use in clinical trials only. It is a multi-sensor wearable device to extend data collection for clinical studies beyond trial sites and into the free-living environment. The watch contains an accelerometer, gyroscope, and a photoplethysmography. The device is not CE (Conformité Européenne) marked or cleared in the United States. The device enables the collection of physiological and environmental data about movement and activity, pulse rate, and skin impedance. Data from the Verily Study Watch will be encrypted and sent securely to the Verily Cloud using a USB synching and charging cradle and wireless connectivity bridge (Verily Study Hub; Figure 2). The Verily Study Watch has been deployed in several studies, including the Baseline Health Study [37], the Parkinson Progression Markers Initiative [38] in the United States, and the Personalized Parkinson Project [39] in the Netherlands.

Figure 2. The Verily Study Watch, along with syncing and charging cradle and Verily Study Hub.

Modus StepWatch

The Modus StepWatch will be placed on the ankle on the corresponding side of the Verily Study Watch during the 4 in-clinic visits. Between visit 2 and visit 4, participants will wear the Modus StepWatch at home for 14 consecutive days for at least 6 hours a day. Participants will be able to choose these 14 consecutive days themselves. To gain insight into the exact wearing times, the participants will create a log where they write down the exact times of wearing the Modus StepWatch.

This device is an ankle-worn wearable medical device (CE class 1 and marked medical in Europe) which will be used as a reference device for measuring participants' ambulation. The onboard 2D accelerometer collects motion data. The collected data can be transferred to the corresponding StepWatch app installed on an iPad. From there, data will be transferred to this study's database. The validity of this device has been obtained in people with PD [40] and COPD [41] as well as in healthy people [42-44].

Assessments

Demographics

During the first visit, demographics, medical history, and medication intake will be registered. Cognitive functions will be assessed during the first and last visit. During each visit, several additional questionnaires on disease symptoms and quality of life will be completed (see Tables 1 and 2 for an overview).

Table 1. Overview of assessments performed by physiotherapist and questionnaires in the Accuracy of Digital Assessment of Performance Trial (ADAPT) study[a].

Assessments	Visit 1	Visit 2[b]	Visit 3[b]	Visit 4[b]
Motor functioning				
MDS-UPDRS-III/IV[c] (PD[d] only)	✓	✓	✓	✓
H&Y scale[e] (PD only)	✓	✓	✓	✓
TUG[f]	✓	✓	✓	✓
6MWT[g] (2×); pre- or post-Borg score fatigue and dyspnea	✓	✓	✓	✓
10MWT[h] (Single context [3×], dual context [3×]	✓	✓	✓	✓
Cognitive functioning and quality of life				
MoCA[i] (with alternative version during follow-up)	✓			✓
MDS-UPDRS-I (PD only)	✓	✓	✓	✓
EQ-5D-5L	✓	✓	✓	✓
Demographics and lifestyle				
Medical history	✓	✓		
Medication	✓			
Arm Hair Index	✓			
Skin tone (Fitzpatrick Scale)	✓			
Autonomic function				
Blood pressure (before 6MWT)	✓	✓	✓	✓
Heart rate (before 6MWT, 0 min after 6MWT, 1 min after 6MWT, 2 min after 6MWT)	✓	✓	✓	✓
SpO2[j] (before 6MWT, 0 min after 6MWT, 1 min after 6MWT, 2 min after 6MWT)	✓	✓	✓	✓

[a]Study Watch sensor data will be recorded during all in-clinic activities, including all walking tests. With the timestamps recorded on the Study Watch for the onset and offset of tasks via the Study Watch graphical user interface, a sensor-based 6-minute walk test will be estimated and compared to the site coordinator's recorded actual 6-minute walk test.

[b]Every fifth week.

[c]MDS-UPDRS-I/II/III/IV: Movement Disorders Society–sponsored revision of the Unified Parkinson's Disease Rating Scale (I) nonmotor aspects of experiences of daily living, (II) motor experiences of the daily living section, (III) motor examination section, and (IV) motor complications section.

[d]PD: Parkinson disease.

[e]H&Y scale: Hoehn and Yahr scale.

[f]TUG: Timed Up and Go test.

[g]6MWT: 6-minute walk test.

[h]10MWT: 10-meter walk test.

[i]MoCA: Montreal Cognitive Assessment.

[j]SpO2: oxygen saturation.

Table 2. Devices and at-home assessments.

Methods	Assessments	Time collected
Verily Study Watch	• Photoplethysmography • Heart rate • IMU[a] including a 3-axis accelerometer and 3-axis gyroscope • Step count • Skin impedance	Continuous data collection, up to 24 h/d
Modus StepWatch	• Step count	All visits[b]
Self-reported patient questionnaires[c]	• ESS[d] • MDS-UPDRS-II[e] (Parkinson disease only) • HADS[f] • PDQ-39[g] (Parkinson disease only) • LAPAQ[h] • CCQ[i] (chronic obstructive pulmonary disease only)	After each visit
At home assessments (walking tests with Verily Study Watch)	• Timed Up and Go test • 6-minute walk test with pre- and post-Borg score	Weekly
Self-reported questionnaires	• FACITF-4[j]	Weekly

[a]IMU: inertial measurement unit.

[b]Wearing at home for 14 consecutive days between visit 2 and visit 4.

[c]Within 2 weeks after each in-clinic visit.

[d]ESS: Epworth Sleepiness Scale.

[e]MDS-UPDRS-II: Movement Disorders Society–sponsored revision of the Unified Parkinson's Disease Rating Scale (II) motor experiences of the daily living section.

[f]HADS: Hospital Anxiety and Depression Scale.

[g]PDQ-39: 39-item Parkinson's Disease Questionnaire.

[h]LAPAQ: Longitudinal Aging Study Amsterdam Physical Activity Questionnaire.

[i]CCQ: Clinical Chronic Obstructive Pulmonary Disease Questionnaire.

[j]FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy.

In-Clinic Measurements

The in-clinic assessments will consist of 3 different walking tests. The first test is the 6MWT which will be performed twice according to the most recent guidelines over a straight course of 10 meters [45]. The participants will be instructed to walk at a comfortable speed that they can sustain for 6 minutes. The physiotherapist measures the walked meters during the 6MWT. Second, the TUG will be performed and will be executed twice [46]. Participants will sit in a chair, stand up, walk for 3 meters at a comfortable speed, turn, walk back, and sit down in the chair again. The physiotherapist will measure the time it takes to complete this task. The third walking test is the 10-meter walk test (10MWT) [47]. This test will be performed 6 times; 3 times without cognitive tasks (single context 10MWT) and 3 times with cognitive tasks (dual context 10MWT). During all 6 times, participants will walk over a straight 10-meter course at a comfortable speed with alternating contexts. The physiotherapist will measure the time it takes to walk between the 2nd and 8th meters of the walkway. During the dual context 10MWT, participants will perform a small cognitive task during walking, for example counting backwards from 100 with steps of 7.

Home Measurements

Participants will wear the Verily Study Watch for 24 hours a day throughout the whole study. The device collects passively recorded data while participants wear it. Additionally, participants will be asked to complete the virtual walk test (VWT) independently at home. The TUG and 6MWT with pre- and post-Borg scores will be performed once a week with the guidance of the graphical user interface on the Verily Study Watch. The Verily Study Watch will provide a notification to the participant on the chosen preset day and time to remind them to perform the VWT. The watch will record the start and end of the 6MWT and TUG from button presses on the watch by the participant. Participants with PD will be asked to perform the walk tests 30 minutes to an hour after medication intake and give a tag on the Verily Study Watch, while participants with COPD can choose a standardized time unrelated to medication intake. The VWT can be postponed to the next day at the same time if desirable.

Participants will choose a course to perform the 6MWT inside their homes where they can walk straight for as many meters as possible. Throughout this study, participants will use the same course every time they perform the VWT. A map will be sent to the Radboudumc research team containing an overview

of the course taken. After each visit, participants will complete a set of validated questionnaires at home, including about quality of life, physical activity, fatigue, sleep, anxiety, and depression in a diagnosis-specific questionnaire [48-55]. These questionnaires will be completed digitally within 2 weeks after each visit. The questionnaire about fatigue will be completed every week.

Intervention

Between visit 2 and visit 4 participants will participate in high-intensity aerobic exercise training according to current physiotherapy guidelines [34,35]. With this intervention, we aim to increase the physical capacity of our participants and, more specifically, the participants' walking capacity to measure the sensitivity to detect changes of the device-assisted 6MWT.

The participants will follow a training session twice a week under the supervision of their physiotherapist. These sessions can be individual sessions or group sessions together with other study participants. Alongside these training sessions, participants will be asked to train independently at home once a week by going outside for a walk. The supervised training sessions will consist of a mix between general physical capacity training and localized muscle function training with a focus on the lower extremities. If needed, the session can be completed with components that are important for the participant, for example, balance training. The physiotherapists will keep a log of each supervised session including the so-called FITT factors: frequency, intensity, timing, and type of training.

Statistical Analyses

The primary aim is to study the measurement properties of the device-assisted 6MWT to assess its ability to obtain physical capacity at home. Our secondary aim is to study these measurement properties of the device-assisted TUG.

The data from the device-assisted 6MWT will be derived from three different situations: (1) during the in-clinic walk tests, (2) during the VWT at home administered via application of the watch, and (3) during free-living where the data are passively recorded.

For our primary aim, we first obtain the measurement agreement between the in-clinic 6-minute walk test distance (6MWD) derived from the Verily Study Watch and the measurements by the physiotherapist. This will be assessed using the intraclass correlation coefficient (ICC) and will be obtained for every study visit. Further, the measurement agreement between the 6MWD of the last virtual 6MWT before the in-clinic assessments and the measurements by the physiotherapist in-clinic will be assessed with the ICC. A Bland-Altman plot will be provided as well. The measurement agreement will be considered "good" when the ICC is at least 0.70 [56].

Second, the test-retest reliability of the 6MWT taken at different visits will be assessed by reporting the ICC. Here, we will use the 6MWD derived from the Verily Study Watch of the 2 in-clinic 6MWTs performed during all 4 visits. The test-retest reliability of the weekly 6MWT at home will also be obtained using the ICC. A Bland-Altman plot will be provided to assess the test-retest reliability too.

Third, we will characterize the performance of the device-assisted 6MWT in capturing changes over time with the physiotherapy intervention. For this comparison, we will use the 6MWD derived from the device-assisted 6MWT during visit 2 and visit 4.

For our secondary aim is the measurement agreement between the in-clinic TUG obtained with the Verily Study Watch and the measurements by the physiotherapist. We will assess this for every study visit using the ICC. Further, the measurement agreement between the last virtual TUG before the in-clinic assessments and the measurements by the physiotherapist will be assessed with the ICC. A Bland-Altman plot will be provided as well.

The TUG derived from the Verily Study Watch of the 2 in-clinic TUGs will be used to obtain the test-retest reliability during all 4 visits. The test-retest reliability of the weekly TUG at home will also be obtained using the ICC. A Bland-Altman plot will be provided too.

Finally, we will characterize the performance of the sensitivity of the device-assisted TUG in capturing changes over time after the physiotherapy intervention. For this comparison, we will use the TUG time derived from the device-assisted TUG during visit 2 and visit 4.

As an exploratory aim, the passively recorded data will be used to relate clinical assessments and free-living–based metrics to patient-reported outcomes.

Sample Size Consideration

No formal sample size calculation was performed. Prior research states that a sample size of at least 50 participants is recommended for validity studies wherein correlation coefficients are estimated [57]. However, larger sample sizes are preferred especially in populations with chronic conditions. Given the fact that we use the ICC as the end point of our primary aim and potential loss of data due to dropouts or device failure, 100 participants with PD and 100 participants with COPD will provide a reasonable sample size for the characterization of performance.

Ethical Considerations

This study is being conducted in conformance with the Good Clinical Practice ICH E6 guideline. Further, this study is conducted in compliance with the Ethical principles for medical research involving human subjects as defined in the Declaration of Helsinki (2007-2008), the Dutch Personal Data Protection Act, and the ISO 14155:2020 (Medical devices). The Medisch Ethische Toetsing Comissie Arnhem Nijmegen approved this study's protocol and communication materials (2021-13165; NL78292.091.21). Written informed consent is obtained before any study procedure is performed. Participants who are not able to give written consent will be excluded from participation.

Results

In total, 89 people with PD and 65 people with COPD were included in this study. Data analysis will start in April 2024, with the first results of the analysis expected in the fourth quarter of 2024.

Discussion

The purpose of the ADAPT study is to evaluate the measurement properties of a device-assisted 6MWT and a device-assisted TUG for assessing physical capacity in the daily lives of people with PD and COPD.

Currently, the 6MWT is used to measure physical capacity but it is performed in clinical settings, where the circumstances are always optimized. That makes it hard to obtain a representative view of a person's physical capacity in their own environment. Wearable technology may offer a solution that enables us to better understand true physical functioning in daily life and its fluctuations throughout the day when deployed at home [23]. Therefore, it is relevant to investigate the measurement properties of a home-based 6MWT when using a wearable device.

This study will lead to unique insights for several reasons. First, the collected data using both regular assessments and continuous data collection using wearable sensors will give us important insights into daily life functioning. Another unique element is the broad inclusion criteria, that allow us to collect data from "real-life" patients and to obtain a more representative view of the true population. Besides that, the repeated measurements in the clinic but also at home and the passively recorded data provide insight into a patient's functioning in daily life. Those include fluctuations regarding medication intake and several other environmental or personal factors, like heart rate and quality of sleep.

The design of this study is complex, which creates potential challenges. This includes the complex logistic distribution of study materials and this study's coordination throughout the country. Using 2 different devices that both have different ways regarding preparation and setup before data collection can take place is also challenging, for both participants and physiotherapists. We have addressed this issue by extensively training the physiotherapists and creating videos about the devices for participants. In case of emergencies or questions, we are easily reachable by email and phone for both physiotherapists and participants.

Another challenge will be the inclusion of participants since we only approach patients who are under treatment within the trained physiotherapists' clinics. Should the inclusion of participants stagnate, we will use our own network to approach participants and see if they are willing to travel to an affiliated practice near their homes. However, even with these solutions, we are aware that participants may feel insecure or not skilled enough about using the devices and decide not to participate or even stop participation. This is compounded by the fact that the vast majority of both people with PD and people with COPD are older.

We also expect a challenge in the analysis of the 6MWT measurements at home. Every participant chooses their own course indoors, which leads to an enormous variety in course shapes, course lengths, and number of turns. Not every participant can walk straight for 10 meters indoors, leading to a shorter course compared to the in-clinic measurements. The study from Fell et al [58] showed that a shorter pathway reduces the 6MWD compared to the traditional 30-meter pathway. We chose to use the 10-meter course to ensure comparability with the 6MWT performed at home. It is more likely that participants can walk for 10 meters straight in their homes than to walk for 30 meters. To gain insight into the courses of our participants, they will create a map of their homes in which they draw their 6MWT course and add the distances of several components of their course.

Additionally, there might be a potential influence of disease severity in the PD cohort when determining the 6MWD from the Verily Study Watch. It is known that people with PD have a significantly reduced step length compared to healthy controls [59]. When analyzing the data, the step length of the participants needs to be defined. The equations used in healthy populations to estimate a person's step length based on body height and age might not be appropriate here. A sensitivity analysis will be performed during the data analysis to check if participants with higher disease severity (ie, a higher Movement Disorders Society–sponsored revision of the Unified Parkinson's Disease Rating Scale part III score) will have a worse correlation between the 6MWD from the Verily Study Watch compared to the measurements of the physiotherapists.

This study design also serves as an important feasibility test for remote VWTs. In recent years, the 6MWT and TUG have been studied at home in people with cardiovascular, pulmonary, and neurological diseases [25,60-62]. Different approaches were used to measure the distance walked and time to complete both tests, for example with wearable sensors [19,63], smartphone apps [25,64-66], and more traditional tools like a rope and a stopwatch [67,68]. Based on their results, administering physical capacity tests at home seems to be a promising tool for clinical management or research. However, these tests should be uncomplicated to perform safely and require little space. An example of a home-based test can be the Parkinson's Disease Virtual Motor Exam which has been deployed to remotely measure the severity of tremor, bradykinesia, and gait impairment [39]. The data from this latter study suggest that people with PD engage with the Parkinson's Disease Virtual Motor Exam and can complete remote active assessments of motor function and yield data of sufficient quality [15]. Since we use the same smartwatch and user interface but with different tests, we expect that the quality of the data is sufficient for our purposes.

With the results of this study, we will gain insight into the measurement properties of the device-assisted 6MWT and TUG in the clinic and at home. When reliable and valid, we will be able to digitally assess a person's physical capacity performed in their own familiar environment and capture daily life functioning. This can contribute to better information that makes it possible to personalize treatment options.

Acknowledgments

The Radboudumc Center of Expertise for Parkinson and Movement Disorders was supported by a Center of Excellence grant from the Parkinson's Foundation. This publication is part of the project ROBUST: Trustworthy AI-based Systems for Sustainable Growth (KICH3.LTP.20.006), which is partly financed by the Dutch Research Council (NWO), Verily Life Sciences LLC, and the Dutch Ministry of Economic Affairs and Climate Policy (EZK; LTP KIC 2020-2023). All content represents the opinion of the authors, which is not necessarily shared or endorsed by their respective employers or sponsors.

Authors' Contributions

All authors read and approved the final paper. DdG, AvH, NMdV, JJPS, TvdZ, BB, SS, NK, PB, RK, and WJM Jr contributed to this study's conception and design, data collection, analysis planning, and paper preparation.

Conflicts of Interest

DdG, TvdZ, and JJPS report no conflict of interest. NMdV reports grants from The Netherlands Organisation for Health Research and Development (ZonMw) and The Michael J. Fox Foundation. BB currently serves as editor in chief for the Journal of Parkinson's Disease; serves on the editorial board of Practical Neurology and Digital Biomarkers; has received honoraria from serving on the scientific advisory board for AbbVie, Biogen, and Union Chimique Belge (UCB); has received fees for speaking at conferences from AbbVie, Zambon, Roche, GE Healthcare, and Bial; and has received research support from the Netherlands Organization for Scientific Research, The Michael J. Fox Foundation, UCB, AbbVie, the Stichting Parkinson Fonds, the Hersenstichting Nederland, the Parkinson's Foundation, Verily Life Sciences, Horizon 2020, the Topsector Life Sciences and Health, the Gatsby Foundation, and the Parkinson Vereniging. SS, NK, PB, WJM Jr, and RK report employment at Verily Life Sciences and equity ownership in Verily Life Sciences.

References

1. van Lummel RC, Walgaard S, Pijnappels M, Elders PJM, Garcia-Aymerich J, van Dieën JH, et al. Physical performance and physical activity in older adults: associated but separate domains of physical function in old age. PLoS One 2015;10(12):e0144048 [FREE Full text] [doi: 10.1371/journal.pone.0144048] [Medline: 26630268]
2. O'Neill D, Forman DE. The importance of physical function as a clinical outcome: assessment and enhancement. Clin Cardiol 2020;43(2):108-117 [FREE Full text] [doi: 10.1002/clc.23311] [Medline: 31825137]
3. Healthy ageing and functional ability. World Health Organization. 2020. URL: https://www.who.int/news-room/questions-and-answers/item/healthy-ageing-and-functional-ability [accessed 2024-04-04]
4. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc 2011;43(7):1334-1359 [FREE Full text] [doi: 10.1249/MSS.0b013e318213fefb] [Medline: 21694556]
5. Sunde S, Hesseberg K, Skelton DA, Ranhoff AH, Pripp AH, Aarønæs M, et al. Associations between health-related quality of life and physical function in older adults with or at risk of mobility disability after discharge from the hospital. Eur Geriatr Med 2021;12(6):1247-1256 [FREE Full text] [doi: 10.1007/s41999-021-00525-0] [Medline: 34106446]
6. LaHue SC, Comella CL, Tanner CM. The best medicine? The influence of physical activity and inactivity on Parkinson's disease. Mov Disord 2016;31(10):1444-1454 [FREE Full text] [doi: 10.1002/mds.26728] [Medline: 27477046]
7. Kuh D, Karunananthan S, Bergman H, Cooper R. A life-course approach to healthy ageing: maintaining physical capability. Proc Nutr Soc 2014;73(2):237-248 [FREE Full text] [doi: 10.1017/S0029665113003923] [Medline: 24456831]
8. Brooks GC, Vittinghoff E, Iyer S, Tandon D, Kuhar P, Madsen KA, et al. Accuracy and usability of a self-administered 6-minute walk test smartphone application. Circ Heart Fail 2015;8(5):905-913 [FREE Full text] [doi: 10.1161/CIRCHEARTFAILURE.115.002062] [Medline: 26283292]
9. Lauzé M, Daneault JF, Duval C. The effects of physical activity in Parkinson's disease: a review. J Parkinsons Dis 2016;6(4):685-698 [FREE Full text] [doi: 10.3233/JPD-160790] [Medline: 27567884]
10. Lamb SE, Keene DJ. Measuring physical capacity and performance in older people. Best Pract Res Clin Rheumatol 2017;31(2):243-254. [doi: 10.1016/j.berh.2017.11.008] [Medline: 29224699]
11. Wright E, Chester V, Kuruganti U. Identifying the optimal parameters to express the capacity-activity interrelationship of community-dwelling older adults using wearable sensors. Sensors (Basel) 2022;22(24):9648 [FREE Full text] [doi: 10.3390/s22249648] [Medline: 36560016]
12. Pitta F, Troosters T, Probst VS, Spruit MA, Decramer M, Gosselink R. Quantifying physical activity in daily life with questionnaires and motion sensors in COPD. Eur Respir J 2006;27(5):1040-1055 [FREE Full text] [doi: 10.1183/09031936.06.00064105] [Medline: 16707399]
13. Prince SA, Adamo KB, Hamel ME, Hardt J, Gorber SC, Tremblay M. A comparison of direct versus self-report measures for assessing physical activity in adults: a systematic review. Int J Behav Nutr Phys Act 2008;5:56 [FREE Full text] [doi: 10.1186/1479-5868-5-56] [Medline: 18990237]

14. Banou E. Kinesia paradoxa: a challenging Parkinson's phenomenon for simulation. Adv Exp Med Biol 2015;822:165-177. [doi: 10.1007/978-3-319-08927-0_18] [Medline: 25416986]
15. Burq M, Rainaldi E, Ho KC, Chen C, Bloem BR, Evers LJW, et al. Virtual exam for Parkinson's disease enables frequent and reliable remote measurements of motor function. NPJ Digit Med 2022;5(1):65 [FREE Full text] [doi: 10.1038/s41746-022-00607-8] [Medline: 35606508]
16. Ascherio A, Schwarzschild MA. The epidemiology of Parkinson's disease: risk factors and prevention. Lancet Neurol 2016;15(12):1257-1272. [doi: 10.1016/S1474-4422(16)30230-7] [Medline: 27751556]
17. Jankovic J, Stacy M. Medical management of levodopa-associated motor complications in patients with Parkinson's disease. CNS Drugs 2007;21(8):677-692. [doi: 10.2165/00023210-200721080-00005] [Medline: 17630819]
18. Espay AJ, Bonato P, Nahab FB, Maetzler W, Dean JM, Klucken J, et al. Technology in Parkinson's disease: challenges and opportunities. Mov Disord 2016;31(9):1272-1282 [FREE Full text] [doi: 10.1002/mds.26642] [Medline: 27125836]
19. Del Din S, Godfrey A, Mazzà C, Lord S, Rochester L. Free-living monitoring of Parkinson's disease: lessons from the field. Mov Disord 2016;31(9):1293-1313 [FREE Full text] [doi: 10.1002/mds.26718] [Medline: 27452964]
20. Horak FB, Mancini M. Objective biomarkers of balance and gait for Parkinson's disease using body-worn sensors. Mov Disord 2013;28(11):1544-1551 [FREE Full text] [doi: 10.1002/mds.25684] [Medline: 24132842]
21. Rovini E, Maremmani C, Cavallo F. How wearable sensors can support Parkinson's disease diagnosis and treatment: a systematic review. Front Neurosci 2017;11:555 [FREE Full text] [doi: 10.3389/fnins.2017.00555] [Medline: 29056899]
22. Patel S, Chen BR, Mancinelli C, Paganoni S, Shih L, Welsh M, et al. Longitudinal monitoring of patients with Parkinson's disease via wearable sensor technology in the home setting. Annu Int Conf IEEE Eng Med Biol Soc 2011;2011:1552-1555. [doi: 10.1109/IEMBS.2011.6090452] [Medline: 22254617]
23. Bloem BR, Post E, Hall DA. An apple a day to keep the Parkinson's disease doctor away? Ann Neurol 2023;93(4):681-685 [FREE Full text] [doi: 10.1002/ana.26612] [Medline: 36708048]
24. Lopez-Campos JL, Calero C, Quintana-Gallego E. Symptom variability in COPD: a narrative review. Int J Chron Obstruct Pulmon Dis 2013;8:231-238 [FREE Full text] [doi: 10.2147/COPD.S42866] [Medline: 23687444]
25. Smith-Turchyn J, Adams SC, Sabiston CM. Testing of a self-administered 6-minute walk test using technology: usability, reliability and validity study. JMIR Rehabil Assist Technol 2021;8(3):e22818 [FREE Full text] [doi: 10.2196/22818] [Medline: 34554105]
26. Doherty A, Jackson D, Hammerla N, Plötz T, Olivier P, Granat MH, et al. Large scale population assessment of physical activity using wrist worn accelerometers: the UK biobank study. PLoS One 2017;12(2):e0169649 [FREE Full text] [doi: 10.1371/journal.pone.0169649] [Medline: 28146576]
27. Liu F, Wanigatunga AA, Schrack JA. Assessment of physical activity in adults using wrist accelerometers. Epidemiol Rev 2022;43(1):65-93 [FREE Full text] [doi: 10.1093/epirev/mxab004] [Medline: 34215874]
28. Sokas D, Paliakaitė B, Rapalis A, Marozas V, Bailón R, Petrėnas A. Detection of walk tests in free-living activities using a wrist-worn device. Front Physiol 2021;12:706545 [FREE Full text] [doi: 10.3389/fphys.2021.706545] [Medline: 34456748]
29. Douma JAJ, Verheul HMW, Buffart LM. Feasibility, validity and reliability of objective smartphone measurements of physical activity and fitness in patients with cancer. BMC Cancer 2018;18(1):1052 [FREE Full text] [doi: 10.1186/s12885-018-4983-4] [Medline: 30373549]
30. Scherrenberg M, Bonneux C, Mahmood DY, Hansen D, Dendale P, Coninx K. A mobile application to perform the six-minute walk test (6MWT) at home: a random walk in the park is as accurate as a standardized 6MWT. Sensors (Basel) 2022;22(11):4277 [FREE Full text] [doi: 10.3390/s22114277] [Medline: 35684898]
31. Trymbulak K, Ding E, Marino F, Wang Z, Saczynski JS. Mobile health assessments of geriatric elements in older patients with atrial fibrillation: the Mobile SAGE-AF Study (M-SAGE). Cardiovasc Digit Health J 2020;1(3):123-129 [FREE Full text] [doi: 10.1016/j.cvdhj.2020.11.002] [Medline: 35265884]
32. Popham S, Burq M, Rainaldi EE, Shin S, Dunn J, Kapur R. An algorithm to classify real-world ambulatory status from a wearable device using multimodal and demographically diverse data: validation study. JMIR Biomed Eng 2023;8:e43726 [FREE Full text] [doi: 10.2196/43726]
33. Kowahl N, Shin S, Barman P, Rainaldi E, Popham S, Kapur R. Accuracy and reliability of a suite of digital measures of walking generated using a wrist-worn sensor in healthy individuals: performance characterization study. JMIR Hum Factors 2023;10:e48270 [FREE Full text] [doi: 10.2196/48270] [Medline: 37535417]
34. Keus S, Graziano M, Munneke M, Paltamaa J, Pelosin E, Domingos J, et al. European physiotherapy guideline for Parkinson's disease. ParkinsonNet. The Netherlands: KNGF; 2014. URL: https://www.parkinsonnet.nl/app/uploads/sites/3/2019/11/eu_guideline_parkinson_development_and_justification.pdf [accessed 2024-04-04]
35. Vreeken HL, van Doormaal MCM, Post MHT, Meerhoff GA, Spruit MA, Beekman E. KNGF richtlijn COPD: Koninklijn Nederlands Genootschap voor Fysiotherapie (KNGF). 2020. URL: https://www.kngf.nl/binaries/content/assets/kennisplatform/onbeveiligd/richtlijnen/copd-2020/product-remake/copd-2020-praktijkrichtlijn.pdf [accessed 2024-04-04]
36. Bloem BR, Munneke M. Revolutionising management of chronic disease: the ParkinsonNet approach. BMJ 2014;348:g1838 [FREE Full text] [doi: 10.1136/bmj.g1838] [Medline: 24647365]
37. Only 500 of the 10,000 diseases that afflict humans today have treatments. Project Baseline. URL: https://www.projectbaseline.com/ [accessed 2022-05-16]

38. Parkinson Progression Marker Initiative. The Parkinson Progression Marker Initiative (PPMI). Prog Neurobiol 2011;95(4):629-635 [FREE Full text] [doi: 10.1016/j.pneurobio.2011.09.005] [Medline: 21930184]
39. Bloem BR, Marks WJ, Silva de Lima AL, Kuijf ML, van Laar T, Jacobs BPF, et al. The personalized Parkinson project: examining disease progression through broad biomarkers in early Parkinson's disease. BMC Neurol 2019;19(1):160 [FREE Full text] [doi: 10.1186/s12883-019-1394-3] [Medline: 31315608]
40. Schmidt AL, Pennypacker ML, Thrush AH, Leiper CI, Craik RL. Validity of the StepWatch step activity monitor: preliminary findings for use in persons with Parkinson disease and multiple sclerosis. J Geriatr Phys Ther 2011;34(1):41-45 [FREE Full text] [doi: 10.1519/JPT.0b013e31820aa921] [Medline: 21937891]
41. Moy ML, Danilack VA, Weston NA, Garshick E. Daily step counts in a US cohort with COPD. Respir Med 2012;106(7):962-969 [FREE Full text] [doi: 10.1016/j.rmed.2012.03.016] [Medline: 22521225]
42. Toth LP, Park S, Pittman WL, Sarisaltik D, Hibbing PR, Morton AL, et al. Validity of activity tracker step counts during walking, running, and activities of daily living. Transl J ACSM 2018;3(7):52-59 [FREE Full text] [doi: 10.1249/tjx.0000000000000057]
43. Hergenroeder AL, Gibbs BB, Kotlarczyk MP, Kowalsky RJ, Perera S, Brach JS. Accuracy of objective physical activity monitors in measuring steps in older adults. Gerontol Geriatr Med 2018;4:2333721418781126 [FREE Full text] [doi: 10.1177/2333721418781126] [Medline: 29977979]
44. Feito Y, Bassett DR, Thompson DL. Evaluation of activity monitors in controlled and free-living environments. Med Sci Sports Exerc 2012;44(4):733-741 [FREE Full text] [doi: 10.1249/MSS.0b013e3182351913] [Medline: 21904249]
45. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166(1):111-117 [FREE Full text] [doi: 10.1164/ajrccm.166.1.at1102] [Medline: 12091180]
46. Mathias S, Nayak US, Isaacs B. Balance in elderly patients: the "get-up and go" test. Arch Phys Med Rehabil 1986;67(6):387-389. [Medline: 3487300]
47. Collen FM, Wade DT, Bradshaw CM. Mobility after stroke: reliability of measures of impairment and disability. Int Disabil Stud 1990;12(1):6-9. [doi: 10.3109/03790799009166594] [Medline: 2211468]
48. Johns MW. A new method for measuring daytime sleepiness: the epworth sleepiness scale. Sleep 1991;14(6):540-545 [FREE Full text] [doi: 10.1093/sleep/14.6.540] [Medline: 1798888]
49. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67(6):361-370. [doi: 10.1111/j.1600-0447.1983.tb09716.x] [Medline: 6880820]
50. Yellen SB, Cella DF, Webster K, Blendowski C, Kaplan E. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. J Pain Symptom Manage 1997;13(2):63-74 [FREE Full text] [doi: 10.1016/s0885-3924(96)00274-6] [Medline: 9095563]
51. Stel VS, Smit JH, Pluijm SMF, Visser M, Deeg DJH, Lips P. Comparison of the LASA physical activity questionnaire with a 7-day diary and pedometer. J Clin Epidemiol 2004;57(3):252-258. [doi: 10.1016/j.jclinepi.2003.07.008] [Medline: 15066685]
52. Ställberg B, Nokela M, Ehrs PO, Hjemdal P, Jonsson EW. Validation of the Clinical COPD Questionnaire (CCQ) in primary care. Health Qual Life Outcomes 2009;7:26 [FREE Full text] [doi: 10.1186/1477-7525-7-26] [Medline: 19320988]
53. Oppe M, Devlin NJ, van Hout B, Krabbe PFM, de Charro F. A program of methodological research to arrive at the new international EQ-5D-5L valuation protocol. Value Health 2014;17(4):445-453 [FREE Full text] [doi: 10.1016/j.jval.2014.04.002] [Medline: 24969006]
54. Jenkinson C, Fitzpatrick R, Peto V, Greenhall R, Hyman N. The Parkinson's Disease Questionnaire (PDQ-39): development and validation of a Parkinson's disease summary index score. Age Ageing 1997;26(5):353-357 [FREE Full text] [doi: 10.1093/ageing/26.5.353] [Medline: 9351479]
55. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord 2008;23(15):2129-2170 [FREE Full text] [doi: 10.1002/mds.22340] [Medline: 19025984]
56. Terwee CB, Bot SDM, de Boer MR, van der Windt DAWM, Knol DL, Dekker J, et al. Quality criteria were proposed for measurement properties of health status questionnaires. J Clin Epidemiol 2007;60(1):34-42. [doi: 10.1016/j.jclinepi.2006.03.012] [Medline: 17161752]
57. Terwee CB, Knol DL, de Vet HCW, Mokkink LB, editors. Validity. In: Measurement in Medicine: A Practical Guide. Cambridge: Cambridge University Press; 2011:150-201.
58. Fell B, Hanekom S, Heine M. A modified Six-Minute Walk Test (6MWT) for low-resource settings-a cross-sectional study. Heart Lung 2022;52:117-122. [doi: 10.1016/j.hrtlng.2021.12.008] [Medline: 35007887]
59. Zanardi APJ, da Silva ES, Costa RR, Passos-Monteiro E, Dos Santos IO, Kruel LFM, et al. Gait parameters of Parkinson's disease compared with healthy controls: a systematic review and meta-analysis. Sci Rep 2021;11(1):752 [FREE Full text] [doi: 10.1038/s41598-020-80768-2] [Medline: 33436993]
60. Holland AE, Malaguti C, Hoffman M, Lahham A, Burge AT, Dowman L, et al. Home-based or remote exercise testing in chronic respiratory disease, during the COVID-19 pandemic and beyond: a rapid review. Chron Respir Dis 2020;17:1479973120952418 [FREE Full text] [doi: 10.1177/1479973120952418] [Medline: 32840385]

61. Hwang R, Fan T, Bowe R, Louis M, Bertram M, Morris N, et al. Home-based and remote functional exercise testing in cardiac conditions, during the COVID-19 pandemic and beyond: a systematic review. Physiotherapy 2022;115:27-35 [FREE Full text] [doi: 10.1016/j.physio.2021.12.004] [Medline: 35180642]
62. Bergquist R, Vereijken B, Mellone S, Corzani M, Helbostad JL, Taraldsen K. App-based self-administrable clinical tests of physical function: development and usability study. JMIR mHealth uHealth 2020;8(4):e16507 [FREE Full text] [doi: 10.2196/16507] [Medline: 32338616]
63. Jehn M, Prescher S, Koehler K, von Haehling S, Winkler S, Deckwart O, et al. Tele-accelerometry as a novel technique for assessing functional status in patients with heart failure: feasibility, reliability and patient safety. Int J Cardiol 2013;168(5):4723-4728. [doi: 10.1016/j.ijcard.2013.07.171] [Medline: 23962782]
64. Portegijs E, Karavirta L, Saajanaho M, Rantalainen T, Rantanen T. Assessing physical performance and physical activity in large population-based aging studies: home-based assessments or visits to the research center? BMC Public Health 2019;19(1):1570 [FREE Full text] [doi: 10.1186/s12889-019-7869-8] [Medline: 31775684]
65. Izmailova ES, Ellis R, Benko C. Remote monitoring in clinical trials during the COVID-19 pandemic. Clin Transl Sci 2020;13(5):838-841 [FREE Full text] [doi: 10.1111/cts.12834] [Medline: 32526077]
66. Buisseret F, Catinus L, Grenard R, Jojczyk L, Fievez D, Barvaux V, et al. Timed up and go and six-minute walking tests with wearable inertial sensor: one step further for the prediction of the risk of fall in elderly nursing home people. Sensors (Basel) 2020;20(11):3207 [FREE Full text] [doi: 10.3390/s20113207] [Medline: 32516995]
67. Du H, Davidson PM, Everett B, Salamonson Y, Zecchin R, Rolley JX, et al. Assessment of a self-administered adapted 6-minute walk test. J Cardiopulm Rehabil Prev 2010;30(2):116-120. [doi: 10.1097/HCR.0b013e3181be7c98] [Medline: 19952771]
68. Motolese F, Magliozzi A, Puttini F, Rossi M, Capone F, Karlinski K, et al. Parkinson's disease remote patient monitoring during the COVID-19 lockdown. Front Neurol 2020;11:567413 [FREE Full text] [doi: 10.3389/fneur.2020.567413] [Medline: 33117262]

Abbreviations

6MWD: 6-minute walk test distance
6MWT: 6-minute walk test
10MWT: 10-meter walk test
ADAPT: Accuracy of Digital Assessment of Performance Trial
CE: Conformité Européenne
COPD: chronic obstructive pulmonary disease
FITT: frequency, intensity, timing, and type of training
ICC: intraclass correlation coefficient
PD: Parkinson disease
TUG: Timed Up and Go test
VWT: virtual walk test

Edited by A Mavragani; submitted 13.12.23; peer-reviewed by S Okita, A Angelucci; comments to author 29.02.24; revised version received 07.03.24; accepted 11.03.24; published 07.05.24.

Please cite as:
de Graaf D, de Vries NM, van de Zande T, Schimmel JJP, Shin S, Kowahl N, Barman P, Kapur R, Marks Jr WJ, van 't Hul A, Bloem B
Measuring Physical Functioning Using Wearable Sensors in Parkinson Disease and Chronic Obstructive Pulmonary Disease (the Accuracy of Digital Assessment of Performance Trial Study): Protocol for a Prospective Observational Study
JMIR Res Protoc 2024;13:e55452
URL: https://www.researchprotocols.org/2024/1/e55452
doi:10.2196/55452
PMID:

Protocol

Vitamin D Deficiency and Its Association With Vitamin D Receptor Gene Variants Among Malaysian Women With Hypertensive Disorders in Pregnancy: Protocol for a Nutrigenomics Study

Yakubu Ibrahim[1,2*], BMLS, MSc; Nurul Iftida Basri[1*], MBChB, DrObGyn; Norshariza Nordin[3*], BSc, MSc, PhD; Amilia Afzan Mohd Jamil[1*], MOG, MD

[1]Department of Obstetrics and Gynaecology, Faculty of Medicine and Health Sciences, Serdang, Malaysia

[2]Department of Medical Laboratory Science, Faculty of Allied Health Sciences, College of Medical Sciences, Ahmadu Bello University, Zaria, Kaduna State, Nigeria

[3]Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang, Malaysia

[*]all authors contributed equally

Corresponding Author:
Nurul Iftida Basri, MBChB, DrObGyn
Department of Obstetrics and Gynaecology
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
Serdang, 43400
Malaysia
Phone: 60 0397699339
Fax: 60 397692640
Email: nurul.iftida@upm.edu.my

Related Article:

This is a corrected version. See correction statement: https://www.researchprotocols.org/2024/1/e59300

Abstract

Background: Vitamin D deficiency has been associated with hypertensive disorders in pregnancy (HDP). The risk of developing HDP was reported to be further augmented among individuals with a vitamin D receptor (VDR) genetic variant. However, the reported roles of *VDR* variants in hypertensive disorders are inconsistent among different populations. Given the relatively higher incidence of vitamin D deficiency among Malaysian pregnant women and the high incidence of HDP in this population, we hypothesize that there may be associations between the risk of vitamin D deficiency and HDP with VDR genetic variants.

Objective: This paper outlines the protocol for a study to determine the association of vitamin D status and *VDR* sequence variants among Malaysian pregnant women with HDP.

Methods: This prospective study consists of two phases. The first phase is a cross-sectional study that will entail gathering medical records, a questionnaire survey, and laboratory testing for vitamin D status, with a planned recruitment of 414 pregnant women. The questionnaire will be utilized to assess the risk factors for vitamin D deficiency. The vitamin D status will be obtained from measurement of the vitamin D (25-hydroxyvitamin D_3) level in the blood. The second phase is a case-control study involving a Malay ethnic cohort with vitamin D deficiency. Participants will be divided into two groups with and without HDP (n=150 per group). Genomic DNA will be extracted from the peripheral blood monocytes of participants using the Qiagen DNA blood kit, and *VDR* sequence variants will be determined using polymerase chain reaction–high-resolution melting (PCR-HRM) analysis. Sanger sequencing will then be used to sequence randomly selected samples corresponding to each identified variant to validate our PCR-HRM results. The *VDR* genotype and mutation frequencies of *BsmI*, *ApaI*, *TaqI*, and *FokI* will be statistically analyzed to evaluate their relationships with developing HDP.

Results: As of December 2023, 340 subjects have been recruited for the phase 1 study, 63% of whom were determined to have vitamin D deficiency. In the phase 2 study, 50 and 22 subjects have been recruited from the control and case groups, respectively. Recruitment is expected to be completed by March 2024 and all analyses should be completed by August 2024.

Conclusions: The outcome of the study will identify the nonmodifiable genetic components contributing to developing vitamin D deficiency leading to HDP. This will in turn enable gaining a better understanding of the contribution of genetic variability to the development of HDP, thus providing more evidence for a need of customized vitamin D supplementation during pregnancy according to the individual variability in the response to vitamin D intake.

Trial Registration: ClinicalTrials.gov NCT05659173; https://clinicaltrials.gov/study/NCT05659173

International Registered Report Identifier (IRRID): DERR1-10.2196/53722

(JMIR Res Protoc 2024;13:e53722) doi:10.2196/53722

KEYWORDS

gestational hypertension; preeclampsia; hypertensive disorder; vitamin D deficiency; vitamin D receptor gene polymorphism; vitamin D sequence

Introduction

Vitamin D deficiency is a global health issue affecting an estimated 1 billion people worldwide across all ethnicities and age groups [1]. Thus, vitamin D deficiency has become a pandemic despite the availability of sunlight in Asia, Africa, the Middle East, and Latin America. The most vulnerable populations at risk of vitamin D deficiency are pregnant women and their fetuses. Several studies have linked low vitamin D status with a higher risk of adverse short- and long-term health outcomes. In addition, risk factors such as dietary habits, cultural and religious practices such as wearing dark veils covering nearly all body parts that discourage sun exposure, and lack of government regulations for vitamin D fortification of foods further worsen the condition [2,3]

Hypertensive disorders in pregnancy (HDP) account for approximately 14% of all causes of maternal mortality globally. The spectrum of HDP includes gestational hypertension (GH); preeclampsia; eclampsia; and hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome. Preeclampsia is a complication of 2%-8% of all pregnancies worldwide, contributing to 16%, 9%, and 1.6%-2.5% maternal deaths globally, in Asia and Africa, and in Malaysia, respectively [4,5]. HDP is one of several disorders associated with vitamin D deficiency [6]. Vitamin D exerts its effect through the nuclear vitamin D receptor (VDR), and several single-nucleotide variants (SNVs; formerly single-nucleotide polymorphisms or SNPs) occur on the VDR gene, such as *BsmI*, *ApaI*, *TaqI*, and *FokI* SNVs. The *BsmI* and *FokI* variants of *VDR* have been reported to affect vitamin D binding and are associated with an increased risk of HDP [7].

In pregnant women, maternal 25-hydroxyvitamin D (25(OH)D) can freely cross the human placenta that expresses VDR and the enzyme CYP27B1, which converts 25(OH)D to its biologically active form 1,25-dihydroxycholecalciferol [8]. VDR is a protein comprising two functional domains (the N-terminal dual zinc finger DNA-binding domain and the C-terminal ligand-binding activity domain) and a linking region [9,10]. The gene encoding VDR is located on chromosome 12 (12q12-14) [11,12]. Several SNVs in the VDR gene have been associated with metabolic disorders and vitamin D deficiency to date, including rs1544410 (*BsmI*), rs7975232 (*ApaI*), and rs731236 (*TaqI*) [12].

Sequence variants in the VDR gene are associated with the dysregulation of metabolic biomarkers such as anthropometric parameters related to insulin resistance, obesity, and cardiovascular diseases, along with atherogenic lipid abnormalities in different populations [12,13]. Such metabolic dysregulation ultimately translates into complications in pregnancy with adverse health consequences for both the pregnant woman and the fetus. Vitamin D exerts its effect through the nuclear VDR. The *TaqI* variant, located at the 3′ untranslated region of the VDR gene, has been shown to affect mRNA stability and VDR expression in tissues. An SNV in *FokI* located near the promoter region causes altered VDR activity due to the change in the amino acid sequence of the protein [14]. A *FokI* variant of the VDR gene is also associated with upregulation of angiotensin II type I receptor and renin gene transcription, leading to hypertension [15]. A variant *BsmI* allele also influences *VDR* mRNA stability, resulting in a reduction in the amount of VDR protein produced in the tissues [16].

Accumulating evidence suggests that genetic variability involving variants of specific maternal susceptibility genes, such as those in the VDR gene, play vital roles in the pathogenesis of HDP [6]. An unfavorable *VDR* genetic background can significantly decrease the effectiveness of vitamin D action, thereby contributing to the development of HDP [6,17].

Moreover, the presence of a *VDR* sequence variant constitutes an important factor contributing to the individual susceptibility to the biological effects of vitamin D. HDP may be apparent in some pregnant women, whereas others present with a relatively milder sequela. Considering the influence of genetic variability and the roles of *BsmI*, *ApaI*, *TaqI*, and *FokI* variants in the etiopathogenesis of HDP, we aim to explore the possible association between the frequencies of these genetic variants and the incidence of HDP in Malaysian pregnant women. Given the estimated high prevalence of vitamin D deficiency among Malaysian pregnant women, we hypothesized that there are sequence variants in the *BsmI* and *FokI* VDR gene fragments (as the most common genotypes associated with HDP) of Malaysian pregnant women with vitamin D deficiency. We further explored associations with *ApaI* and *TaqI* variants given the relative lack of previous research on the potential associations of these genotypes with HDP.

Methods

Objectives

The objectives of this prospective study are to (1) determine the prevalence of vitamin D deficiency and associated risk factors among Malaysian pregnant women; (2) determine the frequencies of *BsmI*, *ApaI*, *TaqI*, and *FokI* genotypes among Malay pregnant women with vitamin D deficiency and HDP; (3) understand and associate the distributions of *VDR* genotype and allele frequencies in relation to vitamin D deficiency among Malay pregnant women; and (4) identify mutations in the *BsmI*, *ApaI*, *TaqI*, and *FokI* VDR gene fragments among Malay pregnant women with HDP.

This study is divided into two phases. Phase 1 is a cross-sectional study involving Malaysian pregnant women to achieve objective 1, whereas phase 2 is a case-control study among Malay pregnant women to achieve objectives 2, 3, and 4.

Settings

This study will be carried out at Hospital Sultan Abdul Aziz Shah (HSAAS), a tertiary university hospital in Selangor, Malaysia. The hospital provides a range of health care services to the neighboring community and serves as the teaching hospital for the Faculty of Medicine and Health Sciences, Universiti Putra Malaysia. All pregnant women attending the Obstetrics and Gynaecology Department of HSAAS who fulfill the inclusion and exclusion criteria will be recruited between November 1, 2022, and March 31, 2024. A systematic random sampling method will be used to recruit the study participants for both the cross-sectional and case-control studies.

Cross-Sectional Study (Phase 1)

Participants and Data

To achieve objective 1, Malaysian pregnant women, at any stage of gestation, with a singleton viable pregnancy at the time of recruitment and who are literate in the English or Malay language will be recruited. Women with a multiple pregnancy and on vitamin D supplementation are excluded. The gestation stage will be determined from the first day of the last menstrual cycle or based on measurement of the fetal crown-rump length determined on an ultrasound scan. Pregnant women taking vitamin D supplements or those who have been diagnosed with chronic diseases that are known to affect vitamin D levels, such as autoimmune disease and cancer, are excluded from the study.

Clinical, sociodemographic, dietary intake, and anthropometric (height, weight, and BMI) data will be collected using a pro forma. The prepregnancy BMI (kg/m^2) will be calculated by dividing the weight (kg) by the square of the height (m^2). Weight will be determined from prepregnancy body weight recall or obtained from the woman's antenatal booking record along with the measured height. Participants will then be interviewed by a single trained interviewer to answer a validated questionnaire to determine their risk factors associated with vitamin D deficiency.

Validation of the Questionnaire

The questionnaire was adapted from the studies of Syed Nor et al [18], Jamil et al [19], and Humayun et al [20] (see Multimedia Appendix 1). Permission was obtained from all authors to adopt their questionnaires and translate them into the Malay language. The translation will be performed by two English-Malay-English translators before the validation test. A pilot test will be carried out among 40 pregnant women (approximately 10% of the calculated sample size) to assess the questionnaire's clarity of meaning, appropriateness of the words used, and its cultural acceptance. Participants recruited for the pilot testing will not be included in the study. The reliability will be measured by calculating the internal consistency and assessing the associations among questions. A Cronbach α value of at least 0.7 indicates good internal consistency of the questionnaire [21].

In addition, the content validity index (CVI) will be calculated to measure the validity of the questionnaire where the relevancy of questions will be assessed by three experts in the field. The item-level CVI will be calculated by assessing each question's validity, in which a score above 0.78 is considered acceptable [22]. The overall validity of the questionnaire will also be measured by calculating the scale-level CVI, in which a score above 0.9 is considered good [22].

Sampling Process

Approximately 5 milliliters of blood will be withdrawn and dispensed into a plain blood bottle for the measurement of $25(OH)D_3$ using an electrochemiluminescence immunoassay (Elecsys Vitamin D Total III assay). This assay kit includes a vitamin D–binding protein (VDBP) labeled with a ruthenium complex as the capture protein to bind $25(OH)D_3$ and $25(OH)D_2$. Cross-reactivity to 24,25(OH)D is blocked by a specific monoclonal antibody.

The sample will first be incubated with pretreatment reagents 1 and 2, where bound 25(OH)D is released from the VDBP. Subsequently, the pretreated sample is incubated with the ruthenium-labeled VDBP to form a complex between 25(OH)D and the ruthenylated VDBP. A specific unlabeled antibody binds to the 24,25(OH)D present in the sample and inhibits cross-reactivity to this vitamin D metabolite. During the third incubation, streptavidin-coated microparticles and 25(OH)D labeled with biotin are added. Unbound ruthenylated-labeled VDBPs become occupied, and a complex consisting of the ruthenylated VDBP and the biotinylated 25(OH)D is formed, which finally binds to the solid phase via the interaction of biotin and streptavidin.

The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with ProCell/ProCell M. Application of a specific voltage to the electrode then induces chemiluminescent emission, which is measured by a photomultiplier. The results are determined via a calibration curve that is specifically generated by a 2-point calibration process and compared to a master curve provided via the reagent barcode or e-barcode.

Quality Control

Per-run control sera (deficient, insufficient, and normal) will be used for sample analysis. All laboratory analytical protocols will be performed with strict adherence to the quality control measures.

Classification of Vitamin D Status

The results will be further classified according to vitamin D status as deficient (30 nmol/L), insufficient (30-50 nmol/L), and normal (≥50 nmol/L), using the 2011 classification guidelines of the Institute of Medicine [23].

Case-Control Study (Phase 2)

Participants and Data

For the second phase of the study, we chose to focus on the Malay ethnic group, who make up the majority of the Malaysian population. Pregnant women of Malay ethnicity who are classified in the vitamin D deficiency group in phase 1 of the study will be recruited for phase 2. Those with a nonviable pregnancy or those who received a diagnosis of chronic hypertension prior to the current pregnancy will be excluded. The remaining participants will then be divided into two groups: those with HDP (GH, preeclampsia, eclampsia, HELLP syndrome) and those with blood pressure in the normal range.

Blood Collection and DNA Extraction

Approximately 5 milliliters of blood will be collected into ethylenediaminetetraacetic acid (EDTA) containers for genetic analysis. The blood samples will be transported to the laboratory under a cold chain. Immediately after collection, the genomic DNA will be extracted using the QIAamp DNA blood kit (Qiagen). The extracted DNA will be checked for purity using an ultraviolet spectrophotometer and the integrity will be checked by running the genomic DNA on a 2% agarose gel using triacetate-EDTA buffer in parallel with DNA ladders (all procured from Vivantis Sdn Bhd Malaysia). The genomic DNA with high quality will be stored at –20 °C pending genetic analysis.

VDR Genotyping

The polymerase chain reaction–high-resolution melting (PCR-HRM) technique will be used to amplify the VDR gene with specific primers. The amplified region of the VDR gene (amplicon) will be stored in a PCR tube. Sets of primers (procured from Apical Scientific and Biotechnology Sdn Bhd Malaysia) spanning the 5′-3′ region of the *VDR* sequence will be synthesized based on published sequences [24], which will be used to run the PCR-HRM analysis to detect *VDR* variants. The extracted DNA will be subjected to PCR-HRM following the manufacturer's protocol using the cycling conditions based on a previous report [24].

Principle of PCR-HRM

PCR-HRM analysis is a sensitive and specific technique for the detection of mutations on double-stranded DNA (dsDNA) samples (amplicons). First, the region of interest on the DNA is amplified in real time using specific primers prior to the HRM phase. The HRM process then begins with slow denaturation of the dsDNA with a temperature range of 50-95 °C in conjunction with an intercalating fluorescent dye, SYBR Green (Roche). When the melting temperature of the dsDNA is reached, the two strands "melt" apart. The midpoint of the melt curve is described as the point when 50% of the DNA is double-stranded and 50% is single-stranded. The shape of the curve is dependent on the characteristics of the dsDNA, which relate to whether it is the homozygous wild-type, homozygous mutant, or heterozygous wild-type and mutant genotype. When the two strands "melt" apart, the fluorescence level drops. As the HRM is monitored in real time, this curve offers a real-time picture of the characteristics of the DNA being tested.

Barcode-Tagged Sequencing Analysis

Barcode-tagged sequencing (BT-Seq) analysis, as a next-generation sequencing approach, will be used to verify the *VDR* SNVs identified among the Malay pregnant women with vitamin D deficiency and HDP according to the PCR-HRM results. BT-Seq services will be sought from TreeCode Sdn Bhd Malaysia. Ten amplicon samples will be selected from each of the identified *VDR* variants as representative samples to serve as the reference genotype for all SNVs detected in the PCR-HRM analysis. The analysis will be performed on each *VDR* variant amplicon that will be synthesized based on published primers spanning the four known VDR SNVs (*BsmI*, *ApaI*, *TaqI*, and *FokI*) using PCR [24]. The amplicons will be run on an agarose gel and the purified products will be cut from the gel before sending to the company providing the BT-Seq service. Discrimination of the three possible genotypes of each genetic variant (common homozygotes, heterozygotes, and rare homozygotes) in 4 distinct groups will be obtained from 180 samples by PCR-HRM analysis. A T-to-C transition in introns 8 and 9 will reflect the presence of SNVs in introns 8 and 9 for *BsmI* and *TaqI*, respectively; a C-to-T transition at the junction of intron 1 and exon 2 reflects the *FokI* variant; and the *ApaI* variant is reflected by a T-to-G transition in intron 8. The corresponding distribution of vitamin D status and the genotype frequency in Hardy-Weinberg equilibrium will be obtained for each SNV.

Sample Size Estimation

Total Sample Size

A total of 414 pregnant women will be recruited for the cross-sectional study (phase 1) to determine the prevalence of vitamin D deficiency and associated risk factors (objective 1). For phase 2, a total of 150 Malaysian pregnant women with HDP will be recruited as the case group and 150 normotensive Malaysian pregnant women with vitamin D deficiency will be recruited as controls.

Sample Size Calculation for the Cross-Sectional Study (Phase 1)

The sample size for the study was calculated using the following formula [25]:

$$n = (Z^2 \times p \times q)/d^2 \textbf{(1)}$$

where n is the minimum sample size, Z is the level of significance at the 95% CI (1.96), p is the prevalence rate, q = 1 − p, and d is the tolerable margin of error (5%).

According to Woon et al [26], the prevalence of vitamin D deficiency among Malaysian pregnant women is 42.6%. Applying equation 1, the sample size is calculated as follows:

$$n = (1.96)^2 \times 0.426 \times (1 - 0.426)/(0.05)^2$$

$$n = (3.8416 \times 0.426 \times 0.574)/0.0025 = 376$$

Therefore, the minimum sample size required for the cross-sectional study after addition of a 10% attrition rate is approximately 414 Malaysian pregnant women.

Sample Size Determination for the Case-Control Study (Phase 2)

The minimum number of participants to be recruited in the case-control study was determined using the following formula [27]:

$$n = r + 1 \times P^* \times (1 - P^*) \times (Z_\beta + Z_{\alpha/2})^2/r \times (P_1 - P_2)^2 \textbf{(2)}$$

where r is the ratio of cases to controls (1 in this instance given the equal numbers in the two groups), P_1 is the proportion of exposed individuals in the cases, P_2 is the proportion of exposed individuals in the controls, P* is the effect size ($P_1 - P_2$), Z_β at 80% power is 0.84, and $Z_{\alpha/2}$ is 1.96 for a .05 significance level at the 95% CI.

According to Caccamo et al [6], the prevalence of vitamin D deficiency among women with GH (P_1) and that among pregnant women without hypertension (P_2) is 21% and 11%, respectively. Therefore, P* is determined to be 0.1 (0.21–0.11). Applying equation 2, the sample size is calculated as:

$$n = (1 + 1) \times (0.1) \times (1 - 0.1) \times (0.84 + 1.96)^2/1 \times (0.1)^2$$

$$n = 141$$

Considering dropout or missing samples, 10% attrition is added to the calculated sample size. Hence, our minimum number of participants in each group (cases and controls) was determined to be 150.

Ethical Considerations

The research protocol has been approved by the Ethics Committee for Research Involving Human Subjects of the Universiti Putra Malaysia (reference number JKEUPM-2021-915). The study will be conducted in accordance with the standards of human experimentation in the Declaration of Helsinki and Malaysian Good Clinical Practice Guideline. This study protocol was also registered with ClinicalTrials.gov (NCT05659173). All eligible participants will be given a patient information sheet consisting of information about the study. Those who agree will be asked to sign a written consent form (available in both the Malay and English languages). Participation is voluntary and participants have the right to withdraw at any time without giving a reason. Any amendment to the protocol or documents will be submitted for review to the ethics committee. To preserve the privacy of the participants, any personal details will be removed from publications. Only anonymized and deidentified information will be made available in future manuscripts related to this work. All data of the study will be kept in a password-protected database on a password-protected desktop computer at the host organization and will only be accessible by the named researchers. As this is an observational cross-sectional and case-control study, there will be no compensation given to the participants given that the study is determined to be of low risk.

Data Analysis Plan

Data obtained from the study will be analyzed using SPSS version 27.0 (IBM Corp). Data entered will be checked for missing or suspicious values. These will subsequently be verified with the participants or omitted as missing values. Descriptive analysis will be used to summarize the sociodemographic data, anthropometric data, clinical data, vitamin D dietary intake, sun exposure, and physical activity. The prevalence of vitamin D deficiency will be expressed in frequency and percentage. The association with sociodemographic data will be analyzed using the χ^2 test, independent *t* test, and ANOVA where applicable.

We will report the comparative prevalence of *BsmI*, *ApaI*, *TaqI*, and *FokIVDR* genotypes among Malay pregnant women with vitamin D deficiency with and without HDP. Similarly, the distributions of *VDR* genotype and allele frequencies according to vitamin D deficiency among Malay pregnant women will be reported as a descriptive analysis. Any mutations found in the *BsmI*, *ApaI*, *TaqI*, and *FokI* VDR gene fragments among Malay pregnant women with HDP will also be described. The associations of vitamin D status, associated risk factors, and VDR genetic variants with HDP will be determined using multivariate logistic regression analysis. The level of significance will be considered at a threshold of $P \leq .05$ at the 95% CI.

Results

As of December 2023, a total of 340 subjects have been recruited for the phase 1 study. Preliminary analysis showed that 63% of the participants were vitamin D–deficient. Other analyses are pending. For the phase 2 study, 50 control subjects and 22 case subjects have been recruited to date. We are expecting to complete the recruitment by March 2024 and to complete all laboratory and questionnaire analyses by August 2024.

Discussion

Projected Significance

The study will provide information on the current prevalence and modifiable risk factors of vitamin D deficiency. The prospective associations of vitamin D deficiency with the study variables will be of immense benefit to physicians and public health experts in formulating policies related to vitamin D supplementation. The outcome will greatly advance our current understanding of vitamin D deficiency in Malaysia and at mechanistic level could be adopted by other low- and middle-income countries to tackle the widespread problem of vitamin D deficiency.

Additionally, this study holds promise for determining the influence of unchangeable genetic components that may impact

vitamin D deficiency and its correlation with HDP. This will constitute a significant new development in the field. Determining the association of the genetic variants will enable gaining a further understanding of the roles of the nonmodifiable components contributing to the risk of vitamin D deficiency that lead to the development of HDP.

Strengths and Limitations

The sample size of this study is one of the highest among similar studies conducted in the study area performed to date [7,17]. In addition, the assessment of both modifiable and nonmodifiable risk factors of vitamin D deficiency will facilitate gaining a deeper understanding of cause and effect, as these factors relate not only to vitamin D deficiency itself but also involve associated genetic variants and the risk of developing HDP.

Potential limitations include bias in recall in answering the vitamin D food frequency components of the questionnaire given that these data are based on the self-reporting of participants. However, efforts have been made to ensure that these challenges are significantly tackled by conducting pre-enrollment interviews with pregnant women for eligibility before their inclusion in the study. As the study will be conducted in a tertiary hospital setting and a convenience sampling strategy is used, only subjects of interest that suit our inclusion criteria will be recruited. Thus, the results of this study may be influenced by the recruited participants group, which may not necessarily replicate the entire Malaysian population. Future studies should adopt a systematic random sampling strategy with a larger sample size and multicentered design to capture pregnant women from broader demographics, including those living in rural areas.

Conclusion

The outcome of this prospective study will determine both modifiable and nonmodifiable factors for vitamin D deficiency and will provide evidence to support targeted vitamin D supplementation programs. Furthermore, the study will help to enhance our understanding of the association of genetic variability in the VDR gene with the risk of developing HDP. These findings could bring together relevant stakeholders in government health authorities, food and drug administrations, and food manufacturing industries to contribute to the establishment of national intervention schemes for the screening, prevention, and treatment of vitamin D deficiency that would be customized for susceptible women of reproductive age.

Acknowledgments

This research was made possible by a grant from the Ministry of Higher Education Malaysia under Fundamental Research Grant Scheme FRGS/1/2022/SKK01/UPM/02/1, awarded to NIB. The funder has no role in the design, data collection, analysis, decision to publish, and preparation of this manuscript.

Data Availability

The data obtained and analyzed during the study will not be made publicly available due to privacy issues but will be available on reasonable request to the corresponding author.

Authors' Contributions

NIB, AAMJ, NN, and YI contributed to the study concept and design. The design of the laboratory analysis was further developed by NN and YI. YI drafted the manuscript with assistance from NIB and AAMJ along with input from NN at various stages. All authors critically reviewed the manuscript and approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Questionnaire.
[DOCX File , 21 KB - resprot_v13i1e53722_app1.docx]

Multimedia Appendix 2
Peer-reviewer report from the Ministry of Higher Education.
[PDF File (Adobe PDF File), 593 KB - resprot_v13i1e53722_app2.pdf]

References

1. Islam QT, Amin MR. Vitamin D deficiency- current status and its impact in clinical medicine. Bangla J Med 2017 Mar 16;28(1):1-3. [doi: 10.3329/bjmed.v28i1.31895]
2. Hussain AN, Alkhenizan AH, El Shaker M, Raef H, Gabr A. Increasing trends and significance of hypovitaminosis D: a population-based study in the Kingdom of Saudi Arabia. Arch Osteoporos 2014 Sep 12;9(1):190. [doi: 10.1007/s11657-014-0190-3] [Medline: 25213798]

3. Al-Shaikh GK, Ibrahim GH, Fayed AA, Al-Mandeel H. Impact of vitamin D deficiency on maternal and birth outcomes in the Saudi population: a cross-sectional study. BMC Pregnancy Childbirth 2016 May 24;16(1):119 [FREE Full text] [doi: 10.1186/s12884-016-0901-4] [Medline: 27221615]
4. Sutan R, Aminuddin NA, Mahdy ZA. Prevalence, maternal characteristics, and birth outcomes of preeclampsia: a cross-sectional study in a single tertiary healthcare center in greater Kuala Lumpur Malaysia. Front Public Health 2022 Oct 17;10:973271 [FREE Full text] [doi: 10.3389/fpubh.2022.973271] [Medline: 36324467]
5. Rana S, Lemoine E, Granger JP, Karumanchi SA. Preeclampsia: pathophysiology, challenges, and perspectives. Circ Res 2019 Mar 29;124(7):1094-1112 [FREE Full text] [doi: 10.1161/CIRCRESAHA.118.313276] [Medline: 30920918]
6. Caccamo D, Cannata A, Ricca S, Catalano LM, Montalto AF, Alibrandi A, et al. Role of vitamin-D receptor (VDR) single nucleotide polymorphisms in gestational hypertension development: a case-control study. PLoS One 2020 Nov 13;15(11):e0239407 [FREE Full text] [doi: 10.1371/journal.pone.0239407] [Medline: 33186385]
7. Lee S, Ling K, Tusimin M, Subramaniam R, Rahim KF, Loh S. Influence of vitamin D binding protein polymorphism, demographics and lifestyle factors on vitamin D status of healthy Malaysian pregnant women. BMC Pregnancy Childbirth 2020 Nov 23;20(1):714 [FREE Full text] [doi: 10.1186/s12884-020-03397-7] [Medline: 33228578]
8. van der Pligt P, Willcox J, Szymlek-Gay E, Murray E, Worsley A, Daly R. Associations of maternal vitamin D deficiency with pregnancy and neonatal complications in developing countries: a systematic review. Nutrients 2018 May 18;10(5):640 [FREE Full text] [doi: 10.3390/nu10050640] [Medline: 29783717]
9. Margolis RN, Christakos S. The nuclear receptor superfamily of steroid hormones and vitamin D gene regulation. An update. Ann N Y Acad Sci 2010 Mar 05;1192(1):208-214. [doi: 10.1111/j.1749-6632.2009.05227.x] [Medline: 20392238]
10. Pike JW, Meyer MB. The vitamin D receptor: new paradigms for the regulation of gene expression by 1,25-dihydroxyvitamin D(3). Endocrinol Metab Clin North Am 2010 Jun;39(2):255-269 [FREE Full text] [doi: 10.1016/j.ecl.2010.02.007] [Medline: 20511050]
11. Szpirer J, Szpirer C, Riviere M, Levan G, Marynen P, Cassiman J, et al. The Sp1 transcription factor gene (SP1) and the 1,25-dihydroxyvitamin D3 receptor gene (VDR) are colocalized on human chromosome arm 12q and rat chromosome 7. Genomics 1991 Sep;11(1):168-173. [doi: 10.1016/0888-7543(91)90114-t] [Medline: 1662663]
12. Karonova T, Grineva E, Belyaeva O, Bystrova A, Jude EB, Andreeva A, et al. Relationship between vitamin D status and vitamin D receptor gene polymorphisms with markers of metabolic syndrome among adults. Front Endocrinol 2018 Aug 16;9:448 [FREE Full text] [doi: 10.3389/fendo.2018.00448] [Medline: 30166978]
13. Schuch NJ, Garcia VC, Vívolo SRGF, Martini LA. Relationship between vitamin D receptor gene polymorphisms and the components of metabolic syndrome. Nutr J 2013 Jul 15;12(1):96 [FREE Full text] [doi: 10.1186/1475-2891-12-96] [Medline: 23855914]
14. Mulligan ML, Felton SK, Riek AE, Bernal-Mizrachi C. Implications of vitamin D deficiency in pregnancy and lactation. Am J Obstet Gynecol 2010 May;202(5):429 [FREE Full text] [doi: 10.1016/j.ajog.2009.09.002] [Medline: 19846050]
15. Awasthi R, Manger PT, Khare RK. Fok I and Bsm I gene polymorphism of vitamin D receptor and essential hypertension: a mechanistic link. Clin Hypertens 2023 Feb 15;29(1):5 [FREE Full text] [doi: 10.1186/s40885-022-00229-y] [Medline: 36788562]
16. Rezavand N, Tabarok S, Rahimi Z, Vaisi-Raygani A, Mohammadi E, Rahimi Z. The effect of VDR gene polymorphisms and vitamin D level on blood pressure, risk of preeclampsia, gestational age, and body mass index. J Cell Biochem 2019 Apr 11;120(4):6441-6448. [doi: 10.1002/jcb.27934] [Medline: 30417411]
17. Lin L, Zhang L, Li C, Gai Z, Li Y. Vitamin D and vitamin D receptor: new insights in the treatment of hypertension. Curr Protein Pept Sci 2019 Sep 20;20(10):984-995. [doi: 10.2174/1389203720666190807130504] [Medline: 31389312]
18. Syed Nor SF, Idris IB, Md Isa Z. Physical inactivity in early pregnancy and the determinants in an urban city setting of Kuala Lumpur, Malaysia. BMC Public Health 2022 Jan 13;22(1):93 [FREE Full text] [doi: 10.1186/s12889-022-12513-5] [Medline: 35027033]
19. Jamil NA, Shahudin NN, Abdul Aziz NS, Jia Qi C, Wan Aminuddin WAA, Mat Ludin AF, et al. Knowledge, attitude and practice related to vitamin D and its relationship with vitamin D status among Malay female office workers. Int J Environ Res Public Health 2019 Nov 27;16(23):4735 [FREE Full text] [doi: 10.3390/ijerph16234735] [Medline: 31783521]
20. Humayun Q, Iqbal R, Azam I, Khan AH, Siddiqui AR, Baig-Ansari N. Development and validation of sunlight exposure measurement questionnaire (SEM-Q) for use in adult population residing in Pakistan. BMC Public Health 2012 Jun 08;12(1):421 [FREE Full text] [doi: 10.1186/1471-2458-12-421] [Medline: 22682277]
21. Cortina JM. What is coefficient alpha? An examination of theory and applications. J Appl Psychol 1993;78(1):98-104. [doi: 10.1037//0021-9010.78.1.98]
22. Shi J, Mo X, Sun Z. Content validity index in scale development. Zhong Nan Da Xue Xue Bao Yi Xue Ban 2012 Feb;37(2):152-155. [doi: 10.3969/j.issn.1672-7347.2012.02.007] [Medline: 22561427]
23. Institute of Medicine, Food and Nutrition Board, Committee to Review Dietary Reference Intakes for Vitamin D and Calcium, Ross AC, Taylor CL, Yaktine AL, et al. Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC: The National Academies Press; 2011.

24. Divanoglou N, Komninou D, Stea EA, Argiriou A, Papatzikas G, Tsakalof A, et al. Association of vitamin D receptor gene polymorphisms with serum vitamin D levels in a Greek rural population (Velestino Study). Lifestyle Genom 2021 Jun 17;14(3):81-90. [doi: 10.1159/000514338] [Medline: 34139712]
25. Cochran WG. Sampling Techniques, 3rd edition. Hoboken, NJ: Wiley; 1977.
26. Woon FC, Chin YS, Ismail IH, Batterham M, Abdul Latiff AH, Gan WY, et al. Vitamin D deficiency during pregnancy and its associated factors among third trimester Malaysian pregnant women. PLoS One 2019 Jun 24;14(6):e0216439 [FREE Full text] [doi: 10.1371/journal.pone.0216439] [Medline: 31233513]
27. Charan J, Biswas T. How to calculate sample size for different study designs in medical research? Indian J Psychol Med 2013 Apr;35(2):121-126 [FREE Full text] [doi: 10.4103/0253-7176.116232] [Medline: 24049221]

Abbreviations

25(OH)D: 25-hydroxyvitamin D
BT-Seq: barcode-tagged sequencing
CVI: content validity index
dsDNA: double-stranded DNA
EDTA: ethylenediaminetetraacetic acid
GH: gestational hypertension
HDP: hypertensive disorders of pregnancy
HELLP: hemolysis, elevated liver enzymes, and low platelets
HSAAS: Hospital Sultan Abdul Aziz Shah
PCR-HRM: polymerase chain reaction–high-resolution melting
SNV: single-nucleotide variant
VDBP: vitamin D–binding protein
VDR: vitamin D receptor

Edited by A Mavragani; submitted 17.10.23; this is a non–peer-reviewed article;accepted 05.02.24; published 26.03.24.

Please cite as:
Ibrahim Y, Basri NI, Nordin N, Mohd Jamil AA
Vitamin D Deficiency and Its Association With Vitamin D Receptor Gene Variants Among Malaysian Women With Hypertensive Disorders in Pregnancy: Protocol for a Nutrigenomics Study
JMIR Res Protoc 2024;13:e53722
URL: https://www.researchprotocols.org/2024/1/e53722
doi:10.2196/53722
PMID:38530345

Protocol

Patient Education and Decision Support for Long-Acting Injectable HIV Antiretroviral Therapy: Protocol for Tool Development and Pilot Testing with Ryan White HIV/AIDS Program Medical Case Management Programs in New York

Mary Kathryn Irvine[1], MPH, DPH; Rebecca Zimba[2,3], MHS; Tigran Avoundjian[1], MPH, PhD; Meghan Peterson[1], MPH; Connor Emmert[1], MPH; Sarah G Kulkarni[2], MPH; Morgan M Philbin[4], MHS, PhD; Elizabeth A Kelvin[2,3], MA, MPH, PhD; Denis Nash[2,3], MPH, PhD

[1]Bureau of Hepatitis, HIV and Sexually Transmitted Infections (BHHS), New York City Department of Health and Mental Hygiene, New York, NY, United States

[2]Institute for Implementation Science in Population Health (ISPH), Graduate School of Public Health and Health Policy, City University of New York (CUNY), New York, NY, United States

[3]Department of Epidemiology and Biostatistics, Graduate School of Public Health and Health Policy, City University of New York (CUNY), New York, NY, United States

[4]Division of Vulnerable Populations, Department of Medicine, University of California San Francisco, San Francisco, CA, United States

Corresponding Author:
Mary Kathryn Irvine, MPH, DPH
Bureau of Hepatitis, HIV and Sexually Transmitted Infections (BHHS)
New York City Department of Health and Mental Hygiene
42-09 28th St.
New York, NY, 11101
United States
Phone: 1 347 396 7712
Fax: 1 347 396 7559
Email: maryk.irvine@gmail.com

Abstract

Background: Long-acting injectable (LAI) HIV antiretroviral therapy (ART) presents a major opportunity to facilitate and sustain HIV viral suppression, thus improving health and survival among people living with HIV and reducing the risk of onward transmission. However, realizing the public health potential of LAI ART requires reaching patients who face barriers to daily oral ART adherence and thus can clinically benefit from alternative treatment modalities. Ryan White HIV/AIDS Program Part A medical case management (MCM) programs provide an array of services to address barriers to HIV care and treatment among economically and socially marginalized people living with HIV. These programs have demonstrated effectiveness in improving engagement along the continuum of care, but findings of limited program impact on durable viral suppression highlight the need to further innovate and hone strategies to support long-term ART adherence.

Objective: This study aims to adapt and expand Ryan White MCM service strategies to integrate LAI ART regimen options, with the larger goal of improving health outcomes in the populations that could most benefit from alternatives to daily oral ART regimens.

Methods: In 3 phases of work involving patient and provider participants, this study uses role-specific focus groups to elicit perceptions of LAI versus daily oral ART; discrete choice experiment (DCE) surveys to quantify preferences for different ART delivery options and related supports; and a nonrandomized trial to assess the implementation and utility of newly developed tools at 6 partnering Ryan White HIV/AIDS Program Part A MCM programs based in urban, suburban, and semirural areas of New York. Findings from the focus groups and DCEs, as well as feedback from advisory board meetings, informed the design and selection of the tools: a patient-facing, 2-page fact sheet, including *frequently asked questions* and a side-by-side comparison of LAI with daily oral ART; a patient-facing informational video available on YouTube (Google Inc); and a patient-provider decision aid. Implementation outcomes, measured through provider interviews, surveys, and service reporting, will guide further specification of strategies to integrate LAI ART options into MCM program workflows.

Results: The study was funded in late April 2021 and received approval from the institutional review board in May 2021 under protocol 20-096. Focus groups were conducted in late 2021 (n=21), DCEs ran from June 2022 to January 2023 (n=378), and tools for piloting were developed by May 2023. The trial (May 2023 through January 2024) has enrolled >200 patients.

Conclusions: This study is designed to provide evidence regarding the acceptability, feasibility, appropriateness, and utility of a package of patient-oriented tools for comparing and deciding between LAI ART and daily oral ART options. Study strengths include formative work to guide tool development, a mixed methods approach, and the testing of tools in real-world safety-net service settings.

Trial Registration: Clinicaltrials.gov NCT05833542; https://clinicaltrials.gov/study/NCT05833542

International Registered Report Identifier (IRRID): DERR1-10.2196/56892

(JMIR Res Protoc 2024;13:e56892) doi:10.2196/56892

KEYWORDS

HIV; implementation science; long-acting injectables; LAI; patient decision aid; medical case management; MCM; antiretroviral therapy; ART

Introduction

Since 1990, the federal Ryan White HIV/AIDS Program (RWHAP) has funded cities and counties (via Part A) to provide HIV medical care and support services for those without alternative resources. The RWHAP is an essential platform for reducing HIV-related health disparities and scaling up evidence-based strategies to strengthen the HIV care continuum [1,2]. RWHAP service recipients account for more than half of the people living with HIV in the United States [1,3-6], and approximately 75% of people receiving HIV medical care in the United States attend facilities with RWHAP funding [2]. The central role of the RWHAP in the US response to HIV has been reaffirmed in the Ending the HIV Epidemic Plan [7]. In New York (NY), RWHAP Part A (RWPA) services primarily represent people who identify as Black (53%) or Latinx (37%), which are groups disproportionately affected by the US HIV epidemic [8,9] and less likely to be virally suppressed once diagnosed with HIV [10]. Among those retained in HIV care in 2022, people enrolled in RWPA services in New York City (NYC) were less likely to be virally suppressed (83% vs 93%) or experience durable viral suppression (defined as all viral loads <200 copies/mL) in 2022 (71% vs 86%) as compared with other people living with HIV in NYC. RWPA medical case management (MCM) programs are specifically designed to reduce barriers to HIV care and treatment through the coordination of medical and social services and the provision of antiretroviral therapy (ART) adherence support. The NYC Health Department oversees RWPA MCM services to >4000 people living with HIV per year in 29 programs in NYC and the suburban and semirural Tri-County area (Putnam, Rockland, and Westchester) north of NYC. Although these programs have shown effectiveness in engaging people in HIV care and treatment, substantial room for improvement in HIV viral suppression outcomes remains, highlighting the need to further innovate and develop strategies to increase long-term ART adherence [11-15].

Long-acting injectable (LAI) ART has been heralded as a major biomedical advance that could close gaps in the HIV care continuum, minimize HIV transmission risk, reduce racial and ethnic HIV outcome disparities, and accelerate the end of the HIV epidemic by making viral suppression attainable for those who struggle with daily oral ART adherence. After phase 3 clinical trials found a long-acting cabotegravir and rilpivirine injectable combination (CABENUVA) to be comparable in safety and efficacy and superior in patient satisfaction to daily oral ART [16-19], the US Food and Drug Administration (FDA) approved a monthly CABENUVA regimen in January 2021 [20] and a bimonthly regimen in February 2022 [21]. LAI ART addresses some important adherence barriers by eliminating the requirement for daily dosing, and patients have also noted that it can remove the daily reminder or stressor of HIV status and mitigate the risk of inadvertent HIV status disclosures [22-30]. However, there are challenges in LAI ART implementation that must be systematically addressed. Commonly reported barriers for patients include concerns over effectiveness [31-36], side effects [31,32,35-37], dosing frequency [33,35,36], getting to a clinic for each injection [34,38,39], and use of needles [32,37]. Providers have voiced concerns related to staffing resources, organizational logistics, patient readiness for LAI ART, adherence to injection appointments, and injection tolerability [35,40,41]. In the face of these challenges, uptake of LAI ART since its FDA approval has fallen short of expectations. As of the end of September 2023, approximately 20,000 people in the United States (including Puerto Rico) were on CABENUVA (Cinthya Avalos Meléndez of ViiV Healthcare, email to author, December 14, 2023). This represents <2% of the approximately 1.1 million people living with diagnosed HIV in the United States and its dependent areas [42]. Optimizing the public health impact of LAI ART will require implementation science to identify and tailor interventions to facilitate LAI uptake and engagement, particularly for the most marginalized patients. Without the necessary groundwork to assess and promote access, acceptability, and uptake in underserved populations, biomedical innovations tend to benefit those who are already relatively advantaged and can even exacerbate health disparities [43-45].

This paper describes the protocol for a mixed methods study designed to prepare RWPA MCM programs for extending LAI ART options to patients who have struggled to achieve or maintain viral suppression on daily oral ART and who have been underrepresented in phase 3 clinical trials. Specifically, we summarize the formative and survey research stages completed to guide the selection and development of LAI ART–related educational and decision-support tools, and we

present the methods for a pilot test to evaluate and refine these tools for future scale-up.

Methods

Study Overview, Aims, and Partners

The Assessing Perceptions and Preferences Around Long-acting Injectables study is organized into 3 consecutive phases of work, each of which corresponds to a specific aim: (1) elicit perceptions, barriers, facilitators, and expectations of LAI versus daily oral ART delivery options in focus groups with RWPA MCM patients, core staff, and prescribing providers; (2) quantify preferences and drivers of engagement in ART delivery and support strategies, including options for LAI and daily oral ART, via discrete choice experiments (DCEs) with approximately 200 patients and 200 providers; and (3) select and pilot strategies to promote LAI ART uptake, adherence, and impact in real-world care settings. Each aim corresponds to distinct data collection activities, as summarized in Table 1.

Table 1. Study data sources, participants, content, data collection periods, and purpose by aim.

Aim	Data source	Participants	Content	Time frame	Purpose
1	Focus groups	1. 16 MCM[a] providers (case managers, patient navigators, administrators, and a prescribing provider) 2. 5 MCM patients	1. Awareness and perceptions about LAI[b] ART[c] 2. Implementation barriers and facilitators (for providers) 3. Acceptability of LAI ART (to patients)	October to December 2021	Inform design of discrete choice experiments and gather preliminary data on LAI ART acceptability or concerns
2	Discrete choice experiment surveys	1. 177 MCM providers 2. 201 MCM patients	1. Preferred program features: type of ART, service location and mode, adherence support, rewards 2. Awareness and acceptability of LAI ART 3. Appropriateness and feasibility of LAI ART (for providers) 4. Case vignettes with questions about LAI ART candidacy and potential benefit (for providers)	June 2022 to January 2023	Understand drivers of decisions about ART regimens and adherence supports; quantify preferences for specific ART regimen, ART delivery, and ART adherence support or reinforcement options
3	Brief provider surveys	• 12 MCM providers (1 administrator and 1 direct service provider per partnering agency)	• Pilot intervention acceptability, appropriateness, and feasibility, and organizational readiness for implementation	3 rounds (baseline, midpoint, and final), May 2023 to February 2024	Quantify role of specific factors for pilot implementation using standard measures for comparison to the literature
3	Individual provider interviews	• 12 MCM providers (1 administrator and 1 direct-service provider per partnering agency)	• Providers' experience of the pilot, barriers and facilitators, or other factors for pilot tool implementation, and any recommendations	September 2023 to February 2024	Qualitatively assess pilot implementation factors and outcomes and desired changes to piloted tools
3	Program data on patients enrolled and pilot-related service delivery	• ≥180 MCM patients from 6 partnering agencies	• Patient descriptive data, assessments of patient ART regimen and adherence, and detail on pilot services delivered (tools and dates used, as well as patient responses on ART regimen choices)	May 2023 to January 2024, with follow-up on LAI ART adherence through September 2024	Quantitatively assess pilot implementation outcomes such as reach, effectiveness, adoption, and implementation and variation by agency, intervention condition, or stage of pilot

[a]MCM: medical case management.

[b]LAI: long-acting injectable.

[c]ART: antiretroviral therapy.

The study functions as an academic-government-provider collaboration, with a university-based lead agency working closely with a health department and 6 NY RWPA MCM service-provider agencies that were engaged as partners from the outset. The 6 provider agencies were purposively selected to represent the full range of NY RWPA MCM service settings (hospitals, community health centers, and social services community-based organizations) and the distinct geographic regions within the NY RWPA eligible metropolitan area. Three of the agencies have headquarters in NYC, which includes 5 counties: New York (Manhattan), Bronx, Kings (Brooklyn), Queens, and Richmond (Staten Island). The other 3 agencies

have headquarters in the Tri-County area north of NYC: Westchester, Rockland, and Putnam. All 6 agencies had an annual caseload of at least 70 RWPA MCM patients at the time of the study proposal development. Although the FDA had not approved LAI ART until after the study proposal was submitted, LAI ART prescription was beginning when the project started and was being considered for some MCM enrollees at the partner agencies by the second year of the project in the months immediately preceding the pilot.

Completed Data Collection

Aim 1 Focus Groups

The first study phase was directed at eliciting patient and provider perceptions and expectations of LAI versus daily oral ART, including barriers and facilitators to LAI ART use or delivery. The focus group guide was designed to explore potential influences (organized by domain from the Consolidated Framework for Implementation Research; CFIR [46]) on LAI ART implementation outcomes. Implementation outcomes were defined using RE-AIM (Reach, Effectiveness, Adoption, Implementation, and Maintenance) measures [47]. The primary purpose of the focus groups was to identify key intervention attributes (features of possible LAI ART implementation tools) to be included in the DCEs.

We set out to conduct focus groups of up to 9 participants each with NYC English-speaking patients, Tri-County English-speaking patients, Spanish-speaking patients, MCM administrators (who determine the use of program resources), MCM direct support service providers (who help develop and carry out patient care plans), and MCM program-affiliated primary care providers (who have the discretion to prescribe LAI ART). Patient focus group eligibility required being aged ≥18 years, currently enrolled in an RWPA MCM program at 1 of the 6 partnering agencies, comfortable conversing in Spanish or English, and virally unsuppressed (viral load ≥200 copies/mL) at most recent viral load test. Providers were eligible if they filled a core MCM role (administrator, support service provider, or prescribing provider) with any of the 6 partnering agencies. Provider focus group recruitment yielded 15 providers in 2 focus groups (administrators and support-service providers) plus 1 individual interview with a prescribing provider. Patient recruitment was more challenging and yielded 1 Tri-County participant and 4 NYC participants after no shows. Partner agencies had relatively few virally unsuppressed adults enrolled in MCM at the time of recruitment and noted that those patients were harder to engage in research. No Spanish-speaking patients were enrolled despite months of recruitment. Each participant received a US $25 gift card in appreciation of their time and input.

Focus group interview discussions were audio-recorded, transcribed, and coded in Dedoose using thematic analysis [48]. In a combined inductive-deductive approach, the qualitative analysts applied predefined codes derived from the CFIR and RE-AIM constructs and used grounded exploration to interpret category meanings [49] and attend to emergent themes salient to participants. Separately for patient and provider transcripts, initial codes were identified in an independent review of 1 focus group transcript by 2 study team members in dialogue with a senior investigator with extensive experience in conducting qualitative research. The draft (patient or provider) codebook was then independently applied to a second transcript, with discrepancies resolved in consensus sessions to optimize inter-rater reliability, yielding the final codebook that was applied to the entire data set. Findings were presented for study advisory board (AB) input and used for consensus- and evidence-based selection of 4 potential intervention attributes (with 3-4 levels each) for inclusion in the DCEs.

Patient and provider participants highlighted the potential for LAI ART options to reduce HIV stigma and adherence burden; providers noted that ART administration via injection by a health care worker offered protection against medication diversion. Both sets of participants mentioned COVID-19 vaccine-related attitudes and insurance preauthorization processes as barriers, and providers expressed concerns about the risks of missed injection appointments. Patients and providers desired more information and clearer messaging about LAI ART. The focus group participants also discussed MCM services that could be expanded to support LAI ART delivery: directly observed therapy, appointment transportation or accompaniment, reminder calls or texts, home visits, and financial incentives (eg, rewards for receiving an injection on time). These strategies, along with perceived LAI ART facilitators (less frequent injections, peer support, and postinjection follow-up communications from MCM staff) were integrated as treatment package features for the DCE surveys.

Aim 2 DCE Surveys

DCE Methods

DCEs offer an efficient means of assessing preferences and priorities for intervention-related attributes [50], which can guide intervention design and packaging to encourage uptake, engagement, and maintenance among the intended users. DCE participants are shown a series of choice sets juxtaposing ≥2 different hypothetical scenarios. Each scenario comprises intervention attributes, further defined by a number of levels, which are randomly combined to create hypothetical intervention alternatives. Participants are asked to choose the single preferred alternative for each choice set presented, recognizing the trade-offs between the desirable or undesirable characteristics of each. Through repetition of this process over several choice sets representing many possible combinations of attribute variations, investigators can identify which attributes and attribute levels participants value the most. Latent class multinomial logit regression is used to estimate utilities, which are measures of preference for levels within attributes. Positive utility values indicate greater preference.

DCE Survey Design

The aforementioned focus groups informed the team's selection of four attributes: (1) type of ART, (2) service location or mode, (3) adherence support, and (4) rewards. The latter 3 were alternative-specific attributes defined according to the type of ART (daily oral or LAI). Focusing on 3 implementation outcomes identified by Proctor et al [51] as salient during the adoption phase of an innovation-decision process, we also included the brief (4-item) *acceptability of intervention measure*

(AIM) on the provider and patient survey and the *intervention appropriateness measure* (IAM) and the *feasibility of intervention measure* (FIM) on the provider survey [52]. Contextual items at the end of the patient survey covered prior awareness of LAI ART and any experience with LAI ART, and contextual items at the end of the provider survey covered the length of time delivering MCM and vignettes about hypothetical patients as potential candidates for LAI ART.

Survey Recruitment

Eligibility for the patient DCE survey required being aged ≥18 years and enrolled in RWPA MCM services at any of the 6 partnering agencies. As with the focus groups, contact attempts for patient recruitment were conducted through MCM program staff at the partnering agencies. Eligibility for the provider DCE survey required having an RWPA MCM care team job role (ie, case manager or care coordinator, patient navigator or community health worker, program administrator with duties beyond clerical or data support, or prescribing provider). Given the target of 200 participants per survey (patient or provider) and the availability of fewer than 50 eligible providers at the 6 partner agencies, all 29 RWPA MCM programs were engaged for the provider survey. We offered the provider survey in English and the patient survey in English, Spanish, and Haitian Creole.

Patient Survey Participants and Preliminary Results

From June 2022 through January 2023, 201 NY RWPA MCM patients with a median age of 54 years (IQR 42-62) and a median MCM enrollment of 31 months (IQR 11-45) completed the DCE. Most patients (183/201, 91%) were Black or Latinx, and 39.3% (79/201) identified as women. Three-quarters (151/201, 75.1%) self-reported perfect adherence to daily oral ART. A two-group latent class analysis identified a smaller subset of patients with a strong preference for daily oral ART and a larger subset preferring LAI ART. Both groups preferred higher value monetary incentives and transportation to primary care or injection appointments over other rewards or supports for adherence. At the time of the survey, 85.6% (172/201) of the participants reported taking daily oral ART. About half of the participants (104/201) indicated that they had heard of LAI ART before taking the survey, but only 4.5% (9/201) reported having tried it.

Provider Survey Participants

From July 2022 through January 2023, 177 NY RWPA MCM staff members completed the DCE. Most provider participants identified as women (127/177, 71.8%), were aged 40 to 59 years (92/177, 52%), and had been providing RWPA MCM services for >2 years (124/177, 70.1%). The largest racial or ethnic group among the participating staff was Latinx or Hispanic (73/177, 41.2%), followed by non-Hispanic Black or African American (50/177, 28.2%), and non-Hispanic White (32/177, 18.1%). The most frequent job types were patient navigator (68/177, 38.4%), case manager or care coordinator (46/177, 26%), program director (33/177, 18.6%), and prescribing provider (21/177, 11.9%). As of the end of 2023, data from the provider DCE survey were in the early analysis stage.

Advisory Board

After receiving notice of the grant award (April 2021), the study team convened an AB for input in July 2021; February, May, and November 2022; and January, April, and August 2023. AB members, who consult on study tools, implementation, results interpretation, and dissemination, include clinical and nonclinical direct-service providers and administrators (from all 6 partnering provider agencies and a seventh interested MCM agency); Health Department staff; external researchers; and members of the HIV Health and Human Services Planning Council of NY (RWPA community planning body). In the January and April 2023 meetings, AB members provided critical input on the tools for inclusion in the pilot, including feedback on the content and visual design of draft versions.

Pilot Testing of ART Regimen Decision-Making Supports

Selection and Design of Tools to Be Piloted

The third aim and phase of this study has focused on the synthesis and application of findings from aims 1 and 2 to develop LAI ART implementation tools and pilot test them with partnering agencies while gathering data to inform tool refinement for future research and scale-up. Tools were developed in consultation with the MCM program staff and other AB members familiar with MCM service settings, MCM patient needs, or decision-support processes. The selection and design of tools for the pilot study were guided by a combination of focus group findings, AB input, and preliminary patient DCE results. In addition to indirectly informing tool development by highlighting the attributes for inclusion in the DCEs, focus group findings and AB input directly influenced the study team's decision to develop patient-facing educational materials. The latter decision stemmed from the focus group participants' emphasis on the need for clearer messaging about LAI ART and AB members' requests for materials that could be reviewed by patients on their own. AB members called attention to a general lack of patient-facing materials about LAI ART beyond the drug manufacturer's consumer-directed materials, which partnering program staff viewed as unrelatable for many of their patients. Finally, the AB advocated for including a patient-facing video to present and compare ART regimen options in an engaging and entertaining medium while minimizing the time required during MCM visits for ART regimen-related education and decision-making processes.

The limited familiarity of patient DCE participants with LAI ART reinforced the need for clear, patient-facing educational materials describing LAI ART and directly comparing it with daily oral ART. Divergent patient preferences for daily oral versus LAI ART suggested a difference in perception between LAI ART phase 3 clinical trial participants and patients seen in our safety-net MCM program settings, which may reflect some of the patient-level factors limiting LAI ART uptake in practice. The mixed reception of LAI ART in the DCE reinforced the potential value of a decision-support tool to assist patients in weighing the advantages and disadvantages of available regimen types and assessing the fit of each option with their individual preferences, needs, challenges, and strengths as well as considering programmatic resources (such as transportation)

that could reduce perceived barriers to treatment success. The study team developed a patient-provider ART regimen decision aid using the Ottawa Decision Support Framework [53] and tailored the tool to suit the RWPA MCM program context, the focus on ART regimen decisions, and the AB's emphasis on brevity and accessibility.

Pilot Trial Design

Primary data collection for the pilot has entailed brief provider surveys and semistructured provider interviews drawing upon the CFIR to assess factors (barriers and facilitators) for pilot tool implementation. In addition, we intend to use the provider interviews and program reporting on pilot enrollment and service delivery to evaluate pilot implementation outcomes, drawing upon RE-AIM measures: reach (types and numbers of patients enrolled), effectiveness (preliminary effects on LAI ART uptake and concordance between treatment plan pursued and patient choice as recorded on the decision aid), adoption (documentation of specific tools' use), implementation (alignment of reported tool use with study condition and guidance on tool use), and maintenance (ART adherence). This pilot study was designed as a nonrandomized, 2-arm trial of newly developed tools with ≥180 RWPA MCM patients. It was structured to allow comparison of an intervention arm including both patient education materials and the decision aid (*decision-aid arm*) with an intervention arm including only the patient education materials and usual care approaches (whatever agencies may already be doing) for ART regimen decision-making (*education-only arm*).

Study Setting and Participants

The pilot test was conducted at the 6 partnering RWPA MCM agencies. The characteristics and study arm assignments of the 6 agencies are summarized in Multimedia Appendix 1. Cluster (agency-level) assignment was used for this study to minimize crossover between intervention conditions and avert the logistical and ethical dilemmas posed by assignment strategies that require providers to administer, maintain, and track different investigator-assigned intervention conditions within a single patient caseload [54-56]. *Provider eligibility:* Pilot-related primary data collection was limited to English-speaking adults responsible for overseeing or delivering RWPA MCM services or prescribing ART for MCM patients at a partnering agency. At each agency, 1 administrative staff member (eg, program director) and 1 direct-service provider (eg, case manager, patient navigator, or prescriber) was engaged to participate in implementation-related data collection through brief surveys and semistructured interviews. *Patient eligibility:* Patients were enrolled in a partnering NY RWPA MCM program, aged ≥18 years, and able to understand materials in English or Spanish. Patient eligibility for an LAI ART prescription could not be directly assessed by the study team and could be assessed differently by different providers or third-party payers; it could also change over time with FDA label indications. However, the study team communicated to partnering programs that patients should not be included in the pilot if they had known or suspected resistance to cabotegravir or rilpivirine, as this was a contraindication for LAI ART available as of the start of this pilot study (CABENUVA). On the basis of AB feedback that translating pilot materials to Spanish without translating to Haitian Creole would be viewed as inequitable, and given a lack of remaining time or resources to provide translations for tools (including audio for the video) in 3 languages, the pilot study was launched with only English-language tool versions.

Intervention Conditions

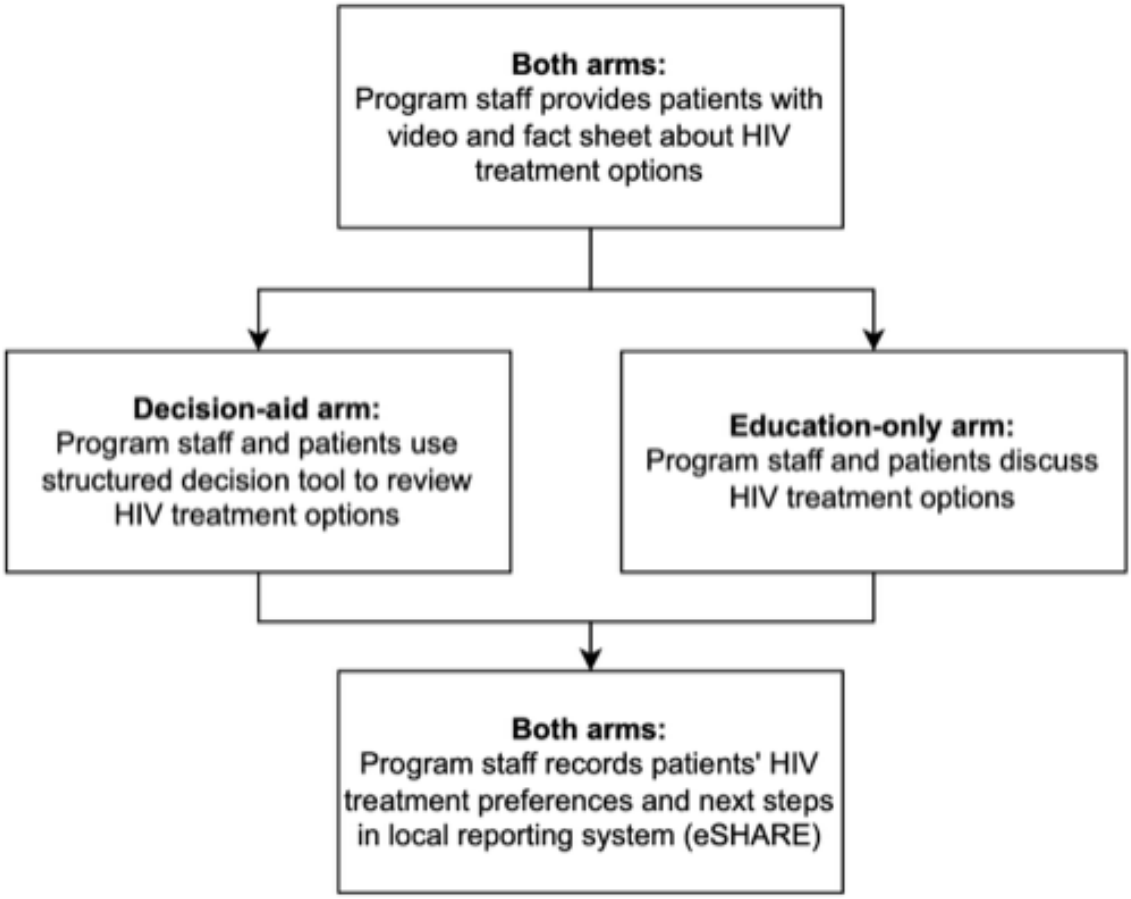
Education-Only Arm

Participants received informational materials (including a fact sheet covering *frequently asked questions* [Multimedia Appendix 2] and a short video [Multimedia Appendix 3]) on their HIV treatment options and related support service options. These materials provide a comparison of the risks and benefits of LAI and oral ART regimens, set expectations about clinic visits, present information about side effects, and include additional resources to assist patients in preparing to discuss HIV treatment and support options with their care coordinator and prescribing provider. All materials are at or below an eighth-grade reading level, use graphics to bolster understanding for different levels of health literacy, and follow accessibility guidelines for font choice and size. Participants receiving this intervention were offered these materials by a care coordinator or patient navigator and were encouraged to review the materials on their own; they could also go over the materials with staff during an MCM program visit.

Decision-Aid Arm

Before or during an MCM visit, participants received informational materials (described in *Education-Only Arm* section) on HIV treatment types and related support service options. During an MCM visit, the participant and patient navigator or care coordinator reviewed the shared decision aid (Multimedia Appendix 4) to weigh the participant's treatment options and their fit to the participant's interests, needs, assets, and constraints. The tool facilitates and records patient-provider agreement on a treatment plan to be integrated into the broader MCM care plan signed by both the patient and provider. Figure 1 illustrates the 2 intervention conditions and the workflow for each.

Figure 1. Intervention arms and workflows for the 2-arm pilot trial. eSHARE: Electronic System for HIV/AIDS Research and Evaluation.



Nonrandom Assignment

We used purposive sampling to assign 3 of the 6 partnering RWPA MCM agencies to the decision-aid arm (which included the educational tools) and 3 to the education-only arm. Specifically, we ensured representation of at least 2 different agency types and MCM program sizes in each arm.

Blinding

Owing to the need to engage service providers in the intervention through study team–led activities (eg, orientation to the project-specific educational materials or the decision aid), study arm assignments were transparent to agency staff and study team members (though not to patients).

Data Collection and Management

Aim 3 (pilot testing) involved repeated primary data collection with 2 providers at each of the 6 partnering agencies and use of secondary data on pilot participants, service delivery, and outcomes. In aim 3 pilot interviews with the implementing providers, oral informed consent was obtained in advance of the interview session by phone or videoconference. The interviews were audio-recorded and transcribed for coding in Dedoose. Aim 3 provider survey data were collected and managed using the NYC Health Department REDCap (Research Electronic Data Capture; Vanderbilt University) server, a web-based application for designing and managing surveys. The REDCap survey data will be analyzed using R (version 4.3.2; R Foundation for Statistical Computing).

Patient data for the pilot are being drawn from the local RWPA data system, the Electronic System for HIV/AIDS Research and Evaluation (eSHARE), in the form of provider-reported enrollments, services, patient characteristics, assessed needs, regimen types, and adherence data required for fee-for-service reimbursement in NY RWPA MCM contracts. eSHARE has been updated by the NYC Health Department to include pilot tools so that partnering MCM agencies could enter pilot activities along with (and as distinct from) other MCM services. No patients were enrolled in the RWPA MCM programs solely for the pilot; rather, patients already enrolled in MCM could be eligible to receive pilot-related services (ART regimen-related information and decision support with the tools developed for the project), along with the array of other MCM services. All patient- and service-level data are protected according to the Centers for Disease Control and Prevention's physical and electronic data security and confidentiality policies [57]. Health Department staff extract and clean eSHARE data monthly, clean and freeze surveillance data sets quarterly, and conduct matches of the program to surveillance data semiannually. The deterministic matching algorithm has been described previously [58]. Through matching with surveillance data, patients are assigned a unique record number used to deduplicate data sets, which are stripped of personal identifiers before analysis.

Study Outcomes

LAI Uptake (Primary Outcome)

The primary outcome is defined as the proportion of pilot participants who start LAI ART (whether initiating ART, transitioning from a prior regimen, or transitioning from a period of nonuse of ART). The denominator includes patients not already on LAI ART at the start of the pilot trial, and the numerator includes any of those in the denominator who began LAI ART during the trial. Using program-reported (eSHARE) data on regimen type, uptake will be measured continuously for up to 9 months (the duration of the pilot trial). *Concordance:* This outcome is defined as the proportion of participants whose intent (as documented via the decision aid) is carried through in terms of their subsequent treatment (self-administered daily oral ART, LAI ART, or some intermediate step such as directly observed therapy to meet the current FDA label requirement for viral suppression). Using eSHARE data on decision aid responses and subsequent regimen type or services related to ART adherence, concordance will be measured from the date of decision aid completion for up to 9 months. *LAI maintenance:* LAI maintenance is defined in terms of adherence to LAI ART, specifically the time from LAI initiation to first deviation from the injection schedule, among trial participants initiating LAI ART during the trial. A deviation includes any injection >1 week ahead of or 1 week after the treatment target date, where the injection target date depends on whether the prescribed regimen is monthly or bimonthly. Using eSHARE data on ART regimen type and adherence (as well as case closure owing to death), maintenance will be measured from the first report of LAI ART to the first reported deviation from the injection schedule or date of death from any cause, whichever comes first, assessed for up to 9 months from the first injection or up to 8 months of follow-up injections (counting from the first possible deviation from a scheduled follow-up injection).

Other Measures

To understand the influences on implementation, we assess provider-perceived acceptability, appropriateness, and feasibility of the tools at 3 points in the pilot: baseline, 4-5 months (midpoint), and 9 months (end of the pilot). Specifically, the provider survey includes the 4-item scales (AIM, IAM, and FIM) that were used in the provider DCE survey [52]. However, for the pilot survey, these 3 measures specifically refer to the pilot tools being implemented. The baseline and midpoint assessments also include a brief measure of organizational readiness for implementing change (ORIC), which captures commitment to change (5 items) and perceived efficacy to change (7 items) [59] based on the theory of organizational readiness for change [60]. As the ORIC measure is anticipatory, it is not part of the final assessment. The semistructured midpoint and end-of-pilot interviews elicit providers' experiences of the piloted tools, including barriers, facilitators, and suggested refinements. Interviews will lend context to the ORIC, AIM, IAM, and FIM results and guide tool refinements.

Sample Size, Data Analysis, and Power Analysis

The original target was to enroll 180 patients or 30 (on average) per partner agency. As of mid-November 2023, 205 patients were enrolled. Using eSHARE data, we will describe trial participant demographics (eg, gender, age, race or ethnicity, income, and housing status) overall and by intervention arm. We will compare LAI ART uptake and, among those starting LAI ART, adherence by intervention arm, to assess the effects of the fuller package with the decision aid versus education alone. We will use log binomial regression to estimate risk ratios for uptake and adherence by intervention arm with generalized estimating equations and a small sample correction (owing to the small number of clusters) to maintain the type I error rate while accounting for clustering by site. To the extent possible given our sample size, we will adjust for potential confounders captured in eSHARE.

The brief provider survey measures will be analyzed through a comparison of responses on the same measures over time (eg, to assess change in perceived feasibility), as well as comparison of responses by intervention arm, agency type, and participant role. AIM, IAM, FIM, and ORIC scores will also be analyzed in relation to the levels of pilot service delivery as documented in eSHARE. To understand the potential for sustainability and scale-up, we will explore qualitative provider interview themes related to the acceptability and feasibility of the intervention. Qualitative and quantitative analyses will be integrated by examining thematic patterns reflecting RE-AIM and CFIR implementation constructs as they explain observed implementation outcomes [61].

Our pilot was designed to assess implementation of the newly developed tools and inform tool refinements. Data from the pilot will be used to generate estimates of LAI ART uptake that can, in turn, inform sample size and power calculations for a larger, controlled study of the refined tools' implementation and treatment outcomes. Accordingly, data from the pilot study will be used to estimate the proportion of patients who start LAI ART and, among those initiating, the proportion who maintain LAI ART. With the original target of 180 patients (now exceeded), we will be able to estimate LAI uptake with precision (95% CI) with the levels of uptake described in Table 2.

Assuming that half of the people who initiate LAI ART maintain it at 9 months, we will have the abovementioned precision estimates for the scenario of 50% LAI ART maintenance across a range of different levels of LAI ART uptake.

Table 2. 95% CIs for long-acting injectable (LAI) antiretroviral therapy (ART) uptake among pilot participants overall and maintenance estimates for those who start on LAI ART under LAI uptake percent assumptions.

LAI ART uptake, (%)	LAI ART uptake, 95% CI	LAI ART maintenance at 50%, 95% CI
5	2.7-9.2	22.7-77.4
10	6.4-15.2	29.0-71.0
15	10.5-20.9	32.4-67.7
20	14.8-26.4	34.5-65.5
30	23.8-37.0	37.0-62.9
40	33.1-47.3	38.8-61.3
50	42.8-57.3	39.9-60.1

Ethical Considerations

This study was approved by the NYC Department of Health and Mental Hygiene IRB (protocol 20-096) and registered with ClinicalTrials.gov (Identifier NCT05833542, preresults). The pilot trial was granted a waiver of patient informed consent in accordance with the pre-2018 requirements set forth in 45 CFR 46.116(d) based on its reliance on secondary data analysis. Any changes to trial eligibility criteria, outcome measures, or analysis plans would be mutually agreed upon between the principal investigators, vetted with the AB, and submitted to the IRB as protocol modifications.

Informed consent was obtained from each participant before their participation in primary data collection: focus groups, DCE surveys, provider pilot interviews, or provider pilot surveys. No individual incentive was offered for provider pilot interviews or provider pilot surveys. Each focus group participant and each DCE survey participant received a US $25 gift card.

The primary data collected for this study are stored on secured servers without participant names or other personal identifiers. Study records can be linked to individual participants only by study team members, who retain a separate key linking study identifiers to other identifiers (eg, eSHARE identifier codes). Patient names are stored in the most secured environment, accessible only to NYC Health Department staff authorized to view names and only during a time-limited, secured session in Citrix, which prohibits access to the internet, email, portable media such as flash drives, or printers. All records used in secondary analyses are also stripped of personal identifiers before their inclusion in data sets for analysis.

Results

The study was funded in late April 2021 and received official IRB approval in May 2021 under protocol 20-096. Focus groups were conducted in late 2021 and DCE data collection took place between June 2022 and January 2023. Patient education and patient-provider decision aid tools were developed by May 2023, and the trial continued through January 2024. Complete outcome data are expected by October 2024 and will be submitted for publication by December 2024. Study results will be reported in accordance with the CONSORT (Consolidated Standards of Reporting Trials) extension to cluster randomized trials and disseminated through scientific conferences, peer-reviewed publications, and meetings with local stakeholders. The investigators have also been sharing this work with colleagues in other jurisdictions and will disseminate the findings via the Ending the Epidemic Dashboard website.

Discussion

Overview

As a biomedical advance that untethers HIV viral suppression from the requirement for daily medication adherence, LAI ART could greatly increase the opportunities for health, survival, transmission prevention, and health equity. However, realizing that potential will depend on reaching those who have difficulty achieving or maintaining viral suppression on daily oral ART regimens. In addition, at this relatively early stage of LAI ART availability through third-party payers, there is little information on how acceptable, appropriate, or feasible this treatment option may be for low-income, predominantly Black and Latinx patients and their HIV service providers. This study is designed to yield insights and field-tested strategies to help optimize the public health impact of LAI ART, with particular attention to the patient groups underrepresented in clinical trials, disproportionately burdened by HIV-related morbidity and mortality, and most able to benefit from gaining access to alternatives to daily oral ART. On the basis of the focus group participants' and AB members' calls for clear patient-facing information and findings of limited LAI ART familiarity and divergent ART regimen-type preferences among patient DCE participants, we prioritized the development and testing of a patient-facing fact sheet and educational video, along with a patient-provider decision aid to guide conversations about treatment options and related supports.

Limitations and Strengths

Agencies were purposively assigned to pilot intervention conditions (with the intent of balancing the characteristics of agencies represented in each condition) rather than through randomization. Additional limitations include a lack of blinding (of agencies, providers, or investigators) to the agencies' assignments and a lack of control over agencies', providers', or patients' exposure to other initiatives or interventions that may affect the outcome. We are aware of at least 1 other NY-based pilot test of LAI-related support strategies [62], as well as a NY State Department of Health clinical quality improvement committee focused on identifying and sharing LAI ART–related resources and best practices. However, the

other NY-based pilot does not directly involve any of the agencies engaged in this trial. To our knowledge, our study is the first and only study to explicitly focus on the integration of LAI ART regimen options in RWPA or other RWHAP MCM service settings and the first to develop patient-directed LAI ART education materials or a patient-provider ART decision aid for use in an RWPA service population.

As with other HIV care quality improvement activities led by the NYC Health Department, agency participation is voluntary, meaning that agencies in the pilot could implement their assigned intervention condition incompletely or decline to implement. To address this limitation, we are tracking multiple implementation measures.

Conclusions

The United States National HIV/AIDS Strategy and National Institutes of Health have called for implementation science to produce evidence-based models of care [63,64]. Reviews of HIV care continuum research have also noted the need for practice-based evidence to inform program and policy development [65-67]. The implementation science design of this study has been selected to facilitate rapid research-to-practice translation of any LAI ART educational or decision-support tools that are found to be acceptable, feasible, and appropriate to these service settings and that show preliminary evidence of patient benefit. Through a robust academic-government-provider partnership, products from this study will be incorporated into local HIV services planning and delivery, as well as into future research.

Acknowledgments

This project was supported by the National Institutes of Health (NIH), grant number R34 MH 126809 (Project Officer Teri Senn), and by the Health Resources and Services Administration (HRSA), grant number H89HA00015 (Project Officer Axel Reyes). The authors would like to thank the 6 partnering provider agencies: State University of New York Downstate Health Sciences University (lead contacts: Lori Hurley and Antoinette Davis), La Casa de Salud (lead contacts: Mohammed Aldhuraibi and Pedro Gonzalez), Together Our Unity Can Health (lead contacts: Julian Palmer and Memunatu Attah-Issah), Open Door Family Medical Centers (lead contacts: Karin Palencia-Lua and José Miranda), Council on Adoptable Children (lead contacts: Denise Barrera and Katie Rivera), and Sun River Health (lead contacts: Aldonza Milian and Lisa Reid). This study also benefited from the support of other Ryan White Part A MCM service providers, Ryan White Part A participants, the HIV Health and Human Services Planning Council of New York, New York City Health Department HIV Care and Treatment Program leadership and quality management staff (Guadalupe Dominguez Plummer, Gina Gambone, Frances Silva, Grace Herndon, and Jacqueline Graham), and the Einstein-Rockefeller-CUNY Center for AIDS Research. The authors are indebted to Jennifer Carmona and Aimee Campbell, who provided early input critical to the grant proposal and the planning of the trial reported here. Finally, the authors would like to recognize the contributions of our other AB members and study team members (including Honoria Guarino, Will You, Chunki Fong, and Javier Lopez-Rios) to the larger Assessing Perceptions and Preferences Around Long-acting Injectables (APPLI) study and specifically the qualitative components and DCEs that guided the development of tools for pilot testing in the study's clinical trial phase. Generative AI (eg, ChatGPT) was not used in the ideation or in the writing process of this protocol. The content of this manuscript is solely the responsibility of the authors and does not necessarily reflect the official views of the funding agencies supporting this project. The NIH and HRSA are not involved in the study design, conduct, or products, or in the decision to submit this work for publication. The cited personal communication from ViiV Healthcare, indicating approximately 20,000 people in the US (including Puerto Rico) on CABENUVA, is based on an estimate derived from the use of information under license from the following IQVIA information service: National Custom Patient with National Longitudinal Patient (LRx) for the period ending 2023-09-29. IQVIA expressly reserves all rights, including rights of copying, distribution, and republication.

Data Availability

The full institutional review board protocol and statistical code will be made available upon request. The NY State Public Health Law prohibits the study team from releasing a public use data set containing information tending to identify the participants in its research. The NYC Health Department staff retain sole custody of study data sets and designated staff are available to answer any inquiries. Any questions or requests for additional information can be emailed to the study contact person.

Authors' Contributions

MKI is the health department (NYC Department of Health and Mental Hygiene [DOHMH]) principal investigator and led the conception of the overall study and the writing of the R34 proposal. RZ (City University of New York [CUNY]) reviewed and edited all drafts of the grant proposal, led the analyses on aim 2 of the larger study, and contributed substantively to the preparation of the manuscript. TA (DOHMH) supervised the DOHMH analysts' work on aims 1 and 3 of the larger study and contributed substantively to the study design and analysis plan. MP (DOHMH) and CE (DOHMH) conducted qualitative data collection for aim 1 and aim 3 and conducted qualitative analyses for aim 1. SGK (CUNY) and MMP (University of California, San Francisco [UCSF]) contributed substantively to the grant proposal and participated in ongoing planning. EAK (CUNY) contributed to the grant proposal and analysis plan and advised on study implementation. RZ (CUNY), TA (DOHMH), MP (DOHMH), and CE (DOHMH) prepared data, facilitated intervention implementation, participated in ongoing planning, and contributed to

communication with service providers and other stakeholders while managing other aspects of the larger study. DN is the university-based, lead agency (CUNY) principal investigator and shares responsibility for the conceptualization and oversight of the overall study and this trial, serves as the primary contact with the grant funding agency, supervises CUNY team members on the grant, and guides dissemination. MKI drafted the manuscript, and all authors (MKI, RZ, TA, MP, CE, SGK, MMP, EAK, and DN) revised it for critically important intellectual content and provided the final approval of the manuscript.

Conflicts of Interest

The authors have reported only federal government grants to their institutions for this work. For work beyond this project, DN has received consulting fees from Gilead Sciences, Inc and Abbvie, Inc, and RZ, SGK, and DN have received research grant funding from Pfizer to their institution.

Multimedia Appendix 1
Partnering agency characteristics and intervention arm assignments for the pilot trial.
[DOCX File , 13 KB - resprot_v13i1e56892_app1.docx]

Multimedia Appendix 2
Long-acting injectable (LAI) antiretroviral therapy (ART) pilot fact sheet.
[PDF File (Adobe PDF File), 109 KB - resprot_v13i1e56892_app2.pdf]

Multimedia Appendix 3
Long-acting injectable (LAI) antiretroviral therapy (ART) pilot video.
[MP4 File (MP4 Video), 43202 KB - resprot_v13i1e56892_app3.mp4]

Multimedia Appendix 4
Long-acting injectable (LAI) antiretroviral therapy (ART) pilot decision aid.
[PDF File (Adobe PDF File), 86 KB - resprot_v13i1e56892_app4.pdf]

References

1. Mandsager P, Marier A, Cohen S, Fanning M, Hauck H, Cheever LW. Reducing HIV-related health disparities in the Health Resources and Services Administration's Ryan White HIV/AIDS Program. Am J Public Health 2018 Nov;108(S4):S246-S250. [doi: 10.2105/AJPH.2018.304689] [Medline: 30383416]
2. Weiser J, Beer L, Frazier EL, Patel R, Dempsey A, Hauck H, et al. Service delivery and patient outcomes in Ryan White HIV/AIDS program-funded and -nonfunded health care facilities in the United States. JAMA Intern Med 2015 Oct;175(10):1650-1659 [FREE Full text] [doi: 10.1001/jamainternmed.2015.4095] [Medline: 26322677]
3. Centers for Disease Control and Prevention. Monitoring selected national HIV prevention and care objectives by using HIV surveillance data—United States and 6 dependent areas, 2015. HIV Surveillance Supplemental Report 2017. 2017 Jul. URL: https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-supplemental-report-vol-22-2.pdf [accessed 2024-02-23]
4. Bradley H, Hall HI, Wolitski RJ, Van Handel MM, Stone AE, LaFlam M, et al. Vital signs: HIV diagnosis, care, and treatment among persons living with HIV--United States, 2011. MMWR Morb Mortal Wkly Rep 2014 Nov 28;63(47):1113-1117 [FREE Full text] [Medline: 25426654]
5. Doshi RK, Milberg J, Isenberg D, Matthews T, Malitz F, Matosky M, et al. High rates of retention and viral suppression in the US HIV safety net system: HIV care continuum in the Ryan White HIV/AIDS Program, 2011. Clin Infect Dis 2015 Jan 01;60(1):117-125. [doi: 10.1093/cid/ciu722] [Medline: 25225233]
6. Part A: grants to eligible metropolitan and transitional grant areas.. HRSA's Ryan White HIV/AIDS Program. 2023 Sep. URL: https://ryanwhite.hrsa.gov/sites/default/files/ryanwhite/resources/program-factsheet-part.pdf [accessed 2024-02-20]
7. Ending the HIV epidemic in the U.S. Office of Infectious Disease and HIV/AIDS Policy, HHS. URL: https://www.hiv.gov/federal-response/ending-the-hiv-epidemic/overview [accessed 2019-03-18]
8. Sullivan PS, Satcher Johnson A, Pembleton ES, Stephenson R, Justice AC, Althoff KN, et al. Epidemiology of HIV in the USA: epidemic burden, inequities, contexts, and responses. Lancet 2021 Mar 20;397(10279):1095-1106. [doi: 10.1016/S0140-6736(21)00395-0] [Medline: 33617774]
9. Allgood KL, Hunt B, Rucker MG. Black: White disparities in HIV mortality in the United States: 1990-2009. J Racial Ethn Health Disparities 2016 Mar;3(1):168-175. [doi: 10.1007/s40615-015-0141-8] [Medline: 26896117]
10. Beer L, Bradley H, Mattson CL, Johnson CH, Hoots B, Shouse RL. Trends in racial and ethnic disparities in antiretroviral therapy prescription and viral suppression in the United States, 2009-2013. J Acquir Immune Defic Syndr 2016 Dec 01;73(4):446-453 [FREE Full text] [doi: 10.1097/QAI.0000000000001125] [Medline: 27391389]

11. Irvine MK, Chamberlin SA, Robbins RS, Myers JE, Braunstein SL, Mitts BJ, et al. Improvements in HIV care engagement and viral load suppression following enrollment in a comprehensive HIV care coordination program. Clin Infect Dis 2015 Jan 15;60(2):298-310 [FREE Full text] [doi: 10.1093/cid/ciu783] [Medline: 25301208]
12. Irvine MK, Chamberlin SA, Robbins RS, Kulkarni SG, Robertson MM, Nash D. Come as you are: improving care engagement and viral load suppression among HIV care coordination clients with lower mental health functioning, unstable housing, and hard drug use. AIDS Behav 2017 Jun;21(6):1572-1579 [FREE Full text] [doi: 10.1007/s10461-016-1460-4] [Medline: 27342990]
13. Nash D, Robertson MM, Penrose K, Chamberlin S, Robbins RS, Braunstein SL, et al. Short-term effectiveness of HIV care coordination among persons with recent HIV diagnosis or history of poor HIV outcomes. PLoS One 2018 Sep 24;13(9):e0204017 [FREE Full text] [doi: 10.1371/journal.pone.0204017] [Medline: 30248136]
14. Robertson MM, Penrose K, Nash D, Harriman G, Braunstein SL, Levin B, et al. Impact of an HIV care coordination program on the timeliness of viral suppression and immune recovery among clients newly diagnosed with HIV. AIDS Behav 2020 Apr;24(4):1237-1242 [FREE Full text] [doi: 10.1007/s10461-019-02732-0] [Medline: 31728695]
15. Robertson MM, Penrose K, Irvine MK, Robbins RS, Kulkarni S, Braunstein SL, et al. Impact of an HIV care coordination program on durable viral suppression. J Acquir Immune Defic Syndr 2019 Jan 01;80(1):46-55 [FREE Full text] [doi: 10.1097/QAI.0000000000001877] [Medline: 30299346]
16. Swindells S, Andrade-Villanueva JF, Richmond GJ, Rizzardini G, Baumgarten A, Masiá M, et al. Long-acting cabotegravir and rilpivirine for maintenance of HIV-1 suppression. N Engl J Med 2020 Mar 19;382(12):1112-1123. [doi: 10.1056/NEJMoa1904398] [Medline: 32130809]
17. Orkin C, Arasteh K, Górgolas Hernández-Mora M, Pokrovsky V, Overton ET, Girard PM, et al. Long-acting cabotegravir and rilpivirine after oral induction for HIV-1 infection. N Engl J Med 2020 Mar 19;382(12):1124-1135. [doi: 10.1056/NEJMoa1909512] [Medline: 32130806]
18. Orkin C, Oka S, Philibert P, Brinson C, Bassa AC, Gusev D, et al. Long-acting cabotegravir + rilpivirine for HIV treatment: FLAIR week 96 results. In: Proceedings of the Conference on Retroviruses and Opportunistic Infections. 2020 Presented at: CROI 2020; March 8-11 2020; Boston, MA URL: https://www.croiconference.org/abstract/long-acting-cabotegravir-rilpivirine-for-hiv-treatment-flair-week-96-results/ [doi: 10.1016/s2352-3018(20)30340-4]
19. Overton ET, Richmond GJ, Rizzardini G, Jaeger H, Orrell C, Nagimova F, et al. Cabotegravir + rilpivirine every 2 months is noninferior to monthly: ATLAS-2M study. In: Proceedings of the Conference on Retroviruses and Opportunistic Infections. 2020 Mar Presented at: CROI 2020; March 8-11, 2020; Boston, MA URL: https://www.croiconference.org/abstract/cabotegravir-rilpivirine-every-2-months-is-noninferior-to-monthly-atlas-2m-study/ [doi: 10.1016/s0140-6736(20)32666-0]
20. FDA approves first extended-release, injectable drug regimen for adults living with HIV. U.S. Food & Drug Administration. 2021 Jan 21. URL: https://www.fda.gov/news-events/press-announcements/fda-approves-first-extended-release-injectable-drug-regimen-adults-living-hiv [accessed 2024-01-26]
21. ViiV healthcare announces us FDA approval of Cabenuva (cabotegravir, rilpivirine) for use every two months, expanding the label of the first and only complete long-acting HIV treatment. ViiV Healthcare. 2022 Feb 1. URL: https://viivhealthcare.com/hiv-news-and-media/news/press-releases/2022/january/viiv-healthcare-announces-fda-approval-of-cabenuva-for-use-every-two-months/ [accessed 2024-01-26]
22. Kilcrease C, Yusuf H, Park J, Powell A, Rn LJ, Rn JO, et al. Realizing the promise of long-acting antiretroviral treatment strategies for individuals with HIV and adherence challenges: an illustrative case series. AIDS Res Ther 2022 Nov 26;19(1):56 [FREE Full text] [doi: 10.1186/s12981-022-00477-w] [Medline: 36435793]
23. Nachega JB, Scarsi KK, Gandhi M, Scott RK, Mofenson LM, Archary M, et al. Long-acting antiretrovirals and HIV treatment adherence. Lancet HIV 2023 May;10(5):e332-e342 [FREE Full text] [doi: 10.1016/S2352-3018(23)00051-6] [Medline: 37062293]
24. Palacios C, Wilpotte C, Adda A, Allaf S, Thibaut P, Chas J, et al. Expectations and acceptability of long-acting injectable antiretrovirals by patients living with HIV/AIDS. Infect Dis Now 2022 Jun;52(4):238-239. [doi: 10.1016/j.idnow.2022.01.010] [Medline: 35172216]
25. Mantsios A, Murray M, Karver TS, Davis W, Margolis D, Kumar P, et al. Efficacy and freedom: patient experiences with the transition from daily oral to long-acting injectable antiretroviral therapy to treat HIV in the context of phase 3 trials. AIDS Behav 2020 Dec;24(12):3473-3481. [doi: 10.1007/s10461-020-02918-x] [Medline: 32410051]
26. Harris S, Nikulina V, Gelpí-Acosta C, Morton C, Newsome V, Gunn A, et al. Prescription drug diversion: predictors of illicit acquisition and redistribution in three U.S. Metropolitan areas. AIMS Public Health 2015 Dec 02;2(4):762-783 [FREE Full text] [doi: 10.3934/publichealth.2015.4.762] [Medline: 26690813]
27. Levi-Minzi MA, Surratt HL. HIV stigma among substance abusing people living with HIV/AIDS: implications for HIV treatment. AIDS Patient Care STDS 2014 Aug;28(8):442-451 [FREE Full text] [doi: 10.1089/apc.2014.0076] [Medline: 24983302]
28. Surratt HL, O'Grady CL, Levi-Minzi MA, Kurtz SP. Medication adherence challenges among HIV positive substance abusers: the role of food and housing insecurity. AIDS Care 2015;27(3):307-314 [FREE Full text] [doi: 10.1080/09540121.2014.967656] [Medline: 25314042]

29. Kennedy CE, Zhao T, Vo AV, Nakubulwa R, Nabakka P, Jackson J, et al. High acceptability and perceived feasibility of long-acting injectable antiretroviral treatment among people living with HIV who are viremic and health workers in Uganda. AIDS Patient Care STDS 2023 Jun;37(6):316-322. [doi: 10.1089/apc.2023.0017] [Medline: 37294280]
30. Garris CP, Czarnogorski M, Dalessandro M, D'Amico R, Nwafor T, Williams W, et al. Perspectives of people living with HIV-1 on implementation of long-acting cabotegravir plus rilpivirine in US healthcare settings: results from the CUSTOMIZE hybrid III implementation-effectiveness study. J Int AIDS Soc 2022 Sep;25(9):e26006 [FREE Full text] [doi: 10.1002/jia2.26006] [Medline: 36097674]
31. Simoni JM, Beima-Sofie K, Mohamed ZH, Christodoulou J, Tapia K, Graham SM, et al. Long-acting injectable antiretroviral treatment acceptability and preferences: a qualitative study among US providers, adults living with HIV, and parents of youth living with HIV. AIDS Patient Care STDS 2019 Mar;33(3):104-111 [FREE Full text] [doi: 10.1089/apc.2018.0198] [Medline: 30844308]
32. Simoni JM, Tapia K, Lee SJ, Graham SM, Beima-Sofie K, Mohamed ZH, et al. A conjoint analysis of the acceptability of targeted long-acting injectable antiretroviral therapy among persons living with HIV in the U.S. AIDS Behav 2020 Apr;24(4):1226-1236 [FREE Full text] [doi: 10.1007/s10461-019-02701-7] [Medline: 31655915]
33. Dandachi D, Dang BN, Lucari B, Swindells S, Giordano TP. Acceptability and preferences for long-acting antiretroviral formulations among people with HIV infection. AIDS Care 2021 Jun;33(6):801-809. [doi: 10.1080/09540121.2020.1764906] [Medline: 32408771]
34. Carillon S, Gallardo L, Linard F, Chakvetadze C, Viard JP, Cros A, et al. Perspectives of injectable long acting antiretroviral therapies for HIV treatment or prevention: understanding potential users' ambivalences. AIDS Care 2020 May;32(sup2):155-161. [doi: 10.1080/09540121.2020.1742869] [Medline: 32189506]
35. Collins AB, Macon EC, Langdon K, Joseph R, Thomas A, Dogon C, et al. Perceptions of long-acting injectable antiretroviral therapy among people living with HIV who use drugs and service providers: a qualitative analysis in Rhode Island. J Urban Health 2023 Oct;100(5):1062-1073. [doi: 10.1007/s11524-023-00755-6] [Medline: 37563518]
36. Fletcher L, Burrowes SA, Khan GK, Sabin L, Johnson S, Kimmel SD, et al. Perspectives on long-acting injectable HIV antiretroviral therapy at an alternative care site: a qualitative study of people with HIV experiencing substance use and/or housing instability. Harm Reduct J 2023 Jan 10;20(1):4 [FREE Full text] [doi: 10.1186/s12954-023-00730-z] [Medline: 36627679]
37. Philbin MM, Parish C, Bergen S, Kerrigan D, Kinnard EN, Reed SE, et al. A qualitative exploration of women's interest in long-acting injectable antiretroviral therapy across six cities in the Women's Interagency HIV Study: intersections with current and past injectable medication and substance use. AIDS Patient Care STDS 2021 Jan;35(1):23-30 [FREE Full text] [doi: 10.1089/apc.2020.0164] [Medline: 33400587]
38. Jolayemi O, Bogart LM, Storholm ED, Goodman-Meza D, Rosenberg-Carlson E, Cohen R, et al. Perspectives on preparing for long-acting injectable treatment for HIV among consumer, clinical and nonclinical stakeholders: a qualitative study exploring the anticipated challenges and opportunities for implementation in Los Angeles County. PLoS One 2022 Feb 3;17(2):e0262926 [FREE Full text] [doi: 10.1371/journal.pone.0262926] [Medline: 35113892]
39. Philbin MM, Parish CL, Kinnard EN, Reed SE, Kerrigan D, Alcaide ML, et al. Multisite study of women living with HIV's perceived barriers to, and interest in, long-acting injectable antiretroviral therapy. J Acquir Immune Defic Syndr 2020 Jul 01;84(3):263-270 [FREE Full text] [doi: 10.1097/QAI.0000000000002337] [Medline: 32530905]
40. Collins LF, Corbin-Johnson D, Asrat M, Morton ZP, Dance K, Condra A, et al. Early experience implementing long-acting injectable cabotegravir/rilpivirine for human immunodeficiency virus-1 treatment at a Ryan White-funded clinic in the US South. Open Forum Infect Dis 2022 Sep;9(9):ofac455 [FREE Full text] [doi: 10.1093/ofid/ofac455] [Medline: 36147599]
41. Mantsios A, Murray M, Karver TS, Davis W, Galai N, Kumar P, et al. Multi-level considerations for optimal implementation of long-acting injectable antiretroviral therapy to treat people living with HIV: perspectives of health care providers participating in phase 3 trials. BMC Health Serv Res 2021 Mar 20;21(1):255 [FREE Full text] [doi: 10.1186/s12913-021-06214-9] [Medline: 33743684]
42. Diagnoses of HIV infection in the United States and dependent areas, 2021. Centers for Disease Control and Prevention. URL: https://www.cdc.gov/hiv/library/reports/hiv-surveillance/vol-34/index.html [accessed 2024-01-25]
43. Singh GK, Azuine RE, Siahpush M. Widening socioeconomic, racial, and geographic disparities in HIV/AIDS mortality in the United States, 1987-2011. Adv Prev Med 2013;2013:657961 [FREE Full text] [doi: 10.1155/2013/657961] [Medline: 23738084]
44. Havlir D, Gandhi M. Implementation challenges for long-acting antivirals as treatment. Curr Opin HIV AIDS 2015 Jul;10(4):282-289 [FREE Full text] [doi: 10.1097/COH.0000000000000158] [Medline: 26049955]
45. Meyers K, Golub SA. Planning ahead for implementation of long-acting HIV prevention: challenges and opportunities. Curr Opin HIV AIDS 2015 Jul;10(4):290-295 [FREE Full text] [doi: 10.1097/COH.0000000000000159] [Medline: 26049956]
46. Damschroder LJ, Aron DC, Keith RE, Kirsh SR, Alexander JA, Lowery JC. Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. Implement Sci 2009 Aug 07;4:50 [FREE Full text] [doi: 10.1186/1748-5908-4-50] [Medline: 19664226]
47. Glasgow RE, Vogt TM, Boles SM. Evaluating the public health impact of health promotion interventions: the RE-AIM framework. Am J Public Health 1999 Sep;89(9):1322-1327. [doi: 10.2105/ajph.89.9.1322] [Medline: 10474547]

48. Braun V, Clarke V. Thematic Analysis: A Practical Guide. Thousand Oaks, CA: SAGE Publications; 2021.
49. Gale NK, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. BMC Med Res Methodol 2013 Sep 18;13:117 [FREE Full text] [doi: 10.1186/1471-2288-13-117] [Medline: 24047204]
50. de Bekker-Grob EW, Ryan M, Gerard K. Discrete choice experiments in health economics: a review of the literature. Health Econ 2012 Feb;21(2):145-172. [doi: 10.1002/hec.1697] [Medline: 22223558]
51. Proctor E, Silmere H, Raghavan R, Hovmand P, Aarons G, Bunger A, et al. Outcomes for implementation research: conceptual distinctions, measurement challenges, and research agenda. Adm Policy Ment Health 2011 Mar;38(2):65-76 [FREE Full text] [doi: 10.1007/s10488-010-0319-7] [Medline: 20957426]
52. Weiner BJ, Lewis CC, Stanick C, Powell BJ, Dorsey CN, Clary AS, et al. Psychometric assessment of three newly developed implementation outcome measures. Implement Sci 2017 Aug 29;12(1):108 [FREE Full text] [doi: 10.1186/s13012-017-0635-3] [Medline: 28851459]
53. Stacey D, Légaré F, Boland L, Lewis KB, Loiselle MC, Hoefel L, et al. 20th anniversary Ottawa decision support framework: part 3 overview of systematic reviews and updated framework. Med Decis Making 2020 Apr;40(3):379-398. [doi: 10.1177/0272989X20911870] [Medline: 32428429]
54. Featherstone K, Donovan JL. Random allocation or allocation at random? Patients' perspectives of participation in a randomised controlled trial. BMJ 1998 Oct 31;317(7167):1177-1180 [FREE Full text] [doi: 10.1136/bmj.317.7167.1177] [Medline: 9794849]
55. Robinson EJ, Kerr C, Stevens A, Lilford R, Braunholtz D, Edwards S. Lay conceptions of the ethical and scientific justifications for random allocation in clinical trials. Soc Sci Med 2004 Feb;58(4):811-824. [doi: 10.1016/s0277-9536(03)00255-7] [Medline: 14672595]
56. Heard K, O'Toole E, Naimpally R, Bressler L. Real-world challenges to randomization and their solutions. Poverty Action Lab. 2017. URL: https://www.povertyactionlab.org/sites/default/files/research-resources/2017.04.14-Real-World-Challenges-to-Randomization-and-Their-Solutions.pdf [accessed 2019-04-04]
57. Data security and confidentiality guidelines for HIV, viral hepatitis, sexually transmitted disease, and tuberculosis programs: standards to facilitate sharing and use of surveillance data for public health action. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. 2011. URL: https://www.cdc.gov/nchhstp/programintegration/docs/PCSIDataSecurityGuidelines.pdf [accessed 2021-09-17]
58. Drobnik A, Pinchoff J, Bushnell G, Ly S, Yuan J, Varma JK, et al. Matching HIV, tuberculosis, viral hepatitis, and sexually transmitted diseases surveillance data, 2000-2010: identification of infectious disease syndemics in New York City. J Public Health Manag Pract 2014;20(5):506-512. [doi: 10.1097/PHH.0b013e3182a95607] [Medline: 24335712]
59. Shea CM, Jacobs SR, Esserman DA, Bruce K, Weiner BJ. Organizational readiness for implementing change: a psychometric assessment of a new measure. Implement Sci 2014 Jan 10;9:7 [FREE Full text] [doi: 10.1186/1748-5908-9-7] [Medline: 24410955]
60. Weiner BJ. A theory of organizational readiness for change. Implement Sci 2009 Oct 19;4:67 [FREE Full text] [doi: 10.1186/1748-5908-4-67] [Medline: 19840381]
61. Creswell JW, Clark VL. Designing and Conducting Mixed Methods Research. Thousand Oaks, CA: SAGE Publications; 2006.
62. The ALAI UP project. Columbia University. URL: https://www.alai-up.org/ [accessed 2023-11-17]
63. National HIV/AIDS Strategy for the United States 2022–2025. The White House. 2021. URL: https://www.whitehouse.gov/wp-content/uploads/2021/11/National-HIV-AIDS-Strategy.pdf [accessed 2023-05-09]
64. NIH Strategic Plan for HIV and HIV-related Research FY2021-2025. Office of AIDS Research, National Institutes of Health. URL: https://www.oar.nih.gov/sites/default/files/NIH_StrategicPlan_FY2021-2025.pdf [accessed 2023-05-09]
65. Dombrowski JC, Irvine M, Nash D, Harriman G, Golden MR. Public health practice-driven research to improve HIV prevention in the United States. J Acquir Immune Defic Syndr 2019 Dec;82 Suppl 3(Suppl 3):S279-S285 [FREE Full text] [doi: 10.1097/QAI.0000000000002194] [Medline: 31764264]
66. Higa DH, Marks G, Crepaz N, Liau A, Lyles CM. Interventions to improve retention in HIV primary care: a systematic review of U.S. studies. Curr HIV/AIDS Rep 2012 Dec;9(4):313-325 [FREE Full text] [doi: 10.1007/s11904-012-0136-6] [Medline: 22996171]
67. Amico KR, Orrell C. Antiretroviral therapy adherence support: recommendations and future directions. J Int Assoc Provid AIDS Care 2013;12(2):128-137 [FREE Full text] [doi: 10.1177/1545109712459041] [Medline: 23334155]

Abbreviations

AB: advisory board
AIM: acceptability of intervention measure
ART: antiretroviral therapy
CFIR: Consolidated Framework for Implementation Research
CONSORT: Consolidated Standards of Reporting Trials

DCE: discrete choice experiment
eSHARE: Electronic System for HIV/AIDS Research and Evaluation
FDA: Food and Drug Administration
FIM: feasibility of intervention measure
IAM: intervention appropriateness measure
IRB: institutional review board
LAI: long-acting injectable
MCM: medical case management
NY: New York
NYC: New York City
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance
RWHAP: Ryan White HIV/AIDS Program
RWPA: Ryan White HIV/AIDS Program Part A

Edited by A Mavragani; submitted 29.01.24; this is a non–peer-reviewed article;accepted 07.02.24; published 27.03.24.

Please cite as:
Irvine MK, Zimba R, Avoundjian T, Peterson M, Emmert C, Kulkarni SG, Philbin MM, Kelvin EA, Nash D
Patient Education and Decision Support for Long-Acting Injectable HIV Antiretroviral Therapy: Protocol for Tool Development and Pilot Testing with Ryan White HIV/AIDS Program Medical Case Management Programs in New York
JMIR Res Protoc 2024;13:e56892
URL: https://www.researchprotocols.org/2024/1/e56892
doi:10.2196/56892
PMID:38536227

Protocol

Global Trends of Medical Misadventures Using International Classification of Diseases, Tenth Revision Cluster Y62-Y69 Comparing Pre–, Intra–, and Post–COVID-19 Pandemic Phases: Protocol for a Retrospective Analysis Using the TriNetX Platform

Rosario Caruso[1,2*], RN, MSN, PhD; Marco Di Muzio[3*], RN, MSN, PhD; Emanuele Di Simone[3], RN, MSN, PhD; Sara Dionisi[4], RN, MSN, PhD; Arianna Magon[1], RN, MSN, PhD; Gianluca Conte[1], RN, MSN, PhD; Alessandro Stievano[5,6], RN, MSN, PhD; Emanuele Girani[7], MSc; Sara Boveri[7], MSc; Lorenzo Menicanti[8*], MD; Mary A Dolansky[9*], RN, MSN, PhD

[1]Health Professions Research and Development Unit, IRCCS Policlinico San Donato, San Donato Milanese, Italy

[2]Department of Biomedical Sciences for Health, University of Milan, Milano, Italy

[3]Department of Clinical and Molecular Medicine, Sapienza University of Rome, Rome, Italy

[4]Nursing, Technical and Rehabilitation Department, DaTeR Azienda Unità Sanitaria Locale di Bologna, Bologna, Italy

[5]Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy

[6]Centre of Excellence for Nursing Scholarship, Rome, Italy

[7]Laboratory of Biostatistics and Data Management, Scientific Directorate, IRCCS Policlinico San Donato, San Donato Milanese, Italy

[8]Scientific Directorate, IRCCS Policlinico San Donato, San Donato Milanese, Italy

[9]Frances Payne Bolton School of Nursing and School of Medicine, Case Western Reserve University, Cleveland, OH, United States

[*]these authors contributed equally

Corresponding Author:
Rosario Caruso, RN, MSN, PhD
Health Professions Research and Development Unit
IRCCS Policlinico San Donato
via morandi 30
San Donato Milanese, 20097
Italy
Phone: 39 025277 ext 4940
Email: rosario.caruso@grupposandonato.it

Abstract

Background: The COVID-19 pandemic has sharpened the focus on health care safety and quality, underscoring the importance of using standardized metrics such as the *International Classification of Diseases, Tenth Revision* (*ICD-10*). In this regard, the *ICD-10* cluster Y62-Y69 serves as a proxy assessment of safety and quality in health care systems, allowing researchers to evaluate medical misadventures. Thus far, extensive research and reports support the need for more attention to safety and quality in health care. The study aims to leverage the pandemic's unique challenges to explore health care safety and quality trends during prepandemic, intrapandemic, and postpandemic phases, using the *ICD-10* cluster Y62-Y69 as a key tool for their evaluation.

Objective: This research aims to perform a comprehensive retrospective analysis of incidence rates associated with *ICD-10* cluster Y62-Y69, capturing both linear and nonlinear trends across prepandemic, intrapandemic, and postpandemic phases over an 8-year span. Therefore, it seeks to understand how these trends inform health care safety and quality improvements, policy, and future research.

Methods: This study uses the extensive data available through the TriNetX platform, using an observational, retrospective design and applying curve-fitting analyses and quadratic models to comprehend the relationships between incidence rates over an 8-year span (from 2015 to 2023). These techniques will enable the identification of nuanced trends in the data, facilitating a deeper understanding of the impacts of the COVID-19 pandemic on medical misadventures. The anticipated results aim to outline complex patterns in health care safety and quality during the COVID-19 pandemic, using global real-world data for robust and generalizable conclusions. This study will explore significant shifts in health care practices and outcomes, with a special focus

on geographical variations and key clinical conditions in cardiovascular and oncological care, ensuring a comprehensive analysis of the pandemic's impact across different regions and medical fields.

Results: This study is currently in the data collection phase, with funding secured in November 2023 through the Ricerca Corrente scheme of the Italian Ministry of Health. Data collection via the TriNetX platform is anticipated to be completed in May 2024, covering an 8-year period from January 2015 to December 2023. This dataset spans pre-pandemic, intra-pandemic, and early post-pandemic phases, enabling a comprehensive analysis of trends in medical misadventures using the ICD-10 cluster Y62-Y69. The final analytics are anticipated to be completed by June 2024. The study's findings aim to provide actionable insights for enhancing healthcare safety and quality, reflecting on the pandemic's transformative impact on global healthcare systems.

Conclusions: This study is anticipated to contribute significantly to health care safety and quality literature. It will provide actionable insights for health care professionals, policy makers, and researchers. It will highlight critical areas for intervention and funding to enhance health care safety and quality globally by examining the incidence rates of medical misadventures before, during, and after the pandemic. In addition, the use of global real-world data enhances the study's strength by providing a practical view of health care safety and quality, paving the way for initiatives that are informed by data and tailored to specific contexts worldwide. This approach ensures the findings are applicable and actionable across different health care settings, contributing significantly to the global understanding and improvement of health care safety and quality.

International Registered Report Identifier (IRRID): PRR1-10.2196/54838

(JMIR Res Protoc 2024;13:e54838) doi:10.2196/54838

KEYWORDS

COVID-19; curve-fitting analyses; health care quality; health care safety; International Classification of Diseases, Tenth Revision; ICD-10; incidence rates; safety; TriNetX

Introduction

A wealth of scholarly research and empirical data underscores the imperative of prioritizing safety and quality in health care [1,2]. Seminal studies in the last 3 decades, such as the Canadian Adverse Events Study and the Harvard Medical Practice Study, have highlighted the rates of adverse events in health care settings, which led to severe, sometimes fatal, consequences for patients [3,4]. Moreover, research conducted in various international contexts has emphasized the necessity of rigorous safety protocols and the urgent need for continuous quality improvement plans [5-7]. The criticality of safety and quality in health care is not merely a theoretical construct but is supported by extensive research, governmental reports, and real-world implications [8]. Ensuring that safety and quality are at the forefront of health care delivery is pivotal for enhancing patient outcomes, reducing costs, and optimizing the effectiveness and efficiency of health care systems globally [9].

The COVID-19 pandemic has served as a watershed moment in the global health care landscape, profoundly influencing safety culture and catalyzing a renewed emphasis on quality improvement plans [10]. The unprecedented strain on health care systems worldwide has necessitated rapid adaptations in safety protocols, resource allocation, and patient care strategies. The pandemic has exposed vulnerabilities in existing health care infrastructures, compelling institutions to reevaluate and fortify their safety measures [11]. For instance, the critical importance of infection control has been magnified, leading to more stringent guidelines for personal protective equipment use, sanitation, and patient isolation [12]. Moreover, the pandemic has accelerated the adoption of telemedicine, which presents its own set of quality and safety considerations. The COVID-19 pandemic has also underscored the importance of data-driven approaches to safety and quality, as health care providers increasingly rely on real-time analytics to make informed decisions in a rapidly changing environment and use data to monitor improvements [13]. In essence, the COVID-19 pandemic has acted as a catalyst for a paradigm shift in health care safety culture, making the continuous improvement of quality not just an institutional goal but a global imperative.

In this evolving landscape of health care safety and quality improvement, the potential use of the *International Classification of Diseases, Tenth Revision* (*ICD-10*) has gained significant attention [14]. *ICD-10* serves as a standardized coding system for diagnosing a wide array of medical conditions, thereby facilitating precise communication among health care providers and enabling robust data collection for research and policy development [15]. This standardization has further enabled the use of expansive data sets for retrospective analyses, thereby contributing to targeted quality improvement initiatives. For instance, platforms such as TriNetX leverage the *ICD-10* coding system to facilitate data-driven decision-making, offering health care institutions invaluable insights into areas requiring intervention or optimization [16]. Consequently, the *ICD-10* framework stands as a pivotal instrument in elevating the culture of safety and the data needed to guide quality improvement plans, particularly in the intricate health care landscape shaped by the ongoing COVID-19 pandemic.

Within the framework of *ICD-10*, the cluster Y62-Y69, designated for "Misadventures to patients during surgical and medical care," serves as a critical proxy for assessing patient safety and quality of care [17]. This particular cluster comprises an array of diagnostic codes that encapsulate a diverse spectrum of medical misadventures, ranging from lapses in sterile precautions to inaccuracies in dosage administration and contamination of medical or biological substances. Using these nuanced codes enables health care practitioners and academic researchers to undertake focused analyses to augment the

standard of medical care. Critically, this categorization facilitates pinpointing potential vulnerabilities in existing safety protocols, thus providing empirically based insights that can be harnessed for the advancement of quality improvement strategies to improve safety.

In light of the urgent need to enhance safety and quality in health care, a comprehensive analysis focusing on the *ICD-10* cluster Y62-Y69 could offer invaluable insights. This research protocol articulates a methodical framework for examining longitudinal trends in the incidence rates associated with this specific cluster. Using the TriNetX platform, the study will encompass an 8-year period and use curve-fitting analyses. The choice of an 8-year time frame for this study serves multiple analytical purposes. First, it provides a sufficient number of data points to establish a robust trendline prior to the onset of the COVID-19 pandemic. These baseline data are crucial for understanding the pre-existing patterns and vulnerabilities in health care safety and quality, as captured by the *ICD-10* cluster Y62-Y69. Second, including data during the pandemic allows for an in-depth examination of how the health care systems adapted their safety protocols and quality improvement plans in response to the unprecedented challenges posed by COVID-19. Finally, extending the study into the postpandemic context offers a timely opportunity to assess the current state of health care safety and quality, including any lasting impacts or improvements catalyzed by the pandemic experience. Therefore, the 8-year span is methodologically sound and contextually relevant, enabling a comprehensive analysis that covers prepandemic, pandemic, and postpandemic phases.

This study aims to describe not only the linear trajectories of these rates but also the dynamics of their rate of change over time. This analytical focus has particular relevance in the context of health care systems' responses to the COVID-19 pandemic, a transformative event that has indelibly impacted global health care. The protocol specifies the analytical methodologies to be deployed, identifies the data repositories for consultation, and outlines the statistical models for rigorous data interpretation. Ultimately, this research protocol aims to provide a robust analytical framework capable of generating empirically substantiated findings regarding the past and current state of safety. The findings are designed to inform targeted interventions for the advancement of health care safety and quality.

Methods

Study Design

This study will adopt an observational, retrospective design, adhering to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines. This is a big data study, leveraging the extensive and diverse data sets available within the TriNetX platform to provide a comprehensive analysis. The Gantt Chart for research activities presents a 6-month project timeline, where the initial 3 months are allocated to retrieving data. This is followed by a period of analysis spanning 2 months. Concurrently, starting in the third month and continuing through to the sixth month, a total of 3 months is devoted to meta-elaboration and scientific writing.

Setting and Data Source

Data will be extracted from the TriNetX platform, a global health research network that provides real-time access to clinical data. The platform's big data capabilities enable the analysis of large, complex data sets, thereby enhancing the robustness and generalizability of the study findings.

This retrospective analysis will be done using TriNetX, a global health research network providing a deidentified data set of electronic medical records regarding demographics, diagnoses, procedures, medications, laboratory values, genomics, and visits. This network comprises routinely collected, aggregated clinical data from around 130 million patients attending 107 health care institutions in 16 countries, with data spanning from 2008 to 2023.

Data include both inpatient and outpatient care. Clinical information is collected using widespread standard terminologies, such as Systematized Nomenclature of Medicine, Logical Observation Identifiers Names and Codes, and *ICD-10*. TriNetX is certified to the International Organization for Standardization 27001:2013 standard and maintains an Information Security Management System to ensure the protection of the health care data it has access to and to meet the requirements of the Health Insurance Portability and Accountability Act (HIPAA) Security Rule.

The cohort for the study includes all patients aged 0 to 89 years old who underwent any *ICD-10-Clinical Modification* diagnosis during the period of observation. The *ICD-10-Clinical Modification* cluster Y62-Y69, which represents "Misadventures to patients during surgical and medical care," has been identified as the outcome of the analysis. The analysis of the incidence rate of the outcome in the years between 2016 and 2023 (4 years before and 4 years after the pandemic) will be conducted globally and for specific geographic areas: North America (United States); Latin America; Europe, Middle East, and Africa; and Asia-Pacific. This analysis will use the corresponding collaborative networks within TriNetX. TriNetX offers natural language processing capabilities, which use machine learning technology from Averbis (located in Freiburg in Breisgau, Germany) to search free text from clinical charts and other records specifically for the geographical areas in the United States.

The analysis will be applied to an oncological cohort and one with cardiovascular diseases to validate the results obtained in the initial phase of the research. The oncological cohort was determined using any *ICD-10* codes related to neoplasms (C00-D49). In contrast, the cardiovascular cohort was identified using codes related to Diseases of the Circulatory System (I00-I99).

The findings will be reported according to the STROBE guideline. One of the primary goals of STROBE is to ensure a clear and transparent account of the reporting of methods and results.

Study Period

The analysis will encompass 8 years of data, now divided into 3 distinct phases to align with the key periods of the COVID-19

pandemic: from 2018 to 2019 (prepandemic phase), from 2020 to May 2023 (intrapandemic phase, aligning with the federal COVID-19 public health emergency declaration period), and from June 2023 to the end of 2023 (early postpandemic phase). This division allows for a precise examination of health care safety and quality trends during the prepandemic phase, the active pandemic phase as defined by the federal public health emergency declaration, and the immediate aftermath of the pandemic. This approach aims to provide a more detailed and contextually relevant understanding of the varying impacts of the COVID-19 pandemic, thus offering a comprehensive view of the health care landscape and its adaptation during these critical periods.

Variables of Interest

This study's primary variables of interest are the incidence rates associated with the *ICD-10* cluster Y62-Y69, a specific set of diagnostic codes designated for capturing "Misadventures to patients during surgical and medical care" [17]. This cluster is of particular importance as it serves as a critical proxy for assessing the safety and quality of health care delivery. It encompasses a wide range of medical misadventures, including but not limited to lapses in sterile precautions, inaccuracies in dosage administration, and contamination of medical or biological substances. Analyzing the incidence rates will enable a comprehensive evaluation of the health care system's performance in minimizing medical misadventures and informing targeted interventions for quality improvement and safety enhancement [18]. The limitations of these data are the self-reporting nature of documenting the "misadventures," with the potential for underreporting.

The incidence rate, which measures the rate of new or first-time cases, is calculated using a time-sensitive approach. The denominator for the incidence rate is the product of the number of patients in the incidence proportion denominator and the number of days covered by the time interval. This ensures that the incidence rate provides a dynamic view of how safety and quality are evolving over time. Importantly, the study also incorporates a "lookback period" to exclude patients who have experienced the event of interest prior to the study period, thereby focusing only on new cases.

Incidence rates are subject to stringent criteria, including demographic matching and time window overlaps, to ensure that the data are accurate and meaningful for targeted interventions. Furthermore, the study acknowledges the potential impact of date shifting by health care organizations to protect patient health information and takes this into consideration in the analysis.

Statistical Analysis

The primary aim of the forthcoming statistical analysis will be to decipher the linear and nonlinear trajectories of incidence rates, with a particular focus on understanding their rate of change over time. Special attention will be dedicated to evaluating the impact of the COVID-19 pandemic on these health care metrics.

The linchpin of the analytical strategy will be the application of curve-fitting analyses [19]. This advanced technique will enable researchers to construct models that elucidate the intricate relationships between the rates and the temporal variables. Specifically, polynomial regression models, including quadratic models, will be used to capture the complexity of the data trends. Quadratic models will be particularly useful for capturing nonlinear trends in the data. These models will be formulated based on the equation $y = ax^2 + bx + c$, where y represents the incidence rate; x represents time; and a, b, and c are coefficients to be estimated. The quadratic term ax^2 will allow us to understand the curvature in the data, providing insights into acceleration or deceleration trends over time. Model diagnostics, such as residual analysis and goodness-of-fit tests, will be conducted to ensure the appropriateness of the quadratic models.

Initially, curve-fitting analyses will be executed on an overall sample characterized by its extensive demographic and clinical diversity. Given the inherent heterogeneity of this sample, a rigorous validation process will be indispensable for confirming the generalizability and applicability of the observed trends.

A series of subgroup analyses will be undertaken to augment the robustness of the findings. These analyses will be stratified by various factors, including but not limited to geographic location. Data for these subgroup analyses will be sourced from the TriNetX network, which amalgamates health care data from a multitude of geographic regions. This approach will facilitate an assessment of the consistency of the observed trends across diverse subpopulations to bolster the external validity of the findings. Further stratification will be conducted based on prevalent epidemiological conditions in the fields of oncology and cardiovascular diseases. Within these conditions, specific groups identified with inclusion and exclusion criteria will be selected as they possess well-documented epidemiological profiles, serving as robust benchmarks for validation. Reperforming the curve-fitting analyses within these disease-specific cohorts will aim to corroborate the trends discerned in the overall sample.

Ethical Considerations

Human Subject Research Ethics Review and Approvals

The study uses data from the TriNetX network, which adheres to international and national data protection and privacy laws, including the HIPAA in the United States and the General Data Protection Regulation in the European Union. These compliance standards ensure that the data are reliably sourced and managed ethically. Each health care organization participating in the TriNetX network is committed to strict ethical standards, including obtaining informed consent for primary data collection with provisions for secondary analysis. Therefore, the study protocol has been approved by the institutional review board of Policlinico San Donato within the Ricerca Corrente funding scheme, affirming adherence to ethical standards and contribution to health care research. No external ethical committee review was deemed necessary due to the aggregated nature of the information, emphasizing the study's compliance with privacy and data protection principles inherent in its observational and secondary data analysis approach.

Informed Consent for Secondary Analysis

The study involves secondary analysis of anonymized data sets obtained from organizations within the TriNetX network. It is important to note that the original informed consent obtained by these organizations (or their respective institutional review boards) allows for secondary analysis without requiring additional consent. This approach ensures that the use of the data respects and upholds the original consent and ethical approvals.

Privacy and Confidentiality Protection

The data included in the study, derived from the TriNetX platform, are aggregated to ensure that individual patient data are not directly used. This aggregation process, in conjunction with the initial ethical compliance by each participating health care organization, guarantees the protection of privacy and confidentiality. The data used in the research are anonymous and deidentified, following strict data protection principles.

Compensation

Compensation is not applicable in the study as it revolves around the secondary analysis of existing anonymized data sets. There is no direct participant interaction, so compensation for participants is not applicable.

Image and Supplementary Material Identification

No individual participants or user identification is possible in any images included in the manuscript or supplementary materials. The study design protects the privacy and anonymity of all individuals involved.

Anticipated Findings

The anticipated results of this comprehensive analysis focusing on the *ICD-10* cluster Y62-Y69 are expected to provide valuable insights into the safety and quality of health care delivery over the study period, spanning prepandemic, intrapandemic, and early postpandemic phases.

Regarding the incidence rates associated with the *ICD-10* cluster Y62-Y69, we anticipate that our analysis will reveal trends and patterns that can be attributed to various factors, including changes in safety protocols, resource allocation, and health care practices during the COVID-19 pandemic. Given the unprecedented challenges and adaptations required by health care systems worldwide, it is reasonable to expect that the pandemic may have had a significant impact on these rates.

In the prepandemic phase, our analysis aims to establish a baseline for the incidence rates, offering insights into the existing vulnerabilities in health care safety and quality captured by the *ICD-10* cluster. This baseline data will be crucial for understanding the context in which subsequent changes occurred.

During the intrapandemic phase, we anticipate observing fluctuations and shifts in the incidence rates. These changes may be indicative of the health care system's responses to the challenges posed by the pandemic, including heightened infection control measures, changes in patient care protocols, and resource allocation adjustments. The pandemic's impact on safety and quality may be reflected in the data.

In the early postpandemic phase, we expect to see how health care systems have adapted and evolved in response to the pandemic's challenges. It is possible that some changes implemented during the pandemic may persist or lead to improvements in safety and quality.

Furthermore, our analysis will include stratified subgroup analyses, which may reveal variations in trends across different geographic regions and within specific disease cohorts (oncology and cardiovascular diseases). These subgroup analyses will help identify whether the observed trends are consistent across diverse populations and clinical contexts. This study aims to provide a nuanced understanding of how the COVID-19 pandemic has influenced safety and quality in health care, as reflected in the incidence rates of the *ICD-10* cluster Y62-Y69. These findings will inform targeted interventions and quality improvement strategies, contributing to the ongoing efforts to enhance health care safety and quality in a rapidly evolving health care landscape.

Results

Our research, supported by the Ricerca Corrente funding from the Italian Ministry of Health to IRCCS Policlinico San Donato (funds secured in November 2023), is currently advancing through the data collection stage. The compilation of data, facilitated by the global health research network TriNetX, is set to encapsulate a comprehensive 8-year timeframe extending from January 2015 to December 2023. This carefully curated dataset documents the healthcare landscape across three critical phases: before the COVID-19 pandemic (pre-pandemic), during the height of the pandemic (intra-pandemic), and the period following the emergency phase of the pandemic (early post-pandemic). Such temporal delineation is pivotal for our investigation into the trends and fluctuations in medical misadventures classified under the ICD-10 cluster Y62-Y69, offering a lens through which to view the nuances of healthcare safety and quality across different global healthcare contexts.

With data collection anticipated to be completed by May 2024, and final analysis expected by June 2024, our study is on track to fulfill its objective of dissecting the intricate patterns of medical misadventures during a period marked by unprecedented global health challenges. The results are anticipated to equip healthcare professionals, policymakers, and stakeholders with the insights necessary to fortify healthcare systems against future adversities, thereby enhancing the overall safety and quality of care delivered to patients worldwide

Discussion

Principal Findings

The primary expectation of this study is to elucidate the linear and nonlinear trajectories of incidence rates associated with the *ICD-10* cluster Y62-Y69 over time. Through the application of curve-fitting analyses, specifically quadratic models, we anticipate revealing intricate patterns in the data that may not be discernible through simpler linear models.

In the context of the COVID-19 pandemic, we expect to observe significant fluctuations in these rates, potentially manifesting

as spikes or declines corresponding to various phases of the pandemic. These observations will be critical for understanding the pandemic's impact on health care safety and quality, particularly in medical misadventures. Furthermore, examining the postpandemic response to these rates will be of particular interest. These results will provide insights into the resilience and adaptability of health care systems in returning to prepandemic safety and quality levels or possibly achieving even better standards.

Upon conducting subgroup analyses, we expect that the trends observed in the overall sample will be validated in specific subpopulations. These subpopulations will be stratified by geographic location and specific epidemiological conditions within oncology and cardiovascular diseases. The validation of trends across these diverse subpopulations will lend greater credibility and generalizability to our findings.

Moreover, we anticipate that our stringent data selection criteria for validating the overall models will yield accurate and meaningful results. These results are expected to inform targeted interventions to improve the safety and quality of health care delivery, fulfilling the study's ultimate objective.

However, it is essential to acknowledge the limitations that may arise from the study. These could include potential biases in the original data documentation and collection and the challenges associated with interpreting complex statistical models. One specific limitation is the retrospective nature of the study, which may introduce recall bias and limit the ability to establish causal relationships. Retrospective studies often rely on existing records and data, which may not have been collected for research purposes, affecting the data's quality and completeness. In addition, despite the application of data selection criteria, the possibility of unmeasured or residual confounding factors cannot be entirely excluded. These factors might influence the observed associations and outcomes. This limitation is characteristic of retrospective studies and should be considered when interpreting our findings. Furthermore, we acknowledge the challenges associated with analyzing data from broad and heterogeneous geographic areas such as Europe, the Middle East, Africa, and Asia-Pacific. The diversity in health care systems, practices, and patient populations across these regions may limit the uniformity and specific applicability of our findings. This variation is important when interpreting our results and their implications in these diverse settings. We recognize this as a limitation of our study and suggest caution in generalizing the findings uniformly across these broad geographic areas.

Despite these limitations, the strength of this study lies in its use of global real-world big data. The TriNetX network provides a rich data set that captures a broad range of demographic and clinical variables, enhancing the study's generalizability and applicability. The use of real-world data allows for a contemporary understanding of medical misadventures, as it reflects on the complexities and variabilities inherent in everyday health care settings. This aspect is a significant advantage over controlled clinical trials, which often operate under idealized conditions that may not be representative of the real world.

Future research will focus on addressing these limitations and possibly using other advanced statistical techniques for a more in-depth analysis. For instance, machine learning algorithms could be used to identify hidden patterns and relationships in the data, providing a more comprehensive understanding of the factors influencing medical misadventures. In line with our future research directions, we aim to delve deeper into specific indicators like complications, side effects, mortality, and morbidity in subsequent studies. These indicators, when analyzed in homogeneous subgroups of patients with and without the presence of the *ICD-10* cluster Y62-Y69, could provide critical insights into the impact of medical misadventures on patient outcomes. This focus will augment our current understanding of relevant safety-related patterns and guide targeted interventions to mitigate such occurrences in health care settings.

Conclusions

The upcoming study is poised to offer a multifaceted exploration of the incidence rates associated with medical misadventures, as defined by the *ICD-10* cluster Y62-Y69. The research is designed to use advanced statistical models, such as quadratic equations, to capture both linear and nonlinear trends over time. This approach will be particularly illuminating in the context of the pre–, intra–, and post–COVID-19 pandemic analyses, a period in history that has introduced unique challenges and disruptions to health care systems globally. Global real-world data stand as a significant strength, offering a more pragmatic view of health care safety and quality that can typically be achieved through controlled clinical trials or other primary studies. The study's findings are anticipated to be of considerable value to health care professionals, policy makers, and researchers alike. The results will not only shed light on the current state of medical misadventures but also provide actionable insights for targeted interventions aimed at improving health care safety and quality.

Acknowledgments

This study was partially supported by Ricerca Corrente funding from the Italian Ministry of Health to Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Policlinico San Donato.

Data Availability

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

Authors' Contributions

RC, MDM, EDS, SB, EG, and MD participated in the conceptualization and methodology of the protocol. RC, MD, and MDM drafted the manuscript, and all authors revised and approved the final version. LM and MAD are the colast authors.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report from the independent reviewers of the “Ricerca Corrente” fund of IRCCS Policlinico San Donato (Italy) and previous version of the protocol.
[PDF File (Adobe PDF File), 1367 KB - resprot_v13i1e54838_app1.pdf]

References

1. Jha AK, Prasopa-Plaizier N, Larizgoitia I, Bates DW, Research Priority Setting Working Group of the WHO World Alliance for Patient Safety. Patient safety research: an overview of the global evidence. Qual Saf Health Care 2010;19(1):42-47 [FREE Full text] [doi: 10.1136/qshc.2008.029165] [Medline: 20172882]
2. Relman A. Book Review Crossing the Quality Chasm: A New Health System for the 21st Century By the Committee on Quality of Health Care in America of the Institute of Medicine. 337 pp. Washington, D.C., National Academy Press, 2001. $44.95. 0-309-07280-8. In: N Engl J Med. Washington (DC): National Academies Press (US); Aug 30, 2001:702-703.
3. Brennan TA, Leape LL, Laird NM, Hebert L, Localio AR, Lawthers AG, et al. Incidence of adverse events and negligence in hospitalized patients. Results of the Harvard medical practice study I. N Engl J Med 1991;324(6):370-376 [FREE Full text] [doi: 10.1056/NEJM199102073240604] [Medline: 1987460]
4. Baker GR, Norton PG, Flintoft V, Blais R, Brown A, Cox J, et al. The Canadian adverse events study: the incidence of adverse events among hospital patients in Canada. CMAJ 2004;170(11):1678-1686 [FREE Full text] [doi: 10.1503/cmaj.1040498] [Medline: 15159366]
5. Alanazi NH, Falqi TA. Healthcare managers' perception on patient safety culture. Glob J Qual Saf Healthc 2023;6(1):6-14 [FREE Full text] [doi: 10.36401/JQSH-22-13] [Medline: 37260855]
6. Jha AK, Larizgoitia I, Audera-Lopez C, Prasopa-Plaizier N, Waters H, Bates DW. The global burden of unsafe medical care: analytic modelling of observational studies. BMJ Qual Saf 2013;22(10):809-815 [FREE Full text] [doi: 10.1136/bmjqs-2012-001748] [Medline: 24048616]
7. Giannetta N, Katigri MR, Azadboni TT, Caruso R, Liquori G, Dionisi S, et al. Knowledge, attitude, and behaviour with regard to medication errors in intravenous therapy: a cross-cultural pilot study. Healthcare (Basel) 2023;11(3):436 [FREE Full text] [doi: 10.3390/healthcare11030436] [Medline: 36767011]
8. Azyabi A, Karwowski W, Davahli MR. Assessing patient safety culture in hospital settings. Int J Environ Res Public Health 2021;18(5):2466 [FREE Full text] [doi: 10.3390/ijerph18052466] [Medline: 33802265]
9. Kilcullen MP, Bisbey TM, Ottosen MJ, Tsao K, Salas E, Thomas EJ. The safer culture framework: an application to healthcare based on a multi-industry review of safety culture literature. Hum Factors 2022;64(1):207-227 [FREE Full text] [doi: 10.1177/00187208211060891] [Medline: 35068229]
10. Brborović O, Brborović H, Hrain L. The COVID-19 pandemic crisis and patient safety culture: a mixed-method study. Int J Environ Res Public Health 2022;19(4):2237 [FREE Full text] [doi: 10.3390/ijerph19042237] [Medline: 35206429]
11. Magon A, Caruso R. Addressing a potential crisis in the Italian national health system. Lancet 2023;401(10384):1262-1263 [FREE Full text] [doi: 10.1016/S0140-6736(23)00450-6] [Medline: 37061260]
12. Waters R. What has the pandemic taught us about our infection control measures? BDJ In Pract 2021;34(5):18-19 [FREE Full text] [doi: 10.1038/s41404-021-0763-y]
13. Zhang Q, Gao J, Wu JT, Cao Z, Zeng DD. Data science approaches to confronting the COVID-19 pandemic: a narrative review. Philos Trans A Math Phys Eng Sci 2022;380(2214):20210127 [FREE Full text] [doi: 10.1098/rsta.2021.0127] [Medline: 34802267]
14. Varela LO, Doktorchik C, Wiebe N, Quan H, Eastwood C. Exploring the differences in ICD and hospital morbidity data collection features across countries: an international survey. BMC Health Serv Res 2021;21(1):308 [FREE Full text] [doi: 10.1186/s12913-021-06302-w] [Medline: 33827567]
15. Jetté N, Quan H, Hemmelgarn B, Drosler S, Maass C, Moskal L, et al. The development, evolution, and modifications of ICD-10: challenges to the international comparability of morbidity data. Med Care 2010;48(12):1105-1110. [doi: 10.1097/MLR.0b013e3181ef9d3e] [Medline: 20978452]
16. Wang W, Wang CY, Wang SI, Wei JCC. Long-term cardiovascular outcomes in COVID-19 survivors among non-vaccinated population: a retrospective cohort study from the TriNetX US collaborative networks. EClinicalMedicine 2022;53:101619 [FREE Full text] [doi: 10.1016/j.eclinm.2022.101619] [Medline: 35971425]
17. 2023 ICD-10-CM Codes Y62-Y69: misadventures to patients during surgical and medical care. ICD10data.com. 2022. URL: https://www.icd10data.com/ICD10CM/Codes/V00-Y99/Y62-Y69 [accessed 2023-09-07]

18. Spronk I, Korevaar JC, Poos R, Davids R, Hilderink H, Schellevis FG, et al. Calculating incidence rates and prevalence proportions: not as simple as it seems. BMC Public Health 2019;19(1):512 [FREE Full text] [doi: 10.1186/s12889-019-6820-3] [Medline: 31060532]
19. Arlinghaus S. Practical Handbook of Curve Fitting. 1st Edition. Boca Raton: CRC Press; 2023.

Abbreviations

ICD-10: International Classification of Diseases, Tenth Revision
HIPAA: Health Insurance Portability and Accountability Act
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

Edited by A Mavragani; submitted 23.11.23; this is a non–peer-reviewed article;accepted 05.02.24; published 17.04.24.

Please cite as:
Caruso R, Di Muzio M, Di Simone E, Dionisi S, Magon A, Conte G, Stievano A, Girani E, Boveri S, Menicanti L, Dolansky MA
Global Trends of Medical Misadventures Using International Classification of Diseases, Tenth Revision Cluster Y62-Y69 Comparing Pre–, Intra–, and Post–COVID-19 Pandemic Phases: Protocol for a Retrospective Analysis Using the TriNetX Platform
JMIR Res Protoc 2024;13:e54838
URL: https://www.researchprotocols.org/2024/1/e54838
doi:10.2196/54838
PMID:38630516

Protocol

Effectiveness and Cost-Effectiveness of Survivorship Care for Survivors of Hodgkin Lymphoma (INSIGHT Study): Protocol for a Multicenter Retrospective Cohort Study With a Quasi-Experimental Design

Eline M J Lammers[1], MD; Josée M Zijlstra[2], MD, PhD; Valesca P Retèl[3], PhD; Berthe M P Aleman[4], MD, PhD; Flora E van Leeuwen[1], PhD; Annelies Nijdam[1], PhD; BETER consortium[5]

[1]Department of Epidemiology, The Netherlands Cancer Institute, Amsterdam, Netherlands

[2]Department of Hematology, Amsterdam UMC, location Vrije Universiteit, Cancer Center, Amsterdam, Netherlands

[3]Department of Health Technology Assessment, The Netherlands Cancer Institute, Amsterdam, Netherlands

[4]Department of Radiation Oncology, The Netherlands Cancer Institute, Amsterdam, Netherlands

[5]See Acknowledgments

Corresponding Author:
Annelies Nijdam, PhD
Department of Epidemiology
The Netherlands Cancer Institute
Plesmanlaan 121
Amsterdam, 1066 CX Amsterdam
Netherlands
Phone: 31 20 5126132
Email: a.nijdam@nki.nl

Abstract

Background: Hodgkin lymphoma (HL) occurs at young ages, with the highest incidence between 20 and 40 years. While cure rates have improved to 80%-90% over the past decades, survivors of HL are at substantial risk of late treatment–related complications, such as cardiovascular diseases, breast cancer, severe infections, and hypothyroidism. To reduce morbidity and mortality from late treatment effects, the Dutch Better care after lymphoma, Evaluation of long-term Treatment Effects and screening Recommendations (BETER) consortium developed a survivorship care program for 5-year survivors of HL that includes risk-based screening for and treatment of (risk factors for) late adverse events. Even though several cancer survivorship care programs have been established worldwide, there is a lack of knowledge about their effectiveness in clinical practice.

Objective: The Improving Nationwide Survivorship care Infrastructure and Guidelines after Hodgkin lymphoma Treatment (INSIGHT) study evaluates whether Dutch BETER survivorship care for survivors of HL decreases survivors' burden of disease from late adverse events after HL treatment and associated health care costs and improves their quality of life.

Methods: The INSIGHT study is a multicenter retrospective cohort study with a quasi-experimental design and prospective follow-up, embedded in the national BETER survivorship care infrastructure. The first BETER clinics started in 2013-2016 and several other centers started or will start BETER clinics in 2019-2024. This allows us to compare survivors who did and those who did not receive BETER survivorship care in the last decade. Survivors in the intervention group are matched to controls (n=450 per group) based on sex, age at diagnosis (±5 years), age in 2013 (±5 years), and treatment characteristics. The primary outcome is the burden of disease in disability-adjusted life years from cardiovascular disease, breast cancer, severe infections, and hypothyroidism. In a cost-effectiveness analysis, we will assess the cost of BETER survivorship care per averted or gained disability-adjusted life year and quality-adjusted life year. Secondary outcomes are BETER clinic attendance, adherence to screening guidelines, and knowledge and distress about late effects among survivors of HL. Study data are collected from a survivor survey, a general practitioner survey, medical records, and through linkages with national disease registries.

Results: The study was funded in November 2020 and approved by the institutional review board of the Netherlands Cancer Institute in July 2021. We expect to finalize recruitment by October 2024, data collection by early 2025, and data analysis by May 2025.

Conclusions: INSIGHT is the first evaluation of a comprehensive survivorship program using real-world data; it will result in new information on the (cost-)effectiveness of survivorship care in survivors of HL in clinical practice. The results of this study will be used to improve the BETER program where necessary and contribute to more effective evidence-based long-term survivorship care for lymphoma survivors.

International Registered Report Identifier (IRRID): PRR1-10.2196/55601

(JMIR Res Protoc 2024;13:e55601) doi:10.2196/55601

KEYWORDS

research design; Hodgkin lymphoma; late effects of cancer treatment; survivorship care; screening; cost-effectiveness analysis

Introduction

Cardiovascular diseases (CVDs) and second malignancies, especially breast cancer, are well-known late complications of Hodgkin lymphoma (HL) treatment. The risks of CVD and breast cancer are highest in survivors of HL treated with chest radiotherapy with or without anthracycline-based chemotherapy [1-8]. In addition, survivors of HL may also face other late treatment effects such as severe infections, associated with (functional) asplenia [3,9], and hypothyroidism after neck radiotherapy [10,11]. Although improved chemotherapy and radiotherapy regimens have increased HL cure rates to 80%-90% over the past decades, the aforementioned treatment-related complications have led to excess morbidity and mortality in survivors of HL [3,4,12-14].

CVD risk is 4-6 times higher in survivors of HL treated in 1965-1995 than in the general population, with up to 50% cumulative CVD incidence 40 years after HL treatment [7]. Female survivors of HL who received chest radiotherapy in the aforementioned period have a 5 times higher breast cancer risk than women in the general population, with a 19% cumulative incidence 30 years after treatment [2]. In addition, infectious disease mortality in survivors of HL treated in 1965-2000 increased 8-fold compared to the general population [3]. Moreover, 25 years after HL treatment, the cumulative incidence of (subclinical) hypothyroidism was 44% in survivors treated between 1961 and 1989 [9]. Individual late treatment–related complication risks depend on the characteristics of patients and HL treatment (radiotherapy location, dose and volume, chemotherapy type and dose, and whether or not splenectomy was performed) and are expected to be lower in more recent treatment years as a result of improved radiotherapy techniques [2,3,5,7,9].

In 2009, the Dutch “Better care after lymphoma, Evaluation of long-term Treatment Effects and screening Recommendations” (BETER) consortium, a collaboration between hemato-oncologists, radiation oncologists, nurse practitioners, epidemiologists, a general practitioner (GP), and patient representatives, was established. While HL generally occurs at a young age (with the highest incidence between 20 and 40 years) and survivors have a long life expectancy where they can develop late effects, structured survivorship care for adult survivors of HL was lacking. Structured survivorship care may lead to the early detection of (risk factors for) late adverse events, enabling timely intervention, possibly leading to a lower burden of disease due to late effects and better quality of life in survivors of HL [15,16]. Therefore, the BETER consortium developed a nationwide infrastructure of outpatient clinics where 5-year survivors of HL are screened for late adverse effects of lymphoma treatment according to nationally approved screening guidelines. Recommendations in the guidelines were based on the available scientific evidence in survivors of HL, and, if this evidence was absent, in other high-risk populations (eg, *BRCA* mutation carriers for breast cancer screening recommendations) or on expert consensus [17,18].

In 2013-2016, the first BETER clinics started inviting 5-year survivors of HL for risk-based screening for late treatment–related complications. Of note, setting up a BETER clinic requires a substantial effort, that is, identification and tracing of patients and setting up local infrastructure, including consulting specialists such as cardiologists [17]. Therefore, several Dutch lymphoma treatment centers were only able to start or will start inviting survivors of HL for survivorship care in 2019-2024.

Other cancer survivorship care programs, especially for survivors of childhood cancer (often also including survivors of childhood HL), have been established in several countries worldwide. However, there is a lack of knowledge about their effectiveness in clinical practice. Studies that evaluated the yield of late events in these programs, almost exclusively concerned with CVD and breast cancer screening results, lacked a comparison group or used hypothetical cohorts or simulation models to estimate the potential health benefits from structured survivorship care [19-25]. The effect of the implementation of cancer survivorship programs on survivors’ burden of disease, quality of life, and cost-effectiveness has never been assessed using real-world data. Therefore, in the Improving Nationwide Survivorship care Infrastructure and Guidelines after Hodgkin lymphoma Treatment (INSIGHT) study, we aim to assess whether BETER survivorship care leads to reduced burden of disease from late adverse events after HL treatment, lower health care costs, better quality of life, and reduced health-related productivity losses compared to the absence of structured survivorship care.

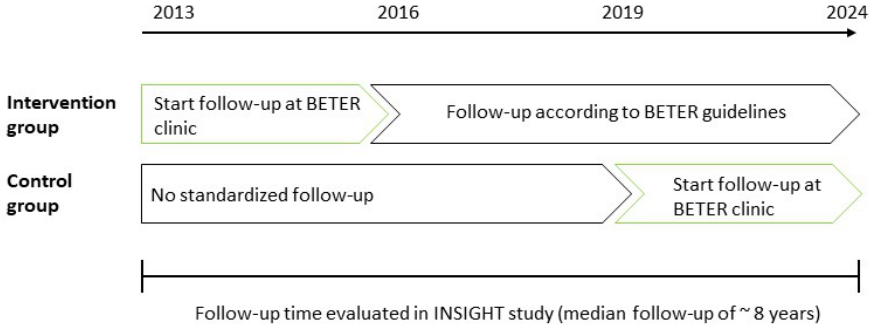
Methods

Design

The INSIGHT study is a retrospective cohort study with a quasi-experimental design and prospective follow-up, embedded in the national BETER survivorship care infrastructure. The first BETER clinics started in 2013-2016 and the number of centers participating in the BETER program increased over the last few years; several centers started or will start a BETER

clinic in 2019-2024. This provides the unique opportunity to evaluate the effectiveness of BETER survivorship care by comparing survivors who did and did not receive BETER survivorship care over the past 6-10 years (expected median follow-up of ~8 years). The intervention group will consist of 450 survivors of HL who were invited to first visit a BETER clinic in 2013-2016. The control group will consist of a matched group of 450 survivors of HL who were eligible for BETER survivorship care as of 2013-2016 but were not invited because they were treated in a lymphoma treatment center not starting a BETER clinic until 2019-2024 (Figure 1).

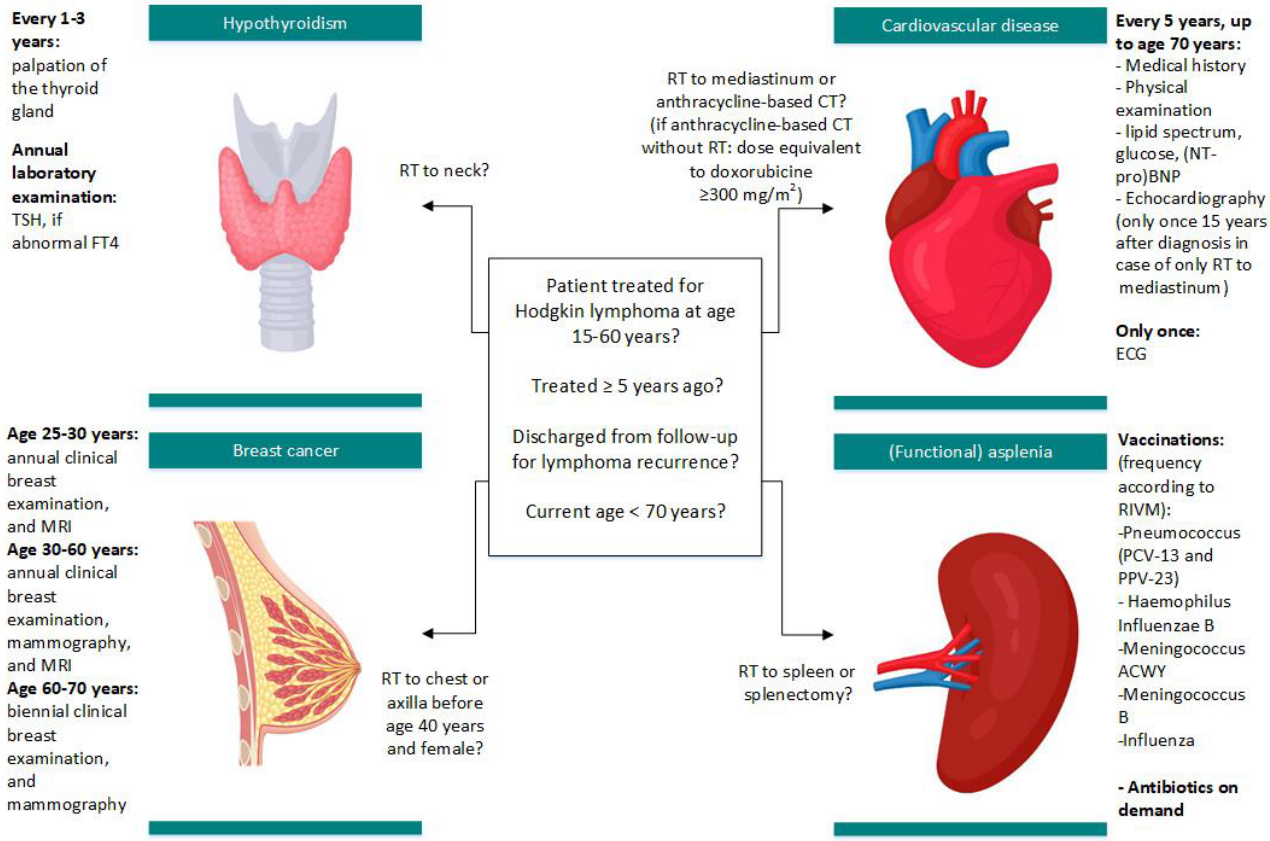
Figure 1. Schematic overview of the INSIGHT cohort study follow-up period among 5-year survivors of Hodgkin lymphoma in the Netherlands. BETER: Better care after lymphoma, Evaluation of long-term Treatment Effects and screening Recommendations.



Study Population

According to the BETER guidelines, survivors of HL are eligible for survivorship care after completion of regular surveillance for HL recurrence (5 years after treatment), if they were 15-60 years at HL diagnosis, and are currently younger than 70 years of age. Figure 2 [17,18,26] shows a simplified overview of BETER eligibility criteria and the screening guidelines [17,18]. Survivors who do not have sufficient understanding of the Dutch language to complete the study survey, have developed an HL relapse during follow-up, whose vital status (and if alive current address) could not be verified, or who live abroad are excluded from the INSIGHT study.

Figure 2. Simplified overview of BETER screening guidelines for 5-year survivors of Hodgkin lymphoma in the Netherlands [17, 18] and guideline asplenia from the National Institute for Public Health and the Environment (RIVM) [26]. CT: chemotherapy; ECG: electrocardiogram; FT4: free thyroxine; MRI: magnetic resonance imaging; (NTpro-)BNP: (N-terminal pro–)B-type natriuretic peptide; RIVM: National Institute for Public Health and the Environment, RT: radiotherapy; TSH: thyroid stimulating hormone.



The study participants in the control group are matched to patients in the intervention group based on the following survivor characteristics: sex, age at diagnosis (±5 years), and age in 2013 (±5 years) and the following treatment

characteristics associated with increased risk of CVD, breast cancer, hypothyroidism, and (functional) asplenia: chest radiotherapy (yes or no), neck radiotherapy (yes or no), spleen radiotherapy or splenectomy (yes or no), and anthracycline-based chemotherapy (yes or no). Controls are selected from the comprehensive database of the previously established retrospective cohort of lymphoma survivors treated in participating BETER centers between 1965 and 2012. This database contains information on basic survivor characteristics and detailed treatment data [17].

Outcomes

The primary outcomes of this study are the burden of disease (in disability-adjusted life years [DALYs]) from CVD including associated risk factors (Table S1 in Multimedia Appendix 1 [17,27-30]), breast cancer, severe infections (defined as fatal or requiring hospitalization) and hypothyroidism, the associated health care costs, and quality of life. In a cost-effectiveness analysis, the cost of BETER survivorship care will be weighed against averted or gained DALYs and quality-adjusted life years (QALYs). In order to assess indirect costs in both groups, health-related productivity losses and overall health care use will be calculated. Furthermore, the incidence rates (including stage and time since HL diagnosis) for the (risk factors for) late adverse events of interest (screen detected or nonscreen detected) will be compared between the intervention and control group.

The secondary outcomes of this study are BETER clinic nonattendance, guideline adherence, and knowledge and distress about late effects among survivors. Both the intervention and control group include survivors who attended the BETER clinic (attenders) and survivors who were invited for BETER survivorship care but chose to not attend (nonattenders). We will describe the reasons for nonattendance to BETER survivorship care and assess possible associations of nonattendance with socioeconomic status, health status, and other patient characteristics. This subanalysis will allow us to place our main study findings in perspective and possibly even improve future attendance rates. Survivors' socioeconomic status will be derived from their zip code based on data from Statistics Netherlands [31]. We assess the BETER clinicians' adherence to the guidelines by comparing the screening diagnostics that were performed in clinical practice to those that are recommended in the BETER guidelines. Finally, we will assess survivors' knowledge about the risk of late complications (risk perception) in both groups and investigate whether this knowledge comes with increased or decreased distress about their risk of late complications.

Follow-Up

For the intervention group, follow-up starts at the first BETER visit (or BETER clinic invitation date for nonattenders) and ends at the study inclusion of its matched control in 2019-2024 or at date of death, whichever comes first. For the control group, follow-up starts at the date their matched intervention group survivor started follow-up and ends at their first BETER visit (or BETER clinic invitation date for nonattenders), or, if earlier, at death. All study data will be stored for at least 20 years. This enables prospective follow-up of our cohort in order to study the long-term effects of screening on the incidence of late adverse events and the associated burden of disease.

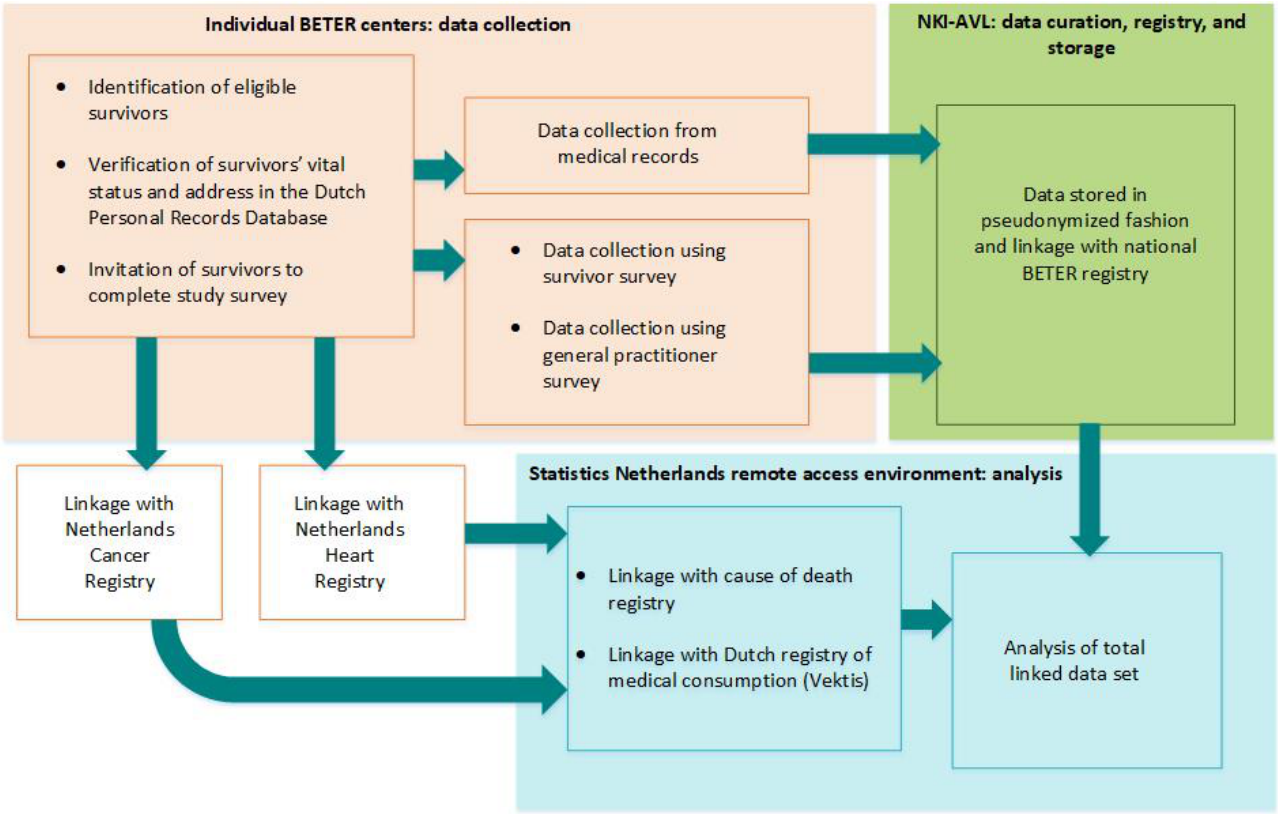
Recruitment and Informed Consent Procedure

For the detailed recruitment and informed consent procedure, refer to the detailed informed consent procedure section in Multimedia Appendix 1. In brief, in intervention centers, study patients are identified and linked to the national Personal Records Database to verify survivors' vital status and current address. Subsequently, eligible survivors are invited for study participation by their (former) treating radiation oncologist or hematologist. In control centers, survivors who match an intervention group survivor are selected from the previously established cohort of survivors of HL from that specific center (Design section) [17]. Matched controls who are alive and do not experience adverse health outcomes in an advanced stage (eg, metastatic breast cancer or end-stage heart failure) are invited to the BETER clinic. After the invitation for BETER survivorship care, these controls are invited for study participation using the same procedures as for the intervention group. Survivors who do not respond to the study invitation will receive reminders; nonattenders receive 1 reminder approximately 4 weeks after the initial invitation and attenders receive 2 reminders after approximately 4 and 8 weeks, respectively. Survivors who died during follow-up are included without informed consent.

Data Collection

Basic survivor characteristics and detailed treatment information for the included survivors are extracted from the comprehensive database of lymphoma survivors treated in participating BETER centers between 1965 and 2012 [17]. For the INSIGHT study, we collect additional data from multiple sources: medical records, a survivor survey, a GP survey, and national registries. We provide explanations on each of the data collection procedures in the upcoming sections Medical Records, Survivor Survey, GP Survey, and Linkage With National Registries and in Figure 3.

Figure 3. Data collection procedures for the INSIGHT cohort study at individual BETER survivorship care clinics for 5-year survivors of Hodgkin lymphoma in the Netherlands and planned linkages with national disease registries. BETER: Better care after lymphoma, Evaluation of long-term Treatment Effects and screening Recommendations; NKI-AVL: The Netherlands Cancer Institute.



Medical Records

For attenders of the BETER clinics in the intervention group, complete follow-up data from the BETER clinic (ie, performed screening tests, results, diagnoses, and subsequent treatments) are collected from the medical records. For attenders in the control group, the date of the first BETER visit and the date of the last regular radiation oncology or hemato-oncology outpatient clinic visit are collected.

Survivor Survey

For attenders of the BETER clinics, the survivor survey includes, among others, the following standardized questionnaires: the EQ-5D-5L questionnaire yields utilities used to calculate QALYs, the 36-Item Short Form Health Survey is used to cross-sectionally assess the quality of life, and the Institute for Medical Technology Assessment Productivity Cost questionnaire is used to assess health-related productivity losses [32-34]. Textbox 1 shows an overview of the total study survey components for attenders of BETER care. The expected survey completion time for attenders of BETER care is 20-55 minutes depending on medical history. Nonattenders of the BETER clinics are asked to complete a survey that contains the following components: (1) a questionnaire assessing reasons to not attend a BETER clinic and possible screening or treatment for late effects elsewhere, (2) a short questionnaire on their current health status and lifestyle, and (3) the 6-item adapted version of the Cancer Worry Scale to determine distress associated with the increased risk of late effects [35]. The expected survey completion time for nonattenders is 10-25 minutes. Attenders in the intervention and control group receive the same survey; the same applies to the nonattenders in the intervention and control group.

Textbox 1. Overview of Improving Nationwide Survivorship care Infrastructure and Guidelines after Hodgkin lymphoma Treatment cohort study survey components for 5-year survivors of Hodgkin lymphoma who attended survivorship care at different Better care after lymphoma, Evaluation of long-term Treatment Effects and screening Recommendations (BETER) centers in the Netherlands. The survey is completed by study participants at enrollment in the period 2021-2024.

- EQ-5D-5L questionnaire (a standardized questionnaire that yields utilities used for calculating quality-adjusted life years)
- 36-Item Short Form Health Survey (standardized quality of life questionnaire)
- Institute for Medical Technology Assessment Productivity Cost Questionnaire (standardized health-related productivity losses questionnaire)
- Medical consumption (including general practitioner care, hospital care, physiotherapist, psychologist, and psychiatrist consultations)
- Knowledge about late adverse effects
- Satisfaction with BETER care and perception of benefit and burdensomeness of BETER care
- 6-item adapted Dutch version of the Cancer Worry Scale to determine distress about late adverse effects
- Current health status (diagnoses of possible late effects, medication use, and lifestyle). These questions are only included when the last BETER clinic visit was > 6 months ago

GP Survey

Each survivor's GP is approached by the survivor's former treating radiation oncologist or hematologist with a request to provide information for the INSIGHT study. Each GP receives a short paper survey enquiring about the survivor's medical history of (risk factors for) CVD, severe infections, vaccination status, hypothyroidism, and, if applicable, cause of death. The GP receives 2 reminders in case of nonresponse.

Linkage With National Registries

For all survivors included in the study (intervention and control group), we will obtain information on the incidence of clinical events of interest through linkage with disease registries. Information on breast cancer diagnoses will be obtained from Netherlands Cancer Registry, information on cardiac interventions and disease episodes will be obtained from the Netherlands Heart Registry, information on hospital admissions for CVD and serious infections and total medical consumption will be obtained from the Dutch health care costs registration (Vektis), and for those who died during follow-up cause of death will be obtained from Statistics Netherlands [36-39]. Furthermore, linkage with the national BETER registry data, containing BETER questionnaire data, will be performed. The BETER questionnaire is completed by survivors before their first BETER visit and contains extensive questions about current health, medical history, and lifestyle, which helps health care providers focus on actual symptoms of late adverse effects and lifestyle during the consultation [17]. The questionnaire answers are registered in the national BETER registry for research into late effects of lymphoma treatment upon survivor's written informed consent [17]. Due to the privacy regulations of Statistics Netherlands, the final linked data set can only be accessed and analyzed in the protected remote environment of Statistics Netherlands.

Ethical Considerations

The study protocol was approved by the institutional review board of the Netherlands Cancer Institute (IRB21-115), and we complied with local ethical approval guidelines at all participating sites. Survivors who opted out of the use of their medical data for the INSIGHT study, or medical research in general, are excluded from the study (refer to the detailed informed consent procedure section in Multimedia Appendix 1). Participating survivors did not receive financial compensation. Patient-identifying information is pseudonymized at the participating sites before storage at the Netherlands Cancer Institute and before data analysis in the Statistics Netherlands remote access environment.

Statistical Analysis

Burden of Disease and Secondary Outcomes

DALYs for the conditions of interest are calculated as the sum of the "years of life lost" (YLL) due to premature mortality and the "years lost due to disability" (YLD) for people living with the condition: DALY=YLL+YLD. The YLL is calculated by the number of deaths multiplied by the standard life expectancy at the age at which death occurs. Standard life expectancy in the Netherlands is available from Statistic Netherlands [40]. To estimate YLD during the follow-up period, the number of cases in that period will be multiplied by the average duration of the disease and a weight factor (disability weight) that reflects the severity of the disease on a scale from 0 (perfect health) to 1 (dead). Disability weights are extracted from the Global Burden of Disease Study 2019 or the most recent Global or preferably Dutch disability weight studies [41].

For continuous outcomes (eg, DALYs and health-related quality of life), multiple linear regression analysis will be used to study differences between the intervention and the control group. Important confounders will be controlled for by matching survivors in the intervention group to survivors in the control group based on patient and treatment characteristics, see Study population section. The influence of other potential confounders (eg, BETER hospital or socioeconomic status) on the regression coefficients will be examined, and these will be included in the model when associated with a ≥10% change in the regression coefficient.

For count data (eg, the incidence of late adverse events), negative binomial regression analysis or Poisson regression analysis (depending on the distribution of the data) will be used. To analyze the time between HL diagnosis and diagnosis of late adverse events, competing risk regression methods will be used, with death treated as a competing risk.

Missing data will be handled by multiple imputation when data are missing (completely) at random. Data analysis will be performed in R and RStudio software (The R Foundation).

Sample Size Calculation

The complete sample size calculation including detailed substantiation can be found in the Detailed sample size calculation section in Multimedia Appendix 1. In brief, in an intention-to-treat analysis, taking a BETER clinic attendance rate of 65% into account (A Nijdam, unpublished data, 2016), the expected difference between the intervention and the control group is 0.40 acquired DALY over a follow-up period of 5 years (our expected median follow-up is longer). With a 2-sided significance level of .05 and 80% power to detect a difference of 0.20 SD (small effect size) and larger, we need 393 patients in each study arm. When we take a 15% loss to follow-up and incomplete data into account, we need 452 patients in each study arm.

Cost-Effectiveness Analysis

To compare direct and indirect health care costs between the intervention and the control group, the Dutch health care costs registration (Vektis) and the handbook of costing studies from the Dutch National Health Care Institute (ZorgInstituut) will be used [39,42]. The effects of BETER survivorship care in comparison to the absence of standardized follow-up will be expressed in costs/DALY and costs/QALY. QALYs are derived by health state utilities. A utility is a standardized score between 0 and 1, with 0 reflecting death and 1 perfect health, measured by the EQ-5D-5L questionnaire [33]. The cost-effectiveness analysis will be performed using a discrete event simulation, where we will incorporate several screening strategies. A discrete event simulation analysis on the patient level will be used to simulate the sequences of events that occur as a continuous process over time and to calculate the mean associated costs and QALYs [43]. Uncertainty around the results will be quantified using nonparametric bootstrapping and cost-effectiveness acceptability curves. These curves will show whether BETER survivorship care is cost-effective or not for various values of the Dutch society's willingness to pay for 1 QALY. A budget impact analysis will be performed to estimate the 5-year financial consequences of the implementation of BETER survivorship care in the Dutch health care system. The following factors will be accounted for in the budget impact analysis: screening costs, the potential number of survivors of HL eligible for screening, and the costs of treatment of late adverse events.

Results

The study was funded in November 2020 and approved by the institutional review board of the Netherlands Cancer Institute in July 2021. The first survivor was included in November 2021, and by November 2023, a total of 445 survivors were included in the study intervention group, and 34 survivors were included in the control group. We expect to finalize recruitment by October 2024, data collection by early 2025, and data analysis by May 2025.

Discussion

Principal Findings

BETER is an internationally unique comprehensive infrastructure for adult oncology survivorship care. The INSIGHT study evaluates the effect of the implementation of BETER survivorship care for survivors of HL on survivors' burden of disease from late adverse events, associated health care costs, and quality of life. It will result in important new information on the (cost-)effectiveness of survivorship care in survivors of HL in clinical practice. With our study results, we will be able to evaluate current BETER screening guidelines and adapt them accordingly, if indicated [17,18]. These study results can therefore be used to improve the BETER survivorship care infrastructure and contribute to more effective evidence-based long-term survivorship care for survivors of HL. Moreover, some results could possibly be extrapolated to other cancer survivors (eg, survivors of breast cancer treated with anthracyclines). Importantly, the knowledge gained in this study can be used to better inform survivors of HL about the possible benefits of screening.

If our study demonstrates the cost-effectiveness of BETER survivorship care, we expect that more hospitals in the Netherlands will be motivated to reallocate resources to overcome the organizational hurdles to implement survivorship care according to the BETER guidelines, thus improving implementation of BETER care.

Taking into account the increasing number of cancer diagnoses, improving survival rates, and increasing health care costs, it is essential to ensure that BETER survivorship care is feasible and cost-effective in the long term. If we are able to identify diagnostic tests that have little added value in terms of diagnostic yield and clinical benefit, we will look into leaving them out in future BETER guidelines. Our results may demonstrate that additional diagnostics not recommended in the guidelines, which do not contribute to the cost-effectiveness of BETER survivorship care, are routinely performed. Also, we may observe that survivors are recalled for surveillance more frequently than advised in the guidelines. We can then provide this feedback to the centers in question, as it is not only important to reduce costs but also to make sure we do not overmedicalize survivors of HL.

Strengths and Limitations

An important strength of this study is the quasi-experimental design, which takes advantage of the situation in which BETER care has been gradually implemented in different lymphoma treatment centers in the Netherlands over the past decade. This provides the unique opportunity to study the added value of BETER survivorship care by comparing survivors who did receive such care over the past 6-10 years with a matched comparison group that did not, thereby minimizing the risk of bias in our observational study. A second strength of this study is the comprehensive data collection on the incidence rates of late adverse events from multiple sources: survivors, survivors' medical records, survivors' GPs (and if necessary medical specialists), and national disease registries. This allows us to verify our data, in order to overcome uncertainties and selection

bias related to patient-reported outcomes and potential missing data, for example, due to failed linkages. Third, very importantly, this study design provided us with a representative study population. As we have identified the entire cohort of 5-year survivors who were treated for HL in the centers participating in BETER, we can also include survivors who died during follow-up [17]. Moreover, we also include the data of survivors who did not respond to the invitation to visit the BETER clinic and those who did not respond to our INSIGHT study invitations. The only survivors not included in our study are those who explicitly objected to the use of their data for the INSIGHT study or medical research in general (expected 2%-7%). Including nonattenders of BETER care in this study enables us to accurately assess the total number of survivors eligible for BETER care and perform the cost-effectiveness analysis from a societal perspective of the Netherlands.

The first limitation of our analysis of patient-reported outcomes such as quality of life and risk perceptions is that our results can be affected by selection bias, as we expect 60%-70% of survivors to complete our study survey. A second limitation may be that our sample size calculation is based on a cumulative difference in the burden of disease of CVD, breast cancer, severe infections, and hypothyroidism. Therefore, we may have limited power to perform subanalyses of parts of the disease-specific screening guidelines separately. A third limitation is that we could only follow survivors treated for HL from 1971 to 2011 who were screened for late adverse events from 2013 onward. As late adverse events of interest may have already developed before the start of the BETER screening program in a substantial proportion of the included survivors, we may underestimate the yield and potential benefit of screening. Finally, the expected study follow-up of approximately 8 years may not be sufficient to accumulate enough events of interest to be able to detect a significant difference in the burden of disease between the groups. Therefore, we plan to prospectively follow our cohort and repeat linkages with disease registries after 5-10 years.

Comparison With Prior Work

The INSIGHT study is not only the first evaluation of survivorship care provided at BETER clinics but also the first cost-effectiveness study of structured cancer survivorship care worldwide that uses real-world data and focuses on multiple types of screening. Previous studies performed on survivors of HL and childhood cancer reported on the screening yield of 1 type of screening, lacked a valid comparison group, or used simulations models or hypothetical cohorts to study its cost-effectiveness [19-25,44].

For example, the study by Chow et al [23] reported on underdiagnosis and undertreatment of hypertension, hypercholesterolemia, and diabetes in adult survivors of childhood cancer at high risk of premature CVD in the United States Childhood Cancer Survivor Study cohort and compared the prevalence rates to the general population [23]. Furthermore, in the St. Jude Lifetime Cohort study of childhood cancer survivors, Armstrong et al [24] and Palmer et al [25] evaluated echocardiographic detection rates of impaired left ventricular ejection fraction and diastolic dysfunction, respectively [24,25]. Howell et al [44] described breast cancer cases detected in the United Kingdom national GP mammography screening program for survivors of HL and compared the findings (eg, stage) to breast cancer cases diagnosed in the general population. Although these studies provide valuable information, the results do not demonstrate the incremental value of screening due to the lack of a valid comparison group.

Chen et al [21] evaluated lipid screening and statin therapy in a hypothetical cohort of 30-year-old 5-year survivors of HL treated with chest irradiation. The authors compared no screening with screening at 1-, 3-, 5-, or 7-year intervals and used Markov models to calculate life expectancy, quality-adjusted life expectancy, and lifetime cost. Wong et al [20] simulated life histories using Markov health states to assess the effect of the implementation of echocardiographic screening followed by angiotensin-converting enzyme inhibitor and β-blocker therapy in survivors of childhood cancer on cost-effectiveness, life expectancy, QALYs, and the cumulative incidence of heart failure 30 years after a cancer diagnosis. An important limitation of the above-mentioned studies is that the actual efficacy of statins, angiotensin-converting enzyme inhibitors, and β-blockers in survivors of HL and childhood cancer is unknown and therefore had to be estimated based on assumptions. Furzer et al [22] used simulation models to evaluate the cost utility of 8 different breast cancer screening strategies for survivors of HL treated with chest radiotherapy, with annual magnetic resonance imaging and mammography from age 25 years onward as a reference (no comparison to population screening only). A limitation of this study is that model assumptions about the efficacy of breast cancer screening at young ages were mostly based on *BRCA1/2* mutation carriers, who are known to have different breast cancer tumor characteristics than other women [45].

The German Hodgkin lymphoma study group described the yield of hypothyroidism with thyroid-stimulating hormone screening in survivors of HL (median time since treatment 6 years, median follow-up of 70 months, IQR 12-243 months) [11]. Our study will examine the efficacy of thyroid-stimulating hormone screening after longer time intervals since HL treatment and will also provide longer follow-up after the start of screening. To our knowledge, no studies describing health gains from vaccinations or prescription of on-demand antibiotics in (functional) asplenic survivors of HL have been published. The current BETER afunctional spleen guideline is based on knowledge about patients who had a splenectomy for other indications and on the known increased mortality from infectious disease after spleen irradiation in survivors of HL [3,9,17,18,26]. This study will provide the opportunity to compare incidences of severe infections among survivors of HL who did and did not receive the recommended vaccinations and antibiotics.

Little is known about the effect of survivorship care on survivors' knowledge about late adverse effects and possible distress about these risks. Signorelli et al [46] performed a systematic review and described that attenders of survivorship care (compared to nonattenders) demonstrated increased knowledge about their treatment and diagnosis, and although not significantly, attenders tended to report more distress associated with the risk of late effects [46]. With our study, we can identify areas of insufficient risk perception in survivors of

HL attending the Dutch survivorship program, with the aim of improving risk communication by BETER health care providers.

Conclusions

INSIGHT is the first evaluation of (cost-)effectiveness of structured cancer survivorship care for survivors of HL based on real-world data. It will result in new knowledge on the (cost-)effectiveness of survivorship care in lymphoma survivors in clinical practice. The results are expected to contribute to more effective evidence-based long-term lymphoma survivorship care and could also be of interest to other survivorship programs.

Acknowledgments

This research was supported by the Netherlands Organization for Health Research and Development (ZonMw; grant number 10330022010009) and an institutional grant from the Dutch Cancer Society and the Dutch Ministry of Health, Welfare and Sport. The INSIGHT study is conducted in close collaboration with the Erasmus Medical Center (CPM Janus and C So-Osman), University Medical Center Utrecht (RJ de Weijer and R Oostvogels), Haaglanden Medical Center (SS Gommers and LCJ te Boome), Amsterdam University Medical Center (JM Zijlstra, MJ Kersten, and LA Daniëls), Verbeeten Institute (MGA Schippers and KMS Verschueren), Amphia hospital (RS Boersma), Leiden University Medical Center (SE Rademakers), University Medical Center Groningen (FG Stedema and WJ Plattel), Haga hospital (R van Os and LH Böhmer), Catharina hospital (M van den Berg and MR Nijziel), Meander Medical Center (AC Kroeze, AW Snijder, and JC Regelink), Gelre hospitals (M Kappert, LS Strobbe, ES Eerenberg, and K Dollenkamp), Máxima MC (HAM van Beek and HS de Lil) and Rijnstate hospital (W Deenik). We refer to the consortium website for the full list of participating BETER hospitals and clinicians [47].

Data Availability

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

Authors' Contributions

EMJL participated in the study design and drafted this manuscript. BMPA, FEvL, and AN designed the study and supervised the drafting of this manuscript. JMZ and VPR participated in the study design and critically reviewed the manuscript. All authors read and approved the final manuscript and take full accountability for its content.

Conflicts of Interest

BMPA reports reimbursement costs for an oral presentation at the International Symposium on Hodgkin Lymphoma (2022) in Cologne, Germany.

Multimedia Appendix 1
Detailed informed consent and recruitment procedure, detailed sample size calculation, and overview of cardiovascular diseases and associated risk factors included in the INSIGHT study.
[DOCX File , 20 KB - resprot_v13i1e55601_app1.docx]

Multimedia Appendix 2
Project peer-review by funder.
[PDF File (Adobe PDF File), 4842 KB - resprot_v13i1e55601_app2.pdf]

References

1. Aleman BMP, van den Belt-Dusebout AW, De Bruin ML, van 't Veer MB, Baaijens MHA, de Boer JP, et al. Late cardiotoxicity after treatment for Hodgkin lymphoma. Blood 2007;109(5):1878-1886 [FREE Full text] [doi: 10.1182/blood-2006-07-034405] [Medline: 17119114]
2. De Bruin ML, Sparidans J, van't Veer MB, Noordijk EM, Louwman MWJ, Zijlstra JM, et al. Breast cancer risk in female survivors of Hodgkin's lymphoma: lower risk after smaller radiation volumes. J Clin Oncol 2009;27(26):4239-4246 [FREE Full text] [doi: 10.1200/JCO.2008.19.9174] [Medline: 19667275]
3. de Vries S, Schaapveld M, Janus CPM, Daniëls LA, Petersen EJ, van der Maazen RWM, et al. Long-term cause-specific mortality in Hodgkin lymphoma patients. J Natl Cancer Inst 2021;113(6):760-769 [FREE Full text] [doi: 10.1093/jnci/djaa194] [Medline: 33351090]
4. de Vries S, Schaapveld M, van Nimwegen FA, Jóźwiak K, Lugtenburg PJ, Daniëls LA, et al. High burden of subsequent malignant neoplasms and cardiovascular disease in long-term Hodgkin lymphoma survivors. Br J Cancer 2018;118(6):887-895 [FREE Full text] [doi: 10.1038/bjc.2017.476] [Medline: 29381685]

5. Schaapveld M, Aleman BMP, van Eggermond AM, Janus CPM, Krol ADG, van der Maazen RWM, et al. Second cancer risk up to 40 years after treatment for Hodgkin's lymphoma. N Engl J Med 2015;373(26):2499-2511 [FREE Full text] [doi: 10.1056/NEJMoa1505949] [Medline: 26699166]
6. van Leeuwen FE, Klokman WJ, Veer MB, Hagenbeek A, Krol AD, Vetter UA, et al. Long-term risk of second malignancy in survivors of Hodgkin's disease treated during adolescence or young adulthood. J Clin Oncol 2000;18(3):487-497. [doi: 10.1200/JCO.2000.18.3.487] [Medline: 10653864]
7. van Nimwegen FA, Schaapveld M, Janus CPM, Krol ADG, Petersen EJ, Raemaekers JMM, et al. Cardiovascular disease after Hodgkin lymphoma treatment: 40-year disease risk. JAMA Intern Med 2015;175(6):1007-1017 [FREE Full text] [doi: 10.1001/jamainternmed.2015.1180] [Medline: 25915855]
8. Wang Y, Ronckers CM, van Leeuwen FE, Moskowitz CS, Leisenring W, Armstrong GT, et al. Subsequent female breast cancer risk associated with anthracycline chemotherapy for childhood cancer. Nat Med 2023;29(9):2268-2277 [FREE Full text] [doi: 10.1038/s41591-023-02514-1] [Medline: 37696934]
9. Cullingford GL, Watkins DN, Watts AD, Mallon DF. Severe late postsplenectomy infection. Br J Surg 1991;78(6):716-721. [doi: 10.1002/bjs.1800780626] [Medline: 2070242]
10. Hancock SL, Cox RS, McDougall IR. Thyroid diseases after treatment of Hodgkin's disease. N Engl J Med 1991;325(9):599-605. [doi: 10.1056/NEJM199108293250902] [Medline: 1861693]
11. Bethge W, Guggenberger D, Bamberg M, Kanz L, Bokemeyer C. Thyroid toxicity of treatment for Hodgkin's disease. Ann Hematol 2000;79(3):114-118. [doi: 10.1007/s002770050565] [Medline: 10803932]
12. Hodgkin lymphoma survival rates. Netherlands Cancer Registry. 2022. URL: https://nkr-cijfers.iknl.nl/viewer/relatieve-overleving-per-jaren-na-diagnose?language=en_GB&viewerId=7007c063-1969-4a3d-85ee-826abdfb068a [accessed 2023-09-26]
13. Borchmann P, Eichenauer DA, Engert A. State of the art in the treatment of Hodgkin lymphoma. Nat Rev Clin Oncol 2012;9(8):450-459. [doi: 10.1038/nrclinonc.2012.91] [Medline: 22688578]
14. Eichenauer DA, Aleman BMP, André M, Federico M, Hutchings M, Illidge T, et al. Hodgkin lymphoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018;29(Suppl 4):iv19-iv29. [doi: 10.1093/annonc/mdy080] [Medline: 29796651]
15. McCabe MS, Faithfull S, Makin W, Wengstrom Y. Survivorship programs and care planning. Cancer 2013;119(Suppl 11):2179-2186 [FREE Full text] [doi: 10.1002/cncr.28068] [Medline: 23695930]
16. Barbui T, Björkholm M, Gratwohl A. Cancer survivorship programs: time for concerted action. Haematologica 2014;99(8):1273-1276 [FREE Full text] [doi: 10.3324/haematol.2014.104059] [Medline: 25082784]
17. Nijdam A, Dekker N, Aleman BMP, van 't Veer MB, Daniels LA, van der Maazen RW, et al. Setting up a national infrastructure for survivorship care after treatment for Hodgkin lymphoma. Br J Haematol 2019;186(4):e103-e108 [FREE Full text] [doi: 10.1111/bjh.15936] [Medline: 31090916]
18. Guidelines for screening for adverse effects after Hodgkin lymphoma. Dutch Society for Radiation Therapy and Oncology (NVRO). 2016. URL: https://richtlijnendatabase.nl/zoek?query=%22na+hodgkinlymfoom%22 [accessed 2023-07-03]
19. Yeh JM, Nohria A, Diller L. Routine echocardiography screening for asymptomatic left ventricular dysfunction in childhood cancer survivors: a model-based estimation of the clinical and economic effects. Ann Intern Med 2014;160(10):661-671 [FREE Full text] [doi: 10.7326/M13-2266] [Medline: 24842413]
20. Wong FL, Bhatia S, Landier W, Francisco L, Leisenring W, Hudson MM, et al. Cost-effectiveness of the children's oncology group long-term follow-up screening guidelines for childhood cancer survivors at risk for treatment-related heart failure. Ann Intern Med 2014;160(10):672-683 [FREE Full text] [doi: 10.7326/M13-2498] [Medline: 24842414]
21. Chen AB, Punglia RS, Kuntz KM, Mauch PM, Ng AK. Cost effectiveness and screening interval of lipid screening in Hodgkin's lymphoma survivors. J Clin Oncol 2009;27(32):5383-5389 [FREE Full text] [doi: 10.1200/JCO.2009.22.8460] [Medline: 19752333]
22. Furzer J, Tessier L, Hodgson D, Cotton C, Nathan PC, Gupta S, et al. Cost-utility of early breast cancer surveillance in survivors of thoracic radiation-treated adolescent Hodgkin lymphoma. J Natl Cancer Inst 2020;112(1):63-70 [FREE Full text] [doi: 10.1093/jnci/djz037] [Medline: 31070751]
23. Chow EJ, Chen Y, Armstrong GT, Baldwin LM, Cai CR, Gibson TM, et al. Underdiagnosis and undertreatment of modifiable cardiovascular risk factors among survivors of childhood cancer. J Am Heart Assoc 2022;11(12):e024735 [FREE Full text] [doi: 10.1161/JAHA.121.024735] [Medline: 35674343]
24. Armstrong GT, Joshi VM, Ness KK, Marwick TH, Zhang N, Srivastava D, et al. Comprehensive echocardiographic detection of treatment-related cardiac dysfunction in adult survivors of childhood cancer: results from the St. Jude Lifetime Cohort Study. J Am Coll Cardiol 2015;65(23):2511-2522 [FREE Full text] [doi: 10.1016/j.jacc.2015.04.013] [Medline: 26065990]
25. Palmer C, Mazur W, Truong VT, Nagueh SF, Fowler JA, Shelton K, et al. Prevalence of diastolic dysfunction in adult survivors of childhood cancer: a report from SJLIFE Cohort. JACC CardioOncol 2023;5(3):377-388 [FREE Full text] [doi: 10.1016/j.jaccao.2022.12.010] [Medline: 37397075]
26. Guideline aplenia. National Institute for Public Health and the Environment (RIVM). URL: https://lci.rivm.nl/richtlijnen/asplenie [accessed 2023-08-11]

27. Tjin-A-Ton JJS, Konings KTS. Dutch college of general practioners (NHG) guideline cardiovascular risk management version 4.0. NHG-Richtlijnen. 2019. URL: https://richtlijnen.nhg.org/standaarden/cardiovasculair-risicomanagement
28. Stouthard MEA, Essink-Bot ML, Bonsel GJ, Barendregt JJM, Kramers PGN, van de Water HPA, Gunning-Schepers LJ, van der Maas PJ. Disability weights for diseases in the Netherlands. In: UvA-DARE. Rotterdam: Department of Public Health, Erasmus University Rotterdam; 1997.
29. Salomon JA, Haagsma JA, Davis A, de Noordhout CM, Polinder S, Havelaar AH, et al. Disability weights for the Global Burden of Disease 2013 study. Lancet Glob Health 2015 Nov;3(11):e712-e723 [FREE Full text] [doi: 10.1016/S2214-109X(15)00069-8] [Medline: 26475018]
30. Groot MT, Baltussen R, Uyl-de Groot CA, Anderson BO, Hortobágyi GN. Costs and health effects of breast cancer interventions in epidemiologically different regions of Africa, North America, and Asia. Breast J 2006;12 Suppl 1:S81-S90. [doi: 10.1111/j.1075-122X.2006.00206.x] [Medline: 16430401]
31. Socioeconomic status based on zip code. Statistics Netherlands. 2019. URL: https://www.cbs.nl/nl-nl/maatwerk/2022/26/sociaal-economische-status-per-postcode-2019
32. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, et al. Translation, validation, and norming of the Dutch language version of the SF-36 health survey in community and chronic disease populations. J Clin Epidemiol 1998;51(11):1055-1068. [doi: 10.1016/s0895-4356(98)00097-3] [Medline: 9817123]
33. Janssen MF, Pickard AS, Golicki D, Gudex C, Niewada M, Scalone L, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Qual Life Res 2013;22(7):1717-1727 [FREE Full text] [doi: 10.1007/s11136-012-0322-4] [Medline: 23184421]
34. Bouwmans C, Krol M, Severens H, Koopmanschap M, Brouwer W, van Roijen LH. The iMTA productivity cost questionnaire: a standardized instrument for measuring and valuing health-related productivity losses. Value Health 2015;18(6):753-758 [FREE Full text] [doi: 10.1016/j.jval.2015.05.009] [Medline: 26409601]
35. Custers JAE, Kwakkenbos L, van de Wal M, Prins JB, Thewes B. Re-validation and screening capacity of the 6-item version of the cancer worry scale. Psychooncology 2018;27(11):2609-2615. [doi: 10.1002/pon.4782] [Medline: 29843189]
36. Netherlands Cancer Registry. URL: https://iknl.nl/en [accessed 2023-10-12]
37. Netherlands Heart Registry. URL: https://nhr.nl/ [accessed 2023-10-12]
38. Causes of death. Statistics Netherlands. URL: https://www.cbs.nl/en-gb/series/time/causes-of-death [accessed 2023-10-12]
39. Vektis. URL: https://www.vektis.nl/ [accessed 2023-10-12]
40. Life expectancy. Statistics Netherlands. 2023. URL: https://opendata.cbs.nl/#/CBS/en/dataset/71950eng/table?dl=71CD6 [accessed 2023-09-26]
41. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 2020;396(10258):1204-1222 [FREE Full text] [doi: 10.1016/S0140-6736(20)30925-9] [Medline: 33069326]
42. van Roijen LH, van der Linden N, Bouwmans C, Kanters T, Swan TS. Guideline for economic evaluations in health care. Zorginstituut Nederland. 2024. URL: https://www.zorginstituutnederland.nl/over-ons/publicaties/publicatie/2024/01/16/richtlijn-voor-het-uitvoeren-van-economische-evaluaties-in-de-gezondheidszorg; [accessed 2024-02-28]
43. Glover MJ, Jones E, Masconi KL, Sweeting MJ, Thompson SG, SWAN Collaborators, SWAN collaborative group. Discrete event simulation for decision modeling in health care: lessons from abdominal aortic aneurysm screening. Med Decis Making 2018;38(4):439-451 [FREE Full text] [doi: 10.1177/0272989X17753380] [Medline: 31665967]
44. Howell SJ, Searle C, Goode V, Gardener T, Linton K, Cowan RA, et al. The UK national breast cancer screening programme for survivors of Hodgkin lymphoma detects breast cancer at an early stage. Br J Cancer 2009;101(4):582-588 [FREE Full text] [doi: 10.1038/sj.bjc.6605215] [Medline: 19672261]
45. Krammer J, Pinker-Domenig K, Robson ME, Gönen M, Bernard-Davila B, Morris EA, et al. Breast cancer detection and tumor characteristics in BRCA1 and BRCA2 mutation carriers. Breast Cancer Res Treat 2017;163(3):565-571 [FREE Full text] [doi: 10.1007/s10549-017-4198-4] [Medline: 28343309]
46. Signorelli C, Wakefield CE, Fardell JE, Wallace WHB, Robertson EG, McLoone JK, et al. The impact of long-term follow-up care for childhood cancer survivors: a systematic review. Crit Rev Oncol Hematol 2017;114:131-138. [doi: 10.1016/j.critrevonc.2017.04.007] [Medline: 28477741]
47. Projectgroep BETER - Beter Na Hodgkin. URL: https://www.beternahodgkin.nl/meer-informatie/over-deze-site/deelnemende-ziekenhuizen/

Abbreviations

BETER: Better care after lymphoma, Evaluation of long-term Treatment Effects and screening Recommendations
CVD: cardiovascular disease
DALY: disability-adjusted life year
GP: general practitioner
HL: Hodgkin lymphoma

INSIGHT: Improving Nationwide Survivorship care Infrastructure and Guidelines after Hodgkin lymphoma Treatment
QALY: quality-adjusted life year
YLD: years lost due to disability
YLL: years of life lost

Edited by A Mavragani; submitted 26.12.23; this is a non–peer-reviewed article;accepted 26.02.24; published 18.04.24.

Please cite as:
Lammers EMJ, Zijlstra JM, Retèl VP, Aleman BMP, van Leeuwen FE, Nijdam A, BETER consortium
Effectiveness and Cost-Effectiveness of Survivorship Care for Survivors of Hodgkin Lymphoma (INSIGHT Study): Protocol for a Multicenter Retrospective Cohort Study With a Quasi-Experimental Design
JMIR Res Protoc 2024;13:e55601
URL: https://www.researchprotocols.org/2024/1/e55601
doi:10.2196/55601
PMID:38635308

Protocol

TAILR (Nursing-Sensitive Events and Their Association With Individual Nurse Staffing Levels) Project: Protocol for an International Longitudinal Multicenter Study

Stefanie Bachnick[1*], PhD; Maria Unbeck[2,3*], PhD; Maryam Ahmadi Shad[4], MSc; Katja Falta[1], BSc; Nicole Grossmann[4], MSc; Daniela Holle[1], PhD; Jana Bartakova[4,5], PhD; Sarah N Musy[4], MSc, PhD; Sarah Hellberg[3,6], MSc; Pernilla Dillner[7,8], MSc; Fatemeh Atoof[9], PhD; Mohammadhossein Khorasanizadeh[10], MSc; Paula Kelly-Pettersson[3,6], PhD; Michael Simon[4], PhD

[1]Department of Nursing Science, University of Applied Sciences, Bochum, Germany

[2]School of Health and Welfare, Dalarna University, Falun, Sweden

[3]Department of Clinical Sciences, Danderyd Hospital, Karolinska Institutet, Stockholm, Sweden

[4]Institute of Nursing Science, Department Public Health, Faculty of Medicine, University of Basel, Basel, Switzerland

[5]Health Economics Facility, Department of Public Health, University of Basel, Basel, Switzerland

[6]Department of Orthopaedics, Danderyd University Hospital, Stockholm, Sweden

[7]Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden

[8]Department of Neonatology, Astrid Lindgren Children's Hospital, Karolinska University Hospital, Stockholm, Sweden

[9]Social Determinants of Health Research Center, Kashan University of Medical Sciences, Kashan, Iran

[10]Trauma Nursing Research Center, Kashan University of Medical Sciences, Kashan, Iran

[*]these authors contributed equally

Corresponding Author:
Stefanie Bachnick, PhD
Department of Nursing Science
University of Applied Sciences
Gesundheitscampus 6 – 8
Bochum, 44801
Germany
Phone: 49 234 77727 748
Email: stefanie.bachnick@hs-gesundheit.de

Abstract

Background: Nursing-sensitive events (NSEs) are common, accounting for up to 77% of adverse events in hospitalized patients (eg, fall-related harm, pressure ulcers, and health care–associated infections). NSEs lead to adverse patient outcomes and impose an economic burden on hospitals due to increased medical costs through a prolonged hospital stay and additional medical procedures. To reduce NSEs and ensure high-quality nursing care, appropriate nurse staffing levels are needed. Although the link between nurse staffing and NSEs has been described in many studies, appropriate nurse staffing levels are lacking. Existing studies describe constant staffing exposure at the unit or hospital level without assessing patient-level exposure to nurse staffing during the hospital stay. Few studies have assessed nurse staffing and patient outcomes using a single-center longitudinal design, with limited generalizability. There is a need for multicenter longitudinal studies with improved potential for generalizing the association between individual nurse staffing levels and NSEs.

Objective: This study aimed (1) to determine the prevalence, preventability, type, and severity of NSEs; (2) to describe individual patient-level nurse staffing exposure across hospitals; (3) to assess the effect of nurse staffing on NSEs in patients; and (4) to identify thresholds of safe nurse staffing levels and test them against NSEs in hospitalized patients.

Methods: This international multicenter study uses a longitudinal and observational research design; it involves 4 countries (Switzerland, Sweden, Germany, and Iran), with participation from 14 hospitals and 61 medical, surgery, and mixed units. The 16-week observation period will collect NSEs using systematic retrospective record reviews. A total of 3680 patient admissions will be reviewed, with 60 randomly selected admissions per unit. To be included, patients must have been hospitalized for at least 48 hours. Nurse staffing data (ie, the number of nurses and their education level) will be collected daily for each shift to assess

the association between NSEs and individual nurse staffing levels. Additionally, hospital data (ie, type, teaching status, and ownership) and unit data (ie, service line and number of beds) will be collected.

Results: As of January 2024, the verification process for the plausibility and comprehensibility of patients' and nurse staffing data is underway across all 4 countries. Data analyses are planned to be completed by spring 2024, with the first results expected to be published in late 2024.

Conclusions: This study will provide comprehensive information on NSEs, including their prevalence, preventability, type, and severity, across countries. Moreover, it seeks to enhance understanding of NSE mechanisms and the potential impact of nurse staffing on these events. We will evaluate within- and between-hospital variability to identify productive strategies to ensure safe nurse staffing levels, thereby reducing NSEs in hospitalized patients. The TAILR (Nursing-Sensitive Events and Their Association With Individual Nurse Staffing Levels) study will focus on the optimization of scarce staffing resources.

International Registered Report Identifier (IRRID): DERR1-10.2196/56262

(JMIR Res Protoc 2024;13:e56262) doi:10.2196/56262

KEYWORDS

adverse events; electronic health record; hospital care; no-harm incidents; nursing care; nursing-sensitive events; nurse staffing; patient safety; systematic record review

Introduction

Overview

The link between patient outcomes and adequate nurse staffing levels has been extensively studied internationally over the last 2 decades. To avoid negative patient outcomes, such as adverse events, adequate staffing levels and combinations of skills and grades are needed. In hospital settings, up to 77% of adverse events are attributed to nursing care [1]. Nursing-sensitive events (NSEs) are part of adverse events that are specifically affected, caused, and influenced by the processes or structures of nursing care, though nursing is not exclusively responsible [2]. Examples of NSEs are hospital-acquired urinary tract infections, pressure ulcers, pneumonia, or deep venous thrombosis [3]. NSEs may be accompanied by additional monitoring or treatment [4]. Compared to studies on adverse events and their characteristics, few studies include all types of NSEs and their prevalence, preventability, and severity [5]. A recently published study exploring NSEs in home care settings found that 73% of the NSEs were preventable, and approximately 37% resulted in temporary harm that required additional health care resources [6]. In addition to the burden on the patient, NSEs generate high medical costs by necessitating additional monitoring or treatment [5,7]. Different methods to identify and assess NSEs are available. Currently, there is no gold standard for identifying and assessing NSEs. However, retrospective record review (RRR) methods, such as the Global Trigger Tool [5] and the Harvard Medical Practice Study methodology [8], seem most promising. Compared to other methods (eg, critical incident reporting systems and patient safety indicators), record review facilitates the detection of more adverse events, thereby minimizing the underreporting of NSEs [9]. To prevent and reduce NSEs and ensure quality nursing care, appropriate nurse staffing levels are needed [8,10]. Nurse staffing refers to the number and qualifications of nurses relative to the care demands of patients, often expressed as staffing levels (eg, nurse-to-patient ratios), skill mix (ie, the composition of the nursing team in terms of qualifications), and grade mix (ie, educational levels of the nursing team) [9]. Providing optimal nurse staffing levels has been a challenge for health care systems worldwide. Having too few nurses increases the risk of NSEs and decreases the quality of care (F Gratwohl, N Grossmann, S Musy, and M Simon, unpublished data, September 2018) [11,12]; it also increases the risk of nurse burnout and job dissatisfaction, which impedes the recruitment and maintenance of the nursing workforce [13]. Evidence suggests that the occurrence of negative patient outcomes is related to staffing [14], but there is a lack of systematic reviews focusing on different types of NSE.

Despite studies that substantiated the link between nurse staffing and NSEs [14-16], operational and methodological challenges have limited the practical impact of this research. Typically, staffing studies describe only constant staffing exposure at the unit or hospital level without assessing individual patient-level exposure to nurse staffing during the hospital stay [17]. Methodological challenges include the omission of important variables (eg, shift patterns, skill mix, and patient turnover) [10,16]; common method variance (ie, dependent and independent variables derived from the same survey of nurses); and simultaneity, which refers to common-cause variables affecting both staffing and outcomes, such as patient severity [16]. Only a few studies have assessed nurse staffing and patient outcomes using a longitudinal study design [10,15,18], and most of these studies were single-center studies; there is a lack of multicenter or international studies allowing generalizability. Therefore, there is a need for multicenter longitudinal studies of the association between individual patient-level exposure to nurse staffing and all types of NSEs, with improved potential for generalization.

To advance the field, there is a strong need to determine the optimal intervention strategies for nurse staffing levels required to reduce the risk of NSEs. This study is the first step in generating data aimed at structuring and planning future intervention strategies.

Objectives

The overall aim of the TAILR (Nursing-Sensitive Events and Their Association With Individual Nurse Staffing Levels) study is to investigate the association between NSEs and individual nurse staffing levels. The specific aims are as follows:

1. To determine the prevalence, preventability, type, and severity of NSEs across sites using structured RRR methodology
2. To describe individual patient-level nurse staffing across hospitals
3. To describe the effect of nurse staffing on NSEs in hospitalized patients
4. To determine thresholds of safe nurse staffing levels and test them against NSEs in hospitalized patients

Methods

Design

TAILR is an international multicenter study with a longitudinal and observational research design, running from 2021 to 2025. Altogether, 4 countries are participating in the study: Switzerland, Sweden, Germany, and Iran. Those countries make up the international TAILR consortium. Except for Switzerland, all data will be collected within the TAILR study. For Switzerland, data from the CroWiS (Crowd Working in der Schweiz) study will be used for data collection and analyses. CroWiS is a multimethod study with the overall aim of investigating the effect of temporary nurses in Switzerland [19].

Setting and Sample

For the different countries, different numbers of hospitals and units are included in the TAILR study. The numbers of participating hospitals and units range from 1 to 4 hospitals and 4 to 21 units, depending on the country. Across all countries, 4 medical, surgical, or mixed units for each hospital are participating in the study, which is a total of 11 hospitals and 49 units. The study also includes acute care hospitals providing elective care. The inclusion criteria for units are as follows: they must have at least 10 patient beds and are either medical or surgical. Units with elevated levels of care, such as intensive or intermediate care, will be excluded, as these units have higher levels of staffing. In Sweden, 1 of the 4 hospitals is a pediatric hospital that is part of a university hospital providing adult care as well. For this pediatric hospital in the TAILR study, 9 units will be included. For pediatric care, neonatal care units will be included, but these data will be analyzed separately in the pediatric cohort. Table 1 shows the setting and sample information for each country.

During the 16-week observation period, 60 admissions will be randomly selected from all eligible admissions per unit and will be reviewed. For adult care, patients ≥18 years of age will be included. For pediatric care, no inclusion criteria for age will be applied. All patients must be hospitalized for at least 48 hours at a TAILR unit, and the admission record must be closed. The stay in the TAILR unit ends after patients have been discharged, when the length of stay exceeds 14 days or when patients are transferred from the TAILR unit for more than 12 hours. If the patient has a length of stay >14 days, the data collection ends at the end of day 14. If a patient is readmitted, this admission is considered a new admission.

Table 1. Number of hospitals, units, and patients, along with shift system information, including the number of shifts for each country and in total.

Country and hospital	Hospital, n	Units, n	Shifts per day, n	Patient admission, n	Number of shifts, n	
					Weekday	Weekend
Germany						
Acute adult care hospital	3	12	3-14	720	Minimum 2880	Minimum 1152
Iran						
Acute adult care hospital	1	4	3	240	1152	192
Sweden						
Acute adult care hospital	3	12	3	720	2880	1152
Pediatric care hospital	1	9	3	560	2160	864
Total	4	21	N/A[a]	1280	5040	2016
Switzerland						
Acute adult care hospital	3	12	3	720	2880	1152
All countries						
Acute adult care hospital	10	40	N/A	2400	Minimum 9792	Minimum 3648
Pediatric care	1	9	N/A	560	2160	864
Total	11	49	N/A	2960	Minimum 11,952	Minimum 4512

[a]N/A: not applicable.

Variables and Measurements

Patient Characteristics and NSEs

Patient characteristics (eg, age and sex), clinically relevant variables (eg, primary diagnosis and patient-based workload for activities of daily living), and NSEs will be collected from patient records using systematic RRR, inspired by commonly used RRR methods. For the collection of the type of NSEs, we will use a set of predefined events (eg, deficiencies in drug management, deterioration of vital signs, health care–associated

infections, gastrointestinal impairment, pain, and pressure ulcer) based on a literature review [3,5,6,20]. Furthermore, there is an option to enter "other" NSEs in the patient record, which allows all types of NSEs to be included. In addition to the type of NSE, preventability, severity, timing, origin, and potential contributing causes will be assessed per NSE. For severity, a slightly modified version of the National Coordinating Council for Medication Error Reporting and Prevention will be used, ranging from "An event that reached the patient but did not cause harm" to "Contributed or resulted in the patient's death."

Staffing Assessment

The shift-level nurse staffing data of the participating units will be collected using routine data or data from unit schedules depending on the hospital. For each day and each shift during the observation period of 16 weeks, each registered nurse (RN), specialist RN, nurse with an associate nursing degree (AND), unqualified helper, and student or trainee directly involved in patient care on the unit will be considered in the staffing assessment. Informal caregivers will be excluded. The assessment also includes whether the staff member is a temporary worker on the unit. We define "temporary" as a staff member deployed from a different unit than the target TAILR unit, a hospital pool, or an external agency. We will not differentiate between temporary nurses who only work for a single or few shifts and nurses who are deployed for weeks or months. To identify shifts with missing nurses, we will clarify whether the number of staff on this shift was as planned or not. If not, the missing number of nurses stratified by nursing degree will be entered.

Patient Counts and Turnovers

To assess the workload of nurses in relation to patient turnover, routine data regarding the number of patients, discharges, admissions, and transfers will be collected. Moreover, we will assess the number of out-of-specialty patients to account for additional workload for nurses.

Unit Survey

The study-specific 26-item unit survey assesses the organizational characteristics of the participating units, such as size (bed count) and service line. Additionally, data about the used care system and the used system to describe nursing care demands, workload, or patient acuity will be part of the unit questionnaire.

Hospital Survey

The study-specific hospital survey (8 items) will be used to collect hospital-level characteristics and statistics, such as ownership status (eg, private, not-for-profit, and public) and type (ie, district, general, and teaching hospital), as well as regulation, financing, and provision of the hospital.

Survey Translation and Validity Testing

The study manual, surveys, and assessments were developed in English. For Germany and Iran, they were translated into German and Farsi (Persian), respectively. Using a modified Brislin protocol, a systematic translation process was conducted [21]. After translation, an expert panel review of bilingual clinical and research nurses fluent in each target language reviewed each item in terms of cultural adaptations. To ensure comprehensibility and to check for response patterns, the entire German and Farsi versions of the NSE assessment sheet were pilot tested with nurses of varying educational levels. For all language versions, adaptations were made, as necessary, for wording and clarity.

Data Collection

The data observation period started in 2022. The data collection covers an observation period of 16 weeks at each hospital, but the start dates for hospital enrollment will be staggered between and within countries. We opted for this stepwise approach to ensure proper supervision and optimal use of resources during the data collection process, considering unit availability. Data will be collected digitally or with paper and pencil.

In Sweden and Switzerland, the random sampling of 60 admissions per unit will be carried out at the end of the 16-week observation period. In Germany and Iran, to use the available data collection resources, a random sampling of 15 admissions for each unit occurred 4 times with an interval of 4 weeks. Therefore, the number of included admissions in Germany and Iran is the same as those in the other participating countries, that is, 60 admissions per unit within 16 weeks of observation. Data will be collected by the internal RNs of the corresponding hospital or RNs who have experience working in the corresponding hospital. All data collectors will receive standardized education with the study manual, PowerPoint presentations, test examples, test records, and discussion sessions. For data quality control, an RN experienced in research for comprehensibility and plausibility will monitor the entered data.

The shift-level staffing assessments will be collected every day (from Monday to Sunday) for every shift (ie, morning, afternoon, night, and intermediated shifts). In Germany and Iran, data will be entered directly into a cloud-based electronic data capture platform by the ward manager of the TAILR unit, a hospital internal RN or a research team member. All data collectors for staffing assessment will receive a 3-hour education session with test entries and discussion sessions. In Sweden, shift data will be generated automatically by the corresponding hospital staffing system. In Switzerland, staffing data will be manually extracted from hospital staffing systems and entered into a secure web platform by members of the research team.

The hospital- and unit-level surveys will be conducted retrospectively after the main data collection. Data will be collected using routine data. If no routine data are available, interviews between TAILR country-specific research group members, unit managers, and hospital managers will be conducted.

Data will be stored in a cloud-based database, with a server in the Netherlands, that complies with the European Union General Data Protection Regulation. Access to the platform is restricted to the TAILR research group members and data collectors at specific sites.

Sample Size

We used 3 hospitals as the basis for sample size considerations. Assuming the same NSE rate of 36.4% as in a Swedish study [5], a sample size of 720 (95% CI 33.3%-39.5%) patients is expected (aim 1). A simulation (500 iterations per cell) of a 3-level generalized linear mixed model with a count variable for each shift above a low staffing threshold, with 15% of patients exposed to 1 or more shifts, was performed. We set the random effects at the unit and hospital level to 0.1, indicating an intraclass correlation coefficient (ICC) of 0.03. Based on an odds ratio of 1.10 and a sample of 60 patients per 4 units in 3 hospitals, the power was 100%. With a lower odds ratio of 1.07, representing the smallest effect of interest for a sample of 60 patients per 4 units in 3 hospitals, the power was still 0.91. As the ICC is unknown, we also assessed ICCs of 0, 0.06, and 0.15, resulting in the power ranging from 90% to 100% for both effect sizes, with a sample of 720 patients. Reducing the number of units to 3 per site, the total sample size was reduced to 540, with the power dropping to 70%-96%, depending on the specification. As the weights will only be known after the study has been conducted [22], this power calculation is based on a generalized linear mixed model without inverse probability weighting.

Data Analysis

Aim 1

A descriptive analysis of the prevalence, preventability, types, and severity of NSEs will be carried out. We will calculate the frequencies and percentages with 95% CIs for NSE type, severity, and preventability. We will calculate the prevalence of NSEs per 1000 patient days and 100 patient admissions. To determine the quality of the review process, we will assess interrater reliability between 2 primary reviewers from a random sample of every tenth of the admissions via the Cohen kappa (κ) coefficient for review stage 1. Agreement between reviewers is defined as (1) agreement on the presence of potential NSEs by calculating Cohen kappa and (2) agreement on the number of NSEs by calculating the weighted Cohen kappa, where high disagreement corresponds to high weights.

Aim 2

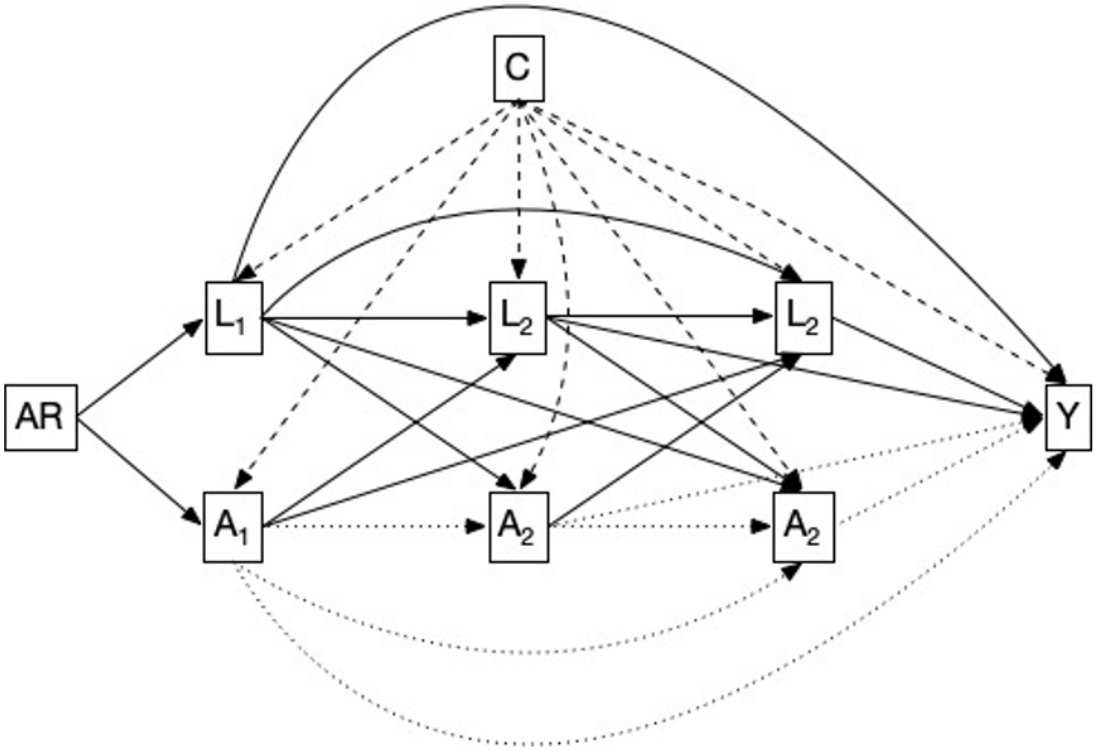
In the first step, a descriptive analysis of the numbers of patients and nurses and the patient-to-nurse ratios for different staff categories (eg, RNs, specialist RNs, nurses with ANDs, and unqualified staff) over time will be conducted. Extreme staffing shifts will be defined as those with 50% more or fewer patients per nurse for each unit based on the shift median.

In the second step, the workload will be modeled with the observed-over-expected (O/E) estimator. The O/E estimator is the observed number of nurse staff on a shift divided by the expected number of nurse staff based on the shift, patient, and unit characteristics; the O/E estimator is an extension of the adjusted staffing measure we used in a previous study [23]. For the O/E estimator, we will predict the number of different staff groups (eg, RNs, nurses with ANDs, and unqualified staff) with a multivariate generalized linear model of the Poisson family, with separate models for each unit. This model will take patient characteristics; primary and secondary diagnoses; shifts; and the number of patients, admissions, transfers, and discharges into account. The observed number of nurse staff per shift will be divided by the expected value derived from the multivariate generalized linear model. The O/E estimator will then be used to describe the staffing variability over time for each patient. Furthermore, the coefficients of the model will allow us to compare units, hospitals, and countries in terms of their nurse staffing provision.

Aim 3

We will evaluate the suspected causative effect of nurse staffing on selected NSEs using a directed acyclic graph describing the hypothesized mechanism over time (Figure 1). Directed acyclic graphs describe a set of time-invariant individual-level confounders, such as age (A) or sex (C), time-variant confounders, such as patient severity on a given shift ($L_{1...n}$); and the time-variant exposure variable of the O/E estimator for nurse staffing ($A_{1...n}$). The minimal adjustment set also includes the admission reason, which determines the unit to which a patient is admitted. To estimate the causal effects, 3 conditions need to be met. The first condition is the "exchangeability assumption." An uncontrolled variable that influences exposure and outcome would violate this assumption. As the supply side (ie, the available nurse staffing resources) is determined by the unit type and relatively fixed rosters, the exposure is primarily driven by the volatility of the demand side (ie, the patients admitted to the unit). Therefore, within units, the exchangeability assumption for the exposure should hold. Indeed, occupancy might influence patient admissions or discharges, potentially creating a backdoor path. We will, therefore, consider occupancy as a variable in a sensitivity analysis. Second, the "positivity" assumption is met by the design, as individual exposure to high- or low-staffed shifts occurs continuously throughout the index admission. We will use descriptive analysis to confirm this assumption. Last, the "consistency assumption" requires that the level of exposure is identical for all patients. Although consistency is provided in the way the exposure is operationalized, the nursing staff will allocate available time between patients according to their needs within shifts. The severity measure will partially account for this. We will use nurse activity data, which are available for some sites, to explore this issue. To estimate a causal effect of nurse staffing exposure on each NSE of interest, we will construct a marginal structural model using inverse probability weighting [24]. According to VanderWeele et al [25], a marginal structural model can assess the joint effects of time-varying exposure. To calculate the weights, we will use the R package "ipw" [26]. To fit the model, we will use a generalized mixed model of the binomial family with the lme4 package in R software (version R-4.3.3; R Foundation for Statistical Computing) [27].

Figure 1. Directed acyclic graph of the staffing and nursing-sensitive events The graph describes a set of time-invariant individual-level confounders, such as age (A) or sex (C); time-variant confounders, such as patient severity on a given shift ($L_{1...n}$); and the time-variant exposure variable of the observed-over-expected estimator for nurse staffing ($A_{1...n}$). The minimal adjustment set also includes the admission reason (AR), which determines the unit to which a patient is admitted. Y: outcome.



Aim 4

To help optimize and predict the necessary nursing staffing needs in hospitals to decrease NSEs, we will develop a simulation using the simmer package in R software. Simmer is a discrete-event simulation (DES) and automation software. DES is a flexible, computer-based modeling methodology characterized by the ability to simulate dynamic behaviors of complex systems and interactions between individuals, populations, and their environments. Compared with aggregate models without interaction, such as decision trees or Markov models, a DES can be more advantageous as an operational research technique to model complex systems at the individual level instead of the cohort level. After we have developed the DES model, we will test it against various data elements from our observational study, including the hospital bed size, number of nursing staff, patient flow structure, nursing practices, and NSEs. The process flow will be translated into a DES model, which will allow us to determine and validate the thresholds of safe nurse staffing levels.

Ethical Considerations

The TAILR study is compliant with the legal and ethical guidelines of the applicable federal, clinical (including participating hospitals), and academic partners (ie, universities and universities of applied sciences). Ethical approval for the proposed study has already been obtained according to national regulations (Germany [Ethik-Kommission Hochschule für Gesundheit, University of Applied Sciences Bochum]: 210602; Sweden [Swedish Ethical Review Authority]: TAILR.SE: 2021-04962; Iran [Ethics Committee of Kashan University of Medical Sciences]: TAILR.IR: IR.KAUMS.REC.1398.032; and Switzerland [Ethikkommission Nordwest- und Zentralschweiz]: CroWiS BASEC 2022-01121).

The study will follow all ethical standards of research conduct outlined in the Declaration of Helsinki and the General Data Protection Regulation for European countries. The project team will handle the patient- and unit-level staffing data with confidentiality. Each patient record included in the record review will receive a unique identification number, and the data in a cloud-based database will be pseudonymized. Participant names will not be disclosed. The published study data will be anonymous, and therefore, there will be no identification of individual participants. The study participants received no compensation.

Results

As of January 2024, the checking of plausibility and comprehensibility of patients' and nurse staffing data is ongoing in all 4 countries. Data analyses are planned to be completed by spring 2024, with the first results expected to be published in late 2024.

Discussion

This paper describes the study protocol for the TAILR study. TAILR is an international multicenter study with a longitudinal and observational design that will consider within- and between-hospital variability to identify productive and urgently needed strategies to ensure safe nurse staffing levels to reduce NSEs. More concretely, TAILR will provide important building

blocks to address and overcome a critical patient safety issue, that is, the lack of staffing guidance in national health policy and at local organizational levels. TAILR provides a unique opportunity to better understand the mechanisms of NSEs and the potential impact of nurse staffing on NSEs. Collecting data on nurse staffing and its association with NSEs in multiple countries, the TAILR study aims to provide a new perspective on optimal nurse staffing levels in hospitals and a unique innovative template for the evaluation of the association between NSEs in patients and individual nurse staffing levels within the international context. This study addresses a gap in current research, as emphasized by repeated calls for research to inform health policies on safe nurse staffing levels [15,28]. This need has been increased due to the COVID-19 pandemic and the increasing pressures to develop and maintain the nursing workforce in the participating countries as well as other countries [29].

TAILR will act as a model for nurse-led improvement strategies for safe staffing within different countries. First, for the participating hospitals, TAILR will create transparency by providing comparative data. Moreover, we will be able to identify hospital structures and processes that facilitate and challenge safe nurse staffing. By conducting workshops with the participating hospitals and stakeholders, the best practices will be identified and described to create applicable solutions based on the study results. Second, based on the workshops with hospitals and stakeholders, TAILR will provide data to develop recommendations that provide cornerstones for safe staffing policies in a country-specific context. Beyond mandatory minimum nurse staffing levels, TAILR will provide highly granular data to describe operational gaps in nurse staffing, which remain undetected in aggregate analysis. Potential safe staffing policies must consider the service line and patient acuity as well as hospital-specific factors, such as nurse pools, clear distribution of nursing and nonnursing tasks between nurses with different educational backgrounds, and the systematic assessment and monitoring of nurse staffing and NSEs. Third, the international TAILR study will create research outputs for the participating countries as well as other countries. For (inter)national stakeholders and the members of the international TAILR consortium, the study results will enable the definition of global quality improvement strategies.

Acknowledgments

We would like to thank all data collectors as well as the hospital and unit coordinators and unit managers.

TAILR.DE (Germany) is funded by the Federal Ministry of Education and Research, Germany (registration number 01GY2001).

Parts of TAILR.CH (Switzerland) are financed by the Swiss National Science Foundation (CroWiS, project 187433).

TAILR.IR (Iran) is funded by Kashan University of Medical Sciences (grant 98064).

Parts of TAILR.SE (Sweden) are funded by the Center for Clinical Research, Region Dalarna (CKFUU-962511) and the Regions´ Patient Insurance Company.

Data Availability

The data that support the findings of this study are available from the corresponding authors, (SB, MU, and MS) upon reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report by the German Federal Ministry of Education and Research.
[PDF File (Adobe PDF File), 94 KB - resprot_v13i1e56262_app1.pdf]

References

1. D'Amour D, Dubois C, Tchouaket, Clarke S, Blais R. The occurrence of adverse events potentially attributable to nursing care in medical units: cross sectional record review. Int J Nurs Stud 2014 Jun;51(6):882-891. [doi: 10.1016/j.ijnurstu.2013.10.017] [Medline: 24238893]
2. Grube J. National voluntary consensus standards for hospital care: an initial performance measure set. JHQ 2004;26(4):58-59. [doi: 10.1097/01445442-200407000-00013]
3. Needleman J, Buerhaus P, Mattke S, Stewart M, Zelevinsky K. Nurse-staffing levels and the quality of care in hospitals. N Engl J Med 2002 May 30;346(22):1715-1722. [doi: 10.1056/nejmsa012247]
4. Griffin FA, Resar RK. IHI Global Trigger Tool for Measuring Adverse Events (Second Edition). Cambridge, Massachusetts: Institute for Healthcare Improvement; 2009:1-42.

5. Hommel A, Magnéli M, Samuelsson B, Schildmeijer K, Sjöstrand D, Göransson KE, et al. Exploring the incidence and nature of nursing-sensitive orthopaedic adverse events: a multicenter cohort study using Global Trigger Tool. Int J Nurs Stud 2020 Feb;102:103473 [FREE Full text] [doi: 10.1016/j.ijnurstu.2019.103473] [Medline: 31810021]
6. Nilsson L, Lindblad M, Johansson N, Säfström L, Schildmeijer K, Ekstedt M, et al. Exploring nursing-sensitive events in home healthcare: a national multicenter cohort study using a trigger tool. Int J Nurs Stud 2023 Feb;138:104434. [doi: 10.1016/j.ijnurstu.2022.104434] [Medline: 36630873]
7. Murphy A, Griffiths P, Duffield C, Brady NM, Scott AP, Ball J, et al. Estimating the economic cost of nurse sensitive adverse events amongst patients in medical and surgical settings. J Adv Nurs 2021 Aug;77(8):3379-3388. [doi: 10.1111/jan.14860] [Medline: 33951225]
8. Bridges J, Griffiths P, Oliver E, Pickering RM. Hospital nurse staffing and staff-patient interactions: an observational study. BMJ Qual Saf 2019 Sep 27;28(9):706-713 [FREE Full text] [doi: 10.1136/bmjqs-2018-008948] [Medline: 30918050]
9. Griffiths P. The association between patient safety outcomes and nurse/healthcare assistant skill mix and staffing levels and factors that may influence staffing requirements. University of Southampton. 2014. URL: http://eprints.soton.ac.uk/367526/ [accessed 2024-03-19]
10. Needleman J, Buerhaus P, Pankratz VS, Leibson CL, Stevens SR, Harris M. Nurse staffing and inpatient hospital mortality. N Engl J Med 2011 Mar 17;364(11):1037-1045. [doi: 10.1056/nejmsa1001025]
11. Cho E, Chin DL, Kim S, Hong O. The relationships of nurse staffing level and work environment with patient adverse events. J Nurs Scholarsh 2016 Jan 07;48(1):74-82. [doi: 10.1111/jnu.12183] [Medline: 26642177]
12. Aiken LH, Sloane DM, Bruyneel L, Van den Heede K, Griffiths P, Busse R, et al. Nurse staffing and education and hospital mortality in nine European countries: a retrospective observational study. The Lancet 2014 May;383(9931):1824-1830. [doi: 10.1016/s0140-6736(13)62631-8]
13. Aiken LH, Clarke SP, Sloane DM, Lake ET, Cheney T. Effects of hospital care environment on patient mortality and nurse outcomes. J Nurs Adm 2009;39(7-8 Suppl):S45-S51. [doi: 10.1097/NNA.0b013e3181aeb4cf] [Medline: 19641438]
14. Dall'Ora C, Saville C, Rubbo B, Turner L, Jones J, Griffiths P. Nurse staffing levels and patient outcomes: a systematic review of longitudinal studies. Int J Nurs Stud 2022 Oct;134:104311 [FREE Full text] [doi: 10.1016/j.ijnurstu.2022.104311] [Medline: 35780608]
15. Needleman J, Shekelle PG. More ward nursing staff improves inpatient outcomes, but how much is enough? BMJ Qual Saf 2019 Aug 17;28(8):603-605. [doi: 10.1136/bmjqs-2018-009266] [Medline: 30996037]
16. Griffiths P, Ball J, Drennan J, Dall'Ora C, Jones J, Maruotti A, et al. Nurse staffing and patient outcomes: strengths and limitations of the evidence to inform policy and practice. A review and discussion paper based on evidence reviewed for the National Institute for Health and Care Excellence Safe Staffing guideline development. Int J Nurs Stud 2016 Nov;63:213-225. [doi: 10.1016/j.ijnurstu.2016.03.012] [Medline: 27130150]
17. Musy SN, Endrich O, Leichtle AB, Griffiths P, Nakas CT, Simon M. Longitudinal study of the variation in patient turnover and patient-to-nurse ratio: descriptive analysis of a swiss university hospital. J Med Internet Res 2020 Apr 02;22(4):e15554 [FREE Full text] [doi: 10.2196/15554] [Medline: 32238331]
18. Griffiths P, Maruotti A, Recio Saucedo A, Redfern OC, Ball JE, Briggs J, Missed Care Study Group. Nurse staffing, nursing assistants and hospital mortality: retrospective longitudinal cohort study. BMJ Qual Saf 2019 Aug 04;28(8):609-617 [FREE Full text] [doi: 10.1136/bmjqs-2018-008043] [Medline: 30514780]
19. CroWiS. URL: https://nursing.unibas.ch/de/forschung/forschungsprojekte/laufende-projekte/crowis/ [accessed 2024-03-19]
20. Blume K, Dietermann K, Kirchner-Heklau U, Winter V, Fleischer S, Kreidl LM, et al. Staffing levels and nursing-sensitive patient outcomes: Umbrella review and qualitative study. Health Serv Res 2021 Oct 01;56(5):885-907 [FREE Full text] [doi: 10.1111/1475-6773.13647] [Medline: 33723857]
21. Jones PS, Lee JW, Phillips LR, Zhang XE, Jaceldo KB. An adaptation of Brislin's translation model for cross-cultural research. Nurs Res 2001;50(5):300-304. [doi: 10.1097/00006199-200109000-00008] [Medline: 11570715]
22. Austin PC. Informing power and sample size calculations when using inverse probability of treatment weighting using the propensity score. Stat Med 2021 Nov 30;40(27):6150-6163 [FREE Full text] [doi: 10.1002/sim.9176] [Medline: 34510501]
23. Bachnick S, Ausserhofer D, Baernholdt M, Simon M, Match RN study group. Patient-centered care, nurse work environment and implicit rationing of nursing care in Swiss acute care hospitals: a cross-sectional multi-center study. Int J Nurs Stud 2018 May;81:98-106. [doi: 10.1016/j.ijnurstu.2017.11.007] [Medline: 29554590]
24. Robins JM, Hernán MA, Brumback B. Marginal structural models and causal inference in epidemiology. Epidemiology 2000 Sep;11(5):550-560. [doi: 10.1097/00001648-200009000-00011] [Medline: 10955408]
25. VanderWeele TJ, Jackson JW, Li S. Causal inference and longitudinal data: a case study of religion and mental health. Soc Psychiatry Psychiatr Epidemiol 2016 Nov 8;51(11):1457-1466. [doi: 10.1007/s00127-016-1281-9] [Medline: 27631394]
26. van der Wal WM, Geskus RB. ipw: an R package for inverse probability weighting. J Stat Soft 2011;43(13):1-23. [doi: 10.18637/jss.v043.i13]
27. Halekoh U, Højsgaard S, Yan J. The package for generalized estimating equations. J Stat Soft 2006;15(2):1-11. [doi: 10.18637/jss.v015.i02]
28. Butler M. Hospital nurse-staffing models and patient- and staff-related outcomes. Cochrane Database Syst Rev 2019;4:1-89. [doi: 10.1002/14651858.CD007019.pub3] [Medline: 31012954]

29. Googe MC. Nurse retention. Orthop Nurs 1982;1(5):45. [doi: 10.1097/00006416-198209000-00010]

Abbreviations

AND: associate nursing degree
CroWiS: Crowd Working in der Schweiz
DES: discrete-event simulation
ICC: intraclass correlation coefficient
NSE: nursing-sensitive event
O/E: observed-over-expected
RN: registered nurse
RRR: retrospective record review
TAILR: Nursing-Sensitive Events and Their Association With Individual Nurse Staffing Levels

Edited by A Mavragani; submitted 19.01.24; this is a non–peer-reviewed article;accepted 06.03.24; published 22.04.24.

Please cite as:
Bachnick S, Unbeck M, Ahmadi Shad M, Falta K, Grossmann N, Holle D, Bartakova J, Musy SN, Hellberg S, Dillner P, Atoof F, Khorasanizadeh M, Kelly-Pettersson P, Simon M
TAILR (Nursing-Sensitive Events and Their Association With Individual Nurse Staffing Levels) Project: Protocol for an International Longitudinal Multicenter Study
JMIR Res Protoc 2024;13:e56262
URL: https://www.researchprotocols.org/2024/1/e56262
doi:10.2196/56262
PMID:38648083

Protocol

Associations Between Stress, Health Behaviors, and Quality of Life in Young Couples During the Transition to Survivorship: Protocol for a Measurement Burst Study

Dalnim Cho[1], PhD; Michael Roth[2], MD; Susan K Peterson[3], MPH, PhD; Kristofer Jennings[4], PhD; Seokhun Kim[5], PhD; Shiao-Pei Weathers[6], MD; Sairah Ahmed[7], MD; J Andrew Livingston[8], MD; Carlos Barcenas[9], MD; Y Nancy You[10], MD; Kathrin Milbury[3], PhD

[1]Department of Health Disparities Research, The University of Texas MD Anderson Cancer Center, Houston, TX, United States
[2]Department of Pediatrics, The University of Texas MD Anderson Cancer Center, Houston, TX, United States
[3]Department of Behavioral Science, The University of Texas MD Anderson Cancer Center, Houston, TX, United States
[4]Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX, United States
[5]The Center for Clinical Research and Evidence-Based Medicine, The University of Texas McGovern Medical School, Houston, TX, United States
[6]Department of Neuro-Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, United States
[7]Department of Lymphoma–Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX, United States
[8]Department of Sarcoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, United States
[9]Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, United States
[10]Department of Colon & Rectal Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX, United States

Corresponding Author:
Dalnim Cho, PhD
Department of Health Disparities Research
The University of Texas MD Anderson Cancer Center
1515 Holcombe Blvd
Houston, TX, 77030
United States
Phone: 1 713 745 8476
Email: dcho1@mdanderson.org

Abstract

Background: Cancer is a life-threatening, stressful event, particularly for young adults due to delays and disruptions in their developmental transitions. Cancer treatment can also cause adverse long-term effects, chronic conditions, psychological issues, and decreased quality of life (QoL) among young adults. Despite numerous health benefits of health behaviors (eg, physical activity, healthy eating, no smoking, no alcohol use, and quality sleep), young adult cancer survivors report poor health behavior profiles. Determining the associations of stress (either cancer-specific or day-to-day stress), health behaviors, and QoL as young adult survivors transition to survivorship is key to understanding and enhancing these survivors' health. It is also crucial to note that the effects of stress on health behaviors and QoL may manifest on a shorter time scale (eg, daily within-person level). Moreover, given that stress spills over into romantic relationships, it is important to identify the role of spouses or partners (hereafter partners) in these survivors' health behaviors and QoL.

Objective: This study aims to investigate associations between stress, health behaviors, and QoL at both within- and between-person levels during the transition to survivorship in young adult cancer survivors and their partners, to identify the extent to which young adult survivors' and their partners' stress facilitates or hinders their own and each other's health behaviors and QoL.

Methods: We aim to enroll 150 young adults (aged 25-39 years at the time of cancer diagnosis) who have recently completed cancer treatment, along with their partners. We will conduct a prospective longitudinal study using a measurement burst design. Participants (ie, survivors and their partners) will complete a daily web-based survey for 7 consecutive days (a "burst") 9 times over 2 years, with the bursts spaced 3 months apart. Participants will self-report their stress, health behaviors, and QoL. Additionally, participants will be asked to wear an accelerometer to assess their physical activity and sleep during the burst period. Finally, dietary intake (24-hour diet recalls) will be assessed during each burst via telephone by research staff.

Results: Participant enrollment began in January 2022. Recruitment and data collection are expected to conclude by December 2024 and December 2026, respectively.

Conclusions: To the best of our knowledge, this will be the first study that determines the interdependence of health behaviors and QoL of young adult cancer survivors and their partners at both within- and between-person levels. This study is unique in its focus on the transition to cancer survivorship and its use of a measurement burst design. Results will guide the creation of a developmentally appropriate dyadic psychosocial or behavioral intervention that improves both young adult survivors' and their partners' health behaviors and QoL and potentially their physical health.

International Registered Report Identifier (IRRID): DERR1-10.2196/53307

(JMIR Res Protoc 2024;13:e53307) doi:10.2196/53307

KEYWORDS

young adult survivors; caregivers; dyadic; couple-based; stress; health behaviors; quality of life; transition to survivorship; measurement-burst

Introduction

Overview

Each year, more than 80,000 adolescents and young adults (aged 15-39 years) are newly diagnosed with cancer in the United States [1], and cancer is the leading cause of disease-related death among adolescents and young adults [2]. Mortality rates in adolescent and young adult patients with cancer have decreased over the past decade, and the 5-year relative survival rate for adolescent and young adult patients with cancer is 85.5% [3]. However, this high relative survival rate may mask the true burden of cancer among adolescent and young adult survivors. Although cancer and its treatment can be a traumatic event for any individual, it may be particularly so for adolescents and young adults because cancer can cause delays and disruptions in their successful developmental transitions across various domains of life: biological or physical (eg, cancer can cause hair loss, infertility, and weight change), psychological (eg, lack of control over life and disruption in progress toward life goals), educational or occupational (eg, disruption in education and unemployment), social or relationship (eg, problems in relationship with significant other and interference with plans for having children), and financial (eg, large debt and bankruptcy) [4-13]. Cancer and its treatment can also cause adverse long-term effects among adolescents and young adults (eg, premature or accelerated aging, cardiotoxicity, and second malignant neoplasms) [14,15] and heightened risk of chronic conditions (eg, cardiovascular disease, hypertension, diabetes, and asthma) [14,16,17], psychological issues (eg, depressive symptoms and fear of cancer recurrence), and lower quality of life (QoL) among adolescents and young adults compared with their peers without cancer [14,18].

Interest in and calls for research on adolescent and young adult cancer survivors have dramatically increased since 2006 when the Adolescent and Young Adult Oncology Progress Review Group published a report about the state of the science regarding cancer among adolescents and young adults [19]. However, adolescents and young adults affected by cancer still have vast unmet health care needs, including psychosocial care needs [7,20-23], and remain an understudied subgroup of patients with cancer. In addition, adolescent and young adult cancer survivors are often considered a single entity, and much of the existing data comes from studies that grouped adolescents and young adults together, although individuals in this age range may face different developmental tasks. Thus, the proposed study focuses on young adult survivors who were diagnosed with cancer at 25 to 39 years old [24], whose primary source of support is more likely to be romantic partners, whereas pediatric and adolescent survivors are more likely to depend on their parents. Due to a lack of existing studies specific to young adult survivors, the literature review below is based on studies among adolescent and young adult survivors.

Stress and Health Behaviors Among Young Adult Survivors

Overview

Strong evidence exists that engaging in healthy behaviors (eg, physical activity, low sedentary behavior, healthy eating, no smoking, no alcohol use, and quality sleep) is critical for cancer survivors' health, as it reduces the likelihood of cardiotoxicity, development of secondary cancers, cancer recurrence, and cancer-specific and all-cause mortality [25-28] and improves QoL [26,29]. However, young adult survivors report poor health behavior profiles. Specifically, young adult survivors report higher rates of unhealthy eating than their peers without cancer [14,16,30], and 26% of young adult survivors versus 18% of their peers without cancer report current smoking [14,16,30]. In addition, 50% to 90% of young adult survivors report at least some alcohol use [30], and 31% of young adult survivors report no leisure-time physical activity [14]. Further, approximately 40% of young adult survivors report experiencing sleep issues (eg, trouble falling or staying asleep in the previous week), and those who report difficulties with sleep also indicate higher levels of psychological distress [31].

While stress can substantially influence negative health outcomes [32] and poor health behaviors [33-35], it remains an understudied factor for young adult survivors' health behaviors. At present, almost nothing is known regarding the association between stress and health behaviors among young adult survivors. To better understand the association between stress and health behaviors in this survivor population, there are three crucial factors to be considered: (1) the transition from active treatment to survivorship; (2) interdependence between survivors and family caregivers, especially partners; and (3) within-person variabilities in stress and health behaviors.

Transition From Active Treatment to Survivorship

Transitioning from active treatment to posttreatment care is critical to cancer survivors' long-term health. However, the transition is challenging because survivors are often lost to systematic follow-up, and opportunities to effectively intervene are missed [36]. Many people finish their primary cancer treatment being unaware of their heightened health risks and are ill-prepared to manage their future health care needs [36]. In particular, young adult survivors struggle with the transition; with the abrupt cessation of intensive support (feelings of abandonment); and with challenges regarding returning to work, study, and social or recreational activities, which is complicated by ongoing disease or treatment impacts and a collective dearth of knowledge and resources on how to cope with these challenges during this time [37]. Thus, beyond cancer or treatment-specific stress (eg, symptom burden and concerns about cancer recurrence), stress regarding postcancer life adjustment needs to be addressed to better understand young adults' survivorship outcomes.

Interdependence Between Survivors and Their Partners

Cancer is often considered a "we-disease" [38]; survivors and their families tend to react to cancer as an interdependent system in which they influence each other's health. As an example of this interdependence, stress experienced by a cancer survivor or by their spouse or partner (hereafter partner) can affect the QoL of the other person in the relationship [38,39]. Beyond cancer care demands and stressors shared with the survivor (eg, concerns about cancer recurrence or progression), partners of survivors may encounter various stressors in their everyday lives (eg, work deadlines and social obligations) that can spill over into the relationship. Thus, neglect of partners' stress and coping and failure to include partners in young adult survivorship interventions may provide only a partial understanding of QoL and the challenges of the transition to survivorship among young adult survivors who have partners. However, to date, to the best of our knowledge, none of the existing interventions developed for and tested among young adult survivors to enhance their psychosocial outcomes (eg, QoL and psychological symptoms) have targeted survivor-partner dyads [40].

Within-Person Variabilities in Stress and Health Behaviors

Although previous studies have significantly advanced our understanding of cancer survivorship issues among young adults, most of these studies were cross-sectional and therefore could not capture potential dynamic changes in stress, health behaviors, and QoL during the transition to survivorship. While a few prospective longitudinal studies in young adult survivors exist [41-44], assessment intervals tend to range between 6 and 12 months and assume that stress, health behaviors, and QoL are fairly stable in the short term. However, evidence indicates that an individual's stress and health behaviors may vary across days of a week [45-53], which may further explain reported short-term (eg, daily) within-person variations in QoL [54]. Moreover, within-person variations in stress, health behaviors, and QoL may exist in survivor-partner dyads [45,46]. Thus, global, aggregated measures of stress, health behaviors, and QoL at the between-person level or over longer time scales at the within-person level (eg, "How much were you stressed out in the *last week*?"; "How much did you drink alcohol in the *past month*?"; and "How was your overall QoL in the *past year*?") may fail to reveal subtle and dynamic changes in stress, health behaviors, and QoL that can occur over shorter time scales (eg, daily intervals) [55].

A measurement burst design can assess both the between- and within-person processes in stress, health behaviors, and QoL. The design incorporates bursts of intensive repeated assessment within a relatively short period of time (eg, daily) that are repeated longitudinally, over more widely spaced intervals (eg, every 3 months), which will enable us to investigate the interaction of within-person processes that transpire over different time intervals [56,57]. However, to date, no published studies have investigated the extent to which young adult survivors and their partners facilitate or hinder each other's short- and long-term adjustment during the transition to survivorship using the measurement burst design.

This Study

Overview

The overarching purpose of this study is to investigate associations between stress, health behaviors, and QoL at both within-person and between-person levels over the transition to survivorship in young adult survivors and their partners to identify the extent to which young adult survivors' and their partners' stress facilitates or hinders their own and each other's health behaviors and QoL. To examine both within-person and between-person changes, we will implement a measurement burst design [56,57], in which participants will be asked to complete a daily survey for 7 consecutive days (a "burst") 9 times over 2 years, with the bursts spaced 3 months apart. Thus, there will be 3 levels: day, burst (3-month interval), and person. We have the following specific aims.

Aim 1

Aim 1 is to determine the within-person effects of stress on health behaviors at both day and burst levels. We hypothesize that on days or during bursts when stress is high, individuals are more likely to report physical inactivity, unhealthy eating, poor sleep quality, smoking (current smokers only), or alcohol use (current drinkers only). We also hypothesize that on days or during bursts when partners' stress is high, survivors are more likely to report these unhealthy behaviors, and vice versa.

Aim 2

Aim 2 is to determine the within-person, day-level, and burst-level effects of stress on QoL and the effects of health behaviors on QoL. We hypothesize that individual's QoL will be high on days or during bursts when their stress is low, when they perform physical activity, and when their sleep quality is good. We also hypothesize that on days or during bursts when partners' stress is low, when partners perform physical activity, and when partners' sleep quality is good, survivors are more likely to report high QoL, and vice versa.

Exploratory Aims

The two exploratory aims are as follows: (1) identifying 2-way cross-level interaction effects between day- or burst-level and person-level stress on health behaviors and QoL—in other words, we will examine whether the extent to which individuals' day- or burst-level stress influences their health behaviors and whether QoL is stable or varies depending on their average person-level stress; and (2) identifying 2-way cross-level interaction effects between day- or burst-level stress and person-level stable factors (eg, sex, race, age at diagnosis, and type of cancer) on health behaviors and QoL—that is, we will examine whether the extent to which individuals' day- or burst-level stress influences their health behaviors and whether QoL is stable or varies depending on their person-level factors.

Methods

Participants and Procedures

We aim to enroll 150 young adult survivors and their partners (ie, 300 individuals). Cancer survivors will be eligible if they (1) were diagnosed with cancer for the first time (ie, no previous history of cancer); (2) were a young adult (aged 25-39 years) at the time of diagnosis; (3) are within 3 months after the completion of treatment (eg, surgery, chemotherapy, and radiation therapy) with curative intent; (4) have no further planned cancer treatment (surgery, chemotherapy, radiation therapy, and immunotherapy) except for hormone therapy; and (5) have a valid phone number and email address. Survivors will be excluded if they (1) do not have significant others and (2) are unable to read, write, or speak English. Partners will be eligible if they (1) are aged ≥18 years; (2) are spouses or romantic partners (either married or not) cohabitating with the young adult survivor; (3) self-identify as the current primary caregivers of the young adult survivors; (4) are able to read, write, and speak English; and (5) have a valid phone number and email address.

During the study period, partners may change (because of separation, divorce, etc). If so, the current (ie, newly identified) partner (identified by the survivor, if applicable) will be contacted after permission is obtained from the survivor, and if interested and eligible, will be enrolled upon providing informed consent. We will record these changes in the dyads. If a member of a dyad drops out of the study, the other member will be asked to complete the study to investigate survivors' or partners' changes in stress, health behaviors, and QoL. If a survivor's cancer recurs during the 2-year study period, the dyad (ie, both the survivor and their partner) will be withdrawn from the study.

Cancer survivors will be recruited at The University of Texas MD Anderson Cancer Center. Potentially eligible survivors will be initially identified by research staff via electronic health records and will be contacted via telephone. Only those who are interested in the study will be further screened. If the survivor is eligible and interested, we will obtain the contact information of their partner for the partner's eligibility screening. If the partner is eligible and interested, the survivor-partner dyad will provide consent remotely via teleconferencing (eg, Zoom). We will also contact young adult cancer support groups and organizations through their websites and social media platforms to recruit non–MD Anderson cancer survivors. Interested individuals can submit a study interest form, and our research staff will contact them for phone screening.

All study procedures will be conducted remotely. After signed electronic consent forms are obtained, both survivors and partners will be asked to individually complete a baseline assessment in the form of a survey questionnaire via Research Electronic Data Capture (REDCap; Vanderbilt University), a secure, web-based app with controlled access designed to support data capture for research studies. This retrospective survey includes demographics, health status, stress, health behaviors, and QoL and will take approximately 1 hour to complete.

The daily survey will also be designed with REDCap, and the first daily survey period (ie, burst) will start within 10 days after completing the baseline survey. All participants will receive a survey link at 6 PM once per day for 7 consecutive days via their email; the brief 5-minute survey can be completed on the participant's electronic device (computer and smartphone). Survivors and partners will receive separate links and be asked to complete their daily reports in the evenings (before going to sleep) regarding stress, health behaviors, and QoL. Survivors and partners will be asked to complete assessments separately. Each survey link will be valid for only 12 hours. Thus, participants will not be able to submit data for a given day early, but they will be able to provide it the next early morning (until 6 AM). Regardless of when data are provided (that evening or the next morning), the questions will be specific to the person's experiences on the day the survey link is received.

During the burst, both survivors and partners will be asked to wear a blinded accelerometer (ActiGraph GT9X Link) on their nondominant wrist for 7 days and to engage in their daily routines as normal. The accelerometer with a prepaid envelope will be sent to the participants' residential address. After wearing the accelerometer for 7 days, participants will return the device using the envelope. Moreover, participants will be asked to choose 2 days (a day to recall a weekday's diet and another day to recall a weekend day's diet) over the 7 days when they are available for a dietary assessment (the Automated Self-Administered 24-hour Dietary Assessment Tool [58]). Participants will be told that research staff will call them on the selected days or times for the assessment.

Before each 7-day daily assessment period, participants will be asked to complete a retrospective survey similar to the baseline survey. We will mail out the accelerometer (with the prepaid envelope) in advance so that participants can wear the accelerometer and begin the 7-day daily survey without delays once they complete the retrospective survey.

Measures

Retrospective Survey Measures

Demographic and Medical Factors and Other Descriptive Factors and Covariates

Both survivors and partners will be asked about demographic (eg, sex, age, level of education and income, and marital or

relationship status) and health and health care information (eg, existing comorbidities, health insurance, and height and weight to calculate BMI). Tumor characteristics will be obtained from self-report and medical records (for MD Anderson patients). Financial toxicity will be assessed with the Comprehensive Score for Financial Toxicity instrument [59], which consists of 12 items scored on a 5-point Likert scale and reveals high internal consistency and test-retest reliability (Cronbach α=.90) in patients with cancer. Financial toxicity will be assessed for both survivors and partners. For partners, the caregiving burden will be assessed with the short form of the Zarit Burden Inventory, a 12-item measure [60], which is validated among cancer caregivers [61]. Each question is scored on a 5-point Likert scale from 0 (never) to 4 (almost always). High scores represent a higher burden.

Stress

All participants will be asked to identify the most stressful event in the past 30 days (open-ended question). Then, the 4-item Perceived Stress Scale [62] will be administered; participants will rate each item from 0 (never) to 4 (very often).

Health Behaviors

For both survivors and partners, self-reported physical activity will be assessed with the Godin Leisure-Time Questionnaire [63], a brief measure assessing aerobic exercise, which is widely used in diverse populations including those with cancer [64]. In addition, we will assess strength exercise (eg, weight lifting and circuit training) with 1 item from the Health Information National Trends Survey [65]. Smoking will be assessed with items adapted from the Patient-Reported Outcomes Measurement Information System (PROMIS) Smoking Initiative [66] and the Health Information National Trends Survey [65], which include smoking behaviors (eg, "Have you smoked at least 100 cigarettes in your entire life?" [yes/no]; if yes, "How old were you when you first started smoking?"; and "Have you ever used an e-cigarette, even one or two times?" [yes/no]). Alcohol use will be assessed with 2 items from the Alcohol Use Disorders Identification Test–Consumption [67] asking about alcohol use frequency and quantity. Eating behaviors will be assessed with the validated, National Cancer Institute Diet History Questionnaire-III, which consists of 135 food and beverage line items and 26 dietary supplement questions [68]. Sleep will be assessed with the Pittsburgh Sleep Quality Index [69], an 18-item self-rated questionnaire that assesses the quality of sleep and sleep disturbances.

Relationship

Relationship will be assessed with 1 item measuring transformation of motivation [70] (indicating motivation for disease management is transformed from self-centered [eg, cancer is my/your problem] to relationship-centered [eg, cancer is our problem]) and with the 5-item Emotional Intimacy Scale, which showed good internal consistency (0.88) and test-retest reliability (0.85) [71].

QoL Measurement

For young adult survivors, we will use the 30-item satisfaction scale from the Late Adolescence and Young Adulthood Survivorship-Related Quality of Life (LAYA-SRQL) [72]. The LAYA-SRQL measure comprises 10 domains, including existential/spirituality, coping, relationship, dependence, vitality, health care, education/career, fertility, intimacy/sexuality, and cognition/memory. Participants can endorse "not applicable" if any item is not relevant to them. To reduce participants' burden, we will use 11 items (ie, approximately 1 item per domain). In addition, both survivors' and partners' QoL will be assessed with the 10-item PROMIS–global health (measuring physical function, pain, fatigue, emotional distress, and social health) [73] so that we can compare the level of QoL between survivors and partners.

Daily Survey Measures

Both survivors and partners will report the following.

Stress

Stress will be assessed by adapting a measure of daily recording of coping with everyday stressful events [74]. Specifically, participants will be asked to report the most stressful event or issue of the day in their own words. Then, the level of distress will be assessed with 1 item asking, "On a scale from 1 to 100 (where 100 is the maximum distress that you could imagine and 1 is a minor annoyance), how stressful would you rate this problem or situation?"

Health Behaviors

The objective level of physical activity will be assessed with the accelerometer, which has strong reliability and validity [75]. Participants will wear a blinded accelerometer on their nondominant wrist for 7 days to assess typical physical activity. The Godin Leisure-Time Questionnaire [63] and the strength exercise item [65] will be asked to assess self-reported physical activity. Dietary intake will be assessed via telephone (from research staff) on 2 preselected days with the Automated Self-Administered 24-hour Dietary Assessment Tool [58], which produces a healthy eating index. The accelerometer will also objectively assess sleep (eg, total sleep time, sleep percentage, and wake after sleep onset). Thus, subjective sleep quality (over the last night) will be assessed with 1 item ("How would you rate your last night's sleep quality overall?") adapted from the Pittsburgh Sleep Quality Index [69]. Daily smoking (yes or no) will be assessed only among current smokers. Daily alcohol use (yes or no) and number of drinks will be assessed only among current drinkers. All of these self-reported measures will be assessed among both survivors and partners, adapting the aforementioned measures with the stem "TODAY, ..."

Relationship

The aforementioned 1 item measuring transformation of motivation [70] and 3 items from the Emotional Intimacy Scale [71] will be assessed with the reference "TODAY."

QoL Measurement

We will assess survivors' QoL with the same 11 items from the LAYA-SRQL. Survivors will be asked to answer each item with the stem "Please indicate the extent to which you are satisfied with this aspect of your life TODAY." Participants can endorse "not applicable" if any item is not relevant to them. For both survivors and partners, the PROMIS-global health

measure (4 items) [76] will also be assessed with the reference "TODAY."

Analytic Plans

We will first conduct extensive descriptive analyses of the retrospective and daily surveys over the 2-year period. Descriptive statistics, for example, means, SDs, and ranges for continuous measures, as well as frequencies and proportions for categorical variables, for the time-varying variables, will be calculated for each burst and for the 2-year period as a whole. Those of the baseline, person-level stable variables (eg, sex) will be calculated once. Preliminary bivariate analyses of the time-varying variables (eg, stress, health behaviors, and QoL) will be performed using within- and between-person correlations between them for each burst and for the 2-year period as a whole. Both correlations between an individual's own variables (eg, individuals' own stress and their health behaviors) and correlations between partners' and survivors' variables (eg, partners' stress and survivors' health behaviors) will be calculated.

For the aims of this study, we will design and fit mixed-effects multilevel models that adapt to the correlation structures of the underlying data process. For continuous (or near-continuous) outcomes (physical activity, eating behaviors, sleep, and QoL), linear mixed-effects models will be considered first, but depending on the distributional properties of the outcome (eg, skewed and censored), generalized linear mixed-effects models with proper distributions such as gamma or censored normal distribution and link functions such as log link will be used accordingly. For categorical outcomes (smoking and alcohol use), a logistic link function and binomial distribution will be used to build mixed-effects logistic regression models. All the models will be multilevel, incorporating burst-level trends, general day-to-day trends (centered), and deviations from the overall mean and day-to-day trends specific to burst (level 2) and to person (level 3) using random effects. Predictors will include survivors' and partners' day-to-day variables (person-burst-centered) to estimate within-person effects at level 1 and their burst-level variables (person-centered) to estimate within-person effects at level 2 (eg, the effect of day- or burst-level stress on health behaviors in Aim 1 and the effect of day- or burst-level health behaviors on QoL in Aim 2), their person-level (averaged) variables to estimate between-person effects at level 3, and a role variable to differentiate survivors' and caregivers' effects in each of those individuals' own effects and partners' effects using interaction terms. For the exploratory aims, 2-way interaction terms between the person-level variables (eg, person-level stress) and the day- or burst-level variables (eg, daily fluctuations of stress), as well as between-level stable demographic and clinical factors and the day- or bust-level variables, will be added to assess moderations for the individuals' day- or burst-level effects. Three-way interaction terms with the role variable added will be used to differentially evaluate each of those 2-way interactions for survivors and partners.

Within this modeling framework, the components of the aims can be estimated and evaluated. For Aim 1, various components of stress will be related to concurrent health behaviors, both within and between individuals and across survivors and partners. The effect of interest is the association between stress components and individual health behaviors (at the burst level and the day level within bursts). Smoking and alcohol use will each be assessed as an indicator of behavior (with a logistic link) and a magnitude of behavior (excluding nonsmokers and nondrinkers, respectively). Linear relationships will be tested, and if model diagnostics indicate a nonlinear fit, a smooth nonlinear association will be assessed. A similar construction will be considered for Aim 2, relating components of stress to QoL and components of behavior to QoL at the burst level and the day level within bursts. Similarly, for the exploratory aim, the effects of interest will be interactions of day- or burst-level stress and aggregate-scale person-level stress or person-level stable factors. For each model, there is a possibility of nonignorable dropout or mortality. To address issues of missingness, we will assume that loss to follow-up is missing at random. Within this context and under a small number of assumptions, the missingness due to death or dropout becomes missing at random and ignorable given the context of the model. The mixed-effects structure, in particular, is robust to many patterns of random missingness. With respect to mortality, we will implement the principal stratification approach [77], wherein participants are weighted by their propensity to survive the study period.

Sample Size and Power Calculation

Assuming a 20% rate of dropout, we expect to have at least 120 dyads complete the study. Most of our assessments will be measured by correlation. With 120 dyads, we expect to have at least 80% power to detect relationships with a partial R^2 of at least 0.26, which is a medium-large effect. A similar construction shows that the 80% detectable level of the partial F is 0.06, which is a small-to-medium effect. The partial F statistic is a scaled version of the partial F statistic in a nested analysis of variance comparison; the scaling factor is the ratio of the numerator's and the denominator's degrees of freedom [78]. As the modeling structure and relative effect sizes (and confidence bounds) will be of primary interest, we will not incorporate a multiple testing structure until the correlation between test statistics can be carefully assessed (which allows for less conservative testing criteria). The R library *pwr* was used in the calculation of these effect sizes.

Ethical Considerations

This study was approved by MD Anderson's institutional review board (Protocol 2021-0165). Written informed consent will be obtained from all participants. Study participant research data, which will be obtained for purposes of statistical analysis and scientific reporting, will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. Participants will receive gift cards as compensation for their time and participation. Each participant will receive up to a US $35 gift card to complete a 7-day daily survey and wear an accelerometer (ie, US $5 gift card per day). Of the 7 days, participants must complete surveys and wear the accelerometer for at least 3 days to receive the compensation. Participants will also receive an additional US $15 gift card for

completing both nutritional assessments and receive a US $40 gift card for each retrospective survey that they complete.

Results

We are currently recruiting participants, having initiated recruitment in January 2022. Recruitment and data collection are expected to conclude by December 2024 and December 2026, respectively. We expect to submit the main study results for publication in 2027.

Discussion

The aim of the proposed study is to investigate associations between stress, health behaviors, and QoL at both within- and between-person levels over the transition to survivorship in young adult survivors and their partners. To date, much is unknown regarding associations between stress, health behaviors, and QoL among young adult survivors. In particular, to the best of our knowledge, there is currently no existing study that investigates these associations among both young adult survivors and their partners. This will also be the first study that determines the interdependence of health behaviors and QoL between young adult survivors and partners, exploring how their stress levels may either facilitate or hinder their own and each other's health behaviors and QoL over the transition to survivorship.

This study has a few limitations. First, recruiting survivor-partner dyads, particularly survivors within a restricted age range (25-39 years old), can be a challenge. We will thoroughly review the recruitment progress, study refusal reasons, and work on addressing enrollment barriers. Second, participants' compliance may be a concern in this intensive longitudinal study. Over the course of the study, we will carefully monitor survey responses and consider reducing the number of retrospective or daily assessments if noncompliance is salient. Finally, this study addresses stress, health behaviors, and QoL of young adult survivors who have partners. Thus, the results of this study may not be generalized to all young adult survivors.

Despite these limitations, this study is novel and promises to generate new knowledge. Specifically, using a sophisticated research design—measurement burst—this study will allow assessment of both within- and between-person level changes in those variables and their relationships [56,57]. If the results of this study could reveal whether and on what time scales higher stress levels or certain types of stressors are associated with unhealthy behaviors and poor QoL, interventions such as just-in-time adaptive intervention [79] might be considered based on the findings. The focus on the transition to survivorship is another strength. By following up with the survivors over the course of 2 years after the completion of their cancer treatment, we can identify the time points when stress, health behaviors, and QoL begin to change (increase or decrease) during the transition. This information will help us target the right time to intervene for this understudied survivor group. Furthermore, the proposed study seeks to shift current individual-focused research in young adult survivors to relationship-focused exploration as it focuses on both survivors and their partners. Thus, the results of this study may guide the creation of a developmentally appropriate couple-based psychosocial or behavioral intervention that improves both young adult survivors' and their partners' QoL.

Acknowledgments

The authors thank Project Koru and Stupid Cancer for their support in the participant recruitment. The authors also thank Sarah Bronson, scientific editor, Research Medical Library, for editing this article. This work was supported by the Department of Defense (W81XWH-21-1-0184).

Data Availability

The data sets generated during this study are not publicly available because they include sensitive information but are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

References

1. Cancer facts and figures 2020. American Cancer Society. Atlanta; 2020. URL: https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2020.html [accessed 2024-01-18]
2. Heron M. Deaths: leading causes for 2017. Natl Vital Stat Rep 2019;68(6):1-75 [FREE Full text]
3. Cancer stat facts: cancer among Adolescents and Young Adults (AYAs) (ages 15-39). Surveillance Epidemiology and End Results Program. 2022. URL: https://seer.cancer.gov/statfacts/html/aya.html [accessed 2023-02-01]
4. Bellizzi KM, Smith A, Schmidt S, Keegan THM, Zebrack B, Lynch CF, et al. Positive and negative psychosocial impact of being diagnosed with cancer as an adolescent or young adult. Cancer 2012;118(20):5155-5162 [FREE Full text] [doi: 10.1002/cncr.27512] [Medline: 22415815]

5. Zebrack B, Kent EE, Keegan THM, Kato I, Smith AW, AYA HOPE Study Collaborative Group. "Cancer sucks," and other ponderings by adolescent and young adult cancer survivors. J Psychosoc Oncol 2014;32(1):1-15 [FREE Full text] [doi: 10.1080/07347332.2013.855959] [Medline: 24428248]
6. Parsons HM, Harlan LC, Lynch CF, Hamilton AS, Wu XC, Kato I, et al. Impact of cancer on work and education among adolescent and young adult cancer survivors. J Clin Oncol 2012;30(19):2393-2400 [FREE Full text] [doi: 10.1200/JCO.2011.39.6333] [Medline: 22614977]
7. Sawyer SM, McNeil R, McCarthy M, Orme L, Thompson K, Drew S, et al. Unmet need for healthcare services in adolescents and young adults with cancer and their parent carers. Support Care Cancer 2017;25(7):2229-2239. [doi: 10.1007/s00520-017-3630-y] [Medline: 28261754]
8. Kirchhoff AC, Yi J, Wright J, Warner EL, Smith KR. Marriage and divorce among young adult cancer survivors. J Cancer Surviv 2012;6(4):441-450 [FREE Full text] [doi: 10.1007/s11764-012-0238-6] [Medline: 22956304]
9. D'Agostino NM, Penney A, Zebrack B. Providing developmentally appropriate psychosocial care to adolescent and young adult cancer survivors. Cancer 2011;117(10 Suppl):2329-2334 [FREE Full text] [doi: 10.1002/cncr.26043] [Medline: 21523754]
10. Stone DS, Ganz PA, Pavlish C, Robbins WA. Young adult cancer survivors and work: a systematic review. J Cancer Surviv 2017;11(6):765-781 [FREE Full text] [doi: 10.1007/s11764-017-0614-3] [Medline: 28478587]
11. Dobinson KA, Hoyt MA, Seidler ZE, Beaumont AL, Hullmann SE, Lawsin CR. A grounded theory investigation into the psychosexual unmet needs of adolescent and young adult cancer survivors. J Adolesc Young Adult Oncol 2016;5(2):135-145. [doi: 10.1089/jayao.2015.0022] [Medline: 26812456]
12. Lu AD, Zheng Z, Han X, Qi R, Zhao J, Yabroff KR, et al. Medical financial hardship in survivors of adolescent and young adult cancer in the United States. J Natl Cancer Inst 2021;113(8):997-1004 [FREE Full text] [doi: 10.1093/jnci/djab013] [Medline: 33839786]
13. Ghazal LV, Gormley M, Merriman JD, Santacroce SJ. Financial toxicity in adolescents and young adults with cancer: a concept analysis. Cancer Nurs 2021;44(6):E636-E651. [doi: 10.1097/NCC.0000000000000972] [Medline: 34694089]
14. Tai E, Buchanan N, Townsend J, Fairley T, Moore A, Richardson LC. Health status of adolescent and young adult cancer survivors. Cancer 2012;118(19):4884-4891 [FREE Full text] [doi: 10.1002/cncr.27445] [Medline: 22688896]
15. Chao C, Bhatia S, Xu L, Cannavale KL, Wong FL, Huang PYS, et al. Incidence, risk factors, and mortality associated with second malignant neoplasms among survivors of adolescent and young adult cancer. JAMA Netw Open 2019;2(6):e195536 [FREE Full text] [doi: 10.1001/jamanetworkopen.2019.5536] [Medline: 31173129]
16. Warner EL, Nam GE, Zhang Y, McFadden M, Wright J, Spraker-Perlman H, et al. Health behaviors, quality of life, and psychosocial health among survivors of adolescent and young adult cancers. J Cancer Surviv 2016;10(2):280-290 [FREE Full text] [doi: 10.1007/s11764-015-0474-7] [Medline: 26248766]
17. Chao C, Xu L, Bhatia S, Cooper R, Brar S, Wong FL, et al. Cardiovascular disease risk profiles in survivors of adolescent and young adult (AYA) cancer: the Kaiser Permanente AYA cancer survivors study. J Clin Oncol 2016;34(14):1626-1633 [FREE Full text] [doi: 10.1200/JCO.2015.65.5845] [Medline: 26951318]
18. Smith AW, Bellizzi KM, Keegan THM, Zebrack B, Chen VW, Neale AV, et al. Health-related quality of life of adolescent and young adult patients with cancer in the United States: the adolescent and young adult health outcomes and patient experience study. JCO 2013;31(17):2136-2145 [FREE Full text] [doi: 10.1200/jco.2012.47.3173] [Medline: 23650427]
19. Closing the gap: research and care imperatives for adolescents and young adults with cancer: report of the adolescent and young adult oncology progress review group (NIH Publication No. 06-6067). U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute, and the LIVESTRONG Young Adult Alliance. Bethesda, MD; 2006. URL: https://www.cancer.gov/types/aya/research/ayao-august-2006.pdf [accessed 2024-01-18]
20. McCarthy MC, McNeil R, Drew S, Orme L, Sawyer SM. Information needs of adolescent and young adult cancer patients and their parent-carers. Support Care Cancer 2018;26(5):1655-1664. [doi: 10.1007/s00520-017-3984-1] [Medline: 29222598]
21. Shay LA, Parsons HM, Vernon SW. Survivorship care planning and unmet information and service needs among adolescent and young adult cancer survivors. J Adolesc Young Adult Oncol 2017;6(2):327-332 [FREE Full text] [doi: 10.1089/jayao.2016.0053] [Medline: 28103126]
22. Bibby H, White V, Thompson K, Anazodo A. What are the unmet needs and care experiences of adolescents and young adults with cancer? a systematic review. J Adolesc Young Adult Oncol 2017;6(1):6-30. [doi: 10.1089/jayao.2016.0012] [Medline: 27454408]
23. Sender A, Friedrich M, Schmidt R, Geue K. Cancer-specific distress, supportive care needs and satisfaction with psychosocial care in young adult cancer survivors. Eur J Oncol Nurs 2020;44:101708. [doi: 10.1016/j.ejon.2019.101708] [Medline: 31874354]
24. Adolescents and young adults with cancer. National Cancer Institute. 2020. URL: https://www.cancer.gov/types/aya [accessed 2021-03-30]
25. Swain CTV, Nguyen NH, Eagles T, Vallance JK, Boyle T, Lahart IM, et al. Postdiagnosis sedentary behavior and health outcomes in cancer survivors: a systematic review and meta-analysis. Cancer 2020;126(4):861-869 [FREE Full text] [doi: 10.1002/cncr.32578] [Medline: 31714596]

26. Otto SJ, Korfage IJ, Polinder S, van der Heide A, de Vries E, Rietjens JAC, et al. Association of change in physical activity and body weight with quality of life and mortality in colorectal cancer: a systematic review and meta-analysis. Support Care Cancer 2015;23(5):1237-1250. [doi: 10.1007/s00520-014-2480-0] [Medline: 25318696]
27. Mustian KM, Adams J, Schwartz RG, Lipshultz SE, Constine LS. Cardiotoxic effects of radiation therapy in Hodgkin's lymphoma and breast cancer survivors and the potential mitigating effects of exercise. In: Rubin P, Constine LS, Marks LB, Okunieff P, editors. Cured II—LENT Cancer Survivorship Research And Education: Late Effects on Normal Tissues. Berlin: Springer; 2008:103-115.
28. Chen JJ, Wu PT, Middlekauff HR, Nguyen KL. Aerobic exercise in anthracycline-induced cardiotoxicity: a systematic review of current evidence and future directions. Am J Physiol Heart Circ Physiol 2017;312(2):H213-H222 [FREE Full text] [doi: 10.1152/ajpheart.00646.2016] [Medline: 27923793]
29. Ferrer RA, Huedo-Medina TB, Johnson BT, Ryan S, Pescatello LS. Exercise interventions for cancer survivors: a meta-analysis of quality of life outcomes. Ann Behav Med 2011;41(1):32-47 [FREE Full text] [doi: 10.1007/s12160-010-9225-1] [Medline: 20931309]
30. Daniel CL, Emmons KM, Fasciano K, Fuemmeler BF, Demark-Wahnefried W. Needs and lifestyle challenges of adolescents and young adults with cancer: summary of an Institute of Medicine and Livestrong Foundation workshop. Clin J Oncol Nurs 2015;19(6):675-681 [FREE Full text] [doi: 10.1188/15.CJON.19-06AP] [Medline: 26583632]
31. Kaul S, Avila JC, Mutambudzi M, Russell H, Kirchhoff AC, Schwartz CL. Mental distress and health care use among survivors of adolescent and young adult cancer: a cross-sectional analysis of the National Health Interview Survey. Cancer 2017;123(5):869-878 [FREE Full text] [doi: 10.1002/cncr.30417] [Medline: 27859009]
32. Dougall AL, Baum A. Stress, health, and illness. In: Baum A, Revenson TA, Singer JE, editors. Handbook of Health Psychology, Second Edition. New York: Psychology Press; 2012:53-78.
33. O'Connor DB, Jones F, Conner M, McMillan B, Ferguson E. Effects of daily hassles and eating style on eating behavior. Health Psychol 2008 Jan;27(1S):S20-S31. [doi: 10.1037/0278-6133.27.1.S20] [Medline: 18248102]
34. Newman E, O'Connor DB, Conner M. Daily hassles and eating behaviour: the role of cortisol reactivity status. Psychoneuroendocrinology 2007;32(2):125-132. [doi: 10.1016/j.psyneuen.2006.11.006] [Medline: 17198744]
35. Jones F, O'Connor DB, Conner M, McMillan B, Ferguson E. Impact of daily mood, work hours, and iso-strain variables on self-reported health behaviors. J Appl Psychol 2007;92(6):1731-1740. [doi: 10.1037/0021-9010.92.6.1731] [Medline: 18020809]
36. Institute of Medicine, National Research Council. In: Hewitt M, Greenfield S, Stovall E, editors. From Cancer Patient to Cancer Survivor: Lost in Transition. Washington, DC: National Academies Press; 2006.
37. Baird H, Patterson P, Medlow S, Allison KR. Understanding and improving survivorship care for adolescents and young adults with cancer. J Adolesc Young Adult Oncol 2019;8(5):581-586. [doi: 10.1089/jayao.2019.0031] [Medline: 31268400]
38. Kayser K, Watson LE, Andrade JT. Cancer as a "we-disease": examining the process of coping from a relational perspective. Fam Syst Health 2007;25(4):404-418. [doi: 10.1037/1091-7527.25.4.404]
39. Bolger N, DeLongis A, Kessler RC, Wethington E. The contagion of stress across multiple roles. J Marriage Fam 1989;51(1):175-183. [doi: 10.2307/352378]
40. Richter D, Koehler M, Friedrich M, Hilgendorf I, Mehnert A, Weißflog G. Psychosocial interventions for adolescents and young adult cancer patients: a systematic review and meta-analysis. Crit Rev Oncol Hematol 2015;95(3):370-386. [doi: 10.1016/j.critrevonc.2015.04.003] [Medline: 25922217]
41. Kwak M, Zebrack BJ, Meeske KA, Embry L, Aguilar C, Block R, et al. Trajectories of psychological distress in adolescent and young adult patients with cancer: a 1-year longitudinal study. J Clin Oncol 2013;31(17):2160-2166 [FREE Full text] [doi: 10.1200/JCO.2012.45.9222] [Medline: 23650425]
42. Cho D, Park CL. Cancer-related identities in people diagnosed during late adolescence and young adulthood. Br J Health Psychol 2015;20(3):594-612. [doi: 10.1111/bjhp.12110] [Medline: 24924918]
43. Zebrack BJ, Corbett V, Embry L, Aguilar C, Meeske KA, Hayes-Lattin B, et al. Psychological distress and unsatisfied need for psychosocial support in adolescent and young adult cancer patients during the first year following diagnosis. Psychooncology 2014;23(11):1267-1275 [FREE Full text] [doi: 10.1002/pon.3533] [Medline: 24664958]
44. Kwak M, Zebrack BJ, Meeske KA, Embry L, Aguilar C, Block R, et al. Prevalence and predictors of post-traumatic stress symptoms in adolescent and young adult cancer survivors: a 1-year follow-up study. Psychooncology 2013;22(8):1798-1806 [FREE Full text] [doi: 10.1002/pon.3217] [Medline: 23135830]
45. Hilpert P, Xu F, Milek A, Atkins DC, Bodenmann G, Bradbury TN. Couples coping with stress: between-person differences and within-person processes. J Fam Psychol 2018;32(3):366-374. [doi: 10.1037/fam0000380] [Medline: 29517246]
46. Shrout PE, Herman CM, Bolger N. The costs and benefits of practical and emotional support on adjustment: a daily diary study of couples experiencing acute stress. Pers Relatsh 2006;13(1):115-134. [doi: 10.1111/j.1475-6811.2006.00108.x]
47. Hawkes G, Houghton J, Rowe G. Risk and worry in everyday life: comparing diaries and interviews as tools in risk perception research. Health Risk Soc 2009;11(3):209-230. [doi: 10.1080/13698570902906439]
48. Maher JP, Dzubur E, Huh J, Intille S, Dunton GF. Within-day time-varying associations between behavioral cognitions and physical activity in adults. J Sport Exerc Psychol 2016;38(4):423-434 [FREE Full text] [doi: 10.1123/jsep.2016-0058] [Medline: 27634288]

49. Conroy DE, Ram N, Pincus AL, Coffman DL, Lorek AE, Rebar AL, et al. Daily physical activity and alcohol use across the adult lifespan. Health Psychol 2015;34(6):653-660 [FREE Full text] [doi: 10.1037/hea0000157] [Medline: 25222084]
50. Conroy DE, Maher JP, Elavsky S, Hyde AL, Doerksen SE. Sedentary behavior as a daily process regulated by habits and intentions. Health Psychol 2013;32(11):1149-1157 [FREE Full text] [doi: 10.1037/a0031629] [Medline: 23477579]
51. Inauen J, Shrout PE, Bolger N, Stadler G, Scholz U. Mind the gap? an intensive longitudinal study of between-person and within-person intention-behavior relations. Ann Behav Med 2016;50(4):516-522 [FREE Full text] [doi: 10.1007/s12160-016-9776-x] [Medline: 26801785]
52. O'Hara RE, Boynton MH, Scott DM, Armeli S, Tennen H, Williams C, et al. Drinking to cope among African American college students: an assessment of episode-specific motives. Psychol Addict Behav 2014;28(3):671-681 [FREE Full text] [doi: 10.1037/a0036303] [Medline: 25134052]
53. Aldridge-Gerry AA, Roesch SC, Villodas F, McCabe C, Leung QK, Da Costa M. Daily stress and alcohol consumption: modeling between-person and within-person ethnic variation in coping behavior. J Stud Alcohol Drugs 2011;72(1):125-134 [FREE Full text] [doi: 10.15288/jsad.2011.72.125] [Medline: 21138719]
54. Willroth EC, John OP, Biesanz JC, Mauss IB. Understanding short-term variability in life satisfaction: the Individual Differences in Evaluating Life Satisfaction (IDELS) model. J Pers Soc Psychol 2020;119(1):229-248 [FREE Full text] [doi: 10.1037/pspp0000261] [Medline: 31478706]
55. Smyth JM, Stone AA. Ecological momentary assessment research in behavioral medicine. J Happiness Stud 2003;4(1):35-52. [doi: 10.1023/a:1023657221954]
56. Stawski RS, MacDonald SWS, Sliwinski MJ. Measurement burst design. In: Krauss SK, editor. The Encyclopedia of Adulthood and Aging. Hoboken: Wiley; 2015:1-5.
57. Sliwinski MJ. Measurement‐burst designs for social health research. Soc Personal Psychol 2008;2(1):245-261. [doi: 10.1111/j.1751-9004.2007.00043.x]
58. Automated Self-Administered 24-Hour (ASA24®) dietary assessment tool. National Cancer Institute. 2016. URL: https://epi.grants.cancer.gov/asa24/ [accessed 2024-01-18]
59. de Souza JA, Yap BJ, Wroblewski K, Blinder V, Araújo FS, Hlubocky FJ, et al. Measuring financial toxicity as a clinically relevant patient-reported outcome: the validation of the Comprehensive Score for Financial Toxicity (COST). Cancer 2017;123(3):476-484 [FREE Full text] [doi: 10.1002/cncr.30369] [Medline: 27716900]
60. Bédard M, Molloy DW, Squire L, Dubois S, Lever JA, O'Donnell M. The Zarit Burden interview: a new short version and screening version. Gerontologist 2001;41(5):652-657 [FREE Full text] [doi: 10.1093/geront/41.5.652] [Medline: 11574710]
61. Higginson IJ, Gao W, Jackson D, Murray J, Harding R. Short-form Zarit caregiver burden interviews were valid in advanced conditions. J Clin Epidemiol 2010;63(5):535-542. [doi: 10.1016/j.jclinepi.2009.06.014] [Medline: 19836205]
62. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav 1983;24(4):385-396. [doi: 10.2307/2136404]
63. Godin G, Shephard RJ. A simple method to assess exercise behavior in the community. Can J Appl Sport Sci 1985;10(3):141-146. [Medline: 4053261]
64. Amireault S, Godin G, Lacombe J, Sabiston CM. The use of the Godin-Shephard leisure-time physical activity questionnaire in oncology research: a systematic review. BMC Med Res Methodol 2015;15:60 [FREE Full text] [doi: 10.1186/s12874-015-0045-7] [Medline: 26264621]
65. Health information national trends survey. National Cancer Institute. 2018. URL: https://hints.cancer.gov/about-hints/default.aspx [accessed 2024-01-18]
66. Edelen MO, Tucker JS, Shadel WG, Stucky BD, Cai L. Toward a more systematic assessment of smoking: development of a smoking module for PROMIS®. Addict Behav 2012;37(11):1278-1284 [FREE Full text] [doi: 10.1016/j.addbeh.2012.06.016] [Medline: 22770824]
67. Bush K, Kivlahan DR, McDonell MB, Fihn SD, Bradley KA. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test. Arch Intern Med 1998;158(16):1789-1795 [FREE Full text] [doi: 10.1001/archinte.158.16.1789] [Medline: 9738608]
68. Diet history questionnaire III. National Cancer Institute. 2018. URL: https://epi.grants.cancer.gov/dhq3/ [accessed 2024-01-18]
69. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28(2):193-213. [doi: 10.1016/0165-1781(89)90047-4] [Medline: 2748771]
70. Zajdel M, Helgeson VS, Seltman HJ, Korytkowski MT, Hausmann LRM. Daily communal coping in couples with type 2 diabetes: links to mood and self-care. Ann Behav Med 2018;52(3):228-238 [FREE Full text] [doi: 10.1093/abm/kax047] [Medline: 29538665]
71. Sinclair VG, Dowdy SW. Development and validation of the emotional intimacy scale. J Nurs Meas 2005;13(3):193-206. [doi: 10.1891/jnum.13.3.193] [Medline: 16605042]
72. Park CL, Wortmann JH, Hale AE, Cho D, Blank TO. Assessing quality of life in young adult cancer survivors: development of the survivorship-related quality of life scale. Qual Life Res 2014;23(8):2213-2224. [doi: 10.1007/s11136-014-0682-z] [Medline: 24729054]

73. Hays RD, Bjorner JB, Revicki DA, Spritzer KL, Cella D. Development of physical and mental health summary scores from the Patient-Reported Outcomes Measurement Information System (PROMIS) global items. Qual Life Res 2009;18(7):873-880 [FREE Full text] [doi: 10.1007/s11136-009-9496-9] [Medline: 19543809]
74. Stone AA, Neale JM. New measure of daily coping: development and preliminary results. J Pers Soc Psychol 1984;46(4):892-906. [doi: 10.1037//0022-3514.46.4.892]
75. Trost SG, McIver KL, Pate RR. Conducting accelerometer-based activity assessments in field-based research. Med Sci Sports Exerc 2005;37(11 Suppl):S531-S543. [doi: 10.1249/01.mss.0000185657.86065.98] [Medline: 16294116]
76. Hays RD, Schalet BD, Spritzer KL, Cella D. Two-item PROMIS® global physical and mental health scales. J Patient Rep Outcomes 2017;1(1):2 [FREE Full text] [doi: 10.1186/s41687-017-0003-8] [Medline: 29757325]
77. Zhang JL, Rubin DB. Estimation of causal effects via principal stratification when some outcomes are truncated by "death". J Educ Behav Stat 2016;28(4):353-368. [doi: 10.3102/10769986028004353]
78. Cohen J. Statistical Power Analysis for the Behavioral Sciences, Second Edition. Hillsdale, N.J: L. Erlbaum Associates; 1988.
79. Nahum-Shani I, Smith SN, Spring BJ, Collins LM, Witkiewitz K, Tewari A, et al. Just-in-Time Adaptive Interventions (JITAIs) in mobile health: key components and design principles for ongoing health behavior support. Ann Behav Med 2018;52(6):446-462 [FREE Full text] [doi: 10.1007/s12160-016-9830-8] [Medline: 27663578]

Abbreviations

LAYA-SRQL: Late Adolescence and Young Adulthood Survivorship-Related Quality of Life
PROMIS: Patient-Reported Outcomes Measurement Information System
QoL: quality of life
REDCap: Research Electronic Data Capture

Edited by A Mavragani; submitted 09.10.23; this is a non–peer-reviewed article;accepted 21.12.23; published 23.04.24.

Please cite as:
Cho D, Roth M, Peterson SK, Jennings K, Kim S, Weathers SP, Ahmed S, Livingston JA, Barcenas C, You YN, Milbury K
Associations Between Stress, Health Behaviors, and Quality of Life in Young Couples During the Transition to Survivorship: Protocol for a Measurement Burst Study
JMIR Res Protoc 2024;13:e53307
URL: https://www.researchprotocols.org/2024/1/e53307
doi:10.2196/53307
PMID:38652520

Protocol

The Use of Medical Services for Low-Acuity Emergency Cases in Germany: Protocol for a Multicenter Observational Pilot Study

Lara Maria Nau[1], MD; Gunter Laux[1], Prof Dr; Attila Altiner[1], Prof Dr; Joachim Szecsenyi[1], Prof Dr; Rüdiger Leutgeb[1], PD Dr

Department of General Practice and Health Services Research, University of Heidelberg, Heidelberg, Germany

Corresponding Author:
Rüdiger Leutgeb, PD Dr
Department of General Practice and Health Services Research
University of Heidelberg
Im Neuenheimer Feld 130
Heidelberg, 69120
Germany
Phone: 49 622156310446
Email: ruediger.leutgeb@med.uni-heidelberg.de

Abstract

Background: The increasing number of requests for help for acutely ill patients and their management is a major problem in the health systems of many countries, but especially in Germany. Rescue coordination centers and ambulances in Germany are increasingly overloaded. As a result, rides as a part of rescue operations have been increasing in length for years, yet a relevant proportion of these operations represent low-acuity calls (LACs). The basic objective of this pilot study is the quantitative analysis of the potential misuse of requests to the rescue control center. Indications for alternative treatment options and how to handle these treatment options in nonacute, non–life-threatening health conditions, such as minor injuries or minor infectious diseases, will be assessed. The identification of these LACs is vital in order to prevent health care resources in emergency medical care becoming inadequate.

Objective: The overarching goal of this study is to determine the percentage of unnecessary rescue missions on site and subsequently to obtain an impression of the paramedics' assessment of alternative treatment options or alternative methods of rescue transportation.

Methods: This will be an exploratory, noninterventional, cross-sectional study with a quantitative approach. The study is multicentric, with 21 ambulances in 12 different locations. The data for this study were collected via a questionnaire, newly developed for this study, for rescue personnel. Additionally, secondary data from the responsible control center will be linked and processed in an initial descriptive analysis. This descriptive analysis will form the basis for a subsequent variance analysis.

Results: Data collection started as projected on September 18, 2023, and was ongoing until end of November 2023. We expect the documentation of several thousand rescue operations. We expect the following study results: (1) many unnecessary rescue operations, (2) immediate on-site assessment of correct care and treatment, and (3) patients' reasons for calling a rescue coordination center.

Conclusions: To our knowledge, this is the first observational study in which acute rescue operations are recorded on site. The focus of this study is on the trained paramedics' assessment of whether rescue operations are necessary or not. Additionally, alternative treatments, such as out-of-hours care service or primary care service, are shown for each individual case. The study also intends to cover the question of which factors are relevant and statistically significantly connected to the misuse of ambulances.

Trial Registration: German Register for Clinical Studies (Deutsches Register für Klinische Studien) DRKS00032510; https://drks.de/search/en/trial/DRKS00032510

International Registered Report Identifier (IRRID): DERR1-10.2196/54002

(JMIR Res Protoc 2024;13:e54002) doi:10.2196/54002

KEYWORDS

emergency medical service; EMS; ambulance misuse; low-acuity calls; emergency department; paramedics; rescue operations

Introduction

The number of outpatient medical treatment cases in Germany has been showing an upward trend for years [1]. Additionally, the number of rescue operations in emergency medical service (EMS) shows a continuous annual increase of about 5%, amounting to almost 16.5 million emergency ambulance and emergency missions in the 2016-2017 observation period [2-5]. This increase can also be observed in the number of rescue operations performed by the ambulance service and is similar in most European countries, as well as in the United States and Australia [6-9]. The steady increase can only partly be accounted for by demographic developments or geographical peculiarities [10,11]. Rather, a not inconsiderable proportion of EMS operations and the resulting transports to an emergency department (ED) do not seem to be indicated from a medical point of view [12-14].

In Germany, patients with minor ailments should generally be treated in medical on-call service centers out of hours when their own general practitioner (GP) is not available. GPs and specialists are obliged to work in medical on-call services; in some regions this is only out of hours, while in other regions it is 24 hours, 7 days a week. The medical on-call services are regulated by the Association of Statutory Health Insurance Physicians, that is, they are self-administered. Everybody, whether seriously or only slightly ill, can consult the ED as well as clinics and the EMS. EDs are also responsible for, preferably, emergency care but also for all other acute patient concerns. [15]. In addition to a lack of professional assessment on the part of those seeking help and ignorance of the responsibilities of the existing emergency and acute patient care structures [16,17], a variety of factors can lead to the EMS and ambulance service being alerted in nonurgent cases. Apart from the possibility of low-threshold and timely care by the ambulance service, these also include the patient-specific perception of their urgency as well as a personal need for safety [18]. Other circumstances that occasionally lead to avoidable requests for ambulance service include nursing home patients with ambulatory care–sensitive conditions, older people with many comorbidities not receiving timely outpatient consultation appointments, and people with mental health problems or somatoform disorders requiring psychological care [19-25].

The increased and undifferentiated use of the EMS means rising costs at the expense of social insurance [26] and a higher workload for emergency medical staff, who are exposed to an extremely high risk of burnout [27,28]. This also leads to overcrowded EDs and therefore to great difficulties treating patients efficiently and at a high quality outside of regular and scheduled consultations [29,30]. Besides this, the response time of the EMS tends to be more and more extended, and statutory provisions consequently cannot be observed [31,32]. Serious doubts concerning the capability of the EMS and the emergency medical system in general are being seen more and more in public debate in recent years.

German policy makers are now seriously addressing this issue after making some local short-term changes; for example, alert keywords have been restricted for ambulances on call. Recently, a German government commission proposed comprehensive modifications to the EMS. These call for extending the EMS's entitlement to services and fees for care and treatment of minor ailments on site, not just transportation (as before). The overall aim is to reorganize and expand the existing components of the EMS [33].

The aim of this prospective cross-sectional study is the quantitative analysis of unnecessary ambulance missions, in addition to the examination of indications for alternative care options in nonacute life-threatening situations instead of transport by the ambulance service to a hospital ED. Alternative health care options should be discussed to help improve care for acute patients and reduce the misuse of ambulances.

Methods

Aim

This study intends to quantify the fraction of low-acuity calls (LACs) in ambulance operations, focusing on alternative treatment options. For this purpose, the trial will evaluate how often EMS personnel rate a different, usually ambulatory treatment as being more suitable because a patient has a non–life-threatening health condition that does not require any urgent medical intervention. In addition, this study aims to identify and quantify the reasons why patients without a life-threatening medical condition or other medical indications are brought to an emergency room by ambulance instead of being transferred to a more suitable location for treatment. Therefore, the 2 main questions the study plans to cover are, first, what kind of treatment patients of the EMS need, if not emergency treatment and urgent conveyance to a hospital, and second, why patients may not receive adequate medical care. A quantitative approach is required to obtain an indication of the dimensions of these individual aspects, as there is usually no standardized documentation by the control center that goes beyond the point of "patient was taken to hospital/patient was referred to GP/refusal of transport/no patient was found," which represents only part of the actual situation. Furthermore, the study will collect and analyze data on operational statistics to determine if conditions like operation time, day of the week, accessibility to a GP, priority, and content of the alert (as set by the dispatcher in the control center) have an impact on the frequency of LAC operations. We will also evaluate socioeconomic factors, such as age and gender of the patient, as well as the impact of the operation area.

Design

The key feature of this exploratory, noninterventional, cross-sectional study is a web-based questionnaire (Table 1) for tablets or smartphones. In the first phase, each individual question on the web-based questionnaire was reviewed by an expert panel at the Department of General Medicine at Heidelberg University Hospital, and in the second phase, the questions were discussed with the heads of operations at the rescue coordination centers, as well as with selected paramedics. The focus was on the feasibility of this pilot study. When this study is rolled out (at large scale) there also will be analyses of interrater reliability.

Table 1. Questionnaire for ambulance crews on emergency cases.

Item	Content
Operation number	• (Free text)
Patient gender	• Male • Female • Gender-diverse
Patient age group (years)	• 18-24 • 25-39 • 40-59 • 60-64 • 65-79 • ≥80
Operation time on a weekend day or holiday[a]	• Yes/no
Operation time during main opening hours of general practitioner care[b]	• Yes/no
Classification of operation area (number of inhabitants)	• Metropolitan (>100,000) • Urban (30,000-100,000) • Suburban (10,000-30,000) • Rural (<10,000)
Working diagnosis	• (Free text)
Treatment or procedure performed (multiple choices possible)	• Being conveyed to a hospital • Referral to a general practitioner or medical on-call service • Continuance at home • Patient refused being conveyed • Therapeutic measures performed • (Free text)
Appropriate treatment or procedure (multiple choices possible; no choice possible)	• Being conveyed to a hospital autonomously • Calling on the medical on-call service autonomously • Consulting the general practitioner for further care • Exclusively counseling • Counseling by telephone possible • Social caretakership • Being conveyed by a patient transport ambulance • (Free text)
Reasons for being conveyed to a hospital without medical indication (multiple choices possible; no choice possible)	• Missed transportation opportunity by patient or relatives • Patient insists on being conveyed by ambulance • Social indication • House call by general practitioner or medical on-call service indicated but not provided • Medical on-call service not favored by patient • Insecurity of team leader • Language barrier • (Free text)

[a]As defined by the state in which the operation took place.

[b]Main opening hours were defined as Monday, Tuesday, and Thursday from 7 AM to 7 PM, and Wednesday and Friday from 7 AM to 2 PM.

The members of the expert panel determined which crucial dimensions of medical emergency treatments will be queried, including (1) working diagnosis, which is the assessment made on site by the ambulance crew with consideration of diagnostics that can be carried out preclinically; (2) procedures, including the ambulance crew's approach to counseling, treatment, patient transport, and referral to other caregivers; (3) adequacy of care, that is, the assessment of the most suitable form of care, which is carried out by the ambulance crew based on the situation on site; and (4) problems that arise, that is, the evaluation of possible reasons why patients are not directed to the form of care that has been assessed as being most suitable.

The training of the paramedics consists of 5 vital elements. The important questions for assessing their concerns about possible rescue operations (Textbox 1) are described in in-person lectures. The five *W* questions are integrated in the questionnaire and special training is provided.

Textbox 1. W questions and example cases.

***W* questions**

- Which typical use cases are presented?
- Who called? (Age and gender should be documented)
- Which concerns were stated? (Assessment of the emergency is an overarching goal of the study)
- When did the concerns occur? (Duration and assessment of the acute situation has to be included in the consideration)
- Where is the location? (Infrastructure, social environment, etc., should be documented)

Examples of possible rescue operation cases integrated into the training

- An ambulance is alerted with high priority because of high blood pressure and vertigo. On site, the crew can rule out current life-threatening conditions, only the blood pressure is slightly elevated beyond the patient's known level after an upsetting argument a few hours before. Anamnesis brings out that the patient is familiar with vertigo and does not have any new kinds of symptoms. So, the ambulance crew cannot find any indication for conveyance at this moment and offers the patient to stay at home unless new kinds of symptoms or decline of general condition occur. The patient prefers to do so, but his daughter presses him to "have a thorough checkup in hospital" and does not concede. The patient is conveyed to the nearest hospital. After the operation, the ambulance crew fills in the questionnaire, describes their working diagnosis as "slightly elevated blood pressure without further symptoms, known vertigo without current worsening" and picks "hospital conveyance" as performed procedure, "consulting the GP in the further course" as appropriate procedure and "patient insists on conveyance by ambulance" (which includes relatives) as reason for hospital conveyance without urgent medical indication.
- An ambulance is alerted under the heading "attendance operation for fire brigade". As there is no patient contact during the whole operation and therefore the operation is excluded from this study, the ambulance crew does not fill in the questionnaire.
- An ambulance and an emergency doctor's car are alerted with high priority because of acute chest pain. On site, the medical examination shows evidence for an acute myocardial infarction and the patient is quickly treated and conveyed to hospital for further treatment. After terminating the operation, the ambulance crew fills in the web-based questionnaire with the items 1-9 only, because they categorize their treatment as appropriate.
- An ambulance is alerted with low priority because of a headache on a Saturday. On site, they find a young woman who is healthy except for a cold that has been lasting for "already six days" accompanied by a sinusitis and a feeling of pressure in her head. The symptoms didn't change during the last days, and she was not satisfied by the advice of her GP and the request to await spontaneous recovery. The ambulance crew repeats the advice of the GP and recommends waiting and see and to contact the GP or alternatively the medical out-of-hours on-call service again if no improvement will occur. The patient insists on an immediate treatment, has never heard of the medical on-call service until now and claims not to be able to drive on her own, so the paramedics call the medical on-call service themselves and ask for a home call. After the operation, they fill in the web-based questionnaire, set their working diagnosis "headache associated with acute sinusitis", pick "referral to GP or medical on-call service" and "continuance at home" as performed procedure, "consulting the GP in the further course" and "exclusively counseling" as well as "counseling telephonically possible" as appropriate procedures and select "missing transportation opportunities by patient and relatives" and add "patient didn't know the medical on-call service" for reasons why the patient has not been directed to the appropriate caregiver straightforward.

We explained all phrases used in the questionnaire (Table 1) to precisely define the terms used. Examples for 2 terms are as follows: "social indication" means, for example, a single, immobile older person, a single mother, or a father of an ill child without his own car and without access to public transportation; "medical on-call service" means an on-call service in a suitable medical practice, self-managed by primary care physicians outside regular consultation hours or when a GP is not available.

The questionnaire will be completed once per operation by the ambulance crew, ideally in consultation with both or all 3 crew members and will represent the assessment of the most qualified crew member. The questionnaire can be filled in until the end of the operation.

The following types of operations are excluded: operations involving minor patients (aged <18 years), secondary transports or interhospital transfers, operations cancelled during the approach, operations with no patient found, provisional operations without a patient (eg, fire service operations), and operations in which the patient dies or is found dead on the incident scene. The inclusion and exclusion criteria are listed in Textbox 2.

Textbox 2. Inclusion and exclusion criteria for emergency case recording.

Inclusion criteria

- Minimum of 1 ambulance involved in the operation (type C according to EN 1789)
- Crew members were recruited and briefed

Exclusion criteria

- Provisional operation without patient (eg, fire service operations)
- Secondary transport/interhospital transfer
- Cancellation during approach
- Minor patients (aged <18 years)
- Patient dies or is found dead on incident scene
- No patient found

Setting

The study takes place in the whole area of responsibility of the integrated emergency control center of Ludwigshafen, Germany. This covers an area of about 1200 km^2 and represents a point of call for over 620,000 inhabitants in 6 administrative districts and independent cities. Its dispatchers answer more than 210,000 calls per year, which result in more than 140,000 EMS operations (average 380 per day) and around 11,000 operations of the fire service annually. The control center has at its disposal 21 ambulances in 12 different locations, as well as 8 emergency doctor's cars, 1 rescue helicopter, and up to 28 patient transport ambulances (figures obtained via oral communication with the management team of the integrated EMS control center of Ludwigshafen on August 29, 2023). The area of responsibility, with its 6 administrative districts and independent cities, includes the core city of Ludwigshafen as the metropolitan zone, a few cities classified as urban regions, several smaller, suburban towns, and several remote rural townships [34]. The classification of the operation areas used in this survey can be found in Table 2.

Table 2. Operation areas of emergency crews.

Operation area	Description
Overall	The area around Ludwigshafen, a city in the federal state of Rhineland-Pfalz, Germany
Metropolitan	The core region of Ludwigshafen
Urban	The cities Speyer, Neustadt, and Frankenthal, as well as the districts Ruchheim and Maudach of Ludwigshafen
Suburban	The cities Bad Dürkheim, Grünstadt, Schifferstadt, Haßloch, Böhl-Iggelheim, Limburgerhof, Mutterstadt, and Bobenheim-Roxheim
Rural	All townships with less than 10,000 inhabitants

Participant Recruitment

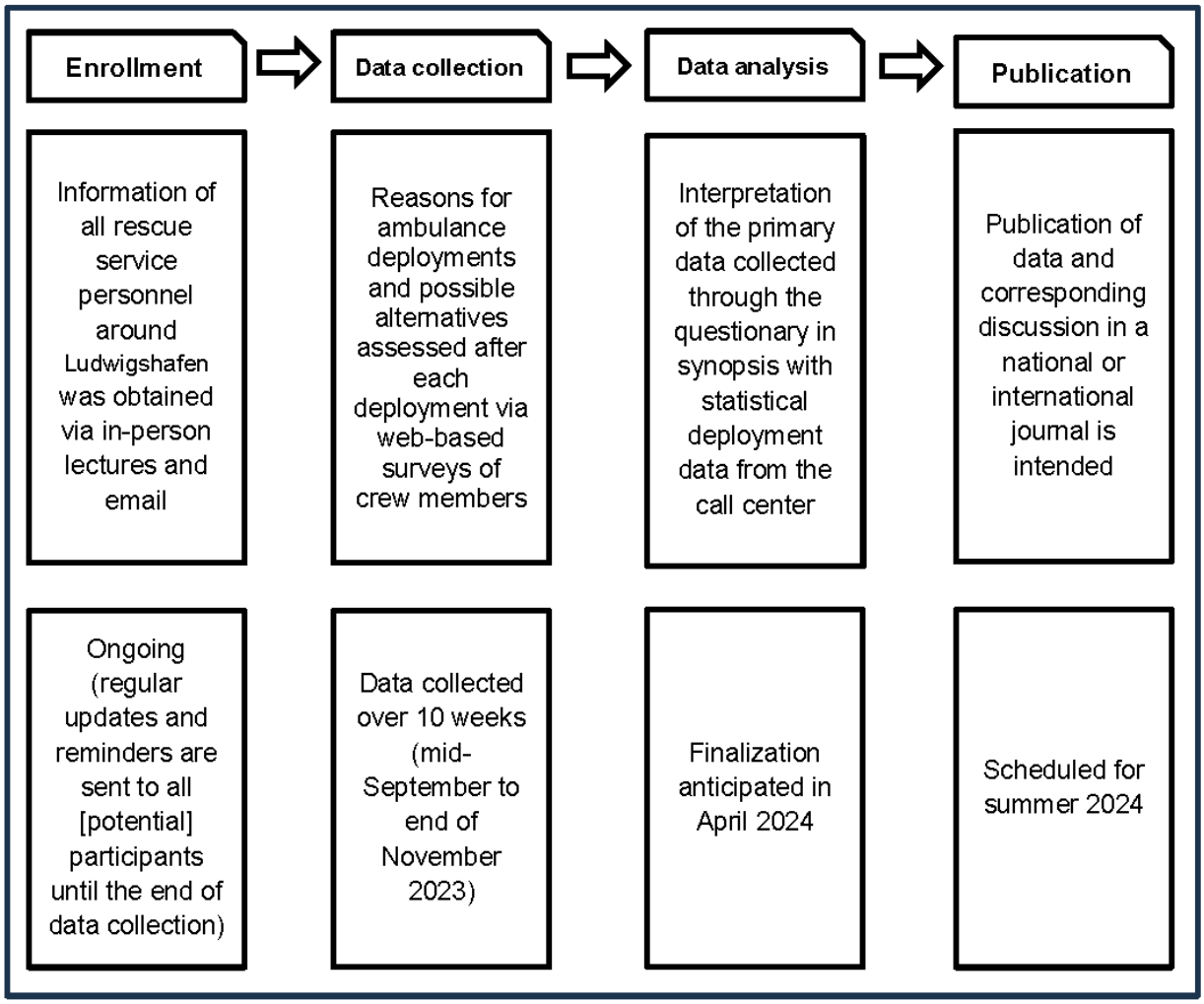
All ambulance crew members under the responsibility of the integrated emergency control center of Ludwigshafen will have access to voluntary participation in this study. LMN, a doctoral student, will run several information sessions integrated into conferences at the individual rescue stations. Additionally, a written invitation with information will be sent to every employee via an email distribution list on the internal communications devices of the quality management system. It will include a thorough description of the study content, clarifications concerning the questionnaire, an informed consent form, and a link and QR code supplying access to the web-based questionnaire. Consent will be obtained in the web-based questionnaire; further participation is only possible after providing informed consent.

Data Collection

During the 10-week period of data collection, access to the web-based questionnaire is available 24 hours a day, 7 days a week. The questionnaire is accessible via the link or QR code and can be filled in using a personal computer, tablet, or smartphone. The questionnaire website has been built exclusively for the study by the department conducting the study. The EMS personnel are encouraged to capture as many operations as possible during this period. The acquisition of the data sets is not bound to a certain time frame after the operations. Although the ambulance crew members must complete the questionnaire only after finishing an operation, the data sets only have to be completed within the period of data collection. The data set of each recorded ambulance operation is directly sent to a dedicated study server within the Department of General Practice and Health Services Research of the University Hospital Heidelberg via secure internet protocols. After closing of primary data collection, additional information and secondary data provided by the control center will be combined with each completely collected data set for interpretation. This comprises the time of day of the alert, the priority of the alert, the keywords of the alert, and a specific feedback code from the ambulance.

The scheduled course of the study is summarized in Figure 1.

Figure 1. Scheduled further course of study.



Research Staff

The research team consists of a doctoral student, several senior researchers, and a computer scientist employed at the Department of General Practice and Health Services Research of the University Hospital Heidelberg, Germany.

Data Management

Data management is performed by the data management team of the Department of General Practice and Health Services Research of the University Hospital Heidelberg. The secondary data are collected by the control center of Ludwigshafen and are unrelated to the described questionnaire; they are governed by their own data management team.

Each data set is directly sent to and filed on a dedicated study server in the Department of General Practice and Health Services Research of the University Hospital Heidelberg. This also applies to the required secondary data transferred from the control center. Data access is granted only to the research staff directly involved in data collection and analysis. There will be no passing on of the unprocessed data to any external institution. Additionally, secondary data from the responsible control center will be linked and processed in the initial descriptive analysis. This descriptive analysis will form the basis for the variance analysis (see Data Analysis section). Working diagnoses will be converted to *International Classification of Diseases, Tenth Edition* codes by a research physician. The free-text entries will be analyzed separately with qualitative methods to obtain a deeper insight into patients' motives for their behavior. Data storage and extraction will be performed with MySQL Community Server x64 (Oracle Corp).

Data Analysis

The two main outcomes for our analyses are the number and percentage of inappropriate emergency calls and the reasons for patients being conveyed to a hospital without a medical indication. This total numbers will be further subdivided according to the paramedics' assessments. Moreover, it is of interest if there are explanatory variables such as patient gender, patient age, operation area, and operation time in the data set that might be associated with inappropriate emergency calls or being conveyed to a hospital without a medical indication. This will be analyzed based on multivariable regression modeling [35]. To calculate frequencies, rates, and percentages, we will use the PROC SQL procedure in SAS (version 9.4, SAS

Institute). To perform the multivariable analyses, we will use the PROC GENMOD procedure in SAS. For qualitative analyses, we will use MAXQDA (version 24.1, VERBI Software).

Ethical Considerations

The ethics committee of the University of Heidelberg revised and approved this study on May 30, 2023 (S-250/2023). The trial has been developed and will be executed according to all relevant national and international rules and regulations under the Declaration of Helsinki (2013 version) and International Council for Harmonisation Good Clinical Practice (E6, R2) guidelines. Consent from all participants will be obtained in the web-based form, and access to the questionnaire will be granted only after approval. Protocol modifications are not scheduled and are not foreseeable; if the need for them arises, they will have to be approved by the ethics committee. In case of modifications, a new study protocol will be released to all study participants via an official email. Due to the anonymous collection of data, participants do not have the choice to opt out after completing the questionnaire. Furthermore, as the questionnaire is anonymous, there is no possibility of inferring the identity of the participant or any other personal information. There is also no way to identify the personal data of patients using the secondary operational data provided by the control center. There is no compensation, financial or otherwise, provided to participants.

Results

Data collection started as projected on September 18, 2023, and was ongoing until end of November 2023. We expect the documentation of several thousand rescue operations. We expect that many of these rescue operations will be unnecessary. Our intention is to train paramedics to give an immediate on-site evaluation of the correct care and treatment. We hope to identify patients' reasons for calling a rescue coordination center so that we can give recommendations in advance on where to find the appropriate treatment options.

Discussion

To the best of our knowledge, this is the first observational study in which acute rescue operations are being recorded on site in Germany. This study was initiated to show how many inappropriate rescue operations, such as those for minor injuries or minor infections, take place in a defined study period. The assessment of these LACs is carried out directly on site by trained rescue personnel and not later in the clinic. The assessment is therefore supplementary and can provide information on operations without the need for a referral, which is a main strength of this study. Another focus is on a preclinical assessment to determine suitable, diverse alternatives to transport by ambulance to an ED for patient conditions that do not require urgent treatment.

One major intent of our study is to complement previous work, which includes several retrospective clinical evaluations and many qualitative studies, such as interview studies, on reasons for calling the EMS in LAC situations as seen through the eyes of patients, as well as of caregivers (mostly EMS personnel), and what circumstances encourage these calls [36-38]. It is known from previous data that around 30% to 35% of all rescue service operations transporting patients to the ED are rated as inadequate and unnecessary [5-8], so a similar proportion of operations with preferred alternative care methods is expected. Most of these inadequate EMS operations involve patients whose health conditions are assessed as being able to be adequately treated by a GP or in general outpatient care [6], which is why there may be a significant difference in the number of primary care–sensitive EMS operations depending on the general availability of and access to general practices and medical out-of-hours care [17]. Additionally, we anticipate that a certain number of transportation operations by ambulance for LACs will take place because of missing transportation alternatives, which has been found to be a relevant reason for ambulance misuse in previous work [39,40]. Previous studies have shown differences in the use of emergency services between urban and rural populations [41], as well as between groups with differences in relevant socioeconomic factors, such as age and personal mobility [42], which may be confirmed in this study.

Several limitations of this study should be noted. The whole system of EMS and acute patient care is complex and includes many variables that cannot be examined in this study. For example, the control centers' process for receiving emergency calls and dispatching ambulances plays a major role during all ambulance operations and the management of acute patients. Assessments of patients' health condition by dispatchers, EMS personnel, and the patients themselves may greatly differ [43]. Misclassification can occur due to different assessment standards because there are usually no uniform classification criteria. There are approaches to harmonizing the triage and dispatching process, such as an intervention in out-of-hours care call centers in Germany that started in 2017 [44], but currently there exist no mandatory and coherent structures in emergency or rescue coordination centers.

In general, studies concerning the EMS in Germany deal with limited generalizability because of huge regional differences in standard operating procedures for treatment, equipment, staffing of rescue resources, and laws and regulations [45]. This is due to the federal structure in Germany and the accountability for civil protection lying mostly with the federal states or even autonomously with the local authorities [46].

Another limitation is the risk of bias. Operations that the ambulance crew rates as having been inappropriately dispatched are more likely to be captured than operations that fulfill the original functions of the EMS. Additionally, recall bias could occur if the questionnaire is not filled in soon after the end of an operation. Our intention was, in any case, to document all rescue operations regardless of urgency.

Nevertheless, the results of this cross-sectional pilot study may form the basis of further evaluations of possible interventions and pilot projects, the implementation of additional services in urgent care, support for change in the way patients are treated, and political change concerning urgent care in general.

Acknowledgments

The authors would like to thank Mr Frank Aluttis for the digital implementation of the questionnaire and the excellent support in all questions concerning the website and data management. Special thanks go to the employees of the rescue services involved in the organizational preparation for the study and to the heads of the control center of Ludwigshafen, Germany, for supporting the realization of the study. There has been no external financial funding in this study. The umbrella organization of the rescue service of Ludwigshafen, Rhineland-Palatinate, as well as the integrated control center of Ludwigshafen, did not support the conceptualization of the study and also provided no nonmaterial or organizational support on account of personal vocational contacts with the responsible parties. The funders did not have a specific role in conceptualization, design, or preparation of the manuscript.

Data Availability

Restrictions apply to the availability of the additionally processed secondary data from the emergency call center of Ludwigshafen, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the emergency call center Ludwigshafen.

Authors' Contributions

LMN developed the study design as well as the questionnaire design and content. She organized the on-site process and implementation of the study at the rescue stations. She was a major contributor in writing the manuscript. RL was a supervisor and co-developed the study, particularly the research question of the study. He was also a major contributor in writing the manuscript. GL provided substantial assistance during the development of the study, especially in all points concerning data management, data privacy, and data analysis. AA and JS advised on the study and critically revised the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

References

1. Radtke R. Ambulante Behandlungsfälle in Deutschland bis 2022 [Outpatient treatment cases in Germany until 2022]. Statista. 2022. URL: https://de.statista.com/statistik/daten/studie/75869/umfrage/gesundheit-anzahl-der-behandlungsfaelle-in-deutschland-seit-2004/ [accessed 2023-09-17]
2. Bedarfsgerechte Steuerung der Gesundheitsversorgung 2018 [Needs-based management of health care in 2018]. Sachverständigenrat Gesundheit und Pflege [Advisory Council of Health and Care]. URL: https://www.svr-gesundheit.de/fileadmin/Gutachten/Gutachten_2018/Kurzfassung_2018.pdf [accessed 2023-09-17]
3. Klein M, Schröder H, Beckers SK, Borgs C, Rossaint R, Felzen M. [Quality of documentation and treatment in the non-physician staffed ambulance: a retrospective analysis of emergency protocols from the city of Aachen]. Anaesthesiologie 2022 Sep;71(9):674-682 [FREE Full text] [doi: 10.1007/s00101-022-01106-x] [Medline: 35316370]
4. Radtke R. Einsatzfahrtenaufkommen in Deutschland nach Einsatzart bis 2017 [Number of rescue trips in Germany by type of operation until 2017]. Statista. 2017. URL: https://de.statista.com/statistik/daten/studie/482380/umfrage/einsatzfahrtaufkommen-im-oeffentlichen-rettungsdienst-nach-einsatzart/ [accessed 2023-09-18]
5. Schehadat MS, Scherer G, Groneberg DA, Kaps M, Bendels MHK. Outpatient care in acute and prehospital emergency medicine by emergency medical and patient transport service over a 10-year period: a retrospective study based on dispatch data from a German emergency medical dispatch centre (OFF-RESCUE). BMC Emerg Med 2021 Mar 09;21(1):29 [FREE Full text] [doi: 10.1186/s12873-021-00424-4] [Medline: 33750317]
6. Andrew E, Nehme Z, Cameron P, Smith K. Drivers of increasing emergency ambulance demand. Prehosp Emerg Care 2020;24(3):385-393. [doi: 10.1080/10903127.2019.1635670] [Medline: 31237460]
7. Hjälte L, Suserud B, Herlitz J, Karlberg I. Initial emergency medical dispatching and prehospital needs assessment: a prospective study of the Swedish ambulance service. Eur J Emerg Med 2007 Jun;14(3):134-141. [doi: 10.1097/MEJ.0b013e32801464cf] [Medline: 17473606]
8. Patton GG, Thakore S. Reducing inappropriate emergency department attendances--a review of ambulance service attendances at a regional teaching hospital in Scotland. Emerg Med J 2013 Jun;30(6):459-461. [doi: 10.1136/emermed-2012-201116] [Medline: 22802457]
9. Olshaker JS, Rathlev NK. Emergency Department overcrowding and ambulance diversion: the impact and potential solutions of extended boarding of admitted patients in the emergency department. J Emerg Med 2006 Apr;30(3):351-356. [doi: 10.1016/j.jemermed.2005.05.023] [Medline: 16677993]

10. Veser A, Sieber F, Groß S, Prückner S. The demographic impact on the demand for emergency medical services in the urban and rural regions of Bavaria, 2012-2032. Z Gesundh Wiss 2015;23(4):181-188 [FREE Full text] [doi: 10.1007/s10389-015-0675-6] [Medline: 26191488]
11. Hanchate AD, Paasche-Orlow MK, Dyer KS, Baker WE, Feng C, Feldman J. Geographic variation in use of ambulance transport to the emergency department. Ann Emerg Med 2017 Oct;70(4):533-543.e7 [FREE Full text] [doi: 10.1016/j.annemergmed.2017.03.029] [Medline: 28559039]
12. Metelmann B, Brinkrolf P, Kliche M, Vollmer M, Hahnenkamp K, Metelmann C. [Emergency medical service, medical on-call service, or emergency department : Germans unsure whom to contact in acute medical events]. Med Klin Intensivmed Notfmed 2022 Mar;117(2):144-151 [FREE Full text] [doi: 10.1007/s00063-021-00820-5] [Medline: 33877425]
13. O'Cathain A, Connell J, Long J, Coster J. 'Clinically unnecessary' use of emergency and urgent care: A realist review of patients' decision making. Health Expect 2020 Feb;23(1):19-40 [FREE Full text] [doi: 10.1111/hex.12995] [Medline: 31663219]
14. Leutgeb R, Engeser P, Berger S, Szecsenyi J, Laux G. Out of hours care in Germany - High utilization by adult patients with minor ailments? BMC Fam Pract 2017 Mar 21;18(1):42 [FREE Full text] [doi: 10.1186/s12875-017-0609-1] [Medline: 28327082]
15. von Stillfried D, Mangiapane S. [Emergency care: need for reform from an outpatient perspective]. Inn Med (Heidelb) 2022 Sep;63(9):905-913 [FREE Full text] [doi: 10.1007/s00108-022-01382-0] [Medline: 35925125]
16. Agarwal S, Banerjee J, Baker R, Conroy S, Hsu R, Rashid A, et al. Potentially avoidable emergency department attendance: interview study of patients' reasons for attendance. Emerg Med J 2012 Dec;29(12):e3. [doi: 10.1136/emermed-2011-200585] [Medline: 22205782]
17. Coster JE, Turner JK, Bradbury D, Cantrell A. Why do people choose emergency and urgent care services? A rapid review utilizing a systematic literature search and narrative synthesis. Acad Emerg Med 2017 Sep;24(9):1137-1149 [FREE Full text] [doi: 10.1111/acem.13220] [Medline: 28493626]
18. Booker MJ, Simmonds RL, Purdy S. Patients who call emergency ambulances for primary care problems: a qualitative study of the decision-making process. Emerg Med J 2014 Jun;31(6):448-452. [doi: 10.1136/emermed-2012-202124] [Medline: 23535018]
19. Horibata K, Takemura Y. Inappropriate use of ambulance services by elderly patients with less urgent medical needs. Tohoku J Exp Med 2015 Feb;235(2):89-95 [FREE Full text] [doi: 10.1620/tjem.235.89] [Medline: 25742927]
20. Inoue Y, Nishi K, Mayumi T, Sasaki J. Factors in avoidable emergency visits for ambulatory care-sensitive conditions among older patients receiving home care in Japan: A retrospective study. Intern Med 2022;61(2):177-183 [FREE Full text] [doi: 10.2169/internalmedicine.7136-21] [Medline: 35034933]
21. Leutgeb R, Berger SJ, Szecsenyi J, Laux G. Potentially avoidable hospitalisations of German nursing home patients? A cross-sectional study on utilisation patterns and potential consequences for healthcare. BMJ Open 2019 Jan 21;9(1):e025269 [FREE Full text] [doi: 10.1136/bmjopen-2018-025269] [Medline: 30670526]
22. Woodhead C, Martin P, Osborn D, Barratt H, Raine R. Health system influences on potentially avoidable hospital admissions by secondary mental health service use: A national ecological study. J Health Serv Res Policy 2022 Jan;27(1):22-30 [FREE Full text] [doi: 10.1177/13558196211036739] [Medline: 34337981]
23. Zúñiga F, Gaertner K, Weber-Schuh SK, Löw B, Simon M, Müller M. Inappropriate and potentially avoidable emergency department visits of Swiss nursing home residents and their resource use: a retrospective chart-review. BMC Geriatr 2022 Aug 11;22(1):659 [FREE Full text] [doi: 10.1186/s12877-022-03308-9] [Medline: 35948872]
24. Lewis J, Weich S, O'Keeffe C, Stone T, Hulin J, Bell N, et al. Use of urgent, emergency and acute care by mental health service users: A record-level cohort study. PLoS One 2023;18(2):e0281667 [FREE Full text] [doi: 10.1371/journal.pone.0281667] [Medline: 36780483]
25. Voss S, Brandling J, Taylor H, Black S, Buswell M, Cheston R, et al. How do people with dementia use the ambulance service? A retrospective study in England: the HOMEWARD project. BMJ Open 2018 Aug 01;8(7):e022549 [FREE Full text] [doi: 10.1136/bmjopen-2018-022549] [Medline: 30068624]
26. Gesundheitsausgaben nach Einrichtungen (Stand 05. April 2023) [Health Expenditures going by institutions]. Statistisches Bundesamt [Federal Statistical Office]. 2023. URL: https://www.destatis.de/DE/Themen/Gesellschaft-Umwelt/Gesundheit/Gesundheitsausgaben/Tabellen/einrichtungen.html [accessed 2023-09-20]
27. Petrino R, Riesgo L, Yilmaz B. Burnout in emergency medicine professionals after 2 years of the COVID-19 pandemic: a threat to the healthcare system? Eur J Emerg Med 2022 Aug 01;29(4):279-284 [FREE Full text] [doi: 10.1097/MEJ.0000000000000952] [Medline: 35620812]
28. Leutgeb R, Frankenhauser-Mannuß J, Scheuer M, Szecsenyi J, Goetz K. Job satisfaction and stressors for working in out-of-hours care - a pilot study with general practitioners in a rural area of Germany. BMC Fam Pract 2018 Jun 22;19(1):95 [FREE Full text] [doi: 10.1186/s12875-018-0777-7] [Medline: 29933743]
29. Bittencourt RJ, Stevanato ADM, Bragança CTNM, Gottems LBD, O'Dwyer G. Interventions in overcrowding of emergency departments: an overview of systematic reviews. Rev Saude Publica 2020;54:66 [FREE Full text] [doi: 10.11606/s1518-8787.2020054002342] [Medline: 32638885]

30. Jacobson T, Salzmann M. Rettungsdienste in ganz Deutschland hoffnungslos überlastet [Emergency medical services in entire Germany desperately overloaded]. World Socialist Web Site. URL: https://www.wsws.org/de/articles/2022/12/18/rett-d18.html [accessed 2023-09-20]
31. Rettungsdienstbericht Bayern 2022 [EMS report Bavaria 2022]. Institut für Notfallmedizin und Medizinmanagement LMU Klinikum München [Institute of Emergency Medicine and Medical Management LMU Hospital Munich]. 2022. URL: https://www.inm-online.de/images/stories/pdf/RD_BERICHT_2022.pdf [accessed 2023-09-20]
32. Jahresbericht 2022 [Annual report 2022]. Berliner Feuerwehr [Berlin Firebrigade]. 2022. URL: https://www.berliner-feuerwehr.de/fileadmin/bfw/dokumente/Publikationen/Jahresberichte/jahresbericht2022.pdf [accessed 2023-09-20]
33. Regierungskommission legt Rettungsdienst-Konzept vor - Lauterbach: Brauchen klare Strukturen [Governmental commission submits concept for EMS - Lauterbach: Have need of more distinct structures]. Federal Ministry for Health. URL: https://www.bundesgesundheitsministerium.de/presse/pressemitteilungen/regierungskommission-legt-rettungsdienst-konzept-vor-pm-07-09-23.html [accessed 2023-09-20]
34. Territorial typologies manual - cluster types. Eurostat. URL: https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Territorial_typologies_manual_-_cluster_types [accessed 2023-09-22]
35. Grant SW, Hickey GL, Head SJ. Statistical primer: multivariable regression considerations and pitfalls. Eur J Cardiothorac Surg 2019 Feb 01;55(2):179-185. [doi: 10.1093/ejcts/ezy403] [Medline: 30596979]
36. Kraaijvanger N, van Leeuwen H, Rijpsma D, Edwards M. Motives for self-referral to the emergency department: a systematic review of the literature. BMC Health Serv Res 2016 Dec 09;16(1):685 [FREE Full text] [doi: 10.1186/s12913-016-1935-z] [Medline: 27938366]
37. O'Cathain A, Simpson R, Phillips M, Knowles E. Tendency to call an ambulance or attend an emergency department for minor or non-urgent problems: a vignette-based population survey in Britain. Emerg Med J 2022 Jun;39(6):436-442 [FREE Full text] [doi: 10.1136/emermed-2020-210271] [Medline: 35273021]
38. Mills B, Hill M, Miles A, Smith E, Afrifa-Yamoah E, Reid D, et al. Calling an ambulance for non-emergency medical situations: Results of a cross-sectional online survey from an Australian nationally representative sample. Emerg Med Australas 2023 Feb;35(1):133-141 [FREE Full text] [doi: 10.1111/1742-6723.14086] [Medline: 36113863]
39. Dejean D, Giacomini M, Welsford M, Schwartz L, Decicca P. Inappropriate ambulance use: A qualitative study of paramedics' views. Healthc Policy 2016 Feb;11(3):67-79 [FREE Full text] [Medline: 27027794]
40. Little GF, Barton D. Inappropriate use of the ambulance service. Eur J Emerg Med 1998 Sep;5(3):307-311. [doi: 10.1097/00063110-199809000-00005] [Medline: 9827832]
41. Wong HT, Lin T, Lin J. Identifying rural-urban differences in the predictors of emergency ambulance service demand and misuse. J Formos Med Assoc 2019 Jan;118(1 Pt 2):324-331 [FREE Full text] [doi: 10.1016/j.jfma.2018.05.013] [Medline: 29908869]
42. Kawakami C, Ohshige K, Kubota K, Tochikubo O. Influence of socioeconomic factors on medically unnecessary ambulance calls. BMC Health Serv Res 2007 Jul 27;7(1):120 [FREE Full text] [doi: 10.1186/1472-6963-7-120] [Medline: 17655772]
43. Booker MJ, Purdy S, Shaw ARG. Seeking ambulance treatment for 'primary care' problems: a qualitative systematic review of patient, carer and professional perspectives. BMJ Open 2017 Aug 03;7(8):e016832 [FREE Full text] [doi: 10.1136/bmjopen-2017-016832] [Medline: 28775192]
44. Schäfer I, Menzel A, Herrmann T, Willms G, Oltrogge J, Lühmann D, et al. Compliance and patient satisfaction with treatment settings recommended by the medical on-call service 116117 in Germany using computer-assisted structured initial assessment: a cross-sectional observational study accompanying the demand intervention. BMJ Open 2023 May 09;13(5):e070475 [FREE Full text] [doi: 10.1136/bmjopen-2022-070475] [Medline: 37160385]
45. Rettungsdienstinformationen [Information on the rescue services]. Stumpf und Kossendey Verlag. URL: https://www.skverlag.de/rettungsdienstschulen/rettungsdienstinfos.html [accessed 2023-09-24]
46. Geier W. Strukturen, Akteure und Zuständigkeiten des deutschen Bevölkerungsschutzes [Structures, actors and jurisdictions of the German civil protection]. Bundeszentrale für politische Bildung [German Federal Agency for Civic Education]. URL: https://www.bpb.de/shop/zeitschriften/apuz/bevoelkerungsschutz-2021/327989/strukturen-akteure-und-zustaendigkeiten-des-deutschen-bevoelkerungsschutzes/ [accessed 2023-09-24]

Abbreviations

EMS: emergency medical service
ED: emergency department
GP: general practitioner
LAC: low-acuity call

Edited by A Mavragani; submitted 27.10.23; peer-reviewed by E Benjamin; comments to author 26.01.24; revised version received 14.02.24; accepted 19.02.24; published 10.04.24.

Please cite as:
Nau LM, Laux G, Altiner A, Szecsenyi J, Leutgeb R
The Use of Medical Services for Low-Acuity Emergency Cases in Germany: Protocol for a Multicenter Observational Pilot Study
JMIR Res Protoc 2024;13:e54002
URL: https://www.researchprotocols.org/2024/1/e54002
doi:10.2196/54002
PMID:38598281

Protocol

Development and Testing of an Electronic Diabetes Diary Integrated With a Hospital Information System for Individuals With Type 2 Diabetes Mellitus: Protocol for a Mixed Methods Study

Geena Skaria[1*], MSc; Bhageerathy Reshmi[1*], MSc, PhD; Sabu K M[1*], MSc, PhD; Sahana Shetty[2*], MD, DM; Vani Lakshmi R[3*], MSc, PhD

[1]Department of Health Information Management, Manipal College of Health Professions, Manipal Academy of Higher Education, Manipal, India
[2]Department of Endocrinology, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, India
[3]Department of Data Science, Prasanna School of Public Health, Manipal Academy of Higher Education, Manipal, India
[*]all authors contributed equally

Corresponding Author:
Bhageerathy Reshmi, MSc, PhD
Department of Health Information Management
Manipal College of Health Professions
Manipal Academy of Higher Education
Manipal, 576104
India
Phone: 91 9880530701
Email: reshmi.b@manipal.edu

Abstract

Background: Type 2 diabetes mellitus (T2DM) is one of the leading noncommunicable diseases that require diabetes self-management (DSM) practices. This study proposes to develop a customized mobile health (mHealth) app integrated with a hospital information system (HIS) to enable real-time, two-way transfer of information between the patient and physician. The captured information in the electronic health record will facilitate physicians to have a chronological account of the patient's diabetes history and enable tweaking of the treatment.

Objective: The objectives of the study are (1) to develop the HIS-integrated Electronic Diabetes Diary (EDDy) per the end-user expectations at a tertiary care hospital in a south Indian state with a high prevalence of T2DM and (2) to evaluate and test adherence to EDDy in the management of T2DM.

Methods: The study will be carried out in 3 phases. Phase 1 involved in-depth interviews with primary end users to gather information regarding their expectations from the hospital-based EDDy. Phase 2 will use this information to develop a customized mHealth app using an iterative model of software development. Phase 3 will involve a pre- and posttest design; the developed app will be tested among consenting patients, where physicians will receive the patients' data through the HIS-integrated mHealth app. The pre- and posttest values will be analyzed for adherence leading to improvement in patients' self-management of blood glucose, user experience, glycemic control, and clinical utility.

Results: Phase 1 was completed on November 28, 2023. Phase 2 commenced in December 2023 and will end in May 2025. Phase 3 will follow afterward.

Conclusions: The proposed app will include a convenient and simple alert system that enables the patient to test glucose values at self-selected intervals, provide grading options to enter diabetic-related complications, enhance patients' knowledge of tracking and managing the complications of diabetes, and help in maintaining the visual representation of glucose values and complications. The simplicity and usability of the modules are its novelty, which may motivate the patients to keep track of their glucose values and help them attain better health outcomes.

Trial Registration: Clinical Trial Registry India CTRI/2023/03/051077; http://tinyurl.com/4tau4ndb

International Registered Report Identifier (IRRID): PRR1-10.2196/50732

(JMIR Res Protoc 2024;13:e50732) doi:10.2196/50732

KEYWORDS

self-management of blood glucose; SMBG; diabetes self-management; DSM; personal health records; electronic diabetes diary; glycemic control; patient adherence; digital health

Introduction

In India, 11.8% of the population have diabetes per the National Diabetes and Diabetic Retinopathy Survey released by the Ministry of Health and Family Welfare in 2019, and this is projected to have a steady rise of 3.8% annually [1]. This prevalence is higher in the southern states and union territories of India [2]. *The Indian Glucose Monitoring Device Market Reports of 2020* [3] suggested that the use of glucometer was always on the rise, and it was specifically noticed that there was an exponential increase in its sale during the COVID-19 pandemic period. Technology-enabled self-management has been increasingly recommended, along with proper medication and lifestyle modification, to tackle diabetes. There are numerous diabetes managements apps available in the Google Play store; however, subscription to such apps is not proportional to the population with diabetes [4]. Literature from other parts of the world suggest that the adoption of digital diabetes-monitoring solutions is expected to reach 21% by 2027 [5].

Diabetes is an irreversible chronic condition that need to be well managed by altering lifestyles, food habits, and physical activities [6]. However, a standard diabetes management regimen may not be feasible to everyone around the globe, as each of these factors varies according to geographical locations and general living conditions [5]. Using customized information that is specific to the local lifestyle may be more effective and easier to ensure adherence. Existing literature suggests that nonadherence to treatment regimen and irregularity in following a diabetes-friendly lifestyle leads to poorly managed diabetes and poor disease outcomes [7]. To enhance the existing measures to manage T2DM, efficient methods needs to be formulated to ensure adherence to treatment regimen [8]. The success of such activities requires active involvement of the patients and caregivers. They should be motivated to follow T2DM management instructions from health care professionals.

This study setting already has an existing system of manual diabetes information documentation that expects its patients to record their self-management of blood glucose (SMBG) practices systematically and submit them to the treating physician during consultation. These glucose monitoring records are used by the physician to evaluate the patient's glycemic status and make appropriate clinical decisions. This study proposes to automate this process and make it more efficient for the patients and physicians. The proposed electronic diary is expected to reduce the loss of documented values, minimize errors, as well as motivate the patients to effectively make use of technology and manage their condition.

A pilot study was conducted to analyze the knowledge and attitude to digital diabetes management practices among 50 existing patients with diabetes, which indicated that ignorance and technological illiteracy are the main reasons behind nonuse of digital apps among them. Those who used digital apps, such as mobile health (mHealth) apps, suggested that the information available is more general in nature and that they find it difficult to navigate and comprehend the information, eventually leading to the discontinuation of its use.

Methods

Overview

The study will be carried out in the outpatient department (OPD) of the endocrinology department at a tertiary care hospital in a south Indian state, and it is divided into 3 phases. In phase 1, a qualitative study was conducted; in phase 2, the mobile app with be developed and integrated with a health information system (HIS); and finally, in phase 3, the developed app will be tested for its feasibility using a pre- and posttest design.

The study is based on the principles of the "theory of change," where stakeholders will be consulted through in-depth interviews (IDIs) to identify the deterrents to acceptance and adherence of electronic diabetes-monitoring practices, potential challenges, as well as ethical issues related to electronic information sharing. This feedback will provide the cues for the development of a customized electronic diabetes-monitoring system. The study would also attempt to identify the reasons that would lead to the discontinuation of electronic monitoring practices among patient with T2DM and address them by developing a more user-friendly mHealth app. This study will also analyze the patient acceptance of the mHealth app and their adherence to SMBG practices.

The model will then be developed and integrated with an HIS. Finally, it will be tested among patients with T2DM regarding their acceptance and adherence to using the Electronic Diabetes Diary (EDDy), its usability, contextual relevance according to user expectation, and clinical utility in terms of glycemic control.

Ethical Considerations

This study has been approved by the Institutional Ethics Committee (IEC; IEC No:223/2022). The participants personal information will be anonymized, and all privacy, confidentiality, and compensation policies will be adhered to as per the IEC guidelines.

Pilot Study

As a precursor to this study, a pilot study was conducted in a tertiary care hospital among 50 patients with T2DM to understand the existing personal record-keeping practices, the challenges they face, and their awareness of personal record keeping. The perception, expectations, and concerns of the target population were studied using a validated questionnaire survey. Patients with T2DM who are within the age group of 40-65 years were included in the study. The study setting encouraged patients with T2DM to document their SMBG values by providing a data sheet to enter the values and asking patients to bring it with them when they come for a doctor's appointment. It is a valuable tool for the doctor to assess the

values and make better clinical decisions in the management of the disease.

A cross-sectional study was conducted, and a purposive sampling technique was followed to select the participants. A mixed-type questionnaire (both open- and close-ended questions) was used to collect data.

Phase 1

Study Design

IDIs with key stakeholders was carried out to identify the reasons for nonadherence, expectations from EDDy, and mandatory requirements to develop the intervention mechanism. The key stakeholders included the following participants:

- Patients with T2DM
- Their caregivers
- Treating doctors
- Diabetes counselors (includes nursing counselors, diet counsellors, and physiotherapists)

Sample Selection

The IDI participants were enrolled according to the following criteria: patients who own an Android smartphone and those who regularly attend doctor's appointments (ie, those who visit the OPD at least once in the last 6 months). Patients who are literate, can understand the local language (Kannada or Tulu) or English, aged 40-65 years, and have hemoglobin A_{1c} values between 7% and 10% were selected to ensure homogeneity. Patients with gestational diabetes and other terminal illnesses were excluded. The IDIs were conducted among the immediate caregivers of the patients (ie, those who are actively involved in the care of the patient). To understand the practical aspects of the treatment and management of patients, physicians, nurses, and counsellors were also interviewed.

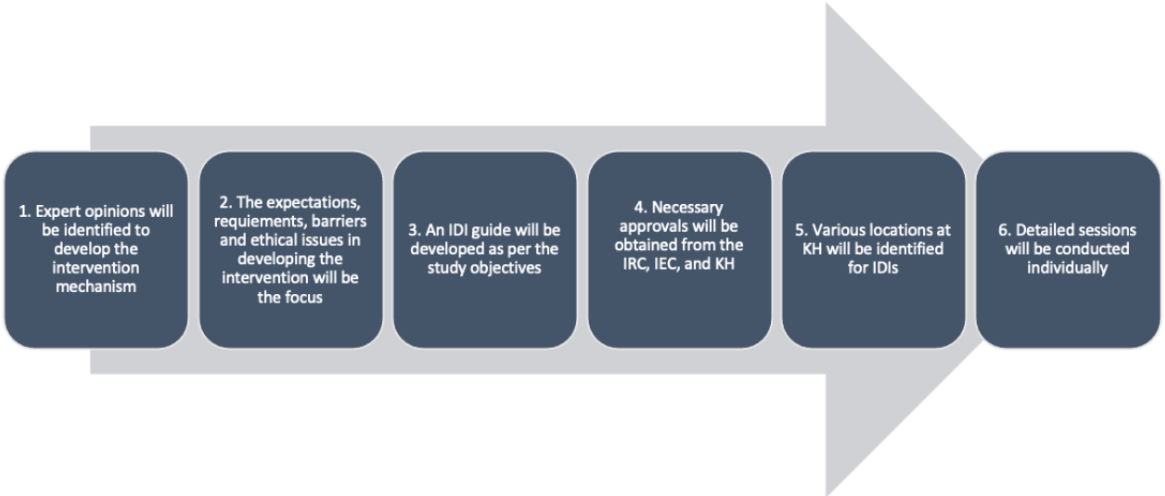
Even with the availability of various diabetes management apps, studies suggest they are not very popular among the general population. The reason for this underuse and nonadherence, along with their expectations from mHealth apps, are the key areas that were addressed among patients with T2DM and their caregivers. The doctors and diabetes counselors were interviewed to understand the challenges they face while managing patients with T2DM and their SMBG practices.

IDI Process

The IDIs focused on the perspectives of patients with T2DM and their caregivers along with physicians and diabetes counselors who are actively involved in the care of patient with T2DM. Additionally, IT and health information management professionals were also consulted on ethical challenges and technical expertise. The IDI guide was designed based on the objectives of the study and the content was validated by experts. The IDI process is shown in Figure 1.

Qualitative data generated during the IDIs will be analyzed by using ATLAS.ti software (version 8; ATLAS.ti), and a report will be prepared. Based on the report, the researchers and the subject experts will identify the most feasible options that will be considered for incorporation into EDDy.

Figure 1. Process of the in-depth interviews (IDIs). IEC: Institutional Ethical Committee; IRC: Institutional Research Committee; KH: Kasturba Hospital.



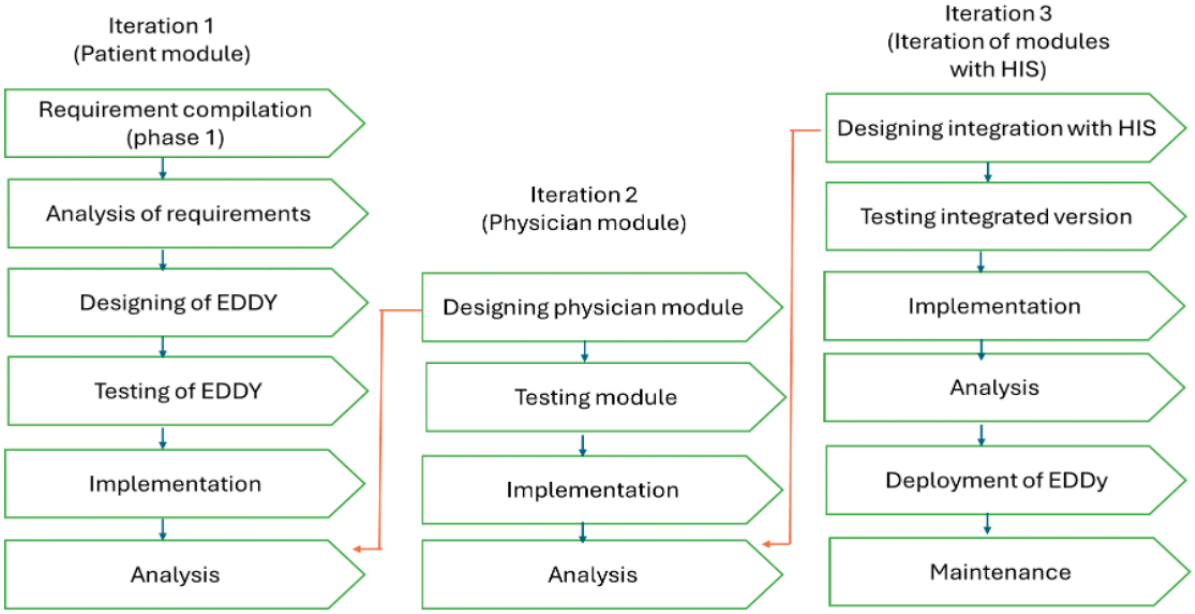
Phase 2

Development of EDDy

Phase 2 is the main part of this research, where the software will be developed based on inputs from the IDIs and the literature. The mobile app will be developed on Android Studio (Google) using an iterative model design.

The iterative model (Figure 2) is one of the Software Development Life Cycle models, where the development of a system goes through repeated cycles (iterative) and is conducted in smaller portions at a time (incremental) [9]. As and when the different modules of the app are developed, they will be tested and reviewed against the end user's expectation, and accordingly, modifications and further development will be done. This process will enable easier debugging and fixing of errors as and when tested.

Figure 2. Iterative model of Software Development Life Cycle. EDDy: Electronic Diabetes Diary; HIS: hospital information system.



The development and testing of the app will involve development, pilot-testing, and debugging at each phase. Each iteration will be subjected to the development, testing implementation, and analysis of each component of EDDy. The components for incorporation into the software will be validated by the following experts:

- An endocrinologist
- Qualitative experts
- The IT team at the hospital

The expected pattern and time period for phase 2 are as follows.

System Development

Step 1: Requirements

This is the phase where the stakeholders' requirements are enquired and compiled, which was primarily covered in phase 1. The captured data will be systematically entered into Microsoft Excel for further evaluation.

Step 2: Analysis

The compiled information will be divided into feasible and nonfeasible items as per the system development and HIS-interfacing requirements. This step will be conducted with the researchers and technical experts.

Step 3: Designing and Development

This step will be done by a software developer with the support of a researcher. Once the feasible requirements are sorted and finalized by the researcher, the design of the app will take place. First, a prototype of the system will be developed, and the requirements for each module of the app will be determined. This step includes the coding of the app based on the design. Android Studio, an open-source program for Android software development, will be used to develop the proposed mobile app. The iteration process has 3 phases, where a patient module and a physician module will be designed, and integration with an HIS will be performed as depicted in Figure 2.

Step 4: Implementation

After development, each module of EDDy will be pilot-tested for its intended use. The modules will be connected to a web-based backend database application to help the validation of content, visualization, and analysis of the data collected.

Step 5: Testing and Quality Assurance

The developed app will undergo a standard testing and quality assurance process to identify and rectify any issues and bugs. Each module will be validated during testing to ensure its intended performance.

Step 6: Analysis of Feedback

A pilot test among 2 potential users will be carried out at each level of iteration, and user experience will be measured using a Likert scale on various aspects of the app's functionality. The parameters that will be measured during the piloting process will be the app's functionality, usability, accessibility, compatibility, and performance under real-life scenarios.

Once the app is fully developed and interfaced with an HIS, it will be installed in the respective systems of the stakeholders and tested for its performance. Gaps and technical glitches will be rectified at each phase.

Step 7: Deployment

The final app will be deployed among end users (patients and physicians).

Step 8: Maintenance

The final app will be integrated into an HIS. Once the module is fully functional, the study will proceed to phase 3.

Expected Outcomes From EDDy

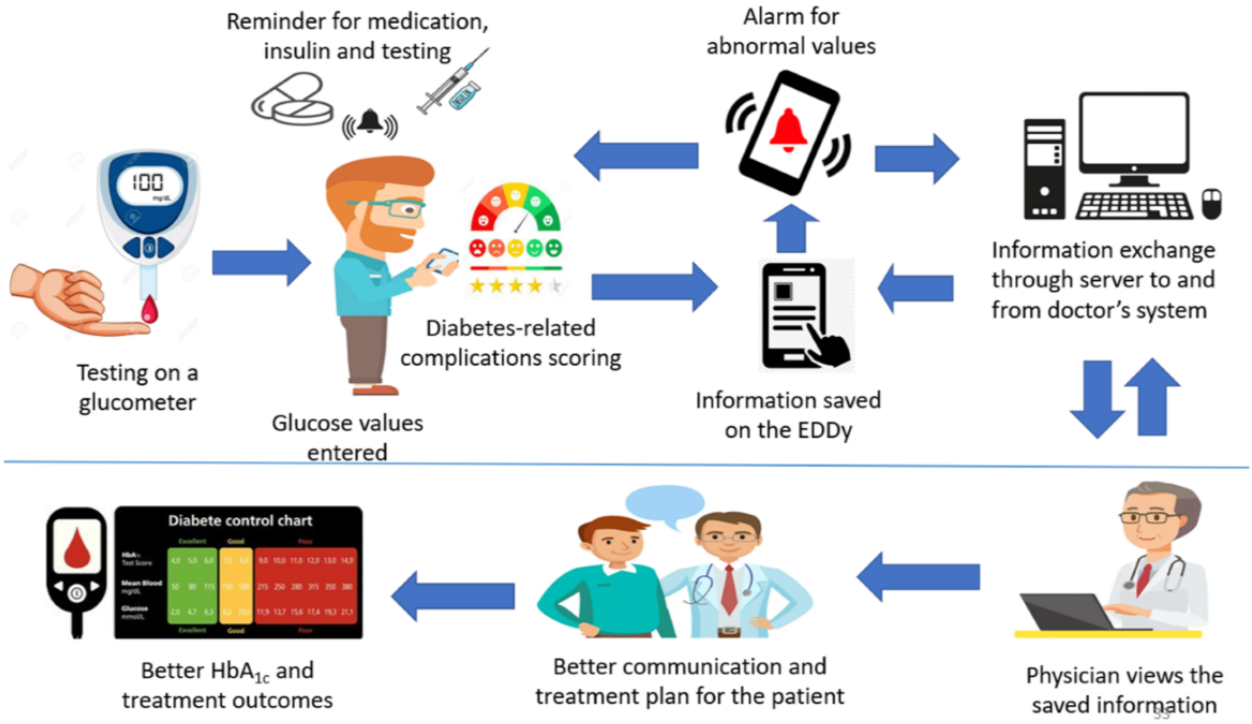
The app is expected to improve the SMBG practices in patients with T2DM. EDDy is expected to motivate the use of the app (*acceptability*) and improve the user experience on the *contextual relevance*. The *ease* of using the customized system and a clinician's feedback mechanism through the physician

module is expected to improve the *clinical utility* of the app. It is expected that adherence to using the app would improve compliance to treatment protocol, thus improving treatment outcomes.

The entry of information into EDDy can be done either by the patient or their caregiver. The entry of SMBG values by the patient is a standard clinical practice in patient management. The current practice is that these self-monitored blood glucose values (SMBG data) is maintained by the patient on a printed form provided by the hospital. It is standard practice that such SMBG data function as a mechanism that helps physicians to optimize medication in routine clinical practice [10].

A researcher will provide instruction to the patient or patient party on how data entry needs to be done on the app. Additionally, a built-in user manual will be provided with the system. This will be developed as a part of the app development. A multilingual *user manual* or *instructional videos* will be developed to assist the patient in using EDDy. The pictogram in Figure 3 represents the workflow of EDDy.

Figure 3. Prototype of EDDy.



Phase 3

Study Design

Phase 3 will involve testing the adherence and usability of the developed app. This phase will use a pre- and posttest design among 48 patients with diabetes selected through purposive sampling.

At a 5% level of significance with 80% power and an effect size of 0.25, the minimum sample size required for a single-group, repeated measures study design involving 1 primary quantitative outcome (adherence) measured across 3 time points (preintervention, after 3 months, and after 6 months; correlation among repeated measures is 0.3) to understand the adherence to EDDy integrated with an HIS is 38 individuals. Incorporating a dropout rate of 20%, the minimum sample size requirement is 48 individuals.

The sample size was computed using G*Power (version 3.1.9; Universität Düsseldorf). The sample size may be amended (if required) based on pilot study findings.

The study setting will be the endocrinology OPD of a tertiary care hospital in coastal Karnataka, India.

Regarding study participants, patients with T2DM who have regular follow-up records will be considered for the study.

This study will analyze the adherence of patients with T2DM to EDDy in comparison to the existing manual method of documentation. Adherence will be evaluated in terms of the following:

- Adherence of entering SMBG values as predetermined by the patient: The study participants will be instructed to fix the frequency that they will monitor their blood glucose; based on this frequency, they will be prompted to conduct the glucometer testing and enter the values into EDDy. The values will be stored in the app and will be transferred to the server on a regular basis as the EDDy is integrated with an HIS.
- Adherence to diabetes self-management (DSM) practices: Pre- and posttest adherence to DSM practices will be analyzed using the same content-validated questionnaire.
- Adherence to routine blood investigations and screening regimen: Pre- and posttest adherence to periodic blood investigation and comorbidity screening will be analyzed.

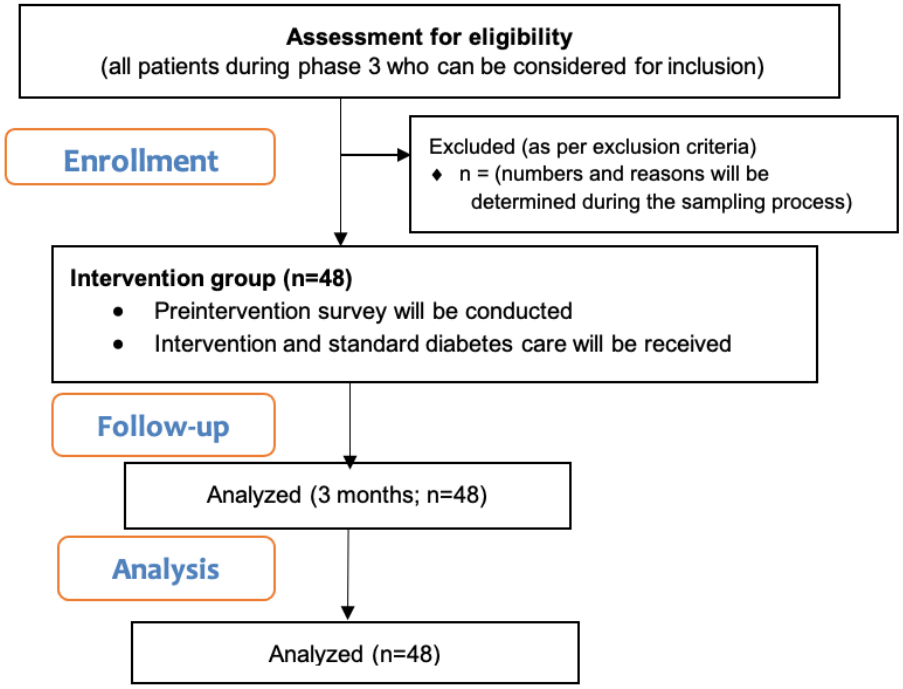
The inclusion and exclusion criteria for sample collection will remain same as that of phase 1.

Phase 3 will be evaluated in 3 intervals:

- First evaluation (preintervention): During enrollment into the study, the patients will undergo an entry survey using a content-validated questionnaire to analyze the current DSM and SMBG practices they follow.
- Second evaluation (follow-up): An interim follow-up will be conducted in the third month.
- Third evaluation (postintervention): The same questionnaire used in the first evaluation will be used to evaluate DSM and SMBG practices after the intervention.

The study participants will be provided with EDDy on their mobile phones and will be trained to use it along with standard diabetes care. Training materials will be a part of the app for patient's ready reference. The pre- and posttest process is shown in Figure 4.

Figure 4. Pre and Posttest Process of development of EDDy.



Analysis

Study participants will be followed up for 6 months and will be analyzed primarily for their adherence to using EDDy. It will be assessed based on patients' willingness to use it, the ease of use, their acceptance of EDDy in terms of the contextual relevance, and the clinical utility. The participants will undergo an exit survey at the end of the study period using a validated questionnaire. It will be specific for assessing the qualitative parameters such as *user experience*, *glycemic control*, *adherence leading to improvement in their SMBG*, and *clinical utility.*

The qualitative outcomes are as follows:

- Ease of use and adherence: User's perception on accessing the various modules in the app, ease of entering information, ease for retrieving information, and ease of comprehending information
- Glycemic control: Adherence in terms of regular monitoring and tracking of blood glucose values to keeps it under check, leading to well-managed T2DM
- Contextual relevance: Relevance of the contents of EDDy in terms of the user expectations and requirements as expressed in phase 1 of the study
- Adherence to SMBG and DSM practices: Reminders and alerts that ensure adherence to medications, insulin injections, regular glucose testing, and comorbidity screening
- Clinical utility: Improvement in treatment outcomes due to adherence to reminders or alerts and monitoring of blood glucose, adherence to medication, and follow-ups

The frequency will be tested based on the Diabetes Co-Conditions Screening Checklist provided by the Association of Diabetes Care & Education Specialists [11].

The following standard tools will be used for assessment, which are modified according to the study requirements and will be content validated by experts:

- Perceived Health Web Site Usability Questionnaire: A 12-item questionnaire that is validated for assessing the usability of health websites for older adults will be used [12].
- Diabetes Self-Management Questionnaire: It describes self-care activities related to diabetes. SMBG practices will be analyzed using this tool. A validated 12-item questionnaire to assess self-care activities associated with glycemic control will be used [13].
- A self-developed, content-validated questionnaire: Adherence will be evaluated, including the regularity of use; ease of use with respect to entering diabetes-related information such as regular testing and entry of glucose levels; adherence to medications or insulin doses; reporting of diabetes-related emergencies or complications, if any; and adherence to periodic screening such as laboratory

investigations, peripheral neuropathies, retinopathy, diabetic foot, and BMI.

The physicians will be interviewed to assess the clinical utility of the app and their experience in using the app using a content-validated questionnaire.

Expected Outcomes

A customized mHealth app that provides adequate information specific to the T2DM management will be developed. This can lead to an effective intervention that will reduce the risk of a person diagnosed with T2DM from developing further disease complications, such as chronic kidney disease, diabetic foot, retinopathies, and peripheral neuropathies, thereby reduce the cost of health care expenditure.

Results

Pilot Study

Out of 50 patients with T2DM (aged 40-50 years), 22 (44%) documented their self-monitored glucose values, whereas the remaining 28 (56%) did not. The percentage score of sources used by patients with diabetes to document the values of self-care activities showed that most of the patients (n=21, 42%) were using a personal diary to document, whereas only 1 (2%) patient each used a diabetes app and mobile notes. Responses from patients with diabetes regarding the necessity of personal health information in diabetes management showed that 31 (62%) patients were not completely aware of personal health information management.

The study results reflected the perception of patients with T2DM about their personal health information documentation practices. Additionally, the study gave a brief outlook about the challenges and barriers that patients face during their DSM activities.

Study Status

Phase 1 was completed on November 28, 2023. Phase 2 of the study, which is the app development, commenced in December 2023 and will end by March 2025. The wireframe model of EDDy is shown in Multimedia Appendix 1. Phase 3 of this study will follow afterward, analyzing the effectiveness of adherence to the app and its usability.

Discussion

Pilot Study Findings

It was evident from the pilot study that there is a strong requirement to promote documentation of SMBG and DSM practices. Overall, the study concluded that there is a scope for strengthening DSM, knowledge development, and improved self-documentation practices by promoting personal health information practices among patients with diabetes. It has the potential to improve the quality of life of patients with diabetes by better promoting self-care.

Expected Findings

When considering a country such as India, which has a very diverse population belonging to different socioeconomic backgrounds, it is difficult to implement a standard practice to tackle a problem. Statistics show that out of 45% of Indians over 45 years of age, about 11.5% are diagnosed with diabetes or high blood sugar levels [3]. Patients belonging to this age group are comparatively less familiar with technology and digital apps. Understanding their requirements and developing a hospital-based electronic diary may promote its use and adherence among them and, eventually, all patients with T2DM.

Considering India's socioeconomic background, the requirements for this population need to be assessed from various angles. It can be demonstrated by analyzing the findings of the study conducted by Walle et al [14] among 422 patients with diabetes in Ethiopia. The study aimed at understanding the willingness of patients with diabetes mellitus to use mHealth app and its associated factors for self-care management in a low-income country as a precursor to digital health implementation in Ethiopia. The study concluded that the mHealth app developers should consider factors such as the patients' age, place of residence, internet connectivity, attitude, perceived ease of use, and perceived usefulness while developing similar apps [14].

The pilot study conducted to analyze the awareness of patients with T2DM also clearly stated that they were aware of the importance of SMBG and DSM practices and the availability of mHealth apps to help them manage their T2DM. However, they were not very keen on using it due to various personal factors.

It was evident from the findings that there is a clear requirement to generate awareness about T2DM management and the use of mHealth apps. It is equally important to understand the challenges that keep them from using available mHealth apps. Based on these observations, if an mHealth app can be developed and the information can be transferred to the patients' records in real time, it will be beneficial for both the patients and the doctors to better manage the condition.

Conclusion

The literature review and pilot study conducted suggests that an easily manageable, personalized diabetes-monitoring system for patients to do regular self-checks and that provides the end users with accurate data on the patient's diabetic history will be beneficial for better management of T2DM. It would enable better sharing of information between patients and doctors, thus improving the communication between patients and doctors, which is significant in the management of diabetes and leads to better treatment outcome. The available apps are not very popular among the end users as they find it difficult to use and understand the contents. To ensure better usability and adherence, a convenient and simple alert system that enables the patient to conduct glucose testing at intervals set by the patients themselves can be designed. The proposed app EDDy will provide grading options to enter the diabetic-related complications (such as neuropathy, retinopathy, diabetic ulcers, etc), thus alerting patients and doctors for prompt action. It is also expected to enhance patients' knowledge of tracking and managing the complications of diabetes and help in maintaining the visual representation of glucose values and complications. The simplicity and usability of the module are its novelty, which

may motivate the patients to keep track of their glucose values and help them to attain better health outcomes.

Acknowledgments

The author would like to acknowledge the participants of the pilot study and Mr Prajwal L Salins and Ms Ashika Shetty.

Data Availability

As this is a study protocol, the results of the pilot study have been reported, and the data will be submitted as required.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Wireframe model of Electronic Diabetes Diary (EDDy).
[PDF File (Adobe PDF File), 225 KB - resprot_v13i1e50732_app1.pdf]

References

1. Sharma NC. Government survey found 11.8% prevalence of diabetes in India. Mint. 2019 Oct 10. URL: https://www.livemint.com/science/health/government-survey-found-11-8-prevalence-of-diabetes-in-india-11570702665713.html [accessed 2024-01-12]
2. Gaikwad L, Bapat SV. Diabetes among senior citizens more prevalent in urban India: LASI report. Down To Earth. 2021 Jan 13. URL: http://tinyurl.com/4tz3ytnt [accessed 2024-01-12]
3. Research and Markets. India glucose monitoring devices market report 2020: historical data 2016-2019, base year of 2020, estimates for 2021 and forecasts 2022-2026. Globe Newswire. 2020 Nov 24. URL: https://www.globenewswire.com/en/news-release/2020/11/24/2132509/28124/en/news [accessed 2024-01-12]
4. Kesavadev J, Krishnan G, Mohan V. Digital health and diabetes: experience from India. Ther Adv Endocrinol Metab 2021 Nov 17;12:20420188211054676 [FREE Full text] [doi: 10.1177/20420188211054676] [Medline: 34820114]
5. Reddy N, Verma N, Dungan K. Monitoring technologies-continuous glucose monitoring, mobile technology, biomarkers of glycemic control. In: Feingold KR, Anawalt B, Blackman MR, editors. Endotext. South Dartmouth, MA: MDText.com, Inc; Jul 8, 2023.
6. Koner S. Technology streamlining diabetes management in India. BioSpectrum. 2021 Oct 4. URL: https://www.biospectrumindia.com/news/17/19698/technology-streamlining-diabetes-management-in-india.html [accessed 2024-01-12]
7. Singh RK, Pattanshetty S, Nair S. Quality of life among type 2 diabetes patients in Udupi taluk: a cross-sectional study. Int J Med Sci Public Health 2016 Jan 26;5(9):1846-1850. [doi: 10.5455/ijmsph.2016.12012016341]
8. Haak T, Hanaire H, Ajjan R, Hermanns N, Riveline JP, Rayman G. Flash glucose-sensing technology as a replacement for blood glucose monitoring for the management of insulin-treated type 2 diabetes: a multicenter, open-label randomized controlled trial. Diabetes Ther 2017 Feb;8(1):55-73 [FREE Full text] [doi: 10.1007/s13300-016-0223-6] [Medline: 28000140]
9. Billingham S, Whitehead AL, Julious SA. Iterative model. JavaTpoint. URL: https://www.javatpoint.com/software-engineering-iterative-model [accessed 2024-01-17]
10. American Diabetes Association. ADA and ADCES update national standards for diabetes self-management education and support. American Diabetes Association. 2022 Jan 20. URL: https://diabetes.org/newsroom/press-releases/2022/ada-and-adces-update-national-standards-for-diabetes-self-management-education-support [accessed 2024-01-12]
11. Rosselli JL. Diabetes Co-Conditions Screening Checklist. Association of Diabetes Care & Education Specialists. 2021. URL: https://www.diabeteseducator.org/docs/default-source/practice/educator-tools/co-conditions/diabetes-co-conditions-screening-chart.pdf?sfvrsn=4 [accessed 2024-01-12]
12. Nahm ES, Resnick B, Mills ME. Development and pilot-testing of the Perceived Health Web Site Usability Questionnaire (PHWSUQ) for older adults. Stud Health Technol Inform 2006;122:38-43. [Medline: 17102214]
13. Schmitt A, Reimer A, Hermanns N, Huber J, Ehrmann D, Schall S, et al. Assessing diabetes self-management with the Diabetes Self-Management Questionnaire (DSMQ) can help analyse behavioural problems related to reduced glycaemic control. PLoS One 2016 Mar 3;11(3):e0150774 [FREE Full text] [doi: 10.1371/journal.pone.0150774] [Medline: 26938980]
14. Walle AD, Ferede TA, Shibabaw AA, Wubante SM, Guadie HA, Yehula CM, et al. Willingness of diabetes mellitus patients to use mHealth applications and its associated factors for self-care management in a low-income country: an input for digital health implementation. BMJ Health Care Inform 2023 May;30(1):e100761 [FREE Full text] [doi: 10.1136/bmjhci-2023-100761] [Medline: 37236653]

Abbreviations

CTRI: Clinical Trial Registry of India
DSM: diabetes self-management
EDDy: Electronic Diabetes Diary
IDI: in-depth interview
IEC: Institutional Ethics Committee
HIS: hospital information system
mHealth: mobile health
OPD: outpatient department
SMBG: self-management of blood glucose
T2DM: type 2 diabetes mellitus

Edited by A Mavragani; submitted 11.07.23; peer-reviewed by B Kalema, M Lee; comments to author 13.10.23; revised version received 03.11.23; accepted 23.11.23; published 23.01.24.

Please cite as:
Skaria G, Reshmi B, K M S, Shetty S, Lakshmi R V
Development and Testing of an Electronic Diabetes Diary Integrated With a Hospital Information System for Individuals With Type 2 Diabetes Mellitus: Protocol for a Mixed Methods Study
JMIR Res Protoc 2024;13:e50732
URL: https://www.researchprotocols.org/2024/1/e50732
doi:10.2196/50732
PMID:38261369

Protocol

Enhancing the Efficiency of a Radiation Oncology Department Using Electronic Medical Records: Protocol for Preparing Radiotherapy

Hao-Shen Cheng[1*], MD; Weir-Chiang You[1*], MD, PhD; Ni-Wei Chen[1*], MS; Mu-Chih Hsieh[1*], MS; Che-Fu Tsai[1*], MS; Chia-Jing Ho[1*], BS; Chien-Chih Chen[1*], MD, PhD

Taichung Veterans General Hospital, Taichung, Taiwan

[*]all authors contributed equally

Corresponding Author:
Chien-Chih Chen, MD, PhD
Taichung Veterans General Hospital
1650 Taiwan Boulevard Sect. 4
Taichung, 40705
Taiwan
Phone: 886 4 2359 2525 ext 5601
Email: chiencheh@gmail.com

Abstract

Background: Electronic medical records (EMRs) streamline medical processes, improve quality control, and facilitate data sharing among hospital departments. They also reduce maintenance costs and storage space needed for paper records, while saving time and providing structured data for future research.

Objective: This study aimed to investigate whether the integration of the radiation oncology information system and the hospital information system enhances the efficiency of the department of radiation oncology.

Methods: We held multidisciplinary discussions among physicians, physicists, medical radiation technologists, nurses, and engineers. We integrated paper records from the radiation oncology department into the existing hospital information system within the hospital. A new electronic interface was designed. A comparison was made between the time taken to retrieve information from either the paper records or the EMRs for radiation preparation. A total of 30 cases were randomly allocated in both the old paper-based system and the new EMR system. The time spent was calculated manually at every step during the process, and we performed an independent 1-tailed *t* test to evaluate the difference between the 2 systems.

Results: Since the system was launched in August 2020, more than 1000 medical records have been entered into the system, and this figure continues to increase. The total time needed for the radiation preparation process was reduced from 286.8 minutes to 154.3 minutes ($P<.001$)—a reduction of 46.2%. There was no longer any need to arrange for a nurse to organize the radiotherapy paper records, saving a workload of 16 hours per month.

Conclusions: The implementation of the integrated EMR system has resulted in a significant reduction in the number of steps involved in radiotherapy preparation, as well as a decrease in the amount of time required for the process. The new EMR system has provided numerous benefits for the department, including a decrease in workload, a simplified workflow, and conserving more patient data within a confined space.

(JMIR Res Protoc 2024;13:e51002) doi:10.2196/51002

KEYWORDS

efficiency; electronic medical records; Hospital Information System; protocol; radiation oncology

Introduction

The advantages of electronic medical records (EMRs) include facilitating medical process management, quality control, and the sharing of medical record data among different departments in a hospital, as well as reducing both costs and storage space for paper medical records [1,2]. The Ministry of Health and Welfare in Taiwan implemented a pilot program for the digitalization of medical records in 2002, and our hospital participated in this program to digitalize our medical records.

However, due to the highly complex nature of the information contained in radiotherapy (RT) treatment plans [3,4], the paper records of RT are not easily integrated into the hospital information system (HIS) [5-7], causing operational difficulties for medical staff across different departments. These difficulties included obtaining information such as a patient's cumulative dose, fractionations, and frequency of treatment through our HIS. Additionally, searching for treatment history in paper records is a time-consuming and inefficient process that can lead to errors, especially as the records are handwritten. Moreover, the software used in a linear accelerator is independent of the HIS in most radiation oncology departments. Doctors and other medical personnel must use 2 different systems, which means they often have repeated tasks. For example, when a physician wants to write an RT certificate for a patient, information such as date of treatment, total dose, and frequency of treatment must be entered into a certificate manually, which is prone to errors and is time-consuming. Integrating the 2 systems would allow doctors to work more efficiently and serve more patients. Structured data can also be used for future quality control and clinical medical research. Furthermore, various monthly and annual reports in an integrated system can allow the department manager to effectively monitor the clinical load in the department, and the data can be used as a reference for manpower deployment and overtime budget application [8].

In line with national policy and the needs of our hospital, an EMR system for the radiation oncology department was established. This study examines how the integration of the RT EMR system with our HIS improved the efficiency of our department and the accuracy of the data. In this study, we demonstrated that by consolidating the 2 separate systems into 1, we were able to significantly increase efficiency, save time, and conserve valuable resources.

Methods

Overview

In January 2020, the first meeting was convened to discuss the implementation of EMRs. Representatives from various staff groups, including physicians, physicists, medical radiation technologists, nurses, and engineers, were appointed to discuss workflow arrangements and functional requirements. The preliminary system was completed in July 2020, followed by internet-based testing and debugging. The updated system was fully deployed in August 2020, replacing the old system entirely. We kept a monthly review of the system in order to debug or improve the user experience.

The first step involved reviewing the paper documents, including graphs, tables, and written records. Staff from different departments held monthly discussions in the Radiation Oncology Department conference room, and the records of our meetings were saved in our database for the future. Our staff and engineers discussed the feasibility of transforming each item into electronic records. In the paper documents, check marks were made under the date in the table upon completion of daily treatment. If daily treatment was not performed, the field would be left blank. The total number of treatment days was calculated manually. Following discussions with the engineers, key information, such as the radiation beam energy, radiation technique, planned target volume and dose, treatment date, and daily treatment status, were selected as items to be included in the electronic records.

The subsequent step involved educating physicians about how to input treatment plan information into the HIS. A new electronic interface was designed for physicians to input crucial data, such as the treatment intent, planned target volume, planned dose, and planned number of treatment days. These data would then be integrated into the EMR.

In addition, daily treatment progress was recorded automatically in the HIS. The total number of treatment days was controlled by the electronic treatment plan entered by the physician, thus preventing unnecessary dose delivery. The EMR retrieved the actual treatment dates from the HIS, thereby providing precise treatment progress information. After several adjustments, the final version of the EMR system was launched in the HIS (Figure 1).

Figure 2 shows the comparison of the preparation processes between paper record usage and the integrated electronic record system. In order to evaluate the results of our integration, a comparison was made between the time taken to retrieve information from either the paper records or the EMRs for radiation preparation. A total of 30 cases were randomly allocated in both the old paper-based (legacy) system and the new EMR system. The time spent was calculated manually at every step during the process, and we performed an independent *t* test to evaluate the difference. All statistical analyses were performed with SPSS (version 23; IBM Corp). A *P* value of <.05 was considered statistically significant. This study explores the benefits of converting paper medical records in the radiation oncology department into EMRs and integrating them with the hospital's existing electronic medical systems. It does not involve personal information or related ethical issues.

Figure 1. The final version of the electronic medical record (EMR), including the records of the past treatment of patients, a review of their past treatment status, and a link to the latest EMRs for tracking their current condition. CBCT: cone-beam computed tomography; CT: computed tomography; ICD9: International Classification of Diseases, Ninth Revision; ICD10: International Statistical Classification of Diseases, Tenth Revision; OBI: on-board imaging.

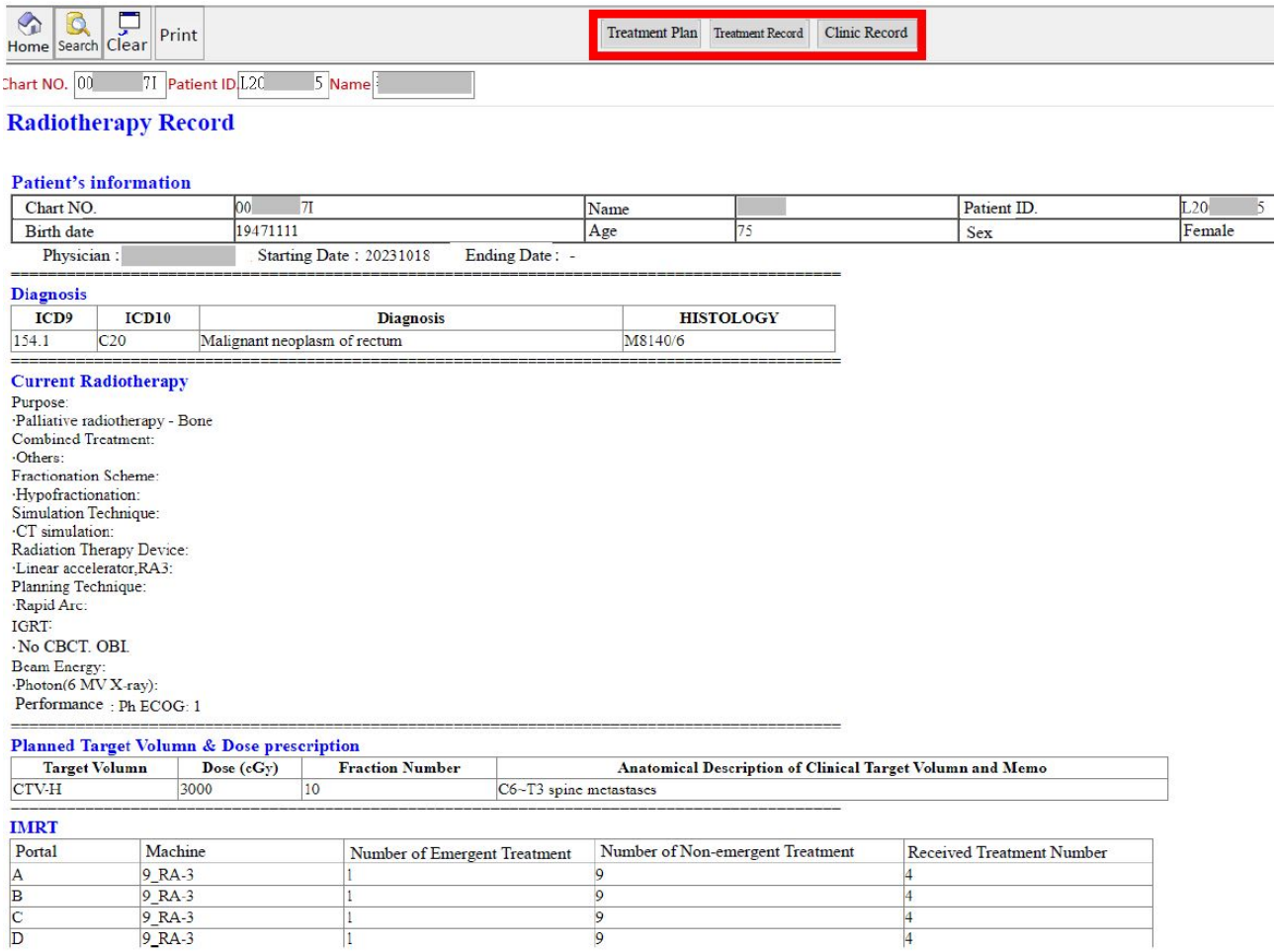

Home Search Clear Print Treatment Plan Treatment Record Clinic Record

Chart NO. 00 7I Patient ID L20 5 Name

Radiotherapy Record

Patient's information

Chart NO.	00 7I	Name		Patient ID.	L20 5
Birth date	19471111	Age	75	Sex	Female

Physician : Starting Date : 20231018 Ending Date : -

Diagnosis

ICD9	ICD10	Diagnosis	HISTOLOGY
154.1	C20	Malignant neoplasm of rectum	M8140/6

Current Radiotherapy

Purpose:
·Palliative radiotherapy - Bone
Combined Treatment:
·Others:
Fractionation Scheme:
·Hypofractionation:
Simulation Technique:
·CT simulation:
Radiation Therapy Device:
·Linear accelerator,RA3:
Planning Technique:
·Rapid Arc:
IGRT:
· No CBCT. OBI.
Beam Energy:
·Photon(6 MV X-ray):
Performance : Ph ECOG: 1

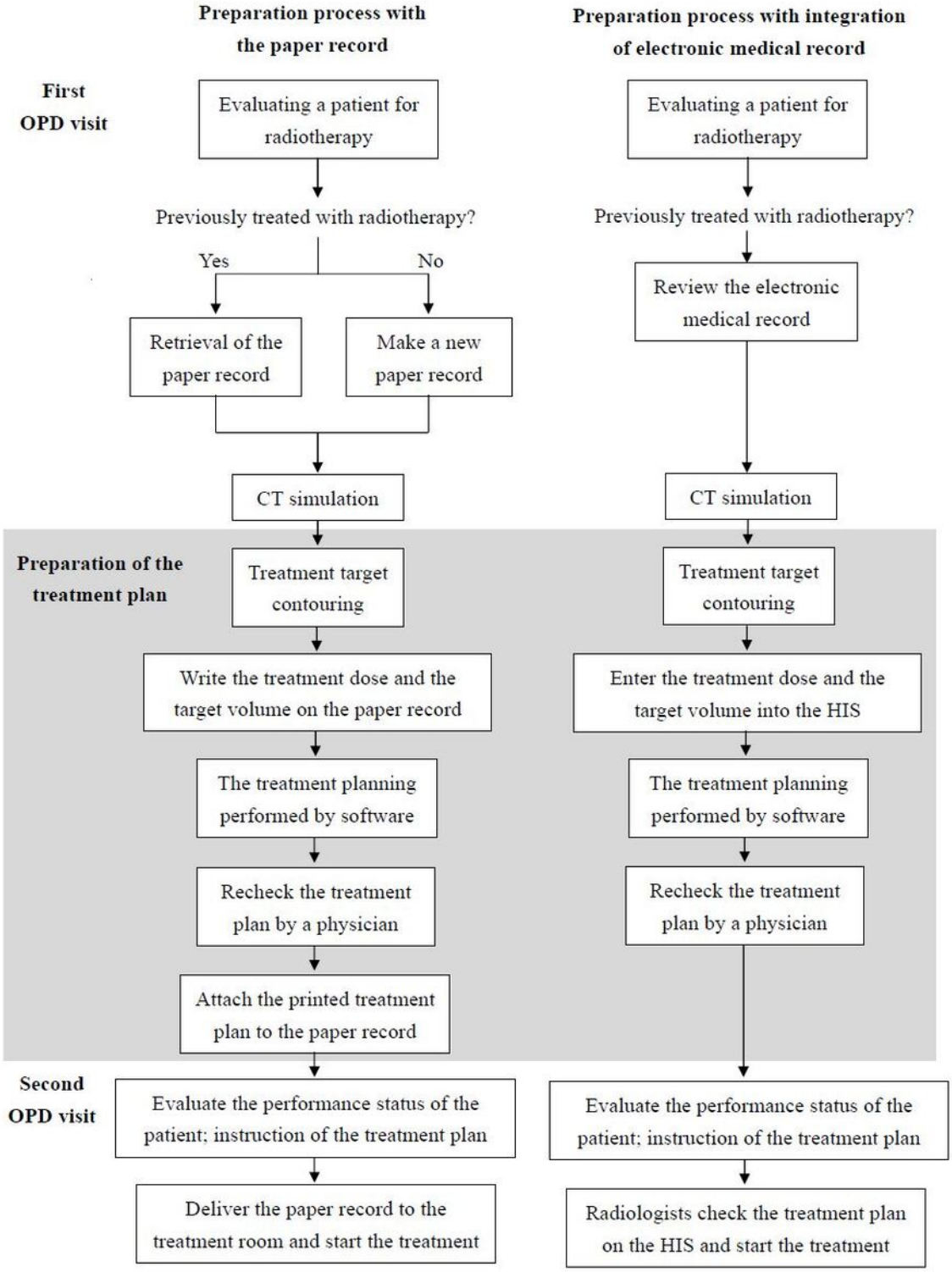
Planned Target Volumn & Dose prescription

Target Volumn	Dose (cGy)	Fraction Number	Anatomical Description of Clinical Target Volumn and Memo
CTV-H	3000	10	C6~T3 spine metastases

IMRT

Portal	Machine	Number of Emergent Treatment	Number of Non-emergent Treatment	Received Treatment Number
A	9_RA-3	1	9	4
B	9_RA-3	1	9	4
C	9_RA-3	1	9	4
D	9_RA-3	1	9	4

Figure 2. Comparison of the preparation processes between paper record usage and the integrated electronic record system. The integration of the electronic record system has led to a significant reduction in the time required for the radiation treatment preparation process. CT: computed tomography; HIS: hospital information system; OPD: outpatient department.



Ethical Considerations

Our research mainly focuses on the integration of the EMR system into the HIS and the efficiency of our new protocol in preparing RT records for new patients. The study does not involve personal or sensitive information related to human participants, so privacy and confidentiality protection considerations for human participants are not applicable [9]. There is no image or identifiable information related to an individual patient.

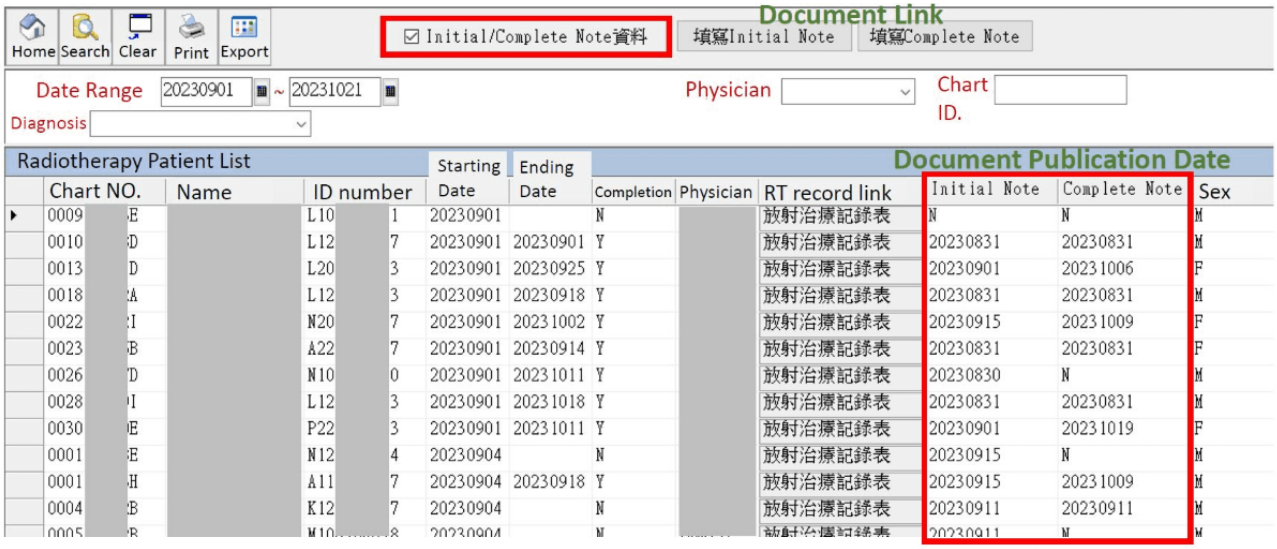
Results

Since launching in August 2020, the system has been highly used, with the number of medical records entered exceeding 1000 and continuing to increase. Integration of the system has

meant that patient lists and their related information are now displayed (Figure 3), allowing physicians to easily check the treatment status of each patient. Physicians can also query the records of past treatments of patients, review their past treatment status, and link their latest EMRs to track their current condition. The new system can also export the files of all patients who have been treated in the past for the purpose of statistical analysis. Additionally, the number of treatment days for each patient can now be automatically calculated. The medical record writing format is now consistent among physicians.

As shown in Figure 2 the integration of the electronic record system has led to a significant reduction in the time required for the radiation treatment preparation process. The new protocol post integration of the EMR streamlines procedures by obviating the need for retrieving previous paper records or generating new ones. Physicians input treatment information directly into the HIS instead of transcribing it onto paper records, eliminating the necessity for printing treatment plans. In addition, physicians can scrutinize the treatment plan and monitor treatment progression seamlessly through the HIS. Radiologists, in turn, can access the treatment plan on the HIS and commence patient treatment, thereby economizing time previously spent awaiting the transportation of paper records. Specifically, the processing time has decreased from 286.8 minutes to 154.3 minutes (P<.001), representing a total reduction of 46.2%.

Figure 3. The list of patients and their related information created by our electronic medical record. Integration of the system allowed the patient lists and their related information to be displayed, allowing physicians to easily check the treatment status of each patient. RT: radiotherapy.



Discussion

Overview

Before the implementation of the EMR system, retrieving RT history was conducted manually, which was time-consuming and burdened nurses with a significant workload. The integration of the electronic system has simplified the process by eliminating several procedures and allowing physicians to instantly access RT records. Many new functions have also been added to this system.

First, the establishment of the new scheduling system allows physicians to modify the treatment schedules of new patients at any time. All staff in the department have the authority to modify the scheduling system. Second, the scheduling system has a hyperlink on the interface, which allows a doctor to view the patient's schedule while browsing the medical records, as well as edit the patient's RT notes. Third, a doctor can easily check the patient's status on the system. The patient list generated by the system can show information about a patient, including contact information, RT starting date or ending date, the number of treatments, and the completion status of RT notes.

The new electronic system has brought several benefits. First, it facilitates communication between physicians and other staff within the department. Clinical RT requires both intensive and extensive communication and cooperation among various groups of staff, including physicians, physicists, medical radiation technologists, nurses, and administrative personnel, in order to proceed smoothly. It is crucial that communication be both correct and instantaneous. With our system, a physician can enter the handover of a patient into the system, and a radiologist can read the handover before the treatment. Staff from different departments can also find the treatment details of a patient on the HIS.

Second, there is no longer a need to arrange for a nurse to organize the RT paper records, which saves a workload of 16 hours each month. Aguirre et al [2] concluded that electronic health records can minimize delays, increase health care workers' satisfaction, and decrease the chances of usability being compromised. Our study also showed that the integration of the radiation oncology EMRs and the HIS simplifies the workflow at our clinic (Figure 2), saving time spent performing radiation preparation procedures and enhancing efficiency. The protocol covered seamless transitions from one stage of the process to the next, ensuring that the entire workflow remained in compliance with standards for RT preparation. Furthermore, Chen et al [10] and Huang et al [11] showed that shortening the preparation time needed before the start of RT improved the treatment effect. Previous research has also shown that, with the assistance of an information system, the work process

becomes smoother. Physicians can be given an automatic reminder or warning, which, in turn can shorten the necessary work preparation time from 12.2 days to 8.9 days [12].

Third, the statistical functions of this information system allowed the manager of the department to obtain accurate information on the number of people treated by each machine, as well as the number of fields per day, the number of simulations, the number of brachytherapy procedures, the number of people waiting for treatment, and the waiting time for each patient. The workload for each physician can also be monitored, and various monthly and annual reports allow the department manager to effectively trace the clinical workload in each treatment room. Monthly and annual reports can also be used as a reference baseline for manpower deployment and overtime budget applications [8]. Having mastery over these data can contribute to a better understanding of the operation of the department, and the information provided by the system can serve as important reference data for decision-making on issues such as whether to purchase new machines or modify manpower.

Additionally, the new system can assist with medical summary writing and education for a resident doctor. Each RT summary requires an average processing time of 10-15 minutes. Currently, with the new system, it only takes about 5 minutes to complete an RT summary because the detailed information on RT is automatically retrieved from the EMR. Doctors simply need to fill in the information about side effects and the treatment response. The system can also remind physicians to finish the initial note and to complete the RT summary when treatment is completed. For educational purposes, an electronic RT summary allows a resident doctor to quickly review the modifications from an attending physician and become familiar with the key points of the appropriate medical record [6,13].

Finally, at least 39,600 sheets of paper were used to prepare RT paper records per year, which is equal to 713 kg of carbon emissions. Furthermore, the demand for storage space tends to increase annually for paper records, but electronic records only require a relatively small physical space to store a large amount of patient data. The implementation of the improved EMR system has freed up space in our department that can now be put to better use. On the other hand, the number of our new patients increased annually. In 2020, we accommodated 1920 new patients, attended to 2118 newcomers in 2021, and extended our services to a total of 2230 fresh patients in 2022. Because the EMR system has decreased the number of radiation therapy transactions per day, physicians and nurses can manage clinical matters more efficiently, allocating more time for meaningful communication with patients. Furthermore, our department is relieved of the necessity to expand storage space for paper records as the EMR system adeptly conserves extensive patient data within a more confined space.

The system offers great flexibility for future expansion and can adapt to changes in clinical practice. We plan to improve the system by introducing an automatic patient registration system, a face recognition system, and an artificial intelligence scheduling system.

Limitations

The challenge of transitioning from paper records to electronic records remains high. The process is time-consuming and requires multidisciplinary team discussions. One limitation of our study is that the multidisciplinary team discussions only included engineers and staff in our department. Ideally, feedback and opinions should also have been collected from other departments in our hospital to improve our EMR system and make it more user-friendly. A survey to assess satisfaction with the new system will be conducted in the future. Any future studies should also have a larger sample size to validate our results. Furthermore, a comparison with other radiation oncology departments would be insightful.

Conclusion

The implementation of the integrated EMR system has resulted in a significant reduction in the number of steps involved in RT preparation, as well as a decrease in the amount of time required for the process. The new EMR system has provided numerous benefits for the department, including a decrease in workload, a simplified workflow, and conserving more patient data within a confined space.

Data Availability

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

Conflicts of Interest

None declared.

References

1. Negro-Calduch E, Azzopardi-Muscat N, Krishnamurthy RS, Novillo-Ortiz D. Technological progress in electronic health record system optimization: systematic review of systematic literature reviews. Int J Med Inform 2021;152:104507 [FREE Full text] [doi: 10.1016/j.ijmedinf.2021.104507] [Medline: 34049051]
2. Aguirre RR, Suarez O, Fuentes M, Sanchez-Gonzalez MA. Electronic health record implementation: a review of resources and tools. Cureus 2019;11(9):e5649 [FREE Full text] [doi: 10.7759/cureus.5649] [Medline: 31700751]
3. Brooks KW, Fox TH, Davis LW. A critical look at currently available radiation oncology information management systems. Semin Radiat Oncol 1997;7(1):49-57. [doi: 10.1053/SRAO00700049] [Medline: 10717196]

4. Bittner MI. Information technology in radiation oncology-a brave new world? Front Oncol 2013;3:116 [FREE Full text] [doi: 10.3389/fonc.2013.00116] [Medline: 23717815]
5. Huang WL, Liu WS, Chen CH, Chang YH, Chang RJ. Study of development of electronic medical records system in radiation oncology. Therapeut Radiol Oncol 2015;22(3):221-230 [FREE Full text]
6. Tsai MH, Cheng CN, Chen HHW. Implementation of an intranet-based radiation oncology information and scheduling system. Therapeut Radiol Oncol 2017;24(3):229-237 [FREE Full text]
7. Wang CY, Leung SW, Wang SR, Ker CY, Chen PC, Hung WC, et al. Integration of radiation oncology information system (MOSAIQ) with health information systems using a one-touch solution. Therapeut Radiol Oncol 2014;21(4):295-304 [FREE Full text]
8. Han Y, Huh SJ, Ju SG, Ahn YC, Lim DH, Lee JE, et al. Impact of an electronic chart on the staff workload in a radiation oncology department. Jpn J Clin Oncol 2005;35(8):470-474 [FREE Full text] [doi: 10.1093/jjco/hyi129] [Medline: 16024532]
9. Institutional Review Board SOPs - Taichung Veterans General Hospital. URL: http://www.vghtc.gov.tw/UnitPage/UnitContentView?WebMenuID=9905d071-6ae5-4bc2-b1fd-b4f655e5b74c&UnitID=eaf3c945-a5d9-493f-938f-37c8449cc2a1&UnitDefaultTemplate=6
10. Chen Z, King W, Pearcey R, Kerba M, Mackillop WJ. The relationship between waiting time for radiotherapy and clinical outcomes: a systematic review of the literature. Radiother Oncol 2008;87(1):3-16 [FREE Full text] [doi: 10.1016/j.radonc.2007.11.016] [Medline: 18160158]
11. Huang J, Barbera L, Brouwers M, Browman G, Mackillop WJ. Does delay in starting treatment affect the outcomes of radiotherapy? A systematic review. J Clin Oncol 2003;21(3):555-563 [FREE Full text] [doi: 10.1200/JCO.2003.04.171] [Medline: 12560449]
12. Lin YH, Hung SK, Lee MS, Chiou WY, Lai CL, Shih YT, et al. Enhancing clinical effectiveness of pre-radiotherapy workflow by using multidisciplinary-cooperating e-control and e-alerts: a SQUIRE-compliant quality-improving study. Medicine (Baltimore) 2017;96(24):e7185 [FREE Full text] [doi: 10.1097/MD.0000000000007185] [Medline: 28614257]
13. Wu RC, Lo V, Morra D, Wong BM, Sargeant R, Locke K, et al. The intended and unintended consequences of communication systems on general internal medicine inpatient care delivery: a prospective observational case study of five teaching hospitals. J Am Med Inform Assoc 2013;20(4):766-777 [FREE Full text] [doi: 10.1136/amiajnl-2012-001160] [Medline: 23355461]

Abbreviations

EMR: electronic medical record
HIS: hospital information system
RT: radiotherapy

Edited by A Mavragani; submitted 18.07.23; peer-reviewed by D Chrimes, SK Suthar; comments to author 18.10.23; revised version received 30.10.23; accepted 23.01.24; published 23.02.24.

Please cite as:
Cheng HS, You WC, Chen NW, Hsieh MC, Tsai CF, Ho CJ, Chen CC
Enhancing the Efficiency of a Radiation Oncology Department Using Electronic Medical Records: Protocol for Preparing Radiotherapy
JMIR Res Protoc 2024;13:e51002
URL: https://www.researchprotocols.org/2024/1/e51002
doi:10.2196/51002
PMID:38393753

Protocol

Machine Learning Model for Readmission Prediction of Patients With Heart Failure Based on Electronic Health Records: Protocol for a Quasi-Experimental Study for Impact Assessment

Monika Nair[1], PhD; Lina E Lundgren[2], PhD; Amira Soliman[3], PhD; Petra Dryselius[4], BSc; Ebba Fogelberg[4], BSc; Marcus Petersson[4], PhD; Omar Hamed[3], MSc; Miltiadis Triantafyllou[5], MD; Jens Nygren[1], Prof Dr

[1]School of Health and Welfare, Halmstad University, Halmstad, Sweden

[2]School of Business, Innovation and Sustainability, Halmstad University, Halmstad, Sweden

[3]School of Information Technology, Halmstad University, Halmstad, Sweden

[4]Cambio Healthcare Systems AB, Linköping, Sweden

[5]Clinical Cardiology at Halmstad Hospital, Halmstad, Sweden

Corresponding Author:
Monika Nair, PhD
School of Health and Welfare
Halmstad University
Kristian IV:s väg 3
Halmstad, 30118
Sweden
Phone: 46 707993854
Email: monika.nair@hh.se

Abstract

Background: Care for patients with heart failure (HF) causes a substantial load on health care systems where a prominent challenge is the elevated rate of readmissions within 30 days following initial discharge. Clinical professionals face high levels of uncertainty and subjectivity in the decision-making process on the optimal timing of discharge. Unwanted hospital stays generate costs and cause stress to patients and potentially have an impact on care outcomes. Recent studies have aimed to mitigate the uncertainty by developing and testing risk assessment tools and predictive models to identify patients at risk of readmission, often using novel methods such as machine learning (ML).

Objective: This study aims to investigate how a developed clinical decision support (CDS) tool alters the decision-making processes of health care professionals in the specific context of discharging patients with HF, and if so, in which ways. Additionally, the aim is to capture the experiences of health care practitioners as they engage with the system's outputs to analyze usability aspects and obtain insights related to future implementation.

Methods: A quasi-experimental design with randomized crossover assessment will be conducted with health care professionals on HF patients' scenarios in a region located in the South of Sweden. In total, 12 physicians and nurses will be randomized into control and test groups. The groups shall be provided with 20 scenarios of purposefully sampled patients. The clinicians will be asked to take decisions on the next action regarding a patient. The test group will be provided with the 10 scenarios containing patient data from electronic health records and an outcome from an ML-based CDS model on the risk level for readmission of the same patients. The control group will have 10 other scenarios without the CDS model output and containing only the patients' data from electronic medical records. The groups will switch roles for the next 10 scenarios. This study will collect data through interviews and observations. The key outcome measures are decision consistency, decision quality, work efficiency, perceived benefits of using the CDS model, reliability, validity, and confidence in the CDS model outcome, integrability in the routine workflow, ease of use, and intention to use. This study will be carried out in collaboration with Cambio Healthcare Systems.

Results: The project is part of the Center for Applied Intelligent Systems Research Health research profile, funded by the Knowledge Foundation (2021-2028). Ethical approval for this study was granted by the Swedish ethical review authority (2022-07287-02). The recruitment process of the clinicians and the patient scenario selection will start in September 2023 and last till March 2024.

Conclusions: This study protocol will contribute to the development of future formative evaluation studies to test ML models with clinical professionals.

International Registered Report Identifier (IRRID): PRR1-10.2196/52744

(JMIR Res Protoc 2024;13:e52744) doi:10.2196/52744

KEYWORDS

artificial intelligence; machine learning; readmission prediction; heart failure; clinical decision support; machine learning model; CHF; congestive heart failure; readmission; prediction; electronic health records; electronic health record; EHR; quasi-experimental study; decision-making process; risk assessment; risk assessment tool; predictive models; predictive model; Sweden; physician; nurse; nurses; clinician; clinicians

Introduction

Care for patients with heart failure (HF) causes a substantial load on the health care system. One of the prominent challenges associated with HF care is the elevated risk of readmissions within 30 days following initial discharge [1]. While this readmission risk underscores that patients receive life-saving care, it also encompasses implications of health care costs, patient's stress, and the impact of socioeconomic determinants on care outcomes [2]. The risk of readmission due to the worsening of HF symptoms is heightened by inappropriate treatment strategies, infectious complications, or prematurely executed discharges. Therefore, readmissions can be reduced by taking steps both during admission and hospitalization and post discharge to ensure compliance with care plans and improved treatment outcomes.

In current practice, clinicians make expert decisions, weighing in the probability of readmission of a patient by evaluating clinical data such as a patient's medical history, medication list, laboratory tests as well as social factors [3]. However, the process of assessing a patient's readiness for discharge introduces an element of subjectivity and uncertainty. Questions surrounding the probability of readmission emerge, prompting deliberation on optimal timing for discharge—whether immediately or with a slight delay. Additionally, the patient's social context plays a critical role; decisions must be made regarding the suitability of home care versus outpatient clinic assignment.

In pursuit of curbing health care costs and mitigating uncertainty novel risk assessment tools, often in the form of predictive models have been developed. Drawing upon statistical, conventional machine learning (ML), and deep learning methodologies, these tools are designed to identify patients at risk of hospital readmission [4-6]. Leveraging risk indicators such as age, illness severity, prior hospitalizations, and other factors, these models predict the likelihood of readmission within a specific time frame. Preventive approaches can then be developed and applied to target the identified high-risk patients. The profound potential for cost savings within the health care domain has fueled substantial interest in rigorous testing and validation of similar models, underscoring the imperative of optimizing patient care while securing resource efficiency.

In this project, our objective is to evaluate the applicability and potential benefits of a previously established ML model for predicting unscheduled readmission of patients with HF within 30 days after discharge from medical care [5]. This model has been further fine-tuned and tailored for practical integration and usage within clinical settings [3,7], encompassing the identification of potential barriers and enablers for implementing a clinical decision support (CDS) tool presenting the model output for clinical use. Refinement also encompassed the augmentation of the model with interpretability features and a comprehensive exploration of the optimal timing and manner in which the model's findings should be presented to users within the clinical domain [7]. The primary aim of the study outlined in this protocol is to investigate how the developed CDS tool alters the decision-making processes of health care professionals in the specific context of discharging patients with HF, and if so, in which ways. Additionally, the aim is to capture the experiences of health care practitioners as they engage with the system's outputs to analyze usability aspects and obtain insights related to future implementation.

Methods

Study Design

The design of this study used the principles of Template for Intervention Description and Replication [8] to support clarity of the description of the intervention and the replicability of its implementation. This study has a quasi-experimental design with a randomized controlled crossover assessment of 2 groups of physicians and nurses working in pairs. This study will be conducted within the health care settings of 1 region in Southern Sweden. The 2 groups will be presented with patient scenarios using purposeful sampling [9] on which they are to make decisions on subsequent care plans and treatment strategies.

HF Care Setting

An HF patient's referral to the hospital can occur through the emergency department, primary care, or home care services. Upon arrival, the patient is allocated to one of the medical departments within either of 2 hospitals in the included region possessing specialized cardiology units. Once admitted, a comprehensive care plan is made, considering the patient's symptoms, prior diagnoses, and relevant test results. This care plan also includes decisions regarding the appropriate timing for discharge. Within the framework of this study, this in-patient scenario, as detailed in a prior work [3], serves as the setting for HF care in which our investigation into the application of the CDS model takes place.

Preparation for This Study

CDS Model

The model is based on comprehensive retrospective electronic health data in a Swedish region [10]. The cohort used for the development consisted of patients diagnosed with HF according to the *ICD-10* (*International Statistical Classification of Diseases, Tenth Revision;* I10.0, I42, I43, and I50), were residents, and receiving care in the region. The patients included were aged ≥40 years and had at least one admission after being diagnosed with HF between January 1, 2017, and December 31, 2019. All-cause hospitalization was considered. For each admission in the cohort, all patient's previous admissions within 5 years were considered from the time of admission as the medical history of the patient (look back period); these admissions are not considered as events in this study but were used only as historical data.

Besides demographic information, variables were collected out of electronic health data related to different categories. These categories can be detailed as follows: comorbidities in which patient conditions related to HF are traced back, for example, hypertension, diabetes, chronic kidney disease, and atrial fibrillation. Diagnoses (including procedures) and medications in the electronic health data system were represented according to standard schemas: *ICD-10-SE* (*Swedish version of the 10th revision of the International Classification of Diseases*) and Anatomical Therapeutic Chemical codes, respectively. Laboratory results were also used, including specific features for some laboratory tests, such as N-terminal prohormone of brain natriuretic peptide, sodium, potassium, ferritin, and estimated glomerular filtration rate. Variables were defined to indicate the level of abnormality in the obtained results of these laboratory tests. Following clinical feedback on model development, features associated with a patient's vital signs collected during the admission such as weight, heart rate, and blood pressure were also considered.

A conventional ML model was developed with *CatBoost*, which resembles gradient-boosting decision trees. The *CatBoost* model makes predictions using a series of decision trees, representing an explainable model [11]. In this study, the *CatBoost* python package (version 1.0.4) was used. The model was trained using a stratified 10-fold cross-validation, such that the training data were further divided into 10 parts where 90% (14,069) of data were used for training and 10% (1842) used for validation. Evaluation of the performance is based on commonly used performance measures such as sensitivity, specificity, F_1-score, receiver operating characteristic curves, the area under the receiver operating characteristic curve, and the area under the precision-recall curve. The performance of the model is presented in a retrospective ML study [7].

The Shapley Additive Explanations (SHAP) technique was adopted to provide more details behind the model decision regarding important features for readmission prediction [12]. SHAP works as a model-agnostic explanation tool and provides local (ie, patient-specific) as well as global explanations (ie, across patient cohorts). SHAP was used to compute explainability outputs for the selected patient scenarios, which were later used as input to the CDS tool. For each prediction, the most important features were listed that were positively or negatively driving toward the readmission risk. The explanations provided were assessed by physicians for clinical relevance.

Stakeholder Study

To prepare for the experiment, an interview study was performed to determine the potential barriers and facilitating factors for the implementation of the CDS tool. In total, 12 interviews with stakeholders were performed in a Swedish health care organization consisting of 2 hospitals, primary care, and partial home care. The views on the CDS tool were collected from different roles such as medical process leaders, medical specialists in cardiology, specialist nurses, physiotherapists, home care physicians, home care nurses, and administrative roles [3]. Interviews were transcribed and thematically analyzed to condense and categorize content.

Explainable Artificial Intelligence Design Process

A design process was carried out to create the user interface of the CDS tool. The initial phases included expert interviews, care process observations, and literature searches about the design of explainable artificial intelligence (AI) systems. There are several design problems to address in creating an interface for such a decision support system, for example, to understand who the intended users are and their needs, what information flows the system shall interact with, and in what part of the care process such information is relevant [13]. Therefore, an iterative design process was adopted, to move forward step by step, while generating and testing different design ideas.

Initial usability tests were conducted after generating a set of low-fidelity prototypes. In total, 5 clinicians (3 physicians and 2 nurses) were individually testing the different prototypes over recorded video calls. The tests evaluated if the prediction score and the explanation presented in the prototypes were understandable, and how clinicians perceived this information given the situation of an AI-model as the source. The tests gave important information on which language to use and what to display in the interface, which was the focus of the next iteration. The initial usability tests further raised questions about where this tool might be needed and who the users could be. Consequently, additional care process observations were made, which led to some changes to the definition of the target users and the place of potential implementation.

All usability test data were analyzed, categorized, and used as input for the further development of the prototype. Thereafter, additional usability testing was performed, following the same procedure as previous tests, however, focusing on exploring how to present more detailed information. Another 5 clinicians (three of them participated in the first usability tests) tested these prototypes over video calls. The outcome of this second round of usability tests was used as input to another design update before a high-fidelity prototype was created. This prototype was tested with 4 clinicians (2 physicians and 2 nurses who also participated in the previous tests).

As the last step of the prototype development, a series of design workshops were conducted with user experience resources, to finalize the prototype and set the details, before a smaller

usability test was performed with 2 clinicians (1 physician and 1 nurse). Their input led to some minor interface changes, and now the development of the CDS tool could begin.

Scenario Creation

From the same data set used to develop the CDS model, 20 patients were selected to constitute the target population in this study by using stratified random sampling. The stratification was made to ensure that there are equal amounts of readmitted patients and control patients. For each of these 20 patients, scenarios comprising narrative reports and clinical data describing demographics, and clinical events and outcomes, including potential readmittance, were recreated retrospectively based on real patient historical data from the regional database of electronic health data.

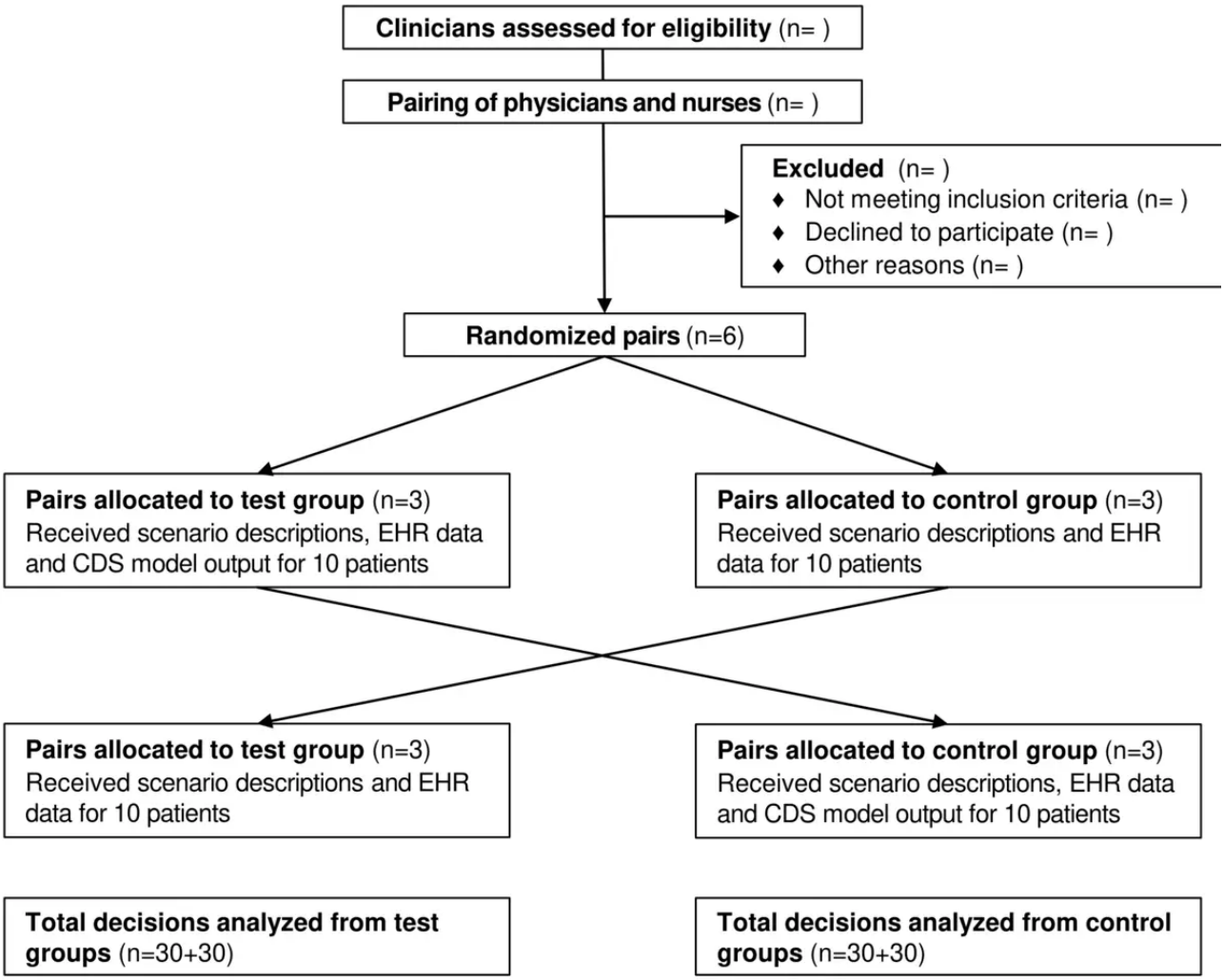
Recruitment

The participants involved in the experimentation will include both physicians (n=6) and nurses (n=6) and will be recruited from the clinical staff at the 2 hospitals based on the following inclusion criteria: a minimum of 3 years of experience in the treatment of patients with HF, and currently active engagement in clinical practice within either of the 2 specialized cardiology departments in the region. This study will use purposeful sampling [9] for recruiting physicians and nurses according to the inclusion criteria, a process led by the hospital. Although there might be a limited availability of staff, physicians and nurses who were involved in the design of this study and the CDS model will be excluded from participation in this study, to prevent bias.

Experimentation and Data Collection

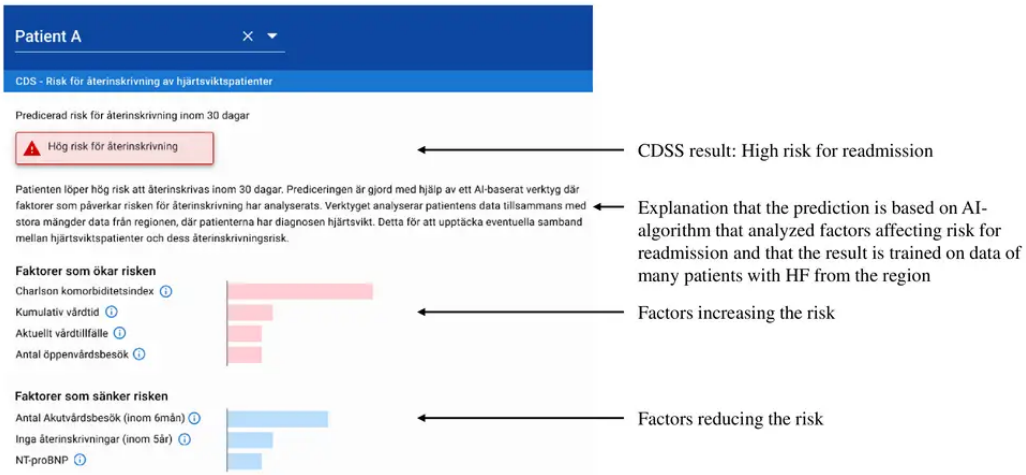
The experiment simulates the decision-making process of a patient's discharge, further treatments, and care plan, based on real historical data. Patient data for model output are preloaded into the CDS model. The participants will be randomly paired with 1 physician and 1 nurse in each pair, reflecting the real-world setup in the decision-making regarding the patient's potential readmission (Figure 1). Pairs will then be randomly assigned into test (n=3) and control (n=3) groups using simple randomization with stratification. The pairs in the test group will be given 10 scenario descriptions, patient electronic health record (EHR) data, and the CDS model output based on each of the 10 patients. The pairs in the control group will be given the same 10 scenario descriptions and EHR data but not the CDS model output. After making decisions based on the 10 scenario descriptions the test group and the control group will switch roles and 10 new scenario descriptions will be given to the groups, again with and without the CDS model output.

Figure 1. Flowchart for the randomized controlled cross-over design. CDS: clinical decision support; EHR: electronic health record.



Before the experiment, each group will be briefly trained in how the CDS model works and how to interpret its output [14,15]. The clinicians will be asked to think aloud so that both the conversation and reasoning during the decision process are recorded. The scenarios will be presented to the clinicians via a text document in a separate computer room at the hospital, and the CDS output in a web-based interface as depicted in Figure 2. The clinicians will be able to either make a decision or request for more information about the patient, which will be provided by an additional clinician who is part of the research group that will be in another room using a chat function on the local information system. This clinician is connected to the EHR system and has access to all patient data. The additional information can include admission notes, laboratory test results, and medication lists, and this procedure will be carefully explained to the clinicians before the experiment. This information will not be available from the beginning, to mimic the real-world information search between different systems or system modules and to research what level of information would be sufficient to decide in both groups; a clinician shall provide extra information about the patient only if requested. Every such request will be documented by the researchers present in the rooms together with the clinicians, observing the decision-making and the experiment. All clinical notes available in the experiment will undergo a deidentification process before this study. The decisions made by the participants will be noted by the observing researcher.

Figure 2. CDS model output showing readmission risk and explanations of model decision for a hypothetical patient. AI: artificial intelligence; CDS: clinical decision support; CDSS: clinical decision support system; HF: heart failure.



At the end of the experiment, each clinician will be interviewed individually by the researcher using the interview questions defined in Multimedia Appendix 1. The dialogue will be audio-recorded and transcribed verbatim.

Outcome Measures

A research-based evaluation framework specifically designed for AI-based decision-support systems [16] has guided and inspired the selection of the outcome measures for this study. The added value of the AI system will be assessed through a mixed methods evaluation design: process efficiency and patient-related outcomes shall be assessed using a quantitative approach, while quality, reliability, trust, and similar parameters shall be addressed through qualitative semistructured interviews. Table 1 provides details on the outcome measures selected for this study.

Table 1. Outcome measures.

Outcome indicator	Goal	Analytic approach
Impact on decision-making		
Decision consistency	To explore decision consistency between the users and the CDS[a] model to research whether having the CDS model increases uniformity among the decisions taken compared to decisions without the model.	• Comparing the taken decisions: • Between the CDS model output and the test group to assess the extent of how much the users agreed with the model output. • Between test and control groups to assess similarity in decisions taken with and without the model output. • Potential decisions: • To discharge, with x, y, and z treatment. • Move to another department (which?). • Take additional tests for an extended investigation. • To send a referral or follow-up at outpatient clinical, primary care, or home care. • To stay for some more days.
Decision quality	To explore whether the CDS model could improve decisions.	• Comparing decisions taken by the test group with: • Historical data—what decision was actually taken for the patient and what event followed afterwards. • Control group's decisions on the same patients to control the influence of the experiment and set up over the decisions taken: do decisions differ from the test group and the historical data?
Work efficiency	To explore performance changes due to using the CDS model output.	• Measuring speed of decision-making for both test and control groups. Comparing the average speed between groups with and without CDS.
Impact on experience with decision-making		
Perceived benefits	Clinicians' attitude toward perceived benefit for patients and clinicians of AI[b].	• Interview with nurses and physicians who were exposed to the CDS model output (Multimedia Appendix 1, Q1).
Knowledge	Knowledge sufficiency and possible gaps.	• Interview with nurses and physicians who were exposed to the CDS model output (Multimedia Appendix 1, Q5).
Confidence	Confidence in making decisions using the algorithm (trust in the algorithm and data, and self-confidence).	• Asking the participants in the test and control groups to take decisions for some patients with and without the CDS model output. Clinicians will be asked to rate their decision confidence and indicate to what extent the CDS output helped them using a 5-point Likert scale (1=not at all, 5=a great deal) [16]. • Interview with nurses and physicians who were exposed to the CDS model output (Multimedia Appendix 1, Q3 and Q7).
Reliability and validity	How reliable and valid are the suggestions by the algorithm—perception?	• Interview with nurses and physicians who were exposed to the CDS model output (Multimedia Appendix 1, Q3).
Perceived service quality	How is the perception of the overall clinician-provided service perceived?	• Interview with nurses and physicians who were exposed to the CDS model output (Multimedia Appendix 1, Q2 and Q6).
Unintended consequences	Unintended consequences are foreseen.	• Interview with nurses and physicians who were exposed to the CDS model output (Multimedia Appendix 1, Q4).
Intention of use	Obtaining an indication of worthiness to continue developing the AI-based system.	• Interview with nurses and physicians who were exposed to the CDS model output (Multimedia Appendix 1, Q1, Q2, and Q6).
Implementation aspects		
Workflow integration	How integrable is the solution into the current workflows?	• Interview with nurses and physicians who were exposed to the CDS model output (Multimedia Appendix 1, Q4 and Q8).

Outcome indicator	Goal	Analytic approach
Usability		
Perceived ease of use	Perception of the features, human-computer interface.	• Interview with nurses and physicians who were exposed to the CDS model output (Multimedia Appendix 1, Q5).

[a]CDS: clinical decision support.

[b]AI: artificial intelligence.

Data Analysis

The quantitative analysis will primarily employ descriptive statistics. The interview data to address the rest of the outcome measures shall be transcribed and thematically analyzed using the thematic coding scheme corresponding but not limited to the outcome measures of this study (Table 1) [16-18].

Ethical Considerations

This study conforms to the principles outlined in the Declaration of Helsinki and will fulfill the following requirements for research: information, consent, confidentiality, and safety of the participants, guided by the ethical principles of autonomy, beneficence, nonmaleficence, and justice. The anonymized patient data used in this study are available (2022-07287-02).

Patients whose data will be used for creating the scenarios will be informed through an advertisement on the university web pages and provided with the possibility to express a will to opt out of this study. The absence of an objection to the use of personal medical data in the research process will be considered as consent to participate.

All participants will receive written and oral information about the studies in which they are directly or indirectly involved. Participants will also be given information about the voluntary nature of the studies, confidentiality, and the ability to withdraw their consent at any time without having to justify why. All personal data will be registered according to the General Data Protection Regulation (GDPR2016/679) and the data will be stored per the Archive Act in Sweden (SFS1990:782).

Results

The project is funded by the Knowledge Foundation and is part of the Center for Applied Intelligent Systems Research Health research profile (280042), which started in July 2021 and ends in 2028. The profile conducts research projects in coproduction with industry about the development, design, and implementation of AI systems in health care. The project HF readmission prediction started in July 2021 and will end in June 2024.

The recruitment process will start in September 2023 and last until March 2024. First, the testing and fine-tuning of this study process using the prototype shall be conducted (planned for September 2023). Then, data will be collected and analyzed during the experiment from October 2023. This study's results are expected to be published. This research will involve several partners: Halmstad University (Sweden), Cambio AB (Sweden), and 1 Swedish region. This research aims to reduce avoidable readmissions of patients with HF.

Discussion

Principal Findings

This study focuses on the ML model for predicting unscheduled readmission of patients with HF within 30 days of discharge [5]. The purpose of the study described in this protocol is to assess the impact of this ML model on decision-making by health care professionals and to capture their experiences in using the model.

A quasi-experimental study shall be conducted with clinicians using the model and results shall be compared against a control group. Throughout the experiment, the researchers shall observe the decision-making process, take measurements, and collect feedback. Such knowledge shall increase an understanding of the potential impact on the decision-making, usability, perceived value if such a model is deployed, and willingness to use such tools in the future. Furthermore, this study will give practical insights into the factors that will potentially influence implementation that could be further used in the implementation process. In addition, concrete outcomes' measures are suggested which can assist in future developments of similar models.

This study has several limitations. First, although the CDS model output shall be provided as a digital interface, the system is not in this version integrated with EHR and it will not be possible to check the actual impact of the CDS model on the workflow. Second, the samples of admissions will be selected using stratified sampling where subgroups will be created for readmission labels assigned to patient encounters. The readmission rate in our data set is 21% (3334 out of 15,911 admissions), thus the chance to obtain enough examples where the readmission label is true will be very low. Accordingly, stratification will be used to divide the population data into 2 subgroups before sampling, then select 10 cases having true as a value for readmission label. Third, this study shall not assess the impact of the use of the model on the cost-efficiency or resource planning. Fourth, the presence of a researcher (an observer) in the computer room while clinicians assess the patient scenarios might influence the results.

To sum up, the findings from this study protocol shall contribute to the development and implementation of a CDS system based on ML models for readmission reduction. The results of this study will be presented at scientific conferences, seminars with professional organizations, articles for media outlets, and submitted to a scientific peer-reviewed journal specialized in health technology.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Interview guide.
[DOCX File , 13 KB - resprot_v13i1e52744_app1.docx]

References

1. Qaddoura A, Yazdan-Ashoori P, Kabali C, Thabane L, Haynes RB, Connolly SJ, et al. Efficacy of hospital at home in patients with heart failure: a systematic review and meta-analysis. PLoS One 2015;10(6):e0129282 [FREE Full text] [doi: 10.1371/journal.pone.0129282] [Medline: 26052944]
2. Patil S, Johnson AE, Khera R, Chhatriwalla AK. Socioeconomic disparities in readmission after heart failure hospitalization. Mayo Clin Proc 2023;2023.
3. Nair M, Andersson J, Nygren JM, Lundgren LE. Barriers and enablers for implementation of an artificial intelligence-based decision support tool to reduce the risk of readmission of patients with heart failure: stakeholder interviews. JMIR Form Res 2023;7:e47335 [FREE Full text] [doi: 10.2196/47335] [Medline: 37610799]
4. Zhou H, Della PR, Roberts P, Goh L, Dhaliwal SS. Utility of models to predict 28-day or 30-day unplanned hospital readmissions: an updated systematic review. BMJ Open 2016;6(6):e011060 [FREE Full text] [doi: 10.1136/bmjopen-2016-011060] [Medline: 27354072]
5. Ashfaq A, Sant'Anna A, Lingman M, Nowaczyk S. Readmission prediction using deep learning on electronic health records. J Biomed Inform 2019;97:103256 [FREE Full text] [doi: 10.1016/j.jbi.2019.103256] [Medline: 31351136]
6. Teo K, Yong CW, Chuah JH, Hum YC, Tee YK, Xia K, et al. Current trends in readmission prediction: an overview of approaches. Arab J Sci Eng 2023;48:11117-11134 [FREE Full text] [doi: 10.1007/s13369-021-06040-5] [Medline: 34422543]
7. Soliman A, Agvall B, Etminani K, Hamed O, Lingman M. The price of explainability in machine learning models for 100-day readmission prediction in heart failure: retrospective, comparative, machine learning study. J Med Internet Res 2023;25:e46934 [FREE Full text] [doi: 10.2196/46934] [Medline: 37889530]
8. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: Template for Intervention Description and Replication (TIDieR) checklist and guide. BMJ 2014;348:g1687 [FREE Full text] [doi: 10.1136/bmj.g1687] [Medline: 24609605]
9. Palinkas LA, Horwitz SM, Green CA, Wisdom JP, Duan N, Hoagwood K. Purposeful sampling for qualitative data collection and analysis in mixed method implementation research. Adm Policy Ment Health 2015;42(5):533-544 [FREE Full text] [doi: 10.1007/s10488-013-0528-y] [Medline: 24193818]
10. Ashfaq A, Lönn S, Nilsson H, Eriksson JA, Kwatra J, Yasin ZM, et al. Data resource profile: regional healthcare information platform in Halland, Sweden. Int J Epidemiol 2020;49(3):738-739f [FREE Full text] [doi: 10.1093/ije/dyz262] [Medline: 31930310]
11. Prokhorenkova L, Gusev G, Vorobev A, Dorogush AV, Gulin A. CatBoost: unbiased boosting with categorical features. Adv Neur Inf Process 2018;31.
12. Lundberg SM, Erion G, Chen H, DeGrave A, Prutkin JM, Nair B, et al. From local explanations to global understanding with explainable AI for trees. Nat Mach Intell 2020;2(1):56-67 [FREE Full text] [doi: 10.1038/s42256-019-0138-9] [Medline: 32607472]
13. Jacobs M, He J, Pradier F, Lam M, Ahn B, McCoy AC, et al. Designing AI for Trust and Collaboration in Time-Constrained Medical Decisions: A Sociotechnical Lens. In: CHI '21: Proceedings of the 2021 CHI Conference on Human Factors in Computing Systems. 2021 Presented at: CHI '21: Proceedings of the 2021 CHI Conference on Human Factors in Computing Systems; May 8-13, 2021; Yokohama, Japan p. 1-14 URL: https://dl.acm.org/doi/proceedings/10.1145/3411764 [doi: 10.1145/3411764.3445385]
14. McCoy A, Das R. Reducing patient mortality, length of stay and readmissions through machine learning-based sepsis prediction in the emergency department, intensive care unit and hospital floor units. BMJ Open Qual 2017;6(2):e000158 [FREE Full text] [doi: 10.1136/bmjoq-2017-000158] [Medline: 29450295]
15. Sun TQ. Adopting artificial intelligence in public healthcare: the effect of social power and learning algorithms. Int J Environ Res Public Health 2021;18(23):12682 [FREE Full text] [doi: 10.3390/ijerph182312682] [Medline: 34886404]
16. Ji M, Genchev GZ, Huang H, Xu T, Lu H, Yu G. Evaluation framework for successful artificial intelligence-enabled clinical decision support systems: mixed methods study. J Med Internet Res 2021;23(6):e25929 [FREE Full text] [doi: 10.2196/25929] [Medline: 34076581]
17. Vanover C, Mihas P, Saldaña J, editors. Analyzing and Interpreting Qualitative Research: After the Interview, 1st Edition. Thousand Oaks, California: SAGE Publications; 2021.
18. Saldaña J. The Coding Manual for Qualitative Researchers, 3rd Edition. London: SAGE; 2015.

Abbreviations

AI: artificial intelligence
CDS: clinical decision support
EHR: electronic health record
HF: heart failure
ICD-10: International Statistical Classification of Diseases, Tenth Revision
ICD-10-SE: Swedish version of the 10th revision of the International Classification of Diseases
ML: machine learning
SHAP: Shapley Additive Explanations

Edited by A Mavragani; submitted 14.09.23; peer-reviewed by S Nilsson; comments to author 02.01.24; revised version received 23.01.24; accepted 24.01.24; published 11.03.24.

Please cite as:
Nair M, Lundgren LE, Soliman A, Dryselius P, Fogelberg E, Petersson M, Hamed O, Triantafyllou M, Nygren J
Machine Learning Model for Readmission Prediction of Patients With Heart Failure Based on Electronic Health Records: Protocol for a Quasi-Experimental Study for Impact Assessment
JMIR Res Protoc 2024;13:e52744
URL: https://www.researchprotocols.org/2024/1/e52744
doi:10.2196/52744
PMID:38466983

Protocol

The Effects of the Processing of Positive Memories Technique on Posttrauma Affect and Cognitions Among Survivors of Trauma: Protocol for a Daily Diary Study

Talya Greene[1,2*], PhD; Ateka A Contractor[3*], PhD; Sheila Daniela Dicker-Oren[2], MA; Andrea Fentem[3], MA; Sharon R Sznitman[4], PhD

[1]Department of Clinical, Educational and Health Psychology, University College London, London, United Kingdom

[2]Department of Community Mental Health, University of Haifa, Haifa, Israel

[3]Department of Psychology, University of North Texas, Denton, TX, United States

[4]School of Public Health, University of Haifa, Haifa, Israel

[*]these authors contributed equally

Corresponding Author:
Talya Greene, PhD
Department of Clinical, Educational and Health Psychology
University College London
1-19 Torrington Place
London, WC1E 7HB
United Kingdom
Phone: 44 020 7679 1897
Email: talya.greene@ucl.ac.uk

Abstract

Background: The Processing of Positive Memories Technique (PPMT) is a promising new treatment approach for posttraumatic stress disorder (PTSD), which involves detailed narration and processing of specific positive autobiographical memories. Indeed, preliminary case-series studies have found reductions in PTSD symptoms, negative affect, and negative cognitions among survivors of trauma who have received PPMT. However, PPMT's effects have not been investigated at the daily level. In this study, we describe the protocol for a study that will examine the daily-level impacts of PPMT in a trauma-exposed, nonclinical community sample.

Objective: This study uses an innovative research protocol that combines case-series design and daily diary approaches to examine changes in daily affect, daily cognitions, and daily PTSD symptoms pre- and post-PPMT. We hypothesize that at the daily level, in comparison to their own pre-PPMT levels, following the PPMT intervention, participants will report (1) a lower count of endorsed daily PTSD symptoms, (2) increases in daily positive affect and decreases in daily negative affect, (3) increases in positive affect reactivity to daily positive events, and (4) decreases in daily posttrauma cognitions.

Methods: We are currently recruiting participants (target n=70) from a metroplex in the southwest United States. Following a screening survey, eligible participants complete a preintervention baseline survey, followed by 21 daily surveys in their natural environments. Then, they receive 4 PPMT sessions on a weekly basis. After the conclusion of the PPMT intervention, participants complete a postintervention outcome survey and 21 daily surveys. To compare daily affect, daily cognitions, and daily PTSD symptoms before and after PPMT, we will use the daily diary report data and conduct multilevel random intercepts and slopes linear regression models.

Results: Data collection was initiated in March 2022 and is expected to end by June 2024. As of November 28, 2023, a total of 515 participants had consented to the study in the screening phase. No analyses will be conducted until data collection has been completed.

Conclusions: Study findings could clarify whether deficits in positive autobiographical memory processes may also characterize PTSD alongside deficits in traumatic memory processes. Furthermore, PPMT could be an additional therapeutic tool for clinicians to help clients reduce posttraumatic distress in their everyday lives.

International Registered Report Identifier (IRRID): DERR1-10.2196/51838

(JMIR Res Protoc 2024;13:e51838) doi:10.2196/51838

KEYWORDS

affect; case series design; cognitions; experience sampling; intensive longitudinal assessment; positive autobiographical memories; posttrauma health; posttraumatic stress disorder; trauma survivors

Introduction

Posttraumatic stress disorder (PTSD) is a psychological condition that can develop following exposure to traumatic events, characterized by intrusive thoughts and re-experiencing symptoms, avoidance of trauma reminders, negative cognitions and mood, and heightened arousal [1]. A proposed mechanism underlying the development and maintenance of PTSD is disruptions in the encoding, consolidation, and retrieval of negatively- and positively-valenced autobiographical memories [2-4]. Evidence suggests that survivors of trauma with PTSD report difficulties accessing and detailing positive autobiographical memories [5-7], akin to reported difficulties with traumatic autobiographical memories [8]. Unsurprisingly, PTSD interventions typically target the content, processes, and phenomenological characteristics of autobiographical memories [9,10]. While such trauma-focused interventions (eg, prolonged exposure and cognitive processing therapy) are effective for many survivors of trauma, a significant proportion of survivors of trauma do not respond to these treatments, and there is a high degree of dropout from these interventions [11]. This highlights the need to develop alternative therapeutic approaches.

While most PTSD interventions address engagement with only traumatic autobiographical memories, only a few other interventions address both traumatic and positive autobiographical memories or only positive autobiographical memories and have been shown to be effective. For instance, Memory Specificity Training (targeting one's ability to retrieve specific autobiographical memories irrespective of valence) is effective for PTSD and posttrauma distress [12,13]. Also, Broad-Minded Affective Coping, a positive emotion induction technique through the retrieval of positive autobiographical memories, improves mood among individuals with PTSD [14]. Such evidence suggests that a focus on positive autobiographical memories may be a helpful target in PTSD interventions.

The PTSD-Positive Memory Model [15,16] outlines that when survivors of trauma repeatedly retrieve, relive, and detail specific positive autobiographical memories, they may experience an improvement in PTSD symptoms, affect, and beliefs over time [15]. This model was foundational to the development of the Processing of Positive Memories Technique (PPMT), which is a 4- to 5-session intervention tailored to PTSD symptoms. During PPMT sessions, survivors of trauma are guided to narrate details of salient positive autobiographical memories; to access and strengthen positive values, affect, strengths, and thoughts associated with these memories; and to engage in positive affective, cognitive, and behavioral changes [17]. PPMT is influenced by positive psychology, a field that emphasizes factors and mechanisms that enhance psychological well-being rather than focusing solely on pathology [18,19]. PPMT draws from positive psychology interventions (eg, sharing positive narratives with others and using mental imagery to re-expereince positive events) [19-21] and from interventions that increase memory retrieval to improve mental health [22]. The detailed session-by-session content of PPMT is outlined by Contractor and colleagues [17].

Practicing PPMT may help survivors of trauma retrieve more positive autobiographical memories over time, which may also translate to retrieving fewer negative autobiographical memories. Consequently, survivors of trauma may be able to better contextualize and integrate traumatic autobiographical memories with existing beliefs [23] and with other memories [2,24], which in turn could aid recovery after a trauma [2,25]. Positive autobiographical memories may also become primary reference points to interpret experiences and influence self-concept [26-28]. Furthermore, by repeatedly retrieving positive autobiographical memories and associated content, survivors of trauma may lessen their focus on negative material, experience more positive affect, and downregulate negative affect [29-32]. This may be especially helpful for survivors of trauma who experience emotional distress from retrieving negative autobiographical memories. In turn, this improved affect may help survivors of trauma positively interpret events [29,33] and note more positive content in their thoughts [34]. Overall, retrieving positive autobiographical memories may improve well-being [35], resilience [36], and adaptive coping [37], serving as a reminder that there are positive values and thoughts to hold on to despite the hardships faced by survivors of trauma.

Pilot studies have shown that PPMT is feasible and may improve therapeutic outcomes for survivors of trauma. Using an experimental design, a 2-session modified-PPMT [38] and a 5-session PPMT protocol [39] were compared to a neutral memory condition among survivors of trauma. In the first study, authors found that participants who repeatedly narrated the content of positive autobiographical memories reported decreases in PTSD symptom severity and negative affect, as well as increases in positive affect across time compared to the control condition [38]. In the second study, authors found that survivors of trauma who repeatedly retrieved positive (and neutral) memories reported less PTSD and depression severity, fewer posttrauma cognitions, and improved affect [39]. Using an open-label pilot trial, the feasibility and effects of the 5-session PPMT were examined among 12 survivors of trauma [40,41]. The authors found that PPMT reduced PTSD symptoms, reduced negative affect, and improved regulation of positive affect, and there were good feasibility indicators for PPMT (eg, PPMT was acceptable).

Critically, no study has examined PPMT's effects using a larger community sample, nor has there been any exploration of whether PPMT is associated with postintervention changes in how survivors of trauma react to events in daily life. We can hypothesize that PPMT may impact individuals' daily-life affect and cognitions; these impacts represent hypothesized

mechanisms through which PPMT may reduce PTSD symptom severity over time. Most studies examining PTSD intervention impacts use case-series designs, in which data are collected from a group of individuals pre- and postintervention and an aggregate assessment of symptomatology pre- and postintervention is conducted and compared. However, this approach has some noteworthy limitations. Affect, cognitions, and PTSD symptoms are dynamic and vary daily in response to trauma reminders and experiences [42-44]; thus, evaluating intervention effectiveness using 2 snapshot assessments of symptomatology is not sufficiently reliable or nuanced. Furthermore, case-series designs do not examine the daily-level mechanisms of change for an intervention. Given that PPMT may impact daily life affect, cognitions, and symptoms, it is crucial that the data enable an examination of these constructs at the daily level.

These limitations can be overcome by integrating case-series designs with a daily diary framework for the pre- and post-PPMT assessments. Daily diary studies are an intensive longitudinal data collection method in which participants provide daily reports of their experiences each day over a period of time. Compared to retrospective assessments, daily diary data are considered more ecologically valid as they are collected in an individual's everyday life rather than in a laboratory, more accurate and robust, and less vulnerable to recall bias [45]. Thus, the proposed study outlines information on the protocol of an ongoing study that combines case-series design and daily diary approaches to provide novel insights into PPMT's effects on daily-level cognitive and affective experiences. This approach can be conceptualized as a special subtype of case-series design that enables an examination of within-person changes at the daily level.

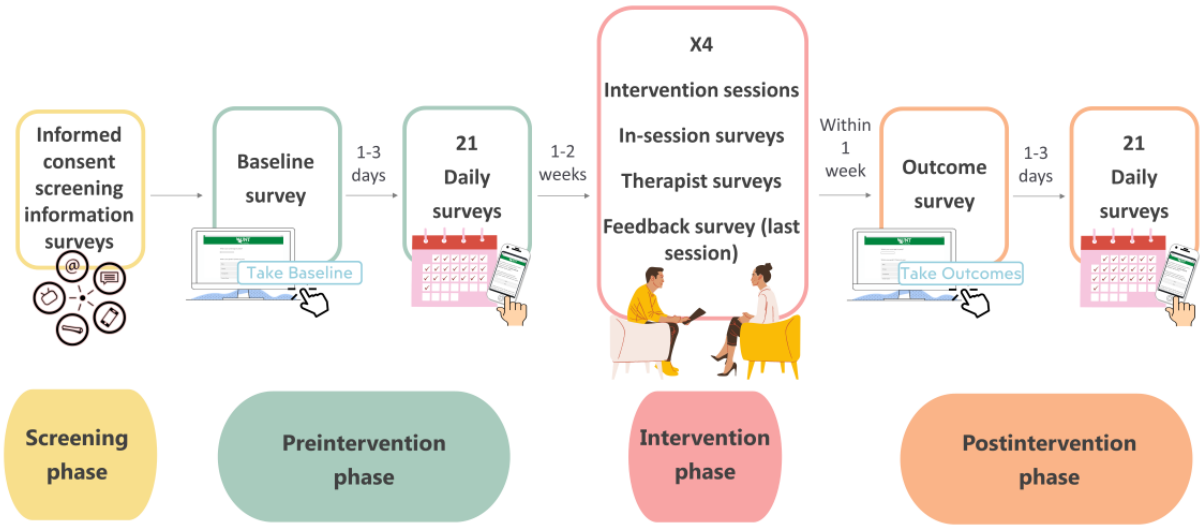
Specifically, the proposed study aims to use daily diary data pre- and post-PPMT to examine changes in daily PTSD, daily affect, and daily cognitions. We hypothesize that at the daily level, participants will report (1) a lower count of endorsed daily PTSD symptoms pre- to post-PPMT, (2) increases in daily positive affect and decreases in daily negative affect pre- to post-PPMT, (3) increases in positive affect reactivity to daily positive events (a within-person index of linear relations between daily positive events and daily positive affect) pre- to post-PPMT, and (4) decreases in daily posttrauma cognitions pre- to post-PPMT. The aim of this study is to detail the proposed research protocol and our hypotheses regarding daily PTSD, daily negative affect, and daily cognitions pre- and post-PPMT. As a supplementary analysis, we will examine if participants report a greater count of retrieved specific positive memories pre- to post-PPMT.

Methods

Study Design

The study involves four phases: (1) screening phase (eligibility survey), (2) preintervention phase (baseline survey and daily surveys), (3) intervention phase (PPMT and weekly surveys), and (4) postintervention phase (outcome survey and daily surveys). Figure 1 provides an illustration of the study procedure. All assessments are completed by participants using a computer or smartphone. Greene and colleagues [46] provide a detailed protocol for the questionnaires. Briefly summed up, following a web-based screening survey, eligible participants are asked to complete a preintervention phase baseline survey followed by 21 daily surveys in their natural environments. Then, they receive 4 PPMT sessions, completing 1 web-based survey per session and a feedback survey in the last session. After the conclusion of the PPMT intervention, participants are asked to complete a postintervention phase outcome survey and 21 daily surveys.

Figure 1. Study procedure: explaining the step-by-step process of the study.



Participants

Participants (target n=70) are currently being recruited from a metroplex in the southwest United States through social media postings, flyers at businesses and public places, and university announcements since March 2022. The inclusion criteria are: (1) being aged between 18 and 65 years; (2) endorsing a trauma with posttrauma symptoms assessed by the Primary Care PTSD Screen for DSM-5 [47]; (3) access to an electronic device (eg, a computer or a smartphone) with internet capabilities; (4)

working knowledge of English; (5) no active suicidal plan, suicidal attempt, homicidal plan, or homicidal attempt (past 3 months including current); (6) being a current resident of the Dallas Fort Worth metroplex; (7) not currently in therapy with a mental health provider; (8) willingness and availability to participate in approximately 10 weeks of this study (including 4 therapy sessions); and (9) willingness to be video-recorded during sessions for quality control purposes.

Procedure

Screening Phase

During this phase, interested participants complete an eligibility survey. First, they read the informed consent document (information about the study, eligibility criteria, compensation, benefits and risks to study participation, and steps to ensure data confidentiality) and provide electronic informed consent if they wish to participate. Next, they answer questions to determine eligibility. Eligible and consenting participants are automatically redirected to a separate survey, wherein they provide contact information for study purposes. Research personnel then contact eligible participants to provide more information on the study (eg, survey timelines and PPMT sessions). No compensation is provided for this study phase.

Preintervention Phase

Participants complete 1 baseline survey and 21 daily surveys as part of this phase. The baseline survey contains questions on demographics, trauma history, PTSD symptoms, and other psychological symptoms, as well as affect and cognitive processes (approximately 30-minute completion time). Eligible participants receive the baseline survey link by email at a date determined to be feasible based on contact with participants. Participants are given up to 48 hours to complete the baseline survey and are sent reminders if they do not complete the survey in a timely manner. Research personnel monitor survey responses for completion, response times to identify unfeasibly short times, accurate participant ID entry, therapy history to confirm they are not currently in therapy, and trauma history.

Participants who complete the baseline survey are asked to complete 21 daily surveys. The daily surveys include questions assessing daily PTSD symptoms, affect, cognitions, and events that occurred in the last 24 hours (approximately 3-5 minutes to complete each survey). The link to the first daily survey is emailed to participants within 1-3 days after completing the baseline survey. Participants receive daily surveys once a day at fixed intervals (at 7:00 PM each day) over a 21-day period, and they have until 11.59 PM to complete each daily survey. Participants are sent text reminders for survey completion to enhance compliance and are contacted if they miss any surveys.

Intervention Phase

PPMT is administered weekly as a 4-session protocol during the intervention phase. The sessions are scheduled within 1-2 weeks after completing the preintervention phase. In session 1, participants receive psychoeducation on PTSD symptoms, an overview of PPMT, and are assessed for psychological symptoms. Sessions 1-4 involve the detailed processing of a salient positive autobiographical memory to elicit "values, affect, strengths, and thoughts" related to that positive memory. Homework assignments include listening to an audio recording of that memory, completing a "values, affect, strengths, and thoughts" log, and engaging in a behavioral activity. In session 4, the therapist also reviews psychological symptoms and addresses termination. Following the completion of session 4, the participants complete a feedback survey on PPMT.

Postintervention Phase

Participants complete 1 outcome survey and 21 daily surveys as part of this phase. Within approximately 1 week after completing the intervention phase, participants complete an outcome survey. The procedural aspects of this phase mimic the preintervention phase. The outcome survey has questions similar to those of the preintervention phase baseline survey (without demographics and trauma history items and with different cue words for the measure examining the count of retrieved memories).

Dropout

Participants who do not complete the outcome survey after 2 days, consecutively miss 4 daily surveys, or miss more than 8 daily surveys (<60% of the daily surveys) in either the preintervention or postintervention phases are considered dropouts for this study, and they do not continue to receive survey links in order to avoid burdening participants with repeated requests to complete the surveys if they no longer wish to participate.

Study's Primary Measures

Overview of Primary Measures

In this section, we outline the measures that relate to the primary outcomes of this study. The primary outcomes of interest are daily positive affect levels, daily positive affect reactivity (within-person index of linear relations between daily positive events and daily positive affect [48]), daily negative affect levels, daily posttrauma cognitions, daily PTSD symptoms, and the number of retrieved specific positive memories as measured pre- and postintervention. Secondary measures (eg, difficulties in positive emotional regulation using the "Difficulties in Emotion Regulation Scale-Positive" and the severity of PTSD symptoms using the "PTSD Checklist for DSM-5") are also administered to allow for the assessment of possible mediators and moderators of treatment effects. Table S1 in Multimedia Appendix 1 [40,47,49-58] provides detailed information on all study measures (including measures for supplemental analyses).

Preintervention Phase Baseline Survey

The number of retrieved specific-positive memories is measured by the Autobiographical Memory Test (AMT) [49,59]. The AMT uses a cued memory recall technique involving the presentation of individual cue words, followed by a prompt to recall a personally meaningful and specific memory of an event that took place within any 24-hour period. For this study, participants are shown cue words and asked to retrieve a personal and specific memory of the cue-word-related event within 60 seconds [59]. The instructions were adapted from previous autobiographical memory studies [49,60,61]. In the preintervention baseline survey, we included 5 cues drawn from

previous studies: friendly, happy, honest, kind, and humorous [62-64]. We will follow coding guidelines to categorize AMT responses [65,66]. AMT responses will be coded as specific (event that occurred at a certain place within 24 hours), extended (event that lasted >1 day), or categorical (summary of repeated events). AMT responses will also be coded as positive or nonpositive following the Coding and Assessment System for Narratives of Trauma [67]. Lastly, AMT responses will be coded as semantic associate (no personal memory) and omission (did not retrieve the memory within 60 seconds or was unable to recall a memory). The AMT demonstrates good psychometrics [68].

Preintervention Phase Daily Surveys

Daily negative and positive events are measured by asking participants to rate their most positive and negative events in the last 24 hours from 0 (not at all unpleasant) to 3 (very unpleasant) [50].

Daily affect levels (ie, positive and negative) are assessed by rating the extent of 4 positive (excited, cheerful, satisfied, and relaxed) and 6 negative (stressed, irritated, anxious, sad, hopeless, and insecure) emotions in the last 24 hours. These emotions were used in a previous daily diary study based on a theoretical circumflex of emotions. The study showed excellent between-person reliability and good within-person reliability [69]. In this study, responses are rated on a 5-point Likert scale ranging from 1 (very slightly or not at all) to 5 (extremely).

Daily posttrauma cognitions are measured by the Brief Version of the Posttraumatic Cognitions Inventory [51], which is a 9-item self-report measure assessing posttrauma cognitions. Responses are provided on a 7-point Likert scale ranging from 1 (totally disagree) to 7 (totally agree), with the time frame modified to “in the last 24 hours.”

Daily PTSD symptom severity is assessed using the Primary Care PTSD Screen for DSM-5 [47], which is a 5-item self-report measure with dichotomous “yes” or “no” items; the time frame is modified to “in the last 24 hours.” We will use the count of endorsed PTSD symptoms as a measure of daily PTSD symptom severity.

Postintervention Phase Outcome Survey

Similar to the preintervention phase baseline survey, the AMT is administered to examine the number of retrieved specific positive memories. Different cue words are used: peaceful, loyal, helpful, safe, and love [62-64].

Postintervention Phase Daily Surveys

The procedural aspects and measures mimic the preintervention phase daily surveys.

Participant Safety and Psychological Distress

There are minimal foreseeable risks associated with this study. Few participants may experience an increase in PTSD severity [70] or suicidal ideation [71], attributed to the sensitive nature of questions targeting trauma reactions and to PPMT itself. To address any such concerns, the study co-principal investigator (co-PI; a licensed clinical psychologist) is training all research personnel on considerations in administering assessments to survivors of trauma, providing clinical training and weekly supervision to study therapists, and training study therapists in anxiety-reduction techniques (eg, guided imagery). Furthermore, study participants receive information on mental health services.

To address any risk factors for self-harm, we are closely monitoring participants during PPMT to assess for any reported suicidal ideation, plan, or attempt (eg, administration of a depression measure every session). Furthermore, the study co-PI is training study therapists to conduct in-depth suicide risk assessments. In the event of suicidal ideation, plan, or attempt reported by participants in session, study therapists conduct a suicide risk assessment and consult with the supervising co-PI to determine if emergency services need to be contacted to ensure participant safety. Also, the participant or therapist may discontinue the study at any time should symptoms worsen or if the participant simply desires to withdraw. Lastly, we are providing information on community mental health centers offering 24-hour access to services and emphasizing contacting 911 or 988 in times of imminent risk.

Treatment Nonresponse or Relapse

Any treatment for posttrauma mental health is associated with some chance of failure to respond or relapse [72]. We are implementing the following procedures to address any such potential concerns. If a participant shows substantial increases in PTSD or depression severity or reports risk factors for self-harm during intervention sessions, we are providing mental health referrals immediately for alternate treatment options, including a 24-hour access local mental health center. Furthermore, research personnel are contacting participants when they miss appointments to check on their health status.

Intervention Training

Therapist Training

The study co-PI trained doctoral students (ie, study therapists) in PPMT. This training included a review of PPMT’s theoretical underpinnings, manuals, and fidelity checklists, as well as practice in PPMT administration. Furthermore, study therapists are required to follow detailed session protocols during each PPMT session. Research assistants were trained in PPMT fidelity ratings; ≥0.81 kappa coefficient and ≥0.8% percent agreement will be considered acceptable interrater reliability (IRR) [73].

Treatment Delivery

All sessions are being video recorded. The co-PI has reviewed all recorded PPMT sessions for 1 participant for each study therapist; she will continue to review 20%-50% of the video-recorded sessions as needed [74]. The co-PI is providing weekly group supervision to study therapists that involves case discussions and feedback.

Fidelity Ratings Across Raters

The authors have created fidelity checklists that include a list of proscribed PPMT components to be recorded as occurring or not occurring. Using these fidelity checklists, 2 trained evaluators will independently code video-recorded sessions for 18-20 participants. These data will be used to compute IRR estimates. If acceptable IRR estimates are not achieved, trained

evaluators will code an additional 20% of sessions. Once acceptable IRR estimates are achieved, the evaluators will solely code the remainder of the treatment sessions for fidelity.

Adherence to PPMT Components

We will compute percentage adherence across sessions for each of the trained study therapists, with the recommended 80%-100% benchmark indicating high fidelity [74].

Data Analysis

Power Analysis

We conducted an a priori power analysis using the *EMAtools R* (Kleiman) package [75] for power curves for multilevel studies. The power analysis was based on two 3-week assessment bursts with 1 questionnaire per day and an estimated intraclass correlation coefficient of 0.36 based on a previous study on daily-level emotions, cognitions, and PTSD [76]. Analysis showed that 70 participants and up to 25% missing data would be sufficient to detect a medium effect size (d=0.5) with 80% power.

Analytical Plan

A paired sample *t* test will be used to examine changes in the count of retrieved specific-positive autobiographical memories pre- versus post-PPMT (comparing the preintervention baseline and postintervention outcome surveys). To examine changes in daily affect, daily cognitions, and daily PTSD symptoms, we will use the daily diary reports pre- and postintervention and conduct multilevel random intercepts and slopes linear regression models for each outcome variable using *MPlus 8*.3 (Muthén and Muthén), *nlme* (Pinheiro et al), and *lme R* (Bates et al) packages, comparing the models pre- and post-PPMT with and without demographic covariates (eg, gender, age, and education). We will also conduct exploratory analyses examining additional variables included in the study as predictors or moderators of post-PPMT outcomes (eg, count of trauma types previously experienced, PTSD severity at baseline, and difficulties in positive emotional regulation).

Missing Data

At the survey level, the web-based questionnaire has been set up with a prompt if questions have been skipped, with the option to continue the survey without completing a particular item or to go back and complete the skipped question. We anticipate a little missing data within the submitted surveys. We will treat surveys that have been submitted with missing data as complete for the purposes of determining dropout and participation compensation. An analysis will be conducted to investigate the pattern of missingness. If data are missing at random or missing completely at random, they will be handled by listwise deletion and models fit by maximum likelihood. If data are not missing at random, then missing data will be imputed using the MICE (van Buuren et al) package in R [77] and fit by maximum likelihood.

Ethical Considerations

The institutional review boards at the University of North Texas (#21-420) and the University of Haifa (#480/21) have approved this study. During the screening phase, interested participants read the informed consent document (information about the study, eligibility criteria, compensation, benefits and risks to study participation, and steps to ensure data confidentiality) and provide electronic informed consent if they wish to participate. Participants are then contacted by research personnel to re-explain any study procedures and obtain or confirm identifying information.

In terms of compensation, participants receive US $1.50 for each completed daily survey and US $10 each for completing each of the baseline and outcome surveys. Participants receive US $10 for completing each of the 4 PPMT session surveys and US $12 toward transportation costs cumulatively for all 4 (attended) intervention sessions. In order to incentivize participants to provide as much data as possible, participants who complete 36 surveys without any missing data receive an additional US $15. The total potential compensation for participation is US $150.

Participants provide personally identifiable information (eg, name and contact information), which is only used for scheduling purposes, study-related communications, and to connect data longitudinally. Each participant receives a unique and randomly generated ID number, which is used on all web-based surveys for this study. At no point is any personally identifiable information linked to participant data. Furthermore, deidentified data will be analyzed for the scientific dissemination of study findings.

Results

Year 1 of the study (October 2021-September 2022) was primarily devoted to recruiting and training research personnel, obtaining ethics approvals, and preparing to launch the study. Year 2 of the study (October 2022-September 2023) has been focused on participant recruitment and data collection. During Year 3 of the study (October 2023-September 2024), we will complete data collection from our targeted sample and start the data cleaning and analysis process. During Year 4 of the study (October 2024-October 2025), we will complete the data analyses and prepare planned scientific outputs (eg, publications and presentations).

Data collection was initiated in March 2022. As of November 28, 2023, a total of 515 participants had consented to the study in the screening phase. Of those, 258 (50.1%) participants were eligible, 92 (35.7%) of which gave their consent by phone and attempted the first daily survey of the study. Of the 92 participants who completed the first daily survey, a total of 58 (63%) participants completed all intervention sessions and ≥13 daily surveys (≥60% of the daily surveys), and 28 (30.4%) participants dropped out in various stages of the study, mostly before the PPMT intervention. As of November 29, 2023, a total of 6 (6.5%) participants are currently participating in various phases of the study. Data collection is expected to end by June 2024. No analyses will be conducted until data collection has been completed.

Discussion

This study aims to examine the daily-level impacts of PPMT, a promising adjunct or alternative to traditional PTSD treatments, in a trauma-exposed, nonclinical community sample. This study combines a case-series design and a daily diary design to examine potential mechanisms of change in PTSD symptoms by assessing daily affect, daily cognitions, and daily PTSD symptoms before and after the PPMT intervention. This approach enables a more nuanced and ecologically valid exploration of changes as compared with retrospective aggregate assessments. We outline the research protocol for this study, including the hypotheses and the proposed analyses. When data collection has been completed (estimated date: June 2024), we will test our hypotheses that, at the daily level, in comparison to their own pre-PPMT levels, following the PPMT intervention, participants will report (1) a lower count of endorsed daily PTSD symptoms, (2) increases in daily positive affect and decreases in daily negative affect, (3) increases in positive affect reactivity to daily positive events, and (4) decreases in daily posttrauma cognitions.

The findings of this proposed study could have significant implications. Results could clarify whether deficits in positive autobiographical memory processes (eg, retrieval and encoding) may also characterize PTSD alongside deficits in traumatic memory processes [7]. If the study's hypotheses are confirmed, PPMT could be an additional therapeutic tool for clinicians to help clients with posttraumatic distress. Unlike other trauma interventions, PPMT exclusively targets positive autobiographical memories in treatment while redirecting attention away from negative content embedded in the positive memories. By uniquely combining positive and symptom-focused techniques and theories, PPMT aims to increase positive elements (eg, values, affect, and thoughts) while simultaneously decreasing PTSD severity [17].

There are some limitations to this study that should be considered. The study uses a self-report approach, which, although it reduces recall bias, is still subject to potential difficulties in the recall of experiences over the course of each day. Relatedly, while it reduces participant burden, the PC-PTSD measure is a PTSD symptom screener and usually is coupled with a comprehensive structured diagnostic interview for PTSD or a self-report measure assessing all 20 PTSD symptoms (which we do not do in this study due to the daily-level methodology and associated participant and time burdens). Furthermore, we are not gathering information on trauma characteristics such as the ages at which the trauma was experienced, the frequency or chronicity of each experienced trauma, or the time since the trauma has elapsed. Such information can impact posttrauma distress [78-80] and may moderate the impacts of PPMT in this study; hence, it should be empirically investigated in future research. In addition, while the research design of one assessment per day enables examination of changes in daily symptoms, affect, and cognition before and after the intervention, it does not have a sampling frequency nor sufficient power to examine fine-grained dynamic interactions between symptoms, affect, and cognition using even more complex modeling techniques. Lastly, our eligibility criterion permits individuals endorsing even 1 PTSD symptom at a clinical level to be included in the study. While such an approach accounts for impairment among individuals endorsing sub-threshold PTSD [81], it may also make it statistically difficult to detect any changes in PTSD symptoms (ie, the floor effect).

In conclusion, this study will contribute to the development of more personalized and alternative PTSD interventions for survivors of trauma who drop out or do not benefit from existing PTSD treatments. Further studies could examine PPMT as an ecological momentary intervention, wherein individuals receive daily reminders and instructions for engaging in therapy-relevant behaviors (eg, processing of positive memories). Such interventions can particularly benefit communities that do not have easy access to mental health services and are underserved in that regard [82]. Finally, this study will give insight into the mechanisms of change in the PPMT intervention through elucidating daily-level changes in affect, cognition, symptoms, and event reactivity.

Acknowledgments

This research was supported by a grant (2020017) from the United States-Israel Binational Science Foundation (BSF). The authors would like to acknowledge the work of Gurleen Kaur for participant recruitment and data collection and the work of Sidonia Compton as a study therapist.

Data Availability

The data sets that will be generated through this study will not be publicly available due to the sensitive nature of the posttrauma daily-level data, however the corresponding author will make deidentified data available on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Supplemental table 1. Timeline information on measures.
[DOCX File , 25 KB - resprot_v13i1e51838_app1.docx]

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR). Washington, DC: American Psychiatric Association Publishing; 2022.
2. Ehlers A, Clark DM. A cognitive model of posttraumatic stress disorder. Behav Res Ther 2000;38(4):319-345. [doi: 10.1016/s0005-7967(99)00123-0] [Medline: 10761279]
3. Contractor AA, Greene T, Dolan M, Weiss NH, Armour C. Relation between PTSD symptom clusters and positive memory characteristics: a network perspective. J Anxiety Disord 2020;69:102157 [FREE Full text] [doi: 10.1016/j.janxdis.2019.102157] [Medline: 31751918]
4. Brewin CR, Holmes EA. Psychological theories of posttraumatic stress disorder. Clin Psychol Rev 2003;23(3):339-376. [doi: 10.1016/s0272-7358(03)00033-3] [Medline: 12729677]
5. Contractor AA, Banducci AN, Dolan M, Keegan F, Weiss NH. Relation of positive memory recall count and accessibility with post-trauma mental health. Memory 2019;27(8):1130-1143 [FREE Full text] [doi: 10.1080/09658211.2019.1628994] [Medline: 31189410]
6. Contractor AA, Caldas SV, Dolan M, Weiss NH. Factors related to positive memory count among trauma-exposed individuals: a scoping review. Trauma Violence Abuse 2022;23(5):1568-1584. [doi: 10.1177/15248380211013130] [Medline: 33960225]
7. Contractor AA, Messman BA, Slavish DC, Weiss NH. Do positive memory characteristics influence daily-level trajectories of posttraumatic stress disorder symptoms? An exploratory daily diary study. Anxiety Stress Coping 2023;36(3):320-338. [doi: 10.1080/10615806.2022.2075856] [Medline: 35561031]
8. Ehlers A. Understanding and treating unwanted trauma memories in posttraumatic stress disorder. Z Psychol 2010;218(2):141-145 [FREE Full text] [doi: 10.1027/0044-3409/a000021] [Medline: 22095462]
9. Schnurr PP. Focusing on trauma-focused psychotherapy for posttraumatic stress disorder. Curr Opin Psychol 2017;14:56-60. [doi: 10.1016/j.copsyc.2016.11.005] [Medline: 28813321]
10. Contractor AA, Weiss NH, Forkus SR, Keegan F. Positive internal experiences in PTSD interventions: a critical review. Trauma Violence Abuse 2022;23(1):101-116 [FREE Full text] [doi: 10.1177/1524838020925784] [Medline: 32468926]
11. Lewis C, Roberts NP, Gibson S, Bisson JI. Dropout from psychological therapies for Post-Traumatic Stress Disorder (PTSD) in adults: systematic review and meta-analysis. Eur J Psychotraumatol 2020;11(1):1709709 [FREE Full text] [doi: 10.1080/20008198.2019.1709709] [Medline: 32284816]
12. Moradi AR, Piltan M, Choobin MH, Azadfallah P, Watson P, Dalgleish T, et al. Proof of concept for the autobiographical Memory Flexibility (MemFlex) intervention for posttraumatic stress disorder. Clin Psychol Sci 2021;9(4):686-698 [FREE Full text] [doi: 10.1177/2167702620982576] [Medline: 34354873]
13. Moradi AR, Moshirpanahi S, Parhon H, Mirzaei J, Dalgleish T, Jobson L. A pilot randomized controlled trial investigating the efficacy of MEmory Specificity Training in improving symptoms of posttraumatic stress disorder. Behav Res Ther 2014;56:68-74. [doi: 10.1016/j.brat.2014.03.002] [Medline: 24705337]
14. Panagioti M, Gooding PA, Tarrier N. An empirical investigation of the effectiveness of the Broad-Minded Affective Coping procedure (BMAC) to boost mood among individuals with PostTraumatic Stress Disorder (PTSD). Behav Res Ther 2012;50(10):589-595. [doi: 10.1016/j.brat.2012.06.005] [Medline: 22835839]
15. Contractor AA, Brown LA, Caldas SV, Banducci AN, Taylor DJ, Armour C, et al. Posttraumatic stress disorder and positive memories: clinical considerations. J Anxiety Disord 2018;58:23-32. [doi: 10.1016/j.janxdis.2018.06.007] [Medline: 30025253]
16. Contractor AA, Banducci AN, Weiss NH. Critical considerations for the positive memory-posttraumatic stress disorder model. Clin Psychol Psychother 2022;29(1):81-91. [doi: 10.1002/cpp.2599] [Medline: 33870586]
17. Contractor AA, Weiss NH, Shea MT. Processing of Positive Memories Technique (PPMT) for posttraumatic stress disorder: a primer. J Psychother Integr 2021;31(2):195-207 [FREE Full text] [doi: 10.1037/int0000239] [Medline: 34483636]
18. Sin NL, Lyubomirsky S. Enhancing well-being and alleviating depressive symptoms with positive psychology interventions: a practice-friendly meta-analysis. J Clin Psychol 2009;65(5):467-487 [FREE Full text] [doi: 10.1002/jclp.20593] [Medline: 19301241]
19. Bolier L, Haverman M, Westerhof GJ, Riper H, Smit F, Bohlmeijer E. Positive psychology interventions: a meta-analysis of randomized controlled studies. BMC Public Health 2013;13:119 [FREE Full text] [doi: 10.1186/1471-2458-13-119] [Medline: 23390882]
20. Wing JF, Schutte NS, Byrne B. The effect of positive writing on emotional intelligence and life satisfaction. J Clin Psychol 2006;62(10):1291-1302. [doi: 10.1002/jclp.20292] [Medline: 16810662]
21. Lambert NM, Gwinn AM, Baumeister RF, Strachman A, Washburn IJ, Gable SL, et al. A boost of positive affect: the perks of sharing positive experiences. J Soc Pers Relat 2012;30(1):24-43 [FREE Full text] [doi: 10.1177/0265407512449400]
22. Raes F, Williams JMG, Hermans D. Reducing cognitive vulnerability to depression: a preliminary investigation of MEmory Specificity Training (MEST) in inpatients with depressive symptomatology. J Behav Ther Exp Psychiatry 2009;40(1):24-38 [FREE Full text] [doi: 10.1016/j.jbtep.2008.03.001] [Medline: 18407245]
23. Resick PA, Schnicke M. Cognitive Processing Therapy for Rape Victims: A Treatment Manual. Newbury Park, California: Sage Publications; 1993.

24. Conway MA, Pleydell-Pearce CW. The construction of autobiographical memories in the self-memory system. Psychol Rev 2000;107(2):261-288. [doi: 10.1037/0033-295x.107.2.261] [Medline: 10789197]
25. Bryant RA, Sutherland K, Guthrie RM. Impaired specific autobiographical memory as a risk factor for posttraumatic stress after trauma. J Abnorm Psychol 2007;116(4):837-841. [doi: 10.1037/0021-843X.116.4.837] [Medline: 18020729]
26. Berntsen D, Rubin DC. The centrality of event scale: a measure of integrating a trauma into one's identity and its relation to post-traumatic stress disorder symptoms. Behav Res Ther 2006;44(2):219-231 [FREE Full text] [doi: 10.1016/j.brat.2005.01.009] [Medline: 16389062]
27. Berntsen D, Rubin DC. When a trauma becomes a key to identity: enhanced integration of trauma memories predicts posttraumatic stress disorder symptoms. Appl Cogn Psychol 2007;21(4):417-431. [doi: 10.1002/acp.1290]
28. Janoff-Bulman R. Shattered Assumptions: Towards a New Psychology of Trauma. New York: Free Press; 1992.
29. Rusting CL, DeHart T. Retrieving positive memories to regulate negative mood: consequences for mood-congruent memory. J Pers Soc Psychol 2000;78(4):737-752. [doi: 10.1037//0022-3514.78.4.737] [Medline: 10794377]
30. Quoidbach J, Mikolajczak M, Gross JJ. Positive interventions: an emotion regulation perspective. Psychol Bull 2015;141(3):655-693. [doi: 10.1037/a0038648] [Medline: 25621978]
31. Tarrier N. Broad Minded Affective Coping (BMAC): a "positive" CBT approach to facilitating positive emotions. Int J Cogn Ther 2010;3(1):64-76. [doi: 10.1521/ijct.2010.3.1.64]
32. Hall KAA, De Raedt R, Timpano KR, Joormann J. Positive memory enhancement training for individuals with major depressive disorder. Cogn Behav Ther 2018;47(2):155-168. [doi: 10.1080/16506073.2017.1364291] [Medline: 28826327]
33. Blaney PH. Affect and memory: a review. Psychol Bull 1986;99(2):229-246. [doi: 10.1037/0033-2909.99.2.229] [Medline: 3515383]
34. Fredrickson BL. The role of positive emotions in positive psychology. The broaden-and-build theory of positive emotions. Am Psychol 2001;56(3):218-226 [FREE Full text] [doi: 10.1037//0003-066x.56.3.218] [Medline: 11315248]
35. Speer ME, Bhanji JP, Delgado MR. Savoring the past: positive memories evoke value representations in the striatum. Neuron 2014;84(4):847-856 [FREE Full text] [doi: 10.1016/j.neuron.2014.09.028] [Medline: 25451197]
36. Philippe FL, Lecours S, Beaulieu-Pelletier G. Resilience and positive emotions: examining the role of emotional memories. J Pers 2009;77(1):139-175. [doi: 10.1111/j.1467-6494.2008.00541.x] [Medline: 19077002]
37. Askelund AD, Schweizer S, Goodyer IM, van Harmelen AL. Positive memory specificity is associated with reduced vulnerability to depression. Nat Hum Behav 2019;3(3):265-273. [doi: 10.1038/s41562-018-0504-3] [Medline: 30953005]
38. Contractor AA, Banducci AN, Jin L, Keegan FS, Weiss NH. Effects of processing positive memories on posttrauma mental health: a preliminary study in a non-clinical student sample. J Behav Ther Exp Psychiatry 2020;66:101516 [FREE Full text] [doi: 10.1016/j.jbtep.2019.101516] [Medline: 31634724]
39. Contractor AA, Messman B, Gould P, Slavish DC, Weiss NH. Impacts of repeated retrieval of positive and neutral memories on posttrauma health: an investigative pilot study. J Behav Ther Exp Psychiatry 2023;81:101887. [doi: 10.1016/j.jbtep.2023.101887] [Medline: 37343425]
40. Contractor AA, Jin L, Weiss NH. Open label pilot study on posttrauma health impacts of the Processing of Positive Memories Technique (PPMT). J Psychother Integr 2023;33(2):213-234. [doi: 10.1037/int0000290] [Medline: 37577256]
41. Contractor AA, Slavish DC, Thornton J, Weiss NH. Positive affect processes and posttraumatic stress disorder symptoms: findings from an open label and uncontrolled pilot study using the positive memory processing technique. J Psychother Integr 2023;33(1):102-122. [doi: 10.1037/int0000292] [Medline: 37193258]
42. Greene T, Gelkopf M, Epskamp S, Fried E. Dynamic networks of PTSD symptoms during conflict. Psychol Med 2018;48(14):2409-2417. [doi: 10.1017/S0033291718000351] [Medline: 29486811]
43. Greene T, Sznitman S, Contractor AA, Prakash K, Fried EI, Gelkopf M. The memory-experience gap for PTSD symptoms: the correspondence between experience sampling and past month retrospective reports of traumatic stress symptoms. Psychiatry Res 2022;307:114315. [doi: 10.1016/j.psychres.2021.114315] [Medline: 34896842]
44. Dornbach-Bender A, Ruggero CJ, Schuler K, Contractor AA, Waszczuk M, Kleva CS, et al. Positive and negative affect in the daily life of World Trade Center responders with PTSD: an ecological momentary assessment study. Psychol Trauma 2020;12(1):75-83 [FREE Full text] [doi: 10.1037/tra0000429] [Medline: 30688510]
45. Shiffman S, Stone AA, Hufford MR. Ecological momentary assessment. Annu Rev Clin Psychol 2008;4(1):1-32. [doi: 10.1146/annurev.clinpsy.3.022806.091415] [Medline: 18509902]
46. Greene T, Contractor AA, Oren SDD, Fentem A, Sznitman S. Daily-level impacts of the processing of positive memories technique on post-trauma affect and cognitions among trauma survivors: a daily diary study protocol. Open Science Framework. URL: https://osf.io/y5az4/ [accessed 2023-12-21]
47. Prins A, Bovin MJ, Kimerling R, Kaloupek DG, Marx BP, Kaiser AP, et al. The Primary Care PTSD screen for DSM-5 (PC-PTSD-5). National Center for PTSD. 2015. URL: https://www.ptsd.va.gov/professional/assessment/screens/pc-ptsd.asp [accessed 2023-12-21]
48. Parrish BP, Cohen LH, Gunthert KC, Butler AC, Laurenceau JP, Beck JS. Effects of cognitive therapy for depression on daily stress-related variables. Behav Res Ther 2009;47(5):444-448 [FREE Full text] [doi: 10.1016/j.brat.2009.02.005] [Medline: 19269627]

49. Henderson D, Hargreaves I, Gregory S, Williams JMG. Autobiographical memory and emotion in a non-clinical sample of women with and without a reported history of childhood sexual abuse. Br J Clin Psychol 2002;41(Pt 2):129-141. [doi: 10.1348/014466502163921] [Medline: 12034001]
50. Hiekkaranta AP, Kirtley OJ, Lafit G, Decoster J, Derom C, de Hert M, et al. Emotion regulation in response to daily negative and positive events in youth: the role of event intensity and psychopathology. Behav Res Ther 2021;144:103916. [doi: 10.1016/j.brat.2021.103916] [Medline: 34224990]
51. Wells SY, Morland LA, Torres EM, Kloezeman K, Mackintosh MA, Aarons GA. The development of a brief version of the Posttraumatic Cognitions Inventory (PTCI-9). Assessment 2019;26(2):193-208. [doi: 10.1177/1073191116685401] [Medline: 28092974]
52. Life Events Checklist for DSM-5 (LEC-5). US Department of Veteran Affairs. URL: https://www.ptsd.va.gov/professional/assessment/te-measures/life_events_checklist.asp [accessed 2023-12-28]
53. PTSD Checklist for DSM-5 (PCL-5). US Department of Veteran Affairs. URL: https://www.ptsd.va.gov/professional/assessment/adult-sr/ptsd-checklist.asp [accessed 2023-12-28]
54. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001;16(9):606-613 [FREE Full text] [doi: 10.1046/j.1525-1497.2001.016009606.x] [Medline: 11556941]
55. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. J Pers Soc Psychol 1988;54(6):1063-1070. [doi: 10.1037//0022-3514.54.6.1063] [Medline: 3397865]
56. Weiss NH, Gratz KL, Lavender JM. Factor structure and initial validation of a multidimensional measure of difficulties in the regulation of positive emotions: the DERS-Positive. Behav Modif 2015;39(3):431-453 [FREE Full text] [doi: 10.1177/0145445514566504] [Medline: 25576185]
57. Luchetti M, Sutin AR. Measuring the phenomenology of autobiographical memory: a short form of the Memory Experiences Questionnaire. Memory 2016;24(5):592-602. [doi: 10.1080/09658211.2015.1031679] [Medline: 25894806]
58. Banducci AN, Fondren A, Bocanegra A, Crespo M, Contractor AA. Processing of Positive Memories Technique: feedback from trauma-exposed clients on Processing of Positive Memories Technique components, format, and feasibility. J Nerv Ment Dis 2023;211(4):289-297 [FREE Full text] [doi: 10.1097/NMD.0000000000001599] [Medline: 36191339]
59. Williams JM, Broadbent K. Autobiographical memory in suicide attempters. J Abnorm Psychol 1986;95(2):144-149. [doi: 10.1037//0021-843x.95.2.144] [Medline: 3711438]
60. Williams JMG, Ellis NC, Tyers C, Healy H, Rose G, MacLeod AK. The specificity of autobiographical memory and imageability of the future. Mem Cognit 1996;24(1):116-125 [FREE Full text] [doi: 10.3758/bf03197278] [Medline: 8822164]
61. Zinbarg RE, Rekart KN, Mineka S. Autobiographical memory in dysphoric and non-dysphoric college students using a computerised version of the AMT. Cogn Emot 2006;20(3-4):506-515. [doi: 10.1080/02699930500341318] [Medline: 26529218]
62. Kleim B, Ehlers A. Reduced autobiographical memory specificity predicts depression and posttraumatic stress disorder after recent trauma. J Consult Clin Psychol 2008;76(2):231-242 [FREE Full text] [doi: 10.1037/0022-006X.76.2.231] [Medline: 18377120]
63. McNally RJ, Lasko NB, Macklin ML, Pitman RK. Autobiographical memory disturbance in combat-related posttraumatic stress disorder. Behav Res Ther 1995;33(6):619-630. [doi: 10.1016/0005-7967(95)00007-k] [Medline: 7654154]
64. Harvey AG, Bryant RA, Dang ST. Autobiographical memory in acute stress disorder. J Consult Clin Psychol 1998;66(3):500-506. [doi: 10.1037//0022-006x.66.3.500] [Medline: 9642888]
65. Sutherland K, Bryant RA. Social problem solving and autobiographical memory in posttraumatic stress disorder. Behav Res Ther 2008;46(1):154-161. [doi: 10.1016/j.brat.2007.10.005] [Medline: 18022601]
66. Griffith JW, Sumner JA, Debeer E, Raes F, Hermans D, Mineka S, et al. An item response theory/confirmatory factor analysis of the autobiographical memory test. Memory 2009;17(6):609-623 [FREE Full text] [doi: 10.1080/09658210902939348] [Medline: 19585345]
67. Fernández-Lansac V, Crespo M. Presentation of the Coding and Assessment System for Narratives of Trauma (CASNOT): application in Spanish battered women and preliminary analyses. Span J Psychol 2017;20:E33. [doi: 10.1017/sjp.2017.31] [Medline: 28743322]
68. Griffith JW, Kleim B, Sumner JA, Ehlers A. The factor structure of the autobiographical memory test in recent trauma survivors. Psychol Assess 2012;24(3):640-646 [FREE Full text] [doi: 10.1037/a0026510] [Medline: 22149328]
69. Kiekens G, Hasking P, Nock MK, Boyes M, Kirtley O, Bruffaerts R, et al. Fluctuations in affective states and self-efficacy to resist non-suicidal self-injury as real-time predictors of non-suicidal self-injurious thoughts and behaviors. Front Psychiatry 2020;11:214 [FREE Full text] [doi: 10.3389/fpsyt.2020.00214] [Medline: 32265760]
70. Foa EB, Zoellner LA, Feeny NC, Hembree EA, Alvarez-Conrad J. Does imaginal exposure exacerbate PTSD symptoms? J Consult Clin Psychol 2002;70(4):1022-1028. [doi: 10.1037//0022-006x.70.4.1022] [Medline: 12182265]
71. Brown LA, McLean CP, Zang Y, Zandberg L, Mintz J, Yarvis JS, et al. Does prolonged exposure increase suicide risk? Results from an active duty military sample. Behav Res Ther 2019;118:87-93 [FREE Full text] [doi: 10.1016/j.brat.2019.04.003] [Medline: 31022593]
72. Watts BV, Schnurr PP, Mayo L, Young-Xu Y, Weeks WB, Friedman MJ. Meta-analysis of the efficacy of treatments for posttraumatic stress disorder. J Clin Psychiatry 2013;74(6):e541-e550. [doi: 10.4088/JCP.12r08225] [Medline: 23842024]

73. McHugh ML. Interrater reliability: the kappa statistic. Biochem Med (Zagreb) 2012;22(3):276-282 [FREE Full text] [Medline: 23092060]
74. Borrelli B. The assessment, monitoring, and enhancement of treatment fidelity in public health clinical trials. J Public Health Dent 2011;71(Suppl 1):S52-S63 [FREE Full text] [doi: 10.1111/j.1752-7325.2011.00233.x] [Medline: 21656954]
75. Kleiman E. EMAtools: data management tools for real-time monitoring/ecological momentary assessment data. R package version 01. 2017. URL: https://cran.r-project.org/web/packages/EMAtools/index.html [accessed 2023-12-21]
76. Pickman LL, Gelkopf M, Greene T. Emotional reactivity to war stressors: an experience sampling study in people with and without different psychiatric diagnoses. Stress Health 2021;37(1):127-139. [doi: 10.1002/smi.2978] [Medline: 32794338]
77. Buuren SV, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. J Stat Soft 2011;45(3):1-67 [FREE Full text] [doi: 10.18637/jss.v045.i03]
78. Cole TA, Reuman L, Lee DJ, Tabke CS, Marx BP, Sloan DM. The effect of time since index trauma on trauma-related beliefs. Psychol Trauma 2022 [FREE Full text] [doi: 10.1037/tra0001249] [Medline: 35666937]
79. Contractor AA, Caldas S, Fletcher S, Shea MT, Armour C. Empirically derived lifespan polytraumatization typologies: a systematic review. J Clin Psychol 2018;74(7):1137-1159. [doi: 10.1002/jclp.22586] [Medline: 29363746]
80. Hagenaars MA, Fisch I, van Minnen A. The effect of trauma onset and frequency on PTSD-associated symptoms. J Affect Disord 2011;132(1-2):192-199 [FREE Full text] [doi: 10.1016/j.jad.2011.02.017] [Medline: 21402413]
81. Zlotnick C, Franklin CL, Zimmerman M. Does "subthreshold" posttraumatic stress disorder have any clinical relevance? Compr Psychiatry 2002;43(6):413-419. [doi: 10.1053/comp.2002.35900] [Medline: 12439826]
82. McDevitt-Murphy ME, Luciano MT, Zakarian RJ. Use of ecological momentary assessment and intervention in treatment with adults. Focus (Am Psychiatr Publ) 2018;16(4):370-375 [FREE Full text] [doi: 10.1176/appi.focus.20180017] [Medline: 31191181]

Abbreviations

AMT: Autobiographical Memory Test
co-PI: coprincipal investigator
IRR: interrater reliability
PPMT: Processing of Positive Memories Technique
PTSD: posttraumatic stress disorder

Edited by A Mavragani; submitted 14.08.23; peer-reviewed by B Hruska, T Benham; comments to author 02.10.23; revised version received 14.12.23; accepted 17.12.23; published 12.01.24.

Please cite as:
Greene T, Contractor AA, Dicker-Oren SD, Fentem A, Sznitman SR
The Effects of the Processing of Positive Memories Technique on Posttrauma Affect and Cognitions Among Survivors of Trauma: Protocol for a Daily Diary Study
JMIR Res Protoc 2024;13:e51838
URL: https://www.researchprotocols.org/2024/1/e51838
doi:10.2196/51838
PMID:38214953

Protocol

Microfragmented Fat and Biphasic Calcium Phosphates for Alveolar Cleft Repair: Protocol for a Prospective, Nonblinded, First-in-Human Clinical Study

Diandra Sabrina Natsir Kalla[1,2], MD; Salem Alkaabi[1,3], DDS; Abul Fauzi[4], DDS; Andi Tajrin[4], DDS; Rifaat Nurrahma[1,5], DDS; Werner E G Müller[6], Prof Dr; Heinz C Schröder[6], Prof Dr; Xiaohong Wang[6], Prof Dr; Tymour Forouzanfar[1,7], Prof Dr; Marco N Helder[1], PhD; Muhammad Ruslin[4], Prof Dr

[1]Department of Oral and Maxillofacial Surgery/Oral Pathology, Amsterdam University Medical Centers and Academic Centre for Dentistry Amsterdam, Vrije Universiteit Amsterdam, Amsterdam Movement Sciences, Amsterdam, Netherlands

[2]Department of Biochemistry, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia

[3]Department of Oral and Maxillofacial Surgery, Fujairah Hospital, Ministry of Health, Fujairah, United Arab Emirates

[4]Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Hasanuddin University, Makassar, Indonesia

[5]Department of Prosthodontics, Faculty of Dentistry, Hasanuddin University, Makassar, Indonesia

[6]ERC Advanced Investigator Grant Research Group at the Institute for Physiological Chemistry, University Medical Center of the Johannes Gutenberg University, Mainz, Germany

[7]Department of Oral and Maxillofacial Surgery, Leiden University Medical Centre, Leiden, Netherlands

Corresponding Author:
Diandra Sabrina Natsir Kalla, MD
Department of Oral and Maxillofacial Surgery/Oral Pathology
Amsterdam University Medical Centers and Academic Centre for Dentistry Amsterdam
Vrije Universiteit Amsterdam, Amsterdam Movement Sciences
De Boelelaan 1117
PO box 7057
Amsterdam, 1007 MB
Netherlands
Phone: 31 20 444 1150
Email: sabrina.diandra@gmail.com

Abstract

Background: Biphasic calcium phosphates (BCP) may serve as off-the-shelf alternatives for iliac crest-derived autologous bone in alveolar cleft reconstructions. To add osteoinductivity to the osteoconductive BCPs to achieve similar regenerative capacity as autologous bone, a locally harvested buccal fat pad will be mechanically fractionated to generate microfragmented fat (MFAT), which has been shown to have high regenerative capacity due to high pericyte and mesenchymal stem cell content and a preserved perivascular niche.

Objective: Our primary objectives will be to assess the feasibility and safety of the BCP-MFAT combination. The secondary objective will be efficacy, which will be evaluated using radiographic imaging and histological and histomorphometric evaluation of biopsies taken 6 months postoperatively, concomitant with dental implant placement.

Methods: Eight patients with alveolar cleft (≥15 years) will be included in this prospective, nonblinded, first-in-human clinical study. MFAT will be prepared intraoperatively from the patient's own buccal fat pad. Regular blood tests and physical examinations will be conducted, and any adverse events (AEs) or serious EAs (SAEs) will be meticulously recorded. Radiographic imaging will be performed prior to surgery and at regular intervals after reconstruction of the alveolar cleft with the BCP-MFAT combination. Biopsies obtained after 6 months with a trephine drill used to prepare the implantation site will be assessed with histological and histomorphometric analyses after methylmethacrylate embedding and sectioning.

Results: The primary outcome parameter will be safety after 6 months' follow-up, as monitored closely using possible occurrences of SAEs based on radiographic imaging, blood tests, and physical examinations. For efficacy, radiographic imaging will be used for clinical grading of the bone construct using the Bergland scale. In addition, bone parameters such as bone volume, osteoid volume, graft volume, and number of osteoclasts will be histomorphometrically quantified. Recruitment started in November 2019, and the trial is currently in the follow-up stage. This protocol's current version is 1.0, dated September 15, 2019.

Conclusions: In this first-in-human study, not only safety but also the histologically and radiographically assessed regenerative potential of the BCP-MFAT combination will be evaluated in an alveolar cleft model. When an SAE occurs, it will be concluded that the BCP-MFAT combination is not yet safe in the current setting. Regarding AEs, if they do not occur at a higher frequency than that in patients treated with standard care (autologous bone) or can be resolved by noninvasive conventional methods (eg, with analgesics or antibiotics), the BCP-MFAT combination will be considered safe. In all other cases, the BCP-MFAT combination will not yet be considered safe.

Trial Registration: Indonesia Clinical Trial Registry INA-EW74C1N; https://tinyurl.com/28tnrr64

International Registered Report Identifier (IRRID): DERR1-10.2196/42371

(JMIR Res Protoc 2024;13:e42371) doi:10.2196/42371

KEYWORDS

microfragmented fat; calcium phosphate; bone regeneration; regenerative medicine; alveolar; bone grafting; bone; graft; alveolar cleft; surgery; surgical; perioperative; mouth; oral surgery; maxillofacial; jaw; oral pathology; oral; dentistry; dental; tooth; teeth; osteo; osteoconductive biphasic calcium phosphate; autograft; operation

Introduction

Alveolar cleft is defined as a bone gap in the primary palate from the nasal sill to the incisive foramen [1]. The defect occurs as a result of disruption of primary palate development between 4 and 12 weeks of gestational age, specifically in the frontonasal prominence [2]. The treatment protocol varies on the basis of the following factors: timing, surgical procedure, and grafting material. Secondary alveolar bone grafting (SABG) is the most preferred and successful method that is usually performed during the mixed dentition period (6-11 years), which allows the provision of support to teeth eruption and facial growth [1]. The iliac crest as a bone graft donor for alveolar cleft reconstruction has gained popularity since it was first introduced by Schmid [3] in 1954, and, in particular, for SABG procedures because it allows harvesting of large amounts of bone for alveolar cleft surgery [4]. Other bone graft sources include the cranium, tibia, and the mandibular symphysis [5]. However, several studies have reported risks of general postoperative complications using autografts, such as pain, prolonged hospital stay, and donor site–specific complications such as scarring, cutaneous nerve injury near the iliac crest, and hematoma after harvesting the cranial bone [6-9]. Therefore, alternative materials are being evaluated for alveolar cleft surgery.

Biphasic calcium phosphate (BCP) is a bioceramic that consists of 2 materials, hydroxyapatite (HA) and β-tricalcium phosphate, mixed in different ratios [10]. It is a biocompatible, easy-to-handle, safe material with a mineral composition comparable to that of human bone tissue [10]. BCP has been mixed in vivo and in vitro with autografts, inducing factors or cells to improve its osteoinductivity [11,12], also in the fields of dentistry and maxillofacial surgery [13-15]. Although calcium phosphate ceramic is not yet considered standard-of-care, it has been used for alveolar cleft reconstruction with satisfactory results [16], reportedly providing support for teeth eruption [17].

Adipose tissue is a source of mesenchymal stem cells, and adipose stem cells (ASCs) can be collected with minimum risk and discomfort from the buccal fat pad (BFP) [18]. The BFP surrounds the buccinators muscle and other superficial muscles such as the masseter, the zygomaticus major, and the zygomaticus minor [19]. Moreover, multiple studies have shown that the cell yield of ASCs per volume is at least 100-500 times that of mesenchymal stem cells in bone marrow aspirates [18,20]. Commonly, ASCs are prepared using enzymatic (collagenase) digestion which, however, is considered “more than minimal manipulation” of the cells by the US Food and Drug Administration and the European Medicines Agency [21]. An alternative method, which also takes considerably less time, involves processing the adipose tissue mechanically into microfragmented fat (MFAT) [22]. MFAT is reported to have similar or even higher secretory activity of regenerative growth factors and cytokines and pericyte content than an enzymatically derived stromal vascular fraction (SVF) [23]. In addition, the MFAT procedure can be applied even in regular hospitals because its harvesting and processing does not require a major invasive surgery, specialized equipment or expensive disposables, or good manufacturing practices–qualified cell culture expansion. Autologous application of MFAT has, among others, been used with success for clinical reconstructions in the maxillofacial area [24].

We hereby describe the protocol of a first-in-human clinical safety trial using BCP mixed with MFAT for alveolar cleft reconstruction. Our hypothesis is that the combination will be a safe, efficient, and effective alternative to conventional autograft since the osteoconductive BCP is supplemented by the regenerative capacity from the MFAT.

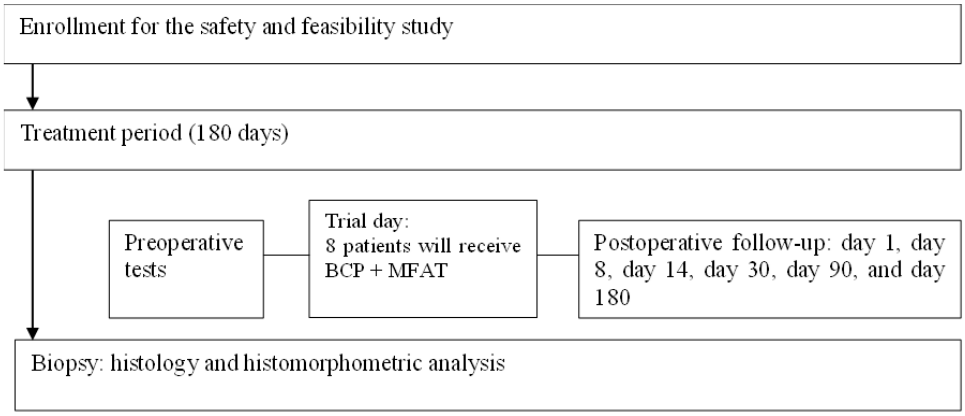
Methods

Study Design

This first-in-human surgical study can be classified as a “stage 1” study in accordance with the IDEAL (innovation, development, exploration, assessment, and long-term study) framework [25]. It is a single-center prospective clinical trial comprising 8 patients, assessing the safety of a combination of MFAT and BCP (BoneCeramic, Straumann) as bone graft material for alveolar cleft reconstruction. The BCP is a synthetic bone graft containing 60% HA and 40% β-tricalcium phosphate, a porosity of 90%, and an interconnected pore size of 100-500 µm. The BCP will be combined in a 1 g:1 cm^3 ratio with MFAT prepared from the patients’ own BFP, which is processed with a 1.2-mm single-use sizing transfer Tulip Gen II Nanofat Kit

(Tulip Medical). The primary end point will be set at 6 months. At each follow-up visit, adverse events (AEs) or serious AEs (SAEs) will be documented, and clinical assessments will be performed at time points specified in the *Interventions* section. After these 6 months, a bone biopsy sample will be taken using a hollow drill during dental implant preparation and subsequently processed for histological or histomorphometric analysis (Figure 1). Finally, a report on safety and proof of concept with regard to bone formation will be made and published.

Figure 1. Simplified diagram of the study protocol (adapted from the SPIRIT [Standard Protocol Items: Recommendations for Interventional Trials] checklist; Multimedia Appendix 1). BCP: biphasic calcium phosphate; MFAT: microfragmented fat.



Ethical Considerations

The clinical trial protocol was approved by the ethical committee of Hasanuddin University, Makassar, Indonesia (1063/UN4.6.4.5.31/PP36/2019) and registered in the Indonesian trial registry (INA-EW74C1N). Informed consent will be obtained from candidates or their parents or legal guardians who are willing to join the trial after being fully educated about the trial procedure. This study complies with the principles of the Declaration of Helsinki. In the informed consent form signed by the patients or their legal representatives, consent to publish their data in a deidentified manner is included.

Inclusion and Exclusion Criteria

Patients will be included on the basis of the following criteria [26]: being healthy male or female participants aged ≥15 years, having unilateral alveolar cleft without any previous history of grafting procedures, being categorized as normal healthy patients for anesthetic risk per the American Society for Anesthesiologists' criteria, and having a normal blood count.

Patients will be excluded on the basis of the following criteria [26]: having poor oral hygiene with mouth plaques; having systemic disease; having systemic or local infection; having received chemotherapy, radiotherapy, immunosuppressives, or anticoagulants that may interfere with the healing process; having received bone growth–inducing factors, malnutrition, or active influenza; and being pregnant.

Interventions

Under general anesthesia and infiltration with lidocaine (1%) with epinephrine (1:100,000 dilution), the surgeon will identify the Stensen's duct with a lacrimal probe and make an incision 2-3 cm below the duct [27]. A dissection penetrating the muscles and the superficial fascia will allow spontaneous herniation of the BFP [27]. This procedure will be carried out bilaterally on both cheeks in order to obtain approximately 3 cm^3 of fat. After vasoconstrictor infiltration with epinephrine (1:100,000), a full mucoperiosteal flap spanning the first molar to the central incisor is lifted. After exposure of the full alveolar cleft and to separate the nasal layer from the oral mucosa, the tissue was meticulously dissected. Following the reflection of a palatal mucoperiosteal flap from either side of the cleft, the palatal tissues are elevated. The oronasal fistula is repaired cranially by elevating and suturing the nasal mucosa [4], thereby creating a pocket for BCP-MFAT deposition.

In parallel with the defect surgery, the harvested fat will be chopped into small pieces with a scissor and soaked in normal saline for 10-15 minutes. The normal saline then will be drained and the chopped fat will be processed into MFAT using 2 syringes (size 10 cm^3) connected with the 1.2-mm single-use sizing transfer Tulip Gen II Nanofat Kit in accordance with the manufacturer's protocol. MFAT will be mixed with BCP (Straumann Bone Ceramic) in a ratio of 1 g:1 cm^3 until it reaches homogenous consistency. The BCP-MFAT mixture will be placed as a graft material into the alveolar cleft defect. If the defect is large and requires more bone graft, another mixture will be prepared with the same mixing ratio. If necessary, a membrane will be used to cover the grafted defect. Finally, the defect will be closed by suturing the palatal mucoperiosteal flaps using absorbable sutures with 3-0 vicryl sutures for mucosa and 4-0 vicryl sutures for nasal reconstruction. All patients will be prescribed antibiotics and analgesics postoperatively.

AE Assessment

Any change in the health of subjects will be documented in their medical history, and required medical care will be provided. Any unexpected physical or laboratory change, symptom, or disease that occurs in a treated patient who has been administered the graft will be documented as an AE. An AE will be graded in accordance with the World Health Organization's classification [28] as either serious or nonserious based on its intensity. The Clavien-Dindo Classification of Surgical Complications will also be used in case of any incidence [29]. In the case of an SAE, a report will be made to the sponsor within 24 hours and to the ethical committee within

3 days from the date of onset. If the SAE concerns severe toxicity or infection associated with graft products, the trial will be terminated immediately.

Sample Size

This is a first-in-human phase I clinical trial aimed to obtain insight on the safety and feasibility of the treatment with the BCP-MFAT combination. We assume that no SAEs or AEs will occur, based on our clinical experience with other applications of MFAT and the well-proven safety of BCP. Upon consultation with a statistician, a sample size of 8 individuals is expected to be sufficient for this trial.

Recruitment

Patients will be recruited from an existing database of the Hasanuddin University Dental Hospital, from general practices of Hasanuddin Dental Hospital and in the area around Makassar. Thereafter, we will determine whether the candidates fulfill the study's inclusion and exclusion criteria. Thorough assessment and training regarding the safety measurements at the research site at Hasanuddin University Dental Hospital will be performed prior to the trial by the ethical and surgical teams.

Since we did not want to enroll children in a safety study with this novel concept in clinical practice, we chose to only include older adolescent and adult patients, being themselves capable of decision-making. Within Indonesia, this age group is more common due to cultural and religious backgrounds causing abstinence from cleft surgeries.

The trial will be conducted at Hasanuddin Dental Hospital. All participants will be asked to sign an informed consent form after risks and possible complications of the procedure (eg, bleeding, infection, cheek asymmetry, parotid duct injury, possibility of facial nerve branches injury, and—although not likely—nonclosure) were appropriately communicated with the patient. Data will be handled and stored in a coded—that is, deidentified—format, so that data cannot be traced back to the patient without a decoding key, which is stored in a locked place and only accessible to the study's principal investigator. Implants will be offered free of charge.

Randomization and Blinding

Since this trial comprises only 1 type of treatment, no randomization or blinding to the treatment is possible.

Data Collection and Access

The research team will be informed about the rules and their responsibilities. All members of the research team, which will collect the data in accordance with the evaluation table (Table 1), will receive training on how data collection should be performed. The data manager will document the data in a patient-coded manner (ie, each patient will be assigned a study-specific code under which the data will be stored in order to conceal their identity), which will subsequently be handed over to the clinical evaluators and investigators. The primary end point is set at 6 months.

Table 1. Patients' assessments.

	Consent form	Orthopantomography	Cone-beam computed tomography or computed tomography	Physical examination	Complete blood count	Thermometry	Biopsy
Preoperative	✓	✓	✓	✓	✓	✓	
Operative day				✓		✓	
Postoperative day 1		✓		✓	✓	✓	
Postoperative day 8		✓	✓	✓	✓	✓	
Postoperative day 14				✓		✓	
Postoperative day 30				✓	✓	✓	
Postoperative day 90		✓		✓		✓	
Postoperative day 180		✓	✓	✓	✓	✓	✓

Posttrial Care

After the primary end point assessment, the participants will be followed up for an additional period of 3 years to ensure their safety and to record whether any delayed side effect occurs as a result of treatment with the BCP-MFAT combination, as previously done in a similar study [26].

Monitoring

Internal monitors of the Ethics and Research Committee, Faculty of Medicine, Hasanuddin University, will evaluate whether the data are accurately collected. Since negligible risk to the patient is expected as both materials (MFAT and BCP) have been tested in other clinical trials [16,17,24], no data safety monitoring board will be installed. A safety report will be submitted every year to the Medical Research Ethics Committee, Faculty of

Medicine, Hasanuddin University. No interim analysis is deemed necessary.

Amendments

If deemed necessary, amendments to this protocol will be submitted to the ethical committee and competent authority and should be approved prior to implementation to ensure the safety and integrity of participants as well as the scientific value of the trial.

Evaluation Methods

Safety Assessment Based on Physical Examination and Laboratory Measurements

When an SAE occurs, it will be concluded that a combination of MFAT and BCP is not yet safe in the current setting. For AEs, if they do not occur at a higher frequency than that in patients treated with standard care (autologous bone) or can be resolved through noninvasive conventional methods (eg, analgesics or antibiotics), the combination of MFAT and BCP will be considered safe. In all other cases, combination of MFAT and BCP will not be considered safe yet.

Radiographic Analysis

To evaluate the success rate of the bone graft, the Bergland scale will be used [30]. This scale will evaluate the integrity and height of the alveolar bone graft and will classify bone height into 4 grades: grade I, bone height is almost normal; grade II, a bone height that is at least 75% of the interalveolar septum; grade III, a bone height of less than 75%; and grade IV, no evidence of bone integration [31].

Histological and Histomorphometric Analysis

Histological and histomorphometric analysis will be performed for at least 3 patients who received dental implants after alveolar cleft reconstruction, in accordance with previously published procedures [32]. Briefly, the implant preparation site will be developed using a trephine burr (2.0 mm × 10.0 mm in length) that allows biopsy specimen collection from the implant site without interfering with the regular procedure. The biopsy specimens will be fixed in 4% phosphate-buffered formaldehyde, dehydrated in an ascending series of ethanol, and embedded in 80% methylmethacrylate (BDH Chemicals) supplemented with 20% dibuthylphtalate (Merck), 8 g/L lucidol CH-50 L (Akzo Nobel), and 22 µL/10 mL N,N-dimethyl-p-toluidine (Merck). The biopsy specimens will be cut into 5-µm-thick sections and subjected to 2 different staining procedures (Goldner's trichrome and Tartrate-resistant acid phosphatase staining). Several histomorphometric parameters (bone volume, osteoid volume, graft volume, and number of osteoclasts) will also be measured for quantitative analysis [32]. Two trained examiners will perform the histologic and histomorphometric analyses. In case of dispute, the biopsies will be reanalyzed to reach consensus.

Statistical Analysis

Since this is a single-arm safety study, statistical analyses will not be performed.

Results

The primary outcome parameter will be safety after 6 months' follow-up, assessed by closely monitoring possible occurrences of AEs or SAEs, radiographic imaging, blood tests, and physical examinations. For efficacy, radiographic imaging will be used for clinical grading of the bone construct using the Bergland scale. In addition, bone parameters such as bone volume, osteoid volume, graft volume, and number of osteoclasts will be histomorphometrically quantified. We expect that the feasibility and safety of the procedure will be apparent, as well as its initial efficacy. Recruitment started in November 2019, and the trial is currently in the follow-up stage. This protocol's current version is 1.0, dated September 15, 2019.

Discussion

In recent years, there has been increasing interest in the use of adipose tissue for cleft lip and palate reconstruction [33]. Its applicability mostly relies on the quantity of the tissue, the ease of surgical harvesting, and the type of surgical reconstruction in which the tissue is used, for example, correction of cleft lip volume asymmetry [34,35], improvement of velopharyngeal insufficiency after cleft lip and palate repair [36,37], or as an extra flap in cleft palate repair [38-41]. In this study, we will make use of the BFP for bone reconstruction. The BFP is a specialized adipose tissue rich in vascular supply, which is easy to harvest via the oral cavity during an intraoral surgery with minimal morbidity and discomfort [42].

Until now, there are only few reports on the use of adipose tissue as a regenerative compound for bony cleft reconstruction—a phase I clinical trial conducted by Khojasteh et al [24] and an animal study using ASCs for alveolar cleft repair [43]. Both studies used collagenase digestion of the tissue and culture expansion to obtain ASCs for personalized cleft reconstructions. An alternative is the SVF derived from adipose tissue via collagenase digestion, which requires a shorter time frame and may yield similar stem cell–like quantities, allowing intraoperative applications [44,45]. A previous clinical study by Prins et al [44] showed that addition of SVF in an intraoperative setting to calcium phosphate ceramics had an additive value on bone formation, implying that SVF can provide osteoinductivity when combined with calcium phosphate. However, so far, regulatory issues and relative expensive SVF production procedures prohibit its wide applicability [22,23]. Mechanically processed fat or MFAT has emerged as a rapid processing alternative to SVF and is being considered minimally manipulated and thereby less regulation restricted [22,23].

This is the first in human study evaluating a combination of MFAT and biphasic BCP as a regenerative graft for alveolar cleft reconstruction [46,47]. BCP is a ceramic scaffold with a balanced ratio between the less-soluble HA and the more-soluble TCP that results in mechanical and biological properties to support bone and cartilage tissue production [48]. It is sufficient for bone reconstruction in non–load-bearing applications and already accepted as standard of care for certain maxillofacial reconstructions [49].

Recently, calcium phosphate has been applied for alveolar cleft surgeries as well [16,17]. Patients within that study were treated at ages of 9-10 years, which is within the optimum age range for SABG [1]. However, we did not want to enroll children in a safety study with this novel concept in clinical practice. Therefore, although we realize that surgeries at a later age will (1) not make optimal use of the growth spurt and (2) may result in cases having larger or even critical size defects (which will not heal unless supplemented with grafts), we chose to only include older adolescent and adult patients, who are themselves capable of being involved in decision-making. We will perform this study in Indonesia because unoperated patients in this age group are difficult to find in Europe.

This is primarily a safety study, so the main conclusions of the study will be based on safety parameters, particularly on the occurrence of AEs or SAEs.

Acknowledgments

We would like to thank Nisrina Ekayani N, DDS, and Citra Dewi Sahrir, DDS, for helping in the administrative process of receiving ethical approval. DSNK received a scholarship from the Indonesia Endowment Fund for Education (LPDP), Ministry of Finance, Republic of Indonesia.

Data Availability

The data generated in the course of this study will be presented in the main manuscript reporting on the trial outcomes in a deidentified manner or provided in a multimedia appendix coupled with that manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 131 KB - resprot_v13i1e42371_app1.pdf]

References

1. Dao AM, Goudy SL. Cleft palate repair, gingivoperiosteoplasty, and alveolar bone grafting. Facial Plast Surg Clin North Am 2016;24(4):467-476. [doi: 10.1016/j.fsc.2016.06.005] [Medline: 27712814]
2. Kyung H, Kang N. Management of alveolar cleft. Arch Craniofac Surg 2015 Aug;16(2):49-52. [doi: 10.7181/acfs.2015.16.2.49] [Medline: 28913221]
3. Schmid E. Die aufbauende kieferkamm plastik. Osterr Z Stomatol 1954 Nov;51(11):582-583. [Medline: 14356661]
4. Kang NH. Current methods for the treatment of alveolar cleft. Arch Plast Surg 2017 May;44(3):188-193 [FREE Full text] [doi: 10.5999/aps.2017.44.3.188] [Medline: 28573092]
5. Santiago PE, Schuster LA, Levy-Bercowski D. Management of the alveolar cleft. Clin Plast Surg 2014 Apr;41(2):219-232. [doi: 10.1016/j.cps.2014.01.001] [Medline: 24607190]
6. Swan MC, Goodacre TEE. Morbidity at the iliac crest donor site following bone grafting of the cleft alveolus. Br J Oral Maxillofac Surg 2006 Apr;44(2):129-133. [doi: 10.1016/j.bjoms.2005.04.015] [Medline: 15961201]
7. Andersen K, Nørholt SE, Knudsen J, Küseler A, Jensen J. Donor site morbidity after reconstruction of alveolar bone defects with mandibular symphyseal bone grafts in cleft patients--111 consecutive patients. Int J Oral Maxillofac Surg 2014 Apr;43(4):428-432. [doi: 10.1016/j.ijom.2013.09.007] [Medline: 24183738]
8. Vura N, Reddy K, Kaluvala VR. Donor site evaluation: anterior iliac crest following secondary alveolar bone grafting. J Clin Diagn Res 2013 Nov;7(11):2627-2630 [FREE Full text] [doi: 10.7860/JCDR/2013/7501.3632] [Medline: 24392424]
9. Baqain ZH, Anabtawi M, Karaky AA, Malkawi Z. Morbidity from anterior iliac crest bone harvesting for secondary alveolar bone grafting: an outcome assessment study. J Oral Maxillofac Surg 2009 Mar;67(3):570-575. [doi: 10.1016/j.joms.2008.09.023] [Medline: 19231782]
10. Kolk A, Handschel J, Drescher W, Rothamel D, Kloss F, Blessmann M, et al. Current trends and future perspectives of bone substitute materials - from space holders to innovative biomaterials. J Craniomaxillofac Surg 2012 Dec;40(8):706-718. [doi: 10.1016/j.jcms.2012.01.002] [Medline: 22297272]
11. Lappalainen O, Karhula S, Haapea M, Kyllönen L, Haimi S, Miettinen S, et al. Bone healing in rabbit calvarial critical-sized defects filled with stem cells and growth factors combined with granular or solid scaffolds. Childs Nerv Syst 2016 Apr 19;32(4):681-688. [doi: 10.1007/s00381-016-3017-2] [Medline: 26782995]
12. Kim K, Park S, Im G. Osteogenic differentiation and angiogenesis with cocultured adipose-derived stromal cells and bone marrow stromal cells. Biomaterials 2014 Jun;35(17):4792-4804. [doi: 10.1016/j.biomaterials.2014.02.048] [Medline: 24655782]

13. Jo D, Cho Y, Seol Y, Lee Y, Lee H, Kim Y. A randomized controlled clinical trial evaluating efficacy and adverse events of different types of recombinant human bone morphogenetic protein-2 delivery systems for alveolar ridge preservation. Clin Oral Implants Res 2019 May;30(5):396-409. [doi: 10.1111/clr.13423] [Medline: 30883942]
14. Jafarian M, Eslaminejad MB, Khojasteh A, Mashhadi Abbas F, Dehghan MM, Hassanizadeh R, et al. Marrow-derived mesenchymal stem cells-directed bone regeneration in the dog mandible: a comparison between biphasic calcium phosphate and natural bone mineral. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2008 May;105(5):e14-e24. [doi: 10.1016/j.tripleo.2008.01.010] [Medline: 18442730]
15. Park J, Oh S, Lee J, Park S, Choi E, Cho K, et al. In vivo bone formation by human alveolar-bone-derived mesenchymal stem cells obtained during implant osteotomy using biphasic calcium phosphate ceramics or Bio-Oss as carriers. J Biomed Mater Res B Appl Biomater 2016 Apr;104(3):515-524. [doi: 10.1002/jbm.b.33416] [Medline: 25939881]
16. de Ruiter A, Janssen N, van Es R, Frank M, Meijer G, Koole R, et al. Micro-structured beta-tricalcium phosphate for repair of the alveolar cleft in cleft lip and palate patients: a pilot study. Cleft Palate Craniofac J 2015 May;52(3):336-340. [doi: 10.1597/13-260] [Medline: 24919123]
17. Janssen NG, Schreurs R, de Ruiter AP, Sylvester-Jensen H, Blindheim G, Meijer GJ, et al. Microstructured beta-tricalcium phosphate for alveolar cleft repair: a two-centre study. Int J Oral Maxillofac Surg 2019 Jun;48(6):708-711. [doi: 10.1016/j.ijom.2018.11.009] [Medline: 30594478]
18. Fraser JK, Wulur I, Alfonso Z, Hedrick MH. Fat tissue: an underappreciated source of stem cells for biotechnology. Trends Biotechnol 2006 Apr;24(4):150-154. [doi: 10.1016/j.tibtech.2006.01.010] [Medline: 16488036]
19. Zhang H, Yan Y, Qi K, Wang J, Liu Z. Anatomical structure of the buccal fat pad and its clinical adaptations. Plast Reconstr Surg 2002 Jun;109(7):2509-2518; discussion 2519. [doi: 10.1097/00006534-200206000-00052] [Medline: 12045584]
20. Baer PC, Geiger H. Adipose-derived mesenchymal stromal/stem cells: tissue localization, characterization, and heterogeneity. Stem Cells Int 2012;2012:812693 [FREE Full text] [doi: 10.1155/2012/812693] [Medline: 22577397]
21. Trivisonno A, Alexander RW, Baldari S, Cohen SR, Di Rocco G, Gentile P, et al. Intraoperative strategies for minimal manipulation of autologous adipose tissue for cell- and tissue-based therapies: concise review. Stem Cells Transl Med 2019 Dec;8(12):1265-1271 [FREE Full text] [doi: 10.1002/sctm.19-0166] [Medline: 31599497]
22. Sesé B, Sanmartín JM, Ortega B, Matas-Palau A, Llull R. Nanofat cell aggregates: a nearly constitutive stromal cell inoculum for regenerative site-specific therapies. Plast Reconstr Surg 2019 Nov;144(5):1079-1088 [FREE Full text] [doi: 10.1097/PRS.0000000000006155] [Medline: 31454336]
23. Vezzani B, Shaw I, Lesme H, Yong L, Khan N, Tremolada C, et al. Higher pericyte content and secretory activity of microfragmented human adipose tissue compared to enzymatically derived stromal vascular fraction. Stem Cells Transl Med 2018 Dec;7(12):876-886 [FREE Full text] [doi: 10.1002/sctm.18-0051] [Medline: 30255987]
24. Khojasteh A, Kheiri L, Behnia H, Tehranchi A, Nazeman P, Nadjmi N, et al. Lateral ramus cortical bone plate in alveolar cleft osteoplasty with concomitant use of buccal fat pad derived cells and autogenous bone: phase I clinical trial. Biomed Res Int 2017;2017:6560234 [FREE Full text] [doi: 10.1155/2017/6560234] [Medline: 29379800]
25. Hirst A, Philippou Y, Blazeby J, Campbell B, Campbell M, Feinberg J, et al. No surgical innovation without evaluation: evolution and further development of the IDEAL framework and recommendations. Ann Surg 2019 Feb;269(2):211-220. [doi: 10.1097/SLA.0000000000002794] [Medline: 29697448]
26. Alkaabi S, Kalla D, Alsabri G, Fauzi A, Jansen N, Tajrin A, et al. Safety and feasibility study of using polyphosphate (PolyP) in alveolar cleft repair: a pilot study. Pilot Feasibility Stud 2021 Nov 08;7(1):199 [FREE Full text] [doi: 10.1186/s40814-021-00939-4] [Medline: 34749808]
27. Kim M, Han W, Kim S. The use of the buccal fat pad flap for oral reconstruction. Maxillofac Plast Reconstr Surg 2017 Dec 25;39(1):5 [FREE Full text] [doi: 10.1186/s40902-017-0105-5] [Medline: 28286743]
28. World alliance for patient safety: WHO draft guidelines for adverse event reporting and learning systems: from information to action. World Health Organization. 2005. URL: https://apps.who.int/iris/handle/10665/69797 [accessed 2023-08-15]
29. Dindo D, Demartines N, Clavien P. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004 Aug;240(2):205-213. [doi: 10.1097/01.sla.0000133083.54934.ae] [Medline: 15273542]
30. Bergland O, Semb G, Abyholm F, Borchgrevink H, Eskeland G. Secondary bone grafting and orthodontic treatment in patients with bilateral complete clefts of the lip and palate. Ann Plast Surg 1986 Dec;17(6):460-474. [doi: 10.1097/00000637-198612000-00005] [Medline: 3548551]
31. Kawakami S, Hiura K, Yokozeki M, Seike T, Nakanishi H, Moriyama K. Prognostic implications of nasal cavity and cleft morphology in secondary bone grafting. Cleft Palate Craniofac J 2002 Nov;39(6):575-581. [doi: 10.1597/1545-1569_2002_039_0575_pionca_2.0.co_2] [Medline: 12401103]
32. Dekker H, Schulten E, Ten Bruggenkate CM, Bloemena E, van Ruijven L, Bravenboer N. Resorption of the mandibular residual ridge: a micro-CT and histomorphometrical analysis. Gerodontology 2018 May 21:A. [doi: 10.1111/ger.12343] [Medline: 29781536]
33. Jones CM, Mackay DR. Autologous fat grafting in cleft lip and palate. J Craniofac Surg 2019;30(3):686-691. [doi: 10.1097/SCS.0000000000005205] [Medline: 31048606]

34. Koonce SL, Grant DG, Cook J, Stelnicki EJ. Autologous fat grafting in the treatment of cleft lip volume asymmetry. Ann Plast Surg 2018 Jun;80(6S Suppl 6):S352-S355. [doi: 10.1097/SAP.0000000000001348] [Medline: 29401128]
35. Zheng D, Zhou J, Yu L, Zhang Y, Wang J. Autologous fat transplantation to improve lip contour in secondary cleft lip deformity. J Craniofac Surg 2020;31(2):343-346. [doi: 10.1097/SCS.0000000000006071] [Medline: 31856127]
36. Foroglou P, Goula OC, Tsimponis A, Georgiadou E, Demiri E. Autologous free fat transfer in patients with velopharyngeal insufficiency. Hell J Nucl Med 2017;20 Suppl:131-135. [Medline: 29324922]
37. Piotet E, Beguin C, Broome M, Iglesias K, Olivier F, Leuchter I, et al. Rhinopharyngeal autologous fat injection for treatment of velopharyngeal insufficiency in patients with cleft palate. Eur Arch Otorhinolaryngol 2015 May;272(5):1277-1285. [doi: 10.1007/s00405-014-3380-0] [Medline: 25411074]
38. Saralaya S, Desai AK, Ghosh R. Buccal fat pad in cleft palate repair-an institutional experience of 27 cases. Int J Pediatr Otorhinolaryngol 2020 Oct;137:110218. [doi: 10.1016/j.ijporl.2020.110218] [Medline: 32658803]
39. Adeyemo WL, Ladeinde AL, Ogunlewe MO, Bamgbose BO. The use of buccal fat pad in oral reconstruction - a review. Niger Postgrad Med J 2004 Sep;11(3):207-211. [Medline: 15505652]
40. Ruslin M, Hajrah-Yusuf A, Tajrin A, Lo L, Forouzanfar T. Utilization of pedicled buccal fat pads for coverage of the lateral relaxing wound: a review of literature and a case series of 15 patients. J Clin Exp Dent 2018 May;10(5):e502-e506 [FREE Full text] [doi: 10.4317/jced.54797] [Medline: 29849977]
41. Adeyemo WL, Ibikunle AA, James O, Taiwo OA. Buccal fat pad: a useful adjunct flap in cleft palate repair. J Maxillofac Oral Surg 2019 Mar;18(1):40-45 [FREE Full text] [doi: 10.1007/s12663-018-1100-9] [Medline: 30728690]
42. Salehi-Nik N, Rezai Rad M, Kheiri L, Nazeman P, Nadjmi N, Khojasteh A. Buccal fat pad as a potential source of stem cells for bone regeneration: a literature review. Stem Cells Int 2017;2017:8354640 [FREE Full text] [doi: 10.1155/2017/8354640] [Medline: 28757880]
43. Pourebrahim N, Hashemibeni B, Shahnaseri S, Torabinia N, Mousavi B, Adibi S, et al. A comparison of tissue-engineered bone from adipose-derived stem cell with autogenous bone repair in maxillary alveolar cleft model in dogs. Int J Oral Maxillofac Surg 2013 May;42(5):562-568. [doi: 10.1016/j.ijom.2012.10.012] [Medline: 23219713]
44. Prins H, Schulten E, Ten Bruggenkate CM, Klein-Nulend J, Helder M. Bone regeneration using the freshly isolated autologous stromal vascular fraction of adipose tissue in combination with calcium phosphate ceramics. Stem Cells Transl Med 2016 Oct;5(10):1362-1374 [FREE Full text] [doi: 10.5966/sctm.2015-0369] [Medline: 27388241]
45. Helder MN, Knippenberg M, Klein-Nulend J, Wuisman PIJM. Stem cells from adipose tissue allow challenging new concepts for regenerative medicine. Tissue Eng 2007 Aug;13(8):1799-1808. [doi: 10.1089/ten.2006.0165] [Medline: 17518736]
46. Lobo SE, Wykrota FHL, Oliveira ACMB, Kerkis I, Mahecha GB, Alves HJ. Quantification of bone mass gain in response to the application of biphasic bioceramics and platelet concentrate in critical-size bone defects. J Mater Sci Mater Med 2009 May;20(5):1137-1147. [doi: 10.1007/s10856-008-3660-6] [Medline: 19112608]
47. Schindler OS, Cannon SR, Briggs TWR, Blunn GW. Composite ceramic bone graft substitute in the treatment of locally aggressive benign bone tumours. J Orthop Surg (Hong Kong) 2008 Apr;16(1):66-74 [FREE Full text] [doi: 10.1177/230949900801600116] [Medline: 18453663]
48. Zizzari V, Zara S, Tetè G, Vinci R, Gherlone E, Cataldi A. Biologic and clinical aspects of integration of different bone substitutes in oral surgery: a literature review. Oral Surg Oral Med Oral Pathol Oral Radiol 2016 Oct;122(4):392-402. [doi: 10.1016/j.oooo.2016.04.010] [Medline: 27496576]
49. Helder MN, van Esterik FAS, Kwehandjaja MD, Ten Bruggenkate CM, Klein-Nulend J, Schulten EAJM. Evaluation of a new biphasic calcium phosphate for maxillary sinus floor elevation: micro-CT and histomorphometrical analyses. Clin Oral Implants Res 2018 May;29(5):488-498 [FREE Full text] [doi: 10.1111/clr.13146] [Medline: 29638012]

Abbreviations

AE: adverse event
ASC: adipose stem cell
BCP: biphasic calcium phosphate
BFP: buccal fat pad
HA: hydroxyapatite
IDEAL: innovation, development, exploration, assessment, and long-term study
MFAT: microfragmented fat
SABG: secondary alveolar bone grafting
SAE: severe adverse event
SVF: stromal vascular fraction

Edited by A Mavragani; submitted 02.09.22; peer-reviewed by H Reychler, N Kandel, H Salem Muthu Sugavanam Sivakumar, J Egger; comments to author 02.02.23; revised version received 08.02.23; accepted 09.02.23; published 15.01.24.

Please cite as:
Natsir Kalla DS, Alkaabi S, Fauzi A, Tajrin A, Nurrahma R, Müller WEG, Schröder HC, Wang X, Forouzanfar T, Helder MN, Ruslin M
Microfragmented Fat and Biphasic Calcium Phosphates for Alveolar Cleft Repair: Protocol for a Prospective, Nonblinded, First-in-Human Clinical Study
JMIR Res Protoc 2024;13:e42371
URL: https://www.researchprotocols.org/2024/1/e42371
doi:10.2196/42371
PMID:38224475

Protocol

Fatigue and Mental Illness Symptoms in Long COVID: Protocol for a Prospective Cohort Multicenter Observational Study

Ligia Pires[1], MD; Cláudia Reis[2], MD; Ana Rita Mesquita Facão[2], MD; Armin Moniri[3,4,5,6], MD, PhD; Ana Marreiros[4], PhD; Marta Drummond[7], MD, PhD; Joana Berger-Estilita[8,9,10], MD, PhD, MME

[1]Serviço de Pneumologia, Hospital de Portimão, Centro Hospitalar Universitário do Algarve, Portimão, Portugal

[2]Serviço de Psiquiatria, Hospital de Portimão, Centro Hospitalar Universitário do Algarve, Portimão, Portugal

[3]Department of Otorhinolaryngology, Sahlgrenska University Hospital, University of Gothenburg, Gothenburg, Sweden

[4]Regenerative Medicine Program, Department of Biomedical Sciences and Medicine, University of Algarve, Faro, Portugal

[5]Algarve Biomedical Center, University of Algarve, Faro, Portugal

[6]Hospital Particular do Algarve, Faro, Portugal

[7]Centro de Responsabilidade Integrada Sono e VNI, Faculdade de Medicina, Universidade do Porto, Porto, Portugal

[8]Institute of Anaesthesiology and Intensive Care, Salem Spital, Hirslanden Medical Group, Bern, Switzerland

[9]Institute for Medical Education, University of Bern, Bern, Switzerland

[10]Centre for Health Technology and Services Research (CINTESIS), Faculty of Medicine, Universidade do Porto, Porto, Portugal

Corresponding Author:
Joana Berger-Estilita, MD, PhD, MME
Institute of Anaesthesiology and Intensive Care
Salem Spital
Hirslanden Medical Group
Schänzlistrasse 39
Bern, 3013
Switzerland
Phone: 41 788438161
Email: joanamberger@gmail.com

Abstract

Background: The aftermath of the COVID-19 pandemic continues to affect millions worldwide, resulting in persisting postvirus complaints and impacting peoples' quality of life. Long COVID, characterized by lingering symptoms like fatigue and mental illness, can extend beyond a few months, necessitating further research to understand its implications.

Objective: This study aims to quantify the degree of physical and psychological fatigue in patients following COVID-19 infection and examine its correlation with mental health disorders.

Methods: Using a consecutive nonrandom sampling technique, we will conduct a prospective cohort multicenter observational study in 5 Portuguese hospitals. Symptomatic adult patients with previous COVID-19 attending follow-up consultations will be enrolled. We will include patients who had mild, moderate, and severe acute disease. We will assess clinical outcomes related to COVID-19, including the type of respiratory support such as high-flow nasal cannula, noninvasive ventilation, and invasive mechanical ventilation. The exclusion criteria will include previous severe psychiatric disorders confirmed by a psychiatrist; refusal or inability to respond to the questionnaire; concomitant neurological disorder; persistent fatigue symptoms during the 6 months before infection; and the need for invasive mechanical ventilation during COVID-19 infection due to a high prevalence of postintensive care syndrome. Our primary outcome is the prevalence of fatigue in patients with post–COVID-19 depression and/or anxiety, as measured by the Chalder Fatigue Scale (CFQ-11) and the Hospital Anxiety and Depression Scale (HADS). The secondary outcomes will include an assessment of health-related quality of life via the EQ-5D questionnaire and an exploration of the prevalence of symptoms of posttraumatic stress disorder (PTSD) using the 14-item Posttraumatic Stress Scale (PTSS-14). We will also examine the association between mental health symptoms and the severity of acute COVID-19. The post–COVID-19 data will be collected at least 6 months after the positive test and no longer than 9 months during the clinical appointment.

Results: We expect our multicenter study on patients post COVID-19 to reveal a significant link between mental illness symptoms and both physical and psychological fatigue. Patients with heightened depression and anxiety may report increased levels of

fatigue. Additionally, we expect to find persistent PTSD symptoms in a subset of participants, indicating the enduring psychological impact of the virus.

Conclusions: This study may underscore the need for integrated care addressing physical and mental health in patients post COVID-19. The observed connections emphasize the importance of considering mental well-being for long-term health outcomes. Despite study limitations, our findings contribute valuable insights for future treatment strategies and highlight the necessity for comprehensive mental health support in post–COVID-19 care. This research provides valuable insights into the mental health implications of COVID-19 and its impact on post–COVID-19 fatigue and the overall well-being of affected individuals.

Trial Registration: ClinicalTrials.gov NCT05323318; https://clinicaltrials.gov/study/NCT05323318

International Registered Report Identifier (IRRID): DERR1-10.2196/51820

(JMIR Res Protoc 2024;13:e51820) doi:10.2196/51820

KEYWORDS

SARS-CoV-2; coronavirus; COVID; long COVID; fatigue; tired; tiredness; anxiety; depression; PTSD; stress; quality of life; mental health; post-COVID-condition; neuropsychological; neuropsychology; psychological; long COVID-19; COVID-19; myalgia; correlation; impairment

Introduction

Despite the World Health Organization (WHO) declaration marking the end of the COVID-19 pandemic on May 5, 2023 [1], millions of people continue to have postvirus complaints. Moreover, the virus remains endemic in many parts of the world. Confirmed COVID-19 cases have exceeded 430 million globally, with 200 million in Europe alone [2]. The causative agent of COVID-19 is the novel SARS-CoV-2 [3]. Although, as the name implies, respiratory symptoms are acute, the term long COVID (or post-COVID syndrome or long-haul COVID-19) began gaining recognition in the scientific and medical communities after the first descriptions of long-lasting symptoms related to mental health, such as anxiety or stress after the first infection [4]. While the definition of long COVID is unclear, the most frequent symptoms are fatigue and dyspnea [5,6]. Other less typical symptoms include cognitive and mental disorders, headache, myalgia, chest and joint pain, smell and taste dysfunction, cough, hair loss, insomnia, wheezing, rhinorrhea, sputum, and cardiac and gastrointestinal issues [4]. These symptoms may persist for up to 6 months after hospital discharge, severely impacting patients' quality of life [7]. Since July 2021, long COVID is considered a disability under the *Americans With Disabilities* Act [8].

Per its definition, long COVID appears within 3 months after the onset of COVID-19, with symptoms lasting for at least 2 months that an alternative diagnosis [9] cannot explain, including, myalgic encephalomyelitis and chronic fatigue syndrome. However, studies have reported different persistent symptoms in contrasting durations and frequencies among survivors of long COVID [10,11]. Long COVID appears like other postviral syndromes observed in other coronavirus diseases. For example, symptoms of fatigue, myalgia, and psychiatric impairments have affected survivors of Middle East respiratory syndrome (MERS) and those with severe acute respiratory syndrome (SARS) for up to 4 years [10,12,13]. Even at 7-year and 15-year follow-ups, pulmonary and bone radiological complications were evident among a proportion of survivors of SARS who were predominantly younger than 40 years [10,14,15]. This is unsettling, as it implies that long COVID may extend beyond just a few months.

Fatigue, a primary persistent symptom of long COVID, has been reported in 10% to 70% of patients [16-19]. It is defined as "a decrease in physical or mental performance that results from changes in central, psychological, or peripheral factors due to the COVID-19 disease" [20]. Thus, post–COVID-19 fatigue depends on conditional and psychophysiological factors comprising the individual's task, environment, physical, and mental capacity, as well as the disease's central, psychological, and peripheral aspects [20].

While fatigue is not traditionally considered a neuropsychiatric disorder, it can be a symptom of many mental health conditions, such as depression, anxiety, and posttraumatic stress disorder (PTSD) [21,22]. Therefore, it is often included in discussions of mental health symptoms in post–COVID-19 syndrome [23]. The term "neuropsychiatric" often refers to a wide range of disorders affecting the brain and mental health. In contrast, "neuropsychological" refers to studying the relationship between brain function and behavior [24]. The primary focus of this study is on psychiatric symptoms, particularly depression and anxiety. However, we will also investigate PTSD, which is a neuropsychiatric disorder involving both neurological and psychiatric aspects. In addition, the health-related quality of life (HRQoL) assessment includes a section that evaluates aspects related to anxiety and depression. While not designed for diagnosing psychiatric disorders, this assessment can help gauge how these symptoms affect a person's overall quality of life, making it more of a general health assessment.

The current literature on long COVID and its mental sequelae has relied on self-reported symptoms through questionnaires administered either in-person or through telephone interviews to comply with public health guidelines. However, the correlation between these self-reported symptoms needs to be clarified. There is an obvious need to accurately characterize the mental sequelae of COVID-19 and the risk factors associated with these outcomes.

This study aims to quantify the degree of physical and psychological fatigue in patients post COVID-19 and assess the correlation of fatigue with other mental sequelae—particularly depression, anxiety, and PTSD. Furthermore, we aim to explore its impact on HRQoL.

Our research questions for this study are outlined in Textbox 1.

Textbox 1. Research questions of the study.

Research Question 1 (primary outcome):

- Do patients with long COVID who experience depression and/or anxiety symptoms have a higher prevalence of fatigue?

Research questions 2 to 4 (secondary outcomes):

- Is there a correlation between the type of fatigue and depression and/or anxiety symptoms among patients post COVID-19?
- Is there a correlation between fatigue and the presence of PTSD symptoms in patients post COVID-19?
- Do patients with fatigue associated with mental health disorders have a lower health-related quality of life (HRQoL) after COVID-19?

Methods

Overview

This protocol adheres to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement [25]. This research is designed as an observational prospective cohort study.

Recruitment

Our study will be conducted in 1 private and 4 public Portuguese hospitals that have established follow-up post–COVID-19 medical consultations. Patients who meet the eligibility criteria will be invited to participate in the study at the end of their appointments in the follow-up clinics. This study will be conducted using a consecutive, nonrandom sampling technique.

Inclusion Criteria

Patients who cumulatively meet the following criteria will be eligible for inclusion: (1) ≥18 years; (2) previous case of COVID-19 at least 6 months after the diagnosis that is duly documented in the clinical record; (3) persistent symptoms after COVID-19 recovery, as defined by the WHO [9]; and (4) SARS-CoV-2 RNA confirmed by a positive real-time reverse-transcription polymerase chain reaction (RT-PCR) on a nasopharyngeal swab or SARS-CoV-2 antigen confirmed with a nasopharyngeal swab by a health care professional within 7 days of initial symptoms.

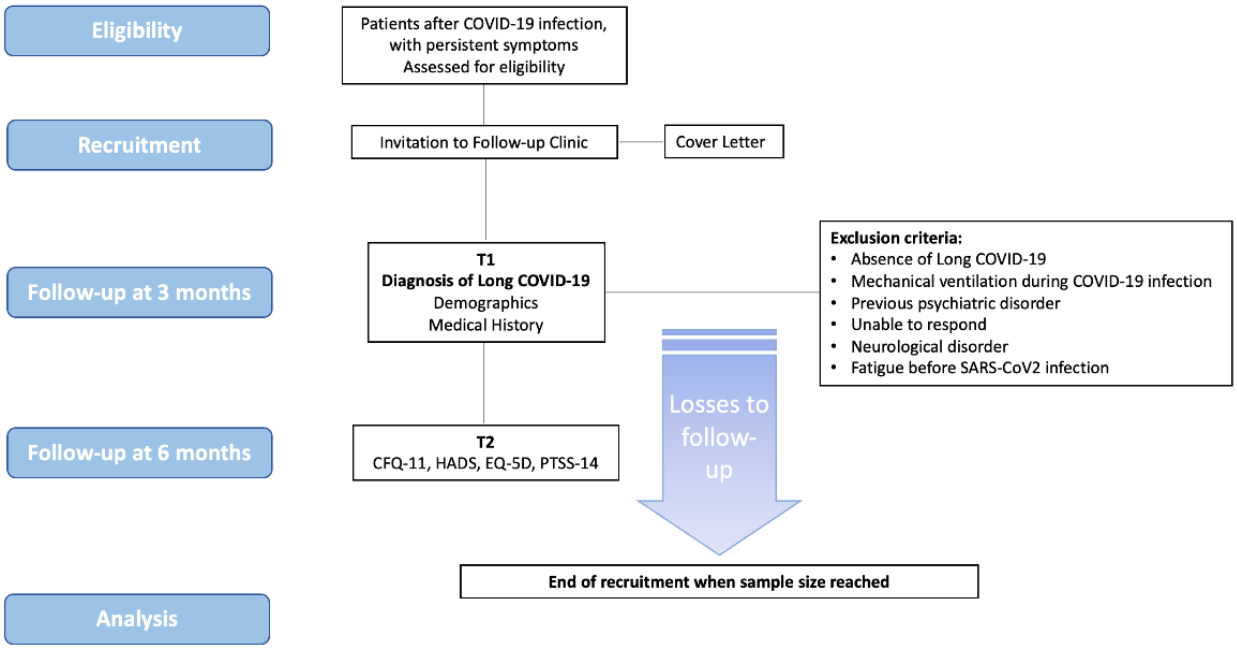
We will implement multiple measures to exclude the possibility of second infections and ensure that the individuals included have persistent symptoms following their initial COVID-19 recovery. Our inclusion criteria stipulate that individuals must have a positive test result for SARS-CoV-2 RNA or antigen within 7 days after their initial infection. Additionally, we will conduct thorough reviews of medical records and clinical assessments to assess symptom presentation and timing, differentiating between persistent cases and new infections. In cases of uncertainty or potential overlap with new infections, we are prepared to conduct repeat testing, which may include RT-PCR and genomic sequencing for accurate classification.

Exclusion Criteria

Patients who meet the following criteria will be excluded from participation: (1) preexisting psychiatric disorders diagnosed by a psychiatrist before contracting COVID-19; (2) inability to respond to the questionnaire; (3) concurrent neurological disorders, such as stroke with sequelae, Alzheimer disease, and Parkinson disease; (4) individuals subjected to invasive mechanical ventilation during their COVID-19 infection; or (5) those experiencing persistent fatigue symptoms within the 6 months before SARS-CoV 2 infection.

The study design and inclusion criteria will be reviewed regularly to ensure they align with current best practices and the latest understanding of COVID-19. A patient enrollment flowchart is presented in Figure 1.

Figure 1. Study flowchart. CFQ-11: Chalder Fatigue Scale; HADS: Hospital Anxiety and Depression Scale; PTSS-14: 14-item Posttraumatic Stress Scale.



Data Collection

Data collection will take place during appointments at the long COVID follow-up clinics in all participating hospitals. Qualified clinical study staff will gather the data using a clinical research form (CRF) (Multimedia Appendix 1). These individuals comprise health care professionals, such as nurses, clinical research coordinators, and health care experts who have received appropriate training and have the necessary expertise to conduct data collection and assessments in a clinical research setting. Their training ensures adherence to research protocols and ethical guidelines, guaranteeing accurate and consistent data gathering during clinical appointments. Two months after hospital discharge, we will mail all patients a letter offering a follow-up consultation in the outpatient clinic. Patients who agree to attend will be offered 2 appointments, consisting of an anamnesis and a physical examination, and given several self-administered tests in the waiting room. We will allocate 15 minutes for the questionnaire completion in the waiting room. In the first visit (T1, 3 months), the following data will be additionally collected: demographic characteristics like age, sex, and BMI (kg/m^2); each participant's medical history, such as the date of the first positive COVID-19 test (PCR or antigen) and smoking, alcohol, and drug consumption status; comorbidities and usual medication intake; and screening of symptoms and severity of the acute disease. Data collection in the second visit (T2, 6 months) will include post–COVID-19 symptoms, the Chalder Fatigue Scale [26] (CFQ-11), the Hospital Anxiety and Depression Scale (HADS) [27], the 14-item Posttraumatic Stress Scale (PTSS-14) adapted to COVID-19, and the EQ-5D [28] questionnaire.

Ethical Considerations

This study involves human participants and has adhered to all applicable ethical standards and procedures. The Algarve University Hospital Centre Ethical Committee approved this study (141/21; Multimedia Appendix 2). The patients' race will not be included in the study because the ethics committee did not approve this differentiation. A paper-based consent form was previously approved by the ethics committee. This consent form has 2 components: information for the participant (regarding the project) and declaration of informed consent (to date and sign, in case of acceptance). The informed consent procedure, mailed to potential participants, will provide them with detailed information about the study's objectives, risks and benefits of participation, and data management practices (Multimedia Appendix 3). The study will follow ethical guidelines and regulations related to informed consent, and participants will have the opportunity to ask questions and provide voluntary consent before enrolling. Participants will be given a month for reflection before written informed consent. As for data management, the study will implement a secure and confidential system that uses data encryption and secure storage procedures to protect participant confidentiality and comply with data protection laws and regulations. Only authorized individuals who have a legitimate need to access the data will be permitted to do so, and any data sharing will be done in compliance with the relevant ethical and legal requirements. As applicable, all procedures from this investigation followed the Declaration of Helsinki. All researchers will comply with the Data Protection Acts of their respective academic institutions.

Primary Outcome

Fatigue

A validated fatigue assessment tool will be used at the follow-up visit to capture a broader range of participants. This will provide a more comprehensive understanding of the relationship between fatigue and mental symptoms in individuals with long COVID. Fatigue will be measured using the CFQ-11 [26]. This is an

11-item self-report measure of physical and mental fatigue. Participants rate their fatigue experienced over the past month compared to their usual energy levels using a 4-point Likert scale ranging from 0 (“less than usual”) to 3 (“much more than usual”) [29]. Scores range from 0 to 33. A bimodal version can also be calculated, where scores range from 0 to 11, with a cutoff score of 4 or more indicating a case of fatigue [29]. Reliability coefficients for the CFQ-11 have been shown to range between 0.8 and 0.9 [29-31] in both patients with chronic fatigue and the general population. This study will use only the Likert scale to reduce the risk of ceiling effect bias.

Secondary Outcomes

Depression and Anxiety

Symptoms of depression and anxiety will be assessed using the HADS [27], a practical, validated tool for assessing symptom severity in anxiety and somatic disorders in psychiatric and primary care settings and the general population [32]. This measure comprises 14 items, 7 measuring symptoms of anxiety and 7 measuring symptoms of depression. The scores are categorized into different ranges: 0 to 7 as “normal,” 8 to 10 as “mild,” 11 to 14 as “moderate,” and 15 to 21 as “severe.” The HADS questionnaire has been validated in many different languages and settings [32-34].

HRQoL Assessment

HRQoL will be assessed using the original EQ-5D questionnaire, which comprises 2 parts. The first part is the EQ-5D-3L questionnaire [28], a health state classification scheme of 5 items (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each having 3 alternatives (1=no problems, 2=moderate problems, and 3=severe problems). The combination of answers for the 5 items represents the health state (given as an index), ranging from 0 (worst possible health state) to 1 (best possible health state). The second part comprises the EuroQol Visual Analog Scale (EQ-VAS), which represents health states in a range from 0 (the worst possible health state) to 100 (the best possible health state). The EQ-5D can distinguish between the health conditions of patients with diverse injuries [35,36] and has been validated in several populations [37].

PTSD Assessment

This study includes an assessment of PTSD as a secondary measure. It aims to evaluate the potential impact of PTSD on the primary outcome of fatigue and provide a better characterization of the study population. Although previous PTSD to COVID-19 infection is an exclusion criterion, some participants may still have experienced PTSD symptoms after their COVID-19 infection, so evaluating the prevalence and severity of these symptoms in the study population could be relevant.

Given that the “gold standard” clinician-administered, semistructured psychiatric interviews to diagnose PTSD symptoms were not feasible during the workload of the COVID-19 follow-up clinic, we chose the patient-reported outcome instrument PTSS-14. This scale was developed based on the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R) criteria for PTSD and subsequently validated for patients following intensive care [38]. Patients were asked to assess the frequency of 10 common PTSD symptoms on a 7-point Likert scale from 1 (never) to 7 (always). Item scores were summed up to a total score (ranging from 10 to 70). A total score above 35 was suggested to indicate clinically relevant PTSD symptoms. A similar 14-item version of PTSS was later developed to reflect the changes in the fourth edition of the DSM (DSM-IV), where a cutoff value of 45 indicated presumable PTSD [39]. We modified the latter to include COVID-19 patients—whenever the term “intensive care unit (ICU)” appeared, we substituted it with “COVID-19.” We applied the same diagnostic cutoff to this adapted scale.

Association of Mental Illness Symptoms With the Severity of Acute COVID-19

COVID-19 severity will be categorized according to the WHO classification [40]. The classification includes the following: mild illness (mild symptoms without the radiographic appearance of pneumonia); pneumonia (having symptoms and the radiographic evidence of pneumonia, with no requirement for supplemental oxygen); severe pneumonia (having pneumonia, including one of the following: respiratory rate >30 breaths/minute, severe respiratory distress, or blood oxygen saturation level ≤93% while at rest and breathing room air); and critical cases (eg, respiratory failure requiring invasive mechanical ventilation or nasal high flow oxygen, septic shock, other organ failure occurrence, or admission to the ICU).

Statistical Analyses

The statistical analysis methodology is designed to align with the study’s defined objectives. All analyses will be conducted using SPSS (version 27; IBM Corp) and R (R Foundation for Statistical Computing) software. The analyses will be carried out in 5 phases, as outlined in Textbox 2.

Textbox 2. The 5 phases of the statistical analyses carried out in this study.

- Phase 1: Characterization of the patient sample
  - 1.1. Sociodemographic analysis of the variables collected at T1 and the variables from the surveyed instruments at T2. This involves descriptive analysis, both univariate and bivariate, which will be differentiated by:
    - 1.1.1. Quantitative variables: mean and SD, coefficient of variation, and median and IQR
    - 1.1.2. Qualitative variables (nominal and ordinal categorical): analysis of distributions through absolute and relative frequencies, including absolute and relative accumulated frequencies
    - 1.1.3. Quantitative variables will be reported alongside appropriate tests for normal distribution to ensure the accuracy and validity of our statistical analyses.
  - 1.2. Bivariate and descriptive analysis using 2D tables will be calculated for all qualitative variables belonging to T1 with all instrument scores collected at T2: Chalder Fatigue Scale (CFQ-11), Hospital Anxiety and Depression Scale (HADS), 14-item Posttraumatic Stress Scale (PTSS-14) adapted to COVID -19, and EQ- 5D plus recorded COVID-19 symptoms. The previous points will be reiterated in this bivariate context, utilizing the computational aid of split->file categorical variables in situations where one variable is metric and the other is categorical.
  - 1.3. Internal consistency and reliability analysis of the T2 instruments: calculation of the Cronbach alpha (general and partial) for all ordinal items and item subgroups differentiated by the subscales defined by the respective authors
- Phase 2: Determination of fatigue incidence caused by long COVID and its relationship with T1 and T2 variables
  - 2.1. Procedures for determining fatigue cutoff points in this cohort of patients:
    - 2.1.1. Bivariate analysis using optimal binning procedures for categorical variables (age class, sex, and BMI) with the total fatigue score, as well as partial scores of physical and psychological fatigue
    - 2.1.2. Multivariate analysis by constructing models in the format of decision trees via the CHAID (chi-square automatic interaction detection) algorithm [41], with total and partial fatigue scores as dependent variables
  - 2.2. Inferential analysis based on variables resulting from 2.1.1 and/or 2.1.2, considering the complexity of variables in T1 and T2:
    - 2.2.1. (1) Chi-Square tests to capture the association of categorical variables; (2) Shapiro-Wilk tests to verify the distribution of quantitative variables; (3) tests for comparing 2 or more population means: parametric analysis of variance (ANOVA) test and nonparametric (Kruskal-Wallis) test; and (4) correlation tests (Spearman or Pearson) to verify the degree of association between T2 instrument scales
- Phase 3: Determination of patient groups based on fatigue differentiation
  - 3.1. Conducting classification analysis using clustering techniques, specifically the 2-step cluster analysis, to explore variables with greater power in differentiating groups of patients
- Phase 4: Exploration of the best combination of T1 and T2 variables capable of discriminating patient fatigue levels through a discriminant multivariate analysis
- Phase 5: Investigation of the association between phase 3 groups and all T2 instrument scales using chi-square association tests

Power and Sample Size

We plan to conduct a prospective multicentric observational study to investigate the prevalence and severity of mental illness symptoms and fatigue in individuals with long COVID. Based on previous studies and expert opinion, we expect the prevalence of fatigue and mental symptoms in this population to be around 50% [42,43]. We aim to detect a minimum effect size of 0.2 with a power of 80% and a significance level of P=.05.

Using these assumptions, we performed a sample size power analysis using a 2-sample t test. We found that a total sample size of 200 participants (100 with adverse mental health symptoms and 100 without) would be required to detect the minimum effect size of 0.2 with 80% power and a significance level of P=.05. The required sample size was calculated using an a priori power analysis with an online calculator [44]. To compensate for a projected 25% loss to follow-up, we aimed for 250 participants.

We plan to recruit participants from multiple hospitals and primary care centers across Portugal, focusing on individuals who have been diagnosed with long COVID and are experiencing mental illness symptoms and/or fatigue. Recruitment will be closely monitored throughout the study to assess the pace at which participants are enrolled. The need for sample size adjustment will be determined based on the observed recruitment rates and the accumulating data. We plan to conduct an interim analysis after the recruitment of the first 100 patients.

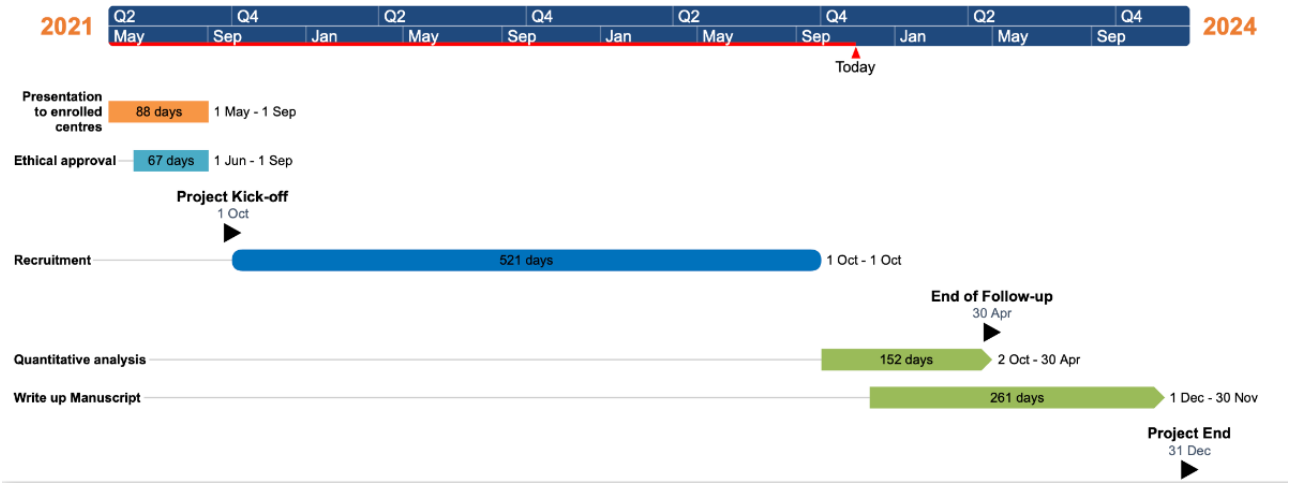
Results

This study received no specific grant from any funding agency in public, commercial, or not-for-profit sectors. Recruitment began in October 2021 at Portimão Hospital and Alvor Hospital,

in June 2022 at Faro Hospital and São Sebastião Hospital, and in October 2022 at Fernando Fonseca Hospital. The deadline for the end of the recruitment period in all centers was December 2023. The preliminary study results will be published in a peer-reviewed international medical journal after October 2023.

The study timeline is shown in Figure 2. This study is included as part of the first author's (LP) PhD thesis. The initial study results were presented at the PhD interview in November 2023. We aim to publish the study in an indexed scientific journal and present the results at national and international congresses.

Figure 2. Study timeline.



We plan to enroll 250 participants, including 100 with adverse mental health symptoms and 100 without, to explore the intricate relationship between adverse mental health symptoms and both physical and psychological fatigue in individuals recovering from long COVID. Preliminary analyses indicate a compelling connection, wherein patients who report heightened levels of depression and anxiety also tend to experience increased fatigue. These findings underscore the importance of considering mental health as a pivotal factor in understanding the enduring impact of COVID-19 beyond the acute phase. In addition to depression and anxiety, our study explores the persistence of PTSD symptoms in a subset of participants. Initial results suggest that, even after recovery from the acute phase of the infection, a proportion of individuals continue to grapple with the psychological repercussions of the virus. This observation aligns with emerging evidence suggesting a prolonged psychological impact of COVID-19, emphasizing the need for comprehensive mental health support for patients after contracting COVID-19. The identified links between mental health symptoms and fatigue have broad implications for the holistic care of this patient population. Understanding these connections can guide targeted interventions, emphasizing the importance of addressing mental well-being alongside physical recovery. As we delve deeper into the data and conduct further analyses, a more nuanced understanding of these relationships will emerge, informing future health care strategies and interventions.

Discussion

Expected Findings

As the COVID-19 pandemic ceases, more patients enter the chronic phase of the disease. Identifying groups at high risk of cognitive and psychiatric dysfunction may allow for targeted intervention to effectively meet their physical, neurological, and psychological health care needs. Our study, conducted in the aftermath of the COVID-19 pandemic, provides a unique opportunity to investigate the persisting health effects of the virus on those who have recovered from the acute phase of the disease. We specifically aim to explore post–COVID-19 fatigue and mental health disorders using specific tools to separate physical and psychological fatigue symptoms. We also use a prospective cohort multicenter study design, which is less prone to bias, and we aim to include both hospitalized and nonhospitalized patients, covering all degrees of acute COVID-19 severity. We anticipate that our research will reveal a significant association between the presence and severity of mental health symptoms, including depression, anxiety, and PTSD, and the degree of physical and psychological fatigue in patients following COVID-19. We expect to observe that patients experiencing more pronounced mental symptoms will report higher levels of physical and psychological fatigue.

The potential links between mental symptoms and fatigue suggest a connection between the mental well-being of patients post COVID-19 and their experience of fatigue, encompassing both physical and psychological dimensions. The existing research has indicated a high prevalence of anxiety and depression symptoms among patients hospitalized with COVID-19 infection, with a quarter of patients experiencing at least mild symptoms of acute stress disorder [42]. Moreover, a study conducted in Iran after the outbreak of COVID-19 found a correlation between the prevalence of chronic fatigue syndrome and PTSD [45]. The study reported that 5.8% of subjects experienced PTSD symptoms 6 months after the onset of SARS-CoV-2 infection. Interestingly, the study also noted that female sex was associated with a higher risk of fatigue. At the same time, variables such as oxygen saturation at admission, primary symptoms, ICU admission, and laboratory test parameters did not show a significant association with fatigue occurrence.

Based on these findings, we anticipate that patients post COVID-19 may exhibit more pronounced symptoms of

depression and anxiety and heightened levels of physical and psychological fatigue. This insight emphasizes the importance of considering mental health as a crucial factor in understanding the long-term effects of COVID-19. It underscores that the impact of the virus extends beyond the acute illness phase and can manifest in persistent mental symptoms that influence patients' overall well-being. Moreover, it can imply that addressing anxiety symptoms in post–COVID-19 care may have a positive impact on reducing fatigue and improving patients' quality of life. We also aim to explore the prevalence and severity of PTSD symptoms in a subset of patients following COVID-19. While this is not the primary focus of our research, assessing the presence of PTSD symptoms in this study population allows for a better characterization of the patient group. Some participants continue to experience PTSD symptoms following COVID-19 infection, suggesting that the psychological impact of the virus can be long-lasting. These findings may shed light on the need for comprehensive mental health support for patients post COVID-19.

The implications of our potential findings are widespread. They underscore the importance of integrated care for patients post COVID-19 that addresses both physical and mental health aspects. Clinicians and health care providers will then be aware of the potential for persistent mental symptoms and their impact on patients' fatigue levels and overall HRQoL.

Limitations

Our study's limitations include the possibility of sampling bias, as individuals with more severe symptoms of fatigue or other mental health symptoms may be less likely to participate. This possibility could result in underrepresentation and bias within the study's findings. To minimize this, we will use diverse recruitment methods across multiple sites and collect data on participants' reasons for declining participation. We will also provide detailed information about the study and its potential benefits to participants while ensuring an ethical and respectful recruitment process sensitive to participants' health concerns and symptoms.

We also acknowledge the limitations related to our exclusion criteria and use of the CFQ-11, which has yet to undergo specific validation for patients with COVID-19. This recognition underscores the importance of future research endeavors to validate the applicability of the CFQ-11 within this patient population, despite its utilization in prior studies [46-48].

While there are valid concerns regarding the exclusion criteria and assessment of psychiatric disorders in our study—including the fact that assessing preexisting fatigue may be difficult—we have devised a plan to mitigate these concerns. We intend to meticulously collect detailed medical histories and review the medical records of all enrolled patients to ensure the precise application of the exclusion criteria. However, a notable limitation of our study arises from the absence of a baseline assessment conducted before the onset of COVID-19 infection. This absence impedes our ability to comprehensively evaluate the influence of COVID-19 on various health parameters, such as fatigue and mental health. The absence of a baseline assessment may also limit our capacity to distinguish between preexisting conditions and post–COVID-19 effects, which is a key consideration in understanding the full spectrum of the virus's impact on individuals. Additionally, while we acknowledge that the measurements used in the study are based on self-report—and therefore subjective—we emphasize that self-reported questionnaires are commonly used in scientific studies. These questionnaires hold significance in assessing the extent of physical and psychological fatigue in patients following COVID-19. Despite these limitations, our study is poised to make a significant contribution to the existing literature by shedding light on the impact of COVID-19 on mental health. This research has the potential to guide future treatment and management strategies, serving as a valuable resource for the health care community.

Conclusion

This study protocol outlines a critical investigation into the lingering physical and psychological effects of long COVID. It emphasizes the importance of understanding the ongoing health challenges individuals face even after recovering from the acute phase of the virus. This study's research questions focus on assessing the potential correlations of mental illness symptoms (ie, physical and psychological fatigue) among patients post COVID-19.

In the aftermath of a global pandemic, this research is timely and crucial. It has the potential to inform health care strategies and interventions that provide targeted and holistic care to individuals grappling with long COVID. Ultimately, this study aims to improve patient outcomes, enhance the quality of life for those affected, and contribute to broader efforts to address the multifaceted health implications of this unprecedented global crisis.

Authors' Contributions

LP conceptualized the study, wrote the first draft of the protocol, and planned the study. CR and RF helped write the first draft of the protocol. AB gave critical input throughout the study.
JB-E wrote the first draft of the protocol and gave critical input throughout the study. AM was responsible for the statistical planning and methodology. MD planned the study. All authors contributed to the manuscript and approved the submitted version. No generative artificial intelligence (AI) was used in any portion of the manuscript writing.

Conflicts of Interest

JB-E is an associate editor for BioMed Central (BMC) Medical Education and has received travel expenses from Medtronic for the "Save the Brain Initiative" training. The remaining authors have no conflicts of interest to disclose.

Multimedia Appendix 1
Study clinical research form (CRF).
[PDF File (Adobe PDF File), 1865 KB - resprot_v13i1e51820_app1.pdf]

Multimedia Appendix 2
Ethical approval.
[PDF File (Adobe PDF File), 126 KB - resprot_v13i1e51820_app2.pdf]

Multimedia Appendix 3
Informed consent form.
[PDF File (Adobe PDF File), 119 KB - resprot_v13i1e51820_app3.pdf]

Multimedia Appendix 4
SPIRIT checklist.
[PDF File (Adobe PDF File), 75 KB - resprot_v13i1e51820_app4.pdf]

References

1. Jee Y. Statement on the fifteenth meeting of the International Health Regulations (2005) Emergency Committee regarding the coronavirus disease (COVID-19) pandemic. World Health Organization. URL: https://www.who.int/news/item/05-05-2023-statement-on-the-fifteenth-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-coronavirus-disease-(covid-19)-pandemic [accessed 2023-05-07]
2. Coronavirus disease (COVID-19) pandemic. World Health Organization. URL: https://www.who.int/europe/emergencies/situations/covid-19 [accessed 2022-09-14]
3. Cevik M, Kuppalli K, Kindrachuk J, Peiris M. Virology, transmission, and pathogenesis of SARS-CoV-2. BMJ 2020 Oct 23;371:m3862. [doi: 10.1136/bmj.m3862] [Medline: 33097561]
4. Soriano JB, Murthy S, Marshall JC, Relan P, Diaz JV, WHO Clinical Case Definition Working Group on Post-COVID-19 Condition. A clinical case definition of post-COVID-19 condition by a Delphi consensus. Lancet Infect Dis 2022 Apr;22(4):e102-e107 [FREE Full text] [doi: 10.1016/S1473-3099(21)00703-9] [Medline: 34951953]
5. Cares-Marambio K, Montenegro-Jiménez Y, Torres-Castro R, Vera-Uribe R, Torralba Y, Alsina-Restoy X, et al. Prevalence of potential respiratory symptoms in survivors of hospital admission after coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. Chron Respir Dis 2021;18:14799731211002240 [FREE Full text] [doi: 10.1177/14799731211002240] [Medline: 33729021]
6. Shah W, Hillman T, Playford ED, Hishmeh L. Managing the long term effects of covid-19: summary of NICE, SIGN, and RCGP rapid guideline. BMJ 2021 Jan 22;372:n136. [doi: 10.1136/bmj.n136] [Medline: 33483331]
7. Nandasena HMRKG, Pathirathna ML, Atapattu AMMP, Prasanga PTS. Quality of life of COVID 19 patients after discharge: systematic review. PLoS One 2022;17(2):e0263941 [FREE Full text] [doi: 10.1371/journal.pone.0263941] [Medline: 35171956]
8. Guidance on “long COVID” as a disability under the ADA, Section 504, and Section 1557. US Department of Health and Human Services. URL: https://www.hhs.gov/civil-rights/for-providers/civil-rights-covid19/guidance-long-covid-disability/index.html#footnote9_x7edz3x [accessed 2022-10-17]
9. Post COVID-19 condition (Long COVID). World Health Organization. 2022 Dec 07. URL: https://www.who.int/europe/news-room/fact-sheets/item/post-covid-19-condition [accessed 2023-01-05]
10. Yong SJ. Long COVID or post-COVID-19 syndrome: putative pathophysiology, risk factors, and treatments. Infect Dis (Lond) 2021 Oct 22;53(10):737-754 [FREE Full text] [doi: 10.1080/23744235.2021.1924397] [Medline: 34024217]
11. Taquet M, Dercon Q, Luciano S, Geddes JR, Husain M, Harrison PJ. Incidence, co-occurrence, and evolution of long-COVID features: A 6-month retrospective cohort study of 273,618 survivors of COVID-19. PLoS Med 2021 Sep;18(9):e1003773 [FREE Full text] [doi: 10.1371/journal.pmed.1003773] [Medline: 34582441]
12. Ngai JC, Ko FW, Ng SS, To KW, Tong M, Hui DS. The long-term impact of severe acute respiratory syndrome on pulmonary function, exercise capacity and health status. Respirology 2010 May 29;15(3):543-550 [FREE Full text] [doi: 10.1111/j.1440-1843.2010.01720.x] [Medline: 20337995]
13. Lee SH, Shin H, Park HY, Kim JL, Lee JJ, Lee H, et al. Depression as a mediator of chronic fatigue and post-traumatic stress symptoms in Middle East respiratory syndrome survivors. Psychiatry Investig 2019 Jan;16(1):59-64 [FREE Full text] [doi: 10.30773/pi.2018.10.22.3] [Medline: 30605995]
14. Zhang P, Li J, Liu H, Han N, Ju J, Kou Y, et al. Correction: Long-term bone and lung consequences associated with hospital-acquired severe acute respiratory syndrome: a 15-year follow-up from a prospective cohort study. Bone Res 2020 Sep 21;8(1):34 [FREE Full text] [doi: 10.1038/s41413-020-00113-1] [Medline: 32983581]
15. Zhao F, Guo K, Li Z. Osteonecrosis of the femoral head in SARS patients: seven years later. Eur J Orthop Surg Traumatol 2013 Aug 13;23(6):671-677. [doi: 10.1007/s00590-012-1054-4] [Medline: 23412187]

16. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020 Feb 07. [doi: 10.1001/jama.2020.1585] [Medline: 32031570]
17. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020 Feb 15;395(10223):497-506 [FREE Full text] [doi: 10.1016/S0140-6736(20)30183-5] [Medline: 31986264]
18. Ceban F, Ling S, Lui LMW, Lee Y, Gill H, Teopiz KM, et al. Fatigue and cognitive impairment in Post-COVID-19 Syndrome: A systematic review and meta-analysis. Brain Behav Immun 2022 Mar;101:93-135 [FREE Full text] [doi: 10.1016/j.bbi.2021.12.020] [Medline: 34973396]
19. Hussain N, Samuelsson CM, Drummond A, Persson CU. Prevalence of fatigue at one-year follow-up from the Gothenburg recovery and rehabilitation after COVID-19 and intensive care unit study. Sci Rep 2022 Jul 12;12(1):11501 [FREE Full text] [doi: 10.1038/s41598-022-14787-6] [Medline: 35821226]
20. Rudroff T, Fietsam AC, Deters JR, Bryant AD, Kamholz J. Post-COVID-19 fatigue: potential contributing factors. Brain Sci 2020 Dec 19;10(12):1012 [FREE Full text] [doi: 10.3390/brainsci10121012] [Medline: 33352638]
21. Schou T, Joca S, Wegener G, Bay-Richter C. Psychiatric and neuropsychiatric sequelae of COVID-19 - A systematic review. Brain Behav Immun 2021 Oct;97:328-348 [FREE Full text] [doi: 10.1016/j.bbi.2021.07.018] [Medline: 34339806]
22. Frontera JA, Simon NM. Bridging knowledge gaps in the diagnosis and management of neuropsychiatric sequelae of COVID-19. JAMA Psychiatry 2022 Aug 01;79(8):811-817. [doi: 10.1001/jamapsychiatry.2022.1616] [Medline: 35767287]
23. Badenoch JB, Rengasamy ER, Watson C, Jansen K, Chakraborty S, Sundaram RD, et al. Persistent neuropsychiatric symptoms after COVID-19: a systematic review and meta-analysis. Brain Commun 2022;4(1):fcab297 [FREE Full text] [doi: 10.1093/braincomms/fcab297] [Medline: 35169700]
24. Bone I. Neuropsychiatry and neuropsychology. J Neurol Neurosurg Psychiatry 2005 Mar 01;76(suppl_1):i1-i1. [doi: 10.1136/jnnp.2004.061622]
25. Chan A, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med 2013 Feb 5;158(3):200-207. [doi: 10.7326/0003-4819-158-3-201302050-00583] [Medline: 23295957]
26. Butler S, Chalder T, Ron M, Wessely S. Cognitive behaviour therapy in chronic fatigue syndrome. J Neurol Neurosurg Psychiatry 1991 Mar 01;54(2):153-158 [FREE Full text] [doi: 10.1136/jnnp.54.2.153] [Medline: 2019842]
27. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983 Jul;67(6):361-370. [doi: 10.1111/j.1600-0447.1983.tb09716.x] [Medline: 6880820]
28. EQ-5D-3L. EuroQol Group. 2022 Jan 11. URL: https://euroqol.org/eq-5d-instruments/eq-5d-3l-about/ [accessed 2022-12-12]
29. Jackson C. The Chalder Fatigue Scale (CFQ 11). Occup Med (Lond) 2015 Jan 04;65(1):86-86. [doi: 10.1093/occmed/kqu168] [Medline: 25559796]
30. Morriss R, Wearden A, Mullis R. Exploring the validity of the Chalder Fatigue scale in chronic fatigue syndrome. J Psychosom Res 1998 Dec;45(5):411-417. [doi: 10.1016/s0022-3999(98)00022-1] [Medline: 9835234]
31. Loge JH, Ekeberg ?, Kaasa S. Fatigue in the general Norwegian population: normative data and associations. J Psychosom Res 1998 Jul;45(1):53-65. [doi: 10.1016/s0022-3999(97)00291-2] [Medline: 9720855]
32. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res 2002 Mar;52(2):69-77. [doi: 10.1016/s0022-3999(01)00296-3] [Medline: 11832252]
33. Stern AF. The hospital anxiety and depression scale. Occup Med (Lond) 2014 Jul;64(5):393-394. [doi: 10.1093/occmed/kqu024] [Medline: 25005549]
34. Snaith RP. The Hospital Anxiety And Depression Scale. Health Qual Life Outcomes 2003;1:29 [FREE Full text] [doi: 10.1186/1477-7525-1-29] [Medline: 12914662]
35. Polinder S, Haagsma JA, Belt E, Lyons RA, Erasmus V, Lund J, et al. A systematic review of studies measuring health-related quality of life of general injury populations. BMC Public Health 2010 Dec 23;10(1):783 [FREE Full text] [doi: 10.1186/1471-2458-10-783] [Medline: 21182775]
36. Berger-Estilita J, Granja C, Gonçalves H, Dias CC, Aragão I, Costa-Pereira A, et al. A new global health outcome score after trauma (GHOST) for disability, cognitive impairment, and health-related quality of life: data from a prospective cross-sectional observational study. Brain Inj 2019 Feb 27;33(7):922-931. [doi: 10.1080/02699052.2019.1581257] [Medline: 30810390]
37. Ferreira LN, Ferreira PL, Pereira LN, Oppe M. The valuation of the EQ-5D in Portugal. Qual Life Res 2014 Mar 8;23(2):413-423. [doi: 10.1007/s11136-013-0448-z] [Medline: 23748906]
38. Stoll C, Kapfhammer HP, Rothenhäusler HB, Haller M, Briegel J, Schmidt M, et al. Sensitivity and specificity of a screening test to document traumatic experiences and to diagnose post-traumatic stress disorder in ARDS patients after intensive care treatment. Intensive Care Med 1999 Jul 22;25(7):697-704. [doi: 10.1007/s001340050932] [Medline: 10470573]
39. Twigg E, Humphris G, Jones C, Bramwell R, Griffiths RD. Use of a screening questionnaire for post-traumatic stress disorder (PTSD) on a sample of UK ICU patients. Acta Anaesthesiol Scand 2008 Feb;52(2):202-208. [doi: 10.1111/j.1399-6576.2007.01531.x] [Medline: 18005373]
40. Son K, Lee T, Hwang S. Disease severity classification and COVID-19 outcomes, Republic of Korea. Bull World Health Organ 2020 Oct 28;99(1):62-66. [doi: 10.2471/blt.20.257758]

41. Ritschard G. CHAID and earlier supervised tree methods. In: McArdle JJ, Ritschard G, editors. Contemporary Issues in Exploratory Data Mining in Behavioral Sciences. New York, NY: Routeledge; 2013:48-74.
42. Mazza MG, De Lorenzo R, Conte C, Poletti S, Vai B, Bollettini I, COVID-19 BioB Outpatient Clinic Study group, et al. Anxiety and depression in COVID-19 survivors: role of inflammatory and clinical predictors. Brain Behav Immun 2020 Oct;89:594-600 [FREE Full text] [doi: 10.1016/j.bbi.2020.07.037] [Medline: 32738287]
43. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet 2021 Jan 16;397(10270):220-232. [doi: 10.1016/S0140-6736(20)32656-8] [Medline: 33428867]
44. Sample size calculators for designing clinical research. Sample Size Calculators. URL: https://sample-size.net/ [accessed 2023-12-30]
45. Simani L, Ramezani M, Darazam IA, Sagharichi M, Aalipour MA, Ghorbani F, et al. Prevalence and correlates of chronic fatigue syndrome and post-traumatic stress disorder after the outbreak of the COVID-19. J Neurovirol 2021 Mar 02;27(1):154-159 [FREE Full text] [doi: 10.1007/s13365-021-00949-1] [Medline: 33528827]
46. Townsend L, Moloney D, Finucane C, McCarthy K, Bergin C, Bannan C, et al. Fatigue following COVID-19 infection is not associated with autonomic dysfunction. PLoS One 2021;16(2):e0247280 [FREE Full text] [doi: 10.1371/journal.pone.0247280] [Medline: 33630906]
47. Verveen A, Müller F, Lloyd A, Moss-Morris R, Omland T, Penninx B, et al. A research agenda for post-COVID-19 fatigue. J Psychosom Res 2022 Mar;154:110726 [FREE Full text] [doi: 10.1016/j.jpsychores.2022.110726] [Medline: 35086054]
48. Nehme M, Chappuis F, Kaiser L, Assal F, Guessous I. The prevalence, severity, and impact of post-COVID persistent fatigue, post-exertional malaise, and chronic fatigue syndrome. J Gen Intern Med 2023 Mar 10;38(3):835-839 [FREE Full text] [doi: 10.1007/s11606-022-07882-x] [Medline: 36357723]

Abbreviations

CFQ-11: Chalder Fatigue Scale
CRF: clinical research form
DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
EQ-VAS: EuroQol Visual Analog Scale
HADS: Hospital Anxiety and Depression Scale
HRQoL: health-related quality of life
ICU: intensive care unit
MERS: Middle East respiratory syndrome
PTSD: posttraumatic stress disorder
PTSS-14: 14-item Posttraumatic Stress Scale
RT-PCR: reverse-transcription polymerase chain reaction
SARS: severe acute respiratory syndrome
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
WHO: World Health Organization

Edited by A Mavragani; submitted 13.08.23; peer-reviewed by M Boarini, A Fuchs; comments to author 24.10.23; revised version received 13.11.23; accepted 06.12.23; published 19.01.24.

Please cite as:
Pires L, Reis C, Mesquita Facão AR, Moniri A, Marreiros A, Drummond M, Berger-Estilita J
Fatigue and Mental Illness Symptoms in Long COVID: Protocol for a Prospective Cohort Multicenter Observational Study
JMIR Res Protoc 2024;13:e51820
URL: https://www.researchprotocols.org/2024/1/e51820
doi:10.2196/51820
PMID:38241071

Protocol

The Impact of Forced Separations Between Women and Their Pets in Domestic Violence Situations and the Effectiveness of Crisis Response: Protocol for a Conceptual Framework

Jasmine Montgomery[1], BSW, MCouns; Janice Lloyd[1], DCR, BSc (Hons), Grad Cert Edu, MEd, PhD; Zhanming Liang[1], Cert SQIL, MBBS, MSc, PhD

College of Public Health, Medical and Veterinary Sciences, James Cook University, Queensland, Australia

Corresponding Author:
Jasmine Montgomery, BSW, MCouns
College of Public Health, Medical and Veterinary Sciences
James Cook University
1 James Cook Drive
Queensland, 4811
Australia
Phone: 61 47814731 ext 07
Email: jasmine.montgomery@my.jcu.edu.au

Abstract

Background: Women are at high risk of experiencing trauma, guilt, and stress when forced to separate from their companion animals when fleeing domestic violence. Where little support is available for women and pets to stay together, women may be forced to delay leaving the abusive relationship or leave the pet with the abuser. Forced separation places both women and pets at substantial risk, where pets may be used as a coercive control measure. However, little evidence exists regarding the extent to which Australian services or policies offer support in these circumstances.

Objective: This research aims to increase the understanding and the impacts of forced separation between women and their pets in domestic violence situations. The research will investigate the effectiveness of service responses for both women and animals, aiming to develop a policy framework that guides service improvement with the goal of enhancing outcomes for women and pets fleeing domestic violence.

Methods: This protocol paper describes the process of developing a conceptual framework of 4 studies that include a scoping review, policy analysis, focus groups, and interviews that guide the design of the qualitative research project.

Results: A scoping review of the literature on forced separation from pets in domestic violence, natural disasters, and homelessness situations has led to the development of a conceptual framework that guided the design of the proposed study. The review also confirmed the necessity of the proposed research project in addressing the lack of Australian national frameworks and guidance available for women and pets seeking formal support in domestic violence situations. As of August 2023, supporting organizations have commenced the distribution of the research flyers. Expected data collection will be completed between August and October 2023. The results are expected to be published in June 2025.

Conclusions: Via a systematic process, the importance of the proposed study in improving the understanding of the impact of forced separation between women and their pets at times of domestic violence and the gaps in best supporting both women and their pets has been confirmed. A study design based on the learnings from previous studies and the focus of the current research has been finalized. The impact of the research project in developing an Australian national framework for best supporting women and their pets in crisis situations is anticipated.

International Registered Report Identifier (IRRID): PRR1-10.2196/52067

(JMIR Res Protoc 2024;13:e52067) doi:10.2196/52067

KEYWORDS

companion animal; domestic violence; forced separation; research protocol; animal welfare; pets; animal abuse; Australia; coercive control; victim; abusive partner; abusive; women; trauma; support; animal

Introduction

In Australia, 69% of households live with a companion animal (pet), and 86% of households with a pet have children [1]. Dogs and cats are the most popular type of pets [1]. The main reason for living with a companion animal is companionship [1]. The relationship is considered beneficial both psychologically and physiologically for humans and animals [2]. Pets are a vital support system providing emotional support or strength at times of domestic violence [3]. Survivors in domestic and family violence situations often live in terror and face threats to themselves and their pets [4]. Sadly, women in domestic violence situations are often faced with the torturous decision to leave their pet with the perpetrator to seek safety or access temporary fostering, resulting in forced separation from their companion animal (Montgomery et al [5], in press), thus losing the emotional support normally received from the relationship [3].

Barrett et al [6] found that decisions to leave or stay in the relationship were impacted by the concerns for the animal's welfare, with 56% of women delaying leaving the relationship to protect their pet. Women with both children and pets were also found to delay leaving an abusive relationship out of concern for the pet's welfare [7]. Most women who delayed were forced to leave their companion animal with the perpetrator when they eventually fled to safety and 47% of women would have fled to safety with their companion animal if support was available [8]. Completing a safety plan when leaving domestic violence situations was often compromised due to a lack of pet-inclusive shelters, often leading to homelessness in order to stay with their pet [7]. When survivors are forced to leave their companion animals with the perpetrator, the risk of coercive control (such as monitoring a person's movements) increases where the companion animal is used as a coercive control tool [9]. The companion animal in this situation may be subject to continued maltreatment [9], often resulting in torture or death [10] and survivors experience additional guilt and trauma [3] as a result. Often, they consider returning to their partner for the sake of their companion animals' safety [8]. Where companion animals have survived domestic violence, signs of distress in the animal have been observed through behavioral changes, such as avoidance and vocalization [4,11]. Devastatingly, in Australia, such behavioral changes often result in euthanasia of the pet [4,11].

The emotional attachment between survivors of domestic violence and their pets may be substantial due to sharing the experience of abuse [4], which makes a deliberate act of cruelty or death of a companion animal particularly torturous [12]. While it is the case that domestic violence is a human issue that affects both men and women, it is recognized as a gender-based issue where men are more likely to perpetrate violence against women and is considered an epidemic problem that requires change in Australia [13]. A recent report on homicide in Australia [14] reveals that, from 1989 to 2020, the incidence of intimate partner homicide is consistently much higher for female survivors than male survivors. The most recent statistic (2019-2020) states that female individuals were the targets in 36 (80%) of the 45 intimate partner homicides. Considering Australia is one of the highest pet ownership countries in the world, where women with children are more likely to have a pet [15], it is vital to address the risks for survivors and their companion animals at times of forced separation because of domestic violence. In such a context, a research project has been developed to investigate the existing policy framework and relevant services that provide support to people and companion animals in domestic violence situations. This protocol paper will explain the process of confirming research gaps and determining research questions and will provide details of the overall project design to be used by the proposed project as informed by the learnings from previously published studies.

Methods

Overview

A scoping review [5] using the keywords "human-animal relationship/bond," "pets," "companion animals," "animal abuse," "violence," "homelessness," "housing," and "disasters," was conducted between March and August 2022. The review focused on identifying empirical studies on the human-animal relationship and crisis or situational change with no date limitation. The review was guided by Arksey and O'Malley's [16] framework for scoping reviews and conformed to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist for scoping reviews [17]. English-language, scholarly peer-reviewed papers that included adults with a strong relationship with a pet and an event or change of situation were a criterion for the scoping review. All methodology types were accepted. Gray literature and certain animal types (rodents, wildlife, zoo animals, and working animals) were excluded. The papers were assessed on their ability to fit within the inclusion criteria. Five databases (MEDLINE Ovid, PsycINFO, Scopus, CINAHL, and Emcare Ovid) were searched, and a total of 42 scholarly papers that met the inclusion criteria were identified and included for data extraction. The scoping review mapped the concept of forced separation between people and their companion animals in areas of crisis or situational change and examined policies that included companion animals. The study design and methods used for the studies were also examined to inform the current project design. Please see the full list of papers included in the scoping review in the Multimedia Appendix 1 [3,4,6-11,18-51].

Scoping Review Findings That Informed the Development of the Protocol

The identified studies in [5] scoping review were predominately quantitative and conducted in the United States, with a focus on the co-occurrence of animal abuse and domestic violence. The lens of research has recently focused on the relationship and animal maltreatment or welfare concerns. Surveys and semistructured interviews were the common forms for collecting quantitative studies and qualitative data respectively. The average sample size consisted of 200 participants for quantitative studies and 20 participants for qualitative studies. The target population was predominantly female adults seeking refuge from domestic violence shelters and support services.

The scoping review [5] confirmed a lack of support for both humans and animals at times of forced separation because of domestic violence. The oversights of the animals' safety and welfare showed that animals were being left with the abuser [18] and women delayed leaving a violent relationship to protect the companion animal [19]. Additional barriers that were identified included geographical locations, lack of available supports [19], lack of awareness of supports, and attachment or fear of separation from the companion animal [4]. As a result of these barriers, the risks to safety, health, and well-being for women, children, and their companion animals have increased.

The scoping review [5] findings revealed survivors were often reluctant to reach out to services due to a lack of trust in accessing support services, veterinary care, and law enforcement. A lack of trust was associated with a fear of being forced to separate from their companion animal [10,18,20,21]. The reluctance to access support, and the responsibility weighing on women to access supports [6,22] is highly concerning. Although many studies in the literature provided implications for service providers, no research was found that investigated the policy frameworks that provide support to people and companion animals in domestic violence situations at any system, organization, societal, or individual level [5].

Ethical Considerations

The following ethical considerations are guided by the Global Women's Institute for the Department of Foreign Affairs and Fair Trade [52], which provides recommendations for projects specific to researching women in domestic violence situations. Ethical approval was granted from the Human Research Ethics Committee (approval H9148). Participation in this study is voluntary and written and verbal consent will be obtained from every participant. The data will be retained for a minimum period of 5 years and will only be accessible to the research team. All data collected will be deidentified and pseudonyms will be provided. All audio recordings for both target populations will be erased after transcription. The primary target population will have the opportunity to review the transcriptions in writing via email. To avoid comprising anonymity and confidentiality for the primary target population, specific locations, age, occupation, culture, and religious discourse in the primary target will not be included in the narrative where there is potential to make the participant identifiable. Consent will be obtained verbally prior to the commencement of the focus group discussion and interviews. Participants are reminded of the voluntary nature of the study and their rights to not answer questions or withdraw their participation from the study. The focus group will be informed that confidentiality is not guaranteed and will be requested to anonymize discussions of their opinions and keep the group discussions private. Confidentiality and anonymity are provided to the interview participants.

Research Focus and Research Questions

The research aims to inform the Australian policy framework by investigating how support services operate across different contexts for adult women and their companion animals affected by forced separation to reduce negative impacts for both people and animals when fleeing domestic violence situations. The research aim will be achieved by the following two objectives:

1. Identifying the impacts of forced separation between adult female survivors of domestic violence and their companion animal's health, safety, and living conditions.
2. Identifying the existing strategies and support services, the perceived effectiveness of these strategies, and areas for improvement to develop recommendations that maximize support to people and their companion animals fleeing domestic violence situations.

The research seeks to answer the following two questions.

1. How does forced separation impact the domestic violence survivor and their companion animal under the existing policy and support framework in Australia?
2. What are the factors and how do these factors influence the extent that the benefits of the existing services currently available to people and their companion animals are realized?

A qualitative design will be used to address the gaps in the literature of a lack of national framework to guide pets and women in domestic violence; the impact of forced separation; and the roles, attitudes, and beliefs of seeking and providing services to better understand the impacts and perceptions of forced separation. The transformative paradigm views privilege and power as a social construction that is embedded through social, political, cultural, economic, gender, age, disability, race, and ethnicity. The transformative worldview is a suitable framework providing the lens of power and oppression with a focus on positive social change [53].

Conceptual Framework

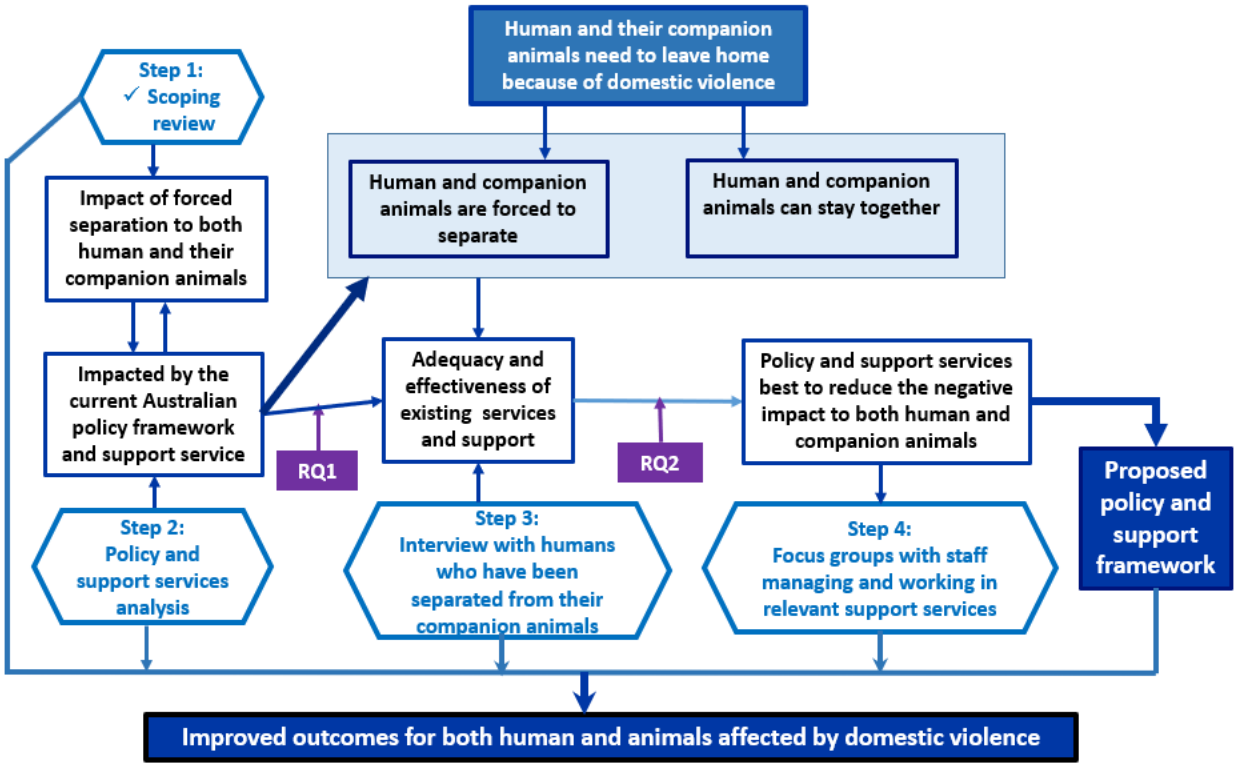
Based on the findings of the scoping review [5] and the role of support services in preventing or minimizing adverse outcomes due to forced separation, a conceptual framework (Figure 1) was developed. The framework indicates that policy and adequate, effective support services are required to improve the outcomes for people and companion animals who must leave their homes because of domestic violence. The scoping review [5] confirms that a policy framework, key supports, and elements required to achieve these outcomes remain unclear. It is important to understand existing policies, support services or providers, and those who use the services in Australia so that improvements can be made to best support people and companion animals fleeing domestic violence. Guided by the conceptual framework created for this study, 4 steps (Figure 1, studies 1-4) need to be implemented to enrich our understanding of the key elements leading to the development of a policy framework on the forced separation of companion animals because of domestic violence that is relevant to the Australian context. The steps include:

1. A scoping review [5] of forced separation at times of crisis or situation (completed).
2. A policy or services analysis and a scanning of the key supports to humans and animals that will analyze the purpose; construction; implementation; and impacts to understand, evaluate, and provide meaning and context [54].

3. Semistructured individual interviews with participants who have accessed a variety of support services (refuges, crisis services, animal welfare services, and mainstream such as women's legal services) will be conducted to increase the understanding and impacts of forced separation on people and companion animals.
4. Focus groups with staff and service providers will be conducted to understand and identify perceptions of the effectiveness and adequacy of service provision.

A critical analysis of steps 2-4 will be completed to compare the findings of the most common types of support, service gaps, and availability of services, leading to the development of an improved policy and support framework.

Figure 1. The conceptual framework. RQ: research question.



RQ 1: How does forced separation impact the domestic violence survivor and their companion animal under the existing policy and support framework in Australia?

RQ 2: What factors and how do these factors influence the extent that the benefits of the existing services currently available to people and their companion animals are realized?

Project Design and Method

Participants: Characteristics and Recruitment

The research project has 2 target populations. The primary target population is female individuals who have or have had considered themselves to have a strong emotional bond in a relationship with their companion animals; have experienced domestic violence; and have been forced to separate from their companion animals or sacrificed their own health, safety, and living arrangements to stay with the animals. The secondary target population is those who have not been directly affected by forced separation and domestic violence but have provided or are currently involved in providing professional support services to the primary target population. Due to the complex and sensitive phenomenon, both target populations are adults, 18 years and older [52].

Both target populations will be recruited through relevant domestic violence or animal welfare organizations. The organizations will be responsible for making direct contact with the potential participants via emails or organization-based advertisements. Potential participants will be encouraged to make direct contact with the principal researcher (first author) should they wish to participate in the study. Both target populations will be geographically recruited nationally across all states and territories in Australia. Due to financial and logistic constraints [55], both target groups are required to be fluent in the English language.

Sampling Strategy

Purposive sampling will be used to gather specific characteristics of survivors who have a strong emotional bond with their companion animals (primary target population) to maximize the richness of the data in addressing the research questions [56]. People who received an invitation from their perspective organization and made contact to participate in the study will need to fit the characteristics of either target population 1 or 2.

Key Stakeholders

To maximize the ethical sensitivity of the research, an advisory group of professionals in the field of domestic violence, advocacy bodies, and animal welfare organizations will be created [52]. Experts participating in the advisory group are

excluded from the secondary target population. The principal researcher candidate and 2 research advisors will hold meetings via Zoom (Zoom Video Communications) prior to ethics submission and after analysis. The advisory group is sought for their expertise regarding sensitivity, recruitment pathways, research questions, and participation sheets. After the analysis, for advice on recommendations based on the findings from the study.

Data Collection Tools

In-depth individual interviews are best suited for "sensitive" populations [52] and web-based options may increase the participant response rate [57]. Hence, the primary target population will be invited to participate in individual semistructured, web-based interviews via Zoom. These interviews are expected to take around 1 hour and will be audio recorded. Focus groups are well suited to discussing beliefs, opinions, and attitudes surrounding programs [52], interventions, and service gaps [58]. Therefore, the secondary target population will be invited to participate in web-based focus groups with audio recordings via Zoom. There will be 4 focus groups nationwide. The focus groups are estimated to last 1 to 2 hours as it is important to allow time during the focus groups for rapport building and voicing opinions [56]. Both types of interviews will be professionally transcribed. Verbal and written consent to participate will be obtained from all participants. All participants will be given the opportunity to review a summary of the transcriptions prior to publication [59].

Sample Size

The average number of participants in related qualitative studies identified in the scoping review was 20 (Montgomery et al [5]). The method of the research project is designed to gather in-depth, rich data or high-quality dialogue [60]. Hence, between 12 and 20 participants will be sampled from the primary target group, with the final number of participants being guided by data saturation of main themes, and no new insights or issues are found [61]. The secondary target population will consist of 4 focus groups throughout Australia. When a group consists of high knowledge, a minimum of 4 participants are required to develop accurate information [62] and the probability of identifying themes with 6 participants is higher than 99% [63]. Due to the expertise and knowledge of the participants, there will be a minimum of 4 and a maximum of 8 participants to allow for space and reflection with each group member [56]. The number of participants for the target populations is supported by a recent systematic review of effective sample sizes for saturation in qualitative research [61].

Data Analysis

Interpretive work is required to identify meanings and themes from participants' opinions, perceptions, and experiences to meet the research aims and overall purpose. Thematic analysis will be used to provide a systematic approach to coding and conceptualizing themes [58]. Areas of analysis will include the impacts and outcomes of forced separation, accessibility of services, types of unmet needs, experiences of accessing services, and benefits of existing services. When the analysis of each step is completed, a critical analysis will be completed to aggregate the data [58] to provide a complete picture of the policy framework [54]. NVivo 12 software (Lumivero) will be used to facilitate the data analysis process.

Results

A scoping review of forced separation of companion animals in crisis situations has been completed, identifying the research gaps and guiding the research questions and design for the research project. As of August 2023, supporting organizations have commenced the distribution of the research flyers. Expected data collection will be completed between August and October 2023. The results are expected to be published in June 2025.

Discussion

Expected Findings

It is expected that the findings will identify the substantial issues experienced by women and pets in domestic violence situations such as psychological distress, grief, loss, and the complexity of decision-making when considering a pet. It is expected that women and pets need to be considered more seriously in Australia and the development of policies and services needs to include the consideration of pets in safety planning, accommodation, and long-term housing as their standard practice.

Comparisons With Prior Work

The research protocol builds on existing knowledge in the literature. We are unaware of any published national Australian frameworks or models that directly relate to responding to women and pets fleeing domestic violence. Previous literature indicates when women are seeking help to flee from domestic violence, the risk of safety increases for both women and their pets. In addition, the pet may be used as a coercive control measure, risking further abuse for both the woman and the animal [18]. The evidence indicates it is vital to address the increased risks to safety when fleeing domestic violence. The prospective data collection of service providers and women using domestic violence and animal welfare services in Australia, as we propose in this study, enables further understanding and development of an Australian framework that is embedded by those with lived experiences to improve outcomes.

Strengths and Limitations

Limitations include the small sample sizes that will not be generalizable to the wider populations, and the exclusion of non–English-speaking populations limits the ability of the research to understand the special needs of the linguistic and cultural populations [55]. The primary target population is recruited from service providers and is considered safe to participate. This is a limitation for women and pets in situations that did not seek formal service provision, had stayed in the relationship, or were not safe from abuse. Bias is more likely to occur in qualitative research than in quantitative methods, resulting in difficulty reaching true objectivity [59]. However, the strength of the qualitative design allows for flexibility and

sensitivity in language, trust, rapport building, exploration of experiences, and collaboration within the community [58] and is appropriate for the study's aims.

Conclusions

A research project guided by a conceptual framework informed by the findings of the scoping review confirms 4 key studies required to better understand the strengths, needs, and gaps of existing policy and support services for women and pets fleeing domestic violence, and the impacts of forced separation from companion animals. Ultimately, the project will develop an Australian national framework that will develop and provide more relevant guidance for supporting women and their pets fleeing domestic violence situations to improve outcomes for both women and their companion animals in Australia.

Acknowledgments

The authors would like to acknowledge Jacqui Watt for her expert advice on domestic violence; the advisory panel members for their contributions regarding animal welfare and domestic violence; and Anna Ludvik, Bridget Brown, Mandy Paterson, Marisa Debattista, and Susan Elvery and the Human Research Ethical Committee and the University Librarians for their contributions. Mentoring support was provided by Diana Mendez and the University Doctoral Cohort Program.

Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Authors' Contributions

As the first author, JM developed the first draft of the manuscript guided by the senior author ZL. Both ZL and JL contributed to writing all sections of the manuscript and critically reviewed and approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Description of the scoping review articles by separation event.
[DOCX File , 33 KB - resprot_v13i1e52067_app1.docx]

References

1. Pets in Australia: a national survey of pets and people. Animal Medicines Australia. 2022. URL: https://animalmedicinesaustralia.org.au/report/pets-in-australia-a-national-survey-of-pets-and-people-2/ [accessed 2022-05-23]
2. The human-animal interaction and human-animal bond. American Veterinary Medical Association. URL: https://www.avma.org/resources-tools/avma-policies/human-animal-interaction-and-human-animal-bond [accessed 2022-08-01]
3. Taylor N, Riggs DW, Donovan C, Signal T, Fraser H. People of diverse genders and/or sexualities caring for and protecting animal companions in the context of domestic violence. Violence Against Women 2019;25(9):1096-1115. [doi: 10.1177/1077801218809942] [Medline: 30419803]
4. Tiplady CM, Walsh DB, Phillips CJC. Intimate partner violence and companion animal welfare. Aust Vet J 2012;90(1-2):48-53. [doi: 10.1111/j.1751-0813.2011.00843.x] [Medline: 22256986]
5. Montgomery J, Liang Z, Lloyd J. A scoping review of forced separation between people and their companion animals. Anthrozoos 2023 (forthcoming). [doi: 10.1080/08927936.2023.2287315]
6. Barrett BJ, Fitzgerald A, Stevenson R, Cheung CH. Animal maltreatment as a risk marker of more frequent and severe forms of intimate partner violence. J Interpers Violence 2020;35(23-24):5131-5156. [doi: 10.1177/0886260517719542] [Medline: 29294833]
7. Collins EA, Cody AM, McDonald SE, Nicotera N, Ascione FR, Williams JH. A template analysis of intimate partner violence survivors' experiences of animal maltreatment: implications for safety planning and intervention. Violence Against Women 2018;24(4):452-476 [FREE Full text] [doi: 10.1177/1077801217697266] [Medline: 29332521]
8. Barrett BJ, Fitzgerald A, Peirone A, Stevenson R, Cheung CH. Help-seeking among abused women with pets: evidence from a Canadian sample. Violence Vict 2018;33(4):604-626. [doi: 10.1891/0886-6708.VV-D-17-00072] [Medline: 30567764]
9. Fitzgerald AJ, Barrett BJ, Stevenson R, Cheung CH. Animal maltreatment in the context of intimate partner violence: a manifestation of power and control? Violence Against Women 2019;25(15):1806-1828. [doi: 10.1177/1077801218824993] [Medline: 30714886]
10. Hardesty JL, Khaw L, Ridgway MD, Weber C, Miles T. Coercive control and abused women's decisions about their pets when seeking shelter. J Interpers Violence 2013;28(13):2617-2639. [doi: 10.1177/0886260513487994] [Medline: 23670287]
11. Tiplady C, Walsh D, Phillips C. "The animals are all i have": domestic violence, companion animals, and veterinarians. Soc Anim 2018;26(5):490-514. [doi: 10.1163/15685306-12341464]

12. Walsh F. Human-animal bonds II: the role of pets in family systems and family therapy. Fam Process 2009;48(4):481-499. [doi: 10.1111/j.1545-5300.2009.01297.x] [Medline: 19930434]
13. The national plan to end violence against women and children 2022-2032. Department of Social Services.: Department of Social Services; 2023. URL: https://www.dss.gov.au/ending-violence [accessed 2023-11-22]
14. Serpell B, Sullivan T, Doherty L. Homicide in Australia 2019-2020. Australian Insititute of Criminology. 2022. URL: https://www.aic.gov.au/publications/sr/sr39 [accessed 2022-09-12]
15. Animal Medicines Australia. Pets in Australia: a national survey of pets and people. Newgate Research. 2019. URL: https://animalmedicinesaustralia.org.au/wp-content/uploads/2019/10/ANIM001-Pet-Survey-Report19_v1.7_WEB_low-res.pdf [accessed 2022-04-14]
16. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. Int J Soc Res Methodol 2005;8(1):19-32. [doi: 10.1080/1364557032000119616]
17. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151(4):264-269 [FREE Full text] [doi: 10.7326/0003-4819-151-4-200908180-00135] [Medline: 19622511]
18. Allen M, Gallagher B, Jones B. Domestic violence and the abuse of pets: researching the link and its implications in Ireland. Practice 2006;18(3):167-181 [FREE Full text] [doi: 10.1080/09503150600904060]
19. Faver CA, Strand EB. To leave or to stay?: battered women's concern for vulnerable pets. J Interpers Violence 2003;18(12):1367-1377. [doi: 10.1177/0886260503258028] [Medline: 14678611]
20. Ascione FR. Battered women's reports of their partners' and their children's cruelty to animals. J Emotional Abuse 1997;1(1):119-133. [doi: 10.1300/j135v01n01_06]
21. Strand EB, Faver CA. Battered women's concern for their pets: a closer look. J Fam Soc Work 2005;9(4):39-58. [doi: 10.1300/j039v09n04_04]
22. Wusinich C, Bond L, Nathanson A, Padgett DK. "If you're gonna help me, help me": barriers to housing among unsheltered homeless adults. Eval Program Plann 2019;76:101673. [doi: 10.1016/j.evalprogplan.2019.101673] [Medline: 31228636]
23. Ascione FR, Weber CV, Thompson TM, Heath J, Maruyama M, Hayashi K. Battered pets and domestic violence: animal abuse reported by women experiencing intimate violence and by nonabused women. Violence Against Women 2007 Apr;13(4):354-373. [doi: 10.1177/1077801207299201] [Medline: 17420515]
24. Carlisle-Frank P, Frank JM, Nielsen L. Selective battering of the family pet. Anthrozoös 2004;17(1):26-42. [doi: 10.2752/089279304786991864]
25. Flynn CP. Woman's best friend: pet abuse and the role of companion animals in the lives of battered women. Violence Against Women 2016 Jun 30;6(2):162-177. [doi: 10.1177/10778010022181778]
26. Hartman CA, Hageman T, Williams JH, Ascione FR. Intimate partner violence and animal abuse in an immigrant-rich sample of mother-child dyads recruited from domestic violence programs. J Interpers Violence 2018 Mar;33(6):1030-1047. [doi: 10.1177/0886260515614281] [Medline: 26611616]
27. Simmons CA, Lehmann P. Exploring the link between pet abuse and controlling behaviors in violent relationships. J Interpers Violence 2007 Sep;22(9):1211-1222. [doi: 10.1177/0886260507303734] [Medline: 17704464]
28. Volant AM, Johnson JA, Gullone E, Coleman GJ. The relationship between domestic violence and animal abuse: an Australian study. J Interpers Violence 2008 Sep;23(9):1277-1295. [doi: 10.1177/0886260508314309] [Medline: 18326483]
29. Applebaum JW, Adams BL, Eliasson MN, Zsembik BA, McDonald SE. How pets factor into healthcare decisions for COVID-19: a one health perspective. One Health 2020 Dec 20;11:100176 [FREE Full text] [doi: 10.1016/j.onehlt.2020.100176] [Medline: 33062838]
30. Canady B, Sansone A. Health care decisions and delay of treatment in companion animal owners. J Clin Psychol Med Settings 2019 Sep;26(3):313-320. [doi: 10.1007/s10880-018-9593-4] [Medline: 30443877]
31. Cleary M, West S, Visentin D, Phipps M, Westman M, Vesk K, et al. The unbreakable bond: the mental health benefits and challenges of pet ownership for people experiencing homelessness. Issues Ment Health Nurs 2021 Aug;42(8):741-746. [doi: 10.1080/01612840.2020.1843096] [Medline: 33196324]
32. Cronley C, Strand EB, Patterson DA, Gwaltney S. Homeless people who are animal caretakers: a comparative study. Psychol Rep 2009 Oct;105(2):481-499. [doi: 10.2466/PR0.105.2.481-499] [Medline: 19928610]
33. Kidd AH, Kidd RM. Benefits and liabilities of pets for the homeless. Psychol Rep 1994 Jun;74(3 Pt 1):715-722. [doi: 10.2466/pr0.1994.74.3.715] [Medline: 8058851]
34. Labrecque J, Walsh CA. Homeless women's voices on incorporating companion animals into shelter services. Anthrozoös 2015 Apr 28;24(1):79-95. [doi: 10.2752/175303711X12923300467447]
35. Scanlon L, Hobson-West P, Cobb K, McBride A, Stavisky J. Homeless people and their dogs: exploring the nature and impact of the human–companion animal bond. Anthrozoös 2021 Feb 14;34(1):77-92. [doi: 10.1080/08927936.2021.1878683]
36. Singer RS, Hart LA, Zasloff RL. Dilemmas associated with rehousing homeless people who have companion animals. Psychol Rep 1995 Dec;77(3 Pt 1):851-857. [doi: 10.2466/pr0.1995.77.3.851] [Medline: 8559923]
37. Slatter J, Lloyd C, King R. Homelessness and companion animals: more than just a pet? Br J Occup Ther 2012 Aug 01;75(8):377-383. [doi: 10.4276/030802212X13433105374350]

38. Shore ER, Petersen CL, Douglas DK. Moving as a reason for pet relinquishment: a closer look. J Appl Anim Welf Sci 2003;6(1):39-52. [doi: 10.1207/S15327604JAWS0601_04] [Medline: 12795858]
39. Brackenridge S, Zottarelli LK, Rider E, Carlsen-Landy B. Dimensions of the human–animal bond and evacuation decisions among pet owners during hurricane Ike. Anthrozoös 2015 Apr 28;25(2):229-238. [doi: 10.2752/175303712X13316289505503]
40. Coombs S, Eberlein A, Mantata K, Turnhout A, Smith CM. Did dog ownership influence perceptions of adult health and wellbeing during and following the Canterbury earthquakes? a qualitative study. Australas J Disaster Trauma Stud 2015;19(2):67-76 [FREE Full text]
41. Farmer AK, DeYoung SE. The pets of Hurricane Matthew: evacuation and sheltering with companion animals. Anthrozoös 2019 May 20;32(3):419-433. [doi: 10.1080/08927936.2019.1598661]
42. Heath SE, Beck AM, Kass PH, Glickman LT. Risk factors for pet evacuation failure after a slow-onset disaster. J Am Vet Med Assoc 2001 Jun 15;218(12):1905-1910 [FREE Full text] [doi: 10.2460/javma.2001.218.1905] [Medline: 11417734]
43. Hunt M, Al-Awadi H, Johnson M. Psychological sequelae of pet loss following Hurricane Katrina. Anthrozoös 2008;21(2):109-121. [doi: 10.2752/175303708X305765]
44. Lowe SR, Rhodes JE, Zwiebach L, Chan CS. The impact of pet loss on the perceived social support and psychological distress of hurricane survivors. J Trauma Stress 2009 Jun;22(3):244-247 [FREE Full text] [doi: 10.1002/jts.20403] [Medline: 19462438]
45. Taylor M, Burns P, Eustace G, Lynch E. The preparedness and evacuation behaviour of pet owners in emergencies and natural disasters. Aust J Emerg Manag 2015;30(2):18-23 [FREE Full text]
46. Thompson CN, Brommer DM, Sherman-Morris K. Pet ownership and the spatial and temporal dimensions of evacuation decisions. Southeastern Geographer 2012;52(3):253-266. [doi: 10.1353/sgo.2012.0025]
47. Thompson K, Trigg J, Smith B. Animal ownership among vulnerable populations in regional South Australia: implications for natural disaster preparedness and resilience. J Public Health Manag Pract 2017;23(1):59-63. [doi: 10.1097/PHH.0000000000000416] [Medline: 27598703]
48. Trigg J, Thompson K, Smith B, Bennett P. A moveable beast: subjective influence of human-animal relationships on risk perception, and risk behaviour during bushfire threat. TQR 2016 Oct 17;21(10):1881-1903. [doi: 10.46743/2160-3715/2016.2494]
49. Trigg J, Thompson K, Smith B, Bennett P. Archetyping relationships with companion animals to understand disaster risk-taking propensity. J Risk Res 2017 Nov 24;22(4):475-496. [doi: 10.1080/13669877.2017.1405458]
50. Yamazaki S. A survey of companion-animal owners affected by the East Japan great earthquake in Iwate and Fukushima prefectures, Japan. Anthrozoös 2015 Jun 16;28(2):291-304. [doi: 10.1080/08927936.2015.11435403]
51. Zottarelli LK. Broken bond: an exploration of human factors associated with companion animal loss during Hurricane Katrina. Sociol Forum 2010;25(1):110-112. [doi: 10.1111/j.1573-7861.2009.01159.x]
52. Ellsberg M, Potts A. Ethical considerations for research and evaluation on ending violence against women and girls. Australian Government Department of Foreign Affairs and Trade. 2018. URL: https://www.dfat.gov.au/sites/default/files/ode-evawg-ethical-considerations-for-research-and-eval.pdf [accessed 2022-05-20]
53. Mertens DM. Transformative paradigm: mixed methods and social justice. J Mix Methods Res 2007;1(3):212-225. [doi: 10.1177/1558689807302811]
54. Bowen GA. Document analysis as a qualitative research method. Qual Res J 2009;9(2):27-40 [FREE Full text] [doi: 10.3316/qrj0902027]
55. Pedemont K. Excluding non-English speaking people from health research including falls research for community-dwelling older people. Aust Orthopt J 2018;50:26-30 [FREE Full text]
56. Dicicco-Bloom B, Crabtree BF. The qualitative research interview. Med Educ 2006;40(4):314-321 [FREE Full text] [doi: 10.1111/j.1365-2929.2006.02418.x] [Medline: 16573666]
57. Harvey WS. Strategies for conducting elite interviews. Qual Res 2011;11(4):431-441 [FREE Full text] [doi: 10.1177/1468794111404329]
58. Davidson PM, Halcomb EJ, Leila G. Focus groups in health research. In: Liamputtong P, editor. Research Methods in Health: Foundations for Evidence-Based Practice. 3rd Edition. Walton Street, Oxford: Oxford University Press; 2017:85-104.
59. Marlow CR. Research Methods for Generalist Social Work. 5th Edition. Asia, Europe, US: Cengage Learning; 2011.
60. Malterud K, Siersma VD, Guassora AD. Sample size in qualitative interview studies: guided by information power. Qual Health Res 2016;26(13):1753-1760. [doi: 10.1177/1049732315617444] [Medline: 26613970]
61. Hennink M, Kaiser BN. Sample sizes for saturation in qualitative research: a systematic review of empirical tests. Soc Sci Med 2022;292:114523 [FREE Full text] [doi: 10.1016/j.socscimed.2021.114523] [Medline: 34785096]
62. Galvin R. How many interviews are enough? do qualitative interviews in building energy consumption research produce reliable knowledge? J Build Eng 2015;1(1):2-12 [FREE Full text] [doi: 10.1016/j.jobe.2014.12.001]
63. Romney AK, Weller SC, Batchelder WH. Culture as consensus: a theory of culture and informant accuracy. Am Anthropol 1986;88(2):313-338. [doi: 10.1525/aa.1986.88.2.02a00020]

Abbreviations

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Edited by A Mavragani; submitted 21.08.23; peer-reviewed by O Harvey, T Howell; comments to author 05.11.23; revised version received 14.12.23; accepted 15.12.23; published 25.01.24.

Please cite as:
Montgomery J, Lloyd J, Liang Z
The Impact of Forced Separations Between Women and Their Pets in Domestic Violence Situations and the Effectiveness of Crisis Response: Protocol for a Conceptual Framework
JMIR Res Protoc 2024;13:e52067
URL: https://www.researchprotocols.org/2024/1/e52067
doi:10.2196/52067
PMID:38271100

Protocol

Validation of an Anti-Müllerian Hormone Cutoff for Polycystic Ovarian Morphology in the Diagnosis of Polycystic Ovary Syndrome in the HARMONIA Study: Protocol for a Prospective, Noninterventional Study

Terhi T Piltonen[1,2], MD, PhD; Deirdre Allegranza[3], BA; Martin Hund[3], MSc, PhD; Katharina Buck[4], Dipl, PhD; Johanna Sillman[3], MSc, PhD; Riikka K Arffman[1,2], MSc, PhD

[1]Department of Obstetrics and Gynecology, Oulu University Hospital, University of Oulu (MRC Oulu, Finland), Oulu, Finland

[2]Research Unit of Clinical Medicine, Medical Research Center, Oulu University Hospital, University of Oulu (MRC Oulu, Finland), Oulu, Finland

[3]Roche Diagnostics International Ltd, Rotkreuz, Switzerland

[4]Roche Diagnostics GmbH, Penzberg, Germany

Corresponding Author:
Terhi T Piltonen, MD, PhD
Department of Obstetrics and Gynecology
Oulu University Hospital
University of Oulu (MRC Oulu, Finland)
Pentti Kaiteran katu 1
Oulu, 90220
Finland
Phone: 358 8 3153051
Email: terhi.piltonen@oulu.fi

Abstract

Background: Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women and is diagnosed using the Rotterdam criteria, including diagnosis of polycystic ovarian morphology (PCOM) by transvaginal ultrasound (TVUS). Due to high cost, availability, and the impact of the operator and ultrasound equipment on the reliability of the antral follicle count (AFC) by TVUS, an unmet need exists for a diagnostic test to determine PCOM without TVUS. A strong positive correlation between elevated anti-Müllerian hormone (AMH) levels and AFCs has been demonstrated in women with PCOS. In addition, recent updates to the international evidence-based PCOS guidelines state that serum AMH can be used as an alternative to TVUS-determined AFC, in the diagnosis of PCOM. The retrospective APHRODITE study derived and validated an AMH cutoff of 3.2 ng/mL for the Elecsys AMH Plus or Elecsys AMH assays (Roche) to diagnose PCOM in patients with PCOS.

Objective: This study aims to further validate, in an independent prospective cohort, the AMH cutoff (3.2 ng/mL) for PCOM determination, which was previously derived and validated in the APHRODITE study.

Methods: This large, prospective, multicenter, population-based, noninterventional study will evaluate the previously established AMH cutoff for the determination of PCOM during the diagnosis of PCOS using the Elecsys AMH Plus immunoassay in an independent population. Participants were women born between July 1985 and December 1987 in Northern Finland; the study partially links to the Northern Finland Birth Cohort 1986. We assessed the enrolled women, determined with the 2023 PCOS Guidelines, for current PCOS status and divided them by phenotype if positive. Each participant had 1 study visit to collect serum samples, record clinical data, and undergo a gynecological examination including TVUS. All data were collected by highly trained midwives or trained gynecologists. Sensitivity, specificity, and agreement measures were used to validate the previously determined cutoff in the whole population and in subpopulations based on phenotype and relevant demographic or clinical factors. The minimum target sample size was approximately 1800 women, including approximately 10% with PCOS.

Results: At the time of manuscript submission, participant recruitment had concluded, and 1803 women were enrolled into the study. Data collection is complete and biostatistical analysis is planned for 2023.

Conclusions: To limit variability, there were few TVUS operators and only 2 TVUS machines of the same type. Additionally, all women who were taking oral contraceptives were excluded from the primary analysis population. Selection bias was limited as this was a population-based study and participants were not seeking treatment for PCOS symptoms. Validating the AMH cutoff

in a large, population-based study will provide further evidence on the utility of the Elecsys AMH Plus or Elecsys AMH assays in PCOM diagnosis as an alternative to TVUS. Measuring AMH for PCOM diagnosis could reduce delayed or missed diagnoses due to operator-dependent TVUS examinations.

Trial Registration: ClinicalTrials.gov NCT05527353; http://tinyurl.com/2f3ffbdz

International Registered Report Identifier (IRRID): DERR1-10.2196/48854

(JMIR Res Protoc 2024;13:e48854) doi:10.2196/48854

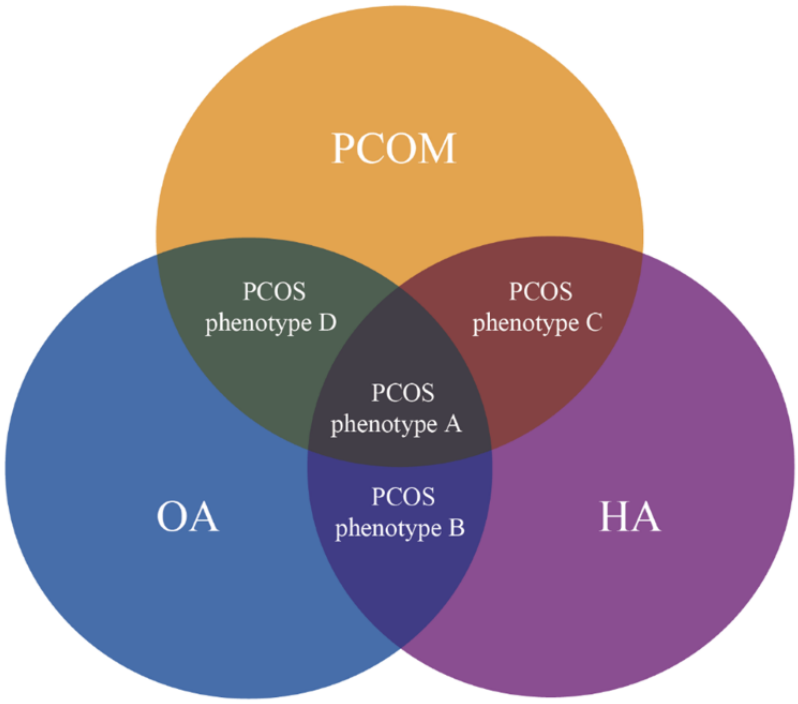
KEYWORDS

anti-Müllerian hormone; immunoassay; polycystic ovarian morphology; polycystic ovary syndrome; transvaginal ultrasound

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders affecting women and is characterized by symptoms of ovarian dysfunction and an excess of androgen, without other specific diagnoses [1-3]. PCOS is the primary cause of female anovulatory infertility and has metabolic, cardiovascular, and psychological implications [4-7]. The diagnosis of PCOS is based on the Rotterdam criteria [8,9], where 2 or more of the following conditions should be met: oligoanovulation or anovulation (OA), clinical or biochemical signs of hyperandrogenism (HA), a combination of both, and polycystic ovarian morphology (PCOM) based on transvaginal ultrasound [10] (TVUS; Figure 1).

Figure 1. Diagnostic criteria and phenotypes of PCOS based on the Rotterdam criteria. HA: hyperandrogenism; OA: oligoanovulation or anovulation; PCOM: polycystic ovarian morphology; PCOS: polycystic ovary syndrome.



Criteria	Phenotypes			
	A	B	C	D
HA	✓	✓	✓	
OA	✓	✓		✓
PCOM	✓		✓	✓

According to the updated guidelines [9], the diagnosis of PCOM is based on a TVUS with a finding of ≥20 follicles of 2-9 mm in size in at least 1 ovary or increased ovarian volume ≥10 mL, but determination of the antral follicle count (AFC) by TVUS

depends on the operator and ultrasound equipment used [11-17]. Due to the expense of the equipment and the regularity of updates needed, in addition to the very high level of specialized training required by operators, TVUS is not available for many physicians seeing women with symptoms of PCOS (eg, general practitioners, gynecologists, and endocrinologists). Thus, there is significant underdiagnosis of PCOS [18] along with a substantial delay in receiving a diagnosis [19-22]; therefore, an unmet medical need exists for a diagnostic test to determine PCOM without the need for TVUS.

Anti-Müllerian hormone (AMH) is a regulator of follicle recruitment from the primordial follicle pool and inhibitor of follicular growth that is expressed by granulosa cells in the preantral and small antral follicles [23,24]. Serum AMH levels correlate well with the 2-9 mm antral follicles found in TVUS examination in the diagnosis of PCOM [25,26]. Elevated levels of AMH are observed in women with PCOS [27-30], and a strong correlation between elevated levels of AMH and increased AFCs has been demonstrated [12,14,26,29], supporting the use of AMH as a biomarker for PCOM.

In the recent, retrospective, case-control APHRODITE study, a cutoff of 3.2 ng/mL for the Elecsys AMH Plus or Elecsys AMH assays (Roche Diagnostics International Ltd) was derived and validated to identify PCOM as part of PCOS diagnosis in women aged 25-45 years [28]. Moreover, a recent study reported the usability of the Elecsys AMH assay to identify PCOS cases in large epidemiological data sets [31]. All previous findings support the use of AMH measurement using the Elecsys AMH Plus assay as a substitute for AFC in the determination of PCOM, thereby reducing the need for TVUS procedures [28,32].

Since APHRODITE was a retrospective, case-control study that validated the derived cutoff in a population with an increased risk of PCOS, it is of interest to further validate the derived cutoff in a prospective, independent, population-based cohort. By validating AMH levels in a large, population-based study using the Roche Elecsys AMH Plus assay, we aim to provide clinicians with the ability to identify PCOM as part of a PCOS diagnosis using a simple blood test, thereby making diagnosis of the disorder more accessible in a primary care setting. Although it is not anticipated that TVUS as a diagnostic method for PCOM will be discarded from PCOS guidelines, AMH testing could be adopted as an alternative method, particularly in primary care.

Methods

Study Design

The prospective, multicenter, population-based, noninterventional HARMONIA (Human Anti-Müllerian Hormone for Diagnosis of PCOS) study aims to validate the AMH cutoff determined and validated in the APHRODITE study for the determination of PCOM during the diagnosis of PCOS using the Elecsys AMH Plus immunoassay. Study enrollment was conducted between May 2020 and October 2022 at 2 sites in Finland: Oulu University Hospital, Department of Obstetrics and Gynecology, Oulu, and Helsinki University Hospital, Helsinki.

Participants

The target population was women born in Northern Finland between July 1, 1985, and December 31, 1987; the study partially links to the Northern Finland Birth Cohort (NFBC) 1986 study population. The prevalence of PCOS in this population is expected to be approximately 10% when applying the diagnostic criteria for PCOS outlined in the 2018 international PCOS guideline [9,33]. The COVID-19 pandemic resulted in a lower enrollment rate than originally expected, and so the cohort was expanded to include a random cohort of women born in the same geographical area up to 18 months after those in the NFBC 1986, to ensure enrollment met the minimum target sample size of approximately 1800 individuals. As the study is population-based, all nonpregnant women from the target population were invited to participate in the study.

Participants were excluded if they were unwilling to undergo gynecological examination including TVUS, refused to have blood drawn, or did not consent to sharing their personal data with Roche Diagnostics International Ltd, who completed the AMH measurement and analysis. Additionally, women who were taking oral contraceptives at the time of study commencement will be excluded from the primary analysis population.

PCOS cases were defined as women fulfilling 2 or more Rotterdam criteria [8,9]. For each participant, the current PCOS status was assessed. PCOS positive cases were further divided into the following phenotypes: phenotype A (HA+, OA+, PCOM+), phenotype B (HA+, OA+, PCOM-), phenotype C (HA+, OA-, PCOM+), and phenotype D (HA-, OA+, PCOM+; Figure 1). PCOM in PCOS cases included the PCOS A, C, and D phenotypes. PCOS phenotype B cases by definition did not meet the criteria for PCOM based on TVUS (phenotype B accounted for approximately 3% of PCOS cases in the APHRODITE study) and were not included in the case group for the primary objective. Controls were defined as women with negative PCOM with an AFC <20, an ovarian volume <10 mL, and no other diagnostic features of PCOS according to the Rotterdam criteria.

Each participant had 1 study visit during which serum samples were collected through blood draw (taken at any stage of the menstrual cycle), clinical data (including questionnaire responses) were recorded, and a gynecological examination including TVUS (Ultrasound System HS60, Samsung Healthcare) was performed to determine PCOM status; all assessments were evaluated by a clinician (Table 1) [34]. All data were collected by highly trained midwives or gynecologists.

Table 1. Baseline characteristics to be recorded by questionnaire and clinical assessment.

Baseline characteristic	Questionnaire	Clinical assessment
General information and medical history	• Participant identification and date of consent • Age at the study visit • Race • Education • History of radiation or chemotherapy (yes or no) or treatment • Long-term illnesses diagnosed by a doctor (self-reported) • Bothersome hair loss experience • Acne (former or current)	Confirmation of fasting for 12 hours before the clinic visit
Medication use	• Medication use (current) • Use and type of hormonal contraceptives (oral, patch, or intrauterine device; former or current)	N/A[a]
Intoxications	• Smoking (current, former, or never; number of cigarettes) • Alcohol (units per week)	N/A
Obstetric history	• Menarche • Cycle (regular, irregular, or absent) • Shortest and longest menstrual cycle length (days) • Last menstrual cycle • Number of live births, fetus mortus, miscarriages, extrauterine pregnancy, and pregnancy terminations • Fertility treatment • Breastfeeding status (no, exclusively, or partially) • Delivery within 6 months from the study visit	From the transvaginal ultrasound report: • Endometrial thickness • Visualization status of the ovaries • Ovarian length, width, height, and volume • Antral follicle count • Dominant follicle presence • Presence of corpus luteum and/or cysts >25 mm and/or other possible reason for increase of the ovarian volume
Anthropomorphic	• N/A	• Height • Weight • Waist circumference • Hip circumference • Systolic blood pressure or diastolic blood pressure • Gynecological ultrasonography (polycystic ovarian morphology) • Hirsutism (Ferriman-Gallwey-Score) • Acne severity grading (1-5) per the Global Acne Severity Scale [34]. Images of the participant will be assessed by a dermatologist

[a]N/A: not applicable.

Sample Processing

A total volume of approximately 5 mL of serum was collected using VACUETTE Tube 9 mL CAT serum clot activator tubes (Greiner Bio One) and stored at –80 °C. Aliquots were sent to the Nordlab in Oulu for measurement of testosterone by liquid chromatography-mass spectrometry (Sciex Qtrap 5500, Ab Sciex). Additional measurements were performed on-site at Oulu (testosterone, sex hormone-binding globulin, follicle-stimulating hormone, luteinizing hormone, thyroid-stimulating hormone, and prolactin) on the COBAS e 411 analyzer (Roche Diagnostics International Ltd), which was used to assess some of the PCOS criteria. Additional aliquots were shipped to Roche Diagnostics GmbH, Penzberg, Germany, for determination of AMH biomarker levels (Textbox 1). AMH levels were measured using the Elecsys AMH Plus assay on the COBAS pro e 801 analyzer (Roche Diagnostics International Ltd). The measuring range of the Elecsys AMH Plus assay is 0.01-23 ng/mL and the coefficient of variance for repeatability is less than 3% [35]. Participants with AMH levels more than 3.2 ng/mL (the cutoff determined and validated in the APHRODITE study [28]) were classified as AMH PCOM positive, and those with results ≤3.2 ng/mL were classified as AMH PCOM negative.

Textbox 1. Laboratory parameters to be measured from blood samples.

Parameters to be measured

- Hemoglobin A1c
- Complete blood count
- Ferritin
- Fasting plasma glucose
- Fasting total cholesterol
- Fasting plasma high-density lipoprotein
- Fasting plasma low-density lipoprotein
- Fasting plasma triglycerides
- Plasma alkaline phosphatase
- Plasma albumin
- Fasting serum C-peptide
- Plasma alanine aminotransferase
- Plasma amylase
- Plasma aspartate aminotransferase
- Plasma bilirubin
- Plasma gamma glutamyltransferase
- Plasma creatinine
- Plasma uric acid
- Fasting serum insulin
- Serum high-sensitivity C-reactive protein
- Testosterone
- Sex hormone-binding globulin
- Follicle-stimulating hormone
- Luteinizing hormone
- Thyroid-stimulating hormone
- Prolactin
- Anti-Müllerian hormone
- Dehydroepiandrosterone sulfate

Data Analysis

At the time of publication submission, the trial was still underway, although data collection was complete. During the planned biostatistical analysis, baseline characteristics and biomarker data will be analyzed for all participants, and by PCOS phenotype and case or control groups. Additionally, the baseline characteristics will be compared between cases and controls using statistical tests, such as Mann-Whitney *U* tests or chi-square tests.

The primary objective of this study, conducted in the PCOM positive population, will be validating the AMH cutoff for PCOM determined in the APHRODITE study. Agreement measures will be calculated, and tables produced to estimate the performance (ie, sensitivity, specificity, and receiver operating characteristic curve) of the prespecified Elecsys AMH cutoff for the prediction of PCOM status. In addition, performance estimates (sensitivity, specificity, and agreement tables) of the Elecsys AMH Plus cutoff will be performed within subpopulations (phenotype and potentially relevant demographic or clinical factors).

Sample Size and Power

The total sample size for the primary analysis was a minimum of approximately 1800 women, of whom approximately 10% will be PCOS positive cases; however, some individuals may need to be excluded from the primary objective analysis due to hormonal contraceptive use. As PCOS phenotype B cases do not meet the criteria for PCOM based on TVUS, some PCOS cases will also be excluded. In addition, some women may need to be excluded if their PCOS or PCOM status cannot be determined (eg, due to the inability to adequately visualize the ovaries). Assuming a significance level of 0.05 (1-sided lower CIs) and a joint power of 80%, approximately 55-88 PCOS

positive cases and approximately 164-262 PCOS negative cases are needed to achieve agreements of 65% and 70%, if the true percentages of agreement are 79%-82.5% and 78%-80%, respectively.

Ethical Considerations

The study complies with all relevant national regulations and institutional policies and was performed in accordance with the principles of the Declaration of Helsinki. Ethical approval was provided by the Ethical Committee of the Northern Ostrobothnia Hospital District (EETTMK 47/2019), and all participants were required to give informed consent for the use of their collected data for scientific purposes. The trial was registered (NCT05527353) on September 2, 2022.

Results

The first patient provided consent on May 7, 2021, and the last patient provided consent on October 28, 2022; therefore, participant recruitment has been completed. At the time of manuscript submission, 1803 women had been enrolled into the study. Biostatistical analysis will commence later in 2023 and it is expected that the results will be published shortly thereafter.

Discussion

This is the first large, prospective, population-based study to validate an AMH level cutoff for determining PCOM status in the diagnosis of PCOS.

Strengths and Limitations

One strength of this study is that all data were collected by highly trained midwives and specialized gynecologists. The TVUS data is robust due to the limited number of TVUS experienced operators performing the ultrasound assessments, and the use of only 2 TVUS machines of the same type. In addition, while most studies on AMH testing are retrospective, using small, non–population-based cohorts from PCOS clinics, HARMONIA is a large, prospective, population-based study. Furthermore, there will be limited bias, as the study is population-based, and participants were not seeking treatment for PCOS symptoms. However, the study also has some limitations. The age of the participants is limited by the study's linkage to the NFBC 1986 (all participants are within a 3-year age range). In the APHRODITE study, it was also found that AMH levels decreased with age among PCOS cases and controls [28]; findings from this study should therefore be evaluated in the context of these results. Furthermore, due to the geographical location of the study and the fertile age of the participants, most women will be White (with a small minority, estimated below 3%, of indigenous Sámi people), and some will be taking hormonal contraceptives. It has also previously been shown that there is some biological variability in AMH during the menstrual cycle [36]. However, a longitudinal study conducted in a population-based cohort demonstrated that AMH may be used as a surrogate marker for identification of PCOM [37]. The samples in this study will be taken at any stage of the menstrual cycle; however, we anticipate that the small variation in cycle phases will not affect the diagnostic performance of the Elecsys AMH Plus assay. Furthermore, studies have shown that women with PCOS may have a higher body mass index, which could affect the precision of TVUS results [38,39]. In addition, the global COVID-19 pandemic may have caused selection bias during enrollment in the original NFBC 1986 population, although this factor applies to the entire cohort. The study results will be analyzed and interpreted in this context.

Benefits of the Study

By validating AMH levels in a large, population-based study, clinicians will be able to identify PCOM as part of PCOS diagnosis using a simple blood test. Thus, if TVUS is necessary only as a means to identify PCOM (rather than for other clinical reasons), this procedure can be replaced, thereby making the diagnosis of PCOM more accessible in a primary care setting. This would lead to much faster diagnoses for patients, as in some health care settings there would be no need to wait for referral, and only patients needing treatment for other specialized health care (eg, fertility, topical skin therapy, or psychological distress) would require referral to a specialist. This would also allow the common health impairments of the women affected to be viewed more holistically, rather than categorizing these women into an infertile population without further consideration of other adverse outcomes (eg, risk of developing type 2 diabetes mellitus or psychological distress). Testing AMH levels could also contribute to reducing missed diagnoses due to operator-dependent TVUS examinations. Following the validation of AMH levels in this study, we do not anticipate that PCOS guidelines will discard TVUS as a diagnostic method for PCOM, but rather advise that AMH testing be adopted as an alternative method.

Acknowledgments

The authors would like to thank Lotta Vuokila for coordination of the study, the study nurses and doctors for the data collection, the Northern Finland Birth Cohort staff for support, Antje Ziegler for data management support, Laura Schlieker and Chad Logan for statistical analysis and study conception support, and Anna-Maria Olziersky and Maria Schoedl for study setup and management support. We thank all study participants for the valuable resources they have offered. Third-party medical writing assistance, under the direction of the authors, was provided by Chloe Fletcher (MSc) and Pozisa Majaja (MSc) of Ashfield MedComms, an Inizio company, and was funded by Roche Diagnostics International Ltd. COBAS, COBAS PRO, and ELECSYS are trademarks of Roche. All other product names and trademarks are the property of their respective owners. This study was funded by Oulu University Hospital, the Academy of Finland (grant 321763), the Novo Nordisk Foundation (grant NNF21OC0070372), the Sigrid Jusélius Foundation, and Roche Diagnostics.

Data Availability

The data sets that will be generated or analyzed during this study will be available for academic research collaborations through the research group at the University of Oulu and the corresponding author on reasonable request. The Women's health study (WENDY) data can also be viewed [40].

Authors' Contributions

TP, DA, MH, JS, and RKA contributed to the study design and conception. TP and RKA acquired the data. TP, DA, MH, KB, JS, and RKA contributed to the data analysis and interpretation, provided critical review of the manuscript, and approved the final manuscript for submission.

Conflicts of Interest

TP received a research grant and honoraria from Roche, and fees or honoraria from Exeltis, MSD, Ferring, Gedeon Richter, and Organon. DA, JS, and MH are employees of Roche Diagnostics International Ltd. MH holds shares in F. Hoffmann-La Roche Ltd. KB is an employee of Roche Diagnostics GmbH. RKA has no competing interests.

References

1. Escobar-Morreale HF. Polycystic ovary syndrome: definition, aetiology, diagnosis and treatment. Nat Rev Endocrinol 2018;14(5):270-284. [doi: 10.1038/nrendo.2018.24] [Medline: 29569621]
2. Glintborg D, Andersen M. Medical treatment and comorbidity in polycystic ovary syndrome: an updated review. Curr Opin Endo Metabol Res 2020;12:33-40. [doi: 10.1016/j.coemr.2020.02.014]
3. Hoeger KM, Dokras A, Piltonen T. Update on PCOS: consequences, challenges, and guiding treatment. J Clin Endocrinol Metab 2021;106(3):e1071-e1083 [FREE Full text] [doi: 10.1210/clinem/dgaa839] [Medline: 33211867]
4. Balen AH, Rutherford AJ. Managing anovulatory infertility and polycystic ovary syndrome. BMJ 2007;335(7621):663-666 [FREE Full text] [doi: 10.1136/bmj.39335.462303.80] [Medline: 17901517]
5. Karjula S, Morin-Papunen L, Auvinen J, Ruokonen A, Puukka K, Franks S, et al. Psychological distress is more prevalent in fertile age and premenopausal women with PCOS symptoms: 15-year follow-up. J Clin Endocrinol Metab 2017;102(6):1861-1869 [FREE Full text] [doi: 10.1210/jc.2016-3863] [Medline: 28323926]
6. Koivuaho E, Laru J, Ojaniemi M, Puukka K, Kettunen J, Tapanainen JS, et al. Age at adiposity rebound in childhood is associated with PCOS diagnosis and obesity in adulthood-longitudinal analysis of BMI data from birth to age 46 in cases of PCOS. Int J Obes (Lond) 2019;43(7):1370-1379 [FREE Full text] [doi: 10.1038/s41366-019-0318-z] [Medline: 30718819]
7. Ollila MME, Kaikkonen K, Järvelin MR, Huikuri HV, Tapanainen JS, Franks S, et al. Self-reported polycystic ovary syndrome is associated with hypertension: a Northern Finland birth cohort 1966 study. J Clin Endocrinol Metab 2019;104(4):1221-1231 [FREE Full text] [doi: 10.1210/jc.2018-00570] [Medline: 30445634]
8. Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 2004;19(1):41-47 [FREE Full text] [doi: 10.1093/humrep/deh098] [Medline: 14688154]
9. Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, et al. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Hum Reprod 2018;33(9):1602-1618 [FREE Full text] [doi: 10.1093/humrep/dey256] [Medline: 30052961]
10. Amer SAKS, Li TC, Bygrave C, Sprigg A, Saravelos H, Cooke ID. An evaluation of the inter-observer and intra-observer variability of the ultrasound diagnosis of polycystic ovaries. Hum Reprod 2002;17(6):1616-1622 [FREE Full text] [doi: 10.1093/humrep/17.6.1616] [Medline: 12042287]
11. Bhide P, Homburg R. Anti-Müllerian hormone and polycystic ovary syndrome. Best Pract Res Clin Obstet Gynaecol 2016;37:38-45. [doi: 10.1016/j.bpobgyn.2016.03.004] [Medline: 27103234]
12. Deb S, Jayaprakasan K, Campbell BK, Clewes JS, Johnson IR, Raine-Fenning NJ. Intraobserver and interobserver reliability of automated antral follicle counts made using three-dimensional ultrasound and SonoAVC. Ultrasound Obstet Gynecol 2009;33(4):477-483 [FREE Full text] [doi: 10.1002/uog.6310] [Medline: 19212944]
13. Dewailly D, Andersen CY, Balen A, Broekmans F, Dilaver N, Fanchin R, et al. The physiology and clinical utility of anti-Müllerian hormone in women. Hum Reprod Update 2014;20(3):370-385 [FREE Full text] [doi: 10.1093/humupd/dmt062] [Medline: 24430863]
14. Lujan ME, Chizen DR, Peppin AK, Dhir A, Pierson RA. Assessment of ultrasonographic features of polycystic ovaries is associated with modest levels of inter-observer agreement. J Ovarian Res 2009;2:6 [FREE Full text] [doi: 10.1186/1757-2215-2-6] [Medline: 19515259]
15. Lujan ME, Jarrett BY, Brooks ED, Reines JK, Peppin AK, Muhn N, et al. Updated ultrasound criteria for polycystic ovary syndrome: reliable thresholds for elevated follicle population and ovarian volume. Hum Reprod 2013;28(5):1361-1368 [FREE Full text] [doi: 10.1093/humrep/det062] [Medline: 23503943]

16. Subirá J, Alberola-Rubio J, Núñez MJ, Escrivá AM, Pellicer A, Montañana V, et al. Inter-cycle and inter-observer variability of the antral follicle count in routine clinical practice. Gynecol Endocrinol 2017;33(7):515-518. [doi: 10.1080/09513590.2017.1291614] [Medline: 28277111]
17. Hillman SC, Dale J. Polycystic ovarian syndrome: an under-recognised problem? Br J Gen Pract 2018;68(670):244 [FREE Full text] [doi: 10.3399/bjgp18X696101] [Medline: 29700037]
18. Gibson-Helm M, Teede H, Dunaif A, Dokras A. Delayed diagnosis and a lack of information associated with dissatisfaction in women with polycystic ovary syndrome. J Clin Endocrinol Metab 2017;102(2):604-612 [FREE Full text] [doi: 10.1210/jc.2016-2963] [Medline: 27906550]
19. Ismayilova M, Yaya S. "I felt like she didn't take me seriously": a multi-methods study examining patient satisfaction and experiences with polycystic ovary syndrome (PCOS) in Canada. BMC Womens Health 2022;22(1):47 [FREE Full text] [doi: 10.1186/s12905-022-01630-3] [Medline: 35197027]
20. Soucie K, Samardzic T, Schramer K, Ly C, Katzman R. The diagnostic experiences of women with polycystic ovary syndrome (PCOS) in Ontario, Canada. Qual Health Res 2021;31(3):523-534. [doi: 10.1177/1049732320971235] [Medline: 33213256]
21. Tomlinson J, Pinkney J, Adams L, Stenhouse E, Bendall A, Corrigan O, et al. The diagnosis and lived experience of polycystic ovary syndrome: a qualitative study. J Adv Nurs 2017;73(10):2318-2326. [doi: 10.1111/jan.13300] [Medline: 28329428]
22. Pellatt L, Hanna L, Brincat M, Galea R, Brain H, Whitehead S, et al. Granulosa cell production of anti-Müllerian hormone is increased in polycystic ovaries. J Clin Endocrinol Metab 2007;92(1):240-245 [FREE Full text] [doi: 10.1210/jc.2006-1582] [Medline: 17062765]
23. Visser JA, de Jong FH, Laven JSE, Themmen APN. Anti-Müllerian hormone: a new marker for ovarian function. Reproduction 2006;131(1):1-9 [FREE Full text] [doi: 10.1530/rep.1.00529] [Medline: 16388003]
24. Bell RJ, Islam RM, Skiba MA, Herbert D, Martinez Garcia A, Davis SR. Substituting serum anti-Müllerian hormone for polycystic ovary morphology increases the number of women diagnosed with polycystic ovary syndrome: a community-based cross-sectional study. Hum Reprod 2021;37(1):109-118 [FREE Full text] [doi: 10.1093/humrep/deab232] [Medline: 34741176]
25. Piltonen T, Morin-Papunen L, Koivunen R, Perheentupa A, Ruokonen A, Tapanainen JS. Serum anti-Müllerian hormone levels remain high until late reproductive age and decrease during metformin therapy in women with polycystic ovary syndrome. Hum Reprod 2005;20(7):1820-1826 [FREE Full text] [doi: 10.1093/humrep/deh850] [Medline: 15802325]
26. Anand S, Kumar A, Prasad A, Trivedi K. Updated meta-analysis on the diagnostic accuracy of serum anti-Mullerian hormone in poly cystic ovary syndrome involving 13 509 subjects. J Obstet Gynaecol Res 2022;48(8):2162-2174. [doi: 10.1111/jog.15233] [Medline: 35394100]
27. Dietz de Loos A, Hund M, Buck K, Meun C, Sillman J, Laven JSE. Antimüllerian hormone to determine polycystic ovarian morphology. Fertil Steril 2021;116(4):1149-1157 [FREE Full text] [doi: 10.1016/j.fertnstert.2021.05.094] [Medline: 34579824]
28. Lie Fong S, Laven JSE, Duhamel A, Dewailly D. Polycystic ovarian morphology and the diagnosis of polycystic ovary syndrome: redefining threshold levels for follicle count and serum anti-Müllerian hormone using cluster analysis. Hum Reprod 2017;32(8):1723-1731 [FREE Full text] [doi: 10.1093/humrep/dex226] [Medline: 28854584]
29. Moolhuijsen LME, Visser JA. AMH in PCOS: controlling the ovary, placenta, or brain? Curr Opin Endocr Metab Res 2020;12:91-97 [FREE Full text] [doi: 10.1016/j.coemr.2020.04.006]
30. Piltonen TT, Komsi E, Morin-Papunen LC, Korhonen E, Franks S, Järvelin MR, et al. AMH as part of the diagnostic PCOS workup in large epidemiological studies. Eur J Endocrinol 2023;188(6):547-554 [FREE Full text] [doi: 10.1093/ejendo/lvad065] [Medline: 37294941]
31. Teede H, Misso M, Tassone EC, Dewailly D, Ng EH, Azziz R, et al. Anti-Müllerian hormone in PCOS: a review informing international guidelines. Trends Endocrinol Metab 2019;30(7):467-478 [FREE Full text] [doi: 10.1016/j.tem.2019.04.006] [Medline: 31160167]
32. Teede H, Misso M, Costello M, Dokras A, Laven J, Moran L, on behalf of the International PCOS Network. International evidence-based guideline for the assessment and management of polycystic ovary syndrome. Monash University on behalf of the NHMRC, Centre for Research Excellence in PCOS and the Australian PCOS Alliance 2018. Melbourne, VIC, Australia; 2018. URL: https://www.monash.edu/__data/assets/pdf_file/0004/1412644/PCOS_Evidence-Based-Guidelines_20181009.pdf [accessed 2023-12-06]
33. Dréno B, Poli F, Pawin H, Beylot C, Faure M, Chivot M, et al. Development and evaluation of a Global Acne Severity Scale (GEA Scale) suitable for France and Europe. J Eur Acad Dermatol Venereol 2011;25(1):43-48. [doi: 10.1111/j.1468-3083.2010.03685.x] [Medline: 20456560]
34. Method sheet: elecsys AMH plus. Roche Diagnostics GmbH. Mannheim, Germany; 2021.
35. Biniasch M, Laubender RP, Hund M, Buck K, De Geyter C. Intra- and inter-cycle variability of anti-Müllerian hormone (AMH) levels in healthy women during non-consecutive menstrual cycles: the BICYCLE study. Clin Chem Lab Med 2021;60(4):597-605 [FREE Full text] [doi: 10.1515/cclm-2021-0698] [Medline: 34717057]

36. Piltonen T, Komsi R, Morin-Papunen L, Korhonen E, Franks S, Järvelin MR, et al. AMH as a surrogate for PCOM: the usability of biological variables to diagnose PCOS in a population-based data set [Abstract no. O14]. 2022 Presented at: Paula Rantakallio Symposium on Birth Cohorts and Longitudinal Studies; June 15-17; Oulu, Finland.
37. Lim SS, Davies MJ, Norman RJ, Moran LJ. Overweight, obesity and central obesity in women with polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod Update 2012;18(6):618-637 [FREE Full text] [doi: 10.1093/humupd/dms030] [Medline: 22767467]
38. Moorthy RS. Transvaginal sonography. Med J Armed Forces India 2000;56(3):181-183. [doi: 10.1016/s0377-1237(17)30160-0]
39. Piltonen TT, Arffman RK, Joham AE. Natural history of polycystic ovary syndrome and new advances in the epidemiology. Semin Reprod Med 2021;39(3-04):94-101. [doi: 10.1055/s-0041-1735211] [Medline: 34464984]
40. Women's health study (WENDY) - a protocol of a population-based study assessing gynecological and metabolic health in women. University of Oulu. URL: https://www.oulu.fi/en/university/faculties-and-units/faculty-medicine/northern-finland-birth-cohorts-and-arctic-biobank/womens-health-study [accessed 2024-01-12]

Abbreviations

AFC: antral follicle count
AMH: anti-Müllerian hormone
HA: hyperandrogenism
HARMONIA: Human Anti-Müllerian Hormone for Diagnosis of PCOS
NFBC: Northern Finland Birth Cohort
OA: oligoanovulation or anovulation
PCOM: polycystic ovarian morphology
PCOS: polycystic ovary syndrome
TVUS: transvaginal ultrasound

Edited by A Mavragani; submitted 09.05.23; peer-reviewed by M Forslund, J Melin, E Elenis; comments to author 21.09.23; revised version received 10.11.23; accepted 23.11.23; published 06.02.24.

Please cite as:
Piltonen TT, Allegranza D, Hund M, Buck K, Sillman J, Arffman RK
Validation of an Anti-Müllerian Hormone Cutoff for Polycystic Ovarian Morphology in the Diagnosis of Polycystic Ovary Syndrome in the HARMONIA Study: Protocol for a Prospective, Noninterventional Study
JMIR Res Protoc 2024;13:e48854
URL: https://www.researchprotocols.org/2024/1/e48854
doi:10.2196/48854
PMID:38319689

Protocol

Let's Agree to Disagree on Operative Versus Nonoperative Treatment for Distal Radius Fractures in Older People: Protocol for a Prospective International Multicenter Cohort Study

Nicole Maria van Veelen[1,2], Dr med; Bryan J M van de Wall[1,2], MD, PhD; Ruben J Hoepelman[3], MD; Frank F A IJpma[4], MD, PhD; Björn-Christian Link[1], PD, Dr med; Reto Babst[1,2], Prof Dr Med; Rolf H H Groenwold[5], PhD; Detlef van der Velde[6], MD, PhD; Nadine Diwersi[7], Dr Med; Mark van Heijl[8], MD, PhD; R Marijn Houwert[3], MD, PhD; Frank J P Beeres[1,2], Prof Dr

[1]Department of Orthopaedic and Trauma Surgery, Luzerner Kantonsspital, Luzern, Switzerland
[2]Department of Health Sciences and Medicine, University of Lucerne, Luzern, Switzerland
[3]Department of Trauma Surgery, Universitair Medisch Centrum Utrecht, Utrecht, Netherlands
[4]Department of Trauma Surgery, Universitair Medisch Centrum Groningen, Groningen, Netherlands
[5]Department of Clinical Epidemiology, Universitair Medisch Centrum Leiden, Leiden, Netherlands
[6]Department of Trauma Surgery, St. Antonius Ziekenhuis, Utrecht, Netherlands
[7]Department of General and Trauma Surgery, Kantonsspital Obwalden, Sarnen, Switzerland
[8]Department of Surgery, Diakonessenhuis Utrecht, Utrecht, Netherlands

Corresponding Author:
Nicole Maria van Veelen, Dr med
Department of Orthopaedic and Trauma Surgery
Luzerner Kantonsspital
Spitalstrasse
Luzern, 6000
Switzerland
Phone: 41 412054770
Email: nicole.vanveelen@luks.ch

Abstract

Background: Distal radius fractures are the most frequently encountered fractures in Western societies, typically affecting patients aged 50 years and older. Although this is a common injury, the best treatment for these fractures in older patients is still under debate.

Objective: This prospective study aims to compare the outcome of operatively and nonoperatively treated distal radius fractures in the older population. Only patients with distal radius fractures for which equipoise regarding the optimal treatment exists will be included.

Methods: This prospective international multicenter observational cohort study will be designed as a natural experiment. Natural experiments are observational studies in which treatment allocation is determined by factors outside the control of the investigators but also (largely) independent of patient characteristics. Patients aged 65 years and older with an acute distal radius fracture will be considered for inclusion. Treatment allocation (operative vs nonoperative) will be based on the local preferences of the treating hospital either in Switzerland or the Netherlands. Hence, the process governing treatment allocation resembles that of randomization. Patients will be identified after treatment has been initiated. Based on the radiographs and baseline information of the patient, an expert panel of 6 certified trauma surgeons from 2 regions will provide their treatment recommendation. Only patients for whom the experts disagree on treatment recommendations will ultimately be included in the study (ie, for whom there is a clinical equipoise). For these patients, both operative and nonoperative treatment of distal radius fractures are viable, and treatment choice is predominantly determined by personal or local preference. The primary outcome will be the Patient-Rated Wrist Evaluation score at 12 weeks. Secondary outcomes will include the Physical Activity Score for the Elderly, the EQ questionnaire, pain, the living situation, range of motion, complications, and radiological outcomes. By including outcomes such as living situation and the Physical Activity Score for the Elderly, which are not relevant for younger cohorts, valuable information to tailor treatment to the needs of the older population can be gained. According to the sample size collection, which was based on the minimal

important clinical difference of the Patient-Rated Wrist Evaluation, 92 patients will have to be included, with at least 46 patients in each treatment group.

Results: Enrollment began in July 2023 and is expected to continue until summer 2024. The final follow-up will be 2 years after the last patient is included.

Conclusions: Although many trials on this topic have previously been published, there remains an ongoing debate regarding the optimal treatment for distal radius fractures in older patients. This observational study, which will use a fairly new methodological study design, will provide further information on treatment outcomes for older patients with distal radius fractures for which to date equipoise exists regarding the optimal treatment.

International Registered Report Identifier (IRRID): DERR1-10.2196/52917

(JMIR Res Protoc 2024;13:e52917) doi:10.2196/52917

KEYWORDS

distal radius fracture; older patients; natural experiment; study protocol; observational study

Introduction

Distal radius fractures are the most common fractures encountered in Western societies, and they typically occur in patients aged 50 years and older [1,2]. Despite being so common, there remains an ongoing discussion on the best treatment for these fractures, especially in older patients, ranging from nonoperative treatment to complex surgery [3].

Previous studies have used varying definitions of "older people" and based this only on chronological age. However, the spectrum of physical demands and capabilities is wide among patients of the same age, which will likely be reflected in the satisfaction and outcome after treatment of distal radius fractures. Additionally, even frail patients may rely on a good function of the wrist to maintain independence if they, for example, require walking aids, and therefore need to fully weight bear on the upper extremity.

This study aims to compare the outcome of operatively and nonoperatively treated distal radius fractures in the older population by evaluating functional and radiological outcomes as well as range of movement, quality of life, and change in independence or living situation. By evaluating the quality of life and patient independency or living situation, we aim to gain more insight into outcomes after distal radius fracture in older patients while considering their individual functional demands.

Therefore, we have designed this study as a prospective international multicenter cohort study in which only patients with distal radius fractures for which equipoise regarding the optimal treatment exists will be included. The primary objective will be to compare clinical outcomes between older patients with distal radius fracture treated operatively and those treated nonoperatively.

Methods

Study Design

Although randomized controlled trials are generally considered the gold standard to investigate the effects of medical treatments, both patients and surgeons can have a strong preference for a certain treatment, which may limit the feasibility of a randomized controlled trial and therefore the generalizability of its results [4,5]. Provided possible incomparability of patients who receive different treatment modalities (ie, confounding) is adequately controlled for, observational studies could provide an alternative source of information.

A natural experiment design uses existing variation in treatment allocation (eg, due to practice variation). Natural experiments are observational studies in which treatment allocation is determined by factors outside the control of the investigators but also (to a large extent) independent of patient characteristics [6,7]. We assume the decisions regarding the treatment of distal radius fractures are largely influenced by the training of the treating surgeons. Since patients with a distal radius fracture generally visit the nearest hospital, treatment allocation is dependent on which surgeon is on call, which is likely independent on patient characteristics. Hence, the process governing treatment allocation arguably resembles that of randomization. Practice variation therefore provides an opportunity to conduct a natural experiment of the effect of operative versus nonoperative treatment of distal radius fractures. In order to further minimize the influence of patient characteristics on treatment decisions, a selection could be made of those patients for whom a panel of physicians disagree regarding the preferred treatment option (ie, for whom there clearly is a clinical equipoise). For these patients, both operative and nonoperative treatment of distal radius fractures are viable, and treatment choice is predominantly determined by personal or local preference.

This study is an international multicenter prospective observational cohort study for which patients will be identified after treatment has been initiated. Outcome data will be prospectively collected. Patients will be recruited from 5 hospitals in countries with a predominant preference for operative (Switzerland) and nonoperative treatment (the Netherlands).

Patient Population

Local investigators will review the list of patients seen in the emergency departments of the participating hospitals to identify eligible patients. The inclusion criteria are all patients 65 years and older with an acute (<14 days after injury) distal radius fracture treated at one of the participating hospitals.

The exclusion criteria are no informed consent provided; patients transferred after initial operative treatment at a nonparticipating hospital; delayed presentation (>14 days after injury); insufficient follow-up (<12 months) or unavailable to follow-up due to residency in other hospital area; concomitant injury to the ipsilateral or contralateral upper extremity; cognitive impairment precluding answering questionnaires; non-German, non-English, and non-Dutch speaking; preexisting comorbidities that preclude operative treatment; pathological fractures; open fractures; and neurovascular injury requiring operative treatment.

Ethical Considerations

This study was approved by the ethics committee of Northwest and Central Switzerland (ID 2022-00142). It will be conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. The study has been registered on ClinicalTrials.gov (ID NCT05631314). The protocol was written in adherence to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guideline. A signed informed consent form is required prior to patient inclusion. The patients will be informed about the aim, content, and requirements of the study by the study leader or delegate either during an initial presentation or at a routine outpatient clinic appointment and will receive an information and consent form. The patients will be given the opportunity to ask questions and clarify any issues prior to giving their consent. No compensation or payments will be provided to project participants. Project data will be handled with the utmost discretion. They will be coded and a file to decode these data will be saved in the research folder only accessible by the principal investigator and project leaders.

Expert Panel

Following the identification of eligible patients and obtainment of informed consent, anonymous radiographs including key images of computer tomography scans if available, and baseline characteristics including information regarding comorbidities and activity levels (details below) will be made available on a secure web-based platform. This will allow the members of the panel to reach a "clinical" decision regarding their treatment recommendation. The panel will be blinded to the actual treatment received and the origin of the case.

The comorbidities, which will be reported to the experts, are cardiomyopathy including valvular disease, history of stroke or other brain injury with persistent neurological deficit, diabetes mellitus, cardiovascular disease, active malignancy, rheumatoid arthritis, and history of alcohol or drug abuse.

Additionally, the experts will be provided with information regarding the usage of the following medications: anticoagulant agents (vitamin K antagonists and new oral anticoagulants), immunosuppressants, and current chemotherapy.

The activity levels are independent, independent with support from family or district nurse or nursing home, and use of a walking aid prior to injury (no, walking stick, frame, and not mobile).

The expert panel will consist of 3 representatives from each "school." All panel members will be certified trauma surgeons. Half of them are generally in favor of conservative treatment ("school A"), while the others are generally in favor of operative treatment ("school B"). Patients will ultimately be included in the study if clinical equipoise is achieved, meaning 2 or more of the experts disagree with the rest of the panel. This is expected to result in 2 comparable groups for which clinical equipoise exists. The actual treatment the patient receives will continue as initially planned by the treating physician (see below).

Intervention

The decision whether operative or nonoperative treatment is chosen is left to the treating trauma surgeon as per the local standard of the participating hospital. Treatment will be initiated before the patient is approached for recruitment. Nonoperative treatment will consist of immobilization in a below the elbow cast for 4-6 weeks with or without prior closed reduction.

Operative intervention will be based on the treating surgeon's experience and preference. It will consist of open reduction and internal plate fixation using volar, dorsal, spanning or a combination of plates, or reduction (open or closed) and fixation with an external fixator with or without Kirschner wires. The participating hospitals in Switzerland will use the 2.4-mm distal radius plate system (Arthrex) for internal plate fixation. Perioperative management including anesthesia, antibiotics, and thromboembolism prophylaxis will follow the national guidelines. Postoperative care and immobilization will be decided by the treating surgeon. When possible, functional aftercare without immobilization will be allowed. Physiotherapy will be provided according to the local standards.

All patients (operative and nonoperative) will be reviewed in the outpatient clinic at 6 and 12 weeks as well as 1 year after treatment or surgery. In addition, patients will be contacted by phone 2 years after treatment or surgery.

Outcomes

Primary Outcome Measure

The primary outcome is the Patient-Rated Wrist Evaluation (PRWE) score measured at 12 weeks. This is a 15-item questionnaire that measures wrist pain and disability in activities of daily living. The score ranges from 0 to 100 with the best score being 0 [8,9].

Secondary Outcome Measures

Functional Outcome

Secondary functional outcome measures will include the PRWE at 1 year, Physical Activity Score for the Elderly, the Numerical Rating Scale for pain, and the EQ-5D-5L questionnaire. The Physical Activity Score for the Elderly is a questionnaire with multiple choice and open questions. The score combines information on household, leisure, and occupational activities. Based on duration, frequency, and intensity level of activities performed the previous week, a score is calculated ranging from 0 to 793, with higher scores reflecting more physical activity [10]. The EQ-5D-5L questionnaire is a questionnaire that measures general health status, with higher scores reflecting a better quality of life. It is based on 5 dimensions (mobility,

self-care, usual activities, pain or discomfort, and anxiety or depression), which are rated on a scale with 5 levels. It also includes the EQ visual analogue scale for patients to state their self-rated health on a scale from 0 to 100, with 0 being the worst health imaginable [11]. The Numerical Rating Scale is a widely used scale to measure pain intensity, ranging from 0 (no pain) to 10 (worst pain imaginable) [4]. The living situation will be assessed at the first presentation, 6 weeks, 12 weeks, 1 year, and 2 years after injury. It will be defined as independent, independent with support from family, district nurse or similar, and nursing home. Range of motion of the wrist (dorsal extension, palmar-flexion, ulnar-, radial-abduction, pro-, and supination) as well as the finger-palm-distance will be assessed 12 weeks after injury. Additionally, the duration of surgery and the occurrence of intraoperative complications will be documented.

Complications

Complications will be assessed at every outpatient visit and after 2 years. They will include infection, nonunion, implant failure, complex regional pain syndrome, and any adverse event needing surgical intervention. For patients treated surgically, the need for implant removal will also be recorded. Infections will be defined according to the guidelines of The Centers for Disease Control and Prevention and subdivided into superficial incisional and deep infections. Deep infections will include both deep incisional and organ or space infections [5]. The diagnosis of complex regional pain syndrome is based on the Budapest clinical diagnostic criteria [12]. Nonunion is defined as a Radius union scoring system score greater than or equal to 6. It will be assessed 1 year after injury. The RUSS score evaluates union on dorso-volar and lateral radiographs by assigning a score of 0 to 2 on each cortex. Zero points are given if the fracture line is visible with no callus, 1 point if a callus is present but the fracture line is still visible, and 2 points if the fracture line is not visible and a bridging callus is present. In surgically treated cases, where the cortex is not visible due to the implant, a score of 0 is given to that cortex [13]. In case of doubt with regard to union, a computer tomography scan will be acquired. Patients with nonunion will be divided into 2 groups based on their symptoms (symptomatic vs asymptomatic).

Radiological Outcome

X-rays will be obtained as per standard hospital protocol at 6 and 12 weeks as well as 1 year after injury. The final radiological outcome will be determined 1 year after injury and will include union, radial inclination, volar tilt, carpal alignment, ulnar variance, and the presence and size of any step or gap in the articular surface.

Timeline and Recruitment

The recruitment procedure is visualized in Figure 1. The follow-up schedule for the patients and time point for the assessment of each outcome are listed in Table 1.

Figure 1. Flowchart of Patient Selection.

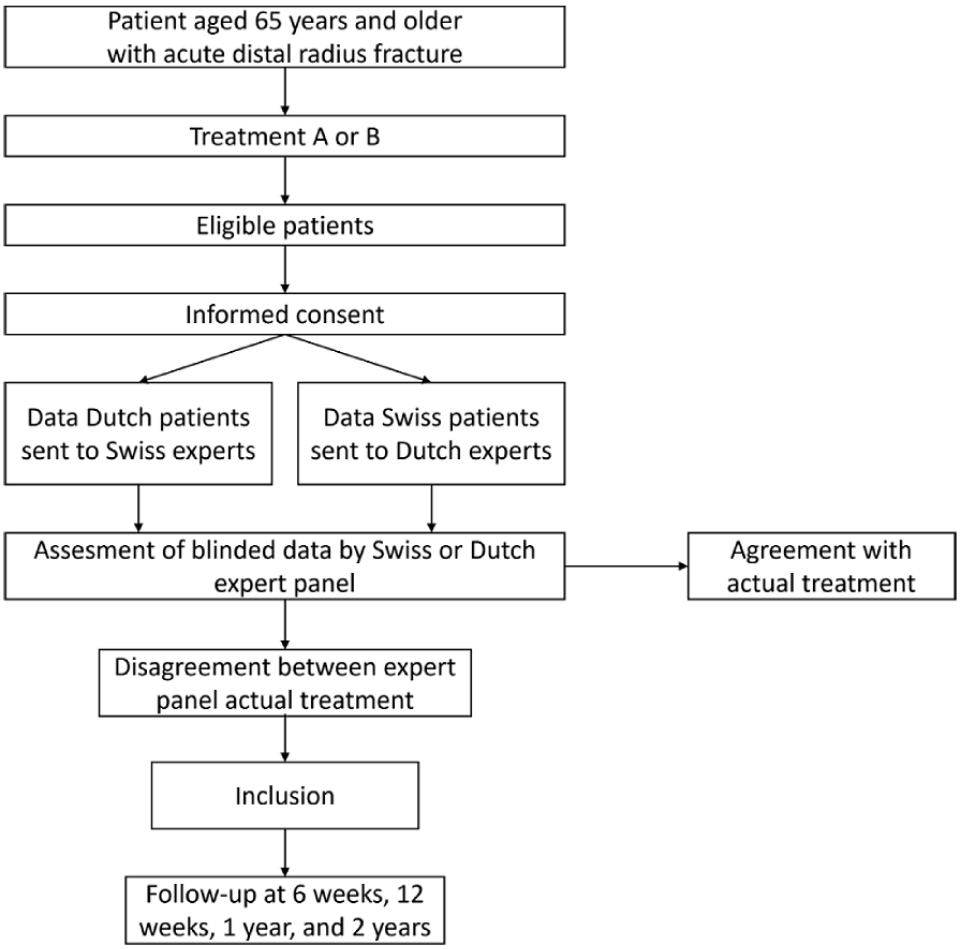


Table 1. Outcome measures.

	First presentation	6 weeks	12 weeks	1 year	2 years
Outpatient clinic		✓	✓	✓	
X-ray	✓	✓			
PRWE[a]	✓		✓	✓	✓
PASE[b]	✓		✓	✓	✓
NRS[c] pain		✓	✓	✓	✓
ROM[d]			✓		
EQ-5D-5L	✓		✓	✓	✓
Complications		✓	✓	✓	✓
Living situation	✓	✓	✓	✓	

[a]PRWE: Patient-Rated Wrist Evaluation.

[b]PASE: Physical Activity Score for the Elderly.

[c]NRS: Numerical Rating Scale.

[d]ROM: range of movement.

Data Collection

In every participating institution, a project leader will fill in all the patient information in the secure web-based database on REDCap (Research Electronic Data Capture; Vanderbilt University). The original data will be collected from the institution's electronic patient records, the picture archiving and communication system, the different questionnaires, and pseudonymized prior to entry in the database.

Health care workers from the participating institutions will get access to REDCap, which enables centralized tracking of potentially eligible patients in compliance with the good clinical practice guidelines for electronic data collection. Every 2-4 weeks, this list of patients will be screened by the project leader, and explanatory and response variables will be entered on the study website. All data will be saved in a research folder that can only be accessed by the principal investigator and the project leader or leaders.

Sample Size Calculation

This study will be a noninferiority study, for which we assume that conservative treatment in older patients with a distal radius fracture is noninferior to operative treatment. The reason for choosing a noninferiority design is as follows. Operative treatment for distal radius fractures inherently exposes patients to additional risks of operation-related complications and costs. This is not the case for conservative treatment. If the study would demonstrate that both treatments are equal with regard to the primary outcome, it would automatically imply that patients should be treated with the lesser invasive treatment of the 2 (in this case, conservative treatment).

The sample size is based on the minimal important clinical difference of the PRWE score, which is 11.5 points (with an average SD 14). Using the minimal important clinical difference (11.5 points) as the noninferiority margin, a statistical significance threshold (α) of 5%, and a power of 90%, 32 patients per group are needed [14]. Taking into account a 30% loss to follow-up (due to the considerable age of the included study population), a total of 92 patients will have to be included, with at least 46 patients in each treatment group.

Statistical Analysis

The statistical software package SPSS (IBM Corp) will be used for analysis. All analyses will be performed according to the intention-to-treat principle. Multiple imputation will be used for missing values. Depending on their distribution, baseline characteristics will be described as means and SDs or median and IQR for continuous variables. Categorical variables will be reported as counts and percentages. Treatment groups will be compared using an independent Student *t* test (2-tailed) or chi-square test, as appropriate.

The primary outcome will be analyzed using a regression analysis with the 12 weeks PRWE score as dependent and treatment as independent variable. Potential confounders (notably age and fracture type) will be included as covariates in the model. Regression coefficients will be calculated with corresponding 95% CI. Regression analysis will also be used for analyzing the secondary outcomes with correction for the previously mentioned confounders.

Results

Patient enrollment started both in the Netherlands and Switzerland in July 2023. To date, 23 patients have given their consent in Switzerland and 59 in the Netherlands. The results of the first expert panel decisions are currently pending. Depending on the rate of equipoise, enrollment is expected to be completed after approximately 1 year. The final follow-up will be 2 years after the inclusion of the last patient.

Discussion

Despite many trials on this topic, the optimal treatment for distal radius fractures in older patients remains debated, and regional preferences continue to influence the treatment chosen. This

provides the perfect situation to perform a natural experiment [6]. The Let's Agree to Disagree on Operative Versus Nonoperative radius study is a prospective international multicenter cohort study that will use a fairly new methodological study design [6]. One of the main benefits of this study design is that patients will be treated as per the local standards. We expect this to lead to high participation rates and prevent the negative effects of a learning curve. By limiting inclusion to those patients, for whom the expert panel disagrees on the treatment method, only those cases in which equipoise is attained are evaluated. We anticipate the 2 patient groups to be comparable as natural randomization based on geographical location will occur. Therefore, confounding is expected to be minimal. Additionally, multivariable analysis will be performed.

Many studies on the treatment of distal radius fractures in older patients have been published and yet no sound conclusion can be drawn. While some authors demonstrated a benefit of volar plating, others were unable to show a difference in functional outcomes between operative and nonoperative treatment [15-19]. Previous studies examined functional outcome based on patient-reported outcome measurements such as the PRWE score or Disabilities of the Arm, Shoulder, and Hand score. None of the studies used a score derived specifically for the older population or evaluated changes in independence or living situation despite the fact that these are very relevant issues for older patients. Additionally, information on the quality of life after treatment is lacking. This study aims to compare the outcome of surgically and nonoperatively treated distal radius fractures in older patients by not only evaluating functional and radiological outcomes but also quality of life and change in independency or living situation. Furthermore, a functional score that was specifically designed to assess the physical activity level of older patients will be used.

One limitation of this study to consider is the relatively new study design. The ratio of opposing opinions among the expert panel to define equipoise was set at 2:4. One could argue that a ratio of 1:5 or 3:3 might be a better choice. A previous study performed with ethical committee members examined which proportion of agreement on the merit of a new treatment was perceived by the members as ethically justifiable to perform a trial investigating the new treatment. This study showed a distribution of 1:4 to suffice for the members to deem the trial ethically justifiable [20]. Based on the findings of that study in combination with an equal number of experts from both regions, the ratio of 2:4 was chosen for this study.

In conclusion, this observational study, designed as a natural study, will provide valuable information on treatment outcomes for those older patients with distal radius fractures for which to date equipoise exists regarding the optimal treatment. By evaluating outcomes pertinent to the older population, such as quality of life and changes in living situation or independence, this study will help tailor treatment to the specific needs of older patients.

Acknowledgments

This project is partially funded by Arthrex GmbH, Munich, Germany. This work is part of the activities of the Natural Experiments Study Group [21].

Conflicts of Interest

None declared.

References

1. Bergh C, Wennergren D, Möller M, Brisby H. Fracture incidence in adults in relation to age and gender: a study of 27,169 fractures in the Swedish Fracture Register in a well-defined catchment area. PLoS One 2020;15(12):e0244291 [FREE Full text] [doi: 10.1371/journal.pone.0244291] [Medline: 33347485]
2. Rundgren J, Bojan A, Navarro CM, Enocson A. Epidemiology, classification, treatment and mortality of distal radius fractures in adults: an observational study of 23,394 fractures from the National Swedish Fracture Register. BMC Musculoskelet Disord 2020;21(1):88 [FREE Full text] [doi: 10.1186/s12891-020-3097-8] [Medline: 32035488]
3. Ansari U, Adie S, Harris IA, Naylor JM. Practice variation in common fracture presentations: a survey of orthopaedic surgeons. Injury 2011;42(4):403-407. [doi: 10.1016/j.injury.2010.11.011] [Medline: 21163480]
4. Ferreira-Valente MA, Pais-Ribeiro JL, Jensen MP. Validity of four pain intensity rating scales. Pain 2011;152(10):2399-2404. [doi: 10.1016/j.pain.2011.07.005] [Medline: 21856077]
5. Anderson DJ, Podgorny K, Berríos-Torres SI, Bratzler DW, Dellinger EP, Greene L, et al. Strategies to prevent surgical site infections in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol 2014;35(6):605-627 [FREE Full text] [doi: 10.1086/676022] [Medline: 24799638]
6. van de Wall BJM, Stadhouder A, Houwert RM, Oner FC, Beeres FJ, Groenwold RHH, NEXT Study Group. Natural experiments for orthopaedic trauma research: an introduction. Injury 2023;54(2):429-434 [FREE Full text] [doi: 10.1016/j.injury.2022.11.028] [Medline: 36402587]
7. Hoepelman RJ, Ochen Y, Beeres FJP, Frima H, Sommer C, Michelitsch C, et al. Let's Agree to Disagree on Operative versus Nonoperative (LADON) treatment for proximal humerus fractures: study protocol for an international multicenter prospective cohort study. PLoS One 2022;17(2):e0264477 [FREE Full text] [doi: 10.1371/journal.pone.0264477] [Medline: 35213647]

8. Kleinlugtenbelt YV, Krol RG, Bhandari M, Goslings JC, Poolman RW, Scholtes VAB. Are the Patient-Rated Wrist Evaluation (PRWE) and the Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire used in distal radial fractures truly valid and reliable? Bone Joint Res 2018;7(1):36-45 [FREE Full text] [doi: 10.1302/2046-3758.71.BJR-2017-0081.R1] [Medline: 29330342]
9. MacDermid JC, Turgeon T, Richards RS, Beadle M, Roth JH. Patient rating of wrist pain and disability: a reliable and valid measurement tool. J Orthop Trauma 1998;12(8):577-586. [doi: 10.1097/00005131-199811000-00009] [Medline: 9840793]
10. Washburn RA, Smith KW, Jette AM, Janney CA. The Physical Activity Scale for the Elderly (PASE): development and evaluation. J Clin Epidemiol 1993;46(2):153-162. [doi: 10.1016/0895-4356(93)90053-4] [Medline: 8437031]
11. Herdman M, Gudex C, Lloyd A, Janssen MF, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20(10):1727-1736 [FREE Full text] [doi: 10.1007/s11136-011-9903-x] [Medline: 21479777]
12. Harden NR, Bruehl S, Perez RSGM, Birklein F, Marinus J, Maihofner C, et al. Validation of proposed diagnostic criteria (the "Budapest Criteria") for complex regional pain syndrome. Pain 2010;150(2):268-274 [FREE Full text] [doi: 10.1016/j.pain.2010.04.030] [Medline: 20493633]
13. Patel SP, Anthony SG, Zurakowski D, Didolkar MM, Kim PS, Wu JS, et al. Radiographic scoring system to evaluate union of distal radius fractures. J Hand Surg Am 2014;39(8):1471-1479. [doi: 10.1016/j.jhsa.2014.05.022] [Medline: 24996677]
14. Walenkamp MMJ, de Muinck Keizer RJ, Goslings JC, Vos LM, Rosenwasser MP, Schep NWL. The minimum clinically important difference of the patient-rated wrist evaluation score for patients with distal radius fractures. Clin Orthop Relat Res 2015;473(10):3235-3241 [FREE Full text] [doi: 10.1007/s11999-015-4376-9] [Medline: 26040969]
15. Martinez-Mendez D, Lizaur-Utrilla A, de-Juan-Herrero J. Intra-articular distal radius fractures in elderly patients: a randomized prospective study of casting versus volar plating. J Hand Surg Eur Vol 2018;43(2):142-147. [doi: 10.1177/1753193417727139] [Medline: 28870129]
16. Saving J, Wahlgren SS, Olsson K, Enocson A, Ponzer S, Sköldenberg O, et al. Nonoperative treatment compared with volar locking plate fixation for dorsally displaced distal radial fractures in the elderly: a randomized controlled trial. J Bone Joint Surg Am 2019;101(11):961-969. [doi: 10.2106/JBJS.18.00768] [Medline: 31169572]
17. Arora R, Lutz M, Deml C, Krappinger D, Haug L, Gabl M. A prospective randomized trial comparing nonoperative treatment with volar locking plate fixation for displaced and unstable distal radial fractures in patients sixty-five years of age and older. J Bone Joint Surg Am 2011;93(23):2146-2153. [doi: 10.2106/JBJS.J.01597] [Medline: 22159849]
18. Ju JH, Jin GZ, Li GX, Hu HY, Hou RX. Comparison of treatment outcomes between nonsurgical and surgical treatment of distal radius fracture in elderly: a systematic review and meta-analysis. Langenbecks Arch Surg 2015;400(7):767-779. [doi: 10.1007/s00423-015-1324-9] [Medline: 26318178]
19. Combined Randomised and Observational Study of Surgery for Fractures in the Distal Radius in the Elderly (CROSSFIRE) Study Group, Lawson A, Naylor JM, Buchbinder R, Ivers R, Balogh ZJ, et al. Surgical plating vs closed reduction for fractures in the distal radius in older patients: a randomized clinical trial. JAMA Surg 2021;156(3):229-237 [FREE Full text] [doi: 10.1001/jamasurg.2020.5672] [Medline: 33439250]
20. Mhaskar R, Bercu BB, Djulbegovic B. At what level of collective equipoise does a randomized clinical trial become ethical for the members of institutional review board/ethical committees? Acta Inform Med 2013;21(3):156-159 [FREE Full text] [doi: 10.5455/aim.2013.21.156-159] [Medline: 24167382]
21. NEXT study group. URL: https://www.next-studygroup.org/ [accessed 2024-01-05]

Abbreviations

PRWE: Patient-Rated Wrist Evaluation
REDCap: Research Electronic Data Capture
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trial

Edited by A Mavragani; submitted 27.09.23; peer-reviewed by M Hogervorst, JB Jupiter; comments to author 05.11.23; revised version received 11.12.23; accepted 11.12.23; published 13.02.24.

Please cite as:
van Veelen NM, van de Wall BJM, Hoepelman RJ, IJpma FFA, Link BC, Babst R, Groenwold RHH, van der Velde D, Diwersi N, van Heijl M, Houwert RM, Beeres FJP
Let's Agree to Disagree on Operative Versus Nonoperative Treatment for Distal Radius Fractures in Older People: Protocol for a Prospective International Multicenter Cohort Study
JMIR Res Protoc 2024;13:e52917
URL: https://www.researchprotocols.org/2024/1/e52917
doi:10.2196/52917
PMID:38349719

Protocol

Genomic, Proteomic, and Phenotypic Biomarkers of COVID-19 Severity: Protocol for a Retrospective Observational Study

Andrew English[1,2], PhD; Darren McDaid[1], BSc; Seodhna M Lynch[1], PhD; Joseph McLaughlin[1], PhD; Eamonn Cooper[1], BSc; Benjamin Wingfield[1], PhD; Martin Kelly[3], MD; Manav Bhavsar[3], MD; Victoria McGilligan[1], PhD; Rachelle E Irwin[1], PhD; Magda Bucholc[1], PhD; Shu-Dong Zhang[1], PhD; Priyank Shukla[1], PhD; Taranjit Singh Rai[1], PhD; Anthony J Bjourson[1], PhD; Elaine Murray[1], PhD; David S Gibson[1], BSc, PhD; Colum Walsh[4], PhD

[1]Personalised Medicine Centre, School of Medicine, Ulster University, Derry/Londonderry, United Kingdom

[2]National Horizons Centre, Teesside University, Middlesbrough, United Kingdom

[3]Western Health Social Care Trust, Londonderry, United Kingdom

[4]Department of Biomedical and Clinical Sciences, Linköping University, Uppsala, Sweden

Corresponding Author:
David S Gibson, BSc, PhD
Personalised Medicine Centre, School of Medicine, Ulster University
C-TRIC Building, Altnagelvin Area Hospital
Glenshane Road
Derry/Londonderry, BT47 6SB
United Kingdom
Phone: 44 028 7161 1249
Email: d.gibson@ulster.ac.uk

Abstract

Background: Health organizations and countries around the world have found it difficult to control the spread of COVID-19. To minimize the future impact on the UK National Health Service and improve patient care, there is a pressing need to identify individuals who are at a higher risk of being hospitalized because of severe COVID-19. Early targeted work was successful in identifying angiotensin-converting enzyme-2 receptors and type II transmembrane serine protease dependency as drivers of severe infection. Although a targeted approach highlights key pathways, a multiomics approach will provide a clearer and more comprehensive picture of severe COVID-19 etiology and progression.

Objective: The COVID-19 Response Study aims to carry out an integrated multiomics analysis to identify biomarkers in blood and saliva that could contribute to host susceptibility to SARS-CoV-2 and the development of severe COVID-19.

Methods: The COVID-19 Response Study aims to recruit 1000 people who recovered from SARS-CoV-2 infection in both community and hospital settings on the island of Ireland. This protocol describes the retrospective observational study component carried out in Northern Ireland (NI; Cohort A); the Republic of Ireland cohort will be described separately. For all NI participants (n=519), SARS-CoV-2 infection has been confirmed by reverse transcription-quantitative polymerase chain reaction. A prospective Cohort B of 40 patients is also being followed up at 1, 3, 6, and 12 months postinfection to assess longitudinal symptom frequency and immune response. Data will be sourced from whole blood, saliva samples, and clinical data from the electronic care records, the general health questionnaire, and a 12-item general health questionnaire mental health survey. Saliva and blood samples were processed to extract DNA and RNA before whole-genome sequencing, RNA sequencing, DNA methylation analysis, microbiome analysis, 16S ribosomal RNA gene sequencing, and proteomic analysis were performed on the plasma. Multiomics data will be combined with clinical data to produce sensitive and specific prognostic models for severity risk.

Results: An initial demographic and clinical profile of the NI Cohort A has been completed. A total of 249 hospitalized patients and 270 nonhospitalized patients were recruited, of whom 184 (64.3%) were female, and the mean age was 45.4 (SD 13) years. High levels of comorbidity were evident in the hospitalized cohort, with cardiovascular disease and metabolic and respiratory disorders being the most significant (P<.001), grouped according to the International Classification of Diseases 10 codes.

Conclusions: This study will provide a comprehensive opportunity to study the mechanisms of COVID-19 severity in recontactable participants.

International Registered Report Identifier (IRRID): DERR1-10.2196/50733

(JMIR Res Protoc 2024;13:e50733) doi:10.2196/50733

KEYWORDS

COVID-19; clinical research; multiomics; comorbidity; severity; electronic health record

Introduction

Background

COVID-19 has a wide spectrum of clinical severity, with approximately 60% of cases thought to be asymptomatic or mildly symptomatic and approximately 5% being critically ill [1]. A severe infection is characterized by respiratory and multiorgan failure [2]. There are several known demographic risk factors, such as age, male sex, diabetes mellitus, and obesity [3], and recently, high-risk genes and genetic variation have gained extensive attention [4-8]. Identifying further biomarkers that reflect the pathophysiology of the disease and aid clinical staff in recognizing COVID-19 severity is critical [9]. This would also help in the development of clinical management systems that can improve patient outcomes [10]. Early work focused on easily accessible laboratory indices, such as elevated C-reactive protein and D-dimer, among others, which have been helpful in the early management of high-risk patients [9,11]. These biomarkers are commonly recorded in electronic care records (ECRs), a technological development that allows the exchange of health information electronically, facilitating effective diagnosis, reducing medical errors, and providing safer care and research [12]. However, the limitations of routine laboratory biomarkers are well documented [13].

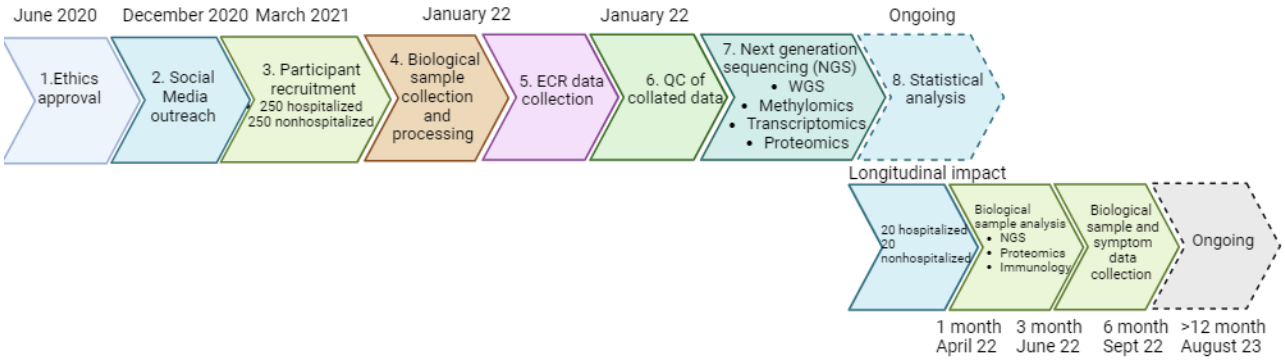
Early work also implicated angiotensin-converting enzyme 2 (ACE2) receptors and type II transmembrane serine protease in viral entry [14,15]. A recent genome-wide association study of 2000 critically ill patients [5] identified dipeptidyl peptidase 9, tyrosine kinase 2, and the antiviral restriction enzyme activators OAS1, OAS2, OAS3. To date, singleomic approaches have been used to identify genomic markers of COVID-19 severity [5,16-18]. Here, we seek to use multiomics analysis using 2 tissue types (blood and saliva) in combination with comprehensive ECRs and self-reported data to build one of the most extensive pictures yet.

Study Aims and Overview

The COVID-19 Response Study (COVRES; NCT05548829) aims to carry out an integrated multiomics analysis of factors contributing to host susceptibility to SARS-CoV-2 among a patient cohort of 1000 people from the geographically isolated island of Ireland. Because of differences in site, governance, and timelines, the protocol in the subsequent section describes the study to be carried out in Northern Ireland (NI-COVRES) by Ulster University and the Western Health and Social Care Trust (WHSCT) only. The Republic of Ireland component (Trinity College Dublin and St James Hospital Dublin) will be described separately.

Figure 1 shows an overview of the main stages and timeline with data for each participant (n=519) on the following: (1) disease status, (2) genome analysis, (3) transcriptome analysis, (4) proteome analysis, (5) methylome analysis, (6) microbiome analysis, (7) immune response, (8) patient history, (9) mental health, and (10) ECR and prospectively on 40 participants at 1, 3, 6, and 12 months postpositive polymerase chain reaction (PCR) analysis to assess persistent inflammatory and immune responses.

Figure 1. Stages of the COVID-19 Response Study implementation. ECR: electronic care record; NGS: next generation sequencing; QC: quality control; WGS: whole genome sequencing.

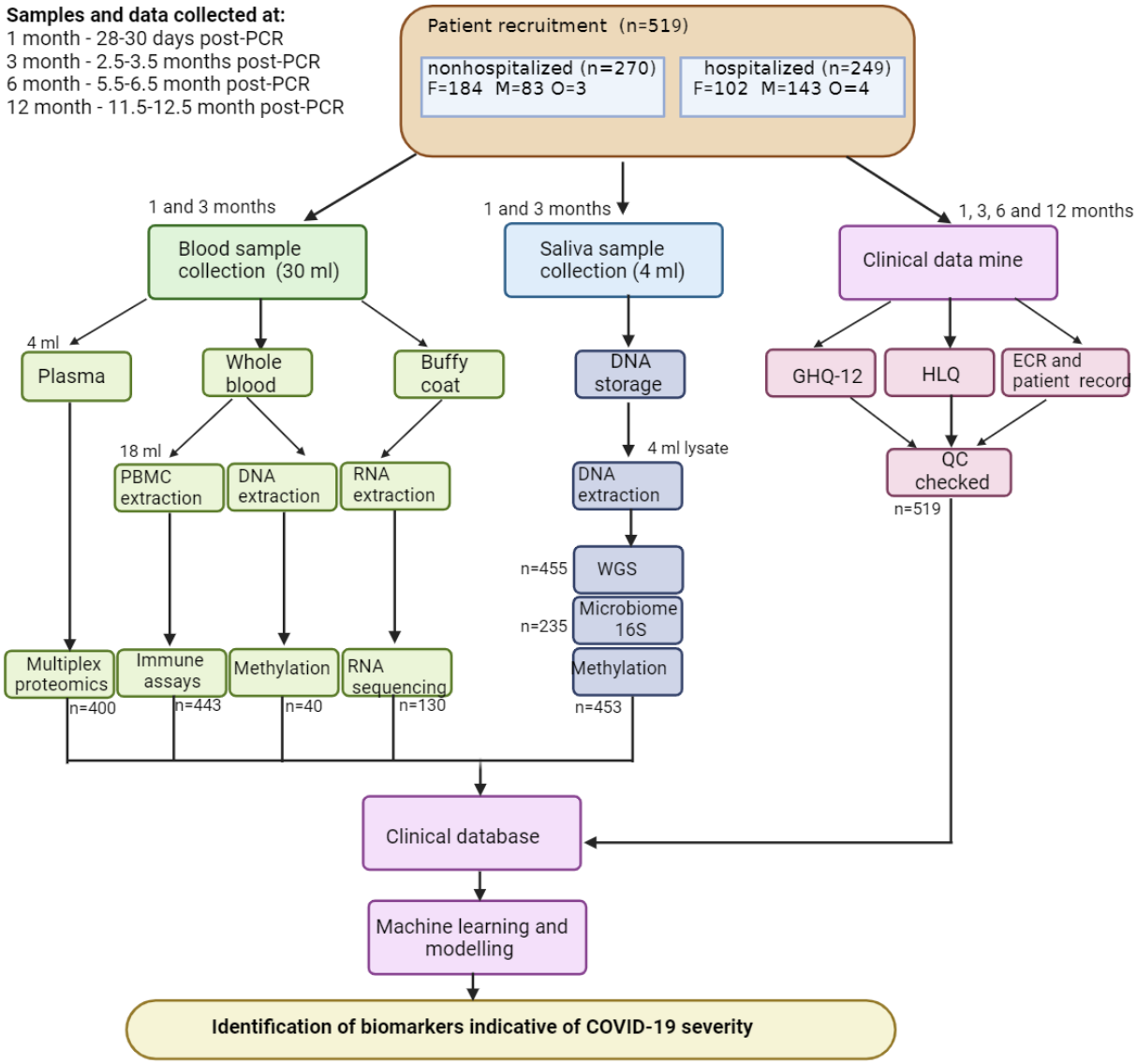


Methods

Status and Timeline of the Study

The main retrospective Cohort A recruitment commenced in December 2020 and was completed in March 2021 (trial registration; NCT05548829), except for the prospective Cohort B (ongoing). Integration of ECR record data was completed in January 2022 at the time of writing, and omics samples are being processed (Figure 2).

Figure 2. Overview of the COVID-19 Response Study sample processing work flow. ECR: electronic care record; FBC: full blood count; GHQ-12: 12-item General Health Questionnaire; HLQ: Health Life Style Questionnaire; MSD: Meso Scale Discovery; PBMC: peripheral blood mononuclear cell; PCR: polymerase chain reaction; TCR: T-cell receptor; QC: quality control; WGS: whole genome sequencing.



Ethical Considerations

Standard operating procedures and participant response questionnaires included standard operating procedures for saliva sample kit preparation, blood collection and processing, downstream sample processing, website management, data protection and participant contact. The COVRES was subsequently approved by the Health and Care Research Wales Ethics Service on July 14, 2020 (Research Ethics Committee ref 20/WA/0179). All the participants provided informed consent to participate.

Social Media Outreach

Social media content (on Twitter [subsequently rebranded X; Twitter, Inc] and Facebook [Meta Platforms, Inc]) and web page visuals were designed, with input from recovered patients, by the project principal investigators, including a range of infographics and short explanatory texts. Information was circulated to local and national news outlets (television, radio, and newspapers) across NI for recruitment purposes. Interested patients contacted the research team and were sent a patient information sheet. Appointments were then organized at least 24 hours later to obtain informed consent and samples.

Participant Recruitment With Inclusion and Exclusion Criteria

Inclusion criteria: patients had to be aged >18 years but could have any BMI or ethnic origin. Exclusion criteria: patients were excluded if they were aged <18 years and had any intellectual disabilities. Hospitalization status was determined if a patient attended or was admitted to the hospital within 14 days of a positive PCR result. Patients were also classified based on the World Health Organization (WHO) scale [19], which reflects severity over the duration of the patient's infection, regardless

of hospitalization status. For example, a patient may have an overall WHO score of 5 and be classified as nonhospitalized as they attended the hospital >14 days from their positive PCR result. After receiving a participant information sheet, patients interested in participating provided written informed consent and were enrolled in the study. A self-report questionnaire established demographic information, lifestyle choices, family history of clinical disorders, and COVID-19 severity and symptoms. This was followed by a 12-item general health questionnaire to help ascertain the patient's mental health after the COVID-19 infection (Figure 2). This data was securely digitalized onto a bespoke database, CovresNIdb, generated on the REDCap (Research Electronic Data Capture; Vanderbilt University) platform [19], to comply with the terms of the ethical considerations, the Human Tissue Act 2004, and general data protection regulations. This process is being repeated for Cohort B (prospective), consisting of 40 participants with stricter timelines followed (1, 3, 6, and 12 mo).

Biological Sample Processing

The WHSCT recruitment team coordinated sample collection appointments at hospital wards, Clinical Translational Research and Innovation Centre clinic rooms, or home visits. Participants and related study code numbers were predetermined depending on hospitalization and logged into encrypted clinical data sheets on a secure server to ensure full data traceability. All whole blood and saliva processing carried out includes recruitment numbers, sample collection types, sample processing, and downstream analysis; n numbers refer to patient numbers for specific omics analyses.

Isolation was carried out in a Category III containment hood with full personal protective equipment. Samples were not deactivated upon receipt or before processing. The participants provided 3×10 mL of whole blood and 2× saliva samples of approximately 2 mL each (Figure 2). Blood was extracted using 21G Vacuette safety needles (Greiner Bio-One Ltd, Gloucestershire) into 3×10 mL ethylenediaminetetraacetic acid–coated Vacuette tubes and centrifuged at 4000 rpm (4 °C) for 15 minutes. The buffy coat was extracted, washed, and stored for RNA sequencing (Figure 2). All samples were frozen at −80 °C; the time to freeze was <2 hours, and none showed signs of hemolysis. Saliva was collected using 1×DNA Genotek (DNA Genotek, Ottawa), Oragene DNA (OG-500), and 1×RNA (CP-190) collection tubes per participant. Samples were considered deactivated once lysed. Peripheral blood mononuclear cells were isolated using the Ficoll gradient separation methods as per [20].

Immune Assays

Whole blood was analyzed at 1 and 3 months post–positive PCR tests. Using the FACSAria III high-speed cell sorter (Becton Dickinson, Oxford, United Kingdom, software version 9) with an 85-µm nozzle fitted, whole blood and peripheral blood mononuclear cell samples were stained for T, B, and natural killer cell populations using CD45 PerCP-Cy5.5, CD3 FITC, CD8 APC-Cy7, CD4 PE-Cy7, CD19 APC, and CD16+CD56 PE (BD Biosciences) before erythrocyte lysis by PharmLyse (BD Biosciences) according to the manufacturer's instructions. T-cell subpopulations were measured using 2 defined panels: panel 1: CD3 FITC, CD4 PE-Cy7, CD8 BV605, CD30 APC, CD45RA V450, CD45RO BV786, and CD183 BB700; panel 2: CD3 FITC, CD4 PE-Cy7, CD8 BV605, CD69 APC, CD45 V450, CD127 BV786, CD152 BB700, CD25 R718, and FoxP3 PE. Cell surface staining was performed before fixing, permeabilizing, and FoxP3 labeling using the Transcription Factor Buffer Set (BD Pharmingen).

DNA Isolation

Saliva samples (whole-genome sequencing [WGS], methylome, and microbiome) were incubated for 2 hours at 56 °C, followed by DNA isolation using PrepIT L2P (DNA Genotek). DNA from whole blood (methylome) was isolated using the DNA Blood 200,360 prefilling H96 Kit (CMG-717, PerkinElmer), and 200 µL of whole blood on the Chemagic 360 system (PerkinElmer) was used. Microbial DNA was extracted from saliva aliquots using a modified protocol from Teng et al [21] using the DNeasy Blood and Tissue Kit (Qiagen). All extracted DNA was evaluated using the Qubit 3.0 fluorometer (Thermo Scientific) and the Nano Drop 1000 spectrophotometer (Thermo Scientific) and sequenced using the Invitrogen Quant-iT PicoGreen dsDNA Assay Kit (P7589) on the Hamilton Microlab Star before storage at −80 °C.

RNA Isolation

RNA was isolated from saliva using the Oragene RNA purification protocol and Qiagen RNeasy Micro Kit (Qiagen), and RNA was extracted from whole blood using the Chemagic 360 system (PerkinElmer) with the Chemagic RNA tissue 360 H96 Kit (CMG-1212). Purity and quantity were assessed, as described in the preceding section for DNA, but with the Invitrogen Quant-iT RiboGreen Assay Kit (R11490). Integrity (RIN) was determined using the Agilent 4200 TapeStation and the RNA ScreenTape (5067-5366), before storage at −80 °C.

Clinical Data

Self-Reported Data on Physical and Mental Well-Being

All participants completed 2 surveys as part of the trial. The 12-item general health questionnaire is a self-administered screening tool designed to detect current mental state disturbances in primary care settings; a score of ≥2 indicates a disorder. The health and lifestyle questionnaire is a survey tool designed by Ulster University to capture key health-related data not present in the ECR. The fields included COVID-19 risk factors, medications, comorbidities, hospitalization information, symptoms at admission, laboratory tests, family history, drinking status, and occupation. The same protocol is being followed for all prospective appointments (ongoing).

Clinical Database Development

The participants' consent forms, as well as data from the self-reported questionnaires, but with all personally identifiable information removed by the project's data controller as per general data protection regulations guidelines, were also recorded in the CovresNIdb database. The data were subjected to quality control (QC) by 2 independent researchers against the original sources. The same protocol is being followed for all prospective appointments (ongoing).

Electronic Care Records

In addition to the self-reported data, consent was also provided by each patient to enrich the database by accessing their NI Electronic Care Record information held by the National Health Service. PCR positive dates, severity (hospitalized because of COVID-19 infection or recovered from COVID-19 infection at home), laboratory results (full blood count, blood pressure, lipids, C-reactive protein, glomerular filtration rate, and troponin), treatment administered, drugs prescribed within the last 6 months, and comorbidity and multimorbidity were recorded for each patient.

Omics Analyses

Genome Analysis

Whole-genome library preparation was performed using the Illumina TruSeq PCR Free Library Prep protocol (20015963) with an input amount of 1 µg on a Hamilton next-generation sequencing Star robotic workstation, and quality was assessed using the Roche KAPA Library Quantification Kit (7960298001) before pooling and sequencing (150bp PE) on an Illumina NovaSeq 6000 instrument using NovaSeq 6000 S4 Reagent Kit v1.5 (20028312), with a mean coverage of 30× as described previously [22]. Sequences are being uploaded to the European Genome-phenome Archive (EGA).

Methylome Analysis

Methylation analysis was performed on DNA samples from saliva (n=450) and whole blood (n=40) using the Illumina Infinium Methylation EPIC, largely as described previously [22]. Data were adjusted for known epigenetic covariates, and surrogate variable analysis was performed via the *sva* inference module [23]. Our in-house-developed tool, CandiMeth [24], will be used to streamline the methylation analysis of gene lists of interest.

Transcriptome Analysis

RNA sequencing library preparation was performed using the Illumina TruSeq Stranded Total RNA Library Prep Globin Kit (20020612) with an input amount of 100 to 1000 ng. Library preparation was automated and processed using a Hamilton next-generation sequencing Star, and quality was assessed using the Roche KAPA Library Quantification Kit (7960298001) and GX Caliper HS Assay (CLS 760,672, 760,517), run on Roche Lightcycler 480 II and PerkinElmer LabChip GX Touch analyzers, respectively. Libraries were pooled and sequenced (75bp PE) on an Illumina NovaSeq 6000 instrument using NovaSeq 6000 S2 Reagent Kit v1.5 (20028314), targeting 50M paired reads. Raw data binary base call format was demultiplexed and converted to the FASTQ format using BCL2FastQ (Illumina). Adapters were trimmed using Skewer [25], and QC was assessed using FASTQC. Spliced Transcripts Alignment to a Reference [26] was used to align reads to the reference genome (GRCh38/hg38) as well as to the transcriptome (version 25; GENCODE). The quality of the RNA alignment was assessed using Picard QC. Gene and isoform quantification will be performed using RNA-Seq by Expectation-Maximization [27], with prospective patient (1 and 3 mo) T-cell receptor sequencing completed following flow cytometry.

Microbiome Analysis

16S ribosomal RNA gene amplicons for sequencing by the Illumina MiSeq system (Illumina) were prepared using the V3 and V4 regions as described by Klindworth et al (2013), with sequencing performed in-house.

Proteome Analysis

Protein analysis of 400 plasma samples (baseline; 186 nonhospitalized and 214 hospitalized), 40 prospective (20 nonhospitalized and 20 hospitalized; 1 and 3 months postinfection), was outsourced to OLINK proteomics (OLINK, Uppsala, Sweden) using the Explore 384 Inflammation panel (Protein Proximity Extension Assay). Ethylenediaminetetraacetic acid plasma samples were thawed at room temperature (20 °C), and 45 µL of each plasma sample was (at random) pipetted into a LightCycle 480Multiwell Plate 96-well white PCR plates (product no. 04729692001; Roche Molecular Systems Inc) with 8 × wells left empty on each plate for internal controls to be added at OLINK. The samples were inactivated as per OLINK's protocol and shipped on dry ice (CO2, −78 °C). Only samples above 0.2 Normalized Protein eXpression and samples that deviated less than 0.3 Normalized Protein eXpression passed QC.

The Meso Scale Discovery plasma multispot assay system comprising V-PLEX COVID-19 serology panel 11, *total IgG*, and *ACE2 neutralization* assays was used to determine viral variant prevalence. Samples were prepared at 1:10 (ACE2) and 1:5000 (neutralization) for specific assays and then treated as described in [28].

The Roche COBAS Elecsys SARS-CoV-2 spike (S) protein receptor binding domain assay was used to determine SARS-CoV-2 antibody presence as per manufacturer's instructions.

Statistics

Univariate and Multivariate Analysis

Only patients from Cohort A (n=507) who had their BMI recorded in the database were selected for the odds ratio analysis. We considered the following risk factors: sex, age, BMI, and disease subgroups. First, univariate analyses (Fisher exact test) were performed to identify risk factors associated with COVID-19 severity.

P values for univariate analyses were generated using the Fisher exact test to compare the frequencies of each potential risk factor between nonhospitalized and hospitalized participants. Variables with a *P* value <.001, that is, sex, age <50 years and >50 years, and cardiovascular, respiratory, endocrine, and musculoskeletal comorbidities, were considered clinically relevant and entered into the multivariable logistic regression model. This and further analysis are being undertaken on Base-R software (R Project for Statistical Computing; version 4.2.2) using the Visdat library.

Demographics Table

The demographic table of the COVRES data (n=519) was generated using IBM SPSS Statistics for Windows (version 27; IBM Corp) [29]. Statistical analysis for the contingency table

was undertaken using a Fisher exact 2-sided test to obtain the required *P* values, and CI rates were set at 95%.

Bioinformatic Analyses

Bioinformatic analyses will focus on using computational approaches to identify genomic, transcriptomic, proteomic, and clinical correlates of severity. Planned analyses primarily include the identification of clinical features, gene variants (host) or Expression quantitative trait loci, transcriptomic signatures, and cytokine profiles associated with disease severity, as well as the differential methylation among the host genomes of the severity groups.

Variant calling will use mathematical models from the Best Practices Genome Analysis Toolkit. Data are being stored according to genomic position in the Genuity Science Genomically Ordered Relational Database to facilitate rapid access by the Clinical Sequence Analyzer user interface and Sequence Miner visualization software. Initial data processing for methylome analysis will be carried out in *GenomeStudio* (version 3.2; Illumina) before the import of idat files into the RnBeads package [30] using RStudio (version 2022.02.0+443) on the R platform (version 4.1.2). QC will be performed using the *greedycut* algorithm, which involves the removal of probes with missing values and poor quality. For RNA-seq, gene and isoform quantification will be performed using RNA-Seq by Expectation-Maximization [27] before further analysis is carried out. 16S ribosomal RNA analysis has been previously described (refer to the preceding section), and OLINK data will be processed in R as per standard pipelines. WGS and transcriptomics data are to be deposited in the EGA pending and shared in collaboration with the International COVID-19 Host Genetics Initiative.

Results

Retrospective Cohort A Demographics

The main demographic characteristics are summarized in Table 1.

Table 1. COVID-19 Response Study Cohort A demographic information.

Cohort A demographics	Nonhospitalized (n=270)	Hospitalized (n=249)	Total (n=519)	*P* value[a]
Sex, n (%)				
Female	184 (64.3)	102 (35.7)	286 (55.1)	<.001
Male	83 (36.7)	143 (63.3)	226 (43.5)	<.001
Other	3 (42.9)	4 (57.1)	7 (1.3)	.72
Age (y) at diagnosis				
Age, mean (SD)	45.4 (13)	56.5 (12.7)	50.7 (14)	<.001[a]
<50, n (%)	169 (62.6)	67 (26.9)	236 (45.5)	<.001
>50, n (%)	101 (37.4)	182 (73.1)	283 (54.5)	<.001
Disease subgroup, n (%)				
Autoimmune[b]	12 (4.4)	26 (10.4)	38 (7.3)	.01
Metabolic[c]	33 (12.2)	94 (37.8)	127 (24.5)	<.001
Respiratory[d]	39 (14.4)	83 (33.3)	122 (23.5)	<.001
Cardiovascular[e]	32 (11.9)	100 (40.2)	132 (25.4)	<.001
Cancer[f]	7 (2.6)	21 (8.4)	28 (5.4)	.003
Gastrointestinal[g]	13 (4.8)	21 (8.4)	34 (6.6)	.11
Musculoskeletal[h]	23 (8.5)	58 (23.3)	81 (15.6)	<.001

[a]*P* value calculated using 2-sided Fisher exact test between nonhospitalized versus hospitalized patients. *P*<.05 was set as statistically significant (n=519); continuous variables used a 2-sided *t* test.

[b]Autoimmune or rheumatic diseases including rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis.

[c]Metabolic and endocrine diseases including thyroid conditions, hypercholesterolemia, or other hyperlipidemia, gout, diabetes, and kidney disorders.

[d]Respiratory disorder and chronic lung diseases including chronic obstructive pulmonary disease, asthma (moderate to severe), interstitial lung disease, cystic fibrosis, sleep apnea, and pulmonary hypertension.

[e]Cardiovascular system disorders including angina, hypertension, stroke, peripheral vascular disease, balloon angioplasty or percutaneous coronary intervention, atrial fibrillation, venous thromboembolism, anemia, and chronic cardiac diseases other than hypertension.

[f]Cancer including leukemia, lymphoma, and malignant solid tumors, and to include current, past, and remission.

[g]Gastrointestinal disorders including gallbladder, liver disease, pancreatic disease, and Inflammatory bowel syndrome.

[h]Musculoskeletal diseases including osteoarthritis and ankylosing spondylitis, excluding subgroup 1 conditions.

As expected, there was a significant difference in the mean age between hospitalized and nonhospitalized patients, as well as between sexes (both $P<.001$). Age bias was also evident, with 62.6% (169/270) of patients aged <50 years in the nonhospitalized subgroup ($P<.001$) and 73.1% (182/249) of patients aged >50 years in the hospitalized subgroup ($P<.001$). As expected, comorbidity incidence was higher in the hospitalized subgroup than in the nonhospitalized subgroup, with autoimmune (12/270, 4.4% nonhospitalized and 26/249, 10.4% hospitalized; $P<.001$), metabolic (33/270, 12.2% nonhospitalized and 94/249, 37.8% hospitalized; $P<.001$), respiratory (39/270, 14.4% nonhospitalized and 83/249, 33.3% hospitalized; $P<.001$), cardiovascular (32/270, 11.9% nonhospitalized and 100/249, 40.2% hospitalized; $P<.001$), and musculoskeletal (23/270, 8.5% nonhospitalized and 58/249, 23.3% hospitalized; $P<.001$) disorders of note. There were no differences between the cohorts for gastrointestinal disorders (Table 1).

Prospective Cohort B Demographics

Data collection is ongoing for 40 participants who are being followed up over 12 months: 20 (8/20, 40% female) hospitalized and 20 nonhospitalized (12/20, 60% female); sex distribution is not significantly different between subgroups ($P=.21$) but average age is (hospitalized: mean 52, SD 17.2 years; nonhospitalized: mean 45.2, SD 13.5 years; $P<.001$; Table 2).

In contrast to the initial recruitment, within this follow-up Cohort B, there was no age bias toward participants older than 50 years ($P=.20$). There was also no significant difference in vaccination status between hospitalization subgroups ($P=.55$), and only cardiovascular disease as a comorbidity was more prevalent in hospitalized patients ($P=.02$), although the numbers are small.

Table 2. COVID-19 Response Study Cohort B multivariate analysis of hospitalized versus nonhospitalized patients analyzing risk factors for COVID-19 severity.

Prospective Cohort B demographics	Nonhospitalized (n=20)	Hospitalized (n=20)	Total (n=40)	*P* value[a]
Female, n (%)	12 (60)	8 (40)	22 (50)	.21
Age (y) at diagnosis				
Age, mean (SD)	45.2 (13.5)	52 (17.2)	48.6 (15.6)	<.001[b]
>50, n (%)	7 (35)	11 (55)	18 (45)	.20
Vaccine status, n (%)	19 (95)	18 (90)	37 (93)	.55
Comorbidity, n (%)				
Autoimmune[c]	3 (15)	6 (30)	9 (23)	.26
Metabolic[d]	4 (20)	9 (45)	13 (33)	.91
Respiratory[e]	2 (10)	7 (35)	9 (26)	.58
Cardiovascular[f]	2 (10)	11 (55)	13 (33)	.02
Cancer[g]	0 (0)	4 (20)	4 (10)	.35
Gastrointestinal[h]	2 (10)	4 (20)	6 (15)	.38
Musculoskeletal[i]	3 (15)	7 (35)	10 (25)	.14

[a]*P* value calculated using 2-sided Fisher exact test between nonhospitalized versus hospitalized patients. $P<.05$ set as statistically significant (n=40); continuous variables used a 2-sided *t* test.

[b]Inclusion criteria for analysis: participants (n=40) were required to have a BMI score recorded.

[c]Autoimmune or rheumatic diseases including rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis.

[d]Metabolic and endocrine diseases including thyroid conditions, hypercholesterolemia, or other hyperlipidemia, gout, diabetes, and kidney disorders.

[e]Respiratory disorder and chronic lung diseases including chronic obstructive pulmonary disease, asthma (moderate to severe), interstitial lung disease, cystic fibrosis, sleep apnea, and pulmonary hypertension.

[f]Cardiovascular system disorders including angina, hypertension, stroke, peripheral vascular disease, balloon angioplasty or percutaneous coronary intervention, atrial fibrillation, venous thromboembolism, anemia, and chronic cardiac diseases other than hypertension.

[g]Cancer including leukemia, lymphoma, and malignant solid tumors, and to include current, past, and remission.

[h]Gastrointestinal disorders including gallbladder, liver disease, pancreatic disease, and Inflammatory bowel syndrome.

[i]Musculoskeletal diseases including osteoarthritis and ankylosing spondylitis, excluding subgroup 1 conditions.

Discussion

Principal Findings

The COVRES provides a novel opportunity to identify multiomics biomarkers from blood and saliva indicative of COVID-19 severity in NI and may provide unique insights into disease mechanisms and identify potential therapeutic targets. The maximum recruitment number (n=519) was reached, and various analyses are ongoing, including WGS and RNA sequencing, proteomic, microbiome, and methylation experiments. We have also collected detailed medical data using the NI Electronic Care Record that will be used to enrich the biomarker data [31]. All Cohort A participants were recruited over a 4-month period (December 1, 2020-March 31, 2021) during the pandemic peak, allowing homogeneous data collection from the same viral variant (B.1.1.7; Figure 1). Compared with other studies, the COVRES has a higher participant number and uses a significantly wider biomarker identification approach. This was achieved while significant pandemic restrictions were in place and was only possible because of our local health trust (WHSCT, National Health Service) collaboration, which facilitated patient access and enabled the recording of laboratory parameters that have not been possible in other studies [32]. A recent multiomics COVID-19 study used proteomics and metabolomics to screen 13 samples at 2 time points and found 10 significant proteins, 32 significant peptides, and 5 metabolites that were dysregulated in severe patients [33]. Recruitment for this study also occurred in early 2021, but the small sample size (n=13) brings into question the generalizability of the findings. Another multiomics study based in the United States sampled 128 individuals between April 6, 2020, and May 1, 2020, and conducted follow-up until June 2020. The authors quantified transcripts, proteins, metabolites, and lipids and made associations with clinical outcomes [34]. Links were made between platelet function, blood coagulation, endotheliopathy, and COVID-19 severity. Our study builds on these smaller studies and may offer increased statistical power and the potential to validate or compare the markers identified.

The COVRES was designed to recruit hospitalized (n=250) patients with COVID-19, classified as having a severe infection, and nonhospitalized (n=250) patients with COVID-19, classified as having a mild infection, within 3 months of sampling. It is worth noting that the recruitment of nonhospitalized patients with COVID-19 makes this cohort particularly valuable, as most trials have only involved patients who have been admitted to the hospital or those who have not [35,36], and few have investigated earlier stages of the disease process, such as preexposure or postexposure and outpatient treatment.

To maximize the impact and benefit to the scientific and health care communities, this study was designed to be cross-border, covering both NI and the Republic of Ireland. The global drive to identify clinical biomarkers of COVID-19 severity has led to many clinical studies and trials that have varied methodologies regarding different control groups, follow-up periods, omics of interest, and laboratory methodologies [37-39]. Studies have also been carried out in different geographic regions without any standardized operating procedures and have been powered according to different end points [40]. This variation makes reproducibility questionable, and it is difficult to apply the findings across geographic regions and variant periods. To align with as many studies as possible, COVRES participants have been classified according to the WHO [41], and to facilitate cross-border collaboration, we coordinated with Trinity College Dublin. We also plan to share our WGS data with the EGA for the advancement of science and improved public health outcomes.

The recruitment of nonhospitalized and hospitalized patients with COVID-19 in NI is the main strength of the COVRES and adds novelty to existing research regarding COVID-19 severity, with the majority recruiting patients based on a positive PCR test result regardless of hospitalization. Sex and age matching was considered, but an exact match was not achieved because of the complexities and limitations of COVID-19 presented regarding patient access [5]. The mean age of the hospitalized COVRES subgroup was 56.5 years (Table 1), which was slightly younger compared with a large UK-wide observational study [42] (20,908 hospitalized), which had a mean age of 62 years. There was no difference between sex (male 49%, female 51%), compared with our sample comprising 43.5% (226/519) men. Another smaller (n=429) UK study found the average age of hospitalized patients with COVID-19 to be 70 years and a male bias of 57%, which is close to our study. Corresponding with our study, they also found the average BMI to be 28 kg/m^2 (overweight-obese) and highly comorbid (Table 2), with the most common comorbidities being type-2 diabetes, hypertension, and respiratory disorders [42,43]. A previous study [43] in England is a good comparison for COVRES NI, as the recruitment protocols and cohort demographics are similar. The similarities in the data are promising and may indicate that our findings could be useful to the wider United Kingdom.

Limitations

COVRES participants were all sampled at a single time point, limiting our ability to assess genomic, proteomic, and immune biomarkers as the disease progresses. Future work will focus on obtaining follow-up samples to enable longitudinal analysis and assess the prognostic capability of markers of interest. Manual data input at some points increases the risk of human error [44], and although QC checks were carried out between 2 WHSCT staff members, there is an inherent risk of incorrect data.

It also needs to be considered that the COVRES cohort represents a COVID-19 population recruited in NI, and the demographics show a low representation of ethnic minority groups; therefore, data may not be able to be generalizable beyond White Irish and UK populations.

Conclusions

The COVRES offers a novel opportunity to study the multiomics mechanisms of COVID-19 severity in recontactable participants. This research has the potential to impact COVID-19 clinical decision-making and therapeutic development. Our WHSCT and industry collaborators enabled rapid and effective

recruitment, allowing us to reach our goal of 500 participants and begin the analysis pipelines immediately. We hope that this paper will not only demonstrate the effectiveness of the study methodology but also raise awareness of the availability of this cohort among researchers in the field and promote future collaboration.

Acknowledgments

This work was supported by a research grant to AJB (principal investigator) and coauthors from the Department for the Economy Northern Ireland under its contribution to Science Foundation Ireland's COVID-19 Rapid Response Call (phase 2), Opportunity-Led Research Awards to TSR and DSG from HSC Research and Development Division, Public Health Agency (COM/5618/20 and COM/5631/20, respectively), and National Core Study: Immunity (NCSi4P program) funding from United Kingdom Research and Innovation to DSG and PS.

The authors would like to extend their sincere gratitude to the participants of this study for their invaluable contribution and to the Western Health Social Care Trust (WHSCT), Northern Ireland, for facilitating access to patients and clinics, Dr Maurice O'Kane for enabling Western Health Social Care Trust laboratory completion of Roche anti–SARS-CoV-2 antibody assays, and Genuity Science (Ireland) Ltd for their funding in kind for the completion of the whole-genome sequencing and methylation analysis.

Data Availability

Data and metadata will be stored according to the Ulster University policy on data management and sharing. Data will be available via Ulster University's Research Data Repository and in accordance with their Research Data Management Policy. Any personal and identifiable information will be redacted, and data queries will be addressed on an individual basis by the research team. Genomics data are being deposited in the European Genome-phenome Archive and will be available upon request.

Authors' Contributions

AE contributed to investigation, formal analysis, writing, resources, and supervision; DM, EC, BW, REI, M Bhavsar, SDZ and PS contributed formal analysis and data curation; SML contributed formal analysis and investigation; JM contributed to investigation, formal analysis and writing; MK and M Bhavsar contributed to conceptualization and project administration; VM contributed to conceptualization, project administration and supervision; TSR contributed to conceptualization, project administration, supervision, and funding acquisition; AJB contributed to conceptualization, project administration, supervision, funding acquisition and resources; EM contributed to conceptualization, project administration, supervision, and funding acquisition; DSG and CW contributed to conceptualization, project administration, supervision, funding acquisition, resources, and writing.

Conflicts of Interest

None declared.

References

1. Heneghan C, Brassey J, Jefferson T. COVID-19: what proportion are asymptomatic? The Centre for Evidence-Based Medicine. 2020 Apr 6. URL: https://www.cebm.net/covid-19/covid-19-what-proportion-are-asymptomatic/ [accessed 2024-01-03]
2. Bhargava A, Fukushima EA, Levine M, Zhao W, Tanveer F, Szpunar SM, et al. Predictors for severe COVID-19 infection. Clin Infect Dis 2020 Nov 05;71(8):1962-1968 [FREE Full text] [doi: 10.1093/cid/ciaa674] [Medline: 32472676]
3. Jordan RE, Adab P, Cheng KK. Covid-19: risk factors for severe disease and death. BMJ 2020 Mar 26;368:m1198. [doi: 10.1136/bmj.m1198] [Medline: 32217618]
4. Zeberg H, Pääbo S. A genomic region associated with protection against severe COVID-19 is inherited from Neandertals. Proc Natl Acad Sci U S A 2021 Mar 02;118(9):e2026309118 [FREE Full text] [doi: 10.1073/pnas.2026309118] [Medline: 33593941]
5. Pairo-Castineira E, Clohisey S, Klaric L, Bretherick AD, Rawlik K, Pasko D, GenOMICC Investigators, ISARIC4C Investigators, COVID-19 Human Genetics Initiative, 23andMe Investigators, BRACOVID Investigators, Gen-COVID Investigators, et al. Genetic mechanisms of critical illness in COVID-19. Nature 2021 Mar;591(7848):92-98. [doi: 10.1038/s41586-020-03065-y] [Medline: 33307546]
6. Mosharaf MP, Reza MS, Kibria MK, Ahmed FF, Kabir MH, Hasan S, et al. Computational identification of host genomic biomarkers highlighting their functions, pathways and regulators that influence SARS-CoV-2 infections and drug repurposing. Sci Rep 2022 Mar 11;12(1):4279 [FREE Full text] [doi: 10.1038/s41598-022-08073-8] [Medline: 35277538]
7. Singh H, Nema R, Kumar A. Chapter 6 - Genomic, proteomic biomarkers and risk factors associated with COVID-19. In: Khan R, Kaushik A, Parihar A, Kumar A, editors. Advanced Biosensors for Virus Detection: Smart Diagnostics to Combat SARS-CoV-2. Cambridge, MA: Academic Press; 2022:95-111.

8. Lynch SM, Guo G, Gibson DS, Bjourson AJ, Rai TS. Role of senescence and aging in SARS-CoV-2 infection and COVID-19 disease. Cells 2021 Nov 30;10(12):3367 [FREE Full text] [doi: 10.3390/cells10123367] [Medline: 34943875]
9. Ponti G, Maccaferri M, Ruini C, Tomasi A, Ozben T. Biomarkers associated with COVID-19 disease progression. Crit Rev Clin Lab Sci 2020 Sep 05;57(6):389-399 [FREE Full text] [doi: 10.1080/10408363.2020.1770685] [Medline: 32503382]
10. Hsu H, Greenwald PW, Laghezza MR, Steel P, Trepp R, Sharma R. Clinical informatics during the COVID-19 pandemic: lessons learned and implications for emergency department and inpatient operations. J Am Med Inform Assoc 2021 Mar 18;28(4):879-889 [FREE Full text] [doi: 10.1093/jamia/ocaa311] [Medline: 33247720]
11. Tjendra Y, Al Mana AF, Espejo AP, Akgun Y, Millan NC, Gomez-Fernandez C, et al. Predicting disease severity and outcome in COVID-19 patients: a review of multiple biomarkers. Arch Pathol Lab Med 2020 Dec 01;144(12):1465-1474 [FREE Full text] [doi: 10.5858/arpa.2020-0471-SA] [Medline: 32818235]
12. Tayefi M, Ngo P, Chomutare T, Dalianis H, Salvi E, Budrionis A, et al. Challenges and opportunities beyond structured data in analysis of electronic health records. WIREs Comput Stats 2021 Feb 14;13(6):e1549. [doi: 10.1002/wics.1549]
13. Pourbagheri-Sigaroodi A, Bashash D, Fateh F, Abolghasemi H. Laboratory findings in COVID-19 diagnosis and prognosis. Clin Chim Acta 2020 Nov;510:475-482 [FREE Full text] [doi: 10.1016/j.cca.2020.08.019] [Medline: 32798514]
14. Singh H, Choudhari R, Nema V, Khan AA. ACE2 and TMPRSS2 polymorphisms in various diseases with special reference to its impact on COVID-19 disease. Microb Pathog 2021 Jan;150:104621 [FREE Full text] [doi: 10.1016/j.micpath.2020.104621] [Medline: 33278516]
15. Strope J, Pharm DH, Figg WD. TMPRSS2: potential biomarker for COVID-19 outcomes. J Clin Pharmacol 2020 Jul;60(7):801-807 [FREE Full text] [doi: 10.1002/jcph.1641] [Medline: 32437018]
16. Fernández-Pato A, Virseda-Berdices A, Resino S, Ryan P, Martínez-González O, Pérez-García F, et al. Plasma miRNA profile at COVID-19 onset predicts severity status and mortality. Emerg Microbes Infect 2022 Dec 27;11(1):676-688 [FREE Full text] [doi: 10.1080/22221751.2022.2038021] [Medline: 35130828]
17. Russell CD, Valanciute A, Gachanja NN, Stephen J, Penrice-Randal R, Armstrong SD, et al. Tissue proteomic analysis identifies mechanisms and stages of immunopathology in fatal COVID-19. Am J Respir Cell Mol Biol 2022 Feb;66(2):196-205. [doi: 10.1165/rcmb.2021-0358oc]
18. Spick M, Lewis HM, Frampas CF, Longman K, Costa C, Stewart A, et al. An integrated analysis and comparison of serum, saliva and sebum for COVID-19 metabolomics. Sci Rep 2022 Jul 13;12(1):11867. [doi: 10.1038/s41598-022-16123-4] [Medline: 35831456]
19. Harvey LA. REDCap: web-based software for all types of data storage and collection. Spinal Cord 2018 Jul 5;56(7):625. [doi: 10.1038/s41393-018-0169-9] [Medline: 29977003]
20. Golke T, Mucher P, Schmidt P, Radakovics A, Repl M, Hofer P, et al. Delays during PBMC isolation have a moderate effect on yield, but severly compromise cell viability. Clin Chem Lab Med 2022 Apr 26;60(5):701-706. [doi: 10.1515/cclm-2022-0003] [Medline: 35085430]
21. Lapsley CR, Irwin R, McLafferty M, Thursby SJ, O'Neill SM, Bjourson AJ, et al. Methylome profiling of young adults with depression supports a link with immune response and psoriasis. Clin Epigenetics 2020 Jun 15;12(1):85 [FREE Full text] [doi: 10.1186/s13148-020-00877-7] [Medline: 32539844]
22. Dhingra R, Kwee LC, Diaz-Sanchez D, Devlin RB, Cascio W, Hauser ER, et al. Evaluating DNA methylation age on the Illumina MethylationEPIC bead chip. PLoS One 2019 Apr 19;14(4):e0207834 [FREE Full text] [doi: 10.1371/journal.pone.0207834] [Medline: 31002714]
23. Leek JT, Parker HS, Jaffe AE, Storey JD, Torres LC. Package 'sva': surrogate variable analysis. Bioconductor. 2023 Dec 12. URL: https://bioconductor.org/packages/devel/bioc/manuals/sva/man/sva.pdf [accessed 2023-12-13]
24. Thursby SJ, Lobo DK, Pentieva K, Zhang SD, Irwin RE, Walsh CP. CandiMeth: powerful yet simple visualization and quantification of DNA methylation at candidate genes. Gigascience 2020 Jun 01;9(6):giaa066 [FREE Full text] [doi: 10.1093/gigascience/giaa066] [Medline: 32568373]
25. Jiang H, Lei R, Ding SW, Zhu S. Skewer: a fast and accurate adapter trimmer for next-generation sequencing paired-end reads. BMC Bioinformatics 2014 Jun 12;15(1):182. [doi: 10.1186/1471-2105-15-182] [Medline: 24925680]
26. Dobin A, Davis CA, Schlesinger F, Drenkow J, Zaleski C, Jha S, et al. STAR: ultrafast universal RNA-seq aligner. Bioinformatics 2013 Jan 01;29(1):15-21 [FREE Full text] [doi: 10.1093/bioinformatics/bts635] [Medline: 23104886]
27. Li B, Dewey CN. RSEM: accurate transcript quantification from RNA-seq data with or without a reference genome. BMC Bioinformatics 2011 Aug 04;12(1):323. [doi: 10.1186/1471-2105-12-323] [Medline: 21816040]
28. Collins ES, Butt AQ, Gibson DS, Dunn MJ, Fearon U, van Kuijk AW, et al. A clinically based protein discovery strategy to identify potential biomarkers of response to anti - TNF - α treatment of psoriatic arthritis. Proteomics Clin Appl 2015 Sep 28;10(6):645-662. [doi: 10.1002/prca.201500051]
29. IBM Corp. IBM SPSS statistics for windows, version 22.0. IBM Corp. 2013. URL: https://www.scirp.org/reference/ReferencesPapers?ReferenceID=2010524 [accessed 2024-01-03]
30. Müller F, Scherer M, Assenov Y, Lutsik P, Walter J, Lengauer T, et al. RnBeads 2.0: comprehensive analysis of DNA methylation data. Genome Biol 2019 Mar 14;20(1):55 [FREE Full text] [doi: 10.1186/s13059-019-1664-9] [Medline: 30871603]

31. Bucholc M, Bradley D, Bennett D, Patterson L, Spiers R, Gibson D, et al. Identifying pre-existing conditions and multimorbidity patterns associated with in-hospital mortality in patients with COVID-19. Sci Rep 2022 Oct 15;12(1):17313 [FREE Full text] [doi: 10.1038/s41598-022-20176-w] [Medline: 36243878]
32. Sáez C, Romero N, Conejero JA, García-Gómez JM. Potential limitations in COVID-19 machine learning due to data source variability: a case study in the nCov2019 dataset. J Am Med Inform Assoc 2021 Feb 15;28(2):360-364 [FREE Full text] [doi: 10.1093/jamia/ocaa258] [Medline: 33027509]
33. Suvarna K, Salkar A, Palanivel V, Bankar R, Banerjee N, Gayathri J Pai M, et al. A multi-omics longitudinal study reveals alteration of the leukocyte activation pathway in COVID-19 patients. J Proteome Res 2021 Oct 01;20(10):4667-4680. [doi: 10.1021/acs.jproteome.1c00215] [Medline: 34379420]
34. Overmyer KA, Shishkova E, Miller IJ, Balnis J, Bernstein MN, Peters-Clarke TM, et al. Large-scale multi-omic analysis of COVID-19 severity. Cell Syst 2021 Jan 20;12(1):23-40.e7 [FREE Full text] [doi: 10.1016/j.cels.2020.10.003] [Medline: 33096026]
35. Caricchio R, Abbate A, Gordeev I, Meng J, Hsue PY, Neogi T, et al. Effect of canakinumab vs placebo on survival without invasive mechanical ventilation in patients hospitalized with severe COVID-19: a randomized clinical trial. JAMA 2021 Jul 20;326(3):230-239 [FREE Full text] [doi: 10.1001/jama.2021.9508] [Medline: 34283183]
36. Salvarani C, Dolci G, Massari M, Merlo DF, Cavuto S, Savoldi L, et al. Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia: a randomized clinical trial. JAMA Intern Med 2021 Jan 01;181(1):24-31 [FREE Full text] [doi: 10.1001/jamainternmed.2020.6615] [Medline: 33080005]
37. Chemaitelly H, Yassine HM, Benslimane FM, Al Khatib HA, Tang P, Hasan MR, et al. mRNA-1273 COVID-19 vaccine effectiveness against the B.1.1.7 and B.1.351 variants and severe COVID-19 disease in Qatar. Nat Med 2021 Sep;27(9):1614-1621. [doi: 10.1038/s41591-021-01446-y] [Medline: 34244681]
38. Tolaney SM, Lydon CA, Li T, Dai J, Standring A, Legor KA, et al. The impact of COVID-19 on clinical trial execution at the Dana-Farber Cancer Institute. J Natl Cancer Inst 2021 Nov 02;113(11):1453-1459 [FREE Full text] [doi: 10.1093/jnci/djaa144] [Medline: 32959883]
39. Robishaw JD, Alter SM, Solano JJ, Shih RD, DeMets DL, Maki DG, et al. Genomic surveillance to combat COVID-19: challenges and opportunities. Lancet Microbe 2021 Sep;2(9):e481-e484. [doi: 10.1016/s2666-5247(21)00121-x]
40. Park JJ, Mogg R, Smith GE, Nakimuli-Mpungu E, Jehan F, Rayner CR, et al. How COVID-19 has fundamentally changed clinical research in global health. Lancet Global Health 2021 May;9(5):e711-e720. [doi: 10.1016/s2214-109x(20)30542-8]
41. de Terwangne C, Laouni J, Jouffe L, Lechien JR, Bouillon V, Place S, et al. Predictive accuracy of COVID-19 world health organization (WHO) severity classification and comparison with a Bayesian-method-based severity score (EPI-SCORE). Pathogens 2020 Oct 24;9(11):880 [FREE Full text] [doi: 10.3390/pathogens9110880] [Medline: 33114416]
42. Goodacre S, Thomas B, Lee E, Sutton L, Loban A, Waterhouse S, et al. Characterisation of 22445 patients attending UK emergency departments with suspected COVID-19 infection: observational cohort study. PLoS One 2020 Nov 25;15(11):e0240206 [FREE Full text] [doi: 10.1371/journal.pone.0240206] [Medline: 33237907]
43. Ken-Dror G, Wade C, Sharma S, Law J, Russo C, Sharma A, et al. COVID-19 outcomes in UK centre within highest health and wealth band: a prospective cohort study. BMJ Open 2020 Nov 16;10(11):e042090 [FREE Full text] [doi: 10.1136/bmjopen-2020-042090] [Medline: 33199428]
44. Menachemi N, Collum TH. Benefits and drawbacks of electronic health record systems. Risk Manag Healthc Policy 2011 May;4:47-55. [doi: 10.2147/rmhp.s12985]

Abbreviations

ACE2: angiotensin-converting enzyme 2
COVRES: COVID-19 Response Study
ECR: electronic care record
EGA: European Genome-phenome Archive
NI: Northern Ireland
PCR: polymerase chain reaction
QC: quality control
REDCap: Research Electronic Data Capture
WGS: whole-genome sequencing
WHO: World Health Organization
WHSCT: Western Health and Social Care Trust

Edited by A Mavragani; submitted 11.07.23; peer-reviewed by P Patel, Y Pan; comments to author 12.09.23; revised version received 23.10.23; accepted 09.11.23; published 14.02.24.

Please cite as:
English A, McDaid D, Lynch SM, McLaughlin J, Cooper E, Wingfield B, Kelly M, Bhavsar M, McGilligan V, Irwin RE, Bucholc M, Zhang SD, Shukla P, Rai TS, Bjourson AJ, Murray E, Gibson DS, Walsh C
Genomic, Proteomic, and Phenotypic Biomarkers of COVID-19 Severity: Protocol for a Retrospective Observational Study
JMIR Res Protoc 2024;13:e50733
URL: https://www.researchprotocols.org/2024/1/e50733
doi:10.2196/50733
PMID:38354037

Protocol

Development and Evaluation of a Community Health Program to Promote Physical Activity Among Vulnerable Community-Dwelling Older Adults: Protocol for a Prospective Cohort Study

Tina Auerswald[1], MSc; Katharina Zwingmann[1], MSc; Torsten Schlesinger[1], Prof Dr; Katrin Müller[1], PhD

Institute of Human Movement Science and Health, Chemnitz University of Technology, Chemnitz, Germany

Corresponding Author:
Tina Auerswald, MSc
Institute of Human Movement Science and Health
Chemnitz University of Technology
Thüringer Weg 11
Chemnitz, 09126
Germany
Phone: 49 371 531 33
Email: tina.auerswald@hsw.tu-chemnitz.de

Abstract

Background: Vulnerable older adults have a high risk of morbidity and mortality. Regular physical activity (PA) can have a positive effect on the health and health-related behavior of this specific target group. However, evidence of the impact and feasibility of community-based PA promotion interventions for vulnerable older adults is still limited.

Objective: The BeTaSen (Bewegungs-Tandems in den Lebenswelten Chemnitzer Seniorinnen und Senioren: ein Beitrag zur kommunalen Gesundheitsförderung) study aims to evaluate the (1) impact as well as the (2) feasibility, acceptance, and usefulness of a 12-month low-threshold PA intervention program for community-dwelling vulnerable older adults.

Methods: For our population-based prospective observational cohort study, a total of 120 vulnerable older adults (aged 75 years or older) in the area of Chemnitz (Germany) will be recruited to participate in (1) weekly neighborhood-based low-threshold PA meetings with trained mentors (activity tandems) and (2) monthly exercise meetings led by trained exercise instructors. Within the intervention, participants will be encouraged to perform the PA independently. Participants will complete assessments, which will include questionnaires as well as objective measurements of their physical, cognitive, and psychosocial health at 3 different time points (baseline, 6 months after the start, and 6 months after the end of the intervention). Additionally, a process evaluation will be performed, including questionnaires and qualitative interviews, involving the participants, mentors, and municipal project partner representatives.

Results: The BeTaSen project process began in October 2021, with the start of data collection and intervention in August 2022 in the first neighborhoods of the city of Chemnitz. A total of 86 participants were recruited at the time of submission of the manuscript. Longitudinal results are expected by 2025.

Conclusions: This study's results will provide insights on (1) the PA behavior of vulnerable older adults as well as the impact of PA interventions on health-related outcomes such as cognitive, physical, and psychosocial health, and (2) the feasible and useful components of community-based PA interventions. Thus, this pilot study contributes to future recommendations and provides a basis for further research, such as the development of feasible and sustainable target group–specific interventions in community settings.

International Registered Report Identifier (IRRID): DERR1-10.2196/51462

(JMIR Res Protoc 2024;13:e51462) doi:10.2196/51462

KEYWORDS

acceptance; ageing; aging; cognitive; cohort; communal health promotion; community based; community dwelling; community-dwelling older adults; elder; elderly; exercise; feasibility; geriatric; gerontology; observational; older adult; older people; older person; physical activity; psychosocial health; psychosocial; vulnerable

Introduction

Overview

The share of older adults in many European countries' total population is increasing [1]. Aging is associated with a number of physical and health-related changes, including a decline in physical and cognitive performance and an increase in neurodegenerative as well as cardiovascular diseases [2]. Furthermore, demographic developments and age-related increases in individual disease risk pose significant (health-related) economic and social challenges for aging societies. This manifests itself in increased hospitalizations [3] and financial burdens on both the health care system and private households due to rising health care costs [4]. Thus, healthy aging, for example, years of life spent in good health and the maintenance of well-being in old age, has enhanced attention in social and health systems [2]; investments in and programs to promote health are increasing in importance. According to current research, vulnerability in older adults (eg, poverty, loneliness, and a low level of education) can adversely affect the health behavior, morbidity, and mortality of older adults [5-9]. German adults with an income of less than 60% of the national average, for example, have a significantly reduced life expectancy compared to those with above-average incomes [8]. Consequently, it is crucial to focus, especially on these target groups, on health promotion programs.

Among other health-promoting interventions, recent studies confirm that regular physical activity (PA), for example, daily walks, can improve individual and biopsychosocial health among healthy as well as vulnerable older adults [10-16]. Moreover, regular PA can also have a positive impact on social connectedness [13], which in turn can improve older adults' cognitive and mental health and seems to be a relevant factor in successful aging [14]. Accordingly, regular PA can be considered a beneficial investment in individual health capital [15] and in healthy aging in general [11]. Furthermore, previous studies and systematic reviews have shown that PA interventions in community settings can improve older adults' physical function and level of PA [16-20], even in those who are vulnerable [16,20]. For example, Giné-Garriga et al [16] find that physical exercise interventions can improve physical function in frail older adults. Other studies conclude that such programs can have positive effects on older adults' cognitive and mental health [21,22]. Recently, studies investigated the impact of community-based PA interventions on older adults' cognitive, psychosocial, and physical health and on their PA behavior in German communities [23,24]. However, many studies involved mostly healthy older adults who did not belong to a vulnerable group, and current research does not address long-term implications or specific group differences.

Thus, more evidence is needed to confirm these positive impacts, especially on vulnerable older adults, and to implement subsequent health promotion programs. Furthermore, despite the well-known positive effects of regular PA, only a small fraction of older adults in Germany are sufficiently physically active in line with the recommendations of the World Health Organization (WHO) [25]. The WHO and the American College of Sports Medicine recommend adults aged 65 years or older perform moderate to vigorous endurance training for a minimum of 150 minutes per week (in bouts of at least 10 minutes each) [26], in addition to flexibility, strength, and balance training twice per week [25]. Among adults aged 65 years or older, 42% meet the recommendations for endurance training, while only 29% meet those for strength training [25]. In a German health monitoring survey, 36% of older adults aged between 60 and 69 years and nearly 45% of older adults aged between 70 and 79 years reported that they do not engage in any regular PA or exercise [27]. Several studies find that vulnerability, for example, a low level of education, physical restrictions, and poor health status, is negatively associated with older adults' PA level (eg, meeting the WHO's recommended level of PA) [25]. This specific group is thus exposed to severe health risks and potentially early care dependency [5-8]. Due to the high share of older adults who are physically inactive, feasible PA promotion programs targeted specifically at previously physically inactive or vulnerable older adults are especially relevant. To determine the feasibility and sustainability of PA programs targeted specifically at vulnerable older adults, further research on contributing factors and barriers is needed. The literature identifies several internal and external barriers for older adults' participation in PA programs: lack of information about PA offers, physical restrictions, lack of social support to begin with PA, lack of language skills and local accessibility, as well as financial costs [28]. Vulnerable older adults (eg, poverty, loneliness, and a low level of education) perceive high barriers to participation in health-related promotion programs, for example, PA programs [29]. In a systemic review, Franco et al [30] identified six major themes that may influence older adults' participation in PA: (1) social influences, (2) physical restrictions, (3) competing priorities, (4) access difficulties, (5) lack of awareness of the personal benefits of PA, and (6) motivation and beliefs [30]. Furthermore, current research recommends providing PA interventions in community settings for vulnerable older adults that are specifically tailored to the target group and embedded in their immediate social-spatial context (districts and neighborhoods) [31-33]. Moreover, previous studies have shown that personal interventions are particularly effective in promoting PA [34] and that motivators such as social and environmental support, convenience of location, and enjoyment of the activity seem to be relevant factors in interventions targeted at community-dwelling older adults [35]. These influencing factors should be considered when developing exercise interventions to promote PA and its associated positive health benefits among vulnerable community-dwelling older adults.

Some studies conclude that community-based PA programs for older adults are feasible, even over a longer period [36-38]. A systematic review carried out by Farrance et al [39], for example, finds long-term adherence rates of nearly 70% for community-based group exercise programs. Nevertheless, there is limited evidence about the long-term adherence measures included in these programs as well as participants' views [39]. Shvedko et al [40] assert that a PA intervention for community-dwelling older adults at risk of loneliness is accepted by older adults and is feasible. Crombie et al [41] also show that a community-based PA intervention is feasible for sedentary

older adults. However, recent evidence about the feasibility and acceptance of community-based PA interventions and of the different components of such interventions, especially among vulnerable older adults, is limited.

In summary, evidence of the impact and feasibility of PA interventions on the health and health-related behavior of vulnerable community-dwelling older adults remains sparse. Therefore, research should focus on the health-related benefits of intervention programs that promote PA among vulnerable older adults as well as on how intervention programs tackle (internal and external) barriers that discourage the participation of vulnerable older adults in PA programs.

For this reason, the aim of this study is to investigate the impact and feasibility of a 12-month low-threshold targeted PA intervention program on community-dwelling vulnerable older adults. This study protocol describes the study's objectives, the design of the intervention, method, data collection, and considerations for analyzing the data from the PA intervention program of the study BeTaSen (Bewegungs-Tandems in den Lebenswelten Chemnitzer Seniorinnen und Senioren: ein Beitrag zur kommunalen Gesundheitsförderung).

Research Objectives and Research Questions

The main goal of the BeTaSen study is to initiate, sustainably maintain, and promote an active and healthy lifestyle for vulnerable older adults who reside in Chemnitz.

The objectives of the BeTaSen study are described in subsequent paragraphs.

Evaluation of the impact of a 12-month low-threshold PA intervention program on health-related outcomes of vulnerable community-dwelling older adults. In this context, the main research questions are as follows: (1) What are the long-term outcomes for older adults after completing a 12-month, target group-specific community-based PA program? Older adults' PA behavior as well as their physical, cognitive, and psychosocial health are of particular interest in this regard. (2) Are any group differences evident in the long-term outcomes of a 12-month target group-specific community-based PA program among older adults (eg, gender, previous disease, and vulnerability)?

Analyzing the feasibility, acceptance, and usefulness of aspects of a community-based PA intervention for vulnerable community-dwelling older adults. In this context, the main research questions are as follows: (1) Which PA-promoting exercises and activities are considered useful by older adults? (2) Is a target group-specific 12-month PA program feasible for vulnerable community-dwelling older adults and the community setting? and (3) What factors promote or inhibit the successful implementation of a target group-specific PA program for vulnerable community-dwelling older adults?

Methods

Participants and Procedure

The pilot study is being implemented in the German city of Chemnitz. Chemnitz is the third-largest city in the federal state of Saxony in the southeastern part of Germany, with a population of 250,398 (in 2023) [42]. In 2022, nearly 30% of the population of Chemnitz was aged 65 years or older; 15% were aged 75 years or older [43]. In 2020, Chemnitz was the city with the highest median age in Europe (52 years) [44]. Forecast calculations expect that by 2030, the Chemnitz region will have the highest share of people aged 65 years or older (nearly 38%) in Europe [1]. According to population forecasts, the share of Chemnitz residents aged 80 years or older will also rise from 8% in 2018 to nearly 11% in 2030 [45]. Due to these demographic developments, there is an urgent need for target group-specific and low-threshold community health promotion programs (eg, PA interventions) to support the healthy aging of vulnerable older adults who live in the city of Chemnitz. This city was furthermore chosen due to its immediate proximity to the Technical University of Chemnitz, which is conducting the study, and its collaboration with the city of Chemnitz's health department, as well as support from various local partners (eg, citizen platforms).

The aim during the study period is to cover at least 4 out of 39 districts in Chemnitz, representing the city's average demographic age (>50 years) and lower socioeconomic districts (compared to the city of Chemnitz's average) [46,47]. The recruitment of participants is planned primarily due to collaboration with local partners. Announcements will be conducted in different communal facilities for older adults (eg, citizen online platforms, assisted living facilities, and citizens' meeting points) through flyers, at information events, in institutional newspapers, and in the personal conversations of the research team with targeted older adults as well as with staff of different social institutions. The study will be announced in various local and district newspapers, and flyers will be distributed in shops, for example, in bakeries and pharmacies. Additionally, older adults who had participated in previous studies and had consented to being informed about future studies will be contacted.

Eligibility to participate in the study will be determined in personal interviews by qualified staff based on the inclusion and exclusion criteria described below.

Inclusion and Exclusion Criteria

The study primarily targets older adults aged 75 years or older who can be considered vulnerable (eg, poverty, loneliness, physical restrictions, and a low level of education) and who reside in the city of Chemnitz.

Residents are eligible to participate in the study if they (1) have at least basic knowledge of the German language, (2) can independently travel to the assessment and intervention locations, which will be meeting points in close proximity to their home, and (3) provide informed consent to participate in the study.

Participants will be excluded from the study if they have a medical condition preventing them from engaging in regular PA or if they had a severe adverse health event within the last 6 months (eg, myocardial infarction, stroke, fracture, surgery, or pneumonia) to ensure their safety during the PA sessions. Additionally, participants will be excluded if they participate in other clinical trials as well as in regular PA programs at least

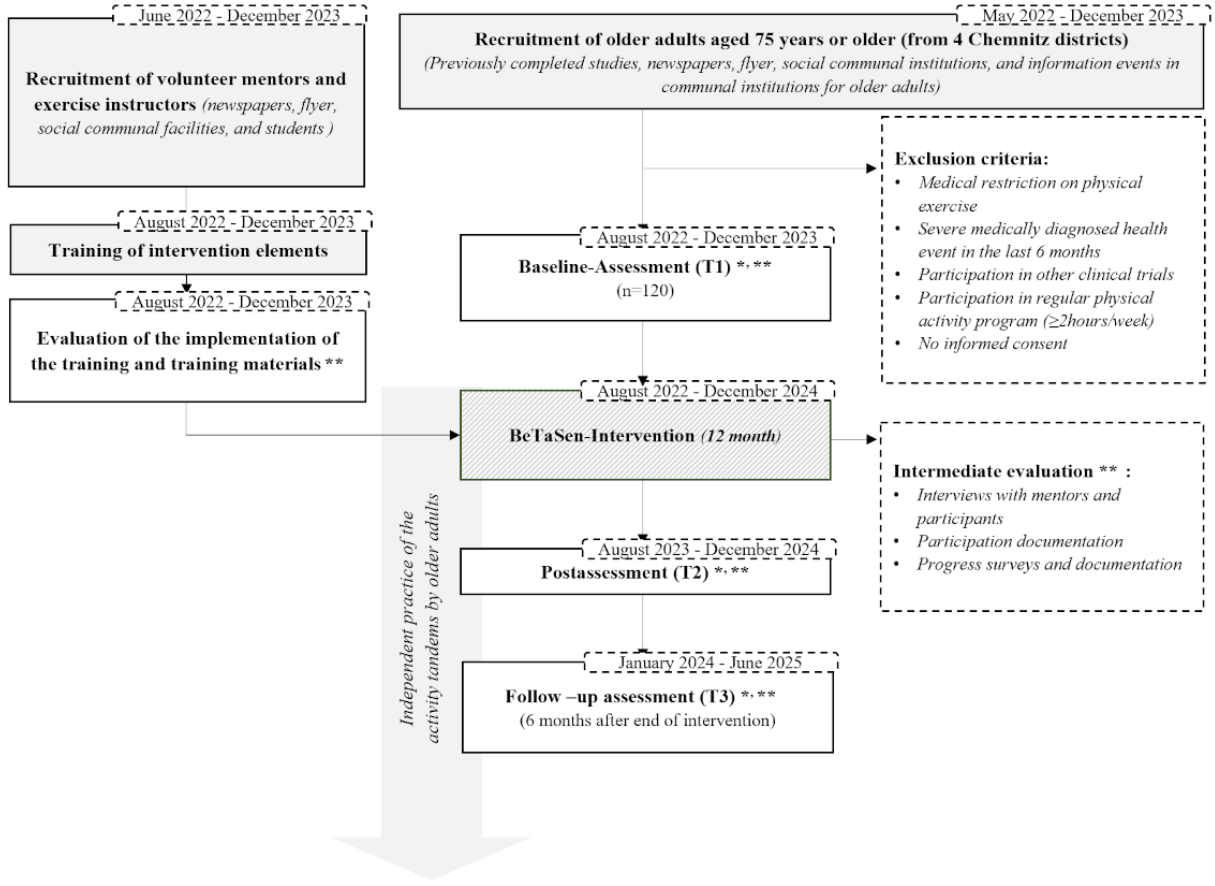
twice a week (eg, regular gym visits or rehabilitation exercise programs) to address older adults who are less physically active and to analyze solely the impact of the intervention.

Study Design

The pilot study is designed as a population-based prospective observational cohort study and is being carried out in 4 different districts in the city of Chemnitz. The first screening for study eligibility will be assessed through a standardized telephone interview with, for example, questions about older adults' age, health conditions, and regular weekly PA exercises. Afterwards, participants will complete an assessment conducted by the research team in their direct neighborhood (eg, in the facilities of community centers), which includes questionnaires and objective measurements of physical and cognitive function and of psychosocial health. In addition to these measurements, participants will wear a pedometer for 7 consecutive days to assess their PA behavior. Measurements will take place at 3 different time points over an 18-month period, namely at the beginning (T1), at the end (T2), and 6 months after the end of the intervention (T3) (Figure 1).

The project was launched in October 2021 and will be completed in September 2025. The first participants were recruited in August 2022.

Figure 1. Study flow of the population-based prospective observational cohort study BeTaSen (Bewegungs-Tandems in den Lebenswelten Chemnitzer Seniorinnen und Senioren: ein Beitrag zur kommunalen Gesundheitsförderung) with a study population of older adults (aged 75 years or older) living in Chemnitz, Germany. *Outcome evalution. **Process evaluation.



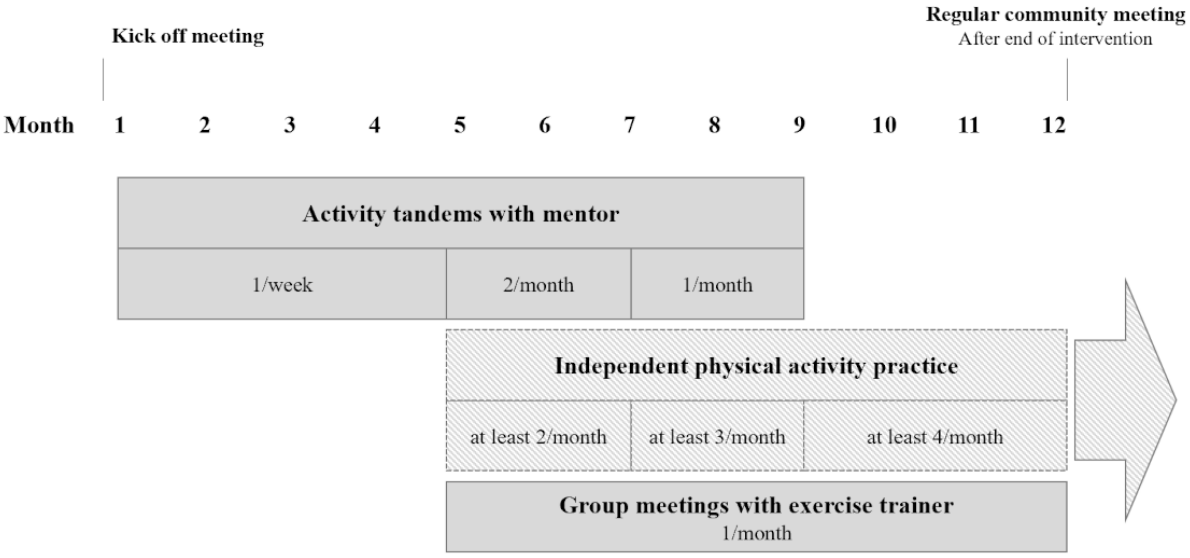
Design and Organization of a Physical Activity–Promoting Intervention

All participants will participate in the target group-specific community-based PA intervention. The pilot study's intervention period is 12 months per participating neighborhood. The participants will be encouraged to continue to engage in PA independently (Figure 2).

The intervention's main component will comprise regular PA meetings organized in so-called "activity tandems," which take place once a week for 30-45 minutes. One activity tandem will include 1 trained voluntary mentor and 3-4 older adults living in the same neighborhood. These activity tandems will primarily engage in low-threshold outdoor PA and exercise together in their neighborhood. For this, easily accessible locations such as urban lawns, walking paths, parks, and fitness trails will be used. In case of bad weather, the PA meetings will be organized in the meeting places of collaborating partners, for example, community centers. Due to the small group size, the content of each tandem lesson can be flexible and tailored to the individual participant's needs. For example, the exercises can be performed at different levels of intensity, or alternative exercises can be selected from a large PA-exercise pool. Additionally, monthly group meetings (eg, 3-4 activity tandems with a total of 12-16 older adults) will be organized in each neighborhood district in the intervention months 5-12 (Figure 2), which will be delivered by trained exercise instructors. In these group meetings, in addition to PA exercises, the following contents will be covered:

knowledge about the positive effects of PA, goal setting and planning, barrier management, and motivational aspects, as well as the sustainable implementation of regular PA in everyday life. Measures like small group sizes, qualified mentors, support material (eg, first aid kits, pulse oximeters, Borg scales), and the accessible, familiar environment of the activity sessions ensure the safety and well-being of participating older adults.

Figure 2. Procedure of the population-based prospective observational cohort study BeTaSen's intervention over a period of 12 months; an example is shown for 1 district (study population: older adults aged 75 years or older living in Chemnitz, Germany). BeTaSen: Bewegungs-Tandems in den Lebenswelten Chemnitzer Seniorinnen und Senioren: ein Beitrag zur kommunalen Gesundheitsförderung).



In total, around 6-8 activity tandems will be created in each of the 4 local districts (approximately 24-32 older adults per district). Thus, the goal is to reach a total of approximately 120 older adults residing in the city of Chemnitz during the project period.

Voluntary mentors (eg, volunteers from Chemnitz, students, and community center staff) will be recruited through various public channels (eg, newspapers, flyers, and mailing lists) in cooperation with municipal partners. The trained mentors should guide the activity tandem groups (eg, demonstrate PA exercises with the help of the manual and walk paths), ensure safety and well-being (eg, through individualized feedback), and encourage the older adults to do independent regular PA exercises. The mentors will also be responsible for communication and the planning of the activity tandem meetings. Researchers on the project team will instruct mentors in a workshop about how to conduct PA meetings, how to appropriately deal with the target group, and how to perform basic first aid procedures. In addition, mentors will be equipped with support materials, such as a manual that includes a range of various low-threshold PA exercises, an overview of district walkways, and additional exercise materials (eg, resistance bands and everyday objects).

The mentors will supervise and support the activity tandems once a week initially at the start of the intervention (intervention months 1-4), later once every 2 weeks (intervention months 5-6), and then once a month (intervention months 7-9). The older adults will thus be gradually encouraged to independently engage in weekly PA activity meetings, as from intervention month 10 onward, they will be prepared for basically independent implementation. Furthermore, older adults will be encouraged to actively participate in the activity tandems, for example, by choosing walkways or suggesting individual exercises. During the intervention period, participants will be given exercise material (eg, brochures) to continue regular PA in their activity tandem and on their own. To ensure that older adults do not overexert themselves as well as to enable them to get a better sense of their exercise limits, their oxygen saturation and heart rate (using a pulse oximeter; Orbisana Healthcare GmbH) as well as a subjective exertion rate (based on the Borg scale; [48]) will be measured at the beginning, middle (during physical exertion), and end of each activity tandem meeting. Based on these measures, participants will receive direct feedback, and the PA exercise intensity can be adjusted individually.

In line with previous literature and findings, the vulnerable target group's potential barriers should be carefully considered when developing the pilot study. To ensure low-threshold accessibility, the activity tandems and monthly group meetings will take place in the older adults' neighborhoods. District plans will be drawn up to identify sitting areas and public toilets, for example, and to pinpoint accessible walkway plans. The activity tandem's PA content will be designed to reflect daily life activities in a very playful, individualized, ability-oriented, and motivational way. Each unit can be freely designed by the mentors and older adults based on the PA, exercise materials, and recommendations provided. Each activity tandem unit should begin with a warm-up, and the components of strength, endurance, coordination, stretching, and relaxation should be addressed regularly in different sessions. In addition, the mentor should include knowledge transfer in each unit, for example,

about the positive effects of PA. Moreover, participation in the PA intervention does not entail any financial costs (eg, materials and participation fees). To promote sustainable participation in the neighborhood meetings and to ensure that the PA meetings are tailored to the vulnerable target group, the activity tandems are purposely organized for a smaller number of older adults. The older adults and mentors of the activity tandems can coordinate the time and location of their weekly meetings flexibly on their own.

Measures

All participants will complete an assessment at baseline (T1), at the end of the 12-month intervention (T2), and 6 months after the end of the intervention (T3). Before each assessment, participants will be asked to fill out a self-administered questionnaire and, for the detection of objective PA behavior, will be given a pedometer to wear for 7 consecutive days. The questionnaire will assess the older adults' psychosocial and physical health and evaluate motivational aspects related to PA in a community setting. Sociodemographic information will be assessed within the questionnaire at T1 only, comprising target group-specific items from the German Health Interview and Examination Survey for Adults [49].

Further measurements will take place in communal facilities in the older adults' neighborhood and will be carried out by qualified staff members. Each assessment will start with the measurement of anthropometric data (height and weight) as well as the registration of current medication intake and existing diagnosed diseases via interview. Using the EQ-5D-3L questionnaire, the participants' subjectively perceived health status in terms of mobility, self-care, regular daily activities, pain, discomfort, anxiety, and depression will then be determined by interview (3 response options: no problems, some problems, and serious problems) [50]. Additionally, their general self-rated health status will be recorded using the vertical visual analog scale EQ-VAS (1-100) [50].

An additional process evaluation will be performed during the intervention period using questionnaires for participants (after a period of 4 weeks) and mentors (after the workshop, 3 months after the intervention). Furthermore, qualitative interviews and informal notes, reports, and documentation of the PA groups will also be obtained from the activity tandems as well as from group meetings (Table 1 for a summary of outcomes).

Table 1. Outcome measurements of the population-based prospective observational cohort study BeTaSen (Bewegungs-Tandems in den Lebenswelten Chemnitzer Seniorinnen und Senioren: ein Beitrag zur kommunalen Gesundheitsförderung). T1 is baseline, T2 is the end of the intervention period (12 months), and T3 is 6 months after the end of the intervention (study population: older adults aged 75 years or older living in Chemnitz, Germany).

Assessment	Instrument or scale	Time of measurement
Outcome		T1, T2, T3
Physical function	• Short Physical Performance Battery (SPPB) • Handgrip strength (handgrip dynamometer)	
Physical activity	• OMRON Walking Style One 2.1. Pedometer (7 days) • PRISCUS-PAQ	
Psychosocial health	• German Depression Scale (DIA-S) • Items of Tilburg Frailty Indicator (TFI) • Items of social support questionnaire (F-SozU)	
Cognitive function	• Montreal Cognitive Assessment (MoCA)	
Process		
Feasibility	• Documentation of activity tandems and group meetings adherence rates • Qualitative interviews and self-administered questionnaire with older adults, mentors, exercise trainers, and communal partners	• Each activity tandem or group session • Monthly during the activity tandem period and after the end of the individual intervention period (older adults); after the end of intervention in the respective neighborhood (mentors, communal partners)
Usefulness	• Qualitative interviews and self-administered questionnaire with older adults, mentors, and exercise trainers	• Monthly during the activity tandem period and after the end of the individual intervention period (older adults); after the end of intervention in the respective neighborhood (mentors, communal partners)
Implementation (barriers and facilitators)	• Qualitative interviews and self-administered questionnaire with mentors, exercise trainers, and communal partners	• Monthly during the activity tandem period and after the end of the individual intervention period (older adults); after the end of intervention in the respective neighborhood (mentors, communal partners)

The main activity and health-related outcomes will be addressed in the following subsections.

PA Behavior

PA behavior will be objectively assessed using the OMRON walking style one 2.1. pedometer (OMRON Cooperation) that records a person's steps, walked kilometers, kilocalories used, and aerobic steps per day over 7 consecutive days. Participants will be instructed to wear the pedometer on their hip during waking times as well as get information about the use and purpose of the pedometer. After the pedometer has been returned, the data will be transferred by study assistants to a Microsoft Excel (Microsoft Corporation) spreadsheet. Activity data for days with at least 500 steps will be included for further analysis, according to Meyer et al [51].

For a subjective evaluation of PA behavior, the PRISCUS-Physical Activity Questionnaire (PRISCUS-PAQ) for older adults aged 70 years or older will be assessed based on interviews during T1, T2, and T3 measurements [52]. PRISCUS-PAQ consists of 10 main items on sedentary behavior, daytime naps, cleaning, and other housework, cycling, gymnastics, group exercise, other PA, walks, and gardening. The total score of the PRISCUS-PAQ reflects the individual's energy expenditure (metabolic equivalent) during the previous week [52].

Physical Performance

The digital grip dynamometer (JAMAR Smart Hand Dynamometer; Performance Health Supply Inc) will be used to assess the participants' handgrip strength. During this test, participants sit upright in a chair without an armrest with their arm bent to 90°. A total of 3 trials are performed per hand, alternating between right and left, with a test duration of 3-5 seconds for each trial. The mean and highest values of the 3 trials for each hand will be analyzed [53]. Additionally, the dominant hand will be queried.

To prove the impact of the exercise intervention on participants physical performance, the widely used, highly reliable, and valid Short Physical Performance Battery (SPPB) will be used [54]. The SPPB includes balance (Romberg, Semi-Tandem, and Tandem), gait speed (4-meter walk), and chair rise tests. Each of these 3 SPPB components is scored from 0 (inability to carry out) to 4 (best performance). There is a potential range between 0 and 12, with higher scores indicating higher functional performance. Participants with cut-off points of less than or equal to 6 points will be classified as "poor performers." Whereas a score of 7-9 points will define the "moderate performers," and the "good performers" will have scores of 9 points or more [55]. In a systematic review and meta-analysis, the SPPB has been shown to be a predictive tool for all-cause mortality [56].

The 2-minute step test (TMST) [57] will be used to assess the participants' endurance capacity. The test starts with a 2-minute rest period. Participants will then stand in front of a wall and raise their thigh to be horizontal to the floor; a mark (strip) will be placed in the position corresponding to the middle of their thigh bone, between the kneecap and frontal prominent pelvis bone. Participants will be instructed to alternately lift their knees as often as they can over a 2-minute period, such that their knees reach the marked location. After completing the TMST, the researcher will record the participants' number of steps, or "steps," as an outcome measure. Before the start of the test, directly after, and 30 seconds after the end of the test, the participant's heart rate in beats per minute and measurement of oxygen saturation in percent (through a pulse oximeter) as well as a subjective rating of perceived exertion (through the Borg scale [48]) will be recorded.

Cognitive Function

The short screening tool Montreal Cognitive Assessment (MoCA) will be used to evaluate the participants' cognitive functions (eg, memory, attention, and basic functions). Participants who achieve a MoCA score between 26 and 30 points will be classified as cognitively healthy; those with a MoCA score of 19-25 will be considered to have mild cognitive impairment; and participants with a MoCA score of less than 19 will be defined as severely cognitively impaired [58].

Psychosocial Health

Psychosocial health outcomes will be assessed using modified, validated, and reliable instruments included in a self-administered questionnaire. Thus, the psychological and social domains of the Tilburg Frailty Indicator [59], the German depression scale for older adults, namely Depression im Alter Skala [60], and modified items of the Fragebogen zur sozialen Unterstützung (social support) [61] will be implemented.

Feasibility and Usefulness

The intervention's feasibility for older adults will be assessed quantitatively based on the adherence rate (number of completed activity tandems and group meetings) during the intervention period. Additionally, participants will be given their own documentation sheet to record their subjective well-being (using a 5-level smiley scale at the beginning, middle, and end of each session) and their level of satisfaction (using a 5-point Likert scale) with each activity tandem meeting. Additional self-administered questionnaires with items to subjectively rate the activity tandem's components will be implemented after every fourth unit. Using a 3-point Likert scale, participants will rate the difficulty of the particular intervention content (eg, strength, endurance, and coordination). In addition, they will be able to use the open response section to indicate which parameters they want to improve and what they want to achieve over the next 4 weeks. Six months into, at the end, and 6 months after the end of the intervention, participants will receive another self-administered questionnaire to assess the intervention's feasibility and sustainability and to identify the optimizing factors of the activity tandems and group meetings.

To evaluate the feasibility of volunteer mentors and the communal context, (1) mentor workshops will be anonymously evaluated using a self-administered questionnaire, and (2) mentors and community project partner representatives will be asked to fill out a self-administered questionnaire (eg, questions on perceived feasibility and sustainability).

Implementation

To assess the implementation of the PA intervention, (1) self-administered questionnaires and (2) qualitative interviews will be conducted with mentors, participants, and community project partner representatives.

Data Management

Participant information will be recorded using an individual identification code. All hard copies will be stored at Chemnitz University of Technology in locked cabinets accessible only to project staff members. Electronic data will be stored on a secured, password-protected computer. The databases will not contain participant identifiers. The data linking participant identifiers and the individual identification codes will be stored separately. Data quality will be ensured through double data entry and range checks for data values. Only project staff members will have access to the final trial data set.

Statistical Analysis

SPSS Statistics (version 29; IBM Corp) and AMOS (version 29; IBM Corp) will be used for all quantitative statistical analyses. To determine the primary outcome at baseline (T1), the study population will be descriptively characterized using the following outcomes: demographics (eg, age, gender, family status, and income), anthropometric comorbidities, PA and health-related behavior (eg, smoking status and alcohol consumption), as well as physical, functional, cognitive, and psychosocial health status. Furthermore, participants' data at the end of the intervention period (T2) and 6 months after its end (T3) will be analyzed to evaluate the long-term impacts, feasibility, and usefulness of the PA intervention. Time effects, group differences (eg, age, gender, vulnerability, and sociodemographic conditions) in terms of physical, cognitive, and psychosocial health, interaction effects, as well as the intervention's feasibility and sustainability, will be analyzed using different parametric or nonparametric statistical methods such as the *t* test, Mann-Whitney *U* test, ANOVA, or Kruskal-Wallis test, depending on the number and size of the group, normal distribution, and homoscedasticity of the sample. Based on current evidence [6-8,25], associations and the strength of the relationship between 2 variables (eg, PA behavior and monthly income and adherence rate and level of education), correlation and regression analyses as well as adjustments for relevant covariates (eg, age, gender, and vulnerable criterion) will be performed. Additionally, multilevel analyses are planned to estimate, for example, the within-person impacts of the intervention program (eg, the impact of PA on well-being).

Qualitative interviews and focus group discussions will be protocolized by researchers and audio recorded, which will be transcribed afterwards. Qualitative data will be analyzed using a qualitative content analysis, according to Mayring and Fenzl [62], with the aim of structured processing of the material by coding relevant interview passages deductively in a theory-driven system of categories. Frequent text material that cannot be assigned to a deductive main category will result in the creation of new (inductive) main categories or subcategories [62]. The coding scheme will subsequently be supplemented with additional categories that emerge from the text material. These newly added categories will either be treated as subcategories of already existing categories or as new main categories. The text material will be coded with the help of MAXQDA (VERBI GmbH).

For this pilot study in the municipal area, the number of participants was calculated based on the project period and the project funding type in terms of feasibility within the study period.

Ethical Considerations

This study was approved by the Ethics Committee of the Chemnitz University of Technology, Faculty of Behavioral and Social Sciences, on May 19, 2022 (101547973). All study participants will be fully informed about the objectives and procedures of the study in German and will be requested to give written informed consent. Additionally, the informed consent contains information about the pseudonymized data collection for the study. Furthermore, the original informed consent allows the secondary analysis without additional consent.

Results

The intervention period of the BeTaSen study started in August 2022 in the first neighborhoods of the City of Chemnitz. Due to the planned staggered launches of the different activity tandems, cross-section data of all participants at T1 (approximately 120 older adults) and initial feasibility data 6 months into the intervention (approximately 60 older adults) will be collected until December 2023. Longitudinal results are expected in the first quarter of 2025. Qualitative and quantitative data on sustainable components for PA interventions among all participating vulnerable older adults are expected in December 2024, after T2, and 6 months after the end of the intervention (T3).

Discussion

The aim of the BeTaSen study is thus to develop, implement, and evaluate a target group-specific PA intervention for community-dwelling older adults living in Chemnitz, the city with the highest median age in Europe [44].

The intervention program was developed especially for the target group of vulnerable community-dwelling older adults on the basis of theoretical aspects [29-35] and considers potential barriers and facilitating factors for initiating and maintaining regular PA. Furthermore, the specific intervention design contains elements promoting long-term use (eg, increasing independent activity sessions over the intervention period, individual goal setting, and knowledge transfer of the effects of PA). Therefore, the intervention concept and their implementation are expected to contribute to (1) increasing or maintaining PA behavior, cognitive and physical function, as well as psychological parameters of older adults, and (2) the feasibility and sustainability of healthy aging in municipalities.

The results of the study will provide insights into (1) the PA behavior of vulnerable older adults as well as the impact of PA interventions on health-related outcomes such as cognitive, physical, and psychosocial health, and (2) feasible and useful

components of community-based PA interventions. Thus, this pilot study bridges a research gap as it focuses on the PA-promotion of vulnerable community-dwelling older adults and implements a low-threshold health promotion concept that may have a sustained impact on the health and health-related behavior of this specific target group. Furthermore, the BeTaSen study will make an important contribution to the state of knowledge of average PA levels and health outcomes, as well as the impact, feasibility, and sustainability of such interventions. As the results of the study will provide insight into the demands, needs, and possible barriers of programs, it can provide a foundation for new interventions and how to deal with difficulties in their implementation.

During and at the end of the project period, interim results and findings will be summarized in information brochures and presented at municipal information events or scientific congresses. When interpreting the results, it should be considered that this research project does not have a randomized, controlled study design since the accessibility of the target group is very restricted and community-based PA programs should be accessible to vulnerable older adults over the entire study period. Nonetheless, the results of the study will provide insights into the within-person impacts of regular PA over a longer time period, and the study design comprises a low-threshold intervention for a highly relevant target population and allows "real-world" applicability. The results of the study will make an important contribution to the research field of aging and movement sciences as well as to the development of health-promoting structures, providing insights into the impact and implementation strategies of community health promotion programs for specific target groups like vulnerable older adults. In addition to publications in scientific journals, the impulses of the study will be implemented into municipal health policies and structures (eg, other neighborhoods, community centers, and health departments) after the end of the project period. Furthermore, the PA program can be distributed throughout Germany through cooperation with the Federal Centre for Health Education and thus shows a high potential for expansion.

Finally, the results will contribute to future recommendations and provide a basis for further research, such as the development of feasible and sustainable target group-specific interventions in community settings.

Acknowledgments

This study is funded by the Federal Centre for Health Education with funds from the statutory health insurance funds as part of the GKV Alliance for Health [63]. The publication is funded by the Deutsche Forschungsgemeinschaft (491193532) and the Chemnitz University of Technology. The authors would like to thank Niki Rodousakis for proofreading the manuscript.

Data Availability

Participants information and data sets generated during and/or analyzed during this study will be stored securely and identified by a coded ID number only to maintain participants' confidentially. Data will be available from the corresponding author on reasonable request.

Authors' Contributions

TA and KM conceptualized the study and conducted the project administration. TA conducted the visualization of the manuscript. TA, KZ, TS, and KM wrote and edited the original draft. TA and KM conducted methodology, investigation, and funding acquisition. KM is responsible for the supervision of the BeTaSen project. All authors read, critically revised, and approved the final manuscript.

Conflicts of Interest

None declared.

References

1. Statistical Office of the European Union. Ageing Europe: Looking at the Lives of Older People in the EU : 2019 Edition. Luxembourg: European Commission Publications Office; 2019.
2. Robert Koch Institute. Gesundheit in deutschland: gesundheitsberichterstattung des bundes. Gemeinsam getragen von RKI und Destatis. 2015. URL: https://www.rki.de/DE/Content/Gesundheitsmonitoring/Gesundheitsberichterstattung/GesInDtld/GesInDtld_node.html [accessed 2024-01-27]
3. Nowossadeck E. Demografische Alterung und Folgen für das Gesundheitswesen. 2012. URL: https://edoc.rki.de/bitstream/handle/176904/3106/2.pdf?sequence=1 [accessed 2024-01-27]
4. Lorenzonii L, Marinoi A, Morgani D, Jamesi C. OECD health working papers. OECD iLibrary. 2019. URL: https://www.oecd-ilibrary.org/social-issues-migration-health/oecd-health-working-papers_18152015 [accessed 2024-01-27]
5. Lehmann SW, Black BS, Shore A, Kasper J, Rabins PV. Living alone with dementia: lack of awareness adds to functional and cognitive vulnerabilities. Int Psychogeriatr 2010;22(5):778-784 [FREE Full text] [doi: 10.1017/S1041610209991529] [Medline: 20478092]

6. Franken G. Allein lebende Personen mit-Demenz. 2017. URL: http://dzd.blog.uni-wh.de/wp-content/uploads/2018/01/Allein-lebende-Menschen-mit-Demenz_final_171204.pdf [accessed 2024-01-27]
7. Lampert T. Soziale ungleichheit und gesundheit im höheren lebensalter. In: Gesundheit und Krankheit im Alter. Eine gemeinsame Veröffentlichung des Statistischen Bundesamtes, des Deutschen Zentrums für Altersfragen und des Robert Koch-Instituts. Berlin, Germany: RKI; 2009.
8. Lampert T, Schenk L. Gesundheitliche konsequenzen des aufwachsens in armut und sozialer benachteiligung. In: Soziale Benachteiligung und Gesundheit bei Kindern und Jugendlichen. Wiesbaden, Germany: VS Verlag für Sozialwissenschaften; 2004:57-83.
9. Sachverständigenrat zur begutachtung der entwicklung im gesundheitswesen. Koordination und Integration | Gutachten | svr-gesundheit.de: SVR Gesundheit Redaktion. 2009. URL: https://www.svr-gesundheit.de/ [accessed 2024-01-27]
10. Cunningham C, O'Sullivan R, Caserotti P, Tully MA. Consequences of physical inactivity in older adults: a systematic review of reviews and meta-analyses. Scand J Med Sci Sports 2020;30(5):816-827. [doi: 10.1111/sms.13616] [Medline: 32020713]
11. Daskalopoulou C, Stubbs B, Kralj C, Koukounari A, Prince M, Prina AM. Physical activity and healthy ageing: a systematic review and meta-analysis of longitudinal cohort studies. Ageing Res Rev 2017;38:6-17 [FREE Full text] [doi: 10.1016/j.arr.2017.06.003] [Medline: 28648951]
12. Warburton DER, Bredin SSD. Health benefits of physical activity: a systematic review of current systematic reviews. Curr Opin Cardiol 2017;32(5):541-556. [doi: 10.1097/HCO.0000000000000437] [Medline: 28708630]
13. Edwards P, Tsouros A. Promoting Physical Activity and Active Living in Urban Environments: The Role of Local Governments. Copenhagen, Denmark: WHO Regional Office for Europe; 2006.
14. Evans IEM, Martyr A, Collins R, Brayne C, Clare L. Social isolation and cognitive function in later life: a systematic review and meta-analysis. J Alzheimers Dis 2019;70(s1):S119-S144 [FREE Full text] [doi: 10.3233/JAD-180501] [Medline: 30372678]
15. Grossman M. On the concept of health capital and the demand for health. J Polit Econ 1972;80:223-255 [FREE Full text] [doi: 10.1086/259880]
16. Giné-Garriga M, Roqué-Fíguls M, Coll-Planas L, Sitjà-Rabert M, Salvà A. Physical exercise interventions for improving performance-based measures of physical function in community-dwelling, frail older adults: a systematic review and meta-analysis. Arch Phys Med Rehabil 2014;95(4):753-769.e3. [doi: 10.1016/j.apmr.2013.11.007] [Medline: 24291597]
17. Chase JAD, Phillips LJ, Brown M. Physical activity intervention effects on physical function among community-dwelling older adults: a systematic review and meta-analysis. J Aging Phys Act 2017;25(1):149-170 [FREE Full text] [doi: 10.1123/japa.2016-0040] [Medline: 27620705]
18. Fitzpatrick SE, Reddy S, Lommel TS, Fischer JG, Speer EM, Stephens H, et al. Physical activity and physical function improved following a community-based intervention in older adults in Georgia senior centers. J Nutr Elder 2008;27(1-2):135-154. [doi: 10.1080/01639360802060223] [Medline: 18928194]
19. Stewart AL, Verboncoeur CJ, McLellan BY, Gillis DE, Rush S, Mills KM, et al. Physical activity outcomes of CHAMPS II: a physical activity promotion program for older adults. J Gerontol A Biol Sci Med Sci 2001;56(8):M465-M470 [FREE Full text] [doi: 10.1093/gerona/56.8.m465] [Medline: 11487597]
20. Lewis M, Peiris CL, Shields N. Long-term home and community-based exercise programs improve function in community-dwelling older people with cognitive impairment: a systematic review. J Physiother 2017;63(1):23-29 [FREE Full text] [doi: 10.1016/j.jphys.2016.11.005] [Medline: 27993488]
21. Tseng CN, Gau BS, Lou MF. The effectiveness of exercise on improving cognitive function in older people: a systematic review. J Nurs Res 2011;19(2):119-131 [FREE Full text] [doi: 10.1097/JNR.0b013e3182198837] [Medline: 21586989]
22. Patel A, Keogh JWL, Kolt GS, Schofield GM. The long-term effects of a primary care physical activity intervention on mental health in low-active, community-dwelling older adults. Aging Ment Health 2013;17(6):766-772. [doi: 10.1080/13607863.2013.781118] [Medline: 23547971]
23. Auerswald T, Hendker A, Ratz T, Lippke S, Pischke CR, Peters M, et al. Impact of activity tracker usage in combination with a physical activity intervention on physical and cognitive parameters in healthy adults aged 60+: a randomized controlled trial. Int J Environ Res Public Health 2022;19(7):3785 [FREE Full text] [doi: 10.3390/ijerph19073785] [Medline: 35409466]
24. Muellmann S, Buck C, Voelcker-Rehage C, Bragina I, Lippke S, Meyer J, et al. Effects of two web-based interventions promoting physical activity among older adults compared to a delayed intervention control group in Northwestern Germany: results of the PROMOTE community-based intervention trial. Prev Med Rep 2019;15:100958 [FREE Full text] [doi: 10.1016/j.pmedr.2019.100958] [Medline: 31410347]
25. Finger JD, Mensink G, Lange C, Manz K, RKI. Gesundheitsfördernde körperliche aktivität in der freizeit bei erwachsenen in deutschland: RKI-bib1 (Robert Koch-Institut). Robert Koch Institute. 2017. URL: https://edoc.rki.de/handle/176904/2650 [accessed 2024-01-27]
26. Nelson ME, Rejeski WJ, Blair SN, Duncan PW, Judge JO, King AC, et al. Physical activity and public health in older adults: recommendation from the American College of Sports Medicine and the American Heart Association. Med Sci Sports Exerc 2007;39(8):1435-1445 [FREE Full text] [doi: 10.1249/mss.0b013e3180616aa2] [Medline: 17762378]

27. Krug S, Jordan S, Mensink GBM, Müters S, Finger J, Lampert T. Körperliche aktivität : ergebnisse der studie zur gesundheit erwachsener in Deutschland (DEGS1). [Physical activity: results of the German health interview and examination survey for adults (DEGS1)]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2013;56(5-6):765-771. [doi: 10.1007/s00103-012-1661-6] [Medline: 23703496]
28. Göhner W, Fuchs R. Änderung des Gesundheitsverhaltens: MoVo-Gruppenprogramme für Körperliche Aktivität und Gesunde Ernährung. Göttingen, Germany: Hogrefe; 2007.
29. Lis K, Olbermann E, von Koenen C, Wisniewski G. Praxishandbuch. Gesundheitsförderung für ältere Menschen in sozial benachteiligten Lebenslagen im Setting Stadtbezirk. Ein Leitfaden mit praktischen Handlungsempfehlungen. 2011. URL: https://www.bundesgesundheitsministerium.de/fileadmin/Dateien/5_Publikationen/Gesundheit/Broschueren/Praxishandbuch_Aelter_werden_in_Eving.pdf [accessed 2024-01-27]
30. Franco MR, Tong A, Howard K, Sherrington C, Ferreira PH, Pinto RZ, et al. Older people's perspectives on participation in physical activity: a systematic review and thematic synthesis of qualitative literature. Br J Sports Med 2015;49(19):1268-1276. [doi: 10.1136/bjsports-2014-094015] [Medline: 25586911]
31. Rütten A, Pfeiffer K. Nationale Bewegungsempfehlungen. Nürnberg, Germany: FAU Erlangen; 2016.
32. Petrescu-Prahova M, Belza B, Kohn M, Miyawaki C. Implementation and maintenance of a community-based older adult physical activity program. Gerontologist 2016;56(4):677-686 [FREE Full text] [doi: 10.1093/geront/gnv024] [Medline: 26035891]
33. Gillette DB, Petrescu-Prahova M, Herting JR, Belza B. A pilot study of determinants of ongoing participation in enhancefitness: a community-based group exercise program for older adults. J Geriatr Phys Ther 2015;38(4):194-201 [FREE Full text] [doi: 10.1519/JPT.0000000000000041] [Medline: 25695473]
34. Richards J, Hillsdon M, Thorogood M, Foster C. Face-to-face interventions for promoting physical activity. Cochrane Database Syst Rev 2013(9):CD010392 [FREE Full text] [doi: 10.1002/14651858.CD010392.pub2] [Medline: 24085592]
35. King WC, Brach JS, Belle S, Killingsworth R, Fenton M, Kriska AM. The relationship between convenience of destinations and walking levels in older women. Am J Health Promot 2003;18(1):74-82. [doi: 10.4278/0890-1171-18.1.74] [Medline: 13677965]
36. Wilcox S, Dowda M, Griffin SF, Rheaume C, Ory MG, Leviton L, et al. Results of the first year of active for life: translation of 2 evidence-based physical activity programs for older adults into community settings. Am J Public Health 2006;96(7):1201-1209 [FREE Full text] [doi: 10.2105/AJPH.2005.074690] [Medline: 16735619]
37. Jancey JM, Clarke A, Howat PA, Lee AH, Shilton T, Fisher J. A physical activity program to mobilize older people: a practical and sustainable approach. Gerontologist 2008;48(2):251-257 [FREE Full text] [doi: 10.1093/geront/48.2.251] [Medline: 18483437]
38. Audsley S, Kendrick D, Logan P, Jones M, Orton E. A randomised feasibility study assessing an intervention to keep adults physically active after falls management exercise programmes end. Pilot Feasibility Stud 2020;6:37 [FREE Full text] [doi: 10.1186/s40814-020-00570-9] [Medline: 32161660]
39. Farrance C, Tsofliou F, Clark C. Adherence to community based group exercise interventions for older people: a mixed-methods systematic review. Prev Med 2016;87:155-166 [FREE Full text] [doi: 10.1016/j.ypmed.2016.02.037] [Medline: 26921655]
40. Shvedko AV, Thompson JL, Greig CA, Whittaker AC. Physical Activity Intervention for Loneliness (PAIL) in community-dwelling older adults: a randomised feasibility study. Pilot Feasibility Stud 2020;6:73 [FREE Full text] [doi: 10.1186/s40814-020-00587-0] [Medline: 32489675]
41. Crombie KM, Leitzelar BN, Almassi NE, Mahoney JE, Koltyn KF. The feasibility and effectiveness of a community-based intervention to reduce sedentary behavior in older adults. J Appl Gerontol 2022;41(1):92-102 [FREE Full text] [doi: 10.1177/0733464820987919] [Medline: 33504249]
42. Bevölkerung des Freistaates Sachsen jeweils am Monatsende ausgewählter Berichtsmonate nach Gemeinden. Statistisches Landesamt des Freistaates Sachsen. 2023. URL: https://www.statistik.sachsen.de/html/bevoelkerungsstand-einwohner.html [accessed 2024-02-09]
43. Corona spezial: bevölkerungsentwicklung in sachsen 2022. Statistisches Landesamt des Freistaates Sachsen. 2022. URL: https://www.statistik.sachsen.de/html/statistischbetrachtet-corona-bevoelkerungsentwicklung.html#a-28815 [accessed 2024-01-27]
44. Are you younger or older than the median age in your region? Statistical Office of the European Union. 2021. URL: https://ec.europa.eu/eurostat/de/web/products-eurostat-news/-/ddn-20211013-2 [accessed 2024-01-27]
45. Bevölkerungsvorausberechnung—anteile der altersgruppen. Bertelsmann Stiftung. 2020. URL: https://www.wegweiser-kommune.de/statistik/chemnitz+anteile-der-altersgruppen+anteil-ab-80-jaehrige-1+2012-2030+balkendiagramm [accessed 2024-01-27]
46. Chemnitz in zahlen—altersstrukturen. FOG-Institut. 2020. URL: https://www.stadtteilkarten-chemnitz.de/altersstrukturen/ [accessed 2024-01-27]
47. Chemnitz in zahlen—sozialstrukturen. FOG-Institut. 2021. URL: https://www.stadtteilkarten-chemnitz.de/sozialstrukturen/ [accessed 2024-01-27]
48. Borg G, Löllgen H. Borg's Perceived Exertion and Pain Scales. Champaign, IL: Human Kinetics; 2001.

49. Gößwald A, Lange M, Kamtsiuris P, Kurth BM. DEGS: studie zur gesundheit erwachsener in Deutschland. Bundesweite quer- und längsschnittstudie im rahmen des gesundheitsmonitorings des Robert Koch-Instituts. [DEGS: German health interview and examination survey for adults. A nationwide cross-sectional and longitudinal study within the framework of health monitoring conducted by the Robert Koch Institute]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2012;55(6-7):775-780. [doi: 10.1007/s00103-012-1498-z] [Medline: 22736155]
50. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med 2001;33(5):337-343. [doi: 10.3109/07853890109002087] [Medline: 11491192]
51. Meyer J, Schnauber J, Heuten W, Wienbergen H, Hambrecht R, Appelrath HJ, et al. Exploring Longitudinal Use of Activity Trackers. : IEEE; 2016 Presented at: 2016 IEEE International Conference on Healthcare Informatics (ICHI); October 04-07, 2016; Chicago, IL p. 198-206. [doi: 10.1109/ichi.2016.29]
52. Trampisch U, Platen P, Burghaus I, Moschny A, Wilm S, Thiem U, et al. Reliabilität des PRISCUS-PAQ : fragebogen zur erfassung körperlicher aktivität von personen im alter von 70 jahren und älter. Z Gerontol Geriat 2010;43(6):399-406. [doi: 10.1007/s00391-010-0118-5]
53. Akter S. Measurement of hand grip strength by digital jamar hand dynamometer: a study on CRP staffs and BHPI students. [dissertation]. University of Dhaka. 2018. URL: http://library.crp-bangladesh.org:8080/xmlui/handle/123456789/520 [accessed 2024-01-27]
54. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol 1994;49(2):M85-M94. [doi: 10.1093/geronj/49.2.m85] [Medline: 8126356]
55. Guralnik JM, Ferrucci L, Pieper CF, Leveille SG, Markides KS, Ostir GV, et al. Lower extremity function and subsequent disability: consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery. J Gerontol A Biol Sci Med Sci 2000;55(4):M221-M231 [FREE Full text] [doi: 10.1093/gerona/55.4.m221] [Medline: 10811152]
56. Pavasini R, Guralnik J, Brown JC, di Bari M, Cesari M, Landi F, et al. Short physical performance battery and all-cause mortality: systematic review and meta-analysis. BMC Med 2016;14(1):215 [FREE Full text] [doi: 10.1186/s12916-016-0763-7] [Medline: 28003033]
57. Rikli RE, Jones CJ. Development and validation of a functional fitness test for community-residing older adults. J Aging Phys Act 1999;7(2):129-161 [FREE Full text] [doi: 10.1123/japa.7.2.129]
58. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005;53(4):695-699. [doi: 10.1111/j.1532-5415.2005.53221.x] [Medline: 15817019]
59. Freitag S, Schmidt S, Gobbens RJJ. Tilburg frailty indicator. German translation and psychometric testing. Z Gerontol Geriatr 2016;49(2):86-93. [doi: 10.1007/s00391-015-0889-9] [Medline: 25953342]
60. Heidenblut S, Zank S. Entwicklung eines neuen depressionsscreenings für den einsatz in der geriatrie. Die "Depression-im-Alter-Skala" (DIA-S). [Development of a new screening instrument for geriatric depression. The Depression in old Age Scale (DIA-S)]. Z Gerontol Geriatr 2010;43(3):170-176. [doi: 10.1007/s00391-009-0067-z] [Medline: 19760357]
61. Fydrich T, Tydecks S, Brähler E, Sommer G. Fragebogen zur Sozialen Unterstützung (F-SozU): Normierung der Kurzform (K-14) [Social Support Questionnaire (F-SozU): Standardization of short form (K-14)]. Zeitschrift für Medizinische Psychologie 2009;18(1):43-48. [doi: 10.1026//0012-1924.45.4.212]
62. Mayring P, Fenzl T. Qualitative inhaltsanalyse. In: Handbuch Methoden der Empirischen Sozialforschung. Wiesbaden, Germany: Springer VS; 2019:633-648.
63. GKV Alliance for Health. URL: https://www.gkv-buendnis.de/ [accessed 2024-02-02]

Abbreviations

BeTaSen: Bewegungs-Tandems in den Lebenswelten Chemnitzer Seniorinnen und Senioren: ein Beitrag zur kommunalen Gesundheitsförderung
MoCA: Montreal Cognitive Assessment
PA: physical activity
PRISCUS-PAQ: PRISCUS-Physical Activity Questionnaire
SPPB: Short Physical Performance Battery
TMST: 2-minute step test
WHO: World Health Organization

Edited by A Mavragani; submitted 01.08.23; peer-reviewed by B Cedeno-Veloz, L Ardigò; comments to author 03.11.23; revised version received 23.11.23; accepted 24.11.23; published 20.02.24.

Please cite as:
Auerswald T, Zwingmann K, Schlesinger T, Müller K
Development and Evaluation of a Community Health Program to Promote Physical Activity Among Vulnerable Community-Dwelling Older Adults: Protocol for a Prospective Cohort Study
JMIR Res Protoc 2024;13:e51462
URL: https://www.researchprotocols.org/2024/1/e51462
doi:10.2196/51462
PMID:38376903

Protocol

Identifying and Validating Alcohol Diagnostics for Injury-Related Trauma in South Africa: Protocol for a Mixed Methods Study

Petal Petersen Williams[1,2,3*], PhD; Megan Prinsloo[4,5,6*], PhD; Margaret M Peden[7,8*], PhD; Ian Neethling[4,5], PhD; Shibe Mhlongo[9,10], MSc; Sithombo Maqungo[11], MBChB, FC Ortho, MMed; Charles Parry[1,12*], PhD; Richard Matzopoulos[4,6*], PhD

[1]Mental Health, Alcohol, Substance use and Tobacco Research Unit, South African Medical Research Council, Cape Town, South Africa
[2]Institute for Life Course Health Research, Department of Global Health, Stellenbosch University, Cape Town, South Africa
[3]Department of Psychiatry and Mental Health, University of Cape Town, Cape Town, South Africa
[4]Burden of Disease Research Unit, South African Medical Research Council, Cape Town, South Africa
[5]Institute for Lifecourse Development, Faculty of Education, Health & Human Sciences, University of Greenwich, London, United Kingdom
[6]School of Public Health, University of Cape Town, Cape Town, South Africa
[7]George Institute for Global Health UK, Imperial College London, London, United Kingdom
[8]WHO Collaborating Centre on Injury Prevention and Trauma Care, London, United Kingdom
[9]Gender and Health Research Unit, South African Medical Research Council, Pretoria, South Africa
[10]Biostatistics Unit, South African Medical Research Council, Pretoria, South Africa
[11]Orthopaedic Trauma Service, Groote Schuur Hospital, University of Cape Town, Cape Town, South Africa
[12]Department of Psychiatry, Stellenbosch University, Cape Town, South Africa
[*]these authors contributed equally

Corresponding Author:
Petal Petersen Williams, PhD
Mental Health, Alcohol, Substance use and Tobacco Research Unit
South African Medical Research Council
PO Box 19070 Francie van Zijl Drive
Tygerberg
Cape Town, 7505
South Africa
Phone: 27 219380337
Email: petal.petersen@mrc.ac.za

Abstract

Background: The burden of alcohol use among patients with trauma and the relative injury risks is not routinely measured in South Africa. Given the prominent burden of alcohol on hospital trauma departments, South Africa needs practical, cost-effective, and accurate alcohol diagnostic tools for testing, surveillance, and clinical management of patients with trauma.

Objective: This study aims to validate alcohol diagnostics for injury-related trauma and assess its use for improving national health practice and policy.

Methods: The Alcohol Diagnostic Validation for Injury-Related Trauma study will use mixed methods across 3 work packages. Five web-based focus group discussions will be conducted with 6 to 8 key stakeholders, each across 4 areas of expertise (clinical, academic, policy, and operational) to determine the type of alcohol information that will be useful for different stakeholders in the injury prevention and health care sectors. We will then conduct a small pilot study followed by a validation study of alcohol diagnostic tools (clinical assessment, breath analysis, and fingerprick blood) against enzyme immunoassay blood concentration analysis in a tertiary hospital trauma setting with 1000 patients. Finally, selected alcohol diagnostic tools will be tested in a district hospital setting with a further 1000 patients alongside community-based participatory research on the use of the selected tools.

Results: Pilot data are being collected, and the protocol will be modified based on the results.

Conclusions: Through this project, we hope to identify and validate the most appropriate methods of diagnosing alcohol-related injury and violence in a clinical setting. The findings from this study are likely to be highly relevant and could influence our primary beneficiaries—policy makers and senior health clinicians—to adopt new practices and policies around alcohol testing

in injured patients. The findings will be disseminated to relevant national and provincial government departments, policy experts, and clinicians. Additionally, we will engage in media advocacy and with our stakeholders, including community representatives, work through several nonprofit partners to reach civil society organizations and share findings. In addition, we will publish findings in scientific journals.

International Registered Report Identifier (IRRID): DERR1-10.2196/52949

(JMIR Res Protoc 2024;13:e52949) doi:10.2196/52949

KEYWORDS

alcohol; diagnostic; surveillance; injuries; violence; road traffic; Africa; South Africa; alcohol misuse; alcohol diagnostics; addiction; mixed methods; trauma; risk; injury; diagnostic tools; diagnostic tool; clinical management; injury; injury prevention; accident; accidents

Introduction

Alcohol indicators obtained from patients seen in emergency departments or admitted to hospitals are one of the key and most cost-effective data sources for estimating the impact of alcohol on communities and health [1] to quantify problem drinking, alcohol-impaired driving, trauma readmissions, and premature death [2]. This assists in identifying high-risk groups that should be targeted for prevention. Effective monitoring of alcohol-related morbidity and mortality requires the collection of alcohol-related indicators, in which regular reports on the key predefined indicators are submitted by hospitals, primary health care units, or emergency services [3,4].

The contribution of alcohol to the global burden of disease is undisputed. In addition to risks such as noncommunicable diseases, infectious diseases, and mental health problems as a result of hazardous and harmful alcohol use [3], the trauma burden of intentional and unintentional risk of injury from alcohol is a major public health concern. Studies from sub-Saharan Africa have highlighted the impact of alcohol on injury and violence [5-8] and concerns over alcohol consumption and alcohol-attributable burden of disease. The lack of attention alcohol-related harm receives from policy makers has been raised [9,10], with calls for stronger and more effective alcohol control measures.

In South Africa, approximately a third (31.2%) of alcohol-attributable deaths in 2012 occurred as a result of injuries, while 15.9% and 12.8% of alcohol-attributable disability-adjusted life years were caused by road traffic injuries and interpersonal violence, respectively [11]. The adult per capita consumption of alcohol in South Africa is extremely high (64.6 g of absolute alcohol per drinker per day). Almost 6 out of 10 South African drinkers older than the age of 15 years are reported to engage in heavy episodic drinking [3], which is strongly associated with increased injury risk.

COVID-19, and the related alcohol bans in South Africa, has brought the impact of alcohol on trauma presenting to health facilities into sharp focus in the country [12]. Moultrie et al [13] and Barron et al [14] demonstrated how a total ban on alcohol during the COVID-19 pandemic resulted in significantly fewer injury deaths. However, the absence of routine and reliable alcohol-related injury surveillance data have been identified as a critical gap, and the government has had to rely on the South African Medical Research Council's (SAMRC) rapid mortality reporting [15] of all injury-related deaths and ad hoc surveillance studies [13,16] to demonstrate the association between the availability of alcohol and alcohol harm. This gap has substantially hindered the ability to provide regular information on changes in the pattern of alcohol-related injuries and limits the ability to measure the impact of policy changes, implementation, and enforcement.

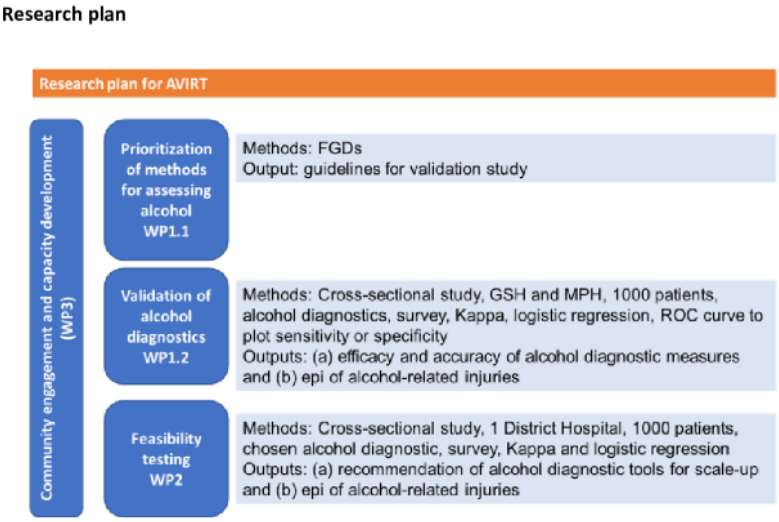
As the country transitions from the COVID-19 crisis response, it is likely that there will be further pressure on the government—from civil society and health and social agencies—to implement more sustained intervention strategies to reduce harmful drinking and to monitor the impact of any interventions on the alcohol-related injury burden. This has highlighted the absence of practical, cost-effective, and accurate alcohol diagnostic tools in the South African trauma setting. Accurate measurement would improve surveillance and influence the clinical management of trauma, inform and improve government policies to address heavy drinking, and assess the impact of alcohol policy reform. The proposed study thus aims to determine the type of information that will be useful for stakeholders in the trauma care and injury prevention sectors, to validate the efficacy of a selection of alcohol diagnostic tools, and to explore their feasibility for wider provincial or national implementation as a routine source of information on the alcohol relatedness of injuries.

Methods

Study Design and Setting

We will use a mixed methods participatory approach across 3 work packages (WPs) to validate alcohol diagnostics for injury-related trauma and assess its use for improving national health practice and policy (Figure 1). Outcomes from this research will inform health practice, policy development, and sustained intervention strategies. A validation study will be conducted in the trauma unit of 2 public health facilities in the Western Cape Province. Further testing will be conducted in 1 hospital setting in the Western Cape Province. These 2 hospitals represent high injury caseloads, particularly for violence and road traffic injuries [17,18].

Figure 1. Diagrammatic illustration of the 3 studies and anticipated outputs. AVIRT: Alcohol Diagnostic Validation for Injury-Related Trauma; GSH: Groote Schuur Hospital; MPH: Mitchell's Plain Hospital.



Research Plan

WP1: Prioritization and Validation of Methods for Assessing Alcohol Use

We will conduct focus group discussions (FGDs) with various stakeholders to ascertain the current alcohol assessment practice in hospitals and the type of information that could assist in the acute management of injured patients and measure alcohol use for public health surveillance. This will be followed by a cross-sectional study to validate the efficacy of three diagnostic tools: (1) clinical assessment, which is based on a clinician's observation of apparent intoxication classifies the alcohol status of a patient into 4 categories as per International Classification of Diseases, Tenth Revision (ICD-10) coding (Y91.0 mild, Y91.1 moderate, Y91.2 severe, and Y91.3 very severe) [19]; (2) breathalyzers provide an estimation of the ethanol content in the breath [20]; and (3) fingerprick test to provide a capillary blood reading in 1-2 minutes and is used to facilitate the clinical process, as well as the use of the ICD-10 Y91 coding [19].

These 3 index tests will be measured against venous blood testing for the presence of ethanol as the reference standard, for which we will use enzyme immunoassay [21] for testing of blood alcohol concentration (BAC). The analysis will be conducted by a private pathology laboratory.

This WP will also describe the epidemiology of alcohol-related injuries among trauma cases presenting at the emergency unit of the selected trauma units through a prospective study. Patients presenting to the trauma units for first-time treatment of their injuries will be interviewed to record patient demographics, the injury intent, and related mechanisms and will be tested for alcohol, using the aforementioned alcohol diagnostic tools. Prior to the validation study, a small pilot study will be conducted over 2 weeks to test the consent procedures, the study questionnaire platform, and the logistics surrounding the blood withdrawal and use of a courier to the contracted laboratory for centrifugation within the 2-hour limit to preserve the alcohol.

WP2: Field Testing Selected Diagnostic Tools

Guided by findings from WP1, the alcohol diagnostic tools will be field tested in a district hospital in a large suburb on the outskirts of Cape Town. This WP aims to test the suitability of validated alcohol diagnostic methods for routine use in a hospital trauma setting on a day-to-day basis.

WP3: Community Engagement and Capacity Development

Engagement with clinicians, operational stakeholders (eg, nongovernmental organizations and emergency services), and individuals working in the policy arena are key to the success of any policy change. These stakeholders will be engaged through the FGDs at the commencement and again at the end to include community and patient representation. Three sets of activities for this phase will thus include:

- Step 1: FGDs on the use of the recommended methods and what would be required for implementation and the role of the measure in health care provision;
- Step 2: workshops or webinars with stakeholders for input on findings and to convey recommendations for uptake and integration; and
- Step 3: community engagement and recommendations for uptake and integration within the health system.

Additionally, capacity development through linking research to policy and practice for increased commitment and support by the government to fund and implement further scale-up of this study in trauma facilities nationally will be threaded through the project.

Study Population and Sampling Procedure

The Applying Research to Policy and Practice for Health (ARCH) stakeholder mapping tool will be used to guide our mapping process [22] to identify stakeholders to participate in FGDs in WP1. FGDs will consist of approximately 6 to 8 participants each, and we anticipate holding 5 FGDs or until theoretical saturation is reached. We will start by making a list of stakeholders in the trauma or injury prevention and alcohol policy fields according to 4 categories: academic, clinical,

operational, and policy stakeholders. Snowballing techniques from the initial core group will be used to identify additional stakeholders. Stakeholders will then be placed in a power-interest matrix based on the information outlined in the mapping [22] in order to categorize South African trauma and injury stakeholders according to their role in the professional landscape, to understand methods of engagement, and to lay out the proposed engagement strategy for the stakeholders throughout the project. FGDs will be exploratory and use a descriptive and contextual design [23]. Participants identified through this process will be invited to take part and required to provide informed consent before participation. FGDs with participants will take place over a 2-month period and will take place digitally to accommodate stakeholders in different locations. These FGDs will be guided by a semistructured interview sheet and run for between 45 and 60 minutes. They will be conducted by a trained facilitator in English.

For inclusion in the WP1 validation study, consenting patients presenting at the trauma units will be 18 years and older and injured <6 to 8 hours prior to arrival at the facility. All new consecutive admissions meeting the inclusion criteria will be tested for alcohol use. Unconscious, ventilated patients, and intoxicated patients with a breathalyzer (BrAC) test result >0.10 mg/L, who will be regarded as too intoxicated for informed consent, will require delayed consent to participate. Patients with severe cognitive impairment will be excluded. If the capacity to consent later is not regained, patients will be excluded. The required sample size to validate and assess the diagnostics' performance is estimated to be 1000 patients. This is based on the eligibility criteria and a targeted sample of cases stratified into a 5-level category variable of intoxication and ICD-10 Y91 severity (Multimedia Appendix 1). From prior studies [24], we expect that 40% will be ineligible for study entry, and a further 60% of the 600 eligible participants will have no alcohol detected or below 0.05 g/100 mL as the legal driving limit. The remaining 4 groups with a positive alcohol detection ("a patient who has a BAC reading of 0.05 g/100 mL" or above) will be closely monitored to ascertain that a minimum of 60 cases per BAC versus ICD-10 Y91/diagnostic measurements code category is captured. Using the expected 60%/40% split in zero versus positive for alcohol, we expect 360 zero alcohol and 240 alcohol-related cases; we do, however, expect that the distribution will vary across BAC categories.

Based on these assumptions, and to test a strict margin that the null hypothesis (k_0=0.7) and the alternative hypothesis (k_1=0.8) will be considered as substantial agreement, further input variables to determining the sample size included the 5 categories with frequencies equal to 0.6 (proportion of 0 alcohol cases) and 0.1 (for each proportion of the 4 remaining alcohol-positive categories). Based on this, we are expecting a sample size of 396 participants at 90% power. This power calculation is based on a significance level of P<.05. Hence, we expect our targeted sample of 600 eligible cases to be enough.

The same sampling strategy will be applied to select patients for the WP2 field testing of validated alcohol diagnostic tools in a district hospital trauma setting and estimated to be approximately 1000 patients. For WP2, the alcohol diagnostic tools will be used in separate data collection periods for ease of use. As the selected district hospital has a monthly average caseload of approximately 561 cases [18], we will plan to collect an approximate sample of 400 eligible cases for 1 alcohol diagnostic tool (breathalyzer), followed by a week's break, then for an additional 400 eligible cases to test a second diagnostic tool (fingerprick test) over the study's planned duration of 90 days.

For WP3, hospital staff from the validation of alcohol diagnostics and field testing will be invited to participate in FGDs (step 1). These will follow the same procedures described previously for the prioritization of methods, and we will include a summary of relevant updated study information. In step 2, national or provincial policy and health management stakeholders and the hospital staff from step 1 will be invited to participate in a feedback workshop to lobby for uptake and implementation nationally and provincially. They will be complemented by approximately 30 key public health, clinician, health management, injury prevention, and policy stakeholders identified using the ARCH stakeholder mapping tool. Step 2 will be held in a hybrid web-based and in-person workshop at the SAMRC in Cape Town after the FGD data have been analyzed. For step 3, we will work with the SAMRC Corporate and Marketing Communications division for policy brief, infographic, and short video design or production. This is for dissemination and engagement with community stakeholders, for research translation and recommendations to national or provincial policy and health management stakeholders, suggesting uptake and integration to other hospital trauma facilities.

Data Collection

The FGDs in WP1 will be conducted to explore stakeholders' knowledge and views on current alcohol indicators collected in trauma settings and gaps in the collection of indicators. We will also obtain opinions from these stakeholders about diagnostic tools, implementation barriers, facilitators, feasibility, acceptability and the appropriateness of collecting routine, and reliable injury surveillance and alcohol-related harm. The findings from this substudy will inform the study on the validation of alcohol diagnostic measures.

For the validation of alcohol diagnostics (WP1), a draft survey questionnaire was adapted from the WHO Collaborative Study on Injuries and Alcohol, a study validated across multicountry sites globally [24]. Information on the injury intent, mechanism, clinical screening according to ICD-10 code Y91, and breathalyzer analysis were retained with additions including the 2 alcohol diagnostic tools (the withdrawal of blood for testing and the fingerprick measure), time of blood withdrawal and fingerprick, the South African Triage Scale, an indication of delayed consent, referring hospital name (if applicable), and hospital folder number.

Fieldworker study nurses will be employed and trained on informed consent and completion of the survey content, and the questionnaire or data capturing on the Kobotools platform [25], using the study's electronic tablet devices. Fieldwork will occur over a 3-month period, with regular monitoring of the caseload

to inform any adjustments to the schedule until the targeted sample of 1000 cases is achieved, of which 600 cases are estimated to be eligible. Study nurses will be required to work midweek during daytime hours as required and during night duty hours of 7 PM to 7 AM over weekends.

Blood samples will be couriered on a regular basis to a Pathcare laboratory near Groote Schuur Hospital. Preservation of the alcohol will be done by centrifuging the samples within 2 hours of blood withdrawal to separate the plasma from the serum and to have it sealed in a separately labeled tube for courier and analysis at a second Pathcare facility identified for blood alcohol testing.

For WP2, the survey questionnaire will be revised for the field testing phase of validated alcohol diagnostics with the addition of questions on the body region injured (head, face, neck, thorax, etc), the nature of injury (fracture, cut, bruise, concussion, etc), the selected alcohol diagnostic tools (Table 1), the patient's drinking history prior to injury, a self-assessment on alcohol intoxication, and information on socioeconomic status.

Table 1. Summary of alcohol diagnostic screening tool measures.

Alcohol diagnostics	Data source
• Clinical assessment: An observational assessment of alcohol intoxication conducted by a trained nurse or medical doctor. The assessment measures the severity of speech impairment, motor coordination, behavioral disturbances, etc through the use of a Likert scale (none to very severe) using ICD-10[a] Y91 codes	• WHO[b] evidence of alcohol involvement is determined by the level of intoxication (ICD-10 Y91 codes) [26]
• Active breathalyzer testing: The blood alcohol concentration measured in breath alcohol (BrAC) mg/L in exhaled breath through a straw. The minimum breath alcohol content detected is 0.03 mg/L BrAC. Alcohol can be detected up to 6-12 hours after the last drink. This method will not be used on ventilated patients • Passive breathalyzer testing: Exhaled breath for all patients to indicate the presence or absence of breath alcohol (yes or no)	• Dräger: SANAS-accredited breathalyzer screener used by blowing through a sterile mouthpiece for a digital reading (active) • Passive: indicate the presence or absence of breath alcohol (yes or no)
• Fingerprick test: Accurate measurement of capillary whole blood samples collected via fingerprick using a lancet. Results displayed in %BAC, mg/L, or µg/dL BrAC. The lowest level of detection is 0.03% BAC	• Fingerprick test: rapid blood alcohol meter
• Blood sample: Detecting the presence or absence of ethanol in the blood [27] using enzyme immunoassay. Venous blood was collected by qualified nurses in a sodium fluoride tube; alcohol levels were reported in g/dL	• Testing with a venous blood sample

[a]ICD-10: International Classification of Diseases, Tenth Revision.

[b]WHO: World Health Organization.

Fieldwork will be based on an idealized week, with a selection of hours across day- and nighttime, during the 3-month period. This is to ensure that the data are representative in terms of the facilities' operating conditions, which are expected to change by time of the month, hour, weekday or weekend, and so forth to assess the suitability of the alcohol diagnostic tools for possible national scale-up.

In WP3, FGDs with participants in step 1 will take place digitally to accommodate stakeholders in different locations. Interview guides will consist of open-ended questions to explore participants' views on the recommended methods, their thoughts on the requirements for implementation (provincially and nationally), and what the role of the measure would be in health care provision more broadly. Specific areas to discuss will include (1) intervention content; (2) intervention delivery; (3) strategies for addressing possible barriers to intervention delivery; (4) research questions around acceptability, feasibility, and sustainability of measuring alcohol-related trauma; and (5) strategies to generate local stakeholder buy-in. These areas of discussion will ensure appropriate information are collected that will inform national stakeholders on the benefits for the adoption of the recommended alcohol diagnostic screening tools for larger implementation [28].

For step 2, the findings from WP1 and WP2, as well as the FGD results from WP3 (step 1) will be shared in a workshop with researchers; clinicians and hospital managers; traffic officials; emergency medical services; police, pathology, and rescue services; and national and provincial policy makers. The output will be a framework to guide the implementation and scale-up of routine diagnostic measuring of alcohol-related trauma. Workshop participants will be asked to evaluate the usefulness of the workshop and their satisfaction with the outcome.

Data Analysis

WP1 and WP3 FGDs will be audio recorded and transcribed verbatim. Thematic analysis will be conducted based on deductive themes focusing on the exploration of current practices, implementation barriers, facilitators, feasibility, acceptability, and appropriateness of conducting alcohol diagnostics in public health facilities (WP1.1) and on acceptability, feasibility, and appropriateness of the recommended measure (WP3). The data will be managed using qualitative data analysis software NVivo (version 12; Lumivero)

and will be presented in line with COREQ (Consolidated Criteria for Reporting Qualitative Research) guidance for reporting qualitative research [29].

For the validation of alcohol diagnostics in WP1 and WP2, data collection will be regularly monitored and managed by the study statistician. The blood alcohol analysis results will be merged into the main database using the unique case ID. The correlation coefficients of the continuous alcohol diagnostic measurements and the blood alcohol tests will be reported and represented graphically. A Kappa statistic [30] will be used to assess the level of agreement between BAC categories and the various alcohol diagnostic tests and the clinical assessment as per ICD-10 (International Classification of Diseases) Y91 codes. Taking into consideration that the alcohol diagnostic measures are ordinal responses, we will use ordinal regression to model the receiver operating characteristic (ROC) curve [31,32]. This diagnostic test plots sensitivity against the specificity of the alcohol diagnostics measures against the gold standard BAC. The area under the ROC curve will also be used to characterize the accuracy of the diagnostic tests, providing all information on its performance, instead of only a single estimate of the test's sensitivity and specificity. The trade-offs between the ROC curve's sensitivity and specificity can then be assessed to inform a decision threshold [33,34] for the alcohol diagnostic methods to be used in phase 2. Any level above 70%, sensitivity and specificity will be acceptable and is usually considered as "fair," followed by 80% as "good" and 90% as "excellent."

If multiple tests meet the same criteria, we will use the area under the curve to determine the best test. We will, however, proceed to test the feasibility of use for both the breathalyzer and the Fingerprick test if they meet the specified sensitivity and specificity criteria. Besides reporting the results of validating the alcohol diagnostic tools, descriptive statistics for analysis will include age and gender, followed by an analysis of the severity of the injury (assessed by the triage scale), the intent of the injury (violence, road traffic, unintentional, and self-harm), the related mechanism of injury (ie, gunshot, stabbing, pedestrian, driver, fall, etc), and BAC categories. Data analysis will be conducted on STATA (version 17; Stata Corp). Data will be presented in line with STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidance for reporting cross-sectional studies [35].

For the field testing (WP2), we will follow the same data management and analysis procedures and packages as for the validation of alcohol diagnostics. Further analysis will include patient demographics, the nature of injury (fracture, sprain, open wound, burn, etc) and body region injured, the intent of the injury (violence, road traffic, unintentional, and self-harm) and the related mechanism of injury (ie, gunshot, stabbing, pedestrian, driver, fall, etc), and triage scale. We will use ordinal regression to analyze the severity of injuries (as indicated by the triage scale) as the outcome, and the level of intoxication (indicated as 0.05 g/100 mL and above) as one of the independent variables. In addition, a multinomial regression will be used to assess the association between the outcome as the type of injury with the level of alcohol intoxication. As information on drinking prior to injury will be recorded to determine the type of alcohol and volume consumed, the dose-response relation between the number of drinks consumed within 6 hours leading up to the injury and the relative risk of being injured will be analyzed and reported. Socioeconomic information on employment status, household income, and suburb of residence will be captured and used to inform alcohol policies.

For the workshop evaluation form in WP3, we will sum each evaluation item to create scores for the evaluation form and will summarize using mean with the SD or median with IQR.

Patient and Public Involvement

Clinicians are an important participant group and were involved in the initial design of the study and as coinvestigators. We will be using a participatory approach through stakeholder engagement initiated in the prioritization of methods to include community and patient representation; then incorporating a synthesis of findings from the validation of alcohol diagnostics and suitability testing to conduct qualitative research on the use of the recommended alcohol diagnostic method. Feedback will be sought on requirements for uptake and integration within the health system, which has a specific focus on community-based participatory research for study synthesis and recommendations. This final uptake activity is iterative and dependent on the outcomes of the formative work. Therefore, the study overall is geared to soliciting participant co-design.

Ethical Considerations

Ethical approval for the study has been granted by the research ethics committee of the South African Medical Research Council (EC005-2/2022) and approval from the Western Cape Health Department. Written informed consent will be obtained from all study participants, and all data will be anonymized. No compensation will be provided for study participation.

Results

Pilot data are being collected, and the protocol will be modified based on the results. The findings will be disseminated to relevant national and provincial government departments, policy experts, and clinicians. We will publish findings in scientific journals, engage in media advocacy, and share findings with our stakeholders, including community representatives, nonprofit partners, and civil society organizations.

Discussion

There is a lack of routine and reliable injury surveillance specifically alcohol-related harm data in South Africa to respond to the related trauma burden. Additionally, research to develop systems or reliable mechanisms to test alcohol-related trauma and to monitor the impact of interventions is lacking. Alcohol is an established risk factor for violence and injuries and accurately monitoring alcohol relatedness in response to interventions, policy changes, and so forth will be necessary to evaluate effectiveness as suggested by the WHO SAFER strategy of "*Monitoring*," 1 of 3 essential strategies aimed at government officials for the purpose of developing evidence-based alcohol policies and action plans to address alcohol harm [36]. The prominent role of alcohol in the trauma

setting has become particularly pronounced during the COVID-19 lockdown, and this study will provide crucial evidence needed for the effective measurement of alcohol-related trauma to improve injury surveillance and clinical management. A few limitations of the study have been identified. First, expert stakeholders included in FGDs will be restricted to known contacts within the field. However, by using the ARCH stakeholder mapping tool to identify appropriate stakeholders, we are confident that we will involve relevant individuals, groups, organizations, and institutions and engage with them in a manner that can contribute to successful research uptake [22]. Second, the validity testing of the alcohol diagnostics will use enzyme immunoassay instead of the gold standard gas chromatography method. The detection of ethanol by gas chromatography, which has the advantage of being able to separate ethanol from other alcohol, is widely considered as the "gold standard" for alcohol measurement [21,27]. Due to the cost implications for this method of testing and the fact that we will not be using the results of this study in medicolegal cases, we will be using enzyme immunoassay [21] for testing of blood alcohol and will consider this as the gold standard for the purpose of this study. Third, validity testing at a tertiary hospital could influence the cut-off period to detect alcohol within the blood due to referrals from primary and secondary health facilities. However, the selected tertiary hospital was specifically selected as the site for validating the alcohol diagnostic tools, as it is a large tertiary hospital situated in Cape Town, South Africa, where the trauma unit is burdened by high injury caseloads, particularly for violence and road traffic injuries [16,17,37]. Through this study, we hope to identify and validate the most appropriate methods of diagnosing alcohol-related injury and violence in clinical settings. The findings from this study are likely to be highly relevant and could influence our primary beneficiaries—policy makers and senior health clinicians—to adopt new practices and policies around alcohol testing in injured patients.

Acknowledgments

This study was supported by the South African Medical Research Council Intramural Early- to Mid-Career Research Flagship Award.

Data Availability

The data generated and analyzed during this study was subject to restricted consent from participants. The data can be made available by the corresponding author upon reasonable request.

Authors' Contributions

PPW and MP conceptualized the paper and are joint first authors. PPW, RM, and MMP developed the first draft. PPW, MP, MMP, IN, S Mhlongo, S Maqungo, CP, and RM edited the subsequent versions of the draft. All authors have reviewed and accepted the final version of the protocol and given their permission for publication. MMP, CP, and RM are joint last or senior authors.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Targeted sampling strategy with minimum sample requirement, prior to eligibility assumptions by blood alcohol concentration reading and Y91 code.
[PDF File (Adobe PDF File), 147 KB - resprot_v13i1e52949_app1.pdf]

References

1. Flynn A, Wells S. Community indicators: assessing the impact of alcohol use on communities. Alcohol Res 2013;35(2):135-149 [FREE Full text] [Medline: 24881322]
2. Rootman DB, Mustard R, Kalia V, Ahmed N. Perceptions and realities of testing for alcohol and other drugs in trauma patients. J Trauma 2007;63(6):1370-1373. [doi: 10.1097/TA.0b013e31815b837a] [Medline: 18212663]
3. Global Status Report on Alcohol and Health 2018. Geneva: World Health Organization. 2018. URL: https://www.who.int/publications/i/item/9789241565639
4. Parry CDH, Trangenstein PJ, Erasmus J, Diedericks A, Harker N. Developing indicators to measure the implementation of the Western Cape alcohol harms reduction strategy in South Africa. Afr J Drug Alcohol Stud 2020;20(2):93-117 [FREE Full text] [doi: 10.4314/ajdas.v20i2.1]
5. Staton CA, Vissoci JRN, Toomey N, Abdelgadir J, Chou P, Haglund M, et al. The impact of alcohol among injury patients in Moshi, Tanzania: a nested case-crossover study. BMC Public Health 2018;18(1):275 [FREE Full text] [doi: 10.1186/s12889-018-5144-z] [Medline: 29466975]

6. Liebenberg J, du Toit-Prinsloo L, Saayman G, Steenkamp V. Prevalence and profile of drugs and alcohol in fatally injured drivers in Pretoria, South Africa. Afr Saf Promot 2021;18(1):61-80 [FREE Full text]
7. Greene MC, Kane JC, Tol WA. Alcohol use and intimate partner violence among women and their partners in sub-Saharan Africa. Glob Ment Health (Camb) 2017;4:e13 [FREE Full text] [doi: 10.1017/gmh.2017.9] [Medline: 29230309]
8. Meel BL. Alcohol-related traumatic deaths in Transki region, South Africa. Internet J Medical Update 2006;1(1):13-18 [FREE Full text] [doi: 10.4314/ijmu.v1i1.39829]
9. Ferreira-Borges C, Parry CDH, Babor TF. Harmful use of alcohol: a shadow over sub-Saharan Africa in need of workable solutions. Int J Environ Res Public Health 2017;14(4):346 [FREE Full text] [doi: 10.3390/ijerph14040346] [Medline: 28346373]
10. Morojele NK, Dumbili EW, Obot IS, Parry CDH. Alcohol consumption, harms and policy developments in sub-Saharan Africa: the case for stronger national and regional responses. Drug Alcohol Rev 2021;40(3):402-419. [doi: 10.1111/dar.13247] [Medline: 33629786]
11. Matzopoulos R, Cois A, Probst C, Parry CDH, Vellios N, Sorsdahl K, et al. Estimating the changing burden of disease attributable to alcohol use in South Africa for 2000, 2006 and 2012. S Afr Med J 2022;112(8b):662-675 [FREE Full text] [doi: 10.7196/SAMJ.2022.v112i8b.16487] [Medline: 36458346]
12. Matzopoulos R, Walls H, Cook S, London L. South Africa's COVID-19 alcohol sales ban: the potential for better policy-making. Int J Health Policy Manag 2020;9(11):486-487 [FREE Full text] [doi: 10.34172/ijhpm.2020.93] [Medline: 32610805]
13. Moultrie TA, Dorrington RE, Laubscher R, Groenewald P, Parry CDH, Matzopoulos R, et al. Unnatural deaths, alcohol bans and curfews: evidence from a quasi-natural experiment during COVID-19. S Afr Med J 2021;111(9):834-837 [FREE Full text] [doi: 10.7196/SAMJ.2021.v111i9.15813] [Medline: 34949245]
14. Barron K, Parry CDH, Bradshaw D, Dorrington R, Groenewald P, Laubscher R, et al. Alcohol, violence and injury-induced mortality evidence from a modern-day prohibition. Rev Econ Stat 2022:1-45 [FREE Full text] [doi: 10.1162/rest_a_01228]
15. Bradshaw D, Laubscher R, Dorrington R, Groenewald P, Moultrie T. Report on weekly deaths in South Africa 1 January—29 December 2020 (week 52). South African Medical Research Council. 2021. URL: https://www.samrc.ac.za/sites/default/files/bod/weeklyreports/weekly29December2020.pdf [accessed 2024-02-13]
16. Navsaria PH, Nicol AJ, Parry CDH, Matzopoulos R, Maqungo S, Gaudin R. The effect of lockdown on intentional and nonintentional injury during the COVID-19 pandemic in Cape Town, South Africa: a preliminary report. S Afr Med J 2020:13183 [FREE Full text] [Medline: 33334392]
17. Nicol AJ, Sorsdahl K, Hoffman R. Violence and substance use at a Cape Town trauma centre. 2013 Presented at: Safety and Violence Initiative (SAVI) of the University of Cape Town inaugural conference; 2013; Cape Town.
18. Parak M. Hospital and Emergency Centre Tracking Information System (HECTIS) trauma data. Western Cape Government. Cape Town, South Africa; 2021. URL: https://www.westerncape.gov.za/news/western-cape-government-launches-safety-dashboard [accessed 2024-02-13]
19. Touquet R, Harris D. Alcohol misuse Y91 coding in ICD-11: rational terminology and logical coding specifically to encourage early identification and advice. Alcohol Alcohol 2012;47(3):213-215 [FREE Full text] [doi: 10.1093/alcalc/ags012] [Medline: 22414920]
20. Hadland SE, Levy S. Objective testing: urine and other drug tests. Child Adolesc Psychiatr Clin N Am 2016;25(3):549-565 [FREE Full text] [doi: 10.1016/j.chc.2016.02.005] [Medline: 27338974]
21. Horvat V, Mandic S, Mandic D, Nestic M, Jonjic J, Majetic-Cetina N. Comparison of enzyme immunoassay and gas chromatography method for determination of whole blood and urine alcohol levels. 2018 Presented at: 3rd Slovenian Congress of Clinical Chemistry with International Participation and 18th International Symposium of Slovenian Association for Clinical Chemistry and Croatian Society of Medical Biochemists; November 13–15, 2008; Ljubljana, Slovenija.
22. Mtika W, Wicox H, De Colombi NF. Stakeholder mapping tool for applying research to policy and practice for health (ARCH). The Global Health Network. 2021. URL: https://arch.tghn.org/stakeholder-mapping-tool-arch-doi/ [accessed 2024-02-13]
23. Moriarty J. Qualitative methods overview. School for Social Care Research. 2011. URL: http://eprints.lse.ac.uk/41199/1/SSCR_Methods_Review_1-1.pdf [accessed 2022-07-04]
24. WHO collaborative study on alcohol and injuries: final report. World Health Organization. 2007. URL: https://www.who.int/publications/i/item/alcohol-and-injury-in-emergency-departments [accessed 2024-02-18]
25. Simple, robust and powerful tools for data collection. Kobotoolbox. 2018. URL: https://www.kobotoolbox.org/ [accessed 2022-07-04]
26. ICD-10 Y91 codes: evidence of alcohol involvement determined by level of intoxication. World Health Organization. 2019. URL: https://www.rxreasoner.com/icd10codes/Y91 [accessed 2024-02-13]
27. Jones AW. Alcohol, its analysis in blood and breath for forensic purposes, impairment effects, and acute toxicity. WIREs Forensic Sci 2019;1(6):e1353 [FREE Full text] [doi: 10.1002/wfs2.1353]
28. Scott SD, Plotnikoff RC, Karunamuni N, Bize R, Rodgers W. Factors influencing the adoption of an innovation: an examination of the uptake of the Canadian Heart Health Kit (HHK). Implementation Sci 2008;3(1):41 [FREE Full text] [doi: 10.1186/1748-5908-3-41]

29. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. Int J Qual Health Care 2007;19(6):349-357 [FREE Full text] [doi: 10.1093/intqhc/mzm042] [Medline: 17872937]
30. Cohen J. Weighted kappa: nominal scale agreement with provision for scaled disagreement or partial credit. Psychol Bull 1968;70(4):213-220. [doi: 10.1037/h0026256] [Medline: 19673146]
31. Hanley JA, McNeil BJ. The meaning and use of the area under a Receiver Operating Characteristic (ROC) curve. Radiology 1982;143(1):29-36 [FREE Full text] [doi: 10.1148/radiology.143.1.7063747] [Medline: 7063747]
32. Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. Radiology 1983;148(3):839-843 [FREE Full text] [doi: 10.1148/radiology.148.3.6878708] [Medline: 6878708]
33. Tosteson AN, Weinstein MC, Wittenberg J, Begg CB. ROC curve regression analysis: the use of ordinal regression models for diagnostic test assessment. Environ Health Perspect 1994;102(Suppl 8):73-78 [FREE Full text] [doi: 10.1289/ehp.94102s873] [Medline: 7851336]
34. Luo J, Xiong C. DiagTest3Grp: an R package for analyzing diagnostic tests with three ordinal groups. J Stat Softw 2012;51(3):1-24 [FREE Full text] [doi: 10.18637/jss.v051.i03] [Medline: 23504300]
35. Cuschieri S. The STROBE guidelines. Saudi J Anaesth 2019;13(Suppl 1):S31-S34 [FREE Full text] [doi: 10.4103/sja.SJA_543_18] [Medline: 30930717]
36. The SAFER Technical Package: Five Areas of Intervention at National and Subnational Levels. Geneva, Switzerland: World Health Organization; 2019. URL: https://www.paho.org/en/documents/safer-technical-package-five-areas-intervention-national-and-subnational-levels [accessed 2024-02-14]
37. Nicol A, Knowlton LM, Schuurman N, Matzopoulos R, Zargaran E, Cinnamon J, et al. Trauma surveillance in Cape Town, South Africa: an analysis of 9236 consecutive trauma center admissions. JAMA Surg 2014;149(6):549-556 [FREE Full text] [doi: 10.1001/jamasurg.2013.5267] [Medline: 24789507]

Abbreviations

ARCH: Applying Research to Policy and Practice for Health
BAC: blood alcohol concentration
COREQ: Consolidated Criteria for Reporting Qualitative Research
FGD: focus group discussion
ICD-10: International Classification of Diseases, Tenth Revision
ROC: receiver operating characteristic
SAMRC: South African Medical Research Council
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology
WP: work package

Edited by A Mavragani; submitted 26.09.23; peer-reviewed by TC Hardcastle; comments to author 25.01.24; revised version received 29.01.24; accepted 30.01.24; published 11.03.24.

Please cite as:
Petersen Williams P, Prinsloo M, Peden MM, Neethling I, Mhlongo S, Maqungo S, Parry C, Matzopoulos R
Identifying and Validating Alcohol Diagnostics for Injury-Related Trauma in South Africa: Protocol for a Mixed Methods Study
JMIR Res Protoc 2024;13:e52949
URL: https://www.researchprotocols.org/2024/1/e52949
doi:10.2196/52949
PMID:38466974

Protocol

Group Acceptance and Commitment Therapy for Recovery From Psychosis: Protocol for a Single-Group Waitlist Trial

Marilyn L Cugnetto[1,2], PhD; Eric M J Morris[1,2], PhD; Siobain F Bonfield[3], DPsych (Clin); Jesse Gates[2,4], MPsych (Clin), PhD; Ilona Morrison[5], BOT; Ellie R Newman[2,3,6], DPsych (Clin); Julia D Nicholls[2,6], BA (Hons), DPsych (Clin); Lisa M Soares[7], DPsych (Clin); Megan T Antonucci[5], MPsych (Clin); Jacinta R Clemente[1], BA (Hons), MPsych; Claire L M Garratt[6], BA (Hons), MPsych (Clin); Eliot Goldstone[7], DPsych (Clin); David A Pavone[1], MPsych (Clin); John Farhall[2,7], MA (ClinPsych), PhD

[1]Mental Health Division, Northern Health, Epping, Victoria, Australia

[2]Department of Psychology, Counselling & Therapy, School of Psychology & Public Health, La Trobe University, Bundoora, Victoria, Australia

[3]Peninsula Health Mental Health Service, Frankston, Victoria, Australia

[4]Orygen, Parkville, Victoria, Australia

[5]St Vincent's Hospital, Melbourne, Victoria, Australia

[6]Alfred Mental and Addiction Health, Melbourne, Victoria, Australia

[7]NorthWestern Mental Health, Royal Melbourne Hospital, Melbourne, Victoria, Australia

Corresponding Author:
Eric M J Morris, PhD
Department of Psychology, Counselling & Therapy
School of Psychology & Public Health
La Trobe University
George Singer Building Rm GS407
Kingsbury Drive
Bundoora, Victoria, 3083
Australia
Phone: 61 03 9479 2472
Email: Eric.Morris@latrobe.edu.au

Abstract

Background: Psychological interventions, along with antipsychotic medications, are recommended for adults diagnosed with a psychotic disorder. While initially designed to mitigate positive symptoms, psychological interventions targeting personal recovery were developed and aligned with the recovery framework that many mental health services have adopted. Acceptance and Commitment Therapy (ACT) for psychosis is one such intervention that shows promise when delivered in an individual format. There is preliminary evidence that ACT for psychosis in a group format improves recovery.

Objective: This trial aims to evaluate the effectiveness of the "Recovery ACT" group program on personal recovery among adults living with a psychotic disorder.

Methods: Our unfunded study is a multiagency, prospective, nonrandomized, waitlist control, single-group trial of the Recovery ACT group program. The program involves 7 weekly group sessions of 90 minutes duration and a 90-minute booster session held 1 month later. We intend to recruit 160 adults living with a psychotic disorder who enroll in a group that is offered as a routine clinical service at participating public mental health services in Melbourne, Victoria, Australia. The 4 assessment time points are 4-6 weeks before the start of the group program, at the start of the group program, at the end of the group program, and at the booster session. There is an optional midgroup assessment and follow-up study. The primary outcome is personal recovery. Secondary outcomes include participants' well-being and psychological flexibility processes. Qualitative data are also collected from participants and facilitators.

Results: Recruitment began in September 2019 and is ongoing until 2024, subsequent to a 24-month disruption due to the COVID-19 pandemic. As of the submission of this paper, 93 participants consented to the evaluation, 65 completed T1 measures, and 40 had a complete data set for the proposed analyses.

Conclusions: This is the first trial evaluating the effectiveness of the Recovery ACT group program on personal recovery for adults living with a psychotic disorder. Findings will contribute to knowledge about psychosocial interventions for adults living with psychosis. This trial may also serve as an example of a partnership between clinicians and academics that can facilitate the translation of research into practice.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12620000223932; https://anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12620000223932

International Registered Report Identifier (IRRID): DERR1-10.2196/49849

(JMIR Res Protoc 2024;13:e49849) doi:10.2196/49849

KEYWORDS

Acceptance and Commitment Therapy; ACT; group therapy; interventions; personal recovery; protocol; psychosis; psychotic disorders; public mental health services

Introduction

Background and Rationale

Schizophrenia spectrum disorders have a prevalence rate of 3.3 per 1000 individuals worldwide [1], with schizophrenia ranking as the twelfth most disabling disorder [2]. Psychotic disorders are typically first diagnosed in young adulthood and can run a chronic course [3]. About two-thirds of individuals diagnosed with a psychotic disorder continue to experience persistent psychotic symptoms despite adhering to antipsychotic medication regimens; about 20% do not respond at all [4]. In addition, there is a high prevalence of comorbid anxiety and mood disorders—about 40% experience anxiety [5,6] and 30%-80% experience depression [6,7]—and other challenges (eg, stigma and social exclusion) that impact well-being and functioning. Persisting psychotic symptoms, comorbid anxiety and depression, and other challenges not only contribute to an individual's level of distress and functioning but also impact a person's ability to fully engage in life [8], referred to as personal recovery [9].

For over 2 decades, psychological and psychosocial interventions have been internationally recommended as adjuncts to pharmacological interventions [10-13]. The leading evidence-based psychological intervention recommended for psychotic disorders is cognitive behavioral therapy for psychosis (CBTp). This intervention involves teaching skills to modify unhelpful thinking patterns that impact behavior [14] and primarily targets reduction in psychotic symptoms and, arguably, distress and functioning as well. While meta-analyses demonstrate that CBTp reduces psychotic symptoms (most notably positive symptoms) with a small effect size [15-17], CBTp does not appear to mitigate distress or improve quality of life [18]. The latter findings continue to be challenged [19,20]. Modifications of CBTp (eg, low-intensity CBTp [21,22] and group CBTp [23]) are promising, though they have yet to amass robust evidence to be recommended in treatment guidelines.

Another promising psychological therapy for psychotic disorders is Acceptance and Commitment Therapy (ACT). This approach involves developing psychological flexibility, which is the ability to be in conscious contact with the present moment, and the capacity to persist with or change behavior based on whether it aligns with one's personal values [24]. Psychological flexibility processes include willingness to be with mental experiences (thoughts, feelings, sensations, etc) instead of engaging in experiential avoidance; cognitive defusion (distancing or observing with openness and curiosity) with mental experiences; engagement in valued actions; and mindfulness (ie, awareness of the present moment) [24]. ACT adapted for individuals living with a psychotic disorder has been implemented in both inpatient and outpatient settings. There is emerging evidence [25] that this intervention not only reduces rehospitalization [26-28] but can also improve quality of life and personal recovery [29].

The first ACT for psychosis group intervention targeting quality of life and social functioning was a 4-session group (2-hour sessions run weekly) known as the "ACT for Life" program, a manualized protocol developed by researchers in the United Kingdom for adults living with psychosis [30,31]. An initial uncontrolled study evaluating this program at a community psychosis service in the United Kingdom [32] demonstrated small improvements in functioning and mood after group completion. A subsequent controlled study [33] demonstrated the positive effects of group participation on well-being over time and greater independence, as indicated by service use changes. Both studies demonstrated that the group was feasible and acceptable to adults living with psychosis.

Building on promising results from individual and group ACT programs for psychosis, the ACT for Life program was adapted for public outpatient mental health services in Melbourne, Victoria, Australia [34]. A pilot of the adapted program, referred to as "Recovery ACT," was implemented by public mental health service clinicians as part of their routine practice and evaluated using pre- and postgroup outcome measures together with qualitative feedback from facilitators and participating consumers [35]. Results from the uncontrolled pilot study involving 9 groups and 90 consumers demonstrated that the program and its evaluation were feasible, acceptable, and safe [35]. Significant increases in personal recovery, well-being, and psychological flexibility were observed from the start to the end of the program. The extent of consumer and clinician interest in the groups, both from the original agency and additional agencies, strongly indicated the feasibility of conducting a more extensive evaluation. Building on this momentum, our clinician-academic partnership agreed to conduct this more stringent trial by incorporating a waitlist control period and an established measure of personal recovery as the primary outcome.

Objectives

The primary aim is to evaluate the effectiveness of the Recovery ACT group program on personal recovery for adults living with a psychotic disorder in routine clinical practice across public mental health organizations in Australia using a single-group, waitlist control design. A secondary aim is to evaluate the effect of the Recovery ACT group program on well-being and psychological flexibility processes (experiential avoidance, cognitive defusion, engagement in valued actions, and mindfulness). The research questions are as follows: (1) What are the clinical benefits and risks of the Recovery ACT group program for adults diagnosed with psychotic disorders as conducted in routine practice in Australia? (2) Are there changes in psychological flexibility processes due to participation in the Recovery ACT group program? (3) Are changes in psychological flexibility processes associated with changes in personal recovery and well-being?

The primary and secondary hypotheses are that the longitudinal trajectory of personal recovery and the secondary outcomes will not significantly change over the waitlist period, then will improve from the start to the end of the group program, and then improve at a less rapid rate from the end of the group to the booster session. A further hypothesis is that changes in psychological flexibility processes during the first half of the group program will be associated with changes in personal recovery and well-being in the second half of the group program.

Methods

Participants and Study Setting

We plan to recruit a minimum of 160 adults (aged between 18 and 65 years) who enroll in a Recovery ACT group program at 1 of 4 public mental health service study sites in Melbourne (NorthWestern Mental Health, St Vincent's Mental Health Service, Alfred Mental and Addiction Health, and Peninsula Health Mental Health Service). The target minimum number of participants at NorthWestern Mental Health is 95 participants, and 32 participants each at the other study sites. The overall recruitment target was based on the minimum sample size needed to complete the intended analyses and an anticipated 60% participant retention rate based on the pilot study [35].

The inclusion criteria are a primary file diagnosis of either schizophrenia spectrum disorder or other psychotic disorder, a mood disorder with psychotic features, or a substance-induced psychotic disorder; currently receiving outpatient mental health care at 1 of the study sites; and current enrollment in a Recovery ACT group program. The exclusion criteria are lack of capacity to consent to the evaluation; lack of proficiency in speaking and comprehending English; a file diagnosis of intellectual disability or borderline personality disorder.

Study Design

This trial is a multiagency, prospective, longitudinal, nonrandomized, waitlist control, single-group study among Australian adults diagnosed with a psychotic disorder who participate in a routine Recovery ACT group program. The design includes 4 assessment time points: the start of the waitlist period (approximately 4-6 weeks before the start of the group program), the start of the group program (0 weeks), the end of the group program (about 6 weeks after the start of the group program), and the booster session (about 10 weeks after the start of the group program). Some participants may complete outcome measures at the midpoint session (T2, which is 3 weeks after the start of the group program) if the study site is resourced to collect data at an additional time point. Quantitative data from facilitators about participants' clinical severity and clinical improvement will be collected before, during, and after the group program, as well as relevant demographic and clinical information collected at baseline from participants' electronic medical records. At either the end of session 7 or the booster session, participants will be asked to provide written consent for study personnel to contact them for a follow-up study. Facilitators will be invited to complete a semistructured interview with senior investigators after each group program to gather qualitative data about the feasibility of the group program in routine practice and to assist in the interpretation of the quantitative measures completed by participants. The protocol development addressed the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials; Multimedia Appendix 1) guidelines [36] and intends to adhere to the CONSORT (Consolidated Standards of Reporting Trials; Figure 1) criteria [37]. We retrospectively registered the trial with the Australian New Zealand Clinical Trials Registry; Table 1 lists the trial registration data set.

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram of the Recovery ACT Trial. ACT: Acceptance and Commitment Therapy.

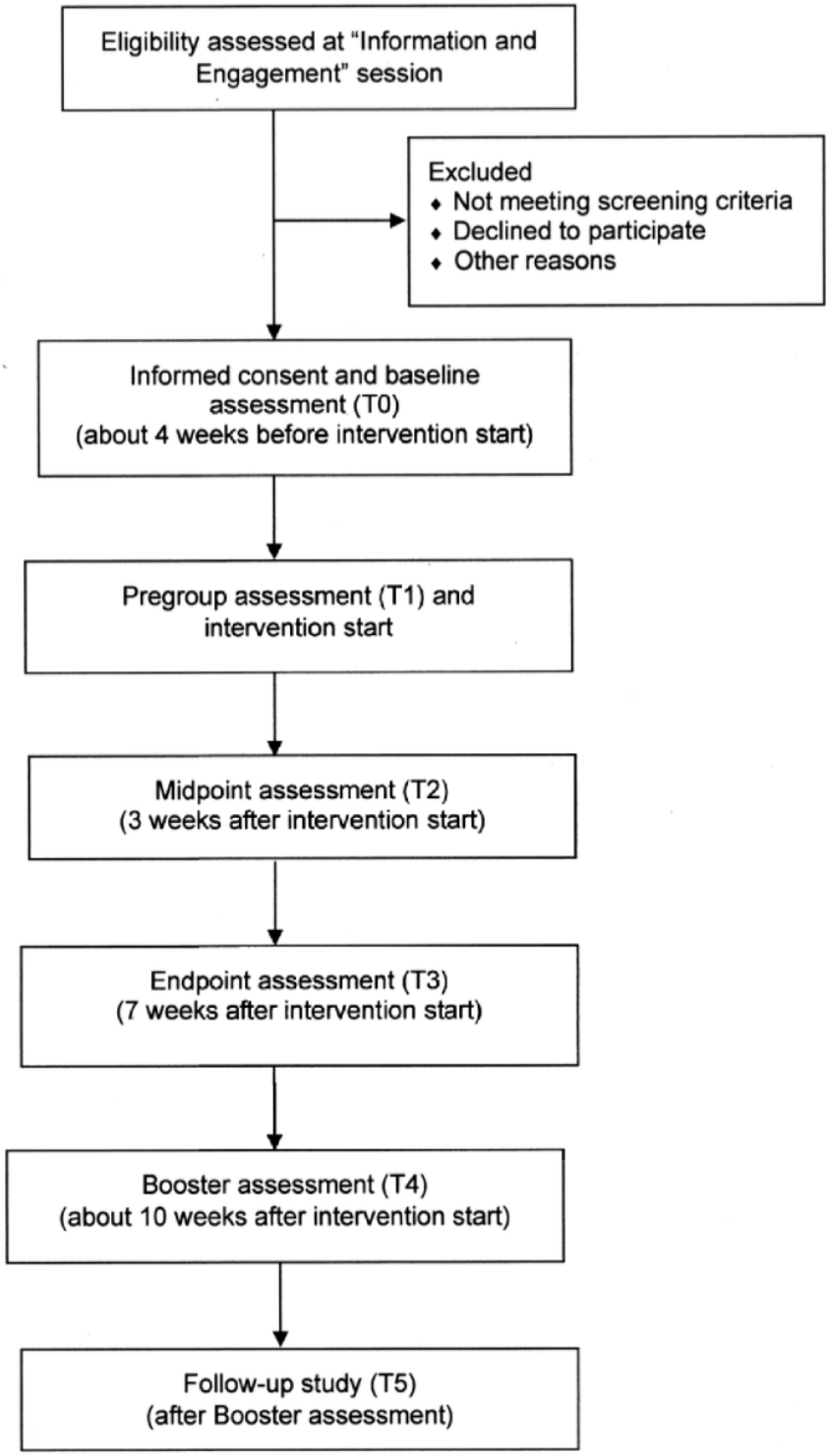


Table 1. World Health Organization Trial registration data set.

Data category	Information
Primary registry and trial identifying number	ANZCTR, ACTRN12620000223932
Date of registration in primary registry	February 24, 2020
Secondary identifying numbers	UTN: U1111-1247-8144
Source of monetary or material support	Royal Melbourne Hospital, NorthWestern Mental Health
Primary sponsor	Royal Melbourne Hospital, NorthWestern Mental Health
Secondary sponsor	La Trobe University
Contact for public enquiries	Dr Eric Morris
Contact for scientific enquiries	Dr Marilyn Cugnetto
Public title	Acceptance and Commitment Therapy (ACT) Group Program for Recovery from Psychosis: A Multi-Agency Evaluation
Scientific title	A Multi-agency Evaluation of the Routine Practice of an Acceptance and Commitment Therapy Group for Recovery from Psychosis
Countries of recruitment	Australia
Heath conditions or problems studied	Psychosis, Mental Health, Schizophrenia
Interventions	Treatment: “Recovery ACT for Psychosis” Group Program; comparator or control: single group, waitlist control period
Key inclusion and exclusion criteria	
Inclusion criteria	Inclusion criteria: Out-patients aged between 18 and 65 years; have a primary file diagnosis of either a schizophrenia spectrum or other psychotic disorder, a mood disorder with psychotic features, or a substance-induced psychotic disorder; are currently receiving outpatient mental health care at one of the study centers; are self-referred or referred by clinical staff to a Recovery ACT group being conducted by a participating center.
Exclusion criteria	Exclusion criteria: lack of capacity to consent to this evaluation; lack of proficiency in speaking and comprehending English; file diagnosis of an intellectual disability (an intellectual development disorder) or borderline personality disorder.
Study type	Interventional
Allocation	• Nonrandomized trial • Intervention assignment: single-group • Masking: open (masking not used)
Primary purpose	Treatment
Phase	N/A[a]
Date of first enrollment	September 13, 2019
Target sample size	160
Recruitment status	Recruiting
Primary outcomes	Personal recovery
Key secondary outcomes	Well-being

[a]N/A: not applicable.

Procedure

Recruitment

Participants will be recruited from current consumers of the services enrolled in a Recovery ACT group program as part of their normal clinical care. Recovery ACT group programs are conducted at all 4 participating sites, either as part of a program of groups offered to consumers or as periodic opportunities. All sites follow the same recruitment plan. Recruitment will continue until the target is met, as long as the clinical services are willing to continue to support the evaluation. Facilitators will describe the group program and the evaluation study at staff meetings and with fellow clinicians at their study site to ensure they are aware that an evaluation of the program is occurring and that consumers will be invited but not obligated to participate. Facilitators will receive all referrals to the group program and contact potential consumers to schedule an “Information and Engagement” session to brief consumers about the group program and confirm their wish to attend. All consumers who enroll in the group program will be screened for eligibility to participate in the evaluation. Consumers who

meet the eligibility criteria will be provided with an explanation of the study, an information sheet, and an evaluation brochure, and those who choose to participate will be required to provide written informed consent.

After the completion of a group program (after the booster session), senior investigators will invite facilitators to participate in a semistructured group interview for evaluation purposes and seek informed consent.

Due to the time elapsed from the initial consent process, all group members will be asked again at either session 7 or the booster session for permission and written consent to contact them in the future to invite them to participate in a follow-up study on the experience of participating in the group.

Intervention

The Recovery ACT group program includes 7 core sessions scheduled weekly and a booster session scheduled approximately 4 weeks later. The duration of all sessions is 90 minutes, and they are delivered in person. The intervention is an adaptation of the ACT for Life program [30] that centers on a core metaphor (passengers on the bus) [38] to facilitate consumers' engagement in value-based actions when relating to their internal experiences (eg, thoughts, feelings, and memories) once they become aware of the internal experiences and are able to defuse (or cognitive distance) from them. The group focuses on developing awareness of internal experiences through metaphors and mindfulness activities and building defusion skills. In the metaphor, the "bus" represents the consumer's life in the present moment, the "bus driver" is the consumer, and the "passengers" on the bus are the consumer's internal experiences. The topics covered during the core sessions include: introduction to noticing (mindfulness) of present experiences and values; enacting the core passengers on the bus metaphor and "specific, meaningful, adaptive, realistic, and time-framed" (SMART) goals; review of values, noticing, and willingness; identification of passengers and different ways of responding to them and development of noticing skills; passengers on the bus and changing relationships with words; review of values and encouragement of sharing value-guided actions; and review of key group messages. Brief contact with consumers between sessions is encouraged to promote completion of home practice and to encourage attendance.

There are no specified criteria for discontinuing or modifying the intervention, as this is an evaluation of a group program as conducted in routine clinical practice at local mental health services. Participants can choose to withdraw from the evaluation and remain in the group program. Participants may be withdrawn from the study due to a protocol violation or an adverse event.

Facilitators will be clinical mental health staff employed at a participating public mental health service who, where possible, have participated in an introductory ACT workshop and completed training in Recovery ACT. The group is led by 2 facilitators, one of whom is experienced (ie, has previously led a Recovery ACT group program) and adheres to the Recovery ACT group program manual [39]. Facilitators will be invited to attend a minimum of 3 "Support and Supervision" sessions while facilitating a group. The goal of these sessions is to enhance fidelity to the Recovery ACT group program manual [39]. In addition, facilitators will complete a fidelity log after each group session.

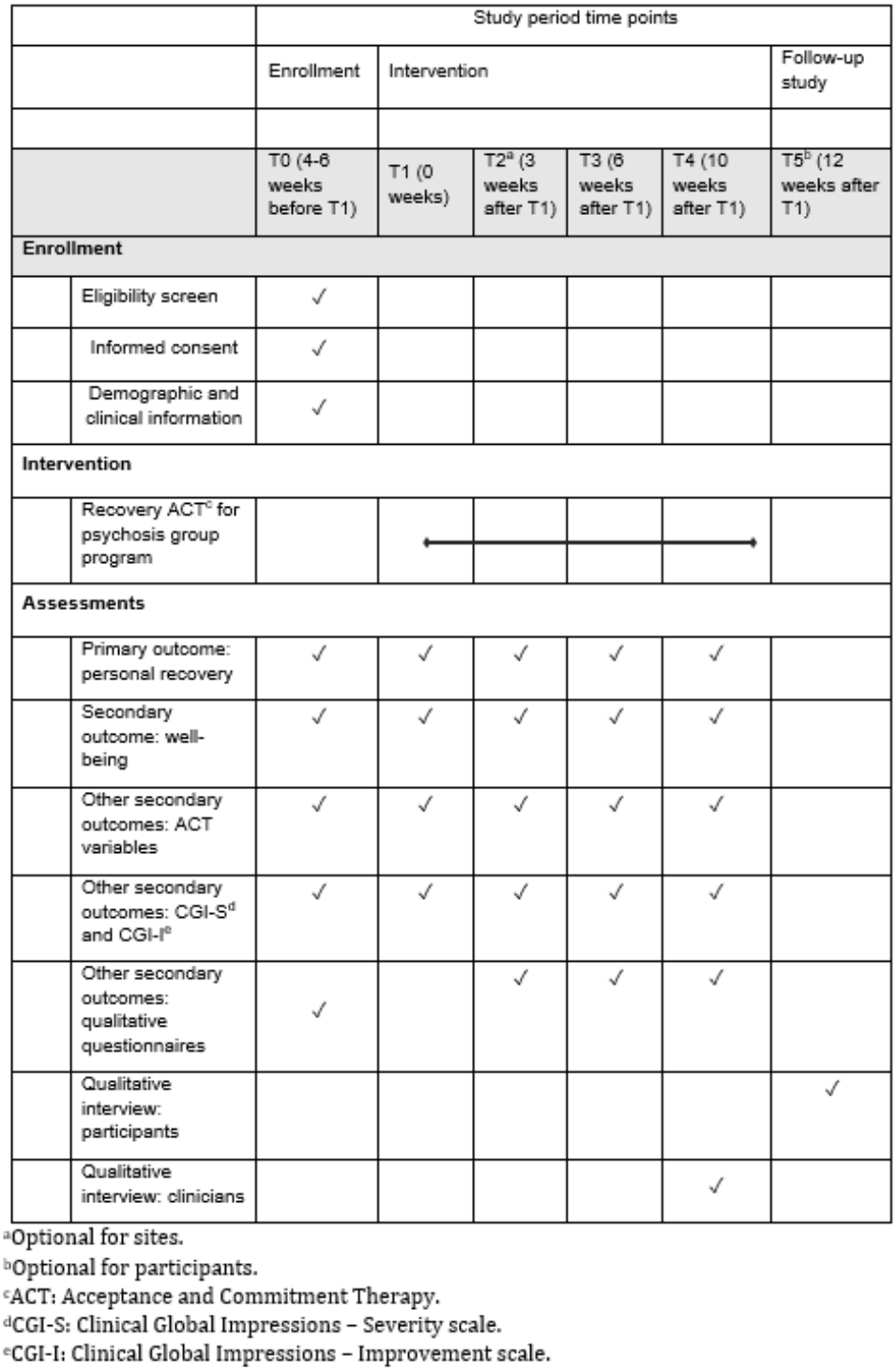
There are no restrictions on concomitant care and interventions, as this is an unfunded evaluation of the Recovery ACT group program that is already offered in routine clinical care at the participating public mental health services. To participate in the Recovery ACT program, participants must be receiving care at the respective public mental health service. As such, participants will receive provisions for ancillary and posttrial care at the public mental health service. The potential risks related to the study are deemed minimal. Facilitators are responsible for participants' clinical care during the group program, including distress related to study procedures. Participants have a key support clinician for out-of-group issues that may arise.

Outcomes

Timeline

The schedule of enrollment, interventions, and assessments is displayed in Figure 2. The quantitative self-report outcome measures are intended to be completed independently at the start of the waitlist period (T0, approximately 4-6 weeks before the start of the group program, typically at the "Information and Engagement" session), at the start of the group program (T1), at the end of the group program (T3, which is 6 weeks after the start of the group program), and at the booster session (T4, about 10 weeks after the start of the group program). Some participants may complete outcome measures at the midpoint session (T2, which is 3 weeks after the start of the group program) if the study site is resourced to collect data at an additional time point. Measures are completed after the group session, except for at T1, when participants complete measures before the start of the group to ensure no exposure to the program's content. Participants can request assistance from facilitators to complete the measures. Demographic and clinical information will be obtained from participants' electronic health records at T0 and will include their date of birth, gender, ethnicity, country of birth, highest level of educational attainment, highest level of employment, current employment status, primary mental health file diagnosis, co-occurring mental health file diagnoses, date of first contact with mental health services, number of listed episodes of outpatient mental health care, and number of psychiatric admissions.

Figure 2. Schedule of enrollment, interventions, and assessments.



		Study period time points					
		Enrollment	Intervention				Follow-up study
		T0 (4-6 weeks before T1)	T1 (0 weeks)	T2[a] (3 weeks after T1)	T3 (6 weeks after T1)	T4 (10 weeks after T1)	T5[b] (12 weeks after T1)
Enrollment							
	Eligibility screen	✓					
	Informed consent	✓					
	Demographic and clinical information	✓					
Intervention							
	Recovery ACT[c] for psychosis group program		←	—	—	→	
Assessments							
	Primary outcome: personal recovery	✓	✓	✓	✓	✓	
	Secondary outcome: well-being	✓	✓	✓	✓	✓	
	Other secondary outcomes: ACT variables	✓	✓	✓	✓	✓	
	Other secondary outcomes: CGI-S[d] and CGI-I[e]	✓	✓	✓	✓	✓	
	Other secondary outcomes: qualitative questionnaires	✓		✓	✓	✓	
	Qualitative interview: participants						✓
	Qualitative interview: clinicians					✓	

[a]Optional for sites.
[b]Optional for participants.
[c]ACT: Acceptance and Commitment Therapy.
[d]CGI-S: Clinical Global Impressions – Severity scale.
[e]CGI-I: Clinical Global Impressions – Improvement scale.

Primary Outcome

The primary outcome is personal recovery, as measured by the 15-item version of the Questionnaire about the Process of Recovery (QPR) [40,41]. The 15-item QPR has good internal consistency (QPR total α=.89), fair to good test-retest reliability (QPR total intracluster correlation coefficient [ICC]=0.74), moderate sensitivity to change, and adequate convergent validity [42]. The QPR is a measure that assesses the 5 core processes of personal recovery that comprise the "Connectedness; Hope and optimism about the future; Identity; Meaning in life; and Empowerment" (CHIME) framework [43], which is currently the strongest conceptualization of personal recovery in serious mental illness. The Recovery ACT group program seeks to support change in these dimensions for participants.

Secondary Outcomes

The secondary outcomes are well-being (Clinical Outcomes in Routine Evaluation 10 [CORE-10]) [44] and 4 psychological flexibility process variables, namely committed action (the Valuing Questionnaire's Progress scale comprised of items 3, 4, 5, 7, and 9) [45], mindfulness (Southampton Mindfulness Questionnaire) [46], cognitive defusion (Cognitive Fusion Questionnaire) [47], and experiential avoidance (Brief Experiential Avoidance Questionnaire) [48].

Other Clinical Outcomes

A facilitator will rate illness severity at enrollment and before the start of the group using the "Clinical Global Impression–Severity" scale and will rate illness improvement at the end of the group and at the booster session using the "Clinical Global Impression–Improvement" scale [49,50].

Consumer and Facilitator Feedback

Permission will be sought from participants to use their responses to routine qualitative feedback questions for evaluation purposes. These questions ask about their hopes and expectations for the group (at T0), helpful and unhelpful aspects of the group (at T2 and T3), requests for remaining sessions (at T2), and reflection on any perceived changes attributed to the group (at T3 and T4). The method of collecting these routine feedback responses is dependent on the site. The baseline feedback questions (at T0) are typically asked and recorded by a facilitator during the "Information and Engagement" session; the feedback questions at other time points are typically written responses by participants. Qualitative data about the group will be sought from facilitators who consent to participate in a semistructured interview after completing a group. The qualitative interview will assess the feasibility of the group, its evaluation in routine practice, and perceptions of the group program's effectiveness.

In addition, during the initial consent process, participants will be asked for written consent to contact them in the future to invite them to participate in a follow-up study involving a qualitative interview exploring their experience of participating in the group.

Statistical Methods and Sample Size

We intend to use an intention-to-treat sample to test a univariate latent growth curve model of the primary outcome from before the start of the waitlist period to the start of the group to the booster session in order to compare the trajectory over the waitlist period to the trajectory over the active treatment period. We selected this method of analysis to strengthen our estimations of associations due to the limitations of the nonrandomized study design chosen as the most realistic option for an evaluation of a program already in routine practice [51]. A minimum sample size of 90 is required to conduct the proposed growth curve structural equation model (5 observed variables and 2 latent variables) with an anticipated medium effect size (0.3), α set at .05, and power (1–β) at .80. Univariate latent growth curve models for each of the 5 secondary outcomes will also be tested. If there are sufficient data, we will test whether the trajectory of the 4 psychological flexibility process variables from the start of the group to the midpoint session (T1 to T2) is significantly associated with the trajectory of personal recovery (T2 to T4) using multivariate growth models. We do not predict a priori any differences associated with the study site. We intend to calculate the ICC after the data are collected to determine the relatedness of the data collected at different study sites.

Randomization and Blinding

This study is a nonrandomized (unblinded) trial that uses a single group, waitlist control, and a quasiexperimental design. All participants serve as their own control. The data for all participants on change in outcomes over the waitlist period (no active intervention) will be used to compare with the data on change in outcomes during the active intervention. The planned statistical methods will strengthen our conclusions. The risk of researcher bias is lessened by the self-report format of the primary and secondary outcomes and the opportunity for participants to submit questionnaires in a sealed envelope.

Data Collection and Management

The data will be collected using deidentified hardcopies of all evaluation documents (quantitative questionnaires completed by participants and facilitators, copies of qualitative feedback forms, and demographic and clinical information forms), and other trial documents (attendance records, fidelity logs, and recruitment logs). Facilitators will assist participants with questionnaire completion if needed. As facilitators will serve a dual role as clinical service providers and study personnel, participants will be provided a sealable envelope to return deidentified self-report questionnaires that will be reviewed by study personnel other than their facilitators if sealed (either at the site or by the study coordinator). If a participant does not attend a group session when data are collected, facilitators will attempt to schedule an appointment to complete study measures.

Deidentified data from hard copy evaluation documents will be entered into a password-protected electronic file maintained on secure computers by the study coordinator. A coding sheet with identifiable participant information will be saved as a password-protected electronic file on the sponsor site's server. Hard copies of consent forms and study documents will be kept in a locked filing cabinet at the Academic Psychology Unit located at the sponsor's site.

Data Monitoring and Adverse Event Reporting

Anticipated risks to participant safety due to participation in the evaluation and the group are deemed minimal based on pilot study data [35]. Therefore, there is no data monitoring committee, and there are no planned interim analyses to identify risks. Adverse events will be monitored by facilitators, site principal investigators, the coordinating principal investigator, and the Interagency Investigator Committee. An adverse event form and guideline are used.

An Interagency Investigator Committee led by the coordinating principal investigator meets quarterly to oversee the trial's progress, monitor any adverse events or serious adverse events related to the procedures or the group program, and discuss any necessary protocol modifications. A study coordinator is responsible for liaising with the site principal investigators, who

are responsible for the evaluation at each site. In addition to the published Recovery ACT group program manual, evaluation procedure manuals were created to ensure that the protocol is adhered to by study personnel at all sites and over the course of the multiyear study.

Ethical Considerations

Melbourne Health's Human Research Ethics Committee (HREC/51498/MH-2019) provided ethics approval for this study. All methods will be performed in accordance with the relevant guidelines and regulations, and written, informed consent will be obtained from participants. The results of the main aim of the study will be published in a peer-reviewed scientific journal and submitted for presentation at clinical and scientific meetings and conferences. The coordinating principal investigator will oversee the publication and presentation of study results, including decisions about authorship. Participants are asked whether they would like to be informed of the main results of the study. Those who express interest and provide contact details will be provided with this information when it is available. Participants who complete quantitative outcome measures will be compensated with a US $6.54 department store voucher at each time point.

Results

Trial enrollment began in September 2019 and was originally planned to continue until at least March 2022. In March 2020, the Victorian Government in Australia introduced public health directions in response to the COVID-19 pandemic that derailed study progress as in-person groups were not permitted for over 20 months at some sites. While study recruitment and follow-up study procedures were broadened to allow for the use of telehealth, the group program format (in-person) was not changed as it would introduce significant variability to the study outcomes. As there remains notable interest from all stakeholders (investigators, facilitators, managers, and consumers), the study will continue to accept enrollments until at least 2024. As of the submission of the manuscript, 93 participants consented to the evaluation, 65 completed T1 measures, and 40 had a complete dataset for the proposed analyses. No data analysis has been conducted. Due to the uncertainty of the trial's viability due to the public health directions during the COVID-19 pandemic, the protocol's publication was delayed. The current protocol version is 8.0 (issue date: July 14, 2021).

Discussion

To our knowledge, this is the first trial in Australia evaluating the effectiveness of an ACT for psychosis group program on personal recovery outcomes. Although limited by the single-group design, its strength lies in the opportunity to evaluate effectiveness in routine practice. External validity is strengthened by the practice settings being spread across 4 public mental health networks in a large city, serving communities with a range of sociodemographic characteristics.

A randomized design was not feasible as the program is offered in routine practice [51], thus limiting causal conclusions. However, the quasiexperimental design includes a waitlist period that provides a baseline comparison to evaluate the effectiveness of the group program and can also allow for process analyses if sufficient data are collected. A further enhancement is a proposed qualitative follow-up study of the experience of the group program, intended to inform program development and assist in the interpretation of quantitative results.

A feature of note is the clinician-initiated origin of the evaluation and the forging of a partnership between clinicians and academics during a previous pilot evaluation that then led to the co-design and collaborative implementation of the trial [34]. This clinician-researcher partnership is likely to not only ensure the practical applicability of program modifications and the feasibility of study procedures, but may also lay the foundations for more rapid implementation into practice should the results warrant it. Nonetheless, as an unfunded study, the project is subject to significant risk of noncompletion as it relies on the participating mental health services supporting facilitators to undertake some evaluation tasks, services continuing to provide the group program over the proposed study period, and the support of the sponsor site to provide a study coordinator.

This study exemplifies an effectiveness-implementation hybrid trial [52]. If successful, the trial will further support psychosocial interventions to improve personal recovery among consumers who experience persisting psychotic symptoms.

Acknowledgments

The authors would like to thank all facilitators, colleagues, and peer reviewers for their contributions to the development of the protocol, including Ms Sheran Kay. The authors also thank all facilitators who offer their service in kind to collect data, as well as local area managers and department heads at each site. The authors are also grateful to all consumers who participated in the trial.

This is an unfunded study. This study received in-kind support from NorthWestern Mental Health-Royal Melbourne Hospital, St Vincent's Hospital-Melbourne, Alfred Mental and Addiction Health, Peninsula Health Mental Health Service, and La Trobe University. Participant gift vouchers are courtesy of La Trobe University.

Data Availability

The data sets generated during or analyzed during this study are not publicly available as the authors do not have research participants' permission to share data.

Authors' Contributions

JF was the initial coordinating principal investigator; EMJM is the current coordinating principal investigator. JF, EMJM, and MLC led the evaluation development, and all authors contributed. All authors contributed to either the conception, design, or acquisition of ethics and governance approval of the evaluation. MLC and JF were major contributors to writing the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Checklist (36).
[PDF File (Adobe PDF File), 250 KB - resprot_v13i1e49849_app1.pdf]

References

1. Saha S, Chant D, Welham J, McGrath J. A systematic review of the prevalence of schizophrenia. PLoS Med 2005;2(5):e141 [FREE Full text] [doi: 10.1371/journal.pmed.0020141] [Medline: 15916472]
2. Charlson FJ, Ferrari AJ, Santomauro DF, Diminic S, Stockings E, Scott JG, et al. Global epidemiology and burden of schizophrenia: findings from the Global Burden of Disease study 2016. Schizophr Bull 2018;44(6):1195-1203 [FREE Full text] [doi: 10.1093/schbul/sby058] [Medline: 29762765]
3. Emsley R, Chiliza B, Asmal L, Harvey BH. The nature of relapse in schizophrenia. BMC Psychiatry 2013;13:50 [FREE Full text] [doi: 10.1186/1471-244X-13-50] [Medline: 23394123]
4. Samara MT, Nikolakopoulou A, Salanti G, Leucht S. How many patients with schizophrenia do not respond to antipsychotic drugs in the short term? An analysis based on individual patient data from randomized controlled trials. Schizophr Bull 2019;45(3):639-646 [FREE Full text] [doi: 10.1093/schbul/sby095] [Medline: 29982701]
5. Kiran C, Chaudhury S. Prevalence of comorbid anxiety disorders in schizophrenia. Ind Psychiatry J 2016;25(1):35-40 [FREE Full text] [doi: 10.4103/0972-6748.196045] [Medline: 28163406]
6. Wilson RS, Yung AR, Morrison AP. Comorbidity rates of depression and anxiety in first episode psychosis: a systematic review and meta-analysis. Schizophr Res 2020;216:322-329. [doi: 10.1016/j.schres.2019.11.035] [Medline: 31791816]
7. Dai J, Du X, Yin G, Zhang Y, Xia H, Li X, et al. Prevalence, demographic and clinical features of comorbid depressive symptoms in drug naïve patients with schizophrenia presenting with first episode psychosis. Schizophr Res 2018;193:182-187. [doi: 10.1016/j.schres.2017.06.029] [Medline: 28651908]
8. Jääskeläinen E, Juola P, Hirvonen N, McGrath JJ, Saha S, Isohanni M, et al. A systematic review and meta-analysis of recovery in schizophrenia. Schizophr Bull 2013;39(6):1296-1306 [FREE Full text] [doi: 10.1093/schbul/sbs130] [Medline: 23172003]
9. Slade M. Mental illness and well-being: the central importance of positive psychology and recovery approaches. BMC Health Serv Res 2010;10:26 [FREE Full text] [doi: 10.1186/1472-6963-10-26] [Medline: 20102609]
10. American Psychiatric Association. The American Psychiatric Association Practice Guideline for the Treatment of Patients with Schizophrenia, Third Edition. Washington, D.C: American Psychiatric Association Publishing; 2020.
11. National Collaborating Centre for Mental Health (UK), National Institute for Health and Care Excellence (UK). Psychosis and Schizophrenia: Treatment and Management. London: National Institute for Health and Care Excellence; 2014.
12. Dixon LB, Dickerson F, Bellack AS, Bennett M, Dickinson D, Goldberg RW, et al. The 2009 schizophrenia PORT psychosocial treatment recommendations and summary statements. Schizophr Bull 2010;36(1):48-70 [FREE Full text] [doi: 10.1093/schbul/sbp115] [Medline: 19955389]
13. Gaebel W, Weinmann S, Sartorius N, Rutz W, McIntyre JS. Schizophrenia practice guidelines: international survey and comparison. Br J Psychiatry 2005;187:248-255 [FREE Full text] [doi: 10.1192/bjp.187.3.248] [Medline: 16135862]
14. Kingdon DG, Turkington D. Cognitive Therapy of Schizophrenia. New York, NY, US: Guilford Press; 2005.
15. Burns AMN, Erickson DH, Brenner CA. Cognitive-behavioral therapy for medication-resistant psychosis: a meta-analytic review. Psychiatr Serv 2014;65(7):874-880. [doi: 10.1176/appi.ps.201300213] [Medline: 24686725]
16. Jauhar S, McKenna PJ, Radua J, Fung E, Salvador R, Laws KR. Cognitive-behavioural therapy for the symptoms of schizophrenia: systematic review and meta-analysis with examination of potential bias. Br J Psychiatry 2014;204(1):20-29 [FREE Full text] [doi: 10.1192/bjp.bp.112.116285] [Medline: 24385461]
17. Bighelli I, Salanti G, Huhn M, Schneider-Thoma J, Krause M, Reitmeir C, et al. Psychological interventions to reduce positive symptoms in schizophrenia: systematic review and network meta-analysis. World Psychiatry 2018;17(3):316-329 [FREE Full text] [doi: 10.1002/wps.20577] [Medline: 30192101]
18. Laws KR, Darlington N, Kondel TK, McKenna PJ, Jauhar S. Cognitive behavioural therapy for schizophrenia—outcomes for functioning, distress and quality of life: a meta-analysis. BMC Psychol 2018;6(1):32 [FREE Full text] [doi: 10.1186/s40359-018-0243-2] [Medline: 30016999]

19. Jauhar S, Laws KR, McKenna PJ. CBT for schizophrenia: a critical viewpoint. Psychol Med 2019;49(8):1233-1236 [FREE Full text] [doi: 10.1017/S0033291718004166] [Medline: 30757979]
20. McKenna P, Leucht S, Jauhar S, Laws K, Bighelli I. The controversy about cognitive behavioural therapy for schizophrenia. World Psychiatry 2019;18(2):235-236 [FREE Full text] [doi: 10.1002/wps.20636] [Medline: 31059624]
21. Hazell CM, Hayward M, Cavanagh K, Strauss C. A systematic review and meta-analysis of low intensity CBT for psychosis. Clin Psychol Rev 2016;45:183-192 [FREE Full text] [doi: 10.1016/j.cpr.2016.03.004] [Medline: 27048980]
22. Waller H, Garety PA, Jolley S, Fornells-Ambrojo M, Kuipers E, Onwumere J, et al. Low intensity cognitive behavioural therapy for psychosis: a pilot study. J Behav Ther Exp Psychiatry 2013;44(1):98-104. [doi: 10.1016/j.jbtep.2012.07.013] [Medline: 22940787]
23. Owen M, Sellwood W, Kan S, Murray J, Sarsam M. Group CBT for psychosis: a longitudinal, controlled trial with inpatients. Behav Res Ther 2015;65:76-85. [doi: 10.1016/j.brat.2014.12.008] [Medline: 25577190]
24. Hayes SC, Strosahl KD, Wilson KG. Acceptance and Commitment Therapy: The Process and Practice of Mindful Change, Second Edition. New York, NY: The Guilford Press; 2012.
25. Cramer H, Lauche R, Haller H, Langhorst J, Dobos G. Mindfulness- and acceptance-based interventions for psychosis: a systematic review and meta-analysis. Glob Adv Health Med 2016;5(1):30-43 [FREE Full text] [doi: 10.7453/gahmj.2015.083] [Medline: 26937312]
26. Bach P, Hayes SC. The use of acceptance and commitment therapy to prevent the rehospitalization of psychotic patients: a randomized controlled trial. J Consult Clin Psychol 2002;70(5):1129-1139. [doi: 10.1037//0022-006x.70.5.1129] [Medline: 12362963]
27. Gaudiano BA, Herbert JD. Acute treatment of inpatients with psychotic symptoms using Acceptance and Commitment Therapy: pilot results. Behav Res Ther 2006;44(3):415-437. [doi: 10.1016/j.brat.2005.02.007] [Medline: 15893293]
28. Tyrberg MJ, Carlbring P, Lundgren T. Brief acceptance and commitment therapy for psychotic inpatients: a randomized controlled feasibility trial in Sweden. Nordic Psychology 2016;69(2):110-125 [FREE Full text] [doi: 10.1080/19012276.2016.1198271]
29. Jansen JE, Gleeson J, Bendall S, Rice S, Alvarez-Jimenez M. Acceptance- and mindfulness-based interventions for persons with psychosis: a systematic review and meta-analysis. Schizophr Res 2020;215:25-37. [doi: 10.1016/j.schres.2019.11.016] [Medline: 31780349]
30. Butler L, Johns LC, Byrne M, Joseph C, O'Donoghue E, Jolley S, et al. Running acceptance and commitment therapy groups for psychosis in community settings. J Contextual Behav Sci 2016;5(1):33-38 [FREE Full text] [doi: 10.1016/j.jcbs.2015.12.001]
31. O'Donoghue EK, Morris EMJ, Oliver JE, Johns LC. ACT for Psychosis Recovery: A Practical Manual for Group-based Interventions Using Acceptance and Commitment Therapy. Oakland, CA: New Harbinger Publications; 2018.
32. Johns LC, Oliver JE, Khondoker M, Byrne M, Jolley S, Wykes T, et al. The feasibility and acceptability of a brief Acceptance and Commitment Therapy (ACT) group intervention for people with psychosis: the 'ACT for life' study. J Behav Ther Exp Psychiatry 2016;50:257-263 [FREE Full text] [doi: 10.1016/j.jbtep.2015.10.001] [Medline: 26480469]
33. Jolley S, Johns LC, O'Donoghue E, Oliver J, Khondoker M, Byrne M, et al. Group acceptance and commitment therapy for patients and caregivers in psychosis services: feasibility of training and a preliminary randomized controlled evaluation. Br J Clin Psychol 2020;59(4):524-551. [doi: 10.1111/bjc.12265] [Medline: 32944971]
34. Gates J, Goldstone E, Clemente J, Cugnetto M, Morris EMJ, Farhall J. Adapting and implementing Acceptance and Commitment Therapy groups to support personal recovery of adults living with psychosis: a qualitative study of facilitators' experiences. Psychosis 2021;14(4):322-332 [FREE Full text] [doi: 10.1080/17522439.2021.1957991]
35. Farhall J, Cugnetto ML, Goldstone E, Gates J, Clemente J, Morris EMJ. Acceptability and feasibility of recovery-oriented group acceptance and commitment therapy for psychosis in routine practice: an uncontrolled pilot study. Behav Cogn Psychother 2024:1-7 [FREE Full text] [doi: 10.1017/s1352465823000589]
36. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med 2013;158(3):200-207 [FREE Full text] [doi: 10.7326/0003-4819-158-3-201302050-00583] [Medline: 23295957]
37. Schulz KF, Altman DG, Moher D, CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ 2010;340:c332 [FREE Full text] [doi: 10.1136/bmj.c332] [Medline: 20332509]
38. Hayes SC, Strosahl K, Wilson KG. Acceptance and Commitment Therapy: An Experiential Approach to Behavior Change. New York: Guilford Press; 1999.
39. Farhall J, Morris E, Goldstone E, Clemente J, Gates J. Recovery ACT: group intervention for psychosis manual. OSFHome. 2019. URL: https://osf.io/7bwgp [accessed 2024-01-23]
40. Neil ST, Kilbride M, Pitt L, Nothard S, Welford M, Sellwood W, et al. The Questionnaire about the Process of Recovery (QPR): a measurement tool developed in collaboration with service users. Psychosis 2009;1(2):145-155. [doi: 10.1080/17522430902913450]
41. Law H, Neil ST, Dunn G, Morrison AP. Psychometric properties of the Questionnaire about the Process of Recovery (QPR). Schizophr Res 2014;156(2-3):184-189. [doi: 10.1016/j.schres.2014.04.011] [Medline: 24816049]

42. Williams J, Leamy M, Pesola F, Bird V, Le Boutillier C, Slade M. Psychometric evaluation of the Questionnaire about the Process of Recovery (QPR). Br J Psychiatry 2015;207(6):551-555 [FREE Full text] [doi: 10.1192/bjp.bp.114.161695] [Medline: 26450585]
43. Leamy M, Bird V, Le Boutillier C, Williams J, Slade M. Conceptual framework for personal recovery in mental health: systematic review and narrative synthesis. Br J Psychiatry 2011;199(6):445-452 [FREE Full text] [doi: 10.1192/bjp.bp.110.083733] [Medline: 22130746]
44. Connell J, Barkham M. CORE-10 user manual, version 1.1. APA PsycNet: American Psychological Association. 2007. URL: https://psycnet.apa.org/doiLanding?doi=10.1037%2Ft71761-000 [accessed 2024-01-31]
45. Smout M, Davies M, Burns N, Christie A. Development of the Valuing Questionnaire (VQ). J Contextual Behav Sci 2014;3(3):164-172 [FREE Full text] [doi: 10.1016/j.jcbs.2014.06.001]
46. Chadwick P, Hember M, Symes J, Peters E, Kuipers E, Dagnan D. Responding mindfully to unpleasant thoughts and images: reliability and validity of the Southampton Mindfulness Questionnaire (SMQ). Br J Clin Psychol 2008;47(Pt 4):451-455. [doi: 10.1348/014466508X314891] [Medline: 18573227]
47. Gillanders DT, Bolderston H, Bond FW, Dempster M, Flaxman PE, Campbell L, et al. The development and initial validation of the cognitive fusion questionnaire. Behav Ther 2014;45(1):83-101 [FREE Full text] [doi: 10.1016/j.beth.2013.09.001] [Medline: 24411117]
48. Gámez W, Chmielewski M, Kotov R, Ruggero C, Suzuki N, Watson D. The brief experiential avoidance questionnaire: development and initial validation. Psychol Assess 2014;26(1):35-45. [doi: 10.1037/a0034473] [Medline: 24059474]
49. Busner J, Targum SD. The clinical global impressions scale: applying a research tool in clinical practice. Psychiatry (Edgmont) 2007;4(7):28-37 [FREE Full text] [Medline: 20526405]
50. Guy W. ECDEU Assessment Manual for Psychopharmacology. Rockville, MD: US Department of Health, Education, and Welfare Public Health Service and Alcohol, Drug Abuse, and Mental Health Administration; 1976.
51. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ 2008;337:a1655 [FREE Full text] [doi: 10.1136/bmj.a1655] [Medline: 18824488]
52. Curran GM, Bauer M, Mittman B, Pyne JM, Stetler C. Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact. Med Care 2012;50(3):217-226 [FREE Full text] [doi: 10.1097/MLR.0b013e3182408812] [Medline: 22310560]

Abbreviations

ACT: Acceptance and Commitment Therapy
CBTp: cognitive behavioral therapy for psychosis
CHIME: Connectedness; Hope and optimism about the future; Identity; Meaning in life; and Empowerment
CONSORT: Consolidated Standards of Reporting Trials
CORE-10: Clinical Outcomes in Routine Evaluation 10
ICC: intracluster correlation coefficient
QPR: Questionnaire about the Process of Recovery
SMART: specific, meaningful, adaptive, realistic, and time-framed
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

Edited by A Mavragani; submitted 13.07.23; peer-reviewed by J D'Arcey, S Althammer ; comments to author 09.09.23; revised version received 19.12.23; accepted 09.01.24; published 18.03.24.

Please cite as:
Cugnetto ML, Morris EMJ, Bonfield SF, Gates J, Morrison I, Newman ER, Nicholls JD, Soares LM, Antonucci MT, Clemente JR, Garratt CLM, Goldstone E, Pavone DA, Farhall J
Group Acceptance and Commitment Therapy for Recovery From Psychosis: Protocol for a Single-Group Waitlist Trial
JMIR Res Protoc 2024;13:e49849
URL: https://www.researchprotocols.org/2024/1/e49849
doi:10.2196/49849
PMID:38498035

Protocol

Applying an Evidence-Based Community Organizing Approach to Strengthen HIV Prevention for Cisgender Women in US South: Protocol for a Mixed Methods Study

Anandi N Sheth[1,2], MSc, MD; Dazon Dixon Diallo[3], MPH, DHL; Celeste Ellison[4], MPH; Deja L Er[1], MPH; Adaora Ntukogu[5], BA; Kelli A Komro[4,6], MA, MPH, PhD; Jessica M Sales[4], MA, PhD

[1]Division of Infectious Diseases, Department of Medicine, Emory University School of Medicine, Atlanta, GA, United States

[2]Ponce de Leon Center, Grady Health System, Atlanta, GA, United States

[3]SisterLove, Inc, Atlanta, GA, United States

[4]Department of Behavioral, Social, and Health Education Sciences, Emory University Rollins School of Public Health, Atlanta, GA, United States

[5]Medical College of Georgia, Augusta, GA, United States

[6]Department of Epidemiology, Emory University Rollins School of Public Health, Atlanta, GA, United States

Corresponding Author:
Anandi N Sheth, MSc, MD
Division of Infectious Diseases
Department of Medicine
Emory University School of Medicine
341 Ponce de Leon Avenue
Atlanta, GA, 30308
United States
Phone: 1 4046166240
Email: ansheth@emory.edu

Abstract

Background: Most new HIV diagnoses among cisgender women in the United States occur in the South. HIV pre-exposure prophylaxis (PrEP), a cornerstone of the federal Ending the HIV Epidemic (EHE) initiative, remains underused by cisgender women who may benefit. Awareness and access to PrEP remain low among cisgender women. Moreover, improving PrEP reach among cisgender women requires effectively engaging communities in the development of appropriate and acceptable patient-centered PrEP care approaches to support uptake. In a community-clinic-academic collaboration, this protocol applies an evidence-based community organizing approach (COA) to increase PrEP awareness and reach among cisgender women in Atlanta.

Objective: The aim of this study is to use and evaluate a COA for engaging community members across 4 Atlanta counties with high-priority EHE designation, to increase PrEP awareness, interest, and connection to PrEP care among cisgender women.

Methods: The COA, consisting of 6 stages, will systematically develop the skills of community members to become leaders and advocates for HIV prevention inclusive of PrEP for cisgender women in their communities. We will use the evidence-based COA to develop and implement a PrEP-specific action plan to create broader community change by raising awareness and interest in PrEP, reducing stigma associated with HIV or PrEP, and connecting women to sexual health clinics providing PrEP services. In the first 4 stages, to prepare for and develop action plans, we will gather data from one-on-one interviews with up to 100 individuals across Atlanta to capture attitudes, motivations, and influences related to women's sexual health with a focus on HIV prevention and PrEP. Informed by the community interviews, we will revise a sexual health curriculum inclusive of PrEP and community-centered engagement. We will then recruit and train community action team members to develop action plans to implement the curriculum during community-located events. In the last 2 stages, we will implement and evaluate COA's effect on PrEP awareness, interest, HIV or PrEP stigma, and connection to PrEP care among cisgender women community members.

Results: This project was funded by the National Institutes of Health and approved by the Emory University institutional review board in July 2021. Data collection began in December 2021 and is ongoing. COA stage 1 of the study is complete with 70 participants enrolled. Community events commenced in November 2023, and data collection will be completed by November 2025. Stage 1 qualitative data analysis is complete with results to be published in 2024. Full study results are anticipated to be reported in 2026.

Conclusions: Through a community-clinic-academic collaboration, this protocol proposes to mount a coordinated approach across diverse Atlanta counties to strengthen HIV prevention for cisgender women and to create a sustainable systems approach to move new sexual health innovations more quickly to cisgender women.

International Registered Report Identifier (IRRID): DERR1-10.2196/56293

(JMIR Res Protoc 2024;13:e56293) doi:10.2196/56293

KEYWORDS

cisgender women; HIV prevention; community engagement; HIV; cisgender; United States; pre-exposure prophylaxis; PrEP; Ending the HIV Epidemic; awareness; community; community-based; prevention; community action team; HIV epidemic; evidence-based; participatory; community-engaged approach; community organizing approach; men who have sex with men

Introduction

Initiatives for ending the HIV epidemic in the United States must include cisgender women. Among ~37,000 people diagnosed with HIV annually in the United States, 19% are cisgender women, with the majority (~60%) of new HIV diagnoses among cisgender women occurring in the South [1,2]. Georgia has the highest rate of new HIV diagnoses (21% occur among cisgender women), and also has one of the highest rates of perinatal HIV infection [1,3]. HIV diagnoses among cisgender women in Georgia and nationally are more evenly distributed across age groups than in men, with magnified disparities by race or ethnicity [2,3]. This highlights the importance of women-tailored HIV prevention care, including pre-exposure prophylaxis (PrEP) to effectively reach all who may benefit. Within Georgia, the Atlanta metropolitan area accounts for over half of all annual HIV diagnoses [3], with 4 counties (Cobb, DeKalb, Fulton, and Gwinnett) identified as a high priority in the federal Ending the HIV Epidemic (EHE) initiative [4]. Reducing HIV in Atlanta is a public health priority, and cisgender women–tailored strategies will be necessary to achieve an end to HIV.

PrEP is dramatically underused by cisgender women. There has been wide-scale endorsement to bring PrEP use to scale through dissemination and implementation efforts in the United States since its approval in 2012 [5-8]. PrEP use has since steadily increased among men but remains flat in women [9]. PrEP is underused in women relative to need, especially in the Southern United States [10]. Women are <5% of US PrEP users, and account for only 2% of the estimated 176,670 cisgender women for whom PrEP is indicated [11,12]. The first steps for increasing PrEP uptake are ensuring that those who can benefit from PrEP are aware of it, and ensuring that PrEP is accessible in settings where they seek health care [13]. Unfortunately, PrEP knowledge is low among cisgender women in the United States, including in the Southern United States) [14-20] and among women's health care providers [21]. Encouragingly, cisgender women report interest in taking PrEP once informed [22,23], and women's providers are willing to prescribe PrEP once trained [21]. Our group previously investigated PrEP awareness and provider PrEP knowledge in 4 Atlanta family planning clinics that were not previously providing PrEP. Clients resided in 103 (91%) of 113 metropolitan Atlanta zip codes (the majority of clients resided in zip codes with HIV prevalence >1%) [14,24]. Only 95 (19%) of 500 cisgender women clients surveyed knew about PrEP, but after a brief provider training, 72 (66%) of 110 cisgender women with PrEP indicators received PrEP counseling during their visits. After receiving PrEP counseling, clients expressed interest in PrEP if it were offered on-site rather than through off-site referral. This study demonstrated the potential reach of sexual health clinics in high HIV burden areas as PrEP delivery sites.

However, PrEP delivery in publicly funded family planning clinics in the South remains low, despite clinical guidelines incorporating PrEP [25]. We previously surveyed nearly 600 providers or staff working in 286 Title X clinics across the South in 2018; only 22% of clinics provided any PrEP services (including through referral), and the Southeastern region (including Atlanta) had the fewest clinics offering PrEP [14,26].

Once clinic capacity for PrEP is built, it does not address low PrEP awareness among cisgender women. Lessons learned from the rollout of other prevention technologies, such as human papillomavirus vaccination [27] and new contraception methods [28], highlight the need to simultaneously address demand barriers that impede use [29]. We are learning that the same applies to scaling PrEP, particularly for cisgender women in Atlanta [14,15,24,26]. To date, efforts to scale PrEP in the United States have largely focused on PrEP awareness for men who have sex with men [8], despite continued low PrEP knowledge among women [15-20]. Our 2018 research found that once informed about PrEP, cisgender women in Atlanta wanted more information and widespread awareness-building specifically for women [30]. Thus, ending the HIV epidemic among women will require addressing uptake barriers through building interest in PrEP and promoting and connecting cisgender women to women-friendly PrEP clinics.

A comprehensive systems-level approach is needed to increase PrEP reach among cisgender women. To create a proactive solution for bridging the chasm from science to practice for PrEP use among cisgender women and building on our existing clinic-academic-community partnerships, we will innovatively use the Interactive Systems Framework (ISF) [31]. The ISF is a multisystem model to guide the dissemination and implementation of prevention programming through the work of 3 interactive systems, "prevention delivery" (implements the innovation in the real world), "prevention support" (provides training and technical assistance to users in the field), and "prevention synthesis and translation" (conducts research and distills information about innovations in user-friendly formats). The ISF has been used successfully by the Centers for Disease Control and Prevention (CDC) in their multisite

capacity-building effort to reduce teen pregnancies in the United States [32], showing its feasibility for building prevention infrastructure to guide large-scale prevention efforts in the area of sexual health for women [32,33]. All 3 systems, and the different stakeholders who populate each system, interact to support each other toward a common goal, which is necessary to mount successful, sustainable, large-scale adoption of new prevention innovations (eg, PrEP, including long-acting PrEP).

The ISF provides a strong model to strengthen access to PrEP care, but it lacks equally robust attention to addressing PrEP awareness and interest. Thus, in this protocol, we innovatively supplemented the ISF with an evidence-based community organizing approach (COA), previously demonstrated effective for addressing underage alcohol use [34,35]. This evidence-based approach can create broader change across the community for any community challenge [36,37]. The COA consists of 6 stages of activities. The first stage is assessing the community through one-on-one conversations with citizens, typically done by a lead community organizer (LCO). The second stage is building the base, in which an action team of approximately 15 citizens is assembled. The action team members are not typically affiliated with formal prevention programs or HIV coalitions and do not need to hold formal positions of power. Rather they are everyday citizens—a retired teacher, minister, stay-at-home parent, coach, and so forth—who care deeply about preventing HIV. The action team is then trained by the LCO on strategies for reducing HIV, including PrEP, and how to take actions to advance those evidence-based strategies (eg, where individuals can go to get these services near them). In the third stage, expanding the base, the action team builds additional rings of supporters connected to the effort. In the fourth stage, the LCO and action team members develop an action plan, wherein they schedule strategic actions designed to accomplish specific organizing outcomes (eg, sharing at community events). Stage 5 involves implementing the plan and carrying out their planned actions. Stage 6 involves assessing results, celebrating accomplishments, and refining the next steps that were planned. Thus, this COA systematically develops the leadership skills of trusted community members to become leaders and advocates for HIV prevention inclusive of PrEP for women in their communities.

We propose to innovatively use this COA to systematically develop the leadership skills and HIV prevention knowledge of individuals to become community advocates for HIV prevention in metro Atlanta to reduce HIV or PrEP-related stigma, build demand for PrEP, and facilitate linkages to women-friendly PrEP clinics. We hypothesize that the COA is feasible to implement and that the PrEP action plan implemented as part of the COA will be associated with increased PrEP awareness and interest, decreased HIV or PrEP stigma, and increased awareness about where women or individuals can get PrEP among cisgender women community members.

Methods

Study Setting

We will implement the COA (Textbox 1) within the 4 Atlanta high-priority EHE counties, in partnership with SisterLove, an Atlanta-based women's HIV and reproductive justice community based organization (CBO) that is internationally recognized for raising sexual health and HIV awareness among women and has deep connections in the community, and additional CBOs identified through our formative work.

Textbox 1. Description of the 6-stage community organizing approach.

Stage 1: assess community

Conduct one-on-one interviews to assess pre-exposure prophylaxis (PrEP) attitudes, motivations, and influences among key community members; use these findings to adapt a sexual health curriculum to address feedback.

Stage 2: build the base

Assemble "action teams" composed of approximately 15 individuals who work or reside across 4 metro Atlanta counties with the help of community-based organization partners and train them on an adapted sexual health curriculum.

Stage 3: expand the base

Identify individuals to engage during implementation (influencers to connect with to recruit women to attend workshops) and resources to contribute (eg, space to conduct the workshops).

Stage 4: develop an action plan

Schedule community education meetings across all 4 counties (5-10 per year per action team member) to reach diverse communities of cisgender women.

Stage 5: implement the action plan

Action team members conduct community events (~150 annually) using the adapted sexual health curriculum.

Stage 6: evaluate the action plan

Monitor the number of events, participant demographics, and fidelity to the sexual health curriculum; collect survey data to evaluate changes in PrEP awareness, interest, stigma, and reach.

Implementation of the COA

Preparing for Action (COA Stages 1-4)

We will first hire and train an LCO. In collaboration with the Emory team, the LCO will assess the community (COA stage 1) through one-on-one conversations with up to 100 individuals across Atlanta; ~25 per EHE county (collaborating CBOs will assist in identifying individuals such as opinion leaders, influential partners in their work, and diverse women in the community). Interviews will capture attitudes, motivations, and influences related to women's health and well-being, as well as their sexual health, with a focus on HIV prevention and PrEP. Interviews will be recorded and transcribed. Using an inductive coding approach, the LCO and Emory team members will code interviews and identify themes salient to address during COA implementation. We will then use findings to adapt SisterLove's existing sexual health curriculum (Healthy Love Workshop [38]) to address community feedback salient to PrEP use among women. Healthy Love is an evidence-based single-session, a small-group intervention for women with core content designed to increase participants' HIV and sexual health knowledge (including prevention strategies), risk perception, and self-efficacy to engage in HIV or sexually transmitted infection (STI) testing and preventative practices. The fundamental information within Healthy Love, specifically related to knowledge, risk perception, and self-efficacy for testing, will be retained, and updates will be made to incorporate information about PrEP.

Next, we will build the base (COA stage 2) by assembling action teams comprised of approximately 15 individuals who work or reside across all 4 counties with the help of CBO partners. Action teams will be essential for reaching diverse groups of women in their community and raising awareness, interest, and connection to PrEP via facilitating educational outreach. Action team members will be asked to commit to at least 1 year of engagement. They will be provided with an annual honorarium for serving in this role, and a certificate of appreciation from SisterLove and Emory teams acknowledging their significant role in reducing HIV in their communities. Action team members will work in coordination under the LCO, but each team will focus their implementation activities on their respective EHE counties. The LCO and SisterLove team will prepare the action teams with training on the adapted sexual health curriculum, supplemented with information on women-friendly places to access PrEP.

To expand the base (COA stage 3) action team members will identify individuals to engage during implementation and resources they might be able to contribute during implementation (eg, space for community education meetings to conduct adapted Healthy Love Workshop, audiences for meetings, and access to influencers to connect with to recruit women to attend meetings). As part of COA stage 4 (developing an action plan), the goal for each action team member is to arrange 5-10 community education events to be held per year in their EHE county. The LCO and action team members (supported by SisterLove and Emory teams) will schedule community education meetings reaching diverse communities of cisgender women, built on the unique reach of each action team member, across the 4 EHE counties.

Implementing and Evaluating the PrEP Action Plan (COA Stages 5-6)

Over 2 years, action team members will collectively conduct ~300 community events (~10 events per action team member per year) with an average of 10 community members attending each event. The action team members will facilitate their planned events (~2 hours each), following the adapted Healthy Love Workshop manual, with the assistance of the LCO, SisterLove, and the Emory team for data collection.

To monitor the implementation of the PrEP action plan, we will use electronic monitoring logs to capture (1) the number of community events scheduled or conducted by each action team member with dates and locations recorded, (2) the number and demographics of participants at each event (gathered through attendance logs at events), and (3) the number of requests for scheduling other community meetings. A study team member will collect monitoring data at each event to ensure the accuracy and completeness of logs and use a fidelity checklist to record fidelity to the adapted sexual health curriculum for each event.

We will collect data via surveys from the ~3000 community event participants to evaluate changes in PrEP awareness, interest, stigma, and reach after participating in a community education event conducted as part of the PrEP action plan. Specifically, all cisgender women participants at community events will be asked to complete brief pre- and posttest surveys that include measures on demographics, knowledge and attitudes about PrEP [15], concerns or barriers to PrEP use [39], and PrEP or HIV stigma [40,41]. Upon arriving at the event, each participant will sign in (name, email, phone number, and social media usernames) on a study laptop. Two additional questions will be asked: (1) "Is it ok to contact you in a few months to ask a few follow-up questions about the workshop—you will receive a US $5 gift card for your time?" and (2) "What is your preferred way to be contacted—text, phone, or email?" Participants will then be assigned a unique identifier to be used in the pre- and posttest surveys which will be administered electronically using a QR code link. The study team member will verify the unique identifier used with the participant ID log which will be stored separately from the participant's contact information. Participants' pretest surveys will be collected at the onset of the event, and posttest surveys will be collected upon completion. Study staff will review surveys upon collection and encourage participants to complete any missing items. Approximately 3 months after participation, ~50% of participants (among those agreeing to be contacted) will be randomly selected per event to participate in a brief survey (via text, email, or phone). Survey questions will be yes or no items assessing PrEP reach since participation in the community event to determine whether the participants has (1) received HIV or STI testing, (2) gone to a clinic for sexual health services, (3) talked to a health care provider about PrEP, (4) started PrEP, and (5) shared information about PrEP with other women (if so, how many). See Table 1 for a full list of evaluation measures.

Table 1. Comprehensive evaluation of pre-exposure prophylaxis (PrEP) action plan implementation on PrEP awareness, interest, and connection to PrEP care.

Method	Data source	Timing	Evaluation measures
Action plan implementation monitoring	Electronic monitoring log to capture the number of events, number of participants, types of PrEP resources shared, and number of requests additional events	Completed for each community event	Number of community events conducted by each action team member; number and demographics of participants at each event; and number of requests for scheduling other community meetings
Fidelity to sexual health curriculum	Fidelity checklist to record fidelity to the adapted sexual health curriculum in real time	Completed for each community event	Overall and individual checklist item
Pre- and posttest assessment of events	Brief paper-pencil pre- and posttest survey completed by ~3000 cisgender women attending community events	All cisgender women who participate in community events before and after the event	Demographics, knowledge, and interest in PrEP, PrEP stigma and attitudes about PrEP, history of PrEP use, and knowledge of PrEP clinics
Follow-up survey after events	Random sample of 50% of community event participants who agree to be contacted will be sent a brief email or text survey	Three months after participating in a community event	Yes or no questions since event: (1) received HIV testing, (2) went to Title X clinic that provides PrEP, (3) talked to a doctor about PrEP, (4) started PrEP, and (5) shared information about PrEP with other women (if so, how many)
PrEP reach among cisgender women seen in area clinics	Number of PrEP prescriptions to cisgender women seen in PrEP-providing clinics shared in community event resource list	Quarterly before, during, and after community events	Changes in number of PrEP prescriptions to women per quarter among PrEP-providing clinics

Statistical Analysis Plan

Descriptive statistics will be conducted on monitoring and fidelity data by year for each of the 2 implementation years. Feasibility of the COA will be determined by (1) successful implementation of ~10 community events per year by each action team member (~15 members), (2) at least 100 community members reached by each action team member per year (as indicated by # of participants attending their events), and (3) high fidelity to the adapted Healthy Love by action team members per year (>80% fidelity: determined by fidelity checklist indicating >80% content completed per event).

For pre-post assessments, scores on scales will be computed according to published guidance [39-42]. Descriptive analyses and paired *t* tests or chi-square tests will be conducted to ascertain pre-post changes in PrEP awareness, interest, stigma, and knowledge of where to access PrEP. For follow-up surveys, descriptive statistics will summarize the connection between PrEP care, connection to HIV testing, and PrEP reach (ie, self-reported initiation of PrEP) among the subset of community event participants who complete a follow-up survey.

We will conduct exploratory logistic regression analyses examining the association between pre-post survey scores (PrEP knowledge, attitudes, barriers, stigma, and prior use of PrEP) on PrEP reach, including demographic factors as covariates. Finally, exploratory descriptive analysis will summarize changes in PrEP reach among cisgender women receiving care at publicly funded family planning clinics in the 4 Atlanta EHE counties (number of PrEP prescriptions to women per quarter among PrEP-providing clinics discussed or shared during community events) for each year before, during, and after PrEP action plan implementation. Given our design, it is not appropriate to conduct comparison tests for this analysis.

Ethical Considerations

This study was approved by the Emory University institutional review board (#00002950). For the community interviews which were all completed via video conferencing, a waiver of documentation of consent was obtained, and the interview was completed after verbal consent. Community interview participants received a US $50 gift card upon completion of an interview. Community event participants who complete pre-post assessments and follow-up surveys will provide written informed consent. Community event participants will receive a US $5 gift card for completion of the 5-item 3-month follow-up text or email survey.

Interviews are conducted by trained research staff and recorded with audio recording devices; we instruct individuals to avoid using their names during the interview. In the event an identifier is used in the recording, all personally identifiable information is redacted from the transcripts during data quality assurance procedures performed by the study team. All audio recordings are professionally transcribed by a trusted vendor with secure web-based file transmission procedures. After transcription, the study team reviews each transcription against the audio recording to ensure verbatim accuracy and to remove identifiable information from the transcripts during this quality assurance procedure. After all transcripts are quality-checked and saved, the audio recordings will be destroyed. A study log kept by the study team will document this process. Transcripts and audio recordings are only stored on secure, password-protected platforms. No personal identifiers will be stored for other data

collection components, except to contact community event participants for follow-up surveys and distribute participant incentives. Personal identifiers will not be linked to any other data and will be destroyed as soon as survey invitations and participant incentives have been distributed.

Results

Study activities were funded by the National Institutes of Health (NIH) and was approved by the institutional review board in July 2021 and data collection began in December 2021 and is ongoing. From December 2021 to October 2022, we hired and trained the LCO and completed 70 community interviews with key stakeholders. Eligible participants worked or resided in Dekalb, Gwinnett, Fulton, or Cobb County in the state of Georgia and were able to provide verbal consent to participate. Participants were primarily female-identifying (n=64, 91%); of 70 total participants, 20 (29%) endorsed being a lay community member, while others reported community involvement through organizations or businesses (n=19, 27% members of a nonprofit organization; n=12, 17% staff at a clinic; n=4, 6% self-employed; n=4, 6% college students; and n=1, 1% affiliated with a faith-based organization). About 10% (n=7) of participants reported involvement in HIV support groups (n=5, 7%) or advocacy groups (n=2, 3%) as their community involvement. Of those who reported race and ethnicity (n=46, 66%), 35 (76%) identified as Black, 7 (15%) identified as White, and 4 (9%) identified as more than 1 race. A total of 4 (9%) participants reported Hispanic or Latino ethnicity which parallels HIV diagnoses by race or ethnicity in Georgia [3].

From October 2022 to December 2022, we analyzed interview data and identified important preliminary themes in these conversations including the need for broad-based, inclusive approaches to discussions about women's sexual health and HIV prevention with accurate, straightforward, and reliable content delivered by trusted, relatable members of the community in safe and easy to access spaces. From December 2022 to June 2023, we collaborated with SisterLove on the adaptation of the Healthy Love sexual health curriculum based on these preliminary community interview findings while taking care to retain fundamental information within Healthy Love, specifically related to HIV knowledge, risk perception, and self-efficacy for testing (COA stage 1). From February 2023 to July 2023, we recruited and trained a diverse group of 15 action team members and gathered feedback on the curriculum adaptation. Additional changes to the curriculum were made based on community feedback from July to August 2023. Community events commenced in November 2023 and data collection will be completed by November 2025. Full trial results are anticipated to be reported by July 2026.

Discussion

Principal Findings

Using a COA that engages and supports community members in educating other community members about their sexual health can broaden and enrich the awareness, and potentially the reach of, HIV prevention, testing, and PrEP into diverse networks of cisgender women. Our findings in assessing the communities in metro Atlanta thus far have affirmed the need for greater emphasis on women-inclusive initiatives delivered by individuals considered relatable within the community who are comfortable and knowledgeable about discussing sexual health with the overarching goal of creating safe spaces for authentic conversations. Taking this into consideration when forming action teams, the LCO, with the assistance of SisterLove and Emory partners, dedicated extra time and attention during stage 1 of the COA to identify, recruit, and train team members to ensure that teams remain representative of women of varying ages, races, ethnicities, and social networks living in EHE high priority counties in metro Atlanta.

Adjustments in the protocol for the adaptation of the evidence-based Healthy Love curriculum by SisterLove, Inc were also made to include the opinions and feedback of the action team members on the revised curriculum content. Initial curriculum revisions were drafted to include content salient to data outcomes from the in-depth community interviews capturing attitudes, motivations, and influences related to women's sexual health, with a focus on HIV prevention and PrEP. The revised draft was then presented to action team members as a community event and their feedback was gathered and later incorporated into the final curriculum to guide action teams in facilitating health education community events.

Moving forward, we anticipate that the evidenced-based COA will be feasible, and participation in its community events will be associated with increases in PrEP awareness and interest, decreases in PrEP or HIV stigma, and greater knowledge about where women can go for PrEP care (eg, PrEP-providing Title X clinics). We also expect that participation in events will be associated with improved PrEP reach among women who participate. These findings will provide critical data related to the COA use to create a potentially sustainable community-engaged approach for disseminating information about new HIV prevention products from trusted members in the community inclusive of cisgender women.

Limitations

Action team members may discontinue participation over time. If this occurs, we will work with our collaborating CBOs and other action team members to recruit new individuals into this role. If a member withdraws before completing community events, other action team members, the LCO, and CBO staff will conduct the remaining scheduled events. We may encounter challenges related to the completion of the follow-up survey. If randomly selected individuals do not complete the survey, we will select another. We expect 90% will indicate willingness to be contacted, and we are only attempting to sample 50% of participants, so we are confident we can achieve our goal sample size.

Conclusions

Through a community-clinic-academic collaboration and innovative application of COA, this protocol proposes to mount a coordinated approach across diverse Atlanta counties to strengthen HIV prevention for cisgender women, and importantly, to create a sustainable systems approach to move

new and sexual health innovations more quickly to cisgender women.

Acknowledgments

The authors would like to thank the study staff, community and clinical partners, and study participants who supported this work. They would like to acknowledge their community action team members for their key role in this study, Athena Carpenter, Ashley Cobb, Aku Dogbe, Muriel “Alea” Grant, Zykeria Holmes, Bailey Ledbetter, Mayra Martinez, Simitri Nassar, Rosie Palmer, Alexis Perkins, and Masonia Traylor. This study is funded by the National Institutes of Health (NIH; R01MH121962).

Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request upon completion of primary analyses.

Conflicts of Interest

None declared.

References

1. HIV surveillance data tables: core indicators for monitoring the ending the HIV epidemic initiative (preliminary data): national HIV surveillance system data reported through June 2023; and preexposure prophylaxis (PrEP) data reported through March 2023. Centers for Disease Control and Prevention. 2023. URL: https://www.cdc.gov/hiv/library/reports/surveillance-data-tables/ [accessed 2023-12-05]
2. HIV surveillance report: diagnoses of HIV infection in the United States and dependent areas, 2021. Centers for Disease Control and Prevention. 2021. URL: http://www.cdc.gov/hiv/library/reports/hiv-surveillance.html [accessed 2023-12-05]
3. HIV/AIDS epidemiology section HIV surveillance summary, Georgia 2018. Georgia Department of Public Health. 2019. URL: https://dph.georgia.gov/document/document/hivepi2018surveillancesummary/download [accessed 2020-12-16]
4. Fauci AS, Redfield RR, Sigounas G, Weahkee MD, Giroir BP. Ending the HIV epidemic: a plan for the United States. JAMA 2019;321(9):844-845 [FREE Full text] [doi: 10.1001/jama.2019.1343] [Medline: 30730529]
5. FDA approves first drug for reducing the risk of sexually acquired HIV infection. HIV.gov. 2012. URL: http://tiny.cc/261kxz [accessed 2024-02-27]
6. HIV prevention programs. Centers for Disease Control and Prevention. 2021. URL: https://www.cdc.gov/nchhstp/highimpactprevention/hiv-prevention-programs.html [accessed 2021-01-04]
7. NIH HIV/AIDS research priorities and guidelines for determining AIDS funding. NIH. 2021. URL: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-137.html [accessed 2021-01-04]
8. Young I, McDaid L. How acceptable are antiretrovirals for the prevention of sexually transmitted HIV?: A review of research on the acceptability of oral pre-exposure prophylaxis and treatment as prevention. AIDS Behav 2014;18(2):195-216 [FREE Full text] [doi: 10.1007/s10461-013-0560-7] [Medline: 23897125]
9. Sullivan PS, Giler RM, Mouhanna F, Pembleton ES, Guest JL, Jones J, et al. Trends in the use of oral emtricitabine/tenofovir disoproxil fumarate for pre-exposure prophylaxis against HIV infection, United States, 2012-2017. Ann Epidemiol 2018;28(12):833-840 [FREE Full text] [doi: 10.1016/j.annepidem.2018.06.009] [Medline: 30037634]
10. Siegler AJ, Mouhanna F, Giler RM, Weiss K, Pembleton E, Guest J, et al. The prevalence of pre-exposure prophylaxis use and the pre-exposure prophylaxis-to-need ratio in the fourth quarter of 2017, United States. Ann Epidemiol 2018;28(12):841-849 [FREE Full text] [doi: 10.1016/j.annepidem.2018.06.005] [Medline: 29983236]
11. Huang YLA, Zhu W, Smith DK, Harris N, Hoover KW. HIV preexposure prophylaxis, by race and ethnicity - United States, 2014-2016. MMWR Morb Mortal Wkly Rep 2018;67(41):1147-1150 [FREE Full text] [doi: 10.15585/mmwr.mm6741a3] [Medline: 30335734]
12. Smith DK, Van Handel M, Grey J. Estimates of adults with indications for HIV pre-exposure prophylaxis by jurisdiction, transmission risk group, and race/ethnicity, United States, 2015. Ann Epidemiol 2018;28(12):850-857.e9 [FREE Full text] [doi: 10.1016/j.annepidem.2018.05.003] [Medline: 29941379]
13. Frost JJ, Gold RB, Bucek A. Specialized family planning clinics in the United States: why women choose them and their role in meeting women's health care needs. Womens Health Issues 2012;22(6):e519-e525 [FREE Full text] [doi: 10.1016/j.whi.2012.09.002] [Medline: 23122212]
14. Sales JM, Cwiak C, Haddad LB, Phillips A, Powell L, Tamler I, et al. Brief report: impact of PrEP training for family planning providers on HIV prevention counseling and patient interest in PrEP in Atlanta, Georgia. J Acquir Immune Defic Syndr 2019;81(4):414-418 [FREE Full text] [doi: 10.1097/QAI.0000000000002057] [Medline: 30985558]
15. Patel AS, Goparaju L, Sales JM, Mehta CC, Blackstock OJ, Seidman D, et al. Brief report: PrEP eligibility among at-risk women in the Southern United States: associated factors, awareness, and acceptability. J Acquir Immune Defic Syndr 2019;80(5):527-532 [FREE Full text] [doi: 10.1097/QAI.0000000000001950] [Medline: 30649036]

16. Edelstein Z, Mensah N, Scanlin K, Cutler B, Myers J. Awareness of HIV prevention innovations among women of color in NYC: HIV self-tests and pre-exposure prophylaxis (PrEP). 2014 Presented at: 142nd APHA Annual Meeting and Exposition; November 15-19, 2014; New Orleans, LA URL: https://apha.confex.com/apha/142am/videogateway.cgi/id/67028?recordingid=67028
17. Auerbach JD, Kinsky S, Brown G, Charles V. Knowledge, attitudes, and likelihood of pre-exposure prophylaxis (PrEP) use among US women at risk of acquiring HIV. AIDS Patient Care STDS 2015;29(2):102-110 [FREE Full text] [doi: 10.1089/apc.2014.0142] [Medline: 25513954]
18. Doblecki-Lewis S, Lester L, Schwartz B, Collins C, Johnson R, Kobetz E. HIV risk and awareness and interest in pre-exposure and post-exposure prophylaxis among sheltered women in Miami. Int J STD AIDS 2016;27(10):873-881 [FREE Full text] [doi: 10.1177/0956462415601304] [Medline: 26384947]
19. Walters SM, Reilly KH, Neaigus A, Braunstein S. Awareness of pre-exposure prophylaxis (PrEP) among women who inject drugs in NYC: the importance of networks and syringe exchange programs for HIV prevention. Harm Reduct J 2017;14(1):40 [FREE Full text] [doi: 10.1186/s12954-017-0166-x] [Medline: 28662716]
20. Collier KL, Colarossi LG, Sanders K. Raising awareness of pre-exposure prophylaxis (PrEP) among women in New York City: community and provider perspectives. J Health Commun 2017;22(3):183-189 [FREE Full text] [doi: 10.1080/10810730.2016.1261969] [Medline: 28248625]
21. Seidman D, Carlson K, Weber S, Witt J, Kelly PJ. United States family planning providers' knowledge of and attitudes towards preexposure prophylaxis for HIV prevention: a national survey. Contraception 2016;93(5):463-469 [FREE Full text] [doi: 10.1016/j.contraception.2015.12.018] [Medline: 26772906]
22. Koren DE, Nichols JS, Simoncini GM. HIV pre-exposure prophylaxis and women: survey of the knowledge, attitudes, and beliefs in an urban obstetrics/gynecology clinic. AIDS Patient Care STDS 2018;32(12):490-494 [FREE Full text] [doi: 10.1089/apc.2018.0030] [Medline: 30036080]
23. Garfinkel DB, Alexander KA, McDonald-Mosley R, Willie TC, Decker MR. Predictors of HIV-related risk perception and PrEP acceptability among young adult female family planning patients. AIDS Care 2017;29(6):751-758 [FREE Full text] [doi: 10.1080/09540121.2016.1234679] [Medline: 27680304]
24. Sales JM, Escoffery C, Hussen SA, Haddad LB, McCumber M, Kwiatkowski E, et al. Pre-exposure prophylaxis implementation in family planning services across the Southern United States: findings from a survey among staff, providers and administrators working in Title X-funded clinics. AIDS Behav 2021;25(6):1901-1912 [FREE Full text] [doi: 10.1007/s10461-020-03120-9] [Medline: 33483899]
25. Committee on Gynecologic Practice. ACOG committee opinion no 595: committee on gynecologic practice: preexposure prophylaxis for the prevention of human immunodeficiency virus. Obstet Gynecol 2014;123(5):1133-1136 [FREE Full text] [doi: 10.1097/01.AOG.0000446855.78026.21] [Medline: 24785877]
26. Piper KN, Escoffery C, Sales JM, Sheth AN. Models of HIV pre-exposure prophylaxis care used in Title X family planning clinics in the Southern U.S. J Adolesc Health 2021;68(3):480-487 [FREE Full text] [doi: 10.1016/j.jadohealth.2020.10.005] [Medline: 33160826]
27. Shah PD, Gilkey MB, Pepper JK, Gottlieb SL, Brewer NT. Promising alternative settings for HPV vaccination of US adolescents. Expert Rev Vaccines 2014;13(2):235-246 [FREE Full text] [doi: 10.1586/14760584.2013.871204] [Medline: 24405401]
28. Delany-Moretlwe S, Mullick S, Eakle R, Rees H. Planning for HIV preexposure prophylaxis introduction: lessons learned from contraception. Curr Opin HIV AIDS 2016;11(1):87-93 [FREE Full text] [doi: 10.1097/COH.0000000000000221] [Medline: 26575146]
29. Boyd M, Murphy D, Bielak D. “Billion dollar bets” to reduce unintended pregnancies: creating economic opportunity for every American. The Bridgespan Group. 2016. URL: https://files.eric.ed.gov/fulltext/ED606530.pdf [accessed 2024-02-27]
30. Sales JM, Phillips AL, Tamler I, Munoz T, Cwiak C, Sheth AN. Patient recommendations for PrEP information dissemination at family planning clinics in Atlanta, Georgia. Contraception 2019;99(4):233-238 [FREE Full text] [doi: 10.1016/j.contraception.2018.12.008] [Medline: 30711352]
31. Wandersman A, Duffy J, Flaspohler P, Noonan R, Lubell K, Stillman L, et al. Bridging the gap between prevention research and practice: the interactive systems framework for dissemination and implementation. Am J Community Psychol 2008;41(3-4):171-181 [FREE Full text] [doi: 10.1007/s10464-008-9174-z] [Medline: 18302018]
32. Lesesne CA, Lewis KM, White CP, Green DC, Duffy JL, Wandersman A. Promoting science-based approaches to teen pregnancy prevention: proactively engaging the three systems of the interactive systems framework. Am J Community Psychol 2008;41(3-4):379-392 [FREE Full text] [doi: 10.1007/s10464-008-9175-y] [Medline: 18302017]
33. Lewis KM, Lesesne CA, Zahniser SC, Wilson MM, Desiderio G, Wandersman A, et al. Developing a prevention synthesis and translation system to promote science-based approaches to teen pregnancy, HIV and STI prevention. Am J Community Psychol 2012;50(3-4):553-571 [FREE Full text] [doi: 10.1007/s10464-012-9510-1] [Medline: 22491824]
34. Kennedy K, Pettigrew D, Komro K, Wagenaar A. Communities mobilizing for change on alcohol: a guide for implementation. Communities Mobilizing for Change on Alcohol. 2021. URL: http://web1.sph.emory.edu/eprc/docs/CMCA%20Handbook%2003-02-17.pdf [accessed 2024-02-27]

35. Komro KA, Wagenaar AC, Boyd M, Boyd BJ, Kominsky T, Pettigrew D, et al. Prevention trial in the Cherokee Nation: design of a randomized community trial. Prev Sci 2015;16(2):291-300 [FREE Full text] [doi: 10.1007/s11121-014-0478-y] [Medline: 24615546]
36. Wagenaar AC, Murray DM, Gehan JP, Wolfson M, Forster JL, Toomey TL, et al. Communities mobilizing for change on alcohol: outcomes from a randomized community trial. J Stud Alcohol 2000;61(1):85-94 [FREE Full text] [doi: 10.15288/jsa.2000.61.85] [Medline: 10627101]
37. Wagenaar AC, Murray DM, Toomey TL. Communities Mobilizing for Change on Alcohol (CMCA): effects of a randomized trial on arrests and traffic crashes. Addiction 2000;95(2):209-217 [FREE Full text] [doi: 10.1046/j.1360-0443.2000.9522097.x] [Medline: 10723849]
38. Diallo DD, Moore TW, Ngalame PM, White LD, Herbst JH, Painter TM. Efficacy of a single-session HIV prevention intervention for black women: a group randomized controlled trial. AIDS Behav 2010;14(3):518-529 [FREE Full text] [doi: 10.1007/s10461-010-9672-5] [Medline: 20135214]
39. Siegler AJ, Wiatrek S, Mouhanna F, Amico KR, Dominguez K, Jones J, et al. Validation of the HIV pre-exposure prophylaxis stigma scale: performance of likert and semantic differential scale versions. AIDS Behav 2020;24(9):2637-2649 [FREE Full text] [doi: 10.1007/s10461-020-02820-6] [Medline: 32157490]
40. Walsh JL. Applying the Information-Motivation-Behavioral Skills model to understand PrEP intentions and use among men who have sex with men. AIDS Behav 2019 Jul;23(7):1904-1916 [FREE Full text] [doi: 10.1007/s10461-018-2371-3] [Medline: 30554396]
41. John SA, Rendina HJ, Starks TJ, Grov C, Parsons JT. Decisional balance and contemplation ladder to support interventions for HIV pre-exposure prophylaxis uptake and persistence. AIDS Patient Care STDS 2019;33(2):67-78 [FREE Full text] [doi: 10.1089/apc.2018.0136] [Medline: 30653348]
42. Golub SA, Fikslin RA, Goldberg MH, Peña SM, Radix A. Predictors of PrEP uptake among patients with equivalent access. AIDS Behav 2019 Jul;23(7):1917-1924 [FREE Full text] [doi: 10.1007/s10461-018-2376-y] [Medline: 30600456]

Abbreviations

CBO: community-based organization
CDC: Centers for Disease Control and Prevention
COA: community organizing approach
EHE: Ending the HIV Epidemic
ISF: Interactive Systems Framework
LCO: lead community organizer
NIH: National Institutes of Health
PrEP: pre-exposure prophylaxis
STI: sexually transmitted infection

Edited by A Mavragani; submitted 11.01.24; peer-reviewed by J Opoku, S Chen; comments to author 12.02.24; revised version received 19.02.24; accepted 23.02.24; published 22.03.24.

Please cite as:
Sheth AN, Dixon Diallo D, Ellison C, Er DL, Ntukogu A, Komro KA, Sales JM
Applying an Evidence-Based Community Organizing Approach to Strengthen HIV Prevention for Cisgender Women in US South: Protocol for a Mixed Methods Study
JMIR Res Protoc 2024;13:e56293
URL: https://www.researchprotocols.org/2024/1/e56293
doi:10.2196/56293
PMID:38517456

Protocol

Investigating Father or Partner Involvement in Family Integrated Care in Neonatal Units: Protocol for a Prospective, Multicenter, Multiphase Study

Rupa Rubinstein[1,2], MBBCHIR, MSci; Katie Gallagher[3], PhD; John Ho[4], MBBS; Julian Bose[5], BSc; Minesh Khashu[6], PhD; Narendra Aladangady[1,2], PhD

[1]Neonatal Unit, Homerton Healthcare NHS Foundation Trust, London, United Kingdom
[2]Blizard Institute, Queen Mary University London, London, United Kingdom
[3]Institute of Women's Health, University College London, London, United Kingdom
[4]Neonatal Unit, Whipps Cross University Hospital, Barts Health, London, United Kingdom
[5]Inspire Cornwall Community Interest Company's DadPad, The Health and Wellbring Innovation Centre, Truro, United Kingdom
[6]Neonatal Unit, University Hospitals Dorset NHS Foundation Trust, Dorset, United Kingdom

Corresponding Author:
Narendra Aladangady, PhD
Neonatal Unit
Homerton Healthcare NHS Foundation Trust
Homerton Row
London, E9 6SR
United Kingdom
Phone: 44 2085105555
Email: n.aladangady@nhs.net

Related Article:

This is a corrected version. See correction statement: https://www.researchprotocols.org/2024/1/e58848

Abstract

Background: Neonatal unit (NU) admissions for premature babies can last for months, which can significantly impact parental mental health (MH) with symptoms of depression, stress, and anxiety. Literature suggests fathers experience comparable MH symptoms to mothers. Family integrated care (FICare) is a culture where parents are collaborators and partners in caring for their hospitalized newborns. FICare improves infant outcomes and maternal MH. Similar reports on fathers are limited.

Objective: The primary aim of this study is to investigate the impact of supporting father or partner engagement in FICare of preterm infants on their MH up to 6 weeks postdischarge. The secondary aim is to investigate the impact on maternal MH.

Methods: This is a 2-phase study: phase 1 to gather baseline information and phase 2 to assess the impact of enhanced father or partner engagement in FICare on their MH, involving 2 NUs (tertiary and level 2). Enhanced FICare will be developed and introduced (eg, information booklet, workbook, classes, and a father peer-support group) alongside standard FICare practices. Father or partner MH will be assessed with semistructured qualitative interviews and validated questionnaires: Generalized Anxiety Disorder Assessment, Patient Health Questionnaire, and Parental Stressor Scale: Neonatal Intensive Care Unit from NU admission to 6 weeks postdischarge. Mothers will be assessed by focus groups and the same questionnaires. Descriptive statistics and appropriate comparative tests, such as the 2-tailed *t* test, will be used to analyze and compare phase 1 and 2 data. Qualitative data will be coded line by line with the use of NVivo (Lumivero) and thematically analyzed. Simultaneously, systematic reviews (SRs) of fathers' experiences of FICare and their MH outcomes will be conducted. The study was approved by the National Research Ethics Committee (22/EM/0140) in August 2022. A parent advisory group was formed to advise on the study methodology, materials, involvement of participant parents, and dissemination of study findings.

Results: A recent SR demonstrated that data saturation is likely to be achieved by interviewing 9 to 17 participants. We will study a maximum of 20 parents of infants born at less than 33 weeks' gestation in each phase. As of October 2023, the study was

ongoing. The SR studies are registered with the PROSPERO database (324275 and 306760). The projected end date for data collection is July 2024; data analysis will be conducted in November 2024 and publication will occur in 2025.

Conclusions: The study aims to demonstrate the feasibility of using a father or partner-sensitive FICare model for parents of premature babies with a positive impact on their MH. It will demonstrate the feasibility of providing FICare to extremely premature babies receiving intensive care. This study may support the development of inclusive FICare guidelines for nonbirthing parents and their extremely premature infants.

Trial Registration: ClinicalTrials.gov: NCT06022991; https://classic.clinicaltrials.gov/ct2/show/NCT06022991

International Registered Report Identifier (IRRID): DERR1-10.2196/53160

(JMIR Res Protoc 2024;13:e53160) doi:10.2196/53160

KEYWORDS

family integrated care; FICare; neonatal intensive care unit; NICU; fathers; premature infants, mental health; pediatric; pediatrics; infant; infants; infancy; baby; babies; neonate; neonates; neonatal; premature; partner; couple; family care; NU admission; NICU admission; engagement

Introduction

In 2019, in England and Wales, 49,489 premature births were recorded, and the majority would have required a neonatal unit (NU) admission [1]. Scientific and technological advancements have led to significant reductions in mortality and morbidity for preterm infants [2], and now the importance of decreasing psychosocial morbidity for the family unit is being addressed. Admission of a critically ill baby to the NU is a deeply traumatic time for parents and may result in parental mental health (MH) difficulties during and after discharge [3,4]. Studies exploring paternal experiences in the NU highlight fathers feeling neglected and in a unique position of stress, trying to balance work and home life to allow the mother to focus on their sick baby [5]. As paternal and maternal MH are closely linked, supporting the fathers could also positively impact maternal MH [6,7]. A recent study has shown reduced paternal stress in relation to the provision of family integrated care (FICare) in single-family rooms, but it only included parents of babies who did not require intensive care [8].

FICare in the NU means that parents are partners and collaborators in the care of their hospitalized baby, rather than observers or visitors. They are included in decision-making and supported to feed, clean, and hold their baby as well as learning how to provide neurodevelopmental care [9,10]. FICare studies that have focused on mothers and infants demonstrate improved neurodevelopmental outcomes [11], improved breastfeeding rates [12], reduced infection rates, and improved maternal MH [13,14]. There is a paucity of similar research regarding fathers [15]. The impact of parental MH on children is a focus of the UK government's "First 1000 days of life" paper [16]. Implementation and improvements to FICare as a method of enhancing "parenting opportunity" are also highlighted in the National Neonatal Critical Care Review in England [17]. Synthesizing the evidence base surrounding the impact of paternal engagement addresses recommendations from National Health Service (NHS) England, the Cross Government 1001 Critical Days Campaign [7], the Neonatal Critical Care Transformation Review, and Care Quality Commission standards to increase the evidence base to support women and their families experiencing perinatal MH problems. This area currently costs the NHS an estimated £1.2 billion (equivalent to US $1.5 billion) per year [16,17]. The UK government has recently recognized the importance of maternal and paternal presence for babies in the NU via the Neonatal Care (Leave and Pay) Act, which achieved royal assent in May 2023 granting parents up to an additional 12 weeks of leave [18]. Hence, we developed a study protocol to investigate and enhance fathers' or partners' involvement in FICare and its impact on their MH.

This study will be the first to report on fathers' experiences of FICare in the NU with extremely premature babies. It will broaden the field of FICare research with respect to fathers from diverse social and cultural backgrounds and will highlight the needs of fathers in the NU. Therefore, it will demonstrate the value of designing a father- or partner-sensitive FICare program. This study will also generate evidence for the feasibility of the introduction of FICare from day 1 while preterm babies are receiving intensive care.

From here on, although the study refers to "fathers," all second parents of any gender or relationship status are included under this term throughout the remaining text.

Methods

Aims

This study aims to undertake an in-depth longitudinal study of the engagement of fathers or partners in FiCare and their experience and MH from NU admission to 6 weeks postdischarge of their premature baby born at 22 to 33 weeks' gestation.

Objectives

Our objectives are to (1) assess baseline fathers' experiences in the NU, their involvement in FICare, and MH status during babies NU admission up to 6 weeks postdischarge, (2) conduct systematic reviews (SRs) of published papers on "Fathers and FiCare in NU" and "Fathers' MH in the NU," (3) develop a program to enhance the involvement of fathers in FiCare, and (4) introduce the program developed to enhance fathers' involvement in FiCare and explore their experiences and effects on their MH.

Outcomes

The primary outcome is paternal MH (stress) assessed by semistructured interviews.

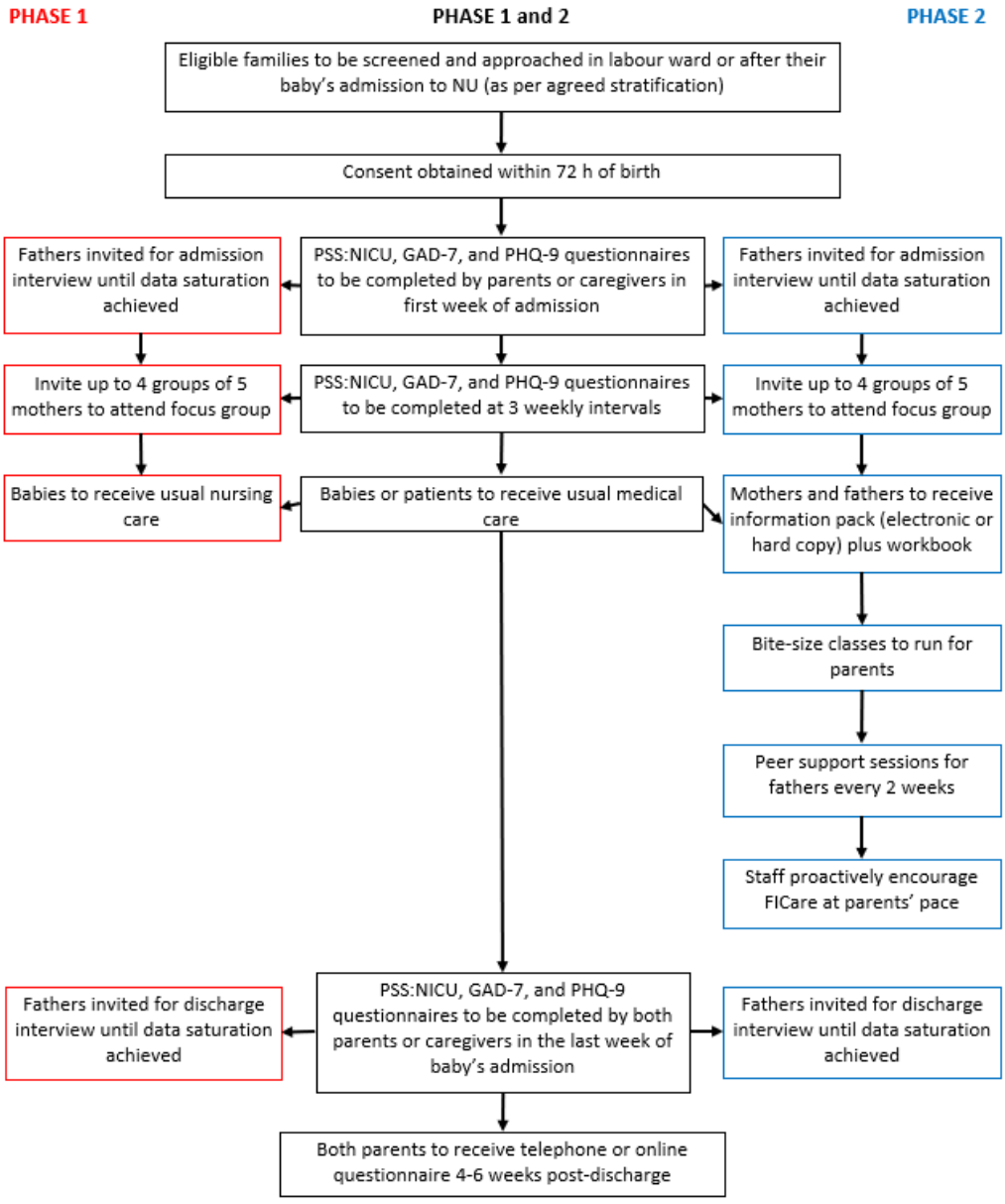
The secondary outcomes are (1) maternal stress, assessed by the Parental Stressor Scale: Neonatal Intensive Care Unit (PSS:NICU) questionnaire; (2) paternal stress, assessed by the PSS:NICU questionnaire; (3) parental anxiety, assessed by the Generalized Anxiety Disorder Assessment-7 (GAD-7); (4) parental depression, assessed by the Personal Health Questionnaire-9 (PHQ-9); and (5); paternal engagement with FICare, assessed via interviews.

Study Design

This is a prospective, multicenter, and multiphase study. Phase 1 will assess baseline fathers' experiences in the NU, their involvement in FICare, and MH status during babies' NU admission up to 6 weeks postdischarge. Simultaneously, an SR of fathers' involvement in FICare and their MH outcomes will be conducted. A program to enhance the involvement of fathers in FICare will be developed using information from the phase 1 study, SR, existing DadPad or Imperial Family Delivered Neonatal Care app, and advice from the parent advisory group (PAG). In the phase 2 study, an enhanced father involvement program in FICare will be implemented and similar assessments as in phase 1 will be conducted (Figure 1). We will provide regular debrief sessions, and research updates or newsletters to keep staff engaged and supportive of the project. This support will be continued throughout the study.

This study has been registered with clinicaltrials.gov (NCT06022991) [19].

Figure 1. Participant flow chart. FICare: family integrated care; GAD-7: Generalized Anxiety Disorder-7; NU: neonatal unit; PHQ-9: Patient Health Questionnaire-9; PSS:NICU: Parental Stressor Scale: Neonatal Intensive Care Unit.



Systematic Reviews

The SR studies have been registered on the PROSPERO database (324275 [20], 306760 [21]) and will follow a similar methodology. A literature search of health care databases including EMBASE, EMCARE, CINAHL, Medline, BNI, PYCHInfo, and Psychology and Behaviour, and a gray literature search will be conducted. Two independent researchers will screen the results at the title and abstract level against the eligibility criteria (Table 1), with mediation by a third researcher available for any disagreements to reevaluate the paper and come to a team agreement. The matrix method will be used for data extraction [22].

Table 1. Eligibility criteria for the systematic reviews.

	Fathers' mental health in the NU[a] [18]	Fathers and FICare[b] in the NU [19]
Studies published from January 1, 2000, to October 14, 2022	✓	✓
Full paper available in English	✓	✓
Study setting is the NU	✓	✓
At least 5 study participants	✓	✓
At least half of the participants are fathers	✓	✓
Addressed paternal mental health	✓	
Addressed FICare		✓

[a]NU: neonatal unit.

[b]FICare: family integrated care.

Study Centers

The study will be conducted at a tertiary NU (level 3) and a local NU (level 2), as defined by the Department of Health [23], in East London, United Kingdom. Average annual admissions are approximately 900 and 600 respectively, with parents from diverse ethnic and socioeconomic backgrounds. Both level 3 and 2 NUs are selected to show the feasibility of delivering enhanced father involvement in FICare in all NUs and the study findings are applicable to all levels of NUs. Although FICare culture is practiced at both sites, a formal program and expectations of FICare are not implemented.

Clinical Staff Involvement

The wider multidisciplinary team was consulted in the study design and consideration of phase 2 study materials. They included physiotherapists, clinical psychologists, occupational therapists, dieticians, and speech and language therapists along with neonatal nursing input. The London neonatal network care coordinator was also consulted regarding the study design and implementation.

Patient and Public Involvement

Patients and the public were involved in the design, conduct, reporting, and dissemination plans of the study. A PAG consisting of parents of preterm infants was developed. They consisted of a diverse socioeconomic and cultural mix of 4 fathers and a mother who had experienced the admission of their premature baby in the NU within the last 4 years. The PAG was involved in developing the study design. The PAG has reviewed and provided feedback on study materials, for example, participant information leaflet. A lay member is included as a coinvestigator (JB, Director of Inspire Cornwall CIC's Neonatal DadPad) of the study.

The PAG was consulted to advise on the burden of intervention and the time required to participate in the research. This has influenced the frequency of questionnaire administration and locations of interviews and focus groups. They will support the development of appropriate phase 2 materials for the information booklet, workbook, and education sessions. The PAG will also support the dissemination of the study findings to research participants, related charity bodies (eg, Bliss), and the wider neonatal community.

Study Participants and Recruitment

Parents of preterm infants will be recruited to the study.

Inclusion Criteria

The inclusion criteria are as follows: (1) parents of 22^{+0} to 32^{+6} weeks preterm infants; (2) infants aged 1 to 7 days; (3) infants with 2 primary caregivers (the father's or partner's participation in the study is a must, and participation from both parents is ideal), and (4) the parents should have conversational English.

Exclusion Criteria

The inclusion criteria are as follows: (1) infant with life-limiting conditions or no realistic chance of survival, (2) infant is likely to be transferred to nonparticipating center within 4 weeks of age, and (3) parents are younger than 16 years.

All parents with babies born between 22^{+0} and 32^{+6} weeks' gestation admitted to the participating centers at less than 7 days of age will be assessed for eligibility. A sequential recruitment strategy will be followed with all eligible parents from the date of recruitment opening until 20 parents have been recruited in each phase. Within each eligible parent, consent and recruitment of the father or partner is essential. Maternal recruitment in addition to the partner, is encouraged but not mandatory.

Sample Size

The sample size of the study is estimated based on qualitative study outcomes. A recent SR of qualitative study demonstrated that to achieve data saturation we need to interview 9 to 17 participants [24]. A focus group of 5 to 7 participants would be

enough for in-depth conversations and 2 or more groups would increase the chances of successful data output [25].

In the first and second phases, up to 20 parents will be recruited (until the fathers' interviews reach data saturation). With a father and mother each, there could be 40 participants per phase. In total, there could be 80 participants in the study.

Phase 1 Study: Baseline Data Collection (9 Months)

Overview

Phase 1 will be conducted as follows: (1) Prior to the introduction of the study to wider NU clinical staff members, staff knowledge, experiences, and opinions about the role of fathers and FICare will be assessed by a questionnaire. (2) Once a parent is recruited, the PSS:NICU [26] and MH questionnaires (GAD-7 [27] and PHQ-9 [28]) will be given to complete within 7 days. (3) Fathers or partners will be invited to participate in 2 semistructured interviews, within 2 weeks of recruitment and immediately prior to discharge. The interviews will explore their MH, experiences of bonding with baby, understanding the neonatal environment, and reflecting on their service expectations. Based on the father's or partner's preference, interviews will be undertaken either in a private room on the NU or digitally via MS Teams at a mutually convenient time. Interviews will be digitally recorded and are anticipated to last up to 1 hour. Data saturation is expected at around 12-15 fathers. (4) The parents will be asked to complete the PSS:NICU, GAD-7, and PHQ-9 questionnaires at 3 weekly intervals, finishing on the week of discharge, to monitor their MH through their NU stay. (5) Up to 4 groups of 5 mothers will be invited to participate in a focus group to assess their wellbeing, experience of the NU, and their perspective on support for and from their partners. This will occur in a room in the NU at a time convenient to the mothers. Groups will be organized until data saturation is reached. (6) Telephone interviews and emailed questionnaires will be completed by parents at 4-6 weeks postdischarge to assess family confidence and bonding after NU discharge.

Description of Questionnaires Used

PSS:NICU Questionnaire

The PSS:NICU was originally developed in 1993 [26]. It assesses neonatal intensive care unit–specific stressors on a Likert scale. Each item can be scored from 0 to 5, with a maximum total score of 230 over the 46 items. Modified versions exist, but the original full-length questionnaire will be used for this study as all subsections are of interest with changes to be implemented.

GAD-7 Questionnaire

The GAD-7 is a 7-item self-administered questionnaire that assesses the presence and severity of symptoms of anxiety over the preceding fortnight. Scores range from 0 to 3 on each item, with a total score ranging from 0 to 21. There are established set points for mild, moderate, and severe anxiety [27].

PHQ-9 Questionnaire

The PHQ-9 is a 9-item self-administered questionnaire that assesses the presence and severity of symptoms of depression over the previous two weeks. It is scored in the same manner as the GAD-7 with total scores ranging from 0 to 27 and with established set points for mild, moderate, and severe symptoms [28].

Washout Period, Phase 2 Preparation (4 Months)

A program to enhance father participation with the FICare model will be developed using the existing Neonatal DadPad or Imperial Family Delivered Neonatal Care app. Both of these apps are currently used in several NHS Trusts to guide fathers through their NU journey. The phase 1 and systematic review findings, along with guidance from the PAG will inform our decision for what is best suited for our local population.

Teaching sessions will be undertaken to educate and upskill all clinical NU staff on the study aims, recruitment, phase 1 study findings, and upcoming phase 2 study, highlighting the importance of fathers' role in the FICare (eg, teaching parents how to safely give nasogastric feeds and nappy changes in a ventilated baby). In addition, there will be regular FICare teaching for staff, including encouragement of parents to attend ward rounds, and with guidance to parents in the workbook (Table 2).

Table 2. Program to enhance father involvement in family integrated care.

Strategies	When	Who
Educational booklet or app, including • Introduction to the neonatal unit • Meeting the multidisciplinary team—tailored to the individual unit • Family integrated care • Taking care of yourselves • Routine care and "observations" • Breastfeeding • Developmental care • Medications • Nutrition and growth • Ventilation and breathing support • Cardiac (heart) conditions • Gastrointestinal and liver (gut) conditions • Brain development • Planning for discharge • Eyes	At parents' disposal	Both parents
Suggested tasks or workbook, including • Kangaroo care • Nappy changes in incubator • Mouth care and cleaning of baby • Reading of observations (heart rate, temperature, respiratory rate) • Helping to weigh baby • Bathing baby • Ward round participation	To work through at parents' pace	Both parents
Peer support sessions—led by specialist clinical psychologists or therapists	Every two weeks	Fathers[a,b]
Ward round participation	Daily	Both parents[a]
Bite-size education classes	2-3 per week at varying times including weekend	Both parents[a,b]

[a]Any parent in the unit is welcome to participate or attend.

[b]Sessions to occur at times to suit fathers with cultural, religious, family, and work obligations, as determined through phase 1 data collection.

Phase 2 Study: Enhanced Father Involvement in FICare (9 Months)

Once a family is recruited, the program developed to enhance the father's involvement in FICare will be implemented to take place at the parents' pace (Table 2). Materials will be freely available to the study participants in a format suited to their needs (electronic or paper copy). All interested parents are encouraged to attend the peer support sessions, ward round participation, and bite-size education classes.

The NU experience and MH status of both parents will be assessed as in the phase 1 study (Figure 1) including assessing their experience of the FICare program. At the end of the phase 2 study, staff knowledge, experiences, and opinions about fathers and FICare will be reassessed and compared with the start of the study.

Statistical Analysis

Qualitative data will be imported into dedicated software packages to facilitate analysis including NVivo (Lumivere) and SPSS (SPSS Inc). Interviews will be transcribed, following which the original recordings will be destroyed.

Interviews and Focus Groups

Data will be uploaded into NVivo to facilitate qualitative data management and thematic analysis. We will use several methods to minimize researcher bias during the study. All interviews will be conducted by 1 person (RR), who will maintain a reflexive diary through the study process. The transcripts will be independently coded by 2 researchers (RR and KG) to find repeated patterns of meaning which provide a detailed understanding of the perspective of the participants [29]. Both researchers will systematically code the data in detail and group them together into broader themes, with themes revisited to ensure that data saturation has been reached. These will then be grouped into broader themes generating a thematic map that will allow us to understand the parents' experiences in NU. The chief investigator (NA) will have control of the data and will be able to access the audio recordings of the interviews at all times to audit the quality of the interview process. Decision trails and coding trees will be used to ensure that coding and decision-making in data analysis are clear and transparent. Any discrepancies will be discussed with a third person (NA). Verbatim (anonymous) quotes will be shared with the results to allow the reader to determine whether the final themes reflect the data. Finally, the research team and participants will be invited to comment on the emerging or final themes during the data analysis.

Questionnaires

For descriptive statistics, the median and mode scores of the PSS:NICU, GAD-7, and PHQ-9 will be used to describe the outcome of the questionnaires. For inference analysis, the difference in median for the PSS:NICU, GAD-7, and PHQ-9 at admission, discharge, and 6 weeks postdischarge will be compared between phase 1 and phase 2 using the Mann-Whitney test and the paired 2-tailed *t* test. The data will be checked for outliers and these will be corrected or removed. However, where these outliers are accurate, a nonparametric statistical analysis will be performed. Depending on the data type, missing data will be replaced with mean, median, or mode. In addition, regression and multiple imputations analysis will also be used to impute or generate missing values.

Staff survey questionnaire responses to individual questions will be presented as a percentage of individuals responding yes or no. The percentage of "yes" responses to each question by the staff at the start and end of the study will be compared by paired *t* test.

Data Storage and Availability

All patient-identifiable data will be stored in a locked office of the principal investigator (PI) of participating sites. Access to identifiable data will be restricted to the PI and research team. The paper questionnaires will be stored securely in a file kept in the locked research office and electronic versions will be stored in a password-protected NHS computer. The electronic version of questionnaires will be emailed by parents to a secure NHS email account. This will also be used if transcription or audio files need to be transferred with third-party transcription services. Third-party services will be vetted as per NHS standards to ensure data protection and confidentiality. The sponsor will have access to the pseudoanonymized data if requested. Anonymized data will be made available on request. Study data will be kept for up to 18 months after the study completion.

Potential Risk to Participants and Mitigation

Considering the nature of the study, it is unlikely to have any adverse events. However, fathers may feel the additional burden of fulfilling their expected NU obligations alongside their breadwinner role and feelings of guilt for being unable to fulfill the expectations set for them [30,31]. To mitigate this difficulty, there is flexibility in when and to what extent fathers would like to be involved in FICare set at their own pace. The questionnaires and interviews may be emotionally challenging. This is being mitigated by the option to attend peer support sessions run by an appropriately trained professional and all parents will have access to the local neonatal psychologist. Interview frameworks were reviewed by the PAG and neonatal psychologist. A protocol is in place for any participants exhibiting severe MH symptoms through questionnaire responses or other forms of communication. Adverse events will be reported to the chief investigator and local research and development office and follow research and development, protocols with consideration of modification of study procedures if required.

Adverse events in the hospital setting will follow local hospital protocols as well as escalation to study PI with consideration of modification of study procedures if required. The risk of psychological distress resulting from study participation has been minimized with the support of a specialist psychotherapist who reviewed the study design and materials. A protocol is in place for any parents exhibiting severe MH symptoms through questionnaire responses or other forms of communication. We do not anticipate any risks to parents as they are simply being encouraged to participate in standard FICare activities that already occur in the participating centers. There is an emphasis that this should occur at the parents' pace.

Dissemination

The study findings will be presented at neonatal and FICare conferences and published in medical and nursing journals. The study findings will also be shared with relevant charities (eg, Bliss), and the study participants if they wish. It will form the basis of a PhD thesis. The PAG will be involved in the dissemination of the study findings.

Ethical Considerations

Participants will be able to withdraw from the study at any point. Anonymized data gathered until this point will be retained for data analysis. Following each interview or focus group, parents will be given 2 weeks to withdraw their data from the study. The study was approved by Leicester, South Research Ethics Committee (22/EM/0140)in August 2022, and written consent will be obtained from participants (see participant information leaflets and consent forms in Multimedia Appendices 1 and 2).

Results

The study is currently ongoing. As of October 2023, 22 families, comprising 22 fathers and 17 mothers had been recruited. The SR studies have been registered with the PROSPERO database (324275 and 306760). The projected end date for data collection is around July 2024, data analysis will occur in November 2024, and publication of the study findings will occur in early 2025.

Discussion

This study will test the hypothesis that if fathers are facilitated to engage more with their baby on the NU and are better supported during the neonatal stay, both parents will experience fewer MH symptoms during their baby's hospitalization and up to 6 weeks postdischarge. Improving parents' MH is shown to allow greater parent-child bonding [32] and more sensitive responsiveness of mothers to their infants' cues [33]. Mothers engaged in the FICare model have greater confidence in caregiving at the point of discharge and seek less medical support after discharge [32]. It is anticipated that these results will translate to fathers or partners.

Unlike many other studies [12,33], this study includes parents of a wide gestational age range of premature infants, including extremely premature infants and those who are invasively ventilated and at the highest risk of adverse outcomes. This is vital as research has found that fathers find the fragile appearance of their premature infants causes significant stress

[34]. A focus of the study methods will be to upskill NU staff to increase awareness and understand the importance of father engagement in FICare and their MH as well as the impact on mother and child, which is in line with the NHS Long Term Plan [17].

Limitations of the study include the need for conversational English. This is required to be able to complete the standardized questionnaires, participate in the interviews and focus groups, and to be able to engage with the phase 2 provisions. The language for the phase 2 materials will be kept as simple to ensure readability and understanding. Exclusion from recruitment based on language will be monitored. The perceived research burden may disproportionately impact parents who have older children, have a greater distance to travel, limited parental leave, or who do not have English as their first language. There may also be cultural barriers to overcome when discussing MH.

A prospective cohort study was the most practical and ethical study design. The sample size and the primary outcome of the study is based on the qualitative data. A bigger sample size will be required for the study to be based on the quantitative or questionnaire data. The quantitative or questionnaire data collected in this study is to support the qualitative data and to test the feasibility of collecting such data longitudinally.

The PSS:NICU questionnaire has been translated into many languages across the world [35,36], and is a well-used tool in neonatal research. It has been validated in mothers and fathers of NICU babies in the United Kingdom [37]. There are limited validated tools to assess paternal and maternal anxiety and depression in the postpartum or NU period. Therefore, simple screening tools that are validated in primary care and the general population for patients with a variety of backgrounds and stages of life were chosen [27,38,39].

Acknowledgments

The authors would like to acknowledge Felix Asamoah for his statistical advice and support. The authors would like to thank the neonatal doctors, nurses, and allied health professionals for their support, and the parents and babies who are participating and will be recruited. The authors are grateful to parent advisory group for their help in reviewing the study methodology and all the participant-facing study materials. The authors received no specific funding for this work. The Homerton Healthcare NHS Foundation Trust sponsors the study and will review and audit the progress and final outcomes of the study.

Data Availability

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

Authors' Contributions

NA, RR, and KG conceptualized the study. RR and NA prepared the first draft of the paper. All authors contributed to the study design, sample size calculation, and writing of the protocol for this study. All authors contributed to revisions of the manuscript and to the final version of the manuscript. All authors have read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Participant information leaflet.
[DOCX File , 48 KB - resprot_v13i1e53160_app1.docx]

Multimedia Appendix 2
Consent form.
[DOCX File , 37 KB - resprot_v13i1e53160_app2.docx]

References

1. Dataset: birth characteristics. Office for National Statistics. 2021. URL: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/livebirths/datasets/birthcharacteristicsinenglandandwales [accessed 2024-02-06]
2. Costeloe KL, Draper ES, Stacey F, Myles J, Hennessy EM. Epicure 2: exploring increased survival of extremely preterm babies. Arch Dis Child 2008;93(Suppl 2):espr13 [FREE Full text]
3. Yaman S, Altay N. Posttraumatic stress and experiences of parents with a newborn in the neonatal intensive care unit. J Reprod Infant Psychol 2014 Dec 24;33(2):140-152 [FREE Full text] [doi: 10.1080/02646838.2014.990872]
4. Shaw RJ, Bernard RS, Storfer-Isser A, Rhine W, Horwitz SM. Parental coping in the neonatal intensive care unit. J Clin Psychol Med Settings 2013 Jun;20(2):135-142 [FREE Full text] [doi: 10.1007/s10880-012-9328-x] [Medline: 22990746]

5. Jeffcoate JA, Humphrey ME, Lloyd JK. Role perception and response to stress in fathers and mothers following pre-term delivery. Soc Sci Med (1967) 1979 Mar;13A(2):139-145. [Medline: 441748]
6. McManus BM, Poehlmann J. Maternal depression and perceived social support as predictors of cognitive function trajectories during the first 3 years of life for preterm infants in Wisconsin. Child Care Health Dev 2012 May;38(3):425-434 [FREE Full text] [doi: 10.1111/j.1365-2214.2011.01253.x] [Medline: 21651608]
7. Leadsom A, Field F, Burstow P, Lucas C. The 1001 critical days: the importance of the conception to age two period. UK Government. 2014. URL: https://www.wavetrust.org/Handlers/Download.ashx?IDMF=e1b25e67-b13b-4e19-a3f6-9093e56d6a31 [accessed 2022-09-17]
8. van Veenendaal NR, van der Schoor SRD, Broekman BFP, de Groof F, van Laerhoven H, van den Heuvel MEN, et al. Association of a family integrated care model with paternal mental health outcomes during neonatal hospitalization. JAMA Netw Open 2022 Jan 04;5(1):e2144720 [FREE Full text] [doi: 10.1001/jamanetworkopen.2021.44720] [Medline: 35072721]
9. Family integrated care: a framework for practice. British Association of Perinatal Medicine. 2021. URL: https://www.bapm.org/resources/ficare-framework-for-practice [accessed 2021-12-01]
10. Programme development: 4 pillars of FICare. Family Integrated Care. URL: https://familyintegratedcare.com/the-ficare-approach/program-development/ [accessed 2023-07-23]
11. Li Y, Gao XY, Xiang XY, Dai HM, Yang L, Shoo MY, et al. [Effect of family integrate care on the development of preterm infants at 18 months of age]. Zhonghua Er Ke Za Zhi 2016 Dec 02;54(12):902-907. [doi: 10.3760/cma.j.issn.0578-1310.2016.12.005] [Medline: 27938589]
12. O'Brien K, Robson K, Bracht M, Cruz M, Lui K, Alvaro R, et al. Effectiveness of Family Integrated Care in neonatal intensive care units on infant and parent outcomes: a multicentre, multinational, cluster-randomised controlled trial. Lancet Child Adolesc Health 2018 Apr;2(4):245-254. [doi: 10.1016/S2352-4642(18)30039-7] [Medline: 30169298]
13. Rey SE, Martinez GH. Manejo racional del nino prematuro. 1983 Presented at: Proceedings of the Conference 1 Curso de Medicine Fetal y Neonatal; 1983; Bogota, Columbia.
14. Levin A. The mother-infant unit at Tallinn Children's Hospital, Estonia: a truly baby-friendly unit. Birth 1994 Mar;21(1):39-44, discussion 45. [doi: 10.1111/j.1523-536x.1994.tb00914.x] [Medline: 8155223]
15. Vora R. What About the Partners? A Literature Review Researching the Fathers' Experience in NICU and how this can be Optimised to Benefit the Whole Family. London, UK: King's College London; Apr 2019.
16. First 1000 days of life; thirteenth report of session 2017-9. UK Government. 2019 Feb 12. URL: https://publications.parliament.uk/pa/cm201719/cmselect/cmhealth/1496/1496.pdf [accessed 2021-03-01]
17. Implementing the recommendations of the neonatal critical care transformation review. NHS England. 2019. URL: https://www.england.nhs.uk/wp-content/uploads/2019/12/Implementing-the-Recommendations-of-the-Neonatal-Critical-Care-Transformation-Review-FINAL.pdf [accessed 2022-09-17]
18. McDonald S. Neonatal care (leave and pay) bill. UK Government. 2022 Sep 07. URL: https://publications.parliament.uk/pa/bills/cbill/58-03/0153/220153.pdf [accessed 2022-09-14]
19. Rubinstein R, Aladangady N. Fathers and partners in family integrated care study (TARGET). National Library of Medicine. 2023 Sep 05. URL: https://clinicaltrials.gov/study/NCT06022991 [accessed 2023-09-05]
20. Rubinstein R, Gallagher K, Aladangady N. Fathers' mental health in the neonatal unit (NICU): a systematic review. National Institute for Health and Care Research. 2022 May 09. URL: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022324275 [accessed 2022-05-09]
21. Rubinstein R, Gallagher K, Aladangady N. Fathers and Family-Integrated Care (FIC) in the Neonatal Unit (NICU): a systematic review. National Institute for Health and Care Research. 2022 May 09. URL: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022306760 [accessed 2022-05-09]
22. Garrard J. Health Sciences Literature Review Made Easy: The Matrix Method, 4th Edition. Burlington, MA: Jones & Bartlett Learning; 2014.
23. Toolkit for high-quality neonatal services. NHS and Department of Health. 2009 Oct. URL: https://drive.google.com/file/d/1BIR2iJNz9K-qRPvFXtPTW3GPWXhldC78/view [accessed 2021-01-30]
24. Hennink M, Kaiser BN. Sample sizes for saturation in qualitative research: a systematic review of empirical tests. Soc Sci Med 2022 Jan;292:114523 [FREE Full text] [doi: 10.1016/j.socscimed.2021.114523] [Medline: 34785096]
25. Krueger RA, Casey MA. Focus Groups: A Practical Guide for Applied Research, 5th Edition. Thousand Oaks, CA: SAGE Publications; 2014.
26. Miles MS, Funk SG, Kasper MA. The stress response of mothers and fathers of preterm infants. Res Nurs Health 1992 Aug;15(4):261-269 [FREE Full text] [doi: 10.1002/nur.4770150405] [Medline: 1496151]
27. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006 May 22;166(10):1092-1097 [FREE Full text] [doi: 10.1001/archinte.166.10.1092] [Medline: 16717171]
28. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001 Sep;16(9):606-613 [FREE Full text] [doi: 10.1046/j.1525-1497.2001.016009606.x] [Medline: 11556941]
29. Attride-Stirling J. Thematic networks: an analytic tool for qualitative research. Qual Res 2016 Nov 07;1(3):385-405 [FREE Full text] [doi: 10.1177/146879410100100307]

30. Noergaard B, Ammentorp J, Garne E, Fenger-Gron J, Kofoed PE. Fathers' stress in a neonatal intensive care unit. Adv Neonatal Care 2018 Oct;18(5):413-422 [FREE Full text] [doi: 10.1097/ANC.0000000000000503] [Medline: 29746269]
31. Janvier A, Asaad MA, Reichherzer M, Cantin C, Sureau M, Prince J, et al. The ethics of family integrated care in the NICU: improving care for families without causing harm. Semin Perinatol 2022 Apr;46(3):151528 [FREE Full text] [doi: 10.1016/j.semperi.2021.151528] [Medline: 34863579]
32. Garfield CF, Lee YS, Kim HN, Rutsohn J, Kahn JY, Mustanski B, et al. Supporting parents of premature infants transitioning from the NICU to home: a pilot randomized control trial of a smartphone application. Internet Interv 2016 May;4(Pt 2):131-137 [FREE Full text] [doi: 10.1016/j.invent.2016.05.004] [Medline: 27990350]
33. Melnyk BM, Feinstein NF, Alpert-Gillis L, Fairbanks E, Crean HF, Sinkin RA, et al. Reducing premature infants' length of stay and improving parents' mental health outcomes with the Creating Opportunities for Parent Empowerment (COPE) neonatal intensive care unit program: a randomized, controlled trial. Pediatrics 2006 Nov;118(5):e1414-e1427 [FREE Full text] [doi: 10.1542/peds.2005-2580] [Medline: 17043133]
34. Ionio C, Colombo C, Brazzoduro V, Mascheroni E, Confalonieri E, Castoldi F, et al. Mothers and fathers in NICU: the impact of preterm birth on parental distress. Eur J Psychol 2016 Nov;12(4):604-621 [FREE Full text] [doi: 10.5964/ejop.v12i4.1093] [Medline: 27872669]
35. De Bernardo G, Svelto M, Giordano M, Sordino D, Riccitelli M. Supporting parents in taking care of their infants admitted to a neonatal intensive care unit: a prospective cohort pilot study. Ital J Pediatr 2017 Apr 17;43(1):36 [FREE Full text] [doi: 10.1186/s13052-017-0352-1] [Medline: 28412958]
36. Kardaş Özdemir F, Küçük Alemdar D. Supporting of the fathers to visit their infants in neonatal intensive care unit decreases their stress level: a pretest-posttest quasi-experimental study. Community Ment Health J 2017 May;53(4):490-495 [FREE Full text] [doi: 10.1007/s10597-016-0066-7] [Medline: 27896502]
37. Franck LS, Cox S, Allen A, Winter I. Measuring neonatal intensive care unit-related parental stress. J Adv Nurs 2005 Mar;49(6):608-615 [FREE Full text] [doi: 10.1111/j.1365-2648.2004.03336.x] [Medline: 15737221]
38. Löwe B, Decker O, Müller S, Brähler E, Schellberg D, Herzog W, et al. Validation and standardization of the Generalized Anxiety Disorder Screener (GAD-7) in the general population. Med Care 2008 Mar;46(3):266-274 [FREE Full text] [doi: 10.1097/MLR.0b013e318160d093] [Medline: 18388841]
39. Costantini L, Pasquarella C, Odone A, Colucci ME, Costanza A, Serafini G, et al. Screening for depression in primary care with Patient Health Questionnaire-9 (PHQ-9): a systematic review. J Affect Disord 2021 Jan 15;279:473-483 [FREE Full text] [doi: 10.1016/j.jad.2020.09.131] [Medline: 33126078]

Abbreviations

FICare: family integrated care
GAD-7: Generalized Anxiety Disorder-7
MH: mental health
NHS: National Health Service
NU: neonatal unit
PAG: parent advisory group
PHQ-9: Patient Health Questionnaire-9
PI: principal investigator
PSS: NICU: Parental Stressor Scale: Neonatal Intensive Care Unit
SR: systematic review

Edited by A Mavragani; submitted 10.10.23; peer-reviewed by V Kain; comments to author 03.01.24; revised version received 10.01.24; accepted 11.01.24; published 25.03.24.

Please cite as:
Rubinstein R, Gallagher K, Ho J, Bose J, Khashu M, Aladangady N
Investigating Father or Partner Involvement in Family Integrated Care in Neonatal Units: Protocol for a Prospective, Multicenter, Multiphase Study
JMIR Res Protoc 2024;13:e53160
URL: https://www.researchprotocols.org/2024/1/e53160
doi:10.2196/53160
PMID:38526549

Protocol

Predictive and Prognostic Biomarkers in Patients With Mycosis Fungoides and Sézary Syndrome (BIO-MUSE): Protocol for a Translational Study

Emma Belfrage[1], MD; Sara Ek[2], PhD; Åsa Johansson[3], MD, PhD; Hanna Brauner[4,5], MD, PhD; Andreas Sonesson[1], MD, PhD; Kristina Drott[6], MD, PhD

[1]Division of Dermatology and Venereology, Department of Clinical Sciences, Lund University, Skåne University Hospital, Lund, Sweden

[2]Department of Immunotechnology, Faculty of Engineering, Lund University, Lund, Sweden

[3]Clinical Genetics and Pathology, Division of Hematology and Transfusion Medicine, Department of Laboratory Medicine, Skåne University Hospital, Lund, Sweden

[4]Division of Dermatology and Venereology, Department of Medicine and Center for Molecular Medicine, Karolinska Institutet, Stockholm, Sweden

[5]Department of Dermatology and Venereology, Karolinska University Hospital, Stockholm, Sweden

[6]Department of Hematology and Transfusion Medicine, Skåne University Hospital, Lund, Sweden

Corresponding Author:
Emma Belfrage, MD
Division of Dermatology and Venereology, Department of Clinical Sciences
Lund University
Skåne University Hospital
Lasarettsgatan 15
Lund, 222 41
Sweden
Phone: 46 707367293
Email: emma.belfrage@med.lu.se

Abstract

Background: Cutaneous T-cell lymphoma (CTCL) is a rare group of lymphomas that primarily affects the skin. Mycosis fungoides (MF) is the most common form of CTCL and Sézary syndrome (SS) is more infrequent. Early stages (IA-IIA) have a favorable prognosis, while advanced stages (IIB-IVB) have a worse prognosis. Around 25% of patients with early stages of the disease will progress to advanced stages. Malignant skin-infiltrating T-cells in CTCL are accompanied by infiltrates of nonmalignant T-cells and other immune cells that produce cytokines that modulate the inflammation. Skin infection, often with *Staphylococcus aureus*, is frequent in advanced stages and can lead to sepsis and death. *S. aureus* has also been reported to contribute to the progression of the disease. Previous reports indicate a shift from Th1 to Th2 cytokine production and dysfunction of the skin barrier in CTCL. Treatment response is highly variable and often unpredictable, and there is a need for new predictive and prognostic biomarkers.

Objective: This prospective translational study aims to identify prognostic biomarkers in the blood and skin of patients with MF and SS.

Methods: The Predictive and Prognostic Biomarkers in Patients With MF and SS (BIO-MUSE) study aims to recruit 120 adult patients with MF or SS and a control group of 20 healthy volunteers. The treatments will be given according to clinical routine. The sampling of each patient will be performed every 3 months for 3 years. The blood samples will be analyzed for lactate dehydrogenase, immunoglobulin E, interleukins, thymus and activation-regulated chemokine, and lymphocyte subpopulations. The lymphoma microenvironment will be investigated through digital spatial profiling and single-cell RNA sequencing. Microbiological sampling and analysis of skin barrier function will be performed. The life quality parameters will be evaluated. The results will be evaluated by the stage of the disease.

Results: Patient inclusion started in 2021 and is still ongoing in 2023, with 18 patients and 20 healthy controls enrolled. The publication of selected translational findings before the publication of the main results of the trial is accepted.

Conclusions: This study aims to investigate blood and skin with a focus on immune cells and the microbiological environment to identify potential new prognostic biomarkers in MF and SS.

Trial Registration: ClinicalTrials.gov NCT04904146; https://www.clinicaltrials.gov/study/NCT04904146
International Registered Report Identifier (IRRID): DERR1-10.2196/55723

(JMIR Res Protoc 2024;13:e55723) doi:10.2196/55723

KEYWORDS

mycosis fungoides; Sézary syndrome; prognostic; predictive; protocol; translational study; cutaneous T-cell lymphomas (CTCL); skin microbiota; immunology; tissue microenvironment; epigenetics; quality of life; skin infection; Staphylococcus aureus; progression of disease; skin barrier; prognostic biomarkers; adult; adults; elderly; spatial; microbiological sampling; blood; study protocol

Introduction

Mycosis Fungoides and Sézary Syndrome

Cutaneous T-cell lymphoma (CTCL) is a rare group of lymphomas that primarily affects the skin [1-3]. The pathogenesis of CTCL is not yet fully understood [3]. The annual incidence of CTCL is 0.7 per 100,000. Mycosis fungoides (MF) is the most prevalent form and comprises 60% of CTCL, with a higher male incidence (1.6:1.0) and a peak age incidence between 50 and 74 years [4]. Since MF often has a chronic course, its prevalence is considerably higher. The skin lesions in MF can be patches, plaques, tumors, or erythroderma. Sézary syndrome (SS) is an aggressive leukemic variant of the disease and constitutes only 5% of CTCL; it is defined as a triad of erythroderma, lymphadenopathy, and the presence of neoplastic T-cells in peripheral blood [5]. The extent of the disease in the skin is measured according to the Modified Severity-Weighted Assessment Tool [6,7]. Both MF and SS are staged according to the same tumor-node-metastasis-blood (TNMB) classification, assessing the involvement of skin, peripheral lymph nodes, peripheral blood, and visceral organs [8].

Prognosis of MF and SS

The TNMB stage at diagnosis remains the most important prognostic factor [9,10]. Many patients with early stages of MF have an indolent disease with a 5-year disease-specific survival of 89% to 98% [8,11]. However, approximately 25% of patients with early stages of disease will later progress to advanced stages [4]. Patients with advanced stages of MF have a 5-year disease-specific survival of 18% to 56% associated with treatment failure [8,10]. The 5-year disease-specific survival of SS is 36% [3,8,10].

Multivariate analyses of cohorts of patients with MF and SS have identified potential adverse prognostic factors in the early stages of disease consisting of male gender, aged >60 years, plaques, folliculotropic disease, and stage N1/NX and negative prognostic factors for advanced disease consisting of male gender, aged >60 years, stages B1/B2 and N2/N3, and visceral involvement [12,13]. The presence of plaque lesions in the early stage of the disease, large cell transformation in the skin, and elevated lactate dehydrogenase are also identified as adverse prognostic factors [11,14,15]. Still, there is an unmet clinical need to identify which patients will progress to an advanced stage of disease, and there is a great need for new reliable prognostic markers.

Treatments for MF and SS

The therapeutic options for MF and SS range from skin-directed therapy (SDT) to systemic treatment, and the selection of appropriate treatment is primarily based on the stage of the disease. There are only a few randomized controlled trials for the treatment of MF and SS, and current recommendations for treatment are mainly based on consensus meetings and international guidelines [4,5,10]. The treatment of the early stages of MF aims at modulating the immune response in the skin through SDT, such as topical corticosteroids and UV light therapy. Local radiation therapy usually has a good effect in all stages. In early stages that are refractory to SDT or in advanced stages, systemic treatment is used, including retinoid derivatives, low-dose methotrexate, and interferon alfa. In patients with lymphoma cells expressing CD30, targeted chemotherapy with brentuximab vedotin can be used. Further, standard chemotherapy such as gemcitabine or doxorubicin can be used; however, this often results in only short remission periods. Extracorporeal photopheresis can be used in erythrodermic stages of MF and SS and mogamulizumab and alemtuzumab can be used in advanced stages of disease. Highly selected patients with advanced stages of disease can be considered for allogeneic stem cell transplantation. Histone deacetylase (HDAC) inhibitors such as vorinostat and romidepsin are approved by the US Food and Drug Administration but are not commonly used in Europe [16,17]. Total skin electron beam therapy can be used in widespread disease in the skin or before allogeneic stem cell transplantation. Treatment response is unpredictable, and there is an unmet clinical need to find reliable predictive markers.

Immunological Changes of the Microenvironment of CTCL in Skin and Blood

Early stages of CTCL derive from mature CD4+ T-cells, or rarely CD8+ T-cells, in the skin. The restriction to the skin suggests that the affected cells are dependent on the specific cutaneous microenvironment, including cytokines and adhesion molecules. Malignant skin-infiltrating cells are accompanied by infiltrates of nonmalignant T-cells and other immune cells. The infiltrating benign immune cells produce a variety of cytokines that modulate cutaneous inflammation and are important constituents of the local environment of the tumor, fostering proliferation, survival, and migration [3]. Attempts to associate a unique cytokine profile of the disease based on skin or blood samples have indicated that a shift from Th1 to Th2 cytokine production accompanies disease progression [18,19], but the mechanisms behind this shift are not completely known [20]. In the advanced stages of the disease, a reduction of

skin-infiltrating CD8+ T-cells has been observed, as well as a shift toward M2 polarized macrophages and increased frequencies of NK cells and B-cells [21,22]. Other major immunological changes also facilitate the environment of the lymphoma cells and impair the host immunological defense [22]. The hypothesis of this study is to further explore these immunological changes through analysis of lymphocyte subpopulations in blood and skin together with cytokine expression in plasma through protein array analysis. We also hypothesize that we will detect other cells, molecules, and factors in the microenvironment of the tumor that could influence the clinical course of CTCL.

Epigenetic Modifications in CTCL

Regulation of DNA transcription is complex, and the mechanisms of regulation of DNA transcription in CTCL are partially unknown. HDACs can regulate the expression of genes and activities of transcription factors involved in malignant transformation and immune defense. HDACs act mainly through alteration of the structural components of chromatin by histone deacetylation, thus affecting the 3D conformation of DNA without changing or interrupting its sequence. Epigenetic drugs such as HDAC inhibitors have shown promising results in patients with advanced disease, emphasizing the impact of epigenetic regulators on the disease. Based on phase II data demonstrating long-term remission in 35% of heavily pretreated patients, HDAC inhibitors have been approved by the US Food and Drug Administration for second-line treatment of CTCL [16,17]. Although the dysregulated function of HDAC inhibitors may have an important role in malignant transformation and in the response to cancer treatment, the in vivo mechanisms behind the effects of HDAC inhibitors in CTCL are largely unknown. However, next-generation sequencing data have shown amino-acid or copy number alterations of 13 chromatin modifiers in 1% to 7% of CTCL cases, respectively, suggesting a mutation-driven epigenetic imbalance in CTCL [23]. Interestingly, HDAC inhibitors have been shown to reprogram the epigenome of host nonmalignant T-cells toward normal patterns, emphasizing the role of the host T-cells for therapy response [24,25].

Microbiological Changes and Skin Barrier Function in MF and SS

Skin infections, often with *Staphylococcus aureus*, are frequently seen in advanced stages of MF and SS. In patients who are immunocompromised, skin infections can lead to sepsis and death. Some studies indicate that a shift from Th1 to Th2 cytokine production and dysfunction of the skin barrier contribute to skin infections [26,27]. The underlying basis for the microbiological changes and the skin barrier function in CTCL need to be further elucidated for their potential role in the pathogenesis and progression.

Goals of This Study

The primary objective of this study is to identify serum-protein markers for 6-month progression-free survival (PFS) and to identify the immune cell profile in blood for 6-month PFS.

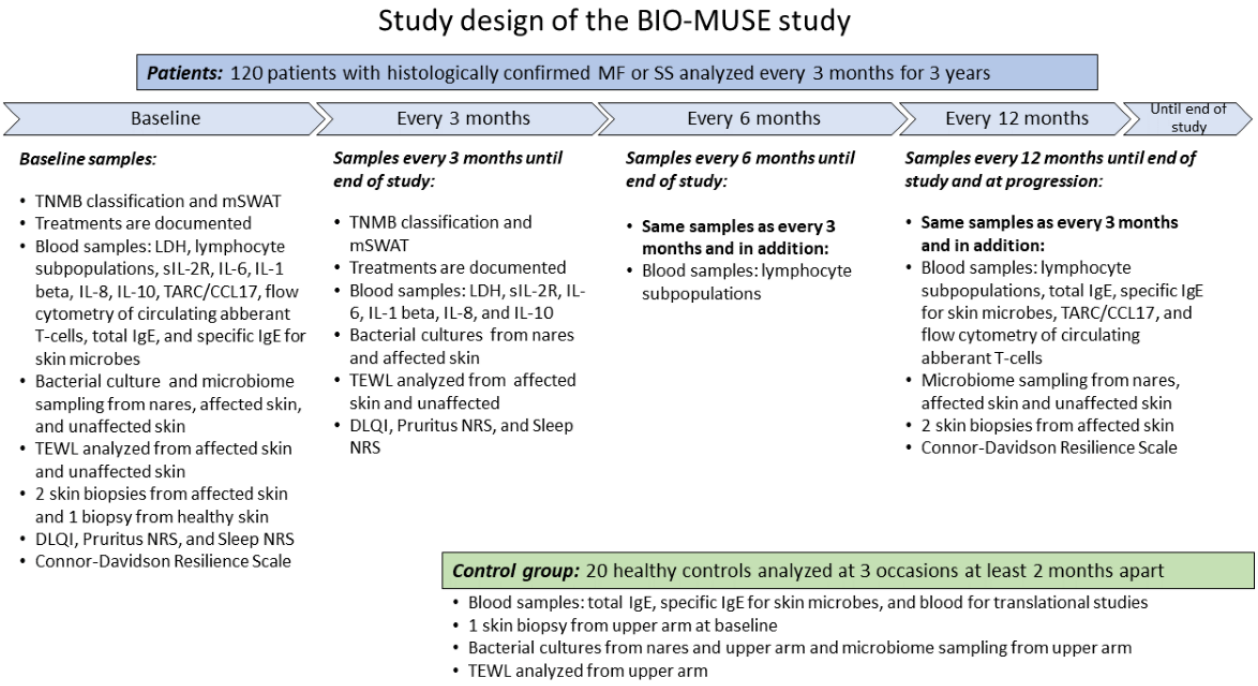
Secondary objectives are to identify the immune cell profile in the skin for 6-month PFS, analyze the lymphoma microenvironment in the skin for 6-month PFS, identify the skin barrier and skin microbiology profiles for 6-months PFS, and identify the epigenetic changes in lymphoma T-cells and host T-cells for 3 months PFS.

Methods

Study Design

The Predictive and Prognostic Biomarkers in Patients With MF and SS (BIO-MUSE) study is a translational prospective study, aiming to include 120 adult patients with MF and SS and a control group of 20 healthy volunteers (Figure 1). Sampling of each patient will be performed every 3 months for 3 years. The control group will be examined on 3 different occasions at least 2 months apart. This study is presently open at Skåne University Hospital and aims to open at Karolinska University Hospital. The multicenter study design enables other Swedish sites to be included, after further ethical approval.

Figure 1. Study design of the BIO-MUSE study. BIO-MUSE: Predictive and Prognostic Biomarkers in Patients With Mycosis Fungoides and Sézary Syndrome; CT: computed tomography; DLQI: Dermatology Life Quality Index; IgE: immunoglobulin E; IL-6: interleukin-6; IL-8: interleukin-8; IL-10: interleukin-10; IL-1beta: interleukin-1beta; LDH: lactate dehydrogenase; MF: mycosis fungoides; mSWAT: Modified Severity-Weighted Assessment Tool; NRS: Numerical Rating Scale; sIL-2R: soluble interleukin-2 receptor; SS: Sézary syndrome; TARC: thymus and activation-regulated chemokine; TEWL: transepidermal water loss; TNMB: tumor-node-metastasis-blood.



Ethical Considerations

This study's protocol is written per the Declaration of Helsinki and the International Council for Harmonisation's good clinical practice guidelines. This study was registered with ClinicalTrials.gov (NCT04904146) and approved by the Swedish Ethics Committee (2019-05130). Written informed consent will be obtained from participants according to the Declaration of Helsinki and International Council for Harmonisation's good clinical practice guidelines.

Eligibility Criteria

Inclusion criteria will be patients aged 18-100 years with histologically confirmed MF and SS (stage IA-IVB) and World Health Organization performance status 0-3. The inclusion criteria for the healthy control group will be healthy adults aged 18-100 years with World Health Organization performance status 0-2 and the absence of any malignant, autoimmune, or infectious disease. The exclusion criteria for both groups are psychiatric illnesses or conditions that could interfere with the ability to understand the requirements of this study.

Stage of Disease and Modified Severity-Weighted Assessment Tool

Patients will be staged according to the TNMB classification [8]. The extent of disease in the skin will be measured according to the Modified Severity-Weighted Assessment Tool [6,7]. Progression or regression will be defined as a shift from one stage to another.

Treatment of MF and SS

The treatments will be given according to clinical routine and national and international guidelines for MF and SS and participation in this study will not affect the choice of treatments. Ongoing treatments will be documented.

Blood Samples for Soluble Interleukin-2 Receptor, Interleukins, and Thymus and Activation-Regulated Chemokine/CCL17

Blood samples in patients will be analyzed for complete blood count, liver and kidney function, lactate dehydrogenase, soluble interleukin-2 receptor, interleukin-6, interleukin-8, interleukin-10, and thymus and activation-regulated chemokine/CCL17 (Multimedia Appendix 1).

Blood Samples for Analysis of Immunoglobulin E Against Specific Antigen

Total immunoglobulin E and specific immunoglobulin E for *S. aureus* enterotoxin A (m80), enterotoxin B (m81), toxic shock syndrome toxin-1 (Rm226), *Malassezia* (m227), and *Candida albicans* (m5) will be analyzed in patients and in the control group (Multimedia Appendices 1 and 2, respectively).

Blood Samples for Analysis of Lymphocyte Subpopulations

Flow cytometry of peripheral blood will be performed in patients to analyze the T-cell subpopulations including naive, effector, and memory T-cells (including Th1, Th2, and Th17 cells) and activated and regulatory T-cells. Monoclonal antibodies recognizing CD4, CD8, CD197, CD45RA, CD25, CD194, CD127, CD45RO, CD183, and CD196 will be used [28]. In

addition, to evaluate the presence of clonal T-cells in peripheral blood and biopsies the following panel: T-cell receptor fluorescein isothiocyanate, TRBC1 phycoerythrin, CD16 electron coupled dye, CD2 PC7, CD3 BV421, CD4PC5.5, CD7 A700, CD8 KrO, CD26 allophycocyanine, and CD45 allophycocyanine-H7 will be used [29] (Multimedia Appendices 1 and 3, respectively).

Serum-Based Profiling of Immune-Related Soluble Proteins

Broad sets of serum-based protein profiling focused on immune-related proteins will be performed in patients. Global protein profiling will be performed using commercially available methods, allowing high-plex analyses of immune-related soluble molecules. State-of-the-art bioinformatic tools will be applied for preprocessing and analysis of data (Multimedia Appendix 1).

Assessment of Tumor Microenvironment by Digital Spatial Profiling and Single-Cell RNA Sequencing

To allow the study of the cellular tumor immune microenvironment, 2 biopsies from affected skin and 1 biopsy from unaffected skin, at least 5 cm away from affected skin, will be taken. In the control group, 1 skin biopsy is taken from the upper arm. The skin biopsies will be formalin-fixed and paraffin-embedded. In addition, blood will be drawn from patients and healthy controls and peripheral blood mononuclear cells will be cryopreserved.

Multiplex analyses of samples taken before and after progression have the potential to contribute to novel biological knowledge as previously discussed in a recent review by the group Kalliara et al [30] and will be performed in samples collected over time. In brief, in skin biopsies, Digital Spatial Profiling will be performed to study immune infiltration in CTCL and how it evolves during the progression of the disease [31]. Single-cell RNA and T-cell receptor sequencing will be applied to sorted CD3+ cells to follow the evolution of the malignant clone over time. Moreover, additional assessments of genetic and epigenetic changes in the tumor and tumor microenvironment will be performed in skin biopsies (Multimedia Appendix 1).

Assessment of Epigenetic Factors in Circulating Tumor Cells Compared to Normal and Host T-Cells

Cell sorting of CD3+ cells from peripheral blood in patients with blood involvement will be performed using FACSAria (BD, Bioscience). When possible, 2-3 million cells will be sorted from each patient to allow the preparation of DNA for epigenetic analysis and RNA for gene expression analysis. Analysis of histone modifications and chromatin accessibility will be performed by ChIP-seq (chromatin immunoprecipitation with sequencing) and ATAC-seq (assay of transposase-accessible chromatin with sequencing), respectively. Moreover, molecular profiling using nCounter analysis (NanoString Technologies, Inc) will be performed to profile cells through expression panels focused on immune profiling and proliferative signaling pathways (Multimedia Appendix 1).

Microbiological Sampling

Microbiological samples will be analyzed from affected skin and from unaffected skin 5 cm away from affected skin, preferably from the upper body, and from nares in patients. In the control group, the microbiological samples will be analyzed from the upper arm and from the nares (Multimedia Appendices 1 and 2, respectively).

Analysis of Skin Barrier Function

Skin barrier function will be measured as transepidermal water loss (TEWL) with a closed chamber TEWL meter, VapoMeter 300 (Delfin Technologies Ltd), according to guidelines [32]. TEWL will be measured on affected skin and on unaffected skin 5 cm away from affected skin, preferably from the upper body. TEWL will be measured on the upper arm in the control group (Multimedia Appendices 1 and 2).

Hematopathology of Skin, Lymph Node, Bone Marrow, and Tumor Biopsies

Hematopathology of skin biopsy will be performed in affected skin from patients and is optional from lymph nodes, bone marrow, and tumors (Multimedia Appendices 1 and 3).

Patient-Oriented Life Quality Measures

Patient-oriented life quality measures will be performed. The Dermatology Life Quality Index [33], Peak Pruritus Numerical Rating Scale [34], Sleep Numerical Rating Scale, and Connor-Davidson Resilience Scale [35] will be used (Multimedia Appendix 1).

Statistical Analysis

The sample profiles from patients with an early stage of disease (stage IA-IIA) will be compared to samples from patients with an advanced stage of disease (stage IIB-IVB) using multivariate analysis with principal component analysis. Individual samples will be compared between the groups using the Mann-Whitney *U* test. Other translational samples will be presented by descriptive statistics. Progression-free and overall survival will be presented using Kaplan-Meier plots.

Results

Patient inclusion started in 2021 and is still ongoing in December 2023, with 18 patients and 20 healthy controls enrolled. Until December 2023, a total of 2 included patients have declined further participation due to the extra visits in this study. Further, 2 patients have died from MF during this study. The publication of selected translational findings before the publication of the main results of the trial is accepted, and data analysis is in progress.

The evaluation of the stage of the disease will be observed every 3 months according to the TNMB classification, where the shift from one stage to another implies progression or treatment response. After the study, patients will be grouped as either early stage of the disease (IA-IIA) or advanced stage of the disease (IIB-IVB). The patients crossing over from the early stage of the disease to the advanced stage of the disease group will be analyzed both individually and as a group. Approximately 30% (36/120) of patients are estimated to be in

the advanced stage of the disease group. The translational samples in the early stage of the disease group will be compared to samples from the advanced stage of the disease group. The treatments directed against MF are documented throughout this study. Excluded patients will be presented along with the final results. Depending on patient numbers, treatment data will be presented descriptively, or if possible, to support data on treatment predictive biomarkers.

Discussion

Principal Findings

This study aims to find potential predictive and prognostic biomarkers in patients with MF and SS. This study will investigate translational samples from skin and blood concerning the stage of the disease over time, which has the advantage of monitoring patients with consecutive samplings to be able to capture changes before and during a possible progression. This study will be able to compare differences in patients with early (IA-IIA) and advanced (IIB-IVB) stages of the disease. It will also be possible to analyze the data separately for patients with MF and SS, respectively. The translational samplings in this study are chosen to be able to detect changes in the immune system and in tumor cells, as well as changes in the skin barrier function and the skin microbiota. There is a clinically unmet need to find new predictive and prognostic biomarkers in MF and SS, and studies further exploring these areas are therefore a high priority. The research team, techniques, and management presented in this protocol have capacities to investigate new aspects and bring new knowledge to the field of CTCL. This study combines a multidisciplinary outpatient clinic with extensive translational research sampling, which has considerable potential to lead to true patient benefit.

Limitations

MF and SS are rare diseases, and the inclusion of the proposed number of patients in this study protocol may take considerable time. To reach the estimated number of patients in this study, inclusion will also start at Karolinska University Hospital, and to expand this study further, cooperations with other centers is ongoing. Another possible limitation is that the control group will be followed for a shorter period compared to the patients.

Comparison With Prior Work

The Prospective Cutaneous Lymphoma International Prognostic Index study is an ongoing international study of a confirmed early-stage MF cohort, which is being followed up to identify prognostic factors in the hope of providing better management and improving survival by identifying patients at risk of disease progression [36].

Conclusions

The BIO-MUSE study is a prospective translational study aiming to identify new prognostic and predictive biomarkers in blood and skin in patients with MF and SS.

Acknowledgments

We thank Anna Porwit, professor emerita, Department of Pathology, Lund University, Skåne University Hospital, Lund, Sweden, for help with planning the hematopathology analysis. We are grateful to Andreas Lennartsson, Department of Biosciences and Nutrition, Karolinska Institutet, Sweden for help with planning the epigenetic analysis. This study was funded by the Stiftelsen Siv-Inger och Per-Erik Anderssons Minnesfond (FBKS-2019-14-(210)), Berta Kamprad foundation (S19 0238), Swedish Cancer Society, Swedish Society for Medical Research (S17-0104), the Swedish Cancer Foundation (190408Fk; 232960), Region Stockholm (clinical research appointment [ref20190859] and ALF medicine [RS2020-0731]), HudFonden (3281), Clas Groschinsky (M19390), Magnus Bergvall (2019-03538), Radiumhemmet (211032), and Karolinska Institutet foundations (2018-02203). The funders had no role in this study's design, data collection and analysis, interpretation of results, paper preparations, or decision to submit the report for publication.

Data Availability

The data sets analyzed during this study are available from corresponding authors upon reasonable request.

Authors' Contributions

KD is the principal investigator of this study. EB and KD are responsible for including patients at Skåne University Hospital, Lund Sweden. HB is responsible for including patients at Karolinska University Hospital, Stockholm. AS is responsible for the microbiological translational part of this study. SE and ÅJ are responsible for the immunology translational part of this study. EB, AS, and KD were the major contributors to writing this paper. All the authors participated in the design of this study and read, commented upon, and approved this final paper.

Conflicts of Interest

EB has received lecturing fees from Novartis. AS has received lecturing and consulting fees from Sanofi, Pfizer, AbbVie, and LEO Pharma. KD has received honoraria from Kyowa Kirin, Roche, and Incyte, and is a shareholder and board member of Respiratorius AB. HB has received honoraria for serving on an advisory board from Kyowa Kirin and a lecturing fee from Janssen-Cilag.

Multimedia Appendix 1
Translational samples and logistics for patients in the Predictive and Prognostic Biomarkers in Patients With Mycosis Fungoides and Sézary Syndrome (BIO-MUSE) study.
[DOCX File , 22 KB - resprot_v13i1e55723_app1.docx]

Multimedia Appendix 2
Translational samples and logistics for the healthy control group in the Predictive and Prognostic Biomarkers in Patients With Mycosis Fungoides and Sézary Syndrome (BIO-MUSE) study.
[DOCX File , 16 KB - resprot_v13i1e55723_app2.docx]

Multimedia Appendix 3
Planned assessments of hematopathology in the skin, lymph node, bone marrow, and tumor biopsies.
[DOCX File , 17 KB - resprot_v13i1e55723_app3.docx]

References

1. Willemze R, Cerroni L, Kempf W, Berti E, Facchetti F, Swerdlow SH, et al. The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas. Blood 2019;133(16):1703-1714 [FREE Full text] [doi: 10.1182/blood-2018-11-881268] [Medline: 30635287]
2. Alaggio R, Amador C, Anagnostopoulos I, Attygalle AD, Araujo IB, Berti E, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: lymphoid neoplasms. Leukemia 2022;36(7):1720-1748 [FREE Full text] [doi: 10.1038/s41375-022-01620-2] [Medline: 35732829]
3. Dummer R, Vermeer MH, Scarisbrick JJ, Kim YH, Stonesifer C, Tensen CP, et al. Cutaneous T cell lymphoma. Nat Rev Dis Primers 2021;7(1):61 [FREE Full text] [doi: 10.1038/s41572-021-00296-9] [Medline: 34446710]
4. Gilson D, Whittaker SJ, Child FJ, Scarisbrick JJ, Illidge TM, Parry EJ, et al. British Association of Dermatologists and U.K. Cutaneous Lymphoma Group guidelines for the management of primary cutaneous lymphomas 2018. Br J Dermatol 2019;180(3):496-526 [FREE Full text] [doi: 10.1111/bjd.17240] [Medline: 30561020]
5. Willemze R, Hodak E, Zinzani PL, Specht L, Ladetto M, ESMO Guidelines Committee. Primary cutaneous lymphomas: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018;29(Suppl 4):iv30-iv40 [FREE Full text] [doi: 10.1093/annonc/mdy133] [Medline: 29878045]
6. Stevens SR, Ke MS, Parry EJ, Mark J, Cooper KD. Quantifying skin disease burden in mycosis fungoides-type cutaneous T-cell lymphomas: the Severity-Weighted Assessment Tool (SWAT). Arch Dermatol 2002;138(1):42-48 [FREE Full text] [doi: 10.1001/archderm.138.1.42] [Medline: 11790166]
7. Olsen EA, Whittaker S, Kim YH, Duvic M, Prince HM, Lessin SR, et al. Clinical end points and response criteria in mycosis fungoides and Sézary syndrome: a consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. J Clin Oncol 2011;29(18):2598-2607 [FREE Full text] [doi: 10.1200/JCO.2010.32.0630] [Medline: 21576639]
8. Olsen E, Vonderheid E, Pimpinelli N, Willemze R, Kim Y, Knobler R, et al. Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC). Blood 2007;110(6):1713-1722 [FREE Full text] [doi: 10.1182/blood-2007-03-055749] [Medline: 17540844]
9. Kim YH, Liu HL, Mraz-Gernhard S, Varghese A, Hoppe RT. Long-term outcome of 525 patients with mycosis fungoides and Sezary syndrome: clinical prognostic factors and risk for disease progression. Arch Dermatol 2003;139(7):857-866 [FREE Full text] [doi: 10.1001/archderm.139.7.857] [Medline: 12873880]
10. Latzka J, Assaf C, Bagot M, Cozzio A, Dummer R, Guenova E, et al. EORTC consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome - update 2023. Eur J Cancer 2023;195:113343 [FREE Full text] [doi: 10.1016/j.ejca.2023.113343] [Medline: 37890355]
11. Agar NS, Wedgeworth E, Crichton S, Mitchell TJ, Cox M, Ferreira S, et al. Survival outcomes and prognostic factors in mycosis fungoides/Sézary syndrome: validation of the revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of cancer staging proposal. J Clin Oncol 2010;28(31):4730-4739 [FREE Full text] [doi: 10.1200/JCO.2009.27.7665] [Medline: 20855822]
12. Benton EC, Crichton S, Talpur R, Agar NS, Fields PA, Wedgeworth E, et al. A Cutaneous Lymphoma International Prognostic Index (CLIPi) for mycosis fungoides and Sezary syndrome. Eur J Cancer 2013;49(13):2859-2868 [FREE Full text] [doi: 10.1016/j.ejca.2013.04.018] [Medline: 23735705]
13. Amorim GM, Corbellini JPN, Quintella DC, Cuzzi T, Ramos-E-Silva M. Evaluation of the Cutaneous Lymphoma International Prognostic Index in patients with early stage mycosis fungoides. An Bras Dermatol 2018;93(5):680-685 [FREE Full text] [doi: 10.1590/abd1806-4841.20187134] [Medline: 30156617]

14. Scarisbrick JJ, Prince HM, Vermeer MH, Quaglino P, Horwitz S, Porcu P, et al. Cutaneous lymphoma international consortium study of outcome in advanced stages of mycosis fungoides and sézary syndrome: effect of specific prognostic markers on survival and development of a prognostic model. J Clin Oncol 2015;33(32):3766-3773 [FREE Full text] [doi: 10.1200/JCO.2015.61.7142] [Medline: 26438120]
15. Zackheim HS, Amin S, Kashani-Sabet M, McMillan A. Prognosis in cutaneous T-cell lymphoma by skin stage: long-term survival in 489 patients. J Am Acad Dermatol 1999;40(3):418-425 [FREE Full text] [doi: 10.1016/s0190-9622(99)70491-3] [Medline: 10071312]
16. Piekarz RL, Frye R, Prince HM, Kirschbaum MH, Zain J, Allen SL, et al. Phase 2 trial of romidepsin in patients with peripheral T-cell lymphoma. Blood 2011;117(22):5827-5834 [FREE Full text] [doi: 10.1182/blood-2010-10-312603] [Medline: 21355097]
17. Coiffier B, Pro B, Prince HM, Foss F, Sokol L, Greenwood M, et al. Results from a pivotal, open-label, phase II study of romidepsin in relapsed or refractory peripheral T-cell lymphoma after prior systemic therapy. J Clin Oncol 2012;30(6):631-636 [FREE Full text] [doi: 10.1200/JCO.2011.37.4223] [Medline: 22271479]
18. Vowels BR, Cassin M, Vonderheid EC, Rook AH. Aberrant cytokine production by Sezary syndrome patients: cytokine secretion pattern resembles murine Th2 cells. J Invest Dermatol 1992;99(1):90-94 [FREE Full text] [doi: 10.1111/1523-1747.ep12611877] [Medline: 1607682]
19. Brunner PM, Jonak C, Knobler R. Recent advances in understanding and managing cutaneous T-cell lymphomas. F1000Res 2020;9:F1000 [FREE Full text] [doi: 10.12688/f1000research.21922.1] [Medline: 32419924]
20. Guenova E, Watanabe R, Teague JE, Desimone JA, Jiang Y, Dowlatshahi M, et al. TH2 cytokines from malignant cells suppress TH1 responses and enforce a global TH2 bias in leukemic cutaneous T-cell lymphoma. Clin Cancer Res 2013;19(14):3755-3763 [FREE Full text] [doi: 10.1158/1078-0432.CCR-12-3488] [Medline: 23785046]
21. Nielsen PR, Eriksen JO, Wehkamp U, Lindahl LM, Gniadecki R, Fogh H, et al. Clinical and histological characteristics of mycosis fungoides and Sézary syndrome: a retrospective, single-centre study of 43 patients from Eastern Denmark. Acta Derm Venereol 2019;99(13):1231-1236 [FREE Full text] [doi: 10.2340/00015555-3351] [Medline: 31620804]
22. Scheffschick A, Nenonen J, Xiang M, Winther AH, Ehrström M, Wahren-Herlenius M, et al. Skin infiltrating NK cells in cutaneous T-cell lymphoma are increased in number and display phenotypic alterations partially driven by the tumor. Front Immunol 2023;14:1168684 [FREE Full text] [doi: 10.3389/fimmu.2023.1168684] [Medline: 37691935]
23. Park J, Yang J, Wenzel AT, Ramachandran A, Lee WJ, Daniels JC, et al. Genomic analysis of 220 CTCLs identifies a novel recurrent gain-of-function alteration in RLTPR (p.Q575E). Blood 2017;130(12):1430-1440 [FREE Full text] [doi: 10.1182/blood-2017-02-768234] [Medline: 28694326]
24. Qu K, Zaba LC, Satpathy AT, Giresi PG, Li R, Jin Y, et al. Chromatin accessibility landscape of cutaneous T cell lymphoma and dynamic response to HDAC inhibitors. Cancer Cell 2017;32(1):27-41.e4 [FREE Full text] [doi: 10.1016/j.ccell.2017.05.008] [Medline: 28625481]
25. Cao K, Wang G, Li W, Zhang L, Wang R, Huang Y, et al. Histone deacetylase inhibitors prevent activation-induced cell death and promote anti-tumor immunity. Oncogene 2015;34(49):5960-5970 [FREE Full text] [doi: 10.1038/onc.2015.46] [Medline: 25745993]
26. Suga H, Sugaya M, Miyagaki T, Ohmatsu H, Kawaguchi M, Takahashi N, et al. Skin barrier dysfunction and low antimicrobial peptide expression in cutaneous T-cell lymphoma. Clin Cancer Res 2014;20(16):4339-4348 [FREE Full text] [doi: 10.1158/1078-0432.CCR-14-0077] [Medline: 24919568]
27. Mirvish JJ, Pomerantz RG, Falo LD, Geskin LJ. Role of infectious agents in cutaneous T-cell lymphoma: facts and controversies. Clin Dermatol 2013;31(4):423-431 [FREE Full text] [doi: 10.1016/j.clindermatol.2013.01.009] [Medline: 23806159]
28. Maecker HT, McCoy JP, Nussenblatt R. Standardizing immunophenotyping for the Human Immunology Project. Nat Rev Immunol 2012;12(3):191-200 [FREE Full text] [doi: 10.1038/nri3158] [Medline: 22343568]
29. Novikov ND, Griffin GK, Dudley G, Drew M, Rojas-Rudilla V, Lindeman NI, et al. Utility of a simple and robust flow cytometry assay for rapid clonality testing in mature peripheral t-cell lymphomas. Am J Clin Pathol 2019;151(5):494-503 [FREE Full text] [doi: 10.1093/ajcp/aqy173] [Medline: 30715093]
30. Kalliara E, Belfrage E, Gullberg U, Drott K, Ek S. Spatially guided and single cell tools to map the microenvironment in cutaneous t-cell lymphoma. Cancers (Basel) 2023;15(8):2362 [FREE Full text] [doi: 10.3390/cancers15082362] [Medline: 37190290]
31. Merritt CR, Ong GT, Church SE, Barker K, Danaher P, Geiss G, et al. Multiplex digital spatial profiling of proteins and RNA in fixed tissue. Nat Biotechnol 2020;38(5):586-599. [doi: 10.1038/s41587-020-0472-9]
32. Pinnagoda J, Tupker RA, Agner T, Serup J. Guidelines for Transepidermal Water Loss (TEWL) measurement. A report from the standardization group of the European Society of Contact Dermatitis. Contact Dermatitis 1990;22(3):164-178 [FREE Full text] [doi: 10.1111/j.1600-0536.1990.tb01553.x] [Medline: 2335090]
33. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. Clin Exp Dermatol 1994;19(3):210-216 [FREE Full text] [doi: 10.1111/j.1365-2230.1994.tb01167.x] [Medline: 8033378]

34. Ständer S, Augustin M, Reich A, Blome C, Ebata T, Phan N, et al. Pruritus assessment in clinical trials: consensus recommendations from the International Forum for the Study of Itch (IFSI) special interest group scoring itch in clinical trials. Acta Derm Venereol 2013;93(5):509-514 [FREE Full text] [doi: 10.2340/00015555-1620] [Medline: 23624777]
35. Connor KM, Davidson JRT. Development of a new resilience scale: the Connor-Davidson Resilience Scale (CD-RISC). Depress Anxiety 2003;18(2):76-82 [FREE Full text] [doi: 10.1002/da.10113] [Medline: 12964174]
36. Scarisbrick JJ, Quaglino P, Prince HM, Papadavid E, Hodak E, Bagot M, et al. The PROCLIPI international registry of early-stage mycosis fungoides identifies substantial diagnostic delay in most patients. Br J Dermatol 2019;181(2):350-357 [FREE Full text] [doi: 10.1111/bjd.17258] [Medline: 30267549]

Abbreviations

ATAC-seq: assay of transposase-accessible chromatin with sequencing
BIO-MUSE: Predictive and Prognostic Biomarkers in Patients With Mycosis Fungoides and Sézary Syndrome
CBC: complete blood count
ChIP-seq: chromatin immunoprecipitation with sequencing
CTCL: cutaneous T-cell lymphoma
HDAC: histone deacetylase
MF: mycosis fungoides
PFS: progression-free survival
SDT: skin-directed therapy
SS: Sézary syndrome
TEWL: transepidermal water loss
TNMB: tumor-node-metastasis-blood

Edited by A Mavragani; submitted 21.12.23; peer-reviewed by D Kumar, K Zhang; comments to author 05.02.24; revised version received 08.02.24; accepted 09.02.24; published 04.04.24.

Please cite as:
Belfrage E, Ek S, Johansson Å, Brauner H, Sonesson A, Drott K
Predictive and Prognostic Biomarkers in Patients With Mycosis Fungoides and Sézary Syndrome (BIO-MUSE): Protocol for a Translational Study
JMIR Res Protoc 2024;13:e55723
URL: https://www.researchprotocols.org/2024/1/e55723
doi:10.2196/55723
PMID:38436589

Protocol

A Bluetooth-Based Smartphone App for Detecting Peer Proximity: Protocol for Evaluating Functionality and Validity

Nancy P Barnett[1], PhD; Alexander W Sokolovsky[1], PhD; Matthew K Meisel[1], PhD; Shannon R Forkus[2], PhD; Kristina M Jackson[1], PhD

[1]Department of Behavioral and Social Sciences, Brown University, Providence, RI, United States

[2]Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, SC, United States

Corresponding Author:
Nancy P Barnett, PhD
Department of Behavioral and Social Sciences
Brown University
Box G-S121
Providence, RI, 02912
United States
Phone: 1 40189636649
Email: Nancy_Barnett@brown.edu

Abstract

Background: While ecological momentary assessment (EMA) is commonly used to study social contexts and social influence in the real world, EMA almost exclusively relies on participant self-report of present circumstances, including the proximity to influential peers. There is the potential for developing a proximity sensing approach that uses small Bluetooth beacons and smartphone-based detection and data collection to collect information about interactions between individuals passively in real time.

Objective: This paper aims to describe the methods for evaluating the functionality and validity of a Bluetooth-based beacon and a smartphone app to identify when ≥2 individuals are physically proximal.

Methods: We will recruit 20 participants aged 18 to 29 years with Android smartphones to complete a 3-week study during which beacon detection and self-report data will be collected using a smartphone app (MEI Research). Using an interviewer-administered social network interview, participants will identify up to 3 peers of the same age who are influential on health behavior (alcohol use in this study). These peers will be asked to carry a Bluetooth beacon (Kontakt asset tag) for the duration of the study; each beacon has a unique ID that, when detected, will be recorded by the app on the participant's phone. Participants will be prompted to respond to EMA surveys (signal-contingent reports) when a peer beacon encounter meets our criteria and randomly 3 times daily (random reports) and every morning (morning reports) to collect information about the presence of peers. In all reports, the individualized list of peers will be presented to participants, followed by questions about peer and participant behavior, including alcohol use. Data from multiple app data sets, including beacon encounter specifications, notification, and app logs, participant EMA self-reports and postparticipation interviews, and peer surveys, will be used to evaluate project goals. We will examine the functionality of the technology, including the stability of the app (eg, app crashes and issues opening the app), beacon-to-app detection (ie, does the app detect proximal beacons?), and beacon encounter notification when encounter criteria are met. The validity of the technology will be defined as the concordance between passive detection of peers via beacon-to-app communication and the participant's EMA report of peer presence. Disagreement between the beacon and self-report data (ie, false negatives and false positives) will be investigated in multiple ways (ie, to determine if the reason was technology-related or participant compliance-related) using encounter data and information collected from participants and peers.

Results: Participant recruitment began in February 2023, and enrollment was completed in December 2023. Results will be reported in 2025.

Conclusions: This Bluetooth-based technology has important applications and clinical implications for various health behaviors, including the potential for just-in-time adaptive interventions that target high-risk behavior in real time.

International Registered Report Identifier (IRRID): DERR1-10.2196/50241

(JMIR Res Protoc 2024;13:e50241) doi:10.2196/50241

KEYWORDS

Bluetooth technology; passive sensing; proximity detection; ecological momentary assessment; social influence; alcohol use; mobile phone

Introduction

Behavioral Influence in Social Contexts

Social context, which refers to immediate temporal, situational, and intrapersonal factors, is important for many health behaviors [1]. Understanding how context influences behavior is an essential first step toward the development of preventive interventions to reduce risk, as it provides essential information on why, with whom, where, and when a person engages in a particular behavior. For alcohol use, the health behavior we will focus on, the presence of peers is a highly influential contextual factor for all ages [2-6]. Recent studies have examined real-time information gathered about individuals and their environment [7-9] via purposeful, self-initiated reports or prompted reports [eg, ecological momentary assessment (EMA)]. Compared with retrospective recall, which can lead to error, EMA methods probe for participant reports in real time, leading to more accurate perceptions of behavior and allowing for the assessment of changes in the social context across a day [10]. However, while EMA as a method can help advance our understanding of the social context, it requires individuals to be both aware of and able to report peer presence or influence. Thus, there is value in research that relies less on self-report and more on passive assessment of the social context.

Use of Technology to Examine Social Contexts

There has been a rapid rise in the passive ambulatory assessment of behavior [11,12] using various technologies, including wearables for physical activity or heart rate [13,14] and alcohol biosensors [15,16]. In addition to wearable sensors, smartphones passively collect data from their built-in sensors in real time [17], including information on location and movement [18-20] and social interactions [20,21]. A smartphone-based technology with potential applications for understanding social contexts is Bluetooth, which is a ubiquitous connectivity protocol embedded in mobile phones and other wearable devices. Designed to underlie communication between digital devices, the unique characteristics of Bluetooth have enabled the development of software that can identify nearby Bluetooth beacons (eg, Apple AirTags or other transmitters, including smartphones themselves), allowing smartphone apps to assess the duration and frequency of interpersonal interactions [22-24].

Despite its promise, little research has applied Bluetooth technology to proximity sensing to study the social contexts of health behavior change. An epidemiological study used smartphone-based Bluetooth sensors to predict behavior change associated with disease spread [25], and another used Bluetooth-based proximity sensing to assess the relationships among sociability, sleep, and mood [26]. A recent study on alcohol use incorporated Bluetooth sensing to examine the social context of young adult drinking, in which the Bluetooth technology captured features such as the number of proximal devices and signal strengths [27]. Recently, researchers have evaluated the performance of Bluetooth-integrated methods to understand disease spread during the COVID-19 pandemic [28-30]. Our goal is to develop and evaluate the stability of a smartphone app that leverages a Bluetooth-based wearable sensing protocol to study the real-world social context of alcohol use but could be applicable to other behaviors in which social contexts act as key determinants.

Study Objective

The objective of this research is to develop technology that will allow for the passive detection of contact between individuals, and specifically between participants and their close friends. In this paper, we describe a smartphone app, Bluetooth-based beacons, and our planned procedures for evaluating the *functionality and validity* of the developed technology. In a companion paper [31], we describe our approach to evaluating participant responses to using the technology in a study on the social context of alcohol (ie, feasibility and acceptability). *Functionality* will be determined by evaluating the stability of the app (ie, low app crashes or other issues) and the success of the beacon detection protocol and app notifications across different devices and in different situations. We will collect data on functionality throughout the study, primarily using app-based data and secondarily using qualitative data from interviews with participants and peers at the completion of data collection. *Validity* will be determined by evaluating the concordance between beacon detection and participant EMA reports of peer presence data sources. Details of the project goals and methods for evaluating the goals are described in Table 1.

Table 1. Project primary goals and methods for evaluating goals.

Goal	Definition	How determined	Data source
Functionality			
Beacon detection	Whether the peer beacons are detected by the participant app consistent with app settings	Tested in participant orientation to confirm that beacons are detected by participant phone	• Beacon Encounter data set • App Log data set
Beacon encounter notifications	Whether the app functions as expected, defined as delivering report notifications with the expected latency when beacon encounter criteria are met	An indication of notification sent by the server when actual encounters are identified	• Beacon Encounter data set • Participant Event data set
App overall stability	Whether the app functions as expected with minimal errors	App error reports (crash and reinstall) and participant error reports	• App Log data set • Participant EMA[a] report data set • Postparticipation interview
Phone and operating system differences	Whether differences across Android phone and operating system versions are noted	Information about participant phones and operating systems	• App Log data set • Baseline survey • Participant postparticipation survey and interview
Validity	Concordance between beacon detection and participant report of peer presence	Cross-classification of beacon encounter and participant self-report data	• Beacon Encounter data set • Participant EMA report data set • Participant postparticipation interview • Peer weekly surveys

[a]EMA: ecological momentary assessment.

Methods

Design

Young adults will participate in a 3-week protocol during which they will complete reports about interactions with peers, including (1) signal-contingent reports triggered by the presence of a Bluetooth beacon being carried by a participant-nominated peer, (2) random reports triggered in time blocks 3 times per day, and (3) a morning report. A baseline assessment will precede field data collection and will aid in identifying peers, and an interview at the end of the study will collect qualitative information and feedback about participant experiences.

Participants

We will recruit up to 5 participants for our pilot study, and we will recruit 20 participants in the main study, with a conservative estimate of 15 completing the full protocol. The inclusion criteria are as follows: (1) be able to read English, (2) own an Android smartphone with OS11 or newer and have it with them throughout the day (typical for the age group between 18 and 29 years), (3) have a data plan (limited or unlimited), (4) be willing to approach peers to participate, and (5) anticipate not deviating from their typical routine during the study period, including leaving the region (as this would likely reduce exposure to selected peers). Additional inclusion criteria related to our substantive research aims are as follows: (1) aged 18 to 29 years; (2) drinking alcohol with others at least once a week, including drinking >4 (women) and >5 drinks (men) per occasion at least once a week in the past month; and (3) not in or seeking treatment for substance use.

We restricted our project to Android phones because there were several barriers that emerged with iOS. First, iOS places significantly more restrictions on apps that can be put on users' phones and the methods by which those apps can be loaded onto devices. Relatedly, when provisional software is distributed via the developer side of the App Store, a very limited number of developer testing accounts are provided, limiting the ability to test the app. Second, iOS takes more control than Android over processes that run in the background of the phone, including notifications, which are critical to the functionality of the app. Third, with the availability of the Apple AirTag we were concerned that implementing an alternative Bluetooth Low Energy (BLE) signal detection network with a different beacon would appear in competition with first-party applications and thus our app would be precluded or significantly delayed in distribution via the App Store. Further, as app development for this project started during the COVID-19 pandemic, there was significant focus placed on using BLE for proximity detection by both Apple and Google, with Apple in particular restricting the use of some features. For these reasons, and given the available resources and time frame of the project, we decided early in the course of the project to exclusively develop for Android phones. We note, however, that while owning an Android phone is a requirement for participants, it is not a requirement for peers.

Procedures

Eligibility and Recruitment

Young adults will be recruited from the community through flyers, email listserves, and social media advertisements. A brief web-based screener will establish their initial eligibility. Eligible participants will provide contact information, and a research assistant (RA) will schedule the in-person baseline session.

Participant Orientation and Baseline Assessment

A 90-minute in-person session will collect informed consent, demographic characteristics, and alcohol use data and identify possible peer participants. The RA will orient the participant to the project procedures, starting with installing the app on the participant's phone and recording device characteristics (device manufacturer, model, and Android operating system version). The RA will assist participants in changing settings on their phones to ensure the app will work optimally, including setting Bluetooth, location, nearby devices, and notifications to *on* or *allow*, and checking that settings that pause activity (eg, pause app activity if unused) or remove permissions are *off*. The RA will demonstrate the app interface, including showing the participants how to initiate reports and respond to notifications. The participants will navigate through each report, view examples of response types (radio buttons and text fields), and practice making entries. They will be instructed to respond as soon as possible after a prompt. We will explain that they are expected to keep their phone on, charged, and nearby. We will verify that the participants are not planning on traveling.

Peer Eligibility and Recruitment

The inclusion criteria for peers are as follows: (1) at least once a week in a typical week, having meaningful in-person social interaction with the participant. The alcohol-related inclusion criteria for peers are as follows: (2) between the ages of 18 and 29 years, and (3) drink with the participant at least twice a month in a typical month. While not all influential people with regard to alcohol use will be same-age peers, research indicates that same-age peers will most likely be present during drinking events (and in social interactions when drinking might occur) [32-34]. To identify possible peers, the RA will conduct a social network interview (SNI) that involves the participant nominating up to 10 people who they are close to, including friends, family members, or anyone they regularly spend time with in person who is close to their age [35,36]. The participants will report on the characteristics of these individuals, including their age, gender identity, whether they live together, relationship (friend, partner or significant other, casual acquaintance or coworker, sibling or cousin, other family member, and other), and frequency of meaningful social interaction ("How often in a typical month do you spend at least 15 consecutive minutes with this person?"). In line with the substantive study goals, we will also assess the frequency of the network member's drinking ("How many times in the past month do you think this person drank alcohol?") and the frequency of drinking with the person ("In the past month, how often did you drink with this person [while both of you were drinking]?"). For this protocol, we will ascertain the participant's perception of the willingness of the peer to participate in this study.

Working with the RA, the participants will identify 3 peers to be invited to participate in the study based on eligibility. During the baseline session, the participant will attempt to contact each of the 3 selected peers to invite them to participate. If the participant contacts the peer with the RA present and the peer agrees to hear more about the study, the participant will, with the peer's agreement, share the peer's contact information with the RA, who will then provide the peer with a web link to the study description and informed consent procedures and will communicate with the peer about their participation from that point forward. If the peer does not respond to the participant in the presence of the RA, the participant will send the peer a brief study description with the web link. If any peer who has received the project description does not respond after 3 days, we will move to the next person on the SNI list and ask the participant to make initial contact with the (new) peer. The participants will be given 5 days to recruit up to 3 peer participants.

Once a peer participant has consented to participate, the RA will arrange a time to give them the beacon and answer any questions. The beacon is 4.4 cm square and 1 cm thick (Figure 1). We will provide a small adhesive patch to allow the peer to attach the beacon to their phone and a ring to facilitate attachment to their keys if they choose. Peers will carry their beacon for 3 weeks of the project. Each beacon is assigned a unique ID that associates the beacon with the participant and peer. The smartphone app reports will begin for the participants once the beacons are distributed to their peers. The peer participants will complete web-based surveys at the end of each of the 3 weeks of data collection, in which they will indicate the days and time of day in the prior week they did not have their Bluetooth beacon with them and times in the prior week they were with the participant. This information will be useful for determining why a beacon was not detected.

Figure 1. The beacons used in this research were asset tags from Kontakt.io.

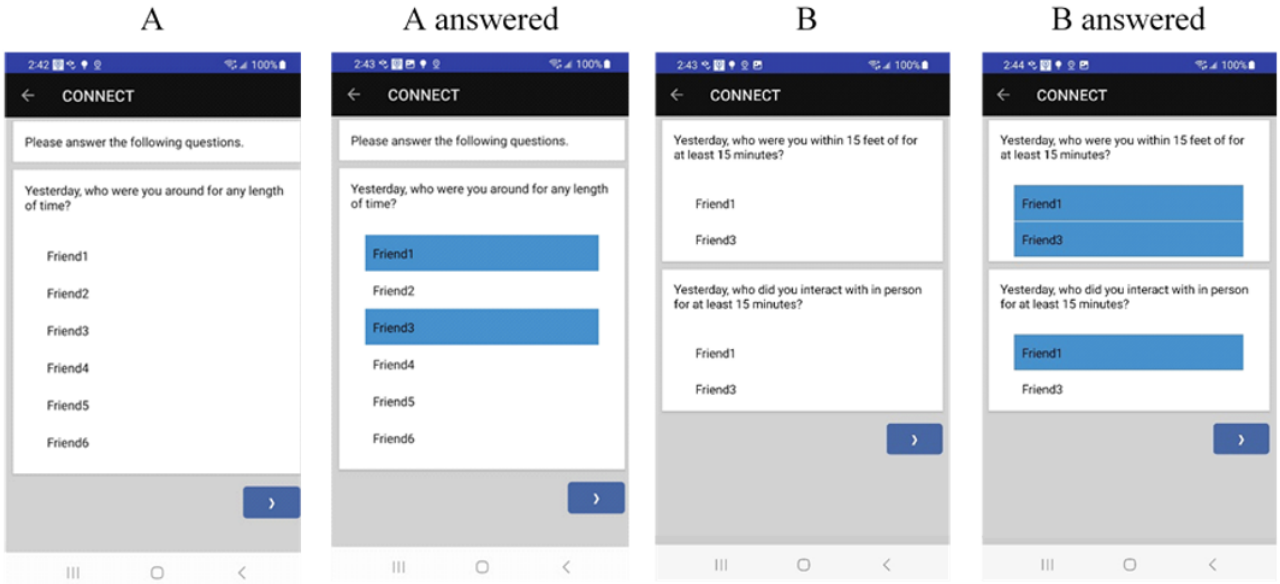
EMA Reports

Overview

Our project will use a custom smartphone app for data collection, developed in conjunction with our developer, MEI Research [37]. The app, which is only available for Android phones, comprises 2 primary components: the participant-facing EMA report delivery component and a background process that continuously scans for the Bluetooth beacons. Researchers create EMA reports and adjust the settings using a web interface. Notification of random and beacon signal-contingent EMA reports is handled locally on-device, so internet connectivity is not needed for either report triggering or beacon detection to function. Content is delivered dynamically from the MEI Research server, which requires cellular or Wi-Fi connectivity. Data are synchronized with the server when the participant opens the app or activates the sync function.

Before the 21-day EMA phase, the names of the SNI-identified peers and information about their associated beacons are uploaded using the researcher-facing web interface into the app so that the customized list of peers is presented to each participant on EMA reports (refer to the examples in Figure 2). This list of peers will have a maximum of 6 names from the SNI. All peers carrying the beacon will be on the list; others on the list may have declined to carry the beacon or may not have been asked. First, names, nicknames, or initials are presented to maximize confidentiality during data collection. Updating this list can occur in real time without involving the participant, thereby avoiding protocol disruptions. EMA reports begin with an item measuring *peer proximity*: “Yesterday/In the past hour, who were you around for any length of time?” The friend list is presented to the participant for them to choose from, with branching logic used to determine the presentation of subsequent questions. The names or nicknames of peers are not included in the researcher data set; numeric peer IDs (also associated with beacon data) ensure deidentification.

Figure 2. Screenshots of 2 items in the morning survey, first presented without answers (A) followed by the item with friends selected (B). Note that image B presents only friends that were selected in question A.



The participants will provide 3 types of EMA reports, completed in 1 to 3 minutes each.

Signal-Contingent

Signal-contingent reports are triggered by the app according to its detection of beacons carried by peer participants (refer to the subsequent section for details on beacon and trigger settings). We will not have constraints on times when these reports are prompted, and reports will expire (ie, will disappear from the app display) after 1 hour.

Random

Random reports are intended to sample experiences outside of drinking events and those prompted by signal-contingent reports, including peer contact and influence. The participants will receive 3 random EMA reports per day between 12 PM and 12 AM (12 to 6 PM, 6 to 9 PM, and 9 PM to 12 AM). We chose these intervals to optimize the measurement of alcohol use and exposure to peers. The participants will be informed of these intervals; missing data because of going to sleep is of low concern. Notifications will be followed by reminders at 15 and 30 minutes and will expire after 1 hour. The notification and in-app display for signal-contingent and random reports appear identical on the EMA app interface to minimize unintentional awareness of peer presence. Although there is no basis on which to project a compliance rate with beacon-triggered surveys, we expect a 70% or higher compliance rate with random surveys [31,38].

Morning

Morning reports will be completed by participants every day. The morning report is always available on the app, with a notification at 10 AM and reminders at 15 and 30 minutes thereafter. The EMA app prioritizes signal-contingent and random reports such that participants are not able to complete morning reports until any pending triggered reports are completed. The morning report items are identical to the signal-contingent and random reports but refer to *yesterday*, whereas the random and signal-contingent reports refer to *in the past hour*. In the morning reports, we also ask about prior-day app functionality related to participant experience (ie, *participant-related functionality*; "Were there times yesterday when you think our system was not working as you expected?"); those who indicate *yes* or *maybe* are asked to describe the issue in a text box. Items also identify possible missing data (eg, "Did you do any of the following yesterday?" with answers "You silenced your phone," "You turned your phone off," "You turned off notifications on your phone or for the EMA app," and "You turned off Bluetooth detection"). During the 3-week EMA period, the study staff will contact the participants once a week to check in, encourage compliance, and address technical issues as needed. The participants can also email, call, or text study staff at any time they have issues or questions.

Postparticipation Assessments

After the 3-week data collection period, the participants will complete a modified 15-item System Usability Scale (SUS [39]) with items adapted to our protocol that assess functionality (eg, "The app drained my battery" and "The app worked as expected") with response options on a 5-point Likert scale from 1=strongly disagree to 5=strongly agree. We will also conduct a semistructured interview to clarify any reported functionality or validity issues. Before the interview, we will examine the participant's beacon encounter data and reports of peer presence, and during the interview, we will clarify discrepant information, including reconciling signal-contingent reports (ie, indicating beacon detection) at times when the participant did not indicate that the peer was present. We will also probe the reasons for noncompliance and whether triggered report noncompletion appears to be systematically related to peer presence. In this final session, participants will be told how to delete the app from their phone.

Ethical Considerations

Human Subject Protections

The procedures were approved by the Brown University Institutional Review Board (protocol number 2022003448).

Informed Consent

The participants and the peer participants will complete informed consent, which includes reviewing detailed consent forms, discussion with the researcher, and documentation of consent.

Privacy and Confidentiality

All information obtained during the assessments will be confidential and will be used solely for research purposes. To protect the data and prevent unauthorized access, all EMA data will be encrypted and will remain so until it is accessed by the project staff using a username and password specific to this project. All files with participant-identifying information will be password-protected and stored separately from the data on a server accessed only by the project staff. To preserve confidentiality, we will deidentify data for both peers and participants using a numeric code. The participants will have the researcher provide credentials for the smartphone app that will not include their names, and we will encourage the participants to use phone passwords.

Compensation

Participants will be paid US $50 for attending the first session, US $5 per day for answering the EMA reports (at least 2 of 4 of the morning and random reports per day), and US $40 for attending the second session. The participants will also receive a weekly bonus of US $20 if they complete at least 80% of the random and morning reports. The most they can receive for participation is US $255. Peer participants will be compensated US $30 for each week they carry the beacon and answer the weekly survey questions, and US $10 for returning the beacon to the research team, so the most they can receive is US $100. All compensation will be provided in the form of an Amazon e-gift card.

Beacons and Parameters for Signal-Contingent Triggers

Beacon Selection and Features

We prioritized 4 criteria in the selection of the beacon used in this study: signal strength, robustness of the application programming interface, size and convenience of carrying, and battery life. The expected functionality of the beacon is primarily advertising (ie, one-way communication comprising transmission of small packets of data over fixed time intervals for detection and localization by a receiver—here, the EMA app used by the participants) [40]. Given these requirements, we selected BLE, an extension of the traditional Bluetooth protocol. Using BLE facilitated the optimization of our first criterion, signal strength. The Bluetooth protocol includes a feature called Received Signal Strength Indication, an indicator of the signal power received by a device detecting BLE signals. This feature, together with the specifications of the transmission source hardware, enables the computation of approximate positioning in the natural environment, including the estimation of distance [41,42]. Many hardware vendors provide these features; a subset of these vendors provides open, nonproprietary documentation of these values [43] and the ability to interface directly with the beacons through a robust application programming interface, our second criterion. After reviewing options, conducting testing, and consulting with the app developer, we selected Kontakt.io, a company with beacons that met the first 2 criteria and have form factors that can be attached to a phone or keyring to ensure that it is carried consistently. We extensively tested the options available from Kontakt.io and determined that the asset tag was most reliably detected by our app and by generic BLE scanner apps. Its battery life is 6 to 12 months and can be monitored on the internet; therefore, even with reuse, there should be no missing data attributable to a depleted battery.

We initially investigated whether we could build the system such that the Bluetooth on the peers' phones would be detected by the app on the participant's phone. For this, an app was needed that could use the BLE functionality within the participant phone to detect and identify the peer phone and prompt the participant to respond within the EMA app. One problem with using the peer phone as the BLE transmitter is that different Bluetooth hardware installed in different phones will report differing RSSI values for the same physical distance since this metric is contingent on the strength of the signal being sent out by the original device. This increases the complexity of the programming logic and would add error into what is a simple threshold check for beacons. Another issue is that we were unable to identify any phone-to-app software with an SDK available to use with our EMA app, whereas beacon detection SDKs were available. There were other considerations, including that in early developmental work concerns were raised by peers about installing an app on their phone, but the most critical were that the resources needed for phone-to-app detection were higher than the beacon-to-app model due to the initial development process, variability of operating systems and hardware, and required ongoing maintenance when relying on operating systems that evolve over time. The key benefits of beacon-to-app detection are the consistency of the technology and lower development costs when using an existing SDK.

EMA Report Triggering by Beacon Proximity

The protocol for peer proximity detection and subsequent triggering of reports involves the detection of *transient encounters* (ie, incidental, brief social interactions between the participant and a peer identified through signal detection), their conversion into *actual encounters* (ie, meaningful social interactions differentiated from incidental encounters using a time criterion), and their termination as *end encounters* (ie, discontinuation of meaningful social interaction; refer to Figure 3 for a representation of the process). The EMA app continuously scans the participants' environments for peer beacons. A transient encounter is recorded when the BLE proximity detection service integrated into our EMA app detects a beacon, defined as detecting a signal from a peer beacon that is at least as strong as the Received Signal Strength Indication criteria that correspond to our proximity criterion (ie, 15 ft, 4.6 m). The peer beacon advertising interval, which is the frequency at which beacons send out signals, was set to 1000 milliseconds (1 second) to ensure that the detection corresponds closely to real-world interactions. However, given that the detection of every signal from the peer beacon by the participants' device during the initial encounter period is not guaranteed, a window

of time for the detection of this signal is needed to ensure that detection occurs (ie, that it is not missed, resulting in a false negative); this window was set at 2 minutes for the transient encounter.

A *transient encounter* is converted into an *actual encounter* when the beacon has been detected for at least 15 minutes (our definition of meaningful interaction) without being undetected (ie, gone) for >2 minutes. A signal-contingent report will be triggered upon the conversion of a transient encounter to an actual encounter. Critically, the algorithm that determines triggering by beacon proximity runs separately for each peer participant, such that a transient and actual encounter with a peer beacon can be initiated even when the participant is in an actual encounter with another peer. Given that there will be 3 peers carrying beacons, it is possible that up to 3 reports could be triggered at a time, although we do not anticipate that this will happen frequently. In addition, given our encounter parameters that require 60 minutes of nondetection before another encounter with the same beacon would occur (refer to the subsequent section for explanation), we do not expect the number of signal-contingent reports to be overwhelming but will evaluate this closely.

A separate criterion to end an actual encounter after 60 minutes of nondetection (vs 2 minutes for a transient encounter end) was selected. We selected 60 minutes to reduce spurious nondetection and accommodate behaviors such as going to the restroom or being in different rooms at a party (which may still be part of an ongoing meaningful interaction despite not meeting the proximity criterion). Although the duration of the time criteria (ie, 15 minutes for the actual encounter and 60 minutes for the end encounter) were somewhat arbitrary, the evaluation of the sensitivity and specificity of the criteria via concordance with self-report is a goal of the study. Subsequent work can trial different definitions based on study findings, as well as what contact is truly influential and whether the length of influential contact varies by relationship type. Table 2 presents our initial criteria (far-right column) based on the best judgment, but the criteria are modifiable within the researcher-accessed interface.

Figure 3. State flow diagram that incorporates the beacon detection, encounter definition, and notifications. PlotProjects is a service and application programming interface used by the app software for the Bluetooth beacon detection.

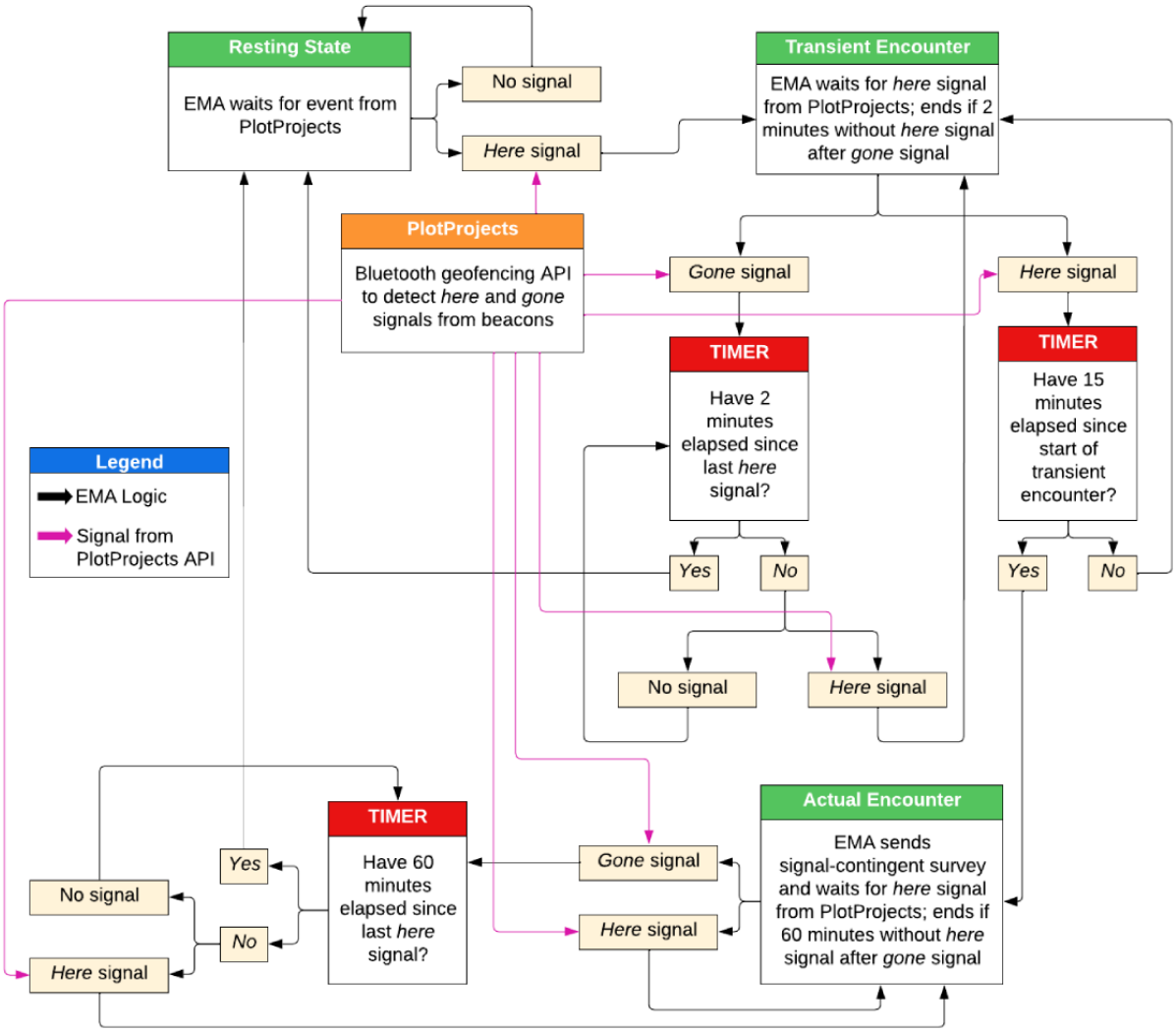


Table 2. Transient and actual beacon encounter terms, definitions, and criteria.

Term	Definition	Criteria
Encounter	Incidental or purposeful social interaction between the participant and a peer is identified through BLE[a] signal detection with a predefined proximity criterion.	15 ft (4.6 m)
Start of a transient encounter	Brief social interaction. A transient encounter begins but does not constitute meaningful interaction until it converts to an actual encounter.	1000 milliseconds
End of the transient encounter	End of a brief social interaction is defined by a given time criterion. Intended to ensure that very brief encounters do not prompt a notification.	2 minutes without beacon contact
Start of an actual encounter	Meaningful social interaction defined by a given criteria of time. A transient encounter is converted to an actual encounter. An actual encounter triggers a signal-contingent report.	15 minutes of beacon contact with no periods >2 minutes without beacon contact
End of the actual encounter	Discontinuation of meaningful social interaction.	60 minutes without beacon contact

[a]BLE: Bluetooth Low Energy.

There are several technology-related considerations for the detection of meaningful interactions. First, an a priori definition of a meaningful social interaction had to balance sensitivity for detecting such events (addressing the *feasibility* of detecting social interactions) with specificity in excluding incidental, nonmeaningful interactions (and reducing the burden of responding to multiple signal-contingent reports). However, our a priori criterion of requiring 15 minutes for a transient encounter to be converted into an actual encounter will miss brief but meaningful interactions (eg, consuming a shot of hard alcohol together, offering alcohol). Importantly, we designed our protocol to minimize missing data associated with such events by including the assessment of past-hour peer presence in our random reports and past-day peer presence in our morning reports. This design will allow us to cross-tabulate the occurrence of self-reported interactions of even short duration (as recorded in the EMA report data set) with the occurrence of all beacon detections, including transient encounters (as recorded in the Beacon Encounter data set).

Data Sets and Calculated Variables

Overview

Data produced by the app, including information about encounter events, participant self-reported data, and metadata, are stored in several data sets. These data sets are supplemented by postparticipation self-report data from (non-EMA) surveys and semistructured interviews. Table 3 contains a description of the data sources; Table 1 links the data sources with the study goals and methods to the evaluate goals.

Table 3. Metadata and calculated variables and associated source data sets that will be used to evaluate research goals.

Metadata or calculated variable	Source data set					
	App log	Beacon Encounter	Participant events	Notification log[a]	EMA[b] report	Postparticipation
Participant ID	✓	✓	✓	✓	✓	✓
Peer ID (corresponds to beacon ID)		✓			✓	✓
Event or Report timestamp	✓	✓	✓	✓	✓	✓
Event type (eg, action delivered, participant report started, report response, and app synced)[c]	✓	✓	✓		✓	
Session ID (helps link together events from different data sets)		✓	✓	✓	✓	
Source of event (eg, morning or random report)			✓	✓	✓	
Corroborative self-report					✓	✓

[a]Contains only notifications for morning and random reports.

[b]EMA: ecological momentary assessment.

[c]Metadata recorded by the app and stored.

Further information about the source data sets are presented in the Multimedia Appendices 1-5.

App Log

This data set contains information about the app version used and (morning, random, beacon-triggered) report items that are programmed into the app. It also contains event types (eg, app opened and app synced) and errors (eg, when the operating system denies permission to the app). We will use information from this data set to determine that the app was installed correctly and that it was functioning as expected during the study.

Beacon Encounters

Variables include participant ID, beacon ID, start and end timestamps of transient and actual encounters, the timestamp when the transient encounter was converted into an actual encounter, and the timestamp for when the report notification was sent. A unique session ID links the elements (start and end) of given (transient and actual) encounters.

Participant Events

Variables include participant ID and types of events (eg, report start, report submit, and report notification) with timestamps. The report start and submit timestamps are present for all reports, including random, morning, and signal-contingent reports. Report notification timestamps (1) duplicate the timestamp of the transient-to-actual conversion reported in the Beacon Encounter data set (which triggers a notification) and (2) indicate whether other notifications are for random or morning reports.

Notification Log

Variables include session ID, report type (ie, random and morning), and timestamps when timed notifications and reminders were scheduled to be sent.

EMA Reports

Data include participant responses to items in the signal-contingent, random, and morning reports, including indicators of who among their peers is or was present and self-reports about app functionality. For example, in each report, we ask, “Who did you interact with in person for at least 15 minutes?” The report type and timestamp will be used to ensure that data responses are aligned with information from other data sets and reports.

Postparticipation Data

Data from the postparticipation interviews and the SUS will be used to evaluate the app’s functionality. Participant interviews will also be used to investigate identified discrepancies between the beacon-derived data and participant reports (ie, validity) and will be supplemented with weekly survey day-level reports from peers about their proximity to participants.

Data Analysis Plan

Functionality of Beacon Detection by the Participant’s Smartphone

We will confirm the detection of the 3 beacons by the participant’s phone during the orientation. We expect to observe smartphone notifications for each beacon when the transient encounter is converted into an actual encounter (after 15 minutes). If notifications are not observed, we will examine the Beacon Encounter data set to determine whether transient encounters are being recorded (ie, whether the beacon is detected by the app) without being converted into an actual encounter. Functionality will be evaluated with 3 metrics: (1) the proportion of participants whose phones detect all beacons during the orientation, (2) the proportion of beacons detected by participant phones, and (3) the latency between exposing the participant phones to the beacons and the start of a transient and actual encounter. These observations will be systematically recorded and aggregated across beacons and participants.

Functionality of the Beacon Encounter Notifications

Data from the Beacon Encounter data set will be used to evaluate functionality in two ways: (1) the proportion of actual encounters for which a signal-contingent notification was shown as sent by the server in the Beacon Encounter data set, and (2) the mean latency in minutes between the conversion to an actual encounter and the sending of the signal-contingent notification. The functionality of notifications for random and morning reports will not be evaluated, as these are commonly used in EMA and are fully functional in the app.

Functionality Related to App Stability

The app log, the EMA data, and the end-of-study interview and survey will be used to assess the participant-experienced functionality. The app log contains details about the events that have occurred within the app, including information about app crashes and app reinstalls. Using data provided by participants in the morning report, participant-related functionality will be determined as follows: (1) the total count (ie, person-days) of participant-reported suspected functionality problems, (2) the person-level proportion of days of suspected functionality problems, and (3) aggregated item-level and overall mean scores on the adapted SUS. Open-ended feedback will also be obtained in the morning report as well as in the end-of-study interviews.

Functionality Related to the Phone and Operating System

The manufacturer, model, and Android operating system of the participant devices will be examined as moderators of the above metrics of functionality. The variables will be evaluated using a series of Mann-Whitney *U* tests (for means and counts) and chi-square tests (for comparing proportions) for each metric. Considering the small sample size, the groups will be driven by the sample of the device itself. For instance, the manufacturer could be binned to *Samsung* (or potentially *Google*) versus *all other manufacturers*; the model could be binned to *currently supported* (ie, receiving ongoing feature and compatibility updates) versus *legacy*; and the operating system could be binned to *Android 13* (the newest) versus *Android 11 or 12* (operating systems that were used during app development). Independent of group comparisons, descriptive findings on functionality will be aggregated for each manufacturer and operating system version.

Validity

We define validity as the concordance between encounters recorded in the Beacon Encounter data set and participant reports of peer presence recorded in the EMA reports (Table 4).

Table 4. Beacon validity: cross-classification of beacon encounter and participant self-report data[a].

	Participant self-report data	
	Positive (participant reports peer within 15 ft, 4.6 m for 15 minutes)	Negative (participant does not report peer nearby)
Beacon detection		
Positive (signal-contingent trigger)	True positive: beacon detected and triggers signal-contingent report and participant reports peer presence in signal-contingent report (*sensitivity*)	False positive[b]: beacon detected and triggers signal-contingent report but participant does not report peer presence in signal-contingent report (*specificity; protocol criterion validation*). This could happen if: • delay or error in notification (*technology failure*) • peer is not actually present (*technology failure*) • peer is present with beacon but the index participant is not aware (*inaccurate index participant self-report*) • peer is present with beacon but not when the participant answers report (*limitation of detection settings*)
Negative (no signal-contingent trigger)	False negative[c]: 1. beacon never detected but participant reports peer presence on next EMA[d] random report (*sensitivity*). This could happen if: • peer is present with beacon but beacon is not detected (*technology failure*) • peer is present without beacon (*peer noncompliance*) • inaccurate index participant self-report 2. peer beacon is detected in transient encounter but criteria for actual encounter are not met so does not trigger signal-contingent report but participant reports peer presence on EMA random report (*specificity; protocol criterion validation*)	True negative: 1. beacon never detected and no report of peer presence on EMA random report (*sensitivity*) 2. peer beacon is detected in transient encounter but does not trigger signal-contingent report (criteria for actual encounter are not met) and no report of peer presence on EMA random report or morning report (*specificity; protocol criterion validation*)

[a]Concordance will be evaluated only when self-report EMA data are available. Therefore, beacon data collected when index participants are not compliant with random or signal-contingent reports will not be usable in the evaluation of concordance, as no self-report of peer proximity will be available.

[b]Reasons for false-positive signal-contingent triggers may not be known to the study team.

[c]Reasons for false-negative signal-contingent triggers may not be known to the study team.

[d]EMA: ecological momentary assessment.

False negative beacon detections will be evaluated in a series of steps: First, we will compute the proportion of (1) days and (2) random reports in which a participant reported peer presence (from the EMA data set), but a corresponding transient or actual encounter does not exist (from the Beacon Encounter data set). If a transient encounter, but not an actual encounter, is recorded, we will compute (3) the proportion of these false negative events that occurred because of the a priori selection of 15 minutes as the threshold delineating a transient versus an actual encounter (based on timestamps of encounter events in the Beacon Encounter data set). For the false negative events that are not associated with a transient encounter, we will further attempt to delineate the reason underlying this false negative as either technology-related (the peer was carrying the beacon but the beacon was not detected) or compliance-related (the peer was not carrying the beacon) by integrating self-report data on compliance from the peer weekly surveys. If sample size and base rates allow, we will also fit a series of generalized linear mixed models [44] regressing concordance at the person level (eg, sex and age) and proximal prior event level (eg, context and alcohol use) predictors to identify systematic factors associated with detection failure. *False positive* beacon detections, as indicated by the triggering of a signal-contingent report when the peer beacon is not present, have never occurred in preliminary testing. Given the factors needed to incur a false positive detection, which should only occur if beacon information was entered incorrectly by the research team, we believe that such events are highly unlikely. However, it is possible that a notification could be delayed by the operating system or other action (eg, if the index participant phone is off), which would result in the participant report being delayed, and thus the participant report would not confirm the peer presence. Beacon detection also could occur when a peer was present but the participant was not aware (eg, at a large party) or if the peer left the area before the participant answered the report. We will compute the proportion of signal-contingent reports in which participants deny a past-hour peer presence. We expect that the participant interviews and the peer surveys will be informative about the conditions under which false positives occur and will improve our understanding and measurement of peer proximity and influence. Ultimately, the detection of an encounter by the protocol when such an interaction did not occur from the participant's perspective provides critical information necessary for the computation of the specificity and positive predictive value of our detection protocol.

Anticipated Sources of Missing Data

With various momentary assessment reports and passive data collection from multiple peers, the source of missing data is important to identify. We expect to have missing data owing to technical issues for the following reasons: (1) the beacons could stop sending a signal because of low battery or hardware failure; (2) the app could crash or be unable to send or receive data; (3) the phone operating system could update, resulting in the app or phone features not working as expected; or (4) the software detection algorithm may stop identifying encounter start and end signals. Missing data may also be because of participant or peer noncompliance, including the following: (1) participant nonresponse to EMA reports, (2) participant changing phone settings or status such that the detection of beacon signals or notifications is interrupted, or (3) peer failure to carry the beacon. Items in the morning report, postparticipation surveys and interviews, and the peer weekly survey will capture times when the participant or peer is aware of these issues occurring. While imperfect, this information should allow us to characterize situations in which the reason for missingness is known and thus maintain the missing-at-random assumption. Situations in which we are not confident about the reason for missing data will be investigated for systematicity using proximal prior predictors in the EMA data set to further maintain the missing-at-random assumption.

Results

Participant enrollment began in February, 2023. As of submission of the manuscript (June 2023), nine participants and 21 peers were enrolled, with data collection anticipated to finish in December, 2023. Data analysis will begin immediately upon completion of data collection.

Discussion

Principal Findings

The research described in this paper will advance the literature by developing and validating a passive detection system for situations in which social influence is important. While this Bluetooth-based technology could be applicable to many research, clinical, or community settings in which social contact is relevant, our substantive goal is to facilitate research characterizing the real-time social context of alcohol use and, in turn, to inform the timing and context of mobile-delivered interventions to reduce hazardous drinking [45,46]. In this paper, we describe our planned procedures for evaluating the functionality and validity of the system, which incorporates multiple components of functionality and uses data from the app and reports from participants and up to 3 of their close peers. Our approach to collecting user-reported information along with passively recorded data is consistent with recommendations for identifying high-risk events and the timing of real-time intervention [47].

Just-in-time adaptive interventions target behavior in the natural environment at a time when behavior is opportune for modification [48]. These tailored mobile-delivered interventions provide the right type and timing of intervention in response to real-time behavior, cognition, or context to prevent negative health outcomes [48-50]. Ideally, interventions could incorporate this BLE-based peer proximity approach to help people who are interested in changing behaviors by identifying contexts that confer greater risk (or alternatively, that protect against risk), alerting these people or others about the risk inherent in their present situation, and including encouragement and information about how to avoid the situation. This approach could be combined with other sensor technology, including location detection or geofencing using GPS to detect proximity to risky locations (eg, alcohol outlets), and other smartphone features (eg, the smartphone accelerometer to measure movement or engagement with messaging and texting apps) [27]. This study will provide much-needed information about the appropriate timing and context for just-in-time adaptive interventions in a scenario that is highly characteristic of young adult drinkers: consuming alcohol with close peers.

Limitations

Limitations related to technology include the need to build the system with a contracted app developer; to the best of our knowledge, there are no systems that researchers could use out of the box for person-proximity detection and EMA report triggering. The system only works with phones that use the Android operating system; iOS imposes barriers to the development of technologies and the distribution of test builds, whereas Android allows for the installation of third-party software outside of the context of Google Services (ie, sideloading). However, Android had multiple operating system updates while our project was under development; each update required a revision of the app and additional testing. This is an unavoidable element of app development that adds considerable time and resources to a project. We considered providing Android phones to participants who did not have them but had concerns that intermittent or limited use of a secondary phone would reduce both compliance and app functionality (eg, fewer notifications being sent to phones frequently in sleep mode). Another technology limitation is our inability to implement a minimum time interval between random and signal-contingent reports or to set a limit on the number of signal-contingent reports a participant receives. We will evaluate the average number of reports and intervals between reports and hope to include adjustments in future iterations.

Our design will not detect influential peers who are not carrying a beacon; therefore, its success will rely largely on how well our SNI identifies influential peers and whether they participate. Our procedures will also poorly detect friends who are influential through interactions other than in-person contact (eg, via social media or text). Influence could also occur more quickly than the time duration estimate that we defined in the protocol; this influential interaction would be missed. During all EMA reports, we collect information about peers who are present but not carrying a beacon (identified a priori) and peers who are present but not on the participant's selected peer list, which will help us to determine how successful our SNI selection process was and address some of the above limitations; we also expect that information collected in the postparticipation interviews will assist us in adjusting procedures for identifying influential peers.

We are relying on self-report to a considerable extent in that we are using it as the ground truth for whether a beacon detection is accurate or not. Self-report can be inaccurate or missing, but it is the standard in the field for describing context and alcohol use, and there are no alternatives that we could use to compare to beacon detection. While we are confident that our informed consent procedure, the provision of a clear rationale to participants and peers, and confidentiality protections will minimize inaccurate reporting, it is possible that social desirability or other person-level or contextual effects in some situations will result in missing or inaccurate reports of peer presence or alcohol use [51,52]. We expect that we will not be able to identify the reason for some disagreements between beacon detection and self-report, but the very robust data sets will allow for sensitivity analyses that will help us identify and understand discrepancies. For example, with morning reports and sensor data, we can compare the concordance between beacon detection and self-report on drinking versus nondrinking evenings. The weekly web-based surveying of peers was designed to minimize burden (and thus increase the likelihood of peer inclusion), but may produce unreliable data about the time spent with the participant.

The success of this research relies on participant and peer compliance, as their reports are needed to evaluate every project goal. Although some degree of noncompliance with EMA is common [38], poor compliance would limit our ability to evaluate functionality (refer to Table 4 for details) independent of systematic bias owing to missingness in the data collected. Although our participant burden is consistent with the current practice in EMA research, our peers must consistently carry a small beacon. Our requirement that peers continuously carry a beacon will likely result in more missing data than if there were an app for peers to install on their phone (which would also be easier to do remotely). Finally, this type of work requires considerable staff time for participant and peer recruitment (up to 3 peers per participant), monitoring incoming EMA and beacon data, and data management and analysis.

Future Work

In addition to the evaluation described herein of functionality and validity, we are collecting participant feedback about our procedures, which will allow us to evaluate feasibility and acceptability. Together, this information will inform a large-scale study with a representative sample, a wider age span, and a broad representation of social context, permitting the study of dynamic intersections of multiple determinants of drinking behavior, including social context, location context, and individual factors (eg, craving, affect, and motivation) that underlie contextual influences [53].

Acknowledgments

This research was supported in part by grants (R21AA027329 [multiple principal investigators NPB and KMJ], K08DA048137 [principal investigator AWS], and K01AA025994 [principal investigator MKM]) from the National Institute on Alcohol Abuse and Alcoholism. The National Institutes of Health had no role in the study design, collection, analysis, or interpretation of the data, writing the manuscript, or the decision to submit the paper for publication.

Data Availability

Data sharing is not applicable to this paper as no data sets were generated or analyzed in this protocol. Once data are generated, data sets will be available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Application (App) log data set.
[PNG File , 135 KB - resprot_v13i1e50241_app1.png]

Multimedia Appendix 2
Beacon encounter data set.
[PNG File , 206 KB - resprot_v13i1e50241_app2.png]

Multimedia Appendix 3
Participant events data set.
[PNG File , 280 KB - resprot_v13i1e50241_app3.png]

Multimedia Appendix 4
Notification log data set.
[PNG File , 298 KB - resprot_v13i1e50241_app4.png]

Multimedia Appendix 5
Ecological momentary assessment report data set.
[PNG File , 314 KB - resprot_v13i1e50241_app5.png]

References

1. Thombs DL, Wolcott BJ, Farkash LG. Social context, perceived norms and drinking behavior in young people. J Subst Abuse 1997;9:257-267. [doi: 10.1016/s0899-3289(97)90020-1] [Medline: 9494953]
2. Borsari B, Carey KB. Peer influences on college drinking: a review of the research. J Subst Abuse 2001 Dec;13(4):391-424. [doi: 10.1016/s0899-3289(01)00098-0] [Medline: 11775073]
3. Trucco EM, Colder CR, Wieczorek WF. Vulnerability to peer influence: a moderated mediation study of early adolescent alcohol use initiation. Addict Behav 2011 Jul;36(7):729-736 [FREE Full text] [doi: 10.1016/j.addbeh.2011.02.008] [Medline: 21420241]
4. Leonard KE, Homish GG. Predictors of heavy drinking and drinking problems over the first 4 years of marriage. Psychol Addict Behav 2008 Mar;22(1):25-35 [FREE Full text] [doi: 10.1037/0893-164X.22.1.25] [Medline: 18298228]
5. Reifman A, Watson WK, McCourt A. Social networks and college drinking: probing processes of social influence and selection. Pers Soc Psychol Bull 2006 Jun 02;32(6):820-832. [doi: 10.1177/0146167206286219] [Medline: 16648206]
6. Jackson KM, Merrill JE, Barnett NP, Colby SM, Abar CC, Rogers ML, et al. Contextual influences on early drinking: characteristics of drinking and nondrinking days. Psychol Addict Behav 2016 Aug;30(5):566-577 [FREE Full text] [doi: 10.1037/adb0000184] [Medline: 27269292]
7. Berg CJ, Haardörfer R, Payne JB, Getachew B, Vu M, Guttentag A, et al. Ecological momentary assessment of various tobacco product use among young adults. Addict Behav 2019 May;92:38-46 [FREE Full text] [doi: 10.1016/j.addbeh.2018.12.014] [Medline: 30579116]
8. O'Donnell R, Richardson B, Fuller-Tyszkiewicz M, Liknaitzky P, Arulkadacham L, Dvorak R, et al. Ecological momentary assessment of drinking in young adults: an investigation into social context, affect and motives. Addict Behav 2019 Nov;98:106019. [doi: 10.1016/j.addbeh.2019.06.008] [Medline: 31247534]
9. Perski O, Keller J, Kale D, Asare BY, Schneider V, Powell D, et al. Understanding health behaviours in context: a systematic review and meta-analysis of ecological momentary assessment studies of five key health behaviours. Health Psychol Rev 2022 Dec 15;16(4):576-601 [FREE Full text] [doi: 10.1080/17437199.2022.2112258] [Medline: 35975950]
10. Ebner-Priemer UW, Trull TJ. Ecological momentary assessment of mood disorders and mood dysregulation. Psychol Assess 2009 Dec;21(4):463-475. [doi: 10.1037/a0017075] [Medline: 19947781]
11. Kuntsche E, Labhart F. The future is now--using personal cellphones to gather data on substance use and related factors. Addiction 2014 Jul;109(7):1052-1053. [doi: 10.1111/add.12540] [Medline: 24754712]
12. Smith A, de Salas K, Lewis I, Schüz B. Developing smartphone apps for behavioural studies: the AlcoRisk app case study. J Biomed Inform 2017 Aug;72:108-119 [FREE Full text] [doi: 10.1016/j.jbi.2017.07.007] [Medline: 28709856]
13. Cheng YC, Huang YC, Huang WL. Heart rate variability as a potential biomarker for alcohol use disorders: a systematic review and meta-analysis. Drug Alcohol Depend 2019 Nov 01;204:107502. [doi: 10.1016/j.drugalcdep.2019.05.030] [Medline: 31494439]
14. Ralevski E, Petrakis I, Altemus M. Heart rate variability in alcohol use: a review. Pharmacol Biochem Behav 2019 Jan;176:83-92. [doi: 10.1016/j.pbb.2018.12.003] [Medline: 30529588]
15. Barnett NP. Alcohol sensors and their potential for improving clinical care. Addiction 2015 Jan 17;110(1):1-3. [doi: 10.1111/add.12764] [Medline: 25515824]
16. Paprocki S, Qassem M, Kyriacou PA. Review of ethanol intoxication sensing technologies and techniques. Sensors (Basel) 2022 Sep 09;22(18):6819 [FREE Full text] [doi: 10.3390/s22186819] [Medline: 36146167]
17. Trull TJ, Ebner-Priemer U. The role of ambulatory assessment in psychological science. Curr Dir Psychol Sci 2014 Dec;23(6):466-470 [FREE Full text] [doi: 10.1177/0963721414550706] [Medline: 25530686]
18. Byrnes HF, Miller BA, Wiebe DJ, Morrison CN, Remer LG, Wiehe SE. Tracking adolescents with global positioning system-enabled cell phones to study contextual exposures and alcohol and marijuana use: a pilot study. J Adolesc Health 2015 Aug;57(2):245-247 [FREE Full text] [doi: 10.1016/j.jadohealth.2015.04.013] [Medline: 26206448]
19. Wray TB, Pérez AE, Celio MA, Carr DJ, Adia AC, Monti PM. Exploring the use of smartphone geofencing to study characteristics of alcohol drinking locations in high-risk gay and bisexual men. Alcohol Clin Exp Res 2019 May;43(5):900-906 [FREE Full text] [doi: 10.1111/acer.13991] [Medline: 30802318]
20. Harari GM, Müller SR, Aung MS, Rentfrow PJ. Smartphone sensing methods for studying behavior in everyday life. Curr Opin Behav Sci 2017 Dec;18:83-90 [FREE Full text] [doi: 10.1016/j.cobeha.2017.07.018]
21. Harari GM, Lane ND, Wang R, Crosier BS, Campbell AT, Gosling SD. Using smartphones to collect behavioral data in psychological science: opportunities, practical considerations, and challenges. Perspect Psychol Sci 2016 Nov;11(6):838-854 [FREE Full text] [doi: 10.1177/1745691616650285] [Medline: 27899727]
22. Deak G, Curran K, Condell J. A survey of active and passive indoor localisation systems. Comput Commun 2012 Sep;35(16):1939-1954. [doi: 10.1016/j.comcom.2012.06.004]

23. Eagle N, Pentland A. Reality mining: sensing complex social systems. Pers Ubiquit Comput 2005 Nov 3;10(4):255-268. [doi: 10.1007/s00779-005-0046-3]
24. Girolami M, Mavilia F, Delmastro F. Sensing social interactions through BLE beacons and commercial mobile devices. Pervasive Mob Comput 2020 Sep;67:101198 [FREE Full text] [doi: 10.1016/j.pmcj.2020.101198] [Medline: 32834802]
25. Madan A, Cebrian M, Lazer D, Pentland A. Social sensing for epidemiological behavior change. In: Proceedings of the 12th ACM international conference on Ubiquitous computing. 2010 Presented at: UbiComp '10; September 26-29, 2010; Copenhagen, Denmark p. 291-300 URL: https://dl.acm.org/doi/10.1145/1864349.1864394 [doi: 10.1145/1864349.1864394]
26. Moturu ST, Khayal I, Aharony N, Pan W, Pentland A. Using social sensing to understand the links between sleep, mood, and sociability. In: Proceedings of the IEEE 3rd International Conference on Privacy, Security, Risk and Trust and 2011 IEEE 3rd International Conference on Social Computing. 2011 Presented at: PASSAT '11; October 9-11, 2011; Boston, MA p. 208-214 URL: https://ieeexplore.ieee.org/document/6113116
27. Meegahapola L, Labhart F, Phan TT, Gatica-Perez D. Examining the social context of alcohol drinking in young adults with smartphone sensing. Proc ACM Interact Mob Wearable Ubiquitous Technol 2021 Sep 14;5(3):1-26. [doi: 10.1145/3478126]
28. Hatke GF, Montanari M, Appadwedula S, Wentz M, Meklenburg J, Ivers L. Using Bluetooth low energy (ble) signal strength estimation to facilitate contact tracing for COVID-19. arXiv Preprint posted online June 28, 2020 2020 [FREE Full text]
29. Maghdid HS, Ghafoor KZ. A smartphone enabled approach to manage COVID-19 lockdown and economic crisis. SN Comput Sci 2020 Aug 14;1(5):271 [FREE Full text] [doi: 10.1007/s42979-020-00290-0] [Medline: 33063052]
30. Shen M, Wei Y, Li T. Bluetooth-based COVID-19 proximity tracing proposals: an overview. arXiv. Preprint posted online August 28, 2020 2020 [FREE Full text]
31. Jackson KM, Meisel MK, Sokolovsky AW, Chen K, Barnett NP. Study protocol for establishing feasibility and acceptability of a bluetooth-based sensor to detect and understand social influence during drinking situations. JMIR Preprint posted online July 7, 2023 2023 [FREE Full text] [doi: 10.2196/preprints.50650]
32. Lau-Barraco C, Linden AN. Drinking buddies: who are they and when do they matter? Addict Res Theory 2014 Mar 14;22(1):57-67 [FREE Full text] [doi: 10.3109/16066359.2013.772585] [Medline: 25429255]
33. Meisel MK, Kenney SR, Barnett NP. Characteristics of prospectively identified negative alcohol-related events among college students. Addict Behav 2018 Mar;78:138-144 [FREE Full text] [doi: 10.1016/j.addbeh.2017.11.025] [Medline: 29172106]
34. DeMartini KS, Prince MA, Carey KB. Identification of trajectories of social network composition change and the relationship to alcohol consumption and norms. Drug Alcohol Depend 2013 Sep 01;132(1-2):309-315 [FREE Full text] [doi: 10.1016/j.drugalcdep.2013.02.020] [Medline: 23523132]
35. Barnett NP, Clark MA, Kenney SR, DiGuiseppi G, Meisel MK, Balestrieri S, et al. Enrollment and assessment of a first-year college class social network for a controlled trial of the indirect effect of a brief motivational intervention. Contemp Clin Trials 2019 Jan;76:16-23 [FREE Full text] [doi: 10.1016/j.cct.2018.10.015] [Medline: 30391343]
36. Longabaugh R, Wirtz PW, Zywiak WH, O'Malley SS. Network support as a prognostic indicator of drinking outcomes: the COMBINE Study. J Stud Alcohol Drugs 2010 Nov;71(6):837-846 [FREE Full text] [doi: 10.15288/jsad.2010.71.837] [Medline: 20946740]
37. Ecological momentary assessment made simple. PiLR Health. URL: https://pilrhealth.com/ [accessed 2024-03-16]
38. Jones A, Remmerswaal D, Verveer I, Robinson E, Franken IH, Wen CK, et al. Compliance with ecological momentary assessment protocols in substance users: a meta-analysis. Addiction 2019 Apr 21;114(4):609-619 [FREE Full text] [doi: 10.1111/add.14503] [Medline: 30461120]
39. Brooke J. Sus: A quick and dirty usability scale. In: Jordan PW, Thomas B, McClelland IL, Weerdmeester B, editors. Usability Evaluation In Industry. London, UK: Taylor & Francis; 1996.
40. Dudhane NA, Pitambare ST. Location Based and Contextual Services Using Bluetooth Beacons: New Way to Enhance Customer Experience. Lect Notes Inf Theory 2015;3(1):31-34 [FREE Full text] [doi: 10.18178/lnit.3.1.31-34]
41. Chai S, An R, Du Z. An indoor positioning algorithm using bluetooth low energy RSSI. In: Proceedings of the 2014 International Conference on Indoor Positioning and Indoor Navigation. 2014 Presented at: IPIN '16; October 27-30, 2014; Busan, South Korea p. 526-533 URL: https://ieeexplore.ieee.org/document/7275525 [doi: 10.2991/amsee-16.2016.72]
42. Wang Y, Yang X, Zhao Y, Liu Y, Cuthbert L. editors. Bluetooth positioning using RSSI and triangulation methods. In: proceedings of the 2013 IEEE 10th Consumer Communications and Networking Conference. 2013 Presented at: CCNC '13; January 11-14, 2013; Las Vegas, NV p. 837-842 URL: https://ieeexplore.ieee.org/abstract/document/6488558 [doi: 10.1109/ccnc.2013.6488558]
43. Beacon transmission power, range, and RSSI. kontakt.io. URL: https://support.kontakt.io/hc/en-gb/articles/4413258518930-Beacon-transmission-power-range-and-RSSI [accessed 2024-01-29]
44. Hedeker D. Generalized linear mixed models. In: Hedeker D, editor. Encyclopedia of Statistics in Behavioral Science. Hoboken, NJ: John Wiley & Sons; 2005.

45. Bendtsen M, McCambridge J, Åsberg K, Bendtsen P. Text messaging interventions for reducing alcohol consumption among risky drinkers: systematic review and meta-analysis. Addiction 2021 May 25;116(5):1021-1033 [FREE Full text] [doi: 10.1111/add.15294] [Medline: 33047865]
46. Berman AH, Gajecki M, Sinadinovic K, Andersson C. Mobile interventions targeting risky drinking among university students: a review. Curr Addict Rep 2016;3:166-174 [FREE Full text] [doi: 10.1007/s40429-016-0099-6] [Medline: 27226948]
47. Beckjord E, Shiffman S. Background for real-time monitoring and intervention related to alcohol use. Alcohol Res 2014;36(1):9-18 [FREE Full text] [Medline: 26258996]
48. Nahum-Shani I, Smith SN, Spring BJ, Collins LM, Witkiewitz K, Tewari A, et al. Just-in-Time Adaptive Interventions (JITAIs) in mobile health: key components and design principles for ongoing health behavior support. Ann Behav Med 2018 May 18;52(6):446-462 [FREE Full text] [doi: 10.1007/s12160-016-9830-8] [Medline: 27663578]
49. Heron KE, Smyth JM. Ecological momentary interventions: incorporating mobile technology into psychosocial and health behaviour treatments. Br J Health Psychol 2010 Feb;15(Pt 1):1-39 [FREE Full text] [doi: 10.1348/135910709X466063] [Medline: 19646331]
50. Spruijt-Metz D, Nilsen W. Dynamic models of behavior for just-in-time adaptive interventions. IEEE Pervasive Comput 2014 Jul;13(3):13-17. [doi: 10.1109/MPRV.2014.46]
51. Sokolovsky AW, Mermelstein RJ, Hedeker D. Factors predicting compliance to ecological momentary assessment among adolescent smokers. Nicotine Tob Res 2014 Mar;16(3):351-358 [FREE Full text] [doi: 10.1093/ntr/ntt154] [Medline: 24097816]
52. Kovalchik SA, Martino SC, Collins RL, Shadel WG, D'Amico EJ, Becker K. Scaled inverse probability weighting: a method to assess potential bias due to event nonreporting in ecological momentary assessment studies. J Educ Behav Stat 2017 Oct 26;43(3):354-381. [doi: 10.3102/1076998617738241]
53. Lau-Barraco C, Braitman AL, Leonard KE, Padilla M. Drinking buddies and their prospective influence on alcohol outcomes: alcohol expectancies as a mediator. Psychol Addict Behav 2012 Dec;26(4):747-758 [FREE Full text] [doi: 10.1037/a0028909] [Medline: 22732054]

Abbreviations

BLE: Bluetooth Low Energy
EMA: ecological momentary assessment
RA: research assistant
SNI: social network interview
SUS: System Usability Scale

Edited by A Mavragani; submitted 25.06.23; peer-reviewed by F Keusch, M Stach, S Wang; comments to author 02.10.23; revised version received 12.12.23; accepted 20.12.23; published 05.04.24.

Please cite as:
Barnett NP, Sokolovsky AW, Meisel MK, Forkus SR, Jackson KM
A Bluetooth-Based Smartphone App for Detecting Peer Proximity: Protocol for Evaluating Functionality and Validity
JMIR Res Protoc 2024;13:e50241
URL: https://www.researchprotocols.org/2024/1/e50241
doi:10.2196/50241
PMID:38578672

Protocol

A Community Needs Assessment and Implementation Planning for a Community Exercise Program for Survivors of Stroke: Protocol for a Pilot Hybrid Type I Clinical Effectiveness and Implementation Study

Elizabeth Wherley Regan[1], DPT, PhD; Pamela Toto[2], OTR, PhD; Jennifer Brach[3], PT, PhD

[1]Department of Exercise Science, Arnold School of Public Health, University of South Carolina, Columbia, SC, United States

[2]Department of Occupational Therapy, School of Health and Rehabilitation Sciences, University of Pittsburgh, Pittsburgh, PA, United States

[3]Department of Physical Therapy, School of Health and Rehabilitation Sciences, University of Pittsburgh, Pittsburgh, PA, United States

Corresponding Author:
Elizabeth Wherley Regan, DPT, PhD
Department of Exercise Science
Arnold School of Public Health
University of South Carolina
1300 Wheat Street Rm 101N
Columbia, SC, 29208
United States
Phone: 1 7046092409
Email: eregan@mailbox.sc.edu

Abstract

Background: Physical activity and exercise are important aspects of maintaining health. People with mobility impairments, including survivors of stroke, are less likely to exercise and at greater risk of developing or worsening chronic health conditions. Increasing accessible, desired options for exercise may address the gap in available physical activity programs, provide an opportunity for continued services after rehabilitation, and cultivate social connections for people after stroke and others with mobility impairments. Existing evidence-based community programs for people after stroke target cardiovascular endurance, mobility, walking ability, balance, and education. While much is known about the effectiveness of these programs, it is important to understand the local environment as implementation and sustainment strategies are context-specific.

Objective: This study protocol aims to evaluate community needs and resources for exercise for adults living with mobility impairments with initial emphasis on survivors of stroke in Richland County, South Carolina. Results will inform a hybrid type I effectiveness and implementation pilot of an evidence-based group exercise program for survivors of stroke.

Methods: The exploration and preparation phases of the EPIS (Exploration, Preparation, Implementation, and Sustainment) implementation model guide the study. A community needs assessment will evaluate the needs and desires of survivors of stroke through qualitative semistructured interviews with survivors of stroke, rehabilitation professionals, and fitness trainers serving people with mobility impairments. Additional data will be collected from survivors of stroke through a survey. Fitness center sites will be assessed through interviews and the Accessibility Instrument Measuring Fitness and Recreation Environments inventory. Qualitative data will be evaluated using content analysis and supported by mean survey results. Data will be categorized by the community (outer context), potential participants (outer context), and fitness center (inner context) and evaluate needs, resources, barriers, and facilitators. Results will inform evidence-based exercise program selection, adaptations, and specific local implementation strategies to influence success. Pilot outcome measures for participants (clinical effectiveness), process, and program delivery levels will be identified. An implementation logic model for interventions will be created to reflect the design elements for the pilot and their complex interactions.

Results: The study was reviewed by the institutional review board and exempt approved on December 19, 2023. The study data collection began in January 2024 and is projected to be completed in June 2024. A total of 17 participants have been interviewed as of manuscript submission. Results are expected to be published in early 2025.

Conclusions: Performing a needs assessment before implementing it in the community allows for early identification of complex relationships and preplanning to address problems that cannot be anticipated in controlled effectiveness research. Evaluation and

preparation prior to implementation of a community exercise program enhance the potential to be successful, valued, and sustained in the community.

International Registered Report Identifier (IRRID): DERR1-10.2196/55432

(JMIR Res Protoc 2024;13:e55432) doi:10.2196/55432

KEYWORDS

community participatory research; need assessment; exercise; survivors of stroke; community; community need; exercise program; stroke; physical activity; PA; mobility impairments; impairment; mobility; health decline; group activity; group exercise

Introduction

Physical activity (PA) and exercise are important aspects of maintaining health and reducing the development and severity of chronic conditions [1]. PA can lower the risk of mortality and reduce the incidence of hypertension, diabetes, heart disease, and some cancers [1]. Older adults have additional benefits of improved quality of life and lower risk of falls [1]. People living with disability are at a greater risk for chronic health conditions and are less likely to exercise than their age-matched peers [2,3]. People with disabilities have limited access to exercise in order to mitigate their health conditions and improve their aerobic capacity [2,4].

For survivors of stroke, reduced PA additionally increases their risk for a recurrent stroke [3]. Up to 80% of the risk of recurrent stroke can be mediated by lifestyle factors including medication management, diet, and exercise [3]. Individuals after stroke with mobility impairments have poor movement economy and higher cardiovascular demands that increases their need to build aerobic capacity over their peers [5]. However, even after receiving inpatient rehabilitation services, deficits remain. After completing inpatient rehabilitation, 80% of stroke survivors can ambulate indoors, but only 27% can perform the essential skills of community ambulation [6]. Despite the remaining deficits, many do not receive additional care in the community [7]. A lack of services after rehabilitation to promote independent community living results in unmet needs for continued physical recovery [4,6,8].

In addition to the physical benefits of PA, structured exercise programs can provide social connection [9,10]. People living with disability, including survivors of stroke, are socially isolated and desire a sense of belonging and social participation [7,10,11]. Increasing accessible, desired options for exercise may address the gap in available PA programs, provide an opportunity for continued services after rehabilitation, and cultivate social connections for people after stroke and others with mobility impairments. Group exercise programs that focus on functional fitness for clinical populations are a worldwide fitness trend and are a suggestion of focus for fitness professionals by the American College of Sports Medicine [12].

Existing evidence-based community programs for people after stroke include Fitness and Mobility Exercise [13], Together in Movement and Exercise [14], and Fit for Function [15]. These programs target fitness with a varied focus on cardiovascular endurance, mobility, walking ability, balance, and education [13-15]. While much is known about the effectiveness of these programs, it is important to understand the local environment as implementation and sustainment strategies are context-specific.

The aim of this study protocol is to evaluate community needs and resources for general and group exercise for adults living with mobility impairments with initial emphasis on survivors of stroke in Richland County, South Carolina. Results will inform an action plan for a hybrid type I implementation study testing the effectiveness and implementation process of a modified evidence-based exercise intervention [16]. Involving the community in the needs assessment and performing the needs assessment with a systematic approach facilitates the success and sustainability of the program [17,18].

Methods

Overview

This project will address the study objective using the EPIS (Exploration, Preparation, Implementation, and Sustainment) framework, concepts of community-based participatory research, and the implementation research logic model [17-19]. The exploration and preparation stages of EPIS seek to determine health needs, identify barriers and facilitators, select an evidence-based program, determine program modifications, and create implementation strategies [17]. These stages are the focus of this protocol. The EPIS implementation and sustainment stages test the evidence-based program and the ability of the program to be maintained in the community after the research process ends [17]. The EPIS framework considers participants inside and outside the organization (inner and outer context) that will offer the community program, the academic and community partners that bridge these contexts, and the characteristics of the program itself [17]. Each stage is dependent on and related to the others [17].

The EPIS exploration and preparation stages (Figures 1 and 2) will be completed as part of this study and include three steps: (1) performing a needs assessment; (2) identifying determinants, selecting an evidence-based exercise program to address, and creating implementation strategies; and (3) determining mechanisms of action for the implementation strategies and their corresponding outcome measures, and creating a logic model [17,19]. Results will inform the implementation protocol and program pilot-testing as a separate study (EPIS implementation and sustainment stages; Figure 1 [17,20]).

Figure 1. Applied EPIS (Exploration, Preparation, Implementation, and Sustainment) framework for implementation studies (adapted from Moullin et al [17], which is published under Creative Commons Attribution 4.0 International License [20]). The exploration and preparation stages will be completed as part of the current needs assessment for community group exercise for people after stroke. The exploration stage performs a needs assessment whose resulting determinants and strategies feed into the preparation stage that results in an implementation logic model and detailed protocol for the pilot study. The implementation and sustainment stages will be completed as a separate study and perform the pilot, evaluate the outcomes, and produce changes and further research for sustainment in the community.

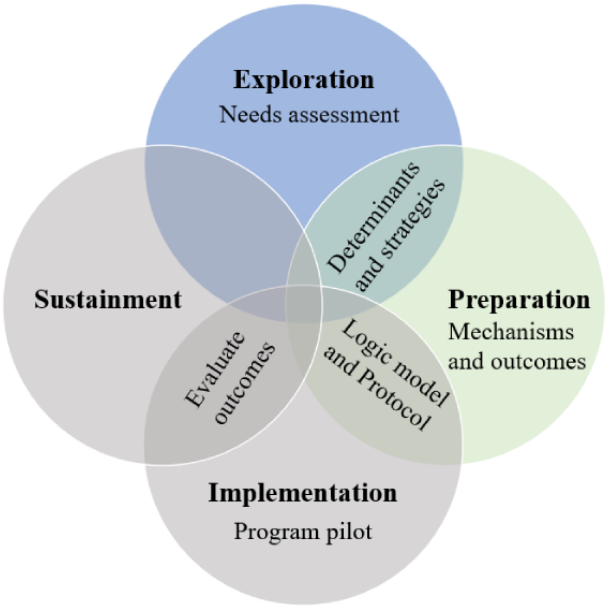
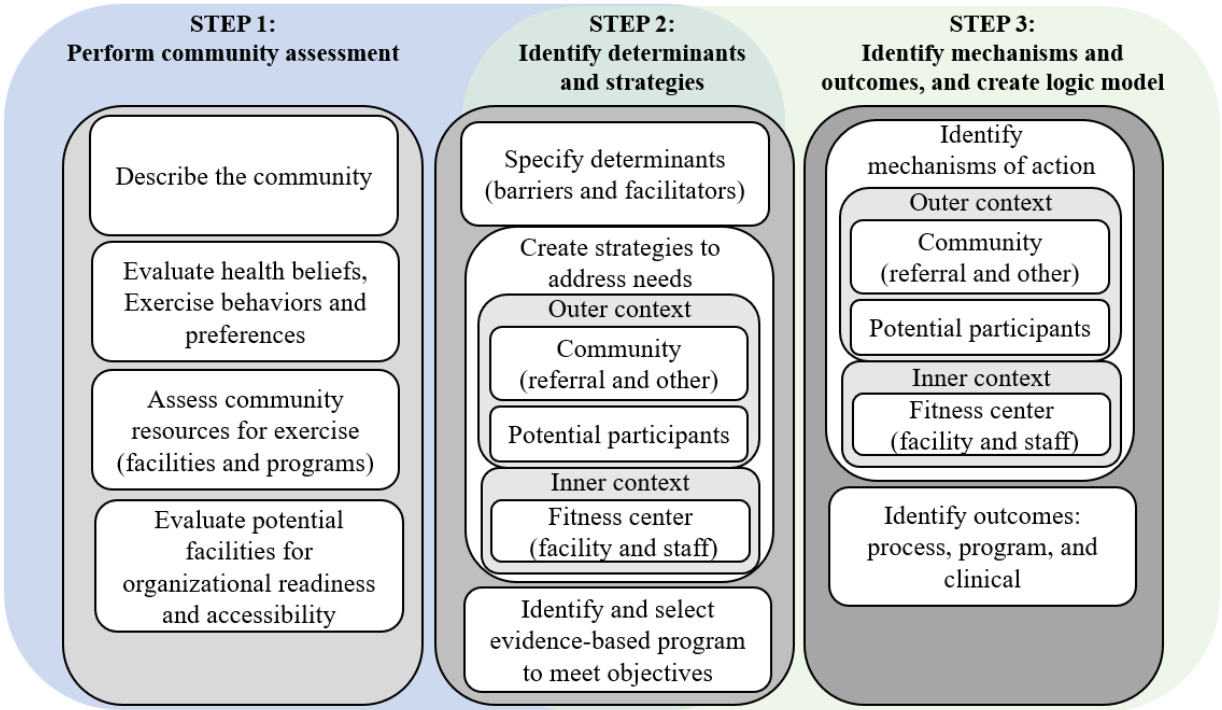


Figure 2. Steps to complete EPIS (Exploration, Preparation, Implementation, and Sustainment) framework: evaluation (blue-textured) and preparation stages (green-solid). This framework will be used as part of the needs assessment for a group exercise program for people after a stroke. Step 1 identifies the actions and data analysis of this study community needs assessment. Step 2 evaluates the results and selects the evidenced-based exercise program. Step 3 details the plans for pilot implementation including the mechanisms of action and the outcome measures.



Step 1: Perform Community Assessment

Describe the Community

A literature review will provide perspective on the communities of Richland and Lexington Counties in South Carolina. Several resources will help provide demographics including United States Census data, Center for Disease Control American Community Survey and Center for Health Statistics, the Behavioral Risk Factor Surveillance System, and County Health Rankings. Prisma Health, the largest nonprofit health system serving Richland County SC, completed a community needs assessment in 2022. This assessment will provide data to

describe the community health concerns and overall health priorities. General demographics, demographics of people living with disabilities, and demographics of survivors of stroke will be described.

Evaluate Health Beliefs, Exercise Behaviors, and Preferences

This step will use semistructured interviews with key stakeholders to assess the culture of the community around health beliefs and exercise behaviors and preferences both for people with mobility impairments and specifically for survivors of stroke. Individual or small group interviews will be conducted with targeted key organizational stakeholders which will include health care providers (physicians, rehabilitation providers, and cardiac rehabilitation providers), other nonprofit or public organizations serving people with disabilities (independent living support services, diabetes educators, vocational rehabilitation, and veterans' organizations) and fitness providers who currently serve people with mobility issues. After initial contact with stakeholders in each category, snowball sampling [21] will identify additional people or organizations to include.

Interview questions will relate to health needs, specific exercise needs, beliefs, contextual factors, exercise services, and gaps. Survivors of stroke will be interviewed in a focus group format at a community stroke survivor support group and additionally in small groups. Care partners will be invited to participate. Interview questions will be the same regardless of format or stakeholder (Textbox 1). Questions will be piloted in the first 2 interviews and revised as needed.

Sample goals are to collect data from a diverse set of viewpoints in order to adequately answer study aims [22]. A pragmatic approach targets 10-15 stakeholders and 10-15 survivors of stroke for the initial sample to achieve.

In addition to the questions in Textbox 1, the stroke survivors focus group will receive additional questions related to specific desires around group exercise (Textbox 2).

Once the focus groups and individual interviews are complete, a survey will be created based on the results. The survey will be distributed to a wider audience in the community and will evaluate desires for general and group exercises and the barriers and facilitators to participation. The survey will be distributed through stakeholder organizations and research contact lists for people with mobility impairments using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at the University of South Carolina.

Textbox 1. Semistructured interview questions for stakeholders to evaluate community health services and exercise beliefs and behaviors as part of the community needs assessment for a group exercise program for people after stroke. Health care providers, organizations serving people with disabilities, fitness professionals, survivors of stroke, and care partners will be interviewed in individual, small group, or focus group formats.

Questions:

1. What is important to this community from a health and quality of life perspective?
2. What are the beliefs about access and treatment for ongoing health care needs?
3. What existing organizations and services address health care and quality of life needs?
    - What are they doing well?
    - What are the gaps in services?
4. What are the beliefs about and interest in exercise for this community?
5. What are the barriers and facilitators to exercise?
6. What are existing community resources for people to exercise and to engage in other ways to improve health?
    - Who is using these resources? Describe the people who engage.
    - What are they doing well?
    - What are the gaps in services?
7. What are your thoughts on funding to support exercise programming on-going? (organizational stakeholders)?

Textbox 2. Semistructured interview questions to evaluate specific exercise interests and preferences for survivors of stroke only as part of the needs assessment for planning a community group exercise program for people after stroke. Interviews will occur in a focus group or small group format.

Semistructured interview questions on exercise interest and preferences (stroke survivors only):

1. What types of exercise activities would you be interested in (endurance, strength, balance/coordination, stretching, and relaxation) Examples given of each type of exercise.
2. In what formats (small group, larger group/Type of group based on mobility: seated vs standing, requiring assistance vs nonrequiring assistance, based on diagnosis or not based on diagnosis)
3. What type of facility (community fitness facility, private gym, community center, senior center, church center) and in what part of the county is desired?
4. How often and what time of day is preferred?
5. What do you think the benefits of an exercise program would be for you individually and others with stroke?
6. What do you think you will like about exercising in a group? What do you think you will dislike about group exercise?
7. What are factors currently and potentially impacting access and engagement in exercise?
    - Are you currently exercising, and if so, what are you doing, and if not, why not?
    - What do you like about exercise or movement?
    - What is your confidence in your ability to exercise independently? With instruction? With assistance?
        - If low confidence, what do you think would increase confidence?
    - How would you be able to get to a group exercise program (transportation)?
    - How much would you be willing to pay for an exercise program?

Assess Community Resources for Exercise

Using results from the community assessment and internet searches, the facilities and program resources available for group and individual exercise for people with mobility impairments in Richland County will be identified. Information gathered will include whether the facility or organization self-identifies as accessible and the goals and mission of the organization.

Evaluate Potential Facilities for Accessibility and Organizational Readiness

A subset of the listing of community resources will be evaluated in more detail to assess accessibility and general organizational readiness for new or modified exercise programs for people with mobility impairments (Textbox 3). Facility management, staff, and fitness providers will be interviewed to determine readiness for change. Interview questions were developed based on the components of the theory of organizational readiness for change [23]. The evaluation will include an accessibility evaluation using the Accessibility Instrument Measuring Fitness and Recreation Environments (AIMFREE) inventory [24].

Textbox 3. Potential location for pilot group exercise program for people after stroke facility evaluation will include facility stakeholder (exercise instructors and management) semistructured interviews in individual or small group format and a comprehensive accessibility inventory.

Methods: (1) Stakeholder interview and (2) Accessibility Instrument Measuring Fitness and Recreation Environments (AIMFREE) accessibility inventory (Rimmer et al [24])

Facility stakeholder interview questions:

1. Describe the interest and priority in the organization to serve those with mobility impairments.
2. What is your openness to adding additional or modified programs for people with mobility impairments?
3. Describe your perception of your organization's ability to support an exercise program for people with mobility impairments both initially and ongoing.
4. What are the resources available to support new programming?
    - Describe your staff who could potentially support these new programs.
    - Would new staff need to be hired?
    - What are your anticipated barriers or facilitators?
    - What types of equipment and space would be available? At what time of day?

AIMFREE accessibility inventory:

The inventory includes both physical space accessibility and behavior and policy evaluations. The AIMFREE inventory can be obtained from the National Center on Health, Physical Activity and Disability (NCHPAD), nchpad.org. The following sections will be completed with the assistance of facility staff and a consultant with mobility impairments. Section E, which evaluates hot tubs, whirlpools, and saunas will be omitted.

- SECTION A: Access Routes and Entrance
- SECTION B: Equipment
- SECTION C: Information
- SECTION D: Locker Rooms and Showers
- SECTION F: Elevators
- SECTION G: Bathrooms
- SECTION H: Professional Behavior
- SECTION I: Professional Support and Training
- SECTION J: Policies
- SECTION K: Programs

Step 1: Data Analysis

Outer Context Description

A narrative summary of the neighborhood characteristics and priorities in the community based on the formal community statistics and health priorities review will be created to provide descriptive background for the remaining data. Community participants will be described with demographic descriptive statistics for each group (referral sources, health care providers, fitness providers, community organizations, and potential participants).

Inner Context Description

General descriptions of fitness facilities including location, program availability, inclusion as part of the mission, and goals of the organizations in Richland County will be summarized. For the subset of facilities that receive detailed reviews, a summary of each facility will be provided. The summary will include the AIMFREE findings.

Qualitative Thematic Analysis and Survey Analysis

Focus group and interview data will be analyzed using deductive-dominant qualitative content analysis using NVivo software (version 12; Luminvero Inc) [25-27]. Captured data will be open-coded and categorized for thematic analysis in the following levels: community (outer context), individual (outer context), and fitness center (inner context). At each level, needs/desires, resources, barriers, and facilitators will be defined by the responses to the categories in Table 1 by 2 researchers and combined by group review and discussion to resolve discrepancies. Any themes newly arising from the data outside of these categories will be included. Survey results will also be mapped to the same categories from Table 1 and combined in an evaluation matrix with the themes from the content analysis.

Table 1. Categories of determinants and implementation strategies for results in the outer context and the inner context of the needs assessment for group exercise for people after stroke. Determinants categories will serve as the organizational structure for qualitative thematic data analysis and implementation strategies categories will serve as the planning structure for the implementation protocol.

Categories and levels	Determinants categories	Implementation strategies categories
Outer context		
Community	• Health care and other potential referral resources and the facilitators and barriers to referral • Other assistance needed from health care or community organizations to support potential new programs.	• Identify referral sources • Create strategies to address barriers to referral • Build strategies to address needs for health care or other community supports vital to the success of the program including champions
Potential participant	• General health and quality of life priorities, services, and organizations to meet related needs and gaps in services. • General exercise resources, use, beliefs, and priorities • General exercise desires and needs • Barriers and facilitators to exercise	• Strategies to address barriers and promote uptake and retention of potential participants
Inner context		
Intervention characteristics	• Group exercise desired format, types of exercise, and frequency	• Identify and select evidence-based exercise program
Organizational (fitness facility)	• Available facilities and programs already meeting the identified individual needs and desires • Accessibility of targeted facilities/organization (physical, behavioral, policy) including gaps and potential future needs • Organizational readiness for change	• Select an organization to pilot the program • Identify organizational strategies for staff, training, equipment, accessibility upgrades, and other needs • Identify an organizational champion

Step 2: Identify Determinants and Implementation Strategies

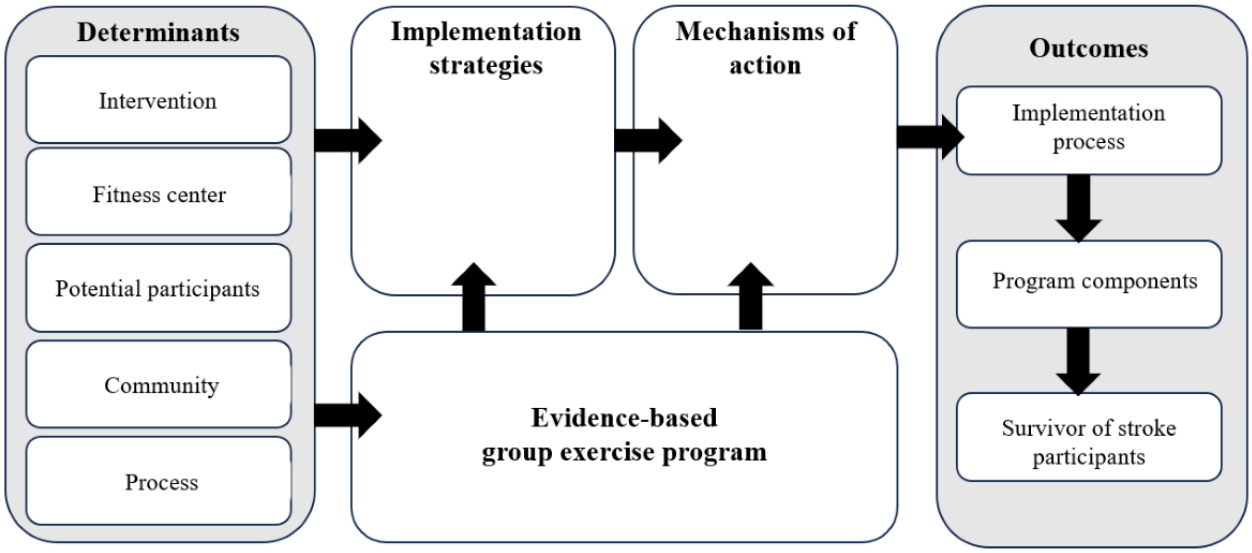
Following the EPIS framework, the preparation stage begins with specifying the determinants based on results in step 1. Determinants include contextual factors for the outer context (potential participants and community) and inner context (fitness facility), process components, and intervention components [19]. From the determinants, an evidenced-based exercise program will be selected, and implementation strategies for exercise programming and related services created (Figure 2 and Table 1) [19]. Implementation strategies are approaches to address the necessary modifications of the exercise program, the training and resources needed for the inner context, and any other required innovations to adapt to the local community.

All results of the qualitative content analysis, triangulation with survey data, and the determinants will be verified through member checking with updates made as necessary.

Step 3: Identify Mechanisms, Outcomes, and Create Logic Model

Identifying the mechanisms of action, selecting outcomes, and creating the logic model addresses the preparation step of the EPIS framework. Mechanisms of action are the implementation strategy processes to affect the outcomes [28]. Examples include education, skill building, efficacy, and motivation [28]. Finally, outcome measures for the participants (clinical effectiveness), implementation process (fidelity), and program components (service) will be identified. A logic model will be created based on the results of steps 2 and 3 to organize the determinants, implementation strategies, exercise programs, mechanisms of action, and outcomes. A logic model demonstrates the study design elements for the hybrid type I model and their complex interactions [19]. The standard logic model format by Smith et al [19] is presented in Figure 3 [19,20].

Figure 3. The implementation research logic model standard form with intervention (adapted from Smith et al [19], which is published under Creative Commons Attribution 4.0 International License [20]). The logic model will serve as a roadmap for the implementation protocol for the evidence-based group exercise program for people after a stroke. Determinants include contextual factors, process components, and intervention components. Implementation strategies are actions to address the unique determinants through mechanisms of action (ie, education and skill building) to ensure success. Outcomes are process, program, and participant-driven.



Ethical Considerations

The study has been reviewed by the University of South Carolina Institutional Review Board and classified as exempt human participant research. Letters of information are provided to participants outlining the study. Data will be collected and stored in REDCap cloud storage or other password-protected cloud storage at the University of South Carolina. Transcripts will be deidentified prior to data analysis. Participants will be compensated with a US $25 gift card upon completion of interviews.

Results

As of March 2024, the project is in process. The literature review has been completed. A total of 4 fitness professionals, 4 physical therapists, 1 physiatrist, 2 directors at Able South Carolina (a nonprofit community organization), 7 survivors of stroke, and 1 care partner have been interviewed. Two potential exercise facilities have been identified.

Discussion

Protocol Goals and Anticipated Outcomes

This protocol will evaluate the desires and needs of the local community for an evidence-based group exercise program for people after stroke and the planning required to implement the program. The use of community-based participatory research at the early stage of implementation planning will enhance the fit and success of the future community program [18]. Involving the community in the planning stages builds trust and identifies shared values toward a common goal [18]. The selection of the evidence-based program will be based on identified needs and desires [17]. The needs assessment will also provide a rationale for required modifications to the standard program [17]. If no evidence-based program meets the majority of the needs of the community, a unique program drawing on available evidence-based resources will be developed.

Performing a needs assessment before implementing it in the community allows for early identification of the complex relationships between the inner and outer contexts of a community program [17,19]. A result is an ability to preplan implementation strategies to address problems that cannot be anticipated in controlled effectiveness research. Capacity building, education and training, and recruitment and retention strategies will be identified and built into the action plan [17,19].

Study Strengths and Limitations

Using the EPIS framework, implementation mapping processes and the implementation logic model are strengths of this protocol [17,19,29]. The use of EPIS and related practical application tools creates a systematic approach to a complex task [17,19,29].

Potential study limitations include difficulty finding willing participants, reduced completion of surveys, and difficulty matching an evidence-based program to the needs of the community. These potential pitfalls are mediated by the ability to leverage existing academic-community relationships, multiple sources of data collection, and the existence of multiple potential evidence-based programs to choose from. Existing evidence-based community programs for people after stroke or for older individuals may be adapted through this process to meet the community's needs and desires.

Conclusions

Performing thorough evaluation and preparation prior to the implementation of a community exercise program will enhance its ability to be successful, valued, and sustained in the community. A robust process that includes community partners, applied theory, and implementation process tools enhance the protocol.

Acknowledgments

This research was supported by the Foundation of Physical Therapy Research's Center of Excellence in Physical Therapy Health Services and Health Policy Research and Training Grant.

Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study

Conflicts of Interest

None declared.

References

1. Piercy KL, Troiano RP, Ballard RM, Carlson SA, Fulton JE, Galuska DA, et al. The physical activity guidelines for Americans. JAMA 2018;320(19):2020-2028 [FREE Full text] [doi: 10.1001/jama.2018.14854] [Medline: 30418471]
2. Martin Ginis KA, van der Scheer JW, Latimer-Cheung AE, Barrow A, Bourne C, Carruthers P, et al. Evidence-based scientific exercise guidelines for adults with spinal cord injury: an update and a new guideline. Spinal Cord 2018;56(4):308-321 [FREE Full text] [doi: 10.1038/s41393-017-0017-3] [Medline: 29070812]
3. Kleindorfer DO, Towfighi A, Chaturvedi S, Cockroft KM, Gutierrez J, Lombardi-Hill D, et al. 2021 guideline for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline from the American Heart Association/American Stroke Association. Stroke 2021;52(7):e364-e467 [FREE Full text] [doi: 10.1161/STR.0000000000000375] [Medline: 34024117]
4. Rimmer J, Lai B. Framing new pathways in transformative exercise for individuals with existing and newly acquired disability. Disabil Rehabil 2017;39(2):173-180 [FREE Full text] [doi: 10.3109/09638288.2015.1047967] [Medline: 26161458]
5. Blokland IJ, Schiphorst LFA, Stroek JR, Groot FP, van Bennekom CAM, van Dieen JH, et al. Relative aerobic load of daily activities after stroke. Phys Ther 2023;103(3):pzad005 [FREE Full text] [doi: 10.1093/ptj/pzad005] [Medline: 37172129]
6. Blennerhassett JM, Levy CE, Mackintosh A, Yong A, McGinley JL. One-quarter of people leave inpatient stroke rehabilitation with physical capacity for community ambulation. J Stroke Cerebrovasc Dis 2018;27(12):3404-3410. [doi: 10.1016/j.jstrokecerebrovasdis.2018.08.004] [Medline: 30185399]
7. Bird ML, Mortenson BW, Chu F, Acerra N, Bagnall E, Wright A, et al. Building a bridge to the community: an integrated knowledge translation approach to improving participation in community-based exercise for people after stroke. Phys Ther 2019;99(3):286-296 [FREE Full text] [doi: 10.1093/ptj/pzy146] [Medline: 30698783]
8. Cho SJ, Kim SR, Cho KH, Shin NM, Oh WO. Effect of a hospital-to-home transitional intervention based on an interaction model of client health behavior for adult patients with stroke. J Community Health Nurs 2023;40(4):273-288. [doi: 10.1080/07370016.2023.2227154] [Medline: 37431105]
9. Morris JH, Oliver T, Kroll T, Joice S, Williams B. Physical activity participation in community dwelling stroke survivors: synergy and dissonance between motivation and capability. a qualitative study. Physiotherapy 2017;103(3):311-321. [doi: 10.1016/j.physio.2016.05.001] [Medline: 27613082]
10. Obembe AO, Eng JJ. Rehabilitation interventions for improving social participation after stroke: a systematic review and meta-analysis. Neurorehabil Neural Repair 2016;30(4):384-392 [FREE Full text] [doi: 10.1177/1545968315597072] [Medline: 26223681]
11. Emerson E, Fortune N, Llewellyn G, Stancliffe R. Loneliness, social support, social isolation and wellbeing among working age adults with and without disability: cross-sectional study. Disabil Health J 2021;14(1):100965 [FREE Full text] [doi: 10.1016/j.dhjo.2020.100965] [Medline: 32843311]
12. Newsome AM, Reed R, Sansone J, Batrakoulis A, McAvoy C, Parrott MW. 2024 ACSM worldwide fitness trends: future directions of the health and fitness industry. ACSM's Health Fit J 2024;28(1):14-26 [FREE Full text] [doi: 10.1249/fit.0000000000000933]
13. Eng JJ. Fitness and mobility exercise (FAME) program for stroke. Top Geriatr Rehabil 2010;26(4):310-323 [FREE Full text] [doi: 10.1097/TGR.0b013e3181fee736] [Medline: 22287825]
14. Merali S, Cameron JI, Barclay R, Salbach NM. Characterising community exercise programmes delivered by fitness instructors for people with neurological conditions: a scoping review. Health Soc Care Community 2016;24(6):e101-e116 [FREE Full text] [doi: 10.1111/hsc.12282] [Medline: 26445890]
15. Richardson J, Tang A, Guyatt G, Thabane L, Xie F, Sahlas D, et al. FIT for FUNCTION: study protocol for a randomized controlled trial. Trials 2018;19:1-15 [FREE Full text]
16. Landes SJ, McBain SA, Curran GM. Reprint of: an introduction to effectiveness-implementation hybrid designs. Psychiatry Res 2020;283:112630 [FREE Full text] [doi: 10.1016/j.psychres.2019.112630] [Medline: 31722790]

17. Moullin JC, Dickson KS, Stadnick NA, Rabin B, Aarons GA. Systematic review of the exploration, preparation, implementation, sustainment (EPIS) framework. Implement Sci 2019;14(1):1 [FREE Full text] [doi: 10.1186/s13012-018-0842-6] [Medline: 30611302]
18. Duran B, Oetzel J, Magarati M, Parker M, Zhou C, Roubideaux Y, et al. Toward health equity: a national study of promising practices in community-based participatory research. Prog Community Health Partnersh 2019;13(4):337-352 [FREE Full text] [doi: 10.1353/cpr.2019.0067] [Medline: 31866589]
19. Smith JD, Li DH, Rafferty MR. The implementation research logic model: a method for planning, executing, reporting, and synthesizing implementation projects. Implement Sci 2020;15(1):84 [FREE Full text] [doi: 10.1186/s13012-020-01041-8] [Medline: 32988389]
20. Attribution 4.0 International (CC BY 4.0). Creative Commons. URL: http://www.w3.org/1999/xlink [accessed 2024-04-09]
21. Etikan I, Alkassim R, Abubakar S. Comparision of snowball sampling and sequential sampling technique. Biom Biostat Int J 2016;3(1):6-7 [FREE Full text] [doi: 10.15406/bbij.2016.03.00055]
22. Levitt HM, Motulsky SL, Wertz FJ, Morrow SL, Ponterotto JG. Recommendations for designing and reviewing qualitative research in psychology: promoting methodological integrity. Qual Psychol 2017;4(1):2-22. [doi: 10.1037/qup0000082]
23. Weiner BJ. A theory of organizational readiness for change. Implement Sci 2009;4(1):67 [FREE Full text] [doi: 10.1186/1748-5908-4-67] [Medline: 19840381]
24. Rimmer JH, Riley B, Wang E, Rauworth A. Development and validation of AIMFREE: accessibility instruments measuring fitness and recreation environments. Disabil Rehabil 2004;26(18):1087-1095. [doi: 10.1080/09638280410001711432] [Medline: 15371034]
25. Elo S, Kyngäs H. The qualitative content analysis process. J Adv Nurs 2008;62(1):107-115. [doi: 10.1111/j.1365-2648.2007.04569.x] [Medline: 18352969]
26. Armat MR, Assarroudi A, Rad M, Sharifi H, Heydari A. Inductive and deductive: ambiguous labels in qualitative content analysis. Qual Rep 2018;23(1):219-221. [doi: 10.46743/2160-3715/2018.2872]
27. Hsieh HF, Shannon SE. Three approaches to qualitative content analysis. Qual Health Res 2005;15(9):1277-1288. [doi: 10.1177/1049732305276687] [Medline: 16204405]
28. Lewis CC, Klasnja P, Powell BJ, Lyon AR, Tuzzio L, Jones S, et al. From classification to causality: advancing understanding of mechanisms of change in implementation science. Front Public Health 2018;6:136 [FREE Full text] [doi: 10.3389/fpubh.2018.00136] [Medline: 29868544]
29. Fernandez ME, Ten Hoor GA, van Lieshout S, Rodriguez SA, Beidas RS, Parcel G, et al. Implementation mapping: using intervention mapping to develop implementation strategies. Front Public Health 2019;7:158 [FREE Full text] [doi: 10.3389/fpubh.2019.00158] [Medline: 31275915]

Abbreviations

AIMFREE: Accessibility Instrument Measuring Fitness and Recreation Environments
EPIS: Exploration, Preparation, Implementation and Sustainment
PA: physical activity
REDCap: Research Electronic Data Capture

Edited by A Mavragani; submitted 12.12.23; peer-reviewed by ML Bird, A Batrakoulis, S Li; comments to author 22.02.24; revised version received 07.03.24; accepted 11.03.24; published 11.04.24.

Please cite as:
Regan EW, Toto P, Brach J
A Community Needs Assessment and Implementation Planning for a Community Exercise Program for Survivors of Stroke: Protocol for a Pilot Hybrid Type I Clinical Effectiveness and Implementation Study
JMIR Res Protoc 2024;13:e55432
URL: https://www.researchprotocols.org/2024/1/e55432
doi:10.2196/55432
PMID:38603776

Protocol

Health Needs Assessment in Home-Living Older Adults: Protocol for a Pre-Post Study

Fifi Kvalsvik[1], PhD; Bente Hamre Larsen[1], MSc; Grethe Eilertsen[2,3], Prof Dr; Helle K Falkenberg[2,4], Prof Dr; Ingvild Dalen[5,6], PhD; Stine Haaland[7], BS; Marianne Storm[1,8,9], Prof Dr

[1]Department of Public Health, Faculty of Health Sciences, University of Stavanger, Stavanger, Norway

[2]Research Group of Older Peoples' Health, University of South-Eastern Norway, Drammen, Norway

[3]Department of Nursing and Health Sciences, University of South-Eastern Norway, Drammen, Norway

[4]National Centre for Optics, Vision and Eye Care, Department of Optometry, Radiography and Lighting Design, Faculty of Health and Social Sciences, University of South-Eastern Norway, Kongsberg, Norway

[5]Section of Biostatistics, Research Department, Stavanger University Hospital, Stavanger, Norway

[6]Department of Quality and Health Technology, Faculty of Health Sciences, University of Stavanger, Stavanger, Norway

[7]Department of Health and Welfare services, Stavanger kommune, Stavanger, Norway

[8]Faculty of Health Sciences and Social Care, Molde University College, Molde, Norway

[9]Research Group of Nursing and Health Sciences, Research Department, Stavanger University Hospital, Stavanger, Norway

Corresponding Author:
Fifi Kvalsvik, PhD
Department of Public Health
Faculty of Health Sciences
University of Stavanger
P.O. Box 8600 Forus
Stavanger, 4036
Norway
Phone: 47 46649888
Email: fifi.kvalsvik@uis.no

Abstract

Background: Conducting a health needs assessment for older adults is important, particularly for early detection and management of frailty. Such assessments can help to improve health outcomes, maintain overall well-being, and support older adults in retaining their independence as they age at home.

Objective: In this study, a systematic approach to health needs assessment is adopted in order to reflect real-world practices in municipal health care and capture the nuances of frailty. The aim is to assess changes in frailty levels in home-living older adults over 5 months and to examine the observable functional changes from a prestudy baseline (t1) to a poststudy period (t2). Additionally, the study explores the feasibility of conducting the health needs assessment from the perspective of home-living older adults and their informal caregivers.

Methods: Interprofessional teams of registered nurses, physiotherapists, and occupational therapists will conduct 2 health needs assessments covering physical, cognitive, psychological, social, and behavioral domains. The study includes 40 home-living older adults of 75 years of age or older, who have applied for municipal health and care services in Norway. A quantitative approach will be applied to assess changes in frailty levels in home-living older adults over 5 months. In addition, we will examine the observable functional changes from t1 to t2 and how these changes correlate to frailty levels. Following this, a qualitative approach will be used to examine the perspectives of participants and their informal caregivers regarding the health needs assessment and its feasibility. The final sample size for the qualitative phase will be determined based on the participant's willingness to be interviewed. The quantitative data consist of descriptive statistics, simple tests, and present plots and correlation coefficients. For the qualitative analysis, we will apply thematic analysis.

Results: The initial baseline assessments were completed in July 2023, and the second health needs assessments are ongoing. We expect the results to be available for analysis in the spring of 2024.

Conclusions: This study has potential benefits for not only older adults and their informal caregivers but also health care professionals. Moreover, it can be used to inform future studies focused on health needs assessments of this specific demographic

group. The study also provides meaningful insights for local policy makers, with potential future implications at the national level.

Trial Registration: ClinicalTrials.gov NCT05837728; https://clinicaltrials.gov/study/NCT05837728

International Registered Report Identifier (IRRID): DERR1-10.2196/55192

(JMIR Res Protoc 2024;13:e55192) doi:10.2196/55192

KEYWORDS

assessment; frailty; healthy aging; health care; home-living older adults; pre-post study; protocol

Introduction

Across the globe, the population is aging rapidly. There are around 1.4 billion people aged 60 years and older in the world today, and this figure will double by 2050 [1]. Norway is no exception to this demographic transition. It is anticipated that the number of people aged 65 years and older will exceed the population aged 0-19 years by 2030 [2]. As is widely known, the older segment of the population tends to have a higher prevalence of chronic diseases and disabilities [3,4]. This implies that the demographic shift could come at a great cost to older adults themselves and society [3,5]. Direct challenges at the societal level may include a strain on public finances and the welfare system, increased demand for health services, and rising health care costs [6,7].

One way to mitigate the impacts of an aging population is to support aging in place [8,9]. The term “aging in place” refers to meeting an older adult’s needs and supporting them to live independently or with some assistance in their own home for as long as possible [8]. Most older adults prefer to live at home because it enables them to maintain their independence, autonomy, and identity, as well as their connection to social support [10]. In addition to being the preferred choice for many older adults, aging in place is viewed as a cost-effective strategy for addressing the aging population’s needs, as it can reduce the expenses associated with institutional care [11]. Given these positive effects, encouraging older adults to continue living at home could be an essential part of the solution to meeting the challenges of population aging.

Many older adults are able to live independently without much support; others, however, may have age-related issues that prevent them from aging in place [12]. These age-related issues often lead to frailty, resulting in increased functional limitations, increased risk of falls, disability, institutionalization, hospitalization, and mortality [13,14]. As frailty progresses, efforts to mitigate, manage, or reverse this decline become increasingly difficult to implement [15]. Hence, there is a broad consensus on the importance of assessing frailty [14,16,17], particularly in relation to older adults aged 70 years and older [16,18]. In general, early assessment of frailty can prevent, reduce onset, or slow its progression in older adults [19], contributing to better quality of life and healthy aging [18,20].

There is currently no consensus on the definition of frailty [17,21]. At its simplest, frailty is a condition that indicates increased vulnerability to negative health outcomes [22]. Despite varying definitions, there is general consensus that frailty is multidimensional and involves complex interactions between physical, psychological, social, cognitive, and behavioral factors [17,19]. The diversity of definitions and the wide range of contributing factors also explain why there is a variety of measures of frailty [16,17].

Incorporating frailty into health needs assessments is, therefore, crucial, as this can help identify specific areas of need, set clear goals to meet those needs, and ultimately contribute to the health promotion of this population [23]. The term “health needs assessment” refers to a systematic method of identifying unmet health and care needs of a population, leading to agreed priorities and resource allocation that will improve health outcomes [24].

While our knowledge of frailty has improved [14], our understanding of the factors that contribute to frailty is still incomplete, and the understanding of how these factors relate to frailty is still limited [19]. These knowledge gaps are a clear indication that considerable efforts are still needed in this area.

Given the complexity of frailty as a construct and its enormous impact on the lives of older adults, adopting a collaborative approach is deemed essential to improving our understanding and achieving meaningful progress. This is further supported by research that highlights the benefits of fostering collaboration between health care professionals, individual service users, families, researchers, and other stakeholders to improve health service outcomes [25-27].

Such collaboration enables all relevant aspects of older adults’ health to be assessed, and essential information can be collected to develop effective, locally applicable, and relevant solutions [28]. With this in mind, we have established partnerships with health care professionals and other stakeholders in a Norwegian municipality, actively involving them in the planning and implementation phase of the project.

Interprofessional teams consisting of registered nurses, physiotherapists, and occupational therapists will be involved in this study. They will perform 2 health needs assessments of home-living older adults, initially at baseline and then after a period of 5 months. These assessments cover several factors, including physical (mobility and sensory), cognitive, psychological (depression), social (loneliness), and behavioral (alcohol consumption). The objectives of our study are 3-fold: first, to assess changes in frailty levels in home-living older adults over 5 months; second, to explore the observable functional changes from a prestudy baseline (t1) to a poststudy period (t2) and how these changes correlate to frailty levels; and finally, to gain deeper insight into the perspectives of older adults and their informal caregivers to enhance the feasibility

of implementing this type of health needs assessment within municipal health and care services.

The research questions that guide the study are (1) What observable changes, if any, can be identified in the frailty levels of home-living older adults over a period of 5 months? (2) Are there identifiable changes in functions that can be observed from t1 to t2, and how these changes relate to frailty levels? and (3) What are the perceptions of home-living older adults regarding the feasibility of the health needs assessment, with regard to its content, delivery, and procedures?

Methods

Study Design

This pre-post study, registered on ClinicalTrials.gov (NCT05837728), is based on a case-only design to conduct health needs assessments, initially at the baseline and then after 5 months. The study is conducted as part of the research project "More good days at home: Advancing health-promoting practices in municipal health care services for older recipients of home care," funded by the Norwegian Research Council (320622).

To gain in-depth insights, we use a 2-step research process. In the first step, a quantitative approach will be applied to examine changes in frailty levels in home-living older adults over 5 months. In addition, we will examine observable functional changes from t1 to t2 and how these changes correlate to frailty levels.

Following this, a qualitative approach will be used to investigate the perspectives of participants and their informal caregivers concerning the health needs assessment and its acceptability.

Setting

This study is placed in the context of the Norwegian health care system, known for its universal health care. This system ensures everyone has equal access to health care regardless of socioeconomic status or geographical location [29]. The system is based on a clearly defined division of responsibilities between the local municipalities and the central government.

The local municipalities are tasked with organizing primary, preventive, and nursing care services [29] and are committed to providing the necessary health services, such as home and personal care, free of charge to all home-living older adults [30]. These services are universally available and tailored to the specific needs of each older adult. To access these services, older adults are required to submit an application to the district office in their municipality [31]. Once the application is submitted, it will be reviewed by health care professionals in the health and welfare services office. After this phase, the health care professionals will reach out to the older adults to proceed further.

While municipalities manage the above care services, central government oversees specialist care, which includes hospital services. This clear division ensures comprehensive health care for all citizens [29]. This study takes place in a municipality in Western Norway with a population of approximately 146,011. In this population, 9874 individuals are older adults aged 75 years or older [32].

Study Sample

Inclusion Criteria

To be eligible for the study, the older adults must be aged 75 years or older and have applied for municipal health and care services. These services may include medical emergency alarms, senior activity centers, home-based nursing services, and practical assistance with daily chores. In addition, older adults who received follow-up care after a hospital stay, were discharged from rehabilitation, or received emergency medical care are also eligible.

Exclusion Criteria

This study does not include home-living older adults who are younger than 75 years of age, have a cognitive impairment, or are undergoing palliative care. In this study, cognitive impairment refers to the inability to understand the study and provide informed consent to participate.

Recruitment

Participant recruitment was conducted in collaboration with 3 health and welfare service departments in a municipality in the western region of Norway between February 1 and June 26, 2023. Health care professionals purposively selected participants according to the eligibility criteria. During their initial phone contact with potential participants, health care professionals used their professional judgment to assess the individual's ability to understand the research project and provide informed consent to participate.

Subsequently, health care professionals asked a designated research team member, a nurse with experience in mental health, to obtain informed consent from those who meet the initial criteria. To ensure consistency in the process, the same nurse visited all potential participants for the consent process. Potential participants were then given time to consider this information before giving their written consent.

The design of our health needs assessment package includes a cognitive assessment. This approach ensures that participants identified with cognitive impairment in the first assessment are not included in the second assessment.

We aim to enroll 40 participants in the quantitative phase of this study, in line with the agreement made with the municipality at the beginning of the project, taking into account their resource limitations. In the next phase, which uses a qualitative approach, we plan to invite all 40 participants for an interview, with the actual number of interviews conducted depending on the participants' consent to participate. To capture diverse perspectives, we will strive to include a group of home-living older adults who differ in terms of age, gender, marital status, living situations, and health care needs.

The aforementioned sample size takes into account the limited resources available for the project, including budget constraints, personnel resources, and time limitations, while ensuring the collection of meaningful data to address the research questions.

Data Collection

To respond to the diverse needs of older adults, we have interprofessional teams consisting of registered nurses, physiotherapists, or occupational therapists to carry out the health needs assessments. The assessment is conducted twice at the participant's home. To facilitate successful implementation, we provided simulation-based training and debriefings. We have also produced webinars available in Norwegian to enhance learning. The link to the webinars can be provided upon request. Our study is ongoing, so we will publish it upon completion.

The interprofessional teams will use an iPad (Apple Inc) to administer assessments covering the various factors—physical (mobility and sensory), cognitive, psychological (depression), social (loneliness), and behavioral (alcohol consumption). The collected data will be registered electronically and directly submitted to Services for Sensitive Data (*Tjenester for Sensitive Data* [TSD]) for secure storage and processing.

After the initial assessment, interprofessional teams will collaboratively review the results to determine whether, and to what extent, the older adult is eligible for assistance and to determine what type of support is available and appropriate for the individual [33]. Examples of such support include practical help with everyday tasks, provision of medical emergency alarms, access to walking aids, recommendations for physiotherapy sessions, referrals to hearing or vision centers, encouragement to participate in senior activity centers, and facilitating contact with primary care physicians.

After 5 months, the same interprofessional teams will conduct the second health needs assessment to determine whether the support provided at the first assessment is suitable for helping participants maintain their quality of life.

With regard to the qualitative approach, we will use 2 data collection methods in order to minimize mono-method bias [34]—in-depth individual interviews and dyadic interviews. We will use a general interview guide approach to collecting data from all the participants, which will give us the flexibility to modify or adapt questions based on responses to previous questions [35]. To maintain consistency, the topics and questions in the 2 interview methods will be identical and guided by the Theoretical Framework of Acceptability (TFA) proposed by Sekhon et al [36]. The questions will include, for example, (1) how the participant thinks and feels about the assessment, (2) what the participant thinks about the effort required to participate in this type of assessment, (3) the participant's understanding of the assessment process, (4) what benefits or value they believe the assessment will have for them, and (5) whether they feel the assessment was conducted respectfully or not. Finally, the interviews will be audio recorded and transcribed verbatim to ensure accuracy in the data analysis.

Measure Descriptions

The selection of measures was informed by a comprehensive review of existing literature, consultation with experts, and input from stakeholders involved in the project. Many of the measures have been validated in different contexts, including the Norwegian context. The study also includes novel scales that will be tested for validity within this particular sample of home-living older adults. The measures in the study are described below, and an overview is given in Table 1.

Table 1. Overview of the measures used in the study.

Variables	Questionnaires and tests used in assessments
Demographics	
Gender	Male, female, or other?
Age	How old are you (years)?
Household	Do you live alone or with others?
Children	Do you have any children?
Residential suitability	Is your residence suitable for your needs?
Transportation	Do you use private or public transport?
Physical function	
Mobility: lower extremity function	To assess the lower extremity function, we will use the SPPB[a], a well-established instrument commonly used in home-living older adults [37-40]. The Norwegian version of SPPB, translated by Bergh et al [41], has been tested for reliability, and the result shows that it has high reliability when used by trained physiotherapists on older populations [42]. Other reasons for using SPPB are that it is fast, safe, and easy to administer; requires little training; and uses simple equipment [43]. The test assesses standing balance, walking, and rising from a chair. The result from the test is quantified by scores. In addition, the test is claimed to be highly sensitive to changes over time [37,44].
Sensory: hearing	To detect hearing impairment, we will use the KAS[b]-Screen interview guide [45]. The questions used in our study stem from the hearing and verbal communication or social life subscales. Previous evaluation and validation found this test to be an adequate tool for detecting hearing impairment in older adults and provides important information on how this impairment can affect the daily life of older adults [45,46].
Sensory: vision	To detect vision impairment, we will use a structured vision assessment tool called KROSS[c] developed by the University of South-Eastern Norway in collaboration with the Vestre Viken Hospital Trust and stroke survivor organizations. The KROSS tool includes assessments of visual acuity, visual field, eye alignment and movements, and visual in attention [47,48].
Cognitive function	
Cognitive function	To identify possible cognitive impairment, the Mini-Cog test will be used. This takes approximately 3 minutes to administer and consists of 2 cognitive tasks: 3-item word recall and a clock drawing test [49]. Mini-Cog was preferred to other cognitive screening tools because it is simple and concise, requires no special equipment, is easily incorporated into general practice and different senior settings, and has high sensitivity and specificity [49,50]. Additionally, it has been suggested that Mini-Cog performs well as a screening test among older adults in communities [51]. The Norwegian version of Mini-Cog was translated by Rostoft et al [52].
Psychological function	
Depression	To assess depression in old age, we will use the 4-item GDS[d]. Although other versions of GDS can be used to identify common symptoms of depression in older individuals, the 4-item GDS is reported to be most suitable for detecting depression in older adults who live at home [53,54]. Overall, the 4-item GDS has been shown to be a valid and reliable tool for evaluating depression in older adults, with a sensitivity of 100% and 62% specificity [54]. Another benefit of using this scale is that it is a relatively short scale, which reduces the burden on the respondent and the time it takes for health professionals to administer the test [54].
Social function	
Loneliness	The validated UCLA[e] 3-Item Loneliness Scale will be used to assess loneliness. This scale is designed to measure loneliness based on individual perceptions of how often a person feels (1) a lack of companionship, (2) left out, and (3) isolated from others [55]. In terms of reliability, this scale has been found to have good internal consistency, and test-retest reliability has shown that the scale produces consistent results over time [56,57]. In terms of validity, it was demonstrated that this scale correlates well with other measures of loneliness and discriminates well between loneliness and other constructs [55]. Additionally, this measure is chosen because it is quick to administer, has been used in large surveys, has been tested in older populations, and measures overall loneliness quite well [55,58]. The Norwegian version of this scale was translated by Arumugam et al [59].
Behavioral function	
Alcohol consumption	For a brief assessment of alcohol consumption, we will use the AUDIT[f] developed by the World Health Organization [60]. Our study will use AUDIT-4, which consists of 3 questions from AUDIT-C and the 10th item of the original scale [61]. In terms of reliability and validity, previous research with different samples has shown that AUDIT-4 has good internal consistency, criterion validity, and convergent validity [62,63].

Variables	Questionnaires and tests used in assessments
Assessment of frailty	To assess frailty, we will use the CFS[g]. The CFS, a tool based on clinical judgment, assesses key areas such as multimorbidity, cognition, and other functional areas [64]. CFS has been shown to be a strong predictor of several outcomes, including falls, length of hospitalization, multimorbidity, and mortality [65]. The CFS was translated into Norwegian by Rostoft et al [66] and has been used to assess frailty in various settings in Norway, including emergencies and intensive care [67,68]. Its simplicity and predictive power in assessing physical health and potential outcomes for frail older adults [17,69] make it an appropriate choice for use in municipal health care settings.

[a]SPPB: Short Physical Performance Battery.

[b]KAS: *Kombinert Alvorlig Sansesvikt* (Combined Serious Sensory Impairment).

[c]KROSS: *Kompetanse om Rehabilitering Om Syn og Slag* (Competence, Rehabilitation of Sight after Stroke).

[d]GDS: Geriatric Depression Scale.

[e]UCLA: University of California, Los Angeles.

[f]AUDIT: Alcohol Use Disorders Identification Test.

[g]CFS: Clinical Frailty Scale.

Outcome Measures

This study has two primary outcome measures: (1) identifying changes in frailty levels of home-living older adults over a period of 5 months and (2) assessing any observed changes in functions from t1 to t2 and how these changes relate to the level of frailty.

In addition to the primary outcome measures, this study will also evaluate the feasibility of the health needs assessment. Emphasis will be placed on the acceptability of the assessment among older adults and their informal caregivers, as well as the practicality of implementation in relation to time and resource constraints.

Data Analysis

Quantitative Analyses

The statistical package SPSS (version 29; IBM Corp) will be used for all statistical analyses. Descriptive statistics will be used to provide an overview of the demographic variables. Given the exploratory nature of this study and the limited sample size, our analysis involves looking at the data from multiple perspectives. The aim is to uncover patterns and relationships that could inform the development of hypotheses for future studies.

To answer the research questions, we will first calculate descriptive statistics for changes in frailty levels between 2 time points, using mean and SD or median and IQR for a skewed distribution. This will be followed by paired comparisons using either 2-tailed *t* test or the Wilcoxon test. We will also examine the association between the changes in frailty and baseline levels by plotting and estimating correlation coefficients (Pearson and Spearman). We will further assess changes in functional variables and the bivariate associations between these changes and the change in frailty.

Qualitative Analyses

The interview transcripts will be read thoroughly and reread to ensure familiarity with the content. NVivo (version 12; Lumivero) software will be used to help organize and code the data. The data analysis will be carried out using a thematic analytical approach based on the guidelines of Braun and Clarke [70].

Patient and Public Involvement

In this study, older adult participants were not involved in developing the study design or objectives. The study design and objectives were developed by the researchers of this study in collaboration with the local municipality stakeholders. The Service User Association for Older Adults in Norway (*Pensjonistforbundet*) contributed insights to the grant application, which was successfully funded by the Research Council of Norway. Furthermore, details about the study design and recruitment procedures were provided to health care professionals prior to data collection.

Ethical Considerations

Ethics approval was obtained from the Regional Committees for Medicine and Health Research Ethics (REK) of West Norway on November 15, 2022 (523455). The project was subsequently approved by the Norwegian Agency for Shared Services in Education and Research (SIKT) on January 19, 2023 (100847), which ensures that adequate safeguards are in place to protect the privacy of participants and to maintain the confidentiality of data. This study will be conducted in accordance with the Declaration of Helsinki guidelines [71] from REK and the Data Protection Impact Assessment (DPIA). It will also be conducted under the principle of informed consent. Prior to data collection, all the participants who agreed to participate in the study will sign a consent form, which includes a description of the study, its objectives, and participants' involvement and rights. Participation in the study is entirely voluntary and participants can withdraw at any time. Additionally, participants are entitled to access the information documented about them and to make necessary corrections to any errors discovered.

Data Management

Overview

The project manager will supervise the day-to-day operation of the project and be responsible for ensuring that DPIA guidelines are followed.

Data Collected From the Frailty Assessment

The collected data will be registered electronically and directly submitted to TSD for secure storage and processing. The code list that links personal identification information to the

individual participant will be secured by the project manager to ensure there is no unauthorized access to the information. Only the selected project team members will have access to the anonymized data sets. No other party will have access to the research data prior to dissemination. Furthermore, other paper-based research data will be anonymized and kept in locked cabinets or archives that are only accessible to project team members.

Data Collected From the Interview

Only a designated member of the research project and the project manager will have access to the audio files stored at Nettskjema. The interview will be transcribed into written text and all personal identifiers will be removed to ensure anonymity. The transcription will be shared with other project team members as appropriate. This data will be retained until December 31, 2026, and then deleted from TSD.

Results

The initial baseline assessments were completed in July 2023, and the second health needs assessments are ongoing. We expect the results to be available for analysis in the spring of 2024.

Discussion

Principal Considerations

Studies have documented that frail older adults have an elevated risk of negative health outcomes [13,14]. Early assessment of frailty in older adults is, therefore, crucial, and is recommended. Despite its recognized importance, assessing frailty is not considered a standard clinical practice in many health care systems [18], including in Norway [72]. This situation is understandable as such an assessment often requires significant resources, which many health care facilities lack [73].

Our study is carefully designed to reflect real-world applications and settings, with a particular focus on municipal health care in Norway, where health care professionals tend to have heavy workloads. These conditions pose a challenge to incorporating additional tasks, such as a frailty assessment, into routine health needs assessments. As mentioned earlier, older adults typically turn to their local municipality for home care services and health care professionals make home visits to assess their care needs. This assessment process uses the standardized tool (The Norwegian Information System for the Nursing and Care Sector [*Individbasert pleie- og omsorgsstatistikk*; IPLOS]), which was developed to optimize care needs assessments in Norway [33]. Despite being a standardized tool, IPLOS has been criticized for being too subjective, as assessments appear to vary widely among health care professionals [74].

In response to these challenges, we aim to refine the health needs assessment process to improve objectivity and consistency, and to highlight the critical needs to incorporate frailty assessments into routine municipal care practices. The path begins with selecting appropriate measurement tools that are meaningful and practical, and training interprofessional teams to implement them. Part of this training process includes the task of conducting assessments and discussing the results to make informed decisions.

Beyond integrating assessments, our study aims to shed light on the dynamic nature of frailty and provide a deeper understanding of the factors that impact its progression. This insight could potentially help older adults and their informal caregivers to manage frailty. Additionally, it can better prepare health care professionals to develop and implement strategies aimed at delaying and mitigating the progression of frailty.

Strengths and Limitations

This study has several strengths. First, it deepens our understanding of frailty as a complex condition and highlights how levels of frailty and related functional changes can differ. Moreover, because the study is designed to reflect the real-world settings and applications, it can help improve health care practices in the municipal sector. The involvement of local stakeholders in the municipality from the planning to the implementation phase ensures that the study remains relevant and applicable, thereby facilitating the translation of knowledge into practice. Additionally, the inclusion of home-living older adults' and their informal caregivers' perspectives can help facilitate improvement in the feasibility of the assessment.

As with other studies, this study has its limitations, particularly with regard to the relatively small sample size and the absence of a control group. This could lead to misinterpretation of the observed changes, either in the support or services for participants, other confounding factors, or due to a habituation effect over the 5-month period. Consequently, this limitation may also potentially impact the internal validity of the study, as well as the construct validity of the study [75]. To address this challenge, we will carefully compare our findings with those of previous studies investigating similar approaches to aiding the interpretation of outcomes.

Despite its inherent limitations, this study will serve as an important first step in developing a more systematic health needs assessment for home-living older adults and the development of health promotion strategies that can improve these older adults' quality of life.

Nonetheless, the results should be interpreted with caution due to the absence of a control group, the limited sample size, and the potential underrepresentation of all home-living older adults. These limitations suggest that the results indicate possible correlations and patterns, rather than confirming a definite relationship or establishing specific cause-and-effect relationships.

Acknowledgments

The authors would like to express their sincere gratitude to the municipality health care professionals who participated and contributed to the design of this study. We would also like to acknowledge other local municipality stakeholders who supported us in planning the recruitment process and implementing the research project.

Data Availability

The data sets generated and analyzed during this study are not publicly available due to ethical considerations inherent in this research but are available from the corresponding author on reasonable request.

Authors' Contributions

All authors made a substantial contribution to this work. FK contributed to the study design and protocol, drafting, writing original draft, and revising and refining the paper. BHL contributed to the study design and data collection tools and feedback and comments on the study protocol. GE contributed to the study design and data collection tools and feedback and comments on the study protocol. HKF contributed to the study design and data collection tools and feedback and comments on the study protocol. ID contributed to the data analysis and statistics and feedback and comments on the study protocol. SH contributed to the study design and collaboration between health care professionals and researchers. MS contributed to the study design, development of data collection tools, prepared all essential documentation for ethical approval, and participated in writing, commenting, and refining the paper. All authors read and approved the final version of the paper.

Conflicts of Interest

None declared.

References

1. Ageing and health. World Health Organization. 2022. URL: https://www.who.int/news-room/fact-sheets/detail/ageing-and-health [accessed 2023-01-31]
2. Gleditsch RL. A historic shift: soon more elderly than children and adolescents. Statistics Norway. 2023. URL: https://www.ssb.no/befolkning/artikler-og-publikasjoner/et-historisk-skifte-flere-eldre-enn [accessed 2023-01-31]
3. Christensen K, Doblhammer G, Rau R, Vaupel JW. Ageing populations: the challenges ahead. Lancet 2009;374(9696):1196-1208 [FREE Full text] [doi: 10.1016/S0140-6736(09)61460-4] [Medline: 19801098]
4. Atella V, Mortari AP, Kopinska J, Belotti F, Lapi F, Cricelli C, et al. Trends in age-related disease burden and healthcare utilization. Aging Cell 2019;18(1):e12861 [FREE Full text] [doi: 10.1111/acel.12861] [Medline: 30488641]
5. Fontana L, Kennedy BK, Longo VD, Seals D, Melov S. Medical research: treat ageing. Nature 2014;511(7510):405-407 [FREE Full text] [doi: 10.1038/511405a] [Medline: 25056047]
6. Sambamoorthi U, Tan X, Deb A. Multiple chronic conditions and healthcare costs among adults. Expert Rev Pharmacoecon Outcomes Res 2015;15(5):823-832 [FREE Full text] [doi: 10.1586/14737167.2015.1091730] [Medline: 26400220]
7. Demographic ageing. European Commission. 2023. URL: https://commission.europa.eu/business-economy-euro/growth-and-investment/structural-reforms/ageing-and-welfare-state-policies_en [accessed 2023-02-01]
8. Horner B, Boldy DP. The benefit and burden of "ageing-in-place" in an aged care community. Aust Health Rev 2008;32(2):356-365 [FREE Full text] [doi: 10.1071/ah080356] [Medline: 18447827]
9. Sixsmith A, Sixsmith J. Ageing in place in the United Kingdom. Ageing Int 2008;32(3):219-235. [doi: 10.1007/s12126-008-9019-y]
10. Wiles JL, Leibing A, Guberman N, Reeve J, Allen RES. The meaning of "aging in place" to older people. Gerontologist 2012;52(3):357-366 [FREE Full text] [doi: 10.1093/geront/gnr098] [Medline: 21983126]
11. Marek KD, Stetzer F, Adams SJ, Popejoy LL, Rantz M. Aging in place versus nursing home care: comparison of costs to Medicare and Medicaid. Res Gerontol Nurs 2012;5(2):123-129. [doi: 10.3928/19404921-20110802-01] [Medline: 21846081]
12. Martin D, Long O, Kessler L. Planning for aging in place: incorporating the voice of elders to promote quality of life. J Hous Elderly 2019;33(4):382-392. [doi: 10.1080/02763893.2019.1593280]
13. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56(3):M146-M156 [FREE Full text] [doi: 10.1093/gerona/56.3.m146] [Medline: 11253156]
14. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet 2013;381(9868):752-762 [FREE Full text] [doi: 10.1016/S0140-6736(12)62167-9] [Medline: 23395245]
15. Puts MTE, Toubasi S, Atkinson E, Ayala AP, Andrew M, Ashe MC, et al. Interventions to prevent or reduce the level of frailty in community-dwelling older adults: a protocol for a scoping review of the literature and international policies. BMJ Open 2016;6(3):e010959 [FREE Full text] [doi: 10.1136/bmjopen-2015-010959] [Medline: 26936911]
16. Morley JE, Vellas B, van Kan GA, Anker SD, Bauer JM, Bernabei R, et al. Frailty consensus: a call to action. J Am Med Dir Assoc 2013;14(6):392-397 [FREE Full text] [doi: 10.1016/j.jamda.2013.03.022] [Medline: 23764209]

17. Dent E, Kowal P, Hoogendijk EO. Frailty measurement in research and clinical practice: a review. Eur J Intern Med 2016;31:3-10 [FREE Full text] [doi: 10.1016/j.ejim.2016.03.007] [Medline: 27039014]
18. Sinha S, McKee A, Dunning J, Wong I, Nicin M, Muscedere J. We can't address what we don't measure consistently: building consensus on frailty in Canada. National Institute on Ageing. 2018. URL: https://www.cfn-nce.ca/wp-content/uploads/2018/10/cfn-nia-frailty-paper-2018-09-24.pdf [accessed 2024-03-23]
19. Levers MJ, Estabrooks CA, Kerr JCR. Factors contributing to frailty: literature review. J Adv Nurs 2006;56(3):282-291. [doi: 10.1111/j.1365-2648.2006.04021.x] [Medline: 17042807]
20. World Report on Aging and Health. Geneva: World Health Organization; 2015.
21. Rockwood K, Fox RA, Stolee P, Robertson D, Beattie BL. Frailty in elderly people: an evolving concept. CMAJ 1994;150(4):489-495 [FREE Full text] [Medline: 8313261]
22. Frieswijk N, Buunk BP, Steverink N, Slaets JPJ. The effect of social comparison information on the life satisfaction of frail older persons. Psychol Aging 2004;19(1):183-190. [doi: 10.1037/0882-7974.19.1.183] [Medline: 15065941]
23. Integrated care for older people (ICOPE): guidance for person-centred assessment and pathways in primary care. World Health Organization. 2017. URL: https://www.who.int/publications/i/item/WHO-FWC-ALC-19.1 [accessed 2024-03-23]
24. Wright J, Williams R, Wilkinson JR. Development and importance of health needs assessment. BMJ 1998;316(7140):1310-1313 [FREE Full text] [doi: 10.1136/bmj.316.7140.1310] [Medline: 9554906]
25. Wegener C, Storm M, Willumsen E. The nursing home as a hub: boundary work as a key to community health promotion. Health Promot Int 2023;38(2):daad020. [doi: 10.1093/heapro/daad020] [Medline: 36951408]
26. Batalden M, Batalden P, Margolis P, Seid M, Armstrong G, Opipari-Arrigan L, et al. Coproduction of healthcare service. BMJ Qual Saf 2016;25(7):509-517 [FREE Full text] [doi: 10.1136/bmjqs-2015-004315] [Medline: 26376674]
27. Eines TF, Storm M, Grønvik CKU. Interprofessional collaboration in a community virtual ward: a focus group study. Scand J Caring Sci 2023;37(3):677-686 [FREE Full text] [doi: 10.1111/scs.13152] [Medline: 36710599]
28. South J, Bagnall AM, Stansfield JA, Southby KJ, Mehta P. An evidence-based framework on community-centred approaches for health: England, UK. Health Promot Int 2019;34(2):356-366 [FREE Full text] [doi: 10.1093/heapro/dax083] [Medline: 29206912]
29. Tikkanen R, Osborn R, Mossialos E, Djordjevic A, Wharton G. International profiles of health care systems. The Commonwealth Fund. 2020. URL: https://www.commonwealthfund.org/sites/default/files/2020-12/International_Profiles_of_Health_Care_Systems_Dec2020.pdf [accessed 2024-03-23]
30. Hoen BT, Abrahamsen DR, Berntsen Ø. Target groups and organisation of the home care service. Statistics Norway. 2023 Jan 17. URL: https://www.ssb.no/en/helse/helsetjenester/artikler/target-groups-and-organisation-of-the-home-care-service [accessed 2024-03-23]
31. omsorgsdepartementet H-o. Lov om kommunale helse- og omsorgstjenester m.m. (helse- og omsorgstjenesteloven). LOVDATA. Norway: Helse- og omsorgsdepartementet; 2011. URL: https://lovdata.no/dokument/NL/lov/2011-06-24-30 [accessed 2024-03-27]
32. Population, by gender, age, statistical variable, year, and region. Statistics Norway. URL: https://www.ssb.no/en/befolkning/folketall/statistikk/befolkning [accessed 2023-06-17]
33. Edvardsen U. Assessment instrument and the allocation of care services in Norway. In: Midford P, Campbell JC, Saito Y, editors. Eldercare Policies in Japan and Scandinavia: Aging Societies East and West. New York, NY: Palgrave Macmillan; 2016:177-195.
34. Podsakoff PM, MacKenzie SB, Lee JY, Podsakoff NP. Common method biases in behavioral research: a critical review of the literature and recommended remedies. J Appl Psychol 2003;88(5):879-903. [doi: 10.1037/0021-9010.88.5.879] [Medline: 14516251]
35. Turner DW. Qualitative interview design: a practical guide for Novice investigators. Qual Rep 2014;15(3):754-760 [FREE Full text] [doi: 10.46743/2160-3715/2010.1178]
36. Sekhon M, Cartwright M, Francis JJ. Acceptability of healthcare interventions: an overview of reviews and development of a theoretical framework. BMC Health Serv Res 2017;17(1):88 [FREE Full text] [doi: 10.1186/s12913-017-2031-8] [Medline: 28126032]
37. Guralnik JM, Ferrucci L, Pieper CF, Leveille SG, Markides KS, Ostir GV, et al. Lower extremity function and subsequent disability: consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery. J Gerontol A Biol Sci Med Sci 2000;55(4):M221-M231 [FREE Full text] [doi: 10.1093/gerona/55.4.m221] [Medline: 10811152]
38. Freiberger E, de Vreede P, Schoene D, Rydwik E, Mueller V, Frändin K, et al. Performance-based physical function in older community-dwelling persons: a systematic review of instruments. Age Ageing 2012;41(6):712-721 [FREE Full text] [doi: 10.1093/ageing/afs099] [Medline: 22885845]
39. Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB. Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. N Engl J Med 1995;332(9):556-561 [FREE Full text] [doi: 10.1056/NEJM199503023320902] [Medline: 7838189]

40. Freire AN, Guerra RO, Alvarado B, Guralnik JM, Zunzunegui MV. Validity and reliability of the short physical performance battery in two diverse older adult populations in Quebec and Brazil. J Aging Health 2012;24(5):863-878. [doi: 10.1177/0898264312438551] [Medline: 22422762]
41. Bergh S, Lyshol H, Selbæk G, Strand BH, Taraldsen K, Thingstad P. Short Physical Performance Battery (SPPB). Legeforeningen.no. 2023. URL: https://www.legeforeningen.no/contentassets/870420284b7d4cb98100191ff93e7983/sppb.pdf [accessed 2023-03-10]
42. Olsen CF, Bergland A. "Reliability of the Norwegian version of the short physical performance battery in older people with and without dementia". BMC Geriatr 2017;17(1):124 [FREE Full text] [doi: 10.1186/s12877-017-0514-4] [Medline: 28599623]
43. Bergland A, Strand BH. Norwegian reference values for the Short Physical Performance Battery (SPPB): the Tromsø study. BMC Geriatr 2019;19(1):216 [FREE Full text] [doi: 10.1186/s12877-019-1234-8] [Medline: 31395008]
44. Ostir GV, Volpato S, Fried LP, Chaves P, Guralnik JM, Women's Health and Aging Study. Reliability and sensitivity to change assessed for a summary measure of lower body function: results from the Women's Health and Aging Study. J Clin Epidemiol 2002;55(9):916-921. [doi: 10.1016/s0895-4356(02)00436-5] [Medline: 12393080]
45. Lyng K, Svingen EM. Kartlegging av alvorlig, kombinert sansetap hos eldre: Evaluering av en sjekklistebasert screeningsmetodikk. Norway: Oslo Metropolitan University—OsloMet; 2001.
46. Haanes GG. Hearing, vision, and lighting conditions among older recipients of home care. University of Oslo. 2016. URL: https://www.duo.uio.no/bitstream/handle/10852/52521/1/PhD-Haanes-DUO.pdf [accessed 2024-03-23]
47. Falkenberg LI, Ormstad HK, Eilertsen G, Langeggen I. Improving outcome in stroke survivors with visual problems: knowledge translation in a multidisciplinary stroke unit intervention study. 2016 Nov Presented at: American Academy of Optometry; November 2016; Anaheim, California, USA URL: https://app.cristin.no/results/show.jsf?id=1994875
48. Mathisen TS, Eilertsen G, Ormstad H, Falkenberg HK. Barriers and facilitators to the implementation of a structured visual assessment after stroke in municipal health care services. BMC Health Serv Res 2021;21(1):497 [FREE Full text] [doi: 10.1186/s12913-021-06467-4] [Medline: 34030691]
49. Borson S, Scanlan J, Brush M, Vitaliano P, Dokmak A. The mini-cog: a cognitive 'vital signs' measure for dementia screening in multi-lingual elderly. Int J Geriatr Psychiatry 2000;15(11):1021-1027. [doi: 10.1002/1099-1166(200011)15:11<1021::aid-gps234>3.0.co;2-6] [Medline: 11113982]
50. Carnero-Pardo C, Cruz-Orduña I, Espejo-Martínez B, Martos-Aparicio C, López-Alcalde S, Olazarán J. Utility of the mini-cog for detection of cognitive impairment in primary care: data from two Spanish studies. Int J Alzheimers Dis 2013;2013:285462 [FREE Full text] [doi: 10.1155/2013/285462] [Medline: 24069544]
51. Yang L, Yan J, Jin X, Jin Y, Yu W, Xu S, et al. Screening for dementia in older adults: comparison of mini-mental state examination, mini-cog, clock drawing test and AD8. PLoS One 2016;11(12):e0168949 [FREE Full text] [doi: 10.1371/journal.pone.0168949] [Medline: 28006822]
52. Rostoft S, Engedal K, Rønning B, Stensrud M, Ommundsen N, Juell S. Mini-cog—instruksjoner for administrering and skåring. legeforeningen.no. 2023. URL: https://www.legeforeningen.no/contentassets/478e85c05e654494896c9d78110ae963/mini-cog_norwegian.pdf [accessed 2023-03-13]
53. Montorio I, Izal M. The geriatric depression scale: a review of its development and utility. Int Psychogeriatr 1996;8(1):103-112. [doi: 10.1017/s1041610296002505] [Medline: 8805091]
54. Li Z, Jeon YH, Low LF, Chenoweth L, O'Connor DW, Beattie E, et al. Validity of the geriatric depression scale and the collateral source version of the geriatric depression scale in nursing homes. Int Psychogeriatr 2015;27(9):1495-1504. [doi: 10.1017/S1041610215000721] [Medline: 25990603]
55. Hughes ME, Waite LJ, Hawkley LC, Cacioppo JT. A short scale for measuring loneliness in large surveys: results from two population-based studies. Res Aging 2004;26(6):655-672 [FREE Full text] [doi: 10.1177/0164027504268574] [Medline: 18504506]
56. Trucharte A, Calderón L, Cerezo E, Contreras A, Peinado V, Valiente C. Three-item loneliness scale: psychometric properties and normative data of the Spanish version. Curr Psychol 2023;42(9):7466-7474 [FREE Full text] [doi: 10.1007/s12144-021-02110-x] [Medline: 34305365]
57. Arimoto A, Tadaka E. Reliability and validity of Japanese versions of the UCLA loneliness scale version 3 for use among mothers with infants and toddlers: a cross-sectional study. BMC Womens Health 2019;19(1):105 [FREE Full text] [doi: 10.1186/s12905-019-0792-4] [Medline: 31349835]
58. Liu T, Lu S, Leung DKY, Sze LCY, Kwok WW, Tang JYM, et al. Adapting the UCLA 3-item loneliness scale for community-based depressive symptoms screening interview among older Chinese: a cross-sectional study. BMJ Open 2020;10(12):e041921 [FREE Full text] [doi: 10.1136/bmjopen-2020-041921] [Medline: 33303463]
59. Arumugam A, Dugstad S, Sandvik M, Overland S, Winje M. UCLA Loneliness Scale, version 3. [UCLA Ensomhetsskala, Versjon 3]. Helsedirektoratet.no. 2023. URL: https://tinyurl.com/2muhtmrt [accessed 2023-03-11]
60. Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG. The Alcohol Use Disorders Identification Test. Geneva: World Health Organization; 2001.

61. Gual A, Segura L, Contel M, Heather N, Colom J. AUDIT-3 and AUDIT-4: effectiveness of two short forms of the alcohol use disorders identification test. Alcohol Alcohol 2002;37(6):591-596 [FREE Full text] [doi: 10.1093/alcalc/37.6.591] [Medline: 12414553]
62. Hilde P, Ingeborg R, Anne B. Are short AUDIT screeners effective in identifying unhealthy drinking of varying severity? a prison population study. Drug Alcohol Depend 2021;229(Pt B):109153. [doi: 10.1016/j.drugalcdep.2021.109153] [Medline: 34800804]
63. Meneses-Gaya C, Zuardi AW, Loureiro SR, Hallak JEC, Trzesniak C, de Azevedo Marques JM, et al. Is the full version of the AUDIT really necessary? study of the validity and internal construct of its abbreviated versions. Alcohol Clin Exp Res 2010;34(8):1417-1424. [doi: 10.1111/j.1530-0277.2010.01225.x] [Medline: 20491736]
64. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173(5):489-495 [FREE Full text] [doi: 10.1503/cmaj.050051] [Medline: 16129869]
65. Church S, Rogers E, Rockwood K, Theou O. A scoping review of the clinical frailty scale. BMC Geriatr 2020;20(1):393 [FREE Full text] [doi: 10.1186/s12877-020-01801-7] [Medline: 33028215]
66. Rostoft S, Engstad TT, Sjøbø B, Flaatten H. Clinical frailty scale—Norwegian. legeforeningen.no. 2023. URL: https://www.legeforeningen.no/contentassets/21ef25cf569d44749573de21a8d6b043/cfs_norsk_horisontal_2021.pdf [accessed 2023-03-10]
67. Engvig A, Wyller TB, Skovlund E, Ahmed MV, Hall TS, Rockwood K, et al. Association between clinical frailty, illness severity and post-discharge survival: a prospective cohort study of older medical inpatients in Norway. Eur Geriatr Med 2022;13(2):453-461 [FREE Full text] [doi: 10.1007/s41999-021-00555-8] [Medline: 34417977]
68. Andersen FH, Haaland Ø, Klepstad P, Flaatten H. Frailty and survival in elderly intensive care patients in Norway. Acta Anaesthesiol Scand 2021;65(8):1065-1072 [FREE Full text] [doi: 10.1111/aas.13836] [Medline: 33896003]
69. Singh M, Stewart R, White H. Importance of frailty in patients with cardiovascular disease. Eur Heart J 2014;35(26):1726-1731 [FREE Full text] [doi: 10.1093/eurheartj/ehu197] [Medline: 24864078]
70. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol 2006;3(2):77-101. [doi: 10.1191/1478088706qp063oa]
71. Goodyear MDE, Krleza-Jeric K, Lemmens T. The declaration of Helsinki. BMJ 2007;335(7621):624-625 [FREE Full text] [doi: 10.1136/bmj.39339.610000.BE] [Medline: 17901471]
72. Husebø BS, Erdal A, Kjellstadli C, Bøe J. Helsehjelp til eldre. Senter for alders- og sykehjemsmedisin. 2017. URL: https://tinyurl.com/52mrfdmn [accessed 2024-03-23]
73. Mirabelli LG, Cosker RM, Kraiss LW, Griffin CL, Smith BK, Sarfati MR, et al. Rapid methods for routine frailty assessment during vascular surgery clinic visits. Ann Vasc Surg 2018;46:134-141. [doi: 10.1016/j.avsg.2017.08.010] [Medline: 28887242]
74. Edvardsen U. Å telle seg til dumskap. In: Assessment Instrument and The Allocation of Care Services in Norway. New York, NY, USA: Springer; Dec 19, 2006.
75. Cook TD, Campbell DT, Shadish WR. Experimental and Quasi-Experimental Designs for Generalized Causal Inference. Boston, MA: Houghton Mifflin; 2002.

Abbreviations

DPIA: Data Protection Impact Assessment
IPLOS: The Norwegian Information System for the Nursing and Care Sector (Individbasert pleie- og omsorgsstatistikk)
REK: Regional Committees for Medicine and Health Research Ethics
SIKT: Shared Services in Education and Research
TFA: Theoretical Framework of Acceptability
TSD: Services for Sensitive Data (Tjenester for Sensitive Data)

Edited by A Mavragani; submitted 05.12.23; peer-reviewed by A Billis; comments to author 06.01.24; revised version received 16.02.24; accepted 23.02.24; published 18.04.24.

Please cite as:
Kvalsvik F, Larsen BH, Eilertsen G, Falkenberg HK, Dalen I, Haaland S, Storm M
Health Needs Assessment in Home-Living Older Adults: Protocol for a Pre-Post Study
JMIR Res Protoc 2024;13:e55192
URL: https://www.researchprotocols.org/2024/1/e55192
doi:10.2196/55192
PMID:38635319

Protocol

Carboplatin in Patients With Metastatic Castration-Resistant Prostate Cancer Harboring Somatic or Germline Homologous Recombination Repair Gene Mutations: Phase II Single-Arm Trial

Rishabh Jain[1], MD; Akash Kumar[1], DM; Atul Sharma[1], DM; Ranjit Kumar Sahoo[1], DM; Aparna Sharma[1], DM; Amlesh Seth[2], MCh; Brusabhanu Nayak[2], MCh; Shamim A Shamim[3], MD; Seema Kaushal[4], MD; Haresh KP[5], MD; Chandan J Das[6], MD; Atul Batra[7], DM

[1]Department of Medical Oncology, Dr BR Ambedkar Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi, India

[2]Department of Urology, All India Institute of Medical Sciences, New Delhi, India

[3]Department of Nuclear Medicine, All India Institute of Medical Sciences, New Delhi, India

[4]Department of Pathology, All India Institute of Medical Sciences, New Delhi, India

[5]Department of Radiation Oncology, Dr BR Ambedkar Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi, India

[6]Department of Radiology, All India Institute of Medical Sciences, New Delhi, India

[7]Department of Medical Oncology, New Delhi, India

Corresponding Author:
Atul Batra, DM
Department of Medical Oncology
160D Dr BR Ambedkar Institute Rotary Cancer Hospital
All India Institute of Medical Sciences
New Delhi, 110029
India
Phone: 91 11 29575043
Email: batraatul85@gmail.com

Abstract

Background: Approximately 20%-25% of patients with metastatic castration-resistant prostate cancer (mCRPC) harbor a deleterious germline or somatic mutation in the homologous recombination repair (HRR) pathway genes, which is involved in the repair of double-stranded DNA damage. Half of these mutations are germline, while the remaining are exclusively somatic. While polyadenosine 5'diphosphoribose [poly (ADP-ribose)] polymerase inhibitors, such as olaparib and rucaparib, are effective in this subgroup, their widespread use is limited due to the associated high cost, especially in resource-constrained settings. Notably, platinum agents like carboplatin have exquisite sensitivity to cells with defective DNA repair machinery. Carboplatin, a conventional, inexpensive chemotherapeutic agent, offers a potential alternative treatment in such patients. Several retrospective small case series support this hypothesis. However, there are no prospective clinical trials of carboplatin in patients with mCRPC with HRR mutations.

Objective: The primary objective is to assess the objective response rate of 3 weekly carboplatin treatments in patients with mCRPC harboring deleterious mutations in the HRR pathway genes and previously treated with a taxane or a novel antiandrogen agent. The secondary objectives include progression-free survival, health-related quality of life, and safety profile of carboplatin.

Methods: Patients diagnosed with mCRPC harboring HRR pathway mutations previously treated with docetaxel or novel antiandrogen agents (abiraterone, enzalutamide, apalutamide, or darolutamide) or both will be eligible. Genes involved directly or indirectly in the HRR pathway will be tested. In this single-arm phase II study, we will screen approximately 200 patients to enroll 49 patients, and carboplatin (dosing at the area under curve=5) will be administered every 3 weeks until progression or intolerable side effects. The primary end point will be assessed as the proportion of patients with a reduction of serum prostate-specific antigen by more than 50% from enrollment. Secondary outcomes include progression-free survival—soft-tissue disease progression (by response evaluation criteria in solid tumors, version 1.1, and bone lesion progression using Prostate Cancer Clinical Trials Working Group 3 criteria), health-related quality of life during carboplatin treatment using the Functional Assessment of Cancer Therapy—Prostate questionnaire and the European Organisation for Research and Treatment of Cancer questionnaire and safety profile of carboplatin (National Cancer Institute's Common Terminology Criteria for Adverse Events version 5.0).

Results: The trial started enrollment in September 2023. This trial is ongoing, and 12 patients have been recruited to date. All 49 participants will be enrolled according to plan.

Conclusions: This prospective phase II trial represents a critical step toward addressing the therapeutic gap in patients with mCRPC harboring HRR pathway mutations, particularly in demographic regions with limited access to poly (ADP-ribose) polymerase inhibitors. Outcomes from this study will inform clinical practice and guide future phase III randomized trials, ultimately improving patient outcomes globally.

Trial Registration: Clinical Trials Registry of India CTRI/2023/04/051507; https://ctri.nic.in/Clinicaltrials/pmaindet2.php?EncHid=Njc0NjU=&Enc=&userName=

International Registered Report Identifier (IRRID): DERR1-10.2196/54086

(JMIR Res Protoc 2024;13:e54086) doi:10.2196/54086

KEYWORDS

carboplatin; mCRPC; prostate cancer; homologous recombinant gene repair; metastatic castration-resistant prostate cancer; incurable; deleterious mutation; synthetic lethality; tumor; DNA; low-income; middle-income; chemotherapeutic; drug; retrospective study; taxane; novel antiandrogen; single-arm study; health-related; quality of life; bone lesion

Introduction

Patients with metastatic prostate cancer are treated with androgen deprivation therapy, chemotherapeutic agents, or novel antiandrogen agents [1]. These patients eventually develop resistance to androgen deprivation therapy, and this state, known as castration-resistant prostate cancer, is incurable despite the advent of several newer therapies [2]. The therapeutic landscape for metastatic castration-resistant prostate cancer (mCRPC) includes chemotherapeutic agents, novel antiandrogen agents, and radioligand therapies [3].

Pritchard et al [4] reported that 11.8% of men with metastatic prostate cancer harbor deleterious germline mutations, primarily in *BRCA2*, followed by *ATM*, *CHEK2*, *BRCA1*, *RAD51D*, and *PALB41* genes. Subsequent studies evaluated the prevalence of deleterious somatic mutations within the homologous recombination repair (HRR) pathway in 25%-30% of patients with mCRPC [5]. Polyadenosine 5'diphosphoribose (poly [ADP-ribose]) polymerase inhibitor (PARP) inhibitors employ a strategy of synthetic lethality, inhibiting the base excision repair pathway, leading to the accumulation of unrepaired DNA breaks within HRR-deficient tumor cells, culminating in cancer cell death [6-8]. Olaparib, a PARP inhibitor, demonstrated an impressive 88% response rate in patients with mCRPC with HRR gene abnormalities, in contrast to a minimal 3% response in those without these mutations [9,10]. The pivotal PROfound trial supported these findings, leading to Food and Drug Administration approval for patients with mCRPC harboring HRR gene mutations [5]. Similar efficacy was observed with other PARP inhibitors, including rucaparib and talazoparib [11,12]. However, most patients with mCRPC harboring HRR gene mutations residing in low- and middle-income countries do not have access to PARP inhibitors due to the high cost.

Interestingly, HRR-deficient tumors also exhibit increased sensitivity to platinum chemotherapeutic agents (eg, carboplatin) due to their reliance on the HRR pathway for DNA double-strand break repair. This vulnerability has been exploited by platinum-containing treatments in breast and ovarian tumors [13,14]. Initial retrospective studies involving carboplatin in unselected patients with mCRPC showed encouraging efficacy, particularly within the subset carrying HRR gene alterations [15-17]. However, these studies are limited by several biases.

Despite a strong scientific rationale and encouraging preliminary data from real-world studies, no prospective study has been reported to assess the role of carboplatin in this subset of patients. Therefore, we planned this phase II single-arm study to evaluate the efficacy of carboplatin in patients with metastatic prostate cancer harboring mutations in the HRR pathway.

Methods

Objectives

This study is an investigator-initiated, prospective phase II, single-arm clinical trial. The primary objective of this study is to assess the prostate-specific antigen (PSA) response rate of 3 weekly carboplatin (dose at area under the curve 5) in patients with mCRPC harboring deleterious or likely deleterious mutations in the HRR genes and previously treated with a taxane or a novel antiandrogen (proportion of patients with more than 50% serum PSA decline).

The secondary objectives are to compare the effect of oral gabapentin with placebo on the following:

- Progression-free survival—soft-tissue disease progression (by response evaluation criteria in solid tumors, version 1.1) and bone lesion progression (by Prostate Cancer Clinical Trials Working Group 3 criteria)
- Health-related quality of life during carboplatin treatment (Functional Assessment of Cancer Therapy—Prostate questionnaire and European Organisation for Research and Treatment of Cancer questionnaire)
- The safety profile of carboplatin (National Cancer Institute's Common Terminology Criteria for Adverse Events, version 5.0)

Study Setting

This study is being conducted in the outpatient department of Dr BR Ambedkar Institute Rotary Cancer Hospital, New Delhi, India, and the National Cancer Institute, Jhajjar, the 2 cancer blocks of the All India Institute of Medical Sciences, New Delhi, a central government-funded tertiary care teaching hospital.

The catchment area includes an over 20 million population from the Northern states of India, with approximately 15,000 patients with cancer being treated every year.

Eligibility Criteria

All the following criteria must be met for enrollment:

- Histological diagnosis of prostate cancer.
- Serum testosterone <50 ng/dL within 28 days before screening.
- Documented current evidence of mCRPC, where metastatic status is defined as at least one documented metastatic lesion on either a bone scan, computed tomography, or magnetic resonance imaging scan.
- Prior treatment with docetaxel or at least one of the novel antiandrogen agents (abiraterone, enzalutamide, apalutamide, or darolutamide) or both.
- Mutation (germline or somatic) in the HRR pathway in either blood or biopsy samples.
- Written informed consent to participate.
- Eastern Cooperative Oncology Group performance status of 0-1.
- Aged older than 18 years.
- Adequate organ function:
  - Absolute neutrophil count ≥1.5 × 109/L
  - Hemoglobin ≥10.0 g/dL with no blood transfusions in the past 28 days.
  - Platelet count ≥100 × 109/L.
  - Total bilirubin ≤1.5 × institutional upper limit of normal (ULN).
  - Aspartate aminotransferase (serum glutamic oxaloacetic transaminase) or alanine aminotransferase (serum glutamic pyruvate transaminase) ≤2.5 × institutional ULN unless liver metastases are present in which case, they must be ≤5 × ULN.
  - Subjects must have an estimated creatinine clearance using the Cockcroft-Gault equation for men of ≥40 mL/minute.

Patients with any of the following will be excluded from the trial:

- Patients with symptomatic brain metastases. A scan to confirm the absence of brain metastases is unnecessary in all patients.
- Patients with spinal cord compression, unless considered to have received definitive treatment for this and evidence of clinically stable disease for 28 days.
- Patients are considered as poor medical risk due to a serious, uncontrolled medical disorder, nonmalignant systemic disease, or active, uncontrolled infection. Examples include but are not limited to uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, extensive interstitial bilateral lung disease on high-resolution computed tomography scan, or any psychiatric disorder that prohibits obtaining informed consent.
- Patients with a known hypersensitivity to carboplatin.

One of this study's investigators will obtain written informed consent from every patient before enrollment, during which the benefits and risks of participation will be informed in the local language (Hindi or English) that the patient comprehends. The study consists of two parts: (1) screening of tumor tissue or blood for mutations in the HRR pathway and (2) administration of carboplatin in patients found to harbor a deleterious or likely deleterious mutation in the HRR pathway.

Screening of mutations in the HRR pathway will be performed in the tumor tissue for the HRR genes using next-generation sequencing. The initial archived biopsy sample will be retrieved after informed consent is obtained. In patients where the initial biopsy sample is inaccessible or deemed to be of inadequate quality for next-generation sequencing, blood samples will be sent to assess germline mutations in the HRR pathway.

Interventions

Patients who agree to participate in this study will be tested for the presence of known deleterious mutations in the archived tumor tissue in genes involved directly or indirectly in HRR pathway: *BRCA1*, *BRCA2*, *ATM*, *BRIP1*, *BARD1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *MSH2*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*.

Those found to have a pathogenic or likely pathogenic mutation in one of these genes will be treated with 3 weekly carboplatin. The dose will be calculated according to the estimated glomerular filtration rate determined by the Cockcroft-Gault equation and then administered at the area under the curve (5) with a dose capped at 750 mg per cycle. Chemotherapy will continue until progression (clinical, biochemical, or radiographic) or intolerable adverse events, whichever occurs earlier. If the patient misses a follow-up visit, this study's team will contact the patient and reinforce adherence to this study.

The relevant concomitant care permitted or prohibited during the trial includes the following. Palliative radiation for patients who develop urgent local complications in previously documented disease sites. The ideal gap between palliative radiotherapy and the first dose of carboplatin would be at least one week, and there would be no capping dose of palliative therapy.

Continuation of protocol therapy, if medically appropriate, should be discussed with the principal investigator at the site. The following medications and treatments are permitted in this study: (1) rescue medications for nausea or vomiting, (2) antibiotics, and (3) bisphosphonates or denosumab.

Certain medications may interact negatively with carboplatin or interfere with its effectiveness. The medications that may have significant interactions or should generally be avoided with carboplatin:

- Aminoglycoside antibiotics: these antibiotics, such as gentamicin or amikacin, may increase the risk of kidney damage when used concomitantly with carboplatin.
- Nonsteroidal anti-inflammatory drug: these drugs, including ibuprofen, naproxen, and aspirin, may increase the risk of bleeding or kidney damage when used concurrently with carboplatin.

- Live vaccines: live vaccines, such as the measles, mumps, rubella vaccine or varicella (chickenpox) vaccine, should generally be avoided during chemotherapy treatment, including carboplatin. These vaccines contain weakened live viruses that may pose a risk to immunocompromised individuals.
- Other nephrotoxic drugs: carboplatin can cause kidney toxicity, and combining it with other medications that have nephrotoxic effects, such as certain antibiotics or antifungal medications, may increase the risk of kidney damage.
- Anticoagulant medications: combining carboplatin with anticoagulants such as warfarin or heparin may increase the risk of bleeding. Close monitoring of blood clotting parameters is essential if these medications must be used together.
- Vaccines containing weakened or killed viruses or bacteria: while certain vaccines may be necessary for specific situations, it is important to discuss with a health care professional, as the timing and administration of vaccines should be carefully considered during chemotherapy treatment.

There are no medications or treatments that are specifically prohibited during this study.

All concomitant medications will be recorded at the time of registration.

Patients meeting either of the following criteria will discontinue this study's treatment:

- Permanent discontinuation of carboplatin by treating physician (unacceptable toxicity or progression of underlying cancer).
- The investigator determines that continuing this study's treatment is not in the patient's best interest.
- Occurrence of an exclusion criterion affecting patient safety.
- Concomitant treatment that is not permitted.
- Failure to comply with the protocol. Suppose a patient consistently fails to attend scheduled assessments in this study. In that case, the investigator will determine the reasons and document the circumstances in the medical records as thoroughly and accurately as possible.
- The patient declines subsequent treatment or withdraws consent.

Posttrial care would be administered based on the treating physician's discretion. Patients will be followed up until disease progression. Data collected for this study comprise clinical characteristics obtained from hospital records and routine laboratory investigations, including but not limited to baseline demographics, outcome measures, treatment details, and adverse events.

Data Collection and Management

The research staff will collect data on site, using premade questionnaires on a paper case record form (CRF). All the parameters assessed in this study are defined a priori in a data dictionary, elucidating standards for data collection. Table 1 outlines the schedule of assessments.

Participating patients will be assessed before initiating a cycle of carboplatin-based chemotherapy and 3 weeks after the last dose of carboplatin. Subjects will be contacted by telephone if they miss their clinic appointment with the treating oncologist. Data entry will be done by using paper CRF. Data will be stored securely with limited access to authorized individuals. Biological samples will be collected as a part of this study at baseline. Formalin-fixed paraffin-embedded prostate tissue samples would be collected for HRR mutation testing. The patients' blood samples would also be collected for germline testing of HRR mutations.

Table 1. Schedule of assessments.

	Screening	Baseline	Every cycle (3 weekly)	3 monthly
Informed consent	✓	—[a]	—	—
Serum testosterone	✓	—	—	—
Clinic assessment	—	✓	✓	—
Concomitant medications	—	✓	✓	—
Adverse events	—	—	✓	—
CBC[b]/LFT[c]/RFT[d]	—	✓	✓	—
Serum PSA[e]	—	✓	✓	—
Quality of life assessments	—	✓	✓	—
PSMA[f] PET[g] scan or CECT[h] chest abdomen and bone scan	—	—	—	✓

[a]Not available.

[b]CBC: complete blood count.

[c]LFT: liver function test.

[d]RFT: renal function test.

[e]PSA: prostate-specific antigen.

[f]PSMA: prostate-specific membrane antigen.

[g]PET: positron emission tomography.

[h]CECT: contrast-enhanced computed tomography.

Statistical Methods

The primary end point (confirmed PSA response rate) will be presented as a proportion to be tested against a 1-sided alternative.

Patient demographics, clinical and treatment characteristics, and other study outcomes will be described using mean, SD and range, or median, IQR and range for continuous variables, frequencies, and percentages for categorical variables, and the Kaplan Meier method for time-to-event variables. The effect sizes and 95% CIs will be presented where possible.

Simon's [18] 2-stage design will be used. The null hypothesis that the true response rate (serum PSA decline of more than 50%) is 20% will be tested against a 1-sided alternative. In the first stage, 24 patients will be accrued. If there are 5 or fewer responses in these 24 patients, this study will be stopped. Otherwise, 25 additional patients will be accrued for a total of 49. The null hypothesis will be rejected if 15 or more responses are observed in 49 patients. This design yields a type I error rate of 5% and a power of 90% when the true response rate is 40%.

To include 49 patients with mCRPC harboring HRR mutations, we must screen approximately 200 patients, assuming a 30% prevalence and tissue inadequacy of 20%. The type of HRR mutation will analyze subgroups. Regression models (using the Cox proportional hazards model) will be used for exploratory analyses.

Oversight and Monitoring

The principal investigator at the All India Institute of Medical Sciences, New Delhi, will coordinate this study and be responsible for data acquisition management and statistical analysis. Investigators from the Department of Medical Oncology at this study's site will constitute the trial steering committee. The trial steering committee will evaluate any serious adverse events and report promptly to the Institute Ethics Sub Committee for Monitoring of Adverse Events in Clinical Trials at the site. Guideline-based collection of adverse event data will be ensured. Additionally, serious adverse reactions will be reported on time to the Institute Ethics Sub Committee for Monitoring of Adverse Events in Clinical Trials at the site. There will be no compensation offered for adverse events or serious adverse events to participants. After the initiation of this study, the trial steering committee will regularly audit the process of consenting, protocol adherence, and data collection biannually. Additionally, the data may be audited or inspected by the Institute Ethics Committee. Amendments made to the protocol will be communicated on time to the Institute Ethics Committee and the Clinical Trials Registry of India. One protocol amendment has been done in which we added the European Organisation for Research and Treatment of Cancer prostate cancer 25 questionnaire to the assessment and included the option of contrast-enhanced computed tomography chest abdomen and bone scan in place of a prostate-specific membrane antigen–positron emission tomography scan.

This trial will be published in a peer-reviewed journal with individual investigators as authors. Full credit will be given to the collaborating investigators and research staff involved in this study. All authors will review and approve this paper before submission and comply with internationally accepted requirements. We also plan to present this study's results at major scientific meetings. The availability of results to all participants will be ensured.

Ethical Considerations

The ethical approval has been obtained from the Institute Ethics Committee of the All India Institute of Medical Sciences, New Delhi who approved this study's protocol on April 20, 2023 (IECPG-255/20.04.2023). Informed consent of each participant in the local language will be taken. The identifying information of participants will be removed as much as possible. Each participant will be given a study identification number, and the CRFs will contain only the deidentified data. Consent forms (with identifying patient data) will be safeguarded in locked compartments at this study's site that can exclusively be accessed by authorized personnel. No monetary compensation will be provided to the enrolled participants. No identification of individual participants or users in any images of the paper or supplementary material is possible.

The protocol and final paper will be published as described by the International Committee of Medical Journal Editors guidelines. No professional writers will be employed to write the final paper. The supplementary material of the final paper will contain the full protocol. The deidentified data set and statistical code will be made available to the corresponding author at a reasonable request.

Results

The trial started enrollment in September 2023. This trial is ongoing, and 12 patients have been recruited to date. All 49 participants will be enrolled according to plan.

Discussion

Relevance of the Study

This prospective phase II study will provide efficacy data of carboplatin in patients with mCRPC with deficient HRR. If this study provides positive results, it will provide a treatment option for patients with mCRPC. Further multicentric phase III noninferiority trials may be conducted to compare the efficacy with PARP inhibitors. Importantly, this study will provide a rationale for using carboplatin in resource-limited settings worldwide.

The limitation of this study is that it will have a screen failure rate of around 70%, as the prevalence of deleterious mutations in the HRR pathway is approximately 30%. Further, the availability of tumor tissue and the quality of archived specimens can also impair the technical ability to detect mutations in the HRR pathway. Therefore, approximately 200 patients with mCRPC will be screened to enroll 49 patients in this study.

There had only been small retrospective trials for using carboplatin in mCRPC. This would be the first phase II trial to evaluate the efficacy of carboplatin in patients with metastatic prostate cancer harboring mutations in the HRR pathway.

Conclusions

This prospective phase II clinical trial addresses a critical unmet need in the management of patients with mCRPC harboring HRR gene mutations. With a focus on evaluating the efficacy of carboplatin, an affordable chemotherapy agent, this study holds promise as a new therapeutic option. The trial's approach builds upon the concept of synthetic lethality, harnessed by both PARP inhibitors and carboplatin. If successful, carboplatin could emerge as a practical and accessible treatment strategy for this specific patient subset, potentially improving their outcomes and quality of life. By bridging the gap between high-cost therapies and broader patient accessibility, this study can potentially transform the landscape of mCRPC treatment, offering hope to patients worldwide.

Acknowledgments

We thank the Indian Council of Medical Research for funding this clinical trial. As an investigator-initiated study, the sponsor is a teaching hospital employing the principal investigator. This study is conducted via the administrative, logistic, and other supports provided by the hospital. ICMR is providing funding for manpower and HRR testing. The protocol is dated August 1, 2023 (version 2.0). All authors declared that they had insufficient or no funding to support open access publication of this manuscript, including from affiliated organizations or institutions, funding agencies, or other organizations. JMIR Publications provided article processing fee (APF) support for the publication of this article.

Data Availability

The supplementary material of the final paper will contain the full protocol. The deidentified data will be available upon reasonable request to the corresponding author after the publication of the final results.

Authors' Contributions

RJ conceptualized the study and drafted and revised the manuscript. AK, Atul S, RKS, SK, Aparna S, BN, SAS, HKP, CJD, and A Seth conceptualized the study. AB conceptualized the study, designed the trial and statistical analysis, and drafted and revised the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Informed consent form.
[DOCX File , 15 KB - resprot_v13i1e54086_app1.docx]

Multimedia Appendix 2
Participant information sheet (PIS).
[DOCX File , 17 KB - resprot_v13i1e54086_app2.docx]

Multimedia Appendix 3
Participant informed consent form (PICF) Hindi.
[DOCX File , 36 KB - resprot_v13i1e54086_app3.docx]

References

1. Sayegh N, Swami U, Agarwal N. Recent advances in the management of metastatic prostate cancer. JCO Oncol Pract 2022;18(1):45-55 [FREE Full text] [doi: 10.1200/OP.21.00206] [Medline: 34473525]
2. Harris WP, Mostaghel EA, Nelson PS, Montgomery B. Androgen deprivation therapy: progress in understanding mechanisms of resistance and optimizing androgen depletion. Nat Clin Pract Urol 2009;6(2):76-85 [FREE Full text] [doi: 10.1038/ncpuro1296] [Medline: 19198621]
3. Lowrance WT, Murad MH, Oh WK, Jarrard DF, Resnick MJ, Cookson MS. Castration-resistant prostate cancer: AUA guideline amendment 2018. J Urol 2018;200(6):1264-1272 [FREE Full text] [doi: 10.1016/j.juro.2018.07.090] [Medline: 30086276]
4. Pritchard CC, Mateo J, Walsh MF, De Sarkar N, Abida W, Beltran H, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N Engl J Med 2016;375(5):443-453 [FREE Full text] [doi: 10.1056/NEJMoa1603144] [Medline: 27433846]
5. de Bono J, Mateo J, Fizazi K, Saad F, Shore N, Sandhu S, et al. Olaparib for metastatic castration-resistant prostate cancer. N Engl J Med 2020;382(22):2091-2102 [FREE Full text] [doi: 10.1056/NEJMoa1911440] [Medline: 32343890]
6. Helleday T. The underlying mechanism for the PARP and BRCA synthetic lethality: clearing up the misunderstandings. Mol Oncol 2011;5(4):387-393 [FREE Full text] [doi: 10.1016/j.molonc.2011.07.001] [Medline: 21821475]
7. Farmer H, McCabe N, Lord CJ, Tutt ANJ, Johnson DA, Richardson TB, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 2005;434(7035):917-921 [FREE Full text] [doi: 10.1038/nature03445] [Medline: 15829967]
8. McLornan DP, List A, Mufti GJ. Applying synthetic lethality for the selective targeting of cancer. N Engl J Med 2014;371(18):1725-1735. [doi: 10.1056/NEJMra1407390] [Medline: 25354106]
9. Mateo J, Carreira S, Sandhu S, Miranda S, Mossop H, Perez-Lopez R, et al. DNA-repair defects and olaparib in metastatic prostate cancer. N Engl J Med 2015;373(18):1697-1708 [FREE Full text] [doi: 10.1056/NEJMoa1506859] [Medline: 26510020]
10. Hussain M, Mateo J, Fizazi K, Saad F, Shore N, Sandhu S, et al. Survival with olaparib in metastatic castration-resistant prostate cancer. N Engl J Med 2020;383(24):2345-2357 [FREE Full text] [doi: 10.1056/NEJMoa2022485] [Medline: 32955174]
11. Loehr A, Patnaik A, Campbell D, Shapiro J, Bryce AH, McDermott R, et al. Response to rucaparib in BRCA-Mutant metastatic castration-resistant prostate cancer identified by genomic testing in the TRITON2 study. Clin Cancer Res 2021;27(24):6677-6686 [FREE Full text] [doi: 10.1158/1078-0432.CCR-21-2199] [Medline: 34598946]
12. de Bono JS, Mehra N, Scagliotti GV, Castro E, Dorff T, Stirling A, et al. Talazoparib monotherapy in metastatic castration-resistant prostate cancer with DNA repair alterations (TALAPRO-1): an open-label, phase 2 trial. Lancet Oncol 2021;22(9):1250-1264 [FREE Full text] [doi: 10.1016/S1470-2045(21)00376-4] [Medline: 34388386]
13. Neff RT, Senter L, Salani R. BRCA mutation in ovarian cancer: testing, implications and treatment considerations. Ther Adv Med Oncol 2017;9(8):519-531 [FREE Full text] [doi: 10.1177/1758834017714993] [Medline: 28794804]
14. Tutt A, Tovey H, Cheang MCU, Kernaghan S, Kilburn L, Gazinska P, et al. Carboplatin in BRCA1/2-mutated and triple-negative breast cancer BRCAness subgroups: the TNT trial. Nat Med 2018;24(5):628-637. [doi: 10.1038/s41591-018-0009-7] [Medline: 29713086]
15. Hager S, Ackermann CJ, Joerger M, Gillessen S, Omlin A. Anti-tumour activity of platinum compounds in advanced prostate cancer-a systematic literature review. Ann Oncol 2016;27(6):975-984 [FREE Full text] [doi: 10.1093/annonc/mdw156] [Medline: 27052650]
16. Mota JM, Barnett E, Nauseef JT, Nguyen B, Stopsack KH, Wibmer A, et al. Platinum-based chemotherapy in metastatic prostate cancer with DNA repair gene alterations. JCO Precis Oncol 2020;4:355-366 [FREE Full text] [doi: 10.1200/po.19.00346] [Medline: 32856010]

17. Schmid S, Omlin A, Higano C, Sweeney C, Chanza NM, Mehra N, et al. Activity of platinum-based chemotherapy in patients with advanced prostate cancer with and without DNA repair gene aberrations. JAMA Netw Open 2020;3(10):e2021692 [FREE Full text] [doi: 10.1001/jamanetworkopen.2020.21692] [Medline: 33112397]
18. Simon R. Optimal two-stage designs for phase II clinical trials. Control Clin Trials 1989;10(1):1-10. [doi: 10.1016/0197-2456(89)90015-9] [Medline: 2702835]

Abbreviations

CRF: case record form
HRR: homologous recombination repair
mCRPC: metastatic castration-resistant prostate cancer
PARP: polyadenosine 5'diphosphoribose (poly [ADP-ribose]) polymerase inhibitor
Poly (ADP-ribose): polyadenosine 5'diphosphoribose
PSA: prostate-specific antigen
ULN: upper limit of normal

Edited by A Mavragani; submitted 29.10.23; peer-reviewed by H Demir, B Biswas, P Mehta; comments to author 14.02.24; revised version received 05.03.24; accepted 06.03.24; published 18.04.24.

Please cite as:
Jain R, Kumar A, Sharma A, Sahoo RK, Sharma A, Seth A, Nayak B, Shamim SA, Kaushal S, KP H, Das CJ, Batra A
Carboplatin in Patients With Metastatic Castration-Resistant Prostate Cancer Harboring Somatic or Germline Homologous Recombination Repair Gene Mutations: Phase II Single-Arm Trial
JMIR Res Protoc 2024;13:e54086
URL: https://www.researchprotocols.org/2024/1/e54086
doi:10.2196/54086
PMID:38453159

Protocol

Investigating SARS-CoV-2 Incidence and Morbidity in Ponce, Puerto Rico: Protocol and Baseline Results From a Community Cohort Study

Chelsea G Major[1,2], MPH; Dania M Rodríguez[1], MS; Liliana Sánchez-González[1], MPH, MD; Vanessa Rodríguez-Estrada[3], BS; Tatiana Morales-Ortíz[3], BS; Carolina Torres[1,4], MPH; Nicole M Pérez-Rodríguez[1], MPH, DrPH; Nicole A Medina-Lópes[1], MPH; Neal Alexander[2], PhD; David Mabey[5], MD; Kyle Ryff[1], MPH; Rafael Tosado-Acevedo[1], PhD; Jorge Muñoz-Jordán[1], PhD; Laura E Adams[1], MPH, DVM; Vanessa Rivera-Amill[3], PhD; Melissa Rolfes[6], MPH, PhD; Gabriela Paz-Bailey[1], MSc, MD, PhD

[1]Division of Vector Borne Diseases, Centers for Disease Control and Prevention, San Juan, Puerto Rico

[2]Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, United Kingdom

[3]Ponce Research Institute, Ponce Health Sciences University, Ponce, Puerto Rico

[4]Kāpili Services, LLC, Alaka`ina Foundation Family of Companies, Orlando, FL, United States

[5]Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, United Kingdom

[6]Influenza Division, Centers for Disease Control and Prevention, Atlanta, GA, United States

Corresponding Author:
Chelsea G Major, MPH
Division of Vector Borne Diseases
Centers for Disease Control and Prevention
1324 Calle Cañada
San Juan, 00920
Puerto Rico
Phone: 1 787 706 2254
Email: lhi5@cdc.gov

Abstract

Background: A better understanding of SARS-CoV-2 infection risk among Hispanic and Latino populations and in low-resource settings in the United States is needed to inform control efforts and strategies to improve health equity. Puerto Rico has a high poverty rate and other population characteristics associated with increased vulnerability to COVID-19, and there are limited data to date to determine community incidence.

Objective: This study describes the protocol and baseline seroprevalence of SARS-CoV-2 in a prospective community-based cohort study (COPA COVID-19 [COCOVID] study) to investigate SARS-CoV-2 infection incidence and morbidity in Ponce, Puerto Rico.

Methods: In June 2020, we implemented the COCOVID study within the Communities Organized to Prevent Arboviruses project platform among residents of 15 communities in Ponce, Puerto Rico, aged 1 year or older. Weekly, participants answered questionnaires on acute symptoms and preventive behaviors and provided anterior nasal swab samples for SARS-CoV-2 polymerase chain reaction testing; additional anterior nasal swabs were collected for expedited polymerase chain reaction testing from participants that reported 1 or more COVID-19–like symptoms. At enrollment and every 6 months during follow-up, participants answered more comprehensive questionnaires and provided venous blood samples for multiantigen SARS-CoV-2 immunoglobulin G antibody testing (an indicator of seroprevalence). Weekly follow-up activities concluded in April 2022 and 6-month follow-up visits concluded in August 2022. Primary study outcome measures include SARS-CoV-2 infection incidence and seroprevalence, relative risk of SARS-CoV-2 infection by participant characteristics, SARS-CoV-2 household attack rate, and COVID-19 illness characteristics and outcomes. In this study, we describe the characteristics of COCOVID participants overall and by SARS-CoV-2 seroprevalence status at baseline.

Results: We enrolled a total of 1030 participants from 388 households. Relative to the general populations of Ponce and Puerto Rico, our cohort overrepresented middle-income households, employed and middle-aged adults, and older children (P<.001). Almost all participants (1021/1025, 99.61%) identified as Latino/a, 17.07% (175/1025) had annual household incomes less than

US $10,000, and 45.66% (463/1014) reported 1 or more chronic medical conditions. Baseline SARS-CoV-2 seroprevalence was low (16/1030, 1.55%) overall and increased significantly with later study enrollment time (P=.003).

Conclusions: The COCOVID study will provide a valuable opportunity to better estimate the burden of SARS-CoV-2 and associated risk factors in a primarily Hispanic or Latino population, assess the limitations of surveillance, and inform mitigation measures in Puerto Rico and other similar populations.

International Registered Report Identifier (IRRID): RR1-10.2196/53837

(JMIR Res Protoc 2024;13:e53837) doi:10.2196/53837

KEYWORDS

cohort studies; COVID-19; epidemiologic studies; Hispanic or Latino; incidence; prospective studies; research methodology; SARS-CoV-2; seroprevalence

Introduction

After the first detection of SARS-CoV-2 in late 2019, the virus has become a significant threat to health and economies globally, particularly in populations with high economic inequality and low access to health resources and infrastructure [1,2]. In the United States, racial and ethnic groups with well-documented socioeconomic disparities have also been disproportionately affected by SARS-CoV-2, with the highest COVID-19 morbidity and mortality rates among American Indian or Alaska Native, non-Hispanic Black, and Hispanic or Latino populations [3,4]. Despite tremendous progress in our understanding of SARS-CoV-2 and the development of COVID-19 treatment and vaccines, control efforts have been hindered by the emergence of new, more contagious variants and vaccine hesitancy [5-9]. A better understanding of risk and risk factors for SARS-CoV-2 infection and transmission dynamics in minority groups and low-resource settings is needed to inform ongoing control efforts and develop strategies to improve health equity.

Puerto Rico, a Caribbean island and US Commonwealth, has a high prevalence of population characteristics associated with increased vulnerability to COVID-19. Among approximately 3.3 million Puerto Rico residents, almost all (99%) identify as Hispanic or Latino, and 43% live below the federal poverty level [10]. Additionally, risk factors for severe COVID-19, including older age and chronic disease, are higher among Puerto Ricans relative to residents of the continental United States, and economic crises and natural disasters have weakened the local health care infrastructure over the past decade [11-13]. As in many regions, facility-based public health surveillance and seroprevalence data from blood banks have been and continue to be the primary sources of SARS-CoV-2 incidence and prevalence data in Puerto Rico [14-16]. While valuable, these data are limited in depth and scope due to reliance on patient health care seeking behavior and passive reporting by providers and diagnostic laboratories. Systematic diagnostic testing and follow-up of a defined population can better capture the spectrum of COVID-19 disease, determine true infection rates, and help identify risk factors for infection and morbidity.

As part of the COVID-19 emergency response efforts, the US Centers for Disease Control and Prevention (CDC) supported multiple community-based cohort studies to better understand SARS-CoV-2 transmission and risk in different settings [17-19]. The ongoing Communities Organized to Prevent Arboviruses (COPA) cohort study in Ponce, Puerto Rico—implemented in 2018 through the collaboration of the Ponce Health Sciences University, Puerto Rico Vector Control Unit, and the CDC Dengue Branch (DB)—was identified as an existing platform that could be expanded to estimate SARS-CoV-2 community infection rates and other COVID-19 research objectives in the region. In June 2020, we implemented the COPA COVID-19 (COCOVID) study, a prospective, community-based cohort to investigate the incidence of and risk factors for SARS-CoV-2 infection and morbidity among COPA participants and other residents of 15 community areas.

In this study, we describe the protocol, baseline population demographics, and seroprevalence of SARS-CoV-2 in the COCOVID cohort. The study included weekly molecular testing and multiantigen serology testing at baseline and every 6 months for SARS-CoV-2. We also collected sociodemographic data, weekly mobility and personal preventive behavior patterns, COVID-19 vaccination status, symptoms, and long-term outcomes among individuals with and without incident SARS-CoV-2 infection during the study period. To date, few longitudinal COVID-19 studies with regular SARS-CoV-2 molecular testing have included the United States or Hispanic or Latino populations [20,21], and none have been conducted in Puerto Rico. Thus, data from the COCOVID study have the potential to enhance general knowledge of SARS-CoV-2 epidemiology in addition to providing unique insights into the COVID-19 epidemic in Puerto Rico, which may have implications for prevention efforts and future epidemics in geographically or demographically similar populations.

Methods

Ethical Considerations

Local ethics review and approval for the COPA project and COCOVID substudy protocols were obtained through the Ponce Medical School Foundation, Inc's institutional review board (study #171110-VR). CDC also reviewed COPA and COCOVID protocols and determined the activities were conducted in a manner consistent with applicable federal law and CDC policy (refer to 45 C.F.R. part 46; 21 C.F.R. part 56).

Adult consent, minor assent, and parental or guardian permission were obtained at enrollment and subsequent 6-month follow-up visits and documented using paper forms. The receipt of consent and assent for all participants was also confirmed daily and

tracked electronically by study coordinators. All participants under the age of 21 years, the age of majority in Puerto Rico, were considered minors except for those emancipated by marriage or judicial decree. Before the interview or specimen collection, staff explained project activities and important points of informed consent to participants, answered any questions raised, and provided a paper copy of the consent form to the household. The household representative (an adult or an emancipated minor that was present at the time of visit) consented to provide household-level information and allow study staff to invite other household members to participate in the study.

All adults and emancipated minors (including household representatives) were asked to provide written consent for each of the following: providing contact information, responding to the COPA annual interview questions and providing blood and nasal swab specimens (where applicable), being contacted weekly for acute illness surveillance (AIS) and annually for cohort follow-up, responding to the COCOVID questionnaire and providing blood specimens every 6 months and nasal swabs weekly, storage of specimens remaining after testing for future studies, and permission for children for which they were the parent or legal guardian to participate in the same project activities.

The adult consent document requested a separate enumeration of each child for which they had parental or guardianship rights to account for any differences in the activities in which each child could participate. For minors aged between 14 and 20 years, written consent was obtained using a designated form simplified from the adult version. Verbal assent was documented in a designated form for minors aged between 7 and 13 years, and only parent or guardian consent was documented for minors aged between 1 and 6 years. All consent and assent forms and questionnaires were available in both Spanish and English and were written at an eighth grade or lower reading level.

This project involved the collection of personal identifying information and included safeguard measures to ensure the privacy and confidentiality of participants. Households and individual participants were assigned project-specific identifiers to track their location of residence and study status. Barcode stickers were used to link specimen tubes and paper forms to each participant's visit during the project. All specimens were securely transported to and stored at the study office site, the CDC DB, and other laboratory sites. All personnel involved in this study were required to complete ethics training requirements set by the institutional review board and adhere to an unwavering code of conduct regarding the confidentiality of patients' information.

Only study personnel have access to participant responses or laboratory results. Study questionnaires, laboratory test results, and other collected data are electronically stored in locations approved by the CDC for storage of personal data, including a limited-access encrypted server and shared drive within the CDC internal network, and, in the case of paper forms, in locked cabinets. Paper records will be maintained for at least 3 years and then destroyed. Where possible, deidentified data sets will be created and used for analysis, and individual participants will not be identified for any presentations or publications based on the study results.

For compensation for the time dedicated to the COCOVID study activities, participants received US $5 each week upon staff receipt of the completed weekly questionnaire and self-collected respiratory specimen, which was given in US $20 installments for every 4 successful transfers of weekly questionnaires and specimens. Participants also received US $20 at each study appointment (enrollment, 6 months, 12 months, 18 months, and 24 months) when they completed serum specimen collection and the questionnaire. If these appointments overlapped with COPA annual follow-up visits (enrollment, 12 months, and 24 months), an additional US $20 (between June 2021 and February 2022) or US $30 (between March and August 2022) in compensation was given for both activities for a total of US $40 or US $50.

Study Overview

In June 2020, we implemented the COCOVID substudy among residents of 15 community areas in Ponce. We aimed to enroll between 900 and 1000 participants for regular surveys and specimen collection, including weekly anterior nasal swab collection for SARS-CoV-2 polymerase chain reaction (PCR) testing and venous blood draws for multiantigen immunoglobulin (Ig) G antibody testing at baseline and every 6 months. Participants were also included in activities for the larger COPA cohort for at least the same period that they were active in the COCOVID study, including weekly reporting of acute COVID-19–like symptoms through SMS text message and additional SARS-CoV-2 PCR testing among symptomatic participants.

COPA Platform

The COPA study established an ongoing cohort of approximately 3800 participants in 38 community areas in Ponce, Puerto Rico (Figure 1) to measure the incidence and prevalence of arboviral infections and evaluate vector control interventions through a cluster randomized controlled trial design [22,23]. Recruitment activities are conducted primarily through house-to-house visits, and random selections of residences in each community area are made until sample size goals are reached or all residences have been approached for recruitment. Eligible individuals are aged between 1 and 50 years, spend 4 or more nights a week in the selected residence, and have no definite plans to move in the next 12 months. Follow-up is conducted annually and includes serum collection for antibody testing for dengue and the administration of a questionnaire (Figure 2). Cohort enrollment began in March 2018.

Figure 1. Map of the 38 Communities Organized to Prevent Arboviruses (COPA) and 15 COPA COVID-19 (COCOVID) community cohort study cluster areas in Ponce, Puerto Rico.

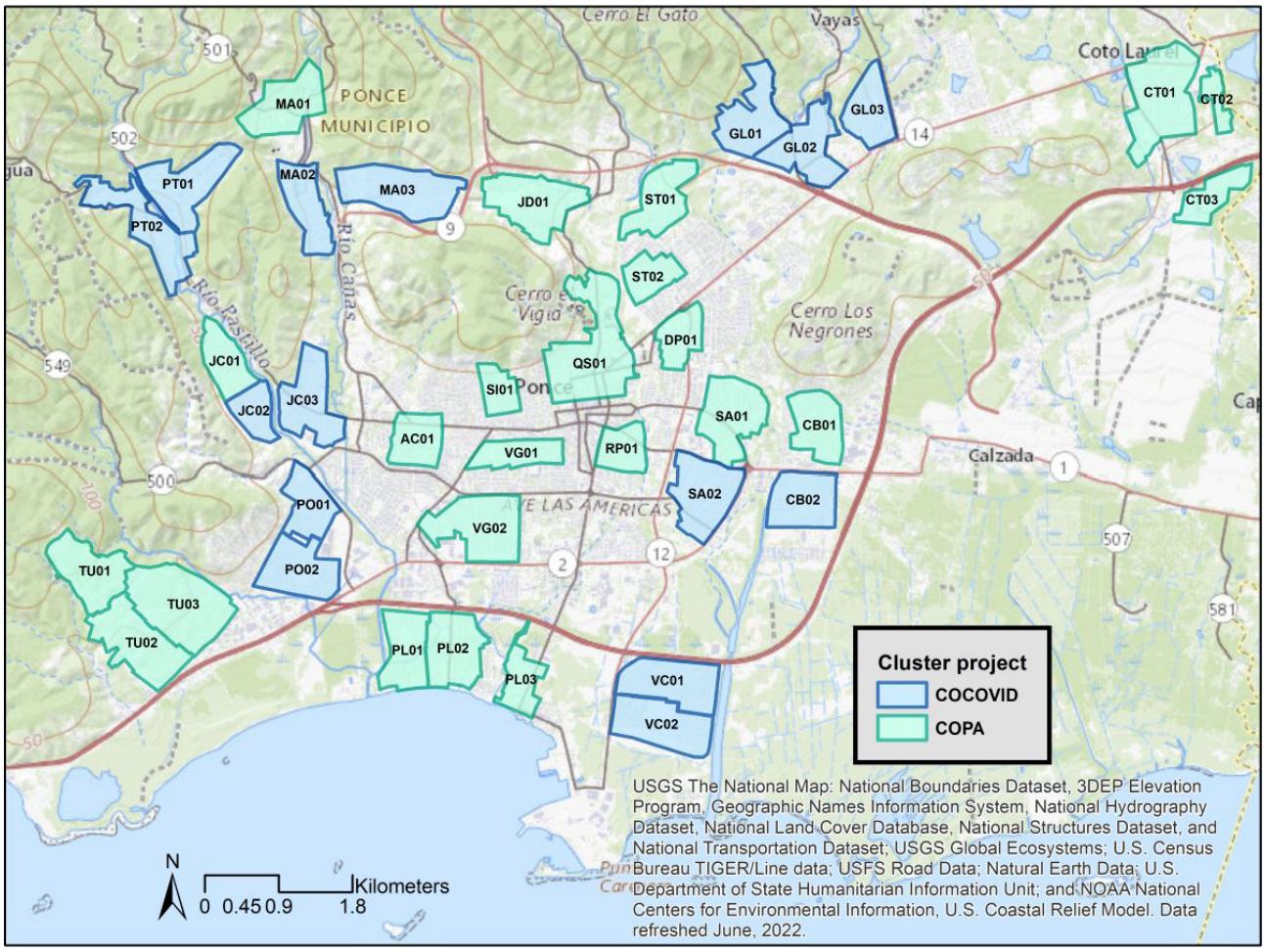
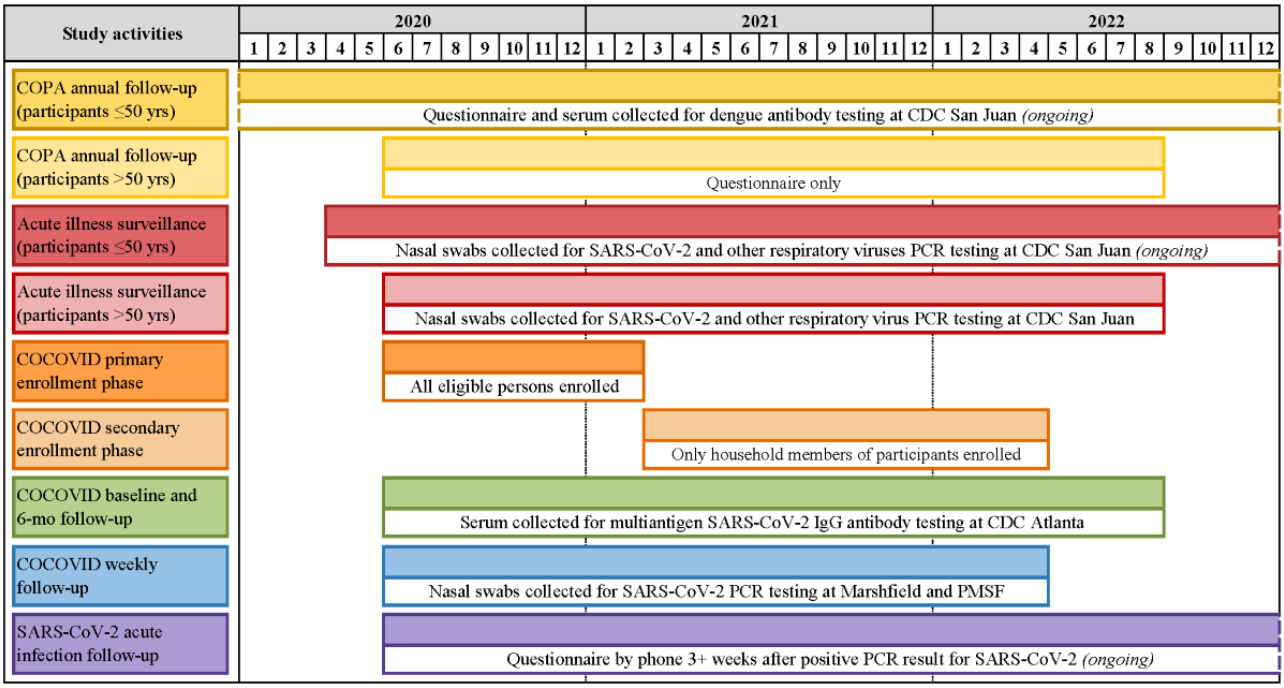


Figure 2. Timeline of key Communities Organized to Prevent Arboviruses (COPA) and COPA COVID-19 (COCOVID) cohort study activities in Ponce, Puerto Rico, between January 2020 and December 2022. CDC: Centers for Disease Control and Prevention; mo: months; PCR: polymerase chain reaction; PMSF: Ponce Medical School Foundation; yrs: years.



In April 2020, questions related to risk and perceptions of COVID-19 were added to the annual questionnaire, and an AIS component was implemented (Figure 2). The AIS component is ongoing and uses an automated SMS text messaging system to contact adult participants weekly to inquire if any household members have experienced fever or other COVID-19–like symptoms (ie, cough, shortness of breath, sore throat, body pain, diarrhea, and loss of taste or smell) in the past 7 days (Figure 2). Participants that report fever are offered testing for dengue virus (DENV) by real-time reverse transcriptase–polymerase chain reaction (rRT-PCR) testing in serum, and those that report any qualifying symptom are offered an anterior nasal swab for SARS-CoV-2 and other respiratory virus rRT-PCR testing. Beginning in December 2021, participants were also asked to provide an additional anterior nasal swab for SARS-CoV-2 rapid antigen testing. To ensure the consistency of the sample collection method for both tests, all nasal swabs are collected by a nurse or medical technologist. At the time of specimen collection, project staff also administer an AIS questionnaire on recent exposures, symptoms, and health care–seeking behaviors.

Study Population and Enrollment

Enrollment activities for the COCOVID substudy for COVID-19 began in late June of 2020. We initially selected 12 of the 38 COPA study communities for COCOVID activities, and an additional 3 community areas were added during the enrollment process to meet sample size goals (Figure 1). We prioritized the selection of community areas with high numbers of individuals aged 18 years or younger and those aged 50 years or older in COPA-participating households to increase the participation of these age groups. We also considered logistical priorities, including proximity to other selected clusters and ease of access to residential areas, in the selection process. Eligibility for COCOVID participation was expanded beyond that of COPA to include residents aged 50 years or older, in addition to spending 4 or more nights per week at a residence in a selected community area and having no definite plans to move in the next 12 months. COCOVID participants agree to participate in COPA annual follow-up questionnaires and, for participants aged between 1 and 50 years, the collection of blood specimens for arbovirus antibody testing for at least the substudy duration; participation in the AIS activities was not required for COCOVID enrollment.

Using a standardized script, study staff contacted households with 1 or more COPA participants by phone to explain the study, offer enrollment to eligible household members, and schedule an initial study visit to complete consent processes and data and specimen collection activities. Enrollment of all eligible household members was encouraged but not required, and participants were also asked to refer family and neighbors residing in the 15 community areas. The primary enrollment phase occurred between June 2020 and February 2021. Subsequently, only the enrollment of members of households with 1 or more active participants was permitted to avoid major changes to study logistics and increases in resource use (secondary enrollment phase, Figure 2). Following the completion of the primary enrollment phase, we planned to continue participants' weekly follow-up activities for a minimum of 12 months (through February 2022) and 6-month activities for a minimum of 18 months (through August 2022).

Sample Size Calculation

The sample size for the COCOVID substudy was based on the primary study objective of estimating community incidence of SARS-CoV-2 infection, which included allowing for comparisons by age group, accounting for potential similarity among participants within cluster areas, and assuming a cumulative incidence of infection of 10%-30% over the study period. Age groups were defined to allow infection risk comparisons of pediatric (1-17 years) and older adult (≥50 years) populations with the general population (18-49 years); gender-based sample size estimates were not made as we assumed our household-based recruitment methods would result in representative samples by gender. Our calculations assumed the enrollment of approximately equal numbers of participants across the 3 age groups and from the initially selected 12 community areas. Additionally, it was assumed that participants who were infected with SARS-CoV-2 before enrollment would not be at lower risk of further infection during the study period.

We expected a high coefficient of variation among the clusters for SARS-CoV-2 transmission, and calculations were made using a range of values from 0.5 to 0.8. We also expected a high intracluster correlation among the responses within a cluster due to the rapid spread of SARS-CoV-2, and calculations were made using values of 0.2 and 0.25. The precision of incidence is estimated by computing the 95% CI for 1 proportion in a cluster sampling design. Scenarios were run considering different cumulative incidence proportions with different intracluster correlations, coefficients of variation, and sample sizes for each cluster. Calculations showed that to reach a CI half width of 0.19 or less, a sample size of 215 participants per age group, or a total of 645 participants, was needed. To account for up to 20%-30% loss to follow-up (a high estimate to also allow for probable unequal recruitment across age groups) and an estimated 5% prevalence of previous SARS-CoV-2 infection at enrollment, we estimated that we needed to enroll a total of 900-1000 participants.

Baseline and 6-Month Follow-Up

Baseline and subsequent 6-month visits took place at the COPA central office facilities, a designated outdoor drive-through site, or the participant's home, depending on local social distancing regulations and participant preferences. After completing informed consent processes, study staff administered a questionnaire on chronic conditions, recent COVID-19 exposures, preventive behaviors, and, for participants that reported an acute COVID–like illness in the past 7 days, symptoms and health care seeking behaviors. Questions on COVID-19 vaccination status were added in January 2021, and questions on employment status and category, long-term COVID-19 symptoms (persisting or appearing more than 1 month after illness onset), and diagnosis of new chronic conditions after an acute SARS-CoV-2 infection were added in September 2021. A trained phlebotomist collected blood for multiantigen SARS-CoV-2 IgG antibody testing by venipuncture using aseptic techniques. Approximately 7.5 milliliters of blood were collected from participants aged between 1 and 4 years,

and approximately 15 milliliters from participants aged 5 years or older.

To reduce study burden, COPA annual activities were conducted at the same time as COCOVID baseline and 6-month follow-up visits, where possible (Figure 2). In these cases, an additional ~7.5 mL of blood for dengue antibody testing were collected during the COCOVID visit for participants aged between 1 and 50 years, and the COPA annual questionnaire was administered to all participants by phone. This questionnaire included questions about household composition and income, demographics, employment status, and COVID-19 risk perception. The 6-month follow-up activities were conducted through August 2022 (Figure 2).

Weekly Follow-Up

Each week, participants self-collected (or had a parent or guardian assist them in collecting) a flocked swab of the anterior nares (anterior nasal swab) and completed a paper questionnaire on new or worsening symptoms, illness among household members, and behaviors such as leaving their home for activities with people outside of their household, places visited, mask use, and social distancing. Before distribution, a unique barcode label was applied to a specimen collection tube and corresponding weekly questionnaire, and questionnaires were prefilled with the participant's name, date of birth, and study identifier. At the enrollment appointment, the first weekly nasal swab specimen and accompanying questionnaire were completed under study staff instruction and supervision, and an initial 4-week supply of paper questionnaires and nasal swab specimen collection supplies were provided. Participants were asked to collect nasal swab specimens and fill out the accompanying questionnaire on a consistent day of the week within 0-12 hours of a scheduled transfer to study staff.

Study staff drove to the participating houses on an agreed-upon day and time for specimen and questionnaire pick-up each week. Households that were unavailable for scheduled pick-up (incidentally or always) were asked to drop off collected specimens and questionnaires at an agreed-upon day and time at the COPA office site. An automated SMS text-messaging system through Twilio MessagingX (Twilio, Inc) was used to send reminders to households on the day of their scheduled pick-up or drop-off for respiratory specimen collection, and study staff contacted participants by phone within 0-2 days if specimen and questionnaire receipt was delayed without notice and to resolve other issues related to received specimens and questionnaires, such as specimen leaks and missing responses. If scheduled receipt of a weekly respiratory specimen was delayed by 4 or more days, no additional opportunities for specimen transfer were offered, and the specimen was considered missing for that week. Additional 4-week supplies of respiratory specimen collection kits and questionnaires were distributed to participants as needed during pick-up and drop-off activities.

Weekly follow-up activities were initially planned to conclude in February 2022, after 12 months of the end of the primary enrollment period. However, investigators agreed to extend the weekly follow-up period due to an increase in SARS-CoV-2 transmission following the introduction of the Omicron variant in Puerto Rico. Study materials and funds were identified to permit a 2-month extension of weekly follow-up to a total of 98 weeks from June 2020 to April 2022 (Figure 2).

Follow-Up for Participants With Symptoms or SARS-CoV-2 Infection

Participants that reported fever, cough, shortness of breath, sore throat, body pain, diarrhea, or loss of taste or smell in the weekly questionnaires (or through the AIS SMS text message system) were asked to participate in a COPA AIS visit to collect additional samples for expedited testing for dengue, SARS-CoV-2, and other respiratory viruses and answer the AIS questionnaire.

Participants with a positive SARS-CoV-2 molecular test from nasal swab specimens collected during weekly COCOVID follow-up or as part of AIS were contacted by phone at least 4 weeks after specimen collection (depending on delays in receipt of positive test results) to complete a follow-up questionnaire on symptoms and illness duration, health care seeking behavior, travel, and other exposures before infection, and to take measures to prevent household transmission while sick (Figure 2).

Specimen Storage, Transport, and Testing

Participants were asked to store weekly anterior nasal swab specimens in their home refrigerators until they were transferred to study staff. Upon receipt of nasal swab specimens, staff stored them in the COPA laboratory refrigerator at 4 °C or according to current CDC specimen storage guidelines. Staff centrifuged whole blood specimens within 4 hours of collection to separate out serum and stored them in the COPA laboratory refrigerator until transport. Specimens were transported by a courier 3 times weekly from the COPA office site to the CDC DB laboratory in San Juan, Puerto Rico, for accessioning, processing, and storage at –70 °C. Frozen nasal swab specimens from COCOVID weekly collection activities were shipped every 1-3 months, and serum aliquots from COCOVID 6-month collection were shipped every 3-6 months to designated laboratories for testing.

Weekly nasal swab specimens were tested by multiplex rRT-PCR assays to detect SARS-CoV-2 RNA, including the Quidel Lyra SARS-CoV-2 Assay [24], Thermo Fisher Scientific TaqPath COVID-19 Combo Kit [25], Thermo Fisher Scientific TaqPath COVID-19, FluA, FluB Combo Kit [26], and Roche Cobas SARS-CoV-2 assay [27]. Cycle threshold values for assay targets were provided for positive specimens, and overall test result interpretations were provided for all tested specimens. Specimens collected between June 2020 and February 2022 were tested by Marshfield Labs in Marshfield, Wisconsin; those collected between March and April 2022 were tested by the Ponce Medical Sciences Foundation Immunology Reference Laboratory in Ponce, Puerto Rico. Whole genome sequencing is ongoing and being performed at CDC headquarters (Atlanta, Georgia) or DB laboratories for weekly nasal swabs that tested positive by rRT-PCR and have sufficiently low cycle threshold values for the nucleocapsid (N) protein target (≤30 for headquarters and ≤27 for DB laboratories). Information on the detected variant lineage (through Pangolin COVID-19 Lineage

Assigner software version 3.1.7; Centre for Genomic Pathogen Surveillance) is provided in accordance with CDC guidance [28].

Serum specimens collected for baseline and 6-month follow-up visits were tested by the Luminex xMAP SARS-CoV-2 multiantigen IgG assay to detect previous infection with SARS-CoV-2 [29]. This assay has 3 antigen targets: the N structural protein, the S1 subunit, and the receptor binding domain (RBD), which are part of the spike (S) protein. Interim guidelines for SARS-CoV-2 testing from the US CDC recommend using anti-N IgG antibody testing to evaluate previous SARS-CoV-2 infection in vaccinated individuals, as COVID-19 vaccines are designed to encode the S protein or a portion of it. Thus, to reduce potential misclassification due to vaccination versus past SARS-CoV-2 infection, specimens were only determined to be positive if IgG antibodies against the N protein, in addition to those against at least 1 of the other 2 targets (S1 and RBD), were detected. The CDC Microbial Pathogenesis and Immune Response Laboratory in Atlanta, Georgia, conducted testing on all serum specimens collected during the study period.

Serum and nasal swab specimens collected for AIS activities were tested at the CDC DB laboratory. Serum samples were tested by the CDC DENV-1-4 rRT-PCR Multiplex Assay to detect RNA for DENVs 1, 2, 3, and 4 and by the DENV Detect IgM Capture enzyme-linked immunosorbent assay kit to detect IgM antibodies for DENV antigens [30,31]. Anterior nasal swabs were tested by an in-house respiratory virus rRT-PCR multiplex assay to detect RNA for SARS-CoV-2, influenza A and B viruses, parainfluenza viruses, adenovirus, respiratory syncytial virus, and human metapneumovirus. The DENV and respiratory virus rRT-PCR assays for AIS specimens were run weekly or more often, and participants with positive results were notified by phone and given recommendations on preventing transmission and following up with their health care providers as needed.

Data Collection and Management

Baseline and 6-Month Questionnaire

Between June 2020 and February 2022, the EpiInfo mobile app was used on Samsung tablets to administer the baseline and 6-month questionnaires and record responses, including participant identifiers and specimen collection data [32]. Beginning in March 2022, the Research Electronic Data Capture (REDCap; Vanderbilt University) mobile application was used to administer these questionnaires [33,34]. Paper questionnaire forms were available for use as a backup in case of electronic data collection failure. Paper forms were entered into the mobile app either daily or every 6 months as part of the data review and cleaning processes. Questionnaire data were transferred daily from tablets to a secure, limited-access CDC server through the Secure Shell File Transfer Protocol.

Weekly Questionnaire

A paper version of the weekly questionnaire was completed by participants and received by study staff at scheduled specimen pick-up and drop-off activities. Staff reviewed the form for completeness and filled out the laboratory section to accompany the corresponding weekly nasal swab specimen. After the specimens were transported to and accessioned by the CDC DB laboratory, the forms were scanned into the CDC laboratory samples database, where they underwent automated data extraction using Microsoft Azure Form Recognizer software or manual data entry in cases of software extraction failure [35].

Preliminary data cleaning was performed in EpiInfo or REDCap daily by study field staff and the data quality team. Additional data cleaning processes were performed weekly using the R environment for statistical computing (R Core Team) and involved data validation and standardization, including the identification of missing forms, data inconsistencies, and variable completeness [36]. Final data checks and standardizations were also performed using R statistical software at 6-month intervals to generate analytic data sets.

Data Analysis

Outcome Measures

The primary outcome measures of interest for this study are (1) the incidence of SARS-CoV-2 infection as defined by detection of SARS-CoV-2 RNA by PCR testing of participant specimens collected as part of weekly follow-up or AIS visits, and (2) the relative risks of incident SARS-CoV-2 infection by participant demographics, health history, and behaviors. Secondary outcomes included the (1) seroprevalence of SARS-CoV-2 defined by detection of N and either S1 or RBD IgG antibodies by enzyme-linked immunosorbent assay, (2) household attack rate among households with at least 2 participants and 1 participant with an incident SARS-CoV-2 infection, and (3) the frequency of illness characteristics and outcomes (ie, symptom status and severity, health care seeking, death, and post–COVID conditions) among participants with incident SARS-CoV-2 infections.

Planned Statistical Analyses

SARS-CoV-2 Infection Incidence and Risk Factors

Using the number of incident SARS-CoV-2 infection events detected through PCR testing divided by the total person-time at risk contributed, we calculated SARS-CoV-2 infection incidence rates overall and approximately every 6 months during the study period (between June 2020 and August 2022). We will also estimate the incidence rates separately for primary and secondary infections, during the circulation of major SARS-CoV-2 variants, and by COVID-19 vaccination status. We will use Poisson regression to estimate adjusted infection risks by age group, primary SARS-CoV-2 variant circulating at the time of infection, previous SARS-CoV-2 infection status, and COVID-19 vaccination status, and identify other potential risk factors for infection in our cohort. Household will be accounted for as a clustering effect in the regression, using the sandwich estimator framework to calculate a clustered SE [37]. We will extrapolate the cumulative incidence of SARS-CoV-2 infections in the cohort to the general population in the Ponce region during the study, using population age and sex estimates from US census data numbers, and compare this extrapolated estimate to surveillance data from the same time period.

SARS-CoV-2 Infection Seroprevalence

Using the overall interpretation for the SARS-CoV-2 IgG antibody testing (positive only when N and either S1 or RBD antibodies are detected), we will estimate the seroprevalence of SARS-CoV-2 infection among participants of the COCOVID cohort approximately every 6 months during the study period, using specimens collected during those periods. The frequency of seroconversion, defined as a positive SARS-CoV-2 IgG antibody test result following a negative result, will be assessed over the study period at the individual and household level. For the period during which both PCR and antibody testing were occurring (between June 2020 and April 2022), we will compare the proportion of participants with seroconversion detected with SARS-CoV-2 incidence estimates from weekly PCR testing. This comparison will be used to evaluate the sensitivity and specificity of repeated serology testing at 6-month intervals in estimating infection incidence. We will also use the results of this comparison to inform estimates of SARS-CoV-2 infection incidence in the cohort that occurred between May and August 2022, when only SARS-CoV-2 IgG test results were available.

Household Attack Rate

We will assess potential household transmission of SARS-CoV-2 among households with at least 2 participating members and 1 participating member with an incident SARS-CoV-2 infection (index case) during study follow-up. Additional household cases will be defined based on the detection of SARS-CoV-2 RNA by PCR testing in a household member within 14 days of the index case. We will calculate a crude household attack rate from the proportion of additional cases among all household members deemed susceptible to acquiring SARS-CoV-2 infection from an index case. To account for household transmissions from nonindex cases and identify factors associated with household transmission, we will consider using a chain binomial transmission model to estimate the household attack rate and identify factors associated with increased and decreased likelihood of intrahousehold transmission [38,39].

Frequency of Illness Characteristics and Outcomes

Among COCOVID participants with incident infections, we will assess the frequency of symptomatic versus asymptomatic infection, self-reported symptoms, illness duration, health care seeking behaviors, and outcomes, including uncomplicated recovery, hospitalization, death, and the development of post–COVID conditions. If sample size permits, we propose using robust Poisson regression models to identify participant demographics, symptoms, and comorbidities associated with seeking care and being diagnosed with COVID-19, severe disease, and the development of self-reported post–COVID-19 conditions [40]. We will compare acute illness events reported in COCOVID weekly questionnaires associated with an incident SARS-CoV-2 infection to those not associated with SARS-CoV-2 infection to identify symptoms and symptom combinations that are highly indicative of infection [41].

Statistical Analyses of Baseline Data

In this study, we describe the baseline characteristics of the COCOVID cohort using data collected from questionnaires applied at COCOVID enrollment or within the previous year for participants previously enrolled in COPA. Frequency statistics are presented overall for the COCOVID cohort and compared to the populations of Ponce and Puerto Rico based on data from the US Census American Community Survey 2021 1-Year estimates [10,42]. Pearson chi-square tests were used for comparisons of the cohort population with those of Ponce and Puerto Rico at a household and individual level; multiple comparisons were conducted for variables with more than 2 categories, and Bonferroni-adjusted *P* values are presented. For the cohort population, individual frequency statistics were also presented by serological evidence of previous SARS-CoV-2 infection at baseline, as indicated by IgG antibody testing by timing of study enrollment, age group, sex, and annual household income. Pearson chi-square or Fisher exact tests, in the case of 1 or more expected values of <5, were used to compare categorical variables by baseline serostatus. A significance level of .05 was assumed for all comparisons, including following Bonferroni adjustment where applicable.

All analyses were conducted using R (version 4.0.4; R Core Team) [36].

Results

During the first phase of enrollment (between June 2020 and February 2021), a total of 1012 individuals from 388 households were enrolled in the COCOVID cohort; an additional 18 members of participating households were enrolled in the secondary enrollment phase, with the last participant enrolled in November 2021. Among 388 households with at least 1 COCOVID participant, 83.03% (1042/1255) of all household members were enrolled, with a mean of 3.2 participants per household; 40.27% (151/375) of households had an annual income under US $20,000 (Table 1). Of the 1030 total participants, 56.21% (579/1030) had previously participated in the COPA study, the mean age was 35.9 (range 1-97) years, and 53.40% (550/1030) were female (Table 2). Most participants identified as Latino/a (1021/1025, 99.61%) and Puerto Rican (1015/1024, 99.12%), and around two-thirds (682/1016, 67.13%) identified as White. There were 719 adult participants (aged 21 years or older; 69.8%) enrolled, of which approximately two-thirds had college or technical school degrees (197/716, 27.51%) or postgraduate study (278/716, 27.36%) and half were employed (380/717, 53.00%). More than half (389/719, 54.10%) of adult participants and 45.66% (463/1014) of all participants reported having been diagnosed with at least 1 chronic health condition.

Table 1. Annual income of households with ≥1 participant in the COPA COVID-19 (COCOVID) cohort study at baseline, between June 2020 and November 2021, compared to those of the Ponce municipality and Puerto Rico populations according to 2020 and 2021 US Census American Community Survey estimates.

Annual household income (US $)[a]	Households with ≥1 COCOVID participant (N=388), n (%)	Households in Ponce municipality (N=50,007), n (%)	*P* value[b]	Households in Puerto Rico (N=1,165,982), n (%)	*P* value[b]
<10,000	61 (16.3)	16,659 (33.3)	<.001	286,499 (24.6)	<.001
10,000-19,999	90 (24)	9,783 (19.6)	.16	250,325 (21.5)	>.99
20,000-29,999	86 (22.9)	6,792 (13.6)	<.001	176,614 (15.1)	<.001
30,000-49,999	90 (24)	7,719 (15.4)	<.001	208,722 (17.9)	.01
>50,000	48 (12.8)	9,054 (18.1)	.04	243,822 (20.9)	<.001

[a]Participants or households who declined to respond or were missing a response were excluded from the denominator in percentage calculations (<4%).

[b]*P* values for characteristics with more than 2 categories were adjusted for multiple comparisons by Bonferroni correction.

Table 2. Demographics of all participants in the COPA COVID-19 (COCOVID) cohort study at baseline, between June 2020 and November 2021, compared to those of the Ponce municipality and Puerto Rico populations according to 2020 and 2021 US Census American Community Survey estimates.

	COCOVID study participant (N=1,030), n (%)	Ponce municipality residents (N=135,084), n (%)	*P* value[a]	Puerto Rico residents (N=3,263,584), n (%)	*P* value[a]
Age group (years)					
1-9	75 (7.3)	11,105 (8.2)	>.99	254,038 (7.8)	>.99
10-17	174 (16.9)	12,603 (9.3)	<.001	291,750 (8.9)	<.001
18-24	119 (11.6)	12,823 (9.5)	.20	316,387 (9.7)	.35
25-34	129 (12.5)	17,660 (13.1)	>.99	402,204 (12.3)	>.99
35-44	181 (17.6)	14,827 (11)	<.001	400,607 (12.3)	<.001
45-54	198 (19.2)	15,391 (11.4)	<.001	415,974 (12.7)	<.001
55-64	52 (5.1)	17,600 (13)	<.001	442,138 (13.5)	<.001
≥65	102 (9.9)	33,075 (24.5)	<.001	740,486 (22.7)	<.001
Female	550 (53.4)	70,555 (52.2)	.47	1,719,593 (52.7)	.67
Identify as Latino or Latina[b]	1021 (99.6)	134,560 (99.6)	.80	3,239,060 (99.2)	.27
Race[b]					
White	682 (68.9)	45,980 (34)	<.001	914,840 (28)	<.001
Black	102 (10.3)	5,171 (3.8)	<.001	200,391 (6.1)	<.001
Other	47 (4.7)	13,477 (10)	<.001	981,183 (30.1)	<.001
Multiple races	159 (16.1)	70,456 (52.2)	<.001	1,167,170 (35.8)	<.001

[a]*P* values for characteristics with more than 2 categories were adjusted for multiple comparisons by Bonferroni correction.

[b]Participants or households who declined to respond or were missing a response were excluded from the denominator in percentage calculations (<4%).

Compared to the overall populations of both Ponce and Puerto Rico, the COCOVID cohort population differed significantly by annual household income, age group, race, education level, and employment status (Tables 1-3). Households with at least 1 COCOVID participant more frequently belonged to middle income groups of US $20,000-US $29,999 (86/375, 22.93% in cohort vs 6792/50,007, 13.58% in Ponce and 176,614/1,165,982, 15.15% in Puerto Rico) and US $30,000-US $49,000 (90/375, 24.00% vs 7719/50,007, 15.44% and 208,722/1,165,982, 17.90%), and less frequently the highest, >US $50,000 (48/375, 12.80% vs 9054/50,007, 18.11% and 243,822/1,165,982, 20.91%), and lowest, <US $10,000 (61/375, 16.27% vs 16,659/50,007, 33.31% and 286,499/1,165,982, 24.57%), income groups (*P*<.05; Table 1). The cohort had relatively high proportions of participants in the age groups of 10-17 years (174/1030, 16.89% in cohort vs 12,603/135,084, 9.33% in Ponce and 291,750/3,263,584, 8.94% in Puerto Rico), 35-44 years (181/1030, 17.57% vs 14,827/135,084, 10.98% and 400,607/3,263,584, 12.28%), and 45-54 years (198/1030, 19.22% vs 15,391/135,084, 11.39% and 415,974/3,263,584, 12.75%), and low proportions of participants in the oldest age groups, 55-64 years (52/1030, 5.05% vs 17,600/135,084, 13.03% and 442,138/3,263,584, 13.55%), and ≥65 years (102/1030, 9.90% vs 33,075/135,084, 24.48% and 740,486/3,263,584, 22.69%; *P*<.001; Table 2). Cohort participants were more frequently identified as White (683/990, 68.99% in the cohort

vs 45,980/135,084, 34.04% in Ponce and 913,840/3,263,584, 28.00% in Puerto Rico) or Black (102/990, 10.30% vs 5171/135,084, 3.83% and 200,391/3,263,584, 6.14%) and less frequently as another race (47/990, 4.75% vs 13,477/135,084, 9.98% and 981,183/3,263,584, 30.06%) or mixed race (159/990, 16.06% vs 70,456/135,084, 52.16% and 1,167,170/3,263,584, 35.76%; *P*<.001). For populations 25 years and older, cohort participants were less likely to have a less than high school education (38/659, 5.77% in cohort vs 19,235/98,553, 19.52% in Ponce and 488,780/2,401,409, 20.35% in Puerto Rico) and more likely to have some college or associate degree (186/659, 28.22% vs 21,209/98,553, 21.52% and 556,795/2,401,409, 23.19%) and a bachelor's degree or higher (268/659, 40.67% vs 31,402/98,553, 31.86% and 683,894/2,401,409, 28.48%; *P*<.001; Table 3). Additionally, cohort participants aged 25 years or older were more likely to be in the labor force relative to Ponce and Puerto Rico residents in the same age group, including in employed (356/644, 55.28% vs 35,976/98,553, 36.50% and 977,860/2,401,409, 40.72%) and unemployed groups (74/644, 11.49% vs 6037/98,553, 6.13% and 119,812/2,401,409, 4.99%; *P*<.001).

At enrollment, 1.55% (16/1030) of COCOVID participants were seropositive for SARS-CoV-2, of which the median age was 46 (IQR 33-51) years, 56.25% (9/16) were male, and half (50.00%, 8/16) reported chronic health conditions (Table 4). There was a significant difference in the timing of study enrollment among participants with and without baseline seropositivity for SARS-CoV-2, with a higher proportion of seropositive participants recruited in the later months of the study (*P*=.003). No significant differences by age group, sex, or household income were observed among participants that were seropositive and those that were seronegative at baseline.

Table 3. Education level and employment status of adult participants aged ≥25 years in the COPA COVID-19 (COCOVID) cohort study at baseline, between June 2020 and November 2021, compared to those of the Ponce municipality and Puerto Rico populations according to 2020 and 2021 US Census American Community Survey estimates.

	COCOVID study participants aged ≥25 years (N=662), n (%)	Ponce municipality residents aged ≥25 years (N=98,553), n (%)	*P* value[a]	Puerto Rico residents aged ≥25 years (N=2,401,409), n (%)	*P* value[a]
Educational attainment[b]					
Less than high school graduate	38 (5.7)	19,235 (19.5)	<.001	488,780 (20.4)	<.001
High school graduate or equivalent	167 (25.3)	26,707 (27.1)	>.99	671,940 (28)	.13
Some college or associate degree	186 (28.2)	21,209 (21.5)	<.001	556,795 (23.2)	.01
Bachelor's degree or higher	268 (40.7)	31,402 (31.9)	<.001	683,894 (28.5)	<.001
Employment status[b]					
Employed	356 (55.3)	35,976 (36.5)	<.001	977,860 (40.7)	<.001
Unemployed	74 (11.5)	6,037 (6.1)	<.001	119,812 (5)	<.001

[a]*P* values for characteristics with more than 2 categories were adjusted for multiple comparisons by Bonferroni correction.

[b]Participants or households who declined to respond or were missing a response were excluded from the denominator in percentage calculations (<4%).

Table 4. Timing of study enrollment and demographics and of participants by serological evidence of previous SARS-CoV-2 infection at baseline, COPA COVID-19 (COCOVID) study, Ponce, Puerto Rico, between June 2020 and November 2021 (N=1030).

	Participants seropositive for SARS-CoV-2 at baseline (N=16), n (%)	Participants seronegative for SARS-CoV-2 at baseline (N=1014), n (%)	Prevalence of seropositivity for SARS-CoV-2 at baseline	*P* value
Timing of study enrollment				.003
June-August 2020	0 (0)	324 (32)	0	
September-November 2020	5 (31.3)	405 (39.9)	1.2	
December 2020–February 2021	10 (62.5)	268 (26.4)	3.6	
March 2021 or later	1 (6.3)	17 (1.7)	5.6	
Age group (years)				.24
1-17	1 (6.3)	248 (24.5)	0.4	
18-34	4 (25)	244 (24.1)	1.6	
35-49	5 (31.3)	301 (29.7)	1.6	
50-64	4 (25)	121 (11.9)	3.2	
≥65	2 (12.5)	100 (9.9)	1.9	
Sex				.46
Female	7 (43.8)	543 (53.6)	1.3	
Male	9 (56.3)	471 (46.5)	1.9	
Annual income for household (US $)[a]				.12
<10,000	3 (18.8)	172 (17)	1.7	
10,000-19,999	5 (31.3)	208 (20.6)	2.3	
20,000-29,999	0 (0)	234 (23.2)	0	
30,000-49,999	5 (31.3)	241 (23.9)	2	
>50,000	3 (18.8)	133 (13.2)	2.2	

[a]Participants that declined to respond were excluded from the denominator in percentage calculations (<3%).

Discussion

Few studies with prospective assessments of incident SARS-CoV-2 infections at the community level have been described to date, and none have been implemented in Puerto Rico or other primarily Latino or Hispanic US populations [17-19,43-45]. The COCOVID community-based cohort study provides a unique opportunity to assess SARS-CoV-2 infection incidence, risk factors, and outcomes in Puerto Rico and also help further characterize asymptomatic infections, household transmission, and serological and molecular testing dynamics. We were able to build the COCOVID study into an existing cohort study platform, allowing for rapid enrollment and the implementation of extensive data collection activities. Prospective follow-up through weekly PCR testing of participants and regular serology testing enabled comprehensive detection of SARS-CoV-2 infections within the cohort population. Additionally, our large sample size and extended follow-up period strengthened our assessment of SARS-CoV-2 incidence and outcomes by time-dependent factors, including lockdown measures, circulating SARS-CoV-2 variants, and COVID-19 vaccination status.

COCOVID surpassed its enrollment goal with 1030 participants with minimum sample size goals (n=215) reached in the 3 age groups of interest (1-17 years, 18-49 years, and ≥50 years). The cohort included participants with characteristics associated with increased COVID-19 morbidity risk [3,46,47], although sometimes with lower frequency than the general populations for Ponce and Puerto Rico. Consistent with these populations, almost all COCOVID participants identified as Latino/a. Chronic health condition prevalence was high among adults in the cohort and in accordance with estimates from the Behavioral Risk Factor Surveillance System [48]. The cohort had relatively low proportions of participants in the oldest (≥65 years) age group and households in the lowest (<US $10,000) annual income group compared to Ponce and Puerto Rico populations. However, these groups still accounted for at least 10% of cohort participants and households, respectively, which should facilitate adjusted analyses and extrapolation of results to the general population. SARS-CoV-2 seroprevalence at enrollment was low and increased among cohort participants enrolled later in the study period. The low but increasing seroprevalence of SARS-CoV-2 observed among study participants at baseline over time is consistent with surveillance data from the region [14]. As a result, there was a limited sample size to assess differences in SARS-CoV-2 seroprevalence by age group and other characteristics, and factors associated with the seroprevalence of SARS-CoV-2 infection will be explored more fully using follow-up data from the study.

We did not use a formal sampling frame, but rather our sampling strategy was determined by logistic constraints to include a limited selection of community areas with primarily single-resident homes and no public housing or large apartment buildings. Additionally, most of our participants were previously enrolled in the larger COPA cohort, whose eligibility was restricted to participants younger than 50 years. This likely led to the observed oversampling of larger, middle-income households and employed, middle-aged adults and their children relative to the overall populations of Ponce and Puerto Rico. Additionally, individuals who agreed to enroll in COCOVID (and COPA) may be more concerned about disease risks and more likely to take measures to prevent SARS-CoV-2 infection than the general populations of Ponce and Puerto Rico. However, there was diversity across sociodemographic indicators in our study population, and the detailed data collected on household and individual characteristics and preventive behaviors can be used to adjust for these potential impacts on SARS-CoV-2–related outcomes and extrapolate our findings to the general population, where possible.

Despite tremendous progress in our understanding of SARS-CoV-2 transmission and control, including the development of effective vaccines, the persistence of health inequities and other challenges underpin the need for more comprehensive data to inform mitigation measures and prevent future outbreaks. The COCOVID study provides a valuable opportunity to investigate community and household SARS-CoV-2 infections in a primarily Hispanic or Latino population with diversity across several risk factors for COVID-19. Study methodology supports thorough detection of asymptomatic and symptomatic infections to help us better estimate the burden of SARS-CoV-2 in the region and assess the limitations of surveillance, which currently remains the primary resource for SARS-CoV-2 data for the island.

Acknowledgments

The authors would like to acknowledge the hard work of our study field team, including Emma Ramírez, Suheil Albizu, Lismarie Santiago Vargas, Aimara Medina, Evelynette Pérez, Juan Santiago, Kasey Kinzel, Nicole León, Wilmarie Rivera, Jared Abraham, Aurora Castillo, and José Molina, and the support of CDC staff and deployers in conducting participant recruitment, data collection, and cleaning activities. We would like to thank Ronald Cancel Santiago, Cindia Díaz, and Oscar Padro for designing and implementing critical data management systems, including those for weekly visit tracking and automated data entry of paper questionnaires.

Authors affiliated with Ponce Health Sciences University and Ponce Research Institute wish to provide acknowledgement of their grant (U01CK000580).

Data Availability

The data sets generated and analyzed during this study are not publicly available due to data security and confidentiality guidelines determined by the study governance board, but are available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

References

1. Bottan N, Hoffmann B, Vera-Cossio D. The unequal impact of the coronavirus pandemic: evidence from seventeen developing countries. PLoS One 2020;15(10):e0239797 [FREE Full text] [doi: 10.1371/journal.pone.0239797] [Medline: 33027272]
2. Sepulveda ER, Brooker AS. Income inequality and COVID-19 mortality: age-stratified analysis of 22 OECD countries. SSM Popul Health 2021;16:100904 [FREE Full text] [doi: 10.1016/j.ssmph.2021.100904] [Medline: 34584934]
3. Mackey K, Ayers CK, Kondo KK, Saha S, Advani SM, Young S, et al. Racial and ethnic disparities in COVID-19-Related infections, hospitalizations, and deaths : a systematic review. Ann Intern Med 2021;174(3):362-373 [FREE Full text] [doi: 10.7326/M20-6306] [Medline: 33253040]
4. COVID data tracker: cases, deaths, and testing. Centers for Disease Control and Prevention. URL: https://covid.cdc.gov/covid-data-tracker/#trends_totalcases [accessed 2022-04-20]
5. Mistry P, Barmania F, Mellet J, Peta K, Strydom A, Viljoen IM, et al. SARS-CoV-2 variants, vaccines, and host immunity. Front Immunol 2021;12:809244 [FREE Full text] [doi: 10.3389/fimmu.2021.809244] [Medline: 35046961]
6. Tian D, Sun Y, Xu H, Ye Q. The emergence and epidemic characteristics of the highly mutated SARS-CoV-2 Omicron variant. J Med Virol 2022;94(6):2376-2383 [FREE Full text] [doi: 10.1002/jmv.27643] [Medline: 35118687]
7. Olney AM, Smith J, Sen S, Thomas F, Unwin HJT. Estimating the effect of social distancing interventions on COVID-19 in the United States. Am J Epidemiol 2021;190(8):1504-1509 [FREE Full text] [doi: 10.1093/aje/kwaa293] [Medline: 33406533]

8. Fischer CB, Adrien N, Silguero JJ, Hopper JJ, Chowdhury AI, Werler MM. Mask adherence and rate of COVID-19 across the United States. PLoS One 2021;16(4):e0249891 [FREE Full text] [doi: 10.1371/journal.pone.0249891] [Medline: 33852626]
9. Robinson E, Jones A, Lesser I, Daly M. International estimates of intended uptake and refusal of COVID-19 vaccines: a rapid systematic review and meta-analysis of large nationally representative samples. Vaccine 2021;39(15):2024-2034 [FREE Full text] [doi: 10.1016/j.vaccine.2021.02.005] [Medline: 33722411]
10. 2020 decennial census: Puerto Rico. U.S. Census Bureau. 2020. URL: https://data.census.gov/cedsci/table?q=Puerto%20Rico&tid=DECENNIALPL2020.P1 [accessed 2021-09-24]
11. Puerto Rico: fast facts. Kaiser Family Foundation. 2017. URL: https://www.kff.org/racial-equity-and-health-policy/fact-sheet/puerto-rico-fast-facts/ [accessed 2021-09-01]
12. Perreira K, Lallemand N, Napoles A, Zuckerman S. Environmental scan of Puerto Rico's health care infrastructure. Urban Institute. 2017. URL: https://www.urban.org/research/publication/environmental-scan-puerto-ricos-health-care-infrastructure [accessed 2024-02-02]
13. García C, Rivera FI, Garcia MA, Burgos G, Aranda MP. Contextualizing the COVID-19 era in Puerto Rico: compounding disasters and parallel pandemics. J Gerontol B Psychol Sci Soc Sci 2021;76(7):e263-e267 [FREE Full text] [doi: 10.1093/geronb/gbaa186] [Medline: 33112945]
14. COVID-19 en CIFRAS en Puerto Rico. Departamento de Salud de Puerto Rico. 2023. URL: https://www.salud.pr.gov/CMS/342 [accessed 2022-04-20]
15. Volkman HR, Pérez-Padilla J, Wong JM, Sánchez-González L, Acevedo-Molina L, Lugo-Menéndez M, et al. Characteristics and clinical outcomes of patients hospitalized with laboratory-confirmed COVID-19-Puerto Rico, march-august 2020. PLoS One 2021;16(12):e0260599 [FREE Full text] [doi: 10.1371/journal.pone.0260599] [Medline: 34855817]
16. Jones JM, Stone M, Sulaeman H, Fink RV, Dave H, Levy ME, et al. Estimated US infection- and vaccine-induced SARS-CoV-2 seroprevalence based on blood donations, july 2020-may 2021. JAMA 2021;326(14):1400-1409 [FREE Full text] [doi: 10.1001/jama.2021.15161] [Medline: 34473201]
17. Dawood FS, Porucznik CA, Veguilla V, Stanford JB, Duque J, Rolfes MA, et al. Incidence rates, household infection risk, and clinical characteristics of SARS-CoV-2 infection among children and adults in Utah and New York City, New York. JAMA Pediatr 2022;176(1):59-67 [FREE Full text] [doi: 10.1001/jamapediatrics.2021.4217] [Medline: 34623377]
18. Karron RA, Hetrich MK, Na YB, Knoll MD, Schappell E, Meece J, et al. Assessment of clinical and virological characteristics of SARS-CoV-2 infection among children aged 0 to 4 years and their household members. JAMA Netw Open 2022;5(8):e2227348 [FREE Full text] [doi: 10.1001/jamanetworkopen.2022.27348] [Medline: 36044218]
19. McLean HQ, McClure DL, King JP, Meece JK, Pattinson D, Neumann G, et al. mRNA COVID-19 vaccine effectiveness against SARS-CoV-2 infection in a prospective community cohort, rural Wisconsin, november 2020 to december 2021. Influenza Other Respir Viruses 2022;16(4):607-612 [FREE Full text] [doi: 10.1111/irv.12970] [Medline: 35178857]
20. Oran DP, Topol EJ. The proportion of SARS-CoV-2 infections that are asymptomatic : a systematic review. Ann Intern Med 2021;174(5):655-662 [FREE Full text] [doi: 10.7326/M20-6976] [Medline: 33481642]
21. Buitrago-Garcia D, Ipekci AM, Heron L, Imeri H, Araujo-Chaveron L, Arevalo-Rodriguez I, et al. Occurrence and transmission potential of asymptomatic and presymptomatic SARS-CoV-2 infections: update of a living systematic review and meta-analysis. PLoS Med 2022;19(5):e1003987 [FREE Full text] [doi: 10.1371/journal.pmed.1003987] [Medline: 35617363]
22. Adams LE, Sánchez-González L, Rodriguez DM, Ryff K, Major C, Lorenzi O, et al. Risk factors for infection with chikungunya and Zika viruses in southern Puerto Rico: a community-based cross-sectional seroprevalence survey. PLoS Negl Trop Dis 2022;16(6):e0010416 [FREE Full text] [doi: 10.1371/journal.pntd.0010416] [Medline: 35696355]
23. Sánchez-González L, Adams LE, Saavedra R, Little EM, Medina NA, Major CG, et al. Assessment of community support for Wolbachia-mediated population suppression as a control method for Aedes aegypti mosquitoes in a community cohort in Puerto Rico. PLoS Negl Trop Dis 2021;15(12):e0009966 [FREE Full text] [doi: 10.1371/journal.pntd.0009966] [Medline: 34871301]
24. Lyra SARS-CoV-2 Assay. QuidelOrtho. 2020. URL: https://www.quidelortho.com/sv/en/products/lyra-assays/lyra-sars-cov-2-assay [accessed 2024-02-02]
25. ThermoFisher S. TaqPath™ COVID-19 combo kit. ThermoFisher Scientific. 2020. URL: https://www.fda.gov/media/136112/download [accessed 2024-02-02]
26. TaqPath™ COVID-19, FluA, FluB combo kit. ThermoFisher Scientific. 2021. URL: https://www.fda.gov/media/145931/download [accessed 2024-02-02]
27. cobas® SARS-CoV-2. Roche. 2022. URL: https://www.fda.gov/media/136049/download [accessed 2024-02-02]
28. Guidance for reporting SARS-CoV-2 sequencing results. U.S. Centers for Disease Control and Prevention. 2021. URL: https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/reporting-sequencing-guidance.html [accessed 2021-11-03]
29. xMAP® SARS-CoV-2 Multi-Antigen IgG Assay (EUA). Luminex. 2020. URL: https://www.luminexcorp.com/?wpdmdl=42625 [accessed 2024-02-02]
30. CDC DENV-1-4 Real-Time RT-PCR multiplex assay. Centers for Disease Control and Prevention. 2019. URL: https://www.cdc.gov/dengue/healthcare-providers/testing/molecular-tests/realtime.html [accessed 2024-02-02]

31. Namekar M, Ellis EM, O'Connell M, Elm J, Gurary A, Park SY, et al. Evaluation of a new commercially available immunoglobulin M capture enzyme-linked immunosorbent assay for diagnosis of dengue virus infection. J Clin Microbiol 2013;51(9):3102-3106 [FREE Full text] [doi: 10.1128/JCM.00351-13] [Medline: 23824771]
32. Dean AG, Arner TG, Sunki GG, Friedman R, Lantinga M, Sangam S, et al. Epi Info™, a database and statistics program for public health professionals. Centers for Disease Control and Prevention. Atlanta, GA, USA; 2011. URL: https://stacks.cdc.gov [accessed 2024-02-02]
33. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: building an international community of software platform partners. J Biomed Inform 2019;95:103208 [FREE Full text] [doi: 10.1016/j.jbi.2019.103208] [Medline: 31078660]
34. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42(2):377-381 [FREE Full text] [doi: 10.1016/j.jbi.2008.08.010] [Medline: 18929686]
35. Microsoft Azure form recognizer. Azure. 2022. URL: https://azure.microsoft.com/en-us/services/form-recognizer/#overview [accessed 2024-02-02]
36. R Core Team. R: a language and environment for statistical computing. R Foundation for Statistical Computing. Vienna, Austria; 2022. URL: https://www.r-project.org/ [accessed 2024-02-02]
37. Zeileis A, Köll S, Graham N. Various versatile variances: an object-oriented implementation of clustered covariances in R. J Stat Soft 2020;95(1):1-36. [doi: 10.18637/jss.v095.i01]
38. Sharker Y, Kenah E. Estimating and interpreting secondary attack risk: binomial considered biased. PLoS Comput Biol 2021;17(1):e1008601 [FREE Full text] [doi: 10.1371/journal.pcbi.1008601] [Medline: 33471806]
39. Li F, Li YY, Liu MJ, Fang LQ, Dean NE, Wong GWK, et al. Household transmission of SARS-CoV-2 and risk factors for susceptibility and infectivity in Wuhan: a retrospective observational study. Lancet Infect Dis 2021;21(5):617-628 [FREE Full text] [doi: 10.1016/S1473-3099(20)30981-6] [Medline: 33476567]
40. Chen W, Qian L, Shi J, Franklin M. Comparing performance between log-binomial and robust Poisson regression models for estimating risk ratios under model misspecification. BMC Med Res Methodol 2018;18(1):63 [FREE Full text] [doi: 10.1186/s12874-018-0519-5] [Medline: 29929477]
41. Antonelli M, Capdevila J, Chaudhari A, Granerod J, Canas LS, Graham MS, et al. Optimal symptom combinations to aid COVID-19 case identification: analysis from a community-based, prospective, observational cohort. J Infect 2021;82(3):384-390 [FREE Full text] [doi: 10.1016/j.jinf.2021.02.015] [Medline: 33592254]
42. 2021: ACS 1-year estimates Puerto Rico public use microdata sample. US Census Bureau. 2021. URL: https://www.census.gov/data/developers/data-sets/census-microdata-api.html [accessed 2024-02-02]
43. Lanata CF, Gil AI, Ecker L, Cornejo R, Rios S, Ochoa M, et al. SARS-CoV-2 infections in households in a peri-urban community of Lima, Peru: a prospective cohort study. Influenza Other Respir Viruses 2022;16(3):386-394 [FREE Full text] [doi: 10.1111/irv.12952] [Medline: 34962079]
44. Miller EM, Law EA, Ajeen R, Karasik J, Mendoza C, Abernathy H, et al. SARS-CoV-2 infection in central North Carolina: protocol for a population-based longitudinal cohort study and preliminary participant results. PLoS One 2021;16(10):e0259070 [FREE Full text] [doi: 10.1371/journal.pone.0259070] [Medline: 34695156]
45. Brasil P, Damasceno L, Fuller T, Bastos LS, Cruz OG, Medeiros F, et al. Cohort-profile: household transmission of SARS-CoV-2 in a low-resource community in Rio de Janeiro, Brazil. BMJ Open 2022;12(12):e067212 [FREE Full text] [doi: 10.1136/bmjopen-2022-067212] [Medline: 36600372]
46. Dessie ZG, Zewotir T. Mortality-related risk factors of COVID-19: a systematic review and meta-analysis of 42 studies and 423,117 patients. BMC Infect Dis 2021;21(1):855 [FREE Full text] [doi: 10.1186/s12879-021-06536-3] [Medline: 34418980]
47. Khanijahani A, Iezadi S, Gholipour K, Azami-Aghdash S, Naghibi D. A systematic review of racial/ethnic and socioeconomic disparities in COVID-19. Int J Equity Health 2021;20(1):248 [FREE Full text] [doi: 10.1186/s12939-021-01582-4] [Medline: 34819081]
48. BRFSS Prevalence and Trends Data. Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Division of Population Health. 2020. URL: https://www.cdc.gov/brfss/brfssprevalence/ [accessed 2023-08-24]

Abbreviations

AIS: acute illness surveillance
CDC: Centers for Disease Control and Prevention
COCOVID: Communities Organized to Prevent Arboviruses COVID-19
COPA: Communities Organized to Prevent Arboviruses
DB: Dengue Branch
DENV: dengue virus
Ig: immunoglobulin

N: nucleocapsid
PCR: polymerase chain reaction
RBD: receptor binding domain
REDCap: Research Electronic Data Capture
rRT-PCR: real-time reverse transcriptase–polymerase chain reaction
S: spike

Edited by A Mavragani; submitted 20.10.23; peer-reviewed by E Meyerowitz, A Fleischauer; comments to author 07.12.23; accepted 19.01.24; published 19.04.24.

Please cite as:
Major CG, Rodríguez DM, Sánchez-González L, Rodríguez-Estrada V, Morales-Ortíz T, Torres C, Pérez-Rodríguez NM, Medina-Lópes NA, Alexander N, Mabey D, Ryff K, Tosado-Acevedo R, Muñoz-Jordán J, Adams LE, Rivera-Amill V, Rolfes M, Paz-Bailey G Investigating SARS-CoV-2 Incidence and Morbidity in Ponce, Puerto Rico: Protocol and Baseline Results From a Community Cohort Study
JMIR Res Protoc 2024;13:e53837
URL: https://www.researchprotocols.org/2024/1/e53837
doi:10.2196/53837
PMID:38640475

Protocol

Capturing the Dynamics of Homelessness Through Ethnography and Mobile Technology: Protocol for the Development and Testing of a Smartphone Technology–Supported Intervention

Marva Foster[1,2], PhD; Gemmae M Fix[2,3], PhD; Justeen Hyde[2,3], PhD; Shawn Dunlap[3], MA; Thomas H Byrne[3,4], PhD; Naomi F Sugie[5], PhD; Randall Kuhn[6], PhD; Sonya Gabrielian[7,8], MD, MPH; Jill S Roncarati[3,9,10], SCD, MPH; Shibei Zhao[3], MS; D Keith McInnes[3,11], MSc, SCD

[1]Center for Healthcare Organization and Implementation Research, VA Boston Healthcare System, Boston, MA, United States

[2]Department of General Internal Medicine, Boston University Chobanian & Avedisian School of Medicine, Boston, MA, United States

[3]Center for Healthcare Organization and Implementation Research, VA Bedford Healthcare System, Bedford, MA, United States

[4]Department of Social Welfare Policy, Boston University School of Social Work, Boston, MA, United States

[5]Department of Criminology, Law and Society, University of California Irvine, Irvine, CA, United States

[6]Department of Community Health Services, Fielding School of Public Health, University of California Los Angeles, Los Angeles, CA, United States

[7]Department of Mental Health, VA Greater Los Angeles, Los Angeles, CA, United States

[8]Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, United States

[9]Department of Health Policy and Management, Harvard TH Chan School of Public Health, Boston, MA, United States

[10]Boston Health Care for the Homeless Program, Boston, MA, United States

[11]Department of Health Law, Policy and Management, Boston University School of Public Health, Boston, MA, United States

Corresponding Author:
Marva Foster, PhD
Center for Healthcare Organization and Implementation Research
VA Boston Healthcare System
150 S Huntington Ave
Boston, MA, 02130
United States
Phone: 1 857 203 6671
Email: marva.foster@va.gov

Abstract

Background: US military veterans who have experienced homelessness often have high rates of housing transition. Disruptions caused by these transitions likely exacerbate this population's health problems and interfere with access to care and treatment engagement. Individuals experiencing homelessness increasingly use smartphones, contributing to improved access to medical and social services. Few studies have used smartphones as a data collection tool to systematically collect information about the daily life events that precede and contribute to housing transitions, in-the-moment emotions, behaviors, geographic movements, and perceived social support.

Objective: The study aims to develop and test a smartphone app to collect longitudinal data from veterans experiencing homelessness (VEH) and to evaluate the feasibility and acceptability of using the app in a population that is unstably housed or homeless.

Methods: This study's design had 3 phases. Phase 1 used ethnographic methods to capture detailed data on day-to-day lived experiences of up to 30 VEH on topics such as housing stability, health, and health behaviors. Phase 2 involved focus groups and usability testing to develop and refine mobile phone data collection methods. Phase 3 piloted the smartphone mobile data collection with 30 VEH. We included mobile ethnography, real-time surveys through an app, and the collection of GPS data in phase 3.

Results: The project was launched in June 2020, and at this point, some data collection and analysis for phases 1 and 2 are complete. This project is currently in progress.

Conclusions: This multiphase study will provide rich data on the context and immediate events leading to housing transitions among VEH. This study will ensure the development of a smartphone app that will match the actual needs of VEH by involving

them in the design process from the beginning. Finally, this study will offer important insights into how best to develop a smartphone app that can help intervene among VEH to reduce housing transitions.

International Registered Report Identifier (IRRID): DERR1-10.2196/53022

(JMIR Res Protoc 2024;13:e53022) doi:10.2196/53022

KEYWORDS

ethnography; homelessness; housing transitions; longitudinal data; military; mobile technology; smartphone; social support; veterans

Introduction

Background and Rationale

US military veterans are at greater risk of homelessness compared to their civilian counterparts [1,2]. Those experiencing homelessness are at increased risk of premature mortality, with a 2-decade–shorter life expectancy than the general population [3]. They experience an elevated burden of mental illness, substance use disorder, hypertension, and cardiovascular disease [4-6] as well as infectious diseases such as HIV or AIDS, tuberculosis, and hepatitis C [7]. Although homelessness is often episodic, it can occur over a long period of time for some. Commonly, those experiencing homelessness transition between different types of accommodations: homeless shelters, doubled-up with family or friends, or staying in places not meant for human habitation (eg, encampments, vehicles, and abandoned buildings) [1]. These frequent housing transitions likely exacerbate poor health, social well-being, and economic vulnerability [8,9]. There is a major gap in detailed, contextual knowledge of these transitions, such as information about in-the-moment emotions, behaviors, geographic movements, and perceived social support.

Having a greater understanding of these in-the-moment experiences may help inform efforts to better identify people who are at risk of an unexpected or unwanted housing transition and intervene to prevent a homeless episode. Without real-time information, it is difficult to understand the point-in-time contextual nuances of an individual's housing transition and provide support to mitigate these transitions. Previous work, whether quantitative or ethnographic, has been limited by the methodological difficulty of retrospectively gathering this type of contextual data about distinct points in time in the past [10,11]. Studies show that perceptions of emotions and behaviors are unreliable when gathered retrospectively [12,13]. Another factor that has limited understanding of the nuances of transition among veterans experiencing homelessness (VEH) is their lack of trust in people generally and in certain entities in particular (eg, "government") [14]. Previous research indicates that smartphones are already being widely used by homeless populations, and those populations view smartphones as a trusted source to communicate and receive information [15,16]. Smartphone technology shows promise for enhancing our understanding of short-term precipitants and helping us gain a better understanding of the in-the-moment experiences that lead to housing transitions.

Smartphone apps support the collection of real-time data, which involves the use of ecological momentary assessment (EMA). EMA allows researchers to measure participants' real-world emotions and behaviors in real-time in their natural environments [17]. Mood has been identified in numerous studies as being predictive of activity; it interacts with social support [18], is an indicator of daily stressors [19], and acts as a mediator of a variety of outcomes [20]. Additionally, technology such as GPS, which can be collected through smartphones, can provide accompanying information on daily changes in geographic movement. When analyzed with other data, this may provide insight on potential factors that precipitate a housing transition. Yet few studies have used smartphone apps to gather detailed, contextual knowledge on housing transitions among VEH. Notably, smartphone ownership among persons experiencing homelessness is growing and almost equivalent to that of the general population [21,22].

Thus, this study is among the first to design and test the feasibility and acceptability of a smartphone app that uses real-time surveys and GPS to collect longitudinal data from a population that is unstably housed. This protocol paper details the specific phases and methods used to prepare for and conduct a longitudinal smartphone data collection study with a sample of veterans.

Objective

We aim to develop and test a smartphone app to collect longitudinal data from VEH and to evaluate the feasibility and acceptability of using the app in a population that is unstably housed or homeless.

Methods

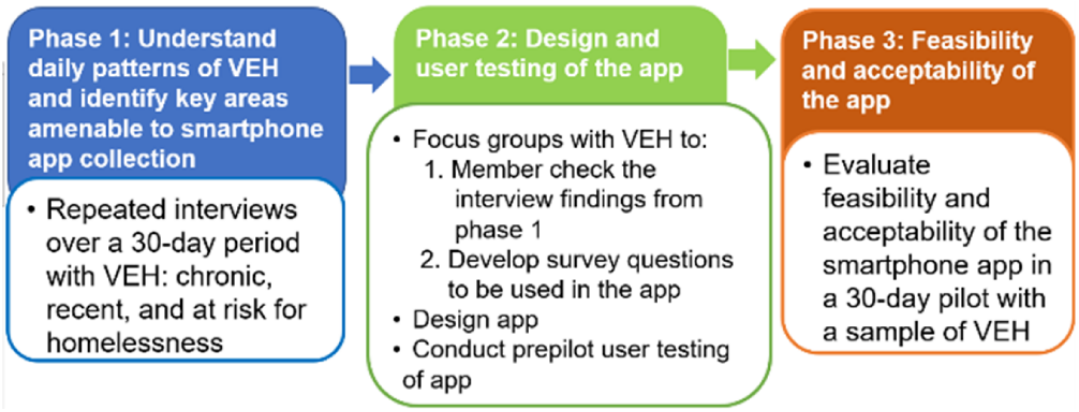
Participating Institutions

The US Department of Veterans Affairs (VA) Center for Healthcare Organization and Implementation Research (CHOIR) leads the study. CHOIR invited university partners to participate to provide the types of additional expertise needed for this initiative. Joining the team are members of Boston University's Software and Application Innovation Lab (SAIL). SAIL is a professional research, software engineering, and consulting lab that acts as both a driver and a collaborative partner for computational and data-oriented research efforts. Also joining are RK, a demographer from the University of California Los Angeles, and NFS, a sociologist from the University of California Irvine. RK brings expertise in defining study populations, including extensive experience studying and conducting interventions for persons experiencing homelessness, and NFS has a depth of expertise in developing smartphone data collection tools for vulnerable populations.

Design

This multistage study involves identifying the needs of VEH, designing an app, and pilot-testing it (Figure 1). Phase 1 involves repeated interviews over a 30-day period to understand app use and contexts of app use among persons at risk for or experiencing either chronic or recent homelessness. Phase 2 involves focus group discussions with VEH to members check the interview findings from phase 1 and develop survey questions to be used in the designed app. Additionally, user testing methods will be used to refine questions as needed. Lastly, in phase 3, we will test the feasibility and acceptability of the developed app with a sample of VEH.

Figure 1. Project design showing the 3 phases of the project. VEH: veterans experiencing homelessness.



Study Settings

The study is being conducted at 2 locations in the northeastern region of the United States to achieve diversity in the participant samples. Site 1 is one of the VA health care system's 172 medical centers, located about 15 miles north of a major city. It is one of the largest providers of services to VEH and provides a range of health and social services to veterans living in suburban and rural areas. This site is a multiservice residential program serving veterans who are experiencing homelessness or at risk for homelessness. Site 2 is located in the center of a dense urban area. This site is a multiservice community-based residential program serving veterans who are experiencing homelessness and at risk for homelessness.

Phase 1: Understand Daily Patterns of VEH and Identify Key Areas Amenable to Smartphone App Collection

Sampling of Participants and Recruitment

Using a convenience sampling strategy, we will recruit participants from 3 locations with a range of experiences with homelessness, including chronic homelessness, a recent onset of homelessness, or being at-risk for homelessness. For the purposes of this study, we define chronic homelessness as having a pattern of multiple episodes (or a single long episode) of homelessness over an extended period (ie, a year or more). We define recent onset as newly homeless, with the period of homelessness having begun in the last 6 months but not having a history of being chronically homeless. Lastly, we define being at risk as being at imminent risk of losing one's housing [23]. Recruitment will begin with the study team hosting informational sessions, followed by sharing and posting flyers at the residential programs at sites 1 and 2. Those who express interest will be approached by study team members during informational sessions or later contacted by telephone. They will then be screened for their current homeless experience (chronic, recent-onset, and at-risk) to confirm that they meet eligibility criteria.

Procedures

A 30-day focused ethnographic data collection design will be used to understand the daily patterns of VEH and identify key areas amenable to smartphone app collection. Individuals will be interviewed multiple times over a 30-day period. This time frame will be consistent with the one planned for the phase 3 pilot study of smartphone-enabled data collection and will offer proof of the concept of engagement in this later work. The focused ethnographic approach will include four different types of interviews. Interview types will include (1) a baseline, historical interview (with structured and open-ended components) that will last between 60 and 90 minutes; (2) long interviews that will focus on a "special topic" (perceptions of health, social services, and technology, including the use of smartphones) of interest to the study and will last approximately 60 minutes; (3) a general short interview, twice a week, that will last approximately 15 minutes; and (4) a final follow-up interview to obtain feedback on participation in the multiweek study. Textbox 1 shows an overview of the interview schedule, and Textbox 2 shows a description of interview topics.

Both the long and short interviews will provide an opportunity to ask VEH their opinions about the most important things to ask on a regular basis that might influence stability in housing, how to ask about sensitive topics like substance use, and about potential concerns with answering questions through a smartphone app.

Textbox 1. Phase 1 30-day illustrative interview schedule.

Weeks and interview schedule

- Week 1: baseline interview 1, short interview 2, short interview 3, and long interview 4
- Week 2: short interview 5, short interview 6, and long interview 7
- Week 3: short interview 8, short interview 9, and long interview 10
- Week 4: short interview 11, short interview 12, and final interview 13

Textbox 2. Interview types and the structured and unstructured ethnographic data collected over the course of the phase 1 30-day interviews.

Interview types and descriptions

- Baseline interview: This interview is designed to:
  - Gain a deeper understanding of participants' housing history using a modified Residential Time-Line Follow-Back Inventory [24].
  - Collect information on key social relationships, military experiences, and employment opportunities that may have influenced the life course of veterans experiencing homelessness.
  - Collect and record demographic information on a short survey form.
- Long qualitative interviews: longer "special topic" interviews to gain insights into 3 different topics
  - Physical and mental health (eg, perception of overall health, experience with physical and mental health conditions and the extent to which they impact everyday life, and perceptions of the impact of health conditions on housing stability) and its impact on housing stability.
  - Access to and use of social services (eg, places participants go for financial, logistical, or social support to meet needs, facilitators, and barriers to accessing different types of support, and perceptions of how support influences housing stability).
  - Use of technology (eg, types and uses of phones, including common apps and phone features).
- Short qualitative interviews: interviews will occur 2-3 times per week, last approximately 15 minutes, and happen between the longer special topic interviews. These interviews will explore participants' feelings, where they slept the night before, and any changes in their lives since the last conversation.
- Final interview: a 60-minute interview to obtain feedback from participants on the experience of engaging with a research team over a prolonged period.

Analysis Phase 1

Quantitative Data Analyses

Demographic characteristics like recent life experiences, homelessness episodes, overall health and health conditions, and social service use of participants will be entered into an Excel (Microsoft Corporation) spreadsheet. We will use descriptive statistics to summarize the characteristics of these participants.

Qualitative Data Analyses

All interviews will be professionally transcribed verbatim. Data will be analyzed using a Rapid Assessment, Response, and Evaluation approach [25], which uses a multidisciplinary team to collect different types of data that can be synthesized and analyzed iteratively and efficiently to generate an understanding of critical health and public health issues. Each participant in phase 1 will have a portfolio of data from their multiweek study period. Analysis will entail attention to both the cumulative story and key changes that might impact housing transitions or health. Once the transcript of each interview is available, a standardized template will be created to systematically summarize data with attention to transitions in housing and health for each participant. The summarized information will be examined to identify patterns, common concepts, and emerging ideas about current events and experiences that influence transitions in housing and health. For each participant, the lead interviewer will compile and analyze the portfolio of data. They will create a summary template that systematically synthesizes the data across the 4 weeks of data collection. This summary template will contain key fields such as transitions in housing and health for each participant, as well as key events such as fluctuations in mood and disposition, social networks, and experience with health and social services. After completion, a second team member, not involved in that participant's data collection, will review the summary template. The team will discuss the data until consensus is reached. This process will ensure consistency, clarity, and rigor. Following this process, team members will be designated to draft questions aligned with transitions in housing, health, and key events. These members will be instructed to first look for validated questions that may be appropriate. If none exist, they will draft questions for group review. Through a series of meetings, the full team will review all drafted questions and make decisions about which ones to include, exclude, and modify for a smartphone app format. This information will be used to inform phase 2 data collection and analysis.

Phase 2: Design and User Testing of the App

Sampling of Participants and Recruitment

Phase 2 will use the same recruitment and consenting strategy as phase 1. Phase 2 focus group participants will be recruited from site 2.

Procedures

Focus Groups

Focus groups will take place at a nearby VA hospital and on-site at the residential program. These discussions will provide an opportunity to build on the phase 1 findings and further explore how to recruit, enroll, and retain VEH in a future, app-based study planned in the next phase. The focus group participants will be asked for their general perceptions of taking part in a research study that uses a smartphone app for data collection and recommendations regarding how to (1) introduce and explain a study that uses the collection of data through a smartphone app, (2) explain the ways in which privacy and confidentiality will be maintained, (3) ask about potentially sensitive topics, such as substance use and relationship conflict, and (4) assess capacity to participate using a smartphone app. Participants will also be provided a brief questionnaire to obtain specific information about their access to and use of technology generally, and specifically smartphones.

We will also inquire about what types of information participants would be willing to provide researchers through their mobile phones, the acceptability of having GPS locations tracked, and any locations where they would not want GPS. We will show the focus group participants a mockup data map of an individual's GPS generated locations and movements to facilitate discussion. We will also inquire about other data collection methods, such as passively collected call logs. We will share with participants mockups of what call log data would look like to researcher team members. We will also emphasize that there will be encryption built into the software to address concerns about privacy. Feedback from the focus groups will be used to adjust the prototype of the smartphone app and guide revisions to phase 3 protocols. Focus group discussions will last approximately 60 minutes and will be facilitated by one of the anthropologists on the study team.

Development and Usability Testing

Smartphone app development will be informed by data from phase 1 ethnographic and phase 2 focus group findings. Usability testing will involve 5 VEH participants reviewing app mockups. Participants will be asked to provide feedback about the home screen, survey screen layouts, survey response options, and settings screen. Usability testing will occur approximately 2-3 months after the focus groups, when the mobile app has reached functionality. SAIL team members will provide mobile phones preloaded with the app. A member of the study team with qualitative expertise will record notes in a data collection template about overall design, ease of use, and specific wording and phrases used in the app during usability testing. Participants will use a smartphone to complete a defined set of tasks, such as turning on the phone, turning GPS off and on, responding to EMA and survey questions, etc. We will follow usability protocols and assessments, including time to complete tasks, participant error rates, software errors, etc. The team member will also ask participants about the burden of answering questions and about issues of privacy and trust. The SAIL development team will incorporate lessons from focus groups and usability assessment into the final version of the smartphone app for the phase 3 pilot. Usability assessments will be conducted by research staff who have been trained in usability assessment procedures by the SAIL mobile development group.

Analysis Phase 2

Phase 2 Focus Groups

The phase 2 focus groups and mobile app design data will include (1) the use of focus groups to gather information about the frequency of data collection, privacy issues, and incentives, and (2) the use of both phase 1 ethnographic data and phase 2 focus group data to develop a smartphone app and perform app usability testing.

Qualitative Data Analyses

All focus groups will be professionally transcribed verbatim. Thematic analysis [26] will be used by the focus group leads to analyze the data, which will be shared with the full team for an analytic discussion. Transcripts will later be combined with the phase 1 data for a global discussion of implications for the phase 3 pilot.

Phase 3: Feasibility and Acceptability Pilot of the App

Sampling of Participants and Recruitment

Phase 3 will use the same recruitment and consenting strategies as the previous phases. Phase 3 participants will also be recruited from sites 1 and 2.

Procedures

Baseline Interview and Demographics

At enrollment in phase 3, study team members will conduct semistructured qualitative interviews to gather structured data on demographics, recent life experiences, homelessness episodes, overall health and well-being, impairments, supportive relationships, and technology use. During the interview period, participants will be guided on how to download the app and will be provided with an orientation on how to use the app. The baseline interview will last about an hour.

30-day Smartphone App Data Collection

We will recruit up to 30 participants who will use the app to daily answer survey questions related to housing transitions, health service usage, medication adherence, emotional states, and social relationships [27,28]. About 2 days a week (Wednesday and Saturday evening), participants will receive a longer app survey with additional questions about health care, substance use, and the ongoing quality of specific social relationships. The questions on substance use and social relationship quality will be based on data collected during the baseline survey and qualitative interview. We will also collect information on veterans' activity space (the local areas within which people move or travel over the course of their daily activities) and proximity to health or social services by using

GPS [29]. GPS data will primarily be used to characterize the overall extent and variability of the activity space.

Follow-Up Interview

At the end of the 30-day pilot, a final follow-up interview will be conducted, using both structured and qualitative components. The interview will be conducted to document participant experiences and perceptions about the app data collection, including issues relating to trust, data security, maintaining phones, and the usability of EMA and mobile surveys. Participants will be allowed to view their survey and GPS data to offer insight into specific ambiguous survey responses and validate the general accuracy of the data set. This information will be used in a later analysis.

Analysis Phase 3

The phase 3 feasibility and acceptability pilot of mobile phone data will include 2 interviews (baseline and follow-up), as well as the mobile survey, GPS, and EMA data.

Qualitative Data Analyses

Baseline and final interview data will be organized and analyzed using the processes described in phase 1. The coding will closely follow the topics covered in the interview guide around performance and effort expectancy, social norms, facilitating factors, and trust.

Quantitative Data Analyses

First, we will use descriptive statistics to summarize the structured items collected from the baseline interviews, including information about participants' demographic characteristics, recent life experiences, homelessness episodes, overall health and health conditions, and social service use. Second, we will use sequence analysis to identify distinct patterns of housing transitions. Third, we will perform convergent integration of the qualitative and quantitative data to assess how contextual characteristics, including mood, activity space size, social support, medication adherence, and usage of health services, are related to housing transition patterns. Fourth, we will use mixed effects regression models to assess how daily changes in contextual characteristics are associated with daily experiences of housing stability (and major health events).

Ethical Considerations

Ethical approval was given by the VA Bedford Institutional Review Board (1626836-16), in accordance with VA guidelines. Written informed consent will be sought from all participants. Phase 1 participants will be provided written informed consent and will receive up to US $185 reimbursement over the course of the study (US $25 for the baseline, follow-up, and long interviews and US $10 for each brief interview). Phase 2 participants will receive US $25 upon completion of their focus group. Phase 3 participants will be offered US $30 for the baseline and follow-up interviews and US $5 per survey completed in the app for a possible total compensation of US $340. Study ID numbers will be assigned to participants to ensure confidentiality. We sought additional protections and obtained a federal Certificate of Confidentiality from the US National Institutes of Health because of the sensitive nature of the study discussions. Certificates of confidentiality protect the privacy of research subjects by prohibiting the disclosure of identifiable, sensitive research information to anyone not connected to the research except when the subject consents or in a few other specific situations. It is not possible to create a minimal data set with this qualitative data.

Results

The project was launched in June 2020, and as of December 2022, we had enrolled 10 participants for phase 1 and 9 participants for phase 2. Data collection and analysis for phases 1 and 2 are complete. This project is currently in progress.

Discussion

Principal Results

VEH are extremely vulnerable to experiencing housing transitions compared to their civilian counterparts [1,2]. A significant gap remains in research approaches to understanding the short-term precipitants and influences upon housing transitions. The use of smartphone apps can help fill the significant gaps in our knowledge, including, (1) the sequence of events leading up to and immediately after housing-related transitions; (2) information about the housing status of veterans not included in administrative systems, such as those who are living double-up or are street homeless; and (3) potential "early warning" signals gleaned from near-real–time reports of mood, activities, social support, and activity spaces (constructed from passively collected GPS data) that may presage increasing housing instability, a homelessness episode, or a major health event. This protocol paper details the specific phases and methods that will be used to develop and test a smartphone app to collect longitudinal data from VEH and to evaluate the feasibility and acceptability of using the app in a population that is unstably housed or homeless. This multiphased research will provide contextual knowledge on how in-the-moment experiences precipitate housing transitions from the perspective of VEH.

Furthermore, engaging participants from a range of housing situations—street homeless, transitional housing, residential treatment programs, and shelters—in the development of the smartphone app will allow us to capture what VEH thinks is significant to include in the app, thus enhancing its potential uptake [30,31]. To our knowledge, this will be the first test of active and passive smartphone-enabled data collection applied to the study of homelessness among veterans. At a minimum, the information gained from this project will lay the groundwork for enhancements to clinical programs that incorporate smartphone data for early intervention or use smartphone tools for 2-way communication between patients and clinical teams to improve care access and engagement for vulnerable populations.

Limitations

While our design methods during phases 1 and 2 will offer rich and nuanced insights to guide the content and design of the smartphone data collection app, there are a few limitations worth noting. First, there are usually difficulties in contacting and recruiting certain VEH, which could bias this study because we

may miss the most vulnerable and extreme cases. Thus, we will work closely with our staff at sites 1 and 2 to reduce selection bias. Second, VEH tends to report a lack of trust due to poor previous experiences with health care providers and mistrust of government institutions. We will try to establish a relationship of trust between the interviewer and VEH participants to obtain the most reliable data possible. Finally, although this will be an evaluation of VEH, our results may be applicable to non-VEH populations, contexts, and activities.

Conclusions

This multiphased study will provide rich data on the context and immediate events leading to housing transitions among VEH. This study will ensure the development of a smartphone app that will match the actual needs of VEH by involving them in the design process from the beginning. Finally, this study will offer important insights on how best to develop a smartphone app that can help intervene among VEH to reduce housing transitions.

Acknowledgments

The authors would like to thank Donald Miller and Jennifer Conti for their expertise during this study. Statements contained in this paper reflect the views of the authors and do not represent the official positions of the US Department of Veterans Affairs or other author affiliate organizations. This research was supported by the Veterans Health Administration Health Services Research and Development Service grant (Investigator Initiated Research 18-244 McInnes). MF is supported by the Veterans Affairs Office of Research and Development Research Supplements to Promote Diversity Award (Investigator Initiated Research 18-244 McInnes).

Data Availability

The underlying data for this study consists of in-depth, qualitative interviews with veterans experiencing homelessness. The data sets generated or analyzed during this study are not publicly available due to participant privacy but may be available from the corresponding author.

Conflicts of Interest

None declared.

References

1. Tsai J, Rosenheck RA. Risk factors for homelessness among US veterans. Epidemiol Rev 2015;37:177-195 [FREE Full text] [doi: 10.1093/epirev/mxu004] [Medline: 25595171]
2. de Sousa T, Andrichik A, Cuellar M, Marson J, Prestera E, Rush K. The 2022 Annual Homelessness Assessment Report (AHAR) to Congress: part 1: point-in-time estimates of homelessness. The US Department of Housing and Urban Development. Washington, DC: Abt Associates; 2022. URL: https://www.huduser.gov/portal/sites/default/files/pdf/2022-ahar-part-1.pdf [accessed 2024-03-28]
3. Schinka JA, Byrne TH. Aging and life expectancy in homeless veterans: nine questions. US Department of Veterans Affairs. 2018. URL: https://tinyurl.com/23kb3y6p [accessed 2024-03-28]
4. Fargo J, Metraux S, Byrne T, Munley E, Montgomery AE, Jones H, et al. Prevalence and risk of homelessness among US veterans. Prev Chronic Dis 2012;9:E45 [FREE Full text] [Medline: 22280960]
5. Goldstein G, Luther JF, Haas GL, Appelt CJ, Gordon AJ. Factor structure and risk factors for the health status of homeless veterans. Psychiatr Q 2010;81(4):311-323. [doi: 10.1007/s11126-010-9140-4] [Medline: 20532627]
6. Goldstein G, Luther JF, Jacoby AM, Haas GL, Gordon AJ. A taxonomy of medical comorbidity for veterans who are homeless. J Health Care Poor Underserved 2008;19(3):991-1005. [doi: 10.1353/hpu.0.0040] [Medline: 18677085]
7. Noska AJ, Belperio PS, Loomis TP, O'Toole TP, Backus LI. Prevalence of human immunodeficiency virus, hepatitis C virus, and hepatitis B virus among homeless and nonhomeless United States veterans. Clin Infect Dis 2017;65(2):252-258 [FREE Full text] [doi: 10.1093/cid/cix295] [Medline: 28379316]
8. Mago VK, Morden HK, Fritz C, Wu T, Namazi S, Geranmayeh P, et al. Analyzing the impact of social factors on homelessness: a fuzzy cognitive map approach. BMC Med Inform Decis Mak 2013;13:94 [FREE Full text] [doi: 10.1186/1472-6947-13-94] [Medline: 23971944]
9. Applewhite SL. Homeless veterans: perspectives on social services use. Soc Work 1997;42(1):19-30. [doi: 10.1093/sw/42.1.19] [Medline: 9009886]
10. Georgiades S. The dire straits of homelessness: dramatic echoes and creative propositions from the field. J Hum Behav Soc Environ 2015;25(6):630-642. [doi: 10.1080/10911359.2015.1011254]
11. Piat M, Polvere L, Kirst M, Voronka J, Zabkiewicz D, Plante MC, et al. Pathways into homelessness: understanding how both individual and structural factors contribute to and sustain homelessness in Canada. Urban Studies 2014;52(13):2366-2382. [doi: 10.1177/0042098014548138]

12. Schwarz N. Retrospective and concurrent self-reports: the rationale for real-time data capture. In: Stone AA, Shiffman S, Atienza AA, Nebeling L, editors. The Science of Real-Time Data Capture: Self-Reports in Health Research. Oxford: Oxford University Press; 2007:11-26.
13. Pennou A, Lecomte T, Potvin S, Khazaal Y. Mobile intervention for individuals with psychosis, dual disorders, and their common comorbidities: a literature review. Front Psychiatry 2019;10:302 [FREE Full text] [doi: 10.3389/fpsyt.2019.00302] [Medline: 31130884]
14. O'Toole TP, Johnson EE, Redihan S, Borgia M, Rose J. Needing primary care but not getting it: the role of trust, stigma and organizational obstacles reported by homeless veterans. J Health Care Poor Underserved 2015;26(3):1019-1031. [doi: 10.1353/hpu.2015.0077] [Medline: 26320930]
15. Gonzalez JMR, Businelle MS, Kendzor D, Staton M, North CS, Swartz M. Using mHealth to increase treatment utilization among recently incarcerated homeless adults (Link2Care): protocol for a randomized controlled trial. JMIR Res Protoc 2018;7(6):e151 [FREE Full text] [doi: 10.2196/resprot.9868] [Medline: 29871852]
16. McInnes DK, Sawh L, Petrakis BA, Rao SR, Shimada SL, Eyrich-Garg KM, et al. The potential for health-related uses of mobile phones and internet with homeless veterans: results from a multisite survey. Telemed J E Health 2014;20(9):801-809. [doi: 10.1089/tmj.2013.0329] [Medline: 25046280]
17. Shiffman S, Stone AA, Hufford MR. Ecological momentary assessment. Annu Rev Clin Psychol 2008;4:1-32. [doi: 10.1146/annurev.clinpsy.3.022806.091415] [Medline: 18509902]
18. Caspi A, Bolger N, Eckenrode J. Linking person and context in the daily stress process. J Pers Soc Psychol 1987;52(1):184-195. [doi: 10.1037//0022-3514.52.1.184] [Medline: 3820071]
19. Bolger N, DeLongis A, Kessler RC, Schilling EA. Effects of daily stress on negative mood. J Pers Soc Psychol 1989;57(5):808-818. [doi: 10.1037//0022-3514.57.5.808] [Medline: 2810026]
20. Brown RT, Goodman L, Guzman D, Tieu L, Ponath C, Kushel MB. Pathways to homelessness among older homeless adults: results from the HOPE HOME Study. PLoS One 2016;11(5):e0155065 [FREE Full text] [doi: 10.1371/journal.pone.0155065] [Medline: 27163478]
21. Rhoades H, Wenzel SL, Rice E, Winetrobe H, Henwood B. No digital divide? Technology use among homeless adults. J Soc Distress Homeless 2017;26(1):73-77 [FREE Full text] [doi: 10.1080/10530789.2017.1305140] [Medline: 31097900]
22. Raven MC, Kaplan LM, Rosenberg M, Tieu L, Guzman D, Kushel M. Mobile phone, computer, and internet use among older homeless adults: results from the HOPE HOME cohort study. JMIR Mhealth Uhealth 2018;6(12):e10049 [FREE Full text] [doi: 10.2196/10049] [Medline: 30530464]
23. McInnes DK, Dunlap S, Fix GM, Foster MV, Conti J, Roncarati JS, et al. Longitudinal high-frequency ethnographic interviewing to simulate and prepare for intensive smartphone data collection among veterans with homeless experience. Front Digit Health 2022;4:897288 [FREE Full text] [doi: 10.3389/fdgth.2022.897288] [Medline: 36033637]
24. Tsemberis S, McHugo G, Williams V, Hanrahan P, Stefancic A. Measuring homelessness and residential stability: the residential time-line follow-back inventory. J Community Psychol 2006;35(1):29-42. [doi: 10.1002/jcop.20132]
25. Trotter RT, Needle RH, Goosby E, Bates C, Singer M. A methodological model for rapid assessment, response, and evaluation: the RARE program in public health. Field Methods 2016;13(2):137-159. [doi: 10.1177/1525822x0101300202]
26. Braun V, Clarke V. Thematic analysis. In: Cooper HM, Camic PM, Long DL, Panter AT, Rindskopf D, Sher KJ, editors. APA Handbook of Research Methods in Psychology, Volume 2: Research Designs: Quantitative, Qualitative, Neuropsychological, and Biological. Washington, D.C: American Psychological Association; 2012:57-71.
27. Justice AC, Dombrowski E, Conigliaro J, Fultz SL, Gibson D, Madenwald T, et al. Veterans Aging Cohort Study (VACS): overview and description. Med Care 2006;44(8 Suppl 2):S13-S24 [FREE Full text] [doi: 10.1097/01.mlr.0000223741.02074.66] [Medline: 16849964]
28. Sherbourne CD, Stewart AL. The MOS social support survey. Soc Sci Med 1991;32(6):705-714. [doi: 10.1016/0277-9536(91)90150-b] [Medline: 2035047]
29. Golledge RG, Stimson RJ. Spatial Behavior: A Geographic Perspective. New York, NY: Guilford Press; 1997.
30. Tremblay M, Hamel C, Viau-Guay A, Giroux D. User experience of the co-design research approach in eHealth: activity analysis with the course-of-action framework. JMIR Hum Factors 2022;9(3):e35577 [FREE Full text] [doi: 10.2196/35577] [Medline: 35943783]
31. Manzini E. Design, When Everybody Designs: An Introduction to Design for Social Innovation. Cambridge, Massachusetts: MIT press; 2015.

Abbreviations

CHOIR: Center for Healthcare Organization and Implementation Research
EMA: ecological momentary assessment
SAIL: Software & Application Innovation Lab
VA: Veterans Affairs
VEH: veterans experiencing homelessness

Edited by A Mavragani; submitted 23.09.23; peer-reviewed by E Rubenstein, A Barker; comments to author 03.01.24; revised version received 23.01.24; accepted 22.02.24; published 22.04.24.

Please cite as:
Foster M, Fix GM, Hyde J, Dunlap S, Byrne TH, Sugie NF, Kuhn R, Gabrielian S, Roncarati JS, Zhao S, McInnes DK
Capturing the Dynamics of Homelessness Through Ethnography and Mobile Technology: Protocol for the Development and Testing of a Smartphone Technology–Supported Intervention
JMIR Res Protoc 2024;13:e53022
URL: https://www.researchprotocols.org/2024/1/e53022
doi:10.2196/53022
PMID:38648101

Protocol

Supportive Care Needs in Chinese, Vietnamese, and Korean Americans With Metastatic Cancer: Mixed Methods Protocol for the DAWN Study

Jacqueline H J Kim[1], PhD; Marjorie Kagawa Singer[2], PhD; Lisa Bang[1], BS; Amy Ko[1], BS; Becky Nguyen[3], MPH, MPA; Sandy Chen Stokes[4], MSN; Qian Lu[5], PhD; Annette L Stanton[6], PhD

[1]Department of Medicine, University of California, Irvine, Irvine, CA, United States

[2]Department of Public Health, University of California, Los Angeles, Los Angeles, CA, United States

[3]Vietnamese American Cancer Foundation, Fountain Valley, CA, United States

[4]Chinese American Coalition for Compassionate Care, Cupertino, CA, United States

[5]Department of Health Disparities Research, The University of Texas MD Anderson Cancer Center, Houston, TX, United States

[6]Department of Psychology, University of California, Los Angeles, Los Angeles, CA, United States

Corresponding Author:
Jacqueline H J Kim, PhD
Department of Medicine
University of California, Irvine
100 Theory
Suite 100
Irvine, CA, 92617
United States
Phone: 1 9498249216
Email: jhjkim@hs.uci.edu

Abstract

Background: Asian Americans with metastatic cancer are an understudied population. The Describing Asian American Well-Being and Needs in Cancer (DAWN) Study was designed to understand the supportive care needs of Chinese-, Vietnamese-, and Korean-descent (CVK) patients with metastatic cancer.

Objective: This study aims to present the DAWN Study protocol involving a primarily qualitative, convergent, mixed methods study from multiple perspectives (patients or survivors, caregivers, and health care professionals).

Methods: CVK Americans diagnosed with solid-tumor metastatic cancer and their caregivers were recruited nationwide through various means (registries, community outreach newsletters, newspapers, radio advertisements, etc). Potentially eligible individuals were screened and consented on the web or through a phone interview. The study survey and interview for patients or survivors and caregivers were provided in English, traditional/simplified Chinese and Cantonese/Mandarin, Vietnamese, and Korean, and examined factors related to facing metastatic cancer, including quality of life, cultural values, coping, and cancer-related symptoms. Community-based organizations assisted in recruiting participants, developing and translating study materials, and connecting the team to individuals for conducting interviews in Asian languages. Health care professionals who have experience working with CVK patients or survivors with metastatic solid cancer were recruited through referrals from the DAWN Study community advisory board and were interviewed to understand unmet supportive care needs.

Results: Recruitment began in November 2020; data collection was completed in October 2022. A total of 66 patients or survivors, 13 caregivers, and 15 health care professionals completed all portions of the study. We completed data management in December 2023 and will submit results for patients or survivors and caregivers to publication outlets in 2024.

Conclusions: Future findings related to this protocol will describe and understand the supportive care needs of CVK patients or survivors with metastatic cancer and will help develop culturally appropriate psychosocial interventions that target known predictors of unmet supportive care needs in Chinese, Vietnamese, and Korean Americans with metastatic cancer.

International Registered Report Identifier (IRRID): DERR1-10.2196/50032

(JMIR Res Protoc 2024;13:e50032) doi:10.2196/50032

KEYWORDS

Asian American; disparities; metastatic cancer; psychosocial; supportive care; unmet needs; well-being

Introduction

Overview

Cancer is the leading cause of death for Asian Americans, the fastest-growing US immigrant group projected to outnumber Hispanic or Latinx immigrants by 2065 [1]. However, only 0.17% of the National Institutes of Health (NIH)–funded clinical research studies have involved Asian American, Native Hawaiian, and Pacific Islander participants (1992-2018) [2], and other foundational funding sources show a similar disparity for Asian Americans [3]. Of the many mental and physical health topics requiring further investigation [3], metastatic cancer survivorship is a significant priority given that Asian Americans are often diagnosed with a distant stage of cancer [4] such as Chinese Americans and Korean Americans with later staged colorectal cancer [5,6]. While progress in treatments and earlier detection have improved cancer survival rates overall [7], metastatic disease remains the major cause of cancer mortality [8]. The provision of quality supportive care is needed for Asian Americans with metastatic cancer, yet very little is known about the needs and preferences of this population. While the National Cancer Institute has funded cancer survivorship science since 1996, a 2020 analysis of NIH-funded research in advanced or metastatic cancer survivorship reported no studies of Asian Americans with metastatic cancer, and past survivorship research typically focused on survivors without detectable disease or active treatment [9,10]. Moreover, Asian-heritage cancer survivors are more likely to experience care-quality disparities [11], with those who are foreign-born especially likely to report unmet supportive needs after controlling for demographic and socioeconomic factors, health system and health care access, and comorbidities [12].

Psychosocial care needs are particularly important to evaluate, as the highest level of psychosocial distress is found in patients with advanced stages of disease [13]. These include anxiety, depression, death anxiety, demoralization, and a perceived inability to cope effectively, which can result in poor quality of life and premature mortality [14,15]. Patients with metastatic cancer have different needs, goals, and physical and psychosocial symptoms compared to patients with earlier-stage cancer, with individuals with metastatic cancer facing greater uncertainty about their prognosis and fear of disease progression [10,16,17]. Evidence suggests early supportive care needs (ie, after diagnosis in active treatment) should also be examined, as it can result in better quality of life and a reduction in functionally impairing symptoms [18].

Chinese-, Vietnamese-, and Korean-descent (CVK) Americans experience greater cancer-specific mortality in contrast to other Asian ethnic groups [19-22] and likely experience difficulties accessing high-quality care due to 46%-60% reporting limited English proficiency [23]. Very little is known about CVK Americans' metastatic cancer survivorship and how similarities in philosophical traditions, values, and norms may guide distinct views about what is optimal for supportive care in metastatic cancer (eg, Confucian-heritage–based interdependent norms for East and Southeast Asian ethnic groups [24,25]). For example, Confucian-heritage individuals' self-concept often includes close others [26,27] and CVK patients' supportive care needs may be influenced by social harmony-based expectations such as self-sacrifice amid profound stress [28,29] or preferring indirect support [30] to minimize direct discussion of stigmatizing subjects such as cancer [31-33]. Supportive interventions or resources that allow for a reduction in directly verbalizing distress may be preferred (eg, writing [34] or use of web-based or social chat platforms [35]). As such, this generative study aimed to produce an initial glance at the supportive care needs and preferences of CVK patients or survivors. Multiple perspectives were sought as cancer survivorship care is coordinated across multiple levels, including close interpersonal relationships, health care organizational settings, and community settings [36]. This protocol outlines the multilevel assessment undertaken through multiple informants and study components.

Objectives

This study aims to present an embedded mixed methods study protocol for examining the supportive care needs and preferences of CVK patients or survivors with metastatic cancer through multiple informants (patients, caregivers, and health care professionals). To our knowledge, this is the first multiperspective study focused on Asian American metastatic cancer survivorship. This protocol will allow for an understanding of the components of the study, and findings from this study will refer to this protocol to showcase how community-engaged collaboration aided the development of culturally relevant, adapted psychosocial interventions or resources targeting known predictors of continued unmet supportive care needs.

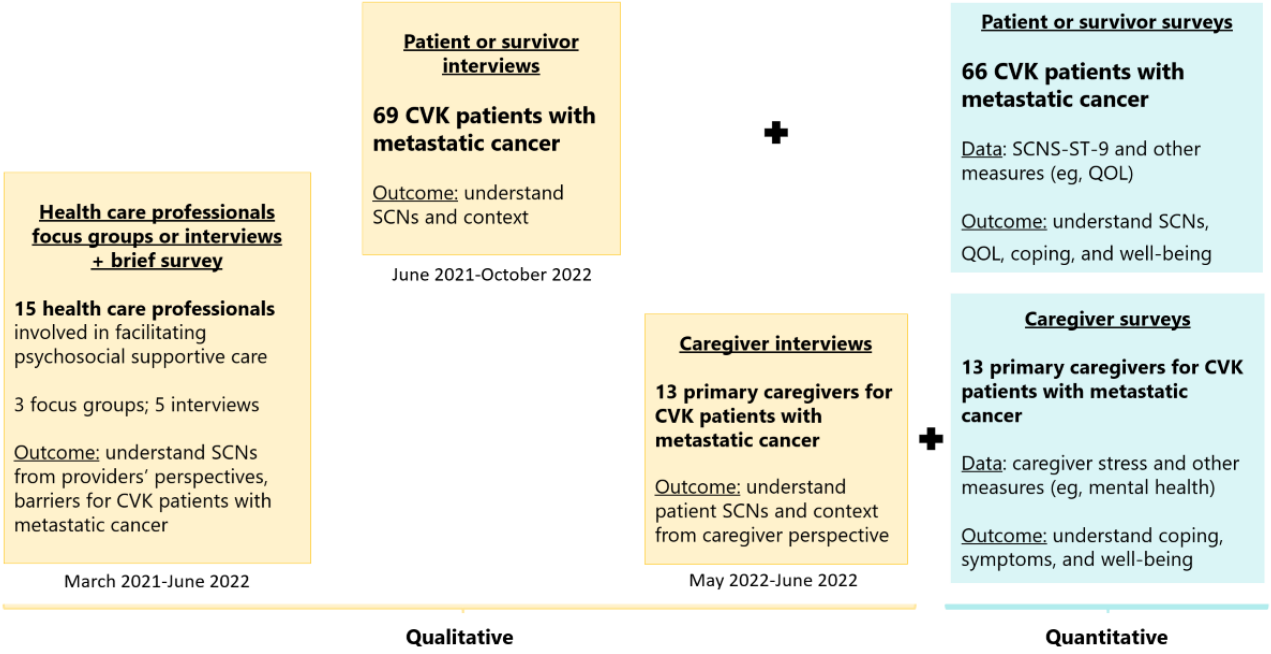
Methods

Overview

We conducted a qualitative (QUAL) and quantitative (quan) convergent mixed methods study on supportive care needs with CVK survivors living in the United States and diagnosed with solid-tumor metastatic cancer (Figure 1). A convergent mixed methods design was selected to provide a rich description of supportive care needs, including any similarities or discrepancies in self-reporting through interview or survey assessment. The strength of a convergent design is its ability to collect both qualitative and quantitative data simultaneously and promptly, which fits well with the generative "snapshot" purpose of this study given the lack of knowledge about conducting research with this understudied population diagnosed with stage IV cancer. With guidance from a qualitative expert (coauthor MKS), the qualitative portion was prioritized to engage an understudied population of cancer survivors who may face cancer-related stigma due to cultural beliefs about cancer. We invited survivors' caregivers to provide their perspective on survivors' supportive care needs through interviews. Health

care professionals' perspectives on the supportive care needs of CVK metastatic cancer patients or survivors and their families were also examined qualitatively. All study materials were matched to participants' language preferences in English, traditional Chinese, simplified Chinese, Vietnamese, and Korean.

Figure 1. Convergent mixed methods design and timeline. CVK: Chinese-, Vietnamese-, and Korean-descent; QOL: quality of life; SCN: supportive care need; SCNS-ST-9: Supportive Care Needs Survey-Screening Tool.



Participants

The study population included CVK individuals with solid-tumor metastatic cancer and caregivers (aged ≥18 years) living in the United States. Patients or survivors and caregivers were primarily recruited through partnered community outreach and supplemented by the University of California, San Francisco CARE (Collaborative Approach for Asian Americans, Native Hawaiians, and Pacific Islanders Research and Education) Registry and the University of California, Los Angeles (UCLA) Cancer Registry. Trained bilingual research assistants who speak English and Chinese (Mandarin or Cantonese), Vietnamese, or Korean called potential patient or survivor and caregiver participants to introduce and explain the study, screen for eligibility, and obtain consent for participation. Patient or survivor and caregiver participants received a US $90 e–gift card upon completing all parts of the study (brief demographic questions, interview, and survey). Patient or survivor participants who started the study but were unable to complete it, or declined to further participate for health reasons were also sent US $90 e–gift cards for their efforts. Health care professionals received a US $100 e–gift card upon completing the study.

Eligibility Criteria

The inclusion criteria for patients or survivors were (1) individuals diagnosed with de novo or recurrent, stage IV, solid tumor metastatic cancer; (2) self-identifying as Chinese, Vietnamese, or Korean and fluent in English, Korean, Cantonese, Mandarin, or Vietnamese; (3) aged 18 years or older; and (4) living in the United States. The inclusion criteria for caregivers were (1) individuals who self-identified or were patient- or survivor-identified as the primary caregiver (a close relative, friend, or partner who is doing most of the work to help take care of daily activities or medical care) for a person diagnosed with de novo or recurrent solid tumor metastatic cancer; (2) aged 18 years or older; and (3) living in the United States. If any patient or survivor or caregiver reported a diagnosis of schizophrenia or bipolar disorder, post hoc exclusion was to be considered based on any evidence of cognitive impairment presented to the research team during interactions or interviews. Health care professionals were eligible if they (1) were involved in facilitating patients' connection to or providing supportive care; (2) have been practicing at their medical or health center-related organization for 6 months or more; and (3) regularly worked with or have worked with at least 2 Chinese, Vietnamese, or Korean American patients with metastatic cancer.

Recruitment

Patient or survivor participants were initially recruited from the Greater Los Angeles Area and Orange County in Southern California. Recruitment was expanded nationwide due to limitations in reach and access resulting from the study being conducted during the height of the COVID-19 pandemic. Advertising and community outreach were focused on locations with a greater presence of Chinese, Vietnamese, and Korean communities (Los Angeles-San Gabriel Valley region, San Francisco Bay Area region, Buena Park, La Palma, Little Saigon area in Orange County, Irvine, Houston, Seattle, New York, etc). A majority of participants were recruited through flyers and community outreach (community organizations, churches, temples, libraries, community centers, senior centers, and ethnic supermarkets), physician referrals, doctor's offices, hospices, coverage on ethnic television, radio, or newspapers, social media

(Facebook and Instagram), and word-of-mouth. Partner community organizations (Chinese American Coalition for Compassionate Care [CACCC] 美華慈心關懷聯盟 and the Vietnamese American Cancer Foundation [VACF] H i Ung Th Vi t M) helped increase word-of-mouth recruitment by using their websites, social media, and radio broadcasts to publicize the research. VACF lay navigators actively distributed study flyers with their community during the organization's events, such as the drive-by COVID-19 relief resource distribution. Participants were also later recruited through the University of California, San Francisco CARE Registry and the UCLA Cancer Registry when open to non-COVID-19 research. Recruitment efforts for caregivers began with paired dyads for more focused qualitative synthesis; thus, we first recruited through patient or survivor participants who identified their primary caregivers and gave assent for contact. Following this, the research team sought to recruit caregivers unpaired with patient or survivor study participants.

Health care professionals were recruited through the Describing Asian American Well-Being and Needs in Cancer (DAWN) Study community advisory board members' referrals of those who may best understand the supportive care needs of CVK adults with metastatic cancer, based mostly in Southern California.

Analysis Plan

The patient or survivor and caregiver interviews were transcribed in English, Mandarin, Cantonese, Korean, and Vietnamese. Asian language transcripts were translated, and English transcripts will be analyzed. The health care professional interviews and focus groups were transcribed in English. All transcription and translation work was reviewed and corrected by the multilingual research team. All qualitative data will be examined for thematic content with reflexive thematic analysis [37,38]. Reflexive thematic analysis is a theoretically flexible approach that allows for the presentation of shared meaning in data by emphasizing researcher reflexivity as a key process in the analysis and acknowledging that the findings are embedded in this context [37,38]. Self-reflexivity will be emphasized before and throughout the analysis and interpretation. Coders and the principal investigator (JHJK) will discuss the influence of their backgrounds and preconceptions and keep memos for a record of analysis and interpretations. As the lead investigator (JHJK) approaches research with a critical realist framework and is a clinical psychologist with knowledge of mental health service use disparities, cultural variations in symptomatology and coping, and stressors faced by immigrant families, findings are likely to be influenced by this perspective.

The research team will first familiarize themselves with the data through independent reading of the interview transcripts and generate initial codes and candidate themes to engage in reflexive thematic analysis. Inductive "bottom-up" coding will be completed first for a full description of participants' perspectives and experiences. Then, deductive "top-down" coding will be performed centered on the research question and any relevant supportive oncology concepts of additional significance. Themes will be reviewed and refined to best represent participant perspectives. Seeking saturation and minimum sample sizes is not compatible with reflexive thematic analysis, and our sampling was pragmatic and acceptable within reflexive thematic analysis (ie, the research team sought to conduct as many qualitative data collections as possible during the project period). Self-reported supportive care needs, demographics, and medical variables will also be summarized with univariate statistics. Chi-square tests will examine any differences in supportive care needs (eg, US- or foreign-born). Joint display results will be produced for the supportive care needs described by CVK patients or survivors. For the health care professionals' parallel-format focus group and interview data, candidate themes were compared across the focus group data and interview data to arrive at final themes.

Data Management and Confidentiality

When participants enrolled in the study, they were assigned a random study ID number to label self-report and interview data. Self-report and interview data were further deidentified. Any potentially identifying records are kept password-protected on a secure server. All analyses will be reported as aggregate data or in an anonymized format for qualitative excerpts.

Data Collection Overview

Patients or Survivors and Caregivers

After obtaining consent, self-reported demographic information (eg, age, sex, ethnicity, education level, income, length of US residency, language use, religion, employment status, insurance status, and subjective social status captured using the community version of the MacArthur Scale of Subjective Social Status [39]), acculturation level (from the Brief Acculturation Scale for Hispanics [40]), and cancer history (eg, type of metastatic cancer, diagnosis date, and treatments) were collected by telephone immediately following the screening call or at another scheduled time. Following the demographic and cancer history questions call, participants were scheduled for a 1-1.5-hour interview over telephone or videoconference through Zoom (Zoom Video Communications). When scheduling and sending reminders for the interview, participants were asked to secure a private location where they could speak freely and confidentially, in addition to a suggestion to use headphones for added privacy. Participants' privacy and comfort with their interview location were confirmed before beginning the interview. In the rare circumstance that the participant needed another location for continued privacy for the interview, participants were offered a break period or to reschedule to continue the interview in a confidential manner. After the interview, participants completed a 30-minute survey on paper or a web-based survey within 1 week of the interview. All participants were encouraged to complete their survey on the same day as the interview, in one sitting, if possible, within 1 week from the interview date. They were reminded to complete the survey through their preferred method of communication. Participants with lower literacy were supported by trained bilingual research assistants over the phone. Caregivers underwent the same study process as patients or survivors (brief demographic questions through phone, 1-hour interview, and 30-minute survey).

Health Care Professionals

Health care professionals were provided study information sheets with the opportunity to ask questions about eligibility before scheduling the 1-hour focus groups or interviews led in English by the principal investigator. Focus groups and parallel key informant interviews took place over Zoom. Focus groups were composed of a minimum of 3 health care professionals to allow for greater depth of responses from each participant attending the focus group, as well as to accommodate scheduling restrictions imposed by their COVID-19 workload. The three focus group compositions were balanced out as much as possible: (1) social worker, bilingual radiation oncologist, and bilingual medical oncologist; (2) social worker, bilingual medical oncologist, and medical oncologist; and (3) chaplain, bilingual hematology oncologist, hematology oncologist, and bilingual medical oncologist. Following the focus groups, parallel-format key informant interviews were the only feasible way to gain additional perspectives due to time limitations from health care professionals' COVID-19 workload—this alternate participation option was pursued when health care professionals could not otherwise participate in the focus groups. In reminders before the interview, participants were asked to secure a private location where they could speak freely and confidentially and were suggested to use headphones for added privacy. Before beginning each focus group or interview, health care professionals confirmed their eligibility and provided oral or web-based survey consent. They also confirmed privacy and comfort with their location of remote participation. The demographics of health care professionals were collected before the interviews through a brief demographic questionnaire on the web. Self-reported demographic information includes age; profession; sex; ethnicity; years since clinical licensure; years since obtaining an MD degree; hospital or clinic affiliation; months employed at the institution, hospital, or clinic; if bilingual in Chinese, Vietnamese, or Korean and if using the endorsed language in clinical practice; years working with patients with metastatic cancer; the number of CVK patients with metastatic cancer seen in the past month and per month before COVID-19; and level of comfort caring for CVK patients with metastatic cancer.

Semistructured Guides for Qualitative Data

Patients or Survivors and Caregivers

All interviews were conducted using semistructured topic guides. Interviews were conducted in English, Chinese (Cantonese or Mandarin), Vietnamese, and Korean by language-matched, trained interviewers and the principal investigator. Interviews lasted 60-90 minutes for both the patients or survivors and their caregivers. Interviews took place through Zoom or telephone calls and were audio-recorded with participants' permission. The main research question domains for patients or survivors and caregivers were (1) cultural influence on coping, needs, and preferences; (2) cultural fit and adequacy of existing or offered supportive care after diagnosis; (3) unmet supportive care needs (physical vs emotional priorities); and (4) psychosocial intervention or resource preferences (modality and timing). Supportive care needs explored included informational, patient care support, daily living, physical, psychological, or emotional, as well as how people's social lives (interpersonal relationships, marriage, sexuality, and spirituality) were affected. Caregivers were asked to provide information regarding their own experiences as well as the patient's or survivor's experiences in these domains and their insights about patients' or survivors' needs. Caregivers were also asked about how their relationship with the patient or survivor had changed or stayed the same if they were married or in a committed relationship. In the fourth domain, participants were asked to rank potential psychosocial interventions based on perceived helpfulness for patients or survivors with metastatic cancer of their ethnicity: writing privately, a website or blog for close family or friends, social media with close family or friends, peer education or support, and professionally trained counseling. Images representing each type of intervention were provided for participants to reference during the interview. For interviews in which participants mentioned end-of-life or openness about mortality, and time permitting, patients or survivors were shown an image of CACCC's Heart to Heart Café cards to ask for their thoughts regarding a culturally based intervention for end-of-life discussions with family or friends. This last intervention image was presented in a tailored manner for each individual because of ethical concerns raised by community and scientific advisors given the known stigma and taboo related to the end of life in Asian cultures [31], the limited scope of the project, and the lack of culturally and linguistically matched supportive or counseling resources available to all participants.

Health Care Professionals

A semistructured interview guide was developed and used for the focus groups and interviews in English. All participants were asked the same questions per the interview guide by the same facilitator. Domains of inquiry included (1) any difference in care provided for CVK patients with metastatic cancer; (2) challenging scenarios for CVK patients with metastatic cancer; (3) health care professionals' perceptions of the most important unmet supportive care needs, barriers to meeting those unmet needs, and potential solutions; and (4) the type of supportive care that would be most helpful and culturally appropriate. Focus group participants were scheduled for an individual follow-up interview if there were any comments to probe for additional clarifying information. Focus group participants' thoughts were shared with parallel-format individual interview participants, as appropriate, to elicit their reactions and thoughts as would occur if they had participated in a focus group.

Survey Measures for Quantitative Data

Overview

All measures for the study were provided in English, Chinese (traditional or simplified), Vietnamese, or Korean. If not already available or needing wording modification, simplified and traditional Chinese, Vietnamese, and Korean versions of measures were developed using a rigorous translation methodology. A total of 2 independent forward translations, 1 independent back translation, and reconciliations of translations were completed with feedback from community partner organization representatives and bilingual research team members from each language group. Feedback from the Chinese,

Vietnamese, and Korean community organization representatives included identifying the best phrasings for the United States context while maintaining the meaning of the original English measure. If not in the public domain, permission was obtained from the measure authors.

Patients or Survivors

The primary survey for a convergent mixed methods examination of patients or survivors with metastatic cancer's supportive care needs was measured by the Supportive Care Needs Survey-Screening Tool [41]. The Functional Assessment of Cancer Therapy General-7 measure was used to assess quality of life [42]. Participants' other patient-reported outcomes were assessed with the National Comprehensive Cancer Network distress thermometer [43], an 8-item Patient Health Questionnaire Depression Scale for depression [44], Generalized Anxiety Disorder Scale for anxiety [45], the Multidimensional Fatigue Symptom Inventory-Short Form physical subscale for fatigue [46], the 6-item Impact of Event Scale for cancer-specific traumatic stress [47], the pain intensity, enjoyment of life, general activity 3-item scale for pain assessment [48], and the 2-item Sleep Condition Indicator for sleep disturbance [49]. Considering the importance of coping in determining quality of life and other patient-reported outcomes, coping was evaluated using the Brief Coping Orientation to Problems Experienced Inventory [50] and the Emotional Approach Coping Scales (emotional processing and emotional expression) [51]. The Mental Health Continuum Short Form examined well-being [52], and other resilience factors were examined with the Gratitude Questionnaire-6 [53], the mindfulness subscale of the Self-Compassion Scale [54], the preparedness subscale of the Quality of Life at the End of Life-Cancer measure [55], the UCLA 3-Item Loneliness Scale [56], and the Social Provisions Scale [57].

We also measured additional exploratory concepts related to cultural factors that may affect supportive care needs and quality of life among CVK adults with metastatic cancer. The Asian American Values Scale was modified as a brief 9-item pilot version to assess how much participants valued family collectivism, conformity to norms, and emotional self-control [58], alongside the harmony subscale of the Brief Collectivism Questionnaire [59]. Other culturally relevant concepts measured include ambivalence of emotional expression with the 4-item Ambivalence Over Emotional Expressiveness Questionnaire [60], internalized metastatic cancer-related stigma (modified Lung Cancer Stigma Inventory subscale) [61], self-perceived burden upon others [32,62], the patient's level of sacrifice for their family using a modified Sacrifice for Close Others Scale [63], and a question about lifetime experience of personal or sociopolitical trauma. All measures were completed in one survey assessment after the interview.

Caregivers

Caregivers filled out the same surveys as patients or survivors for cancer-related coping, mental and physical health symptoms, resilience factors such as gratitude, and cultural values. Additionally, their caregiving relationship was measured with the 4-item Quality of Caregiver-Care Recipient Relationship [64,65] and caregiving stress was measured with the Caregiver Intrapsychic Stress and Strain Scales [66]. All measures were completed in one survey assessment after the interview.

Partnered Community Involvement

The study was conducted in collaboration with community organizations that were cultural and community-based advisors for the research and supported all nonengaged aspects of the study such as prioritizing research questions, informing the design of the study including participant eligibility criteria, recommending culturally relevant concepts to assess (eg, stigma or burden), translating study materials, reviewing the ethics of the research procedures, supporting recruitment efforts, and recommending bilingual research assistant candidates for interviewing participants. The CACCC (美華慈心關懷聯盟) is a coalition in Cupertino, California that addresses issues related to serious illnesses in the Chinese American community and partnered for the Chinese portion of the study. The VACF (H i Ung Th Vi t M) in Orange County, California is an organization that provides cancer education, resources, and services and is involved in research and advocacy for cancer prevention to improve quality of life and outcomes in the Vietnamese community and partnered for the Vietnamese portion of the study. The DAWN Study community advisory board comprising multidisciplinary health care professionals (psychology, oncology, palliative care, or public health), patient advocates, and community-based organizational representatives, also contributed to the development and conduct of the study through quarterly meetings. For example, the eligibility criteria for all participants were informed through community advisory board discussions, with the minimal length of employment for health care professionals set at 6 months for the health care professional to have had time to adjust to their health care system and be able to provide an "insider" perspective. The community advisory board included at least one bilingual representative with cultural knowledge relevant to CVK patients and their families.

Ethical Considerations

Institutional review board approval was obtained from UCLA (20-001554) and the University of California, Irvine (1541;2391). Oral or web-based informed consent was obtained from all participants in this study. Nonregistry-based patient or survivor participants completed a web-based screening and consent form, or expressed interest through email or phone and oral consent was obtained over the phone by trained research assistants. Registry-based patient or survivor participants received a letter or email with the study information sheet and a postage-paid postcard to indicate their interest. Research team members followed up with all potentially eligible registry-based patients or survivors to complete the screening and oral consent by phone if participants had not completed the web-based screening and consent on their own. For all participants who consented through a web-based survey, we ensured informed consent by verbally reconfirming an understanding of the purpose of the study, what participation entails, and rights as participants at the beginning of the first portion of the study.

Results

The study was funded for 2 years, from June 2020 to June 2022, by the NIH-National Cancer Institute with supplement funding from the UCLA Institute of American Cultures and Asian American Studies Center. Recruitment began in November 2020, and data collection was completed in October 2022. A total of 74 patients or survivors enrolled in the study from various US states (66 from California, 3 from Texas, 2 from Washington, 1 from Delaware, 1 from Nevada, and 1 from Connecticut); 69 patients or survivors completed the interview, and 66 patients or survivors completed both the interview and survey. A total of 13 caregivers enrolled in the study (12 from California and 1 from Washington) and completed all portions of the study. All 13 caregivers were linked with a patient or survivor participant in the study; no unlinked caregivers joined the study. A total of 15 health care professionals enrolled in the study, resulting in 3 focus groups and 5 parallel-format interviews. No post hoc exclusions were necessary. We completed the remaining data management in December 2023. A manuscript on health care professionals has been accepted, and manuscripts for convergent mixed method results for patients' or survivors' supportive care needs and caregiver perspectives will be submitted in 2024.

Discussion

This study is one of the first to examine the unmet supportive care needs of Asian Americans with metastatic cancer through interviewing patients or survivors, caregivers, and health care professionals for a more comprehensive understanding, using culturally and linguistically appropriate study materials and community-based participatory research principles. The perspectives of interested parties, which include patients or survivors, caregivers, community members, and health care professionals, will help advocate for this understudied population and inform the next steps to develop, test, and disseminate supportive care resources and interventions that are culturally relevant. By studying adults from Confucian-heritage cultures, this study may uncover cultural factors to be considered in the provision of supportive care. However, given the focus on only CVK adults, the results of this study may not apply to other Asian ethnicities that do not share a Confucian heritage. This research design may be adaptable for other understudied Asian Americans with metastatic cancer to facilitate quality care and intervention development.

Strengths of this study include the involvement of the community through their active participation from the design of the study to the analysis, interpretation, and dissemination of results. Multidisciplinary community advisors who closely work with metastatic cancer survivors and community-based organizations shaped the study to be more culturally appropriate. All steps of the research were available in English, Chinese, Vietnamese, and Korean, and the study was designed to be flexible around participants' schedules (including evenings and weekends) and remove the burden of transportation by being remote.

Challenges encountered in this study include technological and logistical difficulties in offering multiple modalities for participation. Considering that some participants had limited familiarity with technology such as Zoom and SMS text messaging and relied on telephone calls, it was challenging, at times, to connect with individuals to complete every part of the study. Another challenge faced was during the recruitment process, as some participants did not know the staging of their cancer. Diagnoses needed to be clarified through caregivers or with detailed follow-up questions about where the cancer had spread. Though every effort was made to ensure privacy, confidentiality, and independence in participant interviews, one patient strongly preferred that their caregiver be present. Given the patient's physical supportive needs and sporadic difficulty with speech due to cancer, this patient's decision was honored. An explanatory discussion of the research process ensured understanding from both the patient and caregiver that interview and survey responses should be the patient's most direct and honest thoughts. We included this dyad in the study as they were otherwise eligible, and it was deemed the most ethical route per community advisors' recommendations. Lastly, due to COVID-19, opportunities to establish community-based relationships in person were unavailable, and future research participation may be even more plentiful with such efforts. In particular, partnering with locally based community-based organizations and research registries outside of California will be key to reaching a broader US sample, as the majority of the participants in this study were from California.

Acknowledgments

We are grateful to the DAWN Study participants, community advisory board, community organizations, and ethnic media outlets who shared study information broadly. We also thank our community-based interviewers, Sara Kim for translation contributions and Hung Duong for printing service contributions. The research reported in this publication was supported by the National Cancer Institute (K99CA246058), the University of California, Los Angeles Institute of American Cultures and Asian American Studies Center, the National Center for Advancing Translational Science under the University of California, Los Angeles Clinical and Translational Science Institute (UL1TR001881), and the National Institute on Aging (R24AG063718) through the University of California, San Francisco CARE Registry. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Data Availability

The data sets generated during this study are not publicly available. The original consent for study participants did not state such an intention to share the data publicly with others outside of the research team, and some participants are no longer reachable for a reconsent procedure. Confidentiality of participants is of utmost priority, and upon review of the data, there is a possibility that, with known collaborators on this project, demographic characteristics, diagnostic information, interview response patterns, and details, in combination, could make participants recognizable to others in the smaller Asian American network serving metastatic cancer patients or survivors, to participants' health care providers, or to participants' colleagues. Therefore, only restricted data reviews may be discussed with the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

References

1. Budiman A, Ruiz NG. Key facts about Asian Americans, a diverse and growing population. Pew Research Center. 2021. URL: https://www.pewresearch.org/short-reads/2021/04/29/key-facts-about-asian-americans/ [accessed 2024-03-23]
2. Đoàn LN, Takata Y, Sakuma KLK, Irvin VL. Trends in clinical research including Asian American, Native Hawaiian, and Pacific Islander participants funded by the US National Institutes of Health, 1992 to 2018. JAMA Netw Open 2019;2(7):e197432 [FREE Full text] [doi: 10.1001/jamanetworkopen.2019.7432] [Medline: 31339543]
3. Kim JHJ, Lu Q, Stanton AL. Overcoming constraints of the model minority stereotype to advance Asian American health. Am Psychol 2021;76(4):611-626 [FREE Full text] [doi: 10.1037/amp0000799] [Medline: 34410738]
4. Torre LA, Sauer AMG, Chen MS, Kagawa-Singer M, Jemal A, Siegel RL. Cancer statistics for Asian Americans, Native Hawaiians, and Pacific Islanders, 2016: converging incidence in males and females. CA Cancer J Clin 2016;66(3):182-202 [FREE Full text] [doi: 10.3322/caac.21335] [Medline: 26766789]
5. Lin SS, Clarke CA, Prehn AW, Glaser SL, West DW, O'Malley CD. Survival differences among Asian subpopulations in the United States after prostate, colorectal, breast, and cervical carcinomas. Cancer 2002;94(4):1175-1182 [FREE Full text] [Medline: 11920489]
6. Chien C, Morimoto LM, Tom J, Li CI. Differences in colorectal carcinoma stage and survival by race and ethnicity. Cancer 2005;104(3):629-639 [FREE Full text] [doi: 10.1002/cncr.21204] [Medline: 15983985]
7. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68(1):7-30 [FREE Full text] [doi: 10.3322/caac.21442] [Medline: 29313949]
8. Haldar R, Ben-Eliyahu S. Reducing the risk of post-surgical cancer recurrence: a perioperative anti-inflammatory anti-stress approach. Future Oncol 2018;14(11):1017-1021 [FREE Full text] [doi: 10.2217/fon-2017-0635] [Medline: 29623735]
9. Mollica MA, Tesauro G, Tonorezos ES, Jacobsen PB, Smith AW, Gallicchio L. Current state of funded National Institutes of Health grants focused on individuals living with advanced and metastatic cancers: a portfolio analysis. J Cancer Surviv 2021;15(3):370-374. [doi: 10.1007/s11764-021-01008-8] [Medline: 33651327]
10. Mollica MA, Smith AW, Tonorezos E, Castro K, Filipski KK, Guida J, et al. Survivorship for individuals living with advanced and metastatic cancers: National Cancer Institute meeting report. J Natl Cancer Inst 2022;114(4):489-495 [FREE Full text] [doi: 10.1093/jnci/djab223] [Medline: 34878107]
11. Palmer NRA, Kent EE, Forsythe LP, Arora NK, Rowland JH, Aziz NM, et al. Racial and ethnic disparities in patient-provider communication, quality-of-care ratings, and patient activation among long-term cancer survivors. J Clin Oncol 2014;32(36):4087-4094 [FREE Full text] [doi: 10.1200/JCO.2014.55.5060] [Medline: 25403220]
12. John DA, Kawachi I, Lathan CS, Ayanian JZ. Disparities in perceived unmet need for supportive services among patients with lung cancer in the cancer care outcomes research and surveillance consortium. Cancer 2014;120(20):3178-3191 [FREE Full text] [doi: 10.1002/cncr.28801] [Medline: 24985538]
13. Mehnert A, Hartung TJ, Friedrich M, Vehling S, Brähler E, Härter M, et al. One in two cancer patients is significantly distressed: prevalence and indicators of distress. Psychooncology 2018;27(1):75-82. [doi: 10.1002/pon.4464] [Medline: 28568377]
14. Huda N, Shaw MK, Chang HJ. Psychological distress among patients with advanced cancer: a conceptual analysis. Cancer Nurs 2022;45(2):E487-E503. [doi: 10.1097/NCC.0000000000000940] [Medline: 33813528]
15. Hu X, Ma J, Jemal A, Zhao J, Nogueira L, Ji X, et al. Suicide risk among individuals diagnosed with cancer in the US, 2000-2016. JAMA Netw Open 2023;6(1):e2251863 [FREE Full text] [doi: 10.1001/jamanetworkopen.2022.51863] [Medline: 36662522]
16. Ganz PA, Stanton AL. Living with metastatic breast cancer. In: Ganz PA, editor. Improving Outcomes for Breast Cancer Survivors: Perspectives on Research Challenges and Opportunities. Cham, Switzerland: Springer; 2015:243-254.
17. Langbaum T, Smith TJ. Time to study metastatic-cancer survivorship. N Engl J Med 2019;380(14):1300-1302. [doi: 10.1056/NEJMp1901103] [Medline: 30943335]

18. Greer JA, Jacobs JM, El-Jawahri A, Nipp RD, Gallagher ER, Pirl WF, et al. Role of patient coping strategies in understanding the effects of early palliative care on quality of life and mood. J Clin Oncol 2018;36(1):53-60 [FREE Full text] [doi: 10.1200/JCO.2017.73.7221] [Medline: 29140772]
19. Kwong SL, Chen MS, Snipes KP, Bal DG, Wright WE. Asian subgroups and cancer incidence and mortality rates in California. Cancer 2005;104(12 Suppl):2975-2981 [FREE Full text] [doi: 10.1002/cncr.21511] [Medline: 16247792]
20. Trinh QD, Nguyen PL, Leow JJ, Dalela D, Chao GF, Mahal BA, et al. Cancer-specific mortality of Asian Americans diagnosed with cancer: a nationwide population-based assessment. J Natl Cancer Inst 2015;107(6):djv054 [FREE Full text] [doi: 10.1093/jnci/djv054] [Medline: 25794888]
21. Thompson CA, Gomez SL, Hastings KG, Kapphahn K, Yu P, Shariff-Marco S, et al. The burden of cancer in Asian Americans: a report of national mortality trends by Asian ethnicity. Cancer Epidemiol Biomarkers Prev 2016;25(10):1371-1382 [FREE Full text] [doi: 10.1158/1055-9965.EPI-16-0167] [Medline: 27694108]
22. McCracken M, Olsen M, Chen MS, Jemal A, Thun M, Cokkinides V, et al. Cancer incidence, mortality, and associated risk factors among Asian Americans of Chinese, Filipino, Vietnamese, Korean, and Japanese ethnicities. CA Cancer J Clin 2007;57(4):190-205 [FREE Full text] [doi: 10.3322/canjclin.57.4.190] [Medline: 17626117]
23. The rise of Asian Americans. Pew Research Center. 2013. URL: https://www.pewresearch.org/social-trends/2012/06/19/the-rise-of-asian-americans/ [accessed 2024-03-23]
24. Kim BSK, Yang PH, Atkinson DR, Wolfe MM, Hong S. Cultural value similarities and differences among Asian American ethnic groups. Cultur Divers Ethnic Minor Psychol 2001;7(4):343-361. [doi: 10.1037/1099-9809.7.4.343] [Medline: 11759271]
25. Slote WH, De Vos GA, editors. Confucianism and the Family. Albany, New York: State University of New York Press; 1998.
26. Heine SJ. Self as cultural product: an examination of East Asian and North American selves. J Pers 2001;69(6):881-906. [doi: 10.1111/1467-6494.696168] [Medline: 11767822]
27. Markus HR, Kitayama S. Culture and the self: implications for cognition, emotion, and motivation. Psychological Review 1991;98(2):224-253. [doi: 10.1037/0033-295X.98.2.224]
28. Kagawa-Singer M, Wellisch DK. Breast cancer patients' perceptions of their husbands' support in a cross-cultural context. Psychooncology 2003;12(1):24-37. [doi: 10.1002/pon.619] [Medline: 12548646]
29. Ashing KT, Padilla G, Tejero J, Kagawa-Singer M. Understanding the breast cancer experience of Asian American women. Psychooncology 2003;12(1):38-58. [doi: 10.1002/pon.632] [Medline: 12548647]
30. Taylor SE, Sherman DK, Kim HS, Jarcho J, Takagi K, Dunagan MS. Culture and social support: who seeks it and why? J Pers Soc Psychol 2004;87(3):354-362 [FREE Full text] [doi: 10.1037/0022-3514.87.3.354] [Medline: 15382985]
31. Chi HL, Cataldo J, Ho EY, Rehm RS. Please ask gently: using culturally targeted communication strategies to initiate end-of-life care discussions with older Chinese Americans. Am J Hosp Palliat Care 2018;35(10):1265-1272. [doi: 10.1177/1049909118760310] [Medline: 29514489]
32. Yeung NCY, Lu Q, Mak WWS. Self-perceived burden mediates the relationship between self-stigma and quality of life among Chinese American breast cancer survivors. Support Care Cancer 2019;27(9):3337-3345. [doi: 10.1007/s00520-018-4630-2] [Medline: 30617433]
33. Warmoth K, Wong CCY, Chen L, Ivy S, Lu Q. The role of acculturation in the relationship between self-stigma and psychological distress among Chinese American breast cancer survivors. Psychol Health Med 2020;25(10):1278-1292. [doi: 10.1080/13548506.2020.1734638] [Medline: 32174167]
34. Lu Q, Yeung NCY, Tsai W, Kim JHJ. The effects of culturally adapted expressive writing interventions on depressive and anxiety symptoms among Chinese American breast cancer survivors: a randomized controlled trial. Behav Res Ther 2023;161:104244. [doi: 10.1016/j.brat.2022.104244] [Medline: 36592575]
35. Wang Y, Yang L, Xu W, Wang C, Chen J, Wu Y, et al. Effects of a WeChat-based multimodal psychoeducational intervention on psychological well-being and quality of life in acute leukaemia patients in China: a randomised controlled trial. J Cancer Surviv 2022;16(6):1461-1477. [doi: 10.1007/s11764-021-01124-5] [Medline: 34705196]
36. Nekhlyudov L, Mollica MA, Jacobsen PB, Mayer DK, Shulman LN, Geiger AM. Developing a quality of cancer survivorship care framework: implications for clinical care, research, and policy. J Natl Cancer Inst 2019;111(11):1120-1130 [FREE Full text] [doi: 10.1093/jnci/djz089] [Medline: 31095326]
37. Braun V, Clarke V. Reflecting on reflexive thematic analysis. Qual Res Sport Exerc Health 2019;11(4):589-597. [doi: 10.1080/2159676x.2019.1628806]
38. Braun V, Clarke V. Conceptual and design thinking for thematic analysis. Qual Psychol 2022;9(1):3-26. [doi: 10.1037/qup0000196]
39. Adler NE, Epel ES, Castellazzo G, Ickovics JR. Relationship of subjective and objective social status with psychological and physiological functioning: preliminary data in healthy White women. Health Psychol 2000;19(6):586-592. [doi: 10.1037//0278-6133.19.6.586] [Medline: 11129362]
40. Norris AE, Ford K, Bova CA. Psychometrics of a brief acculturation scale for Hispanics in a probability sample of urban Hispanic adolescents and young adults. Hisp J Behav Sci 1996;18(1):29-38. [doi: 10.1177/07399863960181004]

41. Boyes A, Girgis A, Lecathelinais C. Brief assessment of adult cancer patients' perceived needs: development and validation of the 34-item supportive care needs survey (SCNS-SF34). J Eval Clin Pract 2009;15(4):602-606. [doi: 10.1111/j.1365-2753.2008.01057.x] [Medline: 19522727]
42. Yanez B, Pearman T, Lis CG, Beaumont JL, Cella D. The FACT-G7: a rapid version of the functional assessment of cancer therapy-general (FACT-G) for monitoring symptoms and concerns in oncology practice and research. Ann Oncol 2013;24(4):1073-1078 [FREE Full text] [doi: 10.1093/annonc/mds539] [Medline: 23136235]
43. Riba MB, Donovan KA, Ahmed K, Andersen B, Braun I, Breitbart WS, et al. NCCN Guidelines® insights: distress management, version 2.2023: featured updates to the NCCN Guidelines. J Natl Compr Canc Netw 2023;21(5):450-457 [FREE Full text] [doi: 10.6004/jnccn.2023.0026] [Medline: 37156476]
44. Kroenke K, Strine TW, Spitzer RL, Williams JBW, Berry JT, Mokdad AH. The PHQ-8 as a measure of current depression in the general population. J Affect Disord 2009;114(1-3):163-173. [doi: 10.1016/j.jad.2008.06.026] [Medline: 18752852]
45. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006;166(10):1092-1097 [FREE Full text] [doi: 10.1001/archinte.166.10.1092] [Medline: 16717171]
46. Stein KD, Martin SC, Hann DM, Jacobsen PB. A multidimensional measure of fatigue for use with cancer patients. Cancer Pract 1998;6(3):143-152. [doi: 10.1046/j.1523-5394.1998.006003143.x] [Medline: 9652245]
47. Thoresen S, Tambs K, Hussain A, Heir T, Johansen VA, Bisson JI. Brief measure of posttraumatic stress reactions: impact of event scale-6. Soc Psychiatry Psychiatr Epidemiol 2010;45(3):405-412. [doi: 10.1007/s00127-009-0073-x] [Medline: 19479171]
48. Krebs EE, Lorenz KA, Bair MJ, Damush TM, Wu J, Sutherland JM, et al. Development and initial validation of the PEG, a three-item scale assessing pain intensity and interference. J Gen Intern Med 2009;24(6):733-738 [FREE Full text] [doi: 10.1007/s11606-009-0981-1] [Medline: 19418100]
49. Espie CA, Kyle SD, Hames P, Gardani M, Fleming L, Cape J. The sleep condition indicator: a clinical screening tool to evaluate insomnia disorder. BMJ Open 2014;4(3):e004183 [FREE Full text] [doi: 10.1136/bmjopen-2013-004183] [Medline: 24643168]
50. Carver CS. You want to measure coping but your protocol's too long: consider the brief COPE. Int J Behav Med 1997;4(1):92-100. [doi: 10.1207/s15327558ijbm0401_6] [Medline: 16250744]
51. Stanton AL, Kirk SB, Cameron CL, Danoff-Burg S. Coping through emotional approach: scale construction and validation. J Pers Soc Psychol 2000;78(6):1150-1169. [doi: 10.1037//0022-3514.78.6.1150] [Medline: 10870915]
52. Lamers SMA, Westerhof GJ, Bohlmeijer ET, ten Klooster PM, Keyes CLM. Evaluating the psychometric properties of the Mental Health Continuum-Short Form (MHC-SF). J Clin Psychol 2011;67(1):99-110. [doi: 10.1002/jclp.20741] [Medline: 20973032]
53. Mccullough ME, Emmons RA, Tsang JA. The grateful disposition: a conceptual and empirical topography. J Pers Soc Psychol 2002;82(1):112-127. [doi: 10.1037//0022-3514.82.1.112] [Medline: 11811629]
54. Neff KD. The development and validation of a scale to measure self-compassion. Self Identity 2003;2(3):223-250. [doi: 10.1080/15298860309027]
55. Lo C, Burman D, Swami N, Gagliese L, Rodin G, Zimmermann C. Validation of the QUAL-EC for assessing quality of life in patients with advanced cancer. Eur J Cancer 2011;47(4):554-560. [doi: 10.1016/j.ejca.2010.10.027] [Medline: 21126869]
56. Hughes ME, Waite LJ, Hawkley LC, Cacioppo JT. A short scale for measuring loneliness in large surveys: results from two population-based studies. Res Aging 2004;26(6):655-672 [FREE Full text] [doi: 10.1177/0164027504268574] [Medline: 18504506]
57. Cutrona CE, Russell DW. The provisions of social relationships and adaptation to stress. In: Perlman D, Jones WH, editors. Advances in Personal Relationships, Volume 1. Stamford, CT: JAI Press; 1987:37-67.
58. Kim BK, Li LC, Ng GF. The Asian American values scale–multidimensional: development, reliability, and validity. Cultur Divers Ethnic Minor Psychol 2005;11(3):187-201. [doi: 10.1037/1099-9809.11.3.187] [Medline: 16117587]
59. Lui PP, Rollock D. Greater than the sum of its parts: development of a measure of collectivism among Asians. Cultur Divers Ethnic Minor Psychol 2018;24(2):242-259. [doi: 10.1037/cdp0000163] [Medline: 28493735]
60. Tsai W, Lu Q. Perceived social support mediates the longitudinal relations between ambivalence over emotional expression and quality of life among Chinese American breast cancer survivors. Int J Behav Med 2018;25(3):368-373. [doi: 10.1007/s12529-017-9705-9] [Medline: 29238936]
61. Hamann HA, Shen MJ, Thomas AJ, Craddock Lee SJ, Ostroff JS. Development and preliminary psychometric evaluation of a patient-reported outcome measure for lung cancer stigma: the lung cancer stigma inventory (LCSI). Stigma Health 2018;3(3):195-203 [FREE Full text] [doi: 10.1037/sah0000089] [Medline: 30393760]
62. Cousineau N, McDowell I, Hotz S, Hébert P. Measuring chronic patients' feelings of being a burden to their caregivers: development and preliminary validation of a scale. Med Care 2003;41(1):110-118. [doi: 10.1097/00005650-200301000-00013] [Medline: 12544548]
63. Impett EA, Gordon AM. Why do people sacrifice to approach rewards versus to avoid costs? Insights from attachment theory. Pers Relatsh 2010;17(2):299-315. [doi: 10.1111/j.1475-6811.2010.01277.x]

64. Lawrence RH, Tennstedt SL, Assmann SF. Quality of the caregiver–care recipient relationship: does it offset negative consequences of caregiving for family caregivers? Psychol Aging 1998;13(1):150-158. [doi: 10.1037//0882-7974.13.1.150] [Medline: 9533197]
65. Mangen DJ, Bengtson VL, Landry PH, editors. Measurement of Intergenerational Relations. Beverly Hills, CA: Sage Publications; 1988.
66. Pearlin LI, Mullan JT, Semple SJ, Skaff MM. Caregiving and the stress process: an overview of concepts and their measures. Gerontologist 1990;30(5):583-594. [doi: 10.1093/geront/30.5.583] [Medline: 2276631]

Abbreviations

CACCC: Chinese American Coalition for Compassionate Care
CVK: Chinese-, Vietnamese-, and Korean-descent
DAWN: Describing Asian American Well-Being and Needs in Cancer
NIH: National Institutes of Health
UCLA: University of California, Los Angeles
VACF: Vietnamese American Cancer Foundation

Edited by A Mavragani; submitted 16.12.23; peer-reviewed by A Mukherjea, F Lui; comments to author 16.01.24; revised version received 06.02.24; accepted 11.03.24; published 22.04.24.

Please cite as:
Kim JHJ, Kagawa Singer M, Bang L, Ko A, Nguyen B, Chen Stokes S, Lu Q, Stanton AL
Supportive Care Needs in Chinese, Vietnamese, and Korean Americans With Metastatic Cancer: Mixed Methods Protocol for the DAWN Study
JMIR Res Protoc 2024;13:e50032
URL: https://www.researchprotocols.org/2024/1/e50032
doi:10.2196/50032
PMID:38648633

Protocol

Leveraging AI and Machine Learning to Develop and Evaluate a Contextualized User-Friendly Cough Audio Classifier for Detecting Respiratory Diseases: Protocol for a Diagnostic Study in Rural Tanzania

Kahabi Ganka Isangula[1], MD, MPH, PhD; Rogers John Haule[1], DipCIT

School of Nursing and Midwifery, Aga Khan University, Dar Es Salaam, United Republic of Tanzania

Corresponding Author:
Kahabi Ganka Isangula, MD, MPH, PhD
School of Nursing and Midwifery
Aga Khan University
Salama House, 344 Urambo St
PO Box 125
Dar Es Salaam, 255
United Republic of Tanzania
Phone: 255 754030726
Email: kahabi.isangula@aku.edu

Abstract

Background: Respiratory diseases, including active tuberculosis (TB), asthma, and chronic obstructive pulmonary disease (COPD), constitute substantial global health challenges, necessitating timely and accurate diagnosis for effective treatment and management.

Objective: This research seeks to develop and evaluate a noninvasive user-friendly artificial intelligence (AI)–powered cough audio classifier for detecting these respiratory conditions in rural Tanzania.

Methods: This is a nonexperimental cross-sectional research with the primary objective of collection and analysis of cough sounds from patients with active TB, asthma, and COPD in outpatient clinics to generate and evaluate a noninvasive cough audio classifier. Specialized cough sound recording devices, designed to be nonintrusive and user-friendly, will facilitate the collection of diverse cough sound samples from patients attending outpatient clinics in 20 health care facilities in the Shinyanga region. The collected cough sound data will undergo rigorous analysis, using advanced AI signal processing and machine learning techniques. By comparing acoustic features and patterns associated with TB, asthma, and COPD, a robust algorithm capable of automated disease discrimination will be generated facilitating the development of a smartphone-based cough sound classifier. The classifier will be evaluated against the calculated reference standards including clinical assessments, sputum smear, GeneXpert, chest x-ray, culture and sensitivity, spirometry and peak expiratory flow, and sensitivity and predictive values.

Results: This research represents a vital step toward enhancing the diagnostic capabilities available in outpatient clinics, with the potential to revolutionize the field of respiratory disease diagnosis. Findings from the 4 phases of the study will be presented as descriptions supported by relevant images, tables, and figures. The anticipated outcome of this research is the creation of a reliable, noninvasive diagnostic cough classifier that empowers health care professionals and patients themselves to identify and differentiate these respiratory diseases based on cough sound patterns.

Conclusions: Cough sound classifiers use advanced technology for early detection and management of respiratory conditions, offering a less invasive and more efficient alternative to traditional diagnostics. This technology promises to ease public health burdens, improve patient outcomes, and enhance health care access in under-resourced areas, potentially transforming respiratory disease management globally.

International Registered Report Identifier (IRRID): PRR1-10.2196/54388

(JMIR Res Protoc 2024;13:e54388) doi:10.2196/54388

KEYWORDS

artificial intelligence; machine learning; respiratory diseases; cough classifiers; Tanzania; Africa; mobile phone; user-friendly; cough; detecting respiratory disease; diagnostic study; tuberculosis; asthma; chronic obstructive pulmonary disease; treatment; management; noninvasive; rural; cross-sectional research; analysis; cough sound

Introduction

Respiratory diseases impose a significant burden on individuals, communities, and health care systems worldwide. These conditions, which encompass a wide range of disorders such as tuberculosis (TB), asthma, chronic obstructive pulmonary disease (COPD), and lung cancer, not only diminish the quality of life for affected individuals but also lead to substantial economic and health care costs particularly in low- and middle-income countries [1]. Patients with respiratory diseases often struggle with symptoms like coughing, shortness of breath, and chest pain, which can limit their ability to perform daily activities and enjoy a normal life [1,2]. The burden of respiratory diseases extends beyond the physical aspect, as they are frequently associated with emotional distress and psychological challenges, contributing to diminished overall well-being for patients and their families.

From a public health perspective, respiratory diseases account for a significant portion of global morbidity and mortality. The World Health Organization (WHO) reports that respiratory infections alone are responsible for millions of deaths each year, particularly affecting vulnerable populations such as children, the elderly, and individuals with compromised immune systems [3,4]. Moreover, the economic costs associated with respiratory diseases are staggering, encompassing medical expenses lost productivity due to illness, and the burden on health care systems. For instance, the total spending across all respiratory conditions increased by US $71.7 billion in the United States by 2016 from 170.8 billion in 1996 with asthma and COPD contributing US $35.5 billion and US $34.3 billion, respectively, of the total increase [3]. TB, asthma, and COPD are said to be common and rising public health burdens in Africa [5]. Preventive measures such as smoking cessation, improved air quality and vaccination are critical to alleviating this burden, as they can reduce the incidence and severity of respiratory diseases and ultimately improve the overall health and well-being of populations around the world [3]. However, respiratory diseases are relatively neglected in sub-Saharan Africa with no tangible public health programs to address them [5,6]. Consequently, the provision of health care for respiratory diseases appears suboptimal and this was further compromised by the COVID-19 pandemic [5].

Taking TB as an example, the WHO continues to emphasize the need for early detection as a strategic approach for reducing the risk of transmitting the disease to others, improving health outcomes, and reducing distress and economic hardship at the family level [7,8]. Much emphasis is now placed on user-friendly, inexpensive, and contextually feasible diagnostic tools that can effectively identify people who probably have active TB [7,8]. Consequently, countries like Tanzania have started incorporating some of the WHO recommendations about using new user-friendly digital techniques for managing TB into their policies. However, due to the need for improved quality of health care workers with essential knowledge and skills, real adoption of such technologies is still less than intended.

The emergence of the COVID-19 pandemic profoundly impacted the diagnosis and management of other respiratory diseases. With health care systems overwhelmed by the surge in COVID-19 cases, resources, personnel, and laboratory capacities were often diverted away from routine health care services, including the diagnosis of respiratory conditions such as TB, asthma, and COPD [5]. For example, most guidelines recommended limiting the use of pulmonary function tests for fear of transmission of COVID-19 which constrained the use of spirometry testing further compromising the diagnosis of chronic respiratory diseases [9]. Furthermore, the fear of contracting COVID-19 in health care settings led many individuals to postpone or avoid seeking medical care for respiratory symptoms, resulting in delayed diagnoses and exacerbation of preexisting conditions [5]. Diagnostic tests and imaging equipment were sometimes repurposed for COVID-19 testing, leaving fewer resources available for the timely detection of other respiratory ailments. As a result, there has been a concerning backlog in the diagnosis of respiratory diseases, potentially leading to worsened health outcomes and increased burden on health care systems as they work to catch up on missed diagnoses and treatments.

One promising avenue for improving the diagnosis of respiratory diseases is the analysis of cough sounds, which can carry valuable information about the underlying respiratory condition. Most importantly, the recent developments in artificial intelligence (AI) and machine learning (ML) have heightened the need for the application of these powerful tools in the diagnosis of respiratory diseases, particularly, through the development of cough sound classifiers [10,11]. These sophisticated algorithms have the capacity to analyze and interpret patterns within cough sounds, providing valuable insights into a patient's respiratory health [10-17]. By training AI models on large data sets of cough audio recordings from both healthy individuals and those with respiratory conditions such as TB, asthma, or COPD, it becomes possible to identify distinctive acoustic signatures associated with different diseases [12-17]. These AI-driven cough classifiers can discern subtle variations in cough frequency, duration, intensity, and spectral characteristics, enabling early and accurate disease detection [12-17]. A good example of how AI and ML have been proven useful is the documentation of their effectiveness in Western countries toward the detection of TB [12], COVID-19 [13,14], asthma, COPD [15,16], and even pertussis [17] and their values have extended beyond sound classification to interpreting and analysis of medical imaging for TB detection [18,19]. Moreover, the noninvasive nature of cough audio analysis makes it a convenient and cost-effective diagnostic tool, particularly in resource-constrained settings [12-17]. Patients can record their cough sounds using smartphones or dedicated devices, and these

recordings can then be processed by AI algorithms for rapid assessment [20-22]. The potential for remote monitoring is especially valuable in the context of respiratory diseases, as it allows for continuous tracking of a patient's condition and response to treatment.

Coughing is a common indication of respiratory illnesses, resulting from a forceful release of air from the air passages. Nevertheless, the impact of coughing on the respiratory system is recognized to be variable [23,24]. For instance, lung ailments can lead to either constriction or blockage of the airways, which can affect the sound characteristics of coughing [24]. Furthermore, it has been suggested that the glottis behaves differently under various pathological conditions, allowing for the differentiation of coughs associated with asthma, bronchitis, and pertussis [25]. As a result, the automatic classification of acoustic signals linked to cough to detect respiratory diseases like TB, asthma, and COPD seems to be a reasonable scholarly endeavor to pursue. Research suggests that conditions such as TB, asthma, and COPD exhibit specific temporal patterns and frequencies in coughing, which can be effectively analyzed with advanced technology [26,27].

As AI and ML continue to advance, the accuracy and precision of cough audio classifiers are expected to improve and may outperform standard tests enhancing their use in both clinical practice and public health initiatives. For example, a recent study in Europe indicated that the sensitivity and positive predictive value of the AI-based algorithm were superior to pulmonologist-based diagnostic category allocation in each of the 8 disease groups evaluated [28]. In essence, these technologies hold great promise in revolutionizing the way we diagnose and manage respiratory diseases, offering early intervention, personalized treatment, and improved patient outcomes. However, a major shortfall with the application of AI and ML is that they have not been fully exploited in cough audio classification in rural African contexts. Given the burgeoning interest in leveraging AI or ML for health care advancements, there is a critical need for empirical research to explore their potential applications in rural African settings. The gap in noninvasive, efficient diagnostic tools for respiratory diseases in low-income Africa necessitates urgent attention. This study aims to develop and assess an AI-powered cough audio classifier designed to detect respiratory conditions in rural Tanzania. Through a systematic approach to collecting and analyzing cough sounds in outpatient settings, this research aims to improve disease identification accuracy and efficiency, offering accessible, user-friendly diagnostic solutions to support health care providers in low-income areas.

Methods

Design

This is nonexperimental cross-sectional research with the primary objective of collection and analysis of cough sounds from patients with active TB, asthma, and COPD in outpatient clinics to generate and evaluate a noninvasive cough audio classifier. The study combines innovative applications of AI or ML to develop cough audio classifiers using data collected from patients with active diseases and evaluation of the classifiers in routine care against the reference standards. To achieve this, a four-phase research process will be implemented involving (1) cough sound collection for 12 months (phase 1), (2) cough sound analysis and algorithm development for 12 months (phase 2), (3) development of cough audio classifier for 6 months (phase 3), and (4) evaluation of cough audio classifier for 18 months (phase 4). The expected primary outcomes are contextualized user-friendly AI-powered cough audio classifier and a rate of patients with active respiratory diseases notified and linked to treatment. The expected secondary outcomes are health care workers' experience with a cough audio classifier, including perspectives on the acceptability, feasibility, and cost of using a cough audio classifier. The comparison of the cost incurred to implement the audio classifier will be compared to the standards of care. The feasibility indicators will include the perceived acceptability and satisfaction of health care providers and patients toward the cough audio classifier. Findings from this study will be useful in further refinement of the cough audio classifier and definitive trials in the broader community. The research will increase the pool of health experts with skills in the application of AI or ML developing diagnostic tests in Tanzania. It is expected that the cough audio classifier if found effective during future definitive trials, can be trademarked.

Settings

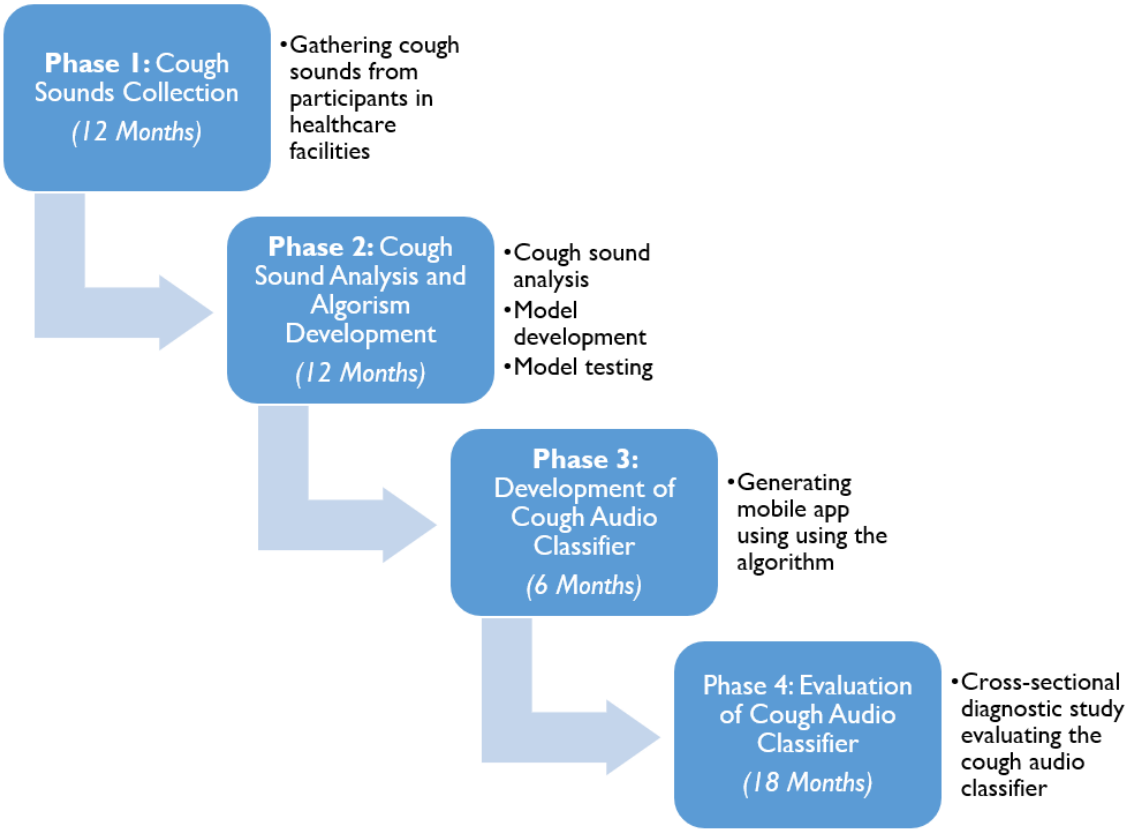
The study will take place across the Shinyanga Region of Tanzania. The Shinyanga Region, predominantly rural with less than 5% urban residency, is detailed further in my prior research [29,30]. More specifically, the study will be conducted in 30 facilities including Shinyanga Referral Hospital, Shinyanga Municipal Hospital, Shinyanga District Council Hospital, Kolandoto Hospital, Kahama Municipal Hospital, Jakaya Kikwete Hospital, Kishapu health centre (HC) Mwadui Hospital, Nindo Dispensary, Tinde HC, Samuye HC, Ngokoro HC, Kambarage HC, Imani Dispensary, Inspire Dispensary, Mwawaza Dispensary, Kizumbi Dispensary, Bubiki Dispensary, Polisi Dispensary, Lubaga Dispensary, Consolata Dispensary, Majengo Dispensary, Maganzo Dispensary, Mwamalili Dispensary, Mwamalili Dispensary, Golden Grace Dispensary, Masekelo Dispensary, Kanisa la Kiinjiri la Kilutheri Tanzania Lutheran Dispensary, Old Shinyanga Dispensary, and Chamaguha Dispensary. These sites are purposefully selected considering ownership (public, private, and faith-based organization), location (urban, peri-urban, and rural), level (hospital, health center, and dispensaries), and access to a wealthy number of clients presenting with coughs. The focus on rural settings stems from the commitment of the principal investigator (PI) to enhancing primary health care [29]; challenges in diagnosing TB, asthma, and COPD due to limited diagnostics; the value of co-designing [30] a cough audio classifier with rural inputs for cultural relevance; and Shinyanga's clear, low-noise environment for optimal cough sound recording.

Study Implementation

Overview

The study implementation is concisely illustrated in Figure 1. A concise summary is provided.

Figure 1. Study implementation framework.



Phase 1: Cough Sounds Collection (12 Months)

The procedures for cough sound collection are adapted from previous research in South Africa [12] considering local contexts. More specifically, cough sound data will be collected from health care facilities using specialized cough sound recording devices equipped with high-quality microphones in a dedicated cross-ventilated room. These devices will be nonintrusive and user-friendly, ensuring patient comfort and compliance. Patients with active TB, asthma, and COPD will be identified in the outpatient department (OPD) clinics and directed to the recording room. During the recording sessions, patients will be instructed to cough into the device several times, producing a diverse set of cough sounds. All audio recordings will be conducted by a health care provider, in selected health care facilities during regular clinic hours, who are trained to operate the recording device. The recording room will not be fitted with additional soundproof materials to mimic the clinical environment where the diagnostic procedures for patients with TB, asthma, and COPD are performed. A comprehensive summary of the audio sound capturing process is detailed in Multimedia Appendix 1 [11,12,31-36].

The research team will adhere to ethical guidelines and ensure the privacy and well-being of participants. The inclusion criteria for patients whose cough sounds will be collected include patients who are older than 18 years of age and with a clinical diagnosis of TB, asthma, or COPD diseases. The exclusion criteria will be patients who provide no consent and those unable to provide a cough sound. The decision to exclude children younger than 18 years of age from our study was driven by the extensive consent process required for minors, compounded by our limited resources. Additionally, previous research has highlighted challenges in collecting cough sounds from this demographic [37-39].

Phase 2: Cough Sound Analysis and Algorithm Development (12 Months)

Once the cough sound data are collected, advanced signal processing and ML techniques will be used to analyze and classify the cough sounds associated with each respiratory disease. By comparing the acoustic features and patterns among the 3 conditions (TB, asthma, and COPD), the study aims to develop a robust algorithm for automated disease discrimination. A proposed approach for audio classification is using TensorFlow applying Librosa software (Librosa Organization) described previously [11,40]. Librosa is an open-source Python package for music and audio analysis and can provide the data and the sampling rate which plays a vital role in audio classification since different sounds have different sample rates [40]. A comprehensive summary of the procedures for cough sound analysis, algorithm or model development, and testing has been summarized in Multimedia Appendix 2 [11,12,34,35,40-46].

The emerging model will be checked whether it correctly predicts the cough sounds. The expected outcome of this process is a reliable model that can assist the research team in developing a mobile app to help health care practitioners identify TB, asthma, and COPD based on cough sound patterns.

Phase 3: Development of Cough Audio Classifier (6 Months)

The developed models for TB, asthma, and COPD will need to be integrated into a noninvasive and user-friendly diagnostic tool. Under the guidance of developers, the development of a mobile app for TB, asthma, and COPD detection will involve the deployment of the developed models to Android with TensorFlow Lite [47]. The sample app will be cloned from GitHub, the sound classification Android app will be imported into Android Studio, and the model will be added (both the soundclassifier.tflite and labels.txt) into the src/main/assets folder replacing the example model that is already there and the app will be built and deployed on the Android device.

Phase 4: Evaluation of Cough Audio Classifier (18 Months)

This will be a cross-sectional diagnostic study evaluating the cough audio classifier for active TB, asthma, and COPD triage and case detection against the reference standards. Clients attending OPD clinics at rural health care facilities and suspected of having TB, asthma, and COPD as per national guidelines will be included in the study, upon written consent. Data will be collected from each of the participating facilities. The results of recorded cough using a cough audio classifier will be compared with the current standard of clinical assessment, spirometry, peak expiratory flow (PEF), GeneXpert, culture and sensitivity, chest x-rays (CXR), clinical assessment, and the specificity and predictive values will be calculated.

Study Design

The study will be a multicenter hospital-based validation cross-sectional diagnostic study evaluating the cough audio classifier for active TB, asthma, and COPD triage and case detection in routine care against the reference standards. This study will involve consecutively enrolled suspects who will be closely evaluated to define their illness. The diagnostic accuracy of automated smartphone-based cough audio will be compared among TB, asthma, and COPD cases and controls. Cases include participants who meet “Definite” or “Probable” TB, asthma, and COPD criteria. Controls include participants who presented with symptoms potentially suggestive of TB, asthma, and COPD, but were not started on treatment and had full clinical resolution at follow-up or had an alternative diagnosis confirmed.

Study Area

The evaluation study will be conducted in similar study settings and the 30 health care facilities in which cough sounds were collected in Shinyanga Region (phase 1).

Participants Recruitment

Patients attending OPD clinics and meeting all eligibility criteria listed in the eligibility criteria will be referred to the study’s research staff primarily by the treating medical officer or nurses during triage at OPD. Once enrolled, participants will be retained in the study by telephone reminders. Research assistants will call the participant to arrange follow-up visits and reminder calls will be placed prior to the expected follow-up visit appointments. If there is significant difficulty with participant retention, the possibility of using community health care workers to conduct home visits will be explored. The participant will be reimbursed for the cost of travel to or from the follow-up appointments.

Eligibility Criteria

Overview

There will be no exceptions to eligibility requirements at the time of enrollment. Questions about eligibility criteria will be administered prior to attempting to enroll the participant. The eligibility criteria for this study have been carefully considered. Patients not meeting the criteria will not be enrolled in the study. Participants will be considered eligible for enrollment in this study if they fulfill all the inclusion criteria and none of the exclusion criteria.

Inclusion Criteria

The criteria for inclusion are (1) patients aged older than 18 years and presenting with cough; (2) clients attending outpatient clinics in the selected study sites; and (3) clients suspected of having tuberculosis, asthma, and COPD as per national guidelines—prioritizing those with cough of any duration.

Exclusion Criteria

The exclusion criteria are (1) refusal to participate and (2) clients who started prescription medications.

Sample Size Estimation

This evaluative study will collect and analyze data for all patients receiving TB, asthma, and COPD care, starting from screening, and ending with the starting of treatment or preventive therapy. A sample size of 348 for each disease condition (a total of 1044) was obtained using the Buderer formula for sensitivity and specificity [48]. Using tuberculosis as an example, the reported sensitivity of 0.98and specificity of 0.84 of using AI in detecting *Mycobacterium tuberculosis* [49,50] and the prevalence of pulmonary TB of 0.335 among patients with presumptive TB [51] were used to compute this sample size at 0.05 precision and 0.1 attrition.

Where n is the required sample size, SN is the anticipated sensitivity, α is the size of the critical region ($1-\alpha$ is the confidence level), $Z1-\alpha 2/$ is the standardized normal variate corresponding to the specified size of the critical region (α), and L is the absolute precision.

Participants’ Service Flow

Patients’ TB, asthma, and COPD service flow all project activities will be consistent with the service standards as outlined in the national policies and guidelines. Currently, in Tanzania, patients’ access to TB, asthma, and COPD services is mainly through facility-based health services. The flow of patients starts with screening for symptoms and signs. Participants who screen positive for TB, asthma, and COPD symptoms (presumptive clients) are either assessed clinically first and referred directly to the laboratory within the same or outside facility for diagnosis (for TB) or receive medical treatment after medical assessments

and investigations (for asthma and COPD). Specifically for TB, health providers then order sputum for smear microscopy or GeneXpert and the sample is collected at the referring entry point or at the laboratory, depending on the client volume and human resources at the site. When the sputum sample is negative, a CXR is ordered to support clinical radiological diagnosis. Sputum samples with positive results are sent to the TB clinic service provider who then liaises with the requesting clinician (at various service delivery points) to ensure that the patient receives their result and initiates TB treatment. Patients may be waiting for their result (same-day diagnosis) or be given an appointment to return to the requesting clinician for follow-up. CXR results are interpreted by trained clinicians if available at the facility level, or by the district TB coordinator. For asthma and COPD, a clinical diagnosis may be made by an attending clinician and medications initiated, occasionally after excluding TB where diagnostic facilities are available.

Clinical Evaluations

A variety of clinical assessments will be conducted, encompassing the collection of demographic and medical data, anthropometric measurements, chest auscultations, spirometry, PEF, and clinical specimen collection. A comprehensive overview of these clinical evaluations is described in Multimedia Appendix 3 [52,53].

Data Management and Analysis

Data Management

Study personnel will be given in-service training by the PI about forms and study procedures before the start of the study and given in-service training periodically throughout the study. Data collection is the responsibility of the research assistants at the site under the supervision of the PI. During the study, the PI will maintain complete and accurate documentation for the study. Data analysis will be the responsibility of the PI, under the mentorship of a biostatistician.

Each subject will be assigned a unique patient ID number. The forms that contain the subjects' names, dates of birth, and contact information will be kept in the PI's office and filed in a secured cabinet. A key linking each participant to their patient ID will be created and kept secured by the PI. All case report forms (CRFs) will be reviewed for accuracy, clarity, and completion, and by the data entry staff for completion. Study-related laboratory reports will be reviewed and signed off by a PI. Data reported on the CRF that are derived from source documents or chart reviews should be consistent with the source documents or the discrepancies should be explained.

Data Capture

Data will be captured using paper CRFs or electronic CRF and transcribed into a secure, password-protected, electronic database. Data capture will be ongoing throughout the period of the study. It is expected that participant CRFs will be reviewed and entered electronically directly or within 7 days of completion of the visit. Data quality control measures will be instituted as outlined in the standard operating procedures, in accordance with data quality control procedures at the study site.

Types of Data

Identifiable information including name and contact information will not be stored electronically, but only on paper. A coded CRF-compliant, secure, password-protected electronic database will house the demographic data, clinical data (including current and past medical history), and laboratory outcome measures (including results of study-related tests or procedures).

Analysis for Outcomes

Results of recorded cough using cough audio classifier will be compared with clinical assessment, GeneXpert, culture and sensitivity, spirometry, PEF and sensitivity, and specificity and predictive values will be calculated. These measures will be collected simultaneously among patients and will serve as benchmarks for comparison purposes. The analysis will be generated for cost, facilitators, and barriers to implementing the cough audio classifier for TB, asthma, and COPD screening in rural community settings.

Audio Classifier-Diagnostic Test

A binomial test will be used to test whether the sensitivity of the audio classifier using the previously reported cut-off is less than 0.8, and receiver operating characteristic analysis will be explored to determine if another cut-off should be used in this patient population. Logistic regression models will be used to determine whether an audio classifier contributes additional information to predicting TB, asthma, and COPD in the presence of clinical and laboratory predictors. Variable assessment will be based on a likelihood ratio test, in which the likelihood of the reduced model will be compared to the likelihood of the full model. As a primary summary measure of discrimination, we will use the c (for concordance) index, a measure that is identical to the area under the receiver operating characteristic curve when the end point is binary.

Risk Factor Analysis

The study will use a similar strategy as described. All models will be adjusted for baseline medical and demographic characteristics of the subjects. Data will be also summarized with respect to the primary and secondary outcome measures, demographics, and baseline characteristics. Quantitative variables will be summarized with standard descriptive statistics while frequency tables will summarize categorical variables. All analyses will be performed in STATA (StataCorp). Before analysis, the outcome will be examined for skew and kurtosis to determine the need for standard transformations to meet normal distribution assumptions. All *P* values are 2-sided and considered statistically significant at a level of .05.

A deductive thematic analysis approach will be used for qualitative data [54] on the barriers and facilitators of cough audio classifier acceptance using NVivo software (Lumivero). More specifically, data transcription and translation will occur simultaneously by the research assistants. After transcription and translation, the interview transcripts will be cross-checked by the PI to ensure that the participants' worldview was not lost during translation. The interview transcripts will then be deidentified, and pseudonyms generated for each participant. The data will then be uploaded into NVivo software for thematic coding. The PI will deductively generate an initial list of codes

from data extracts of the first 3 transcripts. Then, these codes will be reviewed by the research team who had independently reviewed selected transcripts generating a consensual list of codes. The PI will continue coding the rest of the transcripts, refining, and generating more codes upon coming across a new segment of data that could not fit into the initial codes. Codes will then be sorted into potential subthemes and themes, followed by collation of all relevant coded data extracts within identified themes. Throughout coding and refinement, the peer consultation will be maintained to reflect on the subthemes and themes generated.

Ethical Considerations

The study complies with the principles of the Declaration of Helsinki, as amended by 59th World Medical Association General Assembly, Seoul, Korea, October 2008. It will also be conducted in compliance with the approved protocol, the principles of Good Clinical Practice and applicable local laws and guidelines. The study protocol, information, and consent documents will be submitted to the National Institute for Medical Research (Tanzania) for review and approval. Permission will be sought from the President's Office Regional and Local Administrative Government (PORALG), the national TB and leprosy programme (NTLP), and participating health facilities. A comprehensive overview of the informed consent process, along with measures for ensuring confidentiality and data protection, is outlined in Multimedia Appendix 4.

Results

Participants Demographics

The first section of the results will summarize the demographics of participants involved in cough sound collection and evaluation of the cough audio classifier. Participants' gender; age; primary occupations; marital status; presence and duration of cough and other TB, asthma, and COPD symptoms and TB contact and family history; current or chronic medications; and comorbidities are some of the demography that will be presented in a tabular form.

Phase 1: Cough Sounds Collection

The findings will encapsulate a compilation of various cough sounds gathered during the collection process. This compilation will encompass a spectrum of cough characteristics, including frequency, duration, and intensity. Additionally, a summary of the extensive database comprising cough audio recordings, intended for use in subsequent phases, will be provided.

Phase 2: Cough Sound Analysis and Algorithm Development

The findings regarding the methodology and procedures used to analyze patterns and correlations within the cough sound data set, facilitating algorithm development, will be outlined. Additionally, the process, methodologies, and findings related to the initial algorithm development, distinguishing between different cough sounds, and identifying potential classification markers, will be detailed. Furthermore, a summary of the steps taken to refine the algorithms and improve accuracy and efficiency in identifying distinct cough patterns will be provided.

Phase 3: Development of Cough Audio Classifier

The findings will encapsulate an overview of the process and methodologies leading to the successful creation of a functional cough audio classifier, designed as a smartphone-based app, derived from the refined algorithms developed in phase 2. The summary will outline the procedures used to assess the classifier's capacity to accurately differentiate between various types of coughs, specifically identifying those associated with conditions. Similarly, it will highlight the process for evaluating the classifier's adaptability across a broad spectrum of cough variations and its potential for real-time implementation.

Phase 4: Evaluation of Cough Audio Classifier

The study will present findings from a performance evaluation aimed at assessing the accuracy, sensitivity, and specificity of the cough audio classifier in a real-world setting. These results will encompass an evaluation of the classifier's feasibility, acceptability, user experiences, and efficiency among health care providers and patients. Additionally, the study will present findings from a comparative analysis of the cost-effectiveness and practicality of implementing the cough audio classifier in contrast to existing standard practices.

Collectively, these key results from each phase will significantly contribute to a comprehensive understanding of the cough audio classifier's feasibility, accuracy, and its potential for real-world applicability, as developed within this study.

Discussion

Principal Findings

The study aims to enhance the management of TB, asthma, and COPD in health care facilities involved in the research. It aligns with existing patient care pathways for TB, asthma, and COPD by focusing on improving diagnostic capabilities through the integration of services and decentralization, thereby reinforcing referral systems within and between health care facilities. The anticipated primary outcome is the development and validation of a noninvasive, mobile-based cough sound classifier for detecting TB, asthma, and COPD. This research will report on the practical evaluation of the acceptability and effectiveness of the cough audio classifier, with a particular focus on its applicability in rural primary health care settings.

Comparison to Prior Work

The scholarly community is increasingly interested in the potential of AI or ML technologies for developing diagnostic tools. This research aims to develop and explore the feasibility, acceptability, and efficacy of using AI or ML to create cough audio classifiers in Tanzania, marking the first pilot project of its kind in the region. The results of this study will be benchmarked against findings from previous research on cough audio classifiers, some of which have been reviewed in the context of this protocol [13-22], to provide a comparative analysis and contribute to the evolving field of AI or ML applications in health care diagnostics.

Strengths and Limitations

This study represents a groundbreaking effort in the development and evaluation of a noninvasive, user-friendly AI-powered cough audio classifier for 3 respiratory diseases within low-income rural settings. However, conducting a study in rural Tanzania may encounter several limitations. First, access to technology poses a significant challenge. Rural areas may lack the necessary technology infrastructure, including stable internet connections, cough audio processors, reliable power supply for devices, or access to smartphones or suitable devices required for the AI-powered application. To mitigate these challenges, efforts will be made to leverage financial and nonfinancial resources within and beyond Aga Khan University. Second, data quality and quantity could be limited. The availability and quality of cough audio data for training the AI model might be insufficient or biased in rural settings, potentially affecting the model's accuracy. To address this, institutionalized quality assurance measures will be implemented to ensure high-quality data collection. Additionally, the study duration will be adjusted to ensure the collection of sufficient data. Third, language and cultural considerations might impact the classifier's accuracy. The AI model may not be optimized to recognize local dialects or variations in cough sounds due to cultural or linguistic differences. To partly address this, global AI and ML experts and processing protocols will be used to ensure accurate cough audio processing. Fourth, the study targets adults aged 18 years and older, primarily due to the complexities of the consent process, resource constraints, and the difficulties associated with collecting cough audio sounds from children. Given the pilot nature of this research, subsequent studies may consider including children as participants. Consequently, the study aims to exclude participants who have taken prescription medications. This exclusion criterion is based on the premise that prescription medications can markedly modify the characteristics and severity of cough sounds, thereby influencing the precision of our cough audio classifier. Given that certain prescription medications might be available over-the-counter within the study environments, there is a potential for this criterion to substantially diminish the sample size. In response to this challenge, we have expanded the number of health care facilities involved and extended the period of data collection to mitigate the impact on our sample size and ensure robust data acquisition. Finally, limited health care infrastructure in rural areas, including a scarcity of health care facilities and skilled personnel, may hinder the effective implementation of the AI-powered classifier. To counter this, health care workers involved in the study will receive adequate training before engaging in the research. Recognition is made that addressing these limitations are crucial to ensure the successful development, implementation, and evaluation of the AI-powered cough audio classifier for respiratory condition detection in rural Tanzania.

Future Directions

The findings of this study will have a range of social impacts. Although there is a lack of common definitions, conceptualizations and practical tools addressing the acceptability of technological health innovations in sub-Saharan Africa [55], an acknowledgment is made that social and cultural contexts have a significant impact on how humans behave both positively and negatively [56]. This is also the case when we are addressing the adaptation to new innovations among health care providers and community members. Common barriers to acceptance of health innovations may include intrapersonal and interpersonal, community, organizational, and policies or enabling factors [57,58]. Intrapersonal factors encompass attitude, fears, level of income, self-efficacy, and education level, which could play both roles as facilitators and barriers when it comes to the acceptability of these new techniques. For example, a recent review noted fear of a loss of professional autonomy and difficulties in integrating AI into clinical workflows as factors hindering their acceptability [57]. Public fears toward health innovations that they are not fully aware of may also promote negativity toward them [58]. Some of the interpersonal factors include social or family roles and responsibilities, norms, stigma, and community influence. Individuals and communities are seen to be more open to innovations when the intervention is supported by influential people within their communities [58]. Challenges are expected on the issue of acceptability among health care workers and the community since it is a new technology introduced and this can cause some reluctance. Additionally, the issue of smartphone use can be a challenge as some potential health care professionals may not be willing to use their personal devices for clinical diagnostic tasks and patients might not own the smartphone where the app will be installed. Similarly, the sharing of smartphones in the family and at the community level for self-diagnosis can be a potential for spreading communicable respiratory diseases if proper hygiene is not observed. Therefore, this study will navigate through these factors and ensure that they are well-addressed to maximize our outcomes. The focus will be on integrating the end users in the early stages of AI development, offering needs-adjusted training for the use of AI in health care and providing adequate infrastructure [57]. Furthermore, health care providers will be trained as trainer of trainers from the start of the study as they tend to easily pave the way, and consideration of gender roles, ensuring both males and females can participate equally.

Furthermore, the findings will have implications on health economics. Scaling up TB, asthma, and COPD services to achieve national and global targets requires an optimization of available funding. To identify and address the available inefficiencies and consider new interventions at the national level; information on the cost of services is of great necessity. There is a scarcity of data on the cost and technical efficiency of using mobile health (mHealth) for early TB, asthma, and COPD detection in rural communities that once done can aid in the achievement of national goals. Thus, we aim to gather health economics data to assess total and unit costs, cost structure, and cost drivers of this technology provision. The purpose of the health economics component of this study is to inform priority setting within the health sector. This will cover resource allocation across an overall budget or total resource envelope from the health provider's perspective that focuses on costs incurred by the implementing partner but also assesses the costs of services and consumables from other providers (eg, national program) in both financial and costs.

Patient and household expenditures including productivity losses have been barriers to accessing and retention in care. In consultations with health economists, a plan is to collect data on both direct and indirect patient-incurred costs using questionnaires. The study is expected to estimate direct costs incurred by patients such as those related to transport, as well as indirect costs, in terms of productivity losses, related to access to care as well as due to illness-related absenteeism. Together with data on service usage and socioeconomic background, we will be able to analyze patient costs and equity considerations in access and use of care. The study will generate a comprehensive picture of the costs of using mHealth-based cough audio triage testing for active pulmonary TB, asthma, and COPD in health facilities in high-burden settings in Tanzanian communities.

Dissemination Plan

The dissemination of findings will involve communication with key stakeholders, regular reporting through the pertinent channels of the funding agency and the Tanzanian Ministry of Health, engagement in local and international forums, and publication through peer-reviewed open-access journals. By using a methodical and systematic approach to disseminating the study's findings, this research aims to contribute to the expanding knowledge base regarding the use of AI and ML in developing noninvasive diagnostic tools. These tools are designed to assist health care professionals in effectively identifying and distinguishing various diseases, not only within Tanzania but also broadening their application beyond geographical boundaries.

Conclusions

Cough sound classifiers harness the power of advanced technology to offer a promising solution for the early detection and efficient management of various respiratory conditions. By accurately analyzing cough sounds, these innovative tools can identify potential illnesses at an earlier stage than traditional diagnostic methods, facilitating timely intervention and reducing the need for more invasive procedures. This approach not only has the potential to significantly alleviate the burden on public health systems by streamlining the diagnostic process but also aims to improve patient outcomes through faster and more accurate diagnosis. Moreover, the use of cough sound classifiers can democratize health care access, particularly in under-resourced areas, by providing a cost-effective and easily deployable tool for community health workers and primary care settings. Ultimately, the integration of this technology into clinical practice could transform the landscape of respiratory disease management, offering a scalable and efficient solution to global health challenges.

Acknowledgments

The author gratefully acknowledges the technical support received from Amy Strange and Luke Nightingale of the Crick Institute (United Kingdom), as well as Professor Stephen Cose of the Medical Research Council and London School of Hygiene and Tropical Medicine Uganda Research Unit. Additionally, the author expresses sincere gratitude to the leadership of the School of Nursing and Midwifery at the Aga Khan University for offering protected time for the development of this protocol. Finally, we acknowledge using generative artificial intelligence to refine and edit sentences for clarity, while specifying its nonuse in content generation (a sample transcript is provided in Multimedia Appendix 5).

Data Availability

Some data sets generated and analyzed during this study will not be publicly available due ethical reasons and a need to protect participant privacy but will be available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Procedures for capturing cough sounds.
[DOCX File , 588 KB - resprot_v13i1e54388_app1.docx]

Multimedia Appendix 2
Procedures for model development.
[DOCX File , 34 KB - resprot_v13i1e54388_app2.docx]

Multimedia Appendix 3
Guidelines for clinical evaluations.
[DOCX File , 31 KB - resprot_v13i1e54388_app3.docx]

Multimedia Appendix 4
Informed consent process, confidentiality, and data protection.

[DOCX File , 30 KB - resprot_v13i1e54388_app4.docx]

Multimedia Appendix 5
Sample transcript of conversation with generative artificial intelligence.
[PDF File (Adobe PDF File), 68 KB - resprot_v13i1e54388_app5.pdf]

References

1. Ngari MM, Rashid MA, Sanga D, Mathenge H, Agoro O, Mberia JK, et al. Burden of HIV and treatment outcomes among TB patients in rural Kenya: a 9-year longitudinal study. BMC Infect Dis 2023 May 30;23(1):362 [FREE Full text] [doi: 10.1186/s12879-023-08347-0] [Medline: 37254064]
2. Chhabra P, Sharma G, Kannan AT. Prevalence of respiratory disease and associated factors in an urban area of Delhi. Indian J Community Med 2008 Oct;33(4):229-232 [FREE Full text] [doi: 10.4103/0970-0218.43227] [Medline: 19876495]
3. Duan KI, Birger M, Au DH, Spece LJ, Feemster LC, Dieleman JL. Health care spending on respiratory diseases in the United States, 1996-2016. Am J Respir Crit Care Med 2023;207(2):183-192 [FREE Full text] [doi: 10.1164/rccm.202202-0294OC] [Medline: 35997678]
4. Early detection of tuberculosis: an overview of approaches, guidelines and tools: an overview of approaches, guidelines and tools. World Health Organization. 2011. URL: https://www.who.int/publications/i/item/WHO-HTM-STB-PSI-2011.21 [accessed 2023-10-05]
5. Ozoh OB, Ngahane BHM, Zar HJ, Masekela R, Chakaya J, Aluoch J, Pan African Thoracic Society. Lung health in Africa: challenges and opportunities in the context of COVID-19. Am J Physiol Lung Cell Mol Physiol 2021;321(3):L619-L623 [FREE Full text] [doi: 10.1152/ajplung.00322.2021] [Medline: 34378415]
6. Madhi SA, Klugman KP. Acute respiratory infections. In: Jamison DT, Feachem RG, Makgoba MW, editors. Disease and Mortality in Sub-Saharan Africa, 2nd Edition. Washington (DC): The International Bank for Reconstruction and Development / The World Bank; 2006.
7. Global tuberculosis report 2021. World Health Organization. 2021. URL: https://www.who.int/publications/i/item/9789240037021 [accessed 2023-10-10]
8. Using quality improvement approaches to increase TB case detection: program quality and efficiency case study. The Global Fund. 2018. URL: https://www.theglobalfund.org/media/8272/core_pqe-in-tanzania_casestudy_en.pdf [accessed 2023-10-08]
9. Halpin DMG, Criner GJ, Papi A, Singh D, Anzueto A, Martinez FJ, et al. Global initiative for the diagnosis, management, and prevention of chronic obstructive lung disease. The 2020 GOLD Science Committee report on COVID-19 and chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2021;203(1):24-36 [FREE Full text] [doi: 10.1164/rccm.202009-3533SO] [Medline: 33146552]
10. Singh M, Pujar GV, Kumar SA, Bhagyalalitha M, Akshatha HS, Abuhaija B, et al. Evolution of machine learning in tuberculosis diagnosis: a review of deep learning-based medical applications. Electronics 2022;11(17):2634 [FREE Full text] [doi: 10.3390/electronics11172634]
11. Ogola W. MacMachine learning for audio classification. Section.oi. 2021. URL: https://shorturl.at/jvzE1 [accessed 2023-10-10]
12. Pahar M, Klopper M, Reeve B, Warren R, Theron G, Niesler T. Automatic cough classification for tuberculosis screening in a real-world environment. Physiol Meas 2021;42(10):105014 [FREE Full text] [doi: 10.1088/1361-6579/ac2fb8] [Medline: 34649231]
13. Chowdhury NK, Kabir MA, Rahman MM, Islam SMS. Machine learning for detecting COVID-19 from cough sounds: an ensemble-based MCDM method. Comput Biol Med 2022;145:105405 [FREE Full text] [doi: 10.1016/j.compbiomed.2022.105405] [Medline: 35318171]
14. Ren Z, Chang Y, Bartl-Pokorny KD, Pokorny FB, Schuller BW. The acoustic dissection of cough: diving into machine listening-based COVID-19 analysis and detection. J Voice 2022 Jun 15 [FREE Full text] [doi: 10.1016/j.jvoice.2022.06.011] [Medline: 35835648]
15. Yu G, Li Z, Li S, Liu J, Sun M, Liu X, et al. The role of artificial intelligence in identifying asthma in pediatric inpatient setting. Ann Transl Med 2020;8(21):1367 [FREE Full text] [doi: 10.21037/atm-20-2501a] [Medline: 33313112]
16. Kaplan A, Cao H, FitzGerald JM, Iannotti N, Yang E, Kocks JWH, et al. Artificial intelligence/machine learning in respiratory medicine and potential role in asthma and COPD diagnosis. J Allergy Clin Immunol Pract 2021;9(6):2255-2261 [FREE Full text] [doi: 10.1016/j.jaip.2021.02.014] [Medline: 33618053]
17. Pramono RXA, Imtiaz SA, Rodriguez-Villegas E. A cough-based algorithm for automatic diagnosis of pertussis. PLoS One 2016;11(9):e0162128 [FREE Full text] [doi: 10.1371/journal.pone.0162128] [Medline: 27583523]
18. Orjuela-Cañón AD, Jutinico AL, Awad C, Vergara E, Palencia A. Machine learning in the loop for tuberculosis diagnosis support. Front Public Health 2022;10:876949 [FREE Full text] [doi: 10.3389/fpubh.2022.876949] [Medline: 35958865]

19. Becker J, Decker JA, Römmele C, Kahn M, Messmann H, Wehler M, et al. Artificial intelligence-based detection of pneumonia in chest radiographs. Diagnostics (Basel) 2022;12(6):1465 [FREE Full text] [doi: 10.3390/diagnostics12061465] [Medline: 35741276]
20. Subburaj S, Parvez L, Rajagopalan TG. Methods of recording and analysing cough sounds. Pulm Pharmacol 1996;9(5-6):269-279. [doi: 10.1006/pulp.1996.0035] [Medline: 9232663]
21. Korpas J, Vrabec M, Sadlonova J, Salat D, Debreczeni LA. Analysis of the cough sound frequency in adults and children with bronchial asthma. Acta Physiol Hung 2003;90(1):27-34. [doi: 10.1556/APhysiol.90.2003.1.4] [Medline: 12666872]
22. Serrurier A, Neuschaefer-Rube C, Röhrig R. Past and trends in cough sound acquisition, automatic detection and automatic classification: a comparative review. Sensors (Basel) 2022;22(8):2896 [FREE Full text] [doi: 10.3390/s22082896] [Medline: 35458885]
23. Higenbottam T. Chronic cough and the cough reflex in common lung diseases. Pulm Pharmacol Ther 2002;15(3):241-247. [doi: 10.1006/pupt.2002.0341] [Medline: 12099771]
24. Chung KF, Pavord ID. Prevalence, pathogenesis, and causes of chronic cough. Lancet 2008;371(9621):1364-1374. [doi: 10.1016/S0140-6736(08)60595-4] [Medline: 18424325]
25. Korpás J, Sadlonová J, Vrabec M. Analysis of the cough sound: an overview. Pulm Pharmacol 1996;9(5-6):261-268. [doi: 10.1006/pulp.1996.0034] [Medline: 9232662]
26. Zimmer AJ, Ugarte-Gil C, Pathri R, Dewan P, Jaganath D, Cattamanchi A, et al. Making cough count in tuberculosis care. Commun Med (Lond) 2022;2:83 [FREE Full text] [doi: 10.1038/s43856-022-00149-w] [Medline: 35814294]
27. Hall JI, Lozano M, Estrada-Petrocelli L, Birring S, Turner R. The present and future of cough counting tools. J Thorac Dis 2020;12(9):5207-5223 [FREE Full text] [doi: 10.21037/jtd-2020-icc-003] [Medline: 33145097]
28. Topalovic M, Das N, Burgel PR, Daenen M, Derom E, Haenebalcke C, et al. Artificial intelligence outperforms pulmonologists in the interpretation of pulmonary function tests. Eur Respir J 2019;53(4):1801660 [FREE Full text] [doi: 10.1183/13993003.01660-2018] [Medline: 30765505]
29. Isangula KG. Patient trust in doctors in rural Tanzania: meanings, factors and benefits in the context of NCDs and hypertension care: a thesis in fulfilment of the requirements for the degree of doctor of philosophy. Faculty of Medicine, School of Public Health and Community Medicine, The University of New South Wales. Australia; 2018. URL: https://unsworks.unsw.edu.au/entities/publication/a873cdd1-efb6-4aa9-a31c-30f1cf24ad7f/full [accessed 2023-11-10]
30. Isangula K, Pallangyo ES, Ndirangu-Mugo E. Interventions co-designed by healthcare providers and clients for improving therapeutic relationships in maternal and child healthcare: a pilot study using human centered design in rural Tanzania. BMC Nurs 2023;22(1):314 [FREE Full text] [doi: 10.1186/s12912-023-01472-w] [Medline: 37704982]
31. Eni M, Mordoh V, Zigel Y. Cough detection using a non-contact microphone: a nocturnal cough study. PLoS One 2022;17(1):e0262240 [FREE Full text] [doi: 10.1371/journal.pone.0262240] [Medline: 35045111]
32. Drugman T, Urbain J, Bauwens N, Chessini R, Aubriot AS, Lebecque P, et al. Audio and contact microphones for cough detection. arXiv 2020.
33. Audio cough detection. SensiML Toolkit. URL: https://sensiml.com/documentation/application-tutorials/audio-cough-detection.html [accessed 2023-10-20]
34. Pahar M, Klopper M, Warren R, Niesler T. COVID-19 cough classification using machine learning and global smartphone recordings. Comput Biol Med 2021 Aug;135:104572 [FREE Full text] [doi: 10.1016/j.compbiomed.2021.104572] [Medline: 34182331]
35. Pahar M, Miranda I, Diacon A, Niesler T. Automatic non-invasive cough detection based on accelerometer and audio signals. J Signal Process Syst 2022;94(8):821-835 [FREE Full text] [doi: 10.1007/s11265-022-01748-5] [Medline: 35341095]
36. Tacchetti M. User guide for ELAN linguistic annotator version 5.0.0. User Guide for ELAN Linguistic Annotator version 5.0.0. URL: https://www.mpi.nl/corpus/manuals/manual-elan_ug.pdf [accessed 2023-10-20]
37. Hegde S, Sreeram S, Alter IL, Shor C, Valdez TA, Meister KD, et al. Cough sounds in screening and diagnostics: a scoping review. Laryngoscope 2024;134(3):1023-1031. [doi: 10.1002/lary.31042] [Medline: 37672667]
38. Moschovis PP, Sampayo EM, Cook A, Doros G, Parry BA, Lombay J, et al. The diagnosis of respiratory disease in children using a phone-based cough and symptom analysis algorithm: the smartphone recordings of cough sounds 2 (SMARTCOUGH-C 2) trial design. Contemp Clin Trials 2021;101:106278 [FREE Full text] [doi: 10.1016/j.cct.2021.106278] [Medline: 33444779]
39. Sharan RV, Rahimi-Ardabili H. Detecting acute respiratory diseases in the pediatric population using cough sound features and machine learning: a systematic review. Int J Med Inform 2023;176:105093 [FREE Full text] [doi: 10.1016/j.ijmedinf.2023.105093] [Medline: 37224643]
40. Nikhil K. Introduction to PyTorch. In: Deep Learning with Python. Berkeley, CA: Apress; 2017:195-208.
41. Han W, Chan CF, Choy CS, Pun KP. An efficient MFCC extraction method in speech recognition. In: 2006 IEEE International Symposium on Circuits and Systems. 2006 Presented at: 2006 IEEE International Symposium on Circuits and Systems; 2006; Kos, Greece p. 4.
42. Pahar M, Smith LS. Coding and decoding speech using a biologically inspired coding system. 2020 Presented at: 2020 IEEE Symposium Series on Computational Intelligence (SSCI); 2020; Canberra, Australia p. 3025-3032.

43. Chatrzarrin H, Arcelus A, Goubran R, Knoefel F. Feature extraction for the differentiation of dry and wet cough sounds. 2011 Presented at: 2011 IEEE International Symposium on Medical Measurements and Applications; 2011; Bari, Italy.
44. Abadi M, Agarwal A, Barham P, Brevdo E, Chen Z, Citro C, et al. TensorFlow: Large-scale machine learning on heterogeneous distributed systems. arXiv 2016:1603.04467 [FREE Full text]
45. Gelaber JE. Exploring automatic speech recognition with TensorFlow. Universitat Polit`ecnica de Catalunya. 2018. URL: https://imatge.upc.edu/web/sites/default/files/pub/x.pdf [accessed 2023-10-22]
46. Medvedev MS, Okuntsev YV. Using Google TensorFlow machine learning library for speech recognition. J Phys Conf Ser 2019;1399:033033.
47. Build sound classification models for mobile apps with teachable machine and TFLite. TensorFlow. 2020. URL: https://blog.tensorflow.org/2020/12/build-sound-classification-models-for-mobile-apps-with-teachable-machine-and-tflite.html [accessed 2023-10-28]
48. Buderer NM. Statistical methodology: I. Incorporating the prevalence of disease into the sample size calculation for sensitivity and specificity. Acad Emerg Med 1996;3(9):895-900 [FREE Full text] [doi: 10.1111/j.1553-2712.1996.tb03538.x] [Medline: 8870764]
49. Xiong Y, Ba X, Hou A, Zhang K, Chen L, Li T. Automatic detection of mycobacterium tuberculosis using artificial intelligence. J Thorac Dis 2018;10(3):1936-1940 [FREE Full text] [doi: 10.21037/jtd.2018.01.91] [Medline: 29707349]
50. Arifin WN. Sample size calculator. github. 2023. URL: https://wnarifin.github.io/ssc.html [accessed 2023-10-28]
51. Meremo AJ, Kidenya BR, Mshana SE, Kabangila R, Kataraihya JB. High prevalence of tuberculosis among adults with fever admitted at a tertiary hospital in north-western Tanzania. Tanzan J Health Res 2012;14(3):183-188 [FREE Full text] [doi: 10.4314/thrb.v14i3.4] [Medline: 26591755]
52. Asthma: diagnosis. National Heart, Lung, and Blood Institute. URL: https://www.nhlbi.nih.gov/health/asthma/diagnosis [accessed 2023-10-29]
53. COPD: diagnosis. National Heart, Lung, and Blood Institute. URL: https://www.nhlbi.nih.gov/health/copd/diagnosis [accessed 2023-10-29]
54. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol 2006;3(2):77-101. [doi: 10.1191/1478088706qp063oa]
55. Louart S, Hedible GB, Ridde V. Assessing the acceptability of technological health innovations in sub-Saharan Africa: a scoping review and a best fit framework synthesis. BMC Health Serv Res 2023;23(1):930 [FREE Full text] [doi: 10.1186/s12913-023-09897-4] [Medline: 37649024]
56. Germain CB. Human Behavior in the Social Environment. New York: Columbia University Press; 1991.
57. Lambert SI, Madi M, Sopka S, Lenes A, Stange H, Buszello CP, et al. An integrative review on the acceptance of artificial intelligence among healthcare professionals in hospitals. NPJ Digit Med 2023;6(1):111 [FREE Full text] [doi: 10.1038/s41746-023-00852-5] [Medline: 37301946]
58. Yeracaris CA. Social factors associated with the acceptance of medical innovations: a pilot study. J Health Hum Behav 1962;3:193-198. [Medline: 14002572]

Abbreviations

AI: artificial intelligence
COPD: chronic obstructive pulmonary disease
CRF: case report form
CXR: chest x-ray
HC: health centre
mHealth: mobile health
ML: machine learning
NTLP: national TB and leprosy programme
OPD: outpatient department
PEF: peak expiratory flow
PI: principal investigator
PORALG: President's Office Regional and Local Administrative Government
TB: tuberculosis
WHO: World Health Organization

Edited by A Mavragani; submitted 08.11.23; peer-reviewed by Y Li, R Boumans; comments to author 08.02.24; revised version received 14.02.24; accepted 21.02.24; published 23.04.24.

Please cite as:
Isangula KG, Haule RJ
Leveraging AI and Machine Learning to Develop and Evaluate a Contextualized User-Friendly Cough Audio Classifier for Detecting Respiratory Diseases: Protocol for a Diagnostic Study in Rural Tanzania
JMIR Res Protoc 2024;13:e54388
URL: https://www.researchprotocols.org/2024/1/e54388
doi:10.2196/54388
PMID:38652526

Protocol

Exploring the Pathways of Diabetes Foot Complications Treatment and Investigating Experiences From Frontline Health Care Professionals: Protocol for a Mixed Methods Study

Elisavet Andrikopoulou[1], PhD; Panagiotis Chatzistergos[2], PhD; Nachiappan Chockalingam[2], PhD

[1]School of Computing, University of Portsmouth, Portsmouth, United Kingdom

[2]Centre for Biomechanics and Rehabilitation Technologies, Staffordshire University, Stoke on Trent, United Kingdom

Corresponding Author:
Panagiotis Chatzistergos, PhD
Centre for Biomechanics and Rehabilitation Technologies
Staffordshire University
Leek Road, Science Centre
Stoke on Trent, ST4 2DF
United Kingdom
Phone: 44 178229 ext 5920
Email: pchatzistergos@gmail.com

Abstract

Background: Diabetes affects more than 4.3 million individuals in the United Kingdom, with 19% to 34% developing diabetes-related foot ulceration (DFU) during their lifespan, which can lead to an amputation. In the United Kingdom, every week, approximately 169 people have an amputation due to diabetes. Preventing first-ever ulcers is the most effective strategy to reduce the occurrence of diabetes-related amputations, but research in this space is lacking.

Objective: This protocol seeks to document the experiences and perspectives of frontline health care professionals who work with people who have diabetes and diabetes-related foot problems. Special attention is given to their perceptions of barriers to effective care, their views about barriers to effective and inclusive engagement with people with diabetes, and their experience with the first-ever DFU. Another aspect of the study is the focus on whether clinical management is affected by data sharing, data availability, and interoperability issues.

Methods: This is a mixed methods explanatory protocol, which is sequential, and its purpose is to use the qualitative data to explain the initial quantitative data collected through a survey of frontline health care professionals. Data analysis of quantitative data will be completed first and then synthesized with the qualitative data analysis. Qualitative data will be analyzed using the framework method. This study will use joint displays to integrate the data. Ethical approval has been granted by the ethics committee of Staffordshire University.

Results: The quantitative data collection started in March 2023 and will close in May 2024. The qualitative interviews commenced in November 2023 with volunteer participants who initially completed the survey.

Conclusions: This study's survey focuses on data interoperability and the interviews focus more on the perspectives and experiences of clinicians and their perceived barriers for the effective management of diabetes foot ulcers. Including a geographically relevant and diverse cohort of health care professionals that spans a wide range of roles and care settings involved in diabetes-related foot care is very important for the successful application of this protocol. Special care is given to advertise and promote participation as widely as possible. The qualitative part of this protocol is also limited to 30-40 interview participants, as it is not realistic to interview higher numbers, due to time and resource constraints.

International Registered Report Identifier (IRRID): DERR1-10.2196/54852

(JMIR Res Protoc 2024;13:e54852) doi:10.2196/54852

KEYWORDS

diabetic foot; first-ever diabetic foot ulcer; qualitative research; quantitative evaluation; surveys and questionnaires; telephone interviews; primary care; community care; acute care; education of patients; foot ulcer; exploration; diabetes; foot ulceration;

United Kingdom; diabetic foot ulceration; DFU; amputation; complication; complication; perspectives; experiences; health care professionals; barrier; barriers; effective care; foot care; primary ulcers; quality of life

Introduction

Currently, there are more than 4.3 million people diagnosed with diabetes in the United Kingdom [1], and 19% to 34% of them will develop diabetes-related foot ulceration (DFU) in their lifetime [2]. Out of all DFUs, the literature reports that 10% to 56% will result in amputation [3]. In the United Kingdom, every week, approximately 169 people have an amputation due to diabetes [4,5]. The total direct cost of DFU and diabetes-related foot amputations in England alone is between £837 million (US $1.25 billion) and £962 million (US $1.20 billion) and is steadily rising every year [6]. DFU costs the National Health Service (NHS) more than the 3 most common types of cancer combined [6]; hence, DFU is a major challenge for the financial sustainability of the NHS, and effective prevention could significantly reduce its burden.

Understanding the barriers to effective care and their regional variability is critical for service improvement, leading to fewer diabetes-related foot complications and fewer lower limb amputations [7,8]. A survey of health care professionals working with diabetes-related foot complications, conducted in 2018, highlighted delayed access to specialist care as the most important barrier for effective diabetes-related foot care [9,10]. The key contributors to this problem, which were noted by the responders, included inadequate funding and issues in the areas of referral pathways, patient care, and education [9]. More specifically, about half of the responders indicated a lack of necessary resources. Regarding referrals, the responders of that survey identified inefficiencies in the referral pathways leading to preventable delays. In the area of patient care, the survey indicated a lack of coordination and standardization leading to suboptimal care. The responders also noted that the lack of or ineffective patient education compromises their ability for self-care and leaves them unaware of when to seek help [9].

Structured diabetes education programs are extremely important for promoting effective engagement with health care services and for effective self-management of diabetes-related foot complications [11,12]. To be effective, education needs to be offered to people with diabetes as well as to their families or caregivers [11,12]. It also needs to be designed and delivered in a culturally competent manner [13].

People from ethnic minority groups or socioeconomically disadvantaged communities are disproportionately affected by diabetes and diabetes-related foot complications, experiencing higher morbidity and mortality than majority populations or more affluent communities [13]. Understanding the barriers to effective engagement with these groups is extremely important for effective diabetes-related foot care as well as for robust clinical research.

There is overwhelming evidence that populations from geographical regions that are more actively involved in clinical research tend to benefit from it the most. These benefits include the early adoption and tailoring of new highly effective approaches to care that translate to lower disease prevalence and better patient experience [14,15]. At the same time, regional variations in research participation indicate that the areas and communities with the highest diabetes prevalence are also the least likely to participate in research [16,17]. Ineffective communication and engagement with underserved communities are among the key contributors to this disconcerting discrepancy [14,15], highlighting even further the need to address barriers to effective communication and engagement. Understanding the perceptions of health care professionals about these barriers and how these can be overcome can be helpful to this end.

An exciting new approach for effective DFU care proposed in current literature is to shift medical attention from the management of active DFU to supporting people with diabetes to remain ulcer-free for longer. This can be achieved by focusing efforts to prevent the first-ever DFU from happening [18-20].

Preventing first-ever ulcers (also known as primary ulcers) is the most effective way to reduce the number of diabetes-related amputations and protect the quality of life of people with diabetes. This is because 40% of people with healed first DFU reulcerate within a year (60% reulcerate within 3 years), which significantly increases the risk for amputation [2]. The first-ever DFU incidence is also associated with a 250% increase in the 5-year risk of death [21,22].

Integrated care that combines frequent specialist screening with education and offloading interventions (eg, the use of therapeutic footwear or orthoses) is currently used to prevent recurrent DFU [11,23,24] and is likely to be effective also for the prevention of first-ever ulcers. However, their blanket use across all people with diabetes is practically impossible due to the sheer number of people at risk of their first-ever DFU [18,20,25].

According to current international guidelines, a person with diabetes is considered to be at high risk of DFU when they have had their first-ever DFU or diabetes-related amputation [11,26]. However, as it stands, there is no established method to determine when someone is at high risk of developing their first-ever DFU [11].

Clinical research is needed to develop effective strategies to target preventative care for those at imminent risk for first-ever ulceration [11]. However, studying first-ever ulcers remains significantly more challenging than studying recurrent ulcers. This is due to the scarcity of current and geographically relevant data in the literature to support the design and implementation of research in this area. Moreover, due to their relatively low incidence rate [25], any research on first ulcers is likely to require relatively larger numbers of participants, highlighting the need for effective and inclusive recruitment strategies. To maximize the chances of success, research protocols should be informed by the experience of the health care professionals who will have to lead and deliver this research. This includes identifying strengths to be used and limitations and perceived barriers to participation and recruitment to be addressed [9,27].

In this context, this protocol aims to capture the experience and views of frontline health care professionals working with people

with diabetes-related foot complications regarding previously identified barriers to effective care from the literature [9]. These barriers may include the effectiveness of referral pathways, the efficiency of communication between disciplines and NHS services, and the adequacy of patient education The experience of frontline health care professionals regarding the first-ever DFU will be also captured to inform clinical research toward more effective DFU prevention.

The primary objective is to identify the potential areas of improvement regarding DFU care delivery and patient-clinician engagement.

The secondary objectives are to (1) model qualitatively the lived experiences of frontline health care professionals about diabetes foot care and (2) develop a theoretical model that describes the interaction between their lived experience and identified barriers to effective care and engagement with people with diabetes.

Methods

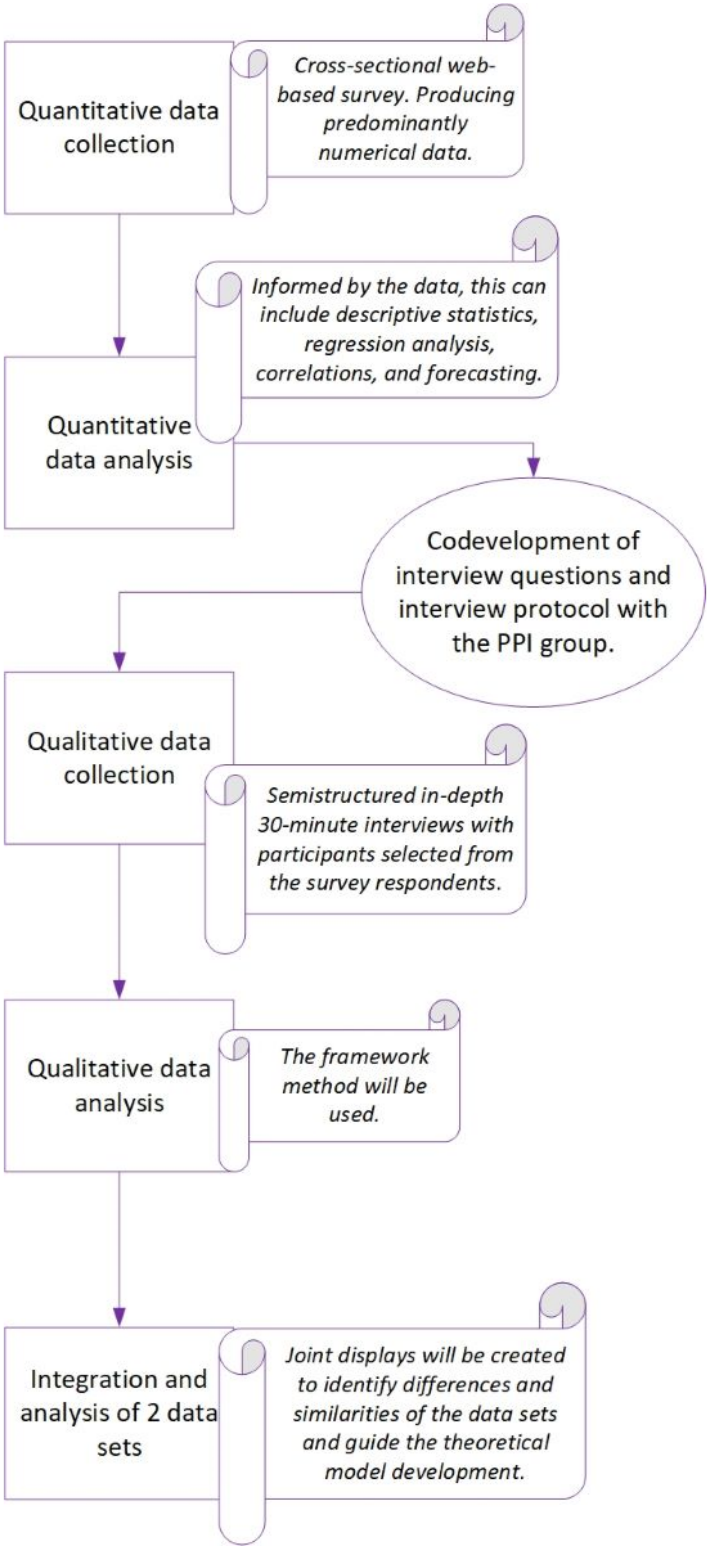
Study Design

In agreement with the Equator's Network mission to improve the reporting of health care research, and in the absence of a comprehensive checklist for mixed methods study design, we have adopted the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement, given that our study is observational [28]. The STROBE statement covers cohort, case-control, and cross-sectional studies and we will follow the relevant statement's sections about the cohort (for our qualitative data) and cross-sectional (for our quantitative data) studies.

This study uses pragmatism and a mixed methods approach, which has been previously used and supported in the field of health informatics [29,30]. The rationale behind choosing mixed methods is that, based on our pragmatic approach, the best way to achieve the aims and objectives was to mix both quantitative and qualitative data, which complement each other enhancing the results of the study [31,32]. This study uses an explanatory design that is sequential, and its purpose is to use the qualitative data to explain the initial quantitative data.

The study has two main components: (1) a survey and (2) semistructured interviews. This study prioritizes the qualitative data as they are used to explain and enhance the findings of the quantitative data [32]. Interview participants were purposefully recruited from the survey responders, mixing the data-gathering methods. Figure 1 illustrates the mixed methods sequential explanatory design stages of this study.

Figure 1. A schematic of the proposed mixed methods sequential explanatory study to capture the experiences and perspectives of frontline health care professionals working in the National Health Service (NHS) in the area of diabetes foot complications. Data collection started in March 2023 and is expected to end in May 2024. PPI: patient and public involvement.



Patients, Sampling, and Recruitment

Recruitment will occur in 2 stages. The first stage includes the recruitment of survey respondents. We aim to attain between 188 and 270 responses that are required for a maximum assumed error of 6% to 5% (90% Cis), respectively [33].

A recruitment strategy, which encompasses a number of different avenues, has been established to enable us to reach out to a diverse audience and maximize the chances of meeting the required target. This includes the distribution of leaflets in relevant scientific conferences, press releases, social media announcements, and dissemination through a network of collaborating NHS trusts and UK universities (and their alumni

associations) that train health care professionals involved in diabetes foot care. Invitation to participate in this survey was also disseminated through the Staffordshire and Shropshire Health Economy Research Partnership [34] through the National Institute for Health and Care Research Clinical Research Network West Midlands [35], special interest groups on diabetes funded by the National Institute for Health and Care Research (Diabesity group), and NHS integrated care boards.

The survey, which is used during this first stage of recruitment, is also used to obtain permission to contact respondents for interviews for the second stage of recruitment. The interviewees will be divided into 3 main cohorts based on their professional work setting (primary, community, or acute care) to discover and model differences in DFU care delivery across contexts. As this study aims for the greatest variation in demographic distribution, the sampling is purposeful [32,36,37]. We intend to interview around 30-40 health care practitioners since the "gold standard" for a purposive sample is to achieve theoretical saturation. It is impossible to predict an absolute number for theoretical saturation; however, based on prior experience and published recommendations, we believe these figures are reasonable given our objectives, scope, and methodology [32,36,38,39].

The interview participants' selection was based on the following criteria in importance ranking to ensure variation in (1) roles within the care pathway for diabetes foot complications, (2) gender, (3) years of experience, and (4) age group.

Inclusion criteria are (1) participant is willing and able to give informed consent for participation in the study, (2) people aged 18 years or older, and (3) any grade or discipline of health care professional working in diabetes foot care.

Exclusion criteria are (1) inadequate spoken English or unable to participate in a web-based interview, (2) health care professionals who are not working in the diabetes foot care field, and (3) health care professionals not working in NHS.

An assumption has been made that everyone who fills the survey and understands English well. Nonetheless, if we suspect that the interviewee's English comprehension and articulation are inadequate, we will exclude them and replace this interview.

Measures

This project will collect quantitative and qualitative data via a web-based survey and further qualitative data from the same group via web-based or telephone interviews.

The survey design was cocreated in conjunction with a patient and public involvement (PPI) group of people with diabetes and diabetes foot complications. The first draft of this survey was cocreated with the 10 health care professionals who also face validated and pilot-tested it. Those health care professionals included a diabetologist, 3 general practitioners, and 6 podiatrists who worked in community, acute, and primary care settings. The survey design can be found in Multimedia Appendix 1. We plan to publish the results of the survey after the analysis is concluded.

Microsoft Excel (Microsoft Corp) will be used for descriptive statistics, while SPSS (IBM Corp) will be used to conduct inferential statistical tests, such as regression analyses and other data-driven tests to assess the association between factors.

For the qualitative component of this protocol, we shall conduct single semistructured interviews (maximum 40 minutes) to explore user experience about the DFU clinical pathway barriers, clinician-patient communication issues, and research participation. We will obtain informed consent and the interviews will be audio recorded and fully transcribed. The interview guide (Multimedia Appendix 2) followed the structure of the NHS Integrated Research Application System guidelines, and it was cocreated with our PPI group.

The framework method [40] will be used for the qualitative data analysis, allowing themes to be produced both inductively (from the interviews) and by adding themes that originate from the survey. The framework method is systematic, comprehensive, and data driven, but it is also adaptable and allows facts to be shown visually [40,41]. The framework method has step-by-step instructions for application, and this study aims to adhere to Gale et al [41] recommendations.

For coding, NVivo (QSR International) will be used. An independent researcher will code a portion of the files (around 25%), and after comparing the themes, the interrater reliability score will be calculated. Following the coding of half of the transcripts, a framework with well-defined and grouped together codes will be created and applied to the remaining transcripts [41]. During data merging, the qualitative data will be interpreted alongside the quantitative.

Having arranged the quantitative and the qualitative data in a format based on thematic relevance to allow merging, further integration will be needed. This study will use joint displays to integrate the data in a similar fashion and to gain a better understanding of the complexity of the observed phenomena [42]. The combined display, should the data collection permit such integration, will have rows representing the participants and columns representing each theme (obstacles in DFU care delivery and research engagement issues, etc), along with the quantitative variables (years of experience, type of employment, etc). This approach may help us better understand the roles of individual themes as enablers or barriers to effective patient care.

Ethics Approval

Ethical approval for this study has been granted by Staffordshire University's ethics committee (approval: SU_22_113). All participants provide informed consent before any quantitative or qualitative data are collected.

All potential responders to the survey are first required to read through the participant information sheet and to fill a specific consent form before accessing the main body of the survey. To ensure that no quantitative data are collected without consent, the participants can only access the survey if they agree to all consenting questions (see consent form in Multimedia Appendix 1).

Consenting to take part in the quantitative part of this mixed methods study does not directly qualify a person to participate also in the follow-up interviews. A separate consenting process

was followed to this end. More specifically, at the end of the survey, it is explained that based on their responses the research team might want to invite them to take part in a semistructured interview. It is explained that the purpose of this interview will be to ask some more specific questions regarding their response to the survey and that the interview will be on the web or over the phone (see follow-up in Multimedia Appendix 1). The questionnaire responder is then asked to indicate whether they consent to be contacted again to arrange the interview. Answering "no" to this question brings the survey to an end, enabling the responder to submit their answers for analysis. Answering "yes" reveals an additional question where the responders are asked to provide their contact details before submitting their survey responses for analysis and exiting the survey. If they are selected to take part in the qualitative data collection, participants who consent to be contacted again are invited to take part in the semistructured interviews. Consent to be interviewed and to have the interview recorded and transcribed is verbally confirmed at the start of each interview. No qualitative data are recorded for survey responders who do not consent to be contacted again. In addition, no qualitative data are recorded for survey responders who consent to be contacted again but fail to provide explicit consent to be interviewed.

All collected personal information will be kept confidential on a password-protected computer. Only members of the research will have access to this information. The contact details of the people who consent to be contacted again will be used to arrange and conduct the interviews and they will be deleted at the end of data collection. Special care will be given during dissemination to ensure that all data are presented in an anonymized form so that no identification of individual participants is possible.

No compensation or financial incentive will be provided to survey responders. Participants taking part in an interview will receive a £10 (US $12.5) shopping voucher.

PPI Involvement

People with diabetes and diabetes foot complications have been involved throughout this research to increase transparency, minimize bias, and maximize clinical relevance. All members of the PPI group were recruited based on posters displayed in Stoke-On-Trend community areas and general practitioner practices as well as social media posts. The selection criteria involved people with diabetes and diabetes foot complications, who are consenting adults, and able to express their opinions.

Early in the design of this study, our aim, objectives, and areas of focus of the survey were discussed within a group of 4 people with diabetes and diabetes foot complications. The final questionnaire was designed based on their feedback. The initial core PPI group has since been extended to include 9 people with diabetes and diabetes foot complications. This extended PPI focus group met at Staffordshire University in June 2023 to discuss plans for the semistructured interviews. Discussions in this meeting enabled identifying topics and specific questions that were important to them. These were then included in the interview script. The final interview script was shared with the members of the PPI group during a separate web-based meeting to ensure that their feedback was correctly used.

Results

So far, this study has had 223 respondents in the web-based survey, and the interview invitations have started. We have invited 30 participants for the interviews, and based on their willingness to be interviewed and their responses, we will keep inviting interviewees, within reason, until theoretical saturation is reached. The study's data collection will close in May 2024. Initial data analysis has commenced, with results expected to be published by the end of 2024.

Discussion

The protocol presented here aims to capture the experience and views of frontline health care professionals working with people with diabetes-related foot complications. Emphasis is given to previously identified barriers to effective care regarding the effectiveness of referral pathways, the efficiency of communication between disciplines and NHS services, and the adequacy of available resources and patient education [9]. This protocol also recognizes the need to help people with diabetes remain ulcer-free for longer [18-20]. With this in mind, the experience of frontline health care professionals regarding the first-ever DFU will be also captured to inform clinical research toward more effective DFU prevention.

To this end, a mixed methods explanatory protocol will be implemented. This protocol is sequential, and its purpose is to use qualitative data to explain the initial quantitative data collected through a survey of frontline health care professionals. Data analysis of quantitative data will be completed first and then synthesized with the qualitative data analysis. Compared to relevant literature, this protocol can offer a more comprehensive overview of the perceptions of frontline clinicians regarding diabetic foot care. It is also the first to include the perspective of health care professionals working in primary care [9].

Regarding the limitations of this protocol, even though special care is given to advertise and promote participation as widely as possible, it is likely that dissemination through institutions that are participating in this research will be more effective, leading to greater numbers of responders. These institutions are based in England, and most of them are based in West Midlands. The inability to attain responses with a representative spread across the country could limit the representativeness of results. This study is also limited to the 30-40 interview participants, as it is not realistic to interview higher numbers, due to time and resource constraints.

Once completed, this study can offer new insight into potential improvements regarding DFU care delivery and patient-clinician engagement toward reduced DFU and amputation rates. It will also provide a contextual evidence base for further studies related to DFU care delivery and DFU care workflow.

Acknowledgments

We would like to acknowledge that this work was supported by the National Institute for Health Research Clinical Research Network West Midlands Improvement and Innovation Strategic Funding. It forms a part of a greater project aiming to establish an ecosystem of research on the first-ever diabetes-related foot ulceration.

Data Availability

The data that will be collected as part of this study will be made available upon reasonable request sent to the corresponding author.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Survey.
[PDF File (Adobe PDF File), 1675 KB - resprot_v13i1e54852_app1.pdf]

Multimedia Appendix 2
Interview guide.
[PDF File (Adobe PDF File), 660 KB - resprot_v13i1e54852_app2.pdf]

References

1. How many people in the UK have diabetes? Diabetes UK. URL: https://www.diabetes.org.uk/about-us/about-the-charity/our-strategy/statistics [accessed 2024-04-02]
2. Armstrong DG, Boulton AJM, Bus SA. Diabetic foot ulcers and their recurrence. N Engl J Med 2017;376(24):2367-2375. [doi: 10.1056/NEJMra1615439] [Medline: 28614678]
3. Lin C, Liu J, Sun H. Risk factors for lower extremity amputation in patients with diabetic foot ulcers: a meta-analysis. PLoS One 2020;15(9):e0239236 [FREE Full text] [doi: 10.1371/journal.pone.0239236] [Medline: 32936828]
4. Us, diabetes and a lot of facts and stats. Diabetes UK. London; 2019. URL: https://www.keep-healthy.com/wp-content/uploads/2020/06/diabetes-facts-stats.pdf [accessed 2024-03-02]
5. Diabetes in the UK 2012: key statistics on diabetes. Diabetes UK. 2011. URL: http://www.diabetes.org.uk/documents/reports/diabetes-in-the-uk-2011-12.pdf [accessed 2024-04-02]
6. Kerr M, Barron E, Chadwick P, Evans T, Kong WM, Rayman G, et al. The cost of diabetic foot ulcers and amputations to the National Health Service in England. Diabet Med 2019;36(8):995-1002. [doi: 10.1111/dme.13973] [Medline: 31004370]
7. Paisey RB, Abbott A, Levenson R, Harrington A, Browne D, Moore J, et al. Diabetes-related major lower limb amputation incidence is strongly related to diabetic foot service provision and improves with enhancement of services: peer review of the South-West of England. Diabet Med 2018;35(1):53-62 [FREE Full text] [doi: 10.1111/dme.13512] [Medline: 29023974]
8. Meffen A, Houghton JSM, Nickinson ATO, Pepper CJ, Sayers RD, Gray LJ. Understanding variations in reported epidemiology of major lower extremity amputation in the UK: a systematic review. BMJ Open 2021;11(10):e053599 [FREE Full text] [doi: 10.1136/bmjopen-2021-053599] [Medline: 34615685]
9. Pankhurst CJW, Edmonds ME. Barriers to foot care in patients with diabetes as identified by healthcare professionals. Diabet Med 2018;35(8):1072-1077. [doi: 10.1111/dme.13653] [Medline: 29696678]
10. McPherson M, Carroll M, Stewart S. Patient-perceived and practitioner-perceived barriers to accessing foot care services for people with diabetes mellitus: a systematic literature review. J Foot Ankle Res 2022;15(1):92 [FREE Full text] [doi: 10.1186/s13047-022-00597-6] [Medline: 36527060]
11. Bus SA, Sacco ICN, Monteiro-Soares M, Raspovic A, Paton J, Rasmussen A, et al. Guidelines on the prevention of foot ulcers in persons with diabetes (IWGDF 2023 update). Diabetes Metab Res Rev 2024;40(3):e3651 [FREE Full text] [doi: 10.1002/dmrr.3651] [Medline: 37302121]
12. Andrikopoulou E, Scott P, Herrera H, Good A. What are the important design features of personal health records to improve medication adherence for patients with long-term conditions? a systematic literature review. BMJ Open 2019;9(9):e028628 [FREE Full text] [doi: 10.1136/bmjopen-2018-028628] [Medline: 31558449]
13. Zeh P, Sandhu HK, Cannaby AM, Sturt JA. The impact of culturally competent diabetes care interventions for improving diabetes-related outcomes in ethnic minority groups: a systematic review. Diabet Med 2012;29(10):1237-1252. [doi: 10.1111/j.1464-5491.2012.03701.x] [Medline: 22553954]
14. Barnard-Kelly KD, Cherñavvsky D. Social inequality and diabetes: a commentary. Diabetes Ther 2020;11(4):803-811 [FREE Full text] [doi: 10.1007/s13300-020-00791-4] [Medline: 32124269]

15. Mitchell C, Fryer K, Guess N, Aminu H, Jackson B, Gordon A, et al. Underserved 'Deep End' populations: a critical analysis addressing the power imbalance in research. Br J Gen Pract 2023;73(732):326-329 [FREE Full text] [doi: 10.3399/bjgp23X733461] [Medline: 37385767]
16. Bower P, Grigoroglou C, Anselmi L, Kontopantelis E, Sutton M, Ashworth M, et al. Is health research undertaken where the burden of disease is greatest? observational study of geographical inequalities in recruitment to research in England 2013-2018. BMC Med 2020;18(1):133 [FREE Full text] [doi: 10.1186/s12916-020-01555-4] [Medline: 32418543]
17. Andrikopoulou E, Scott PJ, Herrera H. Important design features of personal health records to improve medication adherence for patients with long-term conditions: protocol for a systematic literature review. JMIR Res Protoc 2018;7(6):e159 [FREE Full text] [doi: 10.2196/resprot.9778] [Medline: 29954729]
18. Chatzistergos PE, Kumar S, Sumathi CS, Mahadevan S, Vas P, Chockalingam N. Screening for the loss of protective sensation in people without a history of diabetic foot ulceration: validation of two simple tests in India. Diabetes Res Clin Pract 2023;202:110810 [FREE Full text] [doi: 10.1016/j.diabres.2023.110810] [Medline: 37391033]
19. Trocha AK, Gontscharuk V, Icks A, Jeffcoate W. The value of loss of protective pain sensation in predicting a first ulceration of the foot in people with diabetes. Diabet Med 2024 Apr;41(4):e15241. [doi: 10.1111/dme.15241] [Medline: 37845176]
20. Røikjer J, Werkman NCC, Ejskjaer N, van den Bergh JPW, Vestergaard P, Schaper NC, et al. Incidence, hospitalization and mortality and their changes over time in people with a first ever diabetic foot ulcer. Diabet Med 2022;39(4):e14725. [doi: 10.1111/dme.14725] [Medline: 34657300]
21. Sibbald RG, Ayello EA. The reduction of diabetic foot amputations starts with preventing foot ulcers. Adv Skin Wound Care 2018;31(9):389. [doi: 10.1097/01.ASW.0000544473.65179.bf] [Medline: 30134273]
22. Walsh JW, Hoffstad OJ, Sullivan MO, Margolis DJ. Association of diabetic foot ulcer and death in a population-based cohort from the United Kingdom. Diabet Med 2016;33(11):1493-1498. [doi: 10.1111/dme.13054] [Medline: 26666583]
23. Chatzistergos PE, Gatt A, Formosa C, Sinclair JK, Chockalingam N. Effective and clinically relevant optimisation of cushioning stiffness to maximise the offloading capacity of diabetic footwear. Diabetes Res Clin Pract 2023;204:110914 [FREE Full text] [doi: 10.1016/j.diabres.2023.110914] [Medline: 37742803]
24. van Netten JJ, Sacco ICN, Lavery L, Monteiro-Soares M, Paton J, Rasmussen A, et al. Clinical and biomechanical effectiveness of foot-ankle exercise programs and weight-bearing activity in people with diabetes and neuropathy: a systematic review and meta-analysis. Diabetes Metab Res Rev 2024;40(3):e3649 [FREE Full text] [doi: 10.1002/dmrr.3649] [Medline: 37132203]
25. Chamberlain RC, Fleetwood K, Wild SH, Colhoun HM, Lindsay RS, Petrie JR, et al. Foot ulcer and risk of lower limb amputation or death in people with diabetes: a national population-based retrospective cohort study. Diabetes Care 2022;45(1):83-91 [FREE Full text] [doi: 10.2337/dc21-1596] [Medline: 34782354]
26. Crawford F, Cezard G, Chappell FM, Murray GD, Price JF, Sheikh A, et al. A systematic review and individual patient data meta-analysis of prognostic factors for foot ulceration in people with diabetes: the international research collaboration for the Prediction of Diabetic Foot Ulcerations (PODUS). Health Technol Assess 2015;19(57):1-210 [FREE Full text] [doi: 10.3310/hta19570] [Medline: 26211920]
27. Mullan L, Driscoll A, Wynter K, Rasmussen B. Barriers and enablers to delivering preventative and early intervention footcare to people with diabetes: a scoping review of healthcare professionals' perceptions. Aust J Prim Health 2019;25(6):517-525. [doi: 10.1071/PY19115] [Medline: 31718766]
28. STROBE checklist for cohort, case-control, and cross-sectional studies. STROBE. URL: https://www.researchgate.net/publication/294083227_Checklist_S1 [accessed 2024-04-02]
29. Scott PJ, Briggs JS. A pragmatist argument for mixed methodology in medical informatics. J Mix Methods Res 2009;3(3):223-241. [doi: 10.1177/1558689809334209]
30. Andrikopoulou E, Scott P. Personal health records an approach to answer: what works for whom in what circumstances? Stud Health Technol Inform 2022;294:725-729. [doi: 10.3233/SHTI220572] [Medline: 35612192]
31. Teddlie C, Tashakkori A. Foundations of Mixed Methods Research: Integrating Quantitative and Qualitative Approaches in the Social and Behavioral Sciences. Los Angeles, CA: SAGE; 2009.
32. Creswell JW, Plano Clark VL. Designing and Conducting Mixed Methods Research. Los Angeles: Sage Publications; 2017.
33. Bartlett JE, Kotrlik JW, Higgins CC. Determing appropriate sample size in survey research. Inf Technol Learn Perform J 2001;19(1):43-50 [FREE Full text]
34. SSHERPa Research Network Development Survey. Support Staffordshire. URL: https://supportstaffordshire.org.uk/ [accessed 2024-04-02]
35. NIHR Clinical Research Network West Midlands. Birmingham and Solihull ICS. 2021. URL: https://www.birminghamsolihullics.org.uk/about-us/our-partners/nihr-clinical-research-network-west-midlands [accessed 2024-04-02]
36. Collins KMT. Advanced sampling designs in mixed research: current practices and emerging trends in the social and behavioral sciences. In: Tashakkori A, Charles T, editors. SAGE Handbook of Mixed Methods in Social & Behavioral Research. Los Angeles, CA: SAGE Publications; 2010:353-378.
37. Hardon A, Hodgkin C, Fresle D. How to investigate the use of medicines by consumers. World Health Organization and University of Amsterdam. 2004. URL: https://www.kit.nl/wp-content/uploads/2018/08/714_WHO-Consumers.pdf [accessed 2024-04-02]

38. Morse JM. Determining sample size. Qual Health Res 2000;10(1):3-5 [FREE Full text] [doi: 10.1177/104973200129118183]
39. Andrikopoulou E, Scott PJ, Herrera H. Mixed methods protocol for a realist evaluation of electronic personal health records design features and use to support medication adherence (ePHRma). BMJ Health Care Inform 2020;27(1):e100046 [FREE Full text] [doi: 10.1136/bmjhci-2019-100046] [Medline: 31907165]
40. Ritchie J, Spencer L. Qualitative data analysis for applied policy research. In: Huberman AM, Miles MB, editors. The Qualitative Researcher's Companion. Thousand Oaks, California: SAGE Publications, Inc; 2002:305-329.
41. Gale NK, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. BMC Med Res Methodol 2013;13:117 [FREE Full text] [doi: 10.1186/1471-2288-13-117] [Medline: 24047204]
42. Dickson VV, Lee CS, Riegel B. How do cognitive function and knowledge affect heart failure self-care? J Mix Methods Res 2011;5(2):167-189. [doi: 10.1177/1558689811402355]

Abbreviations

DFU: diabetes-related foot ulceration
NHS: National Health Service
PPI: patient and public involvement
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

Edited by A Mavragani; submitted 24.11.23; peer-reviewed by C Pankhurst, L Aljerf; comments to author 24.12.23; revised version received 31.01.24; accepted 11.03.24; published 24.04.24.

Please cite as:
Andrikopoulou E, Chatzistergos P, Chockalingam N
Exploring the Pathways of Diabetes Foot Complications Treatment and Investigating Experiences From Frontline Health Care Professionals: Protocol for a Mixed Methods Study
JMIR Res Protoc 2024;13:e54852
URL: https://www.researchprotocols.org/2024/1/e54852
doi:10.2196/54852
PMID:38656782

Protocol

Real-World Registry on the Pharmacotherapy of Multiple Myeloma and Associated Renal and Pulmonary Impairments in the Greater Gulf Region: Protocol for a Retrospective Real-World Data Study

Abdulnaser Nourallah[1*], MD; Abdulrahman Alshehri[2*], MD; Ayman Alhejazi[3*], MD; Binyam Usman[4*], MD; Ghada ElGohary[5*], MD; Hafiz Malhan[6*], MD; Ibraheem Motabi[7,8*], MD; Khalil Al Farsi[9*], MD; Mohammed Alshuaibi[10*], MD; Mustaqeem Siddiqui[11*], MD; Rasha Ghonema[12*], MD; Ruba Yasin Taha[13*], MD; Tarek Abouzeid[14*], MD; Wesam Ahmed[15,16*], MD; Mohanad Diab[17*], MD; Ahmad Alhuraiji[12*], MD; Magdy Rabea[18*], MD; Mohamed Zahir Chouikrat[19*], MD

[1]Hematology/Medical Oncology Department, Almana General Hospital, Alkhobar, Saudi Arabia

[2]Hematology / Oncology Department, Aseer Central Hospital, Abha, Saudi Arabia

[3]Division of Adult Hematology and Hematopoietic Stem Cell Transplantation, Department of Oncology, King Abdulaziz Medical City, Riyadh, Saudi Arabia

[4]Department of Oncology, King Faisal Specialist Hospital and Research Center, Jeddah, Saudi Arabia

[5]Department of Medicine, Division of Oncology/Hematology, College of Medicine, King Saud University Medical City, Riyadh, Saudi Arabia

[6]Department of Adult Hematology, Prince Mohammed bin Nasser Hospital, Jazan, Saudi Arabia

[7]Adult Hematology & Bone Marrow Transplant Department, Comprehensive Cancer Center at King Fahad Medical City, Riyadh, Saudi Arabia

[8]Alfaisal University, Riyadh, Saudi Arabia

[9]Department of Hematology, Sultan Qaboos University Hospital, Muscat, Oman

[10]Adult Hematology and Oncology Divisions, Department of Medicine, King Abdul-Aziz Hospital, Alahsa, Saudi Arabia

[11]Hematology & Oncology Division at Sheikh Shakhbout Medical City (SSMC), Abu Dhabi, Saudi Arabia

[12]Department of Hematology, Kuwait Cancer Control Center, Kuwait, Kuwait

[13]Department of Hematology-Bone Marrow Transplantation, National Centre for Cancer Care and Research (NCCCR), Hamad Medical Corporation (HMC), Doha, Qatar

[14]Internal Medicine Department, Almouwasat Hospital, Dammam, Saudi Arabia

[15]Cleveland Clinic Abu Dhabi, Oncology Institute, Abu Dhabi, United Arab Emirates

[16]Cleveland Clinic Florida, Oncology Institute, Florida, FL, United States

[17]Hemato-oncology Department, Burjeel Hospital, Abu Dhabi, United Arab Emirates

[18]Medical Affairs Department, Sanofi, Jeddah, Saudi Arabia

[19]Medical Affairs Department, Sanofi, Dubai, United Arab Emirates

[*]all authors contributed equally

Corresponding Author:
Mohamed Zahir Chouikrat, MD
Medical Affairs Department, Sanofi
One JLT building 3rd Floor, Jumeirah Lake Towers
Dubai, 500001
United Arab Emirates
Phone: 971 (0) 50 527 1412
Email: Zahir.Chouikrat@sanofi.com

Abstract

Background: Multiple myeloma (MM) is the second-most common cancer among hematological malignancies. Patients with active disease may experience several comorbidities, including renal insufficiency and asthma, which may lead to treatment failure. The treatment of relapsed or refractory MM (RRMM) has been associated with multiple factors, causing a decline in progression-free survival as well as overall survival with subsequent lines of therapy. Data about the characteristics of this group of patients in the Greater Gulf region are lacking.

Objective: The primary objective of this study is to describe the disease characteristics and various treatment approaches or regimens used in the management of patients with RRMM in the Greater Gulf region.

Methods: We will conduct a regional, retrospective study collecting real-world and epidemiological data on patients with MM in countries of the Greater Gulf region. Medical records will be used to obtain the required data. Around 150 to 170 patients' records are planned to be retrospectively reviewed over 6 months without any cross-sectional or prospective intervention. Cases will be collected from Saudi Arabia, the United Arab Emirates, Kuwait, Oman, and Qatar. Descriptive as well as analytical statistics will be performed on the extracted data. The calculated sample size will allow us to estimate the percentages of RRMM cases with acceptable precision while complying with the challenges in light of data scarcity. We will obtain a comprehensive description of the demographic profile of patients with MM; treatment outcomes; the proportion of patients with MM with renal impairment and asthma, chronic obstructive pulmonary disease, or both at the time of diagnosis and any subsequent point; and data related to treatment lines, regimens, and MM-associated morbidities.

Results: Patient medical records were reviewed between June 2022 and January 2023 for eligibility and data extraction. A total of 148 patients were eligible for study inclusion, of whom 64.2% (n=95) were male and 35.8% (n=53) were female. The study is currently in its final stages of data analysis. The final manuscript is expected to be published in 2024.

Conclusions: Although MM is a predominant hematological disease, data on its prevalence and patients' characteristics in the Greater Gulf region are scarce. Therefore, this study will give us real-world insights into disease characteristics and various management approaches of patients with MM in the Greater Gulf region.

International Registered Report Identifier (IRRID): DERR1-10.2196/49861

(JMIR Res Protoc 2024;13:e49861) doi:10.2196/49861

KEYWORDS

Greater Gulf region; multiple myeloma; pulmonary dysfunction; renal impairment; RRMM; Real-world data

Introduction

Overview

Multiple myeloma (MM) is a malignant clonal cancer of plasma cells of the bone marrow that results in an overproduction of huge amounts of light- and heavy-chain monoclonal immunoglobulins [1,2]. In 2020, MM was revealed as the second most predominant hematological malignancy, representing about 10% of hematologic cancers [1], with 176,404 new cases and 117,077 deaths detected worldwide [3]. The hallmark of monoclonal immunoglobulins in MM is the monoclonal protein (M protein), named after its monoclonal properties, detected in patients with MM's serum and urine [2]. The potential uncontrolled growth of these plasma cells causes destructive bone lesions, kidney injury, anemia, and hypercalcemia [4]. About 15% to 30% of patients have the clinical presentation of hypercalcemia with concomitant renal insufficiency caused by precipitated monoclonal light chains in the collecting tubules [5,6]. However, in asymptomatic patients, the disease is accidentally discovered after detecting anemia or hyperproteinemia [1]. Moreover, around 10% of patients with MM showed a previous history of asthma or chronic obstructive pulmonary disease (COPD). The treatment of MM involves the use of steroids; standard chemotherapy (including cyclophosphamide, melphalan, and bendamustine); proteasome inhibitors such as bortezomib and ixazomib [7]; anti-CD38 monoclonal antibodies (eg, daratumumab and isatuximab), and autologous stem cell transplantation (ASCT) [8].

Guidelines have approved anti-CD38 monoclonal antibodies simultaneously with lenalidomide and dexamethasone for treating relapsed or refractory MM (RRMM) following their remarkable efficacy. Alongside clinical disease complications, the treatment of patients with RRMM relied on 3 key points: the duration of response (DoR), progression-free survival (PFS), and overall survival (OS) reduction with successive lines of therapy [9].

MM shows a socioeconomic burden on the patients as well as their families. Rare data regarding MM in the Middle East have been detected [10]. Nevertheless, the United Arab Emirates (UAE) and Qatar were among the countries with the largest prevalence of MM cases and deaths over the past 30 years across the world [11].

Rationale

The primary objective of this study is to detect the associated characteristics of patients with RRMM and the treatment landscape in the Greater Gulf region. The secondary objectives are to describe MM disease history; assess the prevalence of lenalidomide-refractoriness among patients with RRMM in the Greater Gulf region; assess the prevalence of renal impairment and asthma or COPD among patients with RRMM in countries of the Greater Gulf region, both at diagnosis and throughout the disease course; describe renal response (overall, per treatment line and regimen for patients with renal impairment); describe the overall treatment outcomes for patients with MM and patients with lenalidomide-refractory (per treatment line and regimen); and reveal the percentage of patients with RRMM who are eligible for ASCT.

Methods

Overview

Due to the rarity of MM, this study will be a regional, retrospective study aimed at collecting real-world and epidemiological data from patients with MM's medical records in countries in the Greater Gulf region. In addition, the study will describe the demographic characteristics and treatment

landscape of patients diagnosed with RRMM who have relapsed at least once and maximally 3 times before study entry in the 2 years leading up to data collection. Medical records will be checked for eligibility, and data will be retrieved from all participating countries, including Saudi Arabia, the UAE, Kuwait, Oman, and Qatar.

Participants for whom medical records will be eligible for inclusion, review, and analysis must fulfill the following criteria: male or female patients with RRMM who have relapsed at least once and a maximum of 3 times before study entry in the 2 years leading up to data collection. Patients should be 18 years or older, male or female, diagnosed with RRMM (first, second, and third relapses only, who had 1-3 previous lines of treatment) within a maximum of 2 years before data collection time, and have complete patient medical records from MM diagnosis to date of death or medical abstraction. Patients will be excluded as follows: patients not undergoing treatment for MM or newly diagnosed patients (first-line patients); patients with a history of other malignancies; pregnant patients or those planning for pregnancy; or patients with end-stage renal disease.

This study is based on the secondary use of data; expedited reporting of adverse events or adverse drug reactions is not required. However, the sponsor will report all safety observations made during the conduct of the study in the study report.

All of the data will be obtained from the available records as shown in Textbox 1.

Textbox 1. Study flowchart. All the data will be obtained from the available records. Data will be collected from Saudi Arabia, the United Arab Emirates, Kuwait, Oman, and Qatar.

Evaluation or data points in patients' records

- *Inclusion and exclusion criteria*
- *Patient characteristics*: nationality, gender, age, and race
- *Multiple myeloma (MM) disease history*: year of diagnosis, diagnostic method used, levels of heavy-chain immunoglobulin, hematological biomarkers, other laboratory findings, and symptoms before diagnosis (if available)
- *Cytogenetic abnormalities*
- *MM-associated morbidities*: renal impairment (estimated glomerular filtration rate values or other kidney function tests) and pulmonary impairment (including asthma and chronic obstructive pulmonary disease)
- *Lines of treatment used*: first-line regimens (at diagnosis), second-line regimens (after first relapse), third-line regimens (after second relapse), and fourth-line regimens (after third relapse)
- *Treatment regimens*: monotherapy or combination therapy
- *Reasons for treatment change or discontinuation*
- *Eligibility for stem cell transplant*
- *Lenalidomide refractoriness status*
- *Treatment outcomes*: dates of progression, relapses, and requiring treatment escalation (due to refractoriness or relapse)
- *Time to progression*
- *Minimum residual disease negativity (if applicable)*

Data sources include—but are not limited to—hospital records (medical, clinic, and pharmacy) and office charts; memoranda; evaluation checklists; laboratory reports, radiology reports, and imaging data (eg, ultrasonography and scans on film or digital media); computer printouts; and any other documentation regarding the patient (including the patient diary).

Based on the study by Lecat et al [12], 71% of patients with RRMM became refractory to lenalidomide after an initial response. Considering an observed percentage of 71% (120.7/170) with an absolute precision of 8% and a 95% CI, a sample size of a minimum of 150 patients was calculated based on the below formula:

To estimate an observed percentage of 50% (85/170) with an absolute precision of 8% and a 95% CI, the sample size for this retrospective study was estimated to be 170 patients with the assumption that 10% (15/150) of enrolled patients would not be valuable for the primary analyses due to missing values or unfulfilled inclusion and exclusion criteria.

It is planned to review the medical records of the 170 patients from all participating countries, including Saudi Arabia, the UAE, Kuwait, Oman, and Qatar.

The final study will include 15 medical centers distributed as follows: 10 in Saudi Arabia; 3 in the UAE; and 1 medical center each from Qatar, Oman, and Kuwait.

This study is categorized as a Group E study with no applicable individual case safety reporting; however, either aggregate analysis may provide safety conclusions of interest for the product or, even if the analysis is not intended for safety purposes, it may raise a safety signal. Any potential safety signal will be transmitted to the company's pharmacovigilance department.

All data collected will be analyzed appropriately, and statistical analysis will be carried out by SPSS (version 18 or higher; IBM

Corp). The associated characteristics of RRMM will be described using frequency and percentage with a 95% CI. Other variables will be described using the mean (SD) for continuous variables and counts for categorical variables. Patients' variables will be compared using Mann-Whitney-Wilcoxon tests for continuous variables and chi-square for categorical variables. A probability value of less than 5% (P<.05) will be considered significant.

Primary Analysis

The associated characteristics of RRMM will be described using frequency and percentage with a 95% CI. This analysis will be descriptive and will be conducted on the eligible patients who fulfill the inclusion criteria and who have been selected during the specified study period.

Secondary Analysis

The disease history for MM will be assessed using frequency and percentage with a 95% CI. This analysis will be descriptive and will be conducted on eligible patients. The incidence of lenalidomide-refractoriness among patients with RRMM in the Greater Gulf region and the prevalence of renal impairment and asthma or COPD among patients with RRMM in countries of the Greater Gulf region will be presented using incidence density rates. Comparison will be done using Mann-Whitney-Wilcoxon tests for continuous parameters and chi-square for categorical parameters. The description of renal response (overall, per treatment line and regimen for patients with renal impairment), the overall treatment outcomes for patients with MM and patients with lenalidomide-refractory (per treatment line and regimen), and the percentage of patients with RRMM who are eligible for ASCT will be described using frequency and percentage. Univariate and multivariate analyses will be conducted on lenalidomide-refractoriness among patients with RRMM in the Greater Gulf region and other variables collected.

This section provides specifications for preparing the final statistical analysis plan, which will be issued before the database lock. Therefore, any differences compared to this statistical section should be identified and documented in the final statistical analysis plan.

Statistical Analysis

The data will be analyzed using SPSS version 26 software. Categorical variables will be reported as frequency (n) and percentage (%), while quantitative variables will be reported using descriptive measures such as mean, SD, and range. The chi-square test will be used to determine the association of different risk factors with treatment regimens. A value of P<.05 to determine the significance level will be used. Multivariate logistic regression analysis will be used to analyze the relationship between the dependent variable and multiple predictors or independent variables. PFS and OS will be used accordingly.

Ethical Considerations

This study is being conducted in accordance with the principles established by the 18th World Medical Assembly in Helsinki in 1964, along with all subsequent amendments [13]. All patient data will be handled anonymously to ensure patient confidentiality. In accordance with the institutional review board (IRB) approval obtained for this study, there is no requirement for informed consent. The final study will include 15 medical centers, distributed as follows: 10 in Saudi Arabia; 3 in the UAE; and 1 medical center each from Qatar, Oman, and Kuwait. IRB approvals were obtained from the participating countries. In Saudi Arabia, approval was obtained from Mouwasat Hospital under the IRB NCBE- KACST (H-05-D-12) on October 10, 2022; the Directorate of Health Affairs-Aseer Region (REC-15-06-2022) on June 20, 2022; King Faisal Specialist Hospital and Research Center under IRB 2022-47 on June 22, 2022; King Fahad Medical City under 2 hospitals—Al Mana Hospital (King Fahad Medical City approval as an external site, IRB 22-212E in December 2022) and Alkhobar Comprehensive Cancer Center (22-212 IRB 22-212) on July 26, 2022; King Saud University-Medical City under 22/0626/IRB on August 23, 2022; Prince Mohammed bin Nasser Hospital under 22058 on June 28, 2022; and King Abdullah International Medical Research Center-Al Ahsa and King Abdullah International Medical Research Center-Riyadh (IRB: 1519/22) on August 31, 2022. In UAE, approval was obtained from Burjeel Hospital (DOH/CVDC/2022/1473) on August 11, 2022; Cleveland Clinic Abu Dhabi (DOH/CVDC/2022/1622) on November 10, 2022; and Sheikh Shakhbout Medical City, Abu Dhabi, UAE (DOH/CVDC/2022/740) on April 28, 2022. In Oman, approval was obtained from Sultan Qaboos University Hospital (SQU-EC/174/2022 MREC#2801) on July 13, 2022. In Kuwait, approval was obtained from the ethics committee in the Ministry of Health (2022/1988) on May 17, 2022. In Qatar, approval was obtained from the National Center for Cancer Research (MRC-02-22-37) on October 2, 2022.

Data Analysis

Upon completion of this study, a comprehensive description of the demographic profile of patients with MM, including age, gender, and other relevant data, will be obtained. As well, data on patients undergoing different treatment modalities and regimens, including monotherapy or combination therapy, both overall and for each treatment line, will be collected. Additionally, information on the DoR and time to progression (TTP), both overall and within different treatment lines, will be gathered. This includes assessing the percentage of patients with lenalidomide-refractory in the first, second, and third relapse settings. The study will record the history of MM, including the duration of the disease, laboratory levels of biomarkers, and symptoms before diagnosis. Furthermore, we will investigate the proportion of patients with MM with renal impairment and asthma, COPD, or both at the time of diagnosis and at any point thereafter. These data will be collected for each treatment line and regimen. The changes in estimated glomerular filtration rate and other relevant parameters from baseline to evaluate renal response (whether it remains stable, improves, or worsens) will be analyzed. In addition, information on the proportion of patients prescribed lenalidomide at each treatment line and the treatment regimen for patients with lenalidomide-refractory will be retrieved. TTP and DoR among patients with lenalidomide-refractory in different treatment lines and regimens will be calculated according to the International Myeloma Working Group criteria [2]. For instance, the DoR

will be calculated in the subpopulation experiencing treatment response from the date when the response is first met to the date of the first documented progression, whereas the TTP will be calculated as the length of time from the date of diagnosis or the start of treatment for a disease until disease progression. Moreover, the proportion of patients eligible for ASCT at any time after diagnosis will be determined. The definitions of "relapsed" and "refractory" MM have been varied across clinical studies. While some studies have defined "relapsed" as those patients with recurrent malignancies following a remission or patients who were positively affected by rescue therapy yet experienced disease progression during their follow-up with or without maintenance therapy, others have defined patients with "refractory" MM as those who have a failed response (or showed a limited response) to rescue therapy or who progress within 60 days of their last regimen [14,15]. This study will assess the used definitions and their impact on the OS and PFS of the included patients.

Compliance

RAY-Contract Research Organization (CRO), a third party delegated by Sanofi, is solely responsible for taking all reasonable steps to ensure the proper conduct of the protocol regarding ethics, protocol compliance, and the integrity and validity of the data recorded on the case report form (CRF). The primary responsibility of RAY-CRO is to assist the investigating site in maintaining high standards of ethical, scientific, technical, and regulatory quality throughout the study.

At regular intervals during the study, the site will be contacted, through monitoring visits, letters, or telephone calls, by a representative of the monitoring team to review study progress, investigator and patient compliance with study protocol requirements, and any emergent problems. During these monitoring visits, the following but not exhaustive list of points will be scrutinized by the investigator: IRB approval, documentation and reporting, and quality of data in the CRF.

The main duty of the monitoring team of RAY-CRO will be to assist the investigator and the sponsor in maintaining high ethical, scientific, technical, and regulatory standards throughout the study. Regular monitoring visits, letters, or telephone calls will be made to the site to review study progress, investigator and patient compliance with study protocol requirements, and any emerging issues. During these visits, the investigator will be scrutinized on, but not limited to, the following points: IRB approval, data documentation, and the quality of data in the CRF.

Results

Patient medical records were reviewed between June 2022 and January 2023 for eligibility and data extraction. A total of 148 patients met the study inclusion criteria, of whom 64.2% (n=95) were male and 35.8% (n=53) were female. The study is currently in its final stages of data analysis, and the final manuscript is expected to be published in 2024.

Discussion

Summary

This study is expected to provide reliable data on MM and associated renal and pulmonary impairments in the Greater Gulf region, through the collection of real-world and epidemiological data from the medical records of patients with MM in countries in the Greater Gulf region. In addition, the study will describe the demographic characteristics and treatment landscape of patients diagnosed with RRMM who have relapsed at least once and maximally 3 times before study entry in the 2 years leading up to data collection. All patients who have relapsed at least once and a maximum of 3 times before study entry in the 2 years leading up to data collection will be included. The incidence of lenalidomide-refractoriness among patients with RRMM in the Greater Gulf region, the prevalence of renal impairment and asthma or COPD among patients with RRMM in countries of the Greater Gulf region, renal response, the overall treatment outcomes for patients with MM and patients with lenalidomide-refractory, and the percentage of patients with RRMM who are eligible for ASCT will be presented.

Expected Outcomes and Comparisons With Previous Work

Although MM has been detected at increasing rates in some countries of the Greater Gulf region [11,16], fewer studies have been conducted regarding low-income countries, including the Middle East and North Africa [17]. Nevertheless, the treatment of MM, largely in relapsed cases, poses major challenges. Although new drugs and other therapeutic interventions enhance the prognosis of MM, the availability of these drugs is limited across the Middle East [18]. Hence, this study will provide an overview of the treatment regimens and associated patient characteristics in Greater Gulf countries. Regardless of updated national guidelines established in the Greater Gulf countries, a deficiency in complete data to guide the decision makers of local patients is detected. Educational gaps arise, and bespoke initiatives are required to help oncologists individualize the treatment and translate the evidence-based endorsements into real-world practice [19,20]. With this study, we hope to elucidate the incidence of lenalidomide-refractoriness among patients with RRMM and the overall treatment outcomes for patients with MM and patients with lenalidomide-refractory (per treatment line and regimen) to guide physicians with the best treatment options and better survival outcomes.

Patients who experienced a ≥25% increase in serum or urine M protein have a biochemical relapse, are considered asymptomatic, and are closely monitored without treatment [21]. In contrast, patients with high-risk disease, including those with negative cytogenetics, suboptimal response to previous treatment, or aggressive disease at diagnosis [22], or those who exhibit a rapid escalation in serum or urine M protein levels, for instance, a doubling time of 2 months or less, should initiate therapy immediately [23]. It is expected that if our patients reveal symptomatic relapse, it should be managed based on the criteria of the International Myeloma Working Group. We hope that this study can provide us with the actual management

procedures followed in each country and the consequent responses of those patients.

Regarding the demographic data for MM, age is considered a crucial prognostic factor for patients with MM. Patients aged above 50 years at diagnosis usually exhibit significantly shorter median survival times than younger patients [24]. Nevertheless, recent MM therapy protocols have improved the clinical outcome, particularly in patients younger than 70 years [24,25], while the survival advantage has been recently detected in older patients [26]. This controversial conclusion regarding the improved survival in the older population with MM could be due to the detected variability of the age range included in interventional clinical trials (ie, aged between 60 and 65 years) and the median age of patients with MM at diagnosis (usually around the age of 70 years) in other studies. The median time for diagnosis for these patients usually ranges between 2 and 4 years [23]. According to a study conducted in Jordan, the median age of the included patients was 62 years, the mean OS was 74 months, and the median survival was 38 months [17]. Our anticipated results will provide us with a clear indication of the age range and the influence of age on the prognosis and survival of those patients.

In addition, patients older than the age of 75 years exhibit an increased cumulative incidence of renal insufficiency and cardiovascular disease, from 47.7% at MM diagnosis to 67.8% at the first relapse exhibited. Moreover, in patients with MM aged 75 years or older, the risk of relapse post–second-line therapy increased significantly and alternated by time to the next treatment [11]. Nevertheless, younger patients have exhibited better survival than older populations, particularly those younger than 40 years of age, where they are rarely detected with such comorbid diseases [27]. Additionally, geriatric assessments were recommended to be incorporated into routine clinical practice at the diagnosis of MM and for the exclusion of differential diagnoses in the very elderly. This approach aims to achieve optimum therapy and the adjustment of both dosing and regimens for improved effectiveness and tolerability [28]. As such information is missed among patients with MM in the Greater Gulf countries, this study shall provide us with more details regarding the prognosis of patients aged over 75 years with renal insufficiency, cardiovascular diseases, or both; their management procedure; and the effect of younger age over survival.

For lenalidomide-refractoriness among RRMM, improvement in renal function in patients with RRMM and renal impairment following lenalidomide- or dexamethasone-based treatment has been revealed by many studies [29-31]. Similarly, patients with MM presented with asthma or COPD showed significantly longer time from first- to second-line treatment. Additionally, the OS from first-line therapy was remarkably lower among patients with COPD, with a statistically significant decline in the OS from second-line therapy [32]. As no previous studies in the Middle East and North Africa region have provided the effect of first- or second-line treatment on patients with associated asthma or COPD, this study will assess the OS and PFS in those patients and compare the influence of first- or second-line therapy on survival.

Limitations

Anticipated limitations of this study include the heterogeneity of management guidelines among the included countries, which may restrict the results obtained from real-world data by reflecting actual practice, influenced by patient compliance and environmental factors rather than solely by the efficacy of the drugs. Furthermore, despite the relative consistency of first-line therapy in the countries of the Gulf Cooperation Council, several different treatment options become available after the first relapse. This study may not be able to comprehensively capture the multiple factors influencing the selection of specific regimens at the first stage of progression. Additionally, the proportion of patients receiving anti-CD38 monoclonal antibody therapy such as daratumumab or isatuximab, which has significantly transformed the MM treatment landscape, remains relatively limited to date.

Conclusion

This study will provide a more comprehensive understanding of the management of MM in the Greater Gulf region, with a particular focus on the renal and pulmonary complications that may arise. We will delve into the wider significance of this study, addressing potential predisposing factors and their implications for clinical practice and public health in the region. This study seeks to shed light on how the insights gained can inform healthcare strategies and ultimately enhance the quality of care for patients with MM in this specific geographic area.

Acknowledgments

The authors would like to thank Dr Shimaa Ragab, from RAY-CRO, for her valuable editorial support. The authors also acknowledge Dr Omar M Hussein and Dr Reham Elgarhy, from RAY-CRO, for their valuable review and guidance. The study is conducted by Sanofi Saudi Arabia, Tahlia Street, Nojoud Center, Gate C, Jeddah, Saudi Arabia. Sanofi will provide the basic study material (study outline and protocol template) needed for RAY to develop the study materials, including protocol information, data collection items, a review of the medical manuscript, and approval for journal submission. Furthermore, in accordance with local and international regulations, Sanofi Saudi Arabia will be responsible for the monetary funding for the study conducted and publication, and RAY Clinical Research Organization will ensure operational execution. Also, we confirm that this study protocol was revised by the representative of Sanofi before submission.

Data Availability

Data will be presented in the main manuscript or additional supporting files whenever possible. After completing the study, the data obtained during and/or analyzed during this study will be available upon request through the corresponding author. The authors hereby state that no generative artificial intelligence was used in any portion of the manuscript writing.

Authors' Contributions

The principal investigator for this study is AN, who developed the initial draft of the protocol. Further versions were edited by A Alshehri, A Alhejazi, BU, GE, and HM, while IM, KAF, MA, MS, and RG reviewed the content and development of the paper. All authors provided inputs for the study protocol and approved the final version of the manuscript after their revisions.

Conflicts of Interest

MR and MZC are employees at Sanofi. The authors have no further conflicts to declare.

References

1. Angtuaco EJC, Fassas ABT, Walker R, Sethi R, Barlogie B. Multiple myeloma: clinical review and diagnostic imaging. Radiology 2004;231(1):11-23 [FREE Full text] [doi: 10.1148/radiol.2311020452] [Medline: 14990813]
2. International Myeloma Working Group. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. Br J Haematol 2003;121(5):749-757 [FREE Full text] [Medline: 12780789]
3. Multiple myeloma. Globocan. 2020. URL: https://gco.iarc.fr/today/data/factsheets/cancers/35-Multiple-myeloma-fact-sheet.pdf [accessed 2023-12-29]
4. Cowan AJ, Green DJ, Kwok M, Lee S, Coffey DG, Holmberg LA, et al. Diagnosis and management of multiple myeloma: a review. JAMA 2022;327(5):464-477 [FREE Full text] [doi: 10.1001/jama.2022.0003] [Medline: 35103762]
5. Mikhael J, Singh E, Rice MS. Real-world renal function among patients with multiple myeloma in the United States. Blood Cancer J 2021;11(5):99 [FREE Full text] [doi: 10.1038/s41408-021-00492-6] [Medline: 34021119]
6. Heher EC, Rennke HG, Laubach JP, Richardson PG. Kidney disease and multiple myeloma. Clin J Am Soc Nephrol 2013;8(11):2007-2017 [FREE Full text] [doi: 10.2215/CJN.12231212] [Medline: 23868898]
7. Theodoropoulos N, Lancman G, Chari A. Targeting nuclear export proteins in multiple myeloma therapy. Target Oncol 2020;15(6):697-708 [FREE Full text] [doi: 10.1007/s11523-020-00758-2] [Medline: 33074469]
8. Alanazi F, Kwa FAA, Burchall G, Jackson DE. New generation drugs for treatment of multiple myeloma. Drug Discov Today 2020;25(2):367-379 [FREE Full text] [doi: 10.1016/j.drudis.2019.11.008] [Medline: 31765717]
9. Raab MS, Cavo M, Delforge M, Driessen C, Fink L, Flinois A, et al. Multiple myeloma: practice patterns across Europe. Br J Haematol 2016;175(1):66-76 [FREE Full text] [doi: 10.1111/bjh.14193] [Medline: 27291397]
10. Keykhaei M, Masinaei M, Mohammadi E, Azadnajafabad S, Rezaei N, Moghaddam SS, et al. A global, regional, and national survey on burden and Quality of Care Index (QCI) of hematologic malignancies; global burden of disease systematic analysis 1990-2017. Exp Hematol Oncol 2021;10(1):11 [FREE Full text] [doi: 10.1186/s40164-021-00198-2] [Medline: 33557940]
11. Zhou L, Yu Q, Wei G, Wang L, Huang Y, Hu K, et al. Measuring the global, regional, and national burden of multiple myeloma from 1990 to 2019. BMC Cancer 2021;21(1):606 [FREE Full text] [doi: 10.1186/s12885-021-08280-y] [Medline: 34034700]
12. Lecat CSY, Taube JB, Wilson W, Carmichael J, Parrish C, Wallis G, et al. Defining unmet need following lenalidomide refractoriness: real-world evidence of outcomes in patients with multiple myeloma. Front Oncol 2021 Jul 21;11:703233 [FREE Full text] [doi: 10.3389/fonc.2021.703233] [Medline: 34367987]
13. Goodyear MDE, Krleza-Jeric K, Lemmens T. The declaration of Helsinki. BMJ 2007;335(7621):624-625 [FREE Full text] [doi: 10.1136/bmj.39339.610000.BE] [Medline: 17901471]
14. Vij R, Siegel DS, Jagannath S, Jakubowiak AJ, Stewart AK, McDonagh K, et al. An open-label, single-arm, phase 2 study of single-agent carfilzomib in patients with relapsed and/or refractory multiple myeloma who have been previously treated with bortezomib. Br J Haematol 2012;158(6):739-748 [FREE Full text] [doi: 10.1111/j.1365-2141.2012.09232.x] [Medline: 22845873]
15. Anderson KC, Kyle RA, Rajkumar SV, Stewart AK, Weber D, Richardson P, et al. Clinically relevant end points and new drug approvals for myeloma. Leukemia 2008;22(2):231-239 [FREE Full text] [doi: 10.1038/sj.leu.2405016] [Medline: 17972944]
16. Alaskar A, Alsaeed A, Alsharif FZ, Alhashmi H, Alghamdi M. Multiple myeloma in Saudi Arabia: consensus of the Saudi Lymphoma/Myeloma Group. J Appl Hematol 2019;10(2):37 [FREE Full text] [doi: 10.4103/joah.joah_62_18]
17. Qasem F, Abu-Qamar A, Aqel B, Aladayleh R, Ilham AR, Magableh A, et al. Real world multiple myeloma registry from Jordan, a developing country. Mediterr J Hematol Infect Dis 2022;14(1):e2022031 [FREE Full text] [doi: 10.4084/MJHID.2022.031] [Medline: 35615319]

18. Zhou L, Yu Q, Wei G, Wang L, Huang Y, Hu K, et al. Measuring the global, regional, and national burden of multiple myeloma from 1990 to 2019. BMC Cancer 2021;21(1):606 [FREE Full text] [doi: 10.1186/s12885-021-08280-y] [Medline: 34034700]
19. Fakhri B, Fiala MA, Tuchman SA, Wildes TN. Undertreatment of older patients with newly diagnosed multiple myeloma in the era of novel therapies. Clin Lymphoma Myeloma Leuk 2018;18(3):219-224 [FREE Full text] [doi: 10.1016/j.clml.2018.01.005] [Medline: 29429818]
20. Raje N, Faiman B, Harvey RD, Kurtin SE, Lonial S, Kumar SK, et al. Identifying professional education gaps and barriers in multiple myeloma patient care: findings of the Managing Myeloma Continuing Educational Initiative Advisory Committee. Clin Lymphoma Myeloma Leuk 2014;14(5):356-369 [FREE Full text] [doi: 10.1016/j.clml.2014.04.011] [Medline: 25066040]
21. Lonial S. Relapsed multiple myeloma. Hematology Am Soc Hematol Educ Program 2010;2010:303-309 [FREE Full text] [doi: 10.1182/asheducation-2010.1.303] [Medline: 21239810]
22. Ludwig H, Sonneveld P, Davies F, Bladé J, Boccadoro M, Cavo M, et al. European perspective on multiple myeloma treatment strategies in 2014. Oncologist 2014;19(8):829-844 [FREE Full text] [doi: 10.1634/theoncologist.2014-0042] [Medline: 25063227]
23. Dimopoulos MA, Terpos E, Niesvizky R, Palumbo A. Clinical characteristics of patients with relapsed multiple myeloma. Cancer Treat Rev 2015;41(10):827-835 [FREE Full text] [doi: 10.1016/j.ctrv.2015.07.005] [Medline: 26296679]
24. Ludwig H, Durie BGM, Bolejack V, Turesson I, Kyle RA, Blade J, et al. Myeloma in patients younger than age 50 years presents with more favorable features and shows better survival: an analysis of 10 549 patients from the International Myeloma Working Group. Blood 2008;111(8):4039-4047 [FREE Full text] [doi: 10.1182/blood-2007-03-081018] [Medline: 18268097]
25. Schaapveld M, Visser O, Siesling S, Schaar CG, Zweegman S, Vellenga E. Improved survival among younger but not among older patients with multiple myeloma in the Netherlands, a population-based study since 1989. Eur J Cancer 2010;46(1):160-169 [FREE Full text] [doi: 10.1016/j.ejca.2009.07.006] [Medline: 19682891]
26. Kumar SK, Dispenzieri A, Lacy MQ, Gertz MA, Buadi FK, Pandey S, et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. Leukemia 2014;28(5):1122-1128 [FREE Full text] [doi: 10.1038/leu.2013.313] [Medline: 24157580]
27. Bladé J, Kyle RA, Greipp PR. Presenting features and prognosis in 72 patients with multiple myeloma who were younger than 40 years. Br J Haematol 1996;93(2):345-351 [FREE Full text] [doi: 10.1046/j.1365-2141.1996.5191061.x] [Medline: 8639427]
28. Kaweme NM, Changwe GJ, Zhou F. Approaches and challenges in the management of multiple myeloma in the very old: future treatment prospects. Front Med (Lausanne) 2021;8:612696 [FREE Full text] [doi: 10.3389/fmed.2021.612696] [Medline: 33718400]
29. Dimopoulos MA, Christoulas D, Roussou M, Kastritis E, Migkou M, Gavriatopoulou M, et al. Lenalidomide and dexamethasone for the treatment of refractory/relapsed multiple myeloma: dosing of lenalidomide according to renal function and effect on renal impairment. Eur J Haematol 2010;85(1):1-5 [FREE Full text] [doi: 10.1111/j.1600-0609.2010.01432.x] [Medline: 20192988]
30. Klein U, Neben K, Hielscher T, Heiss C, Ho AD, Goldschmidt H. Lenalidomide in combination with dexamethasone: effective regimen in patients with relapsed or refractory multiple myeloma complicated by renal impairment. Ann Hematol 2011;90(4):429-439 [FREE Full text] [doi: 10.1007/s00277-010-1080-4] [Medline: 20857112]
31. Oehrlein K, Langer C, Sturm I, Pönisch W, Hahn-Ast C, Kuhn S, et al. Successful treatment of patients with multiple myeloma and impaired renal function with lenalidomide: results of 4 German centers. Clin Lymphoma Myeloma Leuk 2012;12(3):191-196 [FREE Full text] [doi: 10.1016/j.clml.2012.01.001] [Medline: 22341857]
32. Rice MS, Naeger S, Singh E. Real-world treatment patterns and outcomes among multiple myeloma patients with asthma and COPD in the United States. Oncol Ther 2021;9(1):195-212 [FREE Full text] [doi: 10.1007/s40487-021-00146-4] [Medline: 33728584]

Abbreviations

ASCT: autologous stem cell transplantation
COPD: chronic obstructive pulmonary disease
CRF: case report form
DoR: duration of response
IRB: institutional review board
M protein: monoclonal protein
MM: multiple myeloma
OS: overall survival
PFS: progression-free survival
RRMM: relapsed or refractory multiple myeloma

TTP: time to progression
UAE: United Arab Emirates

Edited by A Mavragani; submitted 12.06.23; peer-reviewed by M Gasmi ; comments to author 05.10.23; revised version received 17.10.23; accepted 27.11.23; published 24.04.24.

Please cite as:
Nourallah A, Alshehri A, Alhejazi A, Usman B, ElGohary G, Malhan H, Motabi I, Al Farsi K, Alshuaibi M, Siddiqui M, Ghonema R, Taha RY, Abouzeid T, Ahmed W, Diab M, Alhuraiji A, Rabea M, Chouikrat MZ
Real-World Registry on the Pharmacotherapy of Multiple Myeloma and Associated Renal and Pulmonary Impairments in the Greater Gulf Region: Protocol for a Retrospective Real-World Data Study
JMIR Res Protoc 2024;13:e49861
URL: https://www.researchprotocols.org/2024/1/e49861
doi:10.2196/49861
PMID:38657230

Protocol

Tobacco Smoking or Nicotine Phenotype and Severity of Clinical Presentation at the Emergency Department (SMOPHED): Protocol for a Noninterventional Observational Study

Davide Campagna[1,2,3*], MD; Konstantinos Farsalinos[4*], MD; Giorgio Costantino[5*], MD, PhD; Giuseppe Carpinteri[3*], MD; Pasquale Caponnetto[6*], PsyD, PhD; Francesca Cucuzza[3*], MD; Riccardo Polosa[1,2*], MD, PhD; SMOPHED Study Group[7*]

[1]Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy

[2]Center of Excellence for the Acceleration of Harm Reduction, University of Catania, Catania, Italy

[3]Emergency Department, Policlinico Teaching Hospital, Catania, Italy

[4]Department of Public and Community Health, School of Public Health, University of West Attica, Athens, Greece

[5]Scientific Institute for Research, Hospitalization and Healthcare Ca' Granda Ospedale Maggiore Policlinico, Unità Operativa Complessa Pronto Soccorso e Medicina d'Urgenza, University of Milan, Milan, Italy

[6]Department of Educational Sciences, Section of Psychology, University of Catania, Catania, Italy

[7]See Acknowledgments

[*]all authors contributed equally

Corresponding Author:
Davide Campagna, MD
Department of Clinical and Experimental Medicine
University of Catania
Via Santa Sofia
Catania, 95123
Italy
Phone: 39 0953782449
Email: davide.campagna@unict.it

Abstract

Background: In the last few years, several nicotine products have become available as alternatives to smoking tobacco. While laboratory and limited clinical studies suggest that these devices are less toxic compared to classic tobacco cigarettes, very little is known about their epidemiological impact. Visiting the emergency department (ED) often represents the first or even the only contact of patients with the health care system. Therefore, a study conducted at the ED to assess the impact of these products on health can be reliable and reflect a real-life setting.

Objective: The aim of this noninterventional observational study (SMOPHED study) is to analyze the association between the severity of clinical presentation observed during ED visits among patients using various nicotine products and the subsequent outcomes, specifically hospitalization and mortality.

Methods: Outcomes (hospitalization and mortality in the ED) will be examined in relation to various patterns of nicotine products use. We plan to enroll approximately 2000 participants during triage at the ED. These individuals will be characterized based on their patterns of tobacco and nicotine consumption, identified through a specific questionnaire. This categorization will allow for a detailed analysis of how different usage patterns of nicotine products correlate with the clinical diagnosis made during the ED visits and the consequent outcomes.

Results: Enrollment into the study started in March 2024. We enrolled a total of 901 participants in 1 month (approximately 300 potential participants did not provide the informed consent to participate). The data will be analyzed by a statistician as soon as the database is completed. Full data will be published by December 2024.

Conclusions: There is substantial debate about the harm reduction potential of alternative nicotine products in terms of their smoking-cessation and risk-reduction potential. This study represents an opportunity to document epidemiological data on the link between the use of different types of nicotine products and disease diagnosis and severity during an ED visit, and thus evaluate the harm reduction potential claims for these products.

International Registered Report Identifier (IRRID): PRR1-10.2196/54041

(JMIR Res Protoc 2024;13:e54041) doi:10.2196/54041

KEYWORDS

NEWS; National Early Warning Score; emergency department; smoking; nicotine/tobacco use; electronic cigarettes; heated tobacco products

Introduction

Smoking-related diseases are a well-known group of pathologies that are responsible for 8 million deaths per year globally [1]. Despite numerous restrictions, taxation, and communication campaigns, there are still more than 1.3 billion smokers globally. Quitting smoking remains one of the most cost-effective methods to reduce health risks. However, the success rate of smoking cessation methods remains low in real-world settings [2-5]. Additionally, a substantial proportion of smokers are unwilling to use smoking cessation services but would prefer switching to a less harmful alternative product [6,7]. In the last few years, several alternatives to smoking nicotine products have become available, which are commonly referred to as electronic nicotine delivery systems (ENDS), namely e-cigarettes and heated tobacco products (HTPs). While laboratory and limited clinical studies suggest that these products reduce exposure to toxins and may thus reduce health risks [8-12], very little is known about their epidemiological impact.

Several studies have demonstrated a high proportional cigarette smoking prevalence in patients presenting to the emergency department (ED), which is higher than the prevalence in the general population [13-19]. This is expected considering the disease burden caused by smoking, which might result in more ED visits for smokers compared to nonsmokers. Current smoking as well as smoking relapse were found to be significantly associated with ED visits [20-24]. Access to the ED often reflects the first or the only contact of patients with the health care system; thus, the ED visit represents an opportunity to record smoking and nicotine use patterns. However, no studies have systematically recorded use patterns for ENDS in relation to ED visits. Considering the growing popularity of these products and the limited epidemiological evidence on their health effects, a detailed recording of use patterns for all nicotine products is important to monitor their use prevalence, health care system burden, and epidemiological impact.

The National Early Warning Score (NEWS) is a standardized tool used for assessing and responding to acute illness in patients admitted to the ED [24]. The NEWS is based on a straightforward aggregate scoring system, assigning scores to routine physiological measurements taken when patients either present at or are monitored in the hospital. The scoring system is based on six key physiological parameters: (1) respiration rate, (2) oxygen saturation, (3) systolic blood pressure, (4) pulse rate, (5) level of consciousness or new confusion (alert, verbal, pain, unresponsive [AVPU] scale), and (6) temperature.

For patients accessing the ED, the NEWS aids triage nurses in determining the appropriate urgency level for patient examination, which is represented by color codes. This stratification is based on the severity and urgency of the patient's condition.

The aim of this study is to accurately document the patterns of smoking and nicotine product use, including ENDS, in patients visiting the ED. A key focus is to investigate whether the use of ENDS is associated with any measurable differences in disease severity and outcomes compared to conventional tobacco smoking among these patients.

Methods

Study Design

The Smoking or Nicotine Phenotype and Severity of Clinical Presentation at the Emergency Department (SMOPHED) study is an observational study with no intervention or randomization, analyzing the association between the patient's health condition during an ED visit as well as the outcome (hospitalization and death) and different patterns of nicotine products use. Specifically, the study will explore relevant associations according to the smoking and ENDS product use status (current, former, and never use). The pilot phase of the study will take place at a single clinical center, aiming to evaluate its feasibility and analyze the results. Upon successful completion, there are plans to expand the study into a multicenter format involving a national network comprising 10-12 EDs.

Study Population

Inclusion and exclusion criteria are summarized in Textbox 1. Participants will be recruited among patients presenting at the ED of Policlinico Teaching Hospital of Catania, Italy, in 1 month during the diurnal shift. Only patients that access the ED for a nontraumatic reason will be screened, since it is unlikely that smoking or use of other nicotine products can have any causal effect on accident incidence and subsequent diagnosis. The study will take place during daytime working hours owing to organizational constraints. Typically, our ED admits approximately 70-80 patients for nontraumatic issues during a daytime shift, which runs from 8 AM to 8 PM.

We calculated the expected sample size for the study based on available national and regional statistics, providing a practical approach to estimating the study's sample size. The current and former smoking rates in Sicily are estimated at 22.5% and 13.3%, respectively [25], while the combined prevalence of combustion-free products use (e-cigarettes and HTPs) stands at approximately 5% [26]. Considering the annual Catania ED access rate of 80,000 (monthly access rates of 6000-6500) [27], we anticipate recruiting no less than 1500 current smokers and 1000 former smokers per month. Additionally, we expect to enroll no less than 350 users of combined e-cigarettes/HTPs

per month (dual usage is estimated at approximately 50% of the total). Since approximately 70 patients per day access the ED during the diurnal shift for nontraumatic reasons, we expect to enroll approximately 2000 participants in 1 month.

Textbox 1. Inclusion and exclusion criteria for study participation.

Inclusion criteria

- Adult (aged≥18 years)
- Ability to understand and sign the informed consent form

Exclusion criteria

- Accessed the emergency department for a traumatic accident
- Pregnancy

Ethical Considerations

The study will be conducted according to the principles of Good Clinical Practice and the Declaration of Helsinki. Ethical clearance for this protocol was obtained through the ethical review board "Comitato Etico Catania 1" at Policlinico Teaching Hospital of Catania (84/2023/PO del Registro dei pareri del CE) on April 17, 2023. If any amendments to this protocol are required, the chief investigator will be responsible for the decision to amend the protocol and for deciding whether an amendment is substantial or nonsubstantial. Any substantial amendments will be submitted to the research ethics committee for approval before implementation. Informed consent from study participants will be obtained by the investigators through relevant forms. A dedicated website will be created for the study. This website will respect the General Data Protection Regulation policy. Every study team member will access the site with a personal and unique ID and password. The website will create two different databases to guarantee participants' privacy. The first database will record the fiscal code of the participant and will assign a unique ID. The second database will anonymously record the data from each participant using only the participant's ID. It is necessary to create two databases so that additional information on outcomes or other missing data will be recorded at a later time.

Patients will be asked for authorization to use their clinical data in an anonymous format, in accordance with the current privacy directives related to access to the ED. The informed consent model will be shown to participants who must be able to understand and sign it as an inclusion criterion to participate in the study. All collected informed consent forms will be stored at the ED of Policlinico Teaching Hospital of Catania. No financial or other incentives will be provided to the participants.

Data Collection

On arrival at the ED, each patient undergoes a triage phase. A nurse is usually responsible for evaluating the severity of the health condition and the priority for clinical assessment (unless the patient enters the ED by ambulance under a red code). The nurse usually performs this task by collecting vital signs and recording the patient's medical history. This information is then used to assign a color code representing the priority for further assessment. The patient then waits for the medical evaluation in a dedicated room where nurses can monitor the clinical condition of all attending patients. Participants who meet the inclusion criteria will be recruited during this phase and will be administered an electronic questionnaire (see Multimedia Appendix 1) about their smoking and nicotine product use habits and their medical history. This questionnaire serves to typify the patient's use phenotype and quantify exposure to each product.

In addition to the questionnaire, medical data recorded at the triage phase, such as the NEWS, heart rate, blood pressure, blood oxygen saturation, respiratory rate, temperature, and fraction of inspired oxygen, will be collected.

After the assessment and management of each patient in the ED, the final diagnosis, final disposition, and color code at discharge or admission to a ward will be recorded (see Table 1). To avoid compromising the health of patients with severe disease requiring urgent medical attention, potential participants who arrive at the ED under a red code (ie, with a severe acute illness) will be asked to participate only after they are stabilized (ie, the questionnaire, NEWS, and vital signs will be recorded later).

Based on the responses to the questionnaire, participants will be divided in the following 5 smoking subgroups to facilitate analysis: (1) current tobacco smoker, (2) former tobacco smoker, (3) former tobacco smoker now using e-cigarettes and HTPs (exclusive use), (4) current tobacco smoker also using e-cigarettes and HTPs (dual use), and (5) never smokers or e-cigarette/HTP users.

After 1 month, data in the electronic case report form (eCRF) will be extracted for the statistical analysis.

Since the ED is usually very crowded, four study team personnel will work on the study and will screen and recruit patients during the waiting period before the medical examination. The study team will interview potential participants in a dedicated room within the ED area to guarantee privacy. The initial survey will last approximately 5 minutes per patient. This is a reasonable time to collect product use information from each participant. After the medical visit and final disposition, compilation of the eCRF will be completed as provided by the study protocol, with each study member collecting all necessary information about the patients' outcome (discharge or admission to a ward) by the end of their shift. Some patients may stay in the ED beyond the length of a diurnal shift; in such a case, the data will be collected the day after their arrival. Some patients might access the ED

two or more times during the study. To avoid double entries, only the first visit will be included for analysis in the study. The eCRF database will reply with an error if we try to recruit a patient with the same fiscal code a second time (a fiscal code is a unique identifying code in Italy, and it is mandatory to be recorded for each patient during the triage phase in the ED).

Table 1. Data to record in the electronic case report form.

Data type	Value/units
NEWS[a] calculated at the patient's triage phase (conventionally, patients with an acute condition will be recorded as being at high risk, corresponding to NEWS>7)	0-17
Vital signs recorded during triage	
Heart rate	Beats per minute
Blood pressure	mmHg
Blood oxygen saturation	%
Respiratory rate	Breaths per minute
Body temperature	°C
Fraction of inspired oxygen	%
Smoking questionnaire	See Multimedia Appendix 1
Medical history and drug use history	Textual
Length of stay in the ED[b] or in the hospital (if admitted))	Hours and minutes, or days if admitted
Final diagnosis of discharged patients	Textual
Final disposition	Admitted/discharged
Final diagnosis of admitted patients	*ICD-9*[c] codes

[a]NEWS: National Early Warning Score.

[b]ED: emergency department.

[c]*ICD-9: International Classification of Diseases, 9th edition.*

Endpoint and Outcomes

The primary endpoint of the study is the association between the NEWS and product use phenotypes. Our hypothesis is that use of ENDS may be associated with a lower NEWS compared to cigarette smoking. If our hypothesis will be confirmed, the study will be replicated as a multicenter study to validate our findings.

Secondary outcomes will be hospital admissions (vs discharge) and length of stay in the ED and in the hospital (if admitted). Moreover, we will compare the prevalence of acute diseases known to be related to smoking between groups, specifically stroke, acute myocardial infarction, peripheral artery diseases, chronic obstructive pulmonary disease, asthma, and respiratory infections.

Statistical Analysis

Descriptive analysis will be performed by presenting numerical data as mean (SD) and categorical data as n (%). Patients will be classified according to product use as a current tobacco smoker, former tobacco smoker, former tobacco smoker now using e-cigarettes and HTPs (exclusive use), current tobacco smoker also using e-cigarettes and HTPs (dual use), and never smokers/never e-cigarette or HTP users.

Univariate comparisons will be performed using χ^2 tests for categorical variables and the Kruskal-Wallis H test for the NEWS. Regression analyses will be performed to examine the association between the use of different types of products and the NEWS as well as secondary outcomes. Demographics, including age, sex (male or female), and educational level, as well as past medical history will be included as independent variables. Since the majority of ENDS users report current or past smoking, the smoking status of these users will also be recorded along with those who do not report any ENDS use. Therefore, the analysis will be adjusted for the smoking status of ENDS users. Additionally, secondary analyses will be performed for never-smoking ENDS users, if a sufficient number of such participants will be available. All analyses will be performed using SPSS v.25 (IBM) and a P value <.05 will be considered statistically significant.

Dissemination

The intention of the authors is to disseminate the results of the study through articles in high-quality, peer-reviewed journals and through conference abstracts.

Results

In March 2024, we have enrolled a total of 901 participants (approximately 300 potential participants did not provide the informed consent to participate). The data will be analyzed by a statistician as soon as the database is completed. Full data will be published by December 2024.

Discussion

This protocol was designed to evaluate the impact of smoking and the use of other nicotine products on ED visits, including the respective clinical diagnoses and outcomes. Smoking is a leading preventable cause of morbidity and mortality. It is estimated that tobacco use accounts for 3%-6% of all ED visits and 5%-16% of total hospital expenses [28-30]. Smokers with preexisting diseases such as diabetes and asthma are more prone to ED visits than nonsmokers with similar conditions [23,31].

The smoking prevalence among patients at the ED surpasses that of the general population [16,18], indicating the ED as a key setting for managing smoking-related health issues. In recent years, there has been an intense debate about the harm reduction potential of ENDS. Some studies have shown their effectiveness in smoking cessation [32], yet there is scarce epidemiological evidence on the clinical impacts of noncombustible nicotine products. This study will be the first to explore the link between the use of various nicotine products and ED visits, as well as their association with urgent care needs for smoking-related disease.

Approximately one decade ago, our research group conducted the ECLAT study, which was the first randomized controlled trial that established the efficacy and the safety of e-cigarettes as smoking substitutes [33]. Since then, a newer generation of e-cigarettes, which are more efficient in nicotine delivery and more appealing, have shown encouraging results in clinical and real-world settings [34-41]. Therefore, they may represent a viable alternative for individuals unable or unwilling to quit smoking using approved methods. Nonetheless, it is important to thoroughly investigate and document the potential risk-reduction potential of these products in a clinical context.

Little epidemiological evidence exists on the harm reduction potential of ENDS. This study thus represents an opportunity to document epidemiological data on the link between the use of different nicotine products and disease severity during an ED visit, as well as clinical outcomes and associations with specific (ie, smoking-related) diseases. Besides further exploring the epidemiological impact of ENDS on diseases related to smoking, the implications of this study are also directly related to understanding the currently unknown burden of these products on emergency care resource use, particularly in the context of the well-known substantial effects of smoking on increasing ED visits. The systematic tracking of the impacts of nicotine use in this study will help to highlight the magnitude of tobacco and nicotine use in the community in relation to access to emergency health care services, and will enable those responsible for tobacco control policies, programs, research, and surveillance to assess the situation and inform decision-making.

This study, currently conducted in a single hospital, serves as a pilot phase, aiming to evaluate its feasibility and analyze the results. The ultimate objective is to expand this research to additional EDs within a national network.

Documenting the association between ENDS use and ED visits will provide insights on both local and central policy levels, especially when we consider that emergency and urgent care systems struggle with major challenges in developed countries with crowding, long waiting times, and, in general, increasing numbers of ED visits [42]. Therefore, it is important to examine factors associated with ED visits and adverse outcomes, and to assess if ENDS affect the ED burden in a different manner to smoking. At the same time, this study may document the need for routinely recording nicotine use habits for all patients accessing the ED instead of the current norm of recording smoking status only.

This study has several limitations. The brief period of recruitment and the use of only one study site may introduce sampling bias due to seasonality and locality. Therefore, this study may have limited generalizability to all Italian EDs. However, as mentioned above, this represents a pilot study with the purpose of further expanding the protocol to more regions and several EDs from other hospitals. While it is possible to verify exposure to tobacco smoke by measuring exhaled carbon monoxide and exposure to nicotine by measuring salivary cotinine, logistical and financial restrictions within the short duration of an ED presentation, as well as the urgent nature of attendance requested in the ED, preclude us from performing an objective assessment of the smoking status. Although self-report of smoking status has been shown to be accurate in the ED setting [17], a systematic review (despite including studies outside the ED setting) showed some discrepancy between self-report and objective assessment [43]. In addition, determining nicotine exposure would not help to distinguish between the use of tobacco cigarettes and noncombustible nicotine products. Moreover, the responses to questions on past smoking and nicotine use habits may be introducing recall bias. Finally, the exclusion of patients in a critical state who need urgent care will be compensated by a subsequent request to participate in the study once they are stabilized.

In conclusion, this study protocol addresses the need for additional epidemiological evidence on the effects of ENDS on health, with clinical endpoints. The ED setting represents an opportunity to record smoking and nicotine habits, assess the burden of different products, and provide guidance for interventions at both the personal and systematic level.

Acknowledgments

The publication cost of this paper has been supported by the Department of Clinical and Experimental Medicine of the University of Catania, Italy. DC is supported by a ministerial grant PON REACT-EU 2021 GREEN- Bando 3411/2021 of Ministero dell'Universita' e della Ricerca –Piano Nazionale di Ripresa e Resilienza (National Resilience Recovery Plan) EU Community.

The members of the SMOPHED Study Group are Simone Aliotta, Noemi Contino, Adriana Scalia, and Manuela Leonardi. They are affiliated to the Department Of Clinical and Experimental Medicine, University of Catania, Catania, Italy.

Conflicts of Interest

RP has received the following EU and governmental competitive grants: U-BIOPRED, AIR-PROM, Integral Rheumatology & Immunology Specialists Network (IRIS), Ministero dell'Università e della Ricerca (MUR) Piano Nazionale Ripresa Resilienza (PNRR) 3277/2021, PNRR 341/2022, and PNRR 411/2021 funded by NextGenerationEU of the European Commission. RP has also received investigator-initiated grants from Foundation for a Smoke Free World, Pfizer, GlaxoSmithKline, CV Therapeutics, NeuroSearch A/S, Sandoz, Merk Sharp & Dohme, Boehringer Ingelheim, Novartis, Arbi Group Srl, Duska Therapeutics, and Forest Laboratories. He is founder of the Center for Tobacco Prevention and Treatment and of the Center of Excellence for the Acceleration of Harm Reduction at Catania University. He has been consulting for Pfizer, Boehringer Ingelheim, Duska Therapeutics, Forest Laboratories, CV Therapeutics, Sermo Inc, GRG Health, Clarivate Analytics, Guidepoint Expert Network, and GLG Group. He receives textbook royalties from Elsevier and Edra Publishing. He is also Chair of the European Technical Committee for Standardization on "Requirements and test methods for emissions of electronic cigarettes" (CEN/TC 437; WG4) and scientific advisor at RIDE2Med Foundation. The other authors declare no competing interests related to this research.

Multimedia Appendix 1
Questionnaire to be administered to patients.
[DOCX File , 19 KB - resprot_v13i1e54041_app1.docx]

References

1. Fact Sheets: Tobacco. World Health Organization. 2023 Jul 31. URL: https://www.who.int/news-room/fact-sheets/detail/tobacco [accessed 2023-02-10]
2. Moore D, Aveyard P, Connock M, Wang D, Fry-Smith A, Barton P. Effectiveness and safety of nicotine replacement therapy assisted reduction to stop smoking: systematic review and meta-analysis. BMJ 2009 Apr 02;338:b1024 [FREE Full text] [doi: 10.1136/bmj.b1024] [Medline: 19342408]
3. Kotz D, Brown J, West R. 'Real-world' effectiveness of smoking cessation treatments: a population study. Addiction 2014 Mar;109(3):491-499. [doi: 10.1111/add.12429] [Medline: 24372901]
4. Rigotti NA, Pipe AL, Benowitz NL, Arteaga C, Garza D, Tonstad S. Efficacy and safety of varenicline for smoking cessation in patients with cardiovascular disease: a randomized trial. Circulation 2010 Jan 19;121(2):221-229 [FREE Full text] [doi: 10.1161/CIRCULATIONAHA.109.869008] [Medline: 20048210]
5. Casella G, Caponnetto P, Polosa R. Therapeutic advances in the treatment of nicotine addiction: present and future. Ther Adv Chronic Dis 2010 May;1(3):95-106 [FREE Full text] [doi: 10.1177/2040622310374896] [Medline: 23251732]
6. Britton J, Edwards R. Tobacco smoking, harm reduction, and nicotine product regulation. Lancet 2008 Feb 02;371(9610):441-445. [doi: 10.1016/S0140-6736(07)61482-2] [Medline: 17920116]
7. Bell K. Tobacco control, harm reduction and the problem of pleasure. Drug Alc Today 2013;13(2):111-118. [doi: 10.1108/dat-03-2013-0013]
8. Farsalinos KE, Polosa R. Safety evaluation and risk assessment of electronic cigarettes as tobacco cigarette substitutes: a systematic review. Ther Adv Drug Saf 2014 Apr 13;5(2):67-86 [FREE Full text] [doi: 10.1177/2042098614524430] [Medline: 25083263]
9. Glasser AM, Collins L, Pearson JL, Abudayyeh H, Niaura RS, Abrams DB, et al. Overview of electronic nicotine delivery systems: a systematic review. Am J Prev Med 2017 Feb;52(2):e33-e66 [FREE Full text] [doi: 10.1016/j.amepre.2016.10.036] [Medline: 27914771]
10. Marques P, Piqueras L, Sanz M. An updated overview of e-cigarette impact on human health. Respir Res 2021 May 18;22(1):151 [FREE Full text] [doi: 10.1186/s12931-021-01737-5] [Medline: 34006276]
11. Mallock N, Pieper E, Hutzler C, Henkler-Stephani F, Luch A. Heated tobacco products: a review of current knowledge and initial assessments. Front Public Health 2019 Oct 10;7:287 [FREE Full text] [doi: 10.3389/fpubh.2019.00287] [Medline: 31649912]
12. Akiyama Y, Sherwood N. Systematic review of biomarker findings from clinical studies of electronic cigarettes and heated tobacco products. Toxicol Rep 2021;8:282-294 [FREE Full text] [doi: 10.1016/j.toxrep.2021.01.014] [Medline: 33552927]
13. Bernstein SL, Boudreaux ED, Cydulka RK, Rhodes KV, Lettman NA, Almeida S, American College of Emergency Physicians Task Force on Smoking Cessation. Tobacco control interventions in the emergency department: a joint statement of emergency medicine organizations. J Emerg Nurs 2006 Oct;32(5):370-381. [doi: 10.1016/j.jen.2006.06.006] [Medline: 16997023]
14. Boudreaux ED, Kim S, Hohrmann JL, Clark S, Camargo CA. Interest in smoking cessation among emergency department patients. Health Psychol 2005 Mar;24(2):220-224. [doi: 10.1037/0278-6133.24.2.220] [Medline: 15755236]
15. Weiland T, Jelinek GA, Taylor SE, Taylor DM. Tobacco smoking by adult emergency department patients in Australia: a point-prevalence study. Public Health Res Pract 2016 Jul 15;26(3):2631634. [doi: 10.17061/phrp2631634] [Medline: 27421346]
16. Lynch A, Quigley P. ExHALED study: prevalence of smoking and harm levels in an emergency department cohort. Emerg Med Australas 2010 Aug;22(4):287-295. [doi: 10.1111/j.1742-6723.2010.01299.x] [Medline: 20636360]

17. Lowenstein SR, Tomlinson D, Koziol-McLain J, Prochazka A. Smoking habits of emergency department patients: an opportunity for disease prevention. Acad Emerg Med 1995 Mar;2(3):165-171 [FREE Full text] [doi: 10.1111/j.1553-2712.1995.tb03189.x] [Medline: 7497028]
18. Richman PB, Dinowitz S, Nashed A, Eskin B, Cody R. Prevalence of smokers and nicotine-addicted patients in a suburban emergency department. Acad Emerg Med 1999 Aug;6(8):807-810 [FREE Full text] [doi: 10.1111/j.1553-2712.1999.tb01211.x] [Medline: 10463552]
19. Smith PM. Tobacco use among emergency department patients. Int J Environ Res Public Health 2011 Jan;8(1):253-263 [FREE Full text] [doi: 10.3390/ijerph8010253] [Medline: 21318027]
20. Park J, Yeo Y, Ji Y, Kim B, Han K, Cha W, et al. Factors associated with emergency department visits and consequent hospitalization and death in Korea using a population-based national health database. Healthcare 2022 Jul 17;10(7):1324 [FREE Full text] [doi: 10.3390/healthcare10071324] [Medline: 35885850]
21. Agarwal P, Bias TK, Madhavan S, Sambamoorthi N, Frisbee S, Sambamoorthi U. Factors associated with emergency department visits: a multistate analysis of adult fee-for-service Medicaid beneficiaries. Health Serv Res Manag Epidemiol 2016 Apr 27;3(3):233339281664854 [FREE Full text] [doi: 10.1177/2333392816648549] [Medline: 27512721]
22. Kao Y, Celestin MD, Walker CD, Yu Q, Couk J, Moody-Thomas S, et al. Smoking relapse and type 2 diabetes mellitus-related emergency department visits among senior patients with diabetes. Prev Chronic Dis 2019 Dec 19;16:E164 [FREE Full text] [doi: 10.5888/pcd16.190027] [Medline: 31858955]
23. Selya A, Johnson EL, Weber TL, Russo J, Stansbury C, Anshutz D, et al. Smoking is associated with a higher risk of unplanned medical visits among adult patients with diabetes, using retrospective electronic medical record data from 2014 to 2016. BMC Health Serv Res 2020 May 06;20(1):383 [FREE Full text] [doi: 10.1186/s12913-020-05277-4] [Medline: 32375742]
24. Smith GB, Prytherch DR, Meredith P, Schmidt PE, Featherstone PI. The ability of the National Early Warning Score (NEWS) to discriminate patients at risk of early cardiac arrest, unanticipated intensive care unit admission, and death. Resuscitation 2013 Apr;84(4):465-470 [FREE Full text] [doi: 10.1016/j.resuscitation.2012.12.016] [Medline: 23295778]
25. Sorveglianza PASSI. Istituto Superiore di Sanità. URL: https://www.epicentro.iss.it/passi/dati/fumo [accessed 2023-02-10]
26. Sigaretta elettronica e prodotti a tabacco riscaldato, un consumo in lento aumento. Instituto Nazionale di Statistica. URL: https://www.istat.it/it/files//2023/01/TODAY-Sigaretta-elettronica-tabaccoriscaldato.pdf [accessed 2023-02-10]
27. Allegato 2 - Tabella 1. Numero di accessi al PS per dimensione – anno 2017 (Fonte EMUR). URL: https://www.qualitasiciliassr.it/sites/doc/sps/allegato_2_numero_accessi_al_ps.pdf [accessed 2023-02-10]
28. Hauswald M. The cost of smoking: an emergency department analysis. Am J Emerg Med 1989 Mar;7(2):187-190. [doi: 10.1016/0735-6757(89)90136-8] [Medline: 2920083]
29. Bernstein SL. The impact of smoking-related illness in the ED: an attributable risk model. Am J Emerg Med 2002 May;20(3):161-164. [doi: 10.1053/ajem.2002.32645] [Medline: 11992333]
30. Bernstein SL, Becker BM. Preventive care in the emergency department: diagnosis and management of smoking and smoking-related illness in the emergency department: a systematic review. Acad Emerg Med 2002 Jul;9(7):720-729 [FREE Full text] [doi: 10.1111/j.1553-2712.2002.tb02153.x] [Medline: 12093715]
31. Khokhawalla SA, Rosenthal SR, Pearlman DN, Triche EW. Cigarette smoking and emergency care utilization among asthmatic adults in the 2011 Asthma Call-back Survey. J Asthma 2015 Sep 17;52(7):732-739. [doi: 10.3109/02770903.2015.1004337] [Medline: 25563058]
32. Pelletier JH, Strout TD, Baumann MR. A systematic review of smoking cessation interventions in the emergency setting. Am J Emerg Med 2014 Jul;32(7):713-724. [doi: 10.1016/j.ajem.2014.03.042] [Medline: 24768666]
33. Caponnetto P, Campagna D, Cibella F, Morjaria JB, Caruso M, Russo C, et al. EffiCiency and Safety of an eLectronic cigAreTte (ECLAT) as tobacco cigarettes substitute: a prospective 12-month randomized control design study. PLoS One 2013;8(6):e66317 [FREE Full text] [doi: 10.1371/journal.pone.0066317] [Medline: 23826093]
34. Brown J, Beard E, Kotz D, Michie S, West R. Real-world effectiveness of e-cigarettes when used to aid smoking cessation: a cross-sectional population study. Addiction 2014 Sep;109(9):1531-1540 [FREE Full text] [doi: 10.1111/add.12623] [Medline: 24846453]
35. Cox S, Dawkins L, Doshi J, Cameron J. Effects of e-cigarettes versus nicotine replacement therapy on short-term smoking abstinence when delivered at a community pharmacy. Addict Behav Rep 2019 Dec;10:100202 [FREE Full text] [doi: 10.1016/j.abrep.2019.100202] [Medline: 31338412]
36. Lee S, Ahn S, Cheong Y. Effect of electronic cigarettes on smoking reduction and cessation in Korean male smokers: a randomized controlled study. J Am Board Fam Med 2019 Jul 12;32(4):567-574 [FREE Full text] [doi: 10.3122/jabfm.2019.04.180384] [Medline: 31300577]
37. Hajek P, Phillips-Waller A, Przulj D, Pesola F, Myers Smith K, Bisal N, et al. A randomized trial of e-cigarettes versus nicotine-replacement therapy. N Engl J Med 2019 Feb 14;380(7):629-637 [FREE Full text] [doi: 10.1056/NEJMoa1808779] [Medline: 30699054]
38. Lee SM, Tenney R, Wallace AW, Arjomandi M. E-cigarettes versus nicotine patches for perioperative smoking cessation: a pilot randomized trial. PeerJ 2018;6:e5609 [FREE Full text] [doi: 10.7717/peerj.5609] [Medline: 30280019]

39. Hartmann-Boyce J, McRobbie H, Lindson N, Bullen C, Begh R, Theodoulou A, et al. Electronic cigarettes for smoking cessation. Cochrane Database Syst Rev 2021 Apr 29;4(4):CD010216 [FREE Full text] [doi: 10.1002/14651858.CD010216.pub5] [Medline: 33913154]
40. Li J, Hui X, Fu J, Ahmed MM, Yao L, Yang K. Electronic cigarettes versus nicotine-replacement therapy for smoking cessation: a systematic review and meta-analysis of randomized controlled trials. Tob Induc Dis 2022 Oct 20;20(October):90-13 [FREE Full text] [doi: 10.18332/tid/154075] [Medline: 36339933]
41. Li J, Hajek P, Pesola F, Wu Q, Phillips-Waller A, Przulj D, et al. Cost-effectiveness of e-cigarettes compared with nicotine replacement therapy in stop smoking services in England (TEC study): a randomized controlled trial. Addiction 2020 Mar 04;115(3):507-517 [FREE Full text] [doi: 10.1111/add.14829] [Medline: 31597207]
42. Baier N, Geissler A, Bech M, Bernstein D, Cowling TE, Jackson T, et al. Emergency and urgent care systems in Australia, Denmark, England, France, Germany and the Netherlands - Analyzing organization, payment and reforms. Health Policy 2019 Jan;123(1):1-10 [FREE Full text] [doi: 10.1016/j.healthpol.2018.11.001] [Medline: 30503764]
43. Connor Gorber S, Schofield-Hurwitz S, Hardt J, Levasseur G, Tremblay M. The accuracy of self-reported smoking: a systematic review of the relationship between self-reported and cotinine-assessed smoking status. Nicotine Tob Res 2009 Jan;11(1):12-24. [doi: 10.1093/ntr/ntn010] [Medline: 19246437]

Abbreviations

AVPU: alert, verbal, pain, unresponsive
eCRF: electronic case report form
ED: emergency department
ENDS: electronic nicotine delivery system
HTP: heated tobacco product
NEWS: National Early Warning Score
SMOPHED: Smoking or Nicotine Phenotype and Severity of Clinical Presentation at the Emergency Department

Edited by A Mavragani; submitted 27.10.23; peer-reviewed by S Roulet, B Mao; comments to author 19.12.23; revised version received 24.01.24; accepted 19.02.24; published 24.04.24.

Please cite as:
Campagna D, Farsalinos K, Costantino G, Carpinteri G, Caponnetto P, Cucuzza F, Polosa R, SMOPHED Study Group
Tobacco Smoking or Nicotine Phenotype and Severity of Clinical Presentation at the Emergency Department (SMOPHED): Protocol for a Noninterventional Observational Study
JMIR Res Protoc 2024;13:e54041
URL: https://www.researchprotocols.org/2024/1/e54041
doi:10.2196/54041
PMID:38657239

Protocol

Detection of Urinary Misfolded Proteins for Imminent Prediction of Preeclampsia in Pregnant Women With Suspected Cases: Protocol for a Prospective Noninterventional Study

Haiyang Tang[1], MD; Yijia Tian[1], MD; Jing Fang[2], MM; Xiaoying Yuan[3], MM; Minli Yao[3], MM; Yujia Wang[1], MM; Yan Feng[1], MD, PhD; Jia Shu[4], MM; Yan Ni[5], MBBS; Ying Yu[1], MD; Yuanhe Wang[1], MD; Ping Liang[6], MBBS; Xingmin Li[3*], PhD; Xiaoxia Bai[1,7,8,9*], PhD

[1]Women's Hospital, School of Medicine, Zhejiang University, Hangzhou, China

[2]Department of Obstetrics, Lanxi People's Hospital, Jinhua, China

[3]Shuwen Biotech Co, Ltd, Hangzhou, China

[4]Department of Obstetrics, Ningbo Women and Children's Hospital, Ningbo, China

[5]Department of Obstetrics, Quzhou Maternity and Child Health Care Hospital, Quzhou, China

[6]Department of Obstetrics, Xinchang People's Hospital, Shaoxing, China

[7]Traditional Chinese Medicine for Reproductive Health Key Laboratory of Zhejiang Province, Hangzhou, China

[8]Zhejiang Provincial Clinical Research Center for Obstetrics and Gynecology, Hangzhou, China

[9]Key Laboratory of Women's Reproductive Health, Hangzhou, China

[*]these authors contributed equally

Corresponding Author:
Xiaoxia Bai, PhD
Women's Hospital
School of Medicine
Zhejiang University
1 Xueshi Road, Shangcheng District
Hangzhou, 310006
China
Phone: 86 57189995378
Email: baixiaoxia@zju.edu.cn

Abstract

Background: Preeclampsia (PE) is one of the most common hypertensive diseases, affecting 2%-8% of all pregnancies. The high maternal and fetal mortality rates of PE are due to a lack of early identification of affected pregnant women that would have led to closer monitoring and care. Recent data suggest that misfolded proteins might be a promising biomarker for PE prediction, which can be detected in urine samples of pregnant women according to their congophilia (aggregated) characteristic.

Objective: The main purpose of this trial is to evaluate the value of the urine congophilia-based detection of misfolded proteins for the imminent prediction of PE in women presenting with suspected PE. The secondary objectives are to demonstrate that the presence of urine misfolded proteins correlates with PE-related maternal or neonatal adverse outcomes, and to establish an accurate PE prediction model by combining misfolded proteins with multiple indicators.

Methods: At least 300 pregnant women with clinical suspicion of PE will be enrolled in this prospective cohort study. Participants should meet the following inclusion criteria in addition to a suspicion of PE: ≥18 years old, gestational week between 20+0 and 33+6, and single pregnancy. Consecutive urine samples will be collected, blinded, and tested for misfolded proteins and other PE-related biomarkers at enrollment and at 4 follow-up visits. Clinical assessments of PE status and related complications for all participants will be performed at regular intervals using strict diagnostic criteria. Investigators and participants will remain blinded to the results. Follow-up will be performed until 42 days postpartum. Data from medical records, including maternal and fetal outcomes, will be collected. The performance of urine misfolded proteins alone and combined with other biomarkers or clinical variables for the prediction of PE will be statistically analyzed.

Results: Enrollment started in July 2023 and was still open upon manuscript submission. As of March 2024, a total of 251 eligible women have been enrolled in the study and enrollment is expected to continue until August 2024. Results analysis is scheduled to start after all participants reach the follow-up endpoint and complete clinical data are collected.

Conclusions: Upon completion of the study, we expect to derive an accurate PE prediction model, which will allow for proactive management of pregnant women with clinical suspicion of PE and possibly reduce the associated adverse pregnancy outcomes. The additional prognostic value of misfolded proteins is also expected to be confirmed.

Trial Registration: Chinese Clinical Trials Registry ChiCTR2300074878; https://www.chictr.org.cn/showproj.html?proj=202096

International Registered Report Identifier (IRRID): PRR1-10.2196/54026

(JMIR Res Protoc 2024;13:e54026) doi:10.2196/54026

KEYWORDS

preeclampsia; misfolded protein; congophilia; noninvasive; prospective

Introduction

Background

Preeclampsia (PE) is one of the most common hypertensive diseases in pregnancy, characterized by elevated blood pressure accompanied by proteinuria or organ damage after 20 weeks of gestation [1]. The incidence of PE is approximately 2%-8% worldwide [2,3], and each year, an estimated 76,000 women and 500,000 fetuses die from PE and related complications [4]. Symptoms of PE are not specific, including headache, visual impairment, upper abdominal pain, and shortness of breath, among others. In severe cases, PE may develop into eclampsia, which involves seizures or coma [5-7]. PE may also lead to placental abruption; intrauterine growth restriction; hemolysis with a microangiopathic blood smear, elevated liver enzymes, and low platelets (ie, HELLP syndrome, a life-threatening liver and blood clotting disorder); and other serious health consequences for both the pregnant woman and fetus [8,9]. To date, the treatment of PE has mainly involved the use of antihypertensive medications such as methyldopa, labetalol, and hydralazine to lower blood pressure and prevent further maternal complications [10-12], and magnesium sulfate is also administered to prevent seizures in severe cases [13]. However, the only curative treatment of PE is to deliver the placenta. The current clinical strategy for PE is focused on the early screening and close monitoring of high-risk pregnancies, since low-dose aspirin therapy has proven to be effective in reducing the risk of developing PE by 62% [14]. Although potential biomarkers and ultrasonic techniques for detecting PE have been evaluated in recent decades, none has adequate positive or negative predictive value for the prediction of PE [15-17].

With increasing knowledge of the condition, six stages of PE have been proposed [6]. Defective placentation (stage 3) results in oxidative stress, and placental-derived products are released into the maternal blood (stage 4) before PE is diagnosed (stage 5). Recently, an increased level of misfolded proteins in the urine has been identified in patients with PE [18], suggesting that PE might share pathophysiologic features with recognized protein misfolding disorders such as Alzheimer disease. In patients with PE, misfolded proteins such as amyloid beta and transthyretin can accumulate in the circulation to exert neurotoxic effects and activate inflammatory cascades, leading to endothelial dysfunction and oxidative stress. Buhimschi et al [18] demonstrated that a dot test using Congo Red, a synthetic diazo dye with specific affinity for misfolded proteins, to visualize this aggregation feature (ie, congophilia) for detecting the presence of misfolded proteins in urine could serve as a promising diagnostic tool for PE. Li et al [19] subsequently developed a simple and rapid point-of-care testing (POCT) tool to detect the presence of misfolded proteins in urine based on visual observation, which achieved an overall sensitivity of 73.6% that reached up to 83% for severe PE cases.

The traditional approach for PE screening is to identify risk factors based on maternal demographic characteristics and medical history; however, this approach can only identify 35% of total PE cases and 40% of preterm PE cases, with a false-positive rate of approximately 10% [20,21]. A noninvasive laboratory method involving measurement of the ratio of soluble FMS-like tyrosine kinase 1 (sFLT-1) to placental growth factor (PlGF) in the urine proved to be effective in PE diagnosis, achieving a sensitivity of 70%-72.5% with a 5%-14% false-positive rate [22,23]. Thus, combining urine PlGF and sFLT-1 testing with other biomarkers may yield the best predictive performance.

In this trial, we will test a new congophilia-based detection method alone or combined with clinical variables and other urine biomarkers to predict the onset of PE before its clinical manifestation. This work can therefore help clinicians better identify PE earlier, enabling the proactive management and monitoring of pregnant women who exhibit signs or symptoms of PE but do not meet the current diagnostic criteria.

Objective

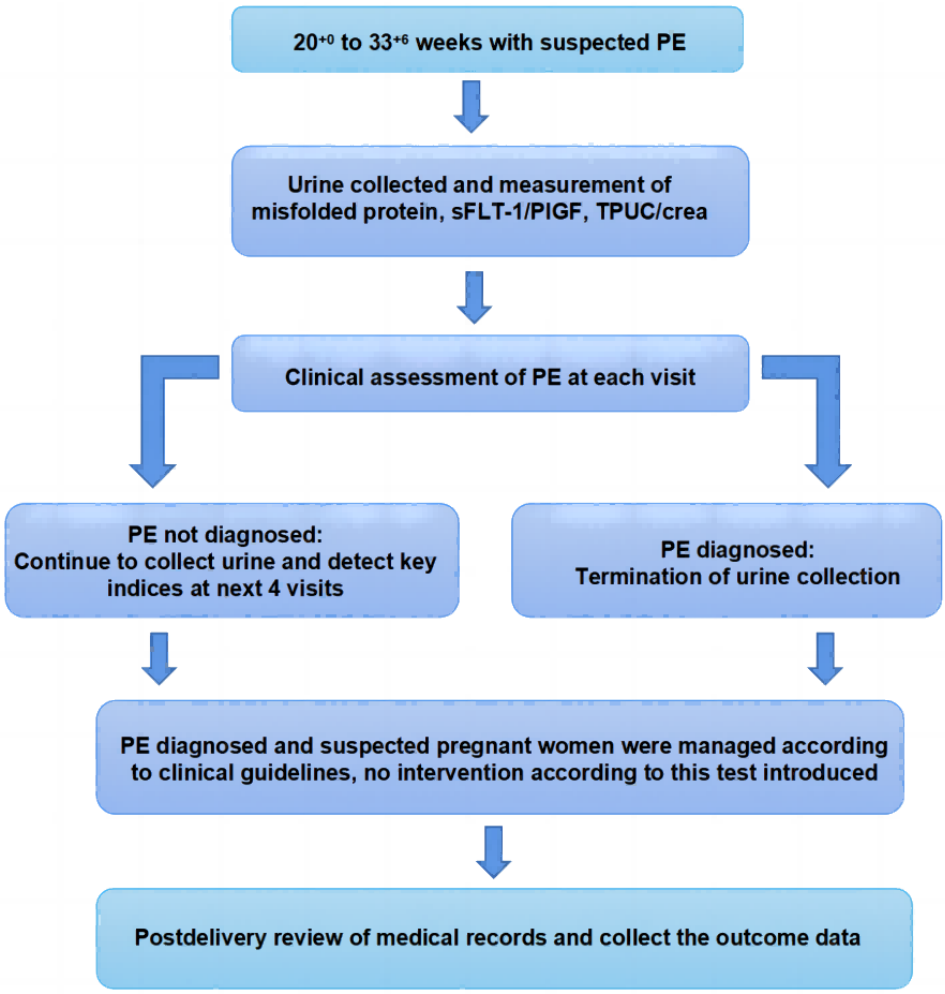
The primary objective of this study is to assess the short-term predictive potential of the new congophilia-based detection tool for PE onset in pregnant women with a clinical suspicion of PE. That is, we aim to confirm whether the urine misfolded protein level can be used to rule in or rule out PE in the short term. The secondary objectives are to evaluate whether the urine misfolded protein level correlates with PE-related maternal or neonatal adverse outcomes and to establish an accurate PE prediction model by combining misfolded protein values and multiple indicators.

Methods

Study Design

This is a prospective noninterventional clinical trial planned in accordance with the principles of evidence-based medicine using the PICO (patient, problem, or population; investigated condition; comparison; and outcome) criteria. The study procedure is outlined in Figure 1.

Figure 1. Flowchart of participants with suspected preeclampsia (PE) in the trial. Eligible pregnant women will be enrolled, and consecutive urine samples will be collected at each visit. Urine samples will be blinded and tested for misfolded proteins and other PE-related biomarkers. No intervention according to the test results will be introduced. Required clinical information will be collected from patients' medical records. crea: creatinine; PlGF: placental growth factor; sFLT-1: soluble FMS-like tyrosine kinase 1; TPUC: Total Protein in Urine.



Ethical Considerations

The trial is being conducted in accordance with ethical principles derived from the Declaration of Helsinki and is in line with Good Clinical Practice and applicable regulatory requirements. The clinical research ethics committee of Women's Hospital, School of Medicine, Zhejiang University has reviewed the trial protocol, and full ethical approval has been granted (IRB-20230198-K). Each woman identified as eligible for the study is required to give written informed consent, including but not limited to, for primary data collection and secondary analyses of research data prior to inclusion in the trial.

Apart from sample collection and required assessments during follow-up, the study does not involve any further impact on the patients' clinical procedures. The patients' PE status will be kept confidential from laboratory technicians, and neither the investigator nor the patient will know the detection results, which ensures that the clinical therapeutic scheme and pregnancy outcomes will not be affected.

Recruitment

Potential participants will be identified by the research team from the antenatal clinic at Women's Hospital, School of Medicine, Zhejiang University. Eligible women must meet all inclusion criteria without violating any of the exclusion criteria (Textbox 1) and will be provided with the participant information and consent form to sign. A research team member will provide a verbal explanation of the trial, including a description of the trial processes, the voluntary nature of the trial, and that a decision of whether or not to participate will not affect normal clinical care. No trial-related procedures will be performed on any individual without their prior written informed consent. All participants will be followed up until 42 days postpartum.

Textbox 1. Inclusion and exclusion criteria for determining trial eligibility.

Inclusion criteria

1. Aged ≥18 years.
2. Gestational week 20+0 to 33+6.
3. Signed written informed consent.
4. Single pregnancy.
5. Clinically suspected preeclampsia (PE), meeting one or more of the following criteria:

(i) new onset of elevated blood pressure (systolic ≥130 mmHg and/or diastolic ≥80 mmHg);

(ii) aggravation of preexisting hypertension (increase of more than 30 mmHg systolic/15 mmHg diastolic from the basic blood pressure in patients without hypertension, or a significant increasing trend or increase beyond the controlled level based on the original treatment for patients with hypertension);

(iii) new onset of proteinuria (no urinary tract infection);

(iv) one or more clinical symptoms indicate suspected PE (other possible causes have been ruled out): upper abdominal pain, headache with impaired vision, fetal growth restriction, thrombocytopenia (platelets count<100×10^9/L), liver function impairment (elevated blood concentrations of liver transaminases up to twice the normal concentration), and renal impairment (serum creatinine>1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease).

Exclusion criteria

1. Confirmed diagnosis of PE/chronic hypertension with PE (superimposed PE).
2. Confirmed diagnosis of eclampsia.
3. Confirmed diagnosis of hemolysis with a microangiopathic blood smear, elevated liver enzymes, and low platelets (HELLP syndrome).
4. Fetal chromosomal abnormalities.
5. Concomitant participation in another clinical study.
6. Received investigational intervention drugs in the past 3 months.
7. Visible hematuria.
8. Preexisting renal disease.

Sample Size

The target negative predictive value (NPV) is 99% and the target positive predictive value (PPV) is 54.0%. A positive test rate of 15% is assumed. The Type I error is set to .05. A sample size of 280 should be sufficient to detect NPV>90% and PPV>25% with 80% power. Therefore, at least 300 eligible participants will be included in this study considering a dropout rate of 6%. To avoid an overrepresentation of cases of late-onset PE, no more than 50% of the enrolled participants will be at 32 weeks gestation or above and no less than 20% of the enrolled participants will be at gestational week below 28+0 at inclusion.

Study Groups: Classification of Cases and Controls

Standard diagnostic criteria [24,25] for PE are new onset of hypertension (systolic blood pressure≥140 mmHg or diastolic blood pressure≥90 mmHg measured on two occasions at least 4 hours apart) and new-onset proteinuria (≥300 mg/day or protein/creatinine ratio ≥0.3 mg/dL) after 20 weeks of gestation. Diagnostic criteria in the absence of proteinuria include any of the following: (1) thrombocytopenia (platelets count<100×10^9/L); (2) liver function impairment (elevated blood concentrations of liver transaminases to twice the normal concentration); (3) renal insufficiency (serum creatinine>1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease); (4) pulmonary edema; and (5) central nervous system abnormalities or visual disturbances.

Cases are defined as patients who develop PE at any time between the first visit to 6 weeks (42 days) postpartum.

Controls are patients who do not develop PE throughout the pregnancy and up to 6 weeks (42 days) postpartum.

Outcome Measures

The primary outcome is the onset of PE after study inclusion. The secondary outcomes are the following maternal and fetal adverse outcomes: maternal death, pulmonary edema, acute renal failure, cerebral hemorrhage, cerebral thrombus, disseminated intravascular coagulation, eclampsia, HELLP syndrome, rupture of placenta, placental abruption, perinatal death, stillbirth, intrauterine growth restriction, small for gestational age, respiratory distress, necrotizing enteritis, intraventricular hemorrhage or subdural and cerebral hemorrhage, neonatal hypoxic encephalopathy, or periventricular leukomalacia. In addition, the date and mode of delivery, fetal weight, and Apgar score are important outcome measures.

Data Collection

Participant data for this study will be collected by investigators and input into an electronic case report form (eCRF). The data will be verified by the principal investigator when suspicious

data entries are noted. The data manager will check the completion of the data for final analysis. The study will include 6 visits plus a postpartum documentation. The first visit starts at enrollment, followed by 4 visits once a week when participants come for their routine prenatal examinations. There will be one visit at delivery as well as one postpartum documentation. On occurrence of pregnancy complications, further visits are possible. The clinical data to be collected during each visit are summarized in Table 1. The time interval between two consecutive visits could be 7±2 days, and adherence to the time schedule is crucial for incorporating participant data into the final analysis.

Table 1. Summary of the data collection procedure and timeline.

Data collected	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Delivery	Postpartum	Unscheduled visit
Inclusion/exclusion criteria	✓							
Informed consent	✓							
General baseline feature	✓							
Chronic history	✓							
Pregnancy history	✓							
Concomitant medication	✓	✓	✓	✓	✓	✓	✓	✓
BMI	✓	✓	✓	✓	✓			✓
Blood pressure	✓	✓	✓	✓	✓		✓	✓
Sampling and detection	✓	✓	✓	✓	✓			✓
Preeclampsia assessment	✓	✓	✓	✓	✓	✓	✓	✓
Laboratory parameters (blood and urine)	✓	✓	✓	✓	✓			✓
Sonographic data	✓	✓	✓	✓	✓			✓
Delivery outcome						✓		
Pregnant woman status						✓	✓	
Fetal/neonatal status						✓	✓	

Sampling and Detection

Urine Sampling and Storage

All enrolled participants will be provided with a sterile cup to collect no less than 5 milliliters of midstream urine at each visit. The sampled urine tubes will be frozen and stored at –20 °C no later than 4 hours after collection. Samples will be shipped frozen to a local laboratory for further analysis.

Urine Coding

At enrollment, each participant will be assigned a specific study number to protect their anonymity. The leading principal investigators will ensure that the participants' anonymity is maintained in the trial database and during the whole research process. Samples collected from one participant at one time will be labeled with the same number to allow tracking and identification of any aliquot prepared from the original urine and for sample programming in laboratory analyzers. The test results will be held securely and separately from the eCRFs, ensuring that clinical decisions will not be influenced by the test results.

Laboratory Detection

Urine samples will be thawed at room temperature and centrifuged at 3000 rpm for 10 minutes. The supernatant will be used for detection.

Urine misfolded proteins will be detected by Pre-Eclampsia Detection Kit (CercaTest RED, Shuwen, China) since misfolded proteins can selectively bind to the Congo Red dye. When a mixture of the Congo Red and urine from a pregnant woman is loaded onto a chromatographic column mounted in a detection cuvette, the presence (positive) or absence (negative) of misfolded proteins can be determined based on the color of the eluent in the cuvette. The eluent will also be applied for quantitative measurement using the HACH DR1900 instrument by detecting the absorbance at a wavelength of 520-600 nanometers.

PlGF and sFLT-1 levels will be detected by the Elecsys PlGF and Elecsys sFlt-1 detection kits (Roche, Germany), respectively. The total urine protein/creatinine ratio will be detected by the Total Protein in Urine/CSF (TPUC) Kit and Creatinine Kit (Mindray, China), all according to the manufacturers' instructions.

Selection of Predictor Variables

According to the objective of this study, the misfolded protein level in urine will be considered as a predictor candidate for PE onset or adverse outcomes. Other preset variables include: (1) demographic factors, including high-risk factors of PE; (2) urine biomarkers reported in the literature; (3) medication; and (4) routine clinical variables or laboratory tests in daily practice (Textbox 2). The determination of valid variables will be based

on the statistical analysis results with a significance level of $P<.05$.

Textbox 2. Preset variable candidates for model development.

Demographic factors

- Age
- BMI
- Conception mode
- Parity
- Preexisting hypertension, diabetes, autoimmune diseases (systemic lupus erythematosus, antiphospholipid syndrome)

Urine biomarkers

- Misfolded proteins
- Placental growth factor
- Soluble FMS-like tyrosine kinase 1
- Total protein
- Creatinine

Medication

- Aspirin
- Antihypertensive drugs

Routine clinical variables or laboratory tests

- Blood pressure
- Aspartate aminotransferase
- Lactate dehydrogenase
- Serum creatinine
- Proteinuria (spot urine protein, 24-hour urine protein)
- Uterine artery pulse index

Statistical Analysis

All variables will be compared between case and control groups. Either parametric or nonparametric tests will be applied for continuous variables and χ^2 tests will be used for categorical variables. Receiver operating characteristic analysis will be used when applicable. Univariable or multivariable logistic regression will be applied to develop the prediction models. All *P* values will be two-tailed. The statistical analysis will be run on SPSS version 27 (IBM) statistical software.

Results

The study is currently in the patient recruitment phase. Study recruitment started in July 2023. As of March 2024, a total of 251 pregnant women with clinical suspicion of PE have been enrolled in the trial, who will be continuously followed up and monitored for their PE status until 42 days postpartum. Statistical analysis is scheduled to start after all participants reach the follow-up endpoint and complete clinical data are collected.

Discussion

Study Implications

Many potential PE biomarkers have been identified using samples from patients with a confirmed diagnosis of PE in comparison with samples obtained from normal pregnancies, which represents a convenient and pragmatic approach for biomarker identification. Although these studies have generated excellent candidate biomarkers for PE detection, there has been less focus on biomarkers that can be used in PE risk prediction. It is possible that biomarkers that are differentially expressed in patients with PE versus those without will fail in a predictive verification study. Thus, a prospective cohort with an uncertain subsequent PE status would provide the best avenue for exploring PE prediction models. To our best knowledge, this is the first prospective study to explore the predictive value of a congophilia-based detection tool in pregnant women with a clinical suspicion of PE in China. The study will be conducted in a high-quality tertiary hospital focused on women's health. Maternal age of 35 years or older; nulliparity; and preexisting hypertension, diabetes, and autoimmune diseases (eg, systemic lupus erythematosus and antiphospholipid syndrome) are the main high-risk factors for PE [25] and will be included as

predictive variables in our analysis. High-risk pregnant women are recommended to use low-dose aspirin to prevent PE; therefore, it is appropriate to consider medication with aspirin as a variable candidate. The crucial biomarkers of PE [22,23], such as PlGF, sFLT-1, and routine clinical variables or laboratory tests, are also under evaluation to build a prediction model. Another important feature of this study is the use of blinding, which ensures that the participants' laboratory data have no influence on the diagnosis of PE as well as the clinical decisions of treatment.

PE remains one of the most severe pregnancy complications associated with substantial maternal and perinatal morbidity. With current pregnancy trends of advancing age and obesity, the morbidity of PE might increase inevitably in the future. Since the only definitive treatment for PE is to terminate the pregnancy, early screening and continuous monitoring during pregnancy are particularly important for pregnant women with high risk of PE. No effective screening test for PE has been identified. The commonly used clinical screening methods are mostly based on blood samples with precise instruments [26-28], which limits the ability for home self-inspection and timely identification of the disease. Congophilia detection represents a promising new approach for the detection of PE by targeting the misfolded proteins in urine, providing a simple, rapid, and cost-effective method for early diagnosis of this complex condition. This method can be performed using small volumes of urine and no additional instrument is needed, making it suitable for use in resource-limited settings and even as a potential home self-test. Therefore, the affordable, noninvasive, and simple use of this POCT detection tool will enable its wide accessibility for bedside use in a central hospital, low-resource settings, and even at home, which would significantly reduce the serious socioeconomic burden attributed to PE.

Limitations

Although use of a prospective cohort in undiagnosed populations provides the best avenue for discovering predictive biomarkers, these markers or their combinations must be rigorously validated in internal/external cohorts to ensure their potential for PE prediction. The single-center nature of this study and prospective recruitment may imply the potential for selection bias. In addition, the enrollment was mainly conducted at prenatal clinics, and this might introduce selection bias regarding the severity of disease, as women with sudden onset of organ complications are more often seen at the emergency clinic. Therefore, future investigations with larger populations, along with assessment of the long-term outcomes of infants will be necessary to ensure the accuracy of the prediction model obtained in this trial and to establish the clinical utility of this tool for routine use in pregnancy care.

Conclusions

This study aims to provide comprehensive evidence on urine misfolded proteins alone or combined with other indicators as a short-term predictive tool for PE. Accurate prediction of PE will allow for proactive management of pregnant women with clinical high risks, and possibly reduce the adverse maternal and fetal outcomes and health care costs associated with hospitalization.

Acknowledgments

We are immensely grateful for the contributions of all investigators from the hospitals and local laboratories; their support is essential for conducting this study. In addition, all study participants are highly appreciated for their nonnegligible contribution to the research. This work is supported by Zhejiang Provincial Ten Thousand Plan for Technological Innovation Leading Talents (2020R52050), the Natural Science Foundation of Zhejiang Province (LQ19H040017), Zhejiang Province Health Innovative Talent Project (A0466), Key Projects of the Science and Technology Co-construction by National Administration of Traditional Chinese Medicine and Zhejiang Provincial Administration of Traditional Chinese Medicine (GZY-ZJ-KJ-23082), and International Cooperation Seed Program Project of Women's Hospital, Medical School of Zhejiang University (GH2024005).

Authors' Contributions

All authors contributed to the overall study design and specific methodologies. The main idea of this study was conceived by XL and XB in collaboration. They jointly take responsibility for the integrity of the data and the accuracy of the data analysis. MY and XY prepared the first draft of the manuscript with considerable input from HT, YT, and JF, and revised the manuscript based on the feedback of other authors. YW, YF, JS, YN, YY, YW, and PL will carry out the recruitment and data collection. All authors have critically reviewed, edited, and approved the final version of the manuscript.

Conflicts of Interest

XL, XY, and MY are employed by Shuwen Biotech. The other authors have no conflicts of interest to declare.

References

1. Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. Lancet 2005;365(9461):785-799. [doi: 10.1016/S0140-6736(05)17987-2] [Medline: 15733721]
2. Jena MK, Sharma NR, Petitt M, Maulik D, Nayak NR. Pathogenesis of preeclampsia and therapeutic approaches targeting the placenta. Biomolecules 2020 Jun 24;10(6):953 [FREE Full text] [doi: 10.3390/biom10060953] [Medline: 32599856]

3. Ives CW, Sinkey R, Rajapreyar I, Tita AT, Oparil S. Preeclampsia-Pathophysiology and clinical presentations: JACC state-of-the-art review. J Am Coll Cardiol 2020 Oct 06;76(14):1690-1702 [FREE Full text] [doi: 10.1016/j.jacc.2020.08.014] [Medline: 33004135]
4. Salam R, Das J, Ali A, Bhaumik S, Lassi Z. Diagnosis and management of preeclampsia in community settings in low and middle-income countries. J Family Med Prim Care 2015;4(4):501-506 [FREE Full text] [doi: 10.4103/2249-4863.174265] [Medline: 26985406]
5. Walker JJ. Pre-eclampsia. Lancet 2000 Oct 07;356(9237):1260-1265. [doi: 10.1016/S0140-6736(00)02800-2] [Medline: 11072961]
6. Redman C. The six stages of pre-eclampsia. Pregnancy Hypertens 2014 Jul;4(3):246. [doi: 10.1016/j.preghy.2014.04.020] [Medline: 26104649]
7. Roberts J, Hubel C. The two stage model of preeclampsia: variations on the theme. Placenta 2009 Mar;30(Suppl A):S32-S37 [FREE Full text] [doi: 10.1016/j.placenta.2008.11.009] [Medline: 19070896]
8. Cruz MO, Gao W, Hibbard JU. Obstetrical and perinatal outcomes among women with gestational hypertension, mild preeclampsia, and mild chronic hypertension. Am J Obstet Gynecol 2011 Sep;205(3):260. [doi: 10.1016/j.ajog.2011.06.033] [Medline: 22071056]
9. Poon LC, Shennan A, Hyett JA, Kapur A, Hadar E, Divakar H, et al. The International Federation of Gynecology and Obstetrics (FIGO) initiative on pre-eclampsia: a pragmatic guide for first-trimester screening and prevention. Int J Gynaecol Obstet 2019 May 20;145(Suppl 1):1-33 [FREE Full text] [doi: 10.1002/ijgo.12802] [Medline: 31111484]
10. James PR, Nelson-Piercy C. Management of hypertension before, during, and after pregnancy. Heart 2004 Dec 01;90(12):1499-1504 [FREE Full text] [doi: 10.1136/hrt.2004.035444] [Medline: 15547046]
11. Duley L, Meher S, Jones L. Drugs for treatment of very high blood pressure during pregnancy. Cochrane Database Syst Rev 2013 Jul 31;2013(7):CD001449 [FREE Full text] [doi: 10.1002/14651858.CD001449.pub3] [Medline: 23900968]
12. Guidelines Review Committee, Sexual and Reproductive Health and Research WHO Team. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia. Geneva: World Health Organization; 2011.
13. Hinduja A. Posterior reversible encephalopathy syndrome: clinical features and outcome. Front Neurol 2020 Feb 14;11:71 [FREE Full text] [doi: 10.3389/fneur.2020.00071] [Medline: 32117030]
14. Rolnik DL, Wright D, Poon LCY, Syngelaki A, O'Gorman N, de Paco Matallana C, et al. ASPRE trial: performance of screening for preterm pre-eclampsia. Ultrasound Obstet Gynecol 2017 Oct 24;50(4):492-495 [FREE Full text] [doi: 10.1002/uog.18816] [Medline: 28741785]
15. Soongsatitanon A, Phupong V. Prediction of preeclampsia using first trimester placental protein 13 and uterine artery Doppler. J Matern Fetal Neonatal Med 2022 Nov 16;35(22):4412-4417. [doi: 10.1080/14767058.2020.1849127] [Medline: 33198548]
16. Yliniemi A, Makikallio K, Korpimaki T, Kouru H, Marttala J, Ryynanen M. Combination of PAPPA, fhCGβ, AFP, PlGF, sTNFR1, and maternal characteristics in prediction of early-onset preeclampsia. Clin Med Insights Reprod Health 2015;9:13-20 [FREE Full text] [doi: 10.4137/CMRH.S21865] [Medline: 26106266]
17. Audibert F, Benchimol Y, Benattar C, Champagne C, Frydman R. Prediction of preeclampsia or intrauterine growth restriction by second trimester serum screening and uterine Doppler velocimetry. Fetal Diagn Ther 2005 Dec 15;20(1):48-53. [doi: 10.1159/000081369] [Medline: 15608460]
18. Buhimschi IA, Nayeri UA, Zhao G, Shook LL, Pensalfini A, Funai EF, et al. Protein misfolding, congophilia, oligomerization, and defective amyloid processing in preeclampsia. Sci Transl Med 2014 Jul 16;6(245):245ra92. [doi: 10.1126/scitranslmed.3008808] [Medline: 25031267]
19. Li X, Liu X, Xu J, Du J, Cuckle H. Late pregnancy screening for preeclampsia with a urinary point-of-care test for misfolded proteins. PLoS One 2020 May 20;15(5):e0233214 [FREE Full text] [doi: 10.1371/journal.pone.0233214] [Medline: 32433710]
20. National Collaborating Centre for Women's and Children's Health (UK). Hypertension in pregnancy: the management of hypertensive disorders during pregnancy. NICE Clinical Guidelines, No. 107. London: RCOG Press; 2010.
21. Wright D, Syngelaki A, Akolekar R, Poon LC, Nicolaides KH. Competing risks model in screening for preeclampsia by maternal characteristics and medical history. Am J Obstet Gynecol 2015 Jul;213(1):62. [doi: 10.1016/j.ajog.2015.02.018] [Medline: 25724400]
22. Tang P, Xu J, Xie B, Wang Q. Use of serum and urinary soluble sFlt-1 and PLGF in the diagnosis of preeclampsia. Hypertens Pregnancy 2017 Feb 11;36(1):48-52. [doi: 10.1080/10641955.2016.1237642] [Medline: 27834501]
23. Zhang K, Zen M, Popovic NL, Lee VW, Alahakoon TI. Urinary placental growth factor in preeclampsia and fetal growth restriction: an alternative to circulating biomarkers? J Obstet Gynaecol Res 2019 Sep;45(9):1828-1836. [doi: 10.1111/jog.14038] [Medline: 31257726]
24. Xie X. Chinese Obstetrics and Gynecology, 9th edition. Beijing: People's Medical Publishing House; 2018:83-91.
25. ACOG. Gestational hypertension and preeclampsia: ACOG Practice Bulletin Summary, Number 222. Obstet Gynecol 2020 Jun;135(6):1492-1495. [doi: 10.1097/AOG.0000000000003892] [Medline: 32443077]

26. Zhong Y, Zhu F, Ding Y. Serum screening in first trimester to predict pre-eclampsia, small for gestational age and preterm delivery: systematic review and meta-analysis. BMC Pregnancy Childbirth 2015 Aug 25;15(1):191 [FREE Full text] [doi: 10.1186/s12884-015-0608-y] [Medline: 26303460]
27. Grill S, Rusterholz C, Zanetti-Dällenbach R, Tercanli S, Holzgreve W, Hahn S, et al. Potential markers of preeclampsia--a review. Reprod Biol Endocrinol 2009 Jul 14;7(1):70 [FREE Full text] [doi: 10.1186/1477-7827-7-70] [Medline: 19602262]
28. Anderson U, Olsson M, Kristensen K, Åkerström B, Hansson S. Review: Biochemical markers to predict preeclampsia. Placenta 2012 Feb;33:S42-S47. [doi: 10.1016/j.placenta.2011.11.021] [Medline: 22197626]

Abbreviations

eCRF: electronic case report form
HELLP: hemolysis, elevated liver enzymes, and low platelets
NPV: negative predictive value
PE: preeclampsia
PICO: patient, problem, or population; investigated condition; comparison; and outcome
PlGF: placental growth factor
POCT: point-of-care testing
PPV: positive predictive value
sFLT-1: soluble FMS-like tyrosine kinase 1

Edited by A Mavragani; submitted 08.11.23; peer-reviewed by G Shen, X Liu; comments to author 13.03.24; revised version received 19.03.24; accepted 21.03.24; published 26.04.24.

Please cite as:
Tang H, Tian Y, Fang J, Yuan X, Yao M, Wang Y, Feng Y, Shu J, Ni Y, Yu Y, Wang Y, Liang P, Li X, Bai X
Detection of Urinary Misfolded Proteins for Imminent Prediction of Preeclampsia in Pregnant Women With Suspected Cases: Protocol for a Prospective Noninterventional Study
JMIR Res Protoc 2024;13:e54026
URL: https://www.researchprotocols.org/2024/1/e54026
doi:10.2196/54026
PMID:38669061

Protocol

Gait Features in Different Environments Contributing to Participation in Outdoor Activities in Old Age (GaitAge): Protocol for an Observational Cross-Sectional Study

Merja Rantakokko[1,2,3], PhD; Emmi Matikainen-Tervola[3], MSc; Eeva Aartolahti[3], PhD; Sanna Sihvonen[3], PhD; Julija Chichaeva[3], MSc; Taija Finni[4], PhD; Neil Cronin[4,5], PhD

[1]Faculty of Sport and Health Sciences, Gerontology Research Center, University of Jyväskylä, Jyväskylä, Finland

[2]The Wellbeing Services County of Central Finland, Jyväskylä, Finland

[3]Institute of Rehabilitation, JAMK University of Applied Sciences, Jyväskylä, Finland

[4]Faculty of Sport and Health Sciences, Neuromuscular Research Centre, University of Jyväskylä, Jyväskylä, Finland

[5]School of Sport and Exercise, University of Gloucestershire, Gloucester, United Kingdom

Corresponding Author:
Merja Rantakokko, PhD
Faculty of Sport and Health Sciences
Gerontology Research Center
University of Jyväskylä
PO BOX 35 (viv)
Jyväskylä, 40014
Finland
Phone: 358 503016860
Email: merja.h.rantakokko@jyu.fi

Abstract

Background: The ability to walk is a key issue for independent old age. Optimizing older peoples' opportunities for an autonomous and active life and reducing health disparities requires a better understanding of how to support independent mobility in older people. With increasing age, changes in gait parameters such as step length and cadence are common and have been shown to increase the risk of mobility decline. However, gait assessments are typically based on laboratory measures, even though walking in a laboratory environment may be significantly different from walking in outdoor environments.

Objective: This project will study alterations in biomechanical features of gait by comparing walking on a treadmill in a laboratory, level outdoor, and hilly outdoor environments. In addition, we will study the possible contribution of changes in gait between these environments to outdoor mobility among older people.

Methods: Participants of the study were recruited through senior organizations of Central Finland and the University of the Third Age, Jyväskylä. Inclusion criteria were community-dwelling, aged 70 years and older, able to walk at least 1 km without assistive devices, able to communicate, and living in central Finland. Exclusion criteria were the use of mobility devices, severe sensory deficit (vision and hearing), memory impairment (Mini-Mental State Examination ≤23), and neurological conditions (eg, stroke, Parkinson disease, and multiple sclerosis). The study protocol included 2 research visits. First, indoor measurements were conducted, including interviews (participation, health, and demographics), physical performance tests (short physical performance battery and Timed Up and Go), and motion analysis on a treadmill in the laboratory (3D Vicon and next-generation inertial measurement units [NGIMUs]). Second, outdoor walking tests were conducted, including walking on level (sports track) and hilly (uphill and downhill) terrain, while movement was monitored via NGIMUs, pressure insoles, heart rate, and video data.

Results: A total of 40 people (n=26, 65% women; mean age 76.3, SD 5.45 years) met the inclusion criteria and took part in the study. Data collection took place between May and September 2022. The first result is expected to be published in the spring of 2024.

Conclusions: This multidisciplinary study will provide new scientific knowledge about how gait biomechanics are altered in varied environments, and how this influences opportunities to participate in outdoor activities for older people.

International Registered Report Identifier (IRRID): RR1-10.2196/52898

(JMIR Res Protoc 2024;13:e52898) doi:10.2196/52898

KEYWORDS

walking; aging; environment; biomechanics; kinematics; spatiotemporal; gait; GaitAge; observational cross-sectional study; gerontology; geriatric; geriatrics; older adult; older adults; elder; elderly; older person; older people; ageing; aging; health disparities; health disparity; assessment; assessments; physical test; physical tests; interview; interviews; biomechanic; activities; outdoor; activity; movement analysis; analysis of walk; posture; free living

Introduction

Overview

The ability to walk is a key issue in maintaining independence in old age. Walking difficulties hinder the ability to manage tasks of daily life and may lead to the need for help and an increased risk of disability and institutionalization [1,2]. With increasing age, changes in gait are common [3]. Walking speed declines with increasing age [4], due to changes in step or stride length, as well as slower cadence. Changes in ankle, knee, and hip motion and center of pressure are also common [4,5]. Gait variability, defined as fluctuations in spatiotemporal characteristics between steps increases with age [3,6] and is associated with increasing risk of developing mobility difficulties [7].

Spatiotemporal and kinematic parameters of gait provide important information, but outcomes are usually based on a treadmill or laboratory overground gait, which may be significantly different from walking outdoors. Only a few studies have examined differences in gait biomechanics between laboratory and outdoor circumstances among older people. In the studies of Schmitt et al [6] and Renggli et al [8] significant differences in several spatiotemporal parameters were found between outdoor walking and treadmill walking. On a treadmill, a decrease in walking speed, an increase in double support duration, shorter stride length, and decreased cadence were found compared to outdoor walking [6,8]. While these assessments provided knowledge about issues such as fall prediction [9] many uncertainties remain. For example, the environment where the activity takes place is typically not recorded, so it is not known whether changes in gait represent a response to some specific environmental demand or whether it is an expression of a person's usual performance. Taking into account environmental features, and using wearable sensors, such as inertial measurement units (IMUs) at the same time could add important information about walking speed and body orientation that is needed to understand how people move and adapt to challenges encountered in different environmental circumstances.

The ability to adapt gait to environmental demands may be crucial for preventing or reducing restrictions in participation on outdoor activities. The concept of life-space mobility gives us an idea about how well people are able to access different community amenities, attend different events, or be physically active, thus describing a person's opportunities for participation outside the home [10]. Life-space mobility refers to the spatial area in which a person moves in daily life, taking into account distance, frequency, and any assistance needed for movement. Restrictions in participating in out-of-home activities are known to correlate, for example, with functional limitations, pain, depression, and chronic conditions [11-13]. Previously it has also been shown that life-space mobility correlates with, for example, quality of life [14,15], physical functioning, and autonomy [16], and that restrictions on it may lead to cognitive decline [17,18], falls and fractures [19], nursing home admission [20], or even mortality [21]. However, research on the association between gait parameters and the impact on life-space mobility is scarce.

Study Objectives

The aim of the "Gait features in different environments contributing to participation in outdoor activities in old Age (GaitAge)" project is to study whether IMUs are valid for detecting traditional (gait cycle event timings) and novel (heading and torso angle) gait parameters among older people in laboratory and outdoor environments. We will focus on how gait parameters change when walking on a treadmill in a laboratory compared to an outdoor environment and in a hilly environment compared to walking in a level outdoor environment. Finally, we will study whether alterations in gait parameters in different environments are associated with outdoor participation (measured via life-space mobility and physical activity) in older people when health and demographics are taken into account.

Methods

Recruitment

Our target was to recruit a total of 40 participants for the study. First, we invited 15 participants from our pilot study conducted between May and June 2021 (not published), who had given their permission to contact them again. These participants were recruited through the University of the Third Age in Jyväskylä by advertising in a public lecture in May 2021. They were contacted again in April 2022 to enquire about their interest in taking part in this study. All of them were willing to take part in the study and met the inclusion criteria.

Additional recruitment to reach a total of 40 participants was done in June 2022 through 5 central Finland senior organizations. Leaders of these organizations were contacted via email and were asked to forward an information letter and invitation to all members of the organizations. Those members who were interested in taking part in the study were asked to contact researchers via email or by phone, after which a short phone interview was scheduled.

A researcher called potential participants and conducted a short telephone interview to screen their suitability and to confirm their willingness to participate. Inclusion criteria were community-dwelling, at least 70 years of age during the current year, able to walk at least 1 km without assistive devices, able

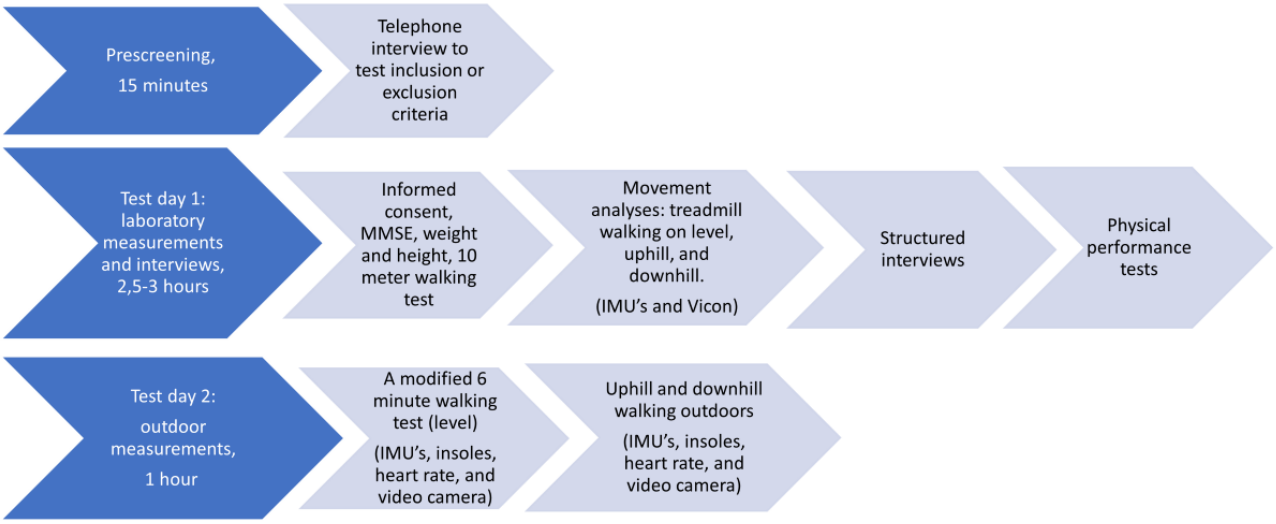
to communicate, and living in central Finland. Exclusion criteria were the use of mobility devices, severe sensory deficit (vision and hearing), neurological conditions (eg, stroke, Parkinson disease and multiple sclerosis), and memory impairment (Mini-Mental State Examination [MMSE]≤23) [22]. Memory impairment was assessed during the initial phone interview by asking about diagnosed memory illness and screened with an MMSE test during the first research visit to the laboratory.

Recruitment continued until 40 participants who met the inclusion criteria and were willing to participate were reached.

Data Collection

The data collection procedure is shown in Figure 1. Data collection took place between May 27, 2022, and September 28, 2022. The data collection protocol included two visits (1) indoor walking measurements and interviews that were conducted at the University of Jyväskylä sport and exercise laboratory and (2) approximately 4 days later, outdoor walking measurements were conducted at the local sports track and hilly terrain next to the sports track. For some participants, the time between indoor and outdoor walking measurements was longer than 3 days due to weather conditions, as it was not possible to perform outdoor measurements when it was raining. One participant was not able to participate in outdoor measurements because of a nonstudy-related injury after the laboratory measurements. All the measurements and interviews were conducted by research group members with help from research assistants trained for the task.

Figure 1. Data collection protocol of GaitAge project. IMU: Inertial measurement unit; MMSE: Mini-Mental State Examination.



Laboratory Measurements and Interviews

Overview

For the indoor research visit, participants were instructed to wear sneakers or running shoes and clothes that were suitable for physical activity, preferably as tight as possible to facilitate the attachment of reflective markers for 3D motion analysis. If the participant did not have shorts or tight leggings, they were provided with tight shorts. Participants were instructed to eat a light meal or breakfast and to avoid alcohol use 24 hours before the measurements.

At the start of the research visit, the MMSE test was conducted and written informed consent was obtained. Participants had the possibility to ask questions about the study and the study protocol was explained to them. After that, weight and height were measured.

10-Meter Walking Test

Indoor walking tests started with a 10-meter walking test to identify participants' walking speed. The time in seconds was measured using photocells placed 10 meters apart in a hallway. Participants were instructed to walk through the photocells at their usual walking speed, starting 2 meters before the first pair of photocells and stopping 2 meters after the second pair of photocells. The test was done once by each participant. Time was changed into walking speed (in m/s) and this information was used to determine the speed for the subsequent treadmill tests.

Next-Generation Inertial Measurement Units

After the 10-meter walking test, next-generation inertial measurement unit (NGIMU) devices (x-io Technologies Limited) were attached. NGIMU is an IMU sensor that includes a triple-axis accelerometer (±16 g; 400 Hz sample rate), triple-axis gyroscope (rotations ±2000°/s; 400 Hz sample rate), and triple-axis magnetometer (magnetic field ±1300 µT). NGIMUs also include analog inputs (8-channel; 0-3.1 V; 10-bit; 1 kHz sampling rate). One NGIMU including housing has dimensions of 56×39×18 mm and weighs 46 g. A total of 8 NGIMU devices were attached to participants with Velcro straps and leukoplast tape.

NGIMUs were placed on both legs above the third metatarsal, on the lateral mid shank, anterior thigh 5 cm above the knee joint, and to the middle of the spine just above the spina iliaca posterior superior and upper half of sternum.

VICON 3D Motion Analysis

3D motion capture (Vicon Motion Systems) was used to obtain ground truth values for indoor walking tests. A total of 16 Vicon Vero cameras were positioned around the space where treadmill walking took place. A total of 26 reflective markers were

attached to participants with 2-sided tape and secured with leukoplast tape and a self-adhesive bandage (Textbox 1). Data were sampled using Nexus software (Vicon Motion Systems).

Textbox 1. Placement (right and left legs and sides of the body) of the reflective markers for indoor 3D motion analysis.

- Hallux
  - Top of hallux nail
- Toe
  - Proximal head of second metatarsal
- Heel
  - Heel, at the same level as toe marker
- Ankle
  - Lateral malleoli
  - Medial malleoli (used only for calibration)
- Shank
  - Midway along the shank, laterally (left and right)
- Knee
  - Knee extension—flexion axis and lateral side
  - Knee extension—flexion axis and medial side
- Thigh
  - Midway between KNEE marker (lateral side) and spina iliaca anterior superios (SIAS)
- SIAS
- Spina iliaca posterior superior
- Thoracic vertebrae 10
- Cervical vertebrae 7 (C7)
- Sternum
  - Lowest part of the sternum
- Clavicula
  - Between the heads of clavicula

NGIMUs and Vicon data were synchronized with an analog trigger, which sent simultaneous pulses to the master NGIMU (400 Hz) and to Nexus software (1000 Hz).

Treadmill Walking Tests

Level Treadmill Walking

First, a safety harness was put on the participant. Second, the participant walked on the treadmill (Gymstick Walking Pad Pro 44 cm×120 cm) for 1-5 minutes for familiarization. Treadmill speed was gradually increased in increments of 0.5 km/h until the participant's walking speed from the 10-meter test was achieved or when the participant indicated that he or she did not wish to increase the speed. Participants were allowed to take support from the front and side rails if necessary for balance at any point during assessments, but they were not allowed to hold the rails during the full measurements.

After familiarization, the treadmill was stopped. The actual test started with 5 seconds of standing still in an anatomical posture. When starting, the speed was gradually increased toward the speed obtained from the 10-meter walking test and once achieved, the participant was asked to walk for 3 minutes at that speed. After 3 minutes, the treadmill was slowed down and the participant was asked to stand again for 5 seconds in an anatomical posture.

Uphill and Downhill Treadmill Walking

The treadmill was inclined or declined by 5° to correspond with the slope of the outdoor hilly walking tests. The order of test (incline or decline first) was randomly determined by a random number generator. The test speed was determined based on 1-5 minutes of walking at the new gradient, whereby participants were asked to indicate their self-selected speed for uphill or downhill walking. The actual test started with 5 seconds of

standing still in an anatomical posture. Then the speed of the treadmill was gradually increased to the test speed, and participants walked for 2 minutes at that speed. After 2 minutes, the treadmill was stopped, and participants again stood for 5 seconds in an anatomical posture.

Structured Interviews

Overview

Following the walking tests, interviews were conducted including structured questions and questionnaires.

Demographic Information

Demographic information included age, gender, perceived financial situation (from very poor to very good), highest educational status, living arrangements (living alone, with spouse, or with someone else), type of housing (apartment block, row house, semidetached, or detached house), and time of residence in the current house.

Health Condition

Health condition was determined via self-report (5-point scale from good to poor) [23] and by asking about illnesses diagnosed by a doctor from a list of chronic conditions, including different cardiovascular, respiratory, musculoskeletal, and eye diseases, hearing impairment, diabetes, cancer, and incontinence and an open-ended question about any other physician-diagnosed chronic conditions. In addition, participants were asked about whether they had artificial joints and if so, in what joint [23].

Functional Vision

Functional vision was assessed using a 7-item vision function questionnaire (VF-7) [24], which is a modified version of the 14-item vision function questionnaire (VF-14) [25]. The VF-7 comprises 7 activities dependent on functional vision and is validated for use in patients with cataracts. Patients are asked how much difficulty they have doing each activity, with or without glasses. The activities are reading small print; seeing steps, stairs, or curbs; reading traffic, street, or store signs; doing fine handwork; cooking; watching television; and driving in darkness. Each question is scored 4, 3, 2, or 1, respectively, if the participant has no, little, moderate, or a great deal of difficulty performing the activity, and 0 if the participant is unable to perform the activity due to poor vision. If a patient does not do an activity for reasons other than his or her vision, the item in question is not included in the scoring. The final score is obtained by averaging responses across all the relevant activities and multiplying by 25. Scores range from 0 (representing maximum impairment) to 100 (representing no impairment).

Trail-Making Test

Trail-making test (TMT) was used to measure executive functioning [26]. The TMT consists of 2 parts. Part A involves drawing connective lines between circles that are spread over a sheet of paper and are numbered from 1 to 25. Part B involves drawing connective lines between circles including numbers and letters in order (1-A-2-B-3-C-4-...etc). Participants are asked to draw the lines as fast as possible without lifting the pen from the paper. The researcher pointed out possible errors as they occurred and the participant continued doing the task. The time to complete the task was recorded. The maximum accepted time for part A was 100 seconds, and for part B 240 seconds or 4 mistakes.

Depressive Symptoms

Depressive symptoms were assessed with the Center for Epidemiologic Studies Depression scale (CES-D) [27] and balance confidence was assessed with the Activities-specific Balance Confidence scale [28]. History of falls during the previous 12 months was self-reported and separated into injurious and noninjurious falls [29].

Outdoor Mobility

Life-Space Mobility

Life-space mobility was assessed with the Finnish version of the University of Alabama at Birmingham Study of Aging Life-Space Assessment (LSA) [10,30]. The LSA establishes self-reported movement patterns according to specific life-space levels, ranging from within one's dwelling to beyond one's town during the 4 weeks preceding the assessment. For each level of life-space (bedroom, home, outside home, neighborhood, town, and beyond town), participants are asked how many days within a week they attained that level and whether they needed help from another person or used assistive devices. A life-space mobility score was calculated (range 0 to 120), reflecting distance, frequency, and independence of movement. Higher scores indicate a larger life-space.

Environmental Features

Environmental features near the participant's home were assessed using "Perceived environmental barriers for outdoor mobility" (PENBOM) questionnaire [31] and with self-evaluation of the home neighborhood environment, including questions about distances to services, closest grocery store, and walking and cycling routes [23].

Physical Activity

Self-reported level of physical activity was assessed with a 6-point scale [32] modified from Grimby [33] and Mattiasson-Nilo et al [34]. The levels varied from "1" hardly any activity and mostly sitting to "6" performing competitive sports.

Walking Ability and Walking Modifications

Walking ability and walking modifications were evaluated using a standardized questionnaire [35]. The participants were asked whether they had difficulties in walking 2 km with response options (1) able to manage without difficulty, (2) able to manage with some difficulty, (3) able to manage with a great deal of difficulty, (4) able to manage only with the help of another person, and (5) unable to manage even with help. Regarding walking modifications, participants were asked "Have you noticed any of the following changes in walking 2 km?" The response options (yes or no) concerned reduced walking frequency, having given up walking 2 km distances, walking more slowly, and resting while walking the 2 km distance.

Physical Performance Tests

Physical performance tests were performed after the interviews. Lower extremity performance was assessed using the short physical performance battery (SPPB) test following the guidelines of the Finnish Institute of Health and Welfare [36,37], which includes 3 subtests, static balance in 3 different positions, 4-meter walking time, and 5 repetitions of sit-to-stand. The balance test was performed without shoes. The walking test was performed at the usual speed and the sit-to-stand test was performed as fast as possible. Both these tests were performed with shoes on. The possible use of a walking aid during the test was also recorded. All subtest results were recorded in seconds and scored from 0 to 4 points, leading to a maximum of 12 points. Higher SPPB test scores indicate better lower extremity performance.

Functional Mobility

Functional mobility was assessed with the Timed Up and Go (TUG) test [38]. In the TUG test, the participant stands up from a chair, walks 3 meters, turns around, walks back, and sits on the chair. The TUG test was performed twice at the usual walking speed, with the shoes on. Time in seconds was measured using a stopwatch. Both results were recorded, and the best result (shorter time in seconds) was used. A lower TUG test time indicates better mobility.

Treadmill walking tests took approximately 1.5 hours including attachment of NGIMUs, instructions and walking tests with breaks, after which the participant had a 15-30 minute coffee break. Interviews and physical performance tests took approximately 45-60 minutes per participant. The total duration of the research visit to the sport and exercise laboratory was 2.5-3 hours.

Outdoor Measurements

Overview

Walking tests outdoors were performed approximately 4 days after the laboratory visit. Participants were instructed to wear good walking shoes (trainers, running shoes, etc) and clothes suitable for physical activity. Outdoor tests were conducted only on days with suitable weather conditions (no rain), thus for some participants the time between indoor and outdoor measures was longer than 4 days (range 2-20).

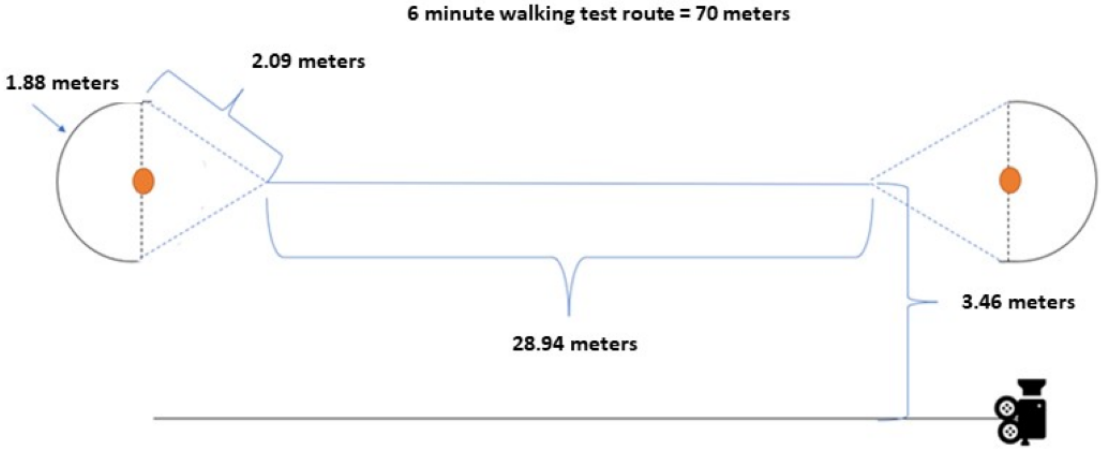
First, participants were equipped with NGIMUs, force-sensitive resistor (FSR)–insoles and a wrist-worn heart rate monitor (Polar Vantage M, Polar, Finland). The same set and placement of NGIMUs were used as in the treadmill walking tests. FSR-insoles were made with two FSRs (18 mm diameter and active area 12.7 mm), which were attached with tape to a thin insole (1-2 mm) and placed under the heel and ball of the foot. The size of the insole was modified according to each participant's feet and FSR-insoles were inserted in participants' shoes replacing the insoles they had in their own shoes. The participants reported that they did not notice having the insoles in their shoes, thus the insoles are not likely to affect the gait parameters. The FSRs were connected to a battery-powered open-source Internet of Things development board (M5StickC PLUS, Interlink Electronics) and force data were sampled at 200 Hz via the board's 12-bit analog-to-digital converter. Internal clocks of the development boards were synchronized before each measurement using an external button connected to the digital pins of the boards. FSR-insoles were connected to a custom mobile phone app via Bluetooth low-energy connection.

The heart rate monitor was placed on the participant's right wrist. The heart rate was measured to monitor exertion during the outdoor walking tests. A GoPro 9 Hero camera (120 Hz; GoPro Inc) was attached to a modified stroller which was pushed alongside the track. A second GoPro Hero camera was placed at the end of the walking track. NGIMUs and GoPro cameras were synchronized with a trigger device, which sent an analog signal to the master NGIMU and simultaneously turned on a light visible by both cameras. For camera calibration, a 5-second video was filmed of a checkerboard calibration matrix located at the same distance from the camera as the participant's walking route.

A Modified 6-Minute Walking Test

Participants walked along a 70 m long route (Figure 2) at the sports track (synthetic track surface) for 6 minutes at a self-selected speed. Rating of perceived exertion was assessed using the Borg scale (range 6-20; 6=no exertion, 20=completely exhausted) [39] at the beginning of the test, after 3 minutes and at the end of the test. A research assistant moved the camera and stroller alongside the participant at a distance of 3.46 meters from the midline of the participant's route. After 6 minutes of walking, the test was stopped and distance was measured to the nearest meter.

Figure 2. Route of a modified 6-minute walking test performed at a sports track.



Uphill and Downhill Walking Outdoors

A walking test in a hilly environment was performed next to the sports track. The steepness of the hill was 5°, and the ground surface was asphalt.

The participants walked at self-selected speed downhill for 20 meters and then after a short break (approximately 10 seconds) walked 20 meters uphill. Downhill and uphill trials were repeated 5 times, that is, 100 meters walking both ways. A research assistant moved the camera and stroller alongside the participant and a second researcher walked behind the participant for safety. Rating of perceived exertion was assessed after every 20 meters, and the heart rate was recorded with the heart rate monitor. Rest breaks were taken between trials as needed.

Data Analysis

Gait Parameters

Several gait parameters will be derived from IMU data. For example, step duration; step length; stance phase duration; swing phase duration; cadence; gait speed; variability of step, swing, or stance duration; and asymmetry of step, swing, or stance duration.

Step duration is defined as time and step length as the length between 2 consecutive contralateral heel strikes. Stride duration is defined as the time between 2 ipsilateral heel strikes. Swing duration is calculated as the time between consecutive toe-off and heel strike of the same foot, and stance duration as the time between consecutive heel strike and toe-off of the same foot. Cadence is defined as steps per minute and step velocity as step length divided by step duration. Variability in gait parameters (within-person differences in steps) is calculated as SD or coefficient of variation (SD divided by mean multiplied by 100%) of certain parameters per participant.

To calculate gait parameters from different IMUs we will use algorithms published in previous literature (eg, [40-43]). New algorithms are developed when necessary.

Vicon Data

Exported 3 dimension motion data are analyzed with open-source Mokka software (Motion kinematic & Kinetic analyzes, biomechanical tool kit, GitHub), where heel strikes and toe-offs are manually determined. In treadmill walking, heel strikes are set to the last frame before the heel marker starts to move backward in the image, that is, at the most anterior point. Toe-offs are set to the last frame before the hallux marker starts to move proximally, that is, at the most posterior point in the image. These analyses are performed by 2 researchers and similarity of identifications is ensured by checking agreement on data. In case of disagreements, event timings are discussed and agreed upon together. Events are then exported to Matlab (b2022; The MathWorks, Inc).

GoPro Camera Data

The GoPro camera data were used as a reference to validate the IMU's in the outdoor environment. From outdoor video data, heel strike and toe-off events and step length are digitized and identified manually. The heel strike is denoted as the first frame when the shoe touches the ground after the swing phase. Toe-off is determined as the last frame when the distal end of the shoe is still on the ground. These analyses are performed by 2 researchers and similarity of identifications is ensured by checking agreement on data. In case of disagreements, event timings are discussed and agreed upon together. ShotCut software (Meltytech, LLC) is used to mark event timings, which are copied to an Excel file (Microsoft Corporation). Timings are converted from frames to seconds using Matlab (MathWorks) and Excel.

Statistical Analyses

To test the validity of IMU sensors, we will use Bland-Altman plots and intra-class correlation coefficients. To compare gait parameters in different environments, we will use appropriate statistical methods depending on data properties, which may include *t* tests and repeated measures ANOVA and mixed effect models. Linear regression analyses are used to study associations with life-space mobility and physical activity. Other statistical testing will be performed where appropriate.

Data Management

All data are handled and registered according to the Finnish Personal Data Act and the European Union Data Protection Act. All data are recorded and analyzed without direct personal recognition information. The research material is carefully

maintained, documented, and stored in password-protected organizational servers.

Ethical Considerations

The study was conducted according to good scientific and clinical practices as laid down by the Declaration of Helsinki. All participants were informed carefully about the study, and they gave their written informed consent prior to any measurements. Data collection included no invasive or potentially physically or psychologically harmful elements beyond what one might experience in everyday life. Only people who were personally able to consent were recruited. Research assistants conducting the data collection were trained for study procedures and the safety of participants during the measurements was ensured. Participants had the possibility to withdraw from the research at any point without any consequences. The ethics committee of the JAMK University of Applied Sciences approved the study (JAMK/40/13.02/2021; January 11, 2021).

Results

The GaitAge data collection is completed. A total of 40 participants participated in indoor measurements and 39 of them in outdoor measurements. Participants were on average 76.3 (range 69-92, SD 5.45) years of age, 65% (n=26) of them were women, and all of them reported being able to walk 2 km without difficulties.

Gait data analyses are underway, and the first results reporting findings of the validation of NGIMUs is expected to be published in spring 2024.

Discussion

Principal Findings

Our project features several strengths. First, for example, a comparison of gait parameters in an outdoor environment and on a treadmill in a laboratory provides fundamental knowledge for studies aiming to use gait parameters to predict progressive neurological problems. We will report how older adults adapt their gait according to variable environmental demands. This study provides findings that can change our view of person-environment interaction processes by providing detailed information about changes in gait parameters in level, uphill, and downhill walking. Second, we will assess whether changes in gait biomechanics induced by environmental demands influence possibilities for general participation in outdoor activities of older people by combining information on gait parameters with life-space mobility. Third, we will explicitly focus on person-environment interaction at the individual level, which will create new study hypotheses and give new perspectives on research in environmental gerontology. Fourth, the study sample of 40 older adults with a comprehensive data set (several walking measures with IMUs, 3D motion analyses and video data, questionnaires, and physical performance tests) will have a multidisciplinary impact by providing information about objective and subjective aspects of gait and mobility in old age.

It should be noted that the study population included older adults without major mobility difficulties or neurological conditions, so the results cannot be generalized to clinical populations. There are also some limitations in the study protocol that will be taken into consideration in forthcoming analyses, for example, differences between measurement protocols for level treadmill walking (3 minutes) and outdoor walking (6 minutes). We will also need additional longitudinal studies to determine whether possible changes in gait in different environments are predictive of changes in mobility capacity.

Conclusions

This research will provide answers to major research questions about the role of the environment in outdoor mobility in old age. This research project could serve as a reference for future research on gait among different patient groups and will serve as a baseline for a longitudinal study, with the aim of exploring whether changes in gait parameters in different environments can be used as early signs of declining health and restricted participation in outdoor activities.

Acknowledgments

The GaitAge project was funded by the Research Council of Finland (330185 to MR). The financial sponsors had no role in the design, implementation, analyses, or reporting of the results. The authors would like to thank Sakari Vekki, Sailee Sansgiri, Olli-Pekka Mattila, and Timo Rantalainen for all the help with data collection and data processing. In addition, we would like to thank Lauri Halme, Mikko Kurkela, Elina Lius, and Marika Salminen for their valuable help with the data collection.

Data Availability

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

Authors' Contributions

MR, TF, and NC performed the concept and design. All authors took part in acquisition of data, drafting the paper, critical revision of the paper, and approved the final paper.

Conflicts of Interest

None declared.

References

1. Hardy SE, Kang Y, Studenski SA, Degenholtz HB. Ability to walk 1/4 mile predicts subsequent disability, mortality, and health care costs. J Gen Intern Med 2011 Feb;26(2):130-135 [FREE Full text] [doi: 10.1007/s11606-010-1543-2] [Medline: 20972641]
2. Rantakokko M, Mänty M, Rantanen T. Mobility decline in old age. Exerc Sport Sci Rev 2013 Jan;41(1):19-25 [FREE Full text] [doi: 10.1097/JES.0b013e3182556f1e] [Medline: 23038241]
3. Jayakody O, Breslin M, Ayers E, Verghese J, Barzilai N, Weiss E, et al. Age-related changes in gait domains: results from the LonGenity study. Gait Posture 2023 Feb;100:8-13 [FREE Full text] [doi: 10.1016/j.gaitpost.2022.11.009] [Medline: 36463714]
4. Ko S, Hausdorff JM, Ferrucci L. Age-associated differences in the gait pattern changes of older adults during fast-speed and fatigue conditions: results from the Baltimore longitudinal study of ageing. Age Ageing 2010 Nov;39(6):688-694 [FREE Full text] [doi: 10.1093/ageing/afq113] [Medline: 20833863]
5. Anderson DE, Madigan ML. Healthy older adults have insufficient hip range of motion and plantar flexor strength to walk like healthy young adults. J Biomech 2014 Mar 21;47(5):1104-1109 [FREE Full text] [doi: 10.1016/j.jbiomech.2013.12.024] [Medline: 24461576]
6. Schmitt AC, Baudendistel ST, Lipat AL, White TA, Raffegeau TE, Hass CJ. Walking indoors, outdoors, and on a treadmill: gait differences in healthy young and older adults. Gait Posture 2021 Oct;90:468-474. [doi: 10.1016/j.gaitpost.2021.09.197] [Medline: 34619613]
7. Brach JS, Studenski SA, Perera S, VanSwearingen JM, Newman AB. Gait variability and the risk of incident mobility disability in community-dwelling older adults. J Gerontol A Biol Sci Med Sci 2007;62(9):983-988 [FREE Full text] [doi: 10.1093/gerona/62.9.983] [Medline: 17895436]
8. Renggli D, Graf C, Tachatos N, Singh N, Meboldt M, Taylor WR, et al. Wearable inertial measurement units for assessing gait in real-world environments. Front Physiol 2020;11:90 [FREE Full text] [doi: 10.3389/fphys.2020.00090] [Medline: 32153420]
9. Ihlen EAF, van Schooten KS, Bruijn SM, van Dieën JH, Vereijken B, Helbostad JL, et al. Improved prediction of falls in community-dwelling older adults through phase-dependent entropy of daily-life walking. Front Aging Neurosci 2018;10:44 [FREE Full text] [doi: 10.3389/fnagi.2018.00044] [Medline: 29556188]
10. Baker PS, Bodner EV, Allman RM. Measuring life-space mobility in community-dwelling older adults. J Am Geriatr Soc 2003 Nov;51(11):1610-1614. [doi: 10.1046/j.1532-5415.2003.51512.x] [Medline: 14687391]
11. Dunlap PM, Rosso AL, Zhu X, Klatt BN, Brach JS. The association of mobility determinants and life space among older adults. J Gerontol A Biol Sci Med Sci 2022 Nov 21;77(11):2320-2328 [FREE Full text] [doi: 10.1093/gerona/glab268] [Medline: 34529773]
12. Lech S, Mümken S, Kessler EM, Gellert P. Life-space mobility among home-living older adults with care needs and clinical depression-a cross-sectional analysis. Int J Geriatr Psychiatry 2023 Jan;38(1):e5875 [FREE Full text] [doi: 10.1002/gps.5875] [Medline: 36647245]
13. Wilkie R, Peat G, Thomas E, Croft P. Factors associated with restricted mobility outside the home in community-dwelling adults ages fifty years and older with knee pain: an example of use of the international classification of functioning to investigate participation restriction. Arthritis Rheum 2007;57(8):1381-1389 [FREE Full text] [doi: 10.1002/art.23083] [Medline: 18050177]
14. Rantakokko M, Portegijs E, Viljanen A, Iwarsson S, Kauppinen M, Rantanen T. Changes in life-space mobility and quality of life among community-dwelling older people: a 2-year follow-up study. Qual Life Res 2016;25(5):1189-1197. [doi: 10.1007/s11136-015-1137-x] [Medline: 26407605]
15. Rantakokko M, Portegijs E, Viljanen A, Iwarsson S, Rantanen T. Life-space mobility and quality of life in community-dwelling older people. J Am Geriatr Soc 2013;61(10):1830-1832 [FREE Full text] [doi: 10.1111/jgs.12473] [Medline: 24117303]
16. Portegijs E, Rantakokko M, Mikkola TM, Viljanen A, Rantanen T. Association between physical performance and sense of autonomy in outdoor activities and life-space mobility in community-dwelling older people. J Am Geriatr Soc 2014;62(4):615-621. [doi: 10.1111/jgs.12763] [Medline: 24655124]
17. De Silva NA, Gregory MA, Venkateshan SS, Verschoor CP, Kuspinar A. Examining the association between life-space mobility and cognitive function in older adults: a systematic review. J Aging Res 2019;2019:3923574 [FREE Full text] [doi: 10.1155/2019/3923574] [Medline: 31275650]
18. Poranen-Clark T, von Bonsdorff MB, Rantakokko M, Portegijs E, Eronen J, Pynnönen K, et al. The temporal association between executive function and life-space mobility in old age. J Gerontol A Biol Sci Med Sci 2018;73(6):835-839 [FREE Full text] [doi: 10.1093/gerona/glx217] [Medline: 29099924]
19. Lo AX, Brown CJ, Sawyer P, Kennedy RE, Allman RM. Life-space mobility declines associated with incident falls and fractures. J Am Geriatr Soc 2014;62(5):919-923 [FREE Full text] [doi: 10.1111/jgs.12787] [Medline: 24731095]
20. Sheppard KD, Sawyer P, Ritchie CS, Allman RM, Brown CJ. Life-space mobility predicts nursing home admission over 6 years. J Aging Health 2013;25(6):907-920 [FREE Full text] [doi: 10.1177/0898264313497507] [Medline: 23965310]

21. Kennedy RE, Sawyer P, Williams CP, Lo AX, Ritchie CS, Roth DL, et al. Life-space mobility change predicts 6-month mortality. J Am Geriatr Soc 2017;65(4):833-838 [FREE Full text] [doi: 10.1111/jgs.14738] [Medline: 28152168]
22. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12(3):189-198. [doi: 10.1016/0022-3956(75)90026-6] [Medline: 1202204]
23. Lundqvist A, Mäki-Opas T. Health 2011 survey—methods. Julkari. Tampere, Finland; 2016. URL: https://www.julkari.fi/handle/10024/130780 [accessed 2024-04-10]
24. Uusitalo RJ, Brans T, Pessi T, Tarkkanen A. Evaluating cataract surgery gains by assessing patients' quality of life using the VF-7. J Cataract Refract Surg 1999;25(7):989-994. [doi: 10.1016/s0886-3350(99)00082-6] [Medline: 10404378]
25. Steinberg EP, Tielsch JM, Schein OD, Javitt JC, Sharkey P, Cassard SD, et al. The VF-14. An index of functional impairment in patients with cataract. Arch Ophthalmol 1994;112(5):630-638. [doi: 10.1001/archopht.1994.01090170074026] [Medline: 8185520]
26. Bowie CR, Harvey PD. Administration and interpretation of the trail making test. Nat Protoc 2006;1(5):2277-2281. [doi: 10.1038/nprot.2006.390] [Medline: 17406468]
27. Radloff LS. CES-D scale: a self-reported scale for research in the general population. Appl Psychol Meas 2016;1(3):385-401. [doi: 10.1177/014662167700100306]
28. Powell LE, Myers AM. The Activities-specific Balance Confidence (ABC) scale. J Gerontol A Biol Sci Med Sci 1995;50A(1):M28-M34. [doi: 10.1093/gerona/50a.1.m28] [Medline: 7814786]
29. Mänty M, Sihvonen S, Hulkko T, Lounamaa A. Iäkkäiden henkilöiden kaatumistapaturmat. Opas kaatumisten ja murtumien ehkäisyyn. Kansanterveyslaitoksen julkaisuja. 2007. URL: https://www.julkari.fi/bitstream/handle/10024/78593/2007b29.pdf?sequence [accessed 2024-04-10]
30. Portegijs E, Iwarsson S, Rantakokko M, Viljanen A, Rantanen T. Life-space mobility assessment in older people in Finland; measurement properties in winter and spring. BMC Res Notes 2014;7:323 [FREE Full text] [doi: 10.1186/1756-0500-7-323] [Medline: 24886670]
31. Rantakokko M, Iwarsson S, Portegijs E, Viljanen A, Rantanen T. Associations between environmental characteristics and life-space mobility in community-dwelling older people. J Aging Health 2015;27(4):606-621. [doi: 10.1177/0898264314555328] [Medline: 25326130]
32. Portegijs E, Sipilä S, Viljanen A, Rantakokko M, Rantanen T. Validity of a single question to assess habitual physical activity of community-dwelling older people. Scand J Med Sci Sports 2017;27(11):1423-1430. [doi: 10.1111/sms.12782] [Medline: 27747944]
33. Grimby G. Physical activity and muscle training in the elderly. Acta Med Scand Suppl 1986;711:233-237. [doi: 10.1111/j.0954-6820.1986.tb08956.x] [Medline: 3535411]
34. Mattiasson-Nilo I, Sonn U, Johannesson K, Gosman-Hedström G, Persson GB, Grimby G. Domestic activities and walking in the elderly: evaluation from a 30-hour heart rate recording. Aging (Milano) 1990;2(2):191-198. [doi: 10.1007/BF03323916] [Medline: 2095860]
35. Mänty M, Heinonen A, Leinonen R, Törmäkangas T, Sakari-Rantala R, Hirvensalo M, et al. Construct and predictive validity of a self-reported measure of preclinical mobility limitation. Arch Phys Med Rehabil 2007;88(9):1108-1113. [doi: 10.1016/j.apmr.2007.06.016] [Medline: 17826454]
36. Lyhyt fyysisen suorituskyvyn testistö. IKINA. URL: https://thl.fi/documents/155392151/190140691/SPPB+lomake+&+ohje.pdf/b989644c-4b2e-432e-877a-f8bb52eab56c/SPPB+lomake+&+ohje.pdf?t=1522992931723) [accessed 2024-02-22]
37. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol 1994 Mar;49(2):M85-M94. [doi: 10.1093/geronj/49.2.m85] [Medline: 8126356]
38. Podsiadlo D, Richardson S. The timed “Up and Go”: a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc 1991 Feb;39(2):142-148. [doi: 10.1111/j.1532-5415.1991.tb01616.x] [Medline: 1991946]
39. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc 1982;14(5):377-381. [Medline: 7154893]
40. Aminian K, Najafi B, Büla C, Leyvraz PF, Robert P. Spatio-temporal parameters of gait measured by an ambulatory system using miniature gyroscopes. J Biomech 2002 May;35(5):689-699. [doi: 10.1016/s0021-9290(02)00008-8] [Medline: 11955509]
41. Bertoli M, Cereatti A, Trojaniello D, Avanzino L, Pelosin E, Del Din S, et al. Estimation of spatio-temporal parameters of gait from magneto-inertial measurement units: multicenter validation among Parkinson, mildly cognitively impaired and healthy older adults. Biomed Eng Online 2018 May 09;17(1):58 [FREE Full text] [doi: 10.1186/s12938-018-0488-2] [Medline: 29739456]
42. Zijlstra W, Hof A. Displacement of the pelvis during human walking: experimental data and model predictions. Gait Posture 1997;6(3):249-262. [doi: 10.1016/s0966-6362(97)00021-0]
43. Zijlstra W, Hof AL. Assessment of spatio-temporal gait parameters from trunk accelerations during human walking. Gait Posture 2003 Oct;18(2):1-10. [doi: 10.1016/s0966-6362(02)00190-x] [Medline: 14654202]

Abbreviations

CES-D: Center for Epidemiologic Studies Depression scale
FSR: force-sensitive resistor
IMU: inertial measurement unit
LSA: Life-Space Assessment
MMSE: Mini-Mental State Examination
NGIMU: next-generation inertial measurement unit
PENBOM: perceived environmental barriers for outdoor mobility
SPPB: short physical performance battery
TMT: trail-making test
TUG: Timed Up and Go
VF-7: 7-item vision function questionnaire
VF-14: 14-item vision function questionnaire

Edited by A Mavragani; submitted 22.09.23; peer-reviewed by J Buekers, P Heyn; comments to author 17.01.24; revised version received 05.02.24; accepted 22.03.24; published 29.04.24.

Please cite as:
Rantakokko M, Matikainen-Tervola E, Aartolahti E, Sihvonen S, Chichaeva J, Finni T, Cronin N
Gait Features in Different Environments Contributing to Participation in Outdoor Activities in Old Age (GaitAge): Protocol for an Observational Cross-Sectional Study
JMIR Res Protoc 2024;13:e52898
URL: https://www.researchprotocols.org/2024/1/e52898
doi:10.2196/52898
PMID:38684085

Protocol

Patient Partnership Tools to Support Medication Safety in Community-Dwelling Older Adults: Protocol for a Nonrandomized Stepped Wedge Clinical Trial

Yan Xiao[1,2], PhD; Kimberley G Fulda[3], DrPH; Richard A Young[4], MD; Z Noah Hendrix[1], MS; Kathryn M Daniel[1†], PhD; Kay Yut Chen[5], PhD; Yuan Zhou[2], PhD; Jennifer L Roye[1], MSN; Ludmila Kosmari[1], MSN; Joshua Wilson[6], MFA; Anna M Espinoza[3], MD; Kathleen M Sutcliffe[7,8,9,10], PhD; Samantha I Pitts[8], MD; Alicia I Arbaje[8,9], MD, MPH, PhD; Michelle A Chui[11], PharmD, PhD; Somer Blair[12], PhD; Dawn Sloan[4], MD; Masheika Jackson[4], MD; Ayse P Gurses[8,9,13], MPH, PhD

[1]College of Nursing and Health Innovation, University of Texas at Arlington, Arlington, TX, United States

[2]College of Engineering, University of Texas at Arlington, Arlington, TX, United States

[3]Department of Family Medicine and Osteopathic Manipulative Medicine and North Texas Primary Care Practice-Based Research Network (NorTex), University of North Texas Health Science Center, Fort Worth, TX, United States

[4]Family Medicine Residency Program, John Peter Smith Health Network, Fort Worth, TX, United States

[5]College of Business, University of Texas at Arlington, Arlington, TX, United States

[6]College of Liberal Arts, University of Texas at Arlington, Arlington, TX, United States

[7]Carey Business School, Johns Hopkins University, Baltimore, MD, United States

[8]School of Medicine, Johns Hopkins University, Baltimore, MD, United States

[9]Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, United States

[10]School of Nursing, Johns Hopkins University, Baltimore, MD, United States

[11]School of Pharmacy, University of Wisconsin-Madison, Madison, WI, United States

[12]Office of Clinical Research, John Peter Smith Health Network, Fort Worth, TX, United States

[13]Whiting School of Engineering, Johns Hopkins University, Baltimore, MD, United States

[†]deceased

Corresponding Author:
Yan Xiao, PhD
College of Nursing and Health Innovation
University of Texas at Arlington
411 S. Nedderman Drive
Arlington, TX, 76019
United States
Phone: 1 817 272 5781
Email: yan.xiao@uta.edu

Abstract

Background: Preventable harms from medications are significant threats to patient safety in community settings, especially among ambulatory older adults on multiple prescription medications. Patients may partner with primary care professionals by taking on active roles in decisions, learning the basics of medication self-management, and working with community resources.

Objective: This study aims to assess the impact of a set of patient partnership tools that redesign primary care encounters to encourage and empower patients to make more effective use of those encounters to improve medication safety.

Methods: The study is a nonrandomized, cross-sectional stepped wedge cluster-controlled trial with 1 private family medicine clinic and 2 public safety-net primary care clinics each composing their own cluster. There are 2 intervention sequences with 1 cluster per sequence and 1 control sequence with 1 cluster. Cross-sectional surveys will be taken immediately at the conclusion of visits to the clinics during 6 time periods of 6 weeks each, with a transition period of no data collection during intervention implementation. The number of visits to be surveyed will vary by period and cluster. We plan to recruit patients and professionals for surveys during 405 visits. In the experimental periods, visits will be conducted with two partnership tools and associated clinic

process changes: (1) a 1-page visit preparation guide given to relevant patients by clinic staff before seeing the provider, with the intention to improve communication and shared decision-making, and (2) a library of short educational videos that clinic staff encourage patients to watch on medication safety. In the control periods, visits will be conducted with usual care. The primary outcome will be patients' self-efficacy in medication use. The secondary outcomes are medication-related issues such as duplicate therapies identified by primary care providers and assessment of collaborative work during visits.

Results: The study was funded in September 2019. Data collection started in April 2023 and ended in December 2023. Data was collected for 405 primary care encounters during that period. As of February 15, 2024, initial descriptive statistics were calculated. Full data analysis is expected to be completed and published in the summer of 2024.

Conclusions: This study will assess the impact of patient partnership tools and associated process changes in primary care on medication use self-efficacy and medication-related issues. The study is powered to identify types of patients who may benefit most from patient engagement tools in primary care visits.

Trial Registration: ClinicalTrials.gov NCT05880368; https://clinicaltrials.gov/study/NCT05880368

International Registered Report Identifier (IRRID): DERR1-10.2196/57878

(JMIR Res Protoc 2024;13:e57878) doi:10.2196/57878

KEYWORDS

primary care; medication safety; communication; patient engagement; human factors; medication; safety; engagement; support; community dwelling; older adults; elderly; protocol; patient safety; self-management; ambulatory; medications; tool; tools; effective; medication safety; data collection; decision; decision making; care; self-efficacy; engagement tool

Introduction

Background

Health care encounters are opportunities for health care professionals (HCPs) to work productively with patients and families to address risks in medication use in ambulatory settings [1,2]. This study assesses a systematic redesign of time-limited primary care encounters to improve medication safety. Adverse drug events (ADEs) account for 6.1 emergency department visits per 1000 population each year in the United States and 38.6% of these visits require hospitalization [3]. Medication safety is recognized as a significant area for improvement by the World Health Organization ("Medication without Harm") [4]. The National Action Plan for ADE Prevention [5] highlighted ADEs associated with insulins, opioids, and anticoagulants, such as those from hypoglycemia, opioid misuse, injurious falls, and bleeding. Older adults are especially vulnerable to ADEs with nearly double the risk compared to younger populations [3]. Patients' roles (including families in this protocol) are critical to medication safety in ambulatory settings [6-8]. An analysis of insulin-related emergency department visits identified patient self-management as the most common precipitant to insulin-related hypoglycemia and errors—patients incorrectly managed their food intake and insulin products at home [9]. Leading contributors to benzodiazepine adverse events were nonmedical use (56%) and self-harm (30%) [10].

Major gaps have been identified in patient and family engagement in medication safety in ambulatory settings [11-15], including cultural barriers that disrupt engagement between HCPs, patients, and families; lack of patients' experience and skills in working with HCPs; and unclear expectations of patient roles in clinical encounters. Older adults often do not take advantage of existing systems for safe medication management practices at home, even for high-risk medications [16]. Patients often have an unvoiced agenda, especially related to concerns, side effects, and uncommunicated methods of managing their conditions [17]. Interventions to bridge these gaps in patient engagement include patient coaching prior to visits [18]; providing patients with instructional brochures, training videos, or prompts of questions to prepare for visits [19-21]; encouraging patients to bring medications and questions to visits [2]; and encouraging patients to ask questions [22-24]. One patient portal-based intervention focused on a dual approach of a previsit agenda-setting questionnaire followed by in-person coaching to prepare for encounters with HCPs [19].

This project uses the patient work system model [25]. The model, similar to those that study and improve the work performance of HCPs [26], focuses on the health-related work of patients and nonprofessionals. The concept of patient work systems broadens the scope for medication safety interventions to encompass patients' home environments [25], including setting expectations and clarifying the roles of patients and families [27], using community resources [28], and incorporating patient perspectives in medication safety improvement [29].

Although the inventions reported so far address several gaps in patient and family engagement, integrated approaches are lacking to systematically target key elements of the joint patient-professional collaborative work to achieve productive interactions. A redesign that acts on multiple aspects of collaborative work is needed to help patients and HCPs set expectations for their partnership appropriate to each patient, along with tools to support collaborative work, and skills training appropriate for the time and resource constraints typical in primary care encounters. Specific aspects of collaborative work are not usually recognized, such as psychological safety in the mostly hierarchical patient-HCP relationship, severe limitation of time, lack of training and knowledge of teamwork concepts, and limited tools for self-efficacy.

Objectives

The primary objective of this study is to assess the impact of a set of patient partnership tools that redesign primary care encounters to encourage and empower patients to make more effective use of those encounters to improve medication safety. Two notable features of the tools are (1) to encourage patients to tell, not just ask, primary care professionals (PCPs) about their medication use at home; and (2) to empower PCPs with tools to nudge patients to become active partners. The tools were developed to leverage the longitudinal relationship between patients and PCPs, instead of focusing on 1-time exposure to the tools. Comparison will be made between usual clinical processes as the control and redesigned clinic processes as the intervention.

Methods

Ethical Considerations

The human participant research protocol was approved by the University of Texas at Arlington Institutional Review Board under a reliance agreement for all study sites (protocol number and version UTA 2019-0439.25 approved on May 10, 2023; contact information: University of Texas at Arlington, Arlington, Texas, US, Angela Luna, IRB Specialist, Office of Regulatory Services, angela.luna@uta.edu). Documentation of patient consent was waived; verbal consent was sufficient and required for data collection (approved verbal consent scripts in Multimedia Appendix 1). The clinics determined that the interventions were part of their standard of care process once implemented. A data and safety monitoring board was appointed with one of the authors (RAY) as the lead to review any adverse events, protocol deviations, and issues with recruitment. The lead physician of each study site was included in the board. Quarterly reviews by the board will be conducted. The trial was registered with ClinicalTrials.gov (number NCT05880368 on May 26, 2023). The clinical leaders at each clinic will decide the types of primary care visits to be included in the interventions, such as annual wellness, disease management follow-up, or acute visits. The leaders will be asked to include all English- or Spanish-speaking patients who are at least 50 years old and have 5 or more medications listed in their electronic health records (EHRs). During each study period, requisite numbers of eligible patients will be recruited by a study coordinator to participate in data collection.

Study Design

The protocol was developed according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement (Multimedia Appendix 2) [30]. The study is a nonrandomized, cross-sectional stepped wedge cluster-controlled trial with 1 private family medicine clinic and 2 public safety-net primary care clinics each composing their own cluster (for a total of 3 clusters). There are 2 intervention sequences with 1 cluster per sequence and 1 control sequence with 1 cluster. We planned the study as a cluster trial because randomization of patients is not feasible when the clinical processes are changed for all patient visits once interventions are in place, not for individual visits. One control sequence is included in the clinic with no intervention planned.

Study Settings

The 3 clinics were in urban settings in a Southwest metropolitan area of the United States. All clinics predominantly serve patients with low socioeconomic status. One clinic is private with 1 family medicine physician. The other 2 clinics are public and part of a safety-net health system with family medicine residency training programs with approximately 15 primary care providers. The clinical and administrative leaders agreed to participate and to the timelines for data collection and implementation.

Interventions

Process redesign will be facilitated by two partnership tools: (1) a 1-page visit preparation guide given to relevant patients by clinic staff before seeing the provider, with the intention to improve communication and shared decision-making, and (2) a library of short educational videos that clinic staff encourage patients to watch on medication safety. The intervention design approach aimed to address multiple elements of collaborative work systems during primary care clinic visits to improve medication safety while minimizing the additional demands on busy PCPs and patients. The tools are expected to be used during typical patient wait times in the exam room and thus are expected to have minimal impact on throughputs. The following goals were considered during the design process: (1) to change collaborative work culture by clarifying patients' roles in contributing to medication use preferences, information accuracy, and in being prepared to participate in shared decision-making; (2) to explicitly recognize fear and reluctance in patient-professional communication by using concepts from the psychological safety literature in teamwork; (3) to set an expectation and to support learning the basics of medication use, such as the refill process and knowledge about tools to reduce unintentional errors; and (4) to encourage problem-solving in community settings, such as contacting pharmacists, who are generally more accessible than primary care providers, with medication-related questions. Participatory design methodologies [31,32] were used in the design and formative evaluation of the tools with older adults and PCPs. Iterative testing was conducted with users, both patients and PCPs. A qualified medical writer wrote the scripts for the videos. Health literacy and patient education experts edited the final versions of the visit prep guide and the scripts for the videos.

The visit preparation guide (Multimedia Appendix 3) contains three sections: ("ask") a list of question prompts for patients to consider about their medications, including one about deprescribing [33]; ("tell") a list of prompts for patients to communicate their medication management views, practices, and concerns; and ("expect") a set of behaviors to encourage collaborative work. The "ask" section had its origin in the approaches used in "Ask Me 3" [23] and EHR-based pre-encounter medication reconciliation [19], with a focus on barriers to self-efficacy in medication use. The "tell" section was designed to overcome communication barriers, such as fear of telling providers about nonadherence with medication regimens. The "expect" section is designed to provide means for providers to recognize and encourage patient collaborative actions, such as bringing medications to clinic visits [34].

The educational videos are less than 2 minutes each in length. The topics and learning objectives are based on interviews, focus groups, professional organization recommendations, and surveys with older adults and PCPs. The final set has 5 videos (length in min:sec): (1) working with your doctor (1:25); (2) taking medicine safely at home (1:33); (3) learning about your medicines (1:36); (4) working with your pharmacist (1:34); and (5) reading prescription labels (1:23). The videos are delivered in exam rooms on touchscreen tablets mounted to either the wall or portable stands.

There is no compensation to patients or clinicians for using the study tools. Participating clinics consider the interventions to be part of their standard of care once implemented, with no plans to compensate for any potential harm because of the trial.

Strategies to Improve Adherence to Interventions

Five points ("moments") of patient encounters during a typical office visit were identified to redesign clinical processes for enhanced patient partnership. The moments all present opportunities for PCPs to partner with patients to improve medication safety and were used to train PCPs on how to incorporate the interventions in the visit process. Two behavioral economics principles were used in developing sample scripts for PCPs: benefits appeal and psychological incentives [35].

1. Rooming, by medical assistants, sets the expectation for active partnership through benefits appeal and psychological incentives. Script examples include "This guide may help you be prepared. Check the items and give it to the doctor" and "I watched all these videos and I like them all. They are very short but will really help you."
2. Greeting, by providers, recognizes and encourages preparation in the patient work system with psychological incentives. Script examples include "Did you bring your meds? Great. I like it when you are prepared!" and "I see you are trying to be prepared. Very good."
3. Agenda setting, by providers, recognizes and encourages collaborative work through psychological incentives. Example scripts include "You used the prep guide. Thank you!" and "Thank you for telling me about your meds! I like it when we can work together better."
4. Closing, by providers, recognizes and encourages patient learning and engagement with psychological incentives. Example scripts include "Did you watch the videos here? Do you want to learn more?" and "That was a good visit – you are a 5-star patient today."
5. Discharge, by medical assistants or nurses, encourages learning through psychological incentives and group effects. Scripts examples include "It is great that you are trying to learn more about your meds" and "We can help you better by working together."

At the discretion of the clinics, gifts of token values are given to patients by staff or providers as part of psychological incentives. Examples of gifts are water bottles, band-aid holders, pill boxes, and medication bags, with a bulk purchase value of about US $1 per item. Staff and providers are informed that although they are encouraged, they are free to decide whether to use the tools and to adapt the suggested partnership enhancement scripts in their clinic encounters.

Outcomes

The primary outcome is self-efficacy in medication use in community settings. Self-efficacy will be measured by a validated tool: Medication Use and Self-Efficacy (MUSE) [36]. MUSE has eight items with a 5-point Likert scale, ranging from "1 – strongly disagree" to "5 – strongly agree": (1) It is easy for me to take my medicine on time; (2) It is easy to remember to take all my medicines; (3) It is easy for me to set a schedule to take my medicines each day; (4) It is easy for me to take my medicines each day; (5) It is easy for me to ask my doctor questions about my medicine; (6) It is easy for me to understand my doctor's instructions for my medicine; (7) It is easy for me to understand instructions on medicine bottles; and (8) It is easy for me to get all the information I need about my medicine. We replaced the word "pharmacist" with "doctor" given that our focus is on interventions in primary care settings. The MUSE score is the sum of the individual responses to the 8 items and ranges between 8 and 40, with 40 indicating "strongly agree" for all 8 items.

Secondary outcomes are a combination of patients' and PCPs' views on communication, collaborative work, and medication reviews. For patients, we will assess their views on collaborative work with seven items selected from five previously published instruments: (1) I know what each of my prescribed medications does (from Patient Activation Measure [37]); (2) I worry about drug interactions between the medications I take (from Medication-Related Problems [38]); (3) During the visit, I was asked to talk about any problems with my medicines or their effects (from Patient Assessment of Chronic Illness Care [39]); (4) During the visit, I was asked questions, either directly or on a survey, about my medicine habits (from Patient Assessment of Chronic Illness Care); (5) I understand what my doctor expects of me regarding my medicines (Psychological Safety Measure [40]); (6) If I make a mistake with my medicines, my doctor does not hold that against me (from Psychological Safety Measure); and (7) My doctor knows the vitamins and supplements I take (from Home Medication Experience Questionnaire [41]).

For providers, we will record the results of medication reviews in a medication review form and capture collaborative work during the visit. The medication review form was adapted from a toolkit published by the Agency for Health Care Research and Quality [42]. The medication review form measures regimen issues (contraindications, drug-drug interactions, and duplications); patient self-management issues (taking expired medications, taking incorrectly, failure to refill, and missed follow-up visits or lab testing); making changes without communicating with the primary care provider (making changes in medications, stopping a prescription, and stopping a supplement); and discrepancies in the medication record (taking medications not in the record, taking medications different from the record, medications active in the patient's record but not taking, or incorrect dose information). For each issue identified, we asked the providers whether they believed it presented a risk to medication safety (no risk, minor risk, or major risk). The collaborative work activities captured are medication changes made in the visit (removal of expired medications, updating prescriptions, replacing prescriptions, prescribing new

medications, regimen simplification, deprescribing, and changes in total number of medications); whether a caregiver is present, and if not, if a caregiver would be helpful; whether the patient brought their prescription and nonprescription medications to the visit; whether the patient knows why and how to take their medications; practices in engaging patients (agenda setting, creating or updating medication list with patients, and using teach-back techniques); and issues impeding the collaborative work (health literacy, language barriers, cognitive impairment, lack of a caregiver, not enough time, patient not knowing their medications).

All outcomes will be assessed immediately after the conclusion of a clinic visit. A research coordinator will survey consenting patients and give a paper form to the provider to collect data on primary and secondary outcomes. Implementation-related measures will be collected in terms of monthly use of the visit preparation guide and access logs of the video library. Protocol deviations will be reported and addressed per University of Texas at Arlington policies.

Study Timeline

Cross-sectional measurements will be taken at 6 time periods of 6 weeks each and will include a transition period of no data collection for intervention clinics (Table 1). Sample sizes will vary by period and cluster. We powered the trial according to the stepped wedge design (clinics A and B only) so that the additional data from the control clinic would add to the power as a supplement. The control clinic is in the same health system as one of the intervention clinics and shares a similar patient population and staff. Using a stepped wedge design allows for the implementation of the intervention at different time points in each clinic, thus providing logistical advantages (like maximizing resources for implementation) and controlling for biases from trends in patient care [43].

Table 1. Design of the nonrandomized, cross-sectional stepped wedge cluster-controlled trial with the schedule of enrollment, interventions, and assessments.

Timepoint (6 weeks[a])	Study period					
	P_1	P_2	P_3	P_4	P_5	P_6
Study sites[b]						
Clinic A	CTRL[c]	N/A[d]	INT[e]	INT	INT	INT
Clinic B	CTRL	CTRL	N/A	INT	INT	INT
Clinic C	CTRL	CTRL	CTRL	CTRL	CTRL	CTRL
Enrollment						
Eligibility screen	Clinics A, B, and C	Clinics B and C	Clinics A and C	Clinics A, B, and C	Clinics A, B, and C	Clinics A, B, and C
Informed consent	Clinics A, B, and C	Clinics B and C	Clinics A and C	Clinics A, B, and C	Clinics A, B, and C	Clinics A, B, and C
Interventions						
Visit Prep Guide	N/A	Clinic A	Clinics A and B	Clinics A and B	Clinics A and B	Clinics A and B
Educational Videos	N/A	Clinic A	Clinics A and B	Clinics A and B	Clinics A and B	Clinics A and B
Assessments						
Medication use self-efficacy	Clinics A, B, and C	Clinics B and C	Clinics A and C	Clinics A, B, and C	Clinics A, B, and C	Clinics A, B, and C
Medication review	Clinics A, B, and C	Clinics B and C	Clinics A and C	Clinics A, B, and C	Clinics A, B, and C	Clinics A, B, and C
Collaborative work	Clinics A, B, and C	Clinics B and C	Clinics A and C	Clinics A, B, and C	Clinics A, B, and C	Clinics A, B, and C

[a]Timepoint is in 6-week periods (P_1-P_6), total 36 weeks.

[b]Study sites (nonrandomized).

[c]CTRL: control.

[d]N/A: not applicable (transition period for implementation; no data collected).

[e]INT: intervention.

Sample Size

The study is a superiority trial, on the hypothesis that interventions will improve patients' self-efficacy in medication use. We powered the trial to detect a difference of 3.8 units on the MUSE scale from pre to postintervention, with a pooled SD of 4.7 (standardized effect size of 0.79) based on a validation study on MUSE [36] using a 2-tailed significance level of 0.05. Power analysis was computed using the R package (version 4.1.0; University of Washington) swCRTdesign [44] via a web-based tool [45]. The transition period was excluded from the sample size calculations. We used 0.07 for intracluster correction and 0.9 for cluster autocorrelation based on study design recommendations [46,47]. With power set at 80%, the

requisite numbers of visits to collect data for each period are in Table 2, with a total sample size of 405.

Table 2. Sample size calculation. Sample size is the number of visits, not the number of patients, using a cross-sectional design.

	Period 1	Period 2	Period 3	Period 4	Period 5	Period 6
Clinic A	15	N/A[a]	35	20	15	15
Clinic B	30	50	N/A	45	30	30
Clinic C	20	20	20	20	20	20

[a]N/A: not applicable (transition period with no data collection efforts).

Recruitment

During each 6-week data collection period, study coordinators will work with study clinics to select recruitment days and identify up to 4 eligible visits per provider on those days. Only 2 visits per provider per shift will be enrolled to avoid disrupting care. Providers will be recruited and consented, informed of identified visits on selected data collection days, and asked to obtain verbal consent from the patients in identified visits to be approached by the study coordinator. The coordinator will then recruit and consent the patient. Patient and clinician participants will be compensated US $10 and US $25, respectively, for each data collection encounter.

Assignment of Interventions and Blinding

Because of the nature of the assessed interventions, we consider blinding not possible for patients or PCPs. Research coordinators who collect data are not blinded to the interventions as they may see interventions, but they are instructed to conduct data collection in consistent procedures regardless of intervention status.

Data Management and Confidentiality

All primary and secondary data collected will be entered into Research Electronic Data Capture (REDCap; Vanderbilt). A quarterly data review will be carried out to assess potential issues with data collection, including missing data and duplicate records. No personal identifying data will be collected.

Statistical Methods for Primary and Secondary Outcomes

Hierarchical models will be used to assess the impact of the interventions on primary and secondary outcomes. Hierarchical models, including linear mixed models, have been described and recommended for use in testing for intervention effects in cross-sectional stepped wedge designs [48,49]. The effect of the intervention is subject to confounding with time due to the staggered entry in stepped wedge designs, and thus the hierarchical modeling structure captures time trends and accounts for the effects of clustering within clinics. Should there be ceiling or floor effects with the total MUSE scores, responses to individual items will be explored. No interim analysis will be conducted. Social determinants of health will be evaluated, including sex, age, race, ethnicity, preferred language, educational level attained, self-reported health literacy, insurance status, and study clinics (private vs public). Associations of these variables with primary outcomes will be assessed, as we anticipate social determinants of health may affect the impact of the interventions. Selected social determinants of health will be assessed through subgroup analyses and model adjustment.

Descriptive statistics, such as medians, IQRs, and proportions, will be tabulated, overall and within clinics, to understand the distribution of the study population. Potential confounding variables were specified prior to data collection and include patient demographics, social determinants of health, time, and clinician. Confounding variables will be evaluated and controlled for in the analysis primarily through model adjustment or stratification. Because the intervention is confounded by time, the model will account for time period as a covariate in the statistical model, following recommendations on mixed models for stepped wedge trials by Li et al [48]. In addition, we included an extra clinic as a control group to assess changes over time in the absence of the intervention.

The study protocol is publicly registered and fully available. Participant level-data will not be made available. Statistical code will be made available upon request.

Dissemination Plan

A writing group will lead publication efforts in peer-reviewed journals and professional conferences. Reports will follow the CONSORT (Consolidated Standards of Reporting Trials) statement and its extensions (for both cluster randomized trials and nonpharmacological interventions) and follow journal authorship guidelines. We will also report implementation-related findings such as uptake patterns of tools over time and qualitative feedback from clinicians and patients at the study sites.

Results

The study was funded in September 2019. The trial started on April 10, 2023, and continued until December 15, 2023. The 3 study sites were in urban settings in a Southwest metropolitan area of the United States. All clinics predominantly serve patients with low socioeconomic status. One clinic is private with 1 family medicine physician. The other 2 clinics are public and part of a safety-net health system with family medicine residency training programs with approximately 15 primary care providers. As of February 15, 2024, we enrolled 405 patients. Data analysis is currently underway and the first results are expected to be submitted for publication in 2024.

Discussion

The trial aims to assess the impact of a set of patient partnership tools that redesign primary care encounters on patient

self-efficacy in medication use in community settings. Secondarily, the trial will provide information on the systematic approach to patient partnership enhancement in collaborative work during primary care visits, from both the patients' and providers' perspectives. We expect the tools and associated process changes in primary care clinics to improve several components of the collaborative work system in terms of self-efficacy, tools, and skills. The intervention is unique compared with prior approaches, such as generic videos on open communication between patients and HCPs or EHR-based tools to help agenda setting [19,22]. If adoption proves successful and MUSE scores rise, the trial will support the innovative approach to improve medication safety in ambulatory settings by improving the value of primary care through collaborative work and partnership. The trial will be carried out in clinics serving vulnerable populations with poor indicators for social determinants of health. The combination of a private family medicine clinic and a primary care clinic in a public safety-net hospital system will provide evidence about the applicability of the approach in a wide range of clinical settings. In addition to the visit prep guide and videos, the trial will also generate other tools for implementation, such as training for PCPs to engage the patient work system and thus improve self-efficacy and ultimately medication safety.

Both the intervention and the assessment approaches are based on collaborative work concepts not previously used to increase patient engagement. Psychological safety in the hierarchical relationship between patients and providers and the clarification of roles and responsibilities have been absent in prior interventions. Although prescribing decisions are important aspects of medication safety, the intervention targets barriers to successful self-management in the patient work system, including patients' home environments.

The trial design has several strengths. The assessment collects data to illuminate both the patient's and PCP's perspectives immediately after an office visit. The data include both patient-centered safety outcomes such as self-efficacy and clinical outcomes such as risks posed by issues identified during medication review. The data also include process measures on collaborative work like psychological safety. The studied patient population is on 5 or more chronic medications and thus is a high-risk group.

The trial has several limitations. Data on ADEs are not collected. Future studies are needed to assess the longer-term impact. The trial is limited in time and thus longitudinal data are not collected on the potential long-term impact of the partnership tools (ie, the impact of repeated exposure over years). The modality of tools (paper visit preparation guides and exam room videos on tablets) is limited and does not leverage consumer and EHR technology in communication and in learning. The number of study clinics is small. However, with stepped wedge design, we expect to control some of the confounding variables, such as seasonality.

Acknowledgments

This trial is supported by a grant from the US Agency for Health Care Quality and Safety (grant number HS027277). The content is solely the responsibility of the authors and does not necessarily represent the official views of the sponsor and funder. The sponsor and funder have no roles in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, with no ultimate authority over any of the above activities other than regulatory authority. The authors thank the following for their contributions: Laura Townsend, Yan Lang, Emily Reeve, Cheryl DeLeon, Monica Patton, Genevieve Walker, Isaac Watemberg, Mai Nguyen, Nicole Hickman, Eva Bustos, Nihita Shah, and Rashmi Rode.

Data Availability

The data sets generated and analyzed during this study are not publicly available to protect patient confidentiality but may be available from the corresponding author upon reasonable request. The assessment instruments and intervention tools are available for noncommercial use.

Authors' Contributions

YX was responsible for writing the protocol, acquiring funding, and planning the study. ZNH, KMD, KGF, APG, RAY, and SB participated in cowriting the protocol. ZNH coordinated data collection procedures across study sites. KMD, KYC, YZ, LK, JW, KGF, AME, APG, SIP, AIA, RAY, and DS were involved in codeveloping intervention tools. JLR, KMS, SIP, AIA, and MAC participated in codeveloping assessment concepts. KGF, APG, RAY, DS, and MJ played a role in coplanning for the study. KGF and SB were responsible for designing the study. KGF, AME, and RAY were involved in recruiting study sites.

Conflicts of Interest

KYC has a potential research conflict of interest due to a financial interest with companies Hewlett-Packard Enterprise, Boostr and DecisionNext. A management plan has been created to preserve objectivity in research in accordance with UTA policy. The authors have no further interests to declare.

Multimedia Appendix 1

Verbal consent scripts.
[PDF File (Adobe PDF File), 136 KB - resprot_v13i1e57878_app1.pdf]

Multimedia Appendix 2
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[DOCX File , 34 KB - resprot_v13i1e57878_app2.docx]

Multimedia Appendix 3
Patient visit guide (English).
[PDF File (Adobe PDF File), 184 KB - resprot_v13i1e57878_app3.pdf]

References

1. Kuriakose R, Aggarwal A, Sohi RK, Goel R, Rashmi NC, Gambhir RS. Patient safety in primary and outpatient health care. J Family Med Prim Care 2020;9(1):7-11 [FREE Full text] [doi: 10.4103/jfmpc.jfmpc_837_19] [Medline: 32110556]
2. Goulding R, Birtwell K, Hann M, Peters S, van Marwijk H, Bower P. Safer Patients Empowered to Engage and Communicate about Health (SPEECH) in primary care: a feasibility study and process evaluation of an intervention for older people with multiple long-term conditions (multimorbidity). BMC Prim Care 2024;25(1):12 [FREE Full text] [doi: 10.1186/s12875-023-02221-3] [Medline: 38178010]
3. Budnitz DS, Shehab N, Lovegrove MC, Geller AI, Lind JN, Pollock DA. US emergency department visits attributed to medication harms, 2017-2019. JAMA 2021;326(13):1299-1309 [FREE Full text] [doi: 10.1001/jama.2021.13844] [Medline: 34609453]
4. Medication without harm: WHO's third global patient safety challenge. World Health Organization. 2017. URL: https://www.who.int/initiatives/medication-without-harm [accessed 2024-04-03]
5. Harris Y, Hu DJ, Lee C, Mistry M, York A, Johnson TK. Advancing medication safety: establishing a national action plan for adverse drug event prevention. Jt Comm J Qual Patient Saf 2015;41(8):351-360. [doi: 10.1016/s1553-7250(15)41046-3] [Medline: 26215524]
6. Hoisnard L, Santos-Eggimann B, Chauvin P, Hiance-Delahaye A, Herr M. Do older adults know the purpose of their medications? a survey among community-dwelling people. Eur J Clin Pharmacol 2019;75(2):255-263. [doi: 10.1007/s00228-018-2575-5] [Medline: 30334201]
7. Dijkstra NE, Sino CG, Schuurmans MJ, Schoonhoven L, Heerdink ER. Medication self-management: considerations and decisions by older people living at home. Res Social Adm Pharm 2022;18(3):2410-2423 [FREE Full text] [doi: 10.1016/j.sapharm.2020.09.004] [Medline: 33627223]
8. Xiao Y, Smith A, Abebe E, Hannum SM, Wessell AM, Gurses AP. Understanding hazards for adverse drug events among older adults after hospital discharge: insights from frontline care professionals. J Patient Saf 2022;18(8):e1174-e1180 [FREE Full text] [doi: 10.1097/PTS.0000000000001046] [Medline: 35617608]
9. Geller AI, Shehab N, Lovegrove MC, Kegler SR, Weidenbach KN, Ryan GJ, et al. National estimates of insulin-related hypoglycemia and errors leading to emergency department visits and hospitalizations. JAMA Intern Med 2014;174(5):678-686 [FREE Full text] [doi: 10.1001/jamainternmed.2014.136] [Medline: 24615164]
10. Moro RN, Geller AI, Weidle NJ, Lind JN, Lovegrove MC, Rose KO, et al. Emergency department visits attributed to adverse events involving benzodiazepines, 2016-2017. Am J Prev Med 2020;58(4):526-535. [doi: 10.1016/j.amepre.2019.11.017] [Medline: 32089287]
11. Kim JM, Suarez-Cuervo C, Berger Z, Lee J, Gayleard J, Rosenberg C, et al. Evaluation of patient and family engagement strategies to improve medication safety. Patient 2018;11(2):193-206. [doi: 10.1007/s40271-017-0270-8] [Medline: 28795338]
12. Mishra SR, Haldar S, Khelifi M, Pollack AH, Wanda P. Must we bust the trust?: understanding how the clinician-patient relationship influences patient engagement in safety. AMIA Annu Symp Proc 2018;2018:1425-1434 [FREE Full text] [Medline: 30815187]
13. Pilla SJ, Park J, Schwartz JL, Albert MC, Ephraim PL, Boulware LE, et al. Hypoglycemia communication in primary care visits for patients with diabetes. J Gen Intern Med 2021;36(6):1533-1542 [FREE Full text] [doi: 10.1007/s11606-020-06385-x] [Medline: 33479925]
14. Zulman DM, Haverfield MC, Shaw JG, Brown-Johnson CG, Schwartz R, Tierney AA, et al. Practices to foster physician presence and connection with patients in the clinical encounter. JAMA 2020;323(1):70-81. [doi: 10.1001/jama.2019.19003] [Medline: 31910284]
15. Byrne JV, Whitaker KL, Black GB. How doctors make themselves understood in primary care consultations: a mixed methods analysis of video data applying health literacy universal precautions. PLoS One 2021;16(9):e0257312 [FREE Full text] [doi: 10.1371/journal.pone.0257312] [Medline: 34547015]
16. Mira JJ, Lorenzo S, Guilabert M, Navarro I, Pérez-Jover V. A systematic review of patient medication error on self-administering medication at home. Expert Opin Drug Saf 2015;14(6):815-838. [doi: 10.1517/14740338.2015.1026326] [Medline: 25774444]

17. Frost J, Gibson A, Ukoumunne O, Vaidya B, Britten N. Does a simple web-based intervention facilitate the articulation of patients' unvoiced agenda for a consultation with their diabetologists? a qualitative study. BMJ Open 2019;9(6):e026588 [FREE Full text] [doi: 10.1136/bmjopen-2018-026588] [Medline: 31203240]
18. Belkora JK, Naguit M, Stupar L, Wiley J, Volz S, O'Donnell S. The effects of coaching patients to list questions before visiting cancer specialists: retrospective evaluation of visit preparation in a rural, underserved setting. J Particip Med 2017;9(1):e15 [FREE Full text] [doi: 10.2196/jopm.8949] [Medline: 36262006]
19. Tai-Seale M, Rosen R, Ruo B, Hogarth M, Longhurst CA, Lander L, et al. Implementation of patient engagement tools in electronic health records to enhance patient-centered communication: protocol for feasibility evaluation and preliminary results. JMIR Res Protoc 2021;10(8):e30431 [FREE Full text] [doi: 10.2196/30431] [Medline: 34435960]
20. Paukkonen L, Oikarinen A, Kähkönen O, Kyngäs H. Patient participation during primary health-care encounters among adult patients with multimorbidity: a cross-sectional study. Health Expect 2021;24(5):1660-1676 [FREE Full text] [doi: 10.1111/hex.13306] [Medline: 34247439]
21. Vasquez TS, Eggly S, Sae-Hau M, DeMairo K, Figueroa L, Gambatese M, et al. Preparing patients to communicate with their doctors about clinical trials as a treatment option: impact of a novel video intervention for patients with a blood cancer and their caregivers. J Cancer Educ 2023;38(5):1562-1570. [doi: 10.1007/s13187-023-02300-0] [Medline: 37097340]
22. Tai-Seale M, Elwyn G, Wilson CJ, Stults C, Dillon EC, Li M, et al. Enhancing shared decision making through carefully designed interventions that target patient and provider behavior. Health Aff (Millwood) 2016;35(4):605-612. [doi: 10.1377/hlthaff.2015.1398] [Medline: 27044959]
23. Shepherd HL, Barratt A, Jones A, Bateson D, Carey K, Trevena LJ, et al. Can consumers learn to ask three questions to improve shared decision making? a feasibility study of the ASK (AskShareKnow) Patient-Clinician Communication Model(®) intervention in a primary health-care setting. Health Expect 2016;19(5):1160-1168 [FREE Full text] [doi: 10.1111/hex.12409] [Medline: 26364752]
24. Brega AG, Hamer MK, Albright K, Brach C, Saliba D, Abbey D, et al. Organizational health literacy: quality improvement measures with expert consensus. Health Lit Res Pract 2019;3(2):e127-e146 [FREE Full text] [doi: 10.3928/24748307-20190503-01] [Medline: 31294314]
25. Holden RJ, Schubert CC, Mickelson RS. The patient work system: an analysis of self-care performance barriers among elderly heart failure patients and their informal caregivers. Appl Ergon 2015;47:133-150 [FREE Full text] [doi: 10.1016/j.apergo.2014.09.009] [Medline: 25479983]
26. Holden RJ, Carayon P, Gurses AP, Hoonakker P, Hundt AS, Ozok AA, et al. SEIPS 2.0: a human factors framework for studying and improving the work of healthcare professionals and patients. Ergonomics 2013;56(11):1669-1686 [FREE Full text] [doi: 10.1080/00140139.2013.838643] [Medline: 24088063]
27. Jallow F, Stehling E, Sajwani-Merchant Z, Daniel KM, Fulda KG, Espinoza AM, et al. A multisite qualitative analysis of perceived roles in medication safety: older adults' perspectives. J Patient Exp 2023;10:23743735231158887 [FREE Full text] [doi: 10.1177/23743735231158887] [Medline: 36865379]
28. White A, Fulda KG, Blythe R, Chui MA, Reeve E, Young R, et al. Defining and enhancing collaboration between community pharmacists and primary care providers to improve medication safety. Expert Opin Drug Saf 2022;21(11):1357-1364 [FREE Full text] [doi: 10.1080/14740338.2022.2147923] [Medline: 36377503]
29. Young RA, Fulda KG, Espinoza A, Gurses AP, Hendrix ZN, Kenny T, et al. Ambulatory medication safety in primary care: a systematic review. J Am Board Fam Med 2022;35(3):610-628 [FREE Full text] [doi: 10.3122/jabfm.2022.03.210334] [Medline: 35641040]
30. Chan AW, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ 2013;346:e7586 [FREE Full text] [doi: 10.1136/bmj.e7586] [Medline: 23303884]
31. Burgess-Limerick R. Participatory ergonomics: evidence and implementation lessons. Appl Ergon 2018;68:289-293 [FREE Full text] [doi: 10.1016/j.apergo.2017.12.009] [Medline: 29409647]
32. Hansen AF, Hasle P, Caroly S, Reinhold K, Järvis M, Herrig AO, et al. Participatory ergonomics: what works for whom and why? a realist review. Ergonomics 2024;67(1):13-33. [doi: 10.1080/00140139.2023.2202842] [Medline: 37070935]
33. Reeve E, Low LF, Shakib S, Hilmer SN. Development and validation of the revised Patients' Attitudes Towards Deprescribing (rPATD) questionnaire: versions for older adults and caregivers. Drugs Aging 2016;33(12):913-928. [doi: 10.1007/s40266-016-0410-1] [Medline: 27785734]
34. Weiss BD, Brega AG, LeBlanc WG, Mabachi NM, Barnard J, Albright K, et al. Improving the effectiveness of medication review: guidance from the health literacy universal precautions toolkit. J Am Board Fam Med 2016;29(1):18-23 [FREE Full text] [doi: 10.3122/jabfm.2016.01.150163] [Medline: 26769873]
35. Shang J, Croson R. A field experiment in charitable contribution: the impact of social information on the voluntary provision of public goods. Econ J 2009;119:1422-1439. [doi: 10.1111/j.1468-0297.2009.02267.x]
36. Cameron KA, Ross EL, Clayman ML, Bergeron AR, Federman AD, Bailey SC, et al. Measuring patients' self-efficacy in understanding and using prescription medication. Patient Educ Couns 2010;80(3):372-376 [FREE Full text] [doi: 10.1016/j.pec.2010.06.029] [Medline: 20650594]

37. Hibbard JH, Stockard J, Mahoney ER, Tusler M. Development of the Patient Activation Measure (PAM): conceptualizing and measuring activation in patients and consumers. Health Serv Res 2004;39(4 Pt 1):1005-1026 [FREE Full text] [doi: 10.1111/j.1475-6773.2004.00269.x] [Medline: 15230939]
38. Snyder ME, Pater KS, Frail CK, Hudmon KS, Doebbeling BN, Smith RB. Utility of a brief screening tool for medication-related problems. Res Social Adm Pharm 2015;11(2):253-264 [FREE Full text] [doi: 10.1016/j.sapharm.2014.08.005] [Medline: 25443640]
39. Cramm JM, Nieboer AP. Factorial validation of the Patient Assessment of Chronic Illness Care (PACIC) and PACIC short version (PACIC-S) among cardiovascular disease patients in the Netherlands. Health Qual Life Outcomes 2012;10:104 [FREE Full text] [doi: 10.1186/1477-7525-10-104] [Medline: 22937991]
40. Edmondson A. Psychological safety and learning behavior in work teams. Adm Sci Q 2016;44(2):350-383. [doi: 10.2307/2666999]
41. Witry MJ, Fadare OO, Pham K. Evaluation of a revised Home Medication Experience Questionnaire (HOME-Qv2). Pharmacy (Basel) 2020;8(3):169 [FREE Full text] [doi: 10.3390/pharmacy8030169] [Medline: 32932876]
42. Brega AG, Barnard J, Mabachi NM, Weiss BD, DeWalt DA, Brach C, et al. AHRQ health literacy universal precautions toolkit, second edition. Agency for Healthcare Research and Quality. 2015. URL: https://www.ahrq.gov/sites/default/files/publications/files/healthlittoolkit2_3.pdf [accessed 2024-04-03]
43. Huynh AK, Lee ML, Farmer MM, Rubenstein LV. Application of a nonrandomized stepped wedge design to evaluate an evidence-based quality improvement intervention: a proof of concept using simulated data on patient-centered medical homes. BMC Med Res Methodol 2016;16(1):143 [FREE Full text] [doi: 10.1186/s12874-016-0244-x] [Medline: 27769177]
44. Voldal EC, Hakhu NR, Xia F, Heagerty PJ, Hughes JP. swCRTdesign: an RPackage for stepped wedge trial design and analysis. Comput Methods Programs Biomed 2020;196:105514 [FREE Full text] [doi: 10.1016/j.cmpb.2020.105514] [Medline: 32554025]
45. Hakhu N, Heagerty P, Hughes J, Voldal E. Stepped Wedge Power Calculation. 2023. URL: https://swcrtdesign.shinyapps.io/stepped_wedge_power_calculation/ [accessed 2024-04-03]
46. Lee YL, Lim YMF, Law KB, Sivasampu S. Intra-cluster correlation coefficients in primary care patients with type 2 diabetes and hypertension. Trials 2020;21(1):530 [FREE Full text] [doi: 10.1186/s13063-020-04349-4] [Medline: 32546189]
47. Hooper R, Bourke L. Cluster randomised trials with repeated cross sections: alternatives to parallel group designs. BMJ 2015;350:h2925 [FREE Full text] [doi: 10.1136/bmj.h2925] [Medline: 26055828]
48. Li F, Hughes JP, Hemming K, Taljaard M, Melnick ER, Heagerty PJ. Mixed-effects models for the design and analysis of stepped wedge cluster randomized trials: an overview. Stat Methods Med Res 2021;30(2):612-639 [FREE Full text] [doi: 10.1177/0962280220932962] [Medline: 32631142]
49. Hussey MA, Hughes JP. Design and analysis of stepped wedge cluster randomized trials. Contemp Clin Trials 2007;28(2):182-191. [doi: 10.1016/j.cct.2006.05.007] [Medline: 16829207]

Abbreviations

ADE: adverse drug event
CONSORT: Consolidated Standards of Reporting Trials
EHR: electronic health record
HCP: health care professional
MUSE: Medication Use and Self-Efficacy
PCP: primary care professional
REDCap: Research Electronic Data Capture
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

Edited by G Eysenbach; submitted 28.02.24; peer-reviewed by K Smith, A Hassan; comments to author 06.03.24; revised version received 20.03.24; accepted 23.03.24; published 29.04.24.

Please cite as:
Xiao Y, Fulda KG, Young RA, Hendrix ZN, Daniel KM, Chen KY, Zhou Y, Roye JL, Kosmari L, Wilson J, Espinoza AM, Sutcliffe KM, Pitts SI, Arbaje AI, Chui MA, Blair S, Sloan D, Jackson M, Gurses AP
Patient Partnership Tools to Support Medication Safety in Community-Dwelling Older Adults: Protocol for a Nonrandomized Stepped Wedge Clinical Trial
JMIR Res Protoc 2024;13:e57878
URL: https://www.researchprotocols.org/2024/1/e57878
doi:10.2196/57878
PMID:38684080

Protocol

Development of a Core Outcome Set for Family and Community Nursing: Protocol for a Delphi Study

Sara Russo[1], BSc, MSc; Rosario Caruso[2,3], MSc, PhD; Gianluca Conte[2], MSc, PhD; Arianna Magon[2], MSc, PhD; Ida Vangone[1,4], BCS, MSc; Barbara Bascape'[5], BSc, MSc; Giulia Maga[1], BSc, MSc; Malgorzata Pasek[6], BSc, MSc; Cristina Arrigoni[7], MSc

[1]Department of Biomedicine and Prevention, University of Rome Tor Vergata, Rome, Italy

[2]Health Professions Researchand Development Unit, Istituto di Ricerca e cura a carattere scientifico Policlinico San Donato, San Donato Milanese, Italy

[3]Department of Biomedical Sciences for Health, University of Milan, Milan, Italy

[4]Nursing Degree Course University of Pavia, Istituto Maugeri Istituto di Ricovero e Cura a Carattere Scientifico, Pavia, Italy

[5]Nursing Degree Course University of Pavia, Istituti Clinici di Pavia e Vigevano, Pavia, Italy

[6]Department of Nursing, Faculty of Health, University of Applied Sciences in Tarnów, Tarnów, Poland

[7]Department of Public Health, Experimental and Forensic Medicine, Section of Hygiene, University of Pavia, Pavia, Italy

Corresponding Author:
Sara Russo, BSc, MSc
Department of Biomedicine and Prevention
University of Rome Tor Vergata
Via Montpellier, 1
Rome, 00133
Italy
Phone: 39 0382433709
Email: sara.russo@grupposandonato.it

Abstract

Background: Family and community nurses (FCNs) play a crucial role in delivering primary care to patients within their homes and communities. A key aspect of their role involves various health interventions, which are influenced by their unique competencies, such as health promotion, advanced clinical knowledge, and strong interpersonal skills. However, it is essential to understand which specific health outcomes these interventions impact to better understand the relationship between FCNs' skills and the health results.

Objective: This study aims to outline the steps we will take to develop a set of core outcomes. These outcomes will be particularly sensitive to the health interventions carried out by FCNs, providing a clearer picture of their practice's impact.

Methods: A Delphi survey will be used for this research, conducted from January to December 2024. The process will involve 5 steps and input from 3 stakeholder categories. These stakeholders will help identify a preliminary list of outcomes that will form the basis of our core outcome set (COS).

Results: This guideline will be beneficial for a wide range of stakeholders involved in COS development, including COS developers, trialists, systematic reviewers, journal editors, policy makers, and patient groups. As of January 2024, we have successfully completed the first stage of the study, with the stakeholder group approving the reported outcomes and assigning participant lists for each stakeholder group.

Conclusions: This study will provide a roadmap for identifying the key health outcomes influenced by the interventions of FCNs. The multistakeholder, multiphase approach will ensure a comprehensive and inclusive process. Ultimately, the findings will enhance our understanding of FCNs' impact on health outcomes, leading to more effective primary care strategies and policies.

International Registered Report Identifier (IRRID): PRR1-10.2196/51084

(JMIR Res Protoc 2024;13:e51084) doi:10.2196/51084

KEYWORDS

clinical knowledge; core outcomes set; Delphi survey; family and community nurse; health interventions; health promotion; primary care; stakeholder engagement

Introduction

Family and community nurses (FCNs) provide primary care services to patients within their homes and communities [1]. Their core activities span a broad spectrum of primary services, including health promotion and primary, secondary, and tertiary prevention, focusing on the health and well-being of communities and populations [2]. These specialized professionals are crucial as they deliver accessible and comprehensive primary care services to individuals and communities, particularly in underserved areas and communities with high rates of chronic diseases [3]. Hence, they play a pivotal role in promoting health, preventing disease, and managing chronic conditions by fostering close collaborations with other health care providers to ensure comprehensive patient care. Although various outcomes linked to the activities of FCNs have been described in recent literature [4-8], a formal core outcome set (COS) is yet to be established [9].

Even though FCNs are primarily employed in primary care settings, they have been recognized as key connectors between the various levels of care and health care providers involved in primary, secondary, and tertiary care levels [10]. Primary care is the first level of contact between a patient and the health care system, focusing on illness prevention, health promotion, and the diagnosis and treatment of common conditions [11]. Secondary care involves specialized medical care provided by health care professionals such as specialists, nurses, and technologists, involving more complex medical procedures and treatments in health care facilities [12]. Tertiary care refers to specialized and complex medical and surgical treatments provided by specialized health care providers in specialized centers. In this intricate scenario, FCNs facilitate a smooth transition of care between the various levels of care in a typical patient journey, addressing the challenges of chronic diseases by providing preventive care, health education, and referrals to specialists when necessary [13,14]. This ability to provide comprehensive care and coordinate with other health care providers enables FCNs to ensure that patients receive seamless and effective care across different health care system levels [15].

The curricular competencies of FCNs, as described in recent literature through the ENhANCE project [16], are primarily based on health promotion, high relational competencies, skills, and advanced clinical knowledge. These competencies define the health domain of FCNs as a specific FCN health intervention. According to Caruso and colleagues [16], to frame an integrated view of the complex relationship between curricular competencies and health outcomes, it is necessary to clarify which specific health outcomes are susceptible to the domains described in defining the role of FCNs.

In essence, aligning a specific domain with a health outcome is crucial for 2 main reasons. First, it allows health care providers and policy makers to determine the effectiveness of the FCN role [17]. Second, linking specific domains to specific health outcomes enables the measurement and comparison of the impact of different domains, thereby informing decisions about which domains are most effective for improving health outcomes [18]. Moreover, matching interventions to outcomes helps ensure that resources are used effectively and efficiently [19]. Health care providers and policy makers can prioritize resource allocation and improve health outcomes for the greatest number of people by focusing on domains that impact health outcomes. Lastly, matching domains to outcomes also promotes accountability and transparency in health care [18]. By clearly documenting the impact of domains on health outcomes, health care providers and policy makers can demonstrate their commitment to improving health and provide evidence of their progress toward this goal. However, even though the nature and classification of the health domain provided by FCNs are clearly recognized in the literature (eg, ENhANCE Project - European Curriculum for Family and Community Nurses) [15], the health outcomes that are susceptible to those interventions remain largely undefined and poorly described, and no COS has been defined in relation to the FCNs [9].

A COS is a standardized and agreed-upon set of outcomes that should be measured and reported in all studies of a particular condition or intervention [20]. A COS helps ensure that the most important and relevant outcomes are measured and reported consistently across studies, allowing for meaningful comparison and synthesis of results [20]. Developing a COS involves a systematic and collaborative process involving stakeholders such as patients, health care providers, researchers, and policy makers. The goal is to identify the most important outcomes, starting from a defined framework and developed from the perspective of patients, ensuring that these outcomes are relevant and meaningful to all stakeholders [20,21].

A COS can improve the quality and comparability of research by standardizing the measured and reported outcomes, informing clinical decision-making, and supporting evidence-based health care. It can also help to reduce the risk of selective reporting of outcomes and publication bias, leading to a more comprehensive understanding of the impact of a domain on health outcomes [20,21]. This COS is therefore labeled as the Family and Community Nursing Core Outcomes Set (FCN-COS), using the approach proposed by Moher and colleagues [22]. This protocol will develop FCN-COS sensitive to the health interventions that characterize the practice of FCNs. The objectives of the study are to (1) determine a consensus with a Delphi survey regarding an FCN-COS and (2) develop an FCN-COS sensitive to the health domains that characterize the practice of FCNs involving stakeholders such as patients, health care providers, researchers, and policy makers.

Methods

Design

This protocol is designed to incorporate a multimethod and multiphase approach from January to December 2024. It adheres to the recommendations of the "Core Outcome Measures in Effectiveness Trials" (COMET) Handbook (version 1.0) [23] and the Guidance on Conducting and Reporting Delphi Studies (CREDES). The development of the FCN-COS guideline will commence in January 2024 and will be carried out in 5 stages.

- Stage 1: compilation of a preliminary, evidence-based list of reviewed outcomes for consideration in the FCN-COS.
- Stage 2: execution of a web-based Delphi survey to validate the classification and work toward a reporting guideline for FCN-COS.
- Stage 3: conducting a final web-based consensus meeting to identify the definitive outcomes for inclusion in the FCN-COS reporting guideline.
- Stage 4: development of a high-quality reporting guideline and a detailed explanatory document, transforming final FCN outcomes into definitive outcomes and domains.
- Stage 5: Postdevelopment activities, including pilot-testing and dissemination of the results.

The process will involve 3 categories of stakeholders: health care professionals, methodological experts, and service users. These stakeholders will contribute to identifying the preliminary list of proposed outcomes, participate in the Delphi survey rounds, contribute to the consensus meeting, and review the materials produced for disseminating the results.

Stage 1

Preliminary List of Outcomes

The practice of FCNs has significantly contributed to the development of comprehensive health interventions. The preliminary list of proposed outcomes is based on the Classification Clinical Care Classification System (CCC, version 2.5), which provides standard terminology for outcomes and domains, facilitating the documentation of nursing assessments in home care settings. This classification comprises 176 nursing diagnoses, including 60 primary outcomes and 116 diagnostic subcategories. The outcomes included in the preliminary list are defined using existing taxonomies [24], supplemented by a summary of outcomes from a recent systematic review [9] (Multimedia Appendix 1 [5,8,13,25-36]). Additionally, the literature review that will serve as a foundation for developing a preliminary list of outcomes [9] will be updated with specific searches in MEDLINE, CINAHL (EBSCO), Global Health (Ovid), Scopus, and Web of Science. The steering committee will approve the final list of outcomes. The Delphi survey will present the outcomes within each domain to participants in a random order.

Preliminary Consensus Meeting

A preliminary consensus meeting has been arranged to define specific methodological aspects of the Delphi survey among the authors of the study protocol. Specifically, an initial web-based consensus meeting was held to define domains. The preliminary outcomes are based on the CCC (version 2.5) taxonomy [24], serving as an evidence-based classification to initiate the preliminary FCN-COS. These preliminary outcomes, developed in the home care setting, have been identified as a crucial starting point [24].

Moreover, a web-based meeting was held in the designing phase of the protocol to discuss strategies for mitigating the risk associated with a low response rate to the Delphi survey. Before starting with the Delphi survey, a brief video will be disseminated among the participants to familiarize them with the project, particularly focusing on the timeline and rounds of discussion.

Stage 2

Delphi Surveys

A web-based Delphi survey will be started to generate consensus regarding the preliminary list of outcomes. We will use the Delphi technique to obtain consensus from the panel of participants through 2 rounds of discussions. Therefore, the first round of discussion will take place from the outcomes identified in the previous stage, inviting participants to add further outcomes not included in the preliminary outcomes. Outcomes identified during the first round will be included in the second round of the Delphi process outcome item. The second round of discussion will take place to provide feedback and identify further outcomes from participants. More precisely, participants will reevaluate their original rating from the first round by including the other participants' overall rating for each outcome. An outcome will be included in the final FCN-COS with a consensus equal to or greater than 80% in all stakeholder groups rating the outcome as critically important.

Participants: Panel Composition

We plan to involve various stakeholder groups, each contributing a balanced mix of skills and competencies. These groups include health care professionals in primary care, health care researchers, nurses actively involved in nursing regulatory authority boards, and service users. The first group will consist of individuals who have experienced primary nursing care within the past 2 years. The second group will focus on research methods to provide robust support for the Delphi survey methodology. Service users will offer feedback based on their experiences in primary care.

Recruitment Process

Potential participants will receive personal emails explaining the project and its objectives. Before initiating the survey, we will organize a web-based meeting to help participants better understand the project's aim. We will then ask them to complete the first round of the Delphi survey within a 2-week time frame. Participation in the survey is optional, and informed consent will be obtained from those who choose to participate. Each participant will be assigned a unique identification number for the 2 rounds of the Delphi survey. We will request the contact authors from each FCN-COS developer stakeholder group to invite their coauthors to provide feedback. This approach ensures that we gather opinions from both clinical and methodological experts in FCN-COS development. At the end of the 2-week

period, we will send reminders to participants to complete the survey.

We will collect demographic data, including age, profession, years of experience, educational background, and previous experiences with COS development. Each stakeholder who completes the first round of the Delphi survey will be invited to participate in the second round. We will obtain their name and informed consent to be recognized as a member of the Delphi group in the publication resulting from this research.

Delphi Scoring and Software

The reporting guideline outcomes listed will use a 9-point scale, with 1-3 labeled as not important for inclusion in the COS, 4-6 labeled as important but not critical for inclusion in the COS, and 7-9 labeled as critical for inclusion in the COS [37]. Participants will also be allowed to score "maybe" if they are unable to offer an opinion as to whether the reporting guideline outcome is important or not. An electronic survey format called "web-based" will be used for managing the Delphi surveys [23].

Data Analysis

Descriptive statistics will be used for each survey round to determine the overall scores for each stakeholder group, considering the 3 categories (not important, important but not critical, and critical) to determine whether outcomes are critical for the FCN-COS. Only responses from participants who will rate at least 50% of the outcomes will be included in the analysis. By comparing the distribution of the mean overall scores from the second Delphi round between participants who attended the consensus meeting and those who did not, selection bias between the Delphi procedure and the consensus meeting (see Stage 3 section) will be evaluated. Data analysis will be performed using SPSS Statistics for Windows (version 28; IBM Corp).

Stage 3

Consensus Meeting

The stakeholder group of 100 people will be included in a web-based interactive consensus meeting. The consensus meeting will be represented through a short study overview as outcomes reported by each stakeholder group. The outcomes where the consensus meeting is reached will be considered first to ratify those results. If a consensus meeting is reached for other outcomes, they will be considered according to the stakeholder groups. An opportunity to discuss each outcome will be given to all participants, defined by an anonymous scoring method, between the ones defined at the consensus meeting. Stakeholders will define the final outcomes based on the review of the responses from Delphi participants. The consensus meeting will be fundamental to identifying the outcomes included in the reporting guideline for FCN-COS development. If 70% of the consensus meeting participants favor the outcome's inclusion, it will be considered consensus. The best form of communication in the consensus meeting will be determined by comprising methods of feedback (eg, track changes) and ensuring disagreements' resolution. In the end, a written report after the consensus meeting will be circulated for comment.

Delphi Round 1

Each outcome will be presented to reflect the outcomes' clarity or ambiguity [23]. Every participant will be asked to score each outcome, and after that, they could add any other outcomes they believed to be added to develop FCN-COS. The research group will revise the entire reporting list of outcomes. Each outcome will have a summarized view, including the scored outcome and its distribution. All outcomes will be carried forward to round 2. The response rate of participants as all the participants completed the survey compared to the sent email invitations. The incomplete answers will also be monitored.

Delphi Round 2

In the second round, each participant who participated in the first round will be shown the number of respondents and the distribution of scores for each outcome. They will be asked to rescore the outcome of the other Delphi participants and to justify any reason for an eventual change (eg, if a participant changed their score from "not critical" to "critical" in the second round). For each outcome, the number of participants who have scored it and the distribution of scores will be summarized. When the second round is completed, the attrition bias will be considered by comparing 2 groups of the first and second rounds. A comparison will be developed between participants who completed the second round and those who completed only the first one. Changes in participants' scores will also be examined, and the reasons for changes between the 2 rounds will be summarized.

Consensus Definition

A consensus will be defined and obtained before participants take part in the Delphi survey, as previously recommended. Reporting outcomes will only be prioritized if they reach 80% of the support from participants scoring "critical" (ie, score 7-9) [23].

Stage 4 (Development of Reporting Guideline and Explanatory Document and Procedure)

The aim of the explanatory document is to provide the background, rationale, and justification for the FCN-COS. This document will be developed concurrently with the reporting guidelines.

In stage 4, stakeholders will concentrate on the development of the reporting guideline for studies developing COS and the accompanying explanatory document. Additionally, a draft recommendation will be created to explain the origin of the outcome (whether from stakeholders or the Delphi survey), the level of consensus achieved (through the Delphi survey and consensus meeting), and a brief rationale for inclusion. The expert panel will review the document and provide feedback on the guideline and explanatory document as needed. The FCN-COS guideline will undergo several revisions until the final draft is deemed complete.

Stage 5 (Pilot-Testing of the FNC-COS)

In the end, in stage 5, we will test the draft completed in the previous stage. Authors will be invited to test the FNC-COS, and the more experienced COS developers will review the

guidelines to improve it. Their feedback will be reached through an anonymous survey incorporated into the final COS guideline.

Ethical Considerations

The University of Pavia Review Board has been consulted and confirmed ethical approval for this study (number 02/int/2023/CdS).

Results

In this study, a comprehensive FCN-COS will be developed through a rigorous multiphase approach. COS developers, trialists, systematic reviewers, journal editors, policy makers, and patient groups will benefit from the COS development, as it will aim to improve the quality and comparability of future research by standardizing, through 5 distinct stages, the measurement and reporting of outcomes in the field of family and community nursing. As the first stage of the study will be successfully completed, with the stakeholder group expected to approve the reported outcomes and assign participant lists for each stakeholder group, this significant milestone will signify the initial step toward establishing a standardized framework for measuring and reporting outcomes in family and community nursing research, which will inform future clinical decision-making and enhance research quality and comparability in this vital domain. The Delphi survey approach will be a sound method for soliciting input from a wide range of stakeholders, including health care professionals, researchers, and service users. The surveys will aim to establish consensus on the importance of various outcomes. This iterative process will be instrumental in refining the list of outcomes and ensuring that the most critical outcomes are identified. The consensus meeting will mark a critical juncture in the development of the FCN-COS. Bringing together a diverse group of stakeholders for an interactive discussion will ensure that the final outcomes selected truly reflect a collective consensus, as well as the development of the reporting guideline and explanatory document. The involvement of an expert panel in reviewing and revising these documents will ensure their quality and clarity. The pilot-testing stage will represent a valuable step in validating the FCN-COS. Inviting authors and experienced COS developers to test the guideline and provide feedback will be a practical approach to identifying any potential issues or areas for improvement. Their insights will contribute to the refinement and usability of the FCN-COS.

Discussion

Overview

To date, no FCN-COS has been developed, and its development could aid in organizing and understanding various interventions within the family and community context [9]. The establishment of FCN-COS will enhance the organization and improvement of FCN interventions, shedding light on the impact of the FCN on health outcomes within a broader family and community context.

This proposed protocol for developing and the future FCN-COS is essential to comprehend how nursing domains are defined by FCN interventions. An example is the “role relationship,” such as parenting skills to ensure child protection. Multidisciplinarity in the health care setting is a priority to ensure continuity of care, involving various health care professionals to better guarantee community health. This can be better illuminated through the FNC-COS, starting from the preliminary version of FCN-COS. The preliminary version of FCN-COS is a crucial starting point. This classification is vital to prioritize the most relevant interventions for FCNs in practice and guide the development of a consensus-based set of core interventions using a Delphi survey approach [24]. This can help ensure that nurses are equipped with the most relevant and evidence-based interventions to provide high-quality care to families and communities.

FCNs provide primary care services to patients in families and communities [1]. Their core activities cover a wide range of primary services, from health promotion to primary, secondary, and tertiary prevention, focusing on the health and well-being of communities and populations [2]. These specialized professionals are important because they provide accessible and comprehensive primary care services to individuals and communities, particularly in underserved areas and communities with high rates of chronic diseases [3]. The FCN is a key role that can bridge the gap between home care settings and hospitals, with autonomy as a self-regulated profession [15]. For this reason, this Delphi process aims to develop a standardized classification of FCN interventions emerging from the unique needs and contexts of FCN practice. In particular, as the FCN’s clinical practice develops in primary, secondary, and tertiary care, defining FCN-COS is a priority that has not yet been developed [9].

The FCN-COS derived from stage 1 is based on the national and international literature [9], and it will need to be adapted for country-specific use in Italy. This will be developed by engaging with a panel of participants in Italy, using a Delphi approach, to define the classification and identification of any outcomes that may be more or less relevant to FCN practice in Italy. In other words, this proposal will be developed as the result of the implementation of the next phases of the protocol to ensure that the FCN is relevant and applicable to the unique needs and contexts of FCN practice in Italy.

Expected Results From the Delphi Study

Having an FCN-COS is highly relevant to sustaining health promotion and salutogenic interventions in the family and community context [2]. FCN-COS is fundamental to try to fill the gaps about the current unavailability of FCN-COS in the Italian context [9]. This protocol, even if developed in Italy, will be fundamental for the international context. In particular, we focused on the international literature review to define the preliminary outcomes of the FCN-COS [9]. After the preliminary outcomes, stage 1 of the study will follow. A standardized scheme of classification and a precise hierarchical classification of interventions are fundamental to facilitate assessments [21].

Furthermore, the social recognition of the FCN could be strengthened by the definition of a COS shared between health care professionals, even internationally [9,24]. The Delphi survey allows the illumination of experts’ opinions through a

series of iterative questionnaires to reach a consensus on defining FCN-COS. The Delphi survey will be conducted ensuring the anonymity of the panel of participants. This is fundamental to reduce the impact of dominant personalities in the debate and decreasing peer pressure [38]. In this sense, every answer will be equally weighted, and the feedback process allows experts to develop a precise idea between one round and another, letting them know the previous ratings of the survey [39].

Limitations

The methodology used is the main limitation in defining FCN-COS. This approach limited the possibility of elaborating on in-depth views of the panel composition about the FCN-COS. However, a web-based system should help researchers optimize the response rate. Despite this, developing the best possible FCN-COS could be possible through future further validation studies to verify the defined FCN-COS in relation to measurable patient-level outcomes and to the previously developed FCN-COS.

Conclusion

The Delphi survey is fundamental to developing a COS sensitive to the health interventions that characterize the practice of FCNs. The FCN-COS will be developed as the main turning point, which can determine a greater quality and comparability of research, inform clinical decision-making, and support evidence-based health care. Furthermore, FCN-COS will be fundamental to define FCN as an emerging health care professional in the field of nursing.

Acknowledgments

This study was partially supported by the University of Pavia (no specific grant) and the Ricerca Corrente funding from the Italian Ministry of Health to IRCCS Policlinico San Donato.

Data Availability

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

Authors' Contributions

SR, CA, and RC conceptualized the study. All authors developed the first draft of the manuscript and are involved in the data collection. All authors contributed to the development of the study protocol and approved the final draft of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Preliminary list of outcomes.
[DOCX File , 107 KB - resprot_v13i1e51084_app1.docx]

References

1. Marcadelli S, Stievano A, Rocco G. Policy proposals for a new welfare: the development of the family and community nurse in Italy as the key to promote social capital and social innovation. Prim Health Care Res Dev 2019;20:e109 [FREE Full text] [doi: 10.1017/S146342361800083X] [Medline: 32799972]
2. Miguélez-Chamorro A, Ferrer-Arnedo C. The family and community nurse: health agent and model for the chronic patient within the community. Enferm Clin 2014;24(1):5-11. [doi: 10.1016/j.enfcli.2013.12.002] [Medline: 24378343]
3. Cockerham WC, Hamby BW, Oates GR. The social determinants of chronic disease. Am J Prev Med 2017;52(1S1):S5-S12 [FREE Full text] [doi: 10.1016/j.amepre.2016.09.010] [Medline: 27989293]
4. Cramm JM, Nieboer AP. Self-management abilities and quality of life among frail community-dwelling individuals: the role of community nurses in the Netherlands. Health Soc Care Community 2017;25(2):394-401. [doi: 10.1111/hsc.12318] [Medline: 26732088]
5. Jin L, Pan R, Huang L, Zhang H, Jiang M, Zhao H. Family nursing with the assistance of network improves clinical outcome and life quality in patients underwent coronary artery bypass grafting: a consolidated standards of reporting trials-compliant randomized controlled trial. Medicine (Baltimore) 2020;99(50):e23488 [FREE Full text] [doi: 10.1097/MD.0000000000023488] [Medline: 33327282]
6. Østergaard B, Mahrer-Imhof R, Shamali M, Nørgaard B, Jeune B, Pedersen KS, et al. Effect of family nursing therapeutic conversations on patients with heart failure and their family members: secondary outcomes of a randomised multicentre trial. J Clin Nurs 2021;30(5-6):742-756. [doi: 10.1111/jocn.15603] [Medline: 33325066]
7. Savini S, Iovino P, Monaco D, Marchini R, Di Giovanni T, Donato G, et al. A family nurse-led intervention for reducing health services' utilization in individuals with chronic diseases: the ADVICE pilot study. Int J Nurs Sci 2021;8(3):264-270 [FREE Full text] [doi: 10.1016/j.ijnss.2021.05.001] [Medline: 34307774]

8. Wood-Baker R, Robinson A, Reid D, Walters EH. Clinical trial of community nurse mentoring to improve self-management in patients with chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2012;7:407-413. [doi: 10.2147/copd.s32220]
9. Dellafiore F, Caruso R, Cossu M, Russo S, Baroni I, Barello S, et al. The state of the evidence about the family and community nurse: a systematic review. Int J Environ Res Public Health 2022;19(7):4382 [FREE Full text] [doi: 10.3390/ijerph19074382] [Medline: 35410065]
10. Magon A, Stievano A, Baroni I, Caruso R. Research, education, workforce, and regulation to transforming nursing practice and leadership: the conundrum of "where to start". Healthcare (Basel) 2023;11(3):378 [FREE Full text] [doi: 10.3390/healthcare11030378] [Medline: 36766953]
11. Kim HS, Suh Y, Kim MS, Yoo BN, Lee EJ, Lee EW, et al. Effects of community-based primary care management on patients with hypertension and diabetes. Asia Pac J Public Health 2019;31(6):522-535. [doi: 10.1177/1010539519867797] [Medline: 31523988]
12. Vos JAM, Wieldraaijer T, van Weert HCPM, van Asselt KM. Survivorship care for cancer patients in primary versus secondary care: a systematic review. J Cancer Surviv 2021;15(1):66-76 [FREE Full text] [doi: 10.1007/s11764-020-00911-w] [Medline: 32815087]
13. Husband J. The evolving role of the community nurse specialist in palliative care. Br J Community Nurs 2008;13(1):26-30. [doi: 10.12968/bjcn.2008.13.1.27980] [Medline: 18399368]
14. Mendes A. A community nurse's role in supporting a 'good' experience of grief. Br J Community Nurs 2017;22(11):566-567. [doi: 10.12968/bjcn.2017.22.11.566] [Medline: 29091507]
15. Bagnasco A, Catania G, Zanini M, Pozzi F, Aleo G, Watson R, et al. Core competencies for family and community nurses: a European e-Delphi study. Nurse Educ Pract 2022;60:103296 [FREE Full text] [doi: 10.1016/j.nepr.2022.103296] [Medline: 35176643]
16. Caruso R, Fida R, Sili A, Arrigoni C. Towards an integrated model of nursing competence: an overview of the literature reviews and concept analysis. Prof Inferm 2016;69(1):35-43. [doi: 10.7429/pi.2016.691035] [Medline: 27191520]
17. Kua CH, Mak VSL, Lee SWH. Health outcomes of deprescribing interventions among older residents in nursing homes: a systematic review and meta-analysis. J Am Med Dir Assoc 2019;20(3):362-372.e11. [doi: 10.1016/j.jamda.2018.10.026] [Medline: 30581126]
18. Suhonen R, Välimäki M, Leino-Kilpi H. A review of outcomes of individualised nursing interventions on adult patients. J Clin Nurs 2008;17(7):843-860. [doi: 10.1111/j.1365-2702.2007.01979.x] [Medline: 18321285]
19. McCullough P. Outcomes of contrast-induced nephropathy: experience in patients undergoing cardiovascular intervention. Catheter Cardiovasc Interv 2006;67(3):335-343. [doi: 10.1002/ccd.20658] [Medline: 16489569]
20. Van den Bussche K, De Meyer D, Van Damme N, Kottner J, Beeckman D. CONSIDER—Core outcome set in IAD research: study protocol for establishing a core set of outcomes and measurements in incontinence-associated dermatitis research. J Adv Nurs 2017;73(10):2473-2483. [doi: 10.1111/jan.13165] [Medline: 27682261]
21. Alkhaffaf B, Metryka A, Blazeby JM, Glenny AM, Adeyeye A, Costa PM, et al. Core outcome set for surgical trials in gastric cancer (GASTROS study): international patient and healthcare professional consensus. Br J Surg 2021;108(10):1216-1224 [FREE Full text] [doi: 10.1093/bjs/znab192] [Medline: 34165555]
22. Moher D, Schulz KF, Simera I, Altman DG. Guidance for developers of health research reporting guidelines. PLoS Med 2010;7(2):e1000217 [FREE Full text] [doi: 10.1371/journal.pmed.1000217] [Medline: 20169112]
23. Williamson PR, Altman DG, Bagley H, Barnes KL, Blazeby JM, Brookes ST, et al. The COMET handbook: version 1.0. Trials 2017;18(Suppl 3):280 [FREE Full text] [doi: 10.1186/s13063-017-1978-4] [Medline: 28681707]
24. Zeffiro V, Sanson G, Vanalli M, Cocchieri A, Ausili D, Alvaro R, et al. Translation and cross-cultural adaptation of the clinical care classification system. Int J Med Inform 2021;153:104534. [doi: 10.1016/j.ijmedinf.2021.104534] [Medline: 34332469]
25. Adamson E, Cruickshank S. A 'good death' at home: community nurses helping to make it possible. Br J Community Nurs 2013 Jan;18(1):40-42. [doi: 10.12968/bjcn.2013.18.Sup9.S40] [Medline: 23299148]
26. Broekema S, Paans W, Roodbol PF, Luttik MLA. Effects of family nursing conversations on families in home health care: a controlled before-and-after study. J Adv Nurs 2021 Jan;77(1):231-243. [doi: 10.1111/jan.14599] [Medline: 33068016]
27. Dening KH, Hibberd P. Exploring the community nurse role in family-centred care for patients with dementia. Br J Community Nurs 2016 Apr;21(4):198-202. [doi: 10.12968/bjcn.2016.21.4.198] [Medline: 27282506]
28. Duncan D. Role of the community nurse in Parkinson's disease and lower urinary disorders. Br J Community Nurs 2021 May 02;26(5):251-254. [doi: 10.12968/bjcn.2021.26.5.251] [Medline: 33939461]
29. Falavigna G, Ippoliti R. The socio-economic planning of a community nurses programme in mountain areas: A Directional Distance Function approach. Socio-Economic Planning Sciences 2020 Sep;71:100770. [doi: 10.1016/j.seps.2019.100770]
30. Holdoway A, Anderson L. What more can community nurses do to manage adult malnutrition. Br J Community Nurs 2019 Jul 01;24(Sup7):S6-S10. [doi: 10.12968/bjcn.2019.24.Sup7.S6] [Medline: 31264455]
31. Murray L. The role of the registered nurse managing pro re nata (PRN) medicines in the care home (nursing): a case study of decision-making, medication management and resident involvement. University of Hertfordshire Research Archive. 2017. URL: https://uhra.herts.ac.uk/handle/2299/17989 [accessed 2024-03-15]

32. Ogston-Tuck S. A silent epidemic: effective pain management in the community. Br J Community Nurs 2014 Jun 02;20(6):286-292. [doi: 10.12968/bjhc.2014.20.6.286]
33. Kelly AM. What can community nurses do for older adults who experience faecal incontinence? Br J Community Nurs 2019 Jan 02;24(1):28-31. [doi: 10.12968/bjcn.2019.24.1.28] [Medline: 30589593]
34. Kent S, Dowling M, Byrne G. Community nurses' child protection role: views of public health nurses in Ireland. Community Pract 2011 Nov;84(11):33-36. [Medline: 23270020]
35. Shafie M, Eyasu M, Muzeyin K, Worku Y, Martín-Aragón S. Prevalence and determinants of self-medication practice among selected households in Addis Ababa community. PLoS One 2018;13(3):e0194122 [FREE Full text] [doi: 10.1371/journal.pone.0194122] [Medline: 29579074]
36. Simonetti V, Comparcini D, Tomietto M, Pavone D, Flacco ME, Cicolini G. Effectiveness of a family nurse-led programme on accuracy of blood pressure self-measurement: a randomised controlled trial. J Clin Nurs 2021 Aug;30(15-16):2409-2419. [doi: 10.1111/jocn.15784] [Medline: 33872417]
37. Kirkham JJ, Gorst S, Altman DG, Blazeby J, Clarke M, Devane D, et al. COS-STAR: a reporting guideline for studies developing core outcome sets (protocol). Trials 2015;16:373 [FREE Full text] [doi: 10.1186/s13063-015-0913-9] [Medline: 26297658]
38. Hasson F, Keeney S, McKenna H. Research guidelines for the Delphi survey technique. J Adv Nurs 2008;32(4):1008-1015. [doi: 10.1046/j.1365-2648.2000.t01-1-01567.x]
39. Gogovor A, Zomahoun HTV, Charif AB, McLean RKD, Moher D, Milat A, et al. Essential items for reporting of scaling studies of health interventions (SUCCEED): protocol for a systematic review and Delphi process. Syst Rev 2020;9(1):11 [FREE Full text] [doi: 10.1186/s13643-019-1258-3] [Medline: 31926555]

Abbreviations

CCC: Clinical Care Classification System
COMET: Core Outcome Measures in Effectiveness Trials
COS: core outcome set
CREDES: Guidance on Conducting and Reporting Delphi Studies
FCN: family and community nurse
FCN-COS: Family and Community Nursing Core Outcomes Set

Edited by A Mavragani; submitted 20.07.23; peer-reviewed by I Milani, M Petralito; comments to author 02.01.24; revised version received 03.01.24; accepted 07.01.24; published 29.03.24.

Please cite as:
Russo S, Caruso R, Conte G, Magon A, Vangone I, Bascape' B, Maga G, Pasek M, Arrigoni C
Development of a Core Outcome Set for Family and Community Nursing: Protocol for a Delphi Study
JMIR Res Protoc 2024;13:e51084
URL: https://www.researchprotocols.org/2024/1/e51084
doi:10.2196/51084
PMID:38551623

Original Paper

Content Validity and Psychometric Properties of the German Version of the Holm and Cordoba Urinary Tract Infection Score for Uncomplicated Urinary Tract Infections in Women: Protocol for a Validation Study

Katharina Piontek[1], PhD; Sophie Nestler[1], MA; Anne Holm[2], PhD; John Brandt Brodersen[2,3,4], PhD; Christian Apfelbacher[1], PhD

[1]Institute of Social Medicine and Health Systems Research, Medical Faculty Magdeburg, Magdeburg, Germany

[2]The Centre of General Practice, University of Copenhagen, Copenhagen, Denmark

[3]The Research Unit for General Practice, Region Zealand, Denmark

[4]Research Unit for General Practice, Department of Community Medicine, Faculty of Health Sciences, UiT The Arctic University of Norway, Tromsø, Norway

Corresponding Author:
Katharina Piontek, PhD
Institute of Social Medicine and Health Systems Research
Medical Faculty Magdeburg
Leipziger Straße 44
Magdeburg, 39120
Germany
Phone: 49 391 67 24307
Email: katharina.piontek@med.ovgu.de

Abstract

Background: Uncomplicated urinary tract infections (UTIs) in women are among the most common bacterial infections in primary care. Given the health threats related to the overuse of antibiotics, alternative options are of increasing importance. Patient-reported outcome measures are valuable tools for including the patients' perspective when evaluating the efficacy of these strategies. Aiming to identify a suitable instrument to measure the severity and bothersomeness of UTI symptoms in women, we performed a systematic review of the literature and identified the Holm and Cordoba Urinary Tract Infection Score (HCUTI), which measures the severity, bothersomeness, and impact of uncomplicated UTIs on daily activities. This instrument showed sufficient content validity but needs translation and further validation before it can be used in German research.

Objective: For use in the German setting, we aim (1) to perform translation and linguistic validation of the HCUTI and (2) to evaluate content validity and psychometric properties of the German version of the HCUTI in a population of women with uncomplicated UTIs.

Methods: The HCUTI will be translated and linguistically validated using the dual-panel method. This process involves a bilingual translation panel and a lay panel to check the comprehensibility of the translation. Content validity of the translated questionnaire will be assessed using cognitive interviews according to the criteria for good content validity as recommended by the COSMIN (Consensus-based Standards for the selection of health Measurement Instruments) group involving women with uncomplicated UTIs and health care professionals. Subsequent psychometric validation of the German version of the HCUTI in a population of women with uncomplicated UTIs will include the assessment of structural validity, internal consistency, test-retest reliability, construct validity, responsiveness, and interpretability.

Results: Results of the translation and linguistic validation process and the results of the content validity study were obtained in September 2023 and will be published separately. Data on the psychometric properties of the German version of the HCUTI are anticipated in mid-2024.

Conclusions: We expect that data from the content validity study will provide important suggestions for potential modifications of the HCUTI for use in the German setting. The final version of the questionnaire will be used for the assessment of its psychometric properties in a large population of women with uncomplicated UTIs.

International Registered Report Identifier (IRRID): PRR1-10.2196/49903

(JMIR Res Protoc 2024;13:e49903) doi:10.2196/49903

KEYWORDS

uncomplicated urinary tract infections; patient-reported outcome measures; PROM; PROMs; content validity; psychometric properties; patient reported; validity; validation; urology; urinary; urinary tract infection; UTI; psychometric; scale; score; scoring; assessment; women's health; internal medicine; women; urinary tract infections; bacterial infection; primary care; infection

Introduction

Background

Patient-reported outcome measures (PROMs) are increasingly used in medical research and patient care since researchers, clinicians, and decisions makers are becoming increasingly aware that the patients' perspective is crucial when evaluating the efficacy of treatments and the quality of health services [1]. PROMs are standardized questionnaires for the assessment of information on health outcomes directly from the patient, including symptoms, physical, emotional, and social functioning, or multidimensional constructs such as health-related quality of life (HRQoL). Initially developed for use in research, the application of PROMs has expanded involving various domains of patient care including clinical decision-making and the evaluation of treatment strategies [1].

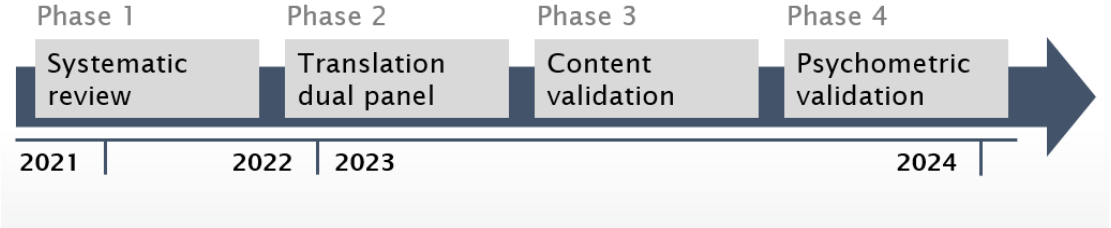
In primary care, uncomplicated urinary tract infections (UTIs) are among the most common bacterial infections in women and an important public health problem [2,3]. UTIs are generally self-limiting but commonly treated with antibiotics since they are bothersome, and antibiotic treatment leads to a more rapid resolution of symptoms [4,5]. Given the health threats related to conservative antibiotic treatment, the development of alternative treatment options is of increasing importance, and evaluating these strategies by considering the patients' perspective is a high priority. For this purpose, PROMs are valuable tools. For uncomplicated UTIs, several disease-specific instruments have been developed and validated, assessing symptom burden [6,7], the impairment of daily activities [6,8], and HRQoL [6]. The selection of a PROM is guided by content-related considerations, including the construct to be measured and the target population, but it is also essential to consider the quality of the measurement properties of available instruments. Aiming to facilitate the selection of high-quality PROMs for research and patient care, the COSMIN (Consensus-based Standards for the selection of health Measurement Instruments) initiative has suggested a methodology for conducting systematic reviews of PROMs [9]. This includes the assessment of the methodological quality of single studies on measurement properties of PROMs using the COSMIN risk of bias checklist [10] and the evaluation of the quality of measurement properties of the PROMs themselves.

A systematic review of the quality of measurement properties of available PROMs for uncomplicated UTIs using the COSMIN methodology was performed [11]. Among the identified PROMs measuring symptom severity and bothersomeness, the Acute Cystitis Symptom Score (ACSS) [6] and the Urinary Tract Infection-Symptom and Impairment Questionnaire (UTI-SIQ-8) [7] can be recommended for use (COSMIN category A). Capturing the broadest spectrum of outcomes, the assessment revealed that the Holm and Cordoba Urinary Tract Infection Score (HCUTI) [12] is a promising tool that warrants further validation (COSMIN category B). The HCUTI comprises 43 items on 3 subscales measuring the following aspects over a 7-day period: symptom severity (18 items), bothersomeness (18 items), and impact on daily activities (7 items). All items are rated on a 4-point Likert scale ranging from 1=none to 4=a lot. The instrument is available in Danish and has sufficient content validity. Data on other important measurement properties, for example, structural validity, are not yet available, indicating the need for further validation studies before the instrument can be used.

Objectives

The objective of this work is to perform translation and linguistic validation of the HCUTI for use in the German setting and to evaluate content validity and psychometric properties of the German version of the HCUTI in a population of women with uncomplicated UTIs. The protocol aims (1) to describe the translation process of the HCUTI from Danish into German language and the linguistic validation, (2) to describe the content validation of the translated HCUTI, and (3) to describe the psychometric validation of the German version of the HCUTI. The timeline is presented in Figure 1.

Figure 1. Study schedule.



Methods

Translation and Linguistic Validation

The HCUTI will be translated from Danish into German language using the dual-panel method [13]. A bilingual translation panel consisting of 4 nonprofessional persons fluently speaking Danish and German will perform the translation in a web-based meeting. A bilingual person with a medical background will moderate the session under the guidance of the study team, and discussion points and decisions about the wording of the single items will be protocolized. To ensure that the original meaning of the items is maintained, the developer of the HCUTI will participate in the translation process. Based on the translations of the single members of the panel, consensus will be sought about the wording during the session. Subsequently, a lay panel involving 4 German native-speaking women who have experienced uncomplicated UTI in their lifetime will review the translation regarding comprehensibility of the instructions, items, and response options, also in a web-based meeting. Changes in wording will be documented in minutes, and the session will be additionally audio recorded for later analysis. Two members of the research team will adapt the questionnaire according to the results of the lay panel. This procedure will result in the German version of the HCUTI, for which content validity and psychometric properties will be assessed.

Assessment of Content Validity

Overview

Following a qualitative approach, the content validity of the German version of the HCUTI will be assessed in cognitive interviews with affected women and interdisciplinary experts.

Recruitment of Participants

Women with uncomplicated UTIs will be recruited through the study team's network. Women being at least 18 years of age who have been diagnosed with uncomplicated UTI in the past 3 years will be included. Experts from relevant disciplines including family practice, urology, gynecology, nursing, health sciences, and psychosomatic medicine will be also recruited through the study team's network.

Procedure

Content validity will be assessed in accordance with the COSMIN criteria [10]. These criteria were developed in 2016 in a Delphi study among 159 experts from 21 countries including participants with expertise in qualitative research, development and evaluation of PROMs, and different professional backgrounds such as clinicians [14]. COSMIN provides a detailed, standardized, and transparent methodology, thereby promoting the selection and use of high-quality PROMs in research.

In individual semistructured interviews, women with uncomplicated UTIs (n=7) and health care professionals (n=7) will complete the questionnaire. The aim is to assess the relevance, comprehensiveness, and comprehensibility of the instructions, items, response options, and recall period from the women's and experts' perspectives. Two trained interviewers will conduct the interviews in a web-based meeting or in-person session following a standardized interview topic guide (Multimedia Appendix 1). The results will be documented for each item using a Microsoft Excel (Microsoft Corp) sheet. All interviews will be recorded and transcribed verbatim. Two researchers will perform data analyses using thematic analyses to identify problems related to relevance, comprehensiveness, and comprehensibility. Single items will be modified if at least 3 interviewees make a specific comment on that item. If required, the questionnaire will be adapted based on the results of the interviews, and all items will be tested in their final form in further qualitative interviews with women with uncomplicated UTIs.

Assessment of Psychometric Properties

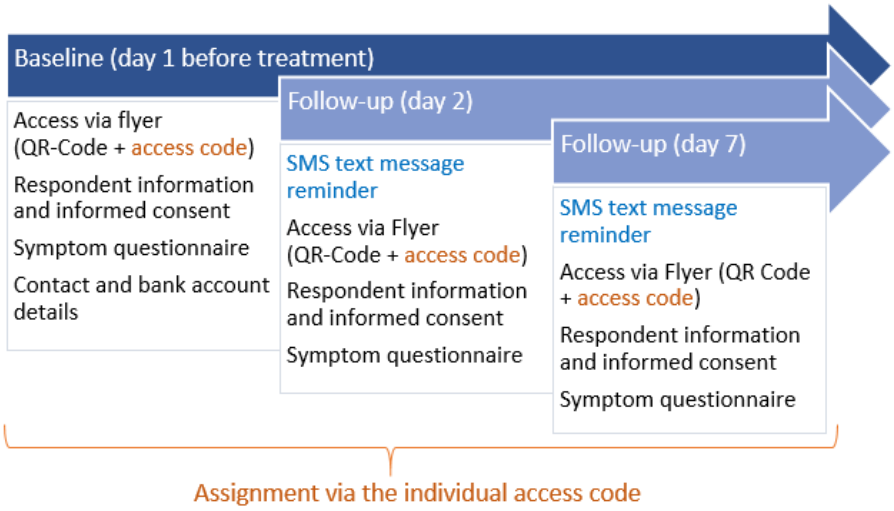
Overview

Once the content validation has been carried out and the final version of the HCUTI has been accepted by the interviewees and experts in terms of relevance, comprehensiveness, and comprehensibility, the psychometric validation study will be carried out in a quantitative web-based survey. For this purpose, the final HCUTI will be used in the target population, and the measurement properties will be analyzed using the survey data set.

Recruitment of Participants

A web-based survey targeting a sample size of >200 will be carried out. The study procedure is displayed in Figure 2. Women with uncomplicated UTIs will be recruited in practices for family medicine, urology, and gynecology. Women being at least 18 years of age with a confirmed diagnosis of acute cystitis or uncomplicated UTI (*International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* [*ICD-10*] codes N30.0, N30.9, and N39.0) will be included. Women with complicated UTI and women with insufficient German language skills will be excluded. Participating women will complete the survey at 3 measurement points: baseline (day 1, before treatment), follow-up 1 (day 2), and follow-up 2 (day 5). Subsequent data analyses on psychometric properties will include the assessment of structural validity, internal consistency, test-retest reliability, construct validity, responsiveness, and interpretability. All analyses will be performed in accordance with the criteria of the COSMIN group [9].

Figure 2. Procedure of the psychometric validation study.



Data Analyses

Structural Validity

Structural validity is defined as the degree to which the scores of an instrument are an adequate reflection of the dimensionality of the construct to be measured [15]. Unidimensionality refers to whether the items in a scale or subscale measure a single construct and is an assumption for internal consistency. The HCUTI is hypothesized to measure symptom severity, bothersomeness, and impact on daily activities, suggesting the unidimensionality of the 3 subscales. Structural validity will be assessed using item response theory and Rasch analysis. Confirmatory factor analyses will be performed to test the unidimensionality of the 3 subscales. The assessed parameters according to the criteria for good measurement properties as recommended by the COSMIN group are depicted in Textbox 1.

Using Rasch analysis, the resulting dimensions will be tested for differential item functioning, which is a method for analyzing measurement equivalence. Differential item functioning of an item is present if the item response differs across groups (eg, sex and race), controlling for an estimate of the construct being measured [16].

Textbox 1. Parameters and criteria for the assessment of structural validity.

- Unidimensionality: Comparative fit index or Tucker-Lewis index or comparable measure >0.95 or root mean square error of approximation <0.06 or standardized root mean square residual <0.08
- Local independency: Residual correlations among the items after controlling for the dominant factor <0.20 or Q3's<0.37
- Monotonicity: Item characteristic curves will be generated for each item; adequate-looking graphs are required or item scalability >0.30
- Model fit: Item response theory: χ^2>0.01 and Rasch: infit and outfit mean squares ≥0.5 and ≤1.5 or *Z* - standardized values >–2 and <2

Internal Consistency

Internal consistency is defined as the extent to which items within an instrument measure various aspects of the same characteristic or construct and is commonly evaluated using Cronbach α [17]. Given unidimensionality, we will analyze Cronbach α for the 3 subscales of the HCUTI. Cronbach α≥.70 is considered sufficient.

Test-Retest Reliability

Test-retest reliability is the degree to which test scores remain unchanged when measuring a stable individual characteristic on different occasions [18]. For the assessment of test-retest reliability, patients will complete the HCUTI before treatment (baseline) and at days 2 and 5 after baseline assessment. To define stable patients, an anchor question from the ACSS [6] on change in symptom severity will be included. Patients are asked if they have perceived any changes in their symptoms. This item is rated on a 5-point Likert scale as follows: 0=now I feel back to normal (all symptoms have gone away), 1=now I feel much better (majority of symptoms has gone away), 2=now I feel only somewhat better (majority of symptoms is still present), 3=no changes, now I feel about the same (no changes in my symptoms), and 4=now I feel worse (my condition is worse).

Based on the rating, participants are categorized into 3 groups as improved, unchanged, or worsened. Test-retest reliability will be assessed for patients whose symptom severity has not changed. The degree of agreement will be assessed using intraclass correlation coefficients. An intraclass correlation coefficient >0.70 is considered sufficient.

Construct Validity

Overview

Construct validity is the degree to which a measurement instrument assesses the intended construct and involves the evaluation of the relationship between the instrument and comparator instruments measuring the same, similar, or dissimilar constructs [10]. To determine construct validity,

hypotheses are formulated a priori, and these hypotheses concern comparisons with other outcome measurement instruments and differences in scores between "known" groups.

Comparison With Other Outcome Measurement Instruments

To determine the convergent validity of the HCUTI, the following comparator instruments will be administered:

The UTI-SIQ-8 is a self-administered questionnaire designed to assess symptom severity and bothersomeness of uncomplicated UTIs with 4 items each. The symptom severity scale is rated on a 5-point Likert scale ranging from 1=not at all to 5=very strong, and the bothersomeness scale is rated on a 5-point Likert scale ranging from 1=not at all to 5=very severe.

The ACSS comprises 4 domains assessing typical symptoms, differential diagnosis, quality of life, and additional symptoms. We will use 2 items of the quality-of-life subscale assessing the impact of UTI symptoms on daily activities and social activities. These items are rated on a 4-point Likert scale ranging from not 0=affected at all to 3=extremely affected.

The EQ-5D-5L is a generic instrument for the measurement of self-reported health status and HRQoL [19]. The EQ-5D-5L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Each dimension has five response levels: 1=no problems, 2=slight problems, 3=moderate problems, 4=severe problems, and 5=unable to or extreme problems. The EQ-5D-5L further includes a vertical EQ visual analog scale capturing the respondents' overall assessment of their health on a scale ranging from 0=worst possible health you can imagine to 100=best possible health you can imagine).

Correlations of the subscales of the HCUTI with the comparator instruments will be examined. A priori formulated hypotheses are tested using Spearman rank correlation coefficients. Following the recommendations of the COSMIN group, correlations with instruments measuring similar constructs should be ≥0.5 (high). Correlations with instruments measuring related but dissimilar constructs should be between 0.3 and 0.5 (moderate). Correlations with instruments measuring unrelated constructs should be <0.3 (low). The hypothesized associations are depicted in Table 1.

Table 1. Hypothesized associations between the subscales of the HCUTI[a] and the comparator instruments.

Comparator instruments	HCUTI subscales		
	Symptom severity	Bothersomeness	Impact on daily activities
UTI-SIQ-8[b] symptom severity	High	Moderate	Moderate
UTI-SIQ-8 bothersomeness	Moderate	High	Moderate
ACSS[c] daily activities item	Moderate	Moderate	High
ACSS social activities item	Moderate	Moderate	High
EQ-5D-5L			
Index: quality of life	Moderate	Moderate	High
Mobility	Moderate	Moderate	Moderate
Self-care	Moderate	Moderate	Moderate
Usual activities	Moderate	Moderate	Moderate
Pain or discomfort	High	Moderate	Moderate
Anxiety or depression	Low	Low	Low
EQ VAS[d]: health status	Moderate	Moderate	Moderate

[a]HCUTI: Holm and Cordoba Urinary Tract Infection Score.

[b]UTI-SIQ-8: Urinary Tract Infection-Symptom and Impairment Questionnaire.

[c]ACSS: Acute Cystitis Symptom Score.

[d]VAS: visual analog scale.

Comparison Between Subgroups (Known-Groups Validity)

Since no clinical ratings or controls will be available due to the design of the study, known-groups validity of the HCUTI will be examined using Kruskal-Wallis test to compare the symptom severity score at baseline assessment between different age groups. We hypothesize no significant differences in symptom severity across age groups.

Responsiveness

Responsiveness to change is defined as the ability of an instrument to detect change over time in the construct to be measured [20,21]. For the assessment of responsiveness, external criteria such as patient reports are needed to determine whether the patient's condition has improved, worsened, or not changed. For symptom severity, the anchor question from the ACSS will be used. We will further include a global rating of change item, which is rated on a 7-point Likert scale as –3=much worse, –2=moderately worse, –1=a little worse, 0=no change, +1=a

little better, +2=moderately better, or +3=much better. This item will be also used to assess changes in bothersomeness and changes in impact on daily activities. Based on the rating of the anchor questions, participants are categorized into 3 groups as improved, unchanged, or worsened. Analyses on responsiveness will be performed at days 2 and 5 after the baseline assessment.

First, we will examine the sensitivity of the HCUTI to changes in patients whose severity of illness has changed. Spearman rank correlations between change scores in the anchor questions and change scores in the subscales of the HCUTI will be calculated to examine if the anchors can be considered as appropriate (>0.3) [22]. Second, receiver operating characteristic curves will be used to assess the ability of the HCUTI subscales to distinguish between patients who have experienced different changes in their condition severity. For this analysis, patients will be grouped based on the anchor question as follows: participants with improvement in symptom severity, bothersomeness, and impact on daily activities ("a little better," "moderately better," or "much better") versus participants with no change or worsening in symptom severity, bothersomeness, and impact on daily activities ("no change," "a little worse," "moderately worse," or "much worse"). Area under the curve values >0.70 indicate sufficient discrimination between groups [9]. The points on the curve maximizing sensitivity and specificity are considered the optimal cutoff value for differentiating between responders and nonresponders. Third, following the construct approach, we hypothesize that improvement in the symptom severity scores of the HCUTI from baseline assessment to days 2 and 5 is related to improvements in the impact on daily activities and social activities as measured with the ACSS. We further hypothesize that improvement in the symptom severity scores of the HCUTI from baseline assessment to days 2 and 5 is related to improvements in the EQ-5D-5L index score and the EuroQol visual analog scale score. Spearman correlation coefficients will be calculated to assess the degree of association between the measures of change. We expect correlations ranging from 0.30 to 0.50.

Interpretability

Interpretability refers to the ease of deriving meaning from an instrument's scores. Interpretability is not considered a measurement property but is an important characteristic for the clinical application of an instrument. Data on the interpretation of changes in the scores are based on the minimal important difference (MID), which denotes the smallest score or change in score that would likely be important from the patient's or clinician's perspective [22]. We will estimate the MID for the 3 subscales of the HCUTI between baseline assessment and days 2 and 5 using an anchor-based approach, a distribution-based approach, and an integrated approach.

Using the anchor-based approach, the MID will be calculated by selecting patients who reported that they felt "a little worse" and "a little better" on the anchor questions. The mean change in scores of the HCUTI subscales in these groups will be calculated.

Applying the distribution-based approach, the MID is estimated based on the distribution of observed scores in the study population at baseline using 2 criteria: half SD and SE of measurement (SEM) [22]. According to these criteria, a change of more than one-half of the outcome score's SD is considered a MID [23]. The SEM is calculated as follows: $SEM=\sigma x\sqrt{(1-rel)}$, where σx=SD of the scale or subscale and rel=reliability of the subscale (internal consistency). A value of 1 SEM is used as a cutoff value for determining the MID [24].

The integrated approach combines the anchor-based approach and the distribution-based approach, taking into account the advantage of both an external criterion and a measure of variability [25]. To determine the MID, the upper bound of a 1-tail 95% CI for the mean score change in the "no change" group is used. The following formula will be used: mean score change in the patient group that did not change+1.645×SE. Patients will be equally grouped as using the classical anchor-based approach.

Ethical Considerations

The study has been approved by the Ethics Committee of the University of Magdeburg, Germany (19/23) and conforms to the principles of the Declaration of Helsinki. Written informed consent is obtained from all participants. The copyright holders gave permission to use the HCUTI for translation and validation. Data collected in the translation process; the content; and the psychometric validation study, including meeting minutes, transcripts, audio records, and survey data are stored in a pseudonymized way. An independent trusted third party at the Medical Faculty of the University of Magdeburg manages data containing personally identifiable information (consent forms and personal data required to pay incentives) and stores these data separately from the study data. A financial incentive is paid to all participants as follows: 50$ for participation in the dual panel or content validity study; 40$ for patients participating in the psychometric validation study; 100$ for physicians participating in the psychometric validation study + 10$ for each included patient.

Results

Results of the translation and linguistic validation process and the results of the content validity study were obtained in September 2023 and will be published separately. Data on the psychometric properties of the German version of the HCUTI are anticipated in mid-2024.

Discussion

Expected Results

The increasing research activities in the development of alternative approaches to conventional antibiotic treatment of uncomplicated UTIs indicate the need for high-quality PROMs to evaluate the efficacy of these strategies. This study will provide data on the content validity and psychometric properties of the German version of the HCUTI. We expect that the German version of the HCUTI is a valid and reliable PROM for the assessment of the symptom severity, bothersomeness, and impact of uncomplicated UTIs on daily activities in women. A tool with sufficient measurement properties that can be used

for the evaluation of novel therapeutic strategies in the German setting will be available.

Challenges

For participation in the web-based survey for the psychometric validation of the HCUTI, strict inclusion criteria in terms of physician-diagnosed cystitis or uncomplicated UTIs according to the respective *ICD-10* codes are applied. This requires collaboration with physicians and is time-consuming. For the recruitment of participating practices, a comprehensive approach is planned, including personal contacts of the study team, personal invitation letters, contact with professional associations, conferences of local physicians, and publications in local medical journals. An incentive will be paid to all participating physicians. To keep the effort for the physicians during data collection as low as possible, they will be asked to confirm the diagnosis on a prepared form and to hand the study information out to the eligible women. The study information includes all data required for study participation, and the women can participate in the survey independently.

In view of the planned analysis, in particular regarding structural validity, responsiveness, and interpretability, a sufficient sample size must be obtained. To maximize the participation rate and minimize the dropout rate, an incentive will be paid to the participating women. For the follow-up assessment, a reminder will be sent via SMS text message to enable prompt completion of the questionnaire using a mobile device. The study procedure will be pretested to evaluate the feasibility of the procedure and the implementation of the survey in LimeSurvey (LimeSurvey GmbH).

To draw attention to our research activities, information on our study, possibilities for participation, and current results will be published on a regular basis at the Institute of Social Medicine and Health Systems Research's website, X (formerly known as Twitter) account, and other social media platforms.

Acknowledgments

This work is funded by Bionorica SE, Germany. The study sponsor has no role in the design of the study, data collection, data management, data analysis, data interpretation, and issues regarding the publication of results.

Data Availability

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

Authors' Contributions

CA, KP, and SN contributed to the conceptualization of the study. KP designed the study protocol and drafted the paper. All authors were involved in revising the draft.

Conflicts of Interest

CA received institutional funding for the submitted work and consultancy fees from the Dr Wolff Group, Bionorica SE, Sanofi, Incyte Biosciences, RHEACELL, and LEO Pharma.

Multimedia Appendix 1
Interview guide.
[DOCX File , 27 KB - resprot_v13i1e49903_app1.docx]

References

1. Churruca K, Pomare C, Ellis LA, Long JC, Henderson SB, Murphy LED, et al. Patient-reported outcome measures (PROMs): a review of generic and condition-specific measures and a discussion of trends and issues. Health Expect 2021;24(4):1015-1024 [FREE Full text] [doi: 10.1111/hex.13254] [Medline: 33949755]
2. Medina M, Castillo-Pino E. An introduction to the epidemiology and burden of urinary tract infections. Ther Adv Urol 2019;11:1756287219832172 [FREE Full text] [doi: 10.1177/1756287219832172] [Medline: 31105774]
3. Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. Nat Rev Microbiol 2015;13(5):269-284 [FREE Full text] [doi: 10.1038/nrmicro3432] [Medline: 25853778]
4. Malterud K, Baerheim A. Peeing barbed wire. Symptom experiences in women with lower urinary tract infection. Scand J Prim Health Care 1999;17(1):49-53. [doi: 10.1080/028134399750002908] [Medline: 10229994]
5. Kaußner Y, Röver C, Heinz J, Hummers E, Debray TPA, Hay AD, et al. Reducing antibiotic use in uncomplicated urinary tract infections in adult women: a systematic review and individual participant data meta-analysis. Clin Microbiol Infect 2022;28(12):1558-1566 [FREE Full text] [doi: 10.1016/j.cmi.2022.06.017] [Medline: 35788049]
6. Alidjanov JF, Abdufattaev UA, Makhsudov SA, Pilatz A, Akilov FA, Naber KG, et al. New self-reporting questionnaire to assess urinary tract infections and differential diagnosis: acute cystitis symptom score. Urol Int 2014;92(2):230-236. [doi: 10.1159/000356177] [Medline: 24457349]

7. Gágyor I, Rentzsch K, Strube-Plaschke S, Himmel W. Psychometric properties of a self-assessment questionnaire concerning symptoms and impairment in urinary tract infections: the UTI-SIQ-8. BMJ Open 2021;11(2):e043328 [FREE Full text] [doi: 10.1136/bmjopen-2020-043328] [Medline: 33589460]
8. Wild DJ, Clayson DJ, Keating K, Gondek K. Validation of a patient-administered questionnaire to measure the activity impairment experienced by women with uncomplicated urinary tract infection: the Activity Impairment Assessment (AIA). Health Qual Life Outcomes 2005;3:42 [FREE Full text] [doi: 10.1186/1477-7525-3-42] [Medline: 16022727]
9. Prinsen CAC, Mokkink LB, Bouter LM, Alonso J, Patrick DL, de Vet HCW, et al. COSMIN guideline for systematic reviews of patient-reported outcome measures. Qual Life Res 2018;27(5):1147-1157 [FREE Full text] [doi: 10.1007/s11136-018-1798-3] [Medline: 29435801]
10. Mokkink LB, de Vet HCW, Prinsen CAC, Patrick DL, Alonso J, Bouter LM, et al. COSMIN risk of bias checklist for systematic reviews of patient-reported outcome measures. Qual Life Res 2018;27(5):1171-1179 [FREE Full text] [doi: 10.1007/s11136-017-1765-4] [Medline: 29260445]
11. Piontek K, Donhauser T, Kann G, Fechtner M, Apfelbacher C, Gabes M. Patient-reported outcome measures for uncomplicated urinary tract infections in women: a systematic review. Qual Life Res 2023;32(8):2137-2153 [FREE Full text] [doi: 10.1007/s11136-023-03358-5] [Medline: 36795285]
12. Holm A, Cordoba G, Siersma V, Brodersen J. Development and validation of a condition-specific diary to measure severity, bothersomeness and impact on daily activities for patients with acute urinary tract infection in primary care. Health Qual Life Outcomes 2017;15(1):57 [FREE Full text] [doi: 10.1186/s12955-017-0629-5] [Medline: 28340586]
13. Swaine-Verdier A, Doward LC, Hagell P, Thorsen H, McKenna SP. Adapting quality of life instruments. Value Health 2004;7(Suppl 1):S27-S30 [FREE Full text] [doi: 10.1111/j.1524-4733.2004.7s107.x] [Medline: 15367241]
14. Terwee CB, Prinsen CAC, Chiarotto A, Westerman MJ, Patrick DL, Alonso J, et al. COSMIN methodology for evaluating the content validity of patient-reported outcome measures: a Delphi study. Qual Life Res 2018;27(5):1159-1170 [FREE Full text] [doi: 10.1007/s11136-018-1829-0] [Medline: 29550964]
15. Mokkink LB, Terwee CB, Patrick DL, Alonso J, Stratford PW, Knol DL, et al. The COSMIN study reached international consensus on taxonomy, terminology, and definitions of measurement properties for health-related patient-reported outcomes. J Clin Epidemiol 2010;63(7):737-745. [doi: 10.1016/j.jclinepi.2010.02.006] [Medline: 20494804]
16. Teresi JA, Fleishman JA. Differential item functioning and health assessment. Qual Life Res 2007;16(Suppl 1):33-42. [doi: 10.1007/s11136-007-9184-6] [Medline: 17443420]
17. Revicki D. Internal consistency reliability. In: Michalos AC, editor. Encyclopedia of Quality of Life and Well-Being Research. Dordrecht: Springer Netherlands; 2014:3305-3306.
18. Vilagut G. Test-retest reliability. In: Michalos AC, editor. Encyclopedia of Quality of Life and Well-Being Research. Dordrecht: Springer Netherlands; 2014:6622-6625.
19. Devlin N, Pickard S, Busschbach J. The development of the EQ-5D-5L and its value sets. In: Devlin N, Roudijk B, Ludwig K, editors. Value Sets for EQ-5D-5L: A Compendium, Comparative Review & User Guide. Cham: Springer International Publishing; 2022:1-12.
20. Terwee CB. Responsiveness to change. In: Michalos AC, editor. Encyclopedia of Quality of Life and Well-Being Research. Dordrecht: Springer Netherlands; 2014:5547-5550.
21. Mokkink L, Terwee C, de Vet H. Key concepts in clinical epidemiology: responsiveness, the longitudinal aspect of validity. J Clin Epidemiol 2021;140:159-162 [FREE Full text] [doi: 10.1016/j.jclinepi.2021.06.002] [Medline: 34116141]
22. Revicki D, Hays RD, Cella D, Sloan J. Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. J Clin Epidemiol 2008;61(2):102-109. [doi: 10.1016/j.jclinepi.2007.03.012] [Medline: 18177782]
23. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care 2003;41(5):582-592 [FREE Full text] [doi: 10.1097/01.MLR.0000062554.74615.4C] [Medline: 12719681]
24. Copay AG, Subach BR, Glassman SD, Polly DW, Schuler TC. Understanding the minimum clinically important difference: a review of concepts and methods. Spine J 2007;7(5):541-546. [doi: 10.1016/j.spinee.2007.01.008] [Medline: 17448732]
25. de Vet HCW, Ostelo RWJG, Terwee CB, van der Roer N, Knol DL, Beckerman H, et al. Minimally important change determined by a visual method integrating an anchor-based and a distribution-based approach. Qual Life Res 2007;16(1):131-142 [FREE Full text] [doi: 10.1007/s11136-006-9109-9] [Medline: 17033901]

Abbreviations

ACSS: Acute Cystitis Symptom Score
COSMIN: Consensus-based Standards for the selection of health Measurement Instruments
HCUTI: Holm and Cordoba Urinary Tract Infection Score
HRQoL: health-related quality of life
ICD-10: International Statistical Classification of Diseases and Related Health Problems, Tenth Revision
MID: minimal important difference

PROM: patient-reported outcome measure
SEM: SE of measurement
UTI: urinary tract infection
UTI-SIQ-8: Urinary Tract Infection-Symptom and Impairment Questionnaire

Edited by A Mavragani; submitted 13.06.23; peer-reviewed by S Morselli, M Rounds; comments to author 03.11.23; revised version received 09.01.24; accepted 25.01.24; published 07.05.24.

Please cite as:
Piontek K, Nestler S, Holm A, Brodersen JB, Apfelbacher C
Content Validity and Psychometric Properties of the German Version of the Holm and Cordoba Urinary Tract Infection Score for Uncomplicated Urinary Tract Infections in Women: Protocol for a Validation Study
JMIR Res Protoc 2024;13:e49903
URL: https://www.researchprotocols.org/2024/1/e49903
doi:10.2196/49903
PMID:

Protocol

Evaluating the Appropriateness of Podcasts to Improve the Knowledge and Awareness of Selected Health Topics Among Undergraduate General Nursing Students: Protocol for an International Feasibility Study

Alanna Denny[1], BSc; Brian Curtin[1], BSc; Simon Taylor-Robinson[2], MD; Griphin Baxter Chirambo[3], MSc, PhD; Liezel Cilliers[4], MEd; Tsung-Shu Joseph Wu[5,6], MSc; Ciara O'Meara[7], BSc, MHSc, MAT, RNT, RGN; Richard Booth[8], MSc, PhD; John O'Donoghue[9,10,11], BSc, MSc, PhD

[1]University College Cork, Cork, Ireland
[2]Imperial College London, London, United Kingdom
[3]Faculty of Health Sciences, Mzuzu University, Mzuzu, Malawi
[4]University of Fort Hare, Alice, Eastern Cape, South Africa
[5]Research Department, Luke International, Mzuzu City, Malawi
[6]Overseas Services Department, Pingtung Christian Hospital, Pingtung County, Taiwan
[7]School of Nursing & Midwifery, University of Galway, Galway, Ireland
[8]Western University, Ontario, ON, Canada
[9]ASSERT Research Centre, University College Cork, Cork, Ireland
[10]Business Information Systems, University College Cork, Cork, Ireland
[11]Malawi eHealth Research Centre, Mzuzu University, Mzuzu City, Malawi

Corresponding Author:
Simon Taylor-Robinson, MD
Imperial College London
Electrical Engineering, South Kensington Campus
London, SW7 2AZ
United Kingdom
Phone: 44 203 312 6199
Fax: 44 203 312 9369
Email: s.taylor-robinson@imperial.ac.uk

Abstract

Background: Podcasts have proven to be a successful alternative source of educational material for students. Given the ability to listen to podcasts 24/7 and while on the go, this technology has the potential to provide informative and educational material to a large number of people at any given time. Podcasts are usually freely available on commonly used mobile devices, such as smartphones, laptops, and tablets.

Objective: This paper describes the impact of health-related podcasts as an intervention tool to support the knowledge and awareness of nursing students on a given topic.

Methods: Pre- and postpodcast questionnaires will gather data regarding the participants' knowledge and awareness of two topics—gestational diabetes and mental health. This intervention will be tested on general nursing undergraduate students. The total number of students (N=2395) from the participating universities are broken down as follows: (1) University College Cork (n=850) and the University of Galway (n=450) in Ireland, (2) Mzuzu University in Malawi (n=719), and (3) University of Fort Hare in South Africa (n=376).

Results: The study received ethical approval from the University College Cork Ethics Committee (2022-027A1). The approval obtained from University College Cork sufficed as ethics coverage for the University of Galway in Ireland. Ethics approval was also received from the Mzuzu University Research Ethics Committee (ID MZUNIREC/DOR/23/28) and the Inter-Faculty Research Ethics Committee of the University of Fort Hare (ID CIL002-21). Data collection is currently underway and will continue until the end of February 2024. The quantitative and qualitative data are expected to be analyzed in March 2024.

Conclusions: Results from this study will allow for an investigation into the impact of podcasts in different settings: a high-income country (Ireland), an upper-middle–income country (South Africa), and a low-to-middle–income country (Malawi). The data gathered from this feasibility study will provide more clarity on the potential utility of podcasts as an intervention tool. We will gather data regarding listener demographics (eg, country of residence, age, gender, and year of study).

International Registered Report Identifier (IRRID): DERR1-10.2196/50735

(JMIR Res Protoc 2024;13:e50735) doi:10.2196/50735

KEYWORDS

podcasting; podcast; nursing student; gestational diabetes; mental health; health; knowledge

Introduction

Overview

The term “podcast” has been used since approximately 2004. It originally stemmed from 2 terms “iPod” and “broadcast” [1]. The groundbreaking iPod device from Apple pioneered the mobility of digital audio information. Although the iPod has never been the only device used for podcast listening, it swiftly grew into one of the most prominent listening devices [2]. A podcast can be listened to on any digital audio listening device, including a computer that supports audio file playing. Therefore, podcasts can be listened to 24/7 and while on the go. These combined attributes have dramatically increased the use of podcasts over the last 20 years [3]. During this period, podcasts have been regarded as effective medical educational instruments [4,5]. Thus, the accessibility and open access of podcasts may be hugely attractive to higher education institutes as a method of teaching and learning.

Chin et al [6] (2017) showed that after listening to the extracurricular audio podcasts on health-related topics, students who completed the study experienced a significant and probably educationally relevant improvement in their knowledge. This aligns with the results of Mitchell et al [7] (2021), which showed an overall increase of 11.54% in knowledge attainment in undergraduate nursing students after listening to a podcast on delirium [7]. Overall, these studies demonstrate the impact of podcasting on knowledge attainment in third-level education.

A study of the literature in 2017 further highlights that podcasts are a popular source of educational material for a wide range of health care professionals, including junior doctors, nurses, and medical students [4]. In particular, third-level nursing education is an area of health care that calls for sophisticated critical thinking abilities and decision-making processes, which may likely influence clinical competency. University staff members can find themselves searching for new and creative ways to present material in an engaging fashion as the demands on their time and the availability of innovative tools for use in nursing education expand. The implementation of podcasting in nursing education is one strategy to enhance learning, as discussed in the literature. Recent research conducted in Northern Ireland on podcasting to improve undergraduate nursing students’ awareness of Parkinson Disease found that “podcasting as an educational resource for undergraduate student nurses is a successful way of developing knowledge for PD [Parkinson disease]” [8].

There has been a rise in research being conducted on podcasting in nursing education [9]. Despite this, there is limited research being undertaken on the use of podcasts in Africa, even though podcasting is a great topic of conversation among interested African communities. Surveys completed by the Reuters Digital News Report that included 2 African countries highlighted that 33% of participants were considered regular podcast users [10]. Notably, 50% believed that podcasts are more informative in terms of providing a better understanding of issues compared to traditional media platforms [10].

This research will allow for an investigation into the impact of podcasts on knowledge and awareness in different settings—a high-income country (Ireland), an upper-middle–income country (South Africa), and a low-to-middle–income country (Malawi).

Knowledge and awareness have often been used synonymously, but in this study, a distinction between these 2 interchangeable words is set. Knowledge has been described as “the fact or condition of knowing something with familiarity gained through experience or association,” the “acquaintance with or understanding of a science, art, or technique,” and “the range of one's information or understanding” [11]. Awareness has been described as “knowledge and understanding that something is happening or exists” [12]. In our study, awareness will be defined as having heard of a term or topic, while knowledge will be defined as a deeper understanding of the area.

The podcast topics are as follows:

Pregnancy

According to the World Health Organization (WHO), approximately 800 women died every day from pregnancy and childbirth-related avoidable causes in 2020 [13]. Of note, nearly 95% of these maternal deaths took place in low- and low-to-middle–income countries, such as Malawi [13]. This highlights the need to raise awareness of pregnancy risk factors, complications, and services available for women to access the care they need.

Gestational Diabetes

The WHO describes gestational diabetes as “hyperglycemia with blood glucose values above normal but below those diagnostic of diabetes,” which occurs during pregnancy [14]. Worldwide, 21.3 million pregnancies are linked to hyperglycemia, and of these, 18.4 million pregnancies are linked to gestational diabetes mellitus [15]. Furthermore, it is estimated that more than 90% of hyperglycemia cases in pregnancy occur in low- and middle-income countries [16]. Gestational diabetes can impact both the fetus and the mother. Long-term

implications for children include an increased risk of obesity and metabolic disruption [17]. Furthermore, women who experience gestational diabetes are at risk for developing type 2 diabetes later in life [17]. This demonstrates that gestational diabetes a potentially preventable condition can have a huge societal burden and devastating long-term outcomes.

HIV/AIDS

The WHO figures highlight how HIV infection remains a significant global health concern with 40.1 million deaths occurring to date [18]. Approximately, 650,000 persons died in 2021 as a result of HIV-related causes, and by the end of 2021, an estimated 38.4 million people were living with HIV [18]. Nearly 60% of new HIV infections worldwide occur in the WHO African Region [18]. The HIV infection is incurable. However, owing to accessibility to effective HIV prevention, diagnosis, treatment, and care, especially for opportunistic infections, HIV infection has evolved into a manageable chronic health disease, allowing those who have it to live long and healthy lives. Unfortunately, the disease continues to take many lives despite the availability of treatment and hence it is an important podcast topic to discuss to increase knowledge and awareness.

Cervical Cancer

According to global estimates, there were 604,000 new cases and 342,000 deaths from cervical cancer in women worldwide in 2020 [19]. New cases of cervical cancer and deaths from cervical cancer that occurred in low- and middle-income countries accounted for around 90% of the global total deaths in 2020 [20]. Nearly 50% of high-grade cervical precancers are caused by 2 human papillomavirus types (16 and 18) [20]. This is an important topic to discuss as cervical cancer is curable if detected early and treated effectively. Preventing cervical cancer is more affordable with the human papillomavirus vaccine, precancer lesions screening, and treatment.

Malnutrition

The WHO defines malnutrition as “undernutrition (wasting, stunting, underweight), inadequate vitamins or minerals, overweight, obesity, and resulting diet-related noncommunicable diseases” [21]. A total of 462 million adults are underweight, compared to 1.9 billion who are overweight or obese [21]. Undernutrition is a contributing factor in about 45% of deaths in children younger than 5 years and mostly takes place in low- and middle-income countries [21]. The prevalence of childhood obesity and overweight is also rising in these same nations. The global burden of malnutrition has substantial and long-lasting effects on people and their families as well as on communities, nations, and the economy; therefore, greater conversation around this area is imperative.

Mental Health

As evidenced by the inclusion of mental health in the United Nations Sustainable Development Goals [22], there has been growing recognition of the crucial role mental health plays in achieving global development goals in recent years [23]. According to Arias et al [24] (2022), 418 million disability-adjusted life years or 16% of all disability-adjusted life years worldwide could be attributed to mental diseases in 2019. Overall, this confirms that the need for action on mental health topics is paramount.

Objective of the Feasibility Study

This paper explores the impact of health-related podcasts as an intervention tool to support the knowledge and awareness of nursing students on a given topic. To address this objective, we aim to answer the following questions:

1. Can podcasts support listeners' knowledge of global health topics?
2. Is knowledge attainment from podcasts different across Ireland, South Africa, and Malawi?
3. Is podcasting effective for supporting awareness in nursing students on global health diseases and issues?

Methods

Research Design

This pre- and postpodcast intervention is a feasibility study. Feasibility studies facilitate researchers’ evaluation of whether an intervention is suitable to undergo additional investigation or whether the concepts and conclusions can be applicable and sustainable to the population [25]. A feasibility method was chosen for this study due to the lack of previously published studies on this specific intervention.

Type of Study and Setting

This study mainly involves quantitative data, but qualitative data will be synthesized for the 1 open-ended question on the survey tool. These questionnaires will be created and managed using Google Forms, as it is compliant with the General Data Protection Regulation. Microsoft Excel will be used to capture qualitative and quantitative data and to execute descriptive statistics in the form of percentages and frequencies [26]. This study will be carried out from March 2023 until March 2024.

The selected podcast topics revolve around global health concerns that exhibit significant variations in understanding and practices across different countries. This is intended to enable in-depth podcast discussions and survey questions that can yield insights into how nursing students use the podcasts. These podcast topics have been chosen to encompass a diversity of health-related topics affecting both high- and low-income countries.

To date, the recordings of the podcasts have been conducted. Video and audio files for 2 out of the 6 podcasts will be available for the study participants. Despite only 2 podcasts being chosen for research purposes, all 6 podcasts will be disseminated on platforms including but not limited to YouTube and Spotify. The podcasts’ duration ranges from approximately 30 to 60 minutes each. Each podcast discusses the risk factors, symptoms, and treatment or management of the global health topic.

Each podcast was created with a panel of international experts along with a chair (AD and BC). The 2 podcasts selected for the study are the gestational diabetes podcast and the mental health podcast. As this is a voluntary feasibility project, we only have the resources to examine 2 of the podcasts. Upon completion of this research, we will determine if podcasting is

an effective method of increasing knowledge and awareness attainment. If the results are positive, we will conduct a broader survey, which will include members of the public and not just nursing students, and will release more podcasts. In addition, mental health and gestational diabetes are widespread issues normally taught in depth in nursing schools and are not confined by geographical locations or socioeconomic status. Likewise, these podcasts had the best audio quality, conversation flow, and in-depth discussion, as decided by the research team. It is evident from the literature that gestational diabetes is a global phenomenon that can impact people from Ireland, South Africa, and Malawi and have potentially long-term preventable implications [16,17]. Similarly, mental health is a global health concern that is gaining increasing attention due to the addition of mental health in the Sustainable Development Goals and the disability-adjusted life years that are attributable to mental disease [23,24]. The selected global health topics are on the list of the top 10 global public health challenges to track in 2023 [27].

Measurement Tools

For the gestational diabetes podcast, a 5-item "Yes-No-I don't know" awareness questionnaire and a 27-item "Yes-No-I don't know" knowledge questionnaire were developed by the researchers. For the mental health podcast, a 4-item "Yes-No-I don't Know" awareness questionnaire and a 26-item "Yes-No-I don't know" knowledge questionnaire were developed by the researchers. The gestational diabetes podcast has 1 additional survey question on awareness and knowledge compared to the mental health podcast, as the podcast discussion on gestational diabetes covered additional items beyond those initially prepared in the semistructured podcast guide.

The knowledge questionnaires for each of these podcasts will address 3 key themes: risk factors, symptoms, and services or treatments. Examples of the questions asked can be found in Table 1.

The only qualitative question asked at the end of each podcast is the following:

"Do you have any further comments on the podcast (duration or formatting), questions asked, or recommendations for future podcasts?"

Table 1. Example of questions asked on knowledge and awareness.

Topic	Area being assessed	Examples of question asked before and after the podcast
Gestational diabetes	Knowledge	Is obesity or BMI a risk factor for gestational diabetes mellitus?
Gestational diabetes	Awareness	Have you heard of metformin?
Mental health	Knowledge	Is a history of mental illness in a blood relative family member a risk factors for mental illness?
Mental health	Awareness	Are you aware of risk factors for mental health problems?

Study Population

The study will collect data from undergraduate general nursing students from 4 universities located across Ireland, South Africa, and Malawi.

Sampling and Sample Sizes

The sample will consist of a cohort of undergraduate nursing students from University College Cork (UCC) and the University of Galway (Ireland), the University of Fort Hare (South Africa), and Mzuzu University (Malawi). These students will be recruited through invitation via the university they are attending. Entry into the study will be entirely voluntary.

The main aim is to compare the pre- and postpodcast scores on knowledge and awareness differences with a paired 2-tailed *t* test. The inputs that will be used are the expected mean (SD) of the paired differences. As this is a feasibility study, a formal sample size calculation is not required [28].

Inclusion and Exclusion Criteria

Exclusion criteria include those who are unable to complete the web-based questionnaires due to a lack of internet connection. These surveys are solely available via Google Forms and are thus inaccessible without an internet connection. Participants will be excluded if they are not a current resident and a registered undergraduate general nursing student of Ireland, South Africa, or Malawi and do not agree to consent to the study. As this is a feasibility study, we are targeting a small cohort of individuals who are convenient to the research team. Inclusion criteria encompass those aged 18 years and older.

Data Collection and Management

Questionnaires will be made using Google Forms, which are stored on UCC's Microsoft OneDrive. The questionnaires will include closed-ended questions using a point scale, with points given to the tick-the-box answers of "Yes", "No," or "I don't know." These questionnaires will be distributed to UCC (Ireland), University of Galway (Ireland), University of Fort Hare (South Africa), and Mzuzu University (Malawi). Regarding the data collection, the investigators will not seek names or emails from the participants, and the data will be fully anonymized. Fully anonymized data are achievable in this study, as participants are not required to complete two different surveys. The pre- and postpodcast questions are on a single Google Form, separated only by the embedded podcast file (not 2 separate survey forms), allowing a direct comparison of survey responses without requiring participant contact details. Once the survey is submitted, the option to withdraw will no longer be available. Answers to our survey (questionnaires) will be stored on UCC-supplied Google Forms and uploaded to OneDrive. Data on knowledge and awareness will be collected from both pre- and postpodcast surveys. Information on gender,

age, year of study, and the university the student is attending will also be stored, along with the consent forms. The UCC-supplied OneDrive will also be used during data collection and data analyses due to the ability to store data generated on the cloud automatically. Data will be stored for a minimum of 10 years. The data will be controlled by the UCC study members. General Data Protection Regulation will be observed at all times with all information anonymized.

Data collection tools will be structured according to the research themes outlined as follows:

Podcast Knowledge

Participants will be asked about their knowledge of the global health topic by assessing knowledge of symptoms, risk factors, and treatment options associated with the disease. The Google Forms will present an individual question on symptoms, risk factors, and treatments and ask respondents to indicate whether they are symptoms, risk factors, and treatment options of the condition with response options "Yes," "No," or "I Don't know." For the prompted symptoms items, "No" and "I Don't Know" responses will be combined and scored 0, and "Yes" responses will be scored 1. Total scores for prompted awareness of warning signs and risk factors as well as knowledge of symptoms, risk factors, treatment options, government policies, or screening programs will be calculated by adding the recorded responses together.

Podcast Awareness

To achieve this objective, terms on awareness will focus on whether participants have previously heard of terminology associated with the specific podcast and are aware of services available for that health topic or whether they have heard of the condition or disease. With regard to awareness assessment, a scoring system will be implemented. For each question item, "No," and "I Don't Know" responses will be combined and scored 0, and "Yes" responses will be scored 1.

Data Analysis

Microsoft Excel and Google Forms will be used to capture raw quantitative data and to execute the descriptive statistics in the form of percentages and frequencies. Descriptive statistics, including percentages, means, and standard deviations will be calculated for participants' survey responses. For the pre- and posttest analysis, a paired 2-tailed *t* test analysis for the questions that assess medical knowledge will be performed. The means of both the pre and posttests will be calculated. The pretest will act as the control, and therefore, *P* values will be determined to identify if the results are statistically significant. This analysis will enable the observation of whether the podcasts were an effective intervention tool by examining a higher posttest mean score. Significance will be defined as $P<.05$.

This is an international feasibility study, and it would be of great interest to analyze participants' country of residence in conjunction with the level of knowledge and awareness gained from the podcast to give us an insight into which country would benefit most from this form of audio learning. To conduct this, we will perform a subgroup analysis in SPSS. Furthermore, men and women have been shown to learn differently, with women preferentially being auditory learners [29]. Therefore, a subgroup analysis on gender will be carried out on SPSS. This research will help to clarify whether podcasting is a useful educational resource that is of benefit to both sexes as an alternative source of learning [30].

For this study, we only have 1 open-ended question, which is "Do you have any further comments on the podcast (duration or formatting), questions asked, or recommendations for future podcasts?" We will conduct a thematic analysis of the responses to open-ended questions [31]. To analyze and describe the comments, a coding frame will be developed. If responses contain 2 or more different statements, these statements or sentences will be coded separately or line by line.

Ethical Considerations

The study received ethical approval from the UCC's Social Research Ethics Committee (ID 2022-027A1). The approval obtained from UCC sufficed as ethics coverage for the University of Galway in Ireland. Ethics approval was also received by the Mzuzu University Research Ethics Committee (ID MZUNIREC/DOR/23/28) and by the Inter-Faculty Research Ethics Committee at the University of Fort Hare (ID CIL002-21) in South Africa. The study will conform with the precepts of the Declaration of Helsinki on Human Rights of 1975. This research will involve participation through remotely answering survey questions and listening to podcasts. The survey is available in the English language only, as it is the official language in Ireland, Malawi, and South Africa. Participation in this research is not likely to cause any harm or pose a risk to the study participants' well-being.

Informed consent will be explicitly sought from the study participants at the beginning of the survey, and participants are required to be 18 years of age and older. Only undergraduate nurses can take part in this research. Participate confidentiality will be upheld throughout the study process. To maintain confidentiality, no emails, names, or contact information will be required.

The study data will be stored on a password-protected laptop to which only the research team will have access. Participation in this study is entirely voluntary, and participants retain the right to withdraw their participation and data at any time while filling out the survey. However, once the survey is submitted, participants cannot withdraw because the survey is anonymous, and we can therefore not identify who completed the survey. Participants will not receive remuneration or compensation for taking part in the study.

Results

Data collection is currently being conducted and will be carried out until February 2024. The quantitative and qualitative data are expected to be analyzed by March 2024.

Discussion

Comparison With Prior Work

This study, to the best of our knowledge, is the first podcast intervention study to compare the impact of podcasting on

nursing education internationally. This is extremely pertinent considering the changing landscape of third-level education, the impact of web learning, and the shift away from conventional approaches [32]. This study may highlight the idea that the next generation may be keener on using this technology, as they have grown up with e-learning and internet-based content.

The implementation of podcasting in nursing education is a strategy that has been considered in previous literature. O'Connor et al [33] (2020) identified that the next generation of nursing students has grown up with technology and thus are mostly learners with diverse digital literacy abilities and perhaps a need for interactive, learner-centred courses. Fortunately, podcasting is emerging as a viable educational option. Abate [34] (2013) demonstrated that when undergraduate nursing students listened to a segmented podcast, they had increased scores on multiple choice exams and case study tests, compared to face-to-face lectures and unsegmented podcasts. Likewise, Burke and Cody [35] (2014) reported that 86% of undergraduate nursing students felt that podcasts enriched their learning, and an astonishing 94% of these students would recommend podcasting for other courses.

Expected Findings

This study will investigate the impact of informational podcasts on the attainment of knowledge and awareness in undergraduate nursing students. It will provide valuable insights into the impact of podcasts in education settings across different countries. We anticipate that results from this study could illuminate whether educational podcasts serve as an impactful learning resource for undergraduate nursing students.

Future Research

Other populations apart from undergraduate general nursing students should be included in further studies to determine the appropriateness of this intervention across third-level education. If the results are positive, this feasibility study will be used to inform future research on podcasting in third-level education.

Strengths and Limitations

The role of social media platforms as a medium to deliver education has been under development for several years. This research will provide a clear contribution focusing on the impact of one such platform—YouTube—for undergraduate nursing students in the areas of knowledge and awareness on a set of given topics. This research is international and will enable a greater understanding of the usefulness of podcasts in a high-income country (Ireland) compared to middle-to-low-income countries (South Africa and Malawi). Nonresponse is one of the limitations of this study. Pre- and postpodcast questionnaires are planned to be administered before and after listening to a podcast recording. This may cause participants to become mentally fatigued and not fill out the questionnaire following the podcast, resulting in a reduced response rate. Another limitation of this study is selection bias. For this study, only general undergraduate nursing students will be used to gather information, and thus, they could skew the results due to the level of knowledge they should already have from their undergraduate studies. The generalisability of the study may be limited by the cohort only being composed of nursing students.

Conclusions

Results from this study will allow for an investigation into the impact of podcasts in different settings, a high-income country (Ireland), an upper-middle–income country (South Africa), and a low-to-middle–income country (Malawi). The data gathered from this feasibility study will provide more clarity on the potential utility of podcasts as an intervention tool. We will gather data regarding listener demographics (ie, country of residence, age, gender, and year of study) to ascertain the outreach of the podcasts, which could shape future studies on podcasts as an educational tool. If the results of our study are positive in terms of an increase in knowledge and awareness, we hope to identify other populations that might benefit from this sort of educational resource.

Acknowledgments

We would like to thank all the wonderful speakers who have contributed their time and knowledge to the creation of these podcasts.

This research received no specific grants from any funding agency in the public, commercial, or not-for-profit sectors. STR was partially funded by a grant from the Wellcome Trust’s Institutional Strategic Support Fund (ISSF) at Imperial College London.

Data Availability

The media data that support the methodology of this study are openly available on Figshare [36]. This is covered by the Creative Commons Attribution license (CC BY 4.0 license).

Authors' Contributions

AD, BC, JOD, and GBC contributed to the design and development of podcasts. LC, GBC, AD, BC, and COM assisted with study recruitment and advertisement. RB, STR, AD, BC, JOD, GBC, COM, and LC edited and reviewed the manuscript. All members of the research team approved the manuscript.

Conflicts of Interest

None declared.

References

1. Hammersley. Audible revolution. The Guardian. URL: https://www.theguardian.com/media/2004/feb/12/broadcasting.digitalmedia [accessed 2004-02-12]
2. Colombo G, Curtis FJ. Absolute Beginner's Guide to Podcasting. Indianapolis, IN: Que Publishing; 2018:-1.
3. Rime J, Pike C, Collins T. What is a podcast? Considering innovations in podcasting through the six-tensions framework. Convergence 2022 Jun 02;28(5):1260-1282. [doi: 10.1177/13548565221104444]
4. Cho D, Cosimini M, Espinoza J. Podcasting in medical education: a review of the literature. Korean J Med Educ 2017 Dec;29(4):229-239 [FREE Full text] [doi: 10.3946/kjme.2017.69] [Medline: 29207454]
5. Brew-Girard E, Brown R, Salter E, Hattersley C, Hodge O, Leonard X, et al. Hunting for Pearls: A Qualitative Analysis of the Reflections of Students Creating Psychiatric Podcasts. AMEP 2023 Oct;Volume 14:1157-1166. [doi: 10.2147/amep.s411072]
6. Chin A, Helman A, Chan T. Podcast use in undergraduate medical education. Cureus 2017 Dec 09;9(12):e1930 [FREE Full text] [doi: 10.7759/cureus.1930] [Medline: 29464137]
7. Mitchell G, Scott J, Carter G, Wilson CB. Evaluation of a delirium awareness podcast for undergraduate nursing students in Northern Ireland: a pre−/post-test study. BMC Nurs 2021 Jan 13;20(1):1-11. [doi: 10.1186/s12912-021-00543-0]
8. Crooks S, Stark P, Carlisle S, McMullan J, Copeland S, Wong WYA, et al. Evaluation of a co-designed Parkinson's awareness audio podcast for undergraduate nursing students in Northern Ireland. BMC Nurs 2023 Oct 09;22(1):370 [FREE Full text] [doi: 10.1186/s12912-023-01544-x] [Medline: 37814245]
9. O'Connor S, Daly CS, MacArthur J, Borglin G, Booth RG. Podcasting in nursing and midwifery education: an integrative review. Nurse Educ Pract 2020 Aug;47:102827. [doi: 10.1016/j.nepr.2020.102827]
10. Reuters Institute Digital News Report 2020. URL: https://reutersinstitute.politics.ox.ac.uk/sites/default/files/2020-06/DNR_2020_FINAL.pdf [accessed 2023-11-29]
11. Knowledge. Meriam-Webster. URL: https://www.merriam-webster.com/dictionary/knowledge [accessed 2023-11-29]
12. Merriam-Webster. Awareness. URL: https://www.merriam-webster.com/dictionary/awareness [accessed 2023-11-29]
13. Maternal mortality. World Health Organization. URL: https://www.who.int/news-room/fact-sheets/detail/maternal-mortality [accessed 2023-11-23]
14. Diabetes. World Health Organization. URL: https://www.who.int/news-room/fact-sheets/detail/diabetes [accessed 2023-11-29]
15. Malanda B. Lessons from WINGS. Diabetes Res Clin Pract 2017 Dec;134:210-211. [doi: 10.1016/j.diabres.2017.11.017] [Medline: 29223254]
16. Guariguata L, Linnenkamp U, Beagley J, Whiting D, Cho N. Global estimates of the prevalence of hyperglycaemia in pregnancy. Diabetes Res Clin Pract 2014 Feb;103(2):176-185. [doi: 10.1016/j.diabres.2013.11.003] [Medline: 24300020]
17. Hod M, Kapur A, Sacks DA, Hadar E, Agarwal M, Di Renzo GC, et al. The International Federation of Gynecology and Obstetrics (FIGO) Initiative on gestational diabetes mellitus: a pragmatic guide for diagnosis, management, and care. Int J Gynaecol Obstet 2015 Oct;131:S173. [doi: 10.1016/s0020-7292(15)30007-2]
18. Data on the size of the HIV epidemic. World Health Organization. URL: https://www.who.int/data/gho/data/themes/hiv-aids/data-on-the-size-of-the-hiv-aids-epidemic [accessed 2023-11-29]
19. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021 Feb 04:209-249 [FREE Full text] [doi: 10.3322/caac.21660] [Medline: 33538338]
20. Cervical cancer. World Health Organization. URL: https://www.who.int/news-room/fact-sheets/detail/cervical-cancer [accessed 2023-11-29]
21. Malnutrition. World Health Organization. URL: https://www.who.int/news-room/fact-sheets/detail/malnutrition [accessed 2023-11-29]
22. The 17 goals, sustainable development. United Nations. URL: https://sdgs.un.org/goals [accessed 2023-11-29]
23. Mental health. World Health Organization. URL: https://www.who.int/health-topics/mental-health#tab=tab_1 [accessed 2023-11-29]
24. Arias D, Saxena S, Verguet S. Quantifying the global burden of mental disorders and their economic value. EClinicalMedicine 2022 Dec;54:101675 [FREE Full text] [doi: 10.1016/j.eclinm.2022.101675] [Medline: 36193171]
25. Bowen DJ, Kreuter M, Spring B, Cofta-Woerpel L, Linnan L, Weiner D, et al. How we design feasibility studies. Am J Prev Med 2009 May;36(5):452-457 [FREE Full text] [doi: 10.1016/j.amepre.2009.02.002] [Medline: 19362699]
26. Google forms: sign-in. Google. URL: https://docs.google.com/forms/ [accessed 2023-12-22]
27. Lucero‐Prisno DE, Shomuyiwa DO, Kouwenhoven MBN, Dorji T, Odey GO, Miranda AV, et al. Top 10 public health challenges to track in 2023: shifting focus beyond a global pandemic. Public Health Chall 2023 May 02;2(2):1-9. [doi: 10.1002/puh2.86]
28. Sluggett JK, Page AT, Chen EYH, Ilomäki J, Corlis M, Van Emden J, et al. Protocol for a non-randomised pilot and feasibility study evaluating a multicomponent intervention to simplify medication regimens for people receiving community-based home care services. BMJ Open 2019 Jul 19;9(7):e025345 [FREE Full text] [doi: 10.1136/bmjopen-2018-025345] [Medline: 31326924]

29. Wehrwein EA, Lujan HL, DiCarlo SE. Gender differences in learning style preferences among undergraduate physiology students. Adv Physiol Educ 2007 Jun;31(2):153-157 [FREE Full text] [doi: 10.1152/advan.00060.2006] [Medline: 17562903]
30. Baharu H. Male and Female EFL Students' Learning Style at Muhammadiyah University of Makassar. ELTWW 2019 Jun 28;6(1):37. [doi: 10.26858/eltww.v6i1.8407]
31. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol 2006 Jan;3(2):77-101. [doi: 10.1191/1478088706qp063oa]
32. Wongwatkit C, Srisawasdi N, Hwang G, Panjaburee P. Influence of an integrated learning diagnosis and formative assessment-based personalized web learning approach on students learning performances and perceptions. Interact Learn Environ 2016 Sep 07;25(7):889-903. [doi: 10.1080/10494820.2016.1224255]
33. O'Connor S, Daly CS, MacArthur J, Borglin G, Booth RG. Podcasting in nursing and midwifery education: an integrative review. Nurse Educ Pract 2020 Aug;47:102827 [FREE Full text] [doi: 10.1016/j.nepr.2020.102827] [Medline: 32763834]
34. Abate KS. The effect of podcast lectures on nursing students' knowledge retention and application. Nurs Educ Perspect 2013;34(3):182-185. [doi: 10.1097/00024776-201305000-00010]
35. Burke S, Cody W. Podcasting in undergraduate nursing programs. Nurse Educ 2014;39(5):256-259. [doi: 10.1097/NNE.0000000000000059] [Medline: 25137450]
36. An international study evaluating the appropriateness of podcasts to improve the knowledge and awareness of selected health topics amongst undergraduate general nursing students: protocol for a feasibility study. Figshare. URL: http://doi.org/10.6084/m9.figshare.24625062 [accessed 2024-01-04]

Abbreviations

UCC: University College Cork
WHO: World Health Organization

Edited by A Mavragani; submitted 17.07.23; peer-reviewed by E Mancinelli, A AL-Asadi; comments to author 12.09.23; revised version received 29.11.23; accepted 11.12.23; published 06.02.24.

Please cite as:
Denny A, Curtin B, Taylor-Robinson S, Chirambo GB, Cilliers L, Wu TSJ, O'Meara C, Booth R, O'Donoghue J
Evaluating the Appropriateness of Podcasts to Improve the Knowledge and Awareness of Selected Health Topics Among Undergraduate General Nursing Students: Protocol for an International Feasibility Study
JMIR Res Protoc 2024;13:e50735
URL: https://www.researchprotocols.org/2024/1/e50735
doi:10.2196/50735
PMID:38319702

Protocol

Comparison of Spontaneous Pushing and Directed Pushing During the Second Stage of Labor Among Chinese Women Without Epidural Analgesia: Protocol for a Noninferior Feasibility Study

Jiasi Yao[1,2], MSc; Heike Roth[3,4], PhD; Debra Anderson[2], PhD; Hong Lu[5], PhD; Huijuan Rong[6], BSc; Kathleen Baird[3,4], PhD

[1]School of Nursing, Hebei Medical University, Shijiazhuang, China

[2]Faculty of Health, University of Technology Sydney, Sydney, Australia

[3]School of Nursing and Midwifery, Faculty of Health, University of Technology Sydney, Sydney, Australia

[4]Collective for Midwifery, Child and Family Health, School of Nursing and Midwifery, Faculty of Health, University of Technology Sydney, Sydney, Australia

[5]School of Nursing, Peking University, Beijing, China

[6]Department of Nursing, The Fourth Hospital of Shijiazhuang, Shijiazhuang, China

Corresponding Author:
Jiasi Yao, MSc
Faculty of Health
University of Technology Sydney
235 Jones Street
Ultimo
Sydney, 2007
Australia
Phone: 61 0415 786 708
Email: jiasi.yao@student.uts.edu.au

Abstract

Background: Maternal pushing during the second stage of labor could influence labor progress and maternal-neonatal outcomes. Although the image of health care providers directing the laboring women to push during the second stage of labor could be commonly observed globally, this practice is not sufficiently researched and is questioned regarding its effectiveness and outcomes on the mother and baby. Meanwhile, a strategy referred to as "spontaneous pushing," which supports women to push by following their bodily urges, has been evaluated in several trials. However, in China, spontaneous pushing is not common practice. Notwithstanding the evaluation of spontaneous pushing, there is a lack of high-quality evidence to support either strategies of directed pushing or spontaneous pushing.

Objective: This study aims to test the feasibility of a future randomized controlled trial to compare the effects of spontaneous pushing and directed pushing during the second stage of labor for maternal and neonatal outcomes in China.

Methods: A nonrandomized, single-group, noninferiority feasibility study will be conducted in a public hospital in Hebei Province, China. In total, 105 women meeting the selection criteria will be recruited to receive the intervention (spontaneous pushing), while 105 sets of medical notes from women who received routine care (directed pushing) will be identified and reviewed to compare outcomes for both cohorts. A mixed methods approach will be used to assess primary outcomes (feasibility and acceptability) and secondary outcomes (effectiveness).

Results: Data collection took place between May and October 2023. A total of 110 women were invited to participate in the intervention of spontaneous pushing. Midwives' interviews were conducted and will be transcribed for analysis in March 2024. The data analysis is planned to be completed by May 2024.

Conclusions: This feasibility study will provide important information by conducting a full-scale clinical trial in the future as well as the potential facilitators and barriers of it. A future randomized controlled trial is likely to have considerable policy and funding impacts regarding pushing management during the second stage of labor and improvement in women's childbirth experience.

Trial Registration: Chinese Clinical Trial Register ChiCTR2300071178; https://tinyurl.com/mudtnbft

International Registered Report Identifier (IRRID): DERR1-10.2196/55701

(JMIR Res Protoc 2024;13:e55701) doi:10.2196/55701

KEYWORDS

spontaneous pushing; directed pushing; labour stage, labour; labor; obstetric; obstetrics; child; birth; delivery; second; feasibility study; China; Chinese; women; protocol; maternal-neonatal outcomes; maternal; healthcare; labouring women; cohort; effectiveness; Midwives; midwife; midwifery; childbirth

Introduction

Background

To achieve physiological childbirth, it is acknowledged that sound maternity practice should aim primarily at giving every woman an opportunity to achieve normality if that is what women choose [1]. More recently, a clinical practice that supports a woman to follow their bodily desire to push during the second stage of labor has been evaluated in several clinical trials [2-5]. This practice is called "spontaneous pushing." However, this is not a new practice; rather, it is a return to previous practice because it is believed that women in the past gave birth unaided. During spontaneous pushing, a woman takes several breaths in between pushes and is encouraged to give several short pushes throughout the duration of 1 uterine contraction [6]. This could occur with open and closed glottis, depending on women's preference [6]. Evidence from a systematic review confirmed that spontaneous pushing did not necessarily lead to a longer duration of the second stage of labor [7]. In addition, women in the spontaneous pushing group are less likely to experience an extended episiotomy and cesarean birth during labor [8].

Meanwhile, in most hospital settings around the world, directing a woman to push during labor is commonly observed [7]. This is usually called "directed pushing." In this context, women are required to follow specific instructions from health care providers and to push in the Valsalva maneuver, involving taking deep breaths and pushing long and hard with closed glottis [7]. At the beginning of the last century in resource-rich countries, promoters of natural birth introduced and advocated this way of directed pushing [9]. They believed that directed pushing could expedite the second stage of labor and avoid the use of forceps, which was commonly used at that time [10]. However, subsequent findings revealed that directed pushing unfavorably alters maternal physiology and contributes to adverse fetal outcomes [11], including poor fetal acid-base balance [12], fetal heart rate increase or decrease [13], low umbilical cord pH and partial pressure of oxygen levels [14], low Apgar scores at 1 and 5 minutes [12], and decreased cerebral oxygenation [15].

Effective spontaneous pushing during the second stage of labor contributes to satisfactory labor progress and improved maternal and neonatal outcomes. The World Health Organization [16] recommends that women in the expulsive phase of the second stage of labor should be encouraged and supported to push spontaneously. Both the Association of Women's Health, Obstetric and Neonatal Nurses and the American College of Nurse-Midwives advocate the use of spontaneous pushing as best practice, which is consistent with physiological birth practices and evidence improved outcomes [17,18]. In a Chinese context, spontaneous pushing has been recommended by a national guideline by the China Maternal and Child Health Association titled *Clinical Practice Guideline for Normal Birth*. The guideline recommends that "women are 'allowed' to push (spontaneously) during a uterine contraction" [19]. Despite the guideline, the routine practice of directed pushing remains in China. Spontaneous pushing is only conducted in an extremely small proportion of hospitals [20]. More evidence is needed to narrow down the gaps between practice guidelines with clinical routine practice. Consequently, high-quality original trials are required to further explore the evidence on pushing management and outcomes in the Chinese context.

Aims

As this study will involve a change of practice in the Chinese context, it is ethically required to conduct a feasibility study before a full-scale randomized controlled trial (RCT) can be performed. Additionally, this study will be conducted as part of a PhD candidature; hence, there are time constraints. This study aims to test the feasibility of a future RCT to compare the effects of spontaneous pushing and directed pushing during the second stage of labor for maternal and neonatal outcomes.

This study will include (1) the preparation program for midwives and (2) the implementation of spontaneous pushing during the second stage of labor for women and a comparison with normal standard care (directed pushing).

Objectives

The primary objective is to test the feasibility of a future RCT to compare the effects of spontaneous pushing and directed pushing for maternal and neonatal outcomes. The secondary objective is to explore the effectiveness of spontaneous pushing and directed pushing for women without an epidural during the second stage of labor.

Methods

Study Design

This feasibility study is a nonrandomized, single-group, noninferiority trial. All participants will receive the intervention (spontaneous pushing). A mixed methods approach will be used to assess the primary and secondary outcomes. This protocol adheres to the SPIRIT (Standard Protocol Items: Recommendations for Intervention Trials) guidelines (Multimedia Appendix 1) [21].

Table 1 illustrates the objectives, outcomes, and the corresponding study design. Tables 2 and 3 illustrate the chart of the study designs, visits, and assessments for both women

and midwives. The flow diagram (Multimedia Appendix 2) demonstrates the enrollment, allocation, follow-up, and assessment process for women to compare the effectiveness of the intervention.

Table 1. Objectives, outcomes, and study design.

Objectives and outcomes	Study design
Primary objective: To test the feasibility of a future RCT[a] to compare the effects of spontaneous pushing and directed pushing for maternal and neonatal outcomes	
Feasibility: recruitment rates, retention rates, and attendance rates of participants	Quantitative study design
Acceptability: women's and midwives' perspectives and acceptability of the intervention	Quantitative study design (survey for women) and qualitative design (interviews for midwives)
Secondary objective: To explore the effectiveness of spontaneous pushing and directed pushing for women without an epidural during the second stage of labor	
Maternal and neonatal outcomes	Quantitative study design

[a]RCT: randomized controlled trial.

Table 2. Chart of the study design, visits, and assessment for women.

Time point	Visit 1: during late pregnancy at clinics	Visit 2: at clinics or admission to the prenatal ward	Visit 3: during the second stage of labor	Visit 4: within 2 hours after birth	Visit 5: during the stay in the postnatal ward
Recruitment					
Eligibility screening	✓	✓			
Informed consent	✓	✓			
Intervention					
Spontaneous pushing			✓		
Assessment					
Case report forms				✓	
Survey for women					✓

Table 3. Chart of the study design, visits, and assessment for midwives.

Time point	Visit 1: before the preparation program	Visit 2: during the preparation program	Visit 3: during women's labor	Visit 4: at the end of the study
Recruitment				
Eligibility screening	✓			
Informed consent	✓			
Intervention				
Preparation program for midwives		✓		
Support women's spontaneous pushing			✓	
Assessment				
Focus group interview for midwives				✓

Sample Size Determination

One of the objectives of the feasibility study is to gain estimates for a sample size calculation in a future RCT [22]. Although a formal sample size calculation is not necessarily needed in a feasibility study, the sample size was calculated based on the duration of the second stage of labor as a parameter outcome in previous studies. Statistical power analysis was used to estimate sample size in PASS (version 15.0; NCSS LLC, USA) software with statistical power at 90%, α at .05, and dropout rate at 20%. The sample size was calculated to be 105 in each group. Based on clinical judgment and the number of laboring women eligible in the site-specific hospital, a sample size of 105 is set for each group.

To cover all 4 shifts of the roster, a total of 6 midwives will be recruited to deliver the intervention. All the midwives recruited to the study will be interviewed at the end of the study to assess midwives' acceptability and experience participating in the study.

Setting

This study will be conducted in a single Birth Centre in the Fourth Hospital of Shijiazhuang, Hebei Province, China. The economic status of the population and the medical resources of Hebei Province is at the average level among all the provinces in China [23], with an annual live birth rate of 762,376 in 2019 [24]. The chosen hospital has one of the largest numbers of annual birth rates in Hebei Province with around 15,600 births in 2022. The default pushing strategy at this hospital is directed pushing, which also aligns with most other hospitals in China.

Participants

All participants will be recruited from the Fourth Hospital of Shijiazhuang, Hebei Province, China. In total, 105 women will be recruited to receive the intervention. At the same time, 105 sets of medical notes will be identified, and relevant information will be extracted to compare health outcomes between the 2 cohorts. These medical notes will be from women who received standard care, that is, "directed pushing" during the second stage and met the same selection criteria as the women in the spontaneous pushing group. The women whose notes will be reviewed will not be recruited into this study, but permission has been obtained from the site-specific hospital to examine the deidentified medical notes. The demographic data, that is, age and the parity and labor care section of the medical notes will be reviewed and examined and parity in 2 cohorts will be matched for further comparison.

Six midwives will be recruited to support spontaneous pushing. They will be rostered to cover all 4 shifts of the roster to ensure that every recruited woman will be supported to push spontaneously by a recruited and trained midwife. All recruited midwives will be interviewed for the qualitative study part.

Eligibility Criteria

The eligibility criteria for women and midwives are presented in Textboxes 1 and 2. The medical note audit will include women who received directed pushing during the second stage of labor and met the same eligibility criteria as the women in the spontaneous pushing group.

Textbox 1. Eligibility criteria for women.

Inclusion criteria

- Older than 18 years of age
- Gestation 37+ weeks at birth
- Single, healthy fetus in cephalic presentation
- No complications during labor

Exclusion criteria

- Administered epidural analgesia
- Any medical or obstetric complication affecting second-stage management
- Unable to comply with guidance
- Undergo cesarean birth during labor

Textbox 2. Eligibility criteria for midwives.

Inclusion criteria

- Qualified with a certificate in maternal and neonatal care by the Ministry of Health, People's Republic of China
- Employed at the Birth Centre of the Fourth Hospital of Shijiazhuang, Hebei Province, China
- Providing care at the birth site
- Willing to participate (not allocated by a manager)
- Have at least 1 year of postregistration practice

Exclusion criteria

- Unwilling to participate
- Allocated by a manager to participate
- Doula or other nonregistered lay birth support person

Recruitment

Recruitment of Women

The researcher (JY) will approach and recruit women into the study during their third trimester of pregnancy. This will allow the women to have enough time to read the information leaflet for the study, ask any questions, and make an informed decision about participating in the study without any undue pressure.

The study will be advertised using posters and information leaflets in the antenatal services of the hospital. The researcher (JY) will approach women while they are in the waiting room awaiting their appointment and will talk to them about the study assessing their willingness to receive further information about the study. Verbal information and a written information sheet outlining the study will be provided to the women to take home and review again before their next visit. At the women's subsequent visit, the researcher (JY) will meet women who are willing to participate, provide them with an opportunity to ask any further questions about the research, and seek their consent to participate in the study by asking them to sign a consent form.

Recruitment of Midwives

Study information will be shared at one of the midwives' regular meetings or workshops and written information will be provided. Midwives will be encouraged to take the information sheet home to review, and those interested in participating in the study will be encouraged to contact the research team.

Upon permission, recruited midwives will be recruited to participate in a preparation program, which will be in a workshop format. The workshop will help to prepare them to provide care to women in the spontaneous pushing group. At the end of the study, the midwives will all be invited to attend a focus group interview to gain their views and thoughts about the implementation of the study, the intervention, and their experience of participating in the study. Midwives will not be rewarded for participating in the study. With permission from the birth center manager, the participation of midwives will occur during their normal working hours.

Patient and Public Involvement

Patients and the public were not directly involved in the development of this protocol. However, the development of the research question and the preparation program content are in accordance with the previously published studies on laboring women's and midwives' experiences and priorities.

Ethical Considerations

Ethics Approval

All the methods will be performed in accordance with the relevant guidelines and regulations. The protocol is approved by 2 ethical committees, the University of Technology Sydney Medical Research Ethics Committee (ETH22-7072) and the Health Research Committee from The Fourth Hospital of Shijiazhuang, Hebei Province, China (20230064). All participants will be provided with informed written consent prior to their enrollment in the study. Deidentified findings of this study will be shared locally via staff forums and education sessions in China; shared through peer-reviewed journal publications, international conferences, and seminar presentations; and included as part of the first author's (JY) PhD thesis.

Informed Consent

Informed consent from both women and midwives will be obtained. A member of the research team (JY) will discuss the study with the women and midwives and provide them with details about the study and obtain written consent. All participants will not receive any type of compensation from the study.

All women participating in the study will be given a study code number, and this will be documented in their medical records and all study documents. A sticker with the logo of this study will be tagged in the top right corner of the participant's medical notes. This will help midwives identify the recruited women when they arrive at the birth center in labor.

Participants' Safety and Withdrawal

A participant (including laboring women or midwives) may choose to withdraw from the study at any time. With consent, data before participant withdrawal will be retained and used in data analysis. Participant withdrawal may happen for several reasons, including but not limited to the following: (1) participant decision, (2) inability to comply with study procedures, and (3) the occurrence of what the participant perceives as an intolerable adverse effect.

In addition, the chief researcher (KB) will exclude a participant if it is considered necessary for any reason, including but not limited to (1) clinical decision, (2) ineligibility (either arising during the study or retrospectively having been overlooked at screening), (3) significant protocol deviation, and (4) significant noncompliance with intervention.

The nature and reason for the withdrawal or discontinuation will be recorded.

Intervention

Preparation Program for Midwives

Before the commencing of the study, a preparation program will be provided to the recruited 6 midwives. The program was developed and informed by the research team's midwifery experience, engagement with the literature and a systematic review [8].

The aim of the midwifery preparation program is to provide midwives with comprehensive and evidence-based practice information on the management of pushing in particular the management of spontaneous pushing during the second stage of labor. This will ensure that midwives feel confident to support women with spontaneous pushing during the second stage of labor. The program will run over 3 weeks and will include 6 sessions, and 5 hours in total over 3 weeks. The training plan is displayed in Table 4.

Table 4. Preparation program for midwives.

Week and session	Topic	Details	Duration (min)
Week 1			
Session 1	Induction	• Introduction of the project and the research team • Midwives to introduce themselves and discuss their expectations of the program, allowing the researcher to answer any questions they may have • The procedure of the feasibility study • The role of the midwife in the feasibility study • Time for question and answers	50
Session 2	Review of the current evidence	• Pushing during the second stage of labor: a scoping review • Directed pushing vs spontaneous pushing: meta-analysis • Discussion	40
Week 2			
Session 3	How to support spontaneous pushing	• Standard procedures of directed pushing management • Strategies to support spontaneous pushing • Comparison of spontaneous pushing and directed pushing • Simulation in pairs • Time for question and answers	90
Session 4	Q&A: Expectations or questions on pushing management	• This session will be conducted digitally using the social media app Tencent meeting • In this session, midwives will be encouraged to share their expectations or questions on managing the second stage of labor • Questions about the process of the study will be answered by the researcher	30
Week 3			
Session 5	Further discussion of the research and participant withdrawal options	• A brief recap of the research and refresh of the training content (highlight the items that directly relate to midwives) • Safety and distress protocol will be explained to midwives • Withdrawal options and their procedures will be explained to midwives	30
Session 6	Scenario-based learning and practice	• Scenario-based learning • Time for question and answers	50 minutes

Strategies to Support Spontaneous Pushing During Labor

Spontaneous pushing encourages a woman to push following her bodily instincts. A standardized step-by-step procedure may not be suitable for every laboring woman. The following strategies are shown to facilitate the spontaneous pushing during labor: (1) encourage woman to select the most comfortable position for her during pushing [7]; (2) offer information about progress of her labor and about any sensations she may feel [25]; (3) affirm to the woman how well her body is working and encourage her to work with and listen to her body urges [25]; (4) support the woman to wait for pushing urges, instead of coaching her to push immediately when the contraction begins [25]; (5) support the woman to push with open glottis, including sighing, moaning, or even crying [26]; and support and encourage the woman to give several short pushes (usually 4 to 6 s) instead of 1 long push (8 to 10 s or even longer) [27].

Outcomes

Overview

The outcomes measured will include 3 domains: feasibility, acceptability, and effectiveness.

Primary Outcomes

The primary outcomes will include (1) feasibility (recruitment rates, retention rates, and attendance rates of participants) and (2) acceptability (women's and midwives' perspectives and acceptability of the intervention).

Secondary Outcomes

Secondary outcomes will include the duration of the second stage of labor, maternal pushing position, mode of birth, rates of cesarean birth, perineal laceration, the rates of episiotomy, newborn Apgar scores, rates of newborn resuscitation, and rates of transfer to the neonatal intensive care unit. Table 5 illustrates the primary and secondary objectives, outcomes, criteria for success, methods for analysis, and measurement tools.

Table 5. Primary and secondary outcome criteria, analysis, and measurement.

Objectives, outcomes, and criteria for success	Methods of analysis	Measurement or tool
Primary objectives: To test the feasibility of a future RCT[a] to compare the effects of spontaneous pushing and directed pushing for maternal and neonatal outcomes		
Recruitment		
Complete recruitment within 6 months	Descriptive	Researcher work log
Women recruited/women accessed×100% > 10%	Descriptive	Researcher work log
Number of women recruited/number of women who bring Information Sheet home×100% > 30%	Descriptive	Researcher work log
Retention		
Loss of follow-up under 30%	Descriptive	Researcher work log
Number of women who completed spontaneous pushing during labor/number of women recruited×100% > 30%	Descriptive	Researcher work log
Number of women who completed the postnatal questionnaire/number of women who completed spontaneous pushing during labor×100% > 80%	Descriptive	Researcher work log
Attendance of participant		
Percentage of completion of all sessions of midwives' preparation program (midwives) > 80%	Descriptive	Researcher work log
Acceptability of the "intervention"		
Overall score of the questionnaire survey above 4 out of 5 (Childbirth Experience Questionnaire above 3 out of 4)	Descriptive	Questionnaire survey
Midwives' focus group	Framework analysis method	Qualitative data
Secondary objectives: To explore the effectiveness of spontaneous pushing and directed pushing for women without an epidural during the second stage of labor		
Duration of the second stage of labor		
From full cervical dilation to the birth of the baby	Mean (SD) or medians for continuous variables	Case report forms
Mode of birth		
Normal vaginal birth, forceps extraction, vacuum extraction, breech delivery, and cesarean birth	n (%) for categorical variables	Case report forms
Perineal laceration		
Intact, I degree, II degree, III degree, and IV degree	n (%) for categorical variables	Case report forms
Episiotomy		
Mediolateral episiotomy, midline episiotomy, and intradermal suture	Mean (SD) or medians for continuous variables	Case report forms
Apgar score		
Apgar scores in 1 minute, 5 minutes, and 10 minutes after birth	Mean (SD) or medians for continuous variables	Case report forms
Admission to neonatal intensive care unit		
Newborn transferred to the neonatal intensive care unit because of any emergency	Mean (SD) or medians for continuous variables	Case report forms
Neonatal resuscitation		
Resuscitation strategies following China Neonatal Resuscitation Guideline	Mean (SD) or medians for continuous variables	Case report forms

[a]RCT: randomized controlled trial.

Data Collection

Overview

The primary and secondary outcomes will be measured using a combination of qualitative and quantitative methods. Three data collection tools will be used during this process.

Case Report Form

A self-designed case report form (CRF) will be used by the researcher (JY) to extract the effectiveness outcomes from a woman's medical notes. These will include the duration of the second stage of labor, maternal pushing position, mode of birth, rates of cesarean birth, perineal laceration, rates of episiotomy, newborn Apgar scores, rates of newborn resuscitation, and rates of transfer to the neonatal intensive care unit. The researcher (JY) will also record on the work log the name of the midwife who supported the recruited woman with spontaneous pushing. As the maternal pushing position is not routinely recorded in medical notes, the researcher (JY) will ask the midwife about a woman's pushing position during labor and will record it on the CRF. Midwives will also be advised to record the maternal pushing position in the labor notes during the preparation sessions.

Survey for Women

A questionnaire with closed-ended and open-ended questions will be used to explore women's satisfaction with pushing, their childbirth experience, and their experience in joining the study. The researcher (JY) will access women during their stay in the postnatal ward for the completion of the survey. In case women withdraw from the study, for personal or medical reasons, a withdrawal note will be recorded in their CRF.

Focus Group With Midwives

The focus group with the midwives will form the qualitative part of the study. At the end of the intervention phase of the study, midwives will be invited to attend a face-to-face focus group to share their experience of supporting women with spontaneous pushing and their experiences of being part of the study. The discussion will be moderated by a senior researcher (HL) from the research team and will be guided by several open-ended questions.

As the primary objective of this study is to explore the feasibility of a future RCT, it is important to fully understand how midwives and women feel about the intervention, the procedure, and the enablers and barriers. The questions in the surveys for women and interviews for midwives will focus on the perceptions of both the women and midwives during the pushing phase of labor as well as their experience of being part of the study.

After a lengthy literature search, it was evident that there was no validated survey tool available that would meet the aims of this study. Therefore, the survey for women was developed based on the principles and domains advocated by Bowen et al [28], Section B "Childbirth Experience Questionnaire" in the survey for women is a freely available tool, which has been published in English and validated in Chinese by Zhu et al [29].

Data Analysis

The data in this study include both quantitative and qualitative data. For quantitative data, "intention-to-treat" analysis will be used. Statistical description will be conducted by the description of mean value, SD, number of cases, and percentage. Pearson chi-square test will be conducted for categorical variables. Independent group 2-tailed *t* test will be conducted for continuous variables. The threshold for statistical significance will be set at .05. For qualitative data, a framework method will be used, which is commonly applied for the thematic analysis of interview transcripts [30]. After a verbatim transcription of the audio recording, the framework method will help to create and apply an analytic framework in the data analysis process in 5 steps (data familiarization, framework identification, indexing, charting, mapping, and interpretation) [31]. The quantitative and qualitative data will be combined in order to compile recommendations from the feasibility in order to conduct a future RCT.

Results

This study will provide both quantitative and qualitative data on the feasibility of a future RCT, including the rate of and ease of recruitment, retention, and attendance of participants during the process. Qualitative results from midwives' focus group interviews will be presented to illustrate midwives' acceptability of the intervention. In addition, a series of labor and birth outcomes will be compared to explore the effectiveness of the intervention.

Data collection took place between May and October 2023. A total of 110 women were invited to participate in the intervention of spontaneous pushing. Midwives' interviews were conducted and will be transcribed for analysis in March 2024. The study is expected to conclude in May 2024.

Discussion

Principal Findings

This is a protocol for a study assessing the feasibility, acceptability, and effectiveness of spontaneous pushing during the second stage of labor among Chinese women without epidural analgesia.

A challenge for this study may likely be the recruitment of laboring women. One of the exclusion criteria for women in this study is "administered epidural analgesia" (Table 3). A large proportion of recruited women may be excluded due to the use of epidural analgesia during labor. The epidural analgesia rate varies from one hospital to another in China [32]. However, the most recently noted rate within the study hospital was around 65% for primiparous women. Despite the anticipated high loss rate of laboring women, this exclusion criterion is set based on the underpinning midwifery philosophy that labor and birth under the use of epidural analgesia is not considered a physiological process. The International Confederation of

Midwives [33] states that "Normal birth is where the woman commences, continues and completes labour with the infant being born spontaneously, in the vertex position at term, without any surgical, medical, or pharmaceutical intervention." The use of epidural analgesia inhibits nerve conduction by blocking painful impulses from the nerves [34]. Although epidural analgesia is considered to be an effective way of pain relief in labor and birth [35], blocking of pain impulses also blocks other impulses conducted by the nerves, including pushing or bearing down urges. At the same time, the "intervention" in this study, spontaneous pushing, encourages laboring woman to feel their bodily urges and push in their most effective way. From this perspective, women who used epidural analgesia during labor may have difficulty feeling their pushing instinct, and hence, they are excluded from this study. The criteria of excluding women who used epidural during labor does not mean to influence women's choices for their pain relief methods. The reasons for this criteria item will be explained beforehand to women to avoid their potential shame of the use of epidural analgesia during labor.

Strengths and Limitations

A strength of this study is the mixed methods that will be used to measure outcome assessment, including quantitative data for effectiveness outcomes and focus group data for acceptability and feasibility outcomes. Another strength of the protocol is that a detailed preparation program for midwives is developed to support spontaneous pushing during labor. A potential limitation of the study is that participants will be both primiparous and multiparous women as we assume that a larger proportion of primiparous women will use epidural analgesia during labor, which will exclude them during the study. Another limitation of the study will be the risk that crossover in clinical context may occur where midwives may facilitate spontaneous pushing when taking care of women from routine practice groups.

Conclusions

This feasibility study will be used to evaluate the feasibility of conducting a full-scale RCT in the future as well as providing an opportunity to explore the potential facilitators and barriers of implementing an RCT. A future RCT will aim to compare the maternal and newborn outcomes between directed pushing and spontaneous pushing in women without epidural analgesia during the second stage of labor. The findings in this study are likely to have considerable policy and funding impacts regarding pushing management during the second stage of labor in line with the World Health Organization's recommendation to improve normality during labor and improve a woman's childbirth experience.

Acknowledgments

The first author (JY) would like to acknowledge the scholarship supported by the China Scholarship Council. This proposed research is being undertaken as a PhD degree and the candidate and supervisors all contributed to the research.

Data Availability

Data sharing is not applicable to this paper currently as no data sets were generated or analyzed during this study.

Authors' Contributions

JY drafted the manuscript protocol. KB and H Roth contributed to the study design and editing. DA and HL helped with the study design. H Rong was a major contributor in assessing the study protocol in hospital settings. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Intervention Trials) checklist.
[PDF File (Adobe PDF File), 78 KB - resprot_v13i1e55701_app1.pdf]

Multimedia Appendix 2
Flow diagram.
[PDF File (Adobe PDF File), 103 KB - resprot_v13i1e55701_app2.pdf]

References

1. Beynon CL. The normal second stage of labour; a plea for reform in its conduct. J Obstet Gynaecol Br Emp 1957 Dec;64(6):815-820. [doi: 10.1111/j.1471-0528.1957.tb08483.x] [Medline: 13502792]
2. Schaffer JI, Bloom SL, Casey BM, McIntire DD, Nihira MA, Leveno KJ. A randomized trial of the effects of coached vs uncoached maternal pushing during the second stage of labor on postpartum pelvic floor structure and function. Am J Obstet Gynecol 2005 May;192(5):1692-1696. [doi: 10.1016/j.ajog.2004.11.043] [Medline: 15902179]

3. Bloom SL, Casey BM, Schaffer JI, McIntire DD, Leveno KJ. A randomized trial of coached versus uncoached maternal pushing during the second stage of labor. Am J Obstet Gynecol 2006 Jan;194(1):10-13. [doi: 10.1016/j.ajog.2005.06.022] [Medline: 16389004]
4. Jahdi F, Shahnazari M, Kashanian M, Farahani MA, Haghani H. A randomized controlled trial comparing the physiological and directed pushing on the duration of the second stage of labor, the mode of delivery and Apgar score. Int J Nurs Midwifery 2011;3(2):159-165 [FREE Full text]
5. Araújo AE, Delgado A, Maia JN, Campos SL, Ferreira CWS, Lemos A. Efficacy of spontaneous pushing with pursed lips breathing compared with directed pushing in maternal and neonatal outcomes. J Obstet Gynaecol 2022;42(5):854-860. [doi: 10.1080/01443615.2021.1945016] [Medline: 34581237]
6. Thomson AM. Maternal behaviour during spontaneous and directed pushing in the second stage of labour. J Adv Nurs 1995;22(6):1027-1034. [doi: 10.1111/j.1365-2648.1995.tb03101.x] [Medline: 8675854]
7. Lemos A, Amorim MMR, Dornelas de Andrade A, de Souza AI, Cabral Filho JE, Correia JB. Pushing/bearing down methods for the second stage of labour. Cochrane Database Syst Rev 2015 Oct 09(10):CD009124. [doi: 10.1002/14651858.CD009124.pub2] [Medline: 26451755]
8. Yao J, Roth H, Anderson D, Lu H, Li X, Baird K. Benefits and risks of spontaneous pushing versus directed pushing during the second stage of labour among women without epidural analgesia: A systematic review and meta-analysis. Int J Nurs Stud 2022 Oct;134:104324. [doi: 10.1016/j.ijnurstu.2022.104324] [Medline: 35908423]
9. Galabin AL. A Manual of Midwifery, 6th edition. London: J. & A. Churchill; 1904.
10. Simkin P, Hanson L, Ancheta R. The Labor Progress Handbook: Early Interventions to Prevent and Treat Dystocia, Fourth Edition. Hoboken, NJ: Wiley Blackwell; 2017.
11. Roberts JE. The "push" for evidence: management of the second stage. J Midwifery Womens Health 2002;47(1):2-15. [doi: 10.1016/s1526-9523(01)00233-1] [Medline: 11874088]
12. Barnett MM, Humenick SS. Infant outcome in relation to second stage labor pushing method. Birth 2007 Mar 31;9(4):221-229. [doi: 10.1111/j.1523-536x.1982.tb01667.x]
13. Caldeyro-Barcia R, Giussi G, Storch E, Poseiro JJ, Lafaurie N, Kettenhuber K, et al. The bearing-down efforts and their effects on fetal heart rate, oxygenation and acid base balance. J Perinat Med 1981;9 Suppl 1:63-67. [doi: 10.1515/jpme.1981.9.s1.63] [Medline: 7229893]
14. Yildirim G, Beji NK. Effects of pushing techniques in birth on mother and fetus: a randomized study. Birth 2008 Mar;35(1):25-30. [doi: 10.1111/j.1523-536X.2007.00208.x] [Medline: 18307484]
15. Aldrich CJ, D'Antona D, Spencer JA, Wyatt JS, Peebles DM, Delpy DT, et al. The effect of maternal pushing on fetal cerebral oxygenation and blood volume during the second stage of labour. Br J Obstet Gynaecol 1995 Jun;102(6):448-453. [doi: 10.1111/j.1471-0528.1995.tb11316.x] [Medline: 7632635]
16. WHO Recommendations: Intrapartum Care for a Positive Childbirth Experience. Geneva, Switzerland: World Health Organization; 2018.
17. American College of Nurse-Midwives, Midwives Alliance of North America, National Association of Certified Professional Midwives. Supporting healthy and normal physiologic childbirth: a consensus statement by the American College of Nurse-Midwives, Midwives Alliance of North America, and the National Association of Certified Professional Midwives. J Midwifery Womens Health 2012;57(5):529-532. [doi: 10.1111/j.1542-2011.2012.00218.x] [Medline: 22954092]
18. Association of Women's Health, Obstetric, and Neonatal Nurses. Nursing Care and Management of the Second Stage of Labor: Evidence-Based Clinical Practice Guideline, 2nd Edition. Washington, D.C: AWHONN; 2008.
19. China Maternal and Child Health Association. Clinical practice guideline of normal birth [Article in Chinese]. Zhonghua Fu Chan Ke Za Zhi 2020 Jun 25;55(6):371-375. [doi: 10.3760/cma.j.cn112141-20200428-00363] [Medline: 32842242]
20. Yan H, Xiu Z, Sen L, Liqian Q, Hong Z, Ruyan P, et al. A survey on the work contents of and services provided by midwives in Zhejiang Province [Article in Chinese]. Chin J Reprod Health 2021;32(6):508-513.
21. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med 2013 Feb 05;158(3):200-207 [FREE Full text] [doi: 10.7326/0003-4819-158-3-201302050-00583] [Medline: 23295957]
22. Pearson N, Naylor PJ, Ashe MC, Fernandez M, Yoong SL, Wolfenden L. Guidance for conducting feasibility and pilot studies for implementation trials. Pilot Feasibility Stud 2020 Oct 31;6(1):167 [FREE Full text] [doi: 10.1186/s40814-020-00634-w] [Medline: 33292770]
23. National Bureau of Statistics of China. China Statistical Yearbook. China: China Statistics Publishing House; 2021.
24. National Health Commission of the People's Republic of China. 2020 Yearbook of Medical Service Statistics. China: National Health Commission of the People's Republic of China; 2021.
25. Sampselle CM, Miller JM, Luecha Y, Fischer K, Rosten L. Provider support of spontaneous pushing during the second stage of labor. J Obstet Gynecol Neonatal Nurs 2005;34(6):695-702 [FREE Full text] [doi: 10.1177/0884217505281904] [Medline: 16282227]
26. Ahmadi Z, Torkzahrani S, Roosta F, Shakeri N, Mhmoodi Z. Effect of breathing technique of blowing on the extent of damage to the perineum at the moment of delivery: a randomized clinical trial. Iran J Nurs Midwifery Res 2017;22(1):62-66 [FREE Full text] [doi: 10.4103/1735-9066.202071] [Medline: 28382061]

27. Parnell C, Langhoff-Roos J, Iversen R, Damgaard P. Pushing method in the expulsive phase of labor. A randomized trial. Acta Obstet Gynecol Scand 1993 Jan;72(1):31-35. [doi: 10.3109/00016349309013345] [Medline: 8382428]
28. Bowen DJ, Kreuter M, Spring B, Cofta-Woerpel L, Linnan L, Weiner D, et al. How we design feasibility studies. Am J Prev Med 2009 May;36(5):452-457 [FREE Full text] [doi: 10.1016/j.amepre.2009.02.002] [Medline: 19362699]
29. Zhu X, Wang Y, Zhou H, Qiu L, Pang R. Adaptation of the Childbirth Experience Questionnaire (CEQ) in China: a multisite cross-sectional study. PLoS One 2019;14(4):e0215373 [FREE Full text] [doi: 10.1371/journal.pone.0215373] [Medline: 31017927]
30. Gale NK, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. BMC Med Res Methodol 2013 Sep 18;13:117 [FREE Full text] [doi: 10.1186/1471-2288-13-117] [Medline: 24047204]
31. Goldsmith LJ. Using framework analysis in applied qualitative research. TQR 2021 Jun 20;26(6):2061-2076 [FREE Full text] [doi: 10.46743/2160-3715/2021.5011]
32. Wang Y. Investigation on the current situation of labour analgesia in Chinese medical institutions [Article in Chinese]. Chin J Pract Nurs 2020;35(12):5.
33. Position statement: keeping birth normal. International Confederation of Midwives. 2014. URL: https://internationalmidwives.org/ [accessed 2024-03-06]
34. Anim-Somuah M, Smyth RM, Cyna AM, Cuthbert A. Epidural versus non-epidural or no analgesia for pain management in labour. Cochrane Database Syst Rev 2018 May 21;5(5):CD000331 [FREE Full text] [doi: 10.1002/14651858.CD000331.pub4] [Medline: 29781504]
35. Aune I, Brøtmet S, Grytskog KH, Sperstad EB. Epidurals during normal labour and birth - midwives' attitudes and experiences. Women Birth 2021 Jul;34(4):e384-e389 [FREE Full text] [doi: 10.1016/j.wombi.2020.08.001] [Medline: 32843237]

Abbreviations

CRF: case report form
RCT: randomized controlled trial
SPIRIT: Standard Protocol Items: Recommendations for Intervention Trials

Edited by A Mavragani; submitted 20.12.23; peer-reviewed by M Foureur, S Manurung; comments to author 07.02.24; revised version received 18.02.24; accepted 26.02.24; published 26.03.24.

Please cite as:
Yao J, Roth H, Anderson D, Lu H, Rong H, Baird K
Comparison of Spontaneous Pushing and Directed Pushing During the Second Stage of Labor Among Chinese Women Without Epidural Analgesia: Protocol for a Noninferior Feasibility Study
JMIR Res Protoc 2024;13:e55701
URL: https://www.researchprotocols.org/2024/1/e55701
doi:10.2196/55701
PMID:38530330

Protocol

Evaluating a Remotely Delivered Cardio-Oncology Rehabilitation Intervention for Patients With Breast Cancer (REMOTE-COR-B): Protocol for a Single-Arm Feasibility Trial

Camille E Short[1,2], PhD; Jonathan C Rawstorn[3], PhD; Tamara L Jones[1], PhD; Lara Edbrooke[2,4], PhD; Sandra C Hayes[5], PhD; Ralph Maddison[3], PhD; Sophie Nightingale[6], MBBS; Hilmy Ismail[7], MD; Richard De Boer[6], MBBS; Fiona Hegi-Johnson[8,9], MBBS, PhD; Aaron L Sverdlov[10,11], MBBS, PhD; Robyn Bell[12]; Irene Halligan[12]; Linda Denehy[2,4], PhD

[1]Melbourne Centre for Behaviour Change, Melbourne School of Psychological Sciences, The University of Melbourne, Melbourne, Australia

[2]Department of Physiotherapy, Melbourne School of Health Sciences, The University of Melbourne, Melbourne, Australia

[3]Institute for Physical Activity and Nutrition, Deakin University, Geelong, Australia

[4]Department of Health Services Research, The Peter MacCallum Cancer Centre, Melbourne, Australia

[5]Cancer Council Queensland, Brisbane, Australia

[6]Department of Surgical Oncology, The Peter MacCallum Cancer Centre, Melbourne, Australia

[7]Department of Anaesthesia, Pain and Perioperative Medicine, The Peter MacCallum Cancer Centre, Melbourne, Australia

[8]Department of Radiation Oncology, The Peter MacCallum Cancer Centre, Melbourne, Australia

[9]Sir Peter MacCallum Department of Oncology, The University of Melbourne, Melbourne, Australia

[10]Newcastle Centre of Excellence in Cardio-Oncology, The University of Newcastle, Hunter Medical Research Institute, Calvary Mater Newcastle, Newcastle, Australia

[11]College of Health, Medicine and Wellbeing, The University of Newcastle, Newcastle, Australia

[12]Consumer representative, Melbourne, Australia

Corresponding Author:
Camille E Short, PhD
Melbourne Centre for Behaviour Change
Melbourne School of Psychological Sciences
The University of Melbourne
Tin Alley
Melbourne, 3010
Australia
Phone: 61 0408 288 786
Email: camille.short@unimelb.edu.au

Abstract

Background: Exercise rehabilitation is a promising strategy for reducing cardiovascular disease risk among patients with breast cancer. However, the evidence is primarily derived from programs based at exercise centers with in-person supervised delivery. Conversely, most patients report a preference for home-based rehabilitation. As such, there is a clear need to explore strategies that can provide real-time supervision and coaching while addressing consumer preferences. Evidence from cardiac rehabilitation has demonstrated the noninferiority of a smartphone-based telerehabilitation approach (REMOTE-CR) to improve cardiorespiratory fitness in people with cardiovascular disease compared to a center-based program.

Objective: This study aims to assess the feasibility, safety, and preliminary efficacy of the REMOTE-CR program adapted for patients with breast cancer at risk of cardiotoxicity (REMOTE-COR-B). We will also assess the satisfaction and usability of REMOTE-COR-B.

Methods: We will conduct a single-arm feasibility study of the REMOTE-COR-B program among patients with stage I-III breast cancer who are at risk of cardiotoxicity (taking treatment type and dose, as well as other common cardiovascular disease risk factors into account) and who are within 24 months of completing primary definitive treatment. Participants (target sample size of 40) will receive an 8-week smartphone-based telerehabilitation exercise program involving remotely delivered real-time supervision and behavior change support. The platform comprises a smartphone and wearable heart rate monitor, as well as a

custom-built smartphone app and web application. Participants will be able to attend remotely monitored exercise sessions during set operating hours each week, scheduled in both the morning and evening. Adherence is the primary outcome of the trial, assessed through the number of remotely monitored exercise sessions attended compared to the trial target (ie, 3 sessions per week). Secondary outcomes include additional trial feasibility indicators (eg, recruitment and retention), safety, satisfaction, and usability, and objective and patient-reported efficacy outcomes (cardiovascular fitness, quality of life, fatigue, self-reported exercise, self-efficacy, habit strength, and motivation). Adherence, feasibility, and safety outcomes will be assessed during the intervention period; intervention satisfaction and usability will be assessed post intervention; and objective and patient-reported efficacy outcomes will be assessed at baseline, post intervention (2-month postbaseline assessment), and at follow-up (5-month postbaseline assessment).

Results: Recruitment for this trial commenced in March 2023, and 7 participants had been recruited as of the submission of the manuscript. The estimated completion date for the project is October 2024, with results expected to be published in mid-2025.

Conclusions: The REMOTE-COR-B intervention is a novel and promising approach to providing exercise therapy to patients with breast cancer at risk of cardiotoxicity who have unique needs and heightened safety risks. This project will provide important information on the extent to which this approach is satisfactory to patients with breast cancer, safe, and potentially effective, which is necessary before larger-scale research or clinical projects.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12621001557820; www.anzctr.org.au/ACTRN12621001557820.aspx

International Registered Report Identifier (IRRID): DERR1-10.2196/53301

(JMIR Res Protoc 2024;13:e53301) doi:10.2196/53301

KEYWORDS

breast cancer survivor; breast cancer; cancer survivor; cancer; cardiac rehabilitation; cardiac; cardiotoxicity; cardiovascular disease; digital health; efficacy; exercise; exercise; feasibility; fitness; rehabilitation intervention; rehabilitation; safety

Introduction

With increased rates of breast cancer survival, especially beyond 5 years, there is now an increased need to focus on the late adverse effects of cancer treatment [1,2]. The adverse impact of cancer treatment on cardiovascular health is one such late effect [3]. Cardiovascular disease (a group of heart and blood vessel disorders [4]) is now a leading cause of death among survivors of breast cancer, and survivors of breast cancer have a higher risk compared to the general population [3,5]. In addition to the overlapping risk factors of cancer and cardiovascular disease, including obesity and physical inactivity [6], the cardiotoxic nature of common breast cancer treatments (including chemotherapy, radiotherapy, and human epidermal growth factor receptor [HER]–targeted therapy) is a contributing factor to this increased risk [3]. Anthracycline-based chemotherapy and trastuzumab are of particular concern, being associated with a 5-fold increase in the risk of heart failure compared to treatment without these agents [7].

Exercise rehabilitation focused on increasing cardiorespiratory fitness is a promising strategy for reducing cardiovascular disease risk among survivors of breast cancer [8]. Lower fitness is associated with an increased risk of cardiovascular disease and all-cause mortality in the general population [9], and fitness declines have been observed during cancer treatment. Following breast cancer, major cardiovascular events tend to emerge initially around 4 years after adjuvant treatments, with a second peak around 10 years post treatment [10]. A recent study in over 4000 women, 12 years after a diagnosis of breast cancer, found that increased physical activity (equivalent to approximately 3 hours of brisk walking per week or ≥9 metabolic equivalent task hours [MET-hrs]) was associated with a 56% reduced risk of cardiovascular events (including heart failure, myocardial infarction, angina, coronary revascularization, peripheral arterial disease, carotid artery disease, transient ischemic attack, stroke, and cardiovascular death) when compared to women who exercised less (<9 MET-hrs per week) [11]. To date, over a dozen randomized controlled trials have demonstrated that exercise rehabilitation can effectively increase cardiorespiratory fitness among survivors of breast cancer [8]. Alongside consistent evidence from randomized controlled trials that exercise also improves quality of life and physical functioning [12], this evidence has led to exercise being recommended in guidelines as a routine part of cancer management [13,14].

While the evidence for exercise rehabilitation improving fitness among survivors of breast cancer is strong, it has primarily been derived from center-based exercise rehabilitation programs, where participants receive real-time in-person supervision. However, reliance on center-based delivery is likely to limit accessibility and uptake [12], as many survivors of breast cancer report a preference for home-based rehabilitation [15]. Even with this preference, it is important to ensure participant safety as well as the suitability and individualization of exercise prescriptions. Particularly because exercise trials typically recruit more “well” survivors of cancer, who are generally younger, less likely to be obese, and who are more physically active (ie, rarely include those most at-risk of cardiovascular disease) [16]. As such, there is a clear need to explore noncenter-based delivery models that can provide real-time supervision and coaching to optimize safety, particularly for high-risk patients with breast cancer (eg, those at high risk of cardiovascular disease). Evidence from the cardiac rehabilitation setting suggests that the use of sensors and mobile technologies is a promising strategy for reducing cardiovascular disease risk

among survivors of breast cancer, warranting investigation [17,18].

Maddison et al [19] developed a smartphone-based exercise telerehabilitation program (REMOTE-CR) that allowed participants to receive real-time remote exercise supervision and coaching from an exercise professional. A noninferiority, randomized trial (n=162) compared REMOTE-CR to a 12-week center-based exercise cardiac rehabilitation program in people with cardiovascular disease [19]. At the 12-week follow-up, REMOTE-CR was shown to be noninferior to center-based exercise cardiac rehabilitation on maximum oxygen uptake (VO_2max; adjusted mean difference [AMD] 0.51, 95% CI 0.97-1.98 mL/kg/minute). At longer-term follow-up (24 weeks), participants allocated to REMOTE-CR were also more likely to be participating in physical activity than those allocated to the center-based program (ie, less sedentary time: AMD –62, 95% CI –118 to –5 minutes/day) [19]. Importantly, per capita costs for delivering REMOTE-CR were 70% lower than center-based exercise cardiac rehabilitation, and although more adverse events were self-reported by the REMOTE-CR group during the intervention period, none were severe, and the majority (42/50, 84%) were not related to program participation. The same approach could be adapted for use in a cardio-oncology setting. However, the extent to which it would be feasible, safe, and effective (ie, positively impact fitness outcomes) for survivors of breast cancer at risk of cardiotoxicity, given their unique needs and risk profile, is unknown.

The overall aim of this study is to determine the feasibility of the REMOTE-COR-B program, a smartphone-based telerehabilitation exercise program for survivors of breast cancer at risk of cardiotoxicity. The secondary objectives of this trial are to determine satisfaction with and usability of REMOTE-COR-B, as well as potential effects on cardiovascular fitness that can be used to inform future, adequately powered trials.

Methods

Ethical Considerations

Ethics clearance was obtained by the Peter MacCallum Cancer Centre Ethics Committee (HREC/60412/PMCC-2020). Informed consent will be obtained from all participants involved in the trial. Participants will be assigned a study ID number. All study materials will be coded with the ID number only. Only the research team will have access to the study database, which contains the information needed to link ID numbers with identifiable information. Participants will be provided with an AUD $25 (US $16.32) gift card at the end of each assessment as an incentive to complete outcome assessments and in acknowledgement of their time. Participants will also be reimbursed for travel expenses or parking costs for attendance at each appointment.

Trial Design

A single-arm feasibility study will be conducted to determine the feasibility, safety, and preliminary efficacy of REMOTE-COR-B (protocol version 7; date August 24, 2023). The trial has been prospectively registered on the Australian New Zealand Clinical Trials Registry (ACTRN12621001557820). The study protocol is reported in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines [20], and the intervention is described according to the Consensus on Exercise Reporting Template (CERT) [21]. Study materials are available on the Open Science Framework [22].

Eligibility and Recruitment

The inclusion and exclusion criteria are provided in Textbox 1. Eligibility will be confirmed using medical data and patient interviews, as appropriate.

Textbox 1. The inclusion and exclusion criteria for the study.

Inclusion criteria

- A diagnosis of stage I-III breast cancer.
- At risk of cardiotoxicity according to predetermined criteria (taking treatment type and dose as well as other common cardiovascular disease risk factors into account, including age, obesity, and the presence of other comorbidities; Figure S1 in Multimedia Appendix 1 [3,6,23-27]).
- Completion of primary definitive anticancer therapy within the last 24 months (which may be surgery, radiotherapy, or chemotherapy depending on the treatment pathway; participants who received both adjuvant and neoadjuvant treatment are eligible).
- Generally participating in less than the REMOTE-COR-B exercise target (ie, <150 minutes of moderate to vigorous intensity aerobic activity per week over <3 sessions per week) [13,14,28].
- An Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 [28]
- Having sufficient reading and writing English skills is required for understanding the participant information sheet and study participation instructions.

Exclusion criteria

- Participants who have been diagnosed with metastatic (stage IV) or recurrent breast cancer.
- Those who have a medical condition where exercise or cardiopulmonary exercise testing is contraindicated (eg, unstable angina, uncontrolled heart failure, or asthma) [21].
- Having an implanted cardiac device [21].
- Being unable to provide informed consent.
- Being unable to fully participate in study assessments due to cognitive or physical impairment.
- Participating in another exercise study or exercise program with similar goals.
- Participating in a clinical trial that presents safety or contamination issues for either trial (to be assessed by the Steering Committee).

Eligible participants will be identified by the breast cancer clinical and research staff at the Peter MacCallum Cancer Centre and the Royal Melbourne Hospital. Potentially eligible patients will receive an email through the REDCap (Research Electronic Data Capture [29,30]) platform and will be provided with an information pack (including a study flyer and participant information and consent form). Patients can indicate their interest in the trial through the REDCap platform or by direct contact with the research team. Trial staff will contact interested patients to provide a verbal explanation of the project and its procedures, answer patients' questions, and complete the eligibility screening. Following confirmation of eligibility, trial staff will obtain informed consent to participate in the study through REDCap, and the baseline assessment will be scheduled. Participants can withdraw from the study at any time without reason or consequence. In addition, the investigator may discontinue a patient from the study at any time if the investigator considers it necessary for any reason.

Adapting the REMOTE-CR Intervention

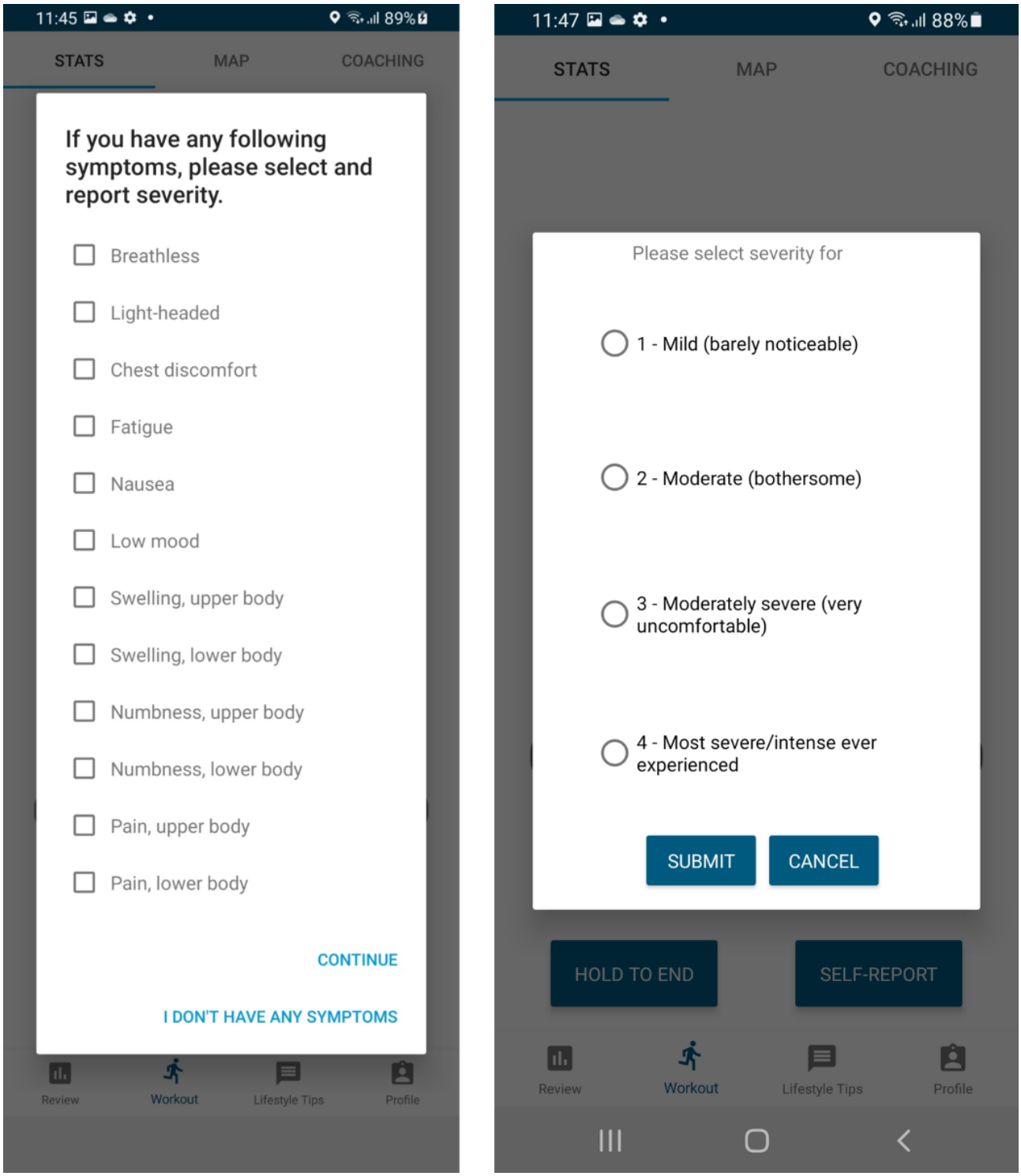
For this study, REMOTE-COR-B was adapted from the original REMOTE-CR platform, which is described in detail elsewhere [31]. In brief, the base platform comprises a smartphone and wearable sensor (currently compatible with BioHarness 3, Zephyr Technology, and H10, Polar Electro), as well as a custom-built smartphone app and web application. The platform facilitates remotely supervised exercise prescriptions that are delivered, monitored, and coached in real-time by an exercise professional. The participant's heart rate and geospatial data are displayed in the smartphone app for self-monitoring and streamed to a web server for review by an exercise professional (along with single-lead electrocardiogram [ECG] data, which are not visible to the participant in the smartphone app). The participant can also use the app to report "red flag" symptoms during exercise (chest pain, breathlessness, and dizziness), allowing the exercise professional to stop the session, make contact, and direct as needed. The exercise professional provides individualized audio coaching, feedback, and social support throughout the session, which is delivered to participants through earphones (text-to-audio feature) to optimize usability. At the end of an exercise session, participants are prompted to report their perceived exertion using the app. Outside of real-time interaction, participants can record exercise training for self-monitoring, receive behavior change education through direct messaging, review all recorded exercise performance data, and set or review goals to encourage behavior change.

Adaptations of REMOTE-CR for Breast Cancer

Following consultation with consumer representatives and the advisory committee, the following changes were made to the base platform for the REMOTE-COR-B trial: (1) expansion of the symptom reporting list to include common breast cancer treatment-related side effects and symptoms (Figure 1); (2) prompts for participants to report their symptoms at the start of each exercise session; (3) ability to report Rating of Perceived Exertion (RPE) both during and after exercise to enhance tailoring of prescription and coaching; (4) expansion of the heart rate data display to include beats per minute (BPM; the raw measurement unit) in addition to heart rate reserve, to allow use when a lack of maximal exercise testing precludes calculation of heart rate reserve; (5) revisions to the behavior change education to provide additional positive reinforcement, breast

cancer–specific content, and messages focused on planning, habit formation, and autonomous motivation; and (6) alternative options for wearing the heart rate monitor if chest irritation or pain is an issue (ie, delay enrollment post treatment, use an adhesive to place the sensor on an unaffected area or at a different location that yields sufficient signal quality, or monitor intensity exclusively through RPE).

Figure 1. Expanded symptom reporting list in REMOTE-COR-B: a single-arm feasibility trial for patients with breast cancer.



The Remote-COR-B Intervention

The REMOTE-COR-B intervention will be delivered over a period of 8 weeks and involves remotely delivered individualized exercise prescriptions, real-time supervision, and behavior change support (eg, goal setting and supportive messages). The aim of the intervention is for participants to attend 3 remotely monitored aerobic exercise sessions per week, with self-directed exercise encouraged (where appropriate) on ≥2 other days to align with current aerobic recommendations for patients with cancer (ie, 150 minutes of moderate to vigorous intensity activity per week) [13,14,28]. The REMOTE-COR-B trial will emphasize aerobic activity, given the focus of the intervention on improving cardiovascular fitness [14,28]. The

intervention is summarized below and described in detail according to the CERT requirements in Table S1 in Multimedia Appendix 2 [21,32,33].

Exercise Prescription

Each participant will be provided with an individualized and progressive exercise prescription based on their age, previous and recent exercise habits, motivation, personal goals, attitudes, values, treatment, and support. Exercise prescription components will include frequency (3 remotely monitored sessions per week), duration (20-60 minutes per session), and intensity (moderate: 40%-60% heart rate reserve [HRR] and RPE 3-5 [34]), with the aim of increasing peak oxygen consumption (VO_2peak). Intensity will be monitored through a combination of HRR and RPE if complete baseline cardiopulmonary exercise testing (CPET) is available (more details are provided in the "Secondary Outcomes" section), or BPM and RPE if baseline CPET is unavailable.

The progression of exercise prescription components will typically occur in the following order: duration, intensity, frequency (additional to remotely monitored sessions), and will be gradually increased as tolerated by the individual, with consideration to symptom status, fitness level, exercise response (based on heart rate data and RPE), and each participant's goals [35]. During the first half of the intervention (ie, weeks 1-4), exercise intensity targets will typically range from RPE 3 to 4 ("moderate" to "somewhat hard") and between 40% and 50% HRR [34]. In the second half of the intervention (ie, weeks 5-8), exercise intensity targets will typically range from RPE 4 to 5 ("somewhat hard" to "hard") and between 50% and 60% HRR [34]. The preferred mode of exercise is walking, though participants may choose other land-based aerobic activities (eg, cycling, jogging, and exercise videos).

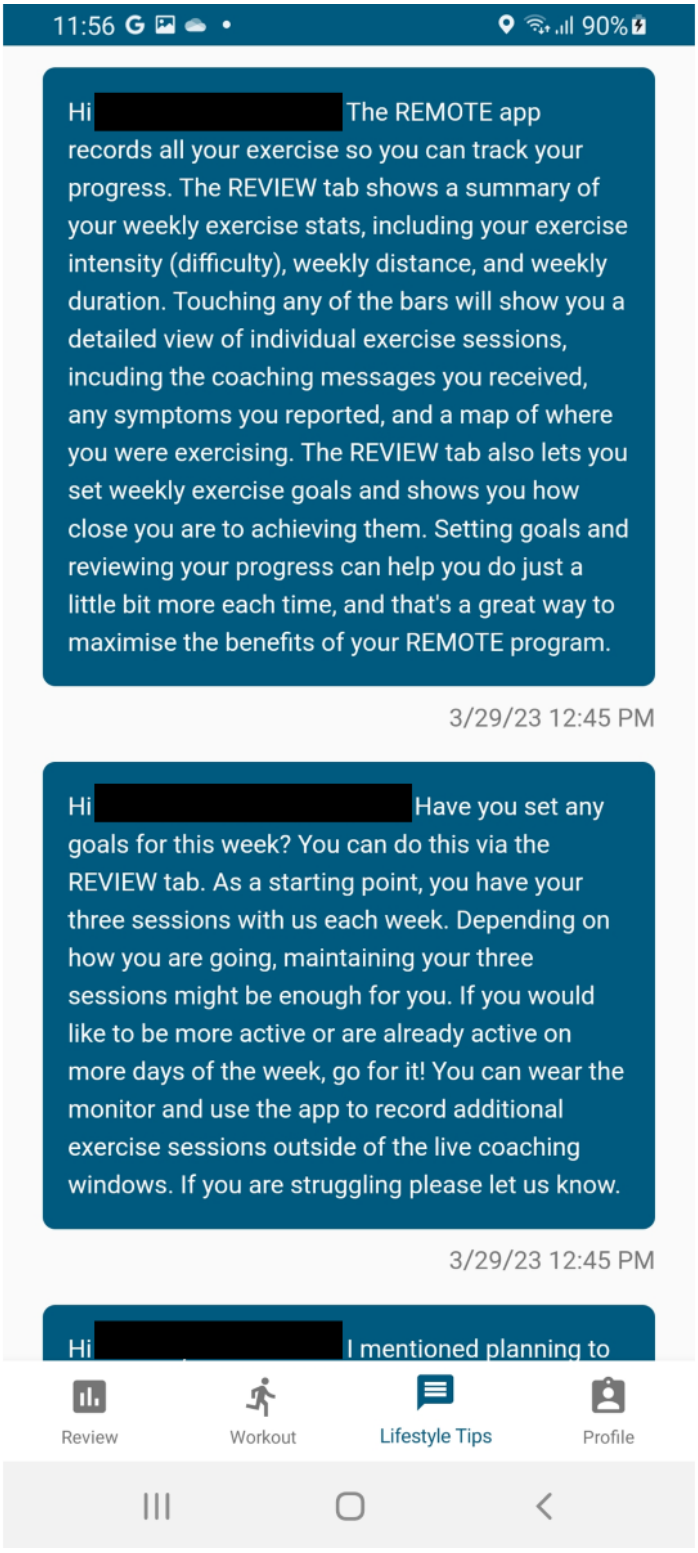
Remote Monitoring and Supervision

Participants will be able to attend remotely monitored exercise sessions during set operating hours each week, scheduled in both the morning (eg, between 6 AM and 10 AM) and evening (eg, between 5:30 PM and 7:30 PM). Participants can complete exercise in any location with an active broadband connection (mobile, Wi-Fi, or Bluetooth). The REMOTE-COR-B mobile app collects heart rate and single-lead ECG through a Polar H10 heart rate transmitter (loaned to participants throughout the study), location, distance, and speed through location services integration, as well as symptoms and RPE through self-report. These data are then transmitted to a cloud-based server and displayed on a companion web application in real-time. Exercise professionals remotely monitor all data in real-time through the web application, provide participants with real-time individualized coaching feedback and support through their smartphone app (through alerts, messages, or telephone calls), respond to adverse events if required, provide postexercise feedback, and modify exercise prescriptions as needed.

Behavior Change Support

Participants will receive behavior change education and support during the 8-week intervention period through push notifications (2-4 per week) delivered through the REMOTE-COR-B mobile app (Figure 2). The messages are based on social cognitive [36], self-determination [37], and habit theories [38] (Table S1 in Multimedia Appendix 2 outlines the specific strategies). Additionally, participants are encouraged to use the built-in data visualization features of the app to review their exercise performance data and set and review goals to encourage behavior change.

Figure 2. Example of behavior change support in REMOTE-COR-B: a single-arm feasibility trial for patients with breast cancer.



Outcomes and Assessment Timing

Data relating to intervention delivery outcomes (eg, adherence, feasibility, and safety) will be collected during the 8-week intervention (Table 1). Satisfaction and usability will be assessed post intervention. Objective and patient-reported efficacy outcomes will be assessed at baseline (within 24 months post completion of primary definition treatment), post intervention (2-month postbaseline assessment), and at follow-up (5-month postbaseline assessment). Demographic and medical data will be collected at baseline through self-reports and medical records. Criteria of success for core feasibility, usability, safety, and efficacy outcomes have been prespecified and are outlined below.

Table 1. Schedule of enrollment, intervention, and assessments for REMOTE-COR-B: a single-arm feasibility trial for patients with breast cancer (based on the SPIRIT [Standard Protocol Items: Recommendations for Interventional Trials] guidelines) [20].

Time point	Study period				
	Enrollment (prebaseline)	Intervention period			Follow-up
		Baseline (0 months)	Intervention (2 months)	Postintervention (2-month postbaseline)	Follow-up (5-month postbaseline)
Enrollment					
Cardiotoxicity screen (including treatment information)	✓				
Eligibility screen	✓				
Informed consent	✓				
Interventions					
Single-arm exercise			✓		
Assessments					
Demographic information	✓	✓			
Intervention adherence			✓		
Feasibility	✓	✓		✓	✓
Safety		✓	✓	✓	✓
Intervention satisfaction				✓	
Intervention usability				✓	
CPET[a]		✓		✓	✓
ISWT[b]		✓		✓	✓
Quality of life		✓		✓	✓
Fatigue		✓		✓	✓
Self-reported exercise		✓		✓	✓
Psychological mechanisms		✓		✓	✓

[a]CPET: cardiopulmonary exercise testing.

[b]ISWT: incremental shuttle walk test.

Primary Outcome

Adherence will be assessed through the number of remotely monitored exercise sessions attended compared to the trial target (ie, 3 sessions per week). Previous research suggests ≥70% adherence is satisfactory to achieve fitness gains [8,12]. As such, participants will be considered adherent to the intervention if they complete ≥17 of 24 remotely monitored exercise sessions.

Secondary Outcomes

Trial Feasibility

Trial feasibility is assessed based on rates of screening, consent, device ownership, retention, and missing data across all assessment points. Prespecified cut points indicating feasibility include cardiac dysfunction risk level is accessible for ≥80% of cases identified; ≥60% of those invited to participate agree to complete eligibility screening [39]; the recruitment goal is reached within the allotted time (1 year); retention is ≥60%; and outcome data are collected for ≥80% of enrolled participants at both the postintervention and follow-up assessments (this is in line with retention observed by the chief investigator Maddison et al [19] in the REMOTE-CR trial).

Safety

Adverse events will be assessed through the frequency and severity of adverse events reported during remotely monitored exercise sessions, any unsupervised exercise sessions, and exercise testing sessions (as outlined in the "Cardiovascular Fitness: VO_2peak" section). Severity will be graded according to the Common Terminology Criteria for Adverse Events 5.0 and the National Health and Medical Research Council guidelines for safety monitoring and reporting [32,40]. Participants will be instructed to immediately report any adverse events that occur during the intervention period (during either supervised or unsupervised exercise sessions) to the study staff (ie, exercise professionals or study coordinators); these will be recorded. All adverse events reported to study staff will be communicated to the study coordinator and the coordinating principal investigator as soon as possible and recorded. The coordinating principal investigator will be responsible for ensuring serious adverse events are reported to the ethics committee and trial sponsor within the appropriate time frames. Participants can also retrospectively report adverse events during the postintervention and follow-up surveys. The trial will be deemed safe if no grade ≥3 adverse events attributed to

participating in the research project are reported. During the intervention period, participants can also self-report symptoms (new, ongoing, or worsening) through the smartphone app at the beginning and end of every exercise session (supervised and unsupervised). Any changes in symptomology will also be recorded.

Satisfaction and Usability

Satisfaction with the intervention and perceived intervention usability will be assessed using the validated 8-item Client Satisfaction Questionnaire (0-32) [41] and the 10-item System Usability Scale (0-100) [42]. The intervention will be deemed satisfactory and usable if mean scores are ≥24 and ≥68, respectively. Issues with wearing the heart rate monitor due to cancer treatment-related discomfort will also be discussed and recorded by the study coordinator in a study-specific form.

Cardiovascular Fitness: VO2peak

Cardiovascular fitness (VO_2peak) will be assessed through CPET and an incremental shuttle walk test (ISWT). The CPET will occur at the Peter MacCallum Cancer Centre (conducted by Peter MacCallum staff) and will involve participants exercising on an exercise bike against increasing resistance, during which time gas exchange analysis will be conducted to measure anaerobic threshold and VO_2peak. Blood pressure and 12-lead ECG will be monitored for signs of an adverse cardiac response. VO_2peak is a gold-standard measure for objectively assessing cardiorespiratory fitness and is an important clinical end point in this population because it is a strong predictor of adverse cardiovascular events and mortality [11]. A change in VO_2peak as small as 6% can be clinically meaningful in terms of cardiovascular outcomes among patients with chronic systolic heart failure [43]. We expect an average improvement in VO_2peak of ≥10%, as this is comparable to what has been achieved in posttreatment supervised exercise interventions among patients with breast cancer [44-46]. Additionally, this level of change is used clinically in a heart failure setting as indicating a clinically meaningful improvement in outcomes [47,48] and is associated with improved health-related quality of life in patients with breast cancer [46].

The ISWT is a valid and reliable field walking test to assess functional exercise capacity [49,50] and is shown to be moderately correlated with CPET-assessed VO_2peak (r=0.61) [51]. Due to possible COVID-19–related difficulties with performing CPETs on all participants, an ISWT will also be performed (conducted by trial staff), as the equipment is easily transportable and the test can be completed outdoors (potentially necessary if a home visit is required due to COVID-19 restrictions and a suitable indoor location is not available). Participants are required to walk around 2 cones placed 9 meters apart (a total of 10 meters of flat course) in time to a set of auditory beeps. Initially, the walking speed is very slow, but each minute, the required walking speed progressively increases. The test concludes when the participant cannot achieve the required speed, experiences clinical indications for test termination, or wishes to stop. The number of shuttles is recorded. Only standardized instructions will be used [50], the walking track will be kept the same for all tests for a participant, and no encouragement will be given throughout. An improvement of ≥48 meters from baseline to postintervention will be considered clinically significant [49]. The intervention will be deemed potentially efficacious for improving cardiovascular fitness if clinically significant changes in VO_2peak (≥10%) or meters walked in the ISWT are achieved.

Quality of Life

Quality of life will be assessed using the validated 38-item Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire [52]. Total health-related quality of life (0-148) and subscale scores (physical, social, emotional, and functional well-being) will be calculated. A clinically important change in total quality of life has been defined as a 6% increase between baseline and postintervention [53].

Fatigue

Fatigue will be assessed using the validated 13-item Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-Fatigue) questionnaire [54]. All items are summed to create a single fatigue score (0-52). A clinically important change in the FACIT-Fatigue has been defined as a 6% increase between baseline and postintervention [53,55].

Self-Reported Exercise

Self-reported exercise will be assessed using the validated 3-item Godin Leisure-Time Exercise Questionnaire (GLTEQ) [56]. Using the GLTEQ, participants self-report how often in the previous 7 days they completed ≥15 minutes of strenuous, moderate, and light physical activity. The number of bouts at each intensity is then multiplied by the corresponding MET value and summed to create a Leisure Score Index (LSI). The proportion of participants considered sufficiently active will also be reported, determined based on prespecified LSI scores (<14 units=insufficiently active or sedentary; between 14 and 23 units=moderately active; and ≥24 units=active or “meeting criteria for being physically active”) [56,57].

Psychological mechanisms

Potential mediators of intervention effects will be assessed, including self-efficacy (Multidimensional Self-Efficacy for Exercise Scale [58]), habit strength (self-reported habit index [59]), motivation type (Behavioural Regulation Questionnaire [60]), and autonomy-supportive exercise environment (The Perceived Environmental Supportiveness Scale [61]).

Data Analysis

Sample Size

We aim to recruit 40 participants over the course of 12 months. This sample size is considered sufficient to test the feasibility of delivering the intervention and other key trial parameters [62]. Notably, with this sample size, we will also have reasonable precision for estimating intervention adherence. For example, with a sample size of 40, if the average adherence rate observed in the study is 70%, we can be sure with 95% confidence that the true population proportion is between 56% and 85%; the 95% CI is ≥14.2. Given the potential reach of the intervention and the fact that adherence to current technology-based behavior change programs is 50% [39], this

finding would warrant further investigation. The target sample size is also equivalent to approximately 20%-30% of the sample size needed to adequately power (80%) a future definitive trial to demonstrate noninferiority in VO_2peak changes between groups (a *P* value of .05); based on differences observed in our formative work [19] and a systematic review [8].

Statistical Methods

The data will be presented descriptively where appropriate; this includes most feasibility outcomes (eg, recruitment rate, proportion of missing data, usability, and satisfaction), including the primary outcome (ie, adherence to the intervention), and safety outcomes (eg, number of adverse events, proportion of serious adverse events).

Changes in VO_2peak, patient-reported outcomes (quality of life and fatigue), and physical activity behavior will be examined in exploratory analyses at all assessment time points using mixed model repeated measures analyses. Unadjusted and age- and treatment pathway–adjusted models will be conducted with standardized coefficients reported with 95% CIs to aid interpretation of clinical significance rather than *P* values given a lack of statistical power. The choice of modeling link will be informed by residual diagnostics. The data for withdrawn participants collected before study withdrawal will be retained for use in intention-to-treat analyses, unless requested otherwise by the participant.

Further exploratory analyses may include (1) examining changes in the proposed psychological mechanisms (eg, self-efficacy) from baseline to postintervention; (2) examining associations between the proposed mechanisms and the study outcomes (eg, adherence to exercise sessions and cardiorespiratory fitness); and (3) examining associations between participant characteristics (potential moderators) and intervention adherence (sessions and intensity), as well as changes in VO_2peak. Given the small sample size and absence of a control group, a formal mediation analysis or moderation analysis will not be undertaken (as per Baron and Kenny [63]). However, the collection of these data will assist with determining the feasibility of mediator and moderator assessment in a larger trial, where a formal mediation analysis and moderator analysis may be undertaken.

Data Management

The data will be preferentially recorded in electronic case record forms (CRF) and through surveys using REDCap data management software, only accessible to trial staff. Hard copy forms will also be available if necessary (stored in a locked filing cabinet). Data collected through hard copy will be scanned and uploaded to REDCap and the secure study network drive as soon as possible. Hard copies will be shredded once the data are safely stored electronically (including a scan of the original). All data will be exported from REDCap at the end of the trial and stored on a password-protected network drive at the University of Melbourne for at least 5 years after the publication of the results. Deidentified data may be shared indefinitely through sites like Open Science or Figshare to ensure scientific transparency and to share knowledge with others.

Results

The recruitment for this trial began in March 2023, and 7 participants had been recruited as of the submission of the manuscript. Recruitment issues were encountered early, and changes to the prespecified protocol (ACTRN12621001557820) have been made to aid recruitment. The original eligibility criteria for the trial required participants to have completed primary, definitive anticancer therapy within 3-12 weeks. In addition, only anthracyclines and no other types of chemotherapy were considered in the cardiotoxic risk assessment. After screening potential participants, it became clear that recruitment would be slower than expected and that many patients at risk of poor heart health would not be eligible for the trial. Before enrolling the first participant, the eligibility criteria were amended so that participants could be up to 6 months post definitive treatment, and a wider range of evidence-based risk factors for cardiotoxicity and cardiovascular disease would be considered (Figure S1 in Multimedia Appendix 1 [3,6,23-27]). A second objective fitness test (the ISWT) was also added, which can be conducted outside of the hospital setting in case COVID-19 disruptions impact access to CPET assessments. Following these changes, the first participant was enrolled in March 2023.

Additional changes have since been made to the protocol to further aid recruitment. These include expanding screening opportunities to identify potentially eligible participants, streamlining the recruitment procedure through REDCap to reduce burden on hospital staff, and expanding eligibility criteria to include patients up to 24 months post definitive treatment. This amendment was recently approved, and the estimated completion date for the project is October 2024, with results expected to be published in mid-2025. Any future protocol amendments will be reported in the main outcomes publication and registered on the Australian New Zealand Clinical Trials Registry.

Discussion

The original intervention underpinning this trial has demonstrated efficacy and noninferiority compared to gold-standard in-clinic cardiac rehabilitation [19]. The adaptation of this intervention for patients with breast cancer who are at risk of cardiotoxicity is a novel and promising approach to providing accessible exercise therapy. This trial will address the extent to which this approach is satisfactory to patients with breast cancer, safe, and potentially effective, given the unique needs and risk profile of this group. The findings will be used to inform features of a future, adequately powered efficacy trial, including but not limited to eligibility and recruitment strategy, app features and functions, and delivery preferences (eg, session timing) [64]. Trial findings might also be used to inform the implementation of this approach in breast cancer services, given that remote strategies are needed now and the strong evidence-based basis behind the base software (REMOTE-CR). By publishing this protocol, we aim to ensure transparency around prespecified outcome criteria, inform

interested parties of the upcoming trial, and aid replication and critical review of study methodology.

Acknowledgments

This study is funded by a National Breast Cancer Foundation grant. TLJ is supported by a postdoctoral fellowship partly funded by the grant. CES is supported by a Victoria Cancer Agency Mid-Career Fellowship. LE is supported by a Victoria Cancer Agency Early Career Research fellowship. JCR received a National Heart Foundation of Australia Postdoctoral Fellowship (102585). ALS is supported by the National Heart Foundation of Australia Future Leader Fellowship (award ID 106025).

The University of Melbourne is the sponsor for the trial. The trial sponsor has responsibility for the quality and integrity of trial data, ensuring appropriate approvals are obtained before the commencement of the trial, and patient safety.

Data Availability

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

Authors' Contributions

CES, JCR, SH, LD, and RM obtained study funding. CES led protocol development with support from all authors. CES led adaptation of the intervention software, with support from JCR, RB, and IH and feedback from SH, LE, RM, and LD. TLJ developed the exercise prescription protocol with input from LE, SH, and LD. CES, TLJ, JCR, and RM developed the behavior change content, which was reviewed and revised by RDB and IH. RDB and IH provided consumer input to the study. SN, RDB, FHJ, and ALS provided clinical expertise in developing cardiotoxicity eligibility criteria. HI oversees cardiopulmonary exercise testing at the Peter MacCallum Cancer Centre. SN and RDB oversee participant recruitment at the study sites. CES and TLJ wrote the original draft of the manuscript. All named authors reviewed, had input into revisions, and approved the final manuscript. Generative AI was not used in any portion of the manuscript writing.

Conflicts of Interest

JCR and RM are inventors of the telerehabilitation platform being examined in this study. They do not receive any related benefits over and above their normal salary.

Multimedia Appendix 1
Cardiotoxicity criteria.
[DOCX File , 17 KB - resprot_v13i1e53301_app1.docx]

Multimedia Appendix 2
Exercise prescription principles of the REMOTE-COR-B trial (based on Consensus on Exercise Reporting Template).
[DOCX File , 27 KB - resprot_v13i1e53301_app2.docx]

References

1. Australian Institute of Health and Welfare. Breast Cancer in Australia: An Overview. Canberra: AIHW; 2012.
2. Lovelace DL, McDaniel LR, Golden D. Long-term effects of breast cancer surgery, treatment, and survivor care. J Midwifery Womens Health 2019;64(6):713-724. [doi: 10.1111/jmwh.13012] [Medline: 31322834]
3. Armenian SH, Lacchetti C, Barac A, Carver J, Constine LS, Denduluri N, et al. Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2017;35(8):893-911 [FREE Full text] [doi: 10.1200/JCO.2016.70.5400] [Medline: 27918725]
4. Cardiovascular diseases (CVDs). World Health Organisation. 2021. URL: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds) [accessed 2024-02-24]
5. Bradshaw PT, Stevens J, Khankari N, Teitelbaum SL, Neugut AI, Gammon MD. Cardiovascular disease mortality among breast cancer survivors. Epidemiology 2016;27(1):6-13 [FREE Full text] [doi: 10.1097/EDE.0000000000000394] [Medline: 26414938]
6. Koene RJ, Prizment AE, Blaes A, Konety SH. Shared risk factors in cardiovascular disease and cancer. Circulation 2016;133(11):1104-1114 [FREE Full text] [doi: 10.1161/CIRCULATIONAHA.115.020406] [Medline: 26976915]
7. Smith LA, Cornelius VR, Plummer CJ, Levitt G, Verrill M, Canney P, et al. Cardiotoxicity of anthracycline agents for the treatment of cancer: systematic review and meta-analysis of randomised controlled trials. BMC Cancer 2010;10:337 [FREE Full text] [doi: 10.1186/1471-2407-10-337] [Medline: 20587042]
8. Scott JM, Nilsen TS, Gupta D, Jones LW. Exercise therapy and cardiovascular toxicity in cancer. Circulation 2018;137(11):1176-1191 [FREE Full text] [doi: 10.1161/CIRCULATIONAHA.117.024671] [Medline: 29530893]

9. Ross R, Blair SN, Arena R, Church TS, Després JP, Franklin BA, et al. Importance of assessing cardiorespiratory fitness in clinical practice: a case for fitness as a clinical vital sign: a scientific statement from the American Heart Association. Circulation 2016;134(24):e653-e699 [FREE Full text] [doi: 10.1161/CIR.0000000000000461] [Medline: 27881567]
10. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;365(9472):1687-1717. [doi: 10.1016/S0140-6736(05)66544-0] [Medline: 15894097]
11. Palomo A, Ray RM, Johnson L, Paskett E, Caan B, Jones L, et al. Associations between exercise prior to and around the time of cancer diagnosis and subsequent cardiovascular events in women with breast cancer: a Women's Health Initiative (WHI) analysis. J Am Coll Cardiol 2017;69(11):1774 [FREE Full text] [doi: 10.1016/s0735-1097(17)35163-x]
12. Buffart LM, Kalter J, Sweegers MG, Courneya KS, Newton RU, Aaronson NK, et al. Effects and moderators of exercise on quality of life and physical function in patients with cancer: An individual patient data meta-analysis of 34 RCTs. Cancer Treat Rev 2017 Jan;52:91-104 [FREE Full text] [doi: 10.1016/j.ctrv.2016.11.010] [Medline: 28006694]
13. Cormie P, Atkinson M, Bucci L, Cust A, Eakin E, Hayes S, et al. Clinical oncology society of Australia position statement on exercise in cancer care. Med J Aust 2018;209(4):184-187. [doi: 10.5694/mja18.00199] [Medline: 29719196]
14. Hayes SC, Newton RU, Spence RR, Galvão DA. The exercise and sports science Australia position statement: exercise medicine in cancer management. J Sci Med Sport 2019;22(11):1175-1199 [FREE Full text] [doi: 10.1016/j.jsams.2019.05.003] [Medline: 31277921]
15. Hardcastle SJ, Cohen PA. Effective physical activity promotion to survivors of cancer is likely to be home based and to require oncologist participation. J Clin Oncol 2017;35(32):3635-3637 [FREE Full text] [doi: 10.1200/JCO.2017.74.6032] [Medline: 28915086]
16. Short CE, James EL, Stacey F, Plotnikoff RC. A qualitative synthesis of trials promoting physical activity behaviour change among post-treatment breast cancer survivors. J Cancer Surviv 2013;7(4):570-581 [FREE Full text] [doi: 10.1007/s11764-013-0296-4] [Medline: 23888337]
17. Beatty AL, Fukuoka Y, Whooley MA. Using mobile technology for cardiac rehabilitation: a review and framework for development and evaluation. J Am Heart Assoc 2013;2(6):e000568 [FREE Full text] [doi: 10.1161/JAHA.113.000568] [Medline: 24185949]
18. Maddison R, Pfaeffli L, Whittaker R, Stewart R, Kerr A, Jiang Y, et al. A mobile phone intervention increases physical activity in people with cardiovascular disease: results from the HEART randomized controlled trial. Eur J Prev Cardiol 2015;22(6):701-709 [FREE Full text] [doi: 10.1177/2047487314535076] [Medline: 24817694]
19. Maddison R, Rawstorn JC, Stewart RAH, Benatar J, Whittaker R, Rolleston A, et al. Effects and costs of real-time cardiac telerehabilitation: randomised controlled non-inferiority trial. Heart 2019;105(2):122-129 [FREE Full text] [doi: 10.1136/heartjnl-2018-313189] [Medline: 30150328]
20. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med 2013;158(3):200-207 [FREE Full text] [doi: 10.7326/0003-4819-158-3-201302050-00583] [Medline: 23295957]
21. Slade SC, Dionne CE, Underwood M, Buchbinder R. Consensus on Exercise Reporting Template (CERT): explanation and elaboration statement. Br J Sports Med 2016;50(23):1428-1437 [FREE Full text] [doi: 10.1136/bjsports-2016-096651] [Medline: 27707738]
22. Short, CE, Jones, TL. REMOTE-COR-B. 2024. URL: https://accounts.osf.io/login?service=https://osf.io/72kdc/ [accessed 2024-02-24]
23. Lyon AR, Dent S, Stanway S, Earl H, Brezden-Masley C, Cohen-Solal A, et al. Baseline cardiovascular risk assessment in cancer patients scheduled to receive cardiotoxic cancer therapies: a position statement and new risk assessment tools from the Cardio-Oncology Study Group of the Heart Failure Association of the European Society of Cardiology in collaboration with the International Cardio-Oncology Society. Eur J Heart Fail 2020 Nov;22(11):1945-1960 [FREE Full text] [doi: 10.1002/ejhf.1920] [Medline: 32463967]
24. Lyon AR, López-Fernández T, Couch LS, Asteggiano R, Aznar MC, Bergler-Klein J, et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). Eur Heart J 2022 Nov 01;43(41):4229-4361. [doi: 10.1093/eurheartj/ehac244] [Medline: 36017568]
25. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiano R, Galderisi M, et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). Eur Heart J 2016 Sep 21;37(36):2768-2801 [FREE Full text] [doi: 10.1093/eurheartj/ehw211] [Medline: 27567406]
26. Bovelli D, Plataniotis G, Roila F, ESMO Guidelines Working Group. Cardiotoxicity of chemotherapeutic agents and radiotherapy-related heart disease: ESMO Clinical Practice Guidelines. Ann Oncol 2010 May;21 Suppl 5:v277-v282 [FREE Full text] [doi: 10.1093/annonc/mdq200] [Medline: 20555097]
27. Florescu M, Cinteza M, Vinereanu D. Chemotherapy-induced cardiotoxicity. Maedica (Bucur) 2013 Mar;8(1):59-67 [FREE Full text] [Medline: 24023601]

28. Campbell KL, Winters-Stone KM, Wiskemann J, May AM, Schwartz AL, Courneya KS, et al. Exercise guidelines for cancer survivors: consensus statement from international multidisciplinary roundtable. Med Sci Sports Exerc 2019;51(11):2375-2390 [FREE Full text] [doi: 10.1249/MSS.0000000000002116] [Medline: 31626055]
29. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: building an international community of software platform partners. J Biomed Inform 2019;95:103208 [FREE Full text] [doi: 10.1016/j.jbi.2019.103208] [Medline: 31078660]
30. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research Electronic Data Capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42(2):377-381 [FREE Full text] [doi: 10.1016/j.jbi.2008.08.010] [Medline: 18929686]
31. Rawstorn JC, Gant N, Meads A, Warren I, Maddison R. Remotely delivered exercise-based cardiac rehabilitation: design and content development of a novel mHealth platform. JMIR Mhealth Uhealth 2016;4(2):e57 [FREE Full text] [doi: 10.2196/mhealth.5501] [Medline: 27342791]
32. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. US Department of Health and Human Services. 2017. URL: https://academy.myeloma.org.uk/wp-content/uploads/2015/04/CTCAE_v5.pdf [accessed 2024-02-24]
33. Slade SC, Dionne CE, Underwood M, Buchbinder R, Beck B, Bennell K, et al. Consensus on Exercise Reporting Template (CERT): modified Delphi study. Phys Ther 2016 Oct;96(10):1514-1524. [doi: 10.2522/ptj.20150668] [Medline: 27149962]
34. Norton K, Norton L, Sadgrove D. Position statement on physical activity and exercise intensity terminology. J Sci Med Sport 2010;13(5):496-502. [doi: 10.1016/j.jsams.2009.09.008] [Medline: 20005170]
35. American College of Sports Medicine. ACSM's Guidelines for Exercise Testing and Prescription, 10th Edition. Philadelphia, PA: Wolters Kluwer; 2018.
36. Bandura A. Health promotion by social cognitive means. Health Educ Behav 2004;31(2):143-164. [doi: 10.1177/1090198104263660] [Medline: 15090118]
37. Deci EL, Ryan RM. Self-determination theory: a macrotheory of human motivation, development, and health. Can Psychol / Psychologie canadienne 2008;49(3):182-185. [doi: 10.1037/a0012801]
38. Gardner B, Lally P, Wardle J. Making health habitual: the psychology of 'habit-formation' and general practice. Br J Gen Pract 2012;62(605):664-666 [FREE Full text] [doi: 10.3399/bjgp12X659466] [Medline: 23211256]
39. Kelders SM, Kok RN, Ossebaard HC, Van Gemert-Pijnen JEWC. Persuasive system design does matter: a systematic review of adherence to web-based interventions. J Med Internet Res 2012;14(6):e152 [FREE Full text] [doi: 10.2196/jmir.2104] [Medline: 23151820]
40. National Health and Medical Research Council. Guidance: Safety Monitoring and Reporting in Clinical Trials Involving Therapeutic Goods. Canberra: National Health and Medical Research Council; 2016.
41. Larsen DL, Attkisson CC, Hargreaves WA, Nguyen TD. Assessment of client/patient satisfaction: development of a general scale. Eval Program Plann 1979;2(3):197-207. [doi: 10.1016/0149-7189(79)90094-6] [Medline: 10245370]
42. Brooke J. SUS: a 'quick and dirty' usability scale. In: Jordan PW, McClelland IL, Thomas B, Weerdmeester BA, editors. Usability Evaluation in Industry. CRC Press: Boca Raton, FL; 1996:189-194.
43. Swank AM, Horton J, Fleg JL, Fonarow GC, Keteyian S, Goldberg L, et al. Modest increase in peak VO2 is related to better clinical outcomes in chronic heart failure patients: results from heart failure and a controlled trial to investigate outcomes of exercise training. Circ Heart Fail 2012;5(5):579-585 [FREE Full text] [doi: 10.1161/CIRCHEARTFAILURE.111.965186] [Medline: 22773109]
44. Hornsby WE, Douglas PS, West MJ, Kenjale AA, Lane AR, Schwitzer ER, et al. Safety and efficacy of aerobic training in operable breast cancer patients receiving neoadjuvant chemotherapy: a phase II randomized trial. Acta Oncol 2014;53(1):65-74 [FREE Full text] [doi: 10.3109/0284186X.2013.781673] [Medline: 23957716]
45. Casla S, López-Tarruella S, Jerez Y, Marquez-Rodas I, Galvão DA, Newton RU, et al. Supervised physical exercise improves VO2max, quality of life, and health in early stage breast cancer patients: a randomized controlled trial. Breast Cancer Res Treat 2015;153(2):371-382. [doi: 10.1007/s10549-015-3541-x] [Medline: 26293147]
46. Courneya KS, Mackey JR, Bell GJ, Jones LW, Field CJ, Fairey AS. Randomized controlled trial of exercise training in postmenopausal breast cancer survivors: cardiopulmonary and quality of life outcomes. J Clin Oncol 2003;21(9):1660-1668. [doi: 10.1200/JCO.2003.04.093] [Medline: 12721239]
47. Edelmann F, Bobenko A, Gelbrich G, Hasenfuss G, Herrmann-Lingen C, Duvinage A, et al. Exercise training in Diastolic Heart Failure (Ex-DHF): rationale and design of a multicentre, prospective, randomized, controlled, parallel group trial. Eur J Heart Fail 2017;19(8):1067-1074 [FREE Full text] [doi: 10.1002/ejhf.862] [Medline: 28516519]
48. Kitzman DW, Brubaker P, Morgan T, Haykowsky M, Hundley G, Kraus WE, et al. Effect of caloric restriction or aerobic exercise training on peak oxygen consumption and quality of life in obese older patients with heart failure with preserved ejection fraction: a randomized clinical trial. JAMA 2016;315(1):36-46 [FREE Full text] [doi: 10.1001/jama.2015.17346] [Medline: 26746456]
49. Parreira VF, Janaudis-Ferreira T, Evans RA, Mathur S, Goldstein RS, Brooks D. Measurement properties of the incremental shuttle walk test. A systematic review. Chest 2014;145(6):1357-1369. [doi: 10.1378/chest.13-2071] [Medline: 24384555]

50. Singh SJ, Morgan MD, Scott S, Walters D, Hardman AE. Development of a shuttle walking test of disability in patients with chronic airways obstruction. Thorax 1992;47(12):1019-1024 [FREE Full text] [doi: 10.1136/thx.47.12.1019] [Medline: 1494764]
51. Granger CL, Denehy L, Parry SM, Martin J, Dimitriadis T, Sorohan M, et al. Which field walking test should be used to assess functional exercise capacity in lung cancer? An observational study. BMC Pulm Med 2015;15:89 [FREE Full text] [doi: 10.1186/s12890-015-0075-2] [Medline: 26264470]
52. Brady MJ, Cella DF, Mo F, Bonomi AE, Tulsky DS, Lloyd SR, et al. Reliability and validity of the Functional Assessment of Cancer Therapy-Breast quality-of-life instrument. J Clin Oncol 1997;15(3):974-986. [doi: 10.1200/JCO.1997.15.3.974] [Medline: 9060536]
53. Eton DT, Cella D, Yost KJ, Yount SE, Peterman AH, Neuberg DS, et al. A combination of distribution- and anchor-based approaches determined minimally important differences (MIDs) for four endpoints in a breast cancer scale. J Clin Epidemiol 2004;57(9):898-910. [doi: 10.1016/j.jclinepi.2004.01.012] [Medline: 15504633]
54. Yellen SB, Cella DF, Webster K, Blendowski C, Kaplan E. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. J Pain Symptom Manage 1997;13(2):63-74 [FREE Full text] [doi: 10.1016/s0885-3924(96)00274-6] [Medline: 9095563]
55. Cella D, Eton DT, Lai JS, Peterman AH, Merkel DE. Combining anchor and distribution-based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy (FACT) anemia and fatigue scales. J Pain Symptom Manage 2002;24(6):547-561 [FREE Full text] [doi: 10.1016/s0885-3924(02)00529-8] [Medline: 12551804]
56. Godin G. The Godin-Shephard Leisure-Time Physical Activity Questionnaire. Health Fitness J Canada 2011;4(1):18-22 [FREE Full text]
57. Amireault S, Godin G, Lacombe J, Sabiston CM. The use of the Godin-Shephard Leisure-Time Physical Activity Questionnaire in oncology research: a systematic review. BMC Med Res Methodol 2015;15:60 [FREE Full text] [doi: 10.1186/s12874-015-0045-7] [Medline: 26264621]
58. Rodgers WM, Wilson PM, Hall CR, Fraser SN, Murray TC. Evidence for a multidimensional self-efficacy for exercise scale. Res Q Exerc Sport 2008;79(2):222-234. [doi: 10.1080/02701367.2008.10599485] [Medline: 18664046]
59. Gardner B, Abraham C, Lally P, de Bruijn GJ. Towards parsimony in habit measurement: testing the convergent and predictive validity of an automaticity subscale of the Self-Report Habit Index. Int J Behav Nutr Phys Act 2012;9:102 [FREE Full text] [doi: 10.1186/1479-5868-9-102] [Medline: 22935297]
60. Wilson PM, Rodgers WM, Fraser SN. Examining the psychometric properties of the Behavioral Regulation in Exercise Questionnaire. Meas Phys Educ Exerc Sci 2002;6(1):1-21. [doi: 10.1207/s15327841mpee0601_1]
61. Markland D, Tobin VJ. Need support and behavioural regulations for exercise among exercise referral scheme clients: the mediating role of psychological need satisfaction. Psychol Sport Exerc 2010;11(2):91-99. [doi: 10.1016/j.psychsport.2009.07.001]
62. Thabane L, Ma J, Chu R, Cheng J, Ismaila A, Rios LP, et al. A tutorial on pilot studies: the what, why and how. BMC Med Res Methodol 2010;10:1 [FREE Full text] [doi: 10.1186/1471-2288-10-1] [Medline: 20053272]
63. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. J Pers Soc Psychol 1986;51(6):1173-1182. [doi: 10.1037//0022-3514.51.6.1173] [Medline: 3806354]
64. Blatch-Jones AJ, Pek W, Kirkpatrick E, Ashton-Key M. Role of feasibility and pilot studies in randomised controlled trials: a cross-sectional study. BMJ Open 2018;8(9):e022233 [FREE Full text] [doi: 10.1136/bmjopen-2018-022233] [Medline: 30257847]

Abbreviations

AMD: adjusted mean difference
BPM: beats per minute
CERT: Consensus on Exercise Reporting Template
CPET: cardiopulmonary exercise testing
CRF: case record forms
ECG: electrocardiogram
FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue Scale
FACT-B: Functional Assessment of Cancer Therapy-Breast
GLTEQ: Godin Leisure-Time Exercise Questionnaire
HER: human epidermal growth factor receptor
HRR: heart rate reserve
ISWT: incremental shuttle walk test
LSI: Leisure Score Index
MET-hrs: metabolic equivalent task hours
REDCap: Research Electronic Data Capture

RPE: Rating of Perceived Exertion
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
VO2max: maximum oxygen uptake
VO2peak: peak oxygen consumption

Edited by A Mavragani; submitted 02.10.23; peer-reviewed by S Schlaepfer, C Lavie, R Krukowski; comments to author 16.01.24; revised version received 18.01.24; accepted 19.01.24; published 05.04.24.

Please cite as:
Short CE, Rawstorn JC, Jones TL, Edbrooke L, Hayes SC, Maddison R, Nightingale S, Ismail H, De Boer R, Hegi-Johnson F, Sverdlov AL, Bell R, Halligan I, Denehy L
Evaluating a Remotely Delivered Cardio-Oncology Rehabilitation Intervention for Patients With Breast Cancer (REMOTE-COR-B): Protocol for a Single-Arm Feasibility Trial
JMIR Res Protoc 2024;13:e53301
URL: https://www.researchprotocols.org/2024/1/e53301
doi:10.2196/53301
PMID:38578682

Protocol

Assessing and Improving the Care of Patients With Heart Failure in Ghana: Protocol for a Prospective Observational Study and the Ghana Heart Initiative-Heart Failure Registry

Felix Awindaogo[1], MD, MSc; Emmanuel Acheamfour-Akowuah[2], MD; Alfred Doku[3], MD, MPH; Collins Kokuro[4*], MD; Francis Agyekum[3*], MD, MSc; Isaac Kofi Owusu[4], MD, Prof Dr

[1]Korle-Bu Teaching Hospital, Accra, Ghana

[2]Directorate of Medicine Kumasi, Komfo Anokye Teaching Hospital, Kumasi, Ghana

[3]Department of Medicine and Therapeutics, University of Ghana Medical School, University of Ghana, Accra, Ghana

[4]Department of Medicine, School of Medicine and Dentistry, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana

[*]these authors contributed equally

Corresponding Author:
Alfred Doku, MD, MPH
Department of Medicine and Therapeutics
University of Ghana Medical School
University of Ghana
22nd Guggisberg Avenue, Korle-Bu
PO Box GP 4236
Accra
Ghana
Phone: 233 244273573
Email: dokukavin@gmail.com

Abstract

Background: Heart failure (HF) is a leading cause of morbidity and mortality globally, with a high disease burden. The prevalence of HF in Ghana is increasing rapidly, but epidemiological profiles, treatment patterns, and survival data are scarce. The national capacity to diagnose and manage HF appropriately is also limited. To address the growing epidemic of HF, it is crucial to recognize the epidemiological characteristics and medium-term outcomes of HF in Ghana and improve the capability to identify and manage HF promptly and effectively at all levels of care.

Objective: This study aims to determine the epidemiological characteristics and medium-term HF outcomes in Ghana.

Methods: We conducted a prospective, multicenter, multilevel cross-sectional observational study of patients with HF from January to December 2023. Approximately 5000 patients presenting with HF to 9 hospitals, including teaching, regional, and municipal hospitals, will be recruited and evaluated according to a standardized protocol, including the use of an echocardiogram and an N-terminal pro-brain natriuretic peptide (NT-proBNP) test. Guideline-directed medical treatment of HF will be initiated for 6 months, and the medium-term outcomes of interventions, including rehospitalization and mortality, will be assessed. Patient data will be collated into a HF registry for continuous assessment and monitoring.

Results: This intervention will generate the necessary information on the etiology of HF, clinical presentations, the diagnostic yield of various tools, and management outcomes. In addition, it will build the necessary capacity and support for HF management in Ghana. As of July 30, 2023, the training and onboarding of all 9 centers had been completed. Preliminary analyses will be conducted by the end of the second quarter of 2024, and results are expected to be publicly available by the middle of 2024.

Conclusions: This study will provide the necessary data on HF, which will inform decisions on the prevention and management of HF and form the basis for future research.

Trial Registration: ISRCTN Registry (United Kingdom) ISRCTN18216214; https:www.isrctn.com/ISRCTN18216214

International Registered Report Identifier (IRRID): DERR1-10.2196/52616

(JMIR Res Protoc 2024;13:e52616) doi:10.2196/52616

KEYWORDS

clinical; cross-sectional; epidemiology; Ghana; heart failure; heart; management; medium-term; monitoring; mortality; outcome; patient data; prevention; protocol; teaching; treatment

Introduction

Overview

Heart failure (HF) is a costly, multifaceted, and life-threatening syndrome characterized by significant morbidity and mortality. Globally, HF affects 64 million people, with a prevalence of 1%-2% of adults in the general population and an estimated incidence of 1-20 cases per 1000 person-years [1].

Sub-Saharan Africa (SSA) has no population-based data; however, in-hospital prevalence ranges from 9.4% to 42.5% [2,3]. HF in SSA mainly affects young people and middle-aged individuals, occurring in people aged between 36 and 62.4 years [4]. It poses a substantial disease burden, with high mortality, rehospitalization rates, and health care costs, primarily attributable to readmissions and prolonged hospitalization periods of 11-13 days [3,5,6].

HF contributes significantly to Ghana's cardiovascular disease burden, with a worse prognosis and a more malignant course [7,8]. It is a leading cause of death among Ghanaian adults; yet, there is a paucity of data on the epidemiological profiles, treatment patterns, and survival rates of patients with HF in Ghana [9-11]. Single-center studies indicate a high prevalence of HF in Ghana [7,8,12].

The diagnosis of HF in most patients is primarily based on clinical manifestations due to the limited availability of diagnostic equipment. Ghana has few cardiologists, who are mainly located in tertiary hospitals [13]. In addition, there is a lack of HF education and training for physicians and nonphysician health workers. While HF management teams or multidisciplinary teams for HF management are the gold standard model for the delivery of care, these teams are nonexistent in Ghana, and most health facilities lack resources for long-term patient follow-up, such as diagnostic equipment, dedicated HF clinics, and protocols [14-17].

A national network of heart failure management teams (NNHFMT) will be established as part of the Ghana Heart Initiative's efforts to improve cardiovascular disease care in Ghana to help mitigate the burden of HF. The NNHFMT is tasked with building the capacity of both secondary and tertiary levels of care to promptly and effectively identify and manage HF by creating heart failure management teams (HFMTs) and establishing a national registry for HF and HF clinics that will be integrated with routine clinical services to provide long-term follow-up and care. The establishment of HF clinics and a national registry will fill a significant gap in HF care and research by providing the most recent epidemiological, management patterns, and medium-term outcomes data on HF.

Objectives

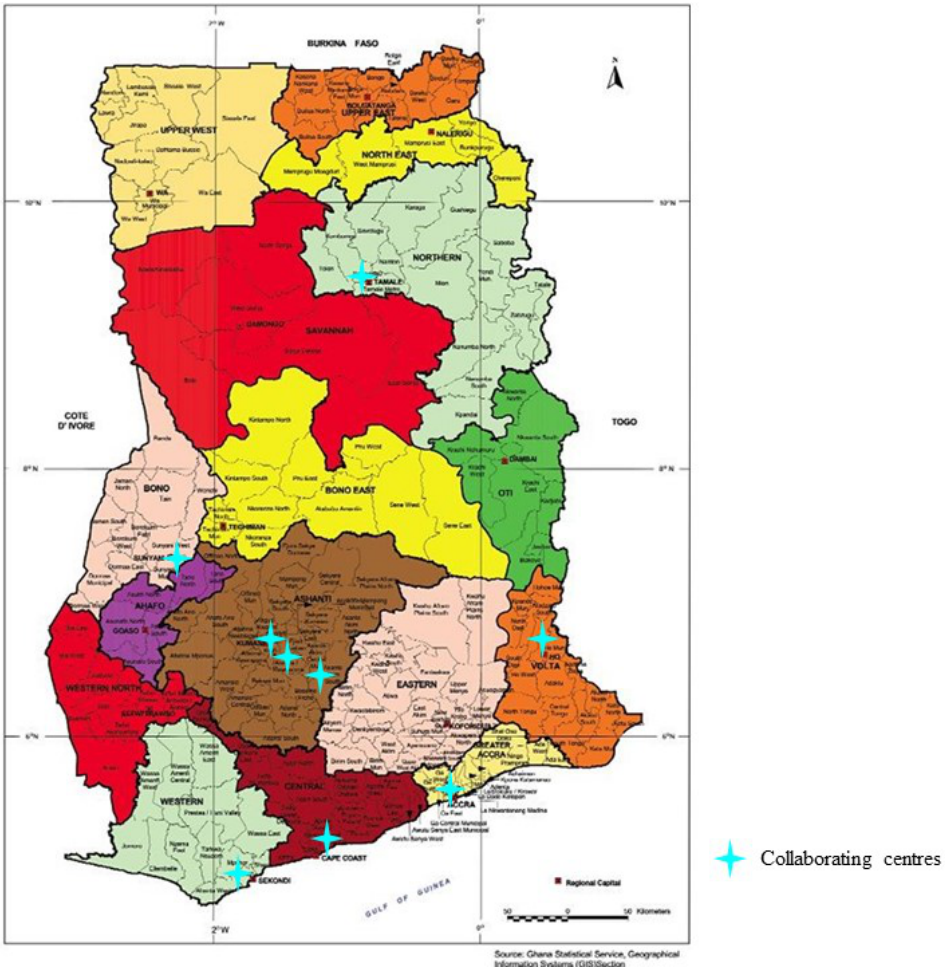
The primary objective of this study is to determine the epidemiological characteristics and medium-term outcomes of HF in Ghana by outlining the epidemiological and clinical characteristics of patients with HF in Ghana, identifying the underlying causes, evaluating the medium-term outcomes of HF in Ghana, and identifying the factors that predict hospitalization and mortality in patients with HF in Ghana. This study also aims to build capacity in the care of patients with HF and form the basis for a national registry for HF in Ghana.

Methods

Overview

An NNHFMT consisting of physicians, nurses, and researchers from 9 collaborating hospitals in Ghana was constituted to achieve the study objectives, with each institutional HFMT led by a cardiologist, 2 supporting cardiologists or physicians, and 2 nurses. The HFMTs will establish HF clinics and integrate them into the routine services of their hospitals; recruit patients with HF and manage them per guidelines and algorithm; and create awareness and train other personnel in the 9 centers on the diagnosis and management of HF. These institutions include 5 teaching hospitals, 3 regional hospitals, and 1 municipal hospital. They include the Korle-Bu Teaching Hospital (KBTH), Komfo Anokye Teaching Hospital (KATH), Tamale Teaching Hospital (TTH), Ho Teaching Hospital (HTH), Cape Coast Teaching Hospital (CCTH), Bono Regional Hospital, Presbyterian Hospital-Agogo, Kumasi South Hospital, and the Effia Nkwanta Regional Hospital (Figure 1) [18].

Figure 1. Map of Ghana showing the location of collaborating centers. Source: Ghana Statistical Service, 2020.

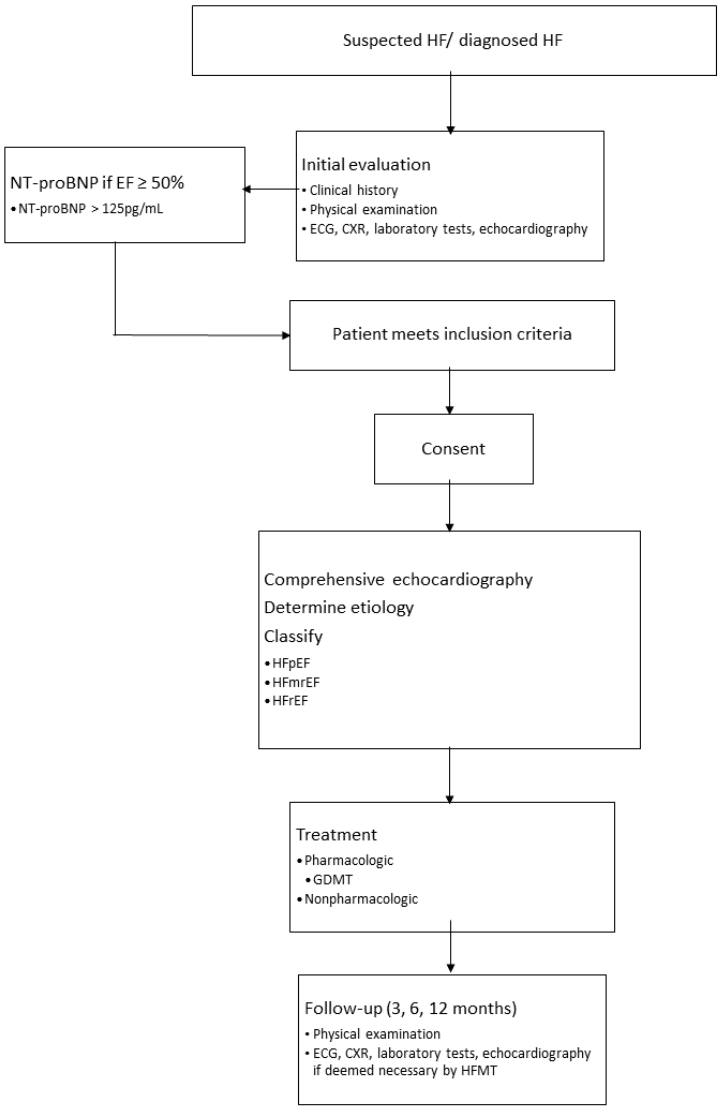


Study Design

This is a prospective, multicenter, and multilevel observational study of patients with HF. Patients presenting with HF will be recruited and evaluated according to a standardized protocol. Guideline-directed treatment for HF will then be prescribed after the diagnosis has been confirmed. The study will conduct a serum N-terminal pro-brain natriuretic peptide (NT-proBNP) and transthoracic echocardiogram for all participants for free, while the cost of treatment and other investigations will be borne by study participants as in routine care. Patients will be followed up prospectively for 6 months to determine the medium-term outcomes of interventions (Figure 2).

Patients will be recruited through the collaborating institutions' emergency rooms, admission wards, and established HF clinics from January to December 2023. The HFMTs of the 2 leading teaching hospitals in Ghana, KBTH and KATH, will be trained using a facilitators' training manual, which will be developed from current international HF guidelines. KBTH and KATH will then provide mentorship and training to the other collaborating hospitals. The HFMT of KBTH will train members of the HFMTs from the TTH, HTH, and Effia-Nkwanta Regional Hospital, while the HFMT of KATH will also train the HFMTs of CCTH, Bono Regional Hospital, Presbyterian Hospital-Agogo, and Kumasi South Hospital. The study will begin in the KBTH and KATH in January 2023, while the other 7 sites will begin recruitment in July 2023, and all areas will end enrollment in December 2023.

Figure 2. Chart outlining study design.



Study Population

Study participants will include patients aged 13 years or older who present with HF in the collaborating hospitals and consent to participate in the study. Patients with a life expectancy less than the expected duration of the registry due to non-HF comorbidities will be excluded.

Based on our estimation of a sample size of 5000 participants, we would be able to determine the mortality and hospitalization rate at 6 months with a 95% CI and a precision of ±1%. Each participating center will recruit 556 participants.

Recruitment of Study Participants

Participants will be recruited through the various departments or units of the collaborating institutions. All patients diagnosed with HF or suspected of having HF will be referred to the HFMTs for evaluation and enrollment. A total of 2 sensitization workshops will be organized at collaborating institutions during the study period: 1 before participants' enrollment and 1 midway through participant recruitment.

Data Collection

Data collection comprises administering questionnaires, reviewing medical records, physical examinations, imaging investigations, including chest x-rays and echocardiography, electrocardiography, and laboratory tests. The methods for data collection in this study are identical in all locations, following standardized operating manuals and tools.

Diagnosis of HF

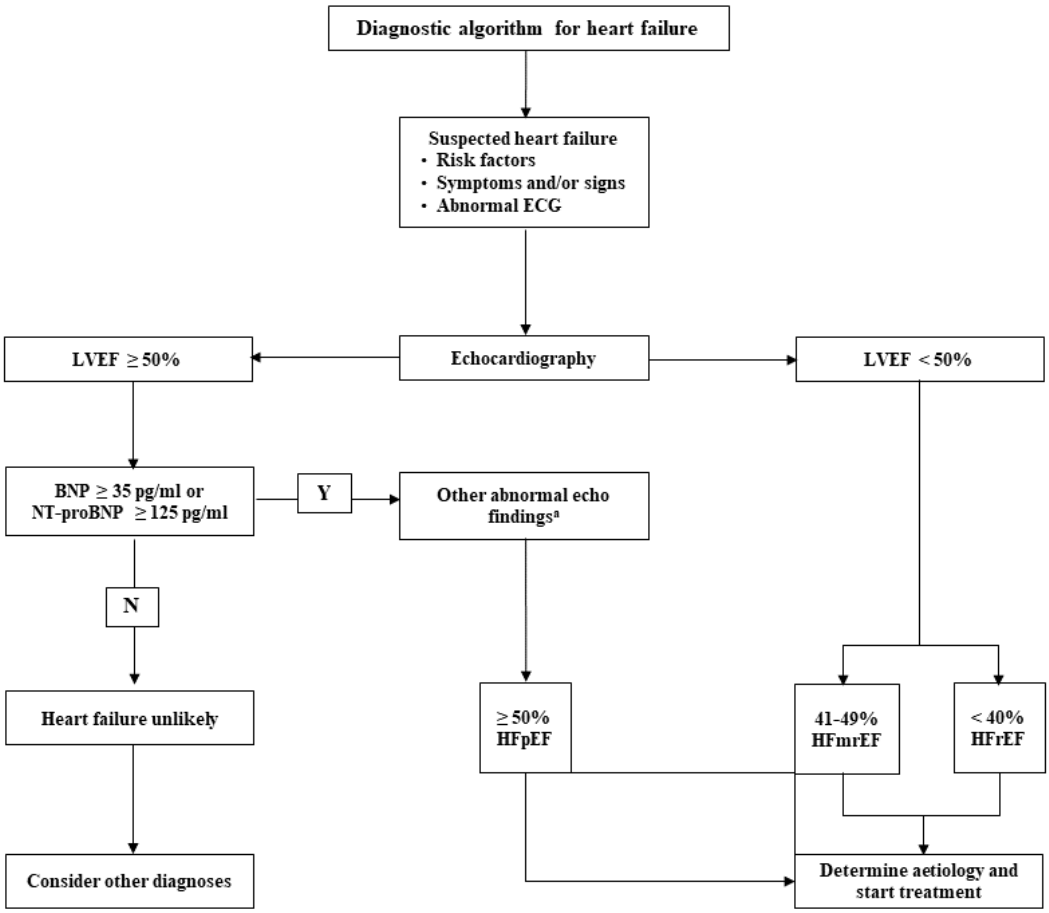
The diagnosis of HF will be made using a modified diagnostic algorithm adopted from the 2021 European Society of Cardiology Guidelines to diagnose and treat acute and chronic HF (Figure 3) [19]. The diagnosis of HF will be made based on the presence of typical symptoms of HF and objective evidence of cardiac dysfunction and categorized into three phenotypes: (1) heart failure with reduced ejection fraction (HFrEF), (2) heart failure with mildly reduced ejection fraction (HFmrEF), and (3) heart failure with preserved ejection fraction (HFpEF) based on the left ventricular ejection fraction (LVEF) [19].

All patients with typical symptoms and specific signs of HF and LVEF≤40% will be categorized as HFrEF, while patients with LVEF of 41%-49 % will be categorized as HFmrEF.

HFpEF will be diagnosed in patients presenting with typical symptoms and specific signs of HF and LVEF≥50%, the presence of elevated natriuretic peptides (NT-proBNP≥125 pg/mL), and objective evidence of cardiac structural and functional abnormalities consistent with the presence of left ventricular (LV) diastolic dysfunction or raised LV filling pressures. Objective evidence of structural or functional abnormalities includes the following:

- LV mass index ≥95 g/m^2 (female), ≥115 g/m^2 (male), and a relative wall thickness >0.42.
- Left atrial volume index >34 mL/m^2 in sinus rhythm (SR) and the presence of atrial fibrillation (AF) left atrial volume >40 mL/m^2.
- E/e' ratio at rest >9.
- NT-proBNP >125 (SR) or >365 (AF) pg/mL OR BNP >35 (SR) or >105 (AF) pg/mL.
- Pulmonary artery systolic pressure >35 mm Hg or tricuspid regurgitant velocity at rest >2.8 m/second.

Figure 3. Modified diagnostic algorithm for heart failure (HF). BNP: brain natriuretic peptide; ECG: electrocardiogram; HFmrEF: heart failure with mildly reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; LVEF: left ventricular ejection fraction.



Etiology of HF

The etiology of HF will be determined based on the history, physical examination, laboratory, electrocardiographic, echocardiographic findings, and other imaging modalities (Table 1).

Table 1. Heart failure (HF) etiology and clinical characteristics.

Etiology of HF	Clinical characteristics	Specific investigations
Hypertension [20-22]	• Persistent elevated systolic BP[a] ≥140 mm Hg and diastolic BP ≥90 mm Hg • Presence of HMOD[b] • Current or previous use of antihypertensive medications	• 24-hour ambulatory BP • Plasma metanephrines and renal artery imaging • Serum renin and aldosterone • TTE[c]
Coronary artery disease [23]	• HF and ACS[d] • A pre-existing history of CCS[e] • Features suggestive of significant CAD[f] on coronary angiography or other imaging	• Invasive coronary angiography • CT[g] coronary angiography • Imaging stress tests (echo, nuclear, and CMR[h])
Valvular heart disease [24]	• Primary valve disease, for example, aortic stenosis • Secondary valve disease, for example, functional regurgitation • Congenital valve disease, for example, bicuspid aortic valve and mitral valve prolapse	• TTE/ TEE[i]/ stress echo • CT/ CMR
Rheumatic heart disease [25,26]	• Primary valve disease, for example, mitral stenosis and mitral regurgitation • Atrial fibrillation	• TTE/ TEE/ stress echo
Dilated cardiomyopathy [27,28]	• Unexplained dilated cardiac chambers with increased left ventricular mass index	• CMR, genetic testing • Trace elements, toxicology, LFTs[j]
Arrhythmia-induced cardiomyopathy [29]	• Mean heart rate above 100 beats per minute • Atrial fibrillation • Premature ventricular contractions burden equal to or greater than 10% • No other cause of LV dysfunction identified	• Ambulatory ECG recording • Electrophysiology study, if indicated
Congenital heart disease	• History of congenital heart disease • Incidental diagnosis of congenital heart disease during investigation for HF	• TTE/ TEE • CMR
Other etiologies of HF [19]	• Clinical features diagnostic of restrictive cardiomyopathy, arrhythmogenic cardiomyopathy, peripartum cardiomyopathy, endomyocardial fibrosis, cor pulmonale, infiltrative cardiomyopathy, pericardial disease, LV noncompaction cardiomyopathy, and toxin-induced cardiomyopathy.	• Serum electrophoresis and serum free light chains. • Echo, CMR, CT-PET[k], endomyocardial biopsy, Serum angiotensin-converting enzyme, fluorodeoxyglucose-PET, and chest CT • Right and left heart catheterization

[a]BP: blood pressure.

[b]HMOD: hypertension-mediated organ damage.

[c]TTE: transthoracic echocardiogram.

[d]ACS: acute coronary syndrome.

[e]CCS: chronic coronary syndrome.

[f]CAD: coronary artery disease.

[g]CT: computed tomography.

[h]CMR: cardiovascular magnetic resonance.

[i]TEE: transesophageal echocardiogram.

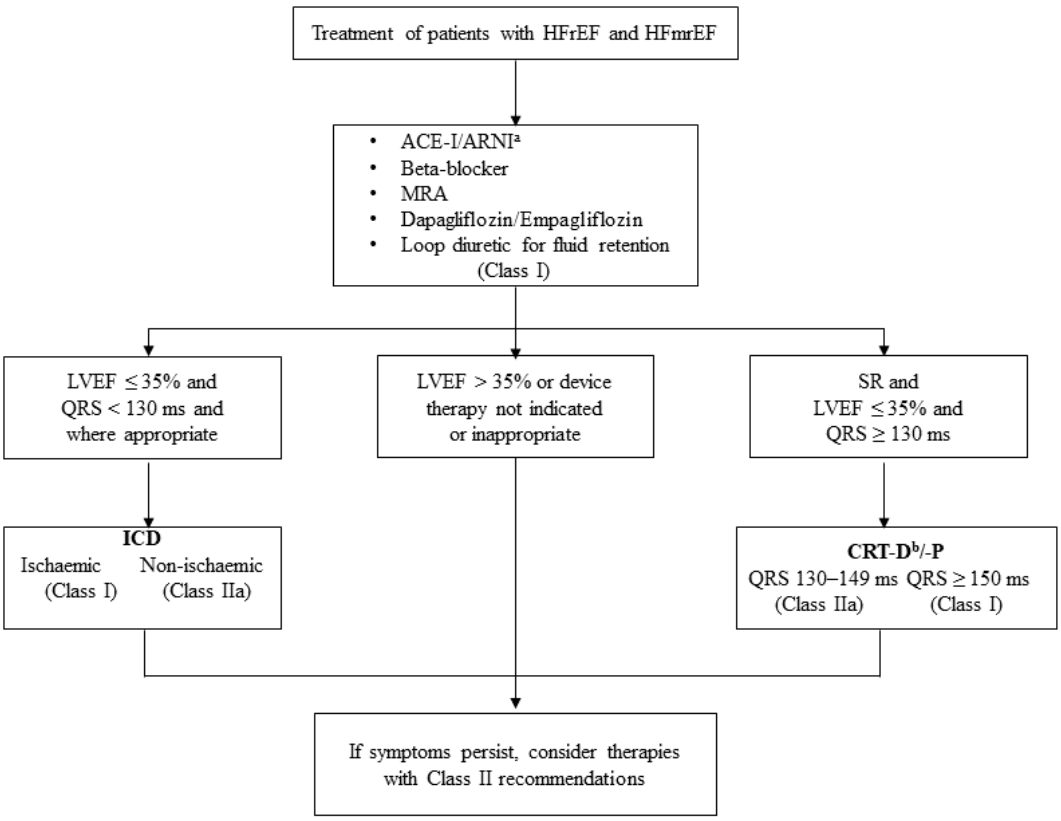
[j]LFT: liver function test.

[k]PET: positron emission tomography.

Treatment of HF

A modified treatment algorithm adopted from the 2021 European Society of Cardiology Guidelines for treating acute and chronic HF (Figure 4) will be used in the treatment of patients [19].

Figure 4. Modified treatment algorithm for treating HFrEF and HFmrEF. a: a replacement for ACE-I/ARB (angiotensin receptor blocker); ACE-I: angiotensin-converting enzyme inhibitor; ARNI: angiotensin receptor-neprilysin inhibitor; CRT-D: cardiac resynchronisation therapy with a defibrillator; CRT-P: cardiac resynchronisation therapy pacemaker; HFmrEF: heart failure with mildly reduced ejection fraction; HFrEF: heart failure with reduced ejection fraction; ICD: implantable cardioverter-defibrillator; MRA: mineralocorticoid receptor antagonist; ms: milliseconds; SR: sinus rhythm.



Data Handling and Analysis

The KoboCollect toolbox (v2022.4.4; [30]) will be used to capture data and upload it onto a cloud database that is only accessible to the principal investigator and the data manager. Collated data will be exported into SPSS (*package 2016*; SPSS Inc) for statistical analysis. Tables, bar charts, and pie charts will be used to present the data. For continuous variables, the central tendency and spread measures will be calculated using the mean (SD), and IQR. Categorical variables will be reported as numbers and percentages. Multivariable regression models will be used explore the relationships between variables and rehospitalization and death. We will perform a Kaplan-Meier analysis to estimate the survival and death rate of patients with HF. The Cox regression analysis will determine the relationship between the risk of death in an individual and selected variables and the significance of these variables. Missing values will be handled based on the type and frequency of missing values. A P value <.05 will be considered statistically significant.

Timelines

The table of timelines (Table 2) below summarizes the key activities of the study from the start to the end of the study.

Table 2. Table of timelines.

	2022	2023												2024	
	December	January	February	March	April	May	June	July	August	September	October	November	December	January-June	June
Training for KBTH and KATH	✓						✓								
Training for other sites								✓			✓				
Sensitization workshops for KBTH and KATH	✓					✓									
Sensitization workshops for other sites								✓			✓				
Enrollment and data collection		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Establishment of HF clinics		✓						✓							
Follow-up				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Preliminary data analysis and reporting										✓					
End of enrollment														✓	
Data analysis									✓	✓	✓	✓	✓	✓	
End of study															✓

Ethical Considerations

Ethical approval has been obtained from the Ethical and Institutional Review Boards of Korle-Bu Teaching Hospital (STC/IRB/000150/2022), Cape Coast Teaching Hospital (CCTHERC/EC/2023/019), Tamale Teaching Hospital (TTH/R&D/SR/229), Ho Teaching Hospital (HTH-REC (30) FC_2023), and Komfo Anokye Teaching Hospital (KATH IRB/AP/166/22). All participants will be informed about the study, its objectives, and the data collection methods. Consent will be obtained from participants who agree to be part of the study and are assured of strict confidentiality and anonymity. Participants will also be informed that participation in the study is entirely voluntary, and all the services they receive at the clinic will continue as usual whether they decide to participate or not. A unique study number will be assigned to each participant, and the collected data will be deidentified. Only the assigned unique number will be used on study documents related to participants. Participants will also be informed that they can withdraw from the study at any time they choose without consequences.

Results

This intervention will generate the necessary information on the etiology of HF, clinical presentations, the diagnostic yield of various tools, and management outcomes. In addition, it will build the necessary capacity and support for HF management in Ghana. As of July 30, 2023, the training of the various health workers in all 9 hospitals has been completed. The KATH and the KBTH acted as supervisory sites and supported the training at 4 and 3 sites, respectively. Preliminary analyses will be conducted by the end of the second quarter of 2024, and results are expected to be publicly available by the middle of 2024.

The test-run of the research and registry instruments and modifications have been completed. Medical equipment (echocardiogram machines and NT-proBNP devices) has been calibrated and distributed to all sites.

Discussion

Overview

HF is one of the leading causes of hospital admissions in developing countries and is predicted to experience the most rapid growth worldwide [2,7,31,32]. This prospective study will answer many clinical questions about HF in Ghana. First, this study will address a notable data scarcity in HF care and research in Ghana by establishing a national HF registry, thus creating a vehicle for the accrual of large, comprehensive, and contemporary data encompassing the sociodemographic, clinical profiles, causes of HF, management of HF, and determinants of outcomes such as mortality and hospitalizations of patients with HF in Ghana. In addition, a national HF registry will also

provide a good opportunity to evaluate adherence to current guidelines and response to treatment among patients with HF in Ghana.

Clinical registries play a crucial role in gathering real-world data, essential for developing evidence for best clinical practice, measuring outcomes, providing feedback to clinicians, and enhancing the quality of care [1,33]. HF registries, like the Swedish Heart Failure Registry, have played a significant role in advancing knowledge and improving the management of HF. Established in 2000 and implemented nationwide in Sweden by 2003, this registry has yielded valuable research outcomes that have led to notable improvements in the understanding and care of patients with HF and under-treatment detection [1]. The NAtional TUnisian REgistry of Heart Failure (NATURE-HF) contributed valuable data that have the potential to enhance the treatment and overall prognosis of individuals with HF in North Africa [34]. Valuable data were also derived from the Abeokuta Heart Failure Clinical Registry of patients presenting with acute HF in Abeokuta, Nigeria, including acute HF presenting at a relatively younger age, commoner in men, and associated with severe symptoms [35].

While the acquisition of realistic data will address the data gap, this pragmatic study will provide capacity building for the management of HF by enhancing the skills and knowledge of health care providers in diagnosing and treating HF and making diagnostic equipment, including echocardiography, electrocardiograms, and point-of-care NT-proBNP devices, available to participating hospitals. Furthermore, participating institutions' HFMTs and HF clinics will broaden the prospect for specialist HF care and long-term follow-up in their regions.

Although numerous HF guidelines are available to aid in managing patients with HF, their generalizability presents variable challenges, as these guidelines may not be appropriate for managing HF in countries with limited health care resources [19]. Therefore, we anticipate that this study will serve as a significant milestone in establishing a standardized approach to managing HF in Ghana and the wider SSA region.

The study will address a notable void within Ghana's ever-evolving HF care and research domain. The study will generate novel and indispensable data that will improve HF care, serve as a foundation for teaching, develop locally tailored HF guidelines, and establish HF research programs.

Strengths and Limitations of This Study

This pragmatic, prospective, multicenter study will generate the most extensive contemporary data on HF in Ghana. The study will also enhance the knowledge and skills of health personnel in diagnosing and managing HF. The project is also designed to establish HF clinics and provide diagnostic services as part of routine health care services in participating hospitals. This study will describe associations rather than establish causality owing to its observational design.

Acknowledgments

The authors are grateful to the teams at all 9 centers for their dedication and sacrifice. This heart failure intervention is part of the Ghana Heart Initiative. The Ghana Heart Initiative is implemented through German International Cooperation (GIZ) and funded by Bayer.

Data Availability

The data sets generated and analyzed during this study will be available from the corresponding author on reasonable request following completion of the study and publication of the findings of the study.

Authors' Contributions

Conceptualization and development of study was done by AD and IKO. First draft by FRA. All authors reviewed and approved the final manuscript; FRA, EAA, CK, FA, AD, and IKO.

Conflicts of Interest

None declared.

References

1. Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC, Coats AJS. Global burden of heart failure: a comprehensive and updated review of epidemiology. Cardiovasc Res 2023;118(17):3272-3287 [FREE Full text] [doi: 10.1093/cvr/cvac013] [Medline: 35150240]
2. Gtif I, Bouzid F, Charfeddine S, Abid L, Kharrat N. Heart failure disease: an African perspective. Arch Cardiovasc Dis 2021;114(10):680-690 [FREE Full text] [doi: 10.1016/j.acvd.2021.07.001] [Medline: 34563468]
3. Ogah OS, Adebiyi A, Sliwa K. Heart failure in Sub-Saharan Africa. In: Rescigno G, Firstenberg MS, editors. Topics in Heart Failure Management. London, UK: IntechOpen; 2019:61-99.
4. Agbor VN, Essouma M, Ntusi NAB, Nyaga UF, Bigna JJ, Noubiap JJ. Heart failure in sub-Saharan Africa: a contemporaneous systematic review and meta-analysis. Int J Cardiol 2018;257:207-215. [doi: 10.1016/j.ijcard.2017.12.048] [Medline: 29506693]

5. Adidja NM, Agbor VN, Aminde JA, Ngwasiri CA, Ngu KB, Aminde LN. Non-adherence to antihypertensive pharmacotherapy in Buea, Cameroon: a cross-sectional community-based study. BMC Cardiovasc Disord 2018;18(1):150 [FREE Full text] [doi: 10.1186/s12872-018-0888-z] [Medline: 30041606]
6. Mensah GA, Roth GA, Sampson UKA, Moran AE, Feigin VL, Forouzanfar MH, et al. Mortality from cardiovascular diseases in sub-Saharan Africa, 1990-2013: a systematic analysis of data from the Global Burden of Disease Study 2013. Cardiovasc J Afr 2015;26(2 Suppl 1):S6-S10 [FREE Full text] [doi: 10.5830/CVJA-2015-036] [Medline: 25962950]
7. Appiah LT, Sarfo FS, Agyemang C, Tweneboah HO, Appiah NABA, Bedu-Addo G, et al. Current trends in admissions and outcomes of cardiac diseases in Ghana. Clin Cardiol 2017;40(10):783-788 [FREE Full text] [doi: 10.1002/clc.22753] [Medline: 28692760]
8. Bonsu KO, Owusu IK, Buabeng KO, Reidpath DD, Kadirvelu A. Clinical characteristics and prognosis of patients admitted for heart failure: a 5-year retrospective study of African patients. Int J Cardiol 2017;238:128-135. [doi: 10.1016/j.ijcard.2017.03.014] [Medline: 28318656]
9. Bragazzi NL, Zhong W, Shu J, Much AA, Lotan D, Grupper A, et al. Burden of heart failure and underlying causes in 195 countries and territories from 1990 to 2017. Eur J Prev Cardiol 2021;28(15):1682-1690 [FREE Full text] [doi: 10.1093/eurjpc/zwaa147] [Medline: 33571994]
10. Owusu AY, Kushitor SB, Ofosu AA, Kushitor MK, Ayi A, Awoonor-Williams JK. Institutional mortality rate and cause of death at health facilities in Ghana between 2014 and 2018. PLoS One 2021;16(9):e0256515 [FREE Full text] [doi: 10.1371/journal.pone.0256515] [Medline: 34496000]
11. Karaye KM, Dokainish H, ElSayed A, Mondo C, Damasceno A, Sliwa K, et al. Clinical profiles and outcomes of heart failure in five African countries: results from INTER-CHF study. Glob Heart 2021;16(1):50 [FREE Full text] [doi: 10.5334/gh.940] [Medline: 34381672]
12. Owusu IK, Adu-Boakye Y. Prevalence and aetiology of heart failure in patients seen at a teaching hospital in Ghana. J Cardiovasc Dis Diagn 2013;1(5):1000131 [FREE Full text] [doi: 10.4172/2329-9517.1000131]
13. Yuyun MF, Sliwa K, Kengne AP, Mocumbi AO, Bukhman G. Cardiovascular diseases in sub-Saharan Africa compared to high-income countries: an epidemiological perspective. Glob Heart 2020;15(1):15 [FREE Full text] [doi: 10.5334/gh.403] [Medline: 32489788]
14. Njoroge JN, Teerlink JR. Pathophysiology and therapeutic approaches to acute decompensated heart failure. Circ Res 2021;128(10):1468-1486 [FREE Full text] [doi: 10.1161/CIRCRESAHA.121.318186] [Medline: 33983837]
15. Dokainish H, Teo K, Zhu J, Roy A, AlHabib KF, ElSayed A, et al. Heart failure in Africa, Asia, the Middle East and South America: the INTER-CHF study. Int J Cardiol 2016;204:133-141. [doi: 10.1016/j.ijcard.2015.11.183] [Medline: 26657608]
16. Morton G, Masters J, Cowburn PJ. Multidisciplinary team approach to heart failure management. Heart 2018;104(16):1376-1382. [doi: 10.1136/heartjnl-2016-310598] [Medline: 29170356]
17. Grady KL, Dracup K, Kennedy G, Moser DK, Piano M, Stevenson LW, et al. Team management of patients with heart failure: a statement for healthcare professionals from the Cardiovascular Nursing Council of the American Heart Association. Circulation 2000;102(19):2443-2456 [FREE Full text] [doi: 10.1161/01.cir.102.19.2443] [Medline: 11067802]
18. Know the 16 regional capitals of Ghana. Daily Graphic Online. 2019. URL: https://www.graphic.com.gh/news/general-news/new-ghana-map-with-16-regional-capitals.html [accessed 2024-02-10]
19. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2021;42(36):3599-3726 [FREE Full text] [doi: 10.1093/eurheartj/ehab368] [Medline: 34447992]
20. Owusu IK, Adu-Boakye Y, Tetteh LA. Hypertensive heart failure in Kumasi, Ghana. Open Sci J Clin Med 2014;2(1):39-43 [FREE Full text]
21. Mancia G, Dominiczak A. The new international society of hypertension guidelines on hypertension. J Hypertens 2020;38(6):981 [FREE Full text] [doi: 10.1097/HJH.0000000000002490] [Medline: 32371786]
22. Williams B, Mancia G, Spiering W, Rosei EA, Azizi M, Burnier M, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. Eur Heart J 2018;39(33):3021-3104 [FREE Full text] [doi: 10.1093/eurheartj/ehy339] [Medline: 30165516]
23. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes: the Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). Eur Heart J 2020;41(3):407-477 [FREE Full text] [doi: 10.1093/eurheartj/ehz425] [Medline: 31504439]
24. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, et al. 2021 ESC/EACTS guidelines for the management of valvular heart disease: developed by the Task Force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2022;43(7):561-632 [FREE Full text] [doi: 10.1093/eurheartj/ehab395] [Medline: 34453165]
25. Reményi B, Wilson N, Steer A, Ferreira B, Kado J, Kumar K, et al. World Heart Federation criteria for echocardiographic diagnosis of rheumatic heart disease—an evidence-based guideline. Nat Rev Cardiol 2012;9(5):297-309 [FREE Full text] [doi: 10.1038/nrcardio.2012.7] [Medline: 22371105]

26. Nunes MCP, Sable C, Nascimento BR, de Lima EM, da Silva JLP, Diamantino AC, et al. Simplified echocardiography screening criteria for diagnosing and predicting progression of latent rheumatic heart disease. Circ Cardiovasc Imaging 2019;12(2):e007928 [FREE Full text] [doi: 10.1161/CIRCIMAGING.118.007928] [Medline: 30704283]
27. Japp AG, Gulati A, Cook SA, Cowie MR, Prasad SK. The diagnosis and evaluation of dilated cardiomyopathy. J Am Coll Cardiol 2016;67(25):2996-3010 [FREE Full text] [doi: 10.1016/j.jacc.2016.03.590] [Medline: 27339497]
28. Pinto YM, Elliott PM, Arbustini E, Adler Y, Anastasakis A, Böhm M, et al. Proposal for a revised definition of dilated cardiomyopathy, hypokinetic non-dilated cardiomyopathy, and its implications for clinical practice: a position statement of the ESC working group on myocardial and pericardial diseases. Eur Heart J 2016;37(23):1850-1858 [FREE Full text] [doi: 10.1093/eurheartj/ehv727] [Medline: 26792875]
29. Huizar JF, Ellenbogen KA, Tan AY, Kaszala K. Arrhythmia-induced cardiomyopathy: JACC State-of-the-Art review. J Am Coll Cardiol 2019;73(18):2328-2344 [FREE Full text] [doi: 10.1016/j.jacc.2019.02.045] [Medline: 31072578]
30. KoboToolBox. URL: https://www.kobotoolbox.org/ [accessed 2024-02-26]
31. Kraus S, Ogunbanjo G, Sliwa K, Ntusi NAB. Heart failure in sub-Saharan Africa: a clinical approach. S Afr Med J 2016;106(1):23-31 [FREE Full text] [doi: 10.7196/samj.2016.v106i1.10325] [Medline: 26933706]
32. Ogah OS, Stewart S, Onwujekwe OE, Falase AO, Adebayo SO, Olunuga T, et al. Economic burden of heart failure: investigating outpatient and inpatient costs in Abeokuta, Southwest Nigeria. PLoS One 2014;9(11):e113032 [FREE Full text] [doi: 10.1371/journal.pone.0113032] [Medline: 25415310]
33. Meltzer SN, Weintraub WS. The role of national registries in improving quality of care and outcomes for cardiovascular disease. Methodist Debakey Cardiovasc J 2020;16(3):205-211 [FREE Full text] [doi: 10.14797/mdcj-16-3-205] [Medline: 33133356]
34. Abid L, Kammoun I, Ben Halima M, Charfeddine S, Ben Slima H, Drissa M, et al. Design and rationale of the national Tunisian registry of heart failure (NATURE-HF): protocol for a multicenter registry study. JMIR Res Protoc 2021;10(10):e12262 [FREE Full text] [doi: 10.2196/12262] [Medline: 34704958]
35. Ogah OS, Stewart S, Falase AO, Akinyemi JO, Adegbite GD, Alabi AA, et al. Contemporary profile of acute heart failure in Southern Nigeria: data from the Abeokuta heart failure clinical registry. JACC Heart Fail 2014;2(3):250-259 [FREE Full text] [doi: 10.1016/j.jchf.2013.12.005] [Medline: 24952692]

Abbreviations

AF: atrial fibrillation
CCTH: Cape Coast Teaching Hospital
HF: heart failure
HFmrEF: heart failure with mildly reduced ejection fraction
HFMT: heart failure management team
HFpEF: heart failure with preserved ejection fraction
HFrEF: heart failure with reduced ejection fraction
HTH: Ho Teaching Hospital
KATH: Komfo Anokye Teaching Hospital
KBTH: Korle-Bu Teaching Hospital
LV: left ventricular
LVEF: left ventricular ejection fraction
NATURE-HF: NAtional TUnisian REgistry of Heart Failure
NNHFMT: national network of heart failure management teams
NT-proBNP: N-terminal pro-brain natriuretic peptide
SR: sinus rhythm
SSA: Sub-Saharan Africa
TTH: Tamale Teaching Hospital

Edited by A Mavragani; submitted 10.09.23; peer-reviewed by L Zakhama, A Kardos; comments to author 19.12.23; revised version received 23.12.23; accepted 24.12.23; published 08.04.24.

Please cite as:
Awindaogo F, Acheamfour-Akowuah E, Doku A, Kokuro C, Agyekum F, Owusu IK
Assessing and Improving the Care of Patients With Heart Failure in Ghana: Protocol for a Prospective Observational Study and the Ghana Heart Initiative-Heart Failure Registry
JMIR Res Protoc 2024;13:e52616
URL: https://www.researchprotocols.org/2024/1/e52616
doi:10.2196/52616
PMID:38588528

Protocol

Investigating Rhythmicity in App Usage to Predict Depressive Symptoms: Protocol for Personalized Framework Development and Validation Through a Countrywide Study

Md Sabbir Ahmed[1], BSc; Tanvir Hasan[1], BSc; Salekul Islam[2], PhD; Nova Ahmed[1], PhD

[1]Design Inclusion and Access Lab, North South University, Dhaka, Bangladesh

[2]Department of Computer Science and Engineering, United International University, Dhaka, Bangladesh

Corresponding Author:
Md Sabbir Ahmed, BSc
Design Inclusion and Access Lab
North South University
Plot # 15, Block B, Bashundhara R/A
Dhaka, 1229
Bangladesh
Phone: 880 1781920068
Email: msg2sabbir@gmail.com

Abstract

Background: Understanding a student's depressive symptoms could facilitate significantly more precise diagnosis and treatment. However, few studies have focused on depressive symptom prediction through unobtrusive systems, and these studies are limited by small sample sizes, low performance, and the requirement for higher resources. In addition, research has not explored whether statistically significant rhythms based on different app usage behavioral markers (eg, app usage sessions) exist that could be useful in finding subtle differences to predict with higher accuracy like the models based on rhythms of physiological data.

Objective: The main objective of this study is to explore whether there exist statistically significant rhythms in resource-insensitive app usage behavioral markers and predict depressive symptoms through these marker-based rhythmic features. Another objective of this study is to understand whether there is a potential link between rhythmic features and depressive symptoms.

Methods: Through a countrywide study, we collected 2952 students' raw app usage behavioral data and responses to the 9 depressive symptoms in the 9-item Patient Health Questionnaire (PHQ-9). The behavioral data were retrieved through our developed app, which was previously used in our pilot studies in Bangladesh on different research problems. To explore whether there is a rhythm based on app usage data, we will conduct a zero-amplitude test. In addition, we will develop a cosinor model for each participant to extract rhythmic parameters (eg, acrophase). In addition, to obtain a comprehensive picture of the rhythms, we will explore nonparametric rhythmic features (eg, interdaily stability). Furthermore, we will conduct regression analysis to understand the association of rhythmic features with depressive symptoms. Finally, we will develop a personalized multitask learning (MTL) framework to predict symptoms through rhythmic features.

Results: After applying inclusion criteria (eg, having app usage data of at least 2 days to explore rhythmicity), we kept the data of 2902 (98.31%) students for analysis, with 24.48 million app usage events, and 7 days' app usage of 2849 (98.17%) students. The students are from all 8 divisions of Bangladesh, both public and private universities (19 different universities and 52 different departments). We are analyzing the data and will publish the findings in a peer-reviewed publication.

Conclusions: Having an in-depth understanding of app usage rhythms and their connection with depressive symptoms through a countrywide study can significantly help health care professionals and researchers better understand depressed students and may create possibilities for using app usage–based rhythms for intervention. In addition, the MTL framework based on app usage rhythmic features may more accurately predict depressive symptoms due to the rhythms' capability to find subtle differences.

International Registered Report Identifier (IRRID): DERR1-10.2196/51540

(JMIR Res Protoc 2024;13:e51540) doi:10.2196/51540

KEYWORDS

depressive symptoms; app usage rhythm; behavioral markers; personalization; multitask learning framework

Introduction

Background

Need for Identification of Depressive Symptoms

Every 40 seconds, a person commits suicide and there are more than 20 attempts worldwide [1]. Among suicide attempters, major depressive disorder (MDD) is common [2], and people having MDD are at greater risk of suicidality [3]. Despite these facts, there is a significant lack of interventions to mitigate depression, due to which the depression rate is increasing. In fact, it is estimated that depression will rank first as a global burden of disease by 2030 [4]. In addition, due to the COVID-19 pandemic, a significantly higher number of people have MDD [5], and such a negative impact may persist for a prolonged period. In Bangladesh, the depression prevalence is higher than the overall rate in South Asia [6]. Compared to Bangladeshi people of any other professions, the depression rate is higher among university students [7] (eg, 82.4% of students have at least mild depression [8]), which is alarming.

To significantly facilitate early interventions to mitigate depression, there is an urgent need for its early identification [9]. A person is identified as depressed if symptoms (eg, hopelessness) appear for a period, such as most days for a minimum of 14 days [10,11]. However, it is difficult to precisely assess depressive symptoms [12]. In fact, primary care providers fail to identify depression in more than 50% of cases [13,14]. Understanding the depressive symptoms, such as those in the 9-item Patient Health Questionnaire (PHQ-9) [15], of a person in real time can significantly facilitate mental health care professionals to understand the illness more precisely, to identify depression early, and to take steps accordingly for intervention.

Pervasive Health Research in Low- and Middle-Income Countries

Although over 80% of the burden of depression is found in low- and middle-income countries (LMICs) [16], there remains a severe scarcity of mental health care professionals in LMICs. In Bangladesh, there are only 565 psychologists [6], although the population is over 165 million [17], with 1.234 million university students [18]. In these cases, a pervasive technology, such as a smartphone-based monitoring system, which is available to a large number of people in LMICs, can play a significant role [19] In addition, to minimize the barriers to health care facilities in low-resource settings, artificial intelligence (AI)–based mobile apps can be useful [20]. However, almost all the studies that have demonstrated a pervasive technology–based automated system to identify depression have been conducted in the context of high-income countries. For instance, all the studies included in a recent systematic review were from countries other than LMICs [21], which indicates how little pervasive health research has been conducted in the context of LMICs. As a result, the models developed based on participants from high-income countries may not be applicable in LMICs, since the behavior (eg, app usage [22]) varies among countries and various factors, such as socioeconomic status [23] and culture [22], impact behavior.

App Usage Rhythm That May Resemble Biobehavioral Rhythm

Zeitgebers, social and environmental cues, help a person's rhythms synchronize well [24], which can impact their daily activities. Rhythms based on pervasive device–sensed physiological data change depending on external cues, such as light exposure, eating time, and physical activity [24]. Similarly, smartphone usage behavior is linked with factors such as eating behavior [25]. In addition, there is a relation of app usage with alertness, chronotype [26], and physiological data, such as sleep [26-28]. Like physiological data, app usage behavioral markers vary depending on the hour of the day [29-31] and exercise [28]. These facts show app usage behavior may also have a rhythmic pattern with reproducible waveforms similar to the rhythms based on physiological data.

Although a recent study extracted parametric rhythmic feature–dominant periods from smartphone usage data [32], the study was limited by not exploring rhythmic features, such as the acrophase, interdaily stability (IS), intradaily variability (IV), and relative amplitude (RA). In addition, the study explored mere screen usage, without any exploration of more informative features [33], such as entropy data–based features. In the case of other previous app usage data–based studies, researchers used descriptive statistical methods [29-31] to determine whether there is any variation over the day and inferential statistical methods [34,35] to find the difference in terms of aggregated data of the 4 time periods, namely morning, afternoon, evening, and night. These approaches have some limitations. First, there is a lack of statistical evidence to show whether there exists any rhythm that could be resolved with the zero-amplitude test [36,37], which is used to detect rhythm in the field of chronobiology. In addition, the mere analysis in presenting the difference between the aggregated data of morning and evening cannot show whether there is a cycle that can repeat over days. The average data may also miss the microscopic view of data [38]. However, an analysis fitting mathematical models (eg, cosinor model) to time series data can present a microscopic view of the data and inferential statistical estimates of the rhythmic properties [38]. In addition, many informative behavioral markers, such as the dominant period, stability in behavior, and the peak time of oscillations in the rhythm, cannot be extracted from just finding the differences between periods (eg, morning vs night).

Potential of App Usage–Based Rhythms in Identifying Depressive Symptoms in LMICs

In human life, physiological changes reappear in a cyclable waveform [38]. Rhythm features based on physiological data have been explored in both the chronobiology [39] and pervasive health [32] areas. Researchers have found a relation between physiological data–based rhythmic markers and health status [32]. These markers can find out subtle differences that enable marker-based features to predict hospital readmission [40] and to identify loneliness and the depression class [32]. This shows the possibility of improving the performance of the models upon the incorporation of app usage rhythmic features to predict the symptoms of depression. However, previous studies [32,40] have mostly relied on wearables to extract rhythmic features,

which are costly and may not be affordable [41] for people with a low income. In contrast, smartphones are economically attainable [42], and app usage data are resource insensitive [33]. As a result, app usage data–based systems may be feasible in LMICs.

Predicting Depression and Depressive Symptoms Through an Unobtrusive Method

Classification of the Depressed and Nondepressed

Most existing research based on AI for mental health has worked on classification problems [43]. Researchers have classified depressed and nondepressed individuals by developing personalized models [44] and using contextually filtered features where the rule mining technique was incorporated [45]. Some other studies (eg, [46,47]) have relied on sensing data (eg, GPS data), along with smartphone data call history, to predict depression. Researchers have also leveraged internet usage data [48], location data retrieved through the campus WiFi infrastructure [49,50], and the GPS [50-52]. Recently, some researchers focused on exploring rhythmic features to assess depression. For instance, Yan et al [32] leveraged rhythm-based features to classify depressed and nondepressed participants. However, the classification does not provide precise information about a participant's depressive status, since scores of all the symptoms are aggregated to keep the participant in a particular group (eg, depressed or moderate depression), resulting in a loss of the complexity of the psychological problem of depression.

Predicting Depression Scores

Compared to classification research problems, there is relatively less research on predicting the depression score (eg, PHQ-9 score=11). Studies in the pervasive health area can be broadly categorized into those that have developed models leveraging data based on both smartphones and wearables [53-56]; only smartphones [53,55]; various sensing devices, along with social media [57]; and subjective and smartphone data [58]. There remain mixed findings on whether the smartphone has superior performance than the wearable. Smartphone-sensed data showed higher performance in a previous study [55] when models were evaluated after splitting training and testing data based on time. However, in the same study [55], researchers found smartphones have inferior performance on another evaluation criterion. Regardless of superiority, both wearables and smartphones show promising performance in the automated assessment of depression [53], which can play a role in real-time remote monitoring of depressed individuals [59]. Wearable- and smartphone-sensed behavioral markers, such as call duration [58] and heart rate [60], as well as inferred markers, such as the circadian rhythm [60], have a significant correlation with the depression score, which may explain the fact of enabling the sensed data to predict depression. However, like the classification, in the prediction of depression scores also, there remains the inability to precisely understand depressive symptoms since a person's depression score (eg, 11) can be found in combination with different frequencies of the appearance of different symptoms.

Predicting Symptoms and Multitask Learning

Researchers have conducted a network analysis of depressive symptoms and presented a possible viable target for intervention [61] and central symptoms for possible focused treatments [62]. The relation of ecological momentary assessment of depressive symptoms with the PHQ-9 score [63] and the relation of depressive symptoms with behavioral data [64] have also been investigated in previous studies. Exploring pervasive device–sensed data, researchers have found a link of higher spending duration in students with higher fatigue, which is a depressive symptom [64]. Although there are studies predicting symptoms of other psychological problems, such as schizophrenia [65] and attention-deficit/hyperactivity disorder (ADHD) [66], few studies [67] have predicted the appearance of depressive symptoms. In a previous study [67], authors predicted depressive symptoms through the data of iPhone users and Android users. However, their study has several limitations. First, their models' performance is low in the case of the maximum depressive symptoms; particularly, the specificity score is around 60% or below 60% in many models developed by leveraging smartphone data. Second, they developed a separate model to predict each symptom, which makes the model resource sensitive. Third, they considered each symptom-predicting task as a separate one, which could be improved by leveraging the shareable information among symptoms through the multitask learning (MTL) framework as MTL has superior performance than the single-task learning (STL) technique [53,65]. However, researchers have grouped all the predicting tasks into a single model in previous studies [53,65], which may lower performance since all tasks do not help each other to improve performance [68].

Objective

To overcome the above-mentioned limitations, the main objective of this study is to explore app usage data–based rhythmicity detection and develop and validate an MTL framework leveraging app usage data–based parametric and nonparametric rhythmic parameters through a countrywide study in Bangladesh. Another objective of this study is to explore whether app usage rhythmic features are related to depressive symptoms.

Methods

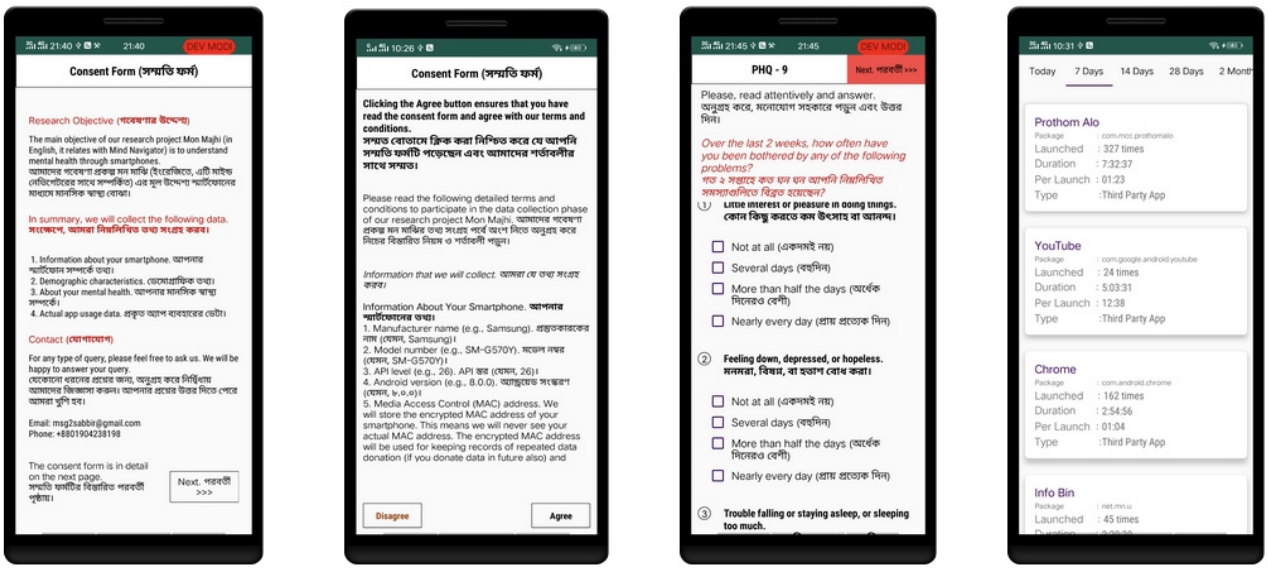
Ethical Considerations

Our study was approved (reference: 2022/OR-NSU/IRB/0704) by the North South University Institutional Review Board/Ethics Review Committee. While collecting data, we presented the consent form in short in Bangla (native language) and English (Figure 1a), where we provided a summary of the data that we collected. In addition, we provided a consent form in detail (Figure 1b) about different matters, including data safety, privacy, and each data item that we collected. Furthermore, before data collection, we briefly described the research to the participants. All participants provided their consent. After collecting data, we provided an incentive of food tokens equivalent to around US $0.30 to almost all participants. For certain participants (<5%) where it was not feasible to give food

tokens, we provided an equivalent gift in other forms (e.g., by book diary).

All participants' data are stored in the Google Firebase database, which only 1 of the researchers can access with 2-factor authentication. We did not collect any personal information from the participants, such as name, email, and phone number. In addition, we did not collect the names of the participants' departments and universities so that they would feel more comfortable in providing data. We reported the number of departments and universities based on our aggregated notes.

Figure 1. Screenshot of the data collection tool showing the (a) consent form in short in Bangla and English, (b) consent form in detail, (c) PHQ-9, and (d) app usage data. PHQ-9: 9-item Patient Health Questionnaire.



(a) Consent form in short (b)Consent form in detail (c) PHQ-9 scale to collect depressive symptoms' data (d) App usage data

Retrieval of App Usage Behavioral Markers

In this study, we will focus on developing our system in such a way that the users of the system and also health care professionals can be informed about depressive symptoms in real time. For instance, a health care professional, with the user's consent to access information, can be notified if our system's automatic prediction in a day shows that the depressive symptoms can worsen. For this research, we used our previously developed app [69], which can retrieve each participant's past 7 days' foreground and background app usage event data within 1 second once the participant provides consent. The average time required to retrieve app usage events is 307.94 milliseconds (SD 1.1 seconds) [33]. For each app usage event, there are data on the app name, package name, and timestamp of the event, which we will use to extract behavioral markers. The app (Figure 1) was used in our previous studies to explore different research problems, including students' academic results [70-72], depression [33-35,73], and loneliness [74,75], showing the app's reliability and validity.

Sample Size Determination and Data Collection

In Bangladesh, there are around 1.234 million university students [18], and an optimal sample that represents the behavior of this population with a 95% CI and a 5% margin of error is 385 university students, as we found with SurveyMonkey [76], which uses the formula for the finite sample size [77]. Using the same formula, we found that the required sample size to represent the 0.448 million female and 0.786 million male student groups each is 384 [18]. Since the depression rate differs between students of public and private universities in Bangladesh [78], we collected data from both types of universities. In the 0.329 million and 0.902 million students of public and private universities, respectively [18], we found that the required sample size in each case is 384. However, there is no fixed sample size that can ensure the generalizable performance of machine learning (ML) models. Therefore, to develop an impactful model, we tried to maximize the number of participants by conducting a countrywide study. In addition, we tried to maximize the number of students from public universities because the largest number of students study there [18].

We collected data from all 8 divisions of Bangladesh using the multistage convenient sampling method. From each division, we collected data from at least 1 university and multiple departments. We tried to maximize the diversity among the participants because the socioeconomic status and many other demographic characteristics vary by region of a country, which can have an impact on mental health [78] and smartphone usage behavior [79,80].

We collected data from a total of 2952 participants from September 2022 to March 2023. While collecting data, first, through our app [69], the participants responded to questions about demographic characteristics (eg, gender) after providing consent. Next, using the same app, they responded to the items of the PHQ-9 [15] based on their experiences of the past 14 days. After saving the responses to all psychological questions, the app automatically retrieved their app usage data, which may take less than 1 second in almost all cases, as shown in our

previous estimation [33]. After retrieval, the app saved the app usage data instantly.

Data Preprocessing and Data Set Description

Our app could not retrieve any app usage data from 14 (0.47%) participants' phones. One of the plausible reasons for this problem could be system problems in the phones, as shared by the participants. Several of these participants shared that they do not use the original version of the phones. In addition, for 2 (0.07%) participants, age values were missing, and we did not impute these values, as age information was not required for the primary purpose of the research. Furthermore, data on 82 (2.77%) participants' professions were missing. We imputed the missing professions based on 2 pieces of information: First, in our study, only 2 (0.07%) participants were not students, and we did not reach out to them for data collection; they provided data by installing the app from Google Play Store, which was based on their own interests, indicating a low probability of having a profession other than "student." Second, all 82 (2.77%) participants provided data when we reached the universities for data collection, as we found by matching the study dates and timestamps of when these participants provided data. Thus, we imputed these 82 participants' profession as "student."

Although the participants were required to provide data at least once, we encouraged them to provide data as many times as possible. After excluding the 14 (0.47%) participants for whom our app could not collect any app usage events and the 2 (0.07%) participants who were not students, 2936 (99.46%) participants remained. Of them, 71 (2.42%) provided data at least twice. However, since there were few participants who provided data twice, in this study, we kept only the first time–provided data for the next steps of the analysis.

Since in this study, we will estimate the circadian rhythm, we followed previous studies to find out the minimum number of days required to estimate the circadian rhythm. Studies have suggested to have data of at least 1 day for estimating the circadian rhythm [81]. However, sensed data of 2 days can estimate the circadian rhythm sufficiently [82]. Researchers have also found that rhythmic features extracted based on the data of 2 days can predict more accurately physiological and mental changes [65]. Therefore, inspired by these previous studies, we excluded 34 (1.15%) participants who had app usage data of less than 2 days.

Finally, after excluding 2 nonstudents, 14 students without any app usage data, and 34 students having app usage data of less than 2 days, we were left with 2902 (98.31%) students' app usage data (Figure 2), which will be analyzed in the next steps. In total, there are 24.48 million foreground and background app usage events of 24.84 million minutes. Of the 2902 participants, 2849 (98.17%) have app usage data of 7 days (Figure 3).

Figure 2. STROBE (Strengthening the Reporting of Observational studies in Epidemiology) flowchart.

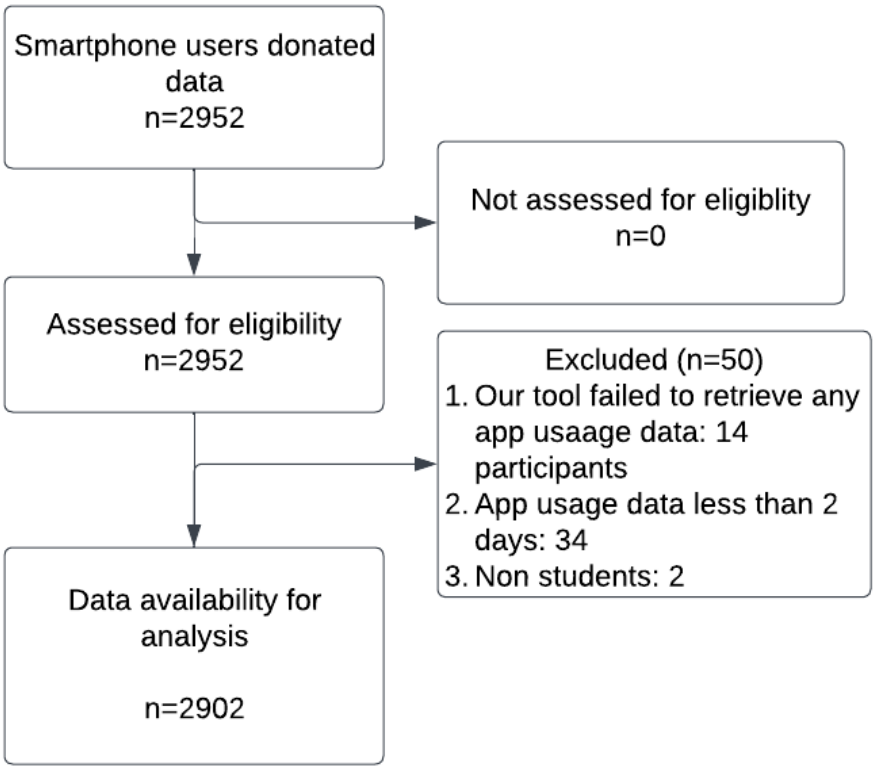
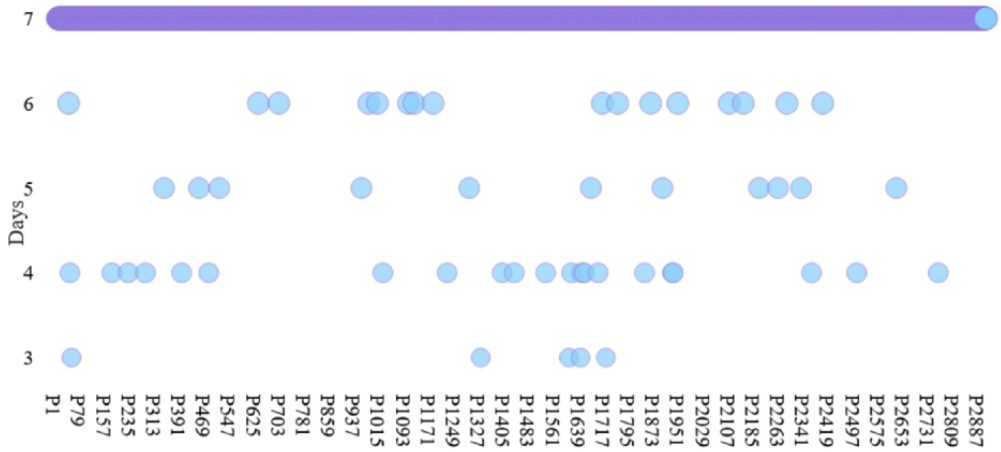


Figure 3. Number of days' data that each participant has for the final analysis. P: participant.



Ground Truth Data to Measure Depressive Symptoms

We used the PHQ-9 (Table 1) [15], which is one of the most commonly used scales to assess depression [21]. In our study, we used the PHQ-9 translated into Bengali [83], which has been validated and is largely used in Bangladesh (eg, [8,78]). The PHQ-9 score of 10 has a sensitivity and specificity of 88% in identifying MDD [15]. Based on this cutoff score, we will categorize the participants as depressed if the PHQ-9 score is at least 10.

In a previous study [67], a person was categorized as having a depressive symptom if that symptom appeared for several days or more. However, we will consider the threshold more than half of the days since the National Institute of Mental Health (NIMH) and the World Health Organization (WHO) define a person as depressed if symptoms appear for a specific time frame, such as most days for a minimum of 14 days [10,11]. In this study, if a participant reports being bothered by a depressive symptom (eg, hopelessness) in the PHQ-9 for more than half of the days or nearly every day of the past 14 days, we will categorize that participant as having that depressive symptom.

Table 1. Depressive symptom for each item of the PHQ-9[a].

Symptom number	Symptom in the PHQ-9
1	Little interest or pleasure in doing things
2	Feeling down, depressed, or hopeless
3	Trouble falling or staying asleep or sleeping too much
4	Feeling tired or having little energy
5	Poor appetite or overeating
6	Feeling bad about yourself or that you are a failure or have let yourself or your family down
7	Trouble concentrating on things, such as reading the newspaper or watching television
8	Moving or speaking so slowly that other people could have noticed or the opposite—being so fidgety or restless that you have been moving around a lot more than usual
9	Thoughts that you would be better off dead or of hurting yourself in some way

[a]PHQ-9: 9-item Patient Health Questionnaire.

Extraction of Behavioral Markers

As we will test the rhythmicity where the time series data are used [36] and explore the rhythmicity of the app usage behavioral markers instead of exploring raw foreground and background app usage events, we will set a time frame of 15 minutes based on which each app usage behavioral marker will be extracted. However, to check the robustness of the findings, we will follow the same process to explore rhythmicity using 2 other time frames as well: 10 minutes and 20 minutes.

In addition to calculating the usage duration, frequency of launching apps, entropy based on duration and entropy based on frequency of launching apps, and app usage sessions [33], we will calculate the following behavioral markers based on which we will extract parametric and nonparametric rhythmic features: relative importance of app categories, personalized top n apps, and cousage of apps.

Relative Importance of App Categories

In pervasive health research, aggregated app usage data (eg, [44-46]) are widely used, where the individual app categories remain unexplored. In our previous studies [33,74], we found that app category–based features are more important than aggregated smartphone usage regardless of category. However, in those studies, features of an app category were extracted independently regardless of the usage behavior of other categories. As a result, the individual category itself may not

provide higher information for the app categories that are less used but contain distinguishable markers. For instance, if a participant launches social media apps 100 times and health and fitness apps only 10 times, data from the health and fitness category may get lower importance. However, data from the health and fitness category can be more important since depressed students use apps that contain features for smoking prevention and body weight reduction, which may not be used more frequently but may contain enough information to be significantly different from those used by nondepressed students [34]. Hence, we will calculate the term frequency–inverse document frequency (TF-IDF), which is a widely used technique in natural language processing [84] where less frequent terms across documents can get more importance. To adapt TF-IDF in the context of app usage, we will use data from all time frames over all days. In each time frame f, the app usage sessions s will work as the set of documents, and in each session (ie, a document) j, the list of categories of the used apps will act as the words.

Let the set of documents of participant i in f be $\{D_{ij}, D_{ij+1}, \ldots D_{is}\}$, where , and n represents the number of participants. We will calculate TF-IDF_{icj} for each app category c based on the participant's data of sessions s.

$$\text{TF-IDF}_{icj} = \text{TF}_{icj} \times \text{IDF}_{icj},$$

where $\text{TF}_{icj} = \log[\text{freq}(c) + 1]$, $\text{IDF}_{icj} =$, freq(c) is the number of times app c was launched in session j, df is the number of sessions where c was used, and s represents the total number of sessions in f. After calculating TF-IDF_{icj} for each session, the mean TF-IDF value will be calculated for each category over the sessions of a time frame. Finally, using that mean value, we will extract the rhythmic features to understand how the relative importance of participant i in using a particular category c varied or remained constant over days and over the periods of a day and whether there was a rhythm in behavioral markers based on the TF-IDF.

To categorize the apps, we will follow relevant previous studies (eg, [30]) and the process in our previous studies [33-35,70,74], where we categorized the apps into more than 20 categories after exploring developers' referred categories in Google Play Store and other app stores and discussing with graduate students of the computer science and engineering (CSE) department.

Personalized Top n Apps

We will calculate entropy based on the usage duration and the frequency of launching the top n apps, which can vary by student. To find the value of n, we will use the probability distribution and plot the probability of using apps on the y axis and the number of apps on the x axis. The point where the curve falls will be considered the threshold (ie, the value of n) to find the top n apps. To find the cutoff value, we will follow a previous study [46] that found cutoff values to exclude the participants having missing values.

Cousage of Apps

A significant portion of app usage consists of switching from one app to another [29]. One plausible reason for such behavior can be changing moods during app usage [85], and the users may do it to seek support, overcome negative emotions, etc. To quantify how participants switch from one app to another, we will calculate the cousage of apps, where the usage of 2 apps will be considered coapp usage if they are used in a single app usage session and also used consecutively. However, in a smartphone, there are many system apps that open automatically to support the function of another app. Users do not need to use those apps intentionally, and as a result, the inclusion of those apps may misrepresent behavior. In addition, to switch from one app to another, the user returns to the home screen of the smartphone, where the launcher app opens automatically. Considering the aforementioned issues, we will exclude these system apps and launcher apps before quantifying the coapp usage.

To find subtle differences in the variation in app usage patterns, we will build a network based on cousage, where each edge will present the cousage of 2 different apps. The weight of the edge will be calculated using point mutual information (PMI).

where $p(A_1, A_2)$ represents the probability of A_1 and A_2 apps to consecutively appear in the same app usage session and $p(A_1)$ and $p(A_2)$ represent the probability of A_1 and A_2 apps, respectively, to appear in that session regardless of consecutiveness. Next, we will calculate the centrality and graph edit distance. The calculation of centrality will help us understand the most influential app in the network that is connected to the maximum number of nodes. The graph edit distance between 2 different sessions of the same time frame will inform whether the behavior differs. Finally, we will use the average data of each session of a time frame to explore the rhythmicity of the centrality and graph edit distance.

Rhythm Analysis and Extraction of Rhythmic Features

The parametric cosinor method is one of the most widely used approaches to find out rhythmic parameters. However, cosinor analysis cannot find out the fragmentation in the rest-activity rhythm [86], which can be detected by extracting nonparametric rhythmic parameters, such as the IS. Therefore, to obtain a comprehensive picture of rhythms, we will conduct both parametric and nonparametric tests and extract the respective rhythmic features, as described later. In this study, to extract rhythms, instead of focusing only on all students' data-based global models, we will also develop individual models and extract the rhythmic parameters for each participant. The main reason is that physiological data–based nonparametric rhythmic [87,88] and parametric rhythmic [89] parameters vary by the characteristics of people, and thus, there may also be a variation in parameters by the individual participant's rhythm that is solely based on app usage data.

Dominant Period

In cosinor analysis, a cosine curve is fitted on the given period (eg, 24 hours) using the least squares method, where the model reduces the difference between observed and estimated values. However, cosinor analysis itself cannot estimate the best-fitting period [90]. Thus, we will empirically investigate through

periodogram analysis and by setting the periods from 1 to 24. Later, the cosinor model will be developed for each given period (eg, 13 hours). The best-fitting period will be counted as the dominant period where the proportion of explained variance is the maximum.

Rhythm Detection

Cosinor analysis is a parametric method, and hence, we will first test normality [91]. Later, we will process the nonnormally distributed data through log transformation. Next, to find out whether a statistically significant rhythm of a participant exists, we will conduct a zero-amplitude test [36] by setting the significance level to .05. To find out whether an individual participant's rhythm differs from the rhythm based on all participants, we will perform population mean cosinor analysis based on all the participants. In addition, we will develop a cosinor model for each participant and then calculate the average of the cosinor rhythmic parameters [90].

MESOR, Amplitude, and Acrophase

After developing the cosinor model, we will extract the following parametric rhythmic parameters for each participant: midline estimating statistic of rhythm (MESOR), amplitude, and acrophase. MESOR is the rhythm-adjusted mean [36], the amplitude presents the difference between the equilibrium position and the peak point of the rhythm oscillation [92], and the acrophase presents the timing of the high values recurring in each cycle of the rhythm [36]. Since the amplitude can present the strength of the rhythm [93], while comparing the diurnal (12-hour period) and circadian (24-hour period) rhythms to determine which rhythm has more strength, we will compare the amplitude. Moreover, we will compare the coefficient of determination as it presents how well a model fits in a given period.

Interdaily Stability and Intradaily Variability

A person's mental state has a relation with the IS and the IV. For example, patients with bipolar disorder have less IS and higher IV [94]. Similar patterns may be found in the IS and the IV based on app usage data, and we will calculate the IS and the IV, based on a previous study [86] on actimetry.

Here, x_i is the behavioral marker's value at a specific time frame, x_m is the mean value of the same behavioral marker in all time frames, and N is the number of time frames.

Here, x_i is the behavioral marker's average value in that time frame over days and p is the number of time frames per day. The range of the IV value is 0-2 and that of the IS value is 0-1 [95]. The higher the IS, the greater the stability, as the name implies. However, the higher the IV, the higher the fragmentation in the rhythm. If a difference remains, for example, if someone sleeps during the daytime and keeps waking up at nighttime, their IV will be higher [86].

M10, L5, and Relative Amplitude

M10 presents the mean value of the most active consecutive 10 hours and provides information about the diurnal activity. Active persons have a higher M10 [86], and a lower M10 can be associated with exercise reduction [86] and also with a negative mental state [86,96]. L5 presents the mean value of the least active 5 consecutive hours of the day. It is a measure of nocturnal activity, and the higher L5 may represent activity during the rest cycle [86]. After calculating M10 and L5, we will calculate the RA = (M10 – L5)/(M10 + L5). As can be understood from the formula of RA, the RA is actually the normalized difference between M10 and L5. The larger the difference between L5 and M10, the larger the RA. People with psychological problems can have a lower RA [65,86].

Statistical Analysis

To explore whether there is any relation between depressive symptoms and app usage rhythmic features, we will perform binomial logistic regression. As having a variance inflation factor (VIF) of more than 5 can create a biased regression model [97], we will eliminate the variable if the VIF of any variable goes beyond 5.

ML Model Development

Participant Similarity and Development of Personalized Models

Most of the existing models (eg, [33,45,46,74]) to predict depression use training data to predict the outcome regardless of the characteristics of the participant whose class will be predicted. These models may have issues regarding generalizability since all individuals have unique characteristics that may not be captured in one-size-fits-all models (ie, 1 set of training data to predict the depression of all test participants). Indeed, through empirical investigation, it has been found that the personalized model performs better than the one-size-fits-all model [98,99]. The one-size-fits-all or global model is likely to capture the general or the "average" characteristics of the participants for the prediction due to which the model may perform well only on the "average" participants and may not work in the case of the participants whose behavior deviates from the "average" participants [100]. However, the personalized model is trained dynamically for each participant, which can facilitate finding the most relevant set of features to predict the outcome of the test participant [98]. Therefore, a personalized model may perform better in predicting depressive symptoms since each of the depressed students has a unique app usage signature [34] and depressed students have statistically significantly different smartphone usage behaviors than nondepressed students [35], as we found in our previous studies [34,35].

In our app to predict depressive symptoms, we will use each participant i's rhythmic parameters based on each of the app usage behavioral markers of m_i to calculate the cosine similarity with all other participants n – 1.

Here, B_i and B_j represent the vectors based on the rhythmic parameter sets m_i and m_j of participants i and j, respectively. The cosine similarity s_{ij} will be close to 1 when there is a higher similarity between participants i and j. After finding the similarities between participant i and all other participants, we will use the most similar N participants to train the MTL framework for participant i. The value of N will be decided empirically through a search on the values 200, 250, 300, and 350.

MTL Framework Development and Validation

Although some similar tasks remain, the development of the model through the MTL framework can facilitate improving the performance of the models through information sharing. In addition, if different models are developed for different tasks, then the system can be resource inefficient. In a previous study [65], researchers used MTL to develop systems for predicting the symptoms of schizophrenia. However, in that system, all symptom prediction tasks were considered the same. In reality, all the tasks included in a model do not help one another improve performance [68]. Therefore, we will find the similarities among the symptoms and use similar symptom prediction tasks in a model, while other similar symptom prediction tasks will be in another model. To group the tasks, we will calculate the correlation coefficients among the symptoms. Symptoms that are highly (coefficients>0.7), moderately (0.4≤coefficients≤0.7) [101], and less than moderately correlated or not correlated will be kept in 3 different groups.

While developing the MTL framework, we will use the hard parameter-sharing technique since in this approach, the model can find a common representation to capture all the tasks that can reduce the potential risk of overfitting [102]. Combining multiple loss functions leads to promising performances [103]. In our study, we will use a weighted loss of the hinge and cross-entropy. However, we will not use a fixed weight. Instead, we will tune the weight using the Bayesian search optimization technique, which selects the next parameter based on the performance of the previously selected one.

To validate the framework, we will use the nested cross-validation (CV) method since this approach is found to have a generalizable performance compared to K-fold CV [104]. In the outer loop, we will use the leave-one-out cross-validation (LOOCV) method, and in the inner loop, we will use a 10-fold CV, where in each interaction, 9 folds will be used for tuning the hyperparameters and the remaining 1 fold will be used for validation. We are aware of the fact using the LOOCV will increase the time complexity since there are 2902 participants and we will be developing a personalized model for each of them. However, we chose to use the LOOCV because it will work like the real-world scenario, where the model will predict a single participant's depressive symptoms at a time. In addition, this process will help in personalizing the model, where we will use only those participants in model training who are similar (in terms of app usage behavior without using any information about depressive symptoms) to the student for whom the model will predict the symptoms, as discussed in detail in the *Participant Similarity and Development of Personalized Models* section. During model development, we will maximize the balanced accuracy as it is based on sensitivity and specificity, and having a higher balanced accuracy can lead to higher precision and F_1-score values.

To understand the robustness of the proposed MTL framework, we will compare it with the performance in the following approaches:

- Comparison with STL-based models: We will compare the performance of the proposed personalized MTL framework with that of STL models. This will resemble the approach presented in a previous study [67], where each symptom was considered a single task. To develop the STL model, we will use ML algorithms, such as the random forest (RF), support vector machine (SVM), decision tree (DT) [105], and logistic regression [106], which are widely used in medical informatics, as shown in systematic reviews [105,106].
- Comparison with the nonpersonalized MTL framework: Since we expect that personalization may provide better performance, as discussed in the *MTL Framework Development and Validation* section, we will compare the performance of the personalized MTL framework with that of a nonpersonalized MTL framework, where we will use n – 1 participants' data for training instead of using a personalized subset of data.
- Comparison with the MTL framework without grouping tasks: To understand how grouping tasks based on similarity impact performance, we will compare the performance of the MTL framework with and without grouping tasks.

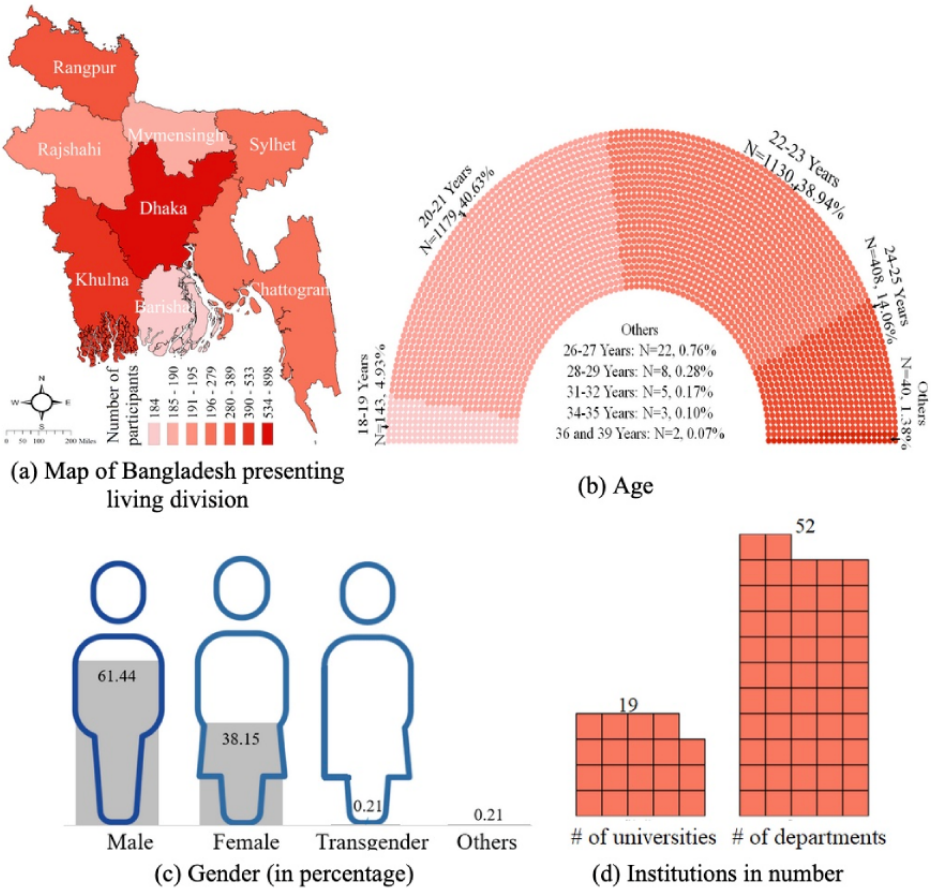
Results

As mentioned earlier, after applying inclusion criteria, we kept the data of 2902 (98.31%) of 2952 students for analysis, with the data of 24.48 million app usage events, and 7 days' app usage of 2849 (98.17%) students.

Figure 4 shows the findings regarding participants' demographic characteristics. The participants were from the 8 divisions of Bangladesh (Figure 4a). Most participants (n=887, 30.56%) were from the Dhaka division, which also reflects the fact that the majority of university students of Bangladesh reside in this division. The participants' age varied from 18 to 39 years, and 2309 (79.57%) participants were aged 20-23 years (Figure 4b). Of the 2902 participants, 1107 (38.15%) and 1783 (61.44%) were female and male participants, respectively (Figure 4c). There were 2430 (83.74%) and 472 (16.26%) students from public and private universities, respectively. The participants belonged to 19 universities (Figure 4d), including specialized universities, studying the following subjects: agriculture, engineering, and textiles. They also belonged to 52 different departments, including arts (eg, Department of Sculpture), business (eg, Department of Management Studies), engineering (eg, Department of Petroleum & Mining Engineering), science (eg, Department of Botany), textiles (eg, Department of Apparel Engineering), public health, and law faculties.

In the remaining part of the study, we will work on rhythm detection, rhythmic feature extraction, and MTL framework development. We expect to publish our findings by June 2024.

Figure 4. Participants' demographic characteristics: (a) map of Bangladesh presenting living divisions, (b) age, (c) gender, and (d) number of different institutions.



Discussion

Significance

By using the data set constructed through a countrywide study on 2902 students having over 24 million app usage events, we will explore whether there is a statistically significant rhythm based on the different app usage behavioral markers. We hypothesize that app usage behavioral markers, such as the relative importance of an app category, have rhythmic patterns with reproducible waveforms because, like physiological data, the markers vary depending on factors such as the time of day [29-31]. In addition, since rhythmic features based on physiological [39,107] and activity [108] data have potential applications in problems such as determining which participants have a higher risk of disease [107], determining sedentary behavior [39], and finding subtle changes in detecting COVID-19 [107], an in-depth exploration of app usage marker–based rhythms may show an alternative source of data to understand the rhythms in human life. App usage marker–based rhythms have the possibility to be used for different purposes. For example, a statistically significant relation between the rhythmicity of app usage and depressive symptoms can create the possibility of using these rhythmic features for an intervention to mitigate depression.

In addition, by predicting depressive symptoms, our study will extend the findings of previous studies since most studies (details in a recent systematic review [43]) in the pervasive health area have developed classification models (eg, to classify depressed and nondepressed individuals) where the complexity of the psychological problem of depression may be lost. For instance, a participant with a PHQ-9 score of 10 has moderate depression [15], and a score of 10 can result from different combinations of the subscores of the 9 symptoms in the PHQ-9. As a result, by classifying participants into a few groups based on the overall score on a scale, it is not possible to precisely determine the depressive symptoms that bother a student. However, it is important to know since each depressive symptom (eg, symptoms in the PHQ-9 [15]) presents a unique phenomenon (eg, anhedonia, sleep disturbance, suicidal ideation) [109]. Therefore, depending on our proposed personalized MTL framework's performance based on real-time data, the proposed app can contribute to early diagnosis of depressive symptoms and precise understanding of a depressed student, which, in turn, may contribute to mitigating depression prevalence.

Our previous pilot studies in Bangladesh on the relation of app usage with depression [35,73] and loneliness [75], classifying depressed and nondepressed students [33] and with and without loneliness [74], showed promising models solely based on resource-insensitive [33] app usage behavioral markers.

Incorporating app usage rhythmic features and also the MTL framework by leveraging the similarities among the symptoms' prediction tasks so that tasks do not hurt one another's performance may help researchers and developers in developing more robust models to predict the symptoms of psychological problems solely through app usage data. In addition, our app's reliance on data retrieved from a smartphone within 1 second [33] may also make it feasible in LMICs since smartphones are more affordable [42] compared to wearables [41] that are usually used to obtain physiological data and extract rhythmic features.

Strengths

The median sample size of previous studies that classified or predicted depression was 58, and none of the studies that developed computational models for prediction tasks had a sample size of over 500, as shown in a recent systematic review [21]. However, we constructed a large data set comprising 2902 students. In addition, the participants of our study are from all 8 divisions of Bangladesh, from both public and private universities and 52 different departments. To the best of our knowledge, this is the largest data set containing data on both app usage and depressive symptoms. Considering these facts, our findings based on the proposed methods may be generalizable, may be robust enough to be impactful in the real world, and may contribute significantly to advancing the knowledge in mobile and pervasive health research areas.

To the best of our knowledge, this will be the first study to explore in depth rhythms based on different app usage behavioral markers, which can create an opportunity to find an alternative source of data to understand the rhythms of daily life without depending on physiological data–based rhythms, which are usually retrieved by costly wearables.

In our recent work based on app usage [33], our developed app had higher performance in predicting depression than the existing systems based on app usage as well. Through feature analysis (for details, please see Ref. [33]), we found that our newly explored behavioral markers (eg, ratio of the hamming distance [33]) were more important than the features used in previous studies. That being said, performance varies depending on the behavioral markers used in a model. Hence, the novel behavioral markers (eg, relative importance of app categories, cousage of apps) we presented in this protocol that were not explored in previous pervasive health research have significance. In addition, to predict depressive symptoms, we will develop a personalized MTL framework. Although an MTL framework has been developed in some previous studies (eg, [65]) to predict a person's mental state, our study will add to this knowledge by showing the performance of a personalized MTL framework.

Limitations

Following previous studies [65,81,82], to analyze rhythms, we have included 2902 participants in this study who had app usage data of at least 2 days and most of whom (n=2849, 98.17%) had app usage data of 7 days. Data of more than 7 days will help us better understand the stability of the rhythms, the rhythm disruption over weeks, and its potential effect on depressive symptoms' appearance. However, we believe our study can work as a primary cursor for future studies to further explore app usage rhythms.

Although our study includes over 2900 students from different divisions of Bangladesh, our proposed app may not be generalizable to every student since behavior varies depending on many factors, such as season, region, [22], and socioeconomic status [23]. We recommend future studies to include participants based on more factors that can impact behavior. Moreover, in our study, although we have included participants from all 8 divisions of Bangladesh, we could not include participants from all 64 districts of the 8 divisions. In addition, including more participants from rural areas could have potential to obtain a more reliable picture of the students' behavior, which, in turn, can be useful to develop a better app.

Conclusion

Predicting depressive symptoms accurately could help in better diagnosis of depression and in taking appropriate steps accordingly. However, existing models regarding symptom prediction are limited by various issues, including low performance (eg, specificity is around or below 60% for most symptoms). Our proposed approach to explore rhythmic features from app usage behavioral markers and the development and validation of the MTL framework through our constructed large-scale data set may provide new insights into rhythms and higher performance in predicting depressive symptoms.

Acknowledgments

This research has been funded by North South University (NSU; ID: NonCTRG-22-26) and the Institute of Advanced Research (IAR; ID: UIU-IAR-01-2022-SE-21) of the United International University (UIU). In addition, the NSU and the IAR (ID: UIU-IAR-01-2022-SE-21) supported publication in *JMIR Research Protocols*. We are grateful to the faculties of universities located in different regions of Bangladesh without whose cordial support, it would not have been possible to conduct this countrywide study. We also thank the participants for their time and willingness to provide data.

Data Availability

Since app usage data are sensitive, making the data publicly available can raise different data privacy and safety concerns (eg, reidentification of the participants [34]). Thus, we do not plan to upload the data to any public data repositories. However, the data can be accessed by sending a reasonable request to the corresponding author.

Conflicts of Interest

None declared.

References

1. Suicide prevention. World Health Organization. URL: https://www.who.int/health-topics/suicide [accessed 2023-03-18]
2. Dong M, Zeng L, Lu L, Li X, Ungvari GS, Ng CH, et al. Prevalence of suicide attempt in individuals with major depressive disorder: a meta-analysis of observational surveys. Psychol Med 2019 Jul;49(10):1691-1704. [doi: 10.1017/S0033291718002301] [Medline: 30178722]
3. Cai H, Xie X, Zhang Q, Cui X, Lin J, Sim K, et al. Prevalence of suicidality in major depressive disorder: a systematic review and meta-analysis of comparative studies. Front Psychiatry 2021;12:690130 [FREE Full text] [doi: 10.3389/fpsyt.2021.690130] [Medline: 34603096]
4. The global burden of disease. World Health Organization. 2008. URL: https://apps.who.int/iris/bitstream/handle/10665/43942/9789241563710_eng.pdf [accessed 2023-03-18]
5. COVID-19 Mental Disorders Collaborators. Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. Lancet 2021 Nov 06;398(10312):1700-1712 [FREE Full text] [doi: 10.1016/S0140-6736(21)02143-7] [Medline: 34634250]
6. Bangladesh WHO special initiative for mental health situational assessment. World Health Organization. 2019. URL: https://www.who.int/docs/default-source/mental-health/special-initiative/who-special-initiative-country-report---bangladesh---2020.pdf?sfvrsn=c2122a0e_2 [accessed 2023-03-18]
7. Hosen I, Al-Mamun F, Mamun MA. Prevalence and risk factors of the symptoms of depression, anxiety, and stress during the COVID-19 pandemic in Bangladesh: a systematic review and meta-analysis. Glob Ment Health (Camb) 2021;8:e47 [FREE Full text] [doi: 10.1017/gmh.2021.49] [Medline: 35145709]
8. Islam MA, Barna SD, Raihan H, Khan MNA, Hossain MT. Depression and anxiety among university students during the COVID-19 pandemic in Bangladesh: a web-based cross-sectional survey. PLoS One 2020;15(8):e0238162 [FREE Full text] [doi: 10.1371/journal.pone.0238162] [Medline: 32845928]
9. Fusar-Poli P, McGorry PD, Kane JM. Improving outcomes of first-episode psychosis: an overview. World Psychiatry 2017 Oct;16(3):251-265 [FREE Full text] [doi: 10.1002/wps.20446] [Medline: 28941089]
10. Depression. National Institute of Mental Health. 2023. URL: https://www.nimh.nih.gov/health/topics/depression [accessed 2023-04-14]
11. Depressive disorder (depression). World Health Organization. 2023. URL: https://www.who.int/news-room/fact-sheets/detail/depression [accessed 2023-04-14]
12. Davidsen AS, Fosgerau CF. What is depression? Psychiatrists' and GPs' experiences of diagnosis and the diagnostic process. Int J Qual Stud Health Well-being 2014 Nov 06;9(1):24866 [FREE Full text] [doi: 10.3402/qhw.v9.24866] [Medline: 25381757]
13. Coyne JC, Schwenk TL, Fechner-Bates S. Nondetection of depression by primary care physicians reconsidered. Gen Hosp Psychiatry 1995 Jan;17(1):3-12. [doi: 10.1016/0163-8343(94)00056-j] [Medline: 7737492]
14. Cepoiu M, McCusker J, Cole MG, Sewitch M, Ciampi A. Recognition of depression in older medical inpatients. J Gen Intern Med 2007 May;22(5):559-564 [FREE Full text] [doi: 10.1007/s11606-006-0085-0] [Medline: 17443361]
15. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001 Sep;16(9):606-613 [FREE Full text] [doi: 10.1046/j.1525-1497.2001.016009606.x] [Medline: 11556941]
16. Depression and other common mental disorders: global health estimates. World Health Organization. 2017. URL: https://apps.who.int/iris/bitstream/handle/10665/254610/WHO-MSD-MER-2017.2-eng.pdf [accessed 2023-03-18]
17. BBS. 2022. URL: http://www.bbs.gov.bd/site/page/47856ad0-7e1c-4aab-bd78-892733bc06eb/Population-&-Housing [accessed 2024-03-02]
18. Chapter – five: madrasah education. BANBEIS. 2021. URL: https://tinyurl.com/4sa7k2jt [accessed 2023-03-18]
19. Delaporte A, Bahia K. Mobile for development: the state of mobile internet connectivity report 2022. GSMA. 2022. URL: https://www.gsma.com/r/somic/ [accessed 2023-04-15]
20. Owoyemi A, Owoyemi J, Osiyemi A, Boyd A. Artificial intelligence for healthcare in Africa. Front Digit Health 2020;2:6 [FREE Full text] [doi: 10.3389/fdgth.2020.00006] [Medline: 34713019]
21. De Angel V, Lewis S, White K, Oetzmann C, Leightley D, Oprea E, et al. Digital health tools for the passive monitoring of depression: a systematic review of methods. NPJ Digit Med 2022 Jan 11;5(1):3 [FREE Full text] [doi: 10.1038/s41746-021-00548-8] [Medline: 35017634]
22. Sekara V, Alessandretti L, Mones E, Jonsson H. Temporal and cultural limits of privacy in smartphone app usage. Sci Rep 2021 Feb 16;11(1):3861 [FREE Full text] [doi: 10.1038/s41598-021-82294-1] [Medline: 33594096]
23. Tu Z, Cao H, Lagerspetz E, Fan Y, Flores H, Tarkoma S, et al. Demographics of mobile app usage: long-term analysis of mobile app usage. CCF Trans Pervasive Comp Interact 2021 Apr 21;3(3):235-252. [doi: 10.1007/s42486-020-00041-3]

24. Quante M, Mariani S, Weng J, Marinac CR, Kaplan ER, Rueschman M, et al. Zeitgebers and their association with rest-activity patterns. Chronobiol Int 2019 Feb;36(2):203-213 [FREE Full text] [doi: 10.1080/07420528.2018.1527347] [Medline: 30365354]
25. Ryu S, Oh H. Duration and content type of smartphone use in relation to diet and adiposity in 53,133 adolescents. Curr Dev Nutrition 2021 Jun;5:1088. [doi: 10.1093/cdn/nzab053_081]
26. Murnane E, Abdullah S, Matthews M, Kay M, Kientz J, Choudhury T, et al. Mobile manifestations of alertness: connecting biological rhythms with patterns of smartphone app use. 2016 Presented at: MobileHCI '16: 18th International Conference on Human-Computer Interaction with Mobile Devices and Services; September 6-9, 2016; Florence, Italy. [doi: 10.1145/2935334.2935383]
27. Abdullah S, Matthews M, Murnane E, Gay G, Choudhury T. Towards circadian computing: "early to bed and early to rise" makes some of us unhealthy and sleep deprived. 2014 Presented at: UbiComp '14: 2014 ACM International Joint Conference on Pervasive and Ubiquitous Computing; September 13-17, 2014; Seattle, WA. [doi: 10.1145/2632048.2632100]
28. Mehrotra A, Müller SR, Harari GM, Gosling SD, Mascolo C, Musolesi M, et al. Understanding the role of places and activities on mobile phone interaction and usage patterns. Proc ACM Interact Mob Wearable Ubiquitous Technol 2017 Sep 11;1(3):1-22. [doi: 10.1145/3131901]
29. Gordon M, Gatys L, Guestrin C, Bigham J, Trister A, Patel K. App usage predicts cognitive ability in older adults. 2019 Presented at: CHI '19: CHI Conference on Human Factors in Computing Systems; May 4-9, 2019; Glasgow, Scotland. [doi: 10.1145/3290605.3300398]
30. Böhmer M, Hecht B, Schöning J, Krüger A, Bauer G. Falling asleep with Angry Birds, Facebook and Kindle: a large scale study on mobile application usage. 2011 Presented at: MobileHCI '11: 13th International Conference on Human Computer Interaction with Mobile Devices and Services; August 30-September 2, 2011; Stockholm, Sweden. [doi: 10.1145/2037373.2037383]
31. Morrison A, Xiong X, Higgs M, Bell M, Chalmers M. A large-scale study of iPhone app launch behaviour. 2018 Presented at: CHI'18: CHI Conference on Human Factors in Computing Systems; April 2- 26, 2018; Montreal, QC. [doi: 10.1145/3173574.3173918]
32. Yan R, Liu X, Dutcher J, Tumminia M, Villalba D, Cohen S, et al. A computational framework for modeling biobehavioral rhythms from mobile and wearable data streams. ACM Trans Intell Syst Technol 2022 Mar 03;13(3):1-27. [doi: 10.1145/3510029]
33. Ahmed MS, Ahmed N. A fast and minimal system to identify depression using smartphones: explainable machine learning–based approach. JMIR Form Res 2023 Aug 10;7:e28848 [FREE Full text] [doi: 10.2196/28848] [Medline: 37561568]
34. Ahmed M, Ahmed N. Exploring unique app signature of the depressed and non-depressed through their fingerprints on apps. In: Lecture Notes of the Institute for Computer Sciences, Social Informatics and Telecommunications Engineering. Cham: Springer International Publishing; 2022:218-239.
35. Ahmed M, Rony R, Hasan T, Ahmed N. Smartphone usage behavior between depressed and non-depressed students: an exploratory study in the context of Bangladesh. 2020 Presented at: UbiComp/ISWC '20 Adjunct: 2020 ACM International Joint Conference on Pervasive and Ubiquitous Computing and 2020 ACM International Symposium on Wearable Computers; September 12-17, 2020; Mexico. [doi: 10.1145/3410530.3414441]
36. Cornelissen G. Cosinor-based rhythmometry. Theor Biol Med Model 2014 Apr 11;11:16 [FREE Full text] [doi: 10.1186/1742-4682-11-16] [Medline: 24725531]
37. Moškon M. CosinorPy: a Python package for cosinor-based rhythmometry. BMC Bioinformat 2020 Oct 29;21(1):485 [FREE Full text] [doi: 10.1186/s12859-020-03830-w] [Medline: 33121431]
38. Bingham C, Arbogast B, Guillaume GC, Lee JK, Halberg F. Inferential statistical methods for estimating and comparing cosinor parameters. Chronobiologia 1982;9(4):397-439. [Medline: 7168995]
39. Miyagi R, Sasawaki Y, Shiotani H. The influence of short-term sedentary behavior on circadian rhythm of heart rate and heart rate variability. Chronobiol Int 2019 Mar 03;36(3):374-380. [doi: 10.1080/07420528.2018.1550422] [Medline: 30501447]
40. Doryab A, Dey AK, Kao G, Low C. Modeling biobehavioral rhythms with passive sensing in the wild: a case study to predict readmission risk after pancreatic surgery. Proc ACM Interact Mob Wearable Ubiquitous Technol 2019 Mar 29;3(1):1-21. [doi: 10.1145/3314395]
41. Elias J. Why wearables are out of reach for people who need them most. Forbes. 2015. URL: https://www.forbes.com/sites/jenniferelias/2015/10/27/the-leftovers-part-i-the-cost-of-activity/?sh=a0e5ffc63c9b [accessed 2023-07-28]
42. Lohchab H. Affordable smartphone sales shoot up as demand grows due to e-learning needs. Economic Times. 2020. URL: https://economictimes.indiatimes.com/tech/hardware/affordable-smartphone-sales-shoot-up-as-demand-grows/articleshow/78241563.cms [accessed 2023-07-28]
43. Abd-Alrazaq A, AlSaad R, Aziz S, Ahmed A, Denecke K, Househ M, et al. Wearable artificial intelligence for anxiety and depression: scoping review. J Med Internet Res 2023 Jan 19;25:e42672 [FREE Full text] [doi: 10.2196/42672] [Medline: 36656625]

44. Xu X, Chikersal P, Dutcher JM, Sefidgar YS, Seo W, Tumminia MJ, et al. Leveraging collaborative-filtering for personalized behavior modeling: a case study of depression detection among college students. Proc ACM Interact Mob Wearable Ubiquitous Technol 2021 Mar 30;5(1):1-27. [doi: 10.1145/3448107]
45. Xu X, Chikersal P, Doryab A, Villalba DK, Dutcher JM, Tumminia MJ, et al. Leveraging routine behavior and contextually-filtered features for depression detection among college students. Proc ACM Interact Mob Wearable Ubiquitous Technol 2019 Sep 09;3(3):1-33. [doi: 10.1145/3351274]
46. Chikersal P, Doryab A, Tumminia M, Villalba DK, Dutcher JM, Liu X, et al. Detecting depression and predicting its onset using longitudinal symptoms captured by passive sensing: A machine learning approach with robust feature selection. ACM Trans Comput-Hum Interact 2021 Jan 20;28(1):1-41. [doi: 10.1145/3422821]
47. Dogrucu A, Perucic A, Isaro A, Ball D, Toto E, Rundensteiner EA, et al. Moodable: on feasibility of instantaneous depression assessment using machine learning on voice samples with retrospectively harvested smartphone and social media data. Smart Health 2020 Jul;17:100118. [doi: 10.1016/j.smhl.2020.100118]
48. Yue C, Ware S, Morillo R, Lu J, Shang C, Bi J, et al. Automatic depression prediction using internet traffic characteristics on smartphones. Smart Health (Amst) 2020 Nov;18:100137 [FREE Full text] [doi: 10.1016/j.smhl.2020.100137] [Medline: 33043105]
49. Ware S, Yue C, Morillo R, Lu J, Shang C, Kamath J, et al. Large-scale automatic depression screening using meta-data from WiFi infrastructure. Proc ACM Interact Mob Wearable Ubiquitous Technol 2018 Dec 27;2(4):1-27. [doi: 10.1145/3287073]
50. Yue C, Ware S, Morillo R, Lu J, Shang C, Bi J, et al. Fusing location data for depression prediction. IEEE Trans Big Data 2021 Jun;7(2):355-370 [FREE Full text] [doi: 10.1109/tbdata.2018.2872569] [Medline: 35498556]
51. Canzian L, Musolesi M. Trajectories of depression: unobtrusive monitoring of depressive states by means of smartphone mobility traces analysis. 2015 Presented at: UbiComp '15: 2015 ACM International Joint Conference on Pervasive and Ubiquitous Computing; September 9-11, 2015; Osaka, Japan p. 1293-1304. [doi: 10.1145/2750858.2805845]
52. Farhan A, Yue C, Morillo R, Ware S, Lu J, Bi J, et al. Behavior vs. introspection: refining prediction of clinical depression via smartphone sensing data. 2016 Presented at: 2016 IEEE Wireless Health (WH); October 25-27, 2016; Bethesda, MD p. 1-8. [doi: 10.1109/wh.2016.7764553]
53. Lu J, Shang C, Yue C, Morillo R, Ware S, Kamath J, et al. Joint modeling of heterogeneous sensing data for depression assessment via multi-task learning. Proc ACM Interact Mob Wearable Ubiquitous Technol 2018 Mar 26;2(1):1-21. [doi: 10.1145/3191753]
54. Mullick T, Radovic A, Shaaban S, Doryab A. Predicting depression in adolescents using mobile and wearable sensors: multimodal machine learning-based exploratory study. JMIR Form Res 2022 Jun 24;6(6):e35807 [FREE Full text] [doi: 10.2196/35807] [Medline: 35749157]
55. Pedrelli P, Fedor S, Ghandeharioun A, Howe E, Ionescu DF, Bhathena D, et al. Monitoring changes in depression severity using wearable and mobile sensors. Front Psychiatry 2020;11:584711 [FREE Full text] [doi: 10.3389/fpsyt.2020.584711] [Medline: 33391050]
56. Ghandeharioun A, Fedor S, Sangermano L, Ionescu D, Alpert J, Dale C, et al. Objective assessment of depressive symptoms with machine learning and wearable sensors data. 2017 Presented at: 2017 Seventh International Conference on Affective Computing and Intelligent Interaction (ACII); October 23-26, 2017; San Antonio, TX p. 325. [doi: 10.1109/acii.2017.8273620]
57. Saha K, Grover T, Mattingly SM, swain VD, Gupta P, Martinez GJ, et al. Person-centered predictions of psychological constructs with social media contextualized by multimodal sensing. Proc ACM Interact Mob Wearable Ubiquitous Technol 2021 Mar 30;5(1):1-32. [doi: 10.1145/3448117]
58. Cao J, Truong AL, Banu S, Shah AA, Sabharwal A, Moukaddam N. Tracking and predicting depressive symptoms of adolescents using smartphone-based self-reports, parental evaluations, and passive phone sensor data: development and usability study. JMIR Ment Health 2020 Jan 24;7(1):e14045 [FREE Full text] [doi: 10.2196/14045] [Medline: 32012072]
59. Doryab A. Critical thinking of mobile sensing for health. Crossroads 2021 Sep 21;28(1):34-37. [doi: 10.1145/3481831]
60. Rykov Y, Thach T, Bojic I, Christopoulos G, Car J. Digital biomarkers for depression screening with wearable devices: cross-sectional study with machine learning modeling. JMIR Mhealth Uhealth 2021 Oct 25;9(10):e24872 [FREE Full text] [doi: 10.2196/24872] [Medline: 34694233]
61. Briganti G, Scutari M, Linkowski P. Network structures of symptoms from the Zung Depression Scale. Psychol Rep 2021 Aug;124(4):1897-1911. [doi: 10.1177/0033294120942116] [Medline: 32686585]
62. Cheung T, Jin Y, Lam S, Su Z, Hall BJ, Xiang Y, International Research Collaboration on COVID-19. Network analysis of depressive symptoms in Hong Kong residents during the COVID-19 pandemic. Transl Psychiatry 2021 Sep 06;11(1):460 [FREE Full text] [doi: 10.1038/s41398-021-01543-z] [Medline: 34489416]
63. Baryshnikov I, Aledavood T, Rosenström T, Heikkilä R, Darst R, Riihimäki K, et al. Relationship between daily rated depression symptom severity and the retrospective self-report on PHQ-9: a prospective ecological momentary assessment study on 80 psychiatric outpatients. J Affect Disord 2023 Mar 01;324:170-174 [FREE Full text] [doi: 10.1016/j.jad.2022.12.127] [Medline: 36586594]

64. Wang R, Wang W, daSilva A, Huckins JF, Kelley WM, Heatherton TF, et al. Tracking depression dynamics in college students using mobile phone and wearable sensing. Proc ACM Interact Mob Wearable Ubiquitous Technol 2018 Mar 26;2(1):1-26. [doi: 10.1145/3191775]
65. Tseng VW, Sano A, Ben-Zeev D, Brian R, Campbell AT, Hauser M, et al. Using behavioral rhythms and multi-task learning to predict fine-grained symptoms of schizophrenia. Sci Rep 2020 Sep 15;10(1):15100 [FREE Full text] [doi: 10.1038/s41598-020-71689-1] [Medline: 32934246]
66. Ware S, Knouse L, Draz I, Enikeeva A. Predicting ADHD symptoms using smartphone sensing data. 2022 Presented at: UbiComp/ISWC '22 Adjunct: 2022 ACM International Joint Conference on Pervasive and Ubiquitous Computing; September 11-15, 2022; Cambridge, UK URL: https://ubicomp-mental-health.github.io/papers/2022/Ware-ADHD.pdf [doi: 10.1145/3544793.3563430]
67. Ware S, Yue C, Morillo R, Lu J, Shang C, Bi J, et al. Predicting depressive symptoms using smartphone data. Smart Health 2020 Mar;15:100093. [doi: 10.1016/j.smhl.2019.100093]
68. Standley T, Zamir A, Chen D, Guibas L, Malik J, Savarese S. Which tasks should be learned together in multi-task learning? 2020 Presented at: ICML'20: 37th International Conference on Machine Learning; July 13-18, 2020; Vienna, Austria p. 9120-9132 URL: http://proceedings.mlr.press/v119/standley20a/standley20a.pdf
69. Ahmed M. Mon Majhi. Google. 2022. URL: https://play.google.com/store/apps/details/?id=net.mn.u [accessed 2023-03-18]
70. Ahmed MS, Rony RJ, Hadi MA, Hossain E, Ahmed N. A minimalistic approach to predict and understand the relation of app usage with students' academic performances. Proc ACM Hum-Comput Interact 2023 Sep 13;7(MHCI):1-28. [doi: 10.1145/3604240]
71. Ahmed M, Jahangir RR, Ahmed N. Identifying high and low academic result holders through smartphone usage data. 2021 Presented at: Asian CHI '21: Asian CHI Symposium 2021; May 8-13, 2021; Yokohama, Japan. [doi: 10.1145/3429360.3468192]
72. Ahmed M, Rony R, Ashhab M, Ahmed N. An empirical study to analyze the impact of Instagram on students' academic results. 2020 Presented at: 2020 IEEE Region 10 Symposium (TENSYMP); June 5-7, 2020; Dhaka, Bangladesh p. 666-669. [doi: 10.1109/tensymp50017.2020.9230945]
73. Ahmed M, Hasan T, Rahman M, Ahmed N. A rule mining and Bayesian network analysis to explore the link between depression and digital behavioral markers of games app usage. In: Lecture Notes of the Institute for Computer Sciences, Social Informatics and Telecommunications Engineering. Cham: Springer Nature Switzerland; 2023:557-569.
74. Ahmed M, Ahmed N. Less is more: leveraging digital behavioral markers for real-time identification of loneliness in resource-limited settings. In: Lecture Notes of the Institute for Computer Sciences, Social Informatics and Telecommunications Engineering. Cham: Springer Nature Switzerland; 2023:460-476.
75. Ahmed S, Khan SS, Ahmed N. Is there any relation between smartphone usage and loneliness during the COVID-19 pandemic?: a study by exploring two objective app usage datasets. EAI Endorsed Trans Perv Health Tech 2023 Aug 02;9:1-15. [doi: 10.4108/eetpht.9.3663]
76. Sample size calculator: understanding sample sizes. SurveyMonkey. URL: https://www.surveymonkey.com/mp/sample-size-calculator/ [accessed 2023-07-06]
77. Sample size calculation when the sampling method is simple random sampling. Uidaho. URL: https://www.webpages.uidaho.edu/ed571/OFFLINE-571-Modules/Offline_Modules/M3-S/Sample_Size_Calculations-Formulas.pdf [accessed 2023-12-22]
78. Hossain MJ, Ahmmed F, Khandokar L, Rahman SMA, Hridoy A, Ripa FA, et al. Status of psychological health of students following the extended university closure in Bangladesh: results from a web-based cross-sectional study. PLOS Glob Public Health 2022;2(3):e0000315 [FREE Full text] [doi: 10.1371/journal.pgph.0000315] [Medline: 36962237]
79. Tu Z, Li R, Li Y, Wang G, Wu D, Hui P, et al. Your apps give you away: distinguishing mobile users by their app usage fingerprints. Proc ACM Interact Mob Wearable Ubiquitous Technol 2018 Sep 18;2(3):1-23. [doi: 10.1145/3264948]
80. Malmi E, Weber I. You are what apps you use: demographic prediction based on user's apps. ICWSM 2021 Aug 04;10(1):635-638. [doi: 10.1609/icwsm.v10i1.14776]
81. Dijk D, Duffy JF. Novel approaches for assessing circadian rhythmicity in humans: a review. J Biol Rhythms 2020 Oct;35(5):421-438 [FREE Full text] [doi: 10.1177/0748730420940483] [Medline: 32700634]
82. Thomas KA, Burr RL. Circadian research in mothers and infants: how many days of actigraphy data are needed to fit cosinor parameters? J Nurs Meas 2008;16(3):201-206 [FREE Full text] [doi: 10.1891/1061-3749.16.3.201] [Medline: 19886472]
83. Chowdhury A, Ghosh S, Sanyal D. Bengali adaptation of Brief Patient Health Questionnaire for screening depression at primary care. J Indian Med Assoc 2004 Oct;102(10):544-547. [doi: 10.1037/t06166-000]
84. Chiny M, Chihab M, Bencharef O, Chihab Y. Netflix recommendation system based on TF-IDF and cosine similarity algorithms. 2021 Presented at: BML'21: 2nd International Conference on Big Data, Modelling and Machine Learning; June 5-6, 2021; Kenitra, Morocco. [doi: 10.5220/0010727500003101]
85. Sarsenbayeva Z, Marini G, van BN, Luo C, Jiang W, Yang K, et al. Does smartphone use drive our emotions or vice versa? A causal analysis. 2020 Presented at: CHI '20: CHI Conference on Human Factors in Computing Systems; April 25-30, 2020; Honolulu HI. [doi: 10.1145/3313831.3376163]

86. Gonçalves BSB, Adamowicz T, Louzada FM, Moreno CR, Araujo JF. A fresh look at the use of nonparametric analysis in actimetry. Sleep Med Rev 2015 Apr;20:84-91. [doi: 10.1016/j.smrv.2014.06.002] [Medline: 25065908]
87. Anderson ST, FitzGerald GA. Sexual dimorphism in body clocks. Science 2020 Sep 04;369(6508):1164-1165. [doi: 10.1126/science.abd4964] [Medline: 32883849]
88. Duarte LL, Menna-Barreto L. Chronotypes and circadian rhythms in university students. Biol Rhythm Res 2021 Mar 23;53(7):1058-1072. [doi: 10.1080/09291016.2021.1903791]
89. Mitchell JA, Quante M, Godbole S, James P, Hipp JA, Marinac CR, et al. Variation in actigraphy-estimated rest-activity patterns by demographic factors. Chronobiol Int 2017;34(8):1042-1056 [FREE Full text] [doi: 10.1080/07420528.2017.1337032] [Medline: 28650674]
90. Mutak A. cosinor2 vignette. R-project. 2018. URL: https://cran.r-project.org/web/packages/cosinor2/vignettes/cosinor2.html [accessed 2023-07-21]
91. Mishra P, Pandey CM, Singh U, Gupta A, Sahu C, Keshri A. Descriptive statistics and normality tests for statistical data. Ann Card Anaesth 2019;22(1):67-72 [FREE Full text] [doi: 10.4103/aca.ACA_157_18] [Medline: 30648682]
92. Khan A, Tian XL. Circadian amplitude. In: Encyclopedia of Gerontology and Population Aging. Cham: Springer International Publishing; 2021:1003-1012.
93. Masubuchi S, Hashimoto S, Endo T, Honma S, Honma K. Amplitude reduction of plasma melatonin rhythm in association with an internal desynchronization in a subject with non-24-hour sleep-wake syndrome. Psychiatry Clin Neurosci 1999 Apr 12;53(2):249-251 [FREE Full text] [doi: 10.1046/j.1440-1819.1999.00535.x] [Medline: 10459702]
94. Jones SH, Hare DJ, Evershed K. Actigraphic assessment of circadian activity and sleep patterns in bipolar disorder. Bipolar Disord 2005 Apr;7(2):176-186. [doi: 10.1111/j.1399-5618.2005.00187.x] [Medline: 15762859]
95. Esaki Y, Obayashi K, Saeki K, Fujita K, Iwata N, Kitajima T. Association between circadian activity rhythms and mood episode relapse in bipolar disorder: a 12-month prospective cohort study. Transl Psychiatry 2021 Oct 13;11(1):525 [FREE Full text] [doi: 10.1038/s41398-021-01652-9] [Medline: 34645802]
96. Mayeli A, LaGoy AD, Smagula SF, Wilson JD, Zarbo C, Rocchetti M, DiAPAson Consortium, et al. Shared and distinct abnormalities in sleep-wake patterns and their relationship with the negative symptoms of schizophrenia spectrum disorder patients. Mol Psychiatry 2023 May 14;28(5):2049-2057. [doi: 10.1038/s41380-023-02050-x] [Medline: 37055512]
97. James G, Witten D, Hastie T, Tibshirani R. An Introduction to Statistical Learning: With Applications in R. New York, NY: Springer; 2021.
98. Ng K, Sun J, Hu J, Wang F. Personalized predictive modeling and risk factor identification using patient similarity. AMIA Jt Summits Transl Sci Proc 2015;2015:132-136 [FREE Full text] [Medline: 26306255]
99. Lee J, Maslove DM, Dubin JA. Personalized mortality prediction driven by electronic medical data and a patient similarity metric. PLoS One 2015;10(5):e0127428 [FREE Full text] [doi: 10.1371/journal.pone.0127428] [Medline: 25978419]
100. Sharafoddini A, Dubin JA, Lee J. Patient similarity in prediction models based on health data: a scoping review. JMIR Med Inform 2017 Mar 03;5(1):e7 [FREE Full text] [doi: 10.2196/medinform.6730] [Medline: 28258046]
101. Durrheim K, Tredoux C. Numbers, Hypotheses & Conclusions: A Course in Statistics for the Social Sciences. 6th ed. Cape Town: Juta and Company; 2004.
102. Ruder S. An overview of multi-task learning in deep neural networks. arXiv Preprint posted online June 15, 2017 [FREE Full text] [doi: 10.48550/arXiv.1706.05098]
103. Mao Y, Wang Z, Liu W, Lin X, Xie P. MetaWeighting: learning to weight tasks in multi-task learning. In: Muresan S, Nakov P, Villavicencio A, editors. Findings of the Association for Computational Linguistics: ACL 2022. Stroudsburg, PA: Association for Computational Linguistics; 2022:3436-3448.
104. Vabalas A, Gowen E, Poliakoff E, Casson AJ. Machine learning algorithm validation with a limited sample size. PLoS One 2019 Nov 7;14(11):e0224365 [FREE Full text] [doi: 10.1371/journal.pone.0224365] [Medline: 31697686]
105. Andaur Navarro CL, Damen JAA, Takada T, Nijman SWJ, Dhiman P, Ma J, et al. Risk of bias in studies on prediction models developed using supervised machine learning techniques: systematic review. BMJ 2021 Oct 20;375:n2281 [FREE Full text] [doi: 10.1136/bmj.n2281] [Medline: 34670780]
106. Bernert RA, Hilberg AM, Melia R, Kim JP, Shah NH, Abnousi F. Artificial intelligence and suicide prevention: a systematic review of machine learning investigations. Int J Environ Res Public Health 2020 Aug 15;17(16):5929 [FREE Full text] [doi: 10.3390/ijerph17165929] [Medline: 32824149]
107. Sarwar A, Agu EO, Almadani A, Sarwar A. CovidRhythm: a deep learning model for passive prediction of COVID-19 using biobehavioral rhythms derived from wearable physiological data. IEEE Open J Eng Med Biol 2023;4:21-30. [doi: 10.1109/ojemb.2023.3261223]
108. Xu Y, Su S, Li X, Mansuri A, McCall WV, Wang X. Blunted rest-activity circadian rhythm increases the risk of all-cause, cardiovascular disease and cancer mortality in US adults. Sci Rep 2022 Nov 30;12(1):20665 [FREE Full text] [doi: 10.1038/s41598-022-24894-z] [Medline: 36450759]
109. Yun J, Yun YH. Health-promoting behavior to enhance perceived meaning and control of life in chronic disease patients with role limitations and depressive symptoms: a network approach. Sci Rep 2023 Mar 24;13(1):4848 [FREE Full text] [doi: 10.1038/s41598-023-31867-3] [Medline: 36964273]

Abbreviations

AI: artificial intelligence
CV: cross-validation
IS: interdaily stability
IV: intradaily variability
LMIC: low- and middle-income country
LOOCV: leave-one-out cross-validation
MDD: major depressive disorder
MESOR: midline estimating statistic of rhythm
ML: machine learning
MTL: multitask learning
PHQ-9: 9-item Patient Health Questionnaire
PMI: point mutual information
RA: relative amplitude
STL: single-task learning
TF-IDF: term frequency–inverse document frequency
VIF: variance inflation factor

Edited by A Mavragani; submitted 06.08.23; peer-reviewed by J Zhu, X Li; comments to author 03.11.23; revised version received 27.12.23; accepted 11.01.24; published 24.04.24.

Please cite as:
Ahmed MS, Hasan T, Islam S, Ahmed N
Investigating Rhythmicity in App Usage to Predict Depressive Symptoms: Protocol for Personalized Framework Development and Validation Through a Countrywide Study
JMIR Res Protoc 2024;13:e51540
URL: https://www.researchprotocols.org/2024/1/e51540
doi:10.2196/51540
PMID:38657238

Protocol

Lack of Diversity in Research on Females with Ehlers-Danlos Syndromes: Recruitment Protocol for a Quantitative Online Survey

Jennifer E Glayzer[1], BSN, PhD; Bethany C Bray[2], PhD; William H Kobak[3], MD; Alana D Steffen[1], PhD; Judith M Schlaeger[1], LAc, CNM, PhD

[1]Department of Human Development Nursing Science, College of Nursing, University of Illinois Chicago, Chicago, IL, United States

[2]Institute for Health Research and Policy, University of Illinois Chicago, Chicago, IL, United States

[3]Department of Obstetrics and Gynecology, College of Medicine, University of Illinois Chicago, Chicago, IL, United States

Corresponding Author:
Jennifer E Glayzer, BSN, PhD
Department of Human Development Nursing Science
College of Nursing
University of Illinois Chicago
845 S. Damen Ave
Chicago, IL, 60622
United States
Phone: 1 2487629576
Email: jglayzer@iu.edu

Abstract

Background: Ehlers-Danlos syndromes (EDS) are a group of connective tissue disorders caused by fragile lax collagen. Current EDS research lacks racial and ethnic diversity. The lack of diversity may be associated with the complexities of conducting a large international study on an underdiagnosed condition and a lack of EDS health care providers who diagnose and conduct research outside of the United States and Europe. Social media may be the key to recruiting a large diverse EDS sample. However, studies that have used social media to recruit have not been able to recruit diverse samples.

Objective: This study aims to discuss challenges, strategies, outcomes, and lessons learned from using social media to recruit a large sample of females with EDS.

Methods: Recruitment on social media for a cross-sectional survey examining dyspareunia (painful sexual intercourse) in females was examined. Inclusion criteria were (1) older than 18 years of age, (2) assigned female at birth, and (3) diagnosed with EDS. Recruitment took place on Facebook and Twitter (now X), from June 1 to June 25, 2019.

Results: A total of 1178 females with EDS were recruited from Facebook (n=1174) and X (n=4). On Facebook, participants were recruited via support groups. A total of 166 EDS support groups were identified, 104 permitted the principal investigator to join, 90 approved posting, and the survey was posted in 54 groups. Among them, 30 of the support groups posted in were globally focused and not tied to any specific country or region, 21 were for people in the United States, and 3 were for people outside of the United States. Recruitment materials were posted on X with the hashtag #EDS. A total of 1599 people accessed the survey and 1178 people were eligible and consented. The average age of participants was 38.6 (SD 11.7) years. Participants were predominantly White (n=1063, 93%) and non-Hispanic (n=1046, 92%). Participants were recruited from 29 countries, with 900 (79%) from the United States and 124 (11%) from Great Britain.

Conclusions: Our recruitment method was successful at recruiting a large sample. The sample was predominantly White and from North America and Europe. More research needs to be conducted on how to recruit a diverse sample. Areas to investigate may include connecting with more support groups from outside the United States and Europe, researching which platforms are popular in different countries, and translating study materials into different languages. A larger obstacle to recruiting diverse samples may be the lack of health care providers that diagnose EDS outside the United States and Europe, making the pool of potential participants small. There needs to be more health care providers that diagnose and treat EDS in countries that are predominantly made up of people of color as well as research that specifically focuses on these populations.

International Registered Report Identifier (IRRID): RR1-10.2196/53646

(JMIR Res Protoc 2024;13:e53646) doi:10.2196/53646

KEYWORDS

Ehlers-Danlos syndrome; hypermobility; social media; recruitment; Facebook; hereditary disease; connective tissue disorders; racial; ethnic; diversity; challenges; strategies; strategy; online; information seeking; cross-sectional survey; dyspareunia; painful sex; United States

Introduction

Overview

Ehlers-Danlos syndromes (EDS) are a group of hereditary connective tissue disorders [1]. The overall prevalence and racial and ethnic breakdowns of EDS are unknown [2]. It is estimated that EDS affects between 1 in 5000 [3] and 1 in 3400 [4] and is thought to be underdiagnosed instead of rare [4,5]. Females are diagnosed at a much higher rate than males with 7 females diagnosed for every 3 males [4]. It is unknown if this is due to the difference in presentation between the 2 sexes or how the condition is passed to offspring [6]. The inability to accurately determine the prevalence of EDS makes it difficult for investigators to recruit large diverse samples for studies, limiting the generalizability of results to participants whose demographics match study samples.

Most EDS studies have been comprised of predominately White samples recruited from the United States and Europe. Recruitment has traditionally been done at clinics or hospitals that treat patients with EDS [7], conferences [8-10], local in-person EDS support groups [11], or big data aggregation of national health records [4,12,13]. These recruitment methods limit the diversity of participants. Recruiting via clinics may limit participation to those who are physically and financially able to travel to the clinics; however, access to clinics is improving with the use of telemedicine. Some studies conducted via hospitals or clinics fail to report race or ethnicity demographics in their results [14-18]. Although national health record studies recruit from a large geographic area, to date they have only been completed in small northern European countries with predominantly White populations [4,12,13]. Extracting data from national health records also limits the types of data that can be analyzed to demographics and health care informatics, lacking metrics not included in patients' charts such as symptom burden and personal experiences. Recruiting via EDS conferences includes only participants who are financially able and healthy enough to travel, excluding those who are of low socioeconomic status and the most ill. Furthermore, health care providers who treat and diagnose EDS and EDS researchers are predominantly located in the United States and Europe [19], which likely decreases the number of people diagnosed outside of these regions and, therefore, the number of people who would be eligible to participate in the research. The Ehlers-Danlos Society is an international nonprofit organization that is involved in raising awareness of EDS as well as supporting EDS research through research grants, patient education conferences, and health care provider symposia. The Ehlers-Danlos Society is based in the United Kingdom and the United States and operates in English, which may be a barrier for non-English speaking health care providers and researchers to participate in research and attend symposia. The Ehlers-Danlos Society is based in the United Kingdom and the United States and operates in English, which may be a barrier for health care providers and researchers in non–English-speaking countries for participating in research and attending symposia. However, the Ehlers-Danlos Society is actively trying to connect with or develop a network of EDS providers and researchers in countries where there are few EDS providers such as Japan [20]. Using social media for recruitment may facilitate the recruitment of diverse samples, increasing the generalizability of results to the global EDS population. However, studies conducted since this study in 2019 had similar results with most participants residing in the United States, Canada, the United Kingdom, and Australia [21-23].

Use of Social Media for EDS Study Recruitment

EDS research has started to use social media for recruitment, but no literature has discussed research methods associated with this approach. A benefit of using social media to recruit is that it can reach a global population in a cost-effective manner [24]. Unable to find care for their symptoms and dismissed by health care providers [25,26], people with EDS often turn to support groups on social media to help them find physicians who diagnose and treat EDS, obtain tips about how to manage symptoms, and feel a sense of belonging [26]. The presence of online EDS support groups allows investigators to access groups of people with EDS. Without these support groups, people with EDS would have been difficult to reach due to the relatively low diagnosis rate. Social media lends itself well to recruiting for sensitive topics, such as medical conditions, because it provides a level of anonymity where individuals may be more comfortable disclosing information than if they had provided information in person [24,27].

Purpose

The purpose of this study is to discuss the challenges, strategies, and outcomes of recruiting people with EDS on social media. We will discuss the protocol used to recruit participants for an online survey examining dyspareunia, pain during sexual intercourse, in people with vaginas who have EDS. The methods for this study in particular were chosen because of the successful recruitment of 1178 participants in 4 weeks, which enabled the research team to identify that vulvodynia occurs in half of females with EDS [28]. For this paper, the term EDS will be used to describe people with hypermobile EDS, hypermobility spectrum disorders, as well as other types of EDS. Not all people who have vaginas identify as female and the use of the terms "female" or "women" to describe all people with vaginas is inaccurate. However, for lack of a better term at this time, we will use the term female to describe people in this study.

Methods

Recruitment

We recruited for an open online survey examining dyspareunia in females who had EDS from June 1 to July 7, 2019. The survey, participant screening, and consent were completed on

Qualtrics (Qualtrics). Details of the survey design and findings are reported elsewhere [28]. Inclusion criteria were (1) a self-reported diagnosis of EDS or a hypermobility spectrum disorder previously confirmed by a health care provider, (2) assigned to the female sex at birth and not had genital gender reassignment surgery, (3) 18 years of age or older, and (4) able to read English. The IP addresses were monitored to prevent people from participating more than once.

Ethical Considerations

The study was approved by the University of Illinois Chicago institutional review board (IRB; #2019-0219). Informed consent took place on Qualtrics and involved participants reading a consent form and then selecting whether they agreed and wanted to participate or not. The study data collected were anonymous, and no protected health information or personal identifiers were collected. No compensation was provided for participation.

Social Media Platform Choice

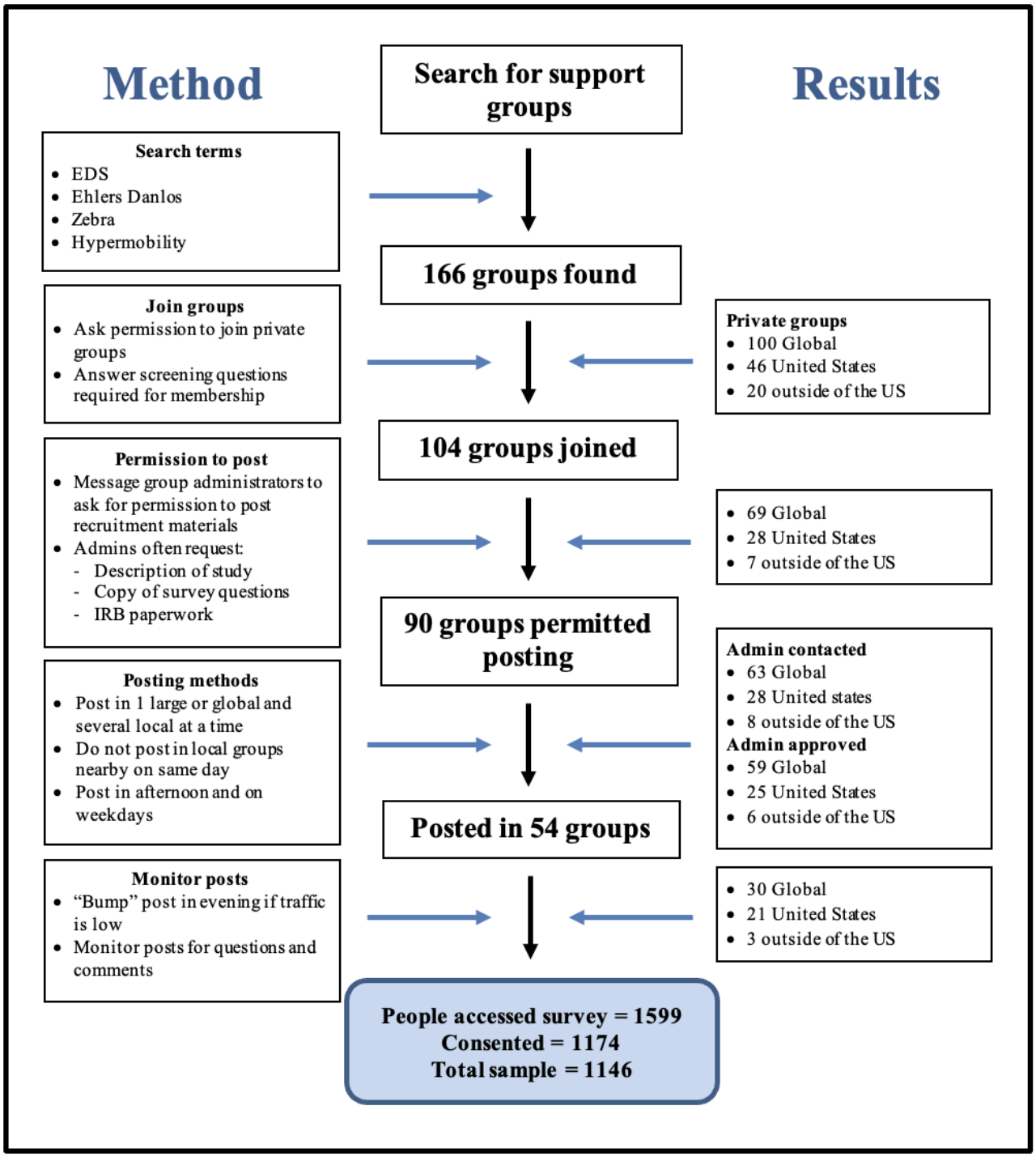
There are 3 basic types of social media platforms—text-based, photo or video-based, and private messaging. The social media quick guide (Table 1) outlines the basic functions and features of the most common social media platforms. Text-based platform posts are centered around text, but images and links can be attached. Image-based platform posts are centered around sharing photos or videos that can include text, but the photo or video is the main part of the post. Private messaging platforms are used to communicate privately between users and cannot be used to post information publicly. Text-based platforms such as Facebook (Meta Platforms) and Twitter (now X; Twitter Inc) facilitate discussion. Facebook works especially well for support groups because of the ability to make groups "private." In private groups, members need to be approved by group administrators to join, group content can only be seen by group members, group content is not searchable via search engines such as Google (Alphabet Inc), and members can be banned for breaking rules. Private groups allow members to discuss sensitive topics with some privacy. X uses hashtags to organize public and private posts. Private posts can only be seen by a user's "friends," people they have identified as knowing. X does not have a group function but instead, information can be searched via hashtags (#). For example, if a user searched for #puppies, all posts that included #puppies in the caption would appear. If a post is private, it would only appear in search results for people who have been identified as friends. Keeping posts private is helpful for discussing sensitive topics but eliminates discussion among members who are not "friends."

Facebook and X were selected for recruitment. Facebook was chosen because of the large number of existing EDS support groups. X was used to explore recruitment on social media via a platform that does not allow group formation. Facebook recruitment protocol and results (Figure 1) outline the recruitment protocol and results used for Facebook.

Table 1. Social media platform quick guide and features of common social media platforms.

Features	Facebook	Reddit	X	Instagram	TikTok	Snapchat	WhatsApp	WeChat
Primary purpose								
Text posts	✓	✓	✓					
Image posts				✓				
Video posts					✓			
Private messaging						✓	✓	✓
Available features								
Private posts	✓		✓	✓	✓			
Group formation	✓	✓						
Private group posts	✓							
Posts searchable by topic or hashtags	✓	✓	✓	✓	✓			

Figure 1. Facebook recruitment protocol and results. EDS: Ehlers-Danlos syndrome; IRB: institutional review board.



Searching for EDS Support Groups in Facebook

Search terms "Ehlers Danlos," "EDS," "Hypermobility," and "Zebra" were used to search for EDS support groups on Facebook. Zebra was used as a search term because it is the mascot for EDS and other rare diseases. Zebra comes from the phrase taught to medical students that if you hear hoof beats think horse and not zebra, as it is more likely to be a horse. When this concept is applied to patients it can cause doctors to miss rare and underdiagnosed diseases such as EDS [29].

Joining EDS Support Groups on Facebook

All support groups the primary investigator (PI) found were private. The PI requested permission to join the private groups. Private Facebook support groups frequently have users answer questions before granting or denying them membership. Groups often require people to have or know someone who has EDS to join. When requesting to join these groups, the PI disclosed that she was a researcher and would like to join the group for the purpose of recruiting for the study. Once the PI joined a group, the administrators of the group were messaged to ask for permission to post the recruitment materials. Messages included information about the PI and the project, and that the

project was approved by an IRB. Although groups did not mandate permission before allowing posting, this approach provided transparency about the PI's motives and helped to build trust between the group and the PI.

Posting Recruitment Material on Facebook

Strategies developed based on previous Facebook use were used to try to reach the most participants possible. Recruitment materials were posted in 3 to 4 groups per day, generally 1 large group of over 1000 members and 3 small groups each with less than 1000 members. Groups in the same geographical area, for example, a Michigan support group and a Great Lakes support group were not posted in on the same day due to the likelihood of membership overlap. Posting recruitment materials in all groups that consented at the same time would limit the visibility of the post to people who were on social media at that time and cause users who are in several groups to see the same post in their feed multiple times and potentially cause them to become annoyed. A feed is like a home page that displays posts from a user's friends and groups of which they are a part. Posts are displayed in chronological order with the newest and most active posts appearing at the top. Active posts are posts that have been commented on or liked. You may comment on your own post to help it move up in a feed; this is called bumping. Posting in different groups over several days will increase the time a post is at the top of a feed for users who are in more than 1 group.

Posting Recruitment Material on X

On X, hashtags related to EDS were searched. Recruitment materials were posted with #EDS by an account specifically made for the study. X posts are limited to 280 characters, requiring a shorter study description than Facebook posts. Prior to posting, the PI interacted with and followed other X accounts related to EDS and pain. X accounts were found by searching for accounts that included search terms in their profile or were included in post hashtags. The same search terms used to search for Facebook support groups were used here. This increased the account's presence and boosted the number of users who would see the posts.

Monitoring Recruitment Posts

All posts on Facebook and X were monitored and any questions or comments were addressed quickly. Responding quickly could keep the post at the top of a user's or group's feed and hopefully address the user's question before they left their social media account and lost interest in participating. Once recruitment goals were met, the PI stopped contacting groups for permission to post and stopped posting recruitment materials.

Statistical Analysis

Recruitment data were analyzed from 3 sources—Facebook search results, Facebook group tracking, and survey response data. Excel (Microsoft Corp) was used to track (1) the name of each group, (2) the size of each group, (3) if permission was given to join the group, (4) who was contacted to ask for permission to post in the group, (5) when the person was contacted, (6) if permission was given to post in the group, and (7) when recruitment materials were posted in the group. Stata Software for Statistics (version 15; StataCorp) was used to analyze descriptive statistics of the search results from the Facebook EDS support groups search. Survey response data were exported from Qualtrics to Excel to be cleaned and then to Stata 15 for analysis. For the original study examining dyspareunia, participants missing key data were not included. For this study, all participants who consented were included. Survey response data were used to analyze participant demographics and their traffic. The traffic of participants was analyzed by calculating the number of participants who accessed the survey during the 6-hour time blocks of 4 AM to 9:59 AM, 10 AM to 3:59 PM, 4 PM to 9:59 PM, and 10 PM to 3:39 AM EST.

Results

Facebook Recruitment

The Facebook recruitment protocol and results (Figure 1) provide the number of groups included in each step of the recruitment process. The EDS support groups search yielded 166 EDS Facebook support groups ranging in size from less than 100 to 33,000. Of the 166 groups found, 104 (63%) gave permission for the PI to join. Common questions asked by group administrators when the PI requested permission to join groups included the following: *Why do you want to join the group?*, *Do you or someone you know have EDS?*, *Do you live in XX city (if the group was focused on a specific geographic area)?*, and *Do you agree to follow the rules of the group?* Group rules often included not taking screenshots of group conversations, not disclosing the identity of members to nonmembers, and no soliciting.

Of the 104 groups that gave permission, 90 (86%) gave permission to post the recruitment materials. Three of the groups that did not permit the PI to join offered to post recruitment materials for the PI. The PI was denied access to post in several groups for cisgendered language in the survey and recruitment materials. These groups preferred the use of specific organs instead of the terms "woman" and "female." Of the 90 groups that gave permission to post, 54 (60%) were posted in before recruitment goals were met. Once the recruitment goals were met posting was stopped by the PI.

When analyzing the data, EDS support groups were divided into 3 categories—global (or no specific geographic location specified); United States for users who resided in the United States (eg, Chicago EDS support group); and outside of the United States for users who resided outside of the United States (eg, Sussex, England EDS support group). The categories of United States and outside of the United States were used because of the high prevalence of US groups and the sparseness of groups from other specific countries. Global groups were separated from the US groups and groups outside of the United States because global groups have different focuses than region-specific groups. Groups specific to a geographic location can be used to help members find local health care providers and members are able to meet in person. Global groups are often focused on broad topics such as comorbid conditions associated with EDS. Global groups were larger in size and more prevalent than the other 2 categories, with 100 global groups found compared to 46 US groups and 20 outside of the US groups. Of the 54 groups in which recruitment materials were posted, 30

(56%) were global groups, 21 (39%) were US groups, and 3 (18%) were outside of the US groups.

User Statistics

There was a total of 110,665 users in the 54 groups posted in; however, this does not take into consideration that users are often members of more than 1 group. The smallest group posted in had 47 members and the largest had 33,170 members. We were unable to calculate a response rate because we were unable to determine how many users saw each post and then accessed the survey. Of the 110,665 people who potentially saw the post, 1599 accessed the survey and 1178 females were eligible, consented, and included in analyses. Of the 1178 consented participants, 1174 were recruited from Facebook and 4 from X. The average age of participants was 38.6 (SD 11.7) years, similar to the average age of participants in big data studies of EDS [4,12,13,30]. Participants were predominantly White (n=1063, 93%), non-Hispanic (n=1046, 92%), and had the most common form of EDS, hypermobile EDS (n=1290,79%) [2]. Participants were recruited from 29 countries with 900 (76%) from the United States and 124 (11%) from Great Britain. The map of the participant's country of residence (Figure 2) shows all the countries from which the participants were recruited. Participant characteristics can be found in the characteristics of the sample (Table 2) [28].

Figure 2. Heat map of countries in which participants reside.

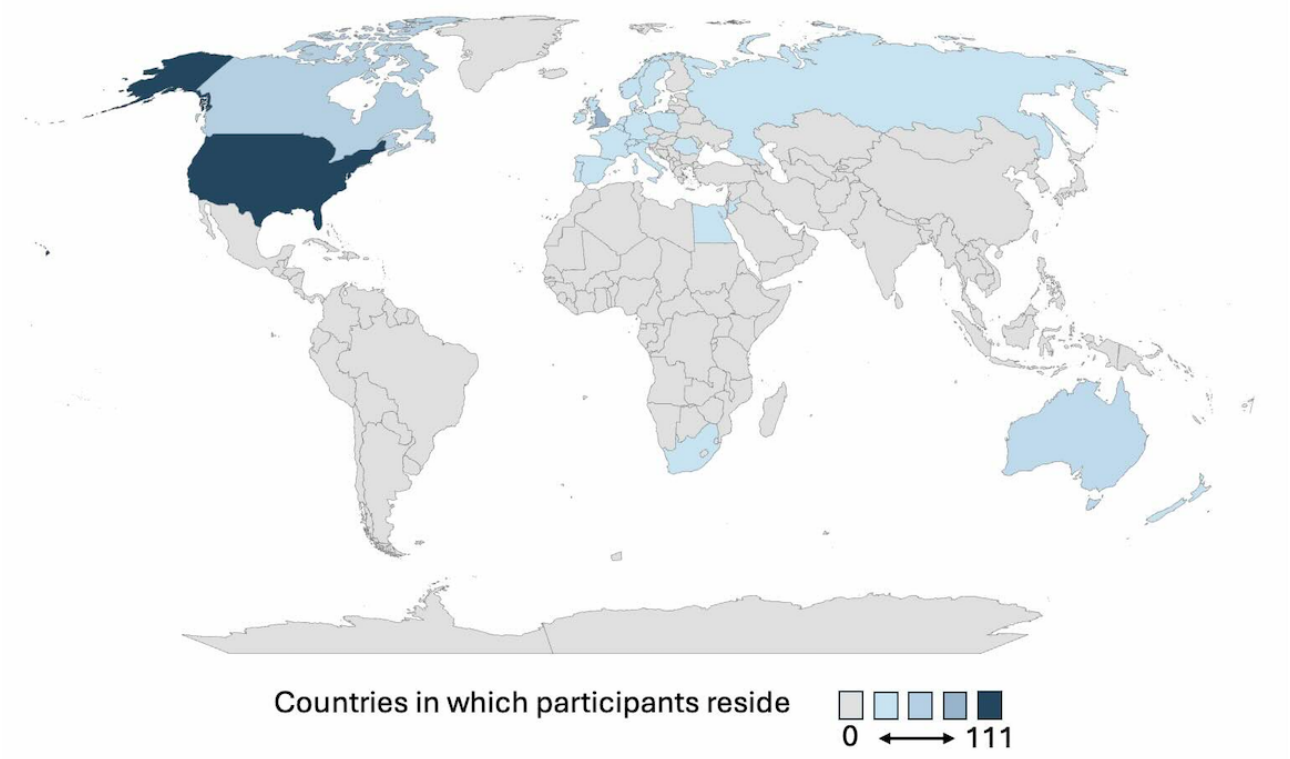


Table 2. Characteristics of the sample (number of females with Ehlers-Danlos syndromes; N=1178) [17].

Demographics	Values
Age (years; n=1141)	
Mean (SD)	38.6 (11.7)
Range	18-76
Sex, n (%)	
Female	1144 (99.8)
Transgender	2 (0.2)
Race[a], n (%)	
White	1063 (92.8)
Black or African American	12 (1.0)
American Indian or Alaskan Native	17 (1.5)
Asian	11 (1.0)
Native Hawaiian or Pacific Islander	3 (0.3)
Other	47 (4.1)
Ethnicity (n=1138), n (%)	
Hispanic or Latino	41 (3.6)
Not Hispanic or Latino	1046 (91.9)
Unknown or not reported	51 (4.5)
Country of residence, n (%)	
Unites States	900 (78.5)
Great Britain	124 (10.8)
Canada	46 (4.0)
Australia	23 (2.0)
Other	66 (5.7)

[a]Participants selected all races they identified with.

Survey Traffic

To examine when participants from different parts of the world accessed the survey and determine optimal posting times for recruiting participants globally, we analyzed what time participants accessed the survey. What time participant accessed the survey was analyzed by time of day and by day of week for the whole sample (N=1178), those residing in North America (n=971), and those residing outside of North America (n=206). The PI posted recruitment materials at different times during the day and night in hopes of recruiting people in different time zones. The North America and non–North America groupings were used for analysis instead of the country of residence due to data sparseness and overlapping time zones of the countries. The busiest time block for recruitment of participants as a whole (n=465, 39%) and among participants in North America (n=411, 42%) was 4 PM to 9:59 PM. Recruitment was busiest from 10 AM to 3:59 PM for participants outside of North America (n=57, 17%). Recruitment of participants outside of North America was more evenly distributed across all time blocks with about 50 participants per time block. The 4 AM to 9:59 AM time block had the least amount of traffic for the whole group (n=130, 11%), participants from North America (n=87, 9%), and participants from outside of North America (n=43, 4%). Monday was the busiest recruitment day for all groups with 301 (25%) participants from the whole sample, 244 (25%) from North America, and 57 (27%) from outside of North America. Saturday through Tuesday were busier than Wednesday through Friday. The day of the week that participants from North America were recruited differed significantly compared to participants from outside of North America (χ^2_6=34.1; P≤.001).

Discussion

Principal Findings

We were able to recruit a large sample in a short amount of time, highlighting the usefulness of using social media, specifically Facebook EDS support groups and X, for recruitment. Our method of recruiting via Facebook can be used to target populations that have access to the internet and use social media. Support groups on social media provide curated groups of people that would otherwise be difficult to find, facilitating recruitment of large groups of participants for rare and underdiagnosed conditions. However, like other EDS studies that recruited via social media, we were not successful at recruiting a diverse sample with our participants being

predominantly from the United States and White. Our results do provide greater detail about the countries participants resided in when they accessed the survey, and their races and ethnicities. Many of the large studies conducted in Northern Europe do not provide demographic details such as race and ethnicity. Providing demographic information is key to assessing the diversity of a sample and evaluate generalizability. Demographic information including race and ethnicity should be included in every study's results. Future directions for research to increase diversity in a sample may include investigators connecting with more support groups from outside of the United States and Europe, use of social media platforms that are popular in other countries, and translating study materials into different languages. More fundamental obstacles potentially include the need for more health care providers that diagnose and treat EDS in countries that are predominantly comprised of people of color, and the need to conduct research that targets these populations.

Challenges That Were Successfully Addressed

Some social media platforms are better than others for recruiting participants. Facebook worked well for recruiting because existing EDS support groups had thousands of members. Posting in these groups allowed the PI to reach many people with EDS with each post. When posting in groups on Facebook, it is easy to see how active a group is based on how frequently people are posting in the group and how many comments and likes the posts receive. Posting in groups on Facebook was chosen over platforms where hashtags (#) are used because these platforms do not have existing groups of people with EDS. On platforms where hashtags are used, the visibility of a post for users is influenced by the number of followers users have. Therefore, for a researcher to reach a lot of people with a post they must create a profile, as well as cultivate a following which can take a fair amount of time. It is also difficult to determine which hashtags are most popular and how people are interacting with hashtags. A better way to share a study on platforms that use hashtags, such as TikTok (ByteDance), is to have existing platform users, with a large group of followers, share the study on their social media page, such as EDS nonprofits.

Our recruitment protocol helped to efficiently keep track of where we were in the recruitment process and within each support group. Documenting the name of each group administrator and when they were contacted allowed the PI to quickly determine what chat conversation was associated with each support group because chats are labeled with users' names and not their affiliated support group. It was also difficult to decide what and when support groups should be posted in. Having the size, where each group was located, and if the group had a specific focus helped determine what groups to post in on a given day. Asking for permission to post recruitment materials in groups was the most labor-intensive aspect of recruitment. On Facebook, messages from users who are not your "friend" are sent to a message request folder that is not easily seen. Typically, when using Facebook Messenger, conversations with "friends" are kept in 1 location and users receive a notification when they receive a new message. This does not happen when a user receives a message from someone who is not a friend. When a message is seen by a recipient in Facebook Messenger, their profile picture appears next to the message. To address the challenge of messages going unseen by group administrators, the PI contacted a different group administrator. Administrators of smaller local groups tended to respond to messages more often and more quickly.

Challenges That Still Need to Be Addressed

Recruiting Participants From Diverse Countries of Residence

Efforts to recruit participants quickly may have led to decisions that decreased the diversity of participants. A total of 21 (45%) of the EDS support groups posted in were US support groups. Anecdotally it seemed easier to recruit from small local EDS support groups because they were more active than global groups, determined by users' engagement such as commenting and liking posts. Support groups that were focused on areas outside of the United States were stricter about allowing people from outside their area to join and post, with 6 (30%) of groups outside of the United States permitting posting compared to 59 (59%) of global groups and 25 (54%) of US groups. Establishing relationships with EDS communities in other countries, to gain permission for research recruitment, may lengthen recruitment. Whether or not establishing these relationships would increase diversity in a sample needs to be assessed. A limitation is that the PI only posted in 3 (50%) of the groups outside of the United States that gave permission before stopping recruiting due to meeting recruitment goals. The decision to post in local US groups over groups based in other countries was based in part on the perception that groups outside of the United States received less traffic. Instead of using groups located outside of the United States, due to perceived low activity, larger more active global groups were targeted. However, it is important to consider that even though a group is global, it may have a large percentage of users from the United States. In the future, global groups and groups outside of the United States should both be a priority for recruiting. It may be beneficial to work with local collaborators, researchers, or advocates who are familiar with the local support groups in their respective countries. Furthermore, social media preferences may differ between countries.

Racial and Ethnic Diversity Within the Sample

Definitions of race and ethnicity vary across the world. This study used the race and ethnicity categories from the US National Institutes of Health with an "other" option added. Identifying racial categories that are used globally and less focused on the United States may make it easier to compare demographics from studies conducted in other countries and may be more inclusive. Our sample was predominately White (n=1063, 93%) The racial and ethnic breakdown of EDS is unknown [2]. In a study looking at EDS diagnoses in hospitalized patients in the United States, 1736 of 2007 (86%) participants were White [30]. However, in the United States, race and ethnicity affect access to care, including receiving an EDS diagnosis and having an inpatient hospital admission, which may cause an overestimation of the percentage of people with EDS who are White. Similarly, there is decreased access to the internet in rural and low-income areas in the United States and abroad. This decreased access disproportionately affects minorities within the United States and people of color abroad,

limiting their participation [31,32]. Big data studies using national health records in predominantly White northern European countries did not report race or ethnicity demographics [4,12,13]. Our high percentage of White participants was likely driven by recruitment from the United States, where structural inequities affect access to care, as well as northern European countries that have predominantly White populations. The lack of access to care and doctors who diagnose EDS outside of North America and Europe [19] likely limits the pool of people from these areas who meet the inclusion criteria of an EDS diagnosis, and therefore, may have impacted the diversity of our study. Similarly, due to the changing terminology for hypermobile EDS and hypermobility spectrum disorders, it is important to include participants with both diagnoses, as a participant's diagnosis may vary based on when or where they were diagnosed, as well as what type of health care provider diagnosed them. There needs to be more health care providers that diagnose and treat EDS in countries that are predominately made up of people of color along with research focused on these specific populations. Research in these groups should be facilitated by members of the EDS community from these groups.

Including LGBTQIA+ Communities

Specific EDS support groups for lesbian, gay, bisexual, transgender, queer or questioning, intersex, asexual, people, as well as those who not listed but identify as part of this community, were targeted for recruitment; however, we were not permitted to post in a few groups because of cisgendered language in our recruitment materials and survey. Facebook EDS support groups preferred the use of gender-neutral language based on the specific organs needed to participate rather than the terms "woman" and "female." To ensure the study is in line with the EDS communities' values and inclusive of nonbinary individuals, researchers should include community representatives in the development of their study.

Limitations

As with other EDS research, our sample was predominately White and from the United States. We were limited by the lack of support groups in countries that were not predominately White. In future research, non-US support groups should receive more focus than US-specific groups. The use of social media platforms likely varies between countries. A wider variety of social media platforms should be explored for use.

The use of social media platforms likely varies between countries. A wider variety of social media platforms should be explored in future research. Additionally, participants were recruited for this survey in 2019, since then there have been many changes in social media including Twitter changing to X and the rise of TikTok. However, the lack of diversity in EDS research persists even as recruitment on social media increases. Identifying recruiting obstacles can help develop methods to overcome them for more diverse and inclusive research.

The survey was conducted without verification of participants' EDS diagnosis and, therefore, may have included people who have not been diagnosed with EDS. For more rigorous and valid results, a participant's EDS diagnosis should be verified; however, this may be difficult via social media. Recruiting via social media may work best for studies that are exploring new areas of research and identifying new phenomena that can then be followed up with more rigorous methods.

During recruitment, an IRB amendment was needed. Until the amendment was approved, recruitment was paused. When recruitment was paused, prospective participants were still able to see recruitment posts, and this caused some confusion. To mitigate confusion, we edited the posts to explain recruitment was temporarily paused. We posted again when recruitment resumed. Commenting on the post that recruitment was live again should have brought the post back up to the top of feeds.

Conclusions

Social media is effective and efficient at recruiting people with EDS for research studies. Text-based platforms that have established EDS support groups such as Facebook are well-suited for recruiting. Specific attention should be paid to recruiting people outside of the United States. Considerations for research on recruitment of participants with EDS include (1) working with local researchers and communities where you wish to recruit from, (2) posting during peak social media traffic time in target areas, and (3) increasing diagnoses and care of patients, which will increase awareness of EDS outside of the United States and Europe. Working with researchers, clinicians, and advocates in areas with support groups outside of the United States may help researchers gain permission to post in groups in these regions and provide guidance on where best to recruit people in their area, as well as ensure survey materials are in line with the EDS community's values. Posting during peak traffic for people outside of North America may help recruit a more global sample. There is still little research on people with EDS outside of the United States and Europe. To engage participants outside of these regions, research materials may need to be translated into other languages. A repository of tools used to evaluate written materials related to EDS in many languages would make it easier for researchers to recruit participants who speak different languages, as well as make results easier to compare across studies. A larger issue may be a lack of EDS providers and researchers in countries outside of the United States and Europe. Research needs to be conducted examining the prevalence of EDS in these areas along with increasing awareness of the condition. Recruiting people with EDS in countries where there are few if any health care providers who diagnose and treat EDS will remain a challenge until awareness of EDS grows and care improves.

Acknowledgments

This research was made possible by Grant (R01HD091210 and F31NR019529) from the National Institutes of Health (NIH), Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and the National Institute for

Nursing Research (NINR). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of NIH, NICHD, or NINR. The final peer-reviewed study is subject to the NIH Public Access Policy. This research was cosponsored by the Rockefeller University Heilbrunn Family Center for Research Nursing through the generosity of the Heilbrunn Family and the National Center for Advancing Translational Sciences, NIH, through Rockefeller University, grant (UL1TR001866); an Ehlers-Danlos Society Microgrant; and Sigma Theta Tau Alpha Lambda Chapter.

Data Availability

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

Conflicts of Interest

None declared.

References

1. Malfait F, Francomano C, Byers P, Belmont J, Berglund B, Black J, et al. The 2017 international classification of the Ehlers-Danlos syndromes. Am J Med Genet C Semin Med Genet 2017;175(1):8-26 [FREE Full text] [doi: 10.1002/ajmg.c.31552] [Medline: 28306229]
2. Tinkle B, Castori M, Berglund B, Cohen H, Grahame R, Kazkaz H, et al. Hypermobile Ehlers-Danlos syndrome (a.k.a. Ehlers-Danlos syndrome type III and Ehlers-Danlos syndrome hypermobility type): clinical description and natural history. Am J Med Genet C Semin Med Genet 2017;175(1):48-69 [FREE Full text] [doi: 10.1002/ajmg.c.31538] [Medline: 28145611]
3. Pyeritz RE. Ehlers-Danlos syndrome. N Engl J Med 2000;342(10):730-732. [doi: 10.1056/NEJM200003093421009] [Medline: 10706904]
4. Demmler JC, Atkinson MD, Reinhold EJ, Choy E, Lyons RA, Brophy ST. Diagnosed prevalence of Ehlers-Danlos syndrome and hypermobility spectrum disorder in Wales, UK: a national electronic cohort study and case-control comparison. BMJ Open 2019;9(11):e031365 [FREE Full text] [doi: 10.1136/bmjopen-2019-031365] [Medline: 31685485]
5. Hakim AJ, Tinkle BT, Francomano CA. Ehlers-Danlos syndromes, hypermobility spectrum disorders, and associated co-morbidities: reports from EDS ECHO. Am J Med Genet C Semin Med Genet 2021;187(4):413-415. [doi: 10.1002/ajmg.c.31954] [Medline: 34793630]
6. Castori M, Camerota F, Celletti C, Grammatico P, Padua L. Ehlers-Danlos syndrome hypermobility type and the excess of affected females: possible mechanisms and perspectives. Am J Med Genet A 2010;152A(9):2406-2408. [doi: 10.1002/ajmg.a.33585] [Medline: 20684008]
7. Rombaut L, Malfait F, De Paepe A, Rimbaut S, Verbruggen G, De Wandele I, et al. Impairment and impact of pain in female patients with Ehlers-Danlos syndrome: a comparative study with fibromyalgia and rheumatoid arthritis. Arthritis Rheum 2011;63(7):1979-1987 [FREE Full text] [doi: 10.1002/art.30337] [Medline: 21391202]
8. Arthur K, Caldwell K, Forehand S, Davis K. Pain control methods in use and perceived effectiveness by patients with Ehlers-Danlos syndrome: a descriptive study. Disabil Rehabil 2016;38(11):1063-1074. [doi: 10.3109/09638288.2015.1092175] [Medline: 26497567]
9. Miller AJ, Stiles LE, Sheehan T, Bascom R, Levy HP, Francomano CA, et al. Prevalence of hypermobile Ehlers-Danlos syndrome in postural orthostatic tachycardia syndrome. Auton Neurosci 2020;224:102637 [FREE Full text] [doi: 10.1016/j.autneu.2020.102637] [Medline: 31954224]
10. Sacheti A, Szemere J, Bernstein B, Tafas T, Schechter N, Tsipouras P. Chronic pain is a manifestation of the Ehlers-Danlos syndrome. J Pain Symptom Manage 1997;14(2):88-93 [FREE Full text] [doi: 10.1016/s0885-3924(97)00007-9] [Medline: 9262038]
11. Voermans NC, Knoop H, Bleijenberg G, van Engelen BG. Pain in Ehlers-Danlos syndrome is common, severe, and associated with functional impairment. J Pain Symptom Manage 2010;40(3):370-378 [FREE Full text] [doi: 10.1016/j.jpainsymman.2009.12.026] [Medline: 20579833]
12. Søborg MLK, Leganger J, Mortensen LQ, Rosenberg J, Burcharth J. Establishment and baseline characteristics of a nationwide Danish cohort of patients with Ehlers-Danlos syndrome. Rheumatology (Oxford) 2017;56(5):763-767 [FREE Full text] [doi: 10.1093/rheumatology/kew478] [Medline: 28077691]
13. Cederlöf M, Larsson H, Lichtenstein P, Almqvist C, Serlachius E, Ludvigsson JF. Nationwide population-based cohort study of psychiatric disorders in individuals with Ehlers-Danlos syndrome or hypermobility syndrome and their siblings. BMC Psychiatry 2016;16:207 [FREE Full text] [doi: 10.1186/s12888-016-0922-6] [Medline: 27377649]
14. Kalisch L, Hamonet C, Bourdon C, Montalescot L, de Cazotte C, Baeza-Velasco C. Predictors of pain and mobility disability in the hypermobile Ehlers-Danlos syndrome. Disabil Rehabil 2020;42(25):3679-3686. [doi: 10.1080/09638288.2019.1608595] [Medline: 31060411]
15. Colman M, Syx D, De Wandele I, Dhooge T, Symoens S, Malfait F. Clinical and molecular characteristics of 168 probands and 65 relatives with a clinical presentation of classical Ehlers-Danlos syndrome. Hum Mutat 2021;42(10):1294-1306. [doi: 10.1002/humu.24258] [Medline: 34265140]

16. Igharo D, Thiel JC, Rolke R, Akkaya M, Weis J, Katona I, et al. Skin biopsy reveals generalized small fibre neuropathy in hypermobile Ehlers-Danlos syndromes. Eur J Neurol 2023;30(3):719-728 [FREE Full text] [doi: 10.1111/ene.15649] [Medline: 36437696]
17. Orenius T, Kautiainen H, Louhi M, Montin L, Bulbena A, Lindgren K. Health-related quality of life and psychological distress in patients with hypermobility type Ehlers-Danlos syndrome. SAGE Open 2022;12(2):1-9 [FREE Full text] [doi: 10.1177/21582440221091237]
18. Bech K, Fogh FM, Lauridsen EF, Sonnesen L. Temporomandibular disorders, bite force and osseous changes of the temporomandibular joints in patients with hypermobile Ehlers-Danlos syndrome compared to a healthy control group. J Oral Rehabil 2022;49(9):872-883 [FREE Full text] [doi: 10.1111/joor.13348] [Medline: 35694904]
19. Healthcare professionals directory. The Ehlers-Danlos Society. 2023. URL: https://tinyurl.com/nhkmkbzf [accessed 2023-02-17]
20. Ehlers-Danlos Japan. The Ehlers-Danlos Society. 2024. URL: https://www.ehlers-danlos.com/affiliate-and-support-group/ehlers-danlos-japan/ [accessed 2024-02-14]
21. Kciuk O, Li Q, Huszti E, McDermott CD. Pelvic floor symptoms in cisgender women with Ehlers-Danlos syndrome: an international survey study. Int Urogynecol J 2023;34(2):473-483. [doi: 10.1007/s00192-022-05273-8] [Medline: 35751670]
22. Pezaro S, Pearce G, Reinhold E. Understanding hypermobile Ehlers-Danlos syndrome and hypermobility spectrum disorders in the context of childbearing: an international qualitative study. Midwifery 2020;88:102749. [doi: 10.1016/j.midw.2020.102749] [Medline: 32535291]
23. Louie A, Meyerle C, Francomano C, Srikumaran D, Merali F, Doyle JJ, et al. Survey of Ehlers-Danlos patients' ophthalmic surgery experiences. Mol Genet Genomic Med 2020;8(4):e1155 [FREE Full text] [doi: 10.1002/mgg3.1155] [Medline: 31989797]
24. Benoit-Piau J, Dumoulin C, Carroll MS, Mayrand MH, Bergeron S, Khalifé S, et al. Efficiency and cost: e-recruitment is a promising method in gynecological trials. J Sex Med 2020;17(7):1304-1311. [doi: 10.1016/j.jsxm.2020.04.005] [Medline: 32434709]
25. Ashtari S, Taylor AD. The internet knows more than my physician: qualitative interview study of people with rare diseases and how they use online support groups. J Med Internet Res 2022;24(8):e39172 [FREE Full text] [doi: 10.2196/39172] [Medline: 36006679]
26. Halverson CME, Clayton EW, Sierra AG, Francomano C. Patients with Ehlers-Danlos syndrome on the diagnostic odyssey: rethinking complexity and difficulty as a hero's journey. Am J Med Genet C Semin Med Genet 2021;187(4):416-424. [doi: 10.1002/ajmg.c.31935] [Medline: 34524722]
27. Gelinas L, Pierce R, Winkler S, Cohen IG, Lynch HF, Bierer BE. Using social media as a research recruitment tool: ethical issues and recommendations. Am J Bioeth 2017;17(3):3-14 [FREE Full text] [doi: 10.1080/15265161.2016.1276644] [Medline: 28207365]
28. Glayzer JE, McFarlin BL, Castori M, Suarez ML, Meinel MC, Kobak WH, et al. High rate of dyspareunia and probable vulvodynia in Ehlers-Danlos syndromes and hypermobility spectrum disorders: an online survey. Am J Med Genet C Semin Med Genet 2021;187(4):599-608 [FREE Full text] [doi: 10.1002/ajmg.c.31939] [Medline: 34747110]
29. Gensemer C, Burks R, Kautz S, Judge DP, Lavallee M, Norris RA. Hypermobile Ehlers-Danlos syndromes: complex phenotypes, challenging diagnoses, and poorly understood causes. Dev Dyn 2021;250(3):318-344 [FREE Full text] [doi: 10.1002/dvdy.220] [Medline: 32629534]
30. Brooks RS, Grady J, Lowder TW, Blitshteyn S. Prevalence of gastrointestinal, cardiovascular, autonomic and allergic manifestations in hospitalized patients with Ehlers-Danlos syndrome: a case-control study. Rheumatology (Oxford) 2021;60(9):4272-4280 [FREE Full text] [doi: 10.1093/rheumatology/keaa926] [Medline: 33410480]
31. Chen R. A demand-side view of mobile internet adoption in the Global South. World Bank Corp. 2021. URL: https://elibrary.worldbank.org/doi/pdf/10.1596/1813-9450-9590 [accessed 2024-03-26]
32. Reddick CG, Enriquez R, Harris RJ, Sharma B. Determinants of broadband access and affordability: an analysis of a community survey on the digital divide. Cities 2020;106:102904 [FREE Full text] [doi: 10.1016/j.cities.2020.102904] [Medline: 32921864]

Abbreviations

EDS: Ehlers-Danlos syndrome
IRB: institutional review board
PI: primary investigator

Edited by A Mavragani; submitted 13.10.23; peer-reviewed by C Halverson, K Robbins; comments to author 05.02.24; revised version received 22.02.24; accepted 13.03.24; published 02.05.24.

Please cite as:
Glayzer JE, Bray BC, Kobak WH, Steffen AD, Schlaeger JM
Lack of Diversity in Research on Females with Ehlers-Danlos Syndromes: Recruitment Protocol for a Quantitative Online Survey
JMIR Res Protoc 2024;13:e53646
URL: https://www.researchprotocols.org/2024/1/e53646
doi:10.2196/53646
PMID:38696252

Corrigenda and Addenda

Correction: Feasibility of a Pediatric Acute Video Consultation Process Among Health Care Professionals in Primary Care in a Rural Setting: Protocol for a Prospective Validation Study

Marta Castillo-Rodenas[1], MD, MSc; Josep Vidal-Alaball[2,3,4], MD, MPH, PhD; Núria Solanas-Bacardit[1], RNC; Clotilde Farràs-Company[5], MD; Aïna Fuster-Casanovas[6], MSc, RPh; Queralt Miró Catalina[3,6], MSc; Francesc López Seguí[7], PhD

[1]Centre d'Atenció Primària Cardona, Gerència Territorial de la Catalunya Central, Institut Català de la Salut, Cardona, Spain

[2]Cap de la Unitat de Suport a la Recerca de la Catalunya Central, Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina, Sant Fruitós de Bages, Spain

[3]Health Promotion in Rural Areas Research Group, Gerència Territorial de la Catalunya Central, Institut Català de la Salut, Sant Fruitós de Bages, Spain

[4]Faculty of Medicine, University of Vic–Central University of Catalonia, Vic, Spain

[5]Direcció del Centre d'Atenció Primària Cardona, Gerència Territorial de la Catalunya Central, Institut Català de la Salut, Cardona, Spain

[6]Unitat de Suport a la Recerca de la Catalunya Central, Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina, Sant Fruitós de Bages, Spain

[7]Chair in ICT and Health, Centre for Health and Social Care Research, University of Vic–Central University of Catalonia, Vic, Spain

Corresponding Author:
Josep Vidal-Alaball, MD, MPH, PhD
Cap de la Unitat de Suport a la Recerca de la Catalunya Central
Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina
Carrer Pica d'Estats, 13-15
Sant Fruitós de Bages, 08272
Spain
Phone: 34 936930040
Email: jvidal.cc.ics@gencat.cat

Related Article:

Correction of: https://www.researchprotocols.org/2024/1/e52946

(JMIR Res Protoc 2024;13:e57937) doi:10.2196/57937

In "Feasibility of a Pediatric Acute Video Consultation Process Among Health Care Professionals in Primary Care in a Rural Setting: Protocol for a Prospective Validation Study" (JMIR Res Protoc 2024;13:e52946) the authors made one correction.

In the original manuscript, the affiliation of author Francesc López Seguí was listed as follows:

> *Centre for Health and Social Care Research, University of Vic–Central University of Catalonia, Vic, Spain*

In the corrected version, it has been changed to read as:

> *Chair in ICT and Health, Centre for Health and Social Care Research, University of Vic–Central University of Catalonia, Vic, Spain*

The correction will appear in the online version of the paper on the JMIR Publications website on March 5, 2024, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

Submitted 29.02.24; this is a non–peer-reviewed article;accepted 29.02.24; published 05.03.24.

Please cite as:
Castillo-Rodenas M, Vidal-Alaball J, Solanas-Bacardit N, Farràs-Company C, Fuster-Casanovas A, Miró Catalina Q, López Seguí F
Correction: Feasibility of a Pediatric Acute Video Consultation Process Among Health Care Professionals in Primary Care in a Rural Setting: Protocol for a Prospective Validation Study
JMIR Res Protoc 2024;13:e57937
URL: https://www.researchprotocols.org/2024/1/e57937
doi:10.2196/57937
PMID:38442371

Corrigenda and Addenda

Correction: Investigating Father or Partner Involvement in Family Integrated Care in Neonatal Units: Protocol for a Prospective, Multicenter, Multiphase Study

Rupa Rubinstein[1,2], MBBCHIR, MSci; Katie Gallagher[3], PhD; John Ho[4], MBBS; Julian Bose[5], BSc; Minesh Khashu[6], MBBS, MD, FRCPCH; Narendra Aladangady[1,2], PhD

[1]Neonatal Unit, Homerton Healthcare NHS Foundation Trust, London, United Kingdom

[2]Blizard Institute, Queen Mary University London, London, United Kingdom

[3]Institute of Women's Health, University College London, London, United Kingdom

[4]Neonatal Unit, Whipps Cross University Hospital, Barts Health, London, United Kingdom

[5]Inspire Cornwall Community Interest Company's DadPad, The Health and Wellbring Innovation Centre, Truro, United Kingdom

[6]Neonatal Unit, University Hospitals Dorset NHS Foundation Trust, Dorset, United Kingdom

Corresponding Author:
Narendra Aladangady, PhD
Neonatal Unit
Homerton Healthcare NHS Foundation Trust
Homerton Row
London, E9 6SR
United Kingdom
Phone: 44 2085105555
Email: n.aladangady@nhs.net

Related Article:

Correction of: https://www.researchprotocols.org/2024/1/e53160

(JMIR Res Protoc 2024;13:e58848) doi:10.2196/58848

In "Investigating Father or Partner Involvement in Family Integrated Care in Neonatal Units With TARGET (Fathers and Partners in Family Integrated Care): Protocol for a Prospective, Multicenter, Multiphase Study" (JMIR Res Protoc 2024;13:e53160), an incorrect title was published.

The title

> *Investigating Father or Partner Involvement in Family Integrated Care in Neonatal Units With TARGET (Fathers and Partners in Family Integrated Care): Protocol for a Prospective, Multicenter, Multiphase Study*

has been revised to:

> *Investigating Father or Partner Involvement in Family Integrated Care in Neonatal Units: Protocol for a Prospective, Multicenter, Multiphase Study*

The reason for this change is that "TARGET" is not defined nor used anywhere in the paper.

The correction will appear in the online version of the paper on the JMIR Publications website on April 3, 2024, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

Submitted 26.03.24; this is a non–peer-reviewed article;accepted 26.03.24; published 03.04.24.

Please cite as:
Rubinstein R, Gallagher K, Ho J, Bose J, Khashu M, Aladangady N
Correction: Investigating Father or Partner Involvement in Family Integrated Care in Neonatal Units: Protocol for a Prospective, Multicenter, Multiphase Study
JMIR Res Protoc 2024;13:e58848
URL: https://www.researchprotocols.org/2024/1/e58848
doi:10.2196/58848
PMID:38569174

Protocol

Safety, Tolerability, and Dose-Limiting Toxicity of Lacosamide in Patients With Painful Chronic Pancreatitis: Protocol for a Phase 1 Clinical Trial to Determine Safety and Identify Side Effects

Evan L Fogel[1], MSc, MD[‡]; Jeffrey J Easler[1], MD; Ying Yuan[2], PhD; Dhiraj Yadav[3], MPH, MD; Darwin L Conwell[3], MSc, MD; Santhi Swaroop Vege[4], MD; Samuel Y Han[5], MS, MD; Walter Park[6], MD; Vanessa Patrick[1], RN; Fletcher A White[7], MSc, PhD

[1]Department of Medicine, School of Medicine, Indiana University, Indianapolis, IN, United States
[2]Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX, United States
[3]Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA, United States
[4]Department of Internal Medicine, Mayo Clinic, Rochester, MN, United States
[5]Department of Medicine, The Ohio State University Wexner Medical Center, Columbus, OH, United States
[6]Department of Medicine, Stanford University Medical Center, Stanford, CA, United States
[7]Department of Anesthesia, School of Medicine, Indiana University, Indianapolis, IN, United States
[‡]The Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC)

Corresponding Author:
Evan L Fogel, MSc, MD
Department of Medicine
School of Medicine
Indiana University
Suite 1602
550 N. University Blvd
Indianapolis, IN, 46202
United States
Phone: 1 317 274 8157
Email: efogel@iu.edu

Abstract

Background: Chronic abdominal pain is the hallmark symptom of chronic pancreatitis (CP), with 50% to 80% of patients seeking medical attention for pain control. Although several management options are available, outcomes are often disappointing, and opioids remain a mainstay of therapy. Opioid-induced hyperalgesia is a phenomenon resulting in dose escalation, which may occur partly because of the effects of opioids on voltage-gated sodium channels associated with pain. Preclinical observations demonstrate that the combination of an opioid and the antiseizure drug lacosamide diminishes opioid-induced hyperalgesia and improves pain control.

Objective: In this phase 1 trial, we aim to determine the safety, tolerability, and dose-limiting toxicity of adding lacosamide to opioids for the treatment of painful CP and assess the feasibility of performance of a pilot study of adding lacosamide to opioid therapy in patients with CP. As an exploratory aim, we will assess the efficacy of adding lacosamide to opioid therapy in patients with painful CP.

Methods: Using the Bayesian optimal interval design, we will conduct a dose-escalation trial of adding lacosamide to opioid therapy in patients with painful CP enrolled in cohorts of size 3. The initial dose will be 50 mg taken orally twice a day, followed by incremental increases to a maximum dose of 400 mg/day, with lacosamide administered for 7 days at each dose level. Adverse events will be documented according to Common Terminology Criteria for Adverse Events (version 5.0).

Results: As of December 2023, we have currently enrolled 6 participants. The minimum number of participants to be enrolled is 12 with a maximum of 24. We expect to publish the results by March 2025.

Conclusions: This trial will test the feasibility of the study design and provide reassurance regarding the tolerability and safety of opioids in treating painful CP. It is anticipated that lacosamide will prove to be safe and well tolerated, supporting a subsequent phase 2 trial assessing the efficacy of lacosamide+opioid therapy in patients with painful CP, and that lacosamide combined with opiates will lower the opioid dose necessary for pain relief and improve the safety profile of opioid use in treating painful CP.

Trial Registration: Clinicaltrials.gov NCT05603702; https://clinicaltrials.gov/study/NCT05603702
International Registered Report Identifier (IRRID): PRR1-10.2196/50513

(JMIR Res Protoc 2024;13:e50513) doi:10.2196/50513

KEYWORDS

abdominal pain; opioid-induced hyperalgesia; pain; abdomen; protocol; toxicity; toxic; lacosamide; pancreas; pancreatitis; opioid

Introduction

Background

Chronic pancreatitis (CP) is a syndrome characterized by inflammation and progressive architectural destruction of the pancreas. This may result in pancreatic fibrosis with concomitant loss of exocrine and endocrine function, regardless of etiology. The most common symptom of CP is debilitating abdominal pain, which may be constant or flare intermittently. The health care and socioeconomic consequences of CP may be substantial. Notably, painful disease exacerbations often prompt medical evaluation. Patients with constant pain often require daily analgesics for pain relief; further, they may experience disability, subsequent loss of productivity, and frequent need for hospitalization [1].

The treatment of abdominal pain is idiosyncratic and typically based on the skill set of the provider or the resources available at an individual institution. The management of pain in patients with CP has traditionally been based on the assumption that all symptoms have a structural basis. However, in a recent review, it was noted that central sensitization and psychological and social factors are now recognized to potentially contribute to chronic pain, supporting the expansion of therapeutic approaches to include nonstructural behavioral interventions [2]. Although the authors recommended avoidance of chronic opioid use in this patient population, opioids remain a mainstay of therapy at many centers in the United States. However, opioid use may present serious risks, including overdose and opioid use disorder. From 1999 to 2014, >165,000 people died of overdose related to opioid pain medication in the United States [3]. In addition, opioid monotherapy is often insufficient for the management of chronic pain of any etiology. Notably, the single-agent maximum-tolerated dose (MTD) of these drugs may reduce pain by only 25% to 40%, owing to incomplete efficacy, dose-limiting adverse effects, or both. The side effects of opioids, including marked detrimental effects on respiratory, gastrointestinal, and cardiovascular functions, may limit the use of opioid analgesia. In 2016, the Centers for Disease Control and Prevention published a guideline for prescribing opioids for chronic pain, noting that nonpharmacological and nonopioid pharmacological therapies are preferred for chronic pain [4]. If opioids are used, they should be combined with nonpharmacological therapy and nonopioid pharmacological therapy, if possible. Therefore, to minimize side effects, clinicians should prescribe the lowest effective opioid dose. Successful development of an opioid-minimizing strategy would provide clinicians with a new tool to lower the prescribed opioid doses. Studies addressing the efficacy of alternative methods for pain management are necessary. We propose an innovative study and intervention that focuses on the safety and tolerability of a novel combination of narcotic and nonnarcotic approach to pain experienced by patients with CP.

Adjuvant drugs, including antidepressants and anticonvulsants, are often used in combination with opiates for the treatment of pain with modest outcomes. One rather pronounced adverse off-target effect of opioids is an increasing sensitivity to noxious stimuli, even evolving a painful response to previously nonnoxious stimuli (allodynia). This condition is clinically known as opioid-induced hyperalgesia (OIH) [5,6]. The underlying pathophysiology of OIH is complex and may be mediated by central [7-9] or peripheral [10] pathways. An intervention targeted against 1 or more of these mechanisms may potentially limit OIH and lead to improved pain control in patients requiring opioids. On the basis of preclinical published data [11], preliminary studies presented subsequently, and clinical observations [12], we hypothesize that therapeutic targeting of the sodium channel NaV1.7 will improve opioid efficacy for controlling pain in patients with CP. Voltage-gated sodium channels (NaVs) play a key role in the initiation and propagation of action potentials in electrically excitable nociceptive neurons. Specific NaVs in these neurons can be activated by nonclassical opioid receptors [11,13]. This activation and augmentation of NaV-dependent pain sensing appears to counter a few classical opioid effects [14-16]. Therefore, neuronal activation of NaV1.7 could be one of the mechanisms that limit opioid effectiveness [11,13,15,16]. The activation of these channels can be blocked with an existing class of Food and Drug Administration (FDA)–approved antiepileptic seizure drugs that modulate NaVs [11,17-20]. The recent identification of neurobiological mechanisms associated with NaV1.7 and opioid efficacy provide the innovative rationale for this combinatorial opioid adjuvant therapy. The basic drug mechanism is that nonclassical opioid receptors function to increase the NaV1.7 current in nociceptive sensory neurons, leading to drug-induced pain, or OIH. The combination of an opioid and specific antiseizure drugs such as carbamazepine, oxcarbazepine, or lacosamide effectively diminishes the opioid-induced NaV1.7 current [11,13,15]. These preclinical observations in several neuropathic pain-induced injury models lay the foundation for changing the management of chronic pain from empirical symptom control to personalized targeting of specific mechanisms responsible for pain.

Lacosamide is a first-in-class FDA-approved modified amino acid antiepileptic drug that targets NaV1.7. It was approved by the FDA after phase 3 trials as adjunctive and monotherapy in adults with refractory partial epileptic seizures [21]. The mechanism of action of lacosamide is thought to be that it enhances the slow inactivation of NaV1.7 without affecting its fast inactivation [17-20]. Lower concentrations of this drug may also bind to fast-inactivated states in a manner similar to other

antiseizure agents but with slower kinetics of binding and unbinding [20]. Therefore, this means that lacosamide only affects neurons that are depolarized or active for long periods, which is typical of neurons not only at the focus of epilepsy but also central to active pain states. We chose lacosamide as our study drug over other sodium channel inhibitors because it has a favorable side effect profile. Carbamazepine use as an adjunct to opioids is limited by its adverse effects; therefore, the reduced side effect profile of lacosamide may make it a better choice for chronic pain management [22]. In addition, carbamazepine is a well-known inducer of hepatic drug metabolism and therefore may result in a variety of drug interactions that might compromise the efficacy and safety of ongoing therapies. Lacosamide, on the other hand, has minimal interaction with hepatic cytochrome P450 drug-metabolizing enzymes [23]. Lacosamide is a *CYP2C19 substrate* [24]. The drug has a negligible first-pass effect, with a bioavailability of approximately 100%. The maximum lacosamide plasma concentrations occur approximately 1 to 4 hours after oral administration, and the pharmacokinetics of lacosamide are dose proportional. Food intake does not affect its absorption. Notably, *CYP2D6* is responsible for the metabolism of most of the commonly prescribed opiate medications, including codeine, tramadol, hydrocodone, and oxycodone [25]. Furthermore, the *CYP3A4* system regulates the excretion of fentanyl, methadone, and buprenorphine. However, patients receiving methadone will be excluded from participation in Safety, Tolerability, and Dose-Limiting Toxicity of Lacosamide in Patients With Painful Chronic Pancreatitis (STTEPP), as this is a μ-opioid agonist and acts as an antagonist of the N-methyl-D-aspartate (NMDA) receptor [26].

Several studies have evaluated lacosamide as a monotherapy for clinical pain conditions such as fibromyalgia and painful diabetic peripheral neuropathy. Although all studies claimed that lacosamide reduced neuropathic pain and was well tolerated, the outcomes were generally inconclusive and provided only marginal benefits [27-31]. Notably, however, all these studies excluded patients who required opioids for pain control. One clinical case report suggested that chemotherapy-induced painful peripheral neuropathy uncontrolled by opioids alone is accompanied by a dramatic reduction in pain when lacosamide was added to opioid therapy [12]. This provides clinical evidence supporting our rationale for the use of lacosamide in combination with opioids to treat neuron-based symptoms. Therefore, we propose to evaluate lacosamide in conjunction with opioids, which is where evidence consistently shows a benefit. Evidence regarding the effect of lacosamide on NMDA receptor has been shown by its ability to prevent seizures and death in NMDA-induced convulsion test paradigms in mice [32].

Objectives

In this protocol, we will evaluate the safety, tolerability, and dose-limiting toxicity (DLT) of the combination of lacosamide and opioid therapy in patients with CP, as well as the feasibility of the performance of this phase 1 pilot study. The MTD will be determined. Lacosamide, an anticonvulsant that is safe and well tolerated in patients with epileptic seizures, may potentially lower the opioid dose necessary for adequate pain relief in patients with CP. The positive outcomes of this pilot study will then support proceeding with a phase 2 efficacy trial assessing the ability of opioid adjuvants to alleviate abdominal pain in this difficult patient population. In addition, we believe that this combination therapy will serve to significantly enhance the safety profile of opioid use in these patients.

Methods

Study Organization

The Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC) has been tasked by the National Institutes of Health (NIH) with the comprehensive clinical, epidemiological, and biological characterization of patients with CP to develop treatments and gain insight into the pathophysiology of CP and its sequelae, including chronic pain, pancreatic exocrine and endocrine insufficiency, and diabetes pancreatic cancer association [33]. All participating clinical centers in the STTEPP trial are CPDPC members and are contributing to a longitudinal cohort study called *Prospective Evaluation of Chronic Pancreatitis for Epidemiologic and Translational Studies* (PROCEED) [34], the first prospective cohort study of pancreatitis in the United States. STTEPP was funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK; R01DK132709) in April 2022 as a multi-institutional prospective ancillary study within the CPDPC. MD Anderson Cancer Center, University of Texas, will serve as the data coordinating center for STTEPP, and the Institutional Review Board (IRB) at MD Anderson will serve as the single-center IRB for this study. The goal of this clinical research study is to determine whether adding the antiseizure medication lacosamide to opioid pain medications will help in managing chronic, ongoing abdominal pain symptoms caused by CP. The safety of this drug combination will also be studied. This is an investigational study.

Lacosamide

Lacosamide is a Schedule V controlled substance approved by the FDA for the management of seizure disorders. A controlled substance is a drug or other substance that is tightly controlled by the government, because it may be abused or cause addiction. All controlled substances in the United States are classified into 5 schedules. Schedule V drugs, including lacosamide, have the lowest potential for misuse and addiction compared with those in other schedules. Although it has been used off-label to treat pain resulting from nervous system damage, this medication is not FDA approved for the management of abdominal pain. Currently, it is being used to treat abdominal pain for research only. There may or may not be benefits for participants in this study. The participant will be closely followed by a study coordinator and site investigator during participation. Although the actual drug therapy will only last for 7 days, the participant may experience improved control of their abdominal pain symptoms during the study. Future patients may also benefit from what is learned in this study.

Ethical Considerations

This study protocol was approved by the University of Texas MD Anderson Cancer Center Institutional Review Board (IRB

ID 2021-1197). Informed consent was obtained from all participants or their legal guardians. All methods were performed in accordance with relevant guidelines and regulations.

Participation is completely voluntary. Before choosing to participate in this study, participants should discuss any concerns they may have with the study team, including side effects, potential expenses, and time commitment. The participant can read the full list of potential side effects in the *Possible Risks* section of the consent form.

The participant may choose not to take part in this study, and they do not have to participate. They may withdraw from the study at any time. The participant has the right to choose whether to participate in this research study. They may decide to stop participating in the study once they have started. Leaving the study early will not result in any loss of benefits that they already have. Instead of participating in this study, they may choose to continue with their current medications and plan of care.

Study Details

Who Is Eligible to Take Part in the Study?

Patients with ongoing chronic abdominal pain related to CP, even with opioid pain medication treatment, were asked to participate in the study.

How Many Participants Are Expected to Take Part in the Study?

Approximately 24 participants will participate in this multicenter study from approximately 5 institutions. Up to 10 participants will be enrolled at Indiana University.

How Long Will the Participation Be? How Long Will It Take to Complete the Study?

If the patient decides to take part in this study, they will complete a screening visit in person to determine if they qualify for enrollment. This visit will take approximately 30 to 60 minutes. After the screening visit, participation will involve an in-person visit that will last 60 minutes. The participant will be asked to take the study medication (provided at no cost) for the 7 days of participating in the study. The participant will also keep a medication diary to confirm when and how they take the study medications and their pain medications. The final study visit will be an in-person follow-up visit on day 8, lasting approximately 60 minutes. The study team will collect medical history and clinical information, draw blood samples, and ask the patient to complete the visit questionnaires as well as medication diaries of all pain medications they take, including the study medication. The research data will be maintained indefinitely.

What Will Be Done to the Patient If They Agree To Be a Research Subject?

If a patient wants to participate in the study, they will be asked to sign the consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization before starting any study procedures. If they agree to participate in the study, the study team will collect several items on the days of their study visits.

Screening Visit

The screening visit will be completed in person and is expected to last 30 to 60 minutes. The protocol for the screening visit has been described in Textbox 1.

Textbox 1. Protocol for screening visit.

- The participant will be asked about the medicines they have used or are now taking, including all prescriptions and nonprescription medications.
- They will also be asked to provide demographic information (eg, age and ethnicity).
- They will have blood (approximately 7 teaspoons) collected for routine safety tests. These blood tests are important to determine whether they are eligible to participate in the study and to monitor for possible side effects of the study drug. They should fast (ie, eat nothing and drink only water) for at least 8 hours before this blood investigation.
- If the patient can become pregnant, they will undergo a urine pregnancy test. To participate in this study, they must not be pregnant.
- The patient will have an electrocardiogram test performed to measure the electrical function of their heart.
- They will be asked to complete 4 questionnaires related to pain and how it affects their daily life.
- They will be given a medication diary to track the medications they take for pain.
- The study team will review their medical records to confirm eligibility to continue in the study.

Enrollment Visit

The enrollment visit will be completed in person on day 0 and is expected to last for 60 minutes. The protocol for enrollment visit day and the treatment days 1 to 7 is described in Textbox 2.

Textbox 2. Protocol for enrollment visit and treatment days.

Enrollment visit day 0

- The patient will be asked if they have any health problems other than chronic pancreatitis and what medical or surgical procedures they have undergone in the past.
- They will be asked to complete 4 questionnaires related to their pain and how it affects their daily life.
- They will be asked about any health problems they may be experiencing.
- They will be asked what medications they are taking, including all prescription and nonprescription medications.
- Patients' vital signs (eg, heart rate, blood pressure, and temperature), height, and weight will be recorded.
- They will have a physical examination.
- If they can become pregnant, they will have a urine pregnancy test.
- Patients will be given a 7-day supply of the study drug and medication diaries to document all medications taken for pain.

Treatment days 1 to 7

- The lacosamide tablets can be stored at room temperature. Patients will take lacosamide by mouth, 2 times a day, approximately 12 hours apart. They will be asked to try and take the tablets at the same time on each of the 7 days of the study. The tablets may be consumed with or without food. Patients will be asked to swallow the tablets whole with a glass of water or any other liquid of their choice and not chew them.
- Patients will be asked to complete daily medication diaries for all medications taken for pain, including the study drug.

Follow-Up Visit

The first follow-up visit will be completed in person on day 8 and is expected to last for 60 minutes. Subsequently, a follow-up visit will be conducted via telephone on day 21. The protocol for these follow-up visits in described in Textbox 3.

Textbox 3. Protocol for follow-up visits.

Follow-up visit on day 8

- Patients will be asked to complete 4 questionnaires related to pain and how it affects their daily life.
- They will be asked about any health problems they may be experiencing.
- They will be asked what medications they have taken, including all prescriptions and nonprescription medications from the enrollment visit day 0.
- Their vital signs will be recorded.
- They will have a physical examination.
- Blood (approximately 7 teaspoons) will be collected for routine safety investigations. They will need to fast before the blood is collected.
- They will have an electrocardiogram test performed to measure the electrical function of their heart.
- They will return any leftover study drug doses to this visit, in the original bottles.

Follow-up on day 21: phone visit

- Patients will be asked about any health problems they may be experiencing.
- They will be asked what medications they have taken, including all prescriptions and nonprescription medications, from the follow-up visit on day 8.

Risks Associated With the Study

Risks of Receiving the Study Drug

There are risks to participating in any research study. One risk is that the study drug does not relieve the abdominal pain. There is a risk of side effects or feeling bad during this study. Side effects vary from person to person. Everyone participating in this study will be carefully monitored for side effects. It is important that the patients tell the study physician about any side effects that they have during this study, even if they do not think it is related to the study drug. The side effects may range from mild to severe. Study physicians and the company that makes the study drug cannot know all the side effects that may occur, and there may be unknown side effects.

Lacosamide Side Effects

Lacosamide intake can result in common, occasional, or rare but serious side effects.

- *Common* side effects (occurring in >20% of the patients):
  - Dizziness

- *Occasional* side effects (occurring in 3%-20% of the patients):
  - Headache, fatigue, sleepiness, skin wound, nausea, vomiting, diarrhea, bruising, tremors, loss of coordination, difficulty in walking, double vision, blurry vision, eye twitching, and injection site pain

- *Rare but serious* side effects (occurring in fewer than 3% of patients):
  - Irregular or slow heartbeat, fainting, fever, difficulty in forming words or speaking, abnormal brain function (eg, affecting balance and coordination), mental status change (eg, memory loss and impaired thinking), suicidal thoughts or behavior, hallucinations (ie, seeing or hearing things that are absent), liver damage because inflammation, abnormal sensation (eg, pins and needles), walking or balance problems (eg, possible falling), and life-threatening allergic reactions (eg, difficulty breathing, low blood pressure, and organ failure)

- Lacosamide may rarely cause low blood cell counts (red or white blood cells).
  - A low red blood cell count (anemia) may cause difficulty in breathing or fatigue. The patient may require a blood transfusion.
  - A low white blood cell count increases the risk of infection (eg, pneumonia or severe blood infection). Infections may occur anywhere and become life-threatening. Symptoms of infection may include fever, pain, redness, and difficulty in breathing.

In other studies of lacosamide, stopping the drug suddenly did not lead to unpleasant physical symptoms. As a Schedule V controlled substance, lacosamide has a very low potential for abuse. No restrictions on activities need to be followed when taking this drug. However, should the patient have a side effect or feel bad during this study, they should call the study physician. The study physician's telephone number is on the front page of the consent form. They should also call the physician if they have a side effect that makes them visit the hospital during the study.

Other Risks

Collecting blood for investigations may cause pain, bleeding, and bruising. The patient may faint and develop an infection with redness and irritation of the vein at the site of blood collection. Frequent blood collection may cause anemia (low red blood cell count), which may necessitate blood transfusions. Undergoing an electrocardiogram (EKG) may cause discomfort while lying on the examination table, and the tape on the EKG pads may cause skin irritation.

The questionnaires may contain questions that are sensitive in nature. They may refuse to answer any question that may make them feel uncomfortable. If the patient has concerns about completing the questionnaire, they are encouraged to contact their physician or the study chair.

The arm cuff used in measuring blood pressure may feel tight or slightly uncomfortable for a short time, and during the measurement, their hand or arm may experience numbness.

Certificate of Confidentiality

This study is covered by a Certificate of Confidentiality (CoC) from the NIH. With this CoC, the researchers may not disclose or use information that may identify the patient in any federal, state, or local civil; criminal; administrative; legislative; or other action, suit, or proceeding or be used as evidence, for example, if there is a court subpoena, unless the patient has consented for this use. Information protected by this CoC cannot be disclosed to anyone else who is not connected with the research, except if there is a federal, state, or local law that requires disclosure (eg, reporting child abuse or communicable diseases but not for federal, state, or local civil; criminal; administrative; legislative; or other proceedings).

The CoC cannot be used to refuse a request for information, for auditing or program evaluation purposes, from personnel of the United States federal or state government agencies sponsoring the project. A CoC does not prevent the patient from voluntarily releasing information about themselves or their involvement in this research. If the patient wants their research information to be released to an insurer, medical care provider, or any other person not connected to the research, they must provide consent to allow the researchers to release it. The CoC will not be used to prevent disclosure for any purpose you have consented.

Pregnancy-Related Risks

Taking part in this study can result in risks to an unborn or breastfeeding baby, so the patient should not become pregnant, breastfeed a baby, or father a child while in this study. They must use birth control during the study if they are sexually active.

- Male patients should tell the physician right away if their partner becomes pregnant or suspects pregnancy.
- If female patients are pregnant, they will not be enrolled in this study. If they become pregnant or suspect pregnancy, they must tell their physician immediately. Pregnancy will result in exclusion from this study.

Risk of Possible Loss of Confidentiality

Every effort will be made to keep patients' personal information confidential; however, we cannot guarantee absolute confidentiality. No information that could identify the patient will be shared in the publication of this study. Patients' personal information may be shared outside the research study if required by law and with individuals or organizations that oversee the conduct of research studies, and these individuals or organizations may not be held to the same legal privacy standards as physicians and hospitals.

There are some types of sharing the CoC does not apply to. The CoC does not stop reporting required by federal, state, or local laws, such as reporting of child or elder abuse, some communicable diseases, and threats to harm oneself or others. The CoC does not stop a government agency who is funding research from checking records or evaluating programs. The CoC also does not prevent their information from being used

for other research when allowed by federal regulations. The CoC also does not stop sharing of information required by the FDA.

Researchers may release information about the patient when they say that it is okay. For example, the patient may still give them permission to release information to insurers, medical providers, or others not connected to the research.

Costs and Compensation

Will Participants or Their Insurers Be Billed for Any Costs of the Study? If so, Which and What Happens if Insurance Does Not Cover the Costs?

The study will pay for the study drug, blood collection, ECGs, physical examinations, and data collection associated with the research study and for the investigations that are performed for research purposes only.

What Happens if the Patient is Hurt or Became Sick as a Result of the Study?

The researchers have taken steps to minimize the known or expected risks. However, they may still experience problems or side effects, even when the researchers are cautious to avoid them. If the patient believes that they have been harmed, they should notify the researchers listed in Section 6 of the consent form. The team at Indiana University Hospital will provide first aid or emergency care. The cost of this first aid or emergency care may be billed to the patient's insurance company. Additional medical care will be provided if the injury is determined to be caused by the research. If they sign the form, they do not give up their right to seek additional compensation if they are harmed because of being in this study.

Of note, it is important that the patients tell the researchers about any injuries, side effects, or other problems that they experience during this study. They may also need to tell their regular physicians. Furthermore, it is the patient's responsibility to determine the extent of their health care coverage. There are no other monetary compensation programs in place for such injuries. They will not be reimbursed for expenses or compensated financially by MD Anderson or the NIH and NIDDK for this injury. They may also contact the Chair of MD Anderson's IRB at 713-792-6477 with questions about study-related injuries.

Are Patients Paid or Given Anything for Being in the Study?

The patient will be paid US $50 at the completion of enrollment visit day 0 and US $100 at the completion of follow-up visit day 8; both payments will be in the form of gift cards.

Patient Eligibility

Relevant to STTEPP, PROCEED study participants are divided into subcohorts to distinguish the natural history of different disease presentations at the time of admission into the cohort [34]. In STTEPP, we will leverage the resources of the CPDPC by approaching participants already enrolled in PROCEED. This approach will facilitate timely accrual, as these participants have demonstrated an interest in research and willingness to participate in CPDPC studies. Although all participants must meet the criteria for diagnosis of suspected or definite CP as per PROCEED definitions [34], study enrollment will not be limited to participants participating in PROCEED. The STTEPP inclusion and exclusion criteria are listed in Textboxes 4 and 5, respectively.

Textbox 4. Inclusion criteria.

1. Written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization for release of personal health information
2. Age ≥18 years at the time of informed consent
3. Suspected (YELLOW 2 or 3) or definite (RED) diagnosis of chronic pancreatitis, as per the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer's *Prospective Evaluation of Chronic Pancreatitis for Epidemiologic and Translational Studies* (PROCEED) study definition with ongoing symptoms of abdominal pain
4. Patients must be maintained on an opioid (except methadone or suboxone) for 4 weeks before enrollment for the treatment of abdominal pain related to pancreatitis, with a daily morphine equivalent dose of 20 mg to 120 mg.
5. Ongoing symptoms of abdominal pain even with opioid use (Visual Analog Score and Brief Pain Inventory average score ≥4, at enrollment)
6. Eastern Cooperative Oncology Group performance status of 0 to 2 (Oken et al [35])
7. Ability to swallow and tolerate oral tablets
8. Females of childbearing potential must have a negative pregnancy test
9. The following laboratory parameters must be met: white blood cell count ≥3.0 K/mm^3, absolute neutrophil count ≥1.5 K/mm^3, hemoglobin ≥9 g/100 ml, platelets ≥75 K/mm^3, creatinine ≤1.5 mg/100 mL, bilirubin ≤1.5 x upper limit of normal (ULN), aspartate transaminase ≤3 ULN, alanine transaminase ≤3 ULN; normal PR interval on baseline 12-lead electrocardiogram.

Textbox 5. Exclusion criteria.

1. Participants with indeterminate chronic pancreatitis (YELLOW 1) as per *Prospective Evaluation of Chronic Pancreatitis for Epidemiologic and Translational Studies* (PROCEED) criteria
2. Treatment with any investigational agent within 30 days before registration or concurrent participation in a clinical trial which involves another investigational agent
3. Rapidly escalating pain that requires parenteral (eg, intravenous or intramuscular) opioid therapy within 30 days of enrollment
4. Known hypersensitivity or allergic reaction to lacosamide, carbamazepine, or oxcarbazepine
5. Pregnant or breastfeeding
6. Diagnosis of epilepsy or a patient who is currently taking antiepileptic drugs
7. Abdominal surgery or pain intervention (eg, endoscopic retrograde cholangiopancreatography with sphincterotomy or stent or stone removal and celiac plexus block) within 90 days of enrollment.
8. Hospitalization for pancreatitis exacerbation or pain management within 90 days of enrollment
9. Patient who currently takes Suboxone or methadone.
10. Other factors which might explain the patient's ongoing symptoms, at the discretion of the enrolling physician.
11. History of autoimmune or traumatic pancreatitis or sentinel attack of acute necrotizing pancreatitis which results in suspected disconnected duct syndrome.
12. Primary pancreatic tumors, pancreatic ductal adenocarcinoma, suspected cystic neoplasm (>1 cm in size or main duct involvement), neuroendocrine tumors, and other uncommon tumors
13. Pancreatic metastasis from other malignancies
14. History of solid organ transplant and HIV or AIDS
15. Known isolated pancreatic exocrine insufficiency (eg, without any eligible inclusion criteria)
16. No medical or psychiatric illnesses or ongoing substance abuse that, in the investigator's opinion, would compromise participant's ability to tolerate study interventions or participate in follow-up.

Objectives and End Point

Our primary objectives are to (1) evaluate the safety, tolerability, and DLT of lacosamide in combination with opioids in patients with CP and (2) assess the feasibility of the performance of a pilot study of adding lacosamide to opioid therapy in patients with CP. As a secondary, exploratory objective, we will assess the efficacy of adding lacosamide to opioid therapy for the treatment of abdominal pain because of CP. The safety end point includes toxicity and DLT of the combination of lacosamide and opioids, defined as grade 3 or 4 toxicities, according to the National Cancer Institute Common Terminology Criteria for Adverse Events v5.0. Tolerability will be assessed by compliance with the intervention. The participants will be evaluated for completing the 7-day trial. The percentage of participants taking 100%, 75%, 50%, and <50% of the study tablets will be recorded. The feasibility end point will include the recruitment rate (ie, the proportion of eligible patients who agree to participate) and the dropout rate, including a qualitative assessment of barriers to retention. The efficacy end point will be assessed using the Visual Analog Score; Brief Pain Inventory, short form, average score; and the Comprehensive Pain Assessment Tool, short form [36] total score. A 50% decrease in pain scores from baseline at study completion will be deemed clinically meaningful. In addition, opioid use will be evaluated, with a decrease of 25% in pain scores from baseline at study completion, identified as clinically significant.

Investigational Plan, Intervention, and Treatment Regimen

We will conduct a dose-escalation trial of lacosamide added to opioid therapy in patients with chronic abdominal pain owing to CP. Participants who meet all the inclusion criteria and none of the exclusion criteria will be included in this dose-finding study. We will use the Bayesian optimal interval (BOIN) [37,38] design to determine the MTD. The BOIN design received a fit-for-purpose designation from the FDA as a drug development tool [39]. The BOIN design is implemented in a simple manner similar to the traditional 3+3 design, but it is more flexible and possesses superior operating characteristics compared to those with more complex model-based designs, such as the continual reassessment method [40]. The target DLT rate for MTD is 0.3, and the maximum sample size is 24. We will enroll and treat patients in cohorts of size 3. The initial dose will be 50 mg taken orally twice a day (100 mg/day), followed by an incremental increase of 100 mg/day in 2 divided doses. The maximum daily dose of lacosamide will be 400 mg/day. The duration of lacosamide administration will be 7 days at each dose level. This target DLT rate and dose-escalation schedule were chosen based on previous trials that had suggested the efficacy and tolerability of comparable doses of lacosamide when used to treat partial seizures and painful diabetic neuropathy. Follow-up laboratory parameters (as obtained at study entry) will be obtained on day 8 (with a 3-day window) after therapy is completed. The trial design is illustrated in Figure 1 and is described as follows:

1. Patients in the first cohort are treated at dose level 1.

2. To assign a dose to the next cohort of patients, dose escalation or de-escalation will be performed according to the rules displayed in Table 1.
3. Repeat step 2 until the maximum sample size of 24 is reached or stop the trial if the number of patients treated at the current dose reaches 15.

In the BOIN design, the number of DLT is the number of patients with at least 1 DLT. When none of the actions (ie, escalation, de-escalation, or elimination) is triggered, the current dose remains unchanged for the next cohort of patients. "N/A" means that a dose cannot be eliminated before treating 3 evaluable patients. After the trial is completed, we will select the MTD based on isotonic regression [38]. This computation is implemented by the "Estimate MTD" tab of the BOIN Design Desktop Program [41]. Notably, each cohort of 3 patients will consist of 3 new patients. Therefore, dose escalation or de-escalation is interpatient (or, more precisely, intercohort), not intrapatient in nature.

Considering the low disease prevalence of CP, including referral bias at academic centers, we chose to avoid the use of eligibility criteria that would narrow the potential recruitment pool. In this phase 1 trial, in which safety, tolerability, and feasibility are the primary outcomes of interest, we propose including all patients with suspected or definitive CP if the above inclusion and exclusion criteria are met. Similarly, although there may be potential variability in patients because of the etiology, duration of CP, or other features of the disease, it is impractical to impose more stringent eligibility criteria during this early phase of the investigation. Doing so would substantially deplete the recruitment pool for this orphan disease and would not be feasible or scientifically justified.

Figure 1. Bayesian optimal interval (BOIN) schema. The BOIN schema is a model-assisted dose-finding design that can be used to determine the maximum-tolerated dose (MTD) of a study drug based on safety or the optimal biological dose (OBD) based on safety and efficacy. DLT: dose-limiting toxicity.

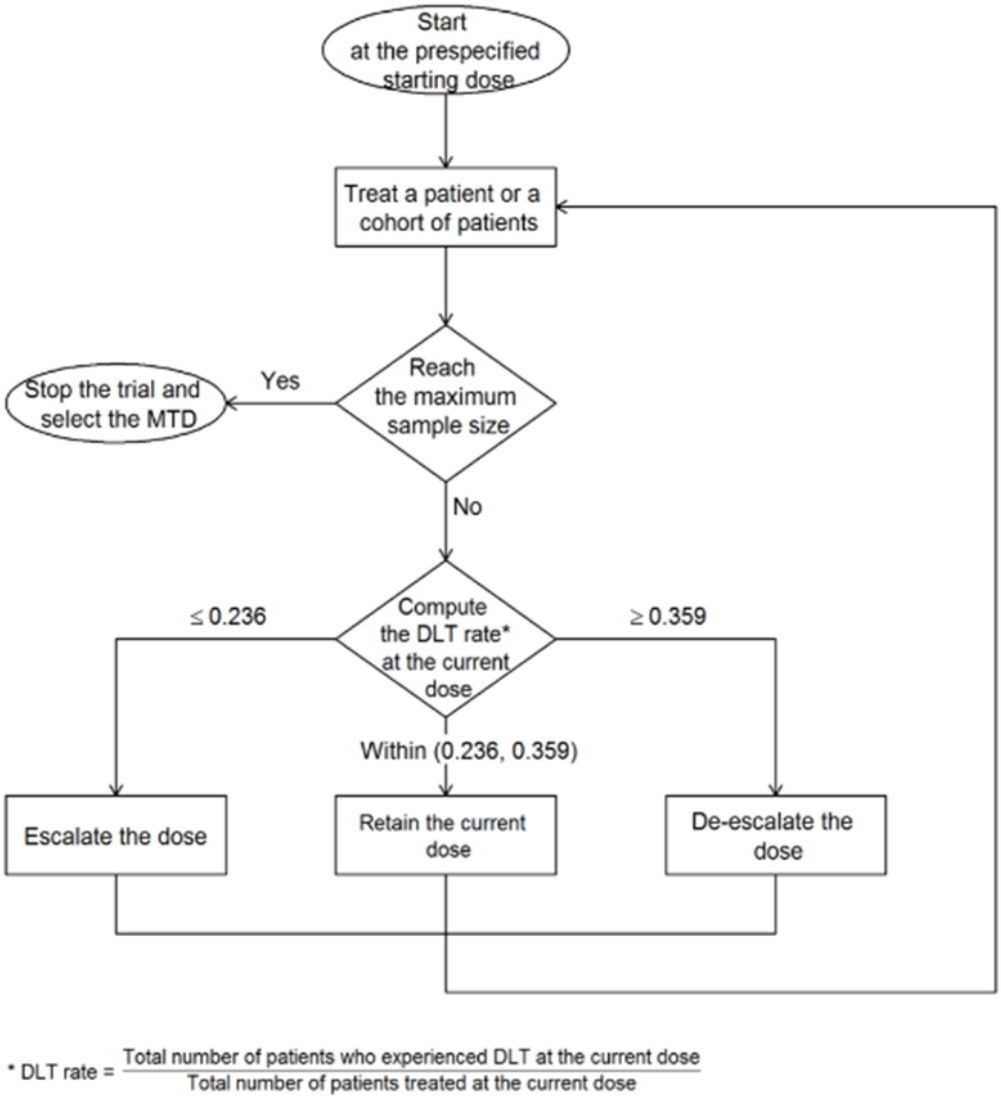


Table 1. Dose-escalation or de-escalation rule for the Bayesian optimal interval design.

Actions	The number of patients treated at the current dose														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Escalate if the number of DLT[a] is ≤	0	0	0	0	1	1	1	1	2	2	2	2	3	3	3
De-escalate if the number of DLT is ≥	1	1	2	2	2	3	3	3	4	4	4	5	5	6	6
Eliminate if the number of DLT is ≥	N/A[b]	N/A	3	3	4	4	5	5	5	6	6	7	7	8	8

[a]DLT: dose-limiting toxicity.

[b]N/A: not applicable.

Drug Dispensing and Compliance

In this phase 1 trial, all enrolled participants will receive the active drug lacosamide. There is no placebo group, and there is no blinding to the treatment or dose received. Following the initial drug purchase, the investigational drug service at each participating institution will purchase additional disbursements on an as-needed basis, depending on patient recruitment. Participants will be provided with drug diaries, which will be reviewed for compliance at the end of the study at the final in-person visit. Patients who miss a dose (defined as beyond 2 hours of the patient's typical drug administration time) will not be instructed to take it later on the same day. Patients will be informed not to take missed doses on the subsequent day (ie, the patient should not take more than the prescribed daily dose).

Study Visits

A screening visit for eligibility in person or via telephone will occur at 7 to 30 days prior to enrollment. There will be 2 in-person study visits. During study visit 1 on day 0, baseline study assessments and questionnaires will be completed in person. Drug treatment days will then occur from days 1 to 7. During study visit 2 on day 8 (with a 3-day window), following completion of the 7-day drug treatment period, participants will have a face-to-face clinic visit, where similar assessments and questionnaires will be completed, as per the study calendar (Table 2). Participants will return all unused drugs during this visit for disposal and to monitor compliance.

Table 2. Study calendar.

	Screening visit, from 7 to 30 days	Enrollment visit, day 0	Treatment days 1-7	Follow-up visit, day 8 (+3-day window)
Required assessments				
Informed consent	✓			
Medical history[a]		✓		
Height and weight		✓		
Physical examination		✓		✓
Vital signs		✓		✓
ECOG[b] performance status	✓	✓		✓
EKG[c]	✓			✓
Blood chemistries[d]	✓			✓
Hemoglobin, absolute neutrophil count, and platelets	✓			✓
Urine pregnancy	✓	✓		
Medication assessment[e]	✓	✓		✓
Adverse event assessment		✓		✓
Questionnaires				
Physician questionnaire		✓		
Study coordinator questionnaire		✓		✓
Patient questionnaire (VAS[f], BPI[g], PROMIS[h], and COMPAT[i])	✓	✓		✓
Medication diary	✓	✓		✓

[a]Medical history and establishment of suspected or definite chronic pancreatitis diagnosis may occur at any time before trial entry.

[b]ECOG: Eastern Cooperative Oncology Group.

[c]EKG: electrocardiogram.

[d]Will include at a minimum: electrolytes, glucose, blood urea nitrogen, creatinine and creatinine clearance, calcium, and hepatic function panel.

[e]Will include detailed use of rescue pain medications and opioids use.

[f]VAS: Visual Analog Score.

[g]BPI: Brief Pain Inventory.

[h]PROMIS: Patient-Reported Outcomes Measurement Information System.

[i]COMPAT: Comprehensive Pain Assessment Tool for Chronic Pancreatitis.

Study Measurements

A site gastroenterologist will review the complete medical history, including medications (particularly opioid use), Eastern Cooperative Oncology Group performance status, physical examination (including vital signs, height, and weight), EKG, and laboratory test results. A site research nurse will collect up to 35 mL of fasting blood using standard protocols. Given the safety or risk protocol of lacosamide and to satisfy inclusion and exclusion criteria, the blood specimens are considered routine safety laboratories and will include electrolytes, glucose, blood urea nitrogen, creatinine, creatinine clearance, calcium, and a hepatic function panel.

The patient, nurse coordinator, and physician case report forms (CRFs) will be completed before study entry. This will be based on a similar CRF currently used in PROCEED. Completion of these forms before enrollment will allow confirmation that the patient is eligible for the study. We will obtain approval from the single-center IRB to share data between protocols with the patients' consent. An additional CRF will be completed by the nurse coordinator in collaboration with the site-specific principal investigator at the follow-up study visit, documenting all side effects noted during the drug treatment phase according to Common Terminology Criteria for Adverse Events (version 5.0).

Safety or Risk Issues

Lacosamide is a Schedule V medication available in tablet, oral solution, and injectable forms. In this study, only the tablet form will be used, and this is available in 50 mg, 100 mg, 150 mg, and 200 mg dosages. For simplicity in drug ordering and distribution, only 50 mg tablets will be used. Lacosamide is FDA approved as monotherapy or adjunctive therapy for partial-onset seizures, with a maximal recommended oral total daily dose of 400 mg, administered in 2 divided doses.

Summary of Known Potential Risks With Study Medication

Side Effects

A complete list of reported side effects from lacosamide trials and postmarketing experience can be found in the medication insert and Amneal Pharmaceuticals website [42]. The common side effects of lacosamide at doses in the range of 200 mg to 400 mg include dizziness (25%), ataxia (6%), fatigue, nausea, diplopia, headache, or tremor (12%-17%). Severe side effects such as cardiac rhythm or conduction abnormalities (first-degree arteriovenous block and atrial fibrillation or flutter, 0.5%) and suicidal ideation or behavior (0.2%) are rare. Case reports have been published regarding episodes of syncope and hypersensitivity reactions.

Prior and Concomitant Medications or Procedures

Relevant information about all concomitant drugs (including prescribed, over-the-counter, or herbal preparations) taken before and during the trial and any dose or dose regimen changes that occur during the trial will be recorded in the source documents and case report form. Owing to the potential drug-to-drug interaction with other CYP3A4 or CYP2C9 inhibitors that may interfere with lacosamide levels, patients taking medications that may interfere with lacosamide metabolism will be monitored carefully. Furthermore, patients taking medications that affect cardiac conduction (eg, sodium channel blockers, β-blockers, and calcium channel blockers), including those that prolong the PR interval, will be carefully observed. We will obtain an EKG before beginning drug therapy and at the end of treatment**.**

The study principal investigators serve as the medical monitors for this trial, overseeing all aspects of the trial, including management of source documentation, adverse event collection, adverse events and protocol deviation reporting, interaction with the Data and Safety Monitoring Board (DSMB), and the creation of corrective and preventive action plans, when necessary. The DSMB will meet to review the study conduct and data relating to safety and efficacy to ensure the continued scientific validity and merit of the study. Following recruitment of the first study participant, summaries will be submitted monthly and reviewed quarterly by the DSMB and will follow the established CPDPC protocols.

Statistical Plan and Analysis

A sample size of 24 was determined and calibrated based on the simulation such that the phase 1 trial has reasonable accuracy (>60% probability) to correctly identify the MTD across a set of practically plausible scenarios. We will use descriptive statistics to summarize the demographic and clinical characteristics of the patients. Safety data will be tabulated by the grade and type of toxicity using descriptive statistics, including mean, SD, and 95% CI. The reduction in pain scores will be summarized by the dose using the mean and 95% CI. As an exploratory analysis, *t* test (2-sided) or Wilcoxon rank-sum test will be used to compare the reduction in pain scores between the doses. The recruitment and dropout rates will be calculated for all patients and by dose and used to determine the feasibility of the treatment. Although the data generated will not have a comparator group (ie, no placebo), these will be helpful in understanding the variability of responses in patients with suspected or definite CP, which in turn will be useful for sample size calculation for a follow-up trial.

Results

As of December 2023, we have currently enrolled 6 participants. The minimum number of participants to be enrolled is 12 with a maximum of 24. We expect to publish the results by March 2025.

Discussion

The management of abdominal pain in patients with CP remains a significant challenge, and innovative approaches to pain management are urgently needed. By potentially limiting OIH, lacosamide may improve pain control in patients requiring opioids. There are no data evaluating the use of lacosamide in patients with CP; this was the impetus of the STTEPP trial. Achieving recruitment goals is a priority. We acknowledge that patients may be unwilling to participate in a dose-finding trial with a low likelihood of long-term therapeutic benefit. Those patients who do note a benefit, however, may choose to be considered for our planned phase 2 trial. The 5 participating centers include experienced researchers, who have led clinical trials in this challenging patient population. In addition, all are members of the CPDPC and participate in PROCEED [38]. This brings substantial synergy to this study because the infrastructure for recruitment and follow-up of study participants is already in place at these institutions. We do not require the study entry to be limited to patients enrolled in PROCEED, to avoid limiting the recruitment pool. However, placing our initial focus on patients participating in PROCEED, particularly those who have demonstrated compliance and return for their follow-up visits, will identify motivated patients who are familiar with the study protocols and the importance of research. The short-term nature of this study should facilitate compliance. Because the safety data of combination therapy with lacosamide and opioids are unknown in patients with CP, this phase 1 trial is necessary. We initially considered the conventional 3+3 design for this study protocol, which suffers several limitations, such as low accuracy in identifying and estimating the MTD and the tendency of underdosing patients. Therefore, we adopted a novel phase 1 trial design (ie, the BOIN design) that allows better statistical learning of the dose-toxicity curve and more reliable identification of the MTD [37].

This study will provide new knowledge regarding the safety, toxicity, and DLT of lacosamide in patients with CP. It is

anticipated that lacosamide will prove to be safe and well tolerated. The results of this pilot study will then support proceeding with a phase 2 trial of assessing the efficacy of lacosamide added to opioid therapy to alleviate abdominal pain caused by CP. We will demonstrate that these pilot trials, in which long-term therapeutic benefits are unlikely, are feasible in this challenging population. This knowledge will facilitate future clinical trials on CP, providing data regarding patient engagement and recruitment that will better inform trial design. Future clinical trials may indicate that a combination of lacosamide and an opioid will achieve better analgesia at lower doses of each drug than either as a single agent.

Acknowledgments

The Safety, Tolerability, and Dose-Limiting Toxicity of Lacosamide in Patients With Painful Chronic Pancreatitis (STTEPP) study is funded by the National Institute of Diabetes and Digestive and Kidney Diseases (1R01DK132709).

In addition, research reported in this publication was further supported by the National Cancer Institute and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) under award numbers related to the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC): U01DK108323 (ELF, JJE, VP), U01DK108328 (YY), U01DK108306 (DY), U01DK108327 (DLC, SYH), U01DK108288 (SSV), U01DK108300 (WP). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Data Availability

Deidentified patient data may be shared with investigators from other institutions for ancillary studies upon request. Requests should be made to the study principal investigator.

Authors' Contributions

ELF and FAW wrote the main manuscript and prepared figures and tables. JJE, YY, DY, DLC, SSV, WP, SYH, and VP reviewed and approved this manuscript.

Conflicts of Interest

DY is a consultant for Pfizer, Inc. and gives research support to AbbVie Pharmaceuticals. SSV has received royalty payments for chapters in *UpToDate* on pancreatitis and received travel and honorarium for the *Orlando Health* scientific meeting in December 2023.

References

1. Mullady DK, Yadav D, Amann ST, O'Connell MR, Barmada MM, Elta GH, et al. Type of pain, pain-associated complications, quality of life, disability and resource utilisation in chronic pancreatitis: a prospective cohort study. Gut 2011 Jan 10;60(1):77-84 [FREE Full text] [doi: 10.1136/gut.2010.213835] [Medline: 21148579]
2. Vege SS, Chari ST. Chronic Pancreatitis. N Engl J Med 2022 Mar 03;386(9):869-878. [doi: 10.1056/nejmcp1809396]
3. Centers for Disease Control and Prevention. Multiple cause of death data on CDC WONDER. US Department of Health and Human Services. 2016. URL: https://wonder.cdc.gov/mcd.html#:~:text=The%20Multiple%20Cause%20of%20Death,multiple%20causes%2C%20and%20demographic%20data [accessed 2023-12-10]
4. Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC clinical practice guideline for prescribing opioids for pain - United States, 2022. MMWR Recomm Rep 2022 Nov 04;71(3):1-95 [FREE Full text] [doi: 10.15585/mmwr.rr7103a1] [Medline: 36327391]
5. Angst MS, Clark JD. Opioid-induced hyperalgesia: a qualitative systematic review. Anesthesiology 2006 Mar;104(3):570-587 [FREE Full text] [doi: 10.1097/00000542-200603000-00025] [Medline: 16508405]
6. Bannister K. Opioid-induced hyperalgesia: where are we now? Curr Opin Support Palliat Care 2015 Jun;9(2):116-121. [doi: 10.1097/SPC.0000000000000137] [Medline: 25872113]
7. Haugan F, Rygh LJ, Tjølsen A. Ketamine blocks enhancement of spinal long-term potentiation in chronic opioid treated rats. Acta Anaesthesiol Scand 2008 May 15;52(5):681-687. [doi: 10.1111/j.1399-6576.2008.01637.x] [Medline: 18419722]
8. Li X, Angst MS, Clark JD. A murine model of opioid-induced hyperalgesia. Brain Res Mol Brain Res 2001 Jan 31;86(1-2):56-62. [doi: 10.1016/s0169-328x(00)00260-6] [Medline: 11165371]
9. Minville V, Fourcade O, Girolami JP, Tack I. Opioid-induced hyperalgesia in a mice model of orthopaedic pain: preventive effect of ketamine. Br J Anaesth 2010 Feb;104(2):231-238 [FREE Full text] [doi: 10.1093/bja/aep363] [Medline: 20031953]
10. Vardanyan A, Wang R, Vanderah TW, Ossipov MH, Lai J, Porreca F, et al. TRPV1 receptor in expression of opioid-induced hyperalgesia. J Pain 2009 Mar;10(3):243-252 [FREE Full text] [doi: 10.1016/j.jpain.2008.07.004] [Medline: 18774343]

11. Due MR, Yang XF, Allette YM, Randolph AL, Ripsch MS, Wilson SM, et al. Carbamazepine potentiates the effectiveness of morphine in a rodent model of neuropathic pain. PLoS One 2014 Sep 15;9(9):e107399 [FREE Full text] [doi: 10.1371/journal.pone.0107399] [Medline: 25221944]
12. Ibrahim SA, Albany Z, Albany C. Significant response to lacosamide in a patient with severe chemotherapy-induced peripheral neuropathy. J Community Support Oncol 2015 May;13(5):202-204. [doi: 10.12788/jcso.0136] [Medline: 26029937]
13. Due MR, Piekarz AD, Wilson N, Feldman P, Ripsch MS, Chavez S, et al. Neuroexcitatory effects of morphine-3-glucuronide are dependent on toll-like receptor 4 signaling. J Neuroinflammation 2012 Aug 16;9(1):200 [FREE Full text] [doi: 10.1186/1742-2094-9-200] [Medline: 22898544]
14. Sutton KG, Martin DJ, Pinnock RD, Lee K, Scott RH. Gabapentin inhibits high-threshold calcium channel currents in cultured rat dorsal root ganglion neurones. Br J Pharmacol 2002 Jan 29;135(1):257-265 [FREE Full text] [doi: 10.1038/sj.bjp.0704439] [Medline: 11786502]
15. Deuis JR, Dekan Z, Wingerd JS, Smith JJ, Munasinghe NR, Bhola RF, et al. Pharmacological characterisation of the highly Na1.7 selective spider venom peptide Pn3a. Sci Rep 2017 Jan 20;7(1):40883 [FREE Full text] [doi: 10.1038/srep40883] [Medline: 28106092]
16. Isensee J, Krahé L, Moeller K, Pereira V, Sexton JE, Sun X, et al. Synergistic regulation of serotonin and opioid signaling contributes to pain insensitivity in Nav1.7 knockout mice. Sci Signal 2017 Jan 10;10(461):eaah4874 [FREE Full text] [doi: 10.1126/scisignal.aah4874] [Medline: 28074005]
17. Sheets PL, Heers C, Stoehr T, Cummins TR. Differential block of sensory neuronal voltage-gated sodium channels by lacosamide [(2R)-2-(acetylamino)-N-benzyl-3-methoxypropanamide], lidocaine, and carbamazepine. J Pharmacol Exp Ther 2008 Jul 31;326(1):89-99. [doi: 10.1124/jpet.107.133413] [Medline: 18378801]
18. Wang Y, Wilson SM, Brittain JM, Ripsch MS, Salomé C, Park KD, et al. Merging structural motifs of functionalized amino acids and α-aminoamides results in novel anticonvulsant compounds with significant effects on slow and fast inactivation of voltage-gated sodium channels and in the treatment of neuropathic pain. ACS Chem Neurosci 2011 Jun 15;2(6):317-322 [FREE Full text] [doi: 10.1021/cn200024z] [Medline: 21765969]
19. Park KD, Yang XF, Dustrude ET, Wang Y, Ripsch MS, White FA, et al. Chimeric agents derived from the functionalized amino acid, lacosamide, and the α-aminoamide, safinamide: evaluation of their inhibitory actions on voltage-gated sodium channels, and antiseizure and antinociception activities and comparison with lacosamide and safinamide. ACS Chem Neurosci 2015 Feb 18;6(2):316-330 [FREE Full text] [doi: 10.1021/cn5002182] [Medline: 25418676]
20. Jo S, Bean BP. Lacosamide inhibition of Nav1.7 voltage-gated sodium channels: slow binding to fast-inactivated states. Mol Pharmacol 2017 Apr 24;91(4):277-286 [FREE Full text] [doi: 10.1124/mol.116.106401] [Medline: 28119481]
21. Ben-Menachem E, Biton V, Jatuzis D, Abou-Khalil B, Doty P, Rudd GD. Efficacy and safety of oral lacosamide as adjunctive therapy in adults with partial-onset seizures. Epilepsia 2007 Jul 16;48(7):1308-1317 [FREE Full text] [doi: 10.1111/j.1528-1167.2007.01188.x] [Medline: 17635557]
22. Wiffen PJ, Derry S, Moore RA, McQuay HJ. Carbamazepine for acute and chronic pain in adults. Cochrane Database Syst Rev 2011 Jan 19(1):CD005451 [FREE Full text] [doi: 10.1002/14651858.CD005451.pub2] [Medline: 21249671]
23. Cawello W. Clinical pharmacokinetic and pharmacodynamic profile of lacosamide. Clin Pharmacokinet 2015 Sep 9;54(9):901-914. [doi: 10.1007/s40262-015-0276-0] [Medline: 25957198]
24. Dean L. Lacosamide therapy and CYP2C19 genotype. In: Pratt VM, Scott SA, Pirmohamed M, Esquivel B, Kattman BL, editors. Medical Genetics Summaries. New York, NY: National Center for Biotechnology Information; 2012.
25. Agarwal D, Udoji MA, Trescot A. Genetic testing for opioid pain management: a primer. Pain Ther 2017 Jun 13;6(1):93-105 [FREE Full text] [doi: 10.1007/s40122-017-0069-2] [Medline: 28409480]
26. Hewitt DJ. The use of NMDA-receptor antagonists in the treatment of chronic pain. Clin J Pain 2000 Jun;16(2 Suppl):S73-S79. [doi: 10.1097/00002508-200006001-00013] [Medline: 10870744]
27. Shaibani A, Biton V, Rauck R, Koch B, Simpson J. Long-term oral lacosamide in painful diabetic neuropathy: a two-year open-label extension trial. Eur J Pain 2009 May 09;13(5):458-463. [doi: 10.1016/j.ejpain.2008.05.016] [Medline: 18619874]
28. Shaibani A, Fares S, Selam JL, Arslanian A, Simpson J, Sen D, et al. Lacosamide in painful diabetic neuropathy: an 18-week double-blind placebo-controlled trial. J Pain 2009 Aug;10(8):818-828 [FREE Full text] [doi: 10.1016/j.jpain.2009.01.322] [Medline: 19409861]
29. Ziegler D, Hidvégi T, Gurieva I, Bongardt S, Freynhagen R, Sen D, Lacosamide SP743 Study Group. Efficacy and safety of lacosamide in painful diabetic neuropathy. Diabetes Care 2010 Apr;33(4):839-841 [FREE Full text] [doi: 10.2337/dc09-1578] [Medline: 20067958]
30. Wymer JP, Simpson J, Sen D, Bongardt S, Lacosamide SP742 Study Group. Efficacy and safety of lacosamide in diabetic neuropathic pain: an 18-week double-blind placebo-controlled trial of fixed-dose regimens. Clin J Pain 2009 Jun;25(5):376-385. [doi: 10.1097/AJP.0b013e318196d2b6] [Medline: 19454870]
31. Hearn L, Derry S, Moore RA. Lacosamide for neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev 2012 Feb 15;2012(2):CD009318 [FREE Full text] [doi: 10.1002/14651858.CD009318.pub2] [Medline: 22336864]

32. Stöhr T, Kupferberg HJ, Stables JP, Choi D, Harris RH, Kohn H, et al. Lacosamide, a novel anti-convulsant drug, shows efficacy with a wide safety margin in rodent models for epilepsy. Epilepsy Res 2007 May;74(2-3):147-154. [doi: 10.1016/j.eplepsyres.2007.03.004] [Medline: 17433624]
33. Serrano J, Andersen DK, Forsmark CE, Pandol SJ, Feng Z, Srivastava S, et al. Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer: from concept to reality. Pancreas 2018 Nov;47(10):1208-1212 [FREE Full text] [doi: 10.1097/MPA.0000000000001167] [Medline: 30325859]
34. Yadav D, Park WG, Fogel EL, Li L, Chari ST, Feng Z, et al. Prospective Evaluation of Chronic Pancreatitis for Epidemiologic and Translational Studies: rationale and study design for PROCEED from the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer. Pancreas 2018 Nov;47(10):1229-1238 [FREE Full text] [doi: 10.1097/MPA.0000000000001170] [Medline: 30325862]
35. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982 Dec;5(6):649-655. [Medline: 7165009]
36. Kuhlmann L, Teo K, Olesen SS, Phillips AE, Faghih M, Tuck N, et al. Development of the Comprehensive Pain Assessment Tool Short Form for chronic pancreatitis: validity and reliability testing. Clin Gastroenterol Hepatol 2022 Apr;20(4):e770-e783 [FREE Full text] [doi: 10.1016/j.cgh.2021.05.055] [Medline: 34089847]
37. Yuan Y, Hess KR, Hilsenbeck SG, Gilbert MR. Bayesian optimal interval design: a simple and well-performing design for phase I oncology trials. Clin Cancer Res 2016 Sep 01;22(17):4291-4301 [FREE Full text] [doi: 10.1158/1078-0432.CCR-16-0592] [Medline: 27407096]
38. Yuan Y, Lin R, Li D, Nie L, Warren KE. Time-to-event bayesian optimal interval design to accelerate phase I trials. Clin Cancer Res 2018 Oct 15;24(20):4921-4930 [FREE Full text] [doi: 10.1158/1078-0432.CCR-18-0246] [Medline: 29769209]
39. Drug development tools: fit-for-purpose initiative. FDA. 2022. URL: https://tinyurl.com/2ffchcak [accessed 2023-12-10]
40. O'Quigley J, Pepe M, Fisher L. Continual reassessment method: a practical design for phase 1 clinical trials in cancer. Biometrics 1990 Mar;46(1):33 [FREE Full text] [doi: 10.2307/2531628]
41. Zhou Y, Lin R, Kuo YW, Lee JJ, Yuan Y. BOIN suite: a software platform to design and implement novel early-phase clinical trials. JCO Clin Cancer Inform 2021 Jan;5:91-101 [FREE Full text] [doi: 10.1200/CCI.20.00122] [Medline: 33439726]
42. Home page. Amneal. URL: https://amneal.com/ [accessed 2024-01-03]

Abbreviations

BOIN: Bayesian optimal interval
CoC: Certificate of Confidentiality
CP: chronic pancreatitis
CPDPC: Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer
CRF: case report form
DLT: dose-limiting toxicity
DSMB: Data and Safety Monitoring Board
EKG: electrocardiogram
FDA: Food and Drug Administration
HIPAA: Health Insurance Portability and Accountability Act
IRB: Institutional Review Board
MTD: maximum-tolerated dose
NaVs: voltage-gated sodium channels
NIDDK: National Institute of Diabetes and Digestive and Kidney Diseases
NIH: National Institutes of Health
NMDA: N-methyl-D-aspartate
OIH: opioid-induced hyperalgesia
PROCEED: Prospective Evaluation of Chronic Pancreatitis for Epidemiologic and Translational Studies
STTEPP: Safety, Tolerability, and Dose-Limiting Toxicity of Lacosamide in Patients With Painful Chronic Pancreatitis

Edited by A Mavragani; submitted 03.07.23; this is a non–peer-reviewed article;accepted 25.10.23; published 07.03.24.

Please cite as:
Fogel EL, Easler JJ, Yuan Y, Yadav D, Conwell DL, Vege SS, Han SY, Park W, Patrick V, White FA
Safety, Tolerability, and Dose-Limiting Toxicity of Lacosamide in Patients With Painful Chronic Pancreatitis: Protocol for a Phase 1 Clinical Trial to Determine Safety and Identify Side Effects
JMIR Res Protoc 2024;13:e50513
URL: https://www.researchprotocols.org/2024/1/e50513
doi:10.2196/50513
PMID:38451604

Protocol

Benefits, Harms, and Stakeholder Perspectives Regarding Opioid Therapy for Pain in Individuals With Metastatic Cancer: Protocol for a Descriptive Cohort Study

Katie Fitzgerald Jones[1*], PhD; Gretchen White[2], PhD; Antonia Bennett[3], PhD; Hailey Bulls[2], PhD; Paula Escott[2], BS; Sarah Orris[2], BS; Elizabeth Escott[2], BS; Stacy Fischer[4], MD; Megan Hamm[2], PhD; Tamar Krishnamurti[2], PhD; Risa Wong[2], MD; Thomas W LeBlanc[5], MD; Jane Liebschutz[2], MD; Salimah Meghani[6], PhD; Cardinale Smith[7], PhD; Jennifer Temel[8], MD; Christine Ritchie[9,10*], MSPH, MD; Jessica S Merlin[2*], PhD

[1]New England Geriatrics Research, Education, and Clinical Center (GRECC), Jamaica Plain, MA, United States
[2]University of Pittsburgh, Pittsburgh, PA, United States
[3]University of North Carolina, Chapel Hill, NC, United States
[4]University of Colorado, Aurora, CO, United States
[5]Duke University School of Medicine, Durham, NC, United States
[6]University of Pennsylvania, Philadelphia, PA, United States
[7]Icahn School of Medicine at Mount Sinai, New York, NY, United States
[8]Division of Hematology/Oncology, Massachusetts General Hospital, Boston, MA, United States
[9]Center for Aging and Serious Illness, Massachusetts General Hospital, Boston, MA, United States
[10]Department of Medicine, Harvard Medical School, Boston, MA, United States
[*]these authors contributed equally

Corresponding Author:
Katie Fitzgerald Jones, PhD
New England Geriatrics Research, Education, and Clinical Center (GRECC)
159 Huntington Ave
Jamaica Plain, MA, 02130
United States
Phone: 1 617 232 9500
Email: katie.jones4@va.gov

Abstract

Background: Opioids are a key component of pain management among patients with metastatic cancer pain. However, the evidence base available to guide opioid-related decision-making in individuals with advanced cancer is limited. Patients with advanced cancer or cancer that is unlikely to be cured frequently experience pain. Opioids are a key component of pain management among patients with metastatic cancer pain. Many individuals with advanced cancer are now living long enough to experience opioid-related harm. Emerging evidence from chronic noncancer pain literature suggests that longer-term opioid therapy may have limited benefits for pain and function, and opioid-related harms are also a major concern. However, whether these benefits and harms of opioids apply to patients with cancer-related pain is unknown.

Objective: This manuscript outlines the protocol for the "Opioid Therapy for Pain in Individuals With Metastatic Cancer: The Benefits, Harms, and Stakeholder Perspectives (BEST) Study." The study aims to better understand opioid decision-making in patients with advanced cancer, along with opioid benefits and harms, through prospective examination of patients' pain experiences and opioid side effects and understanding the decision-making by patients, care partners, and clinicians.

Methods: This is a multicenter, prospective cohort study that aims to enroll 630 patients with advanced cancer, 20 care partners, and 20 clinicians (670 total participants). Patient participants must have an advanced solid cancer diagnosis, defined by the American Cancer Society as cancer that is unlikely to be cured. We will recruit patient participants within 12 weeks after diagnosis so that we can understand opioid benefits, harms, and perspectives on opioid decision-making throughout the course of their advanced cancer (up to 2 years). We will also specifically elicit information regarding long-term opioid use (ie, opioids for ≥90 consecutive days) and exclude patients on long-term opioid therapy before an advanced cancer diagnosis. Lived-experience perspectives related to opioid use in those with advanced cancer will be captured by qualitative interviews with a subset of patients,

clinicians, and care partners. Our data collection will be grounded in a behavioral decision research approach that will allow us to develop future interventions to inform opioid-related decision-making for patients with metastatic cancer.

Results: Data collection began in October 2022 and is anticipated to end by November 2024.

Conclusions: Upon successful execution of our study protocol, we anticipate the development of a comprehensive evidence base on opioid therapy in individuals with advanced cancer guided by the behavioral decision research framework. The information gained from this study will be used to guide interventions to facilitate opioid decisions among patients, clinicians, and care partners. Given the limited evidence base about opioid therapy in people with cancer, we envision this study will have significant real-world implications for cancer-related pain management and opioid-related clinical decision-making.

International Registered Report Identifier (IRRID): DERR1-10.2196/54953

(JMIR Res Protoc 2024;13:e54953) doi:10.2196/54953

KEYWORDS

cancer; cancer-related pain; neoplasm-related pain; opioid analgesics; opioids; pain

Introduction

Patients with advanced cancer or cancer that is unlikely to be cured frequently experience pain [1,2]. Although the overall prevalence of pain and pain severity related to cancer appear to be decreasing, 40% of patients with cancer experienced pain during and up to 3 months after cancer treatment [1,3,4]. When stratified by cancer severity, patients with more advanced disease have higher rates of pain: up to 66%, compared to 39% for patients with localized or curative disease [4]. Although patients with any cancer can experience pain, those with breast, lung, head, and neck cancer experience pain most often [5]. Under- and untreated pain in individuals with cancer is associated with a variety of adverse health consequences, including functional limitations (eg, inability to work), suboptimal health behaviors (eg, reduced physical activity), emotional distress, social isolation, high health care use (eg, emergency department and inpatient admissions), and earlier death [6-9].

Opioids are a key component of pain management among patients with metastatic cancer pain [10]. Although rates of opioid prescribing in advanced cancer have not been well described, people with advanced cancer are prescribed long-term opioid therapy (ie, opioid prescription for at least 90 consecutive days) more often than people with limited-stage disease (66% vs 40%) [11]. A recent study using data from the National Survey on Drug Use and Health found that approximately half of cancer survivors with a recent diagnosis (within 12 months of the National Survey on Drug Use and Health survey) were prescribed an opioid during that year (54%) [12]. National guidelines from the American Society of Clinical Oncology [10] and the National Comprehensive Cancer Network [13] support opioids as a cornerstone of pain management for individuals with advanced cancer, suggesting that the benefits of opioid use outweigh the harms for this patient group.

However, many individuals with advanced cancer are now living long enough to experience opioid-related harm. Indeed, some advanced cancers are considered chronic diseases as patients are surviving longer due to improvements in cancer treatments [14]. For example, the median survival of individuals with metastatic breast cancer in a large national cohort of patients with breast cancer in France was 37 months [15], which has increased steadily over the previous decades [16]. Approximately one-third of individuals with metastatic breast cancer [17] or metastatic prostate cancer [18] survive for at least 5 years. This presents a complex clinical context for treating cancer-related pain with opioids, increasing the need to balance opioid-related benefits and harms.

Emerging evidence from the chronic noncancer pain literature suggests longer-term opioid therapy may have limited benefits for pain and function. For example, a recent meta-analysis of randomized controlled trials of opioids versus placebo for chronic (>3 month) “noncancer” pain observed a small improvement in pain of 0.69 (95% CI 0.56-0.82) on a scale of 0-10 that was less than the prespecified minimum clinically important difference of 1 [19]. Other systematic reviews and meta-analyses have yielded similar findings, including a lack of functional improvement with opioid therapy over placebo [20,21]. Analogous data do not yet exist for patients with advanced cancer; given the unique features of cancer pain and the commonly concurrent noncancer pain experienced by patients with cancer, it is important to better understand pain and pain management in persons with advanced cancer.

Opioid-related harms are also a major concern among people prescribed opioids. In one meta-analysis of 26 studies, 23% of participants decided to discontinue opioids due to side effects (eg, nausea and dizziness) [22]. In the general population, long-term opioid therapy is also associated with more serious harms; 21% to 29% develop opioid misuse, and 8% to 12% may progress to an opioid use disorder. Although more rare, opioid overdoses can occur (256 per 100,000 person-years among people recently prescribed opioids vs 36 per 100,000 years among those not prescribed opioids) [23,24]. In studies of noncancer pain, opioid-related harms are consistently related to both ingestion of high-dose opioids (ie, >90 mg morphine equivalents) and coprescription of sedating medications (benzodiazepines and gabapentin) [25-28]. People with cancer are more likely to be represented in the high-dose opioid groups and frequently experience polypharmacy [29,30]. However, whether these benefits and harms of opioids apply to patients with cancer-related pain is unknown.

This manuscript describes the study protocol for “Opioid Therapy for Pain in Individuals With Metastatic Cancer: The Benefits, Harms, and Stakeholder Perspectives (BEST) Study.”

The study aims to better understand opioid decision-making in patients with advanced cancer, along with opioid benefits and harms, through prospective examination of patients' pain experiences and opioid side effects and understanding the decision-making by patients, care partners, and clinicians.

Methods

Study Design

This is a multicenter, prospective cohort study that aims to enroll 630 patients with advanced cancer, 20 care partners, and 20 clinicians (670 total participants). The data collection is underway at 4 clinical sites. Site selection considered geographic diversity (Northeast, mid-Atlantic, West, and Southeast), the balance of urban versus rural patients, sufficient patient volume to reach the enrollment goal, and the ability to recruit based on previous success in cancer studies. Given well-established health disparities in cancer pain and its treatment, we selected sites that demonstrated a track record of successful recruitment of Black and Hispanic patient participants [31]. None of the chosen sites have opioid stewardship committees or programs, which could have the unintended consequence of limiting opioid prescribing [32]. Additionally, we conducted a comprehensive review of state opioid laws in preparation for the study [33], with most states specifying blanket cancer exemption for any opioid limitation, such as dose or limited day supply.

Participants

Patient participants must have an advanced solid cancer diagnosis, defined by the American Cancer Society as cancer that is unlikely to be cured [2]. An advanced cancer diagnosis can include patients who have distant metastases or a recurrence. Patient participants must be their own decision maker as determined by the electronic medical record (EMR) and enroll within 12 weeks of their advanced cancer diagnosis date. The research team will confirm an advanced cancer diagnosis using medical record documentation of pathology results or radiology and oncology documentation. We will recruit patient participants early after diagnosis so that we can understand opioid benefits, harms, and perspectives on opioid decision-making throughout the course of their advanced cancer (up to 2 years). Lived-experience perspectives related to opioid use in those with advanced cancer will be captured by qualitative interviews with a subset of enrolled patients, clinicians, and care partners.

We will specifically elicit information regarding long-term opioid use (ie, opioids for ≥90 consecutive days) and exclude patients on long-term opioid therapy before an advanced cancer diagnosis. Consistent with previous studies, we confirm opioid use in the medical record and will ask patient participants, "Did you take a strong prescription pain medication known as an opioid or narcotic for at least 90 days in a row during the past year? Examples of opioids include oxycodone, hydrocodone, hydromorphone, morphine, fentanyl, buprenorphine, methadone, and combination products such as oxycodone/acetaminophen." This question is consistent with other commonly used research definitions of long-term or chronic opioid therapy [34,35]. Notably, this long-term opioid use definition also excludes individuals who are receiving methadone or buprenorphine/naloxone (suboxone) for the treatment of opioid use disorder, as the potential benefits and harms of opioid therapy in this population are unique and merit separate investigation [36]. This will allow us to understand the benefits, risk factors for harm, and perspectives on opioid decision-making when a patient with newly diagnosed advanced cancer begins an opioid or continues a newly initiated opioid.

From the larger cohort, we will recruit 40 patient participants with advanced cancer—20 who are prescribed opioids at the time of enrollment and 20 who are not. From that sample of 40 patients, we will aim to obtain consent from care partners of at least 20 patients and clinicians of at least 20 patients.

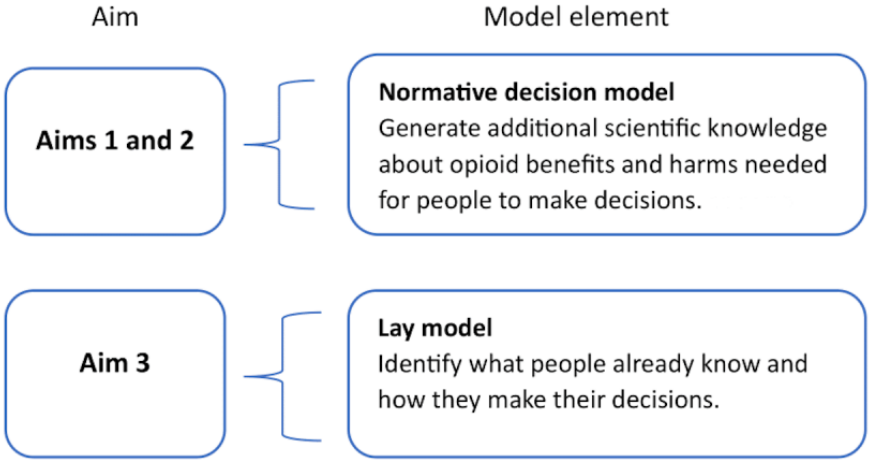
We will exclude individuals younger than 18 years of age, prisoners, pregnant people, and patients currently enrolled in hospice at the time of recruitment from the study. Patient participants do not need to report pain at the time of diagnosis since pain can occur at any point in the cancer trajectory. By including patient participants without pain at the time of diagnosis of metastatic disease, the study has the added benefit of describing the natural history of pain in patients with metastatic cancer for 2 years after diagnosis, filling an existing literature gap [3]. Patients who meet advanced cancer eligibility criteria will be recruited irrespective of their predicted prognosis, due to the inherent challenges of predicting prognosis [37,38].

For qualitative interviews, care partner participants must be a spouse, partner, child, relative, or friend who helps the patient with activities of daily living and health care needs at home, consistent with the National Cancer Institute definition of family caregivers [39]. Clinician participants will be physicians or advanced practice clinicians caring for a patient participant who has opioid prescribing authority and is willing to participate in a qualitative interview.

Theoretical Framework

Our data collection will be grounded in a behavioral decision research (BDR) approach [40] that will allow us to develop future interventions to inform opioid-related decision-making for patients with metastatic cancer. Opioid-related decision-making refers to decisions to initiate opioids or continue opioids over time. The BDR approach consists of 2 components. The first is the characterization of a "normative decision model," which describes the information distilled from existing scientific evidence that experts in the field believe that decision makers (patients, care partners, and clinicians) need to know to be able to make an informed decision. The second is a lay "mental model" of the decision, or what interested parties (ie, patients and care partners) already know and how they currently make their decisions. The normative decision model is a well-established approach for medical decision-making [41], including the development of opioid guidelines [42,43]. Consistent with previous studies, the lay decision model solicits perspectives on what patients, care partners, and clinicians consider foundational knowledge and how they make their decisions [44]. Interventions to support optimal decision-making can bridge the gap between the normative model and the contextual reality of how individuals are currently making those choices. Figure 1 provides the BDR framework-based approach mapped to the study aims.

Figure 1. Study aims mapped to behavioral decision-making model element.



Specific Aims

Using the BDR framework, the objective of this study is to create evidence to guide opioid prescribing in patients with advanced cancer.

The study's aims are as follows:

- Aim 1: To investigate the relationship between opioid therapy and opioid-related benefits.
- Hypothesis 1a: Prescribed opioids will be associated with decreased pain severity and pain interference (coprimary outcomes).
- Aim 2: To investigate risk factors for opioid-related harms.
- Hypothesis 2a: Certain coprescribed medications will be associated with an increased risk of opioid side effects (eg, benzodiazepines and somnolence).
- Hypothesis 2b: Younger age, history of substance use disorder, and history of mood disorders will be associated with a greater risk of opioid misuse and use disorder.
- Aim 3: To understand patient, care partners, and clinician perspectives on opioid-related decision-making.

Study Procedures

Recruitment

Potential patient participants will be identified using EMRs; *International Classification of Diseases, Tenth Revision* diagnosis codes; direct clinician referral; and referral from informational handouts in patient-facing platforms (eg, clinic rooms and chemotherapy teach-back packets). Study sites will develop reports to generate lists of potentially eligible patient participants in accordance with all rules of the HIPAA (Health Insurance Portability and Accountability Act), preparatory to the research exception [45]. The research coordinator will review listed patients' EMRs to verify eligibility following institution-specific procedures for contacting potential patient participants in clinic, over the telephone, or through letters. After receiving permission using one of the methods described above, trained research staff at each site will contact potential patient participants in-clinic or over the telephone to confirm eligibility. Subsequently, research staff will obtain consent, and data will be collected using Research Electronic Data Capture (REDCap; Vanderbilt University), a free and secure web-based application to capture research data [46].

Assessments

Once patients have consented and enrolled in the study, data collection will include patient-reported outcomes (PROs), chart reviews, and interviews. Table 1 provides an overview of the study procedures and time frame.

Table 1. Schedule of research activities.

Study stage	Screening and enrollment	Follow-up			
	Within 12 weeks of the date of diagnosis	Weekly after baseline	Monthly after baseline	Quarterly after baseline	Semiannually after baseline
Prescreening	✓				
Consent, screening, and contact information	✓				
Demographics and medical history	✓				
Baseline and demographics	✓				
Weekly 3-questions pain assessment: pain severity and inference		✓			
Monthly PRO[a] assessment: mood, substance use, symptoms, and opioid misuse (Carey 2-year index)			✓		
Chart reviews: substance use, opioid misuse, and opioid overdose				✓	
Patient calls and chart review: Opioid prescription or dose, benzodiazepine prescription, over or under consumption of opioids					✓
TAPS[b]: substance use and opioid use disorder				✓	
Patient participants, care partners, and clinician interviews				✓	

[a]PRO: patient-reported outcome.

[b]TAPS: Tobacco, Alcohol, Prescription Medication, and Other Substance Use Tool.

Study staff will confirm patient demographics and cancer type from the medical record. Sites will use a chart abstraction tool to gather medication-related data every 6 months. Opioid dose will also be assessed through self-report by reading back the dose and instructions on the opioid bottle and confirmed in the EMR. Patient participants will consent to receiving a phone call from the study staff for pill counts during the latter part of the month of their prescriptions every 3 months.

Patient participants will complete baseline assessments and PROs electronically using REDCap, over the phone, or during clinic visits through a tablet by the study staff. If patient participants are unable to complete PROs, care partners will be permitted to complete the PRO assessments on behalf of the patient participants. We acknowledge that based on systematic reviews in oncology, there may be differences in patient-proxy reports, with proxies having a more negative view of the patient's well-being [47].

The outcome measure for pain will be the Pain, Enjoyment, and General Activity (PEG) scale, a 3-item commonly reliable and validated measure used in oncology populations that asks about pain severity, pain interference in enjoyment of life, and pain interference in general well-being [48-50]. The PEG meets the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials recommendations and has a 7-day recall period [51]. The PEG will be collected weekly to provide longitudinal impact on pain severity, pain interference, and whether opioids precede any change in pain.

Additional monthly PROs will include information on mood (Functional Assessment of Cancer Therapy-General Well-Being Subscale); comorbidities (Self-Administered Comorbidity Questionnaire); functioning (Carey index); and if prescribed opioids, information on opioid misuse (Patient-Reported Outcomes Measurement Information System), opioid side effects (Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events), and substance use (Tobacco, Alcohol, Prescription Medication, and Other Substance Use Tool) [52-56]. These measures were selected because of their favorable psychometrics in the study population, brevity, and similar recall periods. This patient-participant burden is similar to other studies among patients with metastatic cancer [57].

For Aim 3, we will conduct one-on-one interviews with patients, their care partners, and clinicians with the goal of better understanding opioid-related decision-making. These interviews will occur every 3 months for 2 years or until death. The rationale for this frequency is that it strikes a balance between interviewing people often enough for them to remember aspects of opioid decision-making since the last interview but not so often as to ask about opioid-related decisions more frequently than those decisions occur or cause undue participant burden.

Analytic Plan

Aim 1: Data Analysis

This analysis will draw from all patient participants, regardless of whether they are prescribed opioids, so we can compare those who are with those who are not prescribed opioids. We will estimate differences in pain severity and interference between patients treated with opioids versus patients not treated with opioids using linear mixed-effects models, which will allow us to (1) account for repeated measures over time for each patient and (2) adjust for potential confounders. In the linear mixed-effects models, the dependent variables will be based on

the PEG: pain severity (first question is a continuous 0-10 value) and pain interference (mean of 3 PEG items) at each time point. Current opioid prescription, baseline pain severity or interference, and other confounders (ie, factors statistically associated with the exposure and outcome) will be included as fixed effects, while the subject will be included as a random effect.

Power Calculation for Aim 1

Power calculations were performed by simulation to allow a range of parameters to vary in all scenarios. Unlike a randomized trial, in this study we will not have control over the ratio of patients allocated to the 2 comparison groups (eg, there will not be precisely a 1:1 ratio of patients prescribed opioids vs patients not prescribed opioids for comparison). Scenarios were considered where the proportion of patients prescribed opioids was allowed to vary from 30% up to 70%, all assuming a mean baseline PEG of 6 in the patients not prescribed opioids, a reduction in the PEG of 1 point for patients that are prescribed opioids, and a common standard deviation in PEG scores of 2 points [51]. All scenarios considered had at least 90% power to detect a difference of 1 point between groups with a total sample size of 630 patients (allowing for 30%-70% of the population to be prescribe opioids, meaning that with a range of 189 up to 441 patients prescribed opioids during the study period, there is ample power to detect differences between groups). All scenarios had at least 99% power to detect a 2-point difference on the PEG. We acknowledge that up to 40% of patients may drop out during the study due to the morbidity and mortality of patients in palliative care [58]. Data up until the point of attrition will be included in the analysis, and this has also been accounted for in our calculations.

Missing Data for Aim 1

In general, linear mixed-effects models provide unbiased estimates when the data are assumed to be missing at random, meaning that the likelihood of a missing value is not related to the values of the outcome data (in this case, the assumption that missing values for pain are not related to the severity of the patient's pain). The setting of this study will have two basic missingness problems: (1) data that are missing while the patient still lives, either because the survey could not be completed or the patient did not wish to complete the pain instrument; and (2) pain data that are missing because the patient is deceased. The missing at random assumption can never be fully confirmed, so we will perform three sensitivity analyses to see how our results vary under different approaches to handling the missing pain values: (1) multiple imputations; (2) imputing the worst pain value for patients that fail to complete the pain instrument for any reason (including death before the scheduled assessment); and (3) imputing the worst pain value for patients that fail to complete the pain instrument, but omitting patients that have died. It should be noted that in this patient population, death is an expected outcome and not necessarily a negative outcome with respect to end-of-life suffering and pain management.

Aim 2a: Data Analysis

To test our hypothesis that coprescribed medications will be associated with an increased risk of opioid side effects (eg, benzodiazepines and somnolence), we will include only study patient participants who are prescribed opioids. Linear mixed-effects models will be used to assess the relationships between selected risk factors and the corresponding suspected opioid side effects. Each side effect is scored on the respective weekly or monthly assessments. Analyses will be conducted to examine the relationship between coprescribed medications and each of the respective opioid side effects (constipation, nausea, dry mouth, and somnolence) as well as targeted relationships specifically of interest for individual exposures or side effects combinations, including (1) coprescription of other constipating medications and constipation, (2) coprescription of other constipating medications and nausea, (3) coprescription of anticholinergic medications and dry mouth, and (4) coprescription of benzodiazepines with somnolence. We will also examine the association between which opioid is prescribed (ie, morphine vs oxycodone) and each of the same respective opioid side effects (constipation, nausea, dry mouth, and somnolence). The use of linear mixed-effects models will provide estimates of the effect of each risk factor of interest on each of the respective side effects while also allowing the inclusion of longitudinal measurements from patient participants.

Power Calculation for Aim 2a

With an overall sample size of 630, we anticipate approximately 50% (315/630) of the study sample to be prescribed opioids, leaving 315 patient participants available for the analyses pertinent to this hypothesis. We examined a range of scenarios allowing anywhere from 10% to 30% of the eligible participants to have each exposure, performing power analyses to detect a 0.5-point difference in means for each side effect on the 1-5 scale (assuming a SD of 1 point). Power is about 65% if the exposure is rare (10% of patients prescribed opioids) but increases to 87% if the exposure is present in 20% of patients prescribed opioids and 93% if exposure is present in 30% of patients prescribed opioids. Again, we account for up to 40% attrition during the study. Note that patient participants will contribute data until they drop out, and this data will be included in the analysis.

Aim 2: Data Analysis to Test Hypothesis 2b

To test our hypothesis that younger age, history of substance use disorder, and history of mood disorders will be associated with a greater risk of opioid misuse and use disorder, we will perform multivariable Cox regression analyses to assess the respective risk factors of interest. We will use a single prespecified model that includes age, history of substance use disorder, and history of mood disorders using baseline PRO data and chart review.

Power Calculation for Aim 2b

With a total sample size of 630 patients recruited in Aim 1, the power calculation for this subaim assumed a scenario where approximately 50% (315/630) of the patients are prescribed opioids, leaving 315 patients available for this aim. We anticipate opioid misuse will occur in 20% to 30% of patients.

For a rarer event such as opioid use disorder, which is estimated to occur in approximately 10% of the patients, a sample size of 315 patients will be sufficient to support a model with 5 candidate predictor variables.

Missing Data for Aim 2

Unlike Aim 1, missing data should not affect analyses in this aim. The development of opioid-related complications will also be considered an event if it is known to occur and otherwise assumed not to occur during the period patients are under observation.

Aim 3: Data Analysis

The purpose of Aim 3 is to identify what patients, care partners, and clinicians already know and how they make opioid-related decisions to develop the lay model of the BDR. To determine decisional influences, the BDR framework uses the "mental models approach" to elicit these views [59]. To create the BDR framework lay model, we will structure the patient and care partner interviews by focusing on (1) what they already know about opioids, (2) how they make decisions, (3) examining whether this is consistent with or contrary to the normative model of evaluating risks and harms, and (4) how they think decisions around opioid use should ideally be made. The interviews begin with general questions and then become more specific, asking about each topic from the expert model. We will structure the clinician interviews by focusing on (1) their assessment of the patient's pain; (2) approaches to best treating it, including opioids; and (3) their decision-making around opioid prescribing. We will also evaluate whether different patient, care partner, and clinician perspectives are consistent with or contrary to one another.

For the semistructured interviews (40 participants with metastatic cancer from our larger cohort, 20 who are prescribed opioids at the time of enrollment, and 20 who are not), we aim to understand perspectives on deciding to initiate or continue opioid therapy or not. This sample size is based on evidence that suggests thematic saturation is achieved at 8-16 interviews; since we expect up to 40% attrition, this approach will ensure we have at least 20 participants [60]. We will purposively sample [61] to ensure diversity on race, site, and baseline PEG value; we will also recruit some individuals who have a history of a substance use disorder and are therefore at particularly high risk for negative consequences when prescribed opioids.

Similarly, we will recruit patient participants' care partners and clinicians. We will aim for at least 10 people who have care partners who consent to the group prescribed opioids at enrollment and 10 care partners of patient participants who have been prescribed opioids at enrollment. This approach will ensure that we have enough care partners to provide adequate perspective but not severely bias our sample by only allowing the enrollment of individuals who have care partners willing and able to enroll in this study. As described above, we will also purposefully sample 25% of patient participants who do not have care partners so that these perspectives are represented. Interviewing patients and their care partners s and clinicians will allow for triangulation of findings. Additionally, following patients, care partners, and clinicians longitudinally will allow for a detailed understanding of how decision-making changes over the course of metastatic cancer, allow participants to reflect on what they would have liked to know earlier based on what they know now, and provide real-time data on actual decisions (eg, initiation or discontinuation of opioids) on which participants can be asked to comment. Given the challenges inherent in engaging clinicians, we will aim for 15-minute focused interviews.

Trained qualitative researchers will collect and analyze the qualitative data. Interviews will be conducted remotely (through phone or Zoom [Zoom Video Communications], according to the interviewee's preference), and interview recordings will be transcribed verbatim (with details that might identify the interviewee redacted). Coding the data will require a hybrid deductive-inductive approach. A prespecified set of codes will be identified from the normative model. The presence and absence of these codes (eg, the accuracy of knowledge about the relationship between opioids and addiction) will be used to document the consistency between the normative model and stakeholder perspectives. In addition, we will take an inductive analytical approach to identify emergent values and beliefs that are not present in the normative models. Codes will be developed through open coding of the transcripts to determine topics and themes that emerged in the interview transcripts with input on topics or themes that the study team anticipates being relevant, resulting in simultaneously inductive and deductive development of the codebook. A draft codebook including detailed code definitions will be discussed with the study team to ensure that codes reflect both the data as they are emerging as well as relevant topical themes that are important to the team. Codes will be thoroughly checked to determine that definitions are distinct enough to reduce ambiguity in the coding process.

About 25% of the transcripts will be coded by 2 independent, trained qualitative coders to ensure quality and consistency in coding. Coding will then be compared for the purposes of calculating Cohen kappa inter-coder reliability scores [62]. Any coding discrepancies identified during this comparison will be adjudicated by the coders until full agreement on coding is achieved. The finalized coding on these transcripts will be recorded in a single ATLAS.ti file, following which the primary coder will complete the coding of the remaining transcripts according to the codebook and through the adjudication process and discussion by the study team with content and methodologic expertise. This process allows for consistency and quality across transcripts. Once coding is complete and uploaded to ATLAS.ti with quotes associated with codes, we will thematically analyze and determine the relative frequencies of various codes and the most salient themes. The resulting thematic analysis will be discussed with the entire investigator team to use the findings to build lay models of patient, care partner, or clinician decision-making around opioid use for patients with metastatic cancer.

Ethical Considerations

This study has been reviewed and approved by the University of Pittsburgh Institutional Review Board (STUDY20090231), which serves as the institutional review board of record for all research locations. Informed consent is obtained by trained

research staff members at each site. The study was granted a waiver of HIPAA authorization to identify participants who meet study inclusion criteria. The study was granted a waiver to document informed consent for the qualitative interviews conducted in Aim 3. Verbal consent will still be obtained by interviewers before commencing the interview.

Study data will be identifiable while the study is ongoing, as there are many contact points with participants. All study data are segregated by research site, so recruitment team members only have access to the data for participants they have enrolled. The University of Pittsburgh team has access to all study records as the team conducts follow-up assessments. All results that will be published in this study in the future will be done in an aggregate, deidentified manner.

We will reimburse patient participants US $10 for the baseline questionnaire, US $2 per weekly questionnaire, and US $10 per monthly questionnaire (up to US $394 if all questionnaires are completed over the 2 years). Patient participants who complete at least 80% of questionnaires during each year of follow-up will be eligible for an annual bonus payment of US $20. This results in US $434 of total possible compensation for Aims 1 and 2. For Aim 3, patients and care partners will be reimbursed US $30 per interview. Clinicians will not be compensated.

Results

This study was peer-reviewed and funded by the National Institute of Nursing Research in September 2021. Recruitment began in October 2022; we anticipate completing recruitment by November 2024. Follow-up assessments will end by November 2026, at which time we can finalize our data analysis.

Discussion

This paper presents the study protocol for the benefits, harms, and stakeholder perspectives regarding opioid therapy for pain in individuals with metastatic cancers .The study also uses PRO measures, qualitative data collection, and repeated assessments to ascertain how decision-making differs throughout the cancer trajectory, including at the end of life. The protocol is innovative because it addresses the research gap on the benefits and harms of opioids in metastatic cancer in a novel way. This includes our prospective design in patients recently diagnosed with advanced cancer, the collection of data from multiple perspectives (patients, clinicians, and care partners), and the inclusion of a well-known decision-making framework that can facilitate the design of future interventions.

There are several potential challenges or limitations to the research protocol. The first is likely challenges of retention and recruitment that are expected in longitudinal studies, especially in individuals with cancer and serious illnesses. Second, there is a potential for low enrollment or a high rate of missing data due to death, illness, dropout, or participant burden. We have attempted to account for these anticipated issues by having backup recruitment sites and conservative sample size estimates. Third, opioid prescribing is an evolving area of clinical practice and subject to federal and state oversight. It is possible that local and state regulations or institutional policies will change during the study period, resulting in a decrease in opioid prescribing and recruitment issues. Last, prospective investigation of adverse effects such as overdose or opioid-related mortality may be difficult to capture because these events are relatively rare.

At the end of the study, we anticipate the development of a comprehensive evidence base on opioid therapy in individuals with advanced cancer, guided by the BDR framework. The information gained from this study will be used to guide interventions to facilitate opioid decisions among patients, clinicians, and care partners. Given the limited evidence base about opioid therapy in people with cancer, we envision this study will have significant real-world implications for cancer-related pain management and opioid-related clinical decision-making.

Acknowledgments

This work is supported by R01 NR020031-01. The sponsor has no role in study design, in the collection, analysis, and interpretation of data, in the writing of the report, or in the decision to submit the study for publication. JSM is funded by a National Institutes of Health grant (K24DA056837). The views expressed in this article are those of the authors and do not necessarily reflect the views of the National Institutes of Health.

Data Availability

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

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-reviewer report from the National Institute of Nursing Research.
[PDF File (Adobe PDF File), 84 KB - resprot_v13i1e54953_app1.pdf]

References

1. Snijders RAH, Brom L, Theunissen M, van den Beuken-van Everdingen M. Update on prevalence of pain in patients with cancer 2022: a systematic literature review and meta-analysis. Cancers (Basel) 2023;15(3):591 [FREE Full text] [doi: 10.3390/cancers15030591] [Medline: 36765547]
2. Understanding advanced and metastatic cancer. American Cancer Society. 2020. URL: https://www.cancer.org/cancer/managing-cancer/advanced-cancer/what-is.html [accessed 2024-02-06]
3. Evenepoel M, Haenen V, de Baerdemaecker T, Meeus M, Devoogdt N, Dams L, et al. Pain prevalence during cancer treatment: a systematic review and meta-analysis. J Pain Symptom Manage 2022;63(3):e317-e335. [doi: 10.1016/j.jpainsymman.2021.09.011] [Medline: 34563628]
4. van den Beuken-van Everdingen MHJ, Hochstenbach LMJ, Joosten EAJ, Tjan-Heijnen VCG, Janssen DJA. Update on prevalence of pain in patients with cancer: systematic review and meta-analysis. J Pain Symptom Manage 2016;51(6):1070-1090.e9 [FREE Full text] [doi: 10.1016/j.jpainsymman.2015.12.340] [Medline: 27112310]
5. Glare P, Aubrey K, Gulati A, Lee YC, Moryl N, Overton S. Pharmacologic management of persistent pain in cancer survivors. Drugs 2022;82(3):275-291 [FREE Full text] [doi: 10.1007/s40265-022-01675-6] [Medline: 35175587]
6. Azizoddin DR, Schreiber K, Beck MR, Enzinger AC, Hruschak V, Darnall BD, et al. Chronic pain severity, impact, and opioid use among patients with cancer: an analysis of biopsychosocial factors using the CHOIR learning health care system. Cancer 2021;127(17):3254-3263 [FREE Full text] [doi: 10.1002/cncr.33645] [Medline: 34061975]
7. Paice JA, Portenoy R, Lacchetti C, Campbell T, Cheville A, Citron M, et al. Management of chronic pain in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 2016;34(27):3325-3345 [FREE Full text] [doi: 10.1200/jco.2016.68.5206]
8. O'Connor M, Weir J, Butcher I, Kleiboer A, Murray G, Sharma N, et al. Pain in patients attending a specialist cancer service: prevalence and association with emotional distress. J Pain Symptom Manage 2012;43(1):29-38 [FREE Full text] [doi: 10.1016/j.jpainsymman.2011.03.010] [Medline: 21680140]
9. Breivik H, Cherny N, Collett B, de Conno F, Filbet M, Foubert AJ, et al. Cancer-related pain: a pan-European survey of prevalence, treatment, and patient attitudes. Ann Oncol 2009;20(8):1420-1433 [FREE Full text] [doi: 10.1093/annonc/mdp001] [Medline: 19244085]
10. Paice JA, Bohlke K, Barton D, Craig DS, El-Jawahri A, Hershman DL, et al. Use of opioids for adults with pain from cancer or cancer treatment: ASCO guideline. J Clin Oncol 2023;41(4):914-930 [FREE Full text] [doi: 10.1200/JCO.22.02198] [Medline: 36469839]
11. Cuthbert CA, Xu Y, Kong S, Boyne DJ, Hemmelgarn BR, Cheung WY. Patient-level factors associated with chronic opioid use in cancer: a population-based cohort study. Support Care Cancer 2020;28(9):4201-4209. [doi: 10.1007/s00520-019-05224-y] [Medline: 31900614]
12. Jairam V, Yang DX, Verma V, Yu JB, Park HS. National patterns in prescription opioid use and misuse among cancer survivors in the United States. JAMA Netw Open 2020;3(8):e2013605 [FREE Full text] [doi: 10.1001/jamanetworkopen.2020.13605] [Medline: 32804217]
13. Swarm RA, Paice JA, Anghelescu DL, Are M, Bruce JY, Buga S, et al. Adult cancer pain, version 3.2019, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2019;17(8):977-1007 [FREE Full text] [doi: 10.6004/jnccn.2019.0038] [Medline: 31390582]
14. Pituskin E. Cancer as a new chronic disease: oncology nursing in the 21st century. Can Oncol Nurs J 2022;32(1):87-92 [FREE Full text] [Medline: 35280062]
15. Gobbini E, Ezzalfani M, Dieras V, Bachelot T, Brain E, Debled M, et al. Time trends of overall survival among metastatic breast cancer patients in the real-life ESME cohort. Eur J Cancer 2018;96:17-24. [doi: 10.1016/j.ejca.2018.03.015] [Medline: 29660596]
16. Tai P, Yu E, Vinh-Hung V, Cserni G, Vlastos G. Survival of patients with metastatic breast cancer: twenty-year data from two SEER registries. BMC Cancer 2004;4:60 [FREE Full text] [doi: 10.1186/1471-2407-4-60] [Medline: 15345027]
17. Mariotto AB, Etzioni R, Hurlbert M, Penberthy L, Mayer M. Estimation of the number of women living with metastatic breast cancer in the United States. Cancer Epidemiol Biomarkers Prev 2017;26(6):809-815 [FREE Full text] [doi: 10.1158/1055-9965.EPI-16-0889] [Medline: 28522448]
18. Survival rates for prostate cancer. American Cancer Society. 2023. URL: https://www.cancer.org/cancer/types/prostate-cancer/detection-diagnosis-staging/survival-rates.html [accessed 2024-02-06]
19. Busse JW, Wang L, Kamaleldin M, Craigie S, Riva JJ, Montoya L, et al. Opioids for chronic noncancer pain: a systematic review and meta-analysis. JAMA 2018;320(23):2448-2460 [FREE Full text] [doi: 10.1001/jama.2018.18472] [Medline: 30561481]
20. Chou R, Deyo R, Devine B, Hansen R, Sullivan S, Jarvik JG, et al. The effectiveness and risks of long-term opioid treatment of chronic pain. Evid Rep Technol Assess (Full Rep) 2014(218):1-219. [doi: 10.23970/AHRQEPCERTA218] [Medline: 30313000]
21. Nuckols TK, Anderson L, Popescu I, Diamant AL, Doyle B, Di Capua P, et al. Opioid prescribing: a systematic review and critical appraisal of guidelines for chronic pain. Ann Intern Med 2014;160(1):38-47 [FREE Full text] [doi: 10.7326/0003-4819-160-1-201401070-00732] [Medline: 24217469]

22. Noble M, Treadwell JR, Tregear SJ, Coates VH, Wiffen PJ, Akafomo C, et al. Long-term opioid management for chronic noncancer pain. Cochrane Database Syst Rev 2010;2010(1):CD006605 [FREE Full text] [doi: 10.1002/14651858.CD006605.pub2] [Medline: 20091598]
23. Gomes T, Mamdani MM, Dhalla IA, Paterson JM, Juurlink DN. Opioid dose and drug-related mortality in patients with nonmalignant pain. Arch Intern Med 2011;171(7):686-691 [FREE Full text] [doi: 10.1001/archinternmed.2011.117] [Medline: 21482846]
24. Chou R, Turner JA, Devine EB, Hansen RN, Sullivan SD, Blazina I, et al. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. Ann Intern Med 2015;162(4):276-286 [FREE Full text] [doi: 10.7326/M14-2559] [Medline: 25581257]
25. Gomes T, Tadrous M, Mamdani MM, Paterson JM, Juurlink DN. The burden of opioid-related mortality in the United States. JAMA Netw Open 2018;1(2):e180217 [FREE Full text] [doi: 10.1001/jamanetworkopen.2018.0217] [Medline: 30646062]
26. Chua KP, Brummett CM, Conti RM, Bohnert A. Association of opioid prescribing patterns with prescription opioid overdose in adolescents and young adults. JAMA Pediatr 2020;174(2):141-148 [FREE Full text] [doi: 10.1001/jamapediatrics.2019.4878] [Medline: 31841589]
27. Bohnert ASB, Valenstein M, Bair MJ, Ganoczy D, McCarthy JF, Ilgen MA, et al. Association between opioid prescribing patterns and opioid overdose-related deaths. JAMA 2011;305(13):1315-1321 [FREE Full text] [doi: 10.1001/jama.2011.370] [Medline: 21467284]
28. Dunn KM, Saunders KW, Rutter CM, Banta-Green CJ, Merrill JO, Sullivan MD, et al. Opioid prescriptions for chronic pain and overdose: a cohort study. Ann Intern Med 2010;152(2):85-92 [FREE Full text] [doi: 10.7326/0003-4819-152-2-201001190-00006] [Medline: 20083827]
29. Merlin JS, Black AC, Midboe AM, Troszak L, Asch SM, Bohnert A, et al. Long-term opioid therapy trajectories and overdose in patients with and without cancer. BMJ Oncol 2023;2(1):e000023 [FREE Full text] [doi: 10.1136/bmjonc-2022-000023] [Medline: 38259328]
30. Murphy CC, Fullington HM, Alvarez CA, Betts AC, Lee SJC, Haggstrom DA, et al. Polypharmacy and patterns of prescription medication use among cancer survivors. Cancer 2018;124(13):2850-2857 [FREE Full text] [doi: 10.1002/cncr.31389] [Medline: 29645083]
31. Meghani SH, Byun E, Gallagher RM. Time to take stock: a meta-analysis and systematic review of analgesic treatment disparities for pain in the United States. Pain Med 2012;13(2):150-174 [FREE Full text] [doi: 10.1111/j.1526-4637.2011.01310.x] [Medline: 22239747]
32. Perrone J, Weiner SG, Nelson LS. Stewarding recovery from the opioid crisis through health system initiatives. West J Emerg Med 2019;20(2):198-202 [FREE Full text] [doi: 10.5811/westjem.2018.11.39013] [Medline: 30881536]
33. Bulls HW, Bell LF, Orris SR, Goodin BR, Liebschutz JM, Wozniak A, et al. Exemptions to state laws regulating opioid prescribing for patients with cancer-related pain: a summary. Cancer 2021;127(17):3137-3144 [FREE Full text] [doi: 10.1002/cncr.33639] [Medline: 34043811]
34. Karmali RN, Bush C, Raman SR, Campbell CI, Skinner AC, Roberts AW. Long-term opioid therapy definitions and predictors: a systematic review. Pharmacoepidemiol Drug Saf 2020;29(3):252-269 [FREE Full text] [doi: 10.1002/pds.4929] [Medline: 31851773]
35. Hasegawa T, Oguri T, Osawa T, Sawa T, Osaga S, Okuyama T, et al. Opioid dose and survival of patients with incurable nonsmall cell lung cancer: a prospective cohort study. J Palliat Med 2018;21(10):1436-1441. [doi: 10.1089/jpm.2018.0044] [Medline: 29893612]
36. Klimas J, Gorfinkel L, Fairbairn N, Amato L, Ahamad K, Nolan S, et al. Strategies to identify patient risks of prescription opioid addiction when initiating opioids for pain: a systematic review. JAMA Netw Open 2019;2(5):e193365 [FREE Full text] [doi: 10.1001/jamanetworkopen.2019.3365] [Medline: 31050783]
37. Hanson LC, Bull J, Wessell K, Massie L, Bennett RE, Kutner JS, et al. Strategies to support recruitment of patients with life-limiting illness for research: the Palliative Care Research Cooperative Group. J Pain Symptom Manage 2014;48(6):1021-1030 [FREE Full text] [doi: 10.1016/j.jpainsymman.2014.04.008] [Medline: 24863152]
38. Petrillo LA, Shimer SE, Zhou AZ, Sommer RK, Feldman JE, Hsu KE, et al. Prognostic communication about lung cancer in the precision oncology era: a multiple-perspective qualitative study. Cancer 2022;128(16):3120-3128 [FREE Full text] [doi: 10.1002/cncr.34369] [Medline: 35731234]
39. Informal caregivers in cancer (PDQ®)–patient version. National Cancer Institute. 2023. URL: https://www.cancer.gov/about-cancer/coping/family-friends/family-caregivers-pdq#:~:text=and%20after%20treatment.-,Caregivers%20help%20people%20with%20cancer%20during%20and%20after%20treatment.,person%20they%20are%20caring%20for [accessed 2024-02-06]
40. Payne JW, Bettman JR, Luce MF. Chapter 5—Behavioral decision research: an overview. In: Birnbaum MH, editor. Measurement, Judgment and Decision Making. San Diego, CA: Academic Press; 1998:303-359.
41. Enhancing benefit-risk assessment in regulatory decision-making. U.S. Food & Drug Administration. 2022. URL: https://www.fda.gov/industry/prescription-drug-user-fee-amendments/enhancing-benefit-risk-assessment-regulatory-decision-making [accessed 2024-02-06]

42. Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. Prescribing opioids for pain—the New CDC Clinical Practice Guideline. N Engl J Med 2022;387(22):2011-2013 [FREE Full text] [doi: 10.1056/NEJMp2211040] [Medline: 36326116]
43. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. JAMA 2016;315(15):1624-1645 [FREE Full text] [doi: 10.1001/jama.2016.1464] [Medline: 26977696]
44. de Bruine WB, Downs JS, Fischhoff B. Adolescents' thinking about the risks of sexual behaviors. In: Lovett MC, Shah P, editors. Thinking with Data. New Jersey: Lawrence Erlbaum Associates, Inc., Publishers; 2007:421-439.
45. Clinical research and the HIPAA privacy rule. National Institutes of Health. URL: https://privacyruleandresearch.nih.gov/clin_research.asp#:~:text=Under%20the%20%22preparatory%20to%20research,not%20contact%2C%20potential%20study%20participants [accessed 2024-02-06]
46. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research Electronic Data Capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42(2):377-381 [FREE Full text] [doi: 10.1016/j.jbi.2008.08.010] [Medline: 18929686]
47. Roydhouse JK, Wilson IB. Systematic review of caregiver responses for patient health-related quality of life in adult cancer care. Qual Life Res 2017;26(8):1925-1954 [FREE Full text] [doi: 10.1007/s11136-017-1540-6] [Medline: 28293821]
48. Abahussin AA, West RM, Wong DC, Ziegler LE. PROMs for pain in adult cancer patients: a systematic review of measurement properties. Pain Pract 2019;19(1):93-117 [FREE Full text] [doi: 10.1111/papr.12711] [Medline: 29772118]
49. Shi Q, Mendoza TR, Dueck AC, Ma H, Zhang J, Qian Y, et al. Determination of mild, moderate, and severe pain interference in patients with cancer. Pain 2017;158(6):1108-1112. [doi: 10.1097/j.pain.0000000000000890] [Medline: 28267060]
50. Krebs EE, Lorenz KA, Bair MJ, Damush TM, Wu J, Sutherland JM, et al. Development and initial validation of the PEG, a three-item scale assessing pain intensity and interference. J Gen Intern Med 2009;24(6):733-738 [FREE Full text] [doi: 10.1007/s11606-009-0981-1] [Medline: 19418100]
51. Smith SM, Dworkin RH, Turk DC, McDermott MP, Eccleston C, Farrar JT, et al. Interpretation of chronic pain clinical trial outcomes: IMMPACT recommended considerations. Pain 2020;161(11):2446-2461 [FREE Full text] [doi: 10.1097/j.pain.0000000000001952] [Medline: 32520773]
52. McNeely J, Wu LT, Subramaniam G, Sharma G, Cathers LA, Svikis D, et al. Performance of the tobacco, alcohol, prescription medication, and other substance use (TAPS) tool for substance use screening in primary care patients. Ann Intern Med 2016;165(10):690-699 [FREE Full text] [doi: 10.7326/M16-0317] [Medline: 27595276]
53. Weitzner MA, Meyers CA, Gelke CK, Byrne KS, Cella DF, Levin VA. The Functional Assessment of Cancer Therapy (FACT) scale. development of a brain subscale and revalidation of the general version (FACT-G) in patients with primary brain tumors. Cancer 1995;75(5):1151-1161. [doi: 10.1002/1097-0142(19950301)75:5<1151::aid-cncr2820750515>3.0.co;2-q] [Medline: 7850714]
54. You DS, Cook KF, Domingue BW, Ziadni MS, Hah JM, Darnall BD, et al. Customizing CAT administration of the PROMIS misuse of prescription pain medication item bank for patients with chronic pain. Pain Med 2021;22(7):1669-1675 [FREE Full text] [doi: 10.1093/pm/pnab159] [Medline: 33944948]
55. Sangha O, Stucki G, Liang MH, Fossel AH, Katz JN. The Self-Administered Comorbidity Questionnaire: a new method to assess comorbidity for clinical and health services research. Arthritis Rheum 2003;49(2):156-163 [FREE Full text] [doi: 10.1002/art.10993] [Medline: 12687505]
56. Carey EC, Walter LC, Lindquist K, Covinsky KE. Development and validation of a functional morbidity index to predict mortality in community-dwelling elders. J Gen Intern Med 2004;19(10):1027-1033 [FREE Full text] [doi: 10.1111/j.1525-1497.2004.40016.x] [Medline: 15482555]
57. Kutner JS, Blatchford PJ, Taylor DH, Ritchie CS, Bull JH, Fairclough DL, et al. Safety and benefit of discontinuing statin therapy in the setting of advanced, life-limiting illness: a randomized clinical trial. JAMA Intern Med 2015;175(5):691-700 [FREE Full text] [doi: 10.1001/jamainternmed.2015.0289] [Medline: 25798575]
58. Hui D, Glitza I, Chisholm G, Yennu S, Bruera E. Attrition rates, reasons, and predictive factors in supportive care and palliative oncology clinical trials. Cancer 2013;119(5):1098-1105 [FREE Full text] [doi: 10.1002/cncr.27854] [Medline: 23132290]
59. Morgan MG, Fischhoff B, Bostrom A, Atman CJ. Risk Communication: A Mental Models Approach. Cambridge: Cambridge University Press; 2002.
60. Hennink M, Kaiser BN. Sample sizes for saturation in qualitative research: a systematic review of empirical tests. Soc Sci Med 2022;292:114523 [FREE Full text] [doi: 10.1016/j.socscimed.2021.114523] [Medline: 34785096]
61. Benoot C, Hannes K, Bilsen J. The use of purposeful sampling in a qualitative evidence synthesis: a worked example on sexual adjustment to a cancer trajectory. BMC Med Res Methodol 2016;16:21 [FREE Full text] [doi: 10.1186/s12874-016-0114-6] [Medline: 26891718]
62. McHugh ML. Interrater reliability: the kappa statistic. Biochem Med (Zagreb) 2012;22(3):276-282 [FREE Full text] [Medline: 23092060]

Abbreviations

BDR: behavioral decision research

BEST: Benefits, Harms, and Stakeholder Perspectives
EMR: electronic medical record
HIPAA: Health Insurance Portability and Accountability Act
REDCap: Research Electronic Data Capture
PRO: patient-reported outcome
PEG: Pain, Enjoyment, and General Activity

Edited by A Mavragani; submitted 28.11.23; this is a non–peer-reviewed article;accepted 01.02.24; published 13.03.24.

Please cite as:
Jones KF, White G, Bennett A, Bulls H, Escott P, Orris S, Escott E, Fischer S, Hamm M, Krishnamurti T, Wong R, LeBlanc TW, Liebschutz J, Meghani S, Smith C, Temel J, Ritchie C, Merlin JS
Benefits, Harms, and Stakeholder Perspectives Regarding Opioid Therapy for Pain in Individuals With Metastatic Cancer: Protocol for a Descriptive Cohort Study
JMIR Res Protoc 2024;13:e54953
URL: https://www.researchprotocols.org/2024/1/e54953
doi:10.2196/54953
PMID:38478905

Protocol

Designing, Developing, and Testing a Chatbot for Parents and Caregivers of Children and Young People With Rheumatological Conditions (the IMPACT Study): Protocol for a Co-Designed Proof-of-Concept Study

Polly Livermore[1,2,3,4], PhD; Klaudia Kupiec[1], MSc; Lucy R Wedderburn[2,3,4], MBBS, MA, PhD; Andrea Knight[5,6,7], MD, MSCE; Ameenat L Solebo[3,8], PhD; Roz Shafran[3], PhD; Glenn Robert[9], MSc, PhD; N J Sebire[3], MD; Faith Gibson[10,11], MSc, PhD; IMPACT Steering Group[12]

[1]Rheumatology Department, Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom
[2]NIHR Biomedical Research Centre at Great Ormond Street Hospital for Children, London, United Kingdom
[3]University College London Great Ormond Street Institute of Child Health, London, United Kingdom
[4]Centre for Adolescent Rheumatology Versus Arthritis at UCL, UCLH and GOSH, London, United Kingdom
[5]Division of Rheumatology, The Hospital for Sick Children, Toronto, ON, Canada
[6]Neurosciences and Mental Health Program, SickKids Research Institute, Toronto, ON, Canada
[7]Temerty Faculty of Medicine, University of Toronto, Toronto, ON, Canada
[8]Opthamology Department, Great Ormond Street Children's Hospital NHS Foundation Trust, London, United Kingdom
[9]Kings College London, London, United Kingdom
[10]School of Health Sciences, University of Surrey, Surrey, United Kingdom
[11]Director of Research - Nursing and Allied Health, Great Ormond Street Children's Hospital, London, United Kingdom
[12]See Acknowledgments

Corresponding Author:
Polly Livermore, PhD
Rheumatology Department, Great Ormond Street Hospital for Children NHS Foundation Trust
Great Ormond Street
London, WC1N 3JH
United Kingdom
Phone: 44 2074059200
Email: polly.livermore@ucl.ac.uk

Abstract

Background: Pediatric rheumatology is a term that encompasses over 80 conditions affecting different organs and systems. Children and young people with rheumatological chronic conditions are known to have high levels of mental health problems and therefore are at risk of poor health outcomes. Clinical psychologists can help children and young people manage the daily difficulties of living with one of these conditions; however, there are insufficient pediatric psychologists in the United Kingdom. We urgently need to consider other ways of providing early, essential support to improve their current well-being. One way of doing this is to empower parents and caregivers to have more of the answers that their children and young people need to support them further between their hospital appointments.

Objective: The objective of this co-designed proof-of-concept study is to design, develop, and test a chatbot intervention to support parents and caregivers of children and young people with rheumatological conditions.

Methods: This study will explore the needs and views of children and young people with rheumatological conditions, their siblings, parents, and caregivers, as well as health care professionals working in pediatric rheumatology. We will ask approximately 100 participants in focus groups where they think the gaps are in current clinical care and what ideas they have for improving upon them. Creative experience-based co-design workshops will then decide upon top priorities to develop further while informing the appearance, functionality, and practical delivery of a chatbot intervention. Upon completion of a minimum viable product, approximately 100 parents and caregivers will user-test the chatbot intervention in an iterative sprint methodology to determine its worth as a mechanism for support for parents.

Results: A total of 73 children, young people, parents, caregivers, and health care professionals have so far been enrolled in the study, which began in November 2023. The anticipated completion date of the study is April 2026. The data analysis is expected to be completed in January 2026, with the results being published in April 2026.

Conclusions: This study will provide evidence on the accessibility, acceptability, and usability of a chatbot intervention for parents and caregivers of children and young people with rheumatological conditions. If proven useful, it could lead to a future efficacy trial of one of the first chatbot interventions to provide targeted and user-suggested support for parents and caregivers of children with chronic health conditions in health care services. This study is unique in that it will detail the needs and wants of children, young people, siblings, parents, and caregivers to improve the current support given to families living with pediatric rheumatological conditions. It will be conducted across the whole of the United Kingdom for all pediatric rheumatological conditions at all stages of the disease trajectory.

International Registered Report Identifier (IRRID): DERR1-10.2196/57238

(JMIR Res Protoc 2024;13:e57238) doi:10.2196/57238

KEYWORDS

caregivers; chatbot; paediatric rheumatology; parents and caregivers; parents/carers; pediatric; proof-of-concept; quality of life; rheumatology

Introduction

Background

Pediatric rheumatological illnesses are chronic inflammatory conditions that affect the musculoskeletal system [1,2]. While some are rare, juvenile idiopathic arthritis (JIA), the most common rheumatological disease of childhood, currently affects 10,000 children and young people in the United Kingdom [3]. JIA occurs as frequently as juvenile diabetes mellitus and 10 times more frequently than acute lymphoblastic leukemia [4]. Children and young people with rheumatological conditions are well known to experience a high psychological burden, with decreased quality of life, increased pain and disease activity, physical disabilities, school absenteeism, suboptimal medication adherence, and transition challenges [1,5]. Up to two-thirds of young people continue with active disease into adulthood [6,7], with visible and invisible symptoms causing marked psychological ramifications. High levels of mental health comorbidity and consequent risk for adverse health outcomes are common in children and young people with rheumatological conditions [1,8]. The British Society of Paediatric and Adolescent Rheumatology (BSPAR) Standards of Care (2010) include the recommendation that a pediatric clinical psychologist should be part of the core multidisciplinary team [9]. However, a 2021 survey of 15 high-volume pediatric rheumatology UK centers highlighted that 7 centers failed to achieve this [10]. In 2019, the British Society of Rheumatology's (BSR) pediatric and adolescent state of play report [11] highlighted poor access to psychology expertise and recommended increased psychology provision. Early identification of children and young people who are struggling is known to improve outcomes, but current systems fall short of providing adequate emotional and mental health support to those with rheumatological conditions [12].

A review examining the impact of living with a child with a long-term health condition revealed that parents perceive that they are not always supported in their quest for information, and their ultimate responsibility for their child's health can be overwhelming [13]. Parents and caregivers described that when information is not available from health care professionals, they are compelled to search for it elsewhere [14] and feel the need to "take charge," becoming advocates for their child through "tenacious information seeking" [15]. Patient and Public Involvement and Engagement (PPIE) activities revealed that available parental support is currently inequitably distributed and accessed. Charity access is inconsistent, with awareness dependent on clinical teams, other parents, or "internet searching." Education support offered at "family weekends" is limited by geography and capacity. Social media closed groups are only available to those who know about them, and due to the unregulated content, parents were skeptical about the levels of support received.

Rheumatologists and nurse specialists in the United Kingdom identified a lack of clinic time as one of the biggest limitations to asking about emotional and mental health support in appointments, followed by the absence of resources when concerns are raised [10]. While clinic time is limited, waiting lists are too long, and an increase in the number of psychologists is awaited, upskilling parents has the potential to improve their child's psychological well-being and prevent the need for later mental health interventions. The James Lind Alliance also supports this in its 10 identified priority areas for mental health in children and young people, specifically: what methods can parents and caregivers use to identify that their child's mental health is deteriorating and what are the most effective early intervention strategies for supporting them to improve mental resilience [16]. In 2023, 5 UK pediatric rheumatology charities were so worried about mental health that they collaborated to develop and deliver a survey to understand the scale of the problem. The results from this work showed that out of 291 parents and caregivers completing the survey, 218 (82%) parents and caregivers reported their child's diagnosis as impacting their own mental health. It also highlighted that 60% of children and young people have needed mental health support since diagnosis (had help, are undergoing help, or are on a waiting list), and in relation to condition specific difficulties, 81% needed help with needle phobia, 80% are reluctant to take their rheumatology medicines, and 78% are struggling with side effects from medications [17].

At the time of this study application, chatbots were being used as a means of providing useful information in a variety of

settings [18]. Chatbots are typically cloud-based programs that require internet-connected devices, and users interact with them in a number of ways, including through text and voice. In particular, chatbots such as Vincent have proven to be useful to enhance mental health [19], iHelper provides guided self-assessment for stress, anxiety, depression, and self-esteem, and Woebot is a text-based conversational agent providing 2-weeks of self-help, proven to significantly reduce depression [20]. Chatbots are beginning to be used in National Health Service (NHS) services, such as "Ask Olli" for parents at Alderhey [21] and "Oriel Assistant" for patients and staff at Moorfields [22], and evidence showed that most internet users would be receptive to using health chatbots [23]. Since the funding for the study was awarded, chatbot interest has progressed rapidly with the launch of commercially available chatbots. Chatbots potential in health care is also growing, with research progressing in this area. For example, ChatGPT and GPT-4 already show promise in translating radiology reports into plain language for families [24]. The exact deliverable for this study, however, is still work in progress and will be decided by the co-design group, taking into account issues such as digital poverty, scalability, advantages and disadvantages of platforms, data security, and outcome measures.

The "Interventions to improve Mental health supPort in families with children And young people with Chronic rheumaTological conditions" (IMPACT) proof-of-concept study aims to design, develop, and test a chatbot intervention for parents and caregivers of children and young people with rheumatic conditions. It is hoped that by empowering parents and caregivers, we will strengthen the support around children and young people, prevent anxieties and uncertainties from escalating, and improve other aspects of pediatric rheumatological care, such as adherence to therapies. This intervention is not to replace human contact but to be an adjunct when human contact is limited, for example, between appointments and while on holiday.

Study Setup

The research team is led by the principal investigator (PL), who is a senior pediatric rheumatology nurse, and the research facilitator (KK), who has a psychology degree and background in pediatric rheumatology research. This study proposal was submitted for a personal postdoctoral National Institute for Health and Social Care Research (NIHR) Advanced Clinical Academic Fellowship (ACAF; NIHR 302864), awarded in 2023 to PL, the first and currently (at the time of writing) only ACAF award given to a nurse in the United Kingdom. The study timeline is from April 2023 to April 2026.

Patient and Public Involvement and Engagement

A strong and engaged UK-wide steering group of children, young people, parents, caregivers, and health professionals is pivotal to the success of this study. The group is composed of 4 children and young people, 4 parents and caregivers, and 3 health care professionals (a clinical psychologist in pediatric rheumatology, a senior pediatric nurse working in rheumatology research, and a clinical informatics expert). The working group currently includes over 30 children and young people, parents and caregivers, health professionals, and key charity stakeholders who have all been involved in the study proposal since idea conception.

PPIE activities began over 2 years ago and helped shape this study. Initially, children, young people, parents, caregivers, and health professionals were asked whether they needed more support in living with a chronic pediatric rheumatological condition. As conversations proved there was a need to increase support to improve psychosocial well-being, discussions moved over time to consider what this may look like. Initially, the intervention was expected to be tailored toward children and young people; however, as conversations continued, parents and caregivers were open about their need for further support for themselves. A digital intervention was suggested that could help to better prepare their child through their "firsts" (first joint injection, first blood test, or first scan), know the right questions to ask in appointments, know how to have conversations with school, know how to encourage medication adherence, know how to talk about distorted body image due to corticosteroid therapy, know how to encourage home exercises, and know how to identify red flags in their child's mental health and where to go for help. During brainstorming activities, the idea of a "chatbot" was presented by a parent and unanimously selected as a potential targeted intervention. Parents and caregivers particularly liked the anonymity of chatbots and their constant availability.

Regular meetings, both web-based and face-to-face, have ensured key decisions have been agreed upon as a group, for example. whether 2 participants from the same family could be included in the focus groups. Key documentation has been reviewed by both the steering and working groups, and they will continue to be involved from the beginning to the end of the study. The methodology used for this study ensures that the study is directed by children, young people, parents, and caregivers, ultimately for children, young people, parents, and caregivers.

Methods

Methodological Underpinnings

This research study uses experience-based co-design (EBCD) methodology to guide the project, underpinned by the Medical Research Council (MRC)-NIHR Complex Intervention Research Framework [25]. EBCD is a form of participatory research that combines user-centered design and learning theory and is delivered through a 6-stage collaborative process (Textbox 1) [26,27]. These stages will be embedded throughout the study, maximizing the potential to use creativity and ideation to generate wide-ranging ideas and maximize opportunities for innovation, as recommended in the recently updated research framework [25].

Textbox 1. The 6 stages of experience-based co-design (EBCD).

Stage:

- Project set-up
- Staff experiences
- Patient and caregiver experience
- Feedback and co-design
- Co-design teams
- Celebration event

A "trigger film" (short film) is integral to the EBCD methodology and highlights "touch points," which elicit shared reflections. For this study, the focus groups and planned exercises during the workshops will be video recorded, then edited to produce the trigger film. This film is useful to understand some of the key decisions made throughout the study and can be a useful aid for dissemination. Using the EBCD methodology is compliant with the NIHR Participant in Research Experience survey, which recommends that "technology provided to participants should be tested for reliability and ease of use and co-designed with the intended users" [28].

Aim

This proof-of-concept study aims to design, develop, and test a chatbot intervention to provide enhanced support compared to current clinical practice that is accessible, acceptable, and usable for parents and caregivers.

Inclusion and Exclusion Criteria

Children and young people aged 8 years or older with a rheumatological condition diagnosed before the age of 17 years and their siblings will be invited to join focus groups. Parents and caregivers of those with rheumatological conditions will also be invited to parent-specific focus groups. Health professionals who care for pediatric and adolescent rheumatological patients will also be invited to join health care–specific focus groups. Those without rheumatological conditions as a child or young person, siblings, or parents of these will not be included. Members of our steering group are also excluded from participating as research participants in the focus groups, although they are welcomed as facilitators.

Designing EBCD Focus Groups

The "core elements" of the revised MRC-NIHR Framework [25] state that it is imperative to understand key uncertainties, consider the context, and engage stakeholders. Therefore, the aim is to understand, from the perspective of children, young people, siblings, parents, caregivers, and health professionals, what support they think would be useful and whether they think this could be delivered within a chatbot intervention. Focus groups will be used to yield rich qualitative data from a range of individuals from across the United Kingdom. A minimum of 8 focus groups are planned, with approximately 6-12 participants in each group. The parent and caregiver groups will outnumber the child or young person, sibling, and health care professional groups as the intervention is ultimately for parents and caregivers. However, we are also interested in asking participants with rheumatic conditions what they would have found helpful for their parents or caregivers to know, asking siblings for their perspectives, and asking health professionals to discuss where they see more support being offered. Groups will be undertaken remotely or face-to-face, depending on the requests of the majority of participants (in line with NIHR PPIE survey findings) [29].

Parents and caregivers, siblings, children, and young people will be recruited using consecutive sampling. Participants will learn about the study through study advertisement flyers in clinical settings or by being given a flyer. Ethical approval has been granted for local pediatric and adolescent rheumatology centers to display and distribute flyers, and in conjunction with pediatric rheumatology charity social media channels and email lists, this should increase the opportunities for inclusivity across all 4 nations of the United Kingdom. A study-specific website has been developed that encourages interested children, young people, or parents and caregivers to contact the study team to find out more, or if they are unable to access technology, their local team can contact the IMPACT research team on their behalf. Language-specific study documentation and interviews will be offered for those for whom English is not their first language. Staff will be recruited by seeing the study flyers and contacting the study team. A sampling matrix will ensure representation from professional groups and centers.

Consent will be sought for audio and visual recording, the former to guide data analysis, while the video recording will form the trigger film. Thematic analysis [30] will be conducted by 2 members of the research team and discussed with the steering group to identify themes critical to shaping chatbot development using NVivo (QSR International). The final themes will help develop the chatbot.

Developing EBCD Workshops

The working group will meet in 2 face-to-face workshops to discuss the themes and help identify the core components of the chatbot intervention. The workshops will use personas and scenarios developed from the focus group discussion to help inform the chatbot development process. Such creative and participatory methods will allow the shared experiences of the members of the working group to shape the intervention development process. The workshop will be video recorded as recommended in the EBCD methodology, with excerpts of the film used later in the trigger film.

Over the last few years, as chatbot technology has developed at an alarming rate, with large language models now leading the way, their popularity has increased [31]. While it is not possible to be specific regarding the content of the chatbot until the focus groups have been completed and analyzed, a content management system will be developed to inform the chatbot development. It is anticipated that the chatbot may include such functions as (1) frequently asked questions, (2) rheumatology-specific information, (3) information about managing "firsts," (4) parental red-flag identification and signposting, and (5) persuasive argument roleplay. Using agile principles, the exact technologies and approaches used may change as the team learns more about the user requirements. Development of the chatbot will occur within existing recommendations such as the National Institute for Health and Care Excellence Evidence Standards Framework for Digital Health Technologies [32], NHS Digital guidance for cloud security [33], and the Department of Health guidelines for "Putting data, digital, and tech at the heart of transforming the NHS" [34].

User Testing the Agile Sprint Methodology

Chatbots can potentially lead to frustration, anger, dissatisfaction, and, at worst, disengagement with the technology if not designed and developed with key stakeholders [35,36]. This is not a new technology; however, using it for this purpose for parents and caregivers of children and young people with rheumatological conditions is new. Therefore, the crucial step before a larger study must be to determine accessibility, acceptability, and usability through user testing.

User testing will occur through an iterative methodology with short product development cycles and the deployment of the prototype to groups of parents and caregivers. This will ensure user feedback directs incremental iterative software development. This process of "agile development" runs in a cycle of design, develop, test, and refine (termed a "sprint"). Every 3-month cycle, we will user-test, analyze, and develop. At least 25 parents and caregivers will be recruited for each cycle, which is anticipated to be up to 4 cycles in total. While the majority of participants will be naïve to each cycle, some may be invited back to 'test' new modifications in the next cycle. Parents and caregivers will be requested to use the chatbot on a number of occasions for a defined frequency of time.

Eligible parents and caregivers will be those of a child or young person who was diagnosed while being aged 17 years or younger with a chronic pediatric rheumatological condition and who agrees to complete the user metrics throughout the testing period. Flyers in local hospitals will again advertise this part of the study to parents and caregivers, who will then contact the study team for further information. If families are identified as those who do not have access to technology, individual conversations will occur to investigate whether a device may be loaned. All parents and caregivers will be sent an information pack and must provide written consent. Of note, the chatbot technology can integrate "Google Translate," and as such, families who do not have English as a first language will be able to participate.

Usability outcome measures and qualitative experiences will be sought in order to understand the acceptability of the chatbot for progression to a future study. Outcome measure selection will be informed by exploring what success would look like for families. These may include such measures as (1) attrition of participants; (2) engagement and duration of conversations; (3) user satisfaction measures, such as the System Usability Scale (SUS) [37,38], the User Experience Questionnaire (UEQ) [37], and the Net Promoter Score (NPS) [39,40]; and (4) semistructured interviews with the final group of "sprint" participants.

Ethical Considerations

The study will be conducted in accordance with the Principles of Good Clinical Practice and the Declaration of Helsinki. Ethical approval from the Health Research Authority has been received for the study (approval received on August 31, 2023, from the Yorkshire & The Humber–Leeds West Research Ethics Committee, IRAS ID: 329476. REC Reference:23/YH/0172). All participants are asked to provide informed written consent or assent (for those aged 16 years or younger, paired with parental or caregiver's consent) before being enrolled in the study. Consent and assent are requested to audio and video record the focus groups and workshops to enable data analysis and the production of the trigger film, while also requesting to use anonymized quotes and pictures of physical creations in dissemination.

Results

The study is ongoing. As of February 28, 2024, we have enrolled 73 children, young people, parents, caregivers, and health professionals in 12 focus groups so far. We have had over 280 children, young people, siblings, parents, and caregivers reach out to be included in focus groups, and therefore an ethics amendment has been sought to increase our recruitment target. This huge interest validates the need for the study, and already interesting ideas are emerging. Preliminary results will be published from the focus groups by the end of 2024 and from the user testing by the beginning of 2026.

Discussion

The rheumatological conditions of childhood affect the whole family. Children and young people have been shown to suffer with their emotional and mental health as they cope with the implications of a chronic health condition. Parents, caregivers, and siblings of the child have also been shown to experience difficulties as they navigate the new normal family lifestyle and the implications of the health condition on their own lives. Parents and caregivers report that for conditions such as JIA, there is a wealth of information available on the internet; however, it is not always clear how robust and trustworthy this information is, while for rarer pediatric rheumatological conditions, there is much less available information, and searching for what little there is can be upsetting and often futile. Providing information and support in the style of a chatbot has many advantages, including physician-ratified and endorsed information, anonymity, being accessible throughout the day and night, and the ability to integrate new novel functions, such

as the ability to practice difficult conversations with the chatbot enacting as their child or young person. Therefore, the aim of this study is to investigate whether a chatbot intervention could provide additional support to families between appointments without the need for human resources.

If the chatbot proves to be a success, then such an intervention may be useful in other diseases and with other populations. If the chatbot shows that parents and caregivers do not find it useful and its function is limited, this is useful learning in the current rapidly advancing technological climate, and further intervention and development may be commissioned. If the intervention is deemed acceptable, then to draw conclusions regarding the effectiveness of the intervention, a further study would be required. Discussions will begin early to scope out options for embedding the chatbot into NHS services in order to enhance the transition from research to service delivery following further assessment. Links to research outputs will be made available on the IMPACT study website [41].

This study has several limitations; primarily, as a proof-of-concept study, it will be difficult to generalize the findings. Coping with a chronic health condition varies on a daily basis depending on disease severity, treatments and their side effects, social support, and daily mood fluctuations. Therefore, the chatbot may prove useful to families for the short duration of this study, but as there is no external control group, analyzing all variables and drawing sound conclusions could be challenging. Also, due to the technological nature of a chatbot intervention, families who do not have easy access to technology may be disadvantaged; however, we are in the process of scoping local technology resources, which can be loaned out if required. We also set a lower age limit (aged 8 years or older) for child participation. This was to be mindful that the questions we are asking children about what else they would have liked support with would be difficult for most children aged 8 years or younger to answer. However, we are aware that in some instances, parents and caregivers feel their younger child may have liked the opportunity to take part.

We believe this study can have significant future applications and implications, such as learning from family perspectives on how we can improve upon current rheumatological clinical care, providing a responsive and tailored intervention to help support families better, and an understanding of how such technology could be embedded into the wider health care system. This is particularly relevant in today's current climate of limited staffing resources and an interest in delivering care differently. This study also offers an insight into how a chatbot could be used for families who live at a distance from their health care site, thus offering advantages over face-to-face support appointments and providing a resource for families, which may in turn lessen the need to contact the local team for support and thus free up valuable resources. The interest in the study so far, at over 280 families who have reached out in just over three months, over double the planned recruitment for the focus groups, is clear evidence that we need to do more to listen to, engage with, and support families further.

Acknowledgments

The authors would like to thank the children, young people, parents, and caregivers who formed the working group and have been pivotal in getting this study started. We would also like to thank all of the pediatric rheumatology charities who have also supported this work from inception to the present day (particularly Children's Chronic Arthritis Association, Versus Arthritis, National Rheumatoid Arthritis Society, Scottish Network for Arthritis in Children, Lupus UK, and Myositis UK) and all of the rheumatological teams across the United Kingdom for their support so far. We would also like to thank Professor Endacott (National Institute for Health and Social Care Research [NIHR] Director of Nursing and Midwifery) for supporting the fellowship application and this study.

PL (ACAF reference number 302864) is funded by Health Education England/NIHR for this research project. The views expressed in this publication are those of the authors and not necessarily those of the NIHR, NHS, or the UK Department of Health and Social Care.

Data Availability

The anonymized data sets analyzed during this study will be available from the corresponding author upon reasonable request.

Authors' Contributions

PL, KK, AK, ALS, RS, GR, and NJS participated in the design, conception, and revision of this study. KK undertook the design and revision. PL substantially contributed to the conception and design of the protocol and its write-up. PL, KK, LRW, AK, ALS, RS, GR, and NJS have approved the submitted version, agreed to be personally accountable for their own contributions, and ensured that any accuracy and integrity issues that may arise in the future will be appropriately investigated and resolved. The IMPACT Steering Group contributed to the design and conception of the study, reviewed the manuscript, and approved the submitted version. The steering group comprises Eire Byrne, Natalia Kasaru, Morgan Pawlett, Cameron Papantoniou, Emily Earle, Nathanael Bourns, Rachel Pulfree-Blythe, Eunice Kasaru, Emma Piepenstock, Gemma Molyneux and Heather Rostron. Further information is available elsewhere [41].

Conflicts of Interest

PL is currently receiving a personal fellowship award from the NIHR fellowship for nonmedical health care professionals (ACAF reference number 302864), and as Patient and Public Involvement and Engagement (PPIE) co-lead for the NIHR Great Ormond Street Hospital for Children NHS Foundation Trust and Biomedical Research Centre (GOSH BRC), she receives some salary support from the NIHR Biomedical Research Centre at GOSH. PL is also a Senior Center Affiliate at The Centre for Adolescent Rheumatology Versus Arthritis at UCL University College London (UCL), University College London Hospital NHS Foundation Trust (UCLH), and GOSH, which is supported by Versus Arthritis (21593). LRW's contribution was underpinned by grants from the Medical Research Council (MRC; MR/R013926/1), Versus Arthritis (22084, 21593), and Great Ormond Street Hospital Children's Charity (VS0518). AK's contribution is supported by a Canada Research Chair in Mental Health and Chronic Disease of Childhood. ALS is supported by an NIHR Clinician Scientist Award (CS-2018-18-ST2-005). This work is supported by the NIHR GOSH Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the National Health Service (NHS), the NIHR, or the Department of Health.

Multimedia Appendix 1
Reviewer comments.
[PDF File (Adobe PDF File), 1300 KB - resprot_v13i1e57238_app1.pdf]

References

1. Treemarcki EB, Danguecan AN, Cunningham NR, Knight AM. Mental health in pediatric rheumatology: an opportunity to improve outcomes. Rheum Dis Clin North Am 2022;48(1):67-90. [doi: 10.1016/j.rdc.2021.09.012] [Medline: 34798960]
2. Egert Y, Egert T, Costello W, Prakken BJ, Smith EMD, Wulffraat NM. Children and young people get rheumatic disease too. Lancet Child Adolesc Health 2019;3(1):8-9. [doi: 10.1016/S2352-4642(18)30374-2] [Medline: 30473439]
3. Canakinumab for treating systemic juvenile idiopathic arthritis (terminated appraisal). National Institute for Health and Social Care Excellence (NICE). URL: https://www.nice.org.uk/guidance/ta302 [accessed 2013-11-27]
4. Goldmuntz EA, White PH. Juvenile idiopathic arthritis: a review for the pediatrician. Pediatr Rev 2006;27(4):e24-e32. [doi: 10.1542/pir.27-4-e24] [Medline: 16581950]
5. Fawole OA, Reed MV, Harris JG, Hersh A, Rodriguez M, Onel K, et al. Engaging patients and parents to improve mental health intervention for youth with rheumatological disease. Pediatr Rheumatol Online J 2021;19(1):19 [FREE Full text] [doi: 10.1186/s12969-021-00503-7] [Medline: 33622346]
6. Stringer G. Musculoskeletal health. What are musculoskeletal conditions? NHS England. 2019. URL: https://www.england.nhs.uk/ourwork/clinical-policy/ltc/our-work-on-long-term-conditions/musculoskeletal/ [accessed 2020-05-03]
7. Selvaag AM, Aulie HA, Lilleby V, Flatø B. Disease progression into adulthood and predictors of long-term active disease in juvenile idiopathic arthritis. Ann Rheum Dis 2016;75(1):190-195. [doi: 10.1136/annrheumdis-2014-206034] [Medline: 25362042]
8. Knight A, Vickery M, Faust L, Muscal E, Davis A, Harris J, et al. Gaps in mental health care for youth with rheumatologic conditions: a mixed methods study of perspectives from behavioral health providers. Arthritis Care Res (Hoboken) 2019;71(5):591-601 [FREE Full text] [doi: 10.1002/acr.23683] [Medline: 29953741]
9. Davies K, Cleary G, Foster H, Hutchinson E, Baildam E, British Society of Paediatric and Adolescent Rheumatology. BSPAR standards of care for children and young people with juvenile idiopathic arthritis. Rheumatology (Oxford) 2010;49(7):1406-1408 [FREE Full text] [doi: 10.1093/rheumatology/kep460] [Medline: 20173199]
10. Livermore P, Gibson F, Mulligan K, Wedderburn LR, McCann LJ, Gray S. Mapping the current psychology provision for children and young people with juvenile dermatomyositis. Rheumatol Adv Pract 2021;5(3):rkab062 [FREE Full text] [doi: 10.1093/rap/rkab062] [Medline: 34671713]
11. Paediatric and adolescent rheumatology: the state of play. British Society for Rheumatology. London: BSR; 2019. URL: https://www.rheumatology.org.uk/Portals/0/Documents/Policy/Reports/Paediatric_adolescent_report_November_2019.pdf [accessed 2024-03-14]
12. Davis AM, Rubinstein TB, Rodriguez M, Knight AM. Mental health care for youth with rheumatologic diseases—bridging the gap. Pediatr Rheumatol Online J 2017;15(1):85 [FREE Full text] [doi: 10.1186/s12969-017-0214-9] [Medline: 29282086]
13. Smith BA, Kaye DL. Treating parents of children with chronic health conditions: the role of the general psychiatrist. Focus 2012;10(3):255-265 [FREE Full text] [doi: 10.1176/appi.focus.10.3.255]
14. Kepreotes E, Keatinge D, Stone T. The experience of parenting children with chronic health conditions: a new reality. J Nurs Healthc Chron Illness 2010;2(1):51-62. [doi: 10.1111/j.1752-9824.2010.01047.x]
15. Coffey JS. Parenting a child with chronic illness: a metasynthesis. Pediatr Nurs 2006;32(1):51-59. [Medline: 16572539]
16. Mental health in children and young people. James Lind Alliance. URL: https://www.jla.nihr.ac.uk/priority-setting-partnerships/Mental-health-in-children-and-young-people/top-10- [accessed 2018-11-10]
17. Livermore P, Ainsworth S, Beesley R, Douglas S, Earle E, Wilson D, et al. 'The current mental health status of children and young people with JIA, and their wider family': a charity partner collaboration survey. Pediatr Rheumatol Online J 2023;21(1):111 [FREE Full text] [doi: 10.1186/s12969-023-00898-5] [Medline: 37798784]

18. Cameron G, Cameron D, Megaw G, Bond R, Mulvenna M, O'Neill S, et al. Towards a chatbot for digital counselling. 2017 Presented at: HCI '17: Proceedings of the 31st British Computer Society Human Computer Interaction Conference; July 3-6, 2017; Sunderland, UK. [doi: 10.14236/ewic/hci2017.24]
19. Lee M, Ackermans S, van As N, Chang H, Lucas E, IJsselsteijn W. Caring for vincent: a chatbot for self-compassion. 2019 Presented at: CHI '19: Proceedings of the 2019 CHI Conference on Human Factors in Computing Systems; May 4-9, 2019; Glasgow, Scotland, UK p. 1-13. [doi: 10.1145/3290605.3300932]
20. Fitzpatrick KK, Darcy A, Vierhile M. Delivering cognitive behavior therapy to young adults with symptoms of depression and anxiety using a fully automated conversational agent (Woebot): a randomized controlled trial. JMIR Ment Health 2017;4(2):e19 [FREE Full text] [doi: 10.2196/mental.7785] [Medline: 28588005]
21. NHS Alder Hey Children's, NHS Foundation Trust. URL: https://alderhey.nhs.uk/parents-and-patients/alder-play-app [accessed 2023-04-23]
22. Moorfields chatbot to field questions on new £344m eye care facility. Digital Health. URL: https://www.digitalhealth.net/2019/07/moorfields-chatbot-field-questions-new-eye-care-facility/ [accessed 2023-04-23]
23. Nadarzynski T, Miles O, Cowie A, Ridge D. Acceptability of Artificial Intelligence (AI)-led chatbot services in healthcare: a mixed-methods study. Digit Health 2019;5:2055207619871808 [FREE Full text] [doi: 10.1177/2055207619871808] [Medline: 31467682]
24. Lyu Q, Tan J, Zapadka ME, Ponnatapura J, Niu C, Myers KJ, et al. Translating radiology reports into plain language using ChatGPT and GPT-4 with prompt learning: results, limitations, and potential. Vis Comput Ind Biomed Art 2023;6(1):9 [FREE Full text] [doi: 10.1186/s42492-023-00136-5] [Medline: 37198498]
25. Skivington K, Matthews L, Simpson SA, Craig P, Baird J, Blazeby JM, et al. A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance. BMJ 2021;374:n2061 [FREE Full text] [doi: 10.1136/bmj.n2061] [Medline: 34593508]
26. Robert G, Cornwell J, Locock L, Purushotham A, Sturmey G, Gager M. Patients and staff as codesigners of healthcare services. BMJ 2015;350:g7714 [FREE Full text] [doi: 10.1136/bmj.g7714] [Medline: 25670179]
27. EBCD: Experience-Based Co-Design toolkit. The Point of Care Foundation. URL: https://www.pointofcarefoundation.org.uk/resource/experience-based-co-design-ebcd-toolkit/2013 [accessed 2023-10-10]
28. Participant in Research Experience Survey (PRES) 2020/21. National Institute for Health and Care Research. 2021. URL: https://www.nihr.ac.uk/documents/participant-in-research-experience-survey-pres202021/28599 [accessed 2023-10-10]
29. NIHR public involvement feedback survey 2020-2021: the results. National Institute for Health and Care Research. 2022. URL: https://www.nihr.ac.uk/documents/nihr-public-involvement-feedbacksurvey-2020-2021-the-results/29751 [accessed 2023-10-10]
30. Braun V, Clarke V. Thematic Analysis: A Practical Guide. London: Sage Publications; 2021.
31. Ahmed A, Hassan A, Aziz S, Abd-Alrazaq AA, Ali N, Alzubaidi M, et al. Chatbot features for anxiety and depression: a scoping review. Health Informatics J 2023;29(1):14604582221146719 [FREE Full text] [doi: 10.1177/14604582221146719] [Medline: 36693014]
32. Evidence Standards Framework (ESF) for digital health technologies. National Institute of Health and Social Care Excellence (NICE). URL: https://www.nice.org.uk/about/what-we-do/our-programmes/evidence-standards-framework-for-digital-health-technologies [accessed 2023-04-23]
33. NHS and social care data: off-shoring and the use of public cloud services. NHS Digital. URL: https://digital.nhs.uk/data-and-information/looking-after-information/data-security-and-information-governance/nhs-and-social-care-data-off-shoring-and-the-use-of-public-cloud-services [accessed 2023-05-15]
34. Putting data, digital and tech at the heart of transforming the NHS. Department of Health and Social Care. 2021. URL: https://www.gov.uk/government/publications/putting-data-digital-and-tech-at-the-heart-of-transforming-the-nhs [accessed 2023-11-12]
35. Castillo D, Canhoto AI, Said E. The dark side of AI-powered service interactions: exploring the process of co-destruction from the customer perspective. Serv Ind J 2020;41(13-14):900-925. [doi: 10.1080/02642069.2020.1787993]
36. Siglen E, Vetti HH, Lunde ABF, Hatlebrekke TA, Strømsvik N, Hamang A, et al. Ask Rosa—the making of a digital genetic conversation tool, a chatbot, about hereditary breast and ovarian cancer. Patient Educ Couns 2022;105(6):1488-1494 [FREE Full text] [doi: 10.1016/j.pec.2021.09.027] [Medline: 34649750]
37. Holmes S, Moorhead A, Bond R, Zheng H, Coates V, McTear M. Usability testing of a healthcare chatbot: can we use conventional methods to assess conversational user interfaces? 2019 Presented at: ECCE '19: Proceedings of the 31st European Conference on Cognitive Ergonomics; September 10-13, 2019; Belfast, United Kingdom p. 207-214. [doi: 10.1145/3335082.3335094]
38. Rabinowitz AR, Collier G, Vaccaro M, Wingfield R. Development of RehaBot-a conversational agent for promoting rewarding activities in users with traumatic brain injury. J Head Trauma Rehabil 2022;37(3):144-151. [doi: 10.1097/HTR.0000000000000770] [Medline: 35293365]
39. Dosovitsky G, Bunge EL. Bonding with bot: user feedback on a chatbot for social isolation. Front Digit Health 2021;3:735053 [FREE Full text] [doi: 10.3389/fdgth.2021.735053] [Medline: 34713203]

40. Entenberg GA, Areas M, Roussos AJ, Maglio AL, Thrall J, Escoredo M, et al. Using an artificial intelligence based chatbot to provide parent training: results from a feasibility study. Soc Sci 2021;10(11):426 [FREE Full text] [doi: 10.3390/socsci10110426]
41. IMPACT Study: Rheumatological Study for Families. URL: https://www.theimpactstudy.co.uk/ [accessed 2024-03-14]

Abbreviations

ACAF: Advanced Clinical Academic Fellowship
BSPAR: British Society of Paediatric and Adolescent Rheumatology
BSR: British Society of Rheumatology
EBCD: experience-based co-design
IMPACT: Interventions to improve Mental health supPort in families with children And young people with Chronic rheumaTological conditions
JIA: juvenile idiopathic arthritis
MRC: Medical Research Council
NHS: National Health Service
NIHR: National Institute for Health and Social Care Research
NPS: Net Promoter Score
PPIE: Patient and Public Involvement and Engagement
SUS: System Usability Scale
UEQ: User Experience Questionnaire

Edited by A Mavragani; submitted 08.02.24; peer-reviewed by A Hassan; comments to author 26.02.24; revised version received 28.02.24; accepted 04.03.24; published 03.04.24.

Please cite as:
Livermore P, Kupiec K, Wedderburn LR, Knight A, Solebo AL, Shafran R, Robert G, Sebire NJ, Gibson F, IMPACT Steering Group Designing, Developing, and Testing a Chatbot for Parents and Caregivers of Children and Young People With Rheumatological Conditions (the IMPACT Study): Protocol for a Co-Designed Proof-of-Concept Study
JMIR Res Protoc 2024;13:e57238
URL: https://www.researchprotocols.org/2024/1/e57238
doi:10.2196/57238
PMID:38568725

Protocol

Developing and Evaluating a Data-Driven and Systems Approach to Health Promotion Among Vocational Students: Protocol for the Data Health Study

Clara Heinze[1,2], MSc; Rikke Dalgaard Hartmeyer[1], PhD; Anne Sidenius[1], PhD; Lene Winther Ringgaard[1], MSc; Anne-Louise Bjerregaard[3], PhD; Rikke Fredenslund Krølner[2], PhD; Steven Allender[4], PhD, PROF DR; Adrian Bauman[1,5], PhD, PROF DR; Charlotte Demant Klinker[1], PhD

[1]Department of Prevention, Health Promotion and Community Care, Copenhagen University Hospital - Steno Diabetes Center Copenhagen, Herlev, Denmark

[2]National Institute of Public Health, University of Southern Denmark, Copenhagen, Denmark

[3]Steno Diabetes Center Zealand, Holbaek, Denmark

[4]Institute for Health Transformation, Deakin University, Melbourne, Australia

[5]School of Public Health, Sydney University, Sydney, Australia

Corresponding Author:
Clara Heinze, MSc
Department of Prevention, Health Promotion and Community Care
Copenhagen University Hospital - Steno Diabetes Center Copenhagen
Borgmester Ib Juuls Vej 83
Herlev, 2730
Denmark
Phone: 45 28838889
Email: clara.heinze@regionh.dk

Abstract

Background: Vocational school students exhibit significant risk behaviors in terms of poor diet, frequent use of nicotine products, inadequate fruit and vegetable intake, low levels of physical activity, and poor mental health. This makes vocational students vulnerable to the development of noncommunicable diseases. Therefore, effective health promotion programs targeting vocational students are required.

Objective: The Danish study “Data-driven and Systems Approach to Health Promotion Among Vocational Students” (Data Health) aims to develop, implement, and evaluate a systems approach to support vocational schools, municipalities, and local communities in implementing locally relevant health promotion actions among and for vocational students. This paper describes the Data Health program and how implementation and preliminary effectiveness will be evaluated.

Methods: The Data Health program offers an iterative 5-step process to develop changes in the systems that shape health behavior and well-being among vocational students. The program will be implemented and evaluated in 8 Danish vocational schools in 4 municipalities. The implementation of the process and actions will be explored using a systems-based evaluation design that assesses contextual differences and the mechanisms through which the program leads to changes in the systems. Preliminary effectiveness at the individual level (students’ self-reported health behavior and well-being) and organizational level (school organizational readiness reported by school staff) will be assessed using a quasi-experimental design, and cross-sectional data will be collected at all 8 schools simultaneously 4 times during the 2-year study period.

Results: This study was launched in 2021, and data collection is expected to be completed in June 2024. The first results are expected to be submitted for publication in January 2024.

Conclusions: We expect that the Data Health study will make significant contributions to complex intervention research by contributing to the paucity of research studies that have used systems approaches in school settings. The study will also provide evidence of successful elements for systems change and effectiveness to determine whether a national scale-up can be recommended.

Trial Registration: ClinicalTrials.gov NCT05308459; https://clinicaltrials.gov/study/NCT05308459

International Registered Report Identifier (IRRID): DERR1-10.2196/52571

(JMIR Res Protoc 2024;13:e52571) doi:10.2196/52571

KEYWORDS

health promotion; health behavior; well-being; organizational readiness; cocreation; causal loop diagram; systems thinking; systems-based evaluation; vocational schools; youth

Introduction

Social Inequalities in Health

Globally, 71% of all deaths are due to noncommunicable diseases (NCDs), and more comprehensive preventive strategies are needed to reduce NCD mortality worldwide [1]. Social gradients exist in NCD risks (tobacco use, physical inactivity, unhealthy diet, and harmful use of alcohol) and NCD-related premature deaths. Populations with higher educational attainment have better health than those in lower socioeconomic groups [2]. Most students attending vocational schools come from low-income families [3,4], and an ordinary vocational degree is defined as "shortened school education." This makes vocational students vulnerable for NCDs, and already as students, they report a high prevalence of tobacco smoking, inadequate fruit and vegetable consumption, physical inactivity, and obesity [5]. For example, in Denmark, 39% of vocational students are overweight (BMI >25 kg/m^2) compared with 14% of high school students, and this prevalence among vocational students is increasing (2014: 30%; 2019: 39%) [6,7]. Despite this, students in vocational education are an often overlooked but important group to target for health promotion to reduce health inequalities [5].

The Complexity of Health Behavior

The application of health promotion can strengthen the capability of individuals to take action and build the capacity of groups, communities, or organizations to act collectively to exert control over the determinants of health [8]. The determinants of health are complex and influenced by underlying dynamic factors at multiple levels (ie, individual, intrapersonal, organizational, environmental, neighborhood, and structural) [9,10]. Evidence suggests that chancing organizational structures and processes and strengthening relationships between organizations are more likely to maintain healthy behavior among individuals than programs that target individual behavior change only [11]. In addition, multicomponent approaches (a combination of structures, processes, and individual behavior changes) for health promotion are more effective than single-component programs [12,13].

A challenge for health promotion is the "voltage drop" that has been identified when effective programs are scaled up across contexts (eg, schools of different sizes), as different contexts lead to different outcomes [14,15]. Vocational students' health behaviors and well-being vary across educational tracks (technical, business, agriculture and food services, social and health services) and regions [7], requiring the use of local data to identify intervention opportunities and priorities. Data-driven programs that use relevant local data to strengthen intervention design are emerging in health promotion research. These programs explicitly consider local conditions as a means of increasing the strength and relevance of the interventions implemented [16,17].

Approaches to Health Promotion in Schools

Schools are important settings that influence health behaviors [18]. In the Danish vocational school reform in 2015, vocational schools were mandated to engage in health promotion to increase students' healthy behavior and well-being and reduce dropout [19]. There is little evidence on how to support vocational schools to implement effective and sustainable health promotion. Vocational schools have struggled to implement and integrate health promotion into their core business [20], so more knowledge is needed about what approaches are feasible, effective, and sustainable in this setting. In Denmark, the smallest administrative unit, the municipalities, are responsible for health promotion among all citizens within their jurisdiction [21]. This places the 92 Danish municipalities as central to vocational school health promotion, but many schools and their students often cross municipal boundaries, making the responsibility for vocational school health promotion unclear and therefore less of a priority in many Danish municipalities [21]. However, previous research shows that municipalities are keen to work with health promotion at vocational schools but often lack a framework for these activities [22].

The World Health Organization's Health Promoting Schools (HPS) principles [23] state that efforts to improve health should go beyond individual behavior change to consider local contexts, organizational and policy changes (eg, from educating individuals to choosing alternative foods to changing the foods available), or a combination of these [14]. In addition, the HPS principles argue that involving the surrounding community and key community leaders will create a more sustainable environment that can support the maintenance of healthy behavior changes among students [24]. Systems thinking has emerged as a method for understanding and changing the drivers of complex health behavior challenges [10,25]. A systems perspective considers a broad approach that engages different groups of participants to contribute to the design, implementation, and evaluation of actions that disrupt current systems and normalize change [10,26]. Identifying and activating modifiable parts of systems (ie, leverage points) is essential to change structures, goals, and beliefs in the systems and thus achieve sustainable health behavior change [27]. Engaging key stakeholders in coordinated efforts [28] has been conducted in recent attempts to apply systems approaches within health promotion (eg, obesity [17,29-31], reducing dietary inequalities [32] and physical inactivity [33], and tobacco control [34]). In combination, HPS approaches and systems thinking provide a set of methods and perspectives that could be effective and sustainable for school health promotion [35].

Objectives

The Data-Driven and Systems Approach to Health Promotion Among Vocational Students (Data Health) study aims to develop, implement, and evaluate a systems approach informed by local data to support vocational schools, municipalities, and local communities in implementing locally relevant health promotion actions among and for vocational students. This protocol describes the Data Health program and how its implementation and preliminary effectiveness will be evaluated at 8 vocational schools across 4 municipalities in Denmark to determine if national scale-up can be recommended.

Methods

The Vocational School Setting

Vocational education in Denmark prepares students for specific occupations and is divided into four main educational tracks: (1) technical (eg, electrician), (2) business (eg, office assistant), (3) agriculture and food service (eg, farmer or chef), and (4) social and health service (eg, health care assistant). Vocational education alternates between school-based training and workplace-based training, with approximately one-third of the time spent in school [36]. Some schools are multisited and have student populations greater than 6000, whereas other schools are located at a single address with a student population of no more than 100. Almost two-thirds of students are men (64.7%), but the gender distribution varied according to educational track; for example, the proportion of men is 89.3% in technical education but only 12.3% in social and health service education [37]. The average age of students is 24 years; some students enroll directly from primary school (aged 15-17 years), whereas others begin later in adult life (39.8% is aged >25 years) [37].

Recruitment

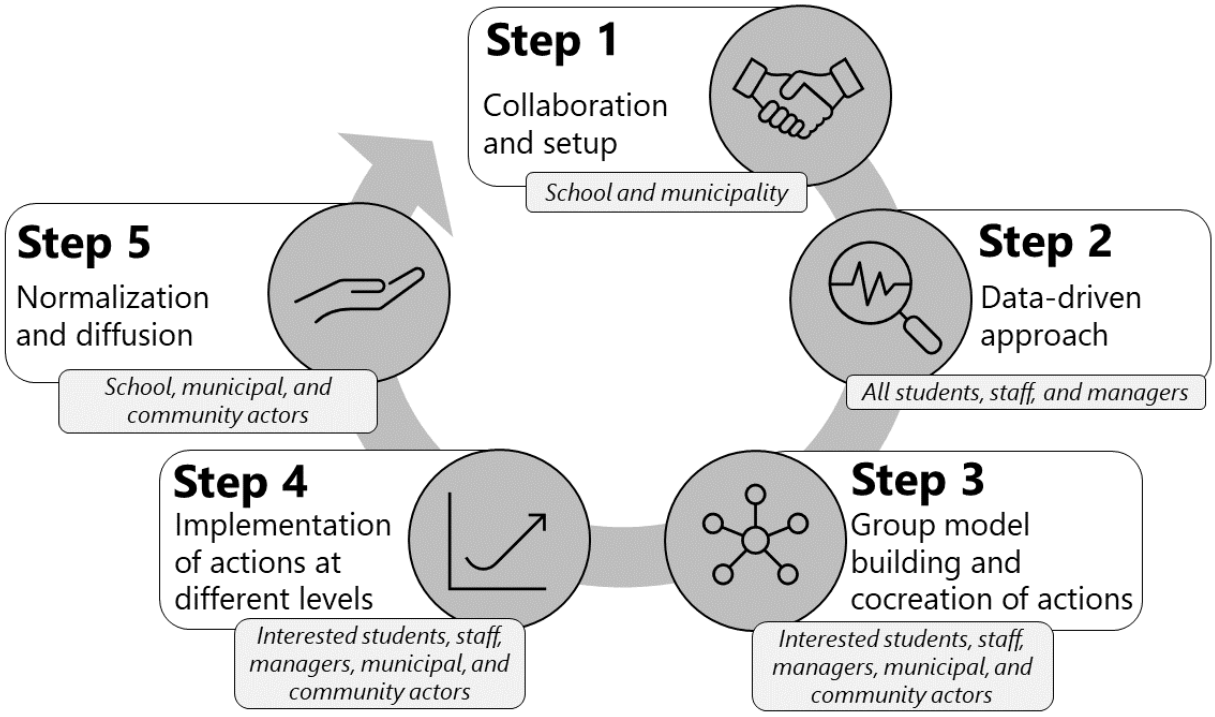
We will use a purposive sampling strategy. A total of 8 vocational schools will be recruited based on the region (Capital Region of Denmark and Region Zealand) and educational track (technical, business, agriculture and food service, and social and health service) to include one vocational school from each educational track in both regions. Simultaneously, the municipalities where the vocational schools are geographically located will be recruited. The enrolled schools and municipalities will be responsible for recruiting community actors with support from the research team, if needed. The role and responsibilities of the actors in the community is described in steps 3 and 4 of the program. In this case, “community actors” refers to individuals, organizations, or companies, both local and national, who can provide resources and social support for the implementation of actions for change.

Content of the Data Health Program

Development

The Data Health program offers an iterative 5-step process (Figure 1) for developing change in the systems to shape vocational students’ health behavior and well-being, combining best practices in health promotion research, including methods from systems science [10,38], data-driven approaches [16,39], and the World Health Organization’s HPS principles [23]. The program was developed by a health promotion research group piloted and formatively evaluated in 1 vocational school and 1 municipality from June 2021 to June 2022. The formative evaluation included observations and interviews and surveys of key participants from both school and municipality. Weekly meetings were held between the evaluator (AS) and the research team to discuss the experiences, barriers, and enablers of implementation. During the formative evaluation, suggestions for program changes were made by exploring the municipality and vocational school environmental contexts and how the program would fit or function within these settings. The research team adjusted and incorporated changes to the program steps throughout the pilot test.

Figure 1. The 5 steps of the Data Health program.



The research team will be responsible for the implementation of steps 1 to 3 of the program but will concurrently build the capacity, motivation, and commitment of the school and municipal program coordinators to be responsible for the implementation of actions and to promote the normalization of the program (steps 4-5).

Step 1: Collaboration and Setup

The Data Health program will begin with the establishment of a formal collaboration agreement between management representatives from the vocational school, the municipality, and the research team. Both the school and the municipality will appoint 1 or 2 staff members as school and municipal program coordinators, respectively. One month of salary will be provided to each school program coordinator (€4000; a currency exchange rate of €1=US $1.09 is applicable) to support program implementation. The roles and responsibilities of the different partners will be clarified and negotiated. Once the collaboration and commitment at the management level has been secured, information about the program will be disseminated by the school management to all staff and students. Dissemination activities include information by email and a kick-off meeting for staff, whereas dissemination for students includes customized posters and flyers distributed in common areas of the school. On the basis of the learnings from the pilot study, we have enhanced the dissemination strategy for the program to boost program visibility at the schools and comprehension among both staff and students.

Step 2: Data-Driven Approach

Local survey data on students' health behaviors and well-being will be collected and analyzed by the research team (see the description of individual outcomes in research question [RQ] 5). To stimulate motivation and interest, the data will be returned to the school and municipality within few weeks in the form of a local health profile. The local health profile covers modifiable health risk factors among vocational students, for example, nicotine use, unhealthy eating habits, physical inactivity, and poor mental health [7]. A simplified version of the health profile will be presented by the research team and the municipal program coordinator at separate meetings for school managers and staff and for students to share and increase their knowledge about health promotion, stimulate discussions and reflections about the results, and promote engagement and motivation for change. On the basis of the data presentations and discussions, the staff and students will be asked to complete a short questionnaire to select the health issue they are most motivated to address. During the pilot, we explored how best to select the specific health issue to be addressed in the remaining steps of the program and who should make this decision. The conclusion was that it is a school management decision, but schools are strongly encouraged to include the perspectives of staff, students, the municipality, and data from the local health profile in the process. To increase the prospect of becoming an iterative model, the local health survey has been designed to match an existing municipal-based health profile system [40] that the school-municipal collaboration can sign up after the research team has withdrawn the program.

Step 3: Group Model Building and Cocreation of Actions

Group Model Building (GMB) is a participatory method from systems science to facilitate a shared understanding of the structures and relationships that shape the system through the creation of causal loop diagrams (CLDs) [38,41]. A CLD helps to build a shared understanding among participants of the cause and effect relationships within a given system and to identify and agree on relevant and important areas for change [41]. In previous community research, this approach has been shown to improve the understanding of the problem, develop consensus

on actions for change among a diverse group of participants, and increase participants' social network [41,42].

GMB is a central part of the Data Health program, as we aim to involve and engage a wide range of participants in developing a CLD and identifying locally adapted actions for change. In this program, the GMB process consists of 3 sessions (GMB1-3), as proposed and applied by an Australian research group at the Institute for Health Transformation, Deakin University [43]. The Data Health research team was trained in the GMB process by this group and then adapted the process and methods to a vocational school setting and vocational students, primarily based on the approaches and results of the pilot test.

In GMB1-2, participants will cocreate a CLD [44] to gain a shared understanding of the perceived causes and drivers of the health issue selected in step 2, for example, poor mental health or physical inactivity. Participants will also identify existing initiatives or programs in the school or community that could have an impact on perceived causes and drivers. GMB1-2 will involve 5 to 10 students, 5 to 10 school staff members, the school and municipal program coordinators, and school management. The school program coordinator will recruit a diverse group of motivated students and staff based on gender, age, and education. The Systems Thinking in Community Knowledge Exchange computer software [45] will be used during this process. At the end of GMB2, participants will identify several community actors who are considered relevant or necessary for the identification and implementation of actions across the school, community, or municipality. These community actors, representing different organizations, sectors and areas of expertise, will then be invited to GMB3 via phone calls. Together with the participants from GMB1-2 and other interested students and staff members, this wider group of participants will identify leverage points in the CLD and prioritize actions to change the system. Within systems thinking, actions can range from minor actions to major actions [27,41]. Minor actions often aim to solve a single issue and can often be implemented quickly with low resource costs (eg, single events), whereas major actions can aim to change paradigms in the way individuals or organizations think and behave and are often more difficult and costly to implement (eg, changes in an organization's goals and beliefs) [27]. The principle in systems thinking is that minor actions can stimulate major actions [27,41].

Participants will identify existing actions or codevelop new actions to change specific elements of the system or the entire system. Actions for further implementation will be selected based on feasibility and expected impact. As a result of GMB3, "action groups" of community actors, staff, and students will be formed, based on motivation, to plan and implement one or more specific actions.

Step 4: Implementation of Actions at Different Levels

In the months following GMB3, the action groups will plan and implement actions for changing the system, assisted by the school and municipal program coordinators. Examples of actions at different levels can be found in the description of program evaluation (implementation of actions [RQ2]). To support the coordinators and action groups, a guide to the development and implementation process has been adapted from previous work [38]. In addition, the Data Health study has reserved funds for each school (€1350) to support the implementation of actions or involvement of community actors to run implementation.

Step 5: Normalization and Diffusion

The school and municipal program coordinators will be responsible for the continuation of the program, and the resources available for this will depend on the priorities of these organizations. The research team will organize meetings between relevant community actors and managers from the school and municipality to encourage the initiated collaborations to remain formalized beyond the program. At these meetings, we will develop a strategy for the continuation of the actions already initiated and a plan for new data collection and development of new local actions. Most municipalities in Denmark have a questionnaire tool [40] for data collection to support the municipalities' work with health behavior and well-being among children and youth. The municipalities will be encouraged to use the tool for future data collection at the program school, as well as at other vocational schools within the municipality.

To increase and maintain momentum for health promotion practices among vocational students, all school and municipal program coordinators and relevant community actors will connect across study sites every 4 months in a community of practice (CoP), initiated by the research team. The CoP is a forum for sharing experiences and learnings on effective strategies for health promotion and collaboration across study sites but will eventually be open to other schools and municipalities interested in implementing the Data Health program.

If all 5 steps are completed as intended, we expect various elements of the Data Health program to be sustained, including the actions implemented, the collaborations initiated, and the organizational practices and motivation to repeat the monitoring to evaluate changes and develop new actions.

Program Evaluation

Research Questions

In total, 5 RQs will comprise the evaluation of the Data Health program:

- RQ1 (process evaluation—steps 2 and 3 of the program): To what extent is the data-driven approach and the GMB process implemented as intended, and what seem to be the most important mechanisms of change and contextual factors?
- RQ2 (implementation of actions—step 4 of the program): What characterizes the planned and initiated actions and what are the unintended consequences related to implementation? Who is involved in the planning and implementation?
- RQ3 (program normalization—step 1 and 5 of the program): What are the opportunities, barriers, and needs for the collaboratives and program to be sustained and normalized?

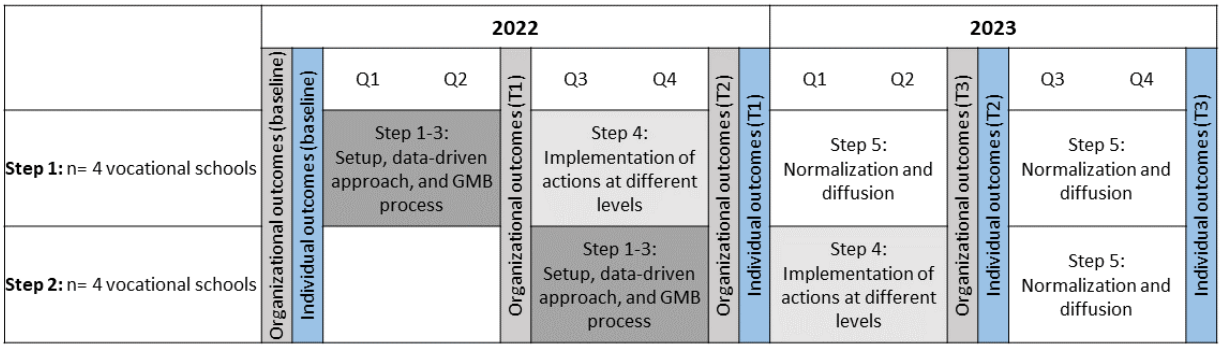
- RQ4 (organizational outcomes): Does the program stimulate organizational changes in schools to work in a more health-promoting direction?
- RQ5 (individual outcomes): Does the program contribute to improvement in health behaviors and well-being among vocational students?

Study Design

To evaluate the implementation of the program, related actions, and systems impact (RQ1-3), we will use a systems-based evaluation design that seeks to understand how the program and the systems adapt to each other [10,46]. Evaluation using a systems perspective needs to adapt as the program unfolds by examining emergent outcomes that result from the interactions of participants [10,46], and it involves examining relationships, interactions, and patterns rather than individual outcomes and static "snapshots" [46,47]. The systems-based evaluation design aims to gain an in-depth understanding of the system as a whole without a "control system." However, it is not possible to include every part of a dynamic system; therefore, it is necessary to define systems boundaries to determine what is considered relevant in terms of what and where to evaluate [46,48]. The starting point for defining the boundaries is the identified primary health issue that each of the 8 program schools has chosen to target. All organizations and interventions relevant to the targeted problem will be considered as part of the system. In terms of system factors, we will focus on modifiable social and physical environmental factors rather than psychological or genetic factors.

We will examine preliminary effectiveness (see descriptions of organizational outcomes [RQ4] and individual outcomes [RQ5]) at the organizational level (ie, school organizational readiness) and at the individual level (ie, students' health behavior and well-being) using a quasi-experimental design with a nonrandomized clustered stepped-wedge strategy. The 8 program schools will be enrolled in 2 steps, matched by educational track (one school from each main track) and geographic location (2 schools from 2 Danish regions). The matched clusters will be assigned to early start (January 2022) or late start (6 months later). This design allows for a sequential roll-out of the program and allows us to control for differences between study sites (vertical control) and secular trends (horizontal control) during the study period [49]. Organizational- and individual-level data will be collected simultaneously at all 8 schools 4 times during the 2-year study period at baseline and at 3 follow-up points (T1, T2, and T3; Figure 2). As systems change takes time to diffuse into individual behavior changes [31], the research team will in due course seek opportunities and funding for longer-term data collection (ie, a 5- and 10-year follow-up).

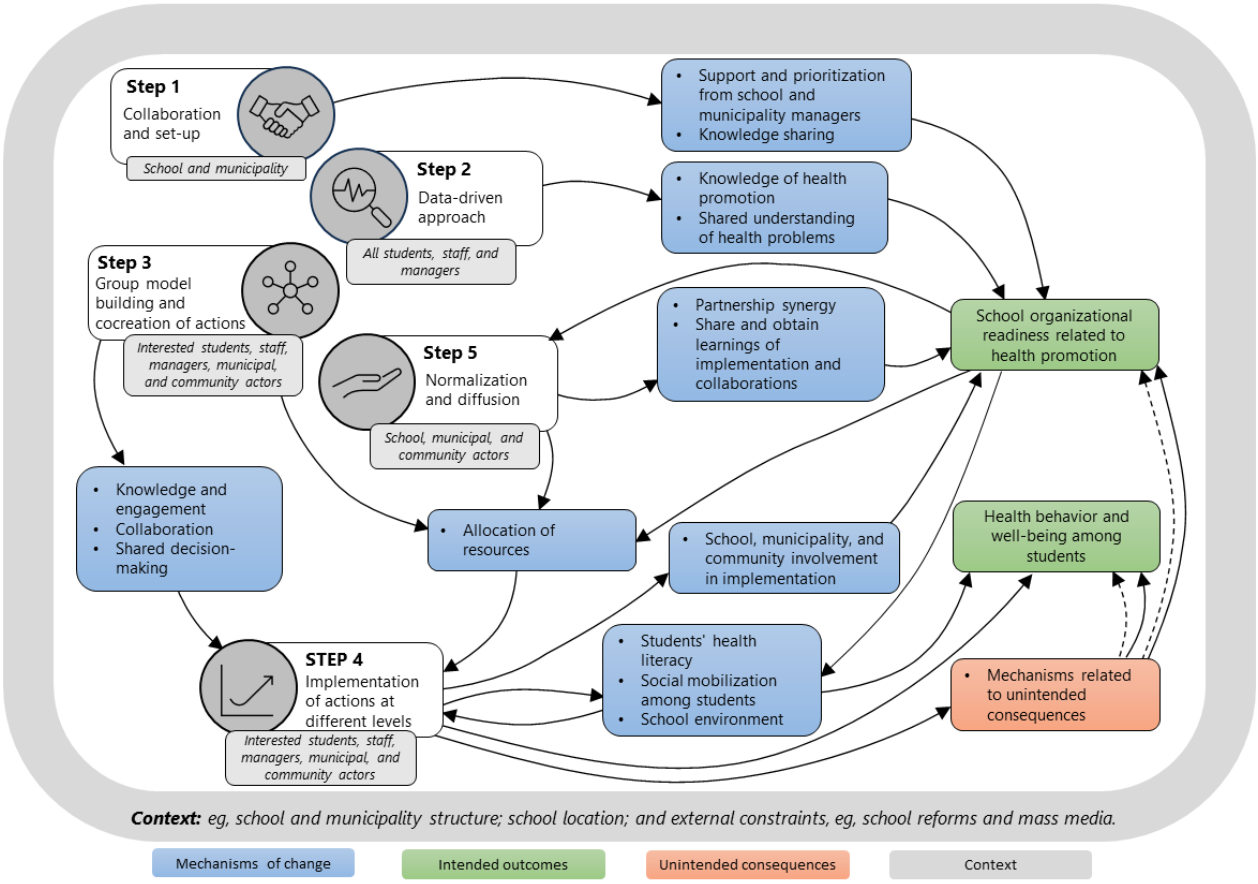
Figure 2. Study design and timeline of the data collection for the effectiveness evaluation. GMB: Group Model Building.



Program Theory

A program theory explains how a program is expected to work and under what conditions [10]. The Data Health program theory (Multimedia Appendix 1) is captured in a series of "if-then" statements and is based on key findings from the pilot test, published literature reporting trial results or theoretical abstractions [8,16,27,50-53], and the research group's experiences and previous research in the field [20,54-57]. Mechanisms of change are the hypothesized causal links between the program components and identified outcomes, triggered within the contexts in which the program is implemented [10]. In total, we hypothesize 6 mechanisms of change as plausible causal links between the data-driven approach and the GMB process and outcomes; these are indicated by mechanisms connected to steps 2 and 3 in Figure 3. To understand the interactions among context, program components, mechanisms, and outcomes; the research group visualized the initial program theory as a systems map, illustrated in Figure 3. The map summarizes our proposed model of how program components are expected to lead to systems change and outcomes. The connecting arrows show how changes in one part of the system are expected to generate changes in other parts of the system. The Data Health program theory and system map will continually be refined and revised as part of the evaluation process.

Figure 3. The Data Health system map.



Process Evaluation (RQ1)

In the process evaluation [58], we will examine whether the data-driven approach and the GMB process (steps 2 and 3 of the program) are being implemented as intended, the associated contextual factors and the mechanisms of change.

Both quantitative and qualitative methods will be used to collect data for the process evaluation (Table 1). Following the Medical Research Council guidelines [58], 5 process evaluation components will be assessed: recruitment, reach, fidelity, dose delivered, and dose received. In addition, we will examine whether the 6 hypothesized mechanisms of change are activated and the extent to which these mechanisms are modified through their interaction with contextual factors. However, we will remain open to other emerging mechanisms.

Table 1. Items, methods, instruments, and frameworks used in evaluation of implementation (research questions 1-3).

Component and items of interest	Methods and data	Applied evaluation instruments and frameworks
Process evaluation—steps 2 and 3 of the program		
Context information		
Examples: • School type • School size • School location • School and municipal structure	• Semistructured interviews with the principal school managers and the municipal program coordinators (after GMB[a]3) • Facts obtained through school and municipality websites	• Medical Research Council guidance [58]
Implementation		
What is delivered: • Recruitment • Reach • Fidelity • Dose • Adaptations	• Registration of participants during meetings and GMB sessions • Exit surveys to all participants (after data presentation meetings, GMB2 and GMB3), semistructured interviews with the school program coordinators (after GMB2) and the principal managers (after GMB3)	• Medical Research Council guidance [58] • COMPACT Stakeholder-driven Community Diffusion Survey [59]
Mechanisms of change		
• Knowledge of health promotion • Shared understanding of health issues • Motivation and engagement • Collaboration • Shared decision-making • Resource allocation • Other emerging mechanisms	• Exit surveys to all participants (after data presentation meetings, GMB2 and GMB3), semistructured interviews with the school program coordinators (after GMB2) and the principal managers (after GMB3)	• Medical Research Council guidance [58] • COMPACT Stakeholder-driven community diffusion survey [59]
Implementation of actions—step 4 of the program		
Actions		
• Number of actions initiated • Primary variable of influence • Action level (beliefs, goals structures, events)	• Semistructured interviews with the school and municipal program coordinators quarterly	• The Systems Thinking in Community Knowledge Exchange computer software [45] • Action Scale Model [27]
Involvement		
• Number of involved participants • Level of involvement in preparation, execution, and implementation of the developed actions	• Semistructured interviews with the school and municipal program coordinators quarterly	• The involvement matrix [53]
Unintended consequences		
• Rippling effects and potential positive and negative unintended consequences of the actions implemented	• The community of practice network will be involved in a process (meetings or workshops) of identifying the rippling effects	• Ripple effect mapping [60]
Program normalization—steps 1 and 5 of the program		
Maintenance of collaboratives		
• Potentials, barriers and needs • Partnership synergy	• Notes from the meetings for program maintenance (6 months after GMB3) • Semistructured interviews with the school manager (after GMB3) and the municipal program coordinator managers (6 months after GMB3)	• Partnership synergy [51]
Program normalization		
• Coherence • Cognitive participation • Collective action • Reflexive monitoring	• Semistructured interviews with the school manager (after GMB3) and the municipal program coordinator managers (6 months after GMB3)	• Normalization process theory framework [61]

[a]GMB: Group Model Building.

Qualitative and quantitative data will be interpreted separately and combined. Quantitative data will be analyzed descriptively, whereas qualitative interviews will be recorded, transcribed, and thematically analyzed in NVivo (Lumivero) [60].

Implementation of Actions (RQ2)

Actions initiated by the school, municipal, or community actors and the consequences of these actions are a direct indicator of systems change. The number of actions initiated and the primary factors in the locally developed CLD that are influenced will be tracked and visually added to the CLD. The Action Scale Model [27] will be used to determine whether the actions address one of four hierarchical levels to change the functioning of the system in the anticipated direction: (1) beliefs (eg, the school creates a local action group as health promotion champions), (2) goals (eg, the school sets new goals for health promotion), (3) structures (eg, school and municipal staff receive training on the complexity of health), and (4) events (eg, a single sport event at schools) [27]. The hierarchical structure suggests that changing beliefs and goals will not only have a greater systemic impact but also be more costly and time consuming than implementing single events [27]. We will also examine which participants (ie, students, school staff and management, municipal staff, and community actors) are involved in the planning and implementation of the actions and how and to what extent they are involved. The involvement levels of the participant groups will be interpreted using the involvement matrix [53].

All actions and involvement will be tracked on a quarterly basis for up to 2 years after GMB3 through semistructured interviews with the school and municipal program coordinators and involved community actors to enable interpretation of the level of system change and engagement across participant groups over time (Table 1).

In addition, an adapted version of "ripple effect mapping" [62] will be used to understand the rippling-initiated actions, effects, and potential positive and negative unintended consequences of the actions implemented. The CoP will be involved in a process to explore and visualize unintended consequences.

Program Normalization (RQ3)

We will explore the opportunities, barriers, and what is needed to integrate the collaboratives and the program into normalized practice (steps 1 and 5 of the program).

The school-municipality collaboration and program normalization will be explored through interviews with school and municipal program coordinators (Table 1). Interview guides inspired by the Partnership Synergy framework [51] will be developed to explore the functioning of the collaborations and the potential for maintenance, and the normalization process theory [61] will be used as a framework for understanding program normalization. In addition, carefully written notes will be taken from the program maintenance meetings, which will be completed as part of step 5 of the program.

Interviews will be recorded and transcribed, and all data will be analyzed thematically in NVivo [60] to understand opportunities, barriers, and needs related to sustaining collaborations and normalizing the program. Finally, we will develop recommendations for the implementation of systems approaches for sustainable health promotion in vocational schools.

Organizational Outcomes (RQ4)

School organizational readiness to address health promotion is selected as a primary organizational outcome. We will apply the "organizational readiness framework" [50] to track change over time. Organizational readiness refers to the extent to which an organization is willing and able to implement change, and the elements in the framework have previously been shown to be related to implementation success [63]. School organizational readiness will be assessed by questionnaires administered to all school staff, supplemented by semistructured interviews with the principal managers at the schools (Table 2).

Table 2. Items, methods, instruments, and frameworks used in evaluation of effectiveness (research questions 4 and 5).

Component and items of interest	Methods and data	Applied evaluation instruments and frameworks
System outcomes		
Organizational readiness		

• Baseline and change in the following:
  • Organizational motivation
  • General capacity
  • Health promotion capacity
	• Questionnaire to staff members (4 times in total)
	• Semistructured interviews with principal managers (after GMB[a]3)
		• Organizational readiness [50]

Individual outcomes		
Health behavior		

• Baseline and changes in the following:
  • Mental health and well-being
  • Physical activity
  • Food intake
  • Nicotine use
  • Alcohol use
	• Questionnaire to all students (4 times in total)	• WHO-5[b] [64] and SGPALS[c] [65]
		• Validated measures from the Danish National Health Survey and the Health Behaviour in School-aged Children study [66]

Health promotion outcomes		

• Baseline and changes in the following:
  • Health literacy
  • Knowledge relevant to the problem of interest
  • Self-empowerment
  • Self-confidence
  • Self-efficacy
  • Behavioral intentions
  • Motivation
  • Social network and interaction
  • Social connectedness
  • Student autonomy
	• Questionnaire to all students (4 times in total)	• HLQ[d] [67]; HLSAC[e] [68] validated measures from the Danish National Health Survey and the Health Behaviour in School-aged Children study [66]

[a]GMB: Group Model Building.

[b]WHO-5: World Health Organization (Five) Well-Being Index.

[c]SGPALS: Saltin-Grimby Physical Activity Level Scale.

[d]HLQ: Health Literacy Questionnaire.

[e]HLSAC: Health Literacy for School-Aged Children.

The questionnaire instrument will adapt and refine existing and tested items [20,69] across 3 dimensions and 10 subdimensions: motivation (relative advantage, compatibility, complexity, and priority), general capacity (culture, climate, and staff capacity), and program-specific capacity (knowledge, skills, and abilities). We will use exploratory and confirmatory factor analyses to initially validate the instrument and assess its internal consistency and convergent validity. The questionnaire will be distributed electronically via email in SurveyXact [70] to all school staff (eg, teachers, counselors, and administrators), and repeated data will be collected 4 times during the study period (Figure 2). Changes in school organizational readiness will be assessed primarily using linear mixed modeling, adjusting for clustering, with school as a random effect and time as a fixed effect.

Interviews with school leaders will contribute to a deeper understanding of how the support and priorities of the school management can stimulate or hinder the school's readiness and willingness to change. The interviews will be recorded, transcribed, and analyzed thematically according to the dimensions and subdimensions of organizational readiness.

To generate a comprehensive understanding of school organizational readiness, a convergent parallel mixed methods design will be used in the analyses [71]. Quantitative and qualitative data will be analyzed independently and then compared, related, and interpreted.

Individual Outcomes (RQ5)

We will explore the indications of effectiveness at the individual level through changes in students' health behaviors and well-being. Items to assess health behavior will primarily consist of validated measures and items used in other national health profile studies in Denmark (Table 2). The research team will preidentify one primary and one secondary outcome indicator item for each targeted health area (ie, dietary behavior, physical activity, alcohol consumption, marijuana and drug use, and well-being). The primary indicator will be an item assessing students' health behavior during school time, and the secondary

indicator will be an item assessing health behavior during leisure time or overall.

Following Bauman and Nutbeam [8], we will assess both health behavior and health promotion outcomes to understand the complexity of health behavior. While health behavior outcomes are expressed in terms of changes in, for example, levels of physical activity or mental well-being, health promotion outcomes are personal, social, and environmental factors that are a means of improving people's ability to change behavior [8]. Therefore, health promotion outcomes are considered intermediate to health behavior (see Table 2 for examples).

The questionnaire data will be collected 4 times (Figure 2). Regardless of the specific health issue each school chooses to address, all students will receive the same questionnaire to identify potential intended and unintended consequences on other health promotion outcomes or behaviors, as suggested in a complex systems sense [46,72]. Electronic questionnaires in SurveyXact [70] will be distributed during school hours by the research team, who will be present in the classrooms so that students can ask questions as they complete the questionnaire. The estimated student population of the 8 program schools is approximately 2000 and, based on previous experience with this procedure [54], we expect that 90% of the students present in class will complete the questionnaire at each of the 4 data collection points. Informed consent will be obtained from all students and can be withdrawn at any time.

Most analyses will be based on cross-sectional data and descriptive in nature, interpreting the mean differences between the intervention and control groups. However, the analyses will also include linear mixed models with time and selected covariates (eg, gender, age, ethnicity, and socioeconomic status) as fixed effects and school as a random effect. It is important to note that the total time of 2 years to assess individual outcomes may be too short to provide conclusive evidence at this level.

Ethical Considerations

The study has been referred to the Capital Region of Denmark's legal center for personal data handling (journal number: P-2021-327). The study will be conducted without approval from the Committees on Health Research Ethics for the Capital Region of Denmark (journal number: 22012766), as this is not required for social health science in Denmark [73]. Participation in research related to the study is voluntary and requires written informed consent from all participants. Consent may be withdrawn at any time. Questionnaire data, key files, audio files, and transcripts of interviews and observations will be stored in a secure folder on the corporate network in accordance with the requirements of the Capital Region of Denmark and European General Data Protection Regulation. Only the principal investigator and those with permission from the principal investigator will have access to data. None of the authors have any financial or competing interests.

Results

This study was launched in 2021, and data collection is expected to be completed in June 2024. The first results will be submitted for publication in January 2024. The results of this research will be disseminated through national and international conferences, peer-reviewed journals, reports, and web-based sources. In addition, key findings will be disseminated through the CoP and other national practice network meetings with stakeholders and policy representatives.

Discussion

Overview

The Data Health study is the first to apply a systems approach to the implementation and evaluation of health promotion programs among vocational school students. The program comprises 5 steps aimed at establishing strong collaborations, building local capacity, identifying leverage points, and generating and implementing collective actions for systems change to improve health and well-being among vocational students. The program will be accompanied by a systems-based evaluation to support the sustainability of program implementation and to determine the scalability of the program. Guided by the Medical Research Council guidance, the evaluation will assess implementation outcomes, contextual differences, and the mechanisms through which the program leads to changes in systems, school organizational readiness, and health behavior and well-being.

Strengths and Limitations

Program Implementation

The steps of the Data Health program are based on systems and health promotion theory, previous health promotion evidence, and formative evaluation at a pilot site. This study has the potential to improve the health behavior and well-being of vocational students and reduce social inequalities in health. The use of systems approaches in communities to address childhood obesity has shown promising results [31,74]. However, adaptation to disadvantaged educational settings may be challenging. One possible challenge is to engage students who are only in school for short periods between workplace-based training. As workplaces are likely to be located across municipalities, it may be difficult to engage students in the GMB process and implementation of actions during workplace training. If possible, we will try to involve the local workplaces in creating collective actions in GMB3 to involve the students, even if they are not physically at the school.

In most health promotion programs, resources often run out before the desired changes in individuals or systems are normalized [75]. The sustainability of actions for system change has been demonstrated in communities, with actions continuing to be implemented years after the reduction in research support [76]. On the basis of locally relevant data and existing capacities and resources, we will test whether the program steps can be successfully sustained. However, sustainable and long-term partnerships between schools, communities, and municipalities can be challenging owing to organizational changes or staff turnover. To address this issue, we will seek to engage and motivate commitment at the management level. In addition, the CoP will serve as an informal capacity building and will expectantly keep the organization as the drivers for systems

change. If the steps in the program prove to be sustainable and effective, the CoP can be used to disseminate knowledge about methods and approaches to other schools and municipalities interested in implementing the Data Health program.

Program Evaluation

This study involves a complex program evaluation. The processes and steps within the Data Health program are systematic but flexible in the sense that the study sites themselves choose the targeted health issue, actions, and process for normalization. The complexity of a systems approach does not allow for a fully randomized controlled trial with a single set of quantitative outcomes [26]. Therefore, we will use a systems-based and quasi-experimental design to test the preliminary effectiveness of the program at an individual and organizational level. We will use mixed methods to account for the complexity and contextual variation. The comprehensive evaluation design of program implementation and outcomes—combining many data sources from different perspectives—will generate new knowledge that can be used in similar or different contexts at the national and international levels.

To our knowledge, few studies have reported on the implementation of systems approaches and sustainment of actions over time [43,77], particularly using GMB as a participatory method. Understanding the use of GMB in a school setting will provide important information for researchers and practitioners regarding enablers and barriers to this approach.

The systems-based evaluation design provides an opportunity to test new system-level evaluation methodologies, such as the Action Scale Model [27], measuring change within complex adaptive systems. There are many uncertainties in studying changes in complex systems, as complex systems are dynamic [26]. Therefore, we recognize that capturing systems change might not be fully comprehensive. To accommodate this, we set systems boundaries to determine what is relevant to capture and will be used to guide the evaluation.

In parallel, we will assess preliminary indications on individual-level outcomes, assessing the effectiveness on students' health behavior and well-being because of systems change. A limitation of this study is that most of the student data will be cross-sectional because of the vocational school structure. The research team will explore the possibility of tracking individuals' educational attainment, employment status, and health registers (compiled by Statistics Denmark [78]) 5 or 10 years postprogram implementation.

This study will test a systems change approach in vocational schools and whether such an approach is suitable for adaptation and scale-up. If this study is shown to be sustainable and effective, the established CoP will support implementation at scale.

Acknowledgments

The authors would like to acknowledge professor Karien Stronks from the Department of Public Health, Academic Medical Centre, University of Amsterdam, for commenting on an earlier draft of this paper and for providing valuable inputs to the study.

Authors' Contributions

CDK, LWR, ALB, and CH conceived the overarching program. AS was responsible for the pilot test and the formative evaluation of the study. CH designed the research design of the study and wrote the main manuscript. RDH, ALB, RFK, AB, and CDK contributed to the research design and writing of the manuscript. LWR, AS, and SA contributed to writing the manuscript. All authors have read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
The Data Health program theory.
[PDF File (Adobe PDF File), 114 KB - resprot_v13i1e52571_app1.pdf]

References

1. Zahra A, Lee EW, Sun LY, Park JH. Cardiovascular disease and diabetes mortality, and their relation to socio-economical, environmental, and health behavioural factors in worldwide view. Public Health 2015 Apr;129(4):385-395. [doi: 10.1016/j.puhe.2015.01.013] [Medline: 25724438]
2. Health for everyone? Social inequalities in health and health systems. Organisation for Economic Co-operation and Development. Paris, France: OECD Publishing; 2019. URL: https://www.oecd-ilibrary.org/docserver/3c8385d0-en.pdf?expires=1705508331&id=id&accname=guest&checksum=06EB8B63F7F510FBC82C2CCB8539577E [accessed 2024-01-12]
3. Foley P. The socio-economic status of vocational education and training students in Australia. National Centre for Vocational Education Research. 2007. URL: https://www.ncver.edu.au/__data/assets/file/0013/3406/sp407.pdf [accessed 2023-09-01]
4. Undervisingsministeriet. Tal, der taler 2009. Børne- og Undervisningsministeriet. 2009. URL: https://uvm.dk/publikationer/statistik/2010-tal-der-taler-2009 [accessed 2023-09-11]

5. Atorkey P, Byaruhanga J, Paul C, Wiggers J, Bonevski B, Tzelepis F. Multiple health risk factors in vocational education students: a systematic review. Int J Environ Res Public Health 2021 Jan 13;18(2):637 [FREE Full text] [doi: 10.3390/ijerph18020637] [Medline: 33451108]
6. Pisinger V, Thorsted A, Jezek AH, Andreas J, Christensen AI, Thygesen LC. Sundhed Og Trivsel På Gymnasiale Uddannelser 2019. Statens Institut for Folkesundhed, SDU. 2019. URL: https://www.sdu.dk/sif/-/media/images/sif/udgivelser/2019/rapport_ung19.pdf [accessed 2023-05-03]
7. UNG19 – sundhed og trivsel på erhvervsuddannelser 2019. Steno Diabetes Center Copenhagen. URL: https://www.sdcc.dk/forskning/forskningsprojekter/Sider/UNG19-%E2%80%93-Sundhed-og-trivsel-p%C3%A5-erhvervsuddannelser-2019.aspx [accessed 2024-01-17]
8. Bauman AE, Nutbeam D. Evaluation in a Nutshell: A Practical Guide to the Evaluation of Health Promotion Programs 3rd edition. Ryde, Australia: McGraw Hill; 2006.
9. Rutter H, Cavill N, Bauman A, Bull F. Systems approaches to global and national physical activity plans. Bull World Health Organ 2019 Feb 01;97(2):162-165 [FREE Full text] [doi: 10.2471/BLT.18.220533] [Medline: 30728623]
10. Skivington K, Matthews L, Simpson SA, Craig P, Baird J, Blazeby JM, et al. A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance. BMJ 2021 Sep 30;374:n2061 [FREE Full text] [doi: 10.1136/bmj.n2061] [Medline: 34593508]
11. Sniehotta FF, Araújo-Soares V, Brown J, Kelly MP, Michie S, West R. Complex systems and individual-level approaches to population health: a false dichotomy? Lancet Public Health 2017 Sep;2(9):e396-e397. [doi: 10.1016/s2468-2667(17)30167-6]
12. Moore D, Benham-Clarke S, Kenchington R, Boyle C, Ford T, Hayes R, et al. Improving behaviour in schools: evidence review. Education Endowment Foundation. 2019. URL: https://files.eric.ed.gov/fulltext/ED612210.pdf [accessed 2023-05-04]
13. Steward-Brown S. What is the evidence on school health promotion in improving health or preventing disease and, specifically, what is the effectiveness of the health promoting schools approach. World Health Organization Regional Office for Europe (Health Evidence Network Report). 2006. URL: http://www.euro.who.int/__data/assets/pdf_file/0007/74653/E88185.pdf?ua=1 [accessed 2019-06-08]
14. Turunen H, Sormunen M, Jourdan D, von Seelen J, Buijs G. Health promoting schools-a complex approach and a major means to health improvement. Health Promot Int 2017 Apr 01;32(2):177-184. [doi: 10.1093/heapro/dax001] [Medline: 28384373]
15. Chambers DA, Glasgow RE, Stange KC. The dynamic sustainability framework: addressing the paradox of sustainment amid ongoing change. Implement Sci 2013 Oct 02;8:117 [FREE Full text] [doi: 10.1186/1748-5908-8-117] [Medline: 24088228]
16. Sigfúsdóttir ID, Thorlindsson T, Kristjánsson AL, Roe KM, Allegrante JP. Substance use prevention for adolescents: the Icelandic model. Health Promot Int 2009 Mar 12;24(1):16-25. [doi: 10.1093/heapro/dan038] [Medline: 19074445]
17. Whelan J, Strugnell C, Allender S, Korn AR, Brown AD, Orellana L, et al. Protocol for the measurement of changes in knowledge and engagement in the stepped wedge cluster randomised trial for childhood obesity prevention in Australia: (Reflexive Evidence and Systems interventions to Prevent Obesity and Non-communicable Disease (RESPOND)). Trials 2020 Sep 04;21(1):763 [FREE Full text] [doi: 10.1186/s13063-020-04692-6] [Medline: 32887655]
18. Pulimeno M, Piscitelli P, Colazzo S, Colao A, Miani A. School as ideal setting to promote health and wellbeing among young people. Health Promot Perspect 2020 Nov 07;10(4):316-324 [FREE Full text] [doi: 10.34172/hpp.2020.50] [Medline: 33312927]
19. Improving vocational education and training. Børne- og Undervisningsministeriet. URL: https://www.uvm.dk/publikationer/engelsksprogede/2014-improving-vocational-education-and-training [accessed 2023-06-01]
20. Hansen AV, Klinker CD. Danske erhvervsskolers: sundhedsfremmende indsatser og implementeringskapacitet. Hjerteforeningen og Steno Diabetes Center Copenhagen. 2017. URL: https://hjerteforeningen.dk/wp-content/uploads/sites/27/2019/01/danske-erhvervsskolers-sundhedsfremmende-indsatser-og-implementeringskapacitet.pdf [accessed 2023-06-01]
21. Simovska V, Nordin LL, Madsen KD. Health promotion in Danish schools: local priorities, policies and practices. Health Promot Int 2016 Jun 08;31(2):480-489. [doi: 10.1093/heapro/dav009] [Medline: 25753051]
22. Rasmussen KH, Hansen AV, Klinker CD, Löfvall S, Heinze C, Jensen PD. Udbredelse af røgfri skoletid på erhvervsskoler. En forundersøgelse til en effektiv tobaksforebyggelsesindsats på erhvervsskoler. Hjerteforeningen og Steno Diabetes Center Copenhagen. 2018. URL: https://research.regionh.dk/en/publications/udbredelse-af-r%C3%B8gfri-skoletid-p%C3%A5-erhvervsskoler-en-forunders%C3%B8gels [accessed 2023-06-01]
23. Simovska V. What do health ‐ promoting schools promote? Processes and outcomes in school health promotion. Health Educ 2012;112(2):84-88. [doi: 10.1108/09654281211214527]
24. Dadaczynski K, Jensen BB, Viig NG, Sormunen M, von Seelen J, Kuchma V, et al. Health, well-being and education: building a sustainable future. The Moscow statement on health promoting schools. Health Educ 2020;120(1):11-19. [doi: 10.1108/HE-12-2019-0058]
25. Rutter H, Savona N, Glonti K, Bibby J, Cummins S, Finegood DT, et al. The need for a complex systems model of evidence for public health. Lancet 2017 Dec 09;390(10112):2602-2604 [FREE Full text] [doi: 10.1016/S0140-6736(17)31267-9] [Medline: 28622953]

26. Egan M, McGill E, Penney T, Anderson de Cuevas R, Er V, Orton L, et al. NIHR SPHR guidance on systems approaches to local public health evaluation. Part 1: introducing systems thinking. National Institute for Health Research School for Public Health Research. 2019. URL: https://sphr.nihr.ac.uk/wp-content/uploads/2018/08/NIHR-SPHR-SYSTEM-GUIDANCE-PART-1-FINAL_SBnavy.pdf [accessed 2023-05-04]
27. Nobles JD, Radley D, Mytton OT, Whole Systems Obesity programme team. The action scales model: a conceptual tool to identify key points for action within complex adaptive systems. Perspect Public Health 2022 Nov 15;142(6):328-337 [FREE Full text] [doi: 10.1177/17579139211006747] [Medline: 33998333]
28. Kreger M, Brindis CD, Manuel DM, Sassoubre L. Lessons learned in systems change initiatives: benchmarks and indicators. Am J Community Psychol 2007 Jun 18;39(3-4):301-320. [doi: 10.1007/s10464-007-9108-1] [Medline: 17510792]
29. Waterlander WE, Luna Pinzon A, Verhoeff A, den Hertog K, Altenburg T, Dijkstra C, et al. A system dynamics and participatory action research approach to promote healthy living and a healthy weight among 10-14-year-old adolescents in Amsterdam: the LIKE programme. Int J Environ Res Public Health 2020 Jul 08;17(14):4928 [FREE Full text] [doi: 10.3390/ijerph17144928] [Medline: 32650571]
30. Maitland N, Williams M, Jalaludin B, Allender S, Strugnell C, Brown A, et al. Campbelltown - changing our future: study protocol for a whole of system approach to childhood obesity in South Western Sydney. BMC Public Health 2019 Dec 18;19(1):1699 [FREE Full text] [doi: 10.1186/s12889-019-7936-1] [Medline: 31852528]
31. Allender S, Orellana L, Crooks N, Bolton KA, Fraser P, Brown AD, et al. Four-year behavioral, health-related quality of life, and BMI outcomes from a cluster randomized whole of systems trial of prevention strategies for childhood obesity. Obesity (Silver Spring) 2021 Jun 05;29(6):1022-1035 [FREE Full text] [doi: 10.1002/oby.23130] [Medline: 33950583]
32. Friel S, Pescud M, Malbon E, Lee A, Carter R, Greenfield J, et al. Using systems science to understand the determinants of inequities in healthy eating. PLoS One 2017;12(11):e0188872 [FREE Full text] [doi: 10.1371/journal.pone.0188872] [Medline: 29190662]
33. Global action plan on physical activity 2018–2030: more active people for a healthier world. World Health Organization. 2018 Jun 1. URL: https://www.who.int/publications/i/item/9789241514187 [accessed 2022-10-07]
34. Best A, Clark PI, Leischow SJ, Trochim WM. Greater than the sum: systems thinking in tobacco control. U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute. 2007 Apr. URL: https://cancercontrol.cancer.gov/brp/tcrb/monographs/monograph-18 [accessed 2023-02-18]
35. Rosas SR. Systems thinking and complexity: considerations for health promoting schools. Health Promot Int 2017 Apr 01;32(2):301-311. [doi: 10.1093/heapro/dav109] [Medline: 26620709]
36. Vocational education and training in Denmark: get access to a career as a skilled worker in Denmark. Ministry of Children and Education, Denmark. URL: https://eng.uvm.dk/upper-secondary-education/vocational-education-and-training-in-denmark [accessed 2023-03-14]
37. Elevtal fordelt på uddannelse - Lav selv tabeller. Undervisningsministeriet. 2022. URL: https://uddannelsesstatistik.dk [accessed 2023-03-14]
38. Allender S, Millar L, Hovmand P, Bell C, Moodie M, Carter R, et al. Whole of systems trial of prevention strategies for childhood obesity: WHO STOPS childhood obesity. Int J Environ Res Public Health 2016 Nov 16;13(11):1143 [FREE Full text] [doi: 10.3390/ijerph13111143] [Medline: 27854354]
39. Crooks N, Strugnell C, Bell C, Allender S. Establishing a sustainable childhood obesity monitoring system in regional Victoria. Health Prom J of Aust 2016 Dec 19;28(2):96-102. [doi: 10.1071/he16020]
40. BørnUngeLiv. URL: https://www.boernungeliv.dk/Public/Forside.aspx?ReturnUrl=%2f [accessed 2023-08-15]
41. Hovmand PS. Community Based System Dynamics. New York, NY: Springer; 2013.
42. Simmons A, Mavoa HM, Bell AC, De Courten M, Schaaf D, Schultz J, et al. Creating community action plans for obesity prevention using the ANGELO (Analysis Grid for Elements Linked to Obesity) framework. Health Promot Int 2009 Dec 16;24(4):311-324 [FREE Full text] [doi: 10.1093/heapro/dap029] [Medline: 19759046]
43. Bolton KA, Fraser P, Lowe J, Moodie M, Bell C, Strugnell C, et al. Generating change through collective impact and systems science for childhood obesity prevention: the GenR8 Change case study. PLoS One 2022 May 11;17(5):e0266654 [FREE Full text] [doi: 10.1371/journal.pone.0266654] [Medline: 35544522]
44. Waterlander WE, Singh A, Altenburg T, Dijkstra C, Luna Pinzon A, Anselma M, et al. Understanding obesity-related behaviors in youth from a systems dynamics perspective: the use of causal loop diagrams. Obes Rev 2021 Jul 27;22(7):e13185 [FREE Full text] [doi: 10.1111/obr.13185] [Medline: 33369045]
45. Hayward J, Morton S, Johnstone M, Creighton D, Allender S. Tools and analytic techniques to synthesise community knowledge in CBPR using computer-mediated participatory system modelling. NPJ Digit Med 2020 Feb 19;3(1):22 [FREE Full text] [doi: 10.1038/s41746-020-0230-x] [Medline: 32133423]
46. Luna Pinzon A, Stronks K, Dijkstra C, Renders C, Altenburg T, den Hertog K, et al. The ENCOMPASS framework: a practical guide for the evaluation of public health programmes in complex adaptive systems. Int J Behav Nutr Phys Act 2022 Mar 28;19(1):33 [FREE Full text] [doi: 10.1186/s12966-022-01267-3] [Medline: 35346233]
47. Dooris M. Healthy settings: challenges to generating evidence of effectiveness. Health Promot Int 2006 Mar;21(1):55-65. [doi: 10.1093/heapro/dai030] [Medline: 16339774]

48. Williams B, Hummelbrunner R. Systems Concepts in Action: A Practitioner's Toolkit. Redwood City, CA: Stanford University Press; 2010.
49. Brown CA, Lilford RJ. The stepped wedge trial design: a systematic review. BMC Med Res Methodol 2006 Nov 08;6(1):54 [FREE Full text] [doi: 10.1186/1471-2288-6-54] [Medline: 17092344]
50. Scaccia JP, Cook BS, Lamont A, Wandersman A, Castellow J, Katz J, et al. A practical implementation science heuristic for organizational readiness: R = MC2. J Community Psychol 2015 Apr 13;43(4):484-501 [FREE Full text] [doi: 10.1002/jcop.21698] [Medline: 26668443]
51. Lasker RD, Weiss ES, Miller R. Partnership synergy: a practical framework for studying and strengthening the collaborative advantage. Milbank Q 2001 Jun 06;79(2):179-1IV [FREE Full text] [doi: 10.1111/1468-0009.00203] [Medline: 11439464]
52. Siokou C, Morgan R, Shiell A. Group model building: a participatory approach to understanding and acting on systems. Public Health Res Pract 2014 Nov 28;25(1):e2511404 [FREE Full text] [doi: 10.17061/phrp2511404] [Medline: 25828443]
53. Smits DW, van Meeteren K, Klem M, Alsem M, Ketelaar M. Designing a tool to support patient and public involvement in research projects: the Involvement Matrix. Res Involv Engagem 2020 Jun 16;6(1):30 [FREE Full text] [doi: 10.1186/s40900-020-00188-4] [Medline: 32550002]
54. Klinker CD, Aaby A, Ringgaard LW, Hjort AV, Hawkins M, Maindal HT. Health literacy is associated with health behaviors in students from vocational education and training schools: a Danish population-based survey. Int J Environ Res Public Health 2020 Jan 20;17(2):671 [FREE Full text] [doi: 10.3390/ijerph17020671] [Medline: 31968667]
55. Hjort AV, Kuipers MA, Stage M, Pisinger C, Klinker CD. Intervention activities associated with the implementation of a comprehensive school tobacco policy at Danish vocational schools: a repeated cross-sectional study. Int J Environ Res Public Health 2022 Sep 30;19(19):12489 [FREE Full text] [doi: 10.3390/ijerph191912489] [Medline: 36231788]
56. Hjort AV, Schreuders M, Rasmussen KH, Klinker CD. Are Danish vocational schools ready to implement "smoke-free school hours"? A qualitative study informed by the theory of organizational readiness for change. Implement Sci Commun 2021 Apr 09;2(1):40 [FREE Full text] [doi: 10.1186/s43058-021-00140-x] [Medline: 33836841]
57. Heinze C, Hjort AV, Elsborg P, Maindal HT, Klinker CD. Smoke-free-school-hours at vocational education and training schools in Denmark: attitudes among managers and teaching staff - a national cross-sectional study. BMC Public Health 2019 Jun 24;19(1):813 [FREE Full text] [doi: 10.1186/s12889-019-7188-0] [Medline: 31234822]
58. Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, et al. Process evaluation of complex interventions: Medical Research Council guidance. BMJ 2015 Mar 19;350:h1258 [FREE Full text] [doi: 10.1136/bmj.h1258] [Medline: 25791983]
59. Korn AR, Appel J, Hammond RA, Hennessy E, Mâsse LC, Must A, et al. Validation and refinement of the stakeholder-driven community diffusion survey for childhood obesity prevention. Implement Sci 2021 Oct 09;16(1):91 [FREE Full text] [doi: 10.1186/s13012-021-01158-4] [Medline: 34627319]
60. Malterud K. Kvalitative metoder i medisinsk forskning — en innføring, 2.utg. Nordic J Nurs Res 2003;23(2):50. [doi: 10.1177/010740830302300212]
61. Murray E, Treweek S, Pope C, MacFarlane A, Ballini L, Dowrick C, et al. Normalisation process theory: a framework for developing, evaluating and implementing complex interventions. BMC Med 2010 Oct 20;8:63 [FREE Full text] [doi: 10.1186/1741-7015-8-63] [Medline: 20961442]
62. Nobles J, Wheeler J, Dunleavy-Harris K, Holmes R, Inman-Ward A, Potts A, et al. Ripple effects mapping: capturing the wider impacts of systems change efforts in public health. BMC Med Res Methodol 2022 Mar 18;22(1):72 [FREE Full text] [doi: 10.1186/s12874-022-01570-4] [Medline: 35300619]
63. Bast LS, Andersen HB, Andersen A, Lauemøller SG, Bonnesen CT, Krølner RF. School coordinators' perceptions of organizational readiness is associated with implementation fidelity in a smoking prevention program: findings from the X:IT II study. Prev Sci 2021 Apr 06;22(3):312-323 [FREE Full text] [doi: 10.1007/s11121-020-01197-1] [Medline: 33404969]
64. Wellbeing measures in primary health care/the DepCare Project: report on a WHO meeting. World Health Organization. Regional Office for Europe. 1998. URL: https://pesquisa.bvsalud.org/portal/resource/pt/who-349766 [accessed 2024-01-17]
65. Grimby G, Börjesson M, Jonsdottir IH, Schnohr P, Thelle DS, Saltin B. The "Saltin-Grimby Physical Activity Level Scale" and its application to health research. Scand J Med Sci Sports 2015 Dec;25 Suppl 4:119-125. [doi: 10.1111/sms.12611] [Medline: 26589125]
66. Health Behaviour in School-aged Children. URL: https://hbsc.org/ [accessed 2022-12-21]
67. Maindal HT, Kayser L, Norgaard O, Bo A, Elsworth GR, Osborne RH. Cultural adaptation and validation of the Health Literacy Questionnaire (HLQ): robust nine-dimension Danish language confirmatory factor model. Springerplus 2016;5(1):1232 [FREE Full text] [doi: 10.1186/s40064-016-2887-9] [Medline: 27536516]
68. Bonde AH, Stjernqvist NW, Klinker CD, Maindal HT, Paakkari O, Elsborg P. Translation and validation of a brief health literacy instrument for school-age children in a Danish context. Health Lit Res Pract 2022 Jan;6(1):e26-e29 [FREE Full text] [doi: 10.3928/24748307-20220106-01] [Medline: 35133944]
69. Duus KS, Brautsch LA, Bonnesen CT, Krølner RF. Sund vægtudvikling hos skolebørn: en kortlægning af kommuners muligheder for at implementere skolebaserede indsatser i region syddanmark. Statens Institut for Folkesundhed. 2021 Jun

9. URL: https://portal.findresearcher.sdu.dk/da/publications/sund-v%C3%A6gtudvikling-hos-skoleb%C3%B8rn-en-kortl%C3%A6gning-af-kommuners-muli [accessed 2022-10-16]
70. SurveyXact. SurveyXact by Ramboll. URL: https://www.surveyxact.dk/ [accessed 2023-09-26]
71. Kettles AM, Creswell JW, Zhang W. Mixed methods research in mental health nursing. J Psychiatr Ment Health Nurs 2011 Aug;18(6):535-542. [doi: 10.1111/j.1365-2850.2011.01701.x] [Medline: 21749560]
72. McGill E, Er V, Penney T, Egan M, White M, Meier P, et al. Evaluation of public health interventions from a complex systems perspective: a research methods review. Soc Sci Med 2021 Mar;272:113697 [FREE Full text] [doi: 10.1016/j.socscimed.2021.113697] [Medline: 33508655]
73. Lov om videnskabsetisk behandling af sundhedsvidenskabelige forskningsprojekter. Retsinformation. 2011. URL: https://www.retsinformation.dk/eli/lta/2011/593#Kap4 [accessed 2023-06-13]
74. Economos CD, Hyatt RR, Must A, Goldberg JP, Kuder J, Naumova EN, et al. Shape Up Somerville two-year results: a community-based environmental change intervention sustains weight reduction in children. Prev Med 2013 Oct;57(4):322-327. [doi: 10.1016/j.ypmed.2013.06.001] [Medline: 23756187]
75. Schell SF, Luke DA, Schooley MW, Elliott MB, Herbers SH, Mueller NB, et al. Public health program capacity for sustainability: a new framework. Implement Sci 2013 Feb 01;8(1):15 [FREE Full text] [doi: 10.1186/1748-5908-8-15] [Medline: 23375082]
76. Ogilvie F. When this community took on the obesity epidemic, it came up with 400 solutions. Australian Broadcasting Corporation News. 2020 Jan 29. URL: https://www.abc.net.au/news/2020-01-29/obesity-epidemic-community-based-solutions-key-to-success/11902898 [accessed 2022-10-16]
77. Jenkins E, Lowe J, Allender S, Bolton KA. Process evaluation of a whole-of-community systems approach to address childhood obesity in western Victoria, Australia. BMC Public Health 2020 Apr 06;20(1):450 [FREE Full text] [doi: 10.1186/s12889-020-08576-x] [Medline: 32252713]
78. Statistics Denmark home page. Statistics Denmark. URL: https://www.dst.dk/en [accessed 2023-03-16]

Abbreviations

CLD: causal loop diagram
CoP: community of practice
GMB: Group Model Building
HPS: health promoting school
NCD: noncommunicable disease
RQ: research question

Edited by A Mavragani; submitted 11.09.23; peer-reviewed by W Al-Chetachi, K Bessems; comments to author 02.12.23; revised version received 15.12.23; accepted 17.12.23; published 06.02.24.

Please cite as:
Heinze C, Hartmeyer RD, Sidenius A, Ringgaard LW, Bjerregaard AL, Krølner RF, Allender S, Bauman A, Klinker CD
Developing and Evaluating a Data-Driven and Systems Approach to Health Promotion Among Vocational Students: Protocol for the Data Health Study
JMIR Res Protoc 2024;13:e52571
URL: https://www.researchprotocols.org/2024/1/e52571
doi:10.2196/52571
PMID:38319698

Protocol

Identification of Anterior Large Vessel Occlusion Stroke During the Emergency Call: Protocol for a Controlled, Nonrandomized Trial

Nicole Wimmesberger[1*], MSc; Diana Rau[1*], MSc; Florian Schuchardt[2*], MD; Simone Meier[2], MD; Matthias L Herrmann[2], MD; Ulrike Bergmann[2]; Erik Farin-Glattacker[1*], Prof Dr; Jochen Brich[2*], MD

[1]Section Health Care Research and Rehabilitation Research, Faculty of Medicine and Medical Center, University of Freiburg, Freiburg im Breisgau, Germany

[2]Department of Neurology and Neurophysiology, Medical Centre - University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany

[*]these authors contributed equally

Corresponding Author:
Nicole Wimmesberger, MSc
Section Health Care Research and Rehabilitation Research, Faculty of Medicine and Medical Center
University of Freiburg
Hugstetter Street 49
Freiburg im Breisgau, 79106
Germany
Phone: 49 0761270 ext 74450
Email: nicole.wimmesberger@uniklinik-freiburg.de

Related Article:

This is a corrected version. See correction statement: https://www.researchprotocols.org/2024/1/e58180

Abstract

Background: Endovascular thrombectomy (ET), combined with intravenous thrombolysis if possible, is an effective treatment option for patients with stroke who have confirmed anterior large vessel occlusion (aLVO). However, ET is mainly limited to comprehensive stroke centers (CSCs), resulting in a lack of ET capacity in remote, sparsely populated areas. Most stroke networks use the "Drip and Ship" or "Mothership" strategy, resulting in either delayed ET or intravenous thrombolysis, respectively.

Objective: This study protocol introduces the *Leitstellen-Basierte Erkennung von Schlaganfall-Patienten für eine Thrombektomie und daraufhin abgestimmte Optimierung der Rettungskette* (LESTOR) strategy, developed to optimize the preclinical part of the stroke chain of survival to improve the clinical outcome of patients with suspected aLVO stroke. This involves refining the dispatch strategy for identifying patients with acute aLVO stroke using a phone-based aLVO query. This includes dispatching emergency physicians and emergency medical services (EMS) to urban emergency sites, as well as dispatching helicopter EMS to remote areas. If a highly suspected aLVO is identified after a standardized aLVO score evaluation during a structured examination at the emergency scene, prompt transport to a CSC should be prioritized.

Methods: The LESTOR study is a controlled, nonrandomized study implementing the LESTOR strategy, with a stepped-wedge, cluster trial design in 6 districts in southwest Germany. In an interprofessional, iterative approach, an aLVO query or dispatch protocol intended for use by dispatchers, followed by a coordinated aLVO examination score for use by EMS, is being developed, evaluated, and pretested in a simulation study. After the training of all participating health care professionals with the corresponding final aLVO query, the LESTOR strategy is being implemented stepwise. Patients otherwise receive usual stroke care in both the control and intervention groups. The primary outcome is the modified Rankin Scale at 90 days in patients with stroke receiving endovascular treatment. We will use a generalized linear mixed model for data analysis. This study is accompanied by a cost-effectiveness analysis and a qualitative process evaluation.

Results: This paper describes and discusses the protocol for this controlled, nonrandomized LESTOR study. Enrollment was completed in June 2023. Data analysis is ongoing and the first results are expected to be submitted for publication in 2024. The project started in April 2020 and will end in February 2024.

Conclusions: We expect that the intervention will improve the clinical outcome of patients with aLVO stroke, especially outside the catchment areas of CSCs. The results of the accompanying process evaluation and the cost-effectiveness analysis will provide further insights into the implementation process and allow for a better interpretation of the results.

Trial Registration: German Clinical Trials Register DRKS00022152; https://drks.de/search/de/trial/DRKS00022152

International Registered Report Identifier (IRRID): DERR1-10.2196/51683

(JMIR Res Protoc 2024;13:e51683) doi:10.2196/51683

KEYWORDS

large vessel occlusion; emergency medical dispatch; lay first responder; emergency call; thrombectomy; stroke; thrombolysis; triage; anterior large vessel occlusion; endovascular thrombectomy; intravenous thrombolysis; modified ranking scale

Introduction

Background

Clinical outcomes of patients with acute ischemic stroke due to the occlusion of the proximal large intracranial arteries (large vessel occlusion [LVO]) remain poor when treated with intravenous thrombolysis (IVT) alone [1]. In recent years, the treatment of patients with acute LVO stroke with endovascular thrombectomy (ET), combined with IVT if possible, has been shown to produce tremendous clinical improvement [2].

In contrast to the widespread access to IVT (usually accessible at any type of stroke center—primary stroke centers [PSCs] or comprehensive stroke centers [CSCs]) in German, ET is mainly limited to CSCs due to the need for technological resources and specialized interventional physicians. This leads to a shortage of ET capacities in remote, sparsely populated areas.

Several strategies exist for the management of patients with suspected LVO in geographic areas not primarily served by a CSC, none of which are superior in terms of stroke outcome [3-6]. Currently, most stroke networks use the “Drip and Ship” (DS) or the “Mothership” (MS) strategy. According to the DS strategy, all patients with acute stroke are transferred to the nearest—in nonurban areas, mostly primary—stroke center to receive IVT if appropriate. Only if imaging indicates LVO and the patient is a candidate for thrombectomy would subsequent transfer to a CSC be initiated.

Following the MS strategy, patients with acute stroke are evaluated on scene with a stroke severity score to assess for possible LVO. Patients with a high probability of LVO stroke bypass the PSC and are transferred directly to the CSC, where both IVT and—in case of proven LVO—ET can be performed. Both the DS and MS strategies present advantages and disadvantages. The DS strategy assumes faster administration of IVT, but IVT is delayed due to the time delay in organizing and performing the transfer to the CSC [7]. On the other hand, the direct transfer to a CSC (MS strategy) results in faster initiation of ET but at the expense of delayed or even denied IVT administration due to longer ground transport times.

Since air rescue is the main means of transport for longer distances (>50 km) in the stroke network in southwest Baden-Wuerttemberg (including sparsely populated areas of the Black Forest region), optimizing the transport allocation process could shorten preclinical times in this region and comparable areas. Data from air rescue missions in Germany showed that parallel dispatch of emergency medical services (EMS) and helicopter emergency medical services (HEMS) resulted in equal arrival times of EMS and HEMS at the emergency site, shortest on-scene time, and reduced transport time to the most appropriate hospital [8]. Hence, to optimize prehospital logistics in the event of an LVO stroke, parallel dispatching of EMS and HEMS would require the identification of patients with possible LVO stroke by dispatchers in the emergency control centers (ECCs). Dispatchers already use simple stroke screening algorithms such as the “Face Arm Speech Time” (FAST) scale [9] as the basis for standardized protocol-based stroke detection in medical emergency calls. However, these simple stroke scales (relying on 1 single stroke symptom only) might be insufficient for reliable LVO detection. Lately, many publications have underlined the high value of cortical signs, such as aphasia and neglect, in combination with hemiparesis, to predict the presence of anterior LVO (aLVO), defined as emergent occlusion of the intracranial carotid artery, the tandem intracranial carotid artery, or the middle cerebral artery (M1 or proximal M2 segment) [10-12]. A recent study consistently showed that the reporting lay first responders mentioned aphasia and conjugate eye deviation (as a symptom of neglect syndrome) during emergency calls for patients with aLVO stroke [13]. It may therefore be possible to develop a stroke query specifically designed for the interaction between dispatchers and the reporting lay first responders to detect cortical signs in patients with aLVO stroke in emergency calls (“aLVO query”).

Considering the requirements and disadvantages of the DS and MS strategies, this study’s authors developed the new *Leitstellen-Basierte Erkennung von Schlaganfall-Patienten für eine Thrombektomie und daraufhin abgestimmte Optimierung der Rettungskette* (LESTOR) strategy. The aim is to optimize the dispatching strategy after the identification of patients with acute stroke with a high probability of aLVO stroke at the dispatcher level by using an aLVO query adapted to the dispatchers’ needs. This includes the dispatch of emergency physicians (EPs) in addition to EMS personnel for urban emergency sites and the parallel dispatch of an air ambulance for nonurban emergency sites for longer distances. A highly qualified EP with the most suitable rescue transport equipment arrives at the scene as quickly as possible for a structured assessment of aLVO probability by applying a standardized aLVO score. If a high suspicion of aLVO persists on-site, transport to a CSC can take place as quickly as possible.

With this strategy, this study's authors want to eliminate the disadvantage of the delayed application of IVT in the MS strategy by enabling an early IVT administration comparable to the DS strategy with the help of the fastest possible transport, even to regions far from the CSC, while maintaining the possibility of rapid access to the MS strategy on ET.

Objective

The LESTOR study aims to investigate whether the implementation of an aLVO query at the dispatcher level with subsequent optimization of dispatch (ie, LESTOR strategy) and a structured assessment at the emergency site improves the clinical outcomes of patients with aLVO stroke. We also compare the health-economic metrics of our approach to established allocation strategies.

Intervention

Development and First Evaluation of the aLVO Query for Dispatchers

To identify patients with aLVO during telephone contact with emergency services, we intend to query the combination of hemiparesis with cortical deficits. Cortical signs (such as aphasia, neglect, and gaze deviation) in combination with hemiparesis predict the presence of aLVO with high sensitivity and specificity [10]. The Ambulance Clinical Triage for Acute Stroke Treatment (ACT-FAST) examination steps apply these fundamentals. The combination of right-sided arm paresis and aphasia or left-sided arm paresis with gaze deviation or neglect, respectively, showed high accuracy for aLVO detection in a prospective validation in EMS [14]. An advantage of the ACT-FAST algorithm is that the examination steps are adjusted to the paretic side, resulting in fewer examination steps compared to undirected scores.

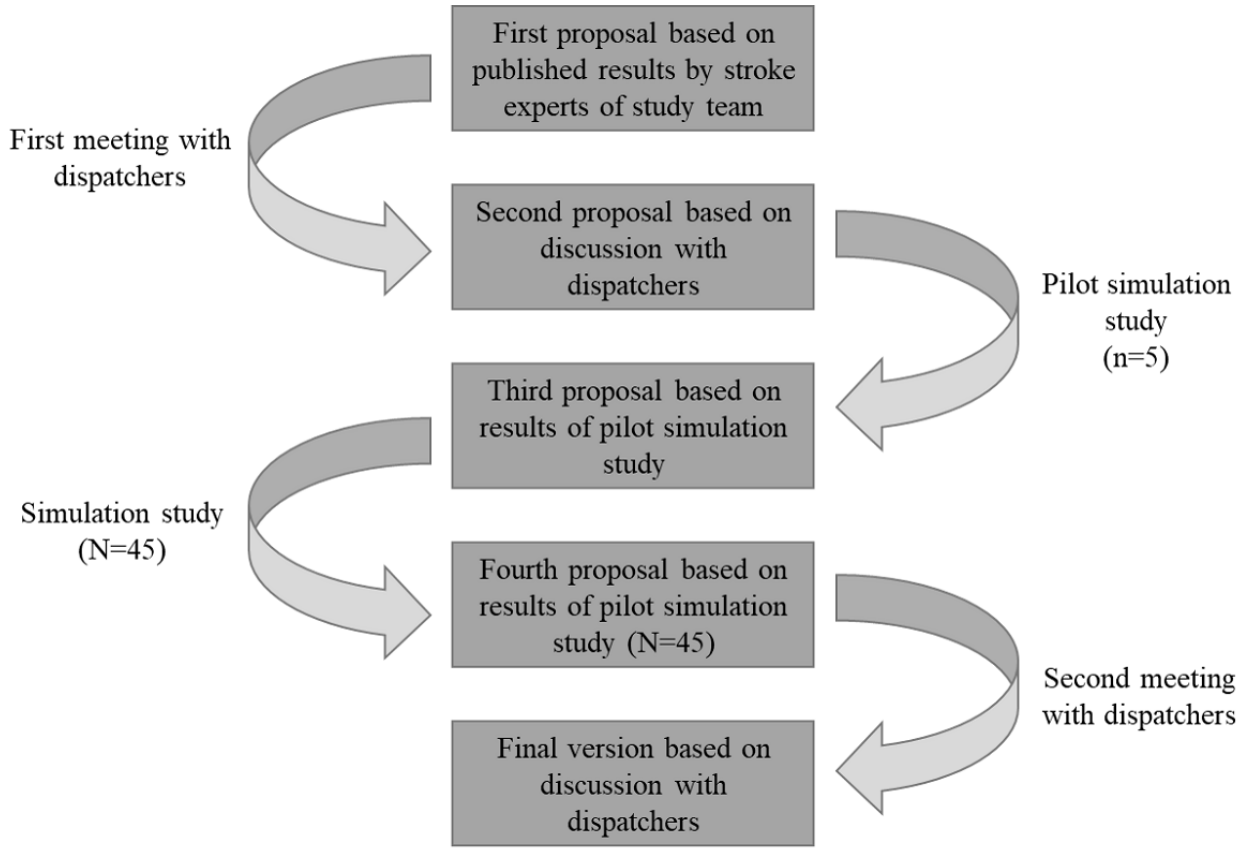
The examination steps for cortical signs and the ACT-FAST algorithm serve as the starting point for the development of the aLVO query for dispatchers. This study's authors focused on adapting the wording of the examination instructions to be comprehensible for the reporting lay first responder during the telephone query and upon collection of the results by the dispatcher on the telephone. The interprofessional development with the dispatchers of the ECCs is decisive since dispatchers are experienced in recognizing serious conditions such as cardiac arrest over the telephone. Given many years of practice in telephone resuscitation, they already have expertise in dealing with complex medical situations and communicating with laypeople who are adapted to these exceptional situations [15].

Through a multistep iteration process, this study's authors constructed an aLVO query for dispatchers aimed at identifying cortical stroke deficits (Figure 1). Stroke experts of this study's team prepared a first proposal based on previously published results [10,16]. Dispatchers (n=6) from the ECC in Freiburg and this study's team adjusted the wording in a consensus meeting about the specific requirements of the emergency call. We then evaluated this second proposal in a simulation study. Simulated patients simulated stroke symptoms with or without aLVO symptoms under controlled conditions. Further, 50 members of the public (potential lay first responders) were confronted with the simulated patients in a randomized block sequence. To ensure blinding, lay first responders simulating the emergency calls were positioned out of sight of dispatchers in another room. The dispatcher conducting the aLVO query with the lay first responder via telephone determined whether the simulated patient presented symptoms suspicious of an aLVO stroke. We recorded these encounters and analyzed this setting with the first participants, which served as a pilot test to check the procedure's comprehensibility and feasibility. Subsequently, this study's team optimized the questions' wording, if necessary. This study's authors then tested this third proposal with the remaining individuals (N=45).

By comparing the dispatcher's decision with the simulated symptoms, this study's team can determine the correct identification. We consider the aLVO query for dispatchers as sufficient if sensitivity and specificity reach at least the values that are achieved with other comparable aLVO screening scores [17] (ie, sensitivity ≥0.75 and specificity ≥0.70). Statistical case number calculations show that assuming this effect, 32 cases would be required to demonstrate significance. We therefore planned conservatively with 45 study participants (considering possible dropouts). If this study's authors do not achieve the abovementioned aims, they will further adapt the aLVO query through more in-depth instructions.

After the simulation study, this study's authors developed the fourth proposal of the aLVO query, which they finally discussed again with dispatchers. The dispatchers and this study's team approved a final version of the aLVO query for dispatchers. By using this complex, multistage procedure, we are striving for the best possible combination of test quality criteria, practical feasibility, and a high level of acceptance during the implementation phase.

Figure 1. Multistage procedure in the development of the aLVO-dispatch protocol. aLVO: anterior large vessel occlusion.



Development of the aLVO-Dispatch Protocol and Integration in the Stroke Detection Protocols in the ECC

We aim at establishing an aLVO-dispatch protocol that queries for eligibility for thrombectomy if the aLVO query is positive. Therefore, the aLVO-dispatch protocol consists of the final aLVO query, which, if aLVO is suspected, is expanded to include a query on the patient's previous state of health and the time window in which the stroke symptoms occurred. The aLVO-dispatch protocol is "LESTOR positive" at the ECC level only, if aLVO is suspected in patients who are not bedridden within the 24-hour window.

All the participating ECCs use electronic dispatch systems with protocol-based dispatching programs. For stroke detection in general, the FAST algorithm is used in all participating ECCs, followed by the immediate dispatch of EMS. We maintain this procedure and implement our aLVO-dispatch protocol directly after completing the first dispatch. Immediately afterward, the dispatcher carries out the aLVO query. If the aLVO-dispatch protocol results in "LESTOR positive," the dispatchers check whether they can optimize the dispatching strategy: within the catchment areas of the CSC, a ground-based EP is dispatched in addition to EMS; outside the catchment area of the CSC, a physician-staffed helicopter is dispatched in parallel. Both protocol-based dispatching programs (FAST and aLVO query) are not mandatory, as the dispatcher can dispatch for unambiguous cases, bypassing the structured dispatching programs to perform faster dispatching.

Development of the aLVO Query for EMS or HEMS

Since EPs and EMS or HEMS need to confirm the aLVO stroke suspicion established by the dispatchers after arrival on the scene, an analogous 2-step procedure is implemented as a secondary survey on scene. In the first step, they apply the FAST scale. If it is positive, they examine cortical symptoms indicative of an aLVO stroke. To enable a comparison between the results of the ECC and EMS or EP or HEMS, as well as to establish a "common" and concerted language at the ECC and EMS or HEMS interface, we closely adapted the examination steps of the aLVO query used in the ECC to the use in EMS or EP or HEMS ("LESTOR Score").

Development of Seminars for Training or Implementation

General Structure of the Seminars

Since the intervention involves neurological examination steps of the patient with stroke that were not previously carried out by the dispatchers or the EMS, EP, or HEMS personnel, this study's authors developed training seminars for all professionals involved in the project. We used didactically carefully designed units for knowledge transfer, including interactive, case-based examples. The didactic training concept builds on principles of the "adult learning theory" (eg, linking to everyday needs and teaching problem-oriented approaches) [18]. Experienced stroke physicians who are part of our study team taught stroke symptoms, recanalizing therapies, and existing referral concepts (DS and MS) with their potential barriers. This study's team then introduced the LESTOR strategy as a new referral concept assessed in this study. aLVO detection, the prerequisite of this

strategy, is visualized with the use of video samples demonstrating simulated patients with hemiparesis and the corresponding cortical symptoms. The stroke experts also taught practical applications of the examination steps and their interpretation, including pitfalls. Due to the COVID-19 pandemic, all the training was held digitally using videoconferencing software. To enable discussions, time slots for discussions were planned at 3 predetermined time points within each seminar.

Adaptions of Seminars for Dispatcher Training

Due to limited practical familiarity with strokes, adjustments for dispatchers included a more detailed description of stroke symptoms, therapies, and referral concepts. Adapted to the dispatchers' workplace situation, we taught the content and application of the aLVO query additionally with a recorded simulated emergency call. To optimize training success, small groups of 4 dispatchers were taught in 4-hour sessions, resulting in 6 to 10 training seminars for each ECC.

Adaptions of Seminars for EMS or HEMS Personnel and EP Training

In the 2-hour seminars for EMS or HEMS personnel and EPs, we introduced the "LESTOR Score" that complements the examination of patients with FAST-positive stroke at the emergency site. To this end, the specifically designed LESTOR app offers additional teaching of the examination steps and algorithm support (see below). Special focus lies on the allocation and prenotification process for patient who are LESTOR positive s.

Supporting Materials

LESTOR App

This study's team has developed a freely available mobile app intended to support the implementation and penetration of the "LESTOR Score" in the EMS or HEMS and for EPs. The main aim of the app is to consolidate knowledge through e-learning modules (eg, instructions, illustrations, and explanatory videos).

Further Materials

Professionals participating in this study can access training and study content digitally to repeat content and train new personnel in the LESTOR approach, including pocket cards and handouts for EPs and EMS or HEMS personnel.

Intervention Implementation

The intervention consists of (1) the implementation of the aLVO-dispatch protocol for suspected stroke at the ECC level, (2) the adjustment of the dispatch in case of a positive aLVO query result, (3) the structured aLVO reassessment on-scene, and (4) the referral strategy of patients with stroke depending on the aLVO probability.

First, after accomplishing stroke dispatch following a positive FAST score, the aLVO-dispatch protocol is started automatically in the ECC, resulting in either "LESTOR negative" (with no further action) or "LESTOR positive" results.

Second, a "LESTOR positive" result of the aLVO-dispatch protocol necessitates a review of the dispatch made: inside the catchment areas of the 2 CSCs, a ground-based EP is dispatched in addition to EMS, whereas outside the catchment area of the 2 CSCs, HEMS is dispatched in parallel.

Third, on the scene, in case of a FAST-positive stroke, EMS, HEMS, or EPs repeat the aLVO query, by applying the aLVO query customized for their situation ("LESTOR Score"), supported by the mobile app or the pocket card.

Finally, the referral strategy of patients with stroke depends on the result of the LESTOR Score on the scene, time window, and preexisting severe impairment due to another disease.

Patients who are "LESTOR positive" without severe impairment due to another disease, and where the duration of symptoms is <24 hours, are transported to the next CSC: via ground-based dispatch when inside the catchment areas of the CSCs, and via air-based dispatch when outside the catchment area of the 2 CSCs. All other patients with stroke are transported to the nearest stroke unit, regardless of whether they are a PSC or CSC.

Methods

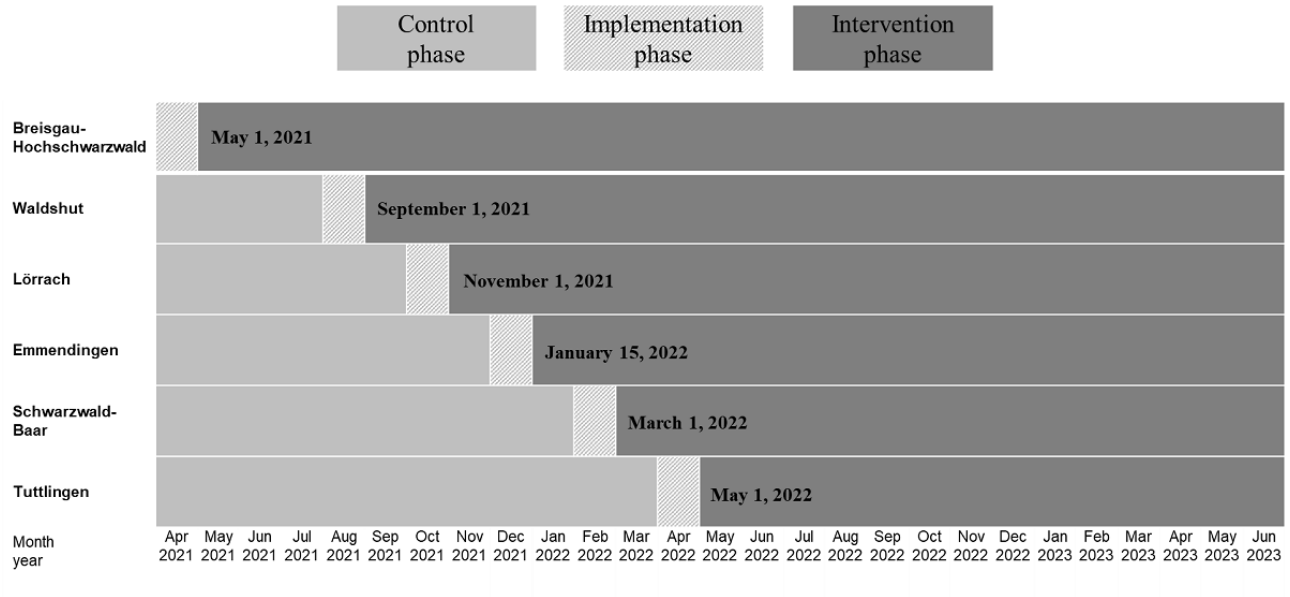
Overview

The LESTOR study comprises various process stages and an accompanying process evaluation. We prospectively registered the trial for the World Health Organization Universal Trial Number and in the German Clinical Trials Register (DRKS00022152) on October 19, 2020.

Study Design

This study's authors performed a controlled, nonrandomized study, introducing the LESTOR strategy with a nonrandomized, stepped wedge, cluster trial design in 6 districts (ie, clusters) in Baden Wuerttemberg in southwest Germany (Figure 2).

Figure 2. Stepped wedge, cluster trial design of the LESTOR study in 6 districts. LESTOR: Leitstellen-Basierte Erkennung von Schlaganfall-Patienten für eine Thrombektomie und daraufhin abgestimmte Optimierung der Rettungskette.



Each cluster includes 1 ECC. Ground emergency medical ambulances are nearly equally distributed across the districts. All 6 districts are supported by 3 air rescue facilities. Further, 6 PSCs and 2 CSCs provide stroke service. The research team sequentially assigns the clusters to the intervention at intervals of 2 to 3 months in an unblinded manner (Figure 2).

This study's team implemented the multicomponent LESTOR approach simultaneously for each cluster's ECC, EMS personnel, EPs, and stroke units. Since HEMS were involved in the intervention from the beginning, this study's authors introduced the LESTOR approach to the 3 air rescue facilities before the implementation of the first cluster.

Each cluster passed through the following phases:

Phase 1 was the control phase (preintervention baseline phase, 3-15 months). During phase 1, ECCs carried out the emergency call and stroke dispatch by local standards: they used the FAST scale for stroke detection, followed by the immediate dispatch of EMS (with additional EP dispatch depending on local conditions). EMS personnel and EPs also used the FAST scale for stroke detection at the scene. The standard allocation for stroke patients was the nearest stroke unit (regardless of whether it is a PSC or CSC). Allocation to CSCs outside their catchment area was based on an individual decision by the EMS or EP to contact the CSC and requires CSC approval. If a helicopter was considered to be the most suitable means of transport on-site, a sequential additional request for the helicopter must be made.

Phase 2 was the implementation phase, when all the professionals involved in acute stroke patient care in a cluster participated in seminars (see above) paralleling the technical implementation of the aLVO query.

Phase 3 was the intervention phase (14-26 months), which follows the intervention's implementation as described above.

Patient Recruitment

In total, 6 districts in Baden Wuerttemberg in southwest Germany participated in the LESTOR study (Breisgau-Hochschwarzwald, Loerrach, Emmendingen, Schwarzwald-Baar, Tuttlingen, and Waldshut) including 6 ECCs; the EMS and EPs of all districts; 3 air rescue facilities; and all the stroke centers of the 6 districts: 2 CSCs (Freiburg im Breisgau and Villingen-Schwenningen) and 6 PSCs—5 of them having a telestroke connection. The maximum distances to CSCs in this study's area were about 120 km by ground and about 80 km by air, while the distances to PSCs were mostly less than 30 km by ground. The distribution of stroke units was specified by the Ministry of Social Affairs in Baden Wuerttemberg, Germany [19].

The 6 districts cover a population of about 1.4 million people living on almost 6000 square kilometers; population density in this area is 233 per square kilometer on average, with the minimum in the district Waldshut (151.4 per square km) and the maximum in the district of Loerrach (283.7 per square km) [20]. According to the Organisation for Economic Co-Operation and Development "Urban-rural classification for NUTS 3 regions" [21], all 6 districts are classified as intermediate regions (rural population between 20% and 50% of the total population). As a regional peculiarity, 5 out of 6 districts have a share of the sparsely populated Black Forest with areas that are difficult to access.

Each district had 1 ECC, operated by the aid organization "Red Cross" and the state administration of each district. EMS was provided in the vast majority by the aid organizations "Deutsches Rotes Kreuz (Red Cross)" and "Malteser," while EPs were organized by the hospitals assuring EP coverage within each district. EMS and EPs were organized at the district level. All 6 districts were supported by 3 air rescue facilities (the German *Deutsche Rettungsflugwacht e. V. Luftrettung*, the Swiss *Rettungsflugwacht Garde Aérienne*, and the Swiss Alpine Air

Ambulance) with 5 helicopters during the day and 4 helicopters at night.

Inclusion and Exclusion Criteria

Inclusion Criteria

Eligible for inclusion were patients aged older than 18 years presenting stroke symptoms that can be treated within 24 hours of the initial symptoms' onset.

Exclusion Criteria

Exclusion criteria were preexisting severe impairment due to another disease (corresponding to level 5 of the modified Rankin Scale [mRS]: "Severe disability; Bedridden, incontinent, requires constant nursing assistance") [22-24], patients in a coma (National Institutes of Health Stroke Scale [25] item of consciousness>2), patients with an unstable clinical status who required emergent life support care, patients hospitalized with acute stroke and suspected aLVO, and patients unlikely to be available for the 90-day follow-up (eg, no fixed home address or visitor from overseas).

Primary and Secondary Outcomes

Primary Outcome

The primary outcome was the mRS score at 90 days in patients with ischemic stroke who received ET. The mRS measures the degree of disability after a stroke with a score ranging from 0 to 6 (0=no deficit; 1=minor deficit without limitations; 2=deficit with limitations; 3=dependence, but independent walking possible; 4=dependence, independent walking no longer possible; 5=being bedridden; and 6=death) [22-24]. The primary outcome was assessed by a structured telephone interview conducted by a central assessor blinded to group allocation.

Secondary Outcomes

Prespecified secondary outcomes were the dichotomization of the mRS (day 90) into scores of 0-2 and 3-6 and the time from emergency call to hospital admission.

Control Variables

Control variables were age, sex, pre-mRS score, and severity of stroke (National Institutes of Health Stroke Scale) [25] at hospital admission.

Data Collection

This study's team asked each participating ECC to share their aLVO-query results with the research team along with time metrics. This study's authors also collected deidentified case data from the 2 ECCs receiving endovascular treatment in a database. A study staff member blinded to group allocation requested the 7-point (0-6) mRS by telephone from patients with stroke receiving endovascular treatment or their guardians 90 days after stroke (unblinded treatment and blinded end point assessment). For the health economic evaluation, this study's authors asked the medical controlling department of the University Medical Centre of Freiburg.

Health Economic Evaluation

This study's team will analyze the costs associated with hospitalization and the intervention for all the patients. Data will be provided by the medical controlling department of the University Medical Centre. This study's authors will also perform a cost-effectiveness analysis, whereby the primary end point (mRS) is related to the total costs.

Power Considerations

A power analysis showed that testing for the statistically significant superiority of the intervention over the control group required far more cases (N=664) than available in the target region during this study's period. This study's authors, therefore, conducted a controlled feasibility study to explore achievable effects and practicability under routine care conditions. This study's team will explore the clinical significance of the intervention effects and refrain from testing for the statistical superiority of the intervention over the control group.

Statistical Analysis

We will use a generalized linear mixed model following the basic model proposed by Hussey and Hughes [26], including the 6 districts as clusters. This study's team will extend the model as proposed by Hemming et al [27] and Li et al [28] to control for the secular trend to avoid potential bias. We will therefore stratify the sample by the 2 stroke centers and add a fixed effect for the secular trend stratified by each of these 2 hospitals, taking into account the control variables. We will assume the same treatment effect in both strata but will exploratively test this assumption by extending the model with an interaction term.

As studies have shown that it is advantageous to examine the full-scale range of mRS—rather than dichotomizing it—this study's authors will account for the ordinal scaling of the mRS [29].

We will conduct exploratory subgroup analyses for cases within and outside of the catchment areas of the 2 CSCs and consider the dichotomous mRS because a favorable clinical outcome is defined as mRS≤2 similar to Goyal et al [2]. In addition, the area under the curve for different mRS cutoff values will be calculated in an exploratory sensitivity analysis.

Missing Values

We will use multiple imputations [30], assuming that the data are missing at random, and perform a full case analysis as a sensitivity analysis for the imputed model.

Process Evaluation

The process evaluation will consist of semistructured, guideline-based individual telephone interviews conducted by trained researchers to assess the implementation process at 2 points in time (in the middle of and at the end of the intervention phase). This study's authors will interview representatives of the ECC, EMS and HEMS personnel, EPs, and first responders. A study nurse will recruit lay first responders of patients receiving ET at the University Hospital of Freiburg to participate in interviews. Key topics for the interviews with medical professionals will be the feasibility of implementation, accessibility, acceptability, appropriateness, fidelity, penetration, and sustainability of the intervention. This study's authors will ask lay first responders about the emergency and personal stress, and the instructions given during the emergency call. Further,

2 independent researchers will use Kuckartz's [31] multistage qualitative content analysis to analyze transcribed data using MAXQDA (VERBI Software GmbH) software.

The results of the first interview round will provide input for a midintervention workshop for all participating medical professionals involved in this study. The workshop aims to discuss the experience and data gained to improve the intervention. The results of the second interview round may help to optimize the intervention for future implementations and projects.

Ethical Considerations

This study's authors did not expect any disadvantages for patients when applying the aLVO query. Even if the aLVO assessment failed and aLVO-positive cases were missed, patients received standard care.

By the local ethics committee, this study's team had established a waiver of consent approach, as a high proportion of patients with stroke with aLVO experienced severe neurological sequelae and had diminished capacity to consent. Moreover, acute psychological distress occurred in approximately 30% of cases during the acute phase, and obtaining consent from relatives, legal guardians, or health care proxies was only possible in a small proportion of cases without causing undue additional psychosocial stress for the representatives [32]. The researchers inform patients using an invitation about a telephone call, which addresses the patient's further neurological course at 90 days after stroke.

For the process evaluation, the interview partners will be informed, in written and verbal form, about this study and must have agreed to the procedure. Project participation will be voluntary and consent can be revoked at any time.

Ethical approval for this study was obtained from the Ethics Committee at the University of Freiburg (416/20; August 10, 2020). The project started in April 2020 and will end in February 2024. All procedures were performed in accordance both with the ethical standards of the institutional or national research committee, and the 1964 Helsinki Declaration and its later amendments or with comparable ethical standards. This study protocol adheres to the recommended SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.

Results

The development phase of this study was completed and the successful integration of the LESTOR strategy into the daily work was in place before patient enrollment. This study was conducted between April 2020 and February 2024, with final data collected by June 2023 and final analyses and results anticipated by mid-2024.

Discussion

Relevance

More than 7 years after the establishment of ET as the standard therapy for aLVO stroke, the best prehospital care and strategy for patients with aLVO stroke, particularly outside the catchment areas of CSCs, remains unclear.

This study aims to evaluate a new strategy, targeting the essential steps of the prehospital section of the stroke chain of survival. The detection of aLVO stroke in the emergency call enables optimization of the dispatch process in terms of human expertise as well as for means of rescue. Involving the lay first responder in the clinical examination of cortical signs for aLVO detection over the telephone represents a major challenge, which this study's authors aim to address with their multistage, interprofessional development process for the aLVO query in the ECC. Re-establishing the aLVO suspicion by EMS, HEMS, or EPs necessitates the introduction of a structured aLVO examination, which the stroke study team closely adapted to the examination steps of the aLVO query used in the ECC ("LESTOR Score"). The LESTOR strategy might enable a delay-free transport to the CSC and could therefore overcome the disadvantage of the MS strategy and still provide an equally fast initiation to thrombolysis as the DS strategy by maintaining the faster access to ET.

As this new strategy does not require any additional human or material resources, other than training time for all the parties involved, it may be easy to implement in comparable regions. The extensive accompanying process evaluation and the health economic evaluation should help to identify determinants of the implementation and thus optimize the transferability.

Limitations

The project faces several challenges. The pieces of training need to reach many dispatchers, EMS and HEMS personnel, and EPs in all 6 districts. Due to the COVID-19 pandemic, the pieces of training were delivered digitally with videoconferencing software. While this enables more flexibility in terms of participation, it may reduce interactions and learning compared to face-to-face sessions. Despite the extensive development of the query, certain known problems with the detection of a stroke in an emergency call cannot be solved, for instance, the misjudgment of strokes as falls or misclassification of aphasia as confusion or reduced vigilance. Moreover, not all callers may be able to understand and perform the instructions for the aLVO query due to stress during the emergency situation or language barriers. Although this study's team plans the trial in an area with 1.4 million inhabitants, the expected number of patients with aLVO stroke during this study's phase is likely to be too small to assess the statistical superiority of the intervention and could therefore be addressed in future trials.

Conclusion

The LESTOR study aims to optimize prehospital care for patients with aLVO stroke with a focus on reducing inequality in aLVO stroke care within and outside of CSC catchment areas. The proposed LESTOR strategy addresses the earliest possible detection of aLVO symptoms in patients suspected of having a stroke, by using the results of the LESTOR query in the emergency call to guide dispatch decisions. This may enable optimization of the dispatch in terms of human expertise as well as for means of rescue and, in case of aLVO suspicion, create the conditions for a fast and direct transport to the CSC,

including the immediate use of air rescue for longer distances to the CSC. The results of the accompanying process evaluation and the cost-effectiveness analysis will provide further insights into the implementation process and allow for a better interpretation of the results.

Acknowledgments

This study's authors acknowledge support from the Open Access Publication Fund of the University of Freiburg. This research was funded by the Innovation Committee of the Federal Joint Committee (*Gemeinsamer Bundesausschuss*) supported by the Innovation Fund (01VSF19053) and has undergone peer review by the funding body. The funding body had no part in the collection, analysis, and interpretation of study data, nor did it play a role either in the writing or submission of this paper for publication.

Data Availability

Data sharing is not applicable to this work as no data sets were generated or analyzed.

Authors' Contributions

NW, DR, FS, and JB wrote this paper with support from EF-G, SM, MLH, and UB. EF-G, FS, and JB conceived and designed this study and supervised this project. All authors reviewed the final paper. Generative AI was not used in any part of this paper's writing process.

Conflicts of Interest

None declared.

References

1. Saqqur M, Uchino K, Demchuk AM, Molina CA, Garami Z, Calleja S, et al. Site of arterial occlusion identified by transcranial Doppler predicts the response to intravenous thrombolysis for stroke. Stroke 2007;38(3):948-954 [FREE Full text] [doi: 10.1161/01.STR.0000257304.21967.ba] [Medline: 17290031]
2. Goyal M, Menon BK, van Zwam WH, Dippel DWJ, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet 2016;387(10029):1723-1731. [doi: 10.1016/S0140-6736(16)00163-X] [Medline: 26898852]
3. Brekenfeld C, Goebell E, Schmidt H, Henningsen H, Kraemer C, Tebben J, et al. 'Drip-and-drive': shipping the neurointerventionalist to provide mechanical thrombectomy in primary stroke centers. J Neurointerv Surg 2018;10(10):932-936. [doi: 10.1136/neurintsurg-2017-013634] [Medline: 29436505]
4. Hubert GJ, Hubert ND, Maegerlein C, Kraus F, Wiestler H, Müller-Barna P, et al. Association between use of a flying intervention team vs patient interhospital transfer and time to endovascular thrombectomy among patients with acute ischemic stroke in nonurban Germany. JAMA 2022;327(18):1795-1805 [FREE Full text] [doi: 10.1001/jama.2022.5948] [Medline: 35510389]
5. Pérez de la Ossa N, Abilleira S, Jovin TG, García-Tornel Á, Jimenez X, Urra X, et al. Effect of direct transportation to thrombectomy-capable center vs local stroke center on neurological outcomes in patients with suspected large-vessel occlusion stroke in nonurban areas: the RACECAT randomized clinical trial. JAMA 2022;327(18):1782-1794 [FREE Full text] [doi: 10.1001/jama.2022.4404] [Medline: 35510397]
6. Seker F, Fiehler J, Möhlenbruch MA, Herweh C, Flottmann F, Ringleb PA, et al. Clinical outcome after endovascular thrombectomy in 3 triage concepts: a prospective, observational study (NEUROSQUAD). Stroke 2021;52(6):e213-e216 [FREE Full text] [doi: 10.1161/STROKEAHA.120.030520] [Medline: 33910365]
7. Romoli M, Paciaroni M, Tsivgoulis G, Agostoni EC, Vidale S. Mothership versus drip-and-ship model for mechanical thrombectomy in acute stroke: a systematic review and meta-analysis for clinical and radiological outcomes. J Stroke 2020;22(3):317-323 [FREE Full text] [doi: 10.5853/jos.2020.01767] [Medline: 33053947]
8. Gries A, Lenz W, Stahl P, Spiess R, Luiz T, BoLuS-Studiengruppe. On-scene times for helicopter services. Influence of central dispatch center strategy. Anaesthesist 2014;63(7):555-562 [Präklinische Versorgungszeiten bei Einsätzen der Luftrettung. Einfluss der Dispositionsstrategie der Rettungsleitstelle]. Der Anaesthesist. [doi: 10.1007/s00101-014-2340-9] [Medline: 24962365]
9. Oostema JA, Carle T, Talia N, Reeves M. Dispatcher stroke recognition using a stroke screening tool: a systematic review. Cerebrovasc Dis 2016;42(5-6):370-377. [doi: 10.1159/000447459] [Medline: 27348228]
10. Beume LA, Hieber M, Kaller CP, Nitschke K, Bardutzky J, Urbach H, et al. Large vessel occlusion in acute stroke. Stroke 2018;49(10):2323-2329 [FREE Full text] [doi: 10.1161/STROKEAHA.118.022253] [Medline: 30355088]

11. Hoglund J, Strong D, Rhoten J, Chang B, Karamchandani R, Dunn C, et al. Test characteristics of a 5-element cortical screen for identifying anterior circulation large vessel occlusion ischemic strokes. J Am Coll Emerg Physicians Open 2020;1(5):908-917 [FREE Full text] [doi: 10.1002/emp2.12188] [Medline: 33145539]
12. Johannes B, Habib P, Schürmann K, Nikoubashman O, Wiesmann M, Schulz JB, et al. Gaze deviation and Paresis Score (GPS) sufficiently predicts emergent large vessel occluding strokes. J Stroke Cerebrovasc Dis 2021;30(3):105518. [doi: 10.1016/j.jstrokecerebrovasdis.2020.105518] [Medline: 33388631]
13. Vuorinen PET, Ollikainen JPJ, Ketola PA, Vuorinen RLK, Setälä PA, Hoppu SE. Emergency medical dispatchers' ability to identify large vessel occlusion stroke during emergency calls. Scand J Trauma Resusc Emerg Med 2021;29(1):97 [FREE Full text] [doi: 10.1186/s13049-021-00914-1] [Medline: 34281596]
14. Zhao H, Smith K, Bernard S, Stephenson M, Ma H, Chandra RV, et al. Utility of severity-based prehospital triage for endovascular thrombectomy: ACT-FAST validation study. Stroke 2021;52(1):70-79 [FREE Full text] [doi: 10.1161/STROKEAHA.120.031467] [Medline: 33349016]
15. Rea TD, Eisenberg MS, Culley LL, Becker L. Dispatcher-assisted cardiopulmonary resuscitation and survival in cardiac arrest. Circulation 2001;104(21):2513-2516 [FREE Full text] [doi: 10.1161/hc4601.099468] [Medline: 11714643]
16. Zhao H, Pesavento L, Coote S, Rodrigues E, Salvaris P, Smith K, et al. Ambulance clinical triage for acute stroke treatment: paramedic triage algorithm for large vessel occlusion. Stroke 2018;49(4):945-951 [FREE Full text] [doi: 10.1161/STROKEAHA.117.019307] [Medline: 29540611]
17. Vidale S, Agostoni E. Prehospital stroke scales and large vessel occlusion: a systematic review. Acta Neurol Scand 2018;138(1):24-31. [doi: 10.1111/ane.12908] [Medline: 29430622]
18. Kaufman DM. Applying educational theory in practice. BMJ 2003;326(7382):213-216 [FREE Full text] [doi: 10.1136/bmj.326.7382.213] [Medline: 12543841]
19. Schlaganfallkonzeption baden-württemberg. Ministerium für Soziales, Gesundheit und Integration. URL: http://tinyurl.com/yrdsmnva [accessed 2024-01-23]
20. Bevölkerungsdichte in den Land- und Stadtkreisen Baden-Württembergs im Jahr 2020 (Einwohner je km²). Statistische Ämter des Bundes und der Länder. URL: https://de.statista.com/statistik/daten/studie/1184779/umfrage/bevoelkerungsdichte-kreise-baden-wuerttemberg/ [accessed 2023-03-07]
21. Urban-rural typology 2021. Eurostat. URL: https://ec.europa.eu/statistical-atlas/viewer/?mids=BKGCNT,C99M01,CNTOVL&o=1,1,0.7&ch=C02,TRC,TYP&center=46.88462,17.0533,4&lcis=C99M01& [accessed 2023-03-07]
22. Rankin J. Cerebral vascular accidents in patients over the age of 60. II. prognosis. Scott Med J 1957;2(5):200-215. [doi: 10.1177/003693305700200504] [Medline: 13432835]
23. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988;19(5):604-607. [doi: 10.1161/01.str.19.5.604] [Medline: 3363593]
24. Saver JL, Filip B, Hamilton S, Yanes A, Craig S, Cho M, et al. Improving the reliability of stroke disability grading in clinical trials and clinical practice: the Rankin Focused Assessment (RFA). Stroke 2010;41(5):992-995 [FREE Full text] [doi: 10.1161/STROKEAHA.109.571364] [Medline: 20360551]
25. NIH Stroke Scale 2003. National Institutes of Health, National Institute of Neurological Disorders and Stroke. URL: https://www.ninds.nih.gov/sites/default/files/documents/NIH_Stroke_Scale_508C_0.pdf [accessed 2023-08-07]
26. Hussey MA, Hughes JP. Design and analysis of stepped wedge cluster randomized trials. Contemp Clin Trials 2007;28(2):182-191. [doi: 10.1016/j.cct.2006.05.007] [Medline: 16829207]
27. Hemming K, Taljaard M, Forbes A. Analysis of cluster randomised stepped wedge trials with repeated cross-sectional samples. Trials 2017;18(1):101 [FREE Full text] [doi: 10.1186/s13063-017-1833-7] [Medline: 28259174]
28. Li F, Hughes JP, Hemming K, Taljaard M, Melnick ER, Heagerty PJ. Mixed-effects models for the design and analysis of stepped wedge cluster randomized trials: an overview. Stat Methods Med Res 2021;30(2):612-639 [FREE Full text] [doi: 10.1177/0962280220932962] [Medline: 32631142]
29. Ganesh A, Luengo-Fernandez R, Wharton RM, Rothwell PM, Oxford Vascular Study. Ordinal vs dichotomous analyses of Modified Rankin Scale, 5-year outcome, and cost of stroke. Neurology 2018;91(21):e1951-e1960 [FREE Full text] [doi: 10.1212/WNL.0000000000006554] [Medline: 30341155]
30. van Buuren S. Flexible Imputation of Missing Data. 2nd Edition. Boca Raton, FL: CRC Press; 2018.
31. Kuckartz U. Qualitative Inhaltsanalyse: Methoden, Praxis, Computerunterstützung. 4th Edition. Weinheim, Basel: Beltz Juventa; 2018.
32. Towfighi A, Ovbiagele B, El Husseini N, Hackett ML, Jorge RE, Kissela BM, et al. Poststroke depression: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2017;48(2):e30-e43 [FREE Full text] [doi: 10.1161/STR.0000000000000113] [Medline: 27932603]

Abbreviations

ACT-FAST: Ambulance Clinical Triage for Acute Stroke Treatment
aLVO: anterior large vessel occlusion

CSC: comprehensive stroke center
DS: Drip and Ship
ECC: emergency control center
EMS: emergency medical services
EP: emergency physician
ET: endovascular thrombectomy
FAST: Face Arm Speech Time
HEMS: helicopter emergency medical services
IVT: intravenous thrombolysis
LESTOR: Leitstellen-Basierte Erkennung von Schlaganfall-Patienten für eine Thrombektomie und daraufhin abgestimmte Optimierung der Rettungskette
LVO: large vessel occlusion
mRS: modified Rankin Scale
MS: Mothership
PSC: primary stroke center
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

Edited by A Mavragani; submitted 09.08.23; peer-reviewed by M Lall, J Hewitt, LH Yao; comments to author 03.11.23; revised version received 24.11.23; accepted 24.11.23; published 13.02.24.

Please cite as:
Wimmesberger N, Rau D, Schuchardt F, Meier S, Herrmann ML, Bergmann U, Farin-Glattacker E, Brich J
Identification of Anterior Large Vessel Occlusion Stroke During the Emergency Call: Protocol for a Controlled, Nonrandomized Trial
JMIR Res Protoc 2024;13:e51683
URL: https://www.researchprotocols.org/2024/1/e51683
doi:10.2196/51683
PMID:38349728

Protocol

Codevelopment and Deployment of a System for the Telemonitoring of Activities of Daily Living Among Older Adults Receiving Home Care Services: Protocol for an Action Design Research Study

Maxime Lussier[1,2*], PhD; Mélanie Couture[3,4*], PhD; Sylvain Giroux[5*], PhD; Aline Aboujaoudé[1,2*], MSc; Hubert Kenfack Ngankam[5*], PhD; Hélène Pigot[5*], PhD; Sébastien Gaboury[6*], PhD; Kevin Bouchard[6*], PhD; Carolina Bottari[2*], PhD; Patricia Belchior[1,7*], PhD; Guy Paré[8*], PhD; Nathalie Bier[1,2*], PhD

[1]Centre de recherche de l'Institut universitaire de gériatrie de Montréal, Université de Montréal, Montreal, QC, Canada

[2]École de réadaptation, Faculté de médecine, Université de Montréal, Montréal, QC, Canada

[3]Centre for Research and Expertise in Social Gerontology, Integrated Health and Social Services University Network for West-Central Montreal, Côte-Saint-Luc, QC, Canada

[4]School of Social Work, Université de Sherbrooke, Sherbrooke, QC, Canada

[5]Computer Science Department, Faculty of Sciences, Université de Sherbrooke, Sherbrooke, QC, Canada

[6]Department of Mathematics and Computer Science, Université du Québec à Chicoutimi, Chicoutimi, QC, Canada

[7]School of Physical and Occupational Therapy, Faculty of Medicine and Health Sciences, McGill University, Montreal, QC, Canada

[8]Research Chair in Digital Health, HEC Montréal, Montréal, QC, Canada

[*]all authors contributed equally

Corresponding Author:
Maxime Lussier, PhD
Centre de recherche de l'Institut universitaire de gériatrie de Montréal
Université de Montréal
4545 Queen Mary Road
Montreal, QC, H3W 1W6
Canada
Phone: 1 514 343 6416
Email: lussier.maxime@gmail.com

Abstract

Background: Telemonitoring of activities of daily living (ADLs) offers significant potential for gaining a deeper insight into the home care needs of older adults experiencing cognitive decline, particularly those living alone. In 2016, our team and a health care institution in Montreal, Quebec, Canada, sought to test this technology to enhance the support provided by home care clinical teams for older adults residing alone and facing cognitive deficits. The Support for Seniors' Autonomy program (SAPA [Soutien à l'autonomie des personnes âgées]) project was initiated within this context, embracing an innovative research approach that combines action research and design science.

Objective: This paper presents the research protocol for the SAPA project, with the aim of facilitating the replication of similar initiatives in the future. The primary objectives of the SAPA project were to (1) codevelop an ADL telemonitoring system aligned with the requirements of key stakeholders, (2) deploy the system in a real clinical environment to identify specific use cases, and (3) identify factors conducive to its sustained use in a real-world setting. Given the context of the SAPA project, the adoption of an action design research (ADR) approach was deemed crucial. ADR is a framework for crafting practical solutions to intricate problems encountered in a specific organizational context.

Methods: This project consisted of 2 cycles of development (alpha and beta) that involved cyclical repetitions of stages 2 and 3 to develop a telemonitoring system for ADLs. Stakeholders, such as health care managers, clinicians, older adults, and their families, were included in each codevelopment cycle. Qualitative and quantitative data were collected throughout this project.

Results: The first iterative cycle, the alpha cycle, took place from early 2016 to mid 2018. The first prototype of an ADL telemonitoring system was deployed in the homes of 4 individuals receiving home care services through a public health institution.

The prototype was used to collect data about care recipients' ADL routines. Clinicians used the data to support their home care intervention plan, and the results are presented here. The prototype was successfully deployed and perceived as useful, although obstacles were encountered. Similarly, a second codevelopment cycle (beta cycle) took place in 3 public health institutions from late 2018 to late 2022. The telemonitoring system was installed in 31 care recipients' homes, and detailed results will be presented in future papers.

Conclusions: To our knowledge, this is the first reported ADR project in ADL telemonitoring research that includes 2 iterative cycles of codevelopment and deployment embedded in the real-world clinical settings of a public health system. We discuss the artifacts, generalization of learning, and dissemination generated by this protocol in the hope of providing a concrete and replicable example of research partnerships in the field of digital health in cognitive aging.

International Registered Report Identifier (IRRID): RR1-10.2196/52284

(JMIR Res Protoc 2024;13:e52284) doi:10.2196/52284

KEYWORDS

action design research; protocol; activities of daily living; older adults; cognitive deficits; telemonitoring; public health care system; home care services

Introduction

Background

In Canada, it is estimated that 2 million people, or 5.4% of the total population, are active users of publicly funded home care services, with more than half of them being aged ≥65 years [1,2]. Home care is considered a priority by the Canadian government and its provincial counterparts [3]. In the province of Quebec, a predominantly French-speaking province in Eastern Canada, the Ministry of Health and Social Services has promoted aging in place since 2003 through a policy known as "Home Support: Always the Option of Choice" ("Chez soi: Le premier choix") [4]. Despite this policy, 40% of older adults in Quebec living with disabilities report unmet home care needs [2], which has been attributed to factors such as the lack of funding, difficulties in recruiting and retaining home care staff, and the increase in care needs in an aging population [5,6]. These challenges, exacerbated by the COVID-19 pandemic, have led to urgent calls in Canada as well as in other countries to better support home care [6,7].

The presence of cognitive deficits is an important risk factor for the loss of functional autonomy [8,9] and is associated with important needs for home care support services [6]. Older adults with cognitive decline, such as those diagnosed with Alzheimer disease, are progressively dependent on others for both instrumental and basic activities of daily living (ADLs), which increases the stress and burden on caregivers (families and relatives) and social and health care services [8,9]. Everyday memory losses and difficulties identifying and recognizing their own limitations affect the ability to recall and report on events, including how they manage their ADLs [10,11]. These individuals may also put themselves at risk by engaging in behaviors that are dangerous to their health and safety, in particular when they live alone (eg, falls, kitchen fires, and medication noncompliance) [12].

Therefore, progressive cognitive decline and its impact on ADLs limit the ability of health and social services to rely on these patients to better understand their home care service needs. This uncertainty can significantly affect intervention plans and resource management [13,14]. On the one hand, this may lead to the costs of some care recipients' needs not being covered by public care services because of a lack of supporting evidence; on the other hand, some services may be offered although they are unnecessary because of clinicians' need to create contingencies to address potential risks [15,16].

In this context, we propose that a key strategy to better understand the needs of older adults with cognitive decline and optimize available human and financial resources lies in the use of digital health technologies, in particular telemonitoring of instrumental and basic ADLs—hereafter referred to as *ADL telemonitoring*.

Telemonitoring of ADLs

ADL telemonitoring is a form of remote monitoring and, as such, a component of telehealth. It is generally used to acquire proxy information about several factors or outcomes relevant to the home care support of older adults, such as functional independence, cognitive state, mobility, risk of falls, and urinary tract infections [13,14,17,18]. The information is based on data collected via several sensors, such as wearables, ambient sensors (eg, motion detectors and contact sensors), radiofrequency identification, and GPS [19]. The resulting profile of the person is based on information collected regarding their behavior in the home over the course of one or several days, such as entering and leaving a room, opening and closing kitchen cupboards, home entrances and exits, and the use of small electrical appliances. Various algorithms can be used to recognize and classify ADLs, including hidden Markov models, linear discriminant analysis, support vector machines, artificial neural networks, and adaptive network fuzzy inference system [20].

ADL telemonitoring can be used in the context of naturalistic scenario-based assessments in which participants are invited to a research laboratory apartment designed to simulate real-life situations. There, participants are usually asked to perform several scripted ADLs, such as cooking a meal, cleaning the apartment, or booking a reservation [21-24].

ADL telemonitoring can also be used in the context of real-life assessments in which participants are asked to continue their daily routine while sensors are installed directly in their homes to collect data on sleeping habits, meal preparation, hygiene,

mobility in the home, periods outside the home, and so on [25,26]. Over time, deviations from previous patterns can be detected and used to assess the ability of an older adult to live independently in the community and detect potential future critical situations [27-30].

Thus, ADL telemonitoring holds great promise to facilitate better understanding of the needs of older adults with cognitive decline, in particular those living alone, in terms of ADL functioning and home care service requirements. Indeed, research in the area of ADL telemonitoring has been expanding over the last 20 years. In a recent umbrella review, Tannou et al [31] identified over 191 experiments in the field and 17 reviews published to date. Despite this dynamism, there is still little available evidence on the effectiveness of ADL telemonitoring and strategies for integrating it successfully into health care systems [31]. Most studies have reported data on prototypes, but very few large-scale deployment studies have been conducted. Therefore, there is a pressing need for more in-depth studies on this subject.

Context and Aim

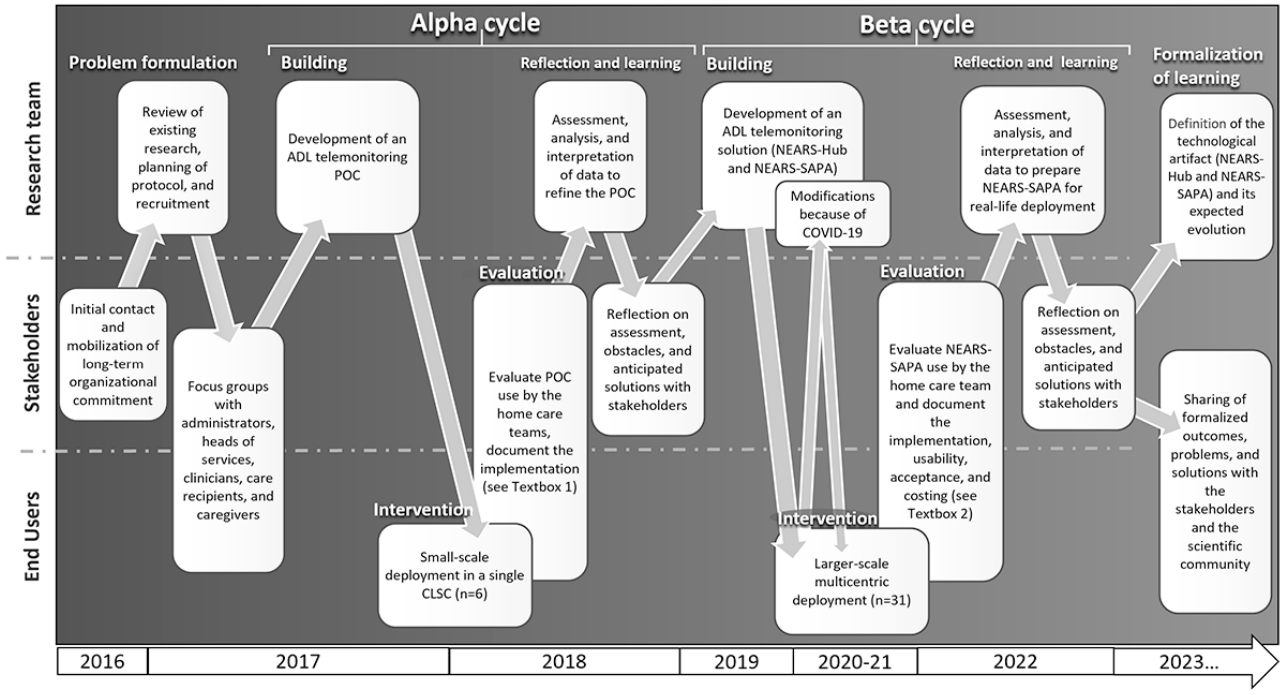
In 2016, the authors were approached by a health institution in the city of Montreal, Quebec, Canada, more specifically by the director of the *Support for Seniors' Autonomy* program (*Soutien à l'Autonomie des Personnes Âgée*s in French; SAPA). SAPA programs aim to support older adults and meet their physical, psychological, and gerontopsychiatric needs both in the community and during hospital stays. The director was searching for innovative ways to support home care clinical teams to better address the needs of older adults with cognitive deficits who live alone. The directorate was also looking for solutions to optimize the use of limited human and financial resources to offer the right service at the right moment. Our team and the top management team decided to engage in a joint research project on ADL telemonitoring, which became the "SAPA Project." The global objectives of the SAPA project were to (1) codevelop an ADL telemonitoring system that addresses the needs of all key stakeholders, (2) deploy the system in a real-world clinical setting and identify the specific use cases, and (3) identify factors that could contribute to ensuring its long-term use in a real-world setting. To foster the project's success, we engaged with all key stakeholders involved in public home care services for older adults with cognitive deficits. We considered that, to ensure the optimal use and adoption of technologies by the health care community, it would be crucial to identify existing solutions or create novel solutions that address the specific needs of all key stakeholders, including the care recipients themselves [32]. To do so, stakeholders had to be involved in every step of the project to align their needs with the technology [33].

Considering the context of the SAPA project, the use of an action design research (ADR) approach was identified as crucial. ADR provides a framework for developing practical solutions to complex problems encountered in a specific organizational setting. It is an iterative process that involves collaborations among researchers, practitioners, and stakeholders in designing [34], deploying, and evaluating interventions that improve the outcomes of a particular problem or issue [35]. This four-stage research process includes (1) problem formulation; (2) building, intervention, and evaluation; (3) reflection and learning; and (4) formalization of learning. ADR proposes the use of multiple cycles of development leading to cyclical repetitions of stages 2 and 3. Carried out in collaboration with the stakeholders (codevelopment process), these cycles allow for the refinement of the technology and related interventions to be implemented subsequently in a real-world setting. The SAPA project underwent 2 iterative technological design cycles entitled "alpha" and "beta." The alpha cycle took place from early 2016 to mid 2018, and the beta cycle took place from late 2018 to late 2022.

A key feature of the SAPA project was its novel methodological approach. In this paper, we present the SAPA research protocol and its various codevelopment and deployment phases for the 2 cycles of ADR. To our knowledge, this represents the first detailed publication of a methodological framework in this field of research. Taking the initiative to share a research design makes it possible to be more transparent about the methodologies used as well as provide an in-depth explanation of the process so that it can be reproduced in the future. It also provides a description of a concrete example of research partnerships in the field of digital health in cognitive aging.

In the following sections, we will present each cycle and stage of the project, which involve multiple research methods as recommended by action research methodologists [36]. Specific methodological details are presented in Multimedia Appendix 1. Figure 1 [35,37] presents an overview of the project's timeline and key elements of each cycle and stage.

Figure 1. Summary of action design research protocol (based on the studies by Sein et al and Schacht et al). ADL: activity of daily living; CLSC: local community services center; NEARS-Hub: Innovative Easy Assistance System–Hub; NEARS-SAPA: Innovative Easy Assistance System–Support for Seniors' Autonomy program; POC: proof of concept.



Note: Stakeholder refers to home care services directorates, administrators, and heads of services. End-users refers to clinicians, care recipient, and caregivers of home care services.

Alpha Cycle

Methods

Background

The SAPA project aimed to provide an in-depth understanding of the potential of ADL telemonitoring in the specific context of the Canadian public health care system, particularly in the province of Quebec. This province has an estimated population of 8.3 million residing in 18 administrative areas referred to as health regions. For a given health region, all public health and social services institutions are networked into integrated health and social services centers (CISSSs [*Centre intégré de santé et de services sociaux*]) or integrated university health and social services centers (CIUSSSs [*Centre intégré universitaire de santé et de services sociaux*]) when located in an area where a university offers an undergraduate medical training program or has an institute in the social services field. These administrative entities are responsible for delivering care and services to the population of an assigned territory via hospitals, residential and long-term care establishments, rehabilitation centers, child and youth protection centers, and local community service centers (CLSC [*Centre local de services communautaires*]). CLSCs offer frontline health and social services, including home care, through dedicated programs.

The alpha cycle of the SAPA project was conducted within the clinical services of the CLSC of one CIUSSS in the city of Montreal referred here as CIUSSS 1.

Problem Formulation

The alpha cycle started with a problem formulation stage aimed at conceptualizing the research problem, securing long-term organizational commitment, and clarifying roles and responsibilities with stakeholders. This stage combined theoretical and experiential knowledge informed by real-life practices [35]. As previously mentioned, the initial problem (ie, the need to support home care clinical teams in meeting the needs of older adults with cognitive difficulties living alone in the community) was brought to the research team by the health institution.

To arrive at a mutual understanding of the problem and prioritize potential technological solutions at the start of the project in late 2016, a descriptive qualitative method was followed [38]. More specifically, individual interviews and focus groups were conducted with key stakeholders (administrators, heads of services, clinicians, older adults, and caregivers; n=23 in total) of 1 specific sector covered by a CLSC of CIUSSS 1 (for more details, see Multimedia Appendix 1, section 1, as well as the study by Couture et al [34]). This sector was chosen by the head administrator as the most appropriate site for project deployment. Participants were questioned about the leverages of and obstacles to the home care of older adults and technology use within this context. At that time, neither the researchers nor the clinical team had a specific technology in mind to address the problem. However, to support the reflection process, several technological solutions were presented to the clinical teams. These included assistive devices and monitoring technologies such as smart home sensors, smart calendars, pill distributors, serious games, and stove safety devices.

One of the main findings was that administrators and clinicians thought that monitoring technologies could help them obtain more objective and reliable information to support their decision-making process to develop an adapted intervention plan with the care recipients [34,39]. More precisely, they

wanted a technology to support their assessment and management of the risks involved in maintaining care recipients at home as long as possible. A second finding was that stakeholders insisted on avoiding the use of cameras or microphones to preserve intimacy and confidentiality [34,39]. They also wanted to avoid wearable technologies as older adults with cognitive deficits would likely forget to wear them. Finally, it was mentioned that an unobtrusive technology requiring little involvement on the part of the older adults would most likely be successfully implemented.

Considering these expectations, ADL telemonitoring seemed to be the most promising technology to fully address the needs expressed by all. At the time of the study, there was no such system available on the market and ready to be deployed in a home care setting. Therefore, we resolved to design a system specifically for this research project based on our previous work [13,24,40-43]. With the stakeholders' approval of the project scope and vision, we secured a long-term organizational commitment as well as funding for the subsequent phases.

Building, Intervention, and Evaluation

Overview

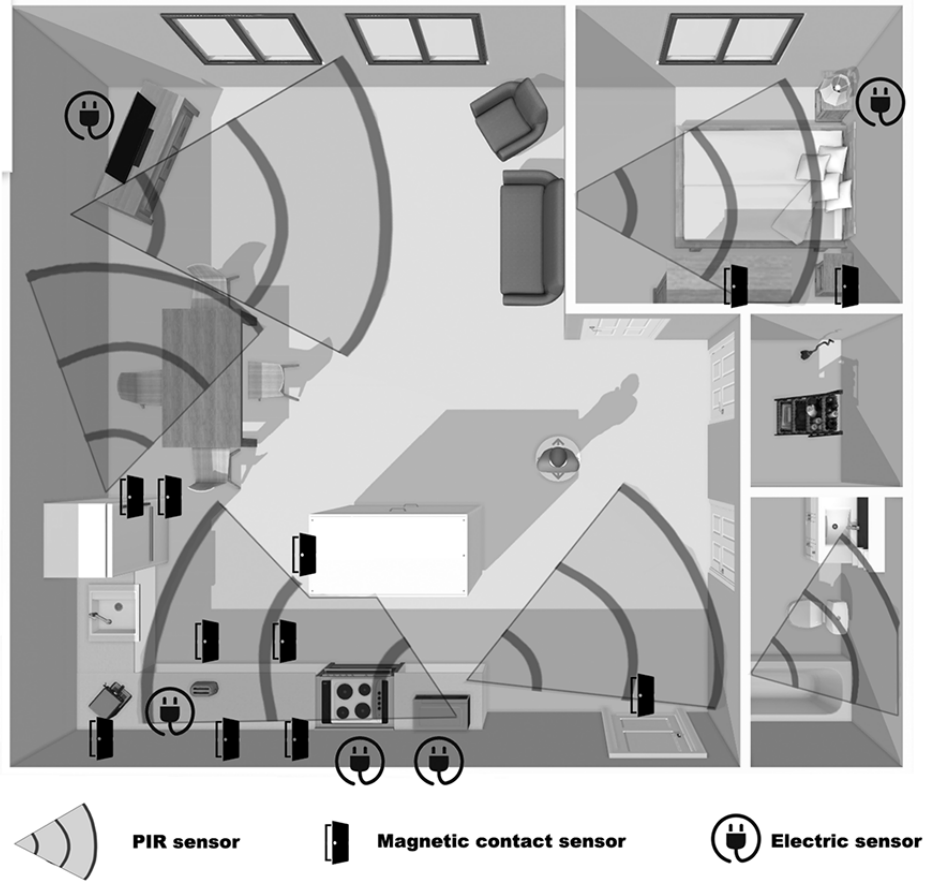
In the second stage of ADR, the initial design of the technological artifact is generated using the problem framing adopted in the first stage [35]. The building, intervention, and evaluation phase, which is an iterative process conducted in the target environment, involves building the technological artifact, intervening in the organization, and evaluating the outcomes. The product of this stage is the design of the artifact.

At this point in the alpha cycle, the overall target and goal of knowledge generation was to design and create an ADL telemonitoring system to support clinicians' decision-making process related to risk management. As is often the case in IT-dominant artifact creation, we opted to develop a proof of concept (POC) that could be quickly developed and tested in the homes of a small sample of older adults receiving home care services (ie, alpha cycle). POC versions are formative and can help validate several anticipated and unanticipated outcomes of technology use and deployment [35]. Early designs serve as lightweight interventions in a limited organizational context.

Building

For the POC, we used a lightweight sensor infrastructure comprising 4 nonintrusive, low-cost, wireless devices similar to the one deployed in the study by Caroux et al [44]. With their consent, sensors were deployed in each participating patient's home: passive infrared sensors, magnetic contact sensors, smart electric switches, and water sensors. Sensors were paired with an Internet of Things device, the VeraPlus Z-Wave Home Controller, which served as the data collection point (ie, a controller). Sensors were positioned in each home so as to capture data on ADLs, including sleeping, cooking, showering, and leaving the home (Figure 2). Multimedia Appendix 1, section 2, provides more details on each sensor's role.

Figure 2. Example of sensor placement in the home. PIR: passive infrared.



Algorithms using an inference system and finite state machine computation models were developed to monitor ADLs such as sleep, periods outside the home, cooking, hygiene, and general activity levels in the home (for more details, see the study by Lussier et al [45]). From these algorithms, it was possible to relay graphical information about the daily habits of the individual to clinicians to support their decision-making process. The information was summarized on a 3-page PDF report sent directly to the clinicians.

Intervention

In the intervention phase, the POC needs to be used firsthand by practitioners from the real-life setting for which it is designed. This participatory process provides opportunities for end users to influence and guide the design.

In early 2017, the POC was presented to clinicians and managers in team meetings in the identified testing sector. Clinicians were invited to identify older home care recipients for whom they thought ADL telemonitoring would be useful. Clinicians who wished to participate filled out a request form about their needs and the care recipient they identified. Complex cases were discussed with the research team to ensure that the needs of the clinician were within the scope of ADL telemonitoring. Recruitment procedures are detailed in Multimedia Appendix 1, section 3.

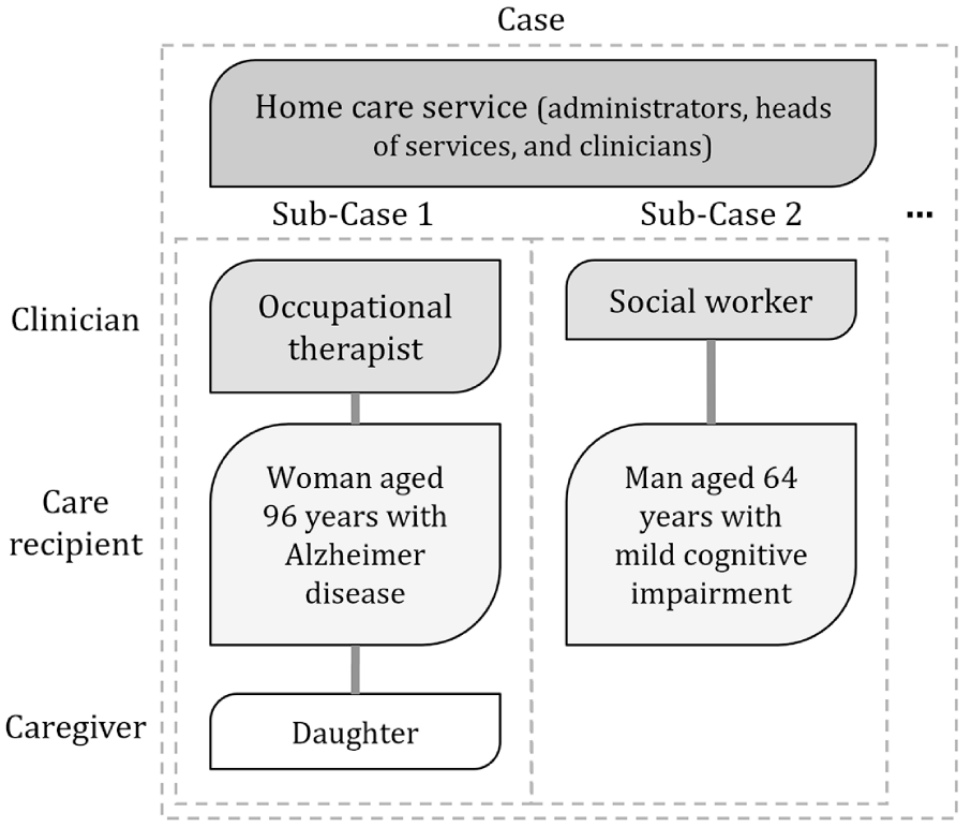
Evaluation

Overview

The general objective of the alpha cycle was to document the feasibility of using ADL telemonitoring in real-life settings and quickly iterate the POC. More specifically, the objectives pursued were to (1) describe the characteristics of the participants and their demands for telemonitoring, (2) describe the use and impact of the POC by the home care teams, and (3) document the facilitators of and barriers to POC use.

To achieve these objectives, a mixed embedded single-case study design was used [46]. Case studies are relevant when the research question requires a comprehensive description of a social phenomenon [46], as is the case here in studying the perspectives of different stakeholders on the feasibility of using technology. The single case was the home care division of CIUSSS 1. The 6 subunits consisted of care recipients (n=6); their clinicians (n=8; 2 were replaced during the project) from home care services; and, when possible, a family caregiver (n=2; Figure 3). These subunits made it possible to shed light on the personalized trajectories of each care recipient as well as the intended and actual use of the system in relation to these trajectories. Multimedia Appendix 1, section 6, provides more details on the subunits and data analysis methods. A mix of quantitative and qualitative data was collected. Textbox 1 provides an overview of the data collection process in the alpha cycle.

Figure 3. Diagram of embedded case study.



Textbox 1. Overview of the alpha cycle data collection, sample, measurements, and variables in the evaluation stage.

Telemonitoring request form filled out by clinicians and with follow-up questions via phone interviews

- Facilitators of and barriers to home care of care recipients
- Demands for telehealth technology

Characteristics of clinicians (n=8) and care recipients (n=6)

- For clinicians: profession
- For care recipients only: age, sex, years of schooling, Mini-Mental State Examination, Montreal Cognitive Assessment, Multiclientele Assessment Tool, Functional Autonomy Measurement System profile, metadata on the home care service received, cognitive evaluation (Rey Auditory Verbal Learning Test; Mini-Geriatric Depression Scale; and Delis-Kaplan Executive Function System Trail Making test, Stroop test, and Tower Test), and Instrumental Activity Profile

Initial individual interviews with care recipients (n=6) and caregivers (n=2)

- Facilitators of and barriers to home care of care recipients
- Anticipated leverages of and obstacles regarding telemonitoring deployment in home care

Total of 3 follow-up focus groups with clinicians after proof of concept installations (n=8)

- Observed facilitators of and barriers to telemonitoring deployment
- Use case, impacts, and general satisfaction regarding deployment

Postdeployment focus groups with administrators (n=2), heads of services (n=5), and clinicians (n=8)

- General facilitators of and barriers to telemonitoring deployment and sustainability
- Impacts of and general satisfaction with telemonitoring

Characteristics of Participants and Demands for ADL Telemonitoring

With the care recipients' consent, their medical history was extracted, including cognitive screening scores as well as needs for home care support, sociodemographic information, and the quantity of home care services required. Metadata were also extracted from the medical records about each service provided by the health network for each care recipient (ie, type of act and its time and duration). Finally, to obtain a more in-depth cognitive profile of each care recipient, a cognitive evaluation, as well as an evaluation of ADL performance, was completed by a research assistant. Multimedia Appendix 1, section 6, provides more details.

Clinicians who identified a care recipient and wished to participate filled out a request form detailing their demands for telemonitoring, the reasons that led them to request remote monitoring for this care recipient, and which ADL they would like to obtain more information about via telemonitoring. Through interviews, they were also asked about facilitators of and barriers to home care for this specific care recipient. After receiving the form, a research assistant called the clinician to provide any further details or clarifications as needed.

Use and Benefits of ADL Telemonitoring

During the follow-up focus groups, clinicians were asked how telemonitoring was used, for which ADL, and how it influenced their decision-making process regarding the recipients' care plan. They were also asked about their satisfaction, whether it was relevant to continue telemonitoring for each care recipient, and why.

Finally, during postdeployment focus groups, administrators, heads of services, and clinicians were asked about their general satisfaction with telemonitoring as well as the benefits it had for clinical practice.

Facilitators of and Barriers to ADL Telemonitoring Deployment

During the initial interviews, care recipients and caregivers were asked whether they foresaw any barriers to and facilitators of the deployment of the ADL telemonitoring system. In addition, to document their perceived needs, they were asked to describe ADLs that were difficult for them to perform, the current help they received, and their unmet care support needs.

In follow-up focus groups, clinicians were asked about the facilitators and obstacles they encountered during deployment.

During postdeployment focus groups, participating clinicians and managers were asked about elements that could promote or hinder deployment of the ADL telemonitoring system in their organization as well as their thoughts regarding the sustainability of this type of system.

Finally, throughout the study, data on several additional factors to be considered were collected: occurrence of adverse events; clinician turnover; reason for care recipient's withdrawal, relocation, or hospitalization; or cause of death.

Ethical Considerations

The alpha cycle was approved by the Centre de recherche de l'Institut universitaire de gériatrie de Montréal research ethics board (CER VN 16-17-22). All participants (ie, care recipients, clinicians, caregivers, and managers) provided informed and

written consent before taking part in the data collection process. Information that could potentially identify participants was securely stored in a locked storage unit or protected by passwords. Whenever possible, data were deidentified through codification. Participants did not receive any monetary compensation.

Results

Overview

The *Reflection and learning* stage of ADR mirror a conventional *Results* section, entailing the analyses and interpretation of the data collected during the evaluation phase. The alpha cycle aimed to develop and deploy the POC in a real-life context as well as quickly reveal anticipated and unanticipated outcomes regarding technology use and deployment. In the following sections, we synthesize the outcomes for each of the 3 objectives. Multimedia Appendix 1, section 5, provides more details on the outcomes.

Characteristics of Participants and Demands for ADL Telemonitoring

The system was deployed in the homes of 4 care recipients with severe cognitive deficits. They all lived alone, and half (2/4, 50%) had family caregivers. Participating clinicians included 3 occupational therapists, 3 nurses, and 2 social workers.

During these interviews, social and health care professionals expressed the need for monitoring data to support their clinical decision-making process. More precisely, they wanted access to technology that could help assess and manage the risks involved in maintaining care recipients at home. In other words, their aim was to gain a better understanding of how care recipients were functioning in their homes. This information would support their intervention plan and help determine which services should be put in place.

Use and Benefits of ADL Telemonitoring

The evaluation stage revealed that the ADL telemonitoring system was used by clinicians to collect additional and reliable data about the home care recipient's ADL routine (for more details, see the study by Lussier et al [15]). In accordance with the demands for ADL telemonitoring, this technology made it possible to gain a better understanding of how care recipients were functioning in their homes, providing an objective measure that complemented other subjective clinical evaluations. More precisely, it was used to confirm or refute hypotheses before developing a comprehensive intervention plan. It was also used to facilitate discussions with the older adults and their families based on consensual information

Overall, clinicians described the monitoring technology as a useful tool for allocating home care services that corresponded to the needs of care recipients and optimizing their autonomy and safety [15].

Facilitators of and Barriers to ADL Telemonitoring Deployment

Overall, the alpha cycle presented several encouraging results regarding the POC's perceived usefulness and reported satisfaction, as well as the feasibility of its deployment in SAPA teams operating in the field [39]. Although the prototype was successfully deployed in 4 care recipients' homes, several obstacles were encountered. In total, 3 main obstacles were identified: the characteristics of some participants, burdensome evaluation protocol, and maturity level of the POC.

First, the technology used for the prototype was suboptimal for some care recipients' profiles. More specifically, a concern was expressed that sensors would exacerbate symptoms of a paranoid personality disorder with invasive thoughts, and consequently, this care recipient was not included in further testing. In addition, the usefulness of the sensors for care recipients presenting important mobility challenges was questioned. For instance, these care recipients performed very few ADLs by themselves and moved around their units in a wheelchair—which decreased monitoring efficiency and accuracy.

Second, the alpha cycle protocol allowed us to better understand the population followed by the CLSC and refine the protocol for evaluating care recipients' characteristics. In fact, our original protocol was too long, formal, and confronting for many care recipients, increasing the risk of a refusal to participate in the study or withdrawal. Thus, it was decided that formal evaluations with care recipients would be reduced as much as possible in subsequent cycles.

Overall, the feedback showed that the prototype was not ready for wider deployment—the installation took too long, data processing was too slow, output analysis was complex and time-consuming, and it was mostly done by hand, among other issues. Finally, despite the lack of real danger, it was decided that water sensors were to be avoided in the future as they were the only type of sensor that generated anxiety in almost all care recipients because of their concerns regarding having wires near water.

Beta Cycle

Methods

Building, Intervention, and Evaluation

Overview

Following the alpha cycle stage and deployment of the POC, CIUSSS 1 was interested in participating in a second cycle of development with a wider deployment. In addition, during the alpha cycle, 2 other institutions from the Greater Montreal area (CIUSSS 2 and CISSS 3) manifested their interest in using the ADL telemonitoring system, and researchers from our team met with managers and clinicians from these institutions. They identified the needs and challenges of home care for older adults with cognitive deficits that were very similar to those encountered by CIUSSS 1. As such, the beta cycle was conducted with CIUSSS 1, CIUSSS 2, and CISSS 3 without repeating the problem formulation stage. Furthermore, a second problem formulation stage was deemed nonrelevant as the alpha cycle results did not indicate a need to refine our understanding of the context.

The general goals of the beta cycle were to further improve the ADL telemonitoring system based on experience gathered during

the POC and deploy this newer version on a wider scale to further document specific use cases and factors that could contribute to ensuring its long-term use in a real-world setting. As the COVID-19 pandemic occurred as deployment for the beta cycle was just starting, many adjustments to the research protocol and monitoring system had to be made. These are summarized in the following sections and detailed in Multimedia Appendix 1, section 6.

Building

Between 2018 and 2019, a blitz of technological developments was undertaken to develop an edge computing based on a distributed architecture that offers more flexibility for integrating new technologies with high performance in data ingestion than the POC developed in the alpha cycle. Details of the system optimization can be found in Multimedia Appendix 1, section 7.

Organized into software modules, the system centralizes data encryption, storage, computation, communication, and system robustness on a single low-power, low-cost computing device. This framework, called the Innovative Easy Assistance System (NEARS)–Hub, integrates nonintrusive sensors in the smart home [47].

Several features were added to build on the alpha cycle learning and address limitations. First, the deployment of sensors was optimized, which not only simplified the installation but also minimized the technicians' presence in the patients' homes. The latter was a particular source of concern for both clinicians and care recipients.

Second, to facilitate rapid data collection, the VeraPlus Z-Wave Home Controller was replaced with a Raspberry Pi 3 linked with a USB Z-Wave controller, offering several options for local data preprocessing and a number of other improvements, such as the automation of collection, maintenance, and data processing; local data storage; and automation of local backups to compensate for service interruptions.

Third, 2 additional types of sensors were integrated into the ecosystem: a heavy-appliance smart electric switch to monitor oven use and pressure mattress sensors that could be added to the bed or couch.

Fourth, a major achievement was compliance with the safety and confidentiality standards required by the Quebec Ministry of Health and Social Services.

Fifth, a web-based user interface supporting advanced data visualization and comparison tools, called NEARS-SAPA, was designed for clinicians, enabling them to monitor (1) 5 significant ADLs (ie, sleep, eating, mobility, activity, and hygiene), (2) relevant object use (eg, fridge, television, and coffee maker), and (3) room occupancy. As a result, the platform provided a broad overview of the ADLs performed by each care recipient as well as some specific information regarding each ADL (eg, the care recipient's sleeping schedule). To compensate for both the inability of research staff to train clinicians because of the pandemic and clinicians' increased workload, the research team simplified reporting, sending a data summary electronically in PDF highlighting the trends and changes in ADLs for each care recipient every 2 months.

Finally, to reduce in-person home visits related to fixing technical problems, a modular and component-based IT infrastructure was built into the NEARS-Hub to solve as many maintenance issues as possible remotely.

Intervention

Strategies based on the alpha cycle were put in place to improve deployment (see Multimedia Appendix 1, section 8, for details). With the involvement of managers from each health institution, it was decided that the project and its opportunities would be presented during regularly scheduled meetings of each targeted profession. Coordinators from different professional teams were asked to promote the project to their colleagues. Although it was not considered an exclusion criterion, clinicians were alerted to poor acceptance and possible adverse outcomes of ADL telemonitoring in individuals with paranoid disorders and extensive mobility challenges.

Evaluation

Overview

For the beta cycle, the objectives were as follows: (1) to describe the characteristics of the participants and their demands for telemonitoring, (2) to describe the use and benefits of the ADL telemonitoring system on a larger scale, (3) to document facilitators of and barriers to its deployment, (4) to evaluate the usability and acceptance of the system, and (5) to estimate the costs related to system deployment and use. To respect COVID-19 sanitary guidelines, interviews and evaluations were conducted through telephone.

Textbox 2 provides an overview of the data collection process used during this cycle. Details can also be found in Multimedia Appendix 1, section 9.

Textbox 2. Overview of the beta cycle data collection, sample, measurements, and variables in the evaluation stage.

Telemonitoring request form filled out by clinicians, with follow-up questions via phone interview

- Facilitators of and barriers to home care of care recipients
- Demands for telehealth technology

Characteristics of clinicians (n=31), care recipients (n=31), and caregivers (n=9)

- For all: demographics
- For care recipients only: Mini-Mental State Examination, Montreal Cognitive Assessment, Multiclientele Assessment Tool, and Functional Autonomy Measurement System profile

Before deployment—individual interviews with clinicians (n=31), care recipients (n=8), and caregivers (n=9)

- Facilitators of and barriers to home care of care recipient
- Anticipated leverages of and obstacles to telemonitoring deployment in home care
- Demands for telehealth technology

During deployment—follow-up individual interviews with clinicians (n=31) every 4 months

- Observed facilitators of and barriers to telemonitoring deployment
- Use case, impacts, and general satisfaction regarding telemonitoring

Questionnaires for clinicians (n=23)

- 10 in-house questions on use
- 7 questions from the System Usability Scale on usability
- 11 questions from the technology acceptance model–2 on acceptance

Questionnaires for care recipients (n=23)

- 3 in-house questions on telemonitoring perceived usefulness
- 8 in-house questions on telemonitoring acceptance

After deployment—focus groups with clinicians (n=8)

- General facilitators of and barriers to telemonitoring deployment and sustainability
- Impacts of and general satisfaction with telemonitoring

After deployment—individual interviews with administrators (n=2)

- General facilitators of and barriers to telemonitoring deployment and sustainability
- Impacts of and general satisfaction with telemonitoring

Estimate of direct, indirect, and intangible costs related to telemonitoring

- Material costs
- Time invested
- Adverse outcomes reported

Characteristics of Participants and Demands for ADL Telemonitoring

For subunit characteristics, we used the same measurements as for the alpha cycle but dropped the cognitive and functional evaluations because of sanitary constraints and adverse reactions reported by clinicians and caregivers from the alpha cycle. For clinicians, age, sex, profession, affiliation, and years of experience in home care services were collected (self-reported). As in the alpha cycle, clinicians who identified a care recipient and wished to participate filled out a request form detailing their demands for ADL telemonitoring. An initial individual interview with the clinician was added before NEARS-SAPA reports were sent to them. This interview was specifically aimed at identifying the demands, facilitators of, and barriers to home care for this specific care recipient.

Use and Impact of ADL Telemonitoring

Qualitative data were similar to those collected in the alpha cycle (Textbox 2), with slight modifications in terms of time points and type of data collection: (1) follow-up focus group interviews with clinicians were replaced with individual

interviews held every 4 months with clinicians following the installation of the sensors and (2) follow-up focus group interviews with administrators and managers were replaced with individual interviews at the end of the cycle.

In addition, after the first follow-up interview, 10 in-house questions specifically related to the ADL telemonitoring system and reported uses were sent to clinicians in the form of a web survey. Finally, 3 in-house questions were administered orally to care recipients regarding their perceptions of the usefulness of the telemonitoring system.

Facilitators of and Barriers to ADL Telemonitoring Deployment

Qualitative data were collected following procedures similar to those in the alpha cycle (Textbox 2), with the same slight modifications as those mentioned previously in terms of time points and type of data collection.

Usability and Acceptance of ADL Telemonitoring

Usability is defined as the effectiveness, efficiency, and satisfaction with which specified users achieve specified goals in particular technological environments [48]. Several measures were added to evaluate the usability of the system. During the initial interview, clinicians were asked whether they foresaw any facilitators of and obstacles to their intended use of the ADL telemonitoring system. During follow-up interviews, they were asked whether there were any barriers to and facilitators of their actual use of the telemonitoring system. A web survey comprising 7 questions from the System Usability Scale [49] was also sent to clinicians. The System Usability Scale is a reliable tool for measuring such usability, and the questions centered on the ADL telemonitoring system and reports. The survey also comprised an 11-question form built from the *perceived usefulness* and *ease of use* sections of the technology acceptance model–2 questionnaire [50]. The technology acceptance model–2 is an information systems theory that maps how users come to accept and use a technology.

To evaluate care recipients' and caregivers' level of acceptance of the presence of the sensors in their homes, they were asked to respond to an oral questionnaire composed of 8 questions developed by the research team.

Cost Estimation of ADL Telemonitoring

We collected metadata on each service provided to care recipients by the CIUSSS and CISSS and recorded them in Intégration CLSC. Intégration CLSC is a provincial ministry database containing personal information and providing data on service requests, users, and interventions concerning services delivered. The database is used to describe frontline services to ensure the quality and efficiency of health and social services. For this study, we examined the monthly count of services received by the care recipients within the time frame of 6 months preceding and 6 months following clinician access to ADL telemonitoring.

Throughout this project, we aimed to document the cost of implementing ADL telemonitoring in the public health care system by totaling direct, indirect, and intangible costs [51,52]. To do so, we documented the material costs (eg, number of devices used, lost material, server maintenance cost, software, licenses, material for fixtures, repairs and maintenance, internet services, and database and server maintenance). We also estimated the time invested by technicians and clinicians over the study period (eg, time for recruitment, needs analyses, installation, training, and technical support). This estimate was validated by the technicians and clinicians during group interviews in the postdeployment phase. The time invested was translated to cost using the common hourly rates for technicians and clinicians. Time dedicated exclusively to research purposes (eg, interviews about the usability of the system) was not included in the deployment costs.

Ethical Considerations

The beta cycle was approved by the Centre de recherche de l'Institut universitaire de gériatrie de Montréal research ethics board, mandated to be the evaluating committee in a multicenter procedure (CER VN 17-18-10). The same protocols and considerations as those in the alpha cycle were followed.

Results

Results corresponds to the *Reflection and learning* stage of ADR. Data collection ended in late 2022. In total, the NEARS-SAPA was installed in 31 care recipients' homes, and 34 clinicians were involved in the beta cycle. Data analyses for the beta cycle are nearing completion, and the results specific to each subobjective will be shared in the future. Three manuscripts currently being written and are expected to be published in 2024-2025.

Discussion

Expected Findings

The aging population and increasing demand for ADL support faced by social and health care services in many countries call for the deployment of innovative solutions to better meet the needs of older adults with cognitive deficits. In close collaboration with 3 public health care institutions in the province of Quebec, we conducted a study designed to arrive at an in-depth understanding of the potential of ADL telemonitoring to support older adults with cognitive decline in the context of a public health care system. More specifically, the objectives of the project were to (1) codevelop an ADL telemonitoring system that addresses the needs of all key stakeholders involved in home care services for older adults with cognitive deficits, including the older adults and their caregivers; (2) deploy ADL telemonitoring in the Quebec public health care system and identify the specific use cases; and (3) identify factors that could contribute to ensuring its long-term use in a real-world setting (ie, participants' characteristics, demands, and use of telemonitoring; facilitators of and obstacles to its deployment; usability and acceptance; and estimated cost of the system). To achieve these objectives, we opted for an innovative research approach with ADR and engaged with all stakeholders involved in home care services throughout 2 iterative cycles of system codevelopment.

The publication of our protocol was part of the completion of the formalization of learning stage, the last ADR stage, comprising the identification of artifacts, generalization of

learning, and dissemination. These 3 components will be addressed in this section.

Identification of Artifacts

In this paper, we report the ADR protocol for the SAPA project and its related artifacts. As a form of ADR result, an artifact encompasses tangible or intangible elements, including objects, documents, processes, or outcomes, shaped by the ADR processes. These artifacts serve as tangible proof of the actions taken and the resulting benefits in the research context. The SAPA project has given rise to IT artifacts such as NEARS-SAPA (a web-based user interface supporting advanced data visualization and comparison tools) and NEARS-Hub (an Internet of Things infrastructure model) [47]. In addition, scientific and clinical artifacts such as the outcomes of the alpha cycle have been published in the form of case studies [15,45]. From data gathered within the beta cycle, our objective is to generate more artifacts, such as presenting comprehensive documentation and analyses of use cases along with factors supporting or limiting the deployment of the ADL telemonitoring system. This endeavor aims to contribute valuable scientific insights into the clinicians' decision-making processes and deployment strategies that will further support the adoption and integration of ADL telemonitoring in real-life home care contexts.

Generalization of Learning

This protocol paper also provides a thorough presentation of the entire project and its intricate phases. It illustrates how ADR principles could apply to the field of ADL telemonitoring, enabling stakeholders to be actively involved in developing technology that is useful, acceptable, and deployable in real-life environments. To our knowledge, a comprehensive ADR protocol spanning 2 cycles of development has not been published so far in the fields of smart environments and ADL telemonitoring. This is surprising as ADR offers a promising framework for developing practical technological solutions to complex problems, such as in health care services [35,37]. In this context, we present the detailed ADR protocol of this project as an outcome or artifact, enabling its replication in similar projects in the future and the generalization of our results.

Furthermore, the SAPA project and ADR protocol are innovative as they include and report the steps involved when ADL telemonitoring is deployed in real life. A recent umbrella review conducted by our team [31] revealed that few real-world deployment studies have been undertaken in the field of smart environments thus far. As an emerging area of research, published studies have primarily focused on the development and conceptualization of technological components, with only a limited number involving small-scale testing in a laboratory context. Consequently, there are limited published data on the deployment strategies required to integrate smart environments into the health care system or community [31], and our project was designed to fill this gap.

To our knowledge, we are the first to have codeveloped and deployed a system in iterative cycles of collaboration with all stakeholders involved in home care support in the context of a public social and health care system. Coconstruction and collaboration are at the heart of ADR principles. Other studies have reported the deployment of similar solutions, but the development or deployment were not carried out using a coconstruction approach in partnership with a health care system and did not consider how stakeholders wish to integrate telemonitoring information into their practice [14,49,53,54]. It has been shown that the codevelopment of technological solutions with all stakeholders and users is an important factor in ensuring that the deployment of sustainable technological solutions proceeds smoothly and leads to their long-term adoption [55]. Our protocol, centered on co-design, use cases, and deployment factors, is parallel to another recently published protocol reporting a clinical trial to document the effectiveness of an ADL telemonitoring platform via a quasi-experimental study [56]. In that study, more than 73 older adults will receive an active and assisted living–based multiservice assistance platform called HomeAssist. The platform includes ADL telemonitoring but also many applications designed for the older adults themselves to help them engage in their daily and social activities. Although the HomeAssist project has not yet been deployed in the home care services context at the time of publication, this type of project is key to advancing the field of ADL telemonitoring, for which very little rigorous experimental data exist thus far [31]. As for ADR procedures, this study illustrates how to realize various cycles of coconstruction and codeployment of a technology in close collaboration with stakeholders.

Although the SAPA project is innovative in terms of its vision and methodology, it operates on a relatively small scale. Therefore, it will be important to conduct larger-scale studies in the future. As a next step, we intend to conduct an evaluative study to determine the benefits of ADL telemonitoring. These benefits could include, for instance, effectiveness in terms of clinician productivity and work, older adults' functional independence, use of other health services, and changes in the living environment, as well as benefits for the institutions in terms of cost-effectiveness [56]. To engage in these types of larger-scale evaluations, we recommend that research teams in the field of ADL telemonitoring rely on recognized models or frameworks of technology implementation and adoption that are well established in the digital health field. For example, the nonadoption, abandonment, scale-up, spread, and sustainability framework by Greenhalgh and Abimbola [55] enables anticipation of the challenges that may arise during the implementation of an eHealth system in a particular environment. As another example, the Clinical Adoption Framework [56] considers the micro-, meso-, and macrodimensions that influence the long-term adoption and sustainability of technological solutions. The use of such frameworks will ensure rigorous development of ADL telemonitoring supported by sophisticated data.

Dissemination

Finally, in terms of dissemination, initial findings from the beta cycle were shared with the participating program managers, heads of services, and clinicians from the CISSS and CIUSSS. Ultimately, the comprehensive results and assessments will be shared with the scientific community, providers of home care services for older adults, managers, and policy makers. There

has been discussion about progressing toward a third cycle of development. The primary objective of such a cycle would be to make NEARS-SAPA fully independent of the research team. Currently, the technology relies on support, supervision, and knowledge transfer from the research team for optimal functionality, posing a significant barrier to broader implementation—including integration into clinical processes—and cost-effectiveness.

Conclusions

This paper reports the protocol for the SAPA project, which used an ADR framework to codevelop and deploy an ADL telemonitoring system in the Canadian public social and health care system. Through 2 ADR iterative cycles, the SAPA project made it possible to consider all stakeholders' needs, expectations, and perceptions in the final telemonitoring strategies proposed as well as the imperatives related to the deployment of such solutions in real test environments. Future studies could follow this protocol and further develop some methodological aspects.

Acknowledgments

This project was made possible through the financial support received from an internal funding program (integrated university health and social services center Centre intégré universitaire de santé et de services sociaux du Centre-Sud-de-l'Île-de-Montréal; alpha cycle), as well as funding from the Canadian Institutes of Health Research and the Natural Sciences and Engineering Research Council of Canada (beta cycle). Part of the technological infrastructure required for both cycles was supported by the Canadian Foundation for Innovation. NB was also supported by a research scholar award from the Fonds de recherche du Québec – Santé. The authors wish to thank Mauricio Chiazzaro, Cédric Démongivert, Yannick Drolet, Renée-Pier Filiou, Paul Guerlin, Catherine Laliberté, Célia Lignon, Maxime Moreau, and Marie-Michelle Ouellet for their valuable contributions to data collection and technological development. The authors also wish to thank their precious collaborators from the health institutions.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Description of specific methodological details for problem formulation, building, intervention, evaluation, and reflection and learning phase for both cycles.
[DOCX File , 54 KB - resprot_v13i1e52284_app1.docx]

References

1. Gilmour H. Unmet home care needs in Canada. Statistics Canada. 2018. URL: https://www150.statcan.gc.ca/n1/pub/82-003-x/2018011/article/00002-eng.pdf [accessed 2024-01-28]
2. Lecours C, Fournier C, Dugas L. Les besoins d'aide non comblés pour les activités de la vie quotidienne chez les personnes avec incapacité au Québec. Zoom Santé. 2016. URL: https://www.ophq.gouv.qc.ca/fileadmin/centre_documentaire/Etudes__analyses_et_rapports/Finances_par_l_Office/zoom-sante-201605-58.pdf [accessed 2024-01-18]
3. Carver LF, Crow B, Rosenberg MW, Puxty J. Core community supports to age in community. Federal, Provincial and Territorial (FPT) Forum of Ministers Responsible for Seniors, Gouvernment of Canada. 2019. URL: https://www.canada.ca/en/employment-social-development/corporate/seniors/forum/core-community-supports.html [accessed 2024-01-18]
4. Publications du ministère de la Santé et des Services sociaux: Chez soi : Le premier choix - La politique de soutien à domicile. Ministère de la Santé et des Services sociaux. 2003. URL: https://publications.msss.gouv.qc.ca/msss/document-001351/ [accessed 2024-01-18]
5. Palmer KS, Stalteri R, Zogo CO, Stall NM, Jüni P, Law S. Home care for older adults during the COVID 19 pandemic: lessons from the Netherlands, Denmark, and Germany to strengthen and expand home care in Canada. CanCOVID. 2022. URL: http://tinyurl.com/352kx6h5 [accessed 2024-01-18]
6. Johnson S, Bacsu J, Abeykoon H, McIntosh T, Jeffery B, Novik N. No place like home: a systematic review of home care for older adults in Canada. Can J Aging 2018 Sep 04;37(4):400-419. [doi: 10.1017/s0714980818000375]
7. Jones A, Maclagan LC, Schumacher C, Wang X, Jaakkimainen RL, Guan J, et al. Impact of the COVID-19 pandemic on home care services among community-dwelling adults with dementia. J Am Med Dir Assoc 2021 Nov;22(11):2258-62.e1 [FREE Full text] [doi: 10.1016/j.jamda.2021.08.031] [Medline: 34571041]
8. Boltz M, Lee KH, Chippendale T, Trotta RL. Pre-admission functional decline in hospitalized persons with dementia: the influence of family caregiver factors. Arch Gerontol Geriatr 2018 Jan;74:49-54. [doi: 10.1016/j.archger.2017.09.006] [Medline: 28957688]
9. Long-term care in ageing societies-challenges and policy options. European Commission. 2013. URL: https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX%3A52013SC0041 [accessed 2024-01-18]

10. De Carolis A, Cipollini V, Corigliano V, Comparelli A, Sepe-Monti M, Orzi F, et al. Anosognosia in people with cognitive impairment: association with cognitive deficits and behavioral disturbances. Dement Geriatr Cogn Dis Extra 2015 Feb 17;5(1):42-50 [FREE Full text] [doi: 10.1159/000367987] [Medline: 25852731]
11. Ito E, Nouchi R, Dinet J, Cheng CH, Husebø BS. The effect of music-based intervention on general cognitive and executive functions, and episodic memory in people with mild cognitive impairment and dementia: a systematic review and meta-analysis of recent randomized controlled trials. Healthcare (Basel) 2022 Aug 03;10(8):1462 [FREE Full text] [doi: 10.3390/healthcare10081462] [Medline: 36011119]
12. Gould E, Maslow K, Lepore M, Lawren Bercaw MP, Leopold J, Lyda-McDonald B. Identifying and meeting the needs of individuals with dementia who live alone. U.S. Administration on Aging. 2021. URL: https://www.researchgate.net/publication/303934162_Identifying_and_Meeting_the_Needs_of_Individuals_With_Dementia_Who_Live_Alone [accessed 2024-01-29]
13. Lussier M, Lavoie M, Giroux S, Consel C, Guay M, Macoir J, et al. Early detection of mild cognitive impairment with in-home monitoring sensor technologies using functional measures: a systematic review. IEEE J Biomed Health Inform 2019 Mar;23(2):838-847. [doi: 10.1109/jbhi.2018.2834317]
14. Rantz MJ, Skubic M, Koopman RJ, Phillips L, Alexander GL, Miller SJ. Using sensor networks to detect urinary tract infections in older adults. In: Proceedings of the 2011 IEEE 13th International Conference on e-Health Networking, Applications and Services. 2011 Presented at: HEALTH '11; June 13–15, 2011; Columbia, MO p. 142-149 URL: https://ieeexplore.ieee.org/document/6026731 [doi: 10.1109/health.2011.6026731]
15. Lussier M, Couture M, Moreau M, Laliberté C, Giroux S, Pigot H, et al. Integrating an ambient assisted living monitoring system into clinical decision-making in home care: an embedded case study. Gerontechnology 2020 Mar 01;19(1):77-92 [FREE Full text] [doi: 10.4017/gt.2020.19.1.008.00]
16. Taylor BJ. Risk management paradigms in health and social services for professional decision making on the long-term care of older people. Br J Soc Work 2005 Nov 18;36(8):1411-1429 [FREE Full text] [doi: 10.1093/bjsw/bch406]
17. Forbes G, Massie S, Craw S. Fall prediction using behavioural modelling from sensor data in smart homes. Artif Intell Rev 2019 Mar 16;53(2):1071-1091. [doi: 10.1007/s10462-019-09687-7]
18. Gokalp H, Clarke M. Monitoring activities of daily living of the elderly and the potential for its use in telecare and telehealth: a review. Telemed J E Health 2013 Dec;19(12):910-923. [doi: 10.1089/tmj.2013.0109] [Medline: 24102101]
19. Li KF. Smart home technology for telemedicine and emergency management. J Ambient Intell Humaniz Comput 2013 May 11;4(5):535-546 [FREE Full text] [doi: 10.1007/s12652-012-0129-8] [Medline: 32218875]
20. Vanus J, Belesova J, Martinek R, Nedoma J, Fajkus M, Bilik P, et al. Monitoring of the daily living activities in smart home care. Hum Cent Comput Inf Sci 2017 Nov 02;7(1):30 [FREE Full text] [doi: 10.1186/s13673-017-0113-6]
21. Jekel K, Damian M, Storf H, Hausner L, Frölich L. Development of a proxy-free objective assessment tool of instrumental activities of daily living in mild cognitive impairment using smart home technologies. J Alzheimers Dis 2016;52(2):509-517 [FREE Full text] [doi: 10.3233/JAD-151054] [Medline: 27031479]
22. Seelye AM, Schmitter-Edgecombe M, Cook DJ, Crandall A. Naturalistic assessment of everyday activities and prompting technologies in mild cognitive impairment. J Int Neuropsychol Soc 2013 Apr;19(4):442-452 [FREE Full text] [doi: 10.1017/S135561771200149X] [Medline: 23351284]
23. Dawadi PN, Cook DJ, Schmitter-Edgecombe M. Automated cognitive health assessment from smart home-based behavior data. IEEE J Biomed Health Inform 2016 Jul;20(4):1188-1194 [FREE Full text] [doi: 10.1109/JBHI.2015.2445754] [Medline: 26292348]
24. Lussier M, Adam S, Chikhaoui B, Consel C, Gagnon M, Gilbert B, et al. Smart home technology: a new approach for performance measurements of activities of daily living and prediction of mild cognitive impairment in older adults. J Alzheimers Dis 2019;68(1):85-96. [doi: 10.3233/JAD-180652] [Medline: 30775978]
25. Dawadi PN, Cook DJ, Schmitter-Edgecombe M. Modeling patterns of activities using activity curves. Pervasive Mob Comput 2016 Jun;28:51-68 [FREE Full text] [doi: 10.1016/j.pmcj.2015.09.007] [Medline: 27346990]
26. Suzuki T, Murase S, Tanaka T, Okazawa T. New approach for the early detection of dementia by recording in-house activities. Telemed J E Health 2007 Feb;13(1):41-44. [doi: 10.1089/tmj.2006.0033] [Medline: 17309353]
27. Akl A, Taati B, Mihailidis A. Autonomous unobtrusive detection of mild cognitive impairment in older adults. IEEE Trans Biomed Eng 2015 May;62(5):1383-1394. [doi: 10.1109/tbme.2015.2389149]
28. Kaye J, Mattek N, Dodge H, Buracchio T, Austin D, Hagler S, et al. One walk a year to 1000 within a year: continuous in-home unobtrusive gait assessment of older adults. Gait Posture 2012 Feb;35(2):197-202 [FREE Full text] [doi: 10.1016/j.gaitpost.2011.09.006] [Medline: 22047773]
29. Akl A, Snoek J, Mihailidis A. Unobtrusive Detection of Mild Cognitive Impairment in Older Adults Through Home Monitoring. IEEE J Biomed Health Inform 2017 Mar;21(2):339-348. [doi: 10.1109/jbhi.2015.2512273]
30. Debes C, Merentitis A, Sukhanov S, Niessen M, Frangiadakis N, Bauer A. Monitoring activities of daily living in smart homes: understanding human behavior. IEEE Signal Process Mag 2016 Mar;33(2):81-94. [doi: 10.1109/MSP.2015.2503881]
31. Tannou T, Lihoreau T, Couture M, Giroux S, Wang RH, Spalla G, et al. Is research on 'smart living environments' based on unobtrusive technologies for older adults going in circles? Evidence from an umbrella review. Ageing Res Rev 2023 Feb;84:101830. [doi: 10.1016/j.arr.2022.101830] [Medline: 36565962]

32. Cresswell KM, Bates DW, Sheikh A. Ten key considerations for the successful implementation and adoption of large-scale health information technology. J Am Med Inform Assoc 2013 Jun;20(e1):e9-13 [FREE Full text] [doi: 10.1136/amiajnl-2013-001684] [Medline: 23599226]
33. Bjørkquist C, Ramsdal H, Ramsdal K. User participation and stakeholder involvement in health care innovation – does it matter? Eur J Innov Manag 2015;18(1):2-18 [FREE Full text] [doi: 10.1108/ejim-08-2013-0081]
34. Couture M, Bandaly S, Giroux S, Lussier M, Bottari C, Pigot H, et al. Expectations of stakeholders regarding technology in home care to optimise the functional autonomy of clients. Gerontechnol 2018 Apr 24;17(s):12. [doi: 10.4017/gt.2018.17.s.012.00]
35. Sein MK, Henfridsson O, Purao S, Rossi M, Lindgren R. Action design research. MIS Q 2011;35(1):37-56 [FREE Full text] [doi: 10.2307/23043488]
36. Gunbayi I. Action research as a mixed methods research: definition, philosophy, types, process, political and ethical issues and pros and cons. J Mix Methods Res 2020(2):16-25 [FREE Full text] [doi: 10.14689/jomes.2020.2.2]
37. Schacht S, Morana S, Maedche A. The evolution of design principles enabling knowledge reuse for projects: an action design research project. J Theor Appl Inf Techno 2015;16(3) [FREE Full text]
38. Sandelowski M. Whatever happened to qualitative description? Res Nurs Health 2000 Aug;23(4):334-340. [doi: 10.1002/1098-240x(200008)23:4<334::aid-nur9>3.0.co;2-g] [Medline: 10940958]
39. Bier N, Lussier M, Couture M, Moreau M, Laliberté C, Aboujaoudé A. Intelligent environments for home support workers: what is their potential for older people at risk of self-neglect? Les environnements intelligents au service des intervenants en soutien à domicile : quel est leur potentiel pour les personnes âgées à risque de négligence de soi? In: Allain P, Aubin G, Banville F, Willems S, editors. Neuropsychologie Clinique et Technologies. Marseille, France: De Boeck Superieur; 2022:415-438.
40. Imbeault H, Gagnon L, Pigot H, Giroux S, Marcotte N, Cribier-Delande P, et al. Impact of AP@LZ in the daily life of three persons with Alzheimer's disease: long-term use and further exploration of its effectiveness. Neuropsychol Rehabil 2018 Jul;28(5):755-778. [doi: 10.1080/09602011.2016.1172491] [Medline: 27126266]
41. Ngankam HK, Pigot H, Parenteau M, Lussier M, Aboujaoudé A, Laliberté C, et al. An IoT architecture of microservices for ambient assisted living environments to promote aging in smart cities. In: Proceedings of the 17th International Conference on How AI Impacts Urban Living and Public Health. 2019 Presented at: ICOST '19; October 14-16, 2019; New York, NY p. 154-167 URL: https://link.springer.com/chapter/10.1007/978-3-030-32785-9_14 [doi: 10.1007/978-3-030-32785-9_14]
42. Giroux S, Bier N, Pigot H, Bouchard B, Bouzouane A, Levasseur M, et al. Cognitive assistance to meal preparation: design, implementation, and assessment in a living lab. In: Proceedings of the AAAI 2015 Symposia. 2015 Presented at: AAAI '15; March 23-25, 2015; Palo Alto, CA URL: https://cdn.aaai.org/ocs/10329/10329-45193-1-PB.pdf
43. Chikhaoui B, Lussier M, Gagnon M, Pigot H, Giroux S, Bier N. Automatic identification of behavior patterns in mild cognitive impairments and Alzheimer's disease based on activities of daily living. In: Proceedings of the 16th International Conference on Smart Homes and Health Telematics, Designing a Better Future: Urban Assisted Living. 2018 Presented at: ICOST '18; July 10-12, 2018; Singapore, Singapore p. 60-72 URL: https://link.springer.com/chapter/10.1007/978-3-319-94523-1_6 [doi: 10.1007/978-3-319-94523-1_6]
44. Caroux L, Consel C, Dupuy L, Sauzéon H. Verification of daily activities of older adults: a simple, non-intrusive, low-cost approach. In: Proceedings of the16th International ACM SIGACCESS Conference on Computers & Accessibility. 2014 Presented at: ASSETS '14; October 4, 2014; New York, NY p. 43-50 URL: https://inria.hal.science/hal-01015280 [doi: 10.1145/2661334.2661360]
45. Lussier M, Aboujaoudé A, Couture M, Moreau M, Laliberté C, Giroux S, et al. Using ambient assisted living to monitor older adults with Alzheimer disease: single-case study to validate the monitoring report. JMIR Med Inform 2020 Nov 13;8(11):e20215 [FREE Full text] [doi: 10.2196/20215] [Medline: 33185555]
46. Yin RK. Case Study Research: Design and Methods. Thousand Oaks, CA: Sage Publications; 2003.
47. Ngankam H, Lussier M, Aboujaoudé A, Pigot H, Gaboury S, Bouchard K. NEARS-hub, a lightweight edge computing for real-time monitoring in smart environments. In: Proceedings of the 2022 International Conference on Ubiquitous Computing & Ambient Intelligence. 2022 Presented at: UCAmI '22; November 30-December 2, 2022; Córdoba, Spain p. 125-138. [doi: 10.1007/978-3-031-21333-5_13]
48. ISO 9241-11: ergonomics of human-system interaction part 11: usability: definitions and concepts. International Organization for Standardization. URL: https://www.iso.org/standard/63500.html [accessed 2024-01-18]
49. Tomita MR, Russ LS, Sridhar R, Naughton BJ. Smart home with healthcare technologies for community-dwelling older adults. In: Al-Qutayri A, editor. Smart Home Systems. Rijeka, Croatia: InTech; 2010:139-158.
50. Venkatesh V, Davis FD. A theoretical extension of the technology acceptance model: four longitudinal field studies. Manag Sci 2000 Feb;46(2):186-204. [doi: 10.1287/mnsc.46.2.186.11926]
51. Colucci L, Bosco M, Fasanaro AM, Gaeta GL, Ricci G, Amenta F. Alzheimer's disease costs: what we know and what we should take into account. J Alzheimers Dis 2014;42(4):1311-1324. [doi: 10.3233/JAD-131556] [Medline: 25024334]
52. WHO guide to identifying the economic consequences of disease and injury. World Health Organization. 2009. URL: https://www.who.int/publications/i/item/9789241598293 [accessed 2024-01-18]

53. Davis MM, Freeman M, Kaye J, Vuckovic N, Buckley DI. A systematic review of clinician and staff views on the acceptability of incorporating remote monitoring technology into primary care. Telemed J E Health 2014 May;20(5):428-438 [FREE Full text] [doi: 10.1089/tmj.2013.0166] [Medline: 24731239]
54. Sauzéon H, Edjolo A, Amieva H, Consel C, Pérès K. Effectiveness of an ambient assisted living (HomeAssist) platform for supporting aging in place of older adults with frailty: protocol for a quasi-experimental study. JMIR Res Protoc 2022 Oct 26;11(10):e33351 [FREE Full text] [doi: 10.2196/33351] [Medline: 36287595]
55. Greenhalgh T, Abimbola S. The NASSS framework - a synthesis of multiple theories of technology implementation. Stud Health Technol Inform 2019 Jul 30;263:193-204. [doi: 10.3233/SHTI190123] [Medline: 31411163]
56. Lau F, Price M. Clinical adoption framework. In: Lau F, Kuziemsky C, editors. Handbook of eHealth Evaluation: An Evidence-Based Approach. Vancouver, CA: University of Victoria; 2017:55-76.

Abbreviations

ADL: activity of daily living
ADR: action design research
CISSS: centre intégré de santé et de services sociaux (integrated health and social services center)
CIUSSS: centre intégré universitaire de santé et de services sociaux (integrated university health and social services center)
CLSC: centre local de services communautaires (local community service center)
NEARS: Innovative Easy Assistance System
POC: proof of concept
SAPA: Soutien à l'autonomie des personnes âgées (Support for Seniors' Autonomy program)

Edited by A Mavragani; submitted 30.08.23; peer-reviewed by E van der Velde, T Karhula; comments to author 20.12.23; revised version received 22.01.24; accepted 24.01.24; published 29.02.24.

Please cite as:
Lussier M, Couture M, Giroux S, Aboujaoudé A, Ngankam HK, Pigot H, Gaboury S, Bouchard K, Bottari C, Belchior P, Paré G, Bier N
Codevelopment and Deployment of a System for the Telemonitoring of Activities of Daily Living Among Older Adults Receiving Home Care Services: Protocol for an Action Design Research Study
JMIR Res Protoc 2024;13:e52284
URL: https://www.researchprotocols.org/2024/1/e52284
doi:10.2196/52284
PMID:38422499

Corrigenda and Addenda

Correction: Mobile Phone Technology for Preventing HIV and Related Youth Health Problems, Sexual Health, Mental Health, and Substance Use Problems in Southwest Uganda (Youth Health SMS)- Protocol for a Pilot Randomized Controlled Trial

Philip Kreniske[1], PhD; Olive Imelda Namuyaba[2], BA; Robert Kasumba[3], MS; Phionah Namatovu[2,3], MPH; Fred Ssewamala[2,3], PhD; Gina Wingood[4], SCD; Ying Wei[5], PhD; Michele L Ybarra[6], PhD; Charlotte Oloya[7], LLB, LLM; Costella Tindyebwa[7], MA; Christina Ntulo[8], MA; Vincent Mujune[7], MPH; Larry W Chang[9], MPH, MD; Claude A Mellins[10], PhD; John S Santelli[11], MPH, MD

[1]Community Health and Social Sciences Department and The Institute for Implementation Science in Population Health, Graduate School of Public Health and Health Policy, City University of New York, New York, NY, United States

[2]International Center for Child Development, Masaka, Uganda

[3]Washington University in St Louis, St Louis, MO, United States

[4]Department of Sociomedical Sciences, Mailman School of Public Health, Columbia University, New York, NY, United States

[5]Department of Biostatistics, Mailman School of Public Health, Columbia University, New York, NY, United States

[6]Center for Innovative Public Health Research, San Clemente, CA, United States

[7]StrongMinds Uganda, Kampala, Uganda

[8]Malachite Center for Mental Health, Kampala, Uganda

[9]Department of Epidemiology, School of Medicine, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States

[10]HIV Center for Clinical and Behavioral Studies, New York State Psychiatric Institute and Columbia University, New York, NY, United States

[11]Heilbrunn Department of Population and Family Health, Mailman School of Public Health, Columbia University, New York, NY, United States

Corresponding Author:
Philip Kreniske, PhD
Community Health and Social Sciences Department and The Institute for Implementation Science in Population Health, Graduate School of Public Health and Health Policy, City University of New York
55 W 125th Street
New York, NY, 10027
United States
Phone: 1 6463649600
Email: philip.kreniske@sph.cuny.edu

Related Article:

Correction of: https://www.researchprotocols.org/2023/1/e49352

(JMIR Res Protoc 2024;13:e55725) doi:10.2196/55725

In “Mobile Phone Technology for Preventing HIV and Related Youth Health Problems, Sexual Health, Mental Health, and Substance Use Problems in Southwest Uganda (Youth Health SMS): Protocol for a Pilot Randomized Controlled Trial” (JMIR Res Protoc 2023;12:e49352), the authors noted two errors:

The affiliation of author Claude A Mellins was:

> *Community Health and Social Sciences Department, Graduate School of Public Health and Health Policy, City University of New York, New York, NY, United States*

It has been revised to:

> *HIV Center for Clinical and Behavioral Studies, New York State Psychiatric Institute and Columbia University, New York, NY, United States*

The affiliation of authors Charlotte Oloya, Costella Tindyebwa and Vincent Mujune was:

> *Malachite Center for Mental Health, Kampala, Uganda*

It has been revised to:

> *StrongMinds Uganda, Kampala, Uganda*

The correction will appear in the online version of the paper on the JMIR Publications website on January 8, 2024, together with the publication of this correction notice. Because this was

made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

Submitted 21.12.23; this is a non–peer-reviewed article;accepted 21.12.23; published 08.01.24.

Please cite as:
Kreniske P, Namuyaba OI, Kasumba R, Namatovu P, Ssewamala F, Wingood G, Wei Y, Ybarra ML, Oloya C, Tindyebwa C, Ntulo C, Mujune V, Chang LW, Mellins CA, Santelli JS
Correction: Mobile Phone Technology for Preventing HIV and Related Youth Health Problems, Sexual Health, Mental Health, and Substance Use Problems in Southwest Uganda (Youth Health SMS)- Protocol for a Pilot Randomized Controlled Trial
JMIR Res Protoc 2024;13:e55725
URL: https://www.researchprotocols.org/2024/1/e55725
doi:10.2196/55725
PMID:38190659

Corrigenda and Addenda

Correction: A Machine Learning Model to Predict Patients' Adherence Behavior and a Decision Support System for Patients With Metastatic Breast Cancer: Protocol for a Randomized Controlled Trial

Marianna Masiero[1,2], PhD; Gea Elena Spada[2], MSc; Virginia Sanchini[1], PhD; Elisabetta Munzone[3], MD; Ricardo Pietrobon[4], PhD; Lucas Teixeira[4], MSc; Mirtha Valencia[4], MSc; Aline Machiavelli[4], MSc; Elisa Fragale[2], MSc; Massimo Pezzolato[1,2], MSc; Gabriella Pravettoni[1,2], PhD

[1]Department of Oncology and Hemato-oncology, University of Milan, Milan, Italy

[2]Applied Research Division for Cognitive and Psychological Science, European Institute of Oncology IRCCS, Milan, Italy

[3]Division of Medical Senology, European Institute of Oncology IRCCS, Milan, Italy

[4]SporeData Inc, Durham, NC, United States

Corresponding Author:
Marianna Masiero, PhD
Department of Oncology and Hemato-oncology
University of Milan
Via Festa del Perdono 7
Milan, 20122
Italy
Phone: 39 0294372099
Email: marianna.masiero@unimi.it

Related Article:

Correction of: https://www.researchprotocols.org/2023/1/e48852

(JMIR Res Protoc 2024;13:e55928) doi:10.2196/55928

In "A Machine Learning Model to Predict Patients' Adherence Behavior and a Decision Support System for Patients With Metastatic Breast Cancer: Protocol for a Randomized Controlled Trial" (JMIR Res Protoc 12(1); e48852) the authors noted one error.

In the Acknowledgments, the last sentences appeared as follows:

> *The 8-item Morisky Medication Adherence Scale content, name, and trademarks are protected by US copyright and trademark laws. Permission for use of the scale and its coding is required. A license agreement is available from MMAS, LLC. The property/identifier issue/registration date/categories are as follows: US registration 5,837,273 August 20, 2019, Trade/Service Mark; US registration TX-8-285-390 June 12, 2016, Copyright; and US registration TX-8-632-533 September 21, 2018, copyright.*
>
> *This project has been funded by a Pfizer grant: Enhancing therapy adherence among patients with metastatic breast cancer (65080791).*

This has been changed to appear as follows:

> *The MMAS-8 Scale, content, name, and trademarks are protected by US copyright and trademark laws. Permission for use of the scale and its coding is required. A license agreement is available from MMAR, LLC., www.moriskyscale.com.*
>
> *This project has been funded by a Pfizer grant: Enhancing therapy adherence among patients with metastatic breast cancer (65080791).*

The correction will appear in the online version of the paper on the JMIR Publications website on January 15, 2024 together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

Submitted 29.12.23; this is a non–peer-reviewed article;accepted 29.12.23; published 15.01.24.

Please cite as:
Masiero M, Spada GE, Sanchini V, Munzone E, Pietrobon R, Teixeira L, Valencia M, Machiavelli A, Fragale E, Pezzolato M, Pravettoni G
Correction: A Machine Learning Model to Predict Patients' Adherence Behavior and a Decision Support System for Patients With Metastatic Breast Cancer: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2024;13:e55928
URL: https://www.researchprotocols.org/2024/1/e55928
doi:10.2196/55928
PMID:38224582

Corrigenda and Addenda

Correction: The Development of a UK Culturally Adapted and Modified Version of the Person Attuned Musical Interactions Manual: Protocol for a 2-Phase Mixed Methods Study

Bryony Waters[1], BSc, MSc; Martin Orrell[1], BMedSci, MBBS, PhD; Orii McDermott[1], ARCM, BA, MMT, PhD

Institute of Mental Health, School of Medicine, University of Nottingham, Nottingham, United Kingdom

Corresponding Author:
Bryony Waters, BSc, MSc
Institute of Mental Health
School of Medicine
University of Nottingham
Jubilee Campus
Innovation Park, Triumph Road
Nottingham, NG7 2TU
United Kingdom
Phone: 44 1158231294
Email: bryony.waters@nottingham.ac.uk

Related Article:

Correction of: https://www.researchprotocols.org/2023/1/e43408

(JMIR Res Protoc 2024;13:e56085) doi:10.2196/56085

In "The Development of a UK Culturally Adapted Version of the Person Attuned Musical Interactions Manual: Protocol for a 2-Phase Mixed Methods Study" (JMIR Res Protoc 2023; 12(1):e43408) the authors made some modifications.

1. The title "The Development of a UK Culturally Adapted Version of the Person Attuned Musical Interactions Manual: Protocol for a 2-Phase Mixed Methods Study" has been revised to:

> *The Development of a UK Culturally Adapted and Modified Version of the Person Attuned Musical Interactions Manual: Protocol for a 2-Phase Mixed Methods Study*

2. *PAMI-United Kingdom* was revised to *PAMI-Modified*, with all subsequent mentions in the paper being changed from *PAMI-UK* to *PAMI-M*.

3. In Table 1, all instances of the word *Dutch* were revised to *Danish*, as the language of the intervention is Danish.

4. Also in Table 1, the phrases in the title and footnote *PAMI-DK* and *PAMI-DK- Person Attuned Musical Interaction Danish Version* have been replaced by *PAMI* and *PAMI-Person Attuned Musical Interactions*, respectively.

5. In the Corresponding Author's address, *Truiumph Road* was corrected to *Triumph Road*.

6. Some sentences were revised to add the words *modified*, *modification* or *modifying* where necessary, as follows:

In the Abstract, in the section Background, "...a team of researchers in the United Kingdom have culturally adapted the tool." has been edited to:

> *...a team of researchers in the United Kingdom have modified and culturally adapted the tool.*

In the Abstract, in the section Objective, "This study aims to investigate the appropriateness of the adapted UK manual for UK care homes and to explore..." has been edited to:

> *This study aims to investigate the appropriateness of the adapted and modified manual for UK care homes and to explore...*

In the Abstract, in the section Conclusions, "This study will be the first to investigate the culturally adapted UK PAMI" has been edited to:

> *This study will be the first to investigate the modified version of PAMI.*

In Background, in the section Person Attuned Musical Interactions Manual, "a UK version of PAMI was developed by a team of researchers at the University of Nottingham" has been edited to:

> *A modified version of PAMI was developed by a team of researchers at the University of Nottingham.*

In Background, in the section Person Attuned Musical Interactions Manual, "The first author's thesis reports the manual development process and the differences between the Danish and UK version of PAMI" has been edited to:

> *The first author's thesis reports the manual development process and the differences between the Danish and Modified version of PAMI.*

In Methods, under the section Training Session, "BW was the researcher who developed the translated PAMI manual as part of her PhD" has been edited to:

> *BW was the researcher who developed the modified PAMI manual as part of her PhD.*

In Methods, under the section Intervention Development, "...the research team liaised with the Danish PAMI team to ensure that any adaptation remained consistent with the PAMI ethos" has been edited to:

> *...the research team liaised with the Danish PAMI team to ensure that any adaptation and modification remained consistent with the PAMI ethos.*

In Discussion, under the section Anticipated Findings, "This study will be the first to investigate the culturally adapted PAMI. Therefore, the data collected in phases 1 and 2 will provide feedback on the appropriateness of the manual for staff..." has been edited to:

> *This study will be the first to investigate the modified PAMI-M. Therefore, the data collected in phases 1 and 2 will provide feedback on the appropriateness of the modified manual for care staff...*

In Discussion, under the section Anticipated Findings, "This study will investigate whether the UK-adapted version of PAMI can benefit residents,..." has been edited to:

> *This study will investigate whether the modified version of PAMI can benefit residents,...*

In Conclusions, the phrase "The study will be the first to investigate the culturally adapted UK PAMI" has been edited to

> *The study will be the first to investigate the modified PAMI.*

In Conclusions, "...and explore participants' experience of using PAMI" has been edited to:

> *...and explore participants' experience of using a modified version of PAMI.*

In the Caption of Figure 2, "PAMI: Person Attuned Musical Interactions" has been edited to:

> *PAMI-M: Person Attuned Musical Interactions-Modified.*

In the caption of Figure 3, the phrase "The manual development process for culturally translating and adapting the Danish Person Attuned Musical Interactions (PAMI) intervention for UK care homes. PAMI-DK: Person Attuned Musical Interactions Danish version; PAMI-UK: Person Attuned Musical Interactions United Kingdom" has been edited to:

> *The manual development process for culturally translating and modifying the Person Attuned Musical Interactions (PAMI) intervention for UK care homes. PAMI: Person Attuned Musical Interactions.*

In the caption of Table 1, "The changes between the Danish and UK Person Attuned Musical Interactions (PAMI)" has been edited to:

> *The changes between the Danish and Modified Person Attuned Musical Interactions (PAMI).*

The correction will appear in the online version of the paper on the JMIR Publications website on January 26, 2024, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

Submitted 05.01.24; this is a non–peer-reviewed article;accepted 05.01.24; published 26.01.24.

Please cite as:
Waters B, Orrell M, McDermott O
Correction: The Development of a UK Culturally Adapted and Modified Version of the Person Attuned Musical Interactions Manual: Protocol for a 2-Phase Mixed Methods Study
JMIR Res Protoc 2024;13:e56085
URL: https://www.researchprotocols.org/2024/1/e56085
doi:10.2196/56085
PMID:38277662

Corrigenda and Addenda

Correction: Vitamin D Deficiency and Its Association With Vitamin D Receptor Gene Variants Among Malaysian Women With Hypertensive Disorders in Pregnancy: Protocol for a Nutrigenomics Study

Yakubu Ibrahim[1,2*], BMLS, MSc; Nurul Iftida Basri[1*], MBChB, DrObGyn; Norshariza Nordin[3*], BSc, MSc, PhD; Amilia Afzan Mohd Jamil[1*], MOG, MD

[1]Department of Obstetrics and Gynaecology, Faculty of Medicine and Health Sciences, Serdang, Malaysia

[2]Department of Medical Laboratory Science, Faculty of Allied Health Sciences, College of Medical Sciences, Ahmadu Bello University, Zaria, Kaduna State, Nigeria

[3]Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang, Malaysia

[*]all authors contributed equally

Corresponding Author:
Nurul Iftida Basri, MBChB, DrObGyn
Department of Obstetrics and Gynaecology
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
Serdang, 43400
Malaysia
Phone: 60 0397699339
Fax: 60 397692640
Email: nurul.iftida@upm.edu.my

Related Article:

Correction of: https://www.researchprotocols.org/2024/1/e53722

(JMIR Res Protoc 2024;13:e59300) doi:10.2196/59300

In "Vitamin D Deficiency and Its Association With Vitamin D Receptor Gene Variants Among Malaysian Women With Hypertensive Disorders in Pregnancy: Protocol for a Nutrigenomics Study (JMIR Res Protoc 2024;13:e53722) the authors noted one error.

The author list was originally:

Yakubu Ibrahim[1,2]; Nurul Iftida[1]; Norshariza Nordin[3]; Amilia Afzan Mohd Jamil[1]

and has been changed to:

Yakubu Ibrahim[1,2]; Nurul Iftida Basri[1]; Norshariza Nordin[3]; Amilia Afzan Mohd Jamil[1]

The correction will appear in the online version of the paper on the JMIR Publications website on April 11, 2024, together with the publication of this correction notice. Because this was made after submission to full-text repositories, the corrected article has also been resubmitted to those repositories.

Submitted 08.04.24; this is a non–peer-reviewed article;accepted 08.04.24; published 11.04.24.

Please cite as:
Ibrahim Y, Basri NI, Nordin N, Mohd Jamil AA
Correction: Vitamin D Deficiency and Its Association With Vitamin D Receptor Gene Variants Among Malaysian Women With Hypertensive Disorders in Pregnancy: Protocol for a Nutrigenomics Study
JMIR Res Protoc 2024;13:e59300
URL: https://www.researchprotocols.org/2024/1/e59300
doi:10.2196/59300
PMID:38603774

Corrigenda and Addenda

Correction: Identification of Anterior Large Vessel Occlusion Stroke During the Emergency Call: Protocol for a Controlled, Nonrandomized Trial

Nicole Wimmesberger[1*], MSc; Diana Rau[1*], MSc; Florian Schuchardt[2*], MD; Simone Meier[2], MD; Matthias L Herrmann[2], MD; Ulrike Bergmann[2]; Erik Farin-Glattacker[1*], Prof Dr; Jochen Brich[2*], MD

[1]Section Health Care Research and Rehabilitation Research, Faculty of Medicine and Medical Center, University of Freiburg, Freiburg im Breisgau, Germany

[2]Department of Neurology and Neurophysiology, Medical Centre - University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany

[*]these authors contributed equally

Corresponding Author:
Nicole Wimmesberger, MSc
Section Health Care Research and Rehabilitation Research, Faculty of Medicine and Medical Center
University of Freiburg
Hugstetter Street 49
Freiburg im Breisgau, 79106
Germany
Phone: 49 0761270 ext 74450
Email: nicole.wimmesberger@uniklinik-freiburg.de

Related Article:

Correction of: https://www.researchprotocols.org/2024/1/e51683

(JMIR Res Protoc 2024;13:e58180) doi:10.2196/58180

In "Identification of Anterior Large Vessel Occlusion Stroke During the Emergency Call: Protocol for a Controlled, Nonrandomized Trial" (JMIR Res Protoc 2024;13:e51683) the authors noted the following error.

In the originally published manuscript, the following authors' degrees were incorrectly listed as:

Florian Schuchardt, PhD

Simone Meier, PhD

Matthias L Herrmann, PhD

Jochen Brich, PD Dr

This has been corrected to:

Florian Schuchardt, MD

Simone Meier, MD

Matthias L Herrmann, MD

Jochen Brich, MD

The correction will appear in the online version of the paper on the JMIR Publications website on April 16, 2024, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

Submitted 08.03.24; this is a non–peer-reviewed article;accepted 13.03.24; published 16.04.24.

Please cite as:
Wimmesberger N, Rau D, Schuchardt F, Meier S, Herrmann ML, Bergmann U, Farin-Glattacker E, Brich J
Correction: Identification of Anterior Large Vessel Occlusion Stroke During the Emergency Call: Protocol for a Controlled, Nonrandomized Trial
JMIR Res Protoc 2024;13:e58180
URL: https://www.researchprotocols.org/2024/1/e58180
doi:10.2196/58180
PMID:38626433

Protocol

Model for Doctor of Nursing Practice Projects Based on Cross-Fertilization Between Improvement and Implementation Sciences: Protocol for Quality Improvement and Program Evaluation Studies

Azizeh Sowan[1], RN, MSN, MBA, MSDA, PhD; Matthew Chinman[2,3], PhD

[1]School of Nursing, The University of Texas Health Science Center at San Antonio, San Antonio, TX, United States

[2]RAND Corporation, Santa Monica, CA, United States

[3]VA Pittsburgh Healthcare System, Pittsburgh, PA, United States

Corresponding Author:
Azizeh Sowan, RN, MSN, MBA, MSDA, PhD
School of Nursing
The University of Texas Health Science Center at San Antonio
7703 Floyd Curl Dr
San Antonio, TX, 7975
United States
Phone: 1 210 567 5799
Fax: 1 210 567 1719
Email: sowan@uthscsa.edu

Abstract

Background: Hundreds of nursing professionals graduate each year from Doctor of Nursing Practice (DNP) programs, entrusted with roles as practice scholars and leaders. Graduates are tasked to lead multidisciplinary knowledge implementation projects to improve safety, quality, and key performance metrics. Nevertheless, there is a continued lack of agreement and faculty dissatisfaction with the format, focus, and results of the DNP graduation projects. The use of a wide range of models and methodologies from different sciences for knowledge implementation introduces challenges to DNP students; affects the scientific rigor of the projects; and results in the overuse, superficial use, or misuse of the models. Quality improvement (QI) and program evaluation studies are substantial investments that may lead to waste and even harm if not well conducted. Traditional QI methodologies, commonly used in DNP projects, were found to be uncertain in improving health care outcomes. The complexity of health care systems calls for cross-fertilization between improvement and implementation sciences to improve health care outcomes.

Objective: This study describes the development, implementation, and evaluation of a hybrid model for QI and program evaluation studies to guide scholarship in the DNP program.

Methods: The hybrid model was based on cross-fertilization between improvement and implementation sciences. The model adapted the Getting to Outcome (GTO) and Knowledge to Action (KTA) models as the overarching process models for knowledge implementation. Within each phase of the GTO and KTA models, expected barriers and facilitators for the implementation and adoption of innovation were identified based on the CFIR (Consolidated Framework for Implementation Research). Accordingly, strategies to facilitate the implementation and adoption of innovations were identified based on a refined list of implementation strategies and QI tools. The choice of these models was based on the top 5 criteria for selecting implementation science theories and frameworks. Seven DNP students used the hybrid model to conduct QI projects. Students evaluated their experiences by responding to a Qualtrics survey.

Results: The hybrid model encouraged a comprehensive systematic way of thinking, provided tools essential to implementation success, emphasized the need for adaptability in implementation, maintained rigor in QI, and guided the sustainability of change initiatives. Some of the challenges faced by students included finding reliable and valid measures, attaining and maintaining staff buy-in, and competing organizational priorities.

Conclusions: Cross-fertilization between improvement and implementation sciences provided a roadmap and systematic thinking for successful QI projects in the DNP program. The integration of the CFIR with the GTO or KTA process models, enforced by

the use of evidence-based implementation strategies and QI tools, reflected the complexity of health care systems and emphasized the need for adaptability in implementation.

International Registered Report Identifier (IRRID): RR1-10.2196/54213

(JMIR Res Protoc 2024;13:e54213) doi:10.2196/54213

KEYWORDS

quality improvement; implementation; Doctor of Nursing Practice; model; methodology; Nursing; Doctor of Nursing; hybrid approach; implementation sciences; scholarship; scholars; Nursing Practice Program; nursing program

Introduction

The Doctor of Nursing Practice (DNP) is the entry-to-practice degree for advanced practice registered nurses and focuses on improving health care outcomes, system practices, and health policy through knowledge implementation [1,2]. According to the American Association of Colleges of Nursing, there were 426 DNP programs in the 50 US states and the District of Columbia, in addition to 70 programs in the planning stage, in 2022 [3]. The number of students enrolled in DNP programs increased from 40,834 to 41,021 from 2021 to 2022 [3]. A core requirement for the degree is the design, implementation, and evaluation of a DNP project [4]. The exponential growth in the number of DNP programs is accompanied by a large inconsistency in the format and focus of the DNP projects [5,6]. To provide clarity, the American Association of Colleges of Nursing recommended that projects focus on knowledge implementation by introducing a change to improve health care outcomes and to have a system focus [2]. Despite these recommendations, a study that included 90 DNP program directors revealed the continued lack of agreement with the format and focus of the DNP projects and reported dissatisfaction of 87% of faculty with the DNP projects [7]. To this end, this study aims to describe a model for designing, implementing, evaluating, and sustaining DNP projects.

At a public university in the Southwest of the United States, our School of Nursing requires DNP projects that are quality improvement (QI) or program evaluation focused. Students over the past 10 years used different theories, models, and methodologies to guide the design, implementation, and evaluation of their projects. Although a difference exists between "models" and "frameworks," these terms will be used interchangeably in this paper. The theories, models, and methodologies used by students include (1) evidence-based practice (EBP) models (eg, Iowa Model and Academic Center for Evidence-Based Practice [ACE] Star Model), (2) implementation science models (eg, Promoting Action on Research Implementation in Health Services [PARiHS] Framework, Knowledge to Action [KTA] Framework, and the Consolidated Framework for Implementation Research [CFIR]), (3) program evaluation models (eg, Logic Models and Getting to Outcomes [GTO] Model), (4) improvement models (eg, Donabedian, Kotter, and Lewin Models), (5) QI methodologies (eg, Plan, Do, Study, Act [PDSA] and Six Sigma—Define, Measure, Analyze, Improve, and Control [DMAIC]), and (7) midrange change theories (eg, Rogers' Diffusion of Innovation).

The use of a wide range of theories, models, and methodologies from different sciences for knowledge implementation and uptake and the absence of criteria to guide that selection introduced challenges to our students in all phases of the project; affected the scientific rigor of the projects; and resulted in the overuse, superficial use, and misuse of the models [8]. This was manifested by several poor practices including a mismatch between the intended use of the guiding model and the complexity of the clinical problem at hand; the selection of inappropriate or least appropriate theory or model to guide the intended change; the selection of multiple (more than 3) models and theories without identifying how the relationship between them supports the different phases of the project; superficial use of the theory or model (ie, selective use of phases, dimensions, or criteria, and the elimination of critical components of a model or a theory); inaccurate representation and application of the dimensions; the lack of using a process model to guide the implementation of a change; and most importantly, the lack of integrating the theory or model into all phases of implementing a change (ie, the theory was mentioned in the planning phase but never used in the implementation, evaluation, or sustainability phases).

The lack of understanding of the intended purposes of these sciences and the interchangeable use of terminologies further complicate the situation. Multimedia Appendix 1 [9-17] provides the definitions of these sciences and associated terminologies. Other terms related to knowledge implementation were well-defined by Graham et al [18]. As shown in Multimedia Appendix 1, the goal of these sciences is to improve health by "producing" or "implementing" knowledge to improve the structure, processes, and outcomes of health care systems [9-17]. For example, implementation science, translation 1 science, and translation 3 science focus on the research, with the goal of "producing and generalizing" new knowledge. QI and EBP, on the other hand, focus on improvement and aim at "applying or implementing" the best available knowledge. Program evaluation is a scientific methodology that aims at either producing or implementing knowledge based on the approach used to conduct the evaluation (ie, research vs QI). On the other hand, most of the models used to guide the conduct of implementation science, QI or improvement science, program evaluation, translation 2 science, and EBP share similar theoretical underpinnings (eg, system theories, change theories, and cognitive theories).

The complexity of health care systems calls for a system-thinking approach to QI. System thinking examines the interrelatedness and interdependence among the system's components to understand the system's behavior and design interventions to improve outcomes. A recent systematic review found the effectiveness of continuous QI methodology for

improving health care outcomes to be uncertain. The uncertainty was related to the complexity of health care systems, in addition to poor application of the methodology [19]. In the same vein, a recent systematic review challenged the legitimacy of PDSA-based QI projects in specifying and achieving predefined improvement aims, highlighted the poor and inconsistent application of the methodology, and called for a theoretical rationale to support the conduct of the methodology and interpretation of the results [20]. Similarly, and to better improve the quality of care, Leeman et al [21] and Check et al [22] called for cross-fertilization between improvement (or QI) and implementation sciences. Implementation science extensively studies best implementation strategies for knowledge implementation and uptake, provides process and determinant models for successful implementation, and focuses on the complexity of the system's components in implementation. QI or improvement science provides useful tools to assess the need for the local context, measures outcomes, and adapt available knowledge at the local level.

The availability of many theories and models for knowledge implementation, the challenges faced by our DNP students in model selection and application, the need for a system thinking approach in QI, the shortcomings of continuous QI and PDSA methodologies in improving health outcomes, and the fact that there is no one best theory to guide all types of projects support the need for cross-fertilization and a hybrid approach in theory and model application between QI and implementation sciences. To this end, this paper describes a hybrid approach to QI in DNP projects by integrating GTO and KTA with the CFIR model and complementing that with the refined list of implementation strategies from Powell et al [23]. A hybrid approach between the different sciences is warranted to deepen our understanding of the interrelated, interdependent contextual factors and the complexity of health care systems, processes, and medical conditions.

The study-specific aims are to (1) describe the development, implementation, and evaluation of a hybrid model between improvement and implementation sciences to guide QI and program evaluation studies in the DNP programs and (2) explore the value of the model and challenges faced in all phases of the DNP projects (planning, implementation, evaluation, and sustainability).

Methods

Overview

The methods section describes the hybrid model and its components; the criteria for selecting GTO, KTA, and the CFIR as process and determinant models; the need to adapt existing models; piloting the hybrid model; and the data analysis plan.

Development of the Hybrid Model

Faculty and the DNP curriculum committee at our School of Nursing recognized the necessity for a standardized and rigorous approach to DNP scholarly projects. This awareness sparked discussions within committee meetings regarding the most effective models to guide DNP projects. The first author of this study (AS) led a task force to develop a comprehensive "DNP Project Guide." The guide encompassed various elements such as the purpose of the DNP program; the focus of the DNP projects; settings of the DNP projects; project format; knowledge dissemination approaches; project timeline; interprofessional collaboration; responsibilities and qualifications of the DNP project committee members; DNP project phases; and a cross-map of DNP project courses, project phases, and milestones. Expanding on this groundwork, the first author (AS) led the development of a new model for DNP scholarly projects and solicited input on its different aspects in subsequent faculty meetings.

Description of the Hybrid Model

The challenges faced by our DNP students in model selection and application call for (1) a "process model" to guide all phases of the DNP project, (2) a "determinant model" to focus attention on the complexity of health care systems, and (3) the application of context- and evidence-based implementation strategies to enhance knowledge uptake and sustainability. Drawing from our expertise in implementation science, QI, and program evaluation, along with input from faculty, a decision was made to use GTO as the overarching process model and the CFIR as the determinant model. KTA was also used as another process model due to its wide adoption in implementation science. These models were complemented by the refined list of implementation strategies and other QI tools from Powell et al [23], as described further below. The choice of these models was based on the top 5 criteria for selecting implementation science theories and frameworks [8]. The criteria include empirical support, application to wide settings or populations, explanatory power, description of a change process, and analytical level (ie, individual, organizational, and system).

In terms of empirical support and application to wide settings or population criteria, the CFIR is the most cited determinant model in implementation science [24], KTA is a widely used process model in implementation science [25], and GTO is a widely used program evaluation model [26]. In terms of explanatory power and description of the change process criteria, the selected models focus on the process of implementation and implementation barriers and facilitators during the full scope of innovation or knowledge implementation, that is, before, during, and after implementation. Regarding the analytic-level criterion, the models consider all levels of implementation for successful adoption. Adoption of innovation occurs at the external, organizational, innovation, and individual levels. Considering the full scope of implementation and the multiple levels of adoption should (1) facilitate engaging the right stakeholders in the implementation process, (2) promote the uptake and ownership of the innovation, (3) build key dimensions of organizational capacities to initiate and sustain a change, (4) foster inter- and intraorganizational collaboration, and therefore (5) provide STEEEP (Safe, Timely, Effective, Efficient, Equitable, and Patient-Centered) care.

The hybrid model consisted of "adapted" versions (described below) of GTO or KTA models as the overarching process model for knowledge implementation. Within each phase of the GTO and KTA models, the expected barriers and facilitators for the implementation and adoption of innovation (ie, best

evidence) were identified based on the CFIR—a determinant model. Accordingly, the implementation strategies to facilitate the implementation and adoption of innovation were identified based on the refined list of implementation strategies and QI tools from Powell et al [23]. Multimedia Appendix 2 [18] illustrates the integration of the CFIR constructs and implementation strategies into each phase of the "adapted" GTO and KTA models.

CFIR Model Overview

The CFIR model is a guide to systematically identify and assess barriers and facilitators to a new program and innovation implementation. The model was guided by studies across 13 fields of research and the analysis of 18 theories and models from different disciplines [27]. It includes 39 constructs that can influence implementation success. These are clustered into 5 domains: intervention characteristics, inner setting, outer setting, individuals' characteristics, and implementation process. These constructs can aid or hurt evidence-based program implementation, depending on their manifestation in organizations. Studies using the CFIR have identified the relationships between different constructs and implementation effectiveness [28,29]. Further, GTO studies have explicitly used the CFIR. In a comparison of community-based sites attempting to implement a drug prevention program with and without GTO, GTO sites had significantly higher average ratings than non-GTO sites for 2 constructs from the CFIR process domain: planning and reflecting and evaluating [30]. In addition, GTO sites had higher ratings of program fidelity, despite having worse CFIR ratings on the culture and available resources constructs. These findings suggest that strong planning, evaluation, and reflection—improved with a process model such as GTO—can aid implementation despite a less desirable implementation climate and further support the need for integrating a process model and a determinant model in QI and program evaluation studies.

GTO Model and the Need for Adaptation

The GTO is a 10-phase action-oriented model for planning, implementing, evaluating, and sustaining innovations and programs. The original phases include (1) needs and resources assessment, (2) goals and desired outcomes, (3) best practices, (4) fit, (5) capacities, (6) planning, (7) process evaluation, (8) outcome evaluation, (9) continuous QI, and (10) sustainability [31].

In our hybrid model (Multimedia Appendix 2), the GTO model was adapted in 5 ways to better guide the implementation of DNP projects (Multimedia Appendix 2). First, "fit" and "capacities" phases were combined and expanded to "fitness and absorptive capacities." Unlike "capacity," absorptive capacity reflects the "dynamic capability of the organization pertaining to knowledge creation and utilization that enhances a firm's ability to gain and sustain a competitive advantage" [32]. Absorptive capacity entails 4 multilevels or dimensions of organizational learning and capabilities, which are knowledge acquisition, assimilation, transformation, and exploitation [32]. An organization's absorptive capacity is critical to its innovative capabilities; is a function of the organization's prior related knowledge; and is influenced by all technical, behavioral, and cultural aspects of the organization [32,33]. Accordingly, the "fitness" phase in the GTO model—the match between the innovation and the organization or user or patient population—is embedded into the organizational absorptive capacity. We decided to keep the term "fitness" in the phase name to remind users of the adapted model to examine fitness at multiple levels (ie, organization, end user, and patient population). According to Cox et al [34], organizational capacity revolves around organizational culture and communication, which in turn are linked to 6 capacity dimensions of leadership, strategy, structure or governance, skills, human capital, and accountability. Effective communication and supportive culture are essential to successful implementation and fundamental for the organization to achieve high performance.

Second, an "implementation" phase was added as part of the cyclic phases after the "planning" phase to move the process to "evaluation." This adaptation is congruent with the action-oriented nature of the GTO model. The third adaptation of the GTO model was clarifying that "process evaluation" means "evaluation of the implementation process." The purpose of this change was to eliminate any confusion between "implementation process evaluation" and the evaluation of "process measures." Although there is some overlap between the 2, "evaluating the implementation process" focuses on 6 main measures of implementation fidelity (the degree to which the innovation was implemented as prescribed in the original protocol), penetration, appropriateness, actual adoption, cost, and sustainability of the innovation [35]. On the other hand, a process measure focuses on the workflow and operations performed to achieve the main outcome metrics. The Institute for Healthcare Improvement identified 3 types of metrics in QI: outcome measures, process measures, and balance measures [36]. The outcome metrics are reflected by the goal of the project. Balance measures track the unintended consequences, if any, resulting from implementing a change or innovations. For example, in implementing a clinical practice guideline (CPG) for cancer screening, an outcome measure would be the cancer screening rate, the process measures might be adherence to CPG use and wait time for a patient to obtain a screening appointment, and a balance measure might be the accuracy of the screening results. Similarly, in implementing a provider in triage model in an emergency department, an outcome measure could be the percentage of patients who left without being seen, process measures could be "door to provider time" and nurse and clinician satisfaction with the provider in triage model, and a balance measure could be "left without treatment" and patient satisfaction with emergency department services. In these 2 examples, it is worth noting that "adherence to CPG use" and "nurse satisfaction" (process measures) could also serve as a proxy for "actual adoption" (adherence to CPG use) and "appropriateness" (clinician satisfaction), which are implementation-related measures. On the other hand, not all process measures reflect implementation-related measures. For example, "time to obtain a screening appointment" and "door to provider time" in the examples above are not 2 of the 6 implementation-related measures.

Fourth, we also changed "outcome evaluation" to "evaluation of measures" to reflect the complexity of measures in QI (ie,

process, balance, and outcomes). Fifth, we combined the "continuous improvement" and "sustainability" phases because continuous QI is a sustainability indicator and a central element of sustainable development [37]. Changes and continuous improvements need to be sustained to achieve their values to consumers of care.

KTA Model and the Need for Adaptation

KTA consists of two interdependent, interrelated phases of (1) knowledge creation that is surrounded by (2) an action cycle [18]. Knowledge creation produces guidance and tools to inform practice, while the action cycle is action oriented to select and implement the best available knowledge to improve practice (ie, the focus of QI). Since improvement science involves the "implementation" of the best available knowledge, the use of KTA to guide QI projects is limited to the action cycle. The KTA framework is based on 31 planned action theories about the process of change [25]. Studies using the KTA model have demonstrated the dynamic, nonlinear aspect of knowledge translation and implementation [25]. However, recent scope reviews that used KTA in behavioral change in rehabilitation and educational interventions for the management of sleep disorders supported the complexity of knowledge implementation and recognized the need to (1) complement the KTA model with determinant models to better assess barriers to implementation and influence implementation outcomes and (2) guide the selection of implementation strategies [38,39]. Along the same line, our hybrid model supports the need for a determinant model (ie, the CFIR) to complement a process model (ie, KTA or GTO) and the need for a refined list of context- and evidence-based implementation and QI strategies to improve implementation fidelity, that is, the list of implementation strategies from Powell et al [23].

A great similarity exists between the original phases of KTA and GTO models (Multimedia Appendix 3). Both models address knowledge implementation starting by identifying the opportunity for improvement (problem) through sustainability. Similar to GTO, KTA was adapted in our hybrid model to better guide the implementation of DNP projects as a process model (Multimedia Appendices 1 and 2). The adaptation (Multimedia Appendix 3) includes (1) adding a "Goals and Desired Outcomes" phase, (2) adding a "Planning" phase, (3) changing "monitor Knowledge use" to "Evaluation of implementation" to capture other crucial aspects of the implementation process, (4) changing "Evaluate outcomes" phase to "Evaluation of Measures" to reflect the complexity of measures in QI, and (5) changing "Sustain knowledge use" to "Sustainability" to emphasize the fact that sustainability is not limited to knowledge "use" but includes sustaining all measures (process, outcome, and balance).

Multimedia Appendix 2 presents the GTO and KTA models with the adapted phases and emphasizes the dynamic nature of QI and program evaluation studies, that is, the need to complete some phases concurrently, adapt subsequent phases based on earlier phases and preliminary results, and the need to adapt and revisit earlier phases.

Integrating CFIR, Implementation Strategies, and QI Tools Into the Adapted Process Models

Multimedia Appendix 2 demonstrates the most important constructs to be considered in each phase of implementation in QI and program evaluation studies based on our expertise in improvement and implementation sciences and program evaluation. Researchers can adapt the list of constructs to fit the needs of the study based on the context of implementation [27]. Our selection of the constructs, and consequently implementation strategies and QI tools, in each phase of the implementation process was also guided by research findings related to core context dimensions in implementation science [40]; heterogeneity in implementation outcomes and dimensions of implementation weaknesses [41]; the relationship among organizational culture, capacity, and communication [34]; stages of knowledge use [42,43]; and strategies for aligning QI science and implementation science [21].

Piloting the Hybrid Model

Students enrolled in the DNP program typically choose models to guide their QI projects based on their familiarity with a model, its previous application in similar studies and clinical contexts, or recommendations from their DNP project mentor. Those without prior exposure to the chosen QI guiding model typically grasp its application with the support of their mentor during the phases of designing, implementing, and evaluating their DNP projects. In this study, none of the involved students had prior experience with KTA, GTO, or the CFIR. The first author (AS) of this study served as the primary mentor for 7 DNP students and with support from a comentor guided students through integrating and applying the hybrid model.

The hybrid model was piloted by 7 DNP students: 5 in the post–Bachelor of Nursing–to-DNP track (BSN-DNP) and 2 in the post–Master of Nursing Science–to-DNP track (MSN-DNP). The 2 tracks have the same program objectives, outcomes, and standards for the DNP project. The only difference concerning the project is the time for completion. Students in the BSN-DNP track complete their projects in 3 semesters, while students in the MSN-DNP track complete their projects in 2 semesters.

The hybrid model was described to all students in the first DNP project course. Students in the BSN-DNP track incorporated GTO as the overarching process model, while students in the MSN-DNP track used KTA. All students used the CFIR as the determinant model, Powell et al [23] refined list of implementation strategies, and different QI tools. The latter included tools such as a swim lane workflow analysis, fishbone analysis, Gantt charts for project management, and control charts of trended data for the main outcome variable before, during, and after implementation. Students were familiar with these tools due to prior application in previous courses. Another required tool that guided project implementation was the TIDieR (template for intervention description and replication) checklist [44]. The primary DNP project mentor (AS, the first author of this study) and the comentor (Amanda Bridges) met with the students monthly to help them apply the hybrid model, monitor progress, maintain rigor and sustainability, and help identify and solve implementation barriers early in the process.

GTO offers a range of tools to facilitate its application. The list of tools is available on the model's website. It is important to note that some of these tools were adapted to fit the nature of QI studies, while others were supplemented with more detailed tools in implementation science (eg, TIDieR). For example, students used a Literature Analysis Table that focused on different available interventions or innovations used to improve the primary project outcome. In addition to the conventional analysis of the literature (covering study design, sample, setting, etc), the analysis focused on the features of each innovation, necessary implementation resources, implementation results, factors contributed to implementation sustainability, and lessons learned.

Model Evaluation

The model was evaluated by students using a Qualtrics survey distributed to students via a link at the end of their DNP projects. All students successfully completed their projects in a variety of inpatient and outpatient settings and thus were eligible to participate in evaluating the hybrid model. The survey included two questions soliciting feedback on (1) the value of the hybrid model in project design, implementation, evaluation, and sustainability and (2) the main challenges faced in all phases of the DNP project. Students received 3 reminders to improve the response rate.

Ethical Considerations

The study was approved by the institutional review board of the University of Texas Health Science Center at San Antonio (IRB; protocol 20210487) as a "non-regulated QI educational project." After the IRB approval, the Qualtrics survey was sent to all students who participated in the pilot. The IRB granted a waiver of consent for educational research. An information sheet was presented at the beginning of the survey with details about the value of responding to the survey, anonymity of responses to maximize objectivity, and confidentiality of the data. Voluntary participation was emphasized in the information letter. Compensation was not offered for participation.

Data Analysis

The 4-stage content analysis methodology by Bengtsson [45] was used to categorize narrative data into themes. To maintain, the transparency, quality, and trustworthiness of the analysis, 2 researchers (AS and Ana Vera) performed the analysis separately and met to discuss the findings and reach a consensus. In the decontextualization phase (stage 1), the 2 researchers read the answers provided by students thoroughly to identify meaning units and generate codes. In the recontextualization stage (stage 2), the researchers went back to the original text to ensure they comprehensively captured all ideas and meanings and revisited the unused text for consideration to be included. In the categorization stage (stage 3), the meaning units were condensed to categories or themes without losing the meaning of the content. In the compilation stage (stage 4), quotes were extracted to support the main themes. As the survey responses were anonymous, we refrained from conducting an "informants check," which involves verifying the alignment between respondents' submitted answers and identified themes or meaning units. However, to mitigate this limitation and to improve the confirmability of the findings, the second researcher (Ana Vera) was a colleague with content analysis expertise who was not involved in the study.

Results

All students designed and implemented projects with QI focus, and none of the projects involved program evaluation. All students (N=7) responded to the survey. Multimedia Appendix 4 presents the themes that represent the value of the hybrid model and challenges reported by students in project design, implementation, and evaluation. The themes are presented in descending order of significance, determined by the quantity of student feedback received for each theme. As per students' feedback, the primary strengths of the hybrid model revolved around its capacity to offer a holistic systematic approach to thinking and the necessary tools for effectively communicating project progress and ensuring implementation fidelity. The model helped students in recognizing how various aspects of implementation are interconnected and supported the complex nature of health care systems and knowledge implementation. The model also maintained rigor in QI, presented a roadmap for a successful project, and empowered the institutionalization of innovation for sustainability. Not surprisingly, the model emphasized the need for adaptability in implementation as it reflected the complexity inherent in health care systems.

Despite these benefits, challenges are inevitable in improvement and implementation endeavors. The challenges reported by students include finding reliable and valid measures, establishing and maintaining staff buy-in, timely access to data, and ensuring the project remains an organizational priority given other competing priorities and organizational changes. Other challenges were related to managing the literature review and selecting the right balance measures.

Discussion

Principal Findings

The need for a theoretical basis for knowledge implementation and uptake has been well supported in the literature [40]. Yet, the availability of a mountain of models and theories for knowledge uptake introduces a burden on researchers and practitioners to choose from [46] and results in a "haphazard selection" or a selection that is "driven by convenience or prior exposure" [8]. Selecting the most appropriate model is crucial to provide systemic thinking for project success; enrich the scientific underpinnings of improvement and implementation endeavors; and minimize "the black box of implementation" and challenges in initiating, implementing, evaluating, and sustaining a change [35]. QI and program evaluation projects are substantial investments that may lead to waste and even harm if not well conducted. The complexity of health care calls for a cross-fertilization between improvement and implementation sciences. This paper presented an improvement-implementation hybrid model to guide scholarship in QI and program evaluation studies.

The hybrid model was successfully implemented to guide QI projects in different inpatient and outpatient settings. The hybrid

model provided a roadmap for rigorous and sustainable QI projects and was crucial to implementation success. Faculty who attended the final presentations of DNP projects using the hybrid model praised the systematic methodology for improving health care outcomes and reinforcing the projects' rigor.

Establishing and maintaining staff buy-in was one of the challenges reported by some students during project implementation. Examples of strategies students implemented to overcome this challenge include the use of project champions, securing leadership support, working on a project that is an organizational priority, creating a sense of urgency to the need of the project, communicating milestones and project progress, conducting rigorous training programs with sufficient support resources for innovation use, and engaging users in every step of the project. However, despite these evidence-backed strategies, sustaining staff enthusiasm and support proved challenging due to competing priorities, notably in projects within acute care settings that experienced significant structural changes, such as transitioning to COVID-19–designated units. Additionally, change in unit directors was a factor in delaying some projects and also impacted staff buy-in. The support of unit directors and charge nurses is essential to project success. These leaders usually act as implementation champions and support students in navigating the system.

Most of the other challenges reported by students in project design, implementation, and evaluation were not related to the hybrid model. For example, managing the literature review and selecting the most appropriate balance measures were expected because of the learning curve to attain these skills in graduate studies. In each DNP project, students complete a comprehensive literature search to identify the best available knowledge and innovations that have been implemented in similar settings to improve the main outcome measure. "Having a manageable set of studies to analyze and synthesize," as reported by students, is a function of selecting the best search terminologies and filters or limits. Similarly, the challenges faced by some students in finding instruments for their process measures (eg, "nurse competence in nasogastric tube care") were not model related. Students had to create these measures based on policies and procedures recommended by professional organizations and test the instruments for face validity before using them in their projects. Nurse competence is a prerequisite to the appropriate use of innovation in these projects. Appropriate use, in turn, reflects "actual adoption"—an implementation-related measure. The lack of sufficient valid and reliable measures for the 6 implementation-related outcomes is well reported in the literature [47-49]. Part of this challenge was related to the fact that the selected process measures are specific to the project. These challenges were acknowledged in the limitation section of the DNP projects.

It is worth noting that following the successful outcomes of this trial project, the DNP curriculum committee and faculty opted to formally incorporate the hybrid model into the DNP program. This structured approach aims to ensure consistent and standardized use of the model across all phases of future DNP projects.

Future Considerations

The substantial diversity in the methodological approaches and rigor of DNP projects across various DNP programs presents significant challenges for faculty, students, and health care organizations. In this study, we aimed to deliberately use well-established, empirically tested, and common models; furnish a structured path for systematic QI planning and implementation; and improve the rigor of QI endeavors. Establishing a standardized and rigorous approach is crucial to prevent any waste associated with unsustainable QI projects, minimize the need for deimplementation, and ultimately improve health care outcomes.

For successful implementation, the hybrid model should be integrated into the DNP curriculum. The frameworks, methodologies, and tools used in the hybrid model (Multimedia Appendix 2) may guide DNP education and curriculum revision. Educators in the DNP program can incorporate many strategies and models in their courses to equip students with sufficient knowledge to design and implement rigorous QI projects. These may include, but are not limited to, team science and team development, best practices and models for stockholders' engagement, best practices and models for optimizing organizational absorptive capacities and capabilities, best practices in sustainability and sustainability models, data visualization in QI, and quality metrics (ie, balance, process, and outcome metrics). The integration of improvement and implementation sciences in 1 model may also advance project dissemination using multiple venues (eg, journals that target implementation science and journals that target improvement science).

Widespread adoption of the hybrid model also necessitates dialogue with clinical partners regarding the value of the model. The hybrid model may allow clinicians and change leaders to consider the full scope of implementation, build key dimensions of organizational absorptive capacity in practice, foster inter- and intraorganizational collaboration, and therefore provide a STEEEP care. However, and based on our experience, some clinical partners are accustomed to specific QI approaches (eg, PDSA, continuous QI, and DMAIC) and expect DNP students to demonstrate these approaches in their proposed projects before endorsing project implementation in their settings.

Equally important is the development of a cadre of faculty capable of guiding students in applying improvement and implementation science principles. Schools of nursing should empower faculty with improvement and implementation science competencies, foster an environment conducive to knowledge sharing among faculty members (eg, faculty huddles), and establish a network of faculty engaged in interdisciplinary QI collaborations. This holistic approach aims to bridge the gap between theoretical understanding and the practical application of QI and implementation science, ensuring that QI initiatives are methodologically sound when implemented in health care settings.

By developing the hybrid model, our intention was not to confine the use of other implementation science models. Model selection in QI and implementation science should be supported by a strong rationale that establishes model relevancy to the

study objectives; pragmatic applicability and fitness to the context, clinical problem, and patient population; model creditability through expert consensus and supporting literature; and other important criteria [8]. Justification for model selection is pivotal to ensure a purposeful and methodologically sound approach, thereby strengthening the credibility of QI and implementation science studies.

Limitations

The hybrid model was created to guide DNP students in QI and program evaluation projects. The model was used by 7 students to pilot its feasibility. All students' projects focused on QI, and none of the projects was program evaluation. Although the model provided many benefits and guided the implementation of rigorous projects, the use of the model by a larger number of students is essential to generalize its use as a guide to all DNP projects that focus on QI and to assess its value in program evaluation studies. While we have not formally sought faculty feedback on the newly developed model, all faculty members acknowledge the necessity of a hybrid improvement-implementation approach in DNP projects. The wide use of the hybrid model in the future will require an assessment of faculty experience regarding the model's value in QI for broader applicability. Future studies should incorporate interviews, alongside surveys, to seek faculty and students' input.

Conclusions

Knowledge implementation and uptake are essential yet complex aspects of health sciences to improve health care and systems outcomes. Improvement endeavors require a hybrid model that integrates improvement and implementation sciences. The integration of the CFIR model with the GTO or KTA process models accompanied by the use of evidence-based implementation strategies and QI tools provided a roadmap and systemic thinking for successful QI projects. The hybrid model can be applied to different inpatient and outpatient settings.

Acknowledgments

We thank Dr Amanda Bridges for comentoring some of the Doctor of Nursing Practice projects and all students who participated in the study. We thank Dr Ana Vera for helping in analyzing the data.

Data Availability

The data sets generated and analyzed during this study are not publicly available due to presenting the data as quotes in Multimedia Appendix 4 but are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Definitions of terms.
[DOCX File , 16 KB - resprot_v13i1e54213_app1.docx]

Multimedia Appendix 2
A hybrid model for quality improvement (QI) and program evaluation studies.
[DOCX File , 70 KB - resprot_v13i1e54213_app2.docx]

Multimedia Appendix 3
Adaptation of Getting to Outcome (GTO) and Knowledge-to-Action (KTA) models.
[DOCX File , 15 KB - resprot_v13i1e54213_app3.docx]

Multimedia Appendix 4
Value of the hybrid model and challenges in project design, implementation, evaluation, and sustainability.
[DOCX File , 17 KB - resprot_v13i1e54213_app4.docx]

References

1. AACN position statement on the practice doctorate in nursing. American Association of Colleges of Nursing. 2004. URL: https://www.aacnnursing.org/Portals/42/News/Position-Statements/DNP.pdf [accessed 2023-10-08]
2. The doctor of nursing practice: current issues and clarifying recommendations: report from the task force on the implementation of the DNP. American Association of Colleges of Nursing. 2015. URL: https://www.pncb.org/sites/default/files/2017-02/AACN_DNP_Recommendations.pdf [accessed 2023-10-08]
3. Fact sheet: the Doctor of Nursing Practice (DNP). American Association of Colleges of Nursing. 2022. URL: https://www.aacnnursing.org/Portals/0/PDFs/Fact-Sheets/DNP-Fact-Sheet.pdf [accessed 2023-10-10]

4. The essentials of doctoral education for advanced nursing practice. American Association of Colleges of Nursing. 2006. URL: https://www.aacnnursing.org/Portals/42/Publications/DNPEssentials.pdf [accessed 2023-10-10]
5. Brown MA, Crabtree K. The development of practice scholarship in DNP programs: a paradigm shift. J Prof Nurs 2013;29(6):330-337. [doi: 10.1016/j.profnurs.2013.08.003] [Medline: 24267927]
6. Nelson JM, Cook PF, Raterink G. The evolution of a doctor of nursing practice capstone process: programmatic revisions to improve the quality of student projects. J Prof Nurs 2013;29(6):370-380 [FREE Full text] [doi: 10.1016/j.profnurs.2012.05.018] [Medline: 24267931]
7. Dols JD, Hernández C, Miles H. The DNP project: quandaries for nursing scholars. Nurs Outlook 2017;65(1):84-93 [FREE Full text] [doi: 10.1016/j.outlook.2016.07.009] [Medline: 27667699]
8. Birken SA, Powell BJ, Shea CM, Haines ER, Kirk MA, Leeman J, et al. Criteria for selecting implementation science theories and frameworks: results from an international survey. Implement Sci 2017;12(1):124 [FREE Full text] [doi: 10.1186/s13012-017-0656-y] [Medline: 29084566]
9. Institute of Medicine (US) Committee to Design a Strategy for Quality Review and Assurance in Medicare. In: Lohr KN, editor. Medicare: A Strategy for Quality Assurance Volume 1. Washington: National Academies Press; 1990.
10. Quality improvement. US Department of Health and Human Services Health Resources and Services Administration. 2011. URL: https://www.ruralcenter.org/sites/default/files/HRSAQIToolkit.pdf [accessed 2023-10-19]
11. Quality measurement and quality improvement. Centers for Medicare & Medicaid Services. URL: https://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/MMS/Quality-Measure-and-Quality-Improvement- [accessed 2023-10-19]
12. Science of Improvement. Institute for Healthcare improvement. URL: http://www.ihi.org/about/Pages/ScienceofImprovement.aspx [accessed 2023-10-20]
13. Glossary of terms. Accreditation Council for Graduate Medical Education. 2010. URL: http://tinyurl.com/yhnk5w5d [accessed 2023-10-20]
14. Rubio DM, Schoenbaum EE, Lee LS, Schteingart DE, Marantz PR, Anderson KE, et al. Defining translational research: implications for training. Acad Med 2010;85(3):470-475 [FREE Full text] [doi: 10.1097/ACM.0b013e3181ccd618] [Medline: 20182120]
15. Definitions under subsection 1 (research objectives), Section I (funding opportunity description), Part II (full text of announcement), of RFA-RM-07-007: institutional clinical and translational science award (U54) Mar 2007. National Institutes of Health. 2007. URL: http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-07-007.html [accessed 2023-10-20]
16. Implementation science news, resources and funding for global health researchers. National Institutes of Health - Fogarty International Center. URL: https://www.fic.nih.gov/ResearchTopics/Pages/ImplementationScience.aspx [accessed 2023-10-20]
17. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. BMJ 1996;312(7023):71-72 [FREE Full text] [doi: 10.1136/bmj.312.7023.71] [Medline: 8555924]
18. Graham ID, Logan J, Harrison MB, Straus SE, Tetroe J, Caswell W, et al. Lost in knowledge translation: time for a map? J Contin Educ Health Prof 2006;26(1):13-24 [FREE Full text] [doi: 10.1002/chp.47] [Medline: 16557505]
19. Hill JE, Stephani AM, Sapple P, Clegg AJ. The effectiveness of continuous quality improvement for developing professional practice and improving health care outcomes: a systematic review. Implement Sci 2020;15(1):23 [FREE Full text] [doi: 10.1186/s13012-020-0975-2] [Medline: 32306984]
20. Knudsen SV, Laursen HVB, Johnsen SP, Bartels PD, Ehlers LH, Mainz J. Can quality improvement improve the quality of care? A systematic review of reported effects and methodological rigor in plan-do-study-act projects. BMC Health Serv Res 2019;19(1):683 [FREE Full text] [doi: 10.1186/s12913-019-4482-6] [Medline: 31585540]
21. Leeman J, Rohweder C, Lee M, Brenner A, Dwyer A, Ko LK, et al. Aligning implementation science with improvement practice: a call to action. Implement Sci Commun 2021;2(1):99 [FREE Full text] [doi: 10.1186/s43058-021-00201-1] [Medline: 34496978]
22. Check DK, Zullig LL, Davis MM, Davies L, Chambers D, Fleisher L, et al. Improvement science and implementation science in cancer care: identifying areas of synergy and opportunities for further integration. J Gen Intern Med 2021;36(1):186-195 [FREE Full text] [doi: 10.1007/s11606-020-06138-w] [Medline: 32869193]
23. Powell BJ, Waltz TJ, Chinman MJ, Damschroder LJ, Smith JL, Matthieu MM, et al. A refined compilation of implementation strategies: results from the Expert Recommendations for Implementing Change (ERIC) project. Implement Sci 2015;10:21 [FREE Full text] [doi: 10.1186/s13012-015-0209-1] [Medline: 25889199]
24. Kirk MA, Kelley C, Yankey N, Birken SA, Abadie B, Damschroder L. A systematic review of the use of the consolidated framework for implementation research. Implement Sci 2016;11:72 [FREE Full text] [doi: 10.1186/s13012-016-0437-z] [Medline: 27189233]
25. Field B, Booth A, Ilott I, Gerrish K. Using the knowledge to action framework in practice: a citation analysis and systematic review. Implement Sci 2014;9:172 [FREE Full text] [doi: 10.1186/s13012-014-0172-2] [Medline: 25417046]
26. Chinman M, Ebener P, Malone PS, Cannon J, D'Amico EJ, Acosta J. Testing implementation support for evidence-based programs in community settings: a replication cluster-randomized trial of getting to outcomes®. Implement Sci 2018;13(1):131 [FREE Full text] [doi: 10.1186/s13012-018-0825-7] [Medline: 30348227]

27. Damschroder LJ, Aron DC, Keith RE, Kirsh SR, Alexander JA, Lowery JC. Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. Implement Sci 2009;4:50 [FREE Full text] [doi: 10.1186/1748-5908-4-50] [Medline: 19664226]
28. Damschroder LJ, Lowery JC. Evaluation of a large-scale weight management program using the consolidated framework for implementation research (CFIR). Implement Sci 2013;8:51 [FREE Full text] [doi: 10.1186/1748-5908-8-51] [Medline: 23663819]
29. Damschroder LJ, Reardon CM, Sperber N, Robinson CH, Fickel JJ, Oddone EZ. Implementation evaluation of the Telephone Lifestyle Coaching (TLC) program: organizational factors associated with successful implementation. Transl Behav Med 2017;7(2):233-241 [FREE Full text] [doi: 10.1007/s13142-016-0424-6] [Medline: 27688249]
30. Cannon JS, Gilbert M, Ebener P, Malone PS, Reardon CM, Acosta J, et al. Influence of an implementation support intervention on barriers and facilitators to delivery of a substance use prevention program. Prev Sci 2019;20(8):1200-1210 [FREE Full text] [doi: 10.1007/s11121-019-01037-x] [Medline: 31473932]
31. Chinman M, Wandersman A, Imm P. Getting to Outcomes 2004: Promoting Accountability Through Methods and Tools for Planning, Implementation and Evaluation. In: RAND Corporation. Santa Monica, CA: RAND Corporation; 2004.
32. Zahra SA, George G. Absorptive capacity: a review, reconceptualization, and extension. Acad Manage Rev 2002;27(2):185-203 [FREE Full text] [doi: 10.5465/amr.2002.6587995]
33. Cohen WM, Levinthal DA. Absorptive capacity: a new perspective on learning and innovation. Adm Sci Q 1990;35(1):128-152. [doi: 10.2307/2393553]
34. Cox K, Jolly S, Staaij S, Stolk C. Understanding the drivers of organizational capacity. RAND Europe. 2018. URL: https://www.rand.org/content/dam/rand/pubs/research_reports/RR2100/RR2189/RAND_RR2189.pdf [accessed 2023-10-20]
35. Proctor E, Silmere H, Raghavan R, Hovmand P, Aarons G, Bunger A, et al. Outcomes for implementation research: conceptual distinctions, measurement challenges, and research agenda. Adm Policy Ment Health 2011;38(2):65-76 [FREE Full text] [doi: 10.1007/s10488-010-0319-7] [Medline: 20957426]
36. How to improve: model for improvement. Institute for Healthcare Improvement. URL: http://www.ihi.org/resources/Pages/HowtoImprove/ScienceofImprovementEstablishingMeasures.aspx [accessed 2023-10-20]
37. Medne A, Lapina I. Sustainability and continuous improvement of organization: review of process-oriented performance indicators. J Open Innov: Technol Mark Complex 2019;5(3):49 [FREE Full text] [doi: 10.3390/joitmc5030049]
38. Romney W, Bellows DM, Tavernite JP, Salbach N, Deutsch JE. Knowledge translation research to promote behavior changes in rehabilitation: use of theoretical frameworks and tailored interventions: a scoping review. Arch Phys Med Rehabil 2022;103(7S):S276-S296 [FREE Full text] [doi: 10.1016/j.apmr.2021.01.076] [Medline: 33561438]
39. King S, Damarell R, Schuwirth L, Vakulin A, Chai-Coetzer CL, McEvoy RD. Knowledge to action: a scoping review of approaches to educate primary care providers in the identification and management of routine sleep disorders. J Clin Sleep Med 2021;17(11):2307-2324 [FREE Full text] [doi: 10.5664/jcsm.9374] [Medline: 33983109]
40. Nilsen P, Bernhardsson S. Context matters in implementation science: a scoping review of determinant frameworks that describe contextual determinants for implementation outcomes. BMC Health Serv Res 2019;19(1):189 [FREE Full text] [doi: 10.1186/s12913-019-4015-3] [Medline: 30909897]
41. Kalolo A, Gautier L, Radermacher R, Srivastava S, Meshack M, de Allegri M. Factors influencing variation in implementation outcomes of the redesigned community health fund in the Dodoma region of Tanzania: a mixed-methods study. BMC Public Health 2021;21(1):1 [FREE Full text] [doi: 10.1186/s12889-020-10013-y] [Medline: 33388037]
42. Skinner K. Developing a tool to measure knowledge exchange outcomes. Can J Program Eval 2007;22(1):49-73 [FREE Full text] [doi: 10.3138/cjpe.022.003]
43. Knott J, Wildavsky A. If dissemination is the solution, what is the problem? Knowledge 1980;1(4):537-578 [FREE Full text] [doi: 10.1177/107554708000100404]
44. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ 2014;348:g1687 [FREE Full text] [doi: 10.1136/bmj.g1687] [Medline: 24609605]
45. Bengtsson M. How to plan and perform a qualitative study using content analysis. NursingPlus Open 2016;2:8-14 [FREE Full text] [doi: 10.1016/j.npls.2016.01.001]
46. Huybrechts I, Declercq A, Verté E, Raeymaeckers P, Anthierens S. The building blocks of implementation frameworks and models in primary care: a narrative review. Front Public Health 2021;9:675171 [FREE Full text] [doi: 10.3389/fpubh.2021.675171] [Medline: 34414155]
47. Weiner BJ, Lewis CC, Stanick C, Powell BJ, Dorsey CN, Clary AS, et al. Psychometric assessment of three newly developed implementation outcome measures. Implement Sci 2017;12(1):108 [FREE Full text] [doi: 10.1186/s13012-017-0635-3] [Medline: 28851459]
48. Walker TJ, Rodriguez SA, Vernon SW, Savas LS, Frost EL, Fernandez ME. Validity and reliability of measures to assess constructs from the inner setting domain of the consolidated framework for implementation research in a pediatric clinic network implementing HPV programs. BMC Health Serv Res 2019;19(1):205 [FREE Full text] [doi: 10.1186/s12913-019-4021-5] [Medline: 30925870]

49. Rabin BA, Lewis CC, Norton WE, Neta G, Chambers D, Tobin JN, et al. Measurement resources for dissemination and implementation research in health. Implement Sci 2016;11:42 [FREE Full text] [doi: 10.1186/s13012-016-0401-y] [Medline: 27000147]

Abbreviations

ACE: Academic Center for Evidence-Based Practice
BSN-DNP: post–Bachelor of Nursing–to–Doctor of Nursing Practice
CFIR: Consolidated Framework for Implementation Research
CPG: clinical practice guideline
DMAIC: Define, Measure, Analyze, Improve, and Control
DNP: Doctor of Nursing Practice
EBP: evidence-based practice
GTO: Getting to Outcome
IRB: institutional review board
KTA: Knowledge to Action
MSN-DNP: post–Master of Nursing Science–to–Doctor of Nursing Practice
PARiHS: Promoting Action on Research Implementation in Health Services
PDSA: Plan, Do, Study, Act
QI: quality improvement
STEEEP: Safe, Timely, Effective, Efficient, Equitable, and Patient-Centered
TIDieR: template for intervention description and replication checklist

Edited by A Mavragani; submitted 01.11.23; peer-reviewed by L Verweij, F Guido-Sanz; comments to author 04.12.23; revised version received 19.12.23; accepted 22.12.23; published 31.01.24.

Please cite as:
Sowan A, Chinman M
Model for Doctor of Nursing Practice Projects Based on Cross-Fertilization Between Improvement and Implementation Sciences: Protocol for Quality Improvement and Program Evaluation Studies
JMIR Res Protoc 2024;13:e54213
URL: https://www.researchprotocols.org/2024/1/e54213
doi:10.2196/54213
PMID:38294860

Protocol

Understanding Employee Voice Behavior Through the Use of Digital Voice Channel in Long-Term Care: Protocol for an Embedded Multiple-Case Study

Anja Kepplinger[1,2], BSc, MSc; Alexander Braun[3,4], MA, MSc, Prof Dr; André Fringer[1,5], Prof Dr, PhD; Martina Roes[1,6], RN, Prof Dr, PhD

[1]Department of Nursing Science, Faculty of Health, Witten/Herdecke University, Witten, Germany

[2]Institute Nursing Science, Department of Health Sciences, IMC University of Applied Sciences Krems, Krems, Austria

[3]Institute Health Management, IMC University of Applied Sciences Krems, Krems, Austria

[4]Institute for Management and Economics in Healthcare, UMIT Tyrole, Hall, Austria

[5]Institute of Nursing, School of Health Sciences, Zurich University of Applied Sciences ZHAW, Winterthur, Switzerland

[6]Deutsches Zentrum für Neurodegenerative Erkrankungen (DZNE), Witten, Germany

Corresponding Author:
Anja Kepplinger, BSc, MSc
Institute Nursing Science, Department of Health Sciences
IMC University of Applied Sciences Krems
Piaristengasse 1
Krems, 3500
Austria
Phone: 43 2732 802 161
Email: anja.kepplinger@fh-krems.ac.at

Abstract

Background: Specific challenges in the health care sector, such as hierarchical structures, shortages of nursing staff, and high turnover of nursing staff, can be addressed by a change process of organizational culture into shared governance. Data from business organizations show that the use of digital voice channels provides employee voice. This approach makes concrete the opportunity for employees to raise their voices by answering surveys and making comments in an anonymous forum, which subsequently positively influences staff turnover and sick leave. Since there is no clear understanding of how a digital voice channel can be used in long-term care to address employee voice, a research gap has been identified.

Objective: The purpose of ADVICE (Understanding Employee Voice Behavior; the acronym for this study) is to understand how the use of a digital voice channel performs in long-term care (residential long-term care and home care facilities). The aim of this study is to understand how the digital voice channel can support staff in making their voices heard and to see what managers need to use the voice channel to change the work environment.

Methods: An embedded multiple-case study will be used to explore the experiences of 2 health care providers who have already implemented a digital voice channel. ADVICE is organized into two main phases: (1) a scoping review and (2) an embedded multiple-case study. For this purpose, focus group interviews with employees, discursive-dialogical interviews with managers, meeting protocols, and data from the digital voice channel will be analyzed. First, all units of analysis from every embedded unit will be separately analyzed and then comprehensively analyzed to obtain a case vignette from every embedded unit (within-analysis). In the second stage, the analyzed data from the embedded units will be compared with each other in a comparative analysis (cross-analysis).

Results: The results will provide insight into how digital voice channels can be used in long-term care to address employee voice. We expect to find how the digital voice channel can empower nurses to speak up and, consequently, create a better work environment. Data collection began in August 2023, and from a current perspective, the first results are expected in summer 2024.

Conclusions: In summary, the results may help to better understand the use of a digital voice channel in the health care sector and its transformative potential for leadership. At the organizational level, research can help to improve the attractiveness of the workplace by understanding how to give employees a voice.

International Registered Report Identifier (IRRID): PRR1-10.2196/48601

(JMIR Res Protoc 2024;13:e48601) doi:10.2196/48601

KEYWORDS

digital voice channel; employee participation; employee voice; health care provider; home care facilities; long-term care; nursing home

Introduction

Overview

The International Council of Nurses points out that there is a need to reduce the dropout rate in nursing and promote the loyalty of employees to their health care provider [1]. Data from the Austrian Work Climate Index that are related to working conditions in the nursing professions describe that 65% of nurses intend to leave their current position, and 15% have plans to change their profession [2]. Furthermore, according to the NORDCARE report on working conditions in long-term care in Austria [3], the working conditions perceived by nurses have declined in recent years. As justifications, the respondents noted the increase in work demands, staff shortages, and lack of time for caring activities. A low level of autonomy, especially among nurses, is highlighted by the collected data. Nursing assistants and home assistants state that they feel left alone with the responsibility for people in need of care. The NORDCARE report [3] findings are corroborated by data from the Austrian Work Climate Index [2], indicating that 44% of employees lack or have inadequate chances to participate in work activities, which may negatively impact on-job satisfaction.

Background

To promote high-quality, person-centered care in the context of challenges related to nursing turnover as well as the different needs and requirements of different generations, health care providers need to invest in creating a productive work environment [4]. To sustainably change the culture in an organization, the interplay of transformational leadership, shared governance, and action processes is needed [5]. In particular, transformational leadership is presented as a leadership style that is action-oriented and enables development and change through shared governance. Shared governance is seen as a management approach in the sense of enabling all stakeholders and employees to have a voice in decision-making processes [5,6].

Recommendations to implement a change process in organizations using transformational leadership and shared governance are supported by the positive impact of the Pathway to Excellence in Long-Term Care (PTE-LTC) program. This is a special Magnet Recognition Program of the American Nurses Credentialing Center for long-term care. The PTE-LTC program is based on 6 pathway standards: professional development, shared decision-making, leadership, well-being, quality, and safety. The goal is to empower and give frontline staff a voice, promote staff participation in improving outcomes, create a sustained culture, strengthen interprofessional collaboration, and ensure the well-being of employees [7]. Key differences between the Magnet Recognition Program and the PTE-LTC program are that the PTE-LTC program includes a person-centered model of care and unlicensed assistive personnel such as nurse assistants [7]. Research indicates that the focus in health care organizations on a better work environment and higher engagement in shared governance decreases rehospitalization and lowers nurse burnout and job dissatisfaction levels [8-10]. A systematic review shows that certified magnet hospitals, compared with nonmagnet hospitals, have higher job satisfaction levels, less burnout, lower turnover, lower rates of nurse shortages, higher quality of care, and better patient outcomes [11].

The “Relationship-Centered Team Nursing Model for Care Delivery in Nursing Homes” is a nursing care delivery model that attempts to address workforce challenges in long-term care. The model describes 4 assumptions. The first is to skillfully manage a multilevel team with a focus on care coordination and communication; the second is to empower and develop staff and delegate appropriately and responsibly; the third is the requisite preparation of nursing staff to deliver person-centered care; and the fourth is nursing leadership. In conclusion, the model addresses an evidence-based approach, clear communication, and staff empowerment [4]. Clear communication means, according to Siegel et al [4], open, clear, and timely communication between staff, residents, their families, and the involved structures.

The PTE-LTC program and the “Relationship-Centered Team Nursing Model for Care Delivery in Nursing Homes” emphasize the importance of empowering frontline staff so that in practice they can have a participatory voice that aims to influence decisions, communicate ideas, communicate residents’ needs and requirements, and initiate change [4,7]. This participatory element of workplace democracy is known as employee voice. Employee voice refers to all organizational structures, mechanisms, or practices in which employees participate and try to influence their work and the performance of their organization [12,13]. The term employee voice has a long tradition in organizational research and is variously defined in the literature [14]. A summary by Dundon et al [15] describes the concept of employee voice in terms of four characteristics: (1) addressing dissatisfaction, opinions, or suggestions; (2) expressing a collective organizational culture; (3) managing decision-making processes; and (4) demonstrating a cooperative relationship between management and employees in an organization [15]. Elizabeth Wolfe Morrison, a professor of management and organization at the Stern School of Business, New York University, defines employee voice as “informal and discretionary communication of ideas, suggestions, concerns, problems, or opinions about work-related issues, with the intent to bring about improvement or change” [14].

The literature on employee voice addresses promotive and prohibitive factors of voice, such as how supervisors respond to that behavior and the effects that voice has. For example, Holland et al [16] and Kee et al [17] show that mechanisms that address the voice of employees can reduce burnout, promote employee well-being [16], and influence organization development through structures that employees are encouraged to explore and give feedback [17]. However, according to Morrison [14], there is a need to consider how informal employee voice behavior is affected by formal opportunities and channels for voicing, both individually and collectively.

Recent developments in digital and communication technology have opened new opportunities to address employee voice [18-20]. For example, the social and economic scientist and sociologist Ellmer and Reichel [19] describe the possibility of a company mirror or digital voice channel. This digital communications technology enables voice by allowing employees to periodically report their work satisfaction through minisurveys and make anonymous comments in miniforums. Ellmer and Reichel [19] show in their case study that employees are encouraged to speak up and discouraged from an affordance perspective. In this context, the affordance perspective refers to the definitions of Gibson [21] and Norman [22] and means analyzing the possibilities for action that an artifact offers to an actor, as well as the constraints. The possibilities that an artifact can support or hinder a person in achieving a goal. These results indicate that the interplay of material and social aspects, that is, the characteristics of the voice channel and the responses of the management embedded in the respective organizational context, lead to employees perceiving the channel as either promoting or restricting speech. This further leads to whether employees feel encouraged or discouraged to speak up or not speak up [19]. In summary, a digital voice channel can have a positive impact on the identification and attachment of the employees with the company, leading to a reduction in turnover and sick leave, which depends on job satisfaction [16], perception of autonomy, the influence of organizational context [23], and the perception of safety [24] and dependencies [19]. These results indicate that a digital voice channel is not sufficient on its own; it must be seen as a part of an overall approach to shared governance [19].

Based on these findings, due to the increasing challenges related to nursing turnover and the different needs and requirements of different generations, new measures are needed to meet the increasing demand for nurses to ensure high-quality, person-centered care.

To date, the use of a digital voice channel in the health care sector has received little attention. Improvements in the health care structure, IT, organization, and legislation are needed to ensure that health care is error-free, efficient, and effective. The Health & Care Expert Council recommends investing in the promotion of digital health literacy, that is, empowering people to deal competently with the digitalization of health care [25]. Available data indicate that in the health care sector, it can be difficult for employees to have a voice due to hierarchical structures [17,26]. For example, Kee et al [17] research how nursing assistants can develop voice behavior that transcends hierarchical levels. The study results show that by training in personal reflection as well as individual coaching, nursing assistants are able to influence organizational structures and initiate change. As a result, it is necessary to understand the wider context of social processes in an organization to address the voice of employees. For example, to know that psychological safety and commitment-based safety management have an impact on whether nurses are willing to raise concerns and be aware that psychological safety is a social-cognitive variable that varies between individuals within the same work context [27-29]. Research also exists regarding the content and structure of simulation training on speaking up in health care organizations [30,31]. It should be noted that the evidence on simulation training has mainly focused on inpatient and emergency settings, operating theaters, and intensive care units and not on long-term care. Martin et al [32] suggest that relying solely on formal channels may discourage some individuals from speaking up, hence the importance of complementing with informal methods. It is recommended to use a combination of both to encourage a greater variety of voices to be heard. Further studies have examined the implementation of a new role called “guardian” to promote voice in the organization. The research indicates that this role should not only focus on formal acts of voice such as support and advice. Instead, a relationship role between the guardian and colleagues is needed, as well as a well-defined role between the existing channels for voice [33]. As Jones et al [34] and O’Donovan and McAuliffe [35] noted, it is unlikely to find a 1-size-fits-all approach to creating a culture where health care professionals can raise their voice. In summary, it must be mentioned that in the health sector, the term employee voice is not used consistently. The existing literature on the use of voice in health care focuses on the use of voice in the context of patient safety and error reporting. In summary, the current review by Lainidi et al [36] points to the lack of a comprehensive theory of employee well-being and communication in the health care sector, which leads to heterogeneous mechanisms and an unclear understanding of the phenomenon of employee voice in health care. Lainidi et al [36] argue that understanding the concepts of voice and silence from both organizational and employee perspectives is crucial, as is the need for different solutions for different contexts. This means that individual approaches and evaluations are needed to gain a deeper understanding of employee voice, especially in the long-term care sector.

In their systematic review, Mair et al [37] note that the published literature focuses on organizational aspects yet neglects the broader social framework that needs to be considered when introducing new technologies. More recently, Krick et al [38] have recommended more evaluations of digital technologies in a real-life setting. It is not about what is technically possible; rather, it is about how new digital technologies in the daily routine can be designed to consider staff needs and preferences [20,39]. Ong et al [40] address this research gap and analyze the implementation of a digital patient feedback system using normalization process theory (NPT) from May and Finch [41] and May et al [42]. NPT is a middle-range theory that provides a sociological framework to understand social processes. The theory was developed to understand how a practice becomes or does not become routinely embedded in social contexts. A total of 4 key components of the theory are of relevance: coherence,

cognitive participation, collective action, and reflexive monitoring. These 4 components define the process of normalization. Coherence refers to the fact that the practice is an ensemble of beliefs, behaviors, and acts that are defined by a set of ideas about its meaning, uses, utility, and socially defined and organized competencies. The nature of embedding depends on the work that defines and organizes a practice as a cognitive and behavioral ensemble and requires that actors collectively invest meaning in it. Cognitive participation means that normalization depends on the work that defines and organizes the actors involved in a practice. Collective action includes the chain of interactions, that is, a place of mental and material work that deals with organizing and enacting a practice. Reflexive monitoring means the continuous formal and informal evaluation of the patterns of collective action and their outcomes by all participants [41,42]. Collectively, NPT provides an appropriate conceptual framework to understand issues relating to routinization of new technology [37,43]; it will therefore be used in the ADVICE (Understanding Employee Voice Behavior; the acronym for this study) study as the theoretical lens.

This study will fill a gap in knowledge because it aims to understand how staff and managers use a digital voice channel in the social context of health care providers who offer long-term care services, to subsequently understand how employee voice behavior is affected by the digital voice channel, and to explore what opportunities arise for the employees and for the organization through a digital voice channel. The digital voice channel is a browser-based software-as-a-service system that organizations can purchase on a subscription basis. The founders of the digital channel provider aim to empower employees to actively participate in the improvement and decision-making processes in their workplace by giving them the opportunity to (1) periodically report on their job satisfaction through minisurveys and (2) post anonymous comments in a miniforum. On the user interface, a dashboard with a graph shows the progression of a sentiment metric over time, allowing analysis of current and past sentiment levels in the organization. The sentiment metric is based on responses to anonymous minisurveys covering 6 categories: well-being, health, collaboration, potential development, work activity, and organizational culture. The standard pool of questions can be supplemented by various additional pools. Employees can select from a Likert scale ranging from 1 to 7 (1=does not apply at all to 7=completely true). To gather votes, a link to minisurveys (ranging from 3 to 10 questions) is sent to all employees through email at specified intervals (weekly or monthly), depending on the organization's preference. Managers are alerted when new votes or anonymous comments are available. This information, combined with the dashboard, can be used to identify and act on trends and dynamics in the team early on, allowing decisions to be made based on this information.

Aim of This Study

The aims of the study are to investigate the phenomenon of the digital voice channel in a real-life context and to explore opportunities and capture experiences to enable a systematic and professional approach in the future. This means that it is about generating new knowledge to make the new techniques usable and normalized in long-term care. The overall question is as follows: How does the use of a digital voice channel support opportunities to affect employee voice behavior in long-term care?

For the planned scoping review, the following question is relevant: Which opportunities are mentioned in the literature to address employee voice in health care providers?

For the embedded multiple-case study, further questions are relevant:

What are the experiences in long-term care with the use of a digital voice channel? How is the normalization process described in long-term care, and how do they differ?

Methods

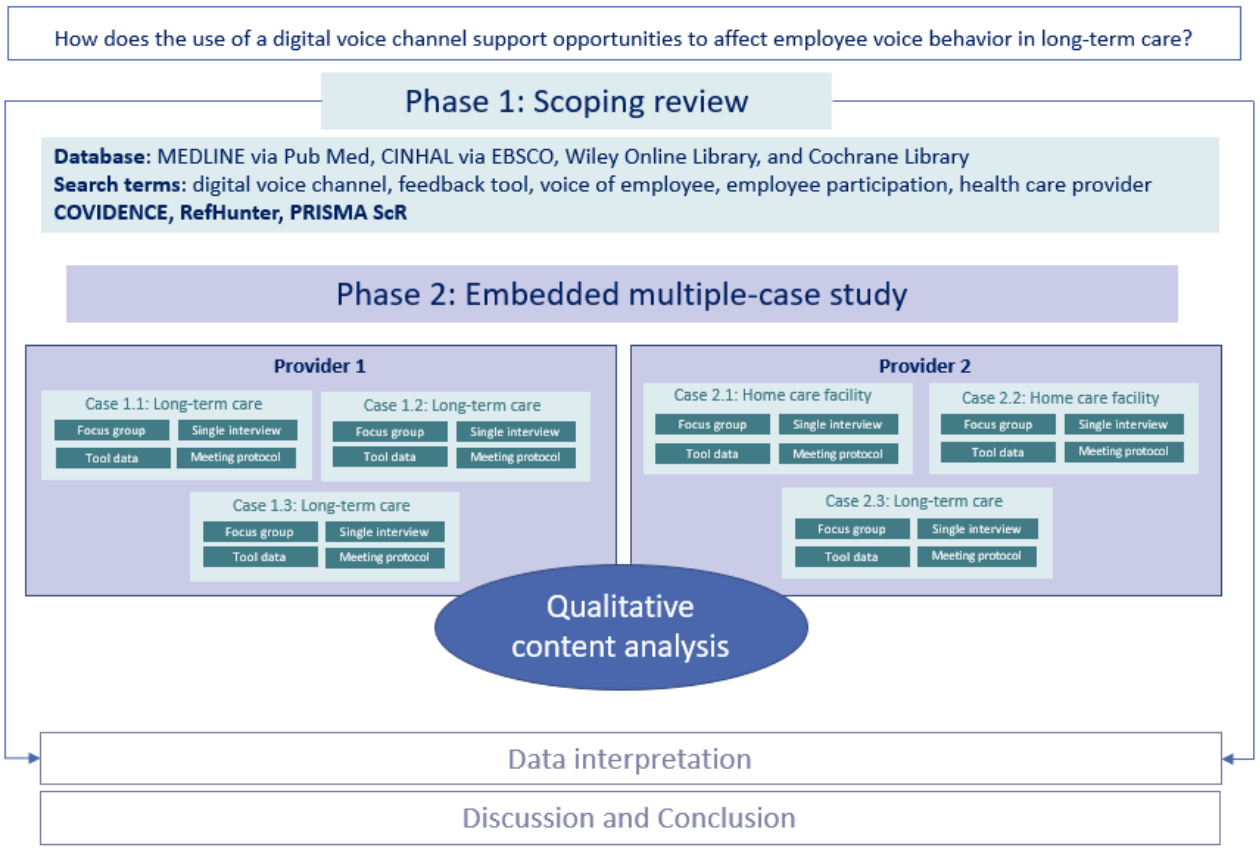
Overview

To answer the research questions, an embedded multiple-case study will be chosen. Case studies can be used to analyze a phenomenon from multiple perspectives in a real-life context [44] to gain a deeper understanding [45]. The case study approach is especially appropriate when there is little understanding of a phenomenon in a certain context [44]. According to Yin [44], case study research is described by 5 components: questions, propositions, cases, data collection, and data analysis. Propositions in ADVICE will result from the scoping review and from NPT. The contexts are 2 health care providers that have already implemented a digital voice channel. These 2 long-term care providers describe the context in which several residential long-term care and home care facilities (cases) operate. Both providers use the same digital voice channel.

To analyze the social processes related to the use of a digital voice channel in health care providers, multiple data sources are necessary to create dense descriptions [44,46]. For this purpose, focus group interviews with employees, discursive-dialogical interviews [47] with managers (plus field notes), meeting protocols, and data from the digital voice channel will be analyzed (units of analysis). The qualitative data and comments in the survey will be analyzed by a deductive-inductive content analysis approach developed by Schreier [48]. Data from the digital voice channel include response rates and frequency of the mentioned topics. These quantitative data are displayed in the digital voice channel and provided by the health care provider. In summary, a phenomenon (digital voice channel) will be analyzed in a real context (2 health care providers) to achieve a deeper understanding of how a digital voice channel becomes a daily routine, that is, normalized [49]. It should be noted that the case definition or units of analysis, as well as other aspects of the research design in a case study, may be revised during data collection [50].

ADVICE is organized into two main phases: (1) the completion of a scoping review and (2) the conduction of an embedded multiple-case study, as shown in Figure 1.

Figure 1. Overview of the research phases of the ADVICE (Understanding Employee Voice Behavior) study.



Phase 1: Scoping Review

The scoping review [51] aims to provide an overview of the literature on employee voice in health care providers and the use of opportunities or interventions such as voice channels, assessments, tools, feedback instruments, feedback training, or meetings to promote having a voice in the organization. To develop the search components, the question is integrated into the PICO (population, interest, and context) schema for qualitative studies [52], as shown in Textbox 1. The scoping review will be conducted using the PRISMA ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) [53].

Textbox 1. PICO schema.

P: population

- Health care provider

I: interest

- Opportunities like digital voice channel

Co: context

- Employee voice

The search process took place in the period ranging from September 2022 to April 2023 in the MEDLINE through PubMed, CINHAL through EBSCO, Embase, Wiley Online Library, and Cochrane Library databases. Furthermore, the reference lists of relevant results will be screened and identified through Google Scholar. The following search terms will be used for the search: digital voice channel, feedback tool, company mirror, feedback, assessment, tool, voice of employee, employee participation, health care provider, long-term care, and home care facilities. Furthermore, the search terms and their synonyms will be linked to search strings using Boolean operators dependent on the databases, as well as MeSH (Medical Subject Headings) terms. After a sensitive search, the research team will consult with each other and adapt the search string. To support the search, the researchers will use the manual for literature search in specialized databases, namely, RefHunter [54]. The inclusion and exclusion criteria shown in Textbox 2 have been derived from the objective and research questions. There will be no restrictions regarding the currency of the literature included.

Textbox 2. Inclusion and exclusion criteria for scoping review.

Inclusion criteria

- Health care provider, residential long-term care, and home care facilities
- Digital voice channel, digital feedback tools, feedback tools, evaluation, assessment, and tools
- Employee voice, employee participation, and team learning
- Qualitative and quantitative studies (all scientific studies)
- English and German

Exclusion criteria

- Other settings similar to business areas
- Summaries and discussions
- Other languages

Covidence is a software for managing and simplifying reviews. The program Covidence supports the review process after the removal of duplicates and enables the screening of the literature by 2 reviewers independently [55]. Specifically, the titles and abstracts will be reviewed against the inclusion and exclusion criteria to identify appropriate studies. In the next step, the full texts of the relevant studies will also be reviewed by 2 reviewers independently. Any disagreements about the eligibility of a study will be resolved by discussion in the research group. For data extraction, a standardized data extraction form will be developed. The form will be tested with the first 3 results and discussed in the research group. The items included in the description of each article will be selected following the Template for Intervention Description and Replication (TIDieR) [56] and Criteria for Reporting and Evaluation of Complex Interventions (CReDECI 2) in health care [57]. Based on the iterative character of the scoping review, all changes will be documented in the protocol [51]. The results of the scoping review will be used to develop propositions and the interview guide used in phase 2 of the ADVICE study.

Phase 2: Embedded Multiple-Case Study

Overview

Based on the results of the scoping review, this research phase aims to go into the field and immerse itself in the day-to-day work of the cases to understand the social processes that involve the promotion of employee voice. A detailed description of the components of Yin's [44] case study research design follows.

Casing

As shown in Figure 1, the ADVICE sample includes 6 different cases that are situated in 2 different contexts (providers 1 and 2). After Sandelowski [50], the cases for a case study are made, not found, through an iterative and theoretical process called casing. The boundary of the cases can be determined by the phenomenon of the use of the digital voice channel and the same scope of long-term care (content boundary). In these cases, the temporal boundary refers to the time of digital voice channel implementation. Starting with the time of implementation in provider 1, (2020) and provider 2 (2021), the end time describes the end of the data collection from the current point of view (2024) [44].

Provider 1 is a health care provider with approximately 1000 employees in different residential long-term care facilities in Austria. A digital voice channel has been used there since 2020. From the current perspective, this health care provider is defined by 3 cases through 3 long-term care facilities.

Provider 2 is a health care provider of several residential long-term care and home care facilities with approximately 5000 employees in Austria. The health care provider has been using a digital voice channel in a pilot phase in a few facilities since 2021. From the recent perspective, this health care provider is defined by 3 cases, namely, 1 residential long-term care and 2 home care facilities. In this case, a long-term residential care facility is an institution where people who need care can live or stay for a period of time under the responsibility of professional health care workers. Home care facilities provide professional care to patients in their own homes. The research team is aware of the different settings (residential long-term care and home care facilities) in the embedded units, which represents a limitation. The use of the different samplings can be argued by the fact that the focus of the analysis is the use of a digital voice channel, as well as employee voice behavior, in long-term care providers. Thus, it is not about the setting of health care providers per se; rather, the commonality is the same setting of long-term care, the same digital voice channel, and therefore, the same organizational culture with different characteristics. Additionally, based on the different settings, additional data, such as individual characteristics of the specific areas and differences, can be generated. The concrete number of employees and number of beds in the embedded units cannot yet be described, as the recruitment phase is only just beginning.

Data Collection

Overview

Based on the recommendation of Yin [44], data collection will take place using multiple sources of evidence. Consequently, data will be collected in the form of focus group interviews, discursive-dialogical interviews [47], meeting protocols, and data from the digital voice channel (anonymous survey data and free comments). During the whole research process, field notes and written memos concerning methodological, personal, and case-related issues will be taken by the first author [58].

These different data are, according to Yin [44], the embedded units of analysis.

Specifically, data from the digital voice channel will be searched concerning the key mechanism of reflexive monitoring drawn from NPT [41,42], for example, how benefits or problems with the digital voice channel are identified or measured.

The Interviews

The interviews will include managers, nurses, and social care professionals in each case. Based on the Austrian Nursing Practice Act, nurses are defined as registered nurses with a diploma and a bachelor's degree (full-time training, 3 years), nursing specialist assistants (full-time training, 2 years), and nursing assistants (full-time training, 1 year). In addition to nurses, social care professionals also work in residential long-term care and home care facilities. There are 3 levels of qualification based on the Social Care Profession Act (home assistant, social care workers, and certified social care workers). Home assistant complete 200 hours of theoretical course and 200 hours of practical training. Social care workers complete a 1200-hour theoretical course and 1200 hours of practical training. Certified social care workers have an 1800-hour theoretical course and 1800 hours of practical training.

It should also be noted that medical care in residential long-term care in Austria varies greatly according to the laws of the individual federal states. In most facilities, it is provided by general practitioners. This means that general practitioners are not employed by the health care provider; they provide medical care by visiting their patients. For example, it is possible for nurses in residential long-term care facilities to have different general practitioners to contact because residents bring their own general practitioners with them. This applies to other health care professionals like physiotherapy, occupational therapy, and speech and language therapy. In summary, this indicates that physicians and health care professionals are not employed in the health care providers and therefore are not using the digital voice channel.

In addition, managers in different positions will be interviewed. The inclusion and exclusion criteria used for the interview participants are summarized in Textbox 3.

The interviews will focus on the following key NPT mechanisms*:* coherence, cognitive participation, and collective action [41]. In the context of ADVICE, coherence means asking about sense-making both as an individual component and as a team component. For example, do the participants see a sense in the use of the digital voice channel or not? Do they see a benefit for themselves and for the team? Cognitive participation includes topics aiming to understand the initiation, promotion, and legitimation of participation. Social norms and formal or informal rules in the team play a role in this key mechanism. For example, are facilitators involved in which role they either have or do not have, and is there a collective commitment in the digital voice channel or not? The collective action mechanism refers to all measures taken to use the digital voice channel. Examples include competencies for workability, such as knowledge work, which is necessary to build trust, and digital competencies [41,59].

Textbox 3. Inclusion and exclusion criteria for interviews.

Inclusion criteria

- Women, men, and diverse
- Nurse (registered nurse, nursing specialist assistant, and nursing assistant)
- Home assistant, social care workers, and certified social care workers
- Manger (nursing director, nursing manager, department manager, deputy manager, head of nursing department, and head of nursing unit or nursing home)
- Employed for at least 6 months in 1 of the 2 health care providers that uses a digital voice channel
- German or English

Exclusion criteria

- Employees who do not work in 1 of the 2 health care providers or who are retired nurses or nursing students
- Employed for less than 6 months in 1 of the 2 health care providers that uses a digital voice channel
- Other languages

During the focus group interviews, nurses will have the opportunity to discuss the use of the digital voice channel. The aim here is to obtain a picture of what nurses need to be able to give a voice and the impact of the voice channel on their voice behavior. Focus group interviews will be conducted with nurses who work in one of the cases of provider 1 or 2 and do not have a management position. Approximately 6 focus groups will be conducted, each with at least 5-6 individuals in each group. Heterogeneity will be considered in the recruitment process. With attention to the professional qualification mix, every professional nursing group will be represented. The focus group interviews will be moderated by the first author with the help of an interview guide based on the results of the scoping review and NPT.

The single interviews will be conducted by the first author in a dialog-discursive interview form based on the interview guide and on the results of the focus group interviews. The reason for choosing dialog-discursive interviews with the help of a semistandardized interview guide is that interviews are

conducted openly on the one hand, while on the other hand, targeted exploratory questions can be asked regarding specific topics. A semistandardized interview guide is intended to be of assistance, whereby the order of the questions, as well as their wording, are flexibly adapted to the interview situation [47]. The semistandardized interview guide will be developed based on the research results of the scoping review and NPT [41,42] using the SPSS principle, according to Helfferich [60]. The number of interviews is based on the fact that at least 1 interview will be conducted at each management level, for approximately 14 interviews in total. It should be mentioned that the data collection will be determined by an iterative approach. Participants will be recruited by the first author through written information as well as through participation in staff meetings to get to know each other directly. Participation will be strictly voluntary. The providers and work councils (employee representation in the health care provider) will provide informed consent before the data collection step.

All interviews will be recorded using a voice recorder. The transcriptions will be performed by the first author, and after the transcriptions, the audio files will be deleted. The transcription of the interviews will follow the content-semantic transcription process word-for-word. Statements in dialect will be, if possible, translated word-for-word into standard German [61]. Before transcription, the interviews will be stripped of any identifiers so that the participants remain anonymous. Table 1 below shows the coding rules used as an example.

Table 1. Exemplary coding rules transcription.

Health care providers and embedded units	Interview	Code
Provider 1		
Case 1.1: long-term care	Focus group interview 1	P1CL1.1F1
Case 1.2: long-term care	Single interview 2	P1CL1.2S2
Provider 2		
Case 2.1: home care facility	Single interview 4	P2CH2.1S4

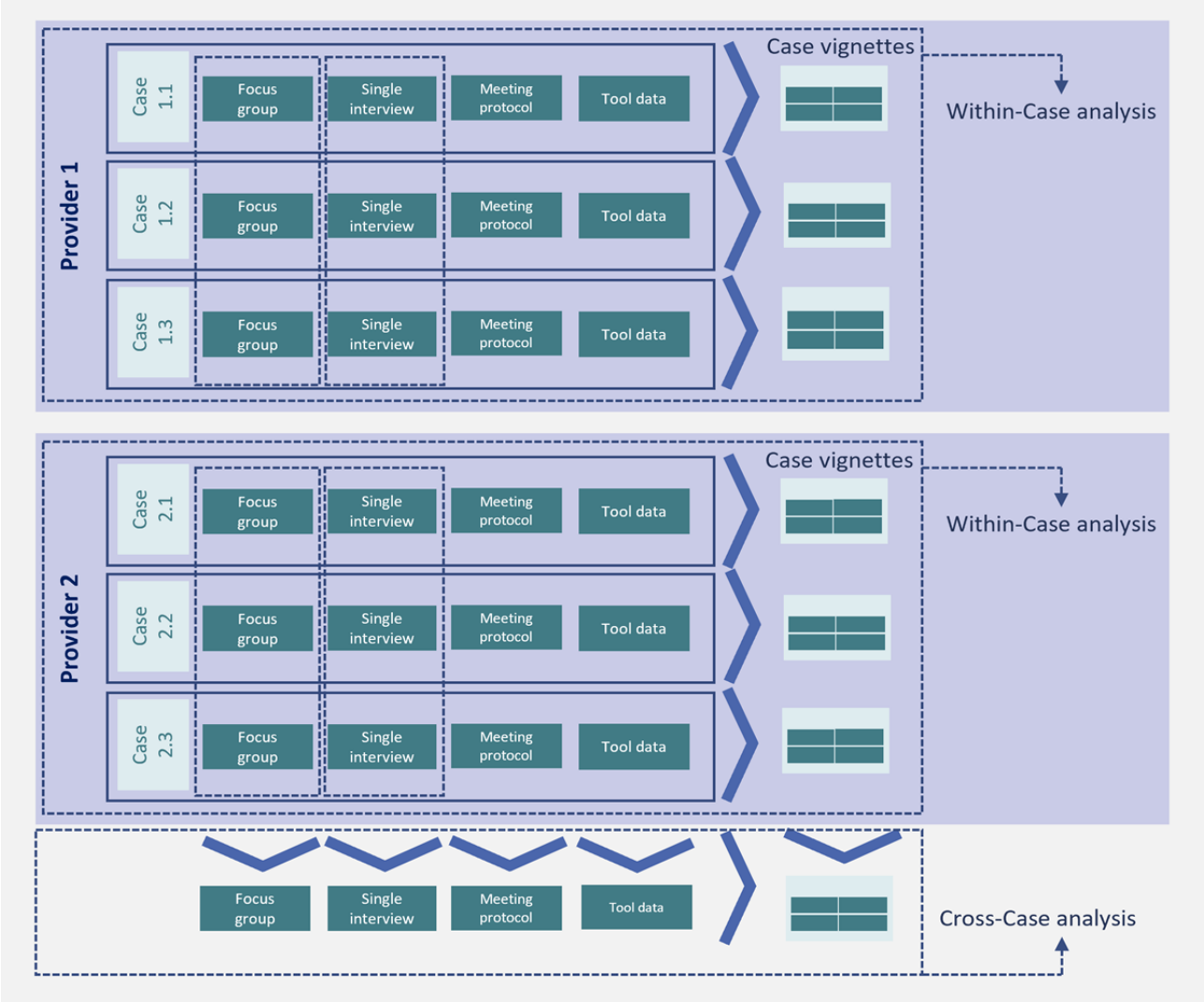
Data From the Digital Voice Channel

Relevant for ADVICE are the response rate, the frequency of topics mentioned, reactions or responses to comments, and, above all, the consistency of the topics mentioned in the interviews. Furthermore, the digital voice channel data ought to corroborate interview statements, for example, indicating infrequent usage of the free comment fields or the absence of any response. It is important to note that this is an iterative process, using different data to get deeper and deeper in understanding the case.

Data Analysis

The principle of data analysis in the case study ADVICE follows the rule of playing with the data and searching for promising patterns, insights, or concepts [44]. Therefore, first, before data analysis, all qualitative and quantitative data will be transferred into MAXQDA Analytics pro software (version 22.2.1; Udo Kuckartz, VERBI software GmbH), where they will be analyzed. Data collection and analysis will be conducted partially in parallel because the case study is an iterative process. The data analysis will be carried out in 2 stages based on the analysis of the individual cases within-case analysis and a subsequent cross-case analysis**,** as shown in Figure 2.

Figure 2. Data analysis.



First, in the *within-case analysis*, the individual cases will be analyzed as independent units, and patterns and peculiarities will be identified. The aim is to obtain an in-depth understanding of the specificities of each case. Therefore, all data from every embedded unit will be comprehensively analyzed. For this step, every unit of analysis (focus group interviews, single interviews, protocols, and data from the digital voice channel) will be repeatedly read and reread by the first author. In this iterative process, first, all focus group interviews will be analyzed in light of these results, and the first author will pursue further data collection within the single interviews. Before the interviews are conducted, the interview guide will be updated based on the results from the focus group interviews. Then, all single interviews from every embedded unit will be interpreted. Afterward, a case description will be written for each case with the results of the interviews (plus data from the digital voice channel). This within-analysis is oriented toward qualitative content analysis with regard to Schreier [48].

Based on the research questions, the first author will derive the categories based on the body of knowledge and then further add to or expand on the inductive codes. To be specific, after the first author has determined the deductive category system based on the theoretical framework, all coding units and context units will be determined in consultation with the research team (ie, sample coding). The category system will then be additionally extended by inductive codes. For example, further categories will be formed that are not represented by the coding guide but are relevant to the understanding of the case. Inductive coding will be performed by the first author and selectively verified with other researchers. In summary, a qualitative content analysis with a theoretical deductive framework will be conducted, that is, a deductive-inductive content analysis [48].

In the subsequent second stage of the cross-case analysis, the analyzed data from the embedded units will be compared with each other in a comparative analysis, and possible distortions caused by individual cases will be identified. The results of the within-analysis will provide content for the case vignettes and serve as a basis for the cross-analysis [44]. In this analysis step, the stacking comparable strategy will be used. This strategy includes case-oriented and variable-oriented cross-case analysis strategies. Each case is analyzed with a standard set of variables (based on the results of the within-analysis). After each case is understood in itself (the results will be the case vignettes), a matrix will be used to analyze each case in depth. From this, patterns and differences will be deduced. The case vignettes will include a case study report title, case description summary

based on the within-case analysis, analyst view, context information, issues, and uniqueness, among others [45,58]. The goal is to understand how the use of the digital voice channel addresses employee voice not only in every embedded single case but also on a meta-level in long-term care. The presentation of the results will follow the format (graphic, matrix, or networks) proposed by Miles et al [58].

Ethical Considerations

All participants will receive overall information about the study and be able to agree to participate and to fill out the informed consent form before the interview. Participation will only take place if the written consent form has been signed by the interviewee. The data will be processed in accordance with the data protection legislation in force, pursuant to the GDPR. The personal data collected (age, sex, professional activity, etc) are processed exclusively in an anonymous form and saved separately from the audio data (such as statements made in interviews).

Ethics approval for the empirical parts of the project was given by the ethics committee of Witten/Herdecke University (S230/2022). The ethics vote was submitted under an expedited procedure in accordance with the rules of procedure of the Ethics Committee of the University of Witten/Herdecke, as it does not raise any difficult ethical or legal issues. Furthermore, no review was requested.

Results

The results will provide insight into how digital voice channels can be used in long-term care to address employee voice. We expect to find how the digital voice channel can empower nurses to speak up and consequently create a better work environment.

The recruitment of the cases from the health care providers took place in consultation with the management and human resources managers. The decision was based, particularly in health care provider 2, on which facilities are already working with the digital voice channel. The recruitment for the focus group interviews and the single interviews began in June 2023.

Data collection began in August 2023, and from a current perspective, the first results are expected in summer 2024.

Discussion

Summary

To retain nurses in a health care organization, it is essential that they have a voice and that their views are heard. Reports from nurses working in the Austrian long-term care sector suggest that working conditions need to be addressed [2,3]. The international PTE-LTC program addresses these challenges. Specifically, this program focuses on empowering nurses, giving them a voice to actively participate in improving outcomes for residents [7]. Employee voice is 1 way of involving employees. It means that employees are able to influence work-related decisions through their feedback [12-15].

The current literature shows that employee voice has a positive impact on reducing burnout, promoting job satisfaction [16], and managing change [11,17]. It is important to note that most of the available data on employee voice in health care focuses on 1 aspect of employee voice, namely speaking up regarding patient safety and managing errors [34-36]. This leads to an unclear understanding of the phenomenon of employee voice in health care [36]. Lainidi et al [36] argue that individual approaches and evaluations are needed to gain a deeper understanding of employee voice, especially in different settings. Recent developments in digital and communication technology have opened new opportunities to address employee voice, for example, as a company mirror or digital voice channel [18-20]. Analyses show that a digital voice channel can have a positive impact on employee identification and commitment to the organization [16]. However, it depends on the organizational culture [16,23,24]. In summary, the research gap is the understanding of employee voice in a specific setting, namely long-term care, and the analysis of the use of a digital voice channel. The NPL [41,42] is used in ADVICE to better understand how the social context influences how the digital voice channel gets used to address employee voice.

We assume that the results will provide insight into how digital voice channels can be used in long-term care to address employee voice. We expect to find how the digital voice channel can empower nurses to speak up and, consequently, create a better work environment. Furthermore, we aim to understand how managers deal with the data from the digital voice channel, whether they use the data, and how they respond to trends and comments in the tool. In summary, the results may help to understand how employee voice behavior is affected by the digital voice channel and to identify what opportunities arise for the employees and for the organization through a digital voice channel.

Strengths and Limitations

We are aware of the different settings, and we try to develop a case understanding of individual cases through our within-case analysis and gain a deeper understanding of employee voice in health care providers by analyzing their similarities and differences. The authors therefore also refer to the NORDCARE report [3], which includes both residential long-term care and mobile care under the term long-term care.

The strength of the method proposed herein lies in the fact that the case study approach addresses the individual experiences of every employee and is oriented to the social processes in the daily routine to understand the use of a new approach to communication (digital voice channel) [44]. These are precisely the aspects that are addressed in the calls for future research on the use of new digital technologies [20,38,39] and employee voice [36]. Potential challenges can be encouraging employees to participate in interviews since these will take up working time, which is very limited due to staff shortages. This challenge can be addressed by attempting to allow the interviews to be completed during duty hours during the recruitment process in consultation with the health care providers. It must be mentioned that the generalizability of case studies is limited based on the high level of specificity and the small number of cases [62]. Furthermore, there is a possibility that, due to the way in which the scope of the data integration of the qualitative and

quantitative data will evolve over the course of the work, the case study will also become a mixed methods case study. This may result from the fact that more attention per individual case and subcase is needed in the data integration process that will occur between the qualitative and quantitative research steps [45]. Both interview bias and selection bias must be considered. Interviewer bias is addressed through constant reflection by the research team. The selection of the health care providers is based on the fact that they are the only ones in Austria who use this digital voice channel. The choice of cases is made by the health care provider themselves. Finally, to avoid conflicts of interest, it must be mentioned that the case selection process is undertaken by the company that provides the digital voice channels. It should be noted that the company is not involved in the research process, and moreover, the name of the company is not explicitly mentioned to avoid conflicts of interest.

Importance of This Study

ADVICE also attempts to address the recommendations of Lainidi et al [36] to consider organizational and employee perspectives to better understand the concepts of voice and silence in a specific context (long-term care). Of course, individual case specifics are considered in the case descriptions, but the main focus is on the digital voice channel used in residential long-term care and home care facilities. At the organizational level, research can help to improve the attractiveness of the workplace by understanding how to give employees a voice.

Acknowledgments

The authors are grateful to Ann Kolanowski, PhD, RN, FAAN (Professor Emerita of Nursing; Professor Emerita of Psychiatry; Penn State Hershey College of Medicine) for her constructive feedback on a draft of this manuscript. This paper is financially supported, thankfully, by the IMC Krems.

Data Availability

Data sharing is not applicable as this is a protocol paper where no data sets were generated or analyzed.

Authors' Contributions

All authors made significant contributions to the research protocol, contributed to editing, and approved the final version of the manuscript. The authors attest that there was no use of generative artificial intelligence technology in the generation of text, figures, or other informational content of this manuscript. DeepL Write (free version; DeepL SE) was only used for spelling and grammar correction.

Conflicts of Interest

None declared.

References

1. International Council of Nurses Policy Brief. The global nursing shortage and nurse retention. International Council of Nurses. 2021. URL: https://www.icn.ch/sites/default/files/inline-files/ICN%20Policy%20Brief_Nurse%20Shortage%20and%20Retention.pdf [accessed 2023-03-13]
2. Arbeitsbedingungen in Pflegeberufen-sonderauswertung des Österreichischen arbeitsklima index. Federal Ministry of Labour, Social Affairs, Health and Consumer Protection. 2021. URL: https://broschuerenservice.sozialministerium.at/Home/Download?publicationId=784 [accessed 2023-10-28]
3. Bauer G, Rodrigues R, Leichsenring K. Arbeitsbedingungen in der langzeitpflege aus sicht der beschäftigten in Österreich. Eine untersuchung auf basis der internationalen NORDCARE-Befragung. Euro Centre Report. 2018. URL: https://www.euro.centre.org/downloads/detail/3288 [accessed 2023-10-28]
4. Siegel EO, Kolanowski AM, Bowers BJ. A fresh look at the nursing home workforce crisis: transforming nursing care delivery models. Res Gerontol Nurs 2023;16(1):5-13 [FREE Full text] [doi: 10.3928/19404921-20230104-01] [Medline: 36692436]
5. Bamford-Wade A, Moss C. Transformational leadership and shared governance: an action study. J Nurs Manag 2010;18(7):815-821 [FREE Full text] [doi: 10.1111/j.1365-2834.2010.01134.x] [Medline: 20946217]
6. Porter-O'Grady T. Re: Joseph, M. and Bogue, R. (2016). A theory-based approach to nursing shared governance. 64. Pp. 339 to 351. Nurs Outlook 2016;64(6):527-529 [FREE Full text] [doi: 10.1016/j.outlook.2016.09.001] [Medline: 27751524]
7. Pathway to excellence in long term care. American Nurses Credentialing Center. 2016. URL: https://www.nursingworld.org/organizational-programs/pathway/overview/pathway-to-excellence-in-long-term-care/#:~:text=The%20Pathway%20to%20Excellence%20in,care%20for%20patients%20may%20apply [accessed 2023-03-13]
8. Aiken LH, Buchan J, Ball J, Rafferty AM. Transformative impact of magnet designation: England case study. J Clin Nurs 2008;17(24):3330-3337 [FREE Full text] [doi: 10.1111/j.1365-2702.2008.02640.x] [Medline: 19146592]

9. Kutney-Lee A, Germack H, Hatfield L, Kelly S, Maguire P, Dierkes A, et al. Nurse engagement in shared governance and patient and nurse outcomes. J Nurs Adm 2016;46(11):605-612 [FREE Full text] [doi: 10.1097/NNA.0000000000000412] [Medline: 27755212]
10. McHugh MD, Kutney-Lee A, Cimiotti JP, Sloane DM, Aiken LH. Nurses' widespread job dissatisfaction, burnout, and frustration with health benefits signal problems for patient care. Health Aff (Millwood) 2011;30(2):202-210 [FREE Full text] [doi: 10.1377/hlthaff.2010.0100] [Medline: 21289340]
11. Rodríguez-García MC, Márquez-Hernández VV, Belmonte-García T, Gutiérrez-Puertas L, Granados-Gámez G. Original research: how magnet hospital status affects nurses, patients, and organizations: a systematic review. Am J Nurs 2020;120(7):28-38. [doi: 10.1097/01.NAJ.0000681648.48249.16] [Medline: 32541337]
12. Lavelle J, Gunnigle P, McDonnell A. Patterning employee voice in multinational companies. Hum Relat 2010;63(3):395-418. [doi: 10.1177/0018726709348935]
13. Wilkinson A, Barry M, Morrison E. Toward an integration of research on employee voice. Hum Resour Manag Rev 2020;30(1):100677. [doi: 10.1016/j.hrmr.2018.12.001]
14. Morrison EW. Employee voice and silence: taking stock a decade later. Annu Rev Organ Psychol Organ Behav 2023;10(1):79-107. [doi: 10.1146/annurev-orgpsych-120920-054654]
15. Dundon T, Wilkinson A, Marchington M, Ackers P. The meanings and purpose of employee voice. Int J Hum Resour Manag 2004;15(6):1149-1170. [doi: 10.1080/0958519041000167733 59]
16. Holland PJ, Allen BC, Cooper BK. Reducing burnout in Australian nurses: the role of employee direct voice and managerial responsiveness. Int J Hum Resour Manag 2013;24(16):3146-3162 [FREE Full text] [doi: 10.1080/09585192.2013.775032]
17. Kee K, van Wieringen M, Beersma B. The relational road to voice: how members of a low-status occupational group can develop voice behavior that transcends hierarchical levels. J Prof Organ 2021;8(3):253-272 [FREE Full text] [doi: 10.1093/jpo/joab011]
18. Dromey J. Going digital? Harnessing social media for employee voice. Research Paper. 2016. URL: https://www.ipa-involve.com/Handlers/Download.ashx?IDMF=dae0f237-9eb2-461e-8a0c-a3dafb237a5e [accessed 2023-03-13]
19. Ellmer M, Reichel A. Mind the channel! an affordance perspective on how digital voice channels encourage or discourage employee voice. Hum Resour Manag J 2020;31(1):259-276. [doi: 10.1111/1748-8583.12297]
20. Zerth J, Jaensch P, Müller S. Technik, pflegeinnovation und implementierungsbedingungen. In: Jacobs K, Kuhlmey A, Klauber J, Schwinger A, editors. Pflege-Report 2021: Sicherstellung der Pflege: Bedarfslagen und Angebotsstrukturen. Berlin, Heidelberg: Springer Berlin Heidelberg; 2021:157-172.
21. Gibson JJ. The Ecological Approach to Visual Perception. Boston, MA: Houghton Mifflin; 1979.
22. Norman DA. The Design of Everyday Things. New York: Doubleday; 1990.
23. Martin G, Parry E, Flowers P. Do social media enhance constructive employee voice all of the time or just some of the time? Hum Resour Manag J 2015;25(4):541-562. [doi: 10.1111/1748-8583.12081]
24. Mao CM, DeAndrea DC. How anonymity and visibility affordances influence employees' decisions about voicing workplace concerns. Manag Commun Q 2018;33(2):160-188 [FREE Full text] [doi: 10.1177/0893318918813202]
25. Gerlach F, Greiner W, Jochimsen B, von Kalle C, Meyer G, Schreyögg J, et al. Digitalisierung für gesundheit–ziele und rahmenbedingungen eines dynamisch lernenden gesundheitssystems. Executive Summary on the SVR-Report 2021. 2021. URL: https://www.svr-gesundheit.de/fileadmin/Gutachten/Gutachten_2021/Executive_Summary_Deutsch.pdf [accessed 2023-03-13]
26. Nembhard IM, Edmondson AC. Making it safe: the effects of leader inclusiveness and professional status on psychological safety and improvement efforts in health care teams. J Organ Behavior 2006;27(7):941-966. [doi: 10.1002/job.413]
27. Alingh CW, van Wijngaarden JDH, van de Voorde K, Paauwe J, Huijsman R. Speaking up about patient safety concerns: the influence of safety management approaches and climate on nurses' willingness to speak up. BMJ Qual Saf 2019;28(1):39-48. [doi: 10.1136/bmjqs-2017-007163] [Medline: 29954948]
28. Weiss M, Morrison EW, Szyld D. I like what you are saying, but only if i feel safe: Psychological safety moderates the relationship between voice and perceived contribution to healthcare team effectiveness. Front Psychol 2023;14:1129359 [FREE Full text] [doi: 10.3389/fpsyg.2023.1129359] [Medline: 37139001]
29. Vauk S, Seelandt JC, Huber K, Grande B, Kolbe M. Exposure to incivility does not hinder speaking up: a randomised controlled high-fidelity simulation-based study. Br J Anaesth 2022;129(5):776-787. [doi: 10.1016/j.bja.2022.07.050] [Medline: 36075775]
30. Barlow M, Morse KJ, Watson B, Maccallum F. Identification of the barriers and enablers for receiving a speaking up message: a content analysis approach. Adv Simul (Lond) 2023;8(1):17 [FREE Full text] [doi: 10.1186/s41077-023-00256-1] [Medline: 37415244]
31. Bienefeld N, Kolbe M, Camen G, Huser D, Buehler PK. Human-AI teaming: leveraging transactive memory and speaking up for enhanced team effectiveness. Front Psychol 2023;14:1208019. [doi: 10.3389/fpsyg.2023.1208019] [Medline: 37599773]
32. Martin GP, Aveling EL, Campbell A, Tarrant C, Pronovost PJ, Mitchell I, et al. Making soft intelligence hard: a multi-site qualitative study of challenges relating to voice about safety concerns. BMJ Qual Saf 2018;27(9):710-717 [FREE Full text] [doi: 10.1136/bmjqs-2017-007579] [Medline: 29459365]

33. Martin GP, Chew S, Dixon-Woods M. Uncovering, creating or constructing problems? Enacting a new role to support staff who raise concerns about quality and safety in the English National Health Service. Health (London) 2021;25(6):757-774 [FREE Full text] [doi: 10.1177/1363459319901296] [Medline: 31984819]
34. Jones A, Blake J, Adams M, Kelly D, Mannion R, Maben J. Interventions promoting employee "speaking-up" within healthcare workplaces: a systematic narrative review of the international literature. Health Policy 2021;125(3):375-384. [doi: 10.1016/j.healthpol.2020.12.016] [Medline: 33526279]
35. O'Donovan R, McAuliffe E. A systematic review exploring the content and outcomes of interventions to improve psychological safety, speaking up and voice behaviour. BMC Health Serv Res 2020;20(1):101 [FREE Full text] [doi: 10.1186/s12913-020-4931-2] [Medline: 32041595]
36. Lainidi O, Jendeby MK, Montgomery A, Mouratidis C, Paitaridou K, Cook C, et al. An integrative systematic review of employee silence and voice in healthcare: what are we really measuring? Front Psychiatry 2023;14:1111579 [FREE Full text] [doi: 10.3389/fpsyt.2023.1111579] [Medline: 37304444]
37. Mair FS, May C, O'Donnell C, Finch T, Sullivan F, Murray E. Factors that promote or inhibit the implementation of e-health systems: an explanatory systematic review. Bull World Health Organ 2012;90(5):357-364 [FREE Full text] [doi: 10.2471/BLT.11.099424] [Medline: 22589569]
38. Krick T, Huter K, Domhoff D, Schmidt A, Rothgang H, Wolf-Ostermann K. Digital technology and nursing care: a scoping review on acceptance, effectiveness and efficiency studies of informal and formal care technologies. BMC Health Serv Res 2019;19(1):400 [FREE Full text] [doi: 10.1186/s12913-019-4238-3] [Medline: 31221133]
39. Seibert K, Domhoff D, Huter K, Krick T, Rothgang H, Wolf-Ostermann K. Application of digital technologies in nursing practice: results of a mixed methods study on nurses' experiences, needs and perspectives. Z Evid Fortbild Qual Gesundhwes 2020;158-159:94-106 [FREE Full text] [doi: 10.1016/j.zefq.2020.10.010] [Medline: 33223491]
40. Ong BN, Hodgson D, Small N, Nahar P, Sanders C. Implementing a digital patient feedback system: an analysis using normalisation process theory. BMC Health Serv Res 2020;20(1):387 [FREE Full text] [doi: 10.1186/s12913-020-05234-1] [Medline: 32381075]
41. May C, Finch T. Implementing, embedding, and integrating practices: an outline of normalization process theory. Sociology 2009;43(3):535-554. [doi: 10.1177/0038038509103208]
42. May CR, Mair F, Finch T, MacFarlane A, Dowrick C, Treweek S, et al. Development of a theory of implementation and integration: normalization process theory. Implement Sci 2009;4:29 [FREE Full text] [doi: 10.1186/1748-5908-4-29] [Medline: 19460163]
43. McEvoy R, Ballini L, Maltoni S, O'Donnell CA, Mair FS, Macfarlane A. A qualitative systematic review of studies using the normalization process theory to research implementation processes. Implement Sci 2014;9:2 [FREE Full text] [doi: 10.1186/1748-5908-9-2] [Medline: 24383661]
44. Yin RK. Case Study Research and Applications: Design and Methods. 6th Edition. Los Angeles: SAGE Publications; 2018.
45. Creswell JW. Research Design: Qualitative, Quantitative, and Mixed Methods Approaches. 3rd Edition. Los Angeles: SAGE Publications; 2009.
46. Fringer A, Schnepp W. Case study methodik-methodologie-forschungsstrategie. J Qual Res Nurs Health Sci 2015;01:62-70 [FREE Full text]
47. Mey G, Mruck K. Qualitative interviews. In: Naderer G, Balzer E, editors. Qualitative Marktforschung in Theorie und Praxis. Grundlagen, Methoden und Anwendungen. Qualitative Interviews. Wiesbaden: Gabler; 2007.
48. Schreier M. Ways of doing qualitative content analysis: disentangling terms and terminologies. Forum Qual Soc Res 2014;15(1):27.
49. Baker GR. The contribution of case study research to knowledge of how to improve quality of care. BMJ Qual Saf 2011;20(Suppl_1):i30-i35 [FREE Full text] [doi: 10.1136/bmjqs.2010.046490] [Medline: 21450767]
50. Sandelowski M. "Casing" the research case study. Res Nurs Health 2011;34(2):153-159. [doi: 10.1002/nur.20421] [Medline: 21381044]
51. Peters MDJ, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. Int J Evid Based Healthc 2015;13(3):141-146. [doi: 10.1097/XEB.0000000000000050] [Medline: 26134548]
52. Systematic reviews-research guide. Murdoch University. 2022. URL: https://libguides.murdoch.edu.au/systematic/defining#s-lib-ctab-22166366-4 [accessed 2023-03-13]
53. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med 2018;169(7):467-473 [FREE Full text] [doi: 10.7326/M18-0850] [Medline: 30178033]
54. Nordhausen T, Hirt J. 10 Schritte zur systematischen Literaturrecherche. RefHunter. Systematische Literaturrecherche. URL: https://refhunter.org/research_support/rechercheschritte/ [accessed 2023-03-13]
55. Program, for screening and data extraction from literature. Covidence. URL: https://www.covidence.org/ [accessed 2023-03-13]
56. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ 2014;348:g1687 [FREE Full text] [doi: 10.1136/bmj.g1687] [Medline: 24609605]

57. Möhler R, Köpke S, Meyer G. Criteria for reporting the development and evaluation of complex interventions in healthcare: revised guideline (CReDECI 2). Trials 2015;16:204 [FREE Full text] [doi: 10.1186/s13063-015-0709-y] [Medline: 25935741]
58. Miles MB, Huberman AM, Saldaña J. Qualitative Data Analysis: A Methods Sourcebook. Fourth edition, International student edition. Thousand Oaks, Kalifornien, Vereinigte Staaten: SAGE; 2020.
59. Johnson MJ, May CR. Promoting professional behaviour change in healthcare: what interventions work, and why? A theory-led overview of systematic reviews. BMJ Open 2015;5(9):e008592 [FREE Full text] [doi: 10.1136/bmjopen-2015-008592] [Medline: 26423853]
60. Helfferich C. Die Qualität qualitativer Daten: Manual für die Durchführung qualitativer Interviews. Wiesbaden: VS Verlag für Sozialwissenschaften | Springer Fachmedien Wiesbaden GmbH; 2005.
61. Dresing T, Pehl T. Praxisbuch Interview, 8. Auflage. Wiesbaden: VS Verlag für Sozialwissenschaften; 2018. URL: https://www.audiotranskription.de/wp-content/uploads/2020/11/Praxisbuch_08_01_web.pdf [accessed 2023-01-05]
62. Widdowson M. Case study research methodology. Int J Trans Anal Res Pract 2011;2(1):25-34 [FREE Full text]

Abbreviations

ADVICE: Understanding Employee Voice Behavior (acronym for the study)
CReDECI 2: Criteria for Reporting and Evaluation of Complex Interventions
MeSH: Medical Subject Headings
NPT: normalization process theory
PICO: population, interest, and context
PRISMA ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
PTE-LTP: Pathway to Excellence in Long Term Care
TIDieR: Template for Intervention Description and Replication

Edited by A Mavragani; submitted 29.04.23; peer-reviewed by L Peterson, M Kolbe; comments to author 13.10.23; revised version received 02.11.23; accepted 30.11.23; published 02.02.24.

Please cite as:
Kepplinger A, Braun A, Fringer A, Roes M
Understanding Employee Voice Behavior Through the Use of Digital Voice Channel in Long-Term Care: Protocol for an Embedded Multiple-Case Study
JMIR Res Protoc 2024;13:e48601
URL: https://www.researchprotocols.org/2024/1/e48601
doi:10.2196/48601
PMID:38306164

Protocol

Understanding the Acceptability of Broadly Neutralizing Antibodies for HIV Prevention Among At-Risk Populations and Feasibility Considerations for Product Introduction in India: Protocol for a Qualitative Study

Joyeeta Mukherjee[1], PhD; Shruta Rawat[2], MSc; Saif ul Hadi[1], MA; Pritha Aggarwal[1], MSc; Venkatesan Chakrapani[3], MD, PhD; Pratyasha Rath[4], MA; Pallavi Manchi[4], MA; Srikrishnan Aylur[5], MBA; Shelly Malhotra[6], MA; Margaret Keane[6], MS, MBA; Alok Gangaramany[4], MBA

[1]International AIDS Vaccine Initiative, Gurugram, India

[2]The Humsafar Trust, Mumbai, India

[3]Centre for Sexuality and Health Research And Policy, Chennai, India

[4]The Final Mile, Mumbai, India

[5]Yeshwant Rao Gaitonde Centre for AIDS Research and Education, Chennai, India

[6]International AIDS Vaccine Initiative, New York, NY, United States

Corresponding Author:
Joyeeta Mukherjee, PhD
International AIDS Vaccine Initiative
Unit no. 810, 8th Floor, Emaar Capital Tower - 1
Mehrauli Gurugram Road
Gurugram, 122002
India
Phone: 91 8588838927
Email: jmukherjee@iavi.org

Abstract

Background: Acceptability and preference research play a crucial role in the design, evaluation, and implementation of any new prevention product in any geographical setting. They also play a critical role in the development of clinical guidelines and policies. A wide range of acceptability studies have been conducted in diverse general and key populations for various new HIV prevention products worldwide. As clinical development strategies are being developed for clinical studies of broadly neutralizing antibodies (bNAbs) as potential HIV prevention products, appropriately tailoring them to address the type of HIV epidemic at hand would be critical for efficient uptake within in-country public health systems and decrease adoption and adherence challenges. Accomplishing this will require comprehensive acceptability and feasibility studies to inform multisectoral efforts that increase access to these products and national policies supportive of access to health care for those in most need. Thus, it is both opportune and important to undertake focused efforts toward informing product development strategies.

Objective: This study aims to understand preferences for product attributes and key behavioral factors influencing adoption and uptake of bNAb prevention products among end-users including female sex workers, men who have sex with men, transgender women, people who inject drugs, and adolescent girls and young women in India and understand the key health system and programmatic perspectives toward the introduction of bNAb prevention products from health service providers and policy makers in India.

Methods: A multisite study will be conducted in Delhi, Mumbai, and Chennai to capture the differences in perspectives among diverse end-users and key informants across the country. The study will use a multimethods design using focus group discussions, in-depth interviews, simulated behavioral experiments, and key informant interviews. A total of 30 focus group discussions, 45 in-depth interviews, 15 simulated behavioral experiments sessions, and 15 key informant interviews will be conducted across 3 sites.

Results: The data collected and analyzed will enable insights on which specific product attributes matter the most to the populations and why some attributes are less preferred; contextual drivers of preferences and choices at individual, interpersonal, social, and structural levels; and relative positioning of bNAb products among other potential HIV prevention products. Insights

from the health service providers and policy makers will provide a critical understanding of the need perception of the potential product in the existing product landscape and what additional efforts and resources are required for potential introduction, delivery, and uptake of the bNAb products in the Indian context.

Conclusions: Insights generated from the abovementioned objectives will represent perspectives of populations of interest across geographies in India, will provide an overview of the acceptability of bNAb products and the feasibility of their introduction in this region, and will inform product development strategies.

International Registered Report Identifier (IRRID): DERR1-10.2196/47700

(JMIR Res Protoc 2024;13:e47700) doi:10.2196/47700

KEYWORDS

HIV; key populations; acceptability; feasibility; product attributes; end-user preferences; broadly neutralizing antibodies; simulated behavioral experiments; qualitative study

Introduction

HIV Prevention Product Landscape

HIV/AIDS has been one of the most devastating epidemics in human history. Since the official recognition of *AIDS* in the early 1980s, a total of 77 million people have been infected globally and approximately half of them have succumbed to the disease. Although effective and affordable antiretroviral (ARV) treatment has transformed HIV from a *death sentence* to a chronic, manageable disease, people with HIV have shorter life expectancy than those without the virus. New infections continue to fuel the epidemic while disproportionately affecting low- and middle-income countries. India has the third largest HIV epidemic in the world, with 2.1 million people currently living with HIV, and the sixth highest incidence with 88,000 new infections per year [1]. In addition, the high variability and ever-changing face of the virus along with the persistent marginalization and stigmatization of populations most at risk remain critical challenges in controlling the spread of HIV infection [2].

Current HIV prevention strategies include a range of behavioral and biomedical interventions, including behavior change campaigns, promotion of consistent use of male and female condoms, use of clean needles and syringes, opioid substitution therapy (eg, buprenorphine), voluntary male medical circumcision, and biomedical tools such as the use of ARV medication as preexposure prophylaxis (PrEP), and the treatment of people living with HIV to reduce viral load to undetectable levels and prevent onward transmission (treatment as prevention). There are several new HIV prevention products in the pipeline that have the potential to reduce the spread of HIV infection, including next-generation ARVs, especially long-acting ARVs [3], intravaginal (dapivirine) ring [4], preventive vaccines, and broadly neutralizing monoclonal antibodies (bNAbs) [5-11]. Multiple studies have highlighted that a single product will not be preferred by all end- users under all circumstances [12,13] because there is a constant evolution in the life journeys, social contexts, and product attributes. Thus, different products may be preferred by end-users at different times. Introduction of a new product does not necessarily mean that the importance or relevance of existing products has been replaced. It is important to identify the unique value of novel interventions and understand end-user perspectives to highlight their value addition to the current prevention landscape. There is a need to create a toolbox and choice sets that will cater to the unique needs of end-users [14]. bNAbs are antibodies that can potentially be used to fight against multiple strains of HIV and are poised to have advantages over other preventive drugs such as the ability to target and act against a broad spectrum of viral strains, longer half-life and hence less frequent dosage, no risk of development of resistance to ARVs used for treatment, and comparatively safe with rare cases of adverse side effects [11,15-19]. More than 200 different bNAbs targeting HIV have been isolated to date, varying significantly in their coverage of global HIV isolates (breadth) as well as the amount required to neutralize the virus (potency). bNAbs have been proven to be safe for humans and can work effectively in preventing HIV infection. The antibody-mediated prevention trial found that an antibody called VRC01 could prevent HIV infection with specific HIV strains when administered every 8 weeks to adults [20]. In addition, combinations of bNAbs engineered with extended half-lives and increased potency are also being developed and tested in trials to ensure lower dosage and lesser frequency that would make the end product accessible and affordable. The World Health Organization (WHO) has also recently published the preferred product characteristics for monoclonal antibodies for HIV prevention [21], and it highlights that based on the needs of various target populations, the antibodies should have longer lasting duration of protection, have minimal side effects, and be delivered as injections, among others. In India, most of the abovementioned prevention options have not yet been rolled out as a part of the national policy, and hence, there is a need to understand the acceptability for bNAbs and their preference vis-à-vis other potential options.

Acceptability and Feasibility Studies for bNAbs

Value of Acceptability and Feasibility Studies

Acceptability and preference research play a crucial role in the design, evaluation, and implementation of any new product in any geographical setting. They also play a critical role in the development of clinical guidelines and policies [22]. A wide range of acceptability studies have been conducted in diverse general and key populations for HIV prevention products including women, adolescent boys and girls, men who have sex with men (MSM), female sex workers (FSWs), people who inject drugs (PWID), and transgender women (TGW) [23-26]. These studies have focused on prevention products such as oral and injectable PrEP, vaginal and rectal microbicides, vaginal

rings, and future HIV vaccines [22,26-29]. The main drivers of prevention product adoption and uptake include product effectiveness, cost, absence of side effects, and multipurpose protection against sexually transmitted diseases and pregnancy [30]. Acceptability studies have shown that emotional and intuitive decision-making for a product choice is also driven by factors such as sexual satisfaction, dimensions of trust, self-efficacy, and sociocultural environments [26,31]. There is evidence for differential preference for prevention products among different populations. For example, in South Africa, FSWs preferred injectable products over oral PrEP and microbicide gel, adolescents preferred a potential HIV vaccine and expressed dislike for a vaginal ring, and MSM preferred rectal microbicides [24,25]. Relative importance of specific product attributes also varied across target populations. For example, the route of PrEP administration was found to be the most important attribute for prospective end-users in Peru, Ukraine, India, and Botswana; FSWs in Kenya; and young women in South Africa [32], whereas the PrEP dispensing site was the most important attribute for participants from Uganda and MSM in South Africa and the second most important attribute for FSWs in Ukraine [32].

There are several standard qualitative methods for assessing the acceptability of an intervention for the target population and setting. Two common methods are focus group discussions (FGDs) and in-depth interviews (IDIs). Moderated FGDs allow for understanding of group dynamics including similarities and differences and allow to probe further on particular topics as they come up in the discussion. This type of interaction generally results in a deeper understanding of the forces in a community that may impede or facilitate the implementation of effective interventions. IDIs are conducted in a one-on-one setting with members of the target communities. They allow for deeper probing to understand more details, have nuanced understanding of sensitive topics, and have an opportunity to monitor changes in tone and body language, which is also an important factor in eliciting key responses.

For the successful development and adoption of any product, it is critical that perspectives from all service providers including health care professionals and community "gatekeepers" are taken into account in the development process [33,34]. Thus, there is a need to gather evidence from diverse populations and multitude of related stakeholders across geographies in India and focus on understanding their perspectives on potential new products such as bNAbs and preferences of different product attributes. These are often conducted through key informant interviews (KIIs).

In India, acceptability and feasibility studies have been conducted for various microbicides and PrEP [35-42]. These studies have been scattered over time and have been restricted to a few geographical locations and key populations. Thus, there is a need to gather evidence from diverse populations and multitude of related stakeholders across geographies in India and also focus on perspectives with respect to the potential new product—bNAbs.

Behavioral Science for Contextualized Understanding of End-User Decision-Making

Apart from the aforementioned methods, there are other qualitative research methods that are necessary to complement some of the emerging insights from the potential end-users. It has often been observed that studies conducted to explore preferences for hypothetical products or willingness to participate in hypothetical trials have shown differences in the stated preferences and intentions versus the eventual decisions and observed behavior of end-users [43-45]. In Kenya, an observational cohort study reported a 90% willingness to participate in future trials; however, during actual trial recruitment, only 30% were willing to actually enroll [44]. In a real-time scenario, end-users may be presented with multiple contextual trade-offs as well as nonconscious factors that may influence their decision-making, and hence, stated versus revealed preferences may be different [45]. It has also been reported that hypothetical choice experiments with end-users provide relatively satisfactory predictive results for positive choices, but they are less effective for predicting negative choices [43]. Thus, to premeditate and elicit the "say-do" gap, one of the useful methods deployed by behavioral scientists is to identify and analyze shortcuts known as heuristics in action, which take off the cognitive load of decision-making and help anticipate and explain potential avenues for gaps between the stated intention and action [46,47].

The cognitive process marking the final behaviors exhibited and decisions made by prospective end-users may be a mix of conscious and nonconscious factors and, hence, cannot always be brought out through in-person discussions alone. Therefore, the application of behavioral science in a simulated context has been found to be extremely beneficial for deciphering the key drivers of decisions and behaviors. In such a situation, the participants in a study do not just have to talk about their past or future decisions but have to actively make a decision in real time in a simulated environment. This provides researchers with a better understanding of the decision pathways of prospective end-users as well as potential aspects of say-do gaps to inform the design and development of products. Toward this, Ethnolab is a behavioral research methodology that often uses a Conundrum game [48] to deploy scenarios based on the preliminary qualitative research findings in a simulated environment and observe user choices in real time. The method has been used in several sociobehavioral and acceptability studies for health programs and interventions, including voluntary male medical circumcision decision-making in Zimbabwe and Zambia [48]; understanding HIV prevention for adolescent girls and young women (AGYW) in South Africa [49]; and estimating the impact of nonconscious drivers of human behavior among pregnant women and mothers of infants as well as with frontline workers on reproductive, maternal, newborn, and child health outcomes in Uttar Pradesh [50].

Population of Interest

As noted previously, India has the third largest HIV epidemic in the world, with 2.1 million people living with HIV, and the sixth highest number of new infections at 88,000 per year [2]. Therefore, ensuring the acceptability and feasibility of any new

potential HIV prevention product in the regional Indian context and needs is critical. The HIV epidemic in India is concentrated among key populations such as FSWs, MSM, PWID, and TGW. The average national prevalences from the government studies range from 1% to 6% (PWID: 6.3%, TGW: 3.1%, MSM: 2.7%, and FSWs: 1.6%) with high interstate variations [51], and access to HIV prevention and treatment services for these populations remain hindered by sociobehavioral and structural barriers including multilayered stigma, discrimination, and marginalization [52,53]. In addition to epidemiological and behavioral diversity across regions and key populations, the rapidly evolving nature of the epidemic as well as changes in risk behaviors owing to the rise in the use of new communication technologies also necessitate systematic and structured inquiry into the health system and end-user contexts and preferences impacting the eventual adoption and uptake of new HIV prevention products such as bNAbs. In addition, although there has been a steady decline in HIV prevalence in India over the last decade, the decline among men has been significantly more rapid than that among women [54]. Similarly, significant gender-based gaps persist in knowledge on HIV prevention among young people (aged 15-24 years); although 75% of the women had heard of HIV (as compared with 89% of men), only 43% of the women in the country knew where to get tested for HIV, and of them, only 14% were ever tested and received results [54]. In addition, the prevalence of intimate partner violence among women of reproductive age (15-49 years) remains high at 22% [54]. Thus, in addition to key populations, it also becomes important to understand the perspectives of AGYW to cover diverse viewpoints and preferences for HIV prevention products, specifically bNAbs.

Study Objectives

The study objectives are as follows:

1. To understand preferences for product attributes and key behavioral factors influencing the adoption and uptake of bNAb prevention products among end-users including FSW, MSM, TGW, PWID, and AGYW populations in India
2. To understand key health system and programmatic perspectives toward the introduction of bNAb prevention products from health service providers and policy makers in India

Methods

Study Population and Sites

The study populations include potential end-user populations such as FSWs, MSM, TGW, PWID, and AGYW and key stakeholders such as health service providers (including frontline health care workers, community-based organization [CBO] or nongovernmental organization [NGO] representatives, and lead community representatives) and policy makers (including national, state, and district level officials or program managers).

The multisite study will be conducted in Delhi, Mumbai, and Chennai regions to ensure coverage of perceptions from North, West, and South India, including differences in perspectives among diverse end-users and stakeholders. These sites also have very high HIV prevalence among the study populations [51].

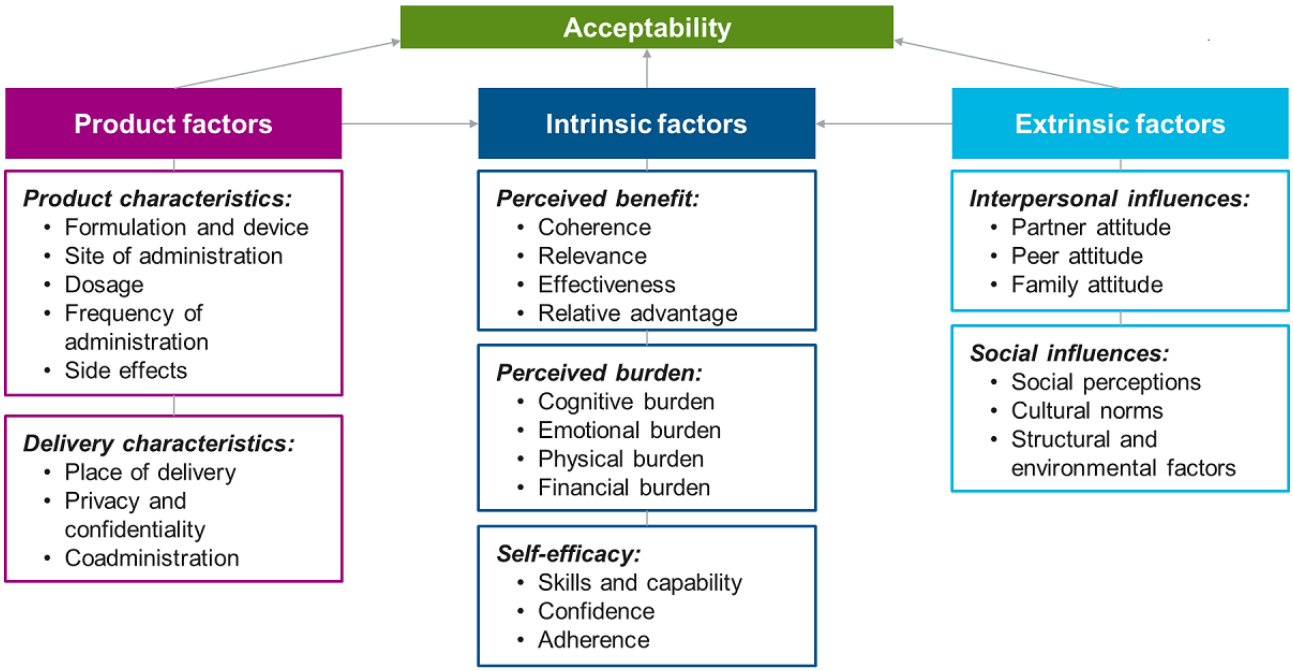
Conceptual Framework

Conceptual Framework for Acceptability

Acceptability may be defined as the extent to which people delivering or receiving a health care intervention consider it to be appropriate based on anticipated or experienced cognitive and emotional responses to the intervention [55]. Several theoretical frameworks are available for understanding acceptability of new HIV prevention products or technologies [41,42,55-57] at the individual and community levels. A recent systematic review proposed a model of acceptability of health interventions, the Theoretical Framework of Acceptability (TFA) [55]. According to TFA, intention to use a health intervention is determined by seven factors: (1) perceived effectiveness, (2) intervention coherence, (3) affective attitudes, (4) burden, (5) ethicality, (6) self-efficacy, and (7) opportunity costs. It was chosen to adapt the TFA to guide exploration of acceptability of bNAbs in this study as it can readily incorporate individual- and community-level influences on attitudes and behavior. The study design was also informed by the conceptual framework developed by Mensch et al [56] to incorporate the various factors operating at individual, interpersonal, community, and structural levels in influencing a person's product-related attitudes and perceptions. In addition to adopting aspects from the social-ecological model, the framework emphasizes the role of actual product-related factors, including product attributes, which also play a role in defining an individual's preferences [56]. Thus, guided by these frameworks, an adapted conceptual framework was used to design this study. In this adaptation, the constructs were embedded within three domains (Figure 1) [55,56]:

1. Product factors: those related to the potential product characteristics (formulation, device, site of administration, dosage, frequency of administration, and side effects) and delivery characteristics (place of delivery, privacy and confidentiality, and coadministration)
2. Intrinsic factors: those related to a person's individual traits and not influenced by external factors. These include a person's those related to a person's individual traits and not influenced by external factors. These include a person's *perceived benefit* of the product (coherence, relevance, effectiveness as well as relative positioning, and advantage of the product among other options), *perceived burden* in using the product (cognitive burden—complexity of dosage and time; emotional burden—fear, anxiety, and discreteness; physical burden—pain, side effects, and impact on sex; and financial burden—cost, travel, and opportunity loss), and *self-efficacy* (skills and capability, confidence, and adherence)
3. Extrinsic factors: those related to external influences including *interpersonal influences* (peer, partner, and family attitude) and *social/structural influences* (social perceptions—stigma and discrimination, cultural norms, and structural or environmental factors).

Figure 1. Conceptual framework for acceptability (adapted from the Theoretical Framework of Acceptability and the conceptual framework for product acceptability).

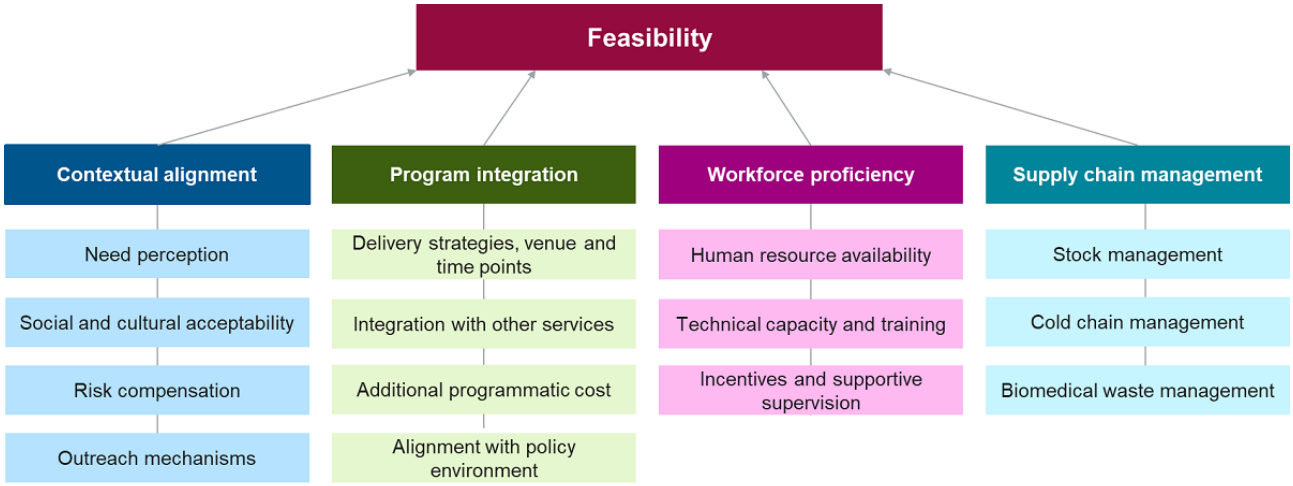


Conceptual Framework for Feasibility

There are multiple factors at the health systems and programmatic levels that service providers such as frontline health care providers, policy makers, and program managers at national, state, and district levels would consider as key issues that are needed for introduction and uptake of bNAbs as HIV prevention products in the future. Thus, complementing the study's conceptual framework for acceptability, which will be used among the end-users, there is a need to have a conceptual framework to assess the feasibility. For this purpose, the framework shown in Figure 2 [58] was adapted from the WHO Framework on Health Systems, which was also used by the WHO for reviewing the impact of new vaccine introduction on immunization and health systems. The broad themes include the following:

1. Contextual alignment: This will enable an understanding of the need perception of the current product, its social and cultural acceptability, the outreach mechanisms that will be needed, and whether there is any risk compensation because of the introduction of this new product.
2. Program integration: This is toward understanding delivery strategies, venues, and time points; possibility of integration with already existing services; additional programmatic costs required; and alignment with the existing policy environment in India.
3. Health care workforce: This will explore the availability of adequate human resources—their distribution and workload, existing technical capacity and additional training needs, and incentives and supportive supervision required to successfully implement the introduction of a potential new product.
4. Integrated supply chain: This will be toward assessing the health systems' readiness in terms of robust stock management, cold chain availability, and biomedical waste management.

Figure 2. Framework for the assessment of feasibility of introduction of potential broadly neutralizing antibody products for HIV prevention (adapted from a study by World Health Organization).



Study Design

Data Collection Methods

Overview

To understand preferences with regard to product attributes and key behavioral factors influencing the adoption and uptake of bNAb prevention products, this study will use a multimethods design [59] to provide a holistic approach based on complementarity and corroboration [60] by including the following qualitative methods:

- FGDs
- IDIs
- Simulated behavioral experiments (SBE)
- KIIs.

Data Collection Through FGDs

FGDs will be conducted among various groups such as FSWs, MSM, PWID, TGW, and AGYW. These discussions aim to understand the preferences and aspirations of prospective end-users regarding characteristics of HIV prevention products. In addition, the research seeks to uncover the key factors influencing their decision-making process including influential individuals and other contextual factors. Furthermore, the aim is to correlate these insights with what motivates or dissuades them from favoring specific HIV prevention options over others. This will be conducted in a small group of 7 to 8 participants. The end-users will also be asked about specific delivery preferences that would guide their adoption of and adherence to novel HIV biomedical prevention tools. FGDs allow the members of the group to collectively brainstorm on the issues, choices, drivers, and solutions, sometimes called a "synergistic group effect" [61]. This also allows for assessing participant behavior in a group setting wherein not only the individual respondent's views are deliberated on, but the voices of the community as a whole are also accounted for.

Data Collection Through IDIs

IDIs will be conducted with additional participants from all the target populations through one-to-one discussions and will cover aspects similar to the FGDs. However, these will provide an opportunity to gather deeper insights as the interviewer can probe more, note the changes in respondent's tone and body language, and also have views that are not influenced by group dynamics or social desirability [62].

Data Collection Through SBEs

SBEs will be conducted in small groups of 5 to 6 end-users to delve deeper into the causative factors of decision-making and potential avenues for intention-action gaps by using interdisciplinary concepts from behavioral economics and decision science. SBEs will use the insights generated from the FGDs and IDIs to construct a range of decision scenarios that end-users could face in deciding their preferences for a potential prevention product. SBEs will then use a game-based research technique (Ethnolab) to understand the context, emotions, and decision levers that influence decision-making based on these scenarios. Ethnolab is designed to minimize the impact of biases in decision-making, such as fear of value judgment, social desirability, and expectation of higher self-control in the future, which make respondents claim behaviors that may not play out in real life, thereby giving rise to "say-do" gaps [48]. Ethnolab would allow participants to not only discuss preferred attributes but also make real-time decisions revealing their preferences through multiple test scenarios. One of the critical objectives is to decipher the patterns of preference exhibited by different respondents across divergent contexts. Therefore, Ethnolab will help to identify the following:

- Past experiences that have led to decision-making criteria, values, norms, or beliefs that influence health behaviors and product preference
- Present goals around health management, relationship management, and life management and how they influence attribute selection
- Factors that could lead to preference reversal.

Data Collection Through KIIs

In addition, to better understand the environmental, market, programmatic, and policy contexts at the national, state, and local levels, along with decision-making factors and pathways informing HIV policy, KIIs will be conducted with policy makers and health service providers to understand their

perspectives on drivers for the adoption and uptake of health innovations. Efforts will also be directed toward seeking their input on implementation and access issues as well as health systems challenges on non–cold chain versus cold chain product requirements and other parameters related to effective delivery and adoption of biomedical interventions to prevent HIV.

Sample Selection

The following sample selection criteria will be followed for the abovementioned methods.

End-Users

The inclusion criteria for the various target groups are:

- Inclusion criteria for MSM, TGW, PWID, and FSWs in the FGDs and IDIs were as follows: Aged at least 18 years, self-identifies as MSM, TGW, PWID, or FSW, and willing to provide informed consent.
- Inclusion criteria for AGYW in the FGD and IDIs were as follows: Aged 18 to 24 years and willing to provide informed consent. According to the Joint United Nations Programme on HIV and AIDS definition, AGYW fall into the age group of 15 to 24 years [63]. However, given the ethical considerations with respect to minor adolescent girls (15-17 y) in the Indian context and keeping in mind their relatively lower exposure to HIV prevention services, it was decided that for the purpose of this study, only adolescent girls aged 18 to 19 years and adult young women aged 20 to 24 years will be included. Efforts will be made during data collection and data analysis to ensure that perspectives from participants aged 18 to 19 years and those aged 20 to 24 years are disaggregated to bring out the unique highlights from these populations.
- For FGDs, diverse typologies and subgroups of MSM (kothis [feminine/primarily receptive role], panthis [masculine and primarily insertive role] , double-deckers or versatile, gay, and bisexual men), FSWs (brothel or bar based, street based, internet or social media based, and home based), TGW (gharana based and nongharana and those in sex work and those who are not), PWID (who use different types of injectable drugs), and AGYW across the age group (adolescents aged 18-19 years and young women aged 20-24 years) will be recruited.
- To explore diverse perspectives, maximum variation purposive sampling [64] will be used to recruit individuals from diverse backgrounds such as engaging in sex work; being from lower and middle class; and being single, living with male or female partners, heterosexually married, and representative of male and female PWID groups.

Key Informants

For KIIs, the inclusion criteria will be as follows:

- Key informants should be aged >18 years, ≥5 years of experience as a community leader or ≥3 years of working experience with population of interest or as a part of the HIV program, and willing to provide informed consent.
- Key informants will include information-rich individuals who have worked with key populations or have some experience of working with AGYW or in the field of HIV. These may include health service providers (physicians, counselors, nurses, CBO or NGO representatives, and community leaders) and policy makers (program managers and district or state or national level officials).

Sample Size

A total of 30 FGDs (2 FGDs per end-user group per site; for 5 end-user groups across 3 sites) and 45 IDIs (3 IDIs per end-user group per site; for 5 end-user groups across 3 sites) will be conducted in Delhi, Mumbai, and Chennai to investigate factors at individual, interpersonal, and sociostructural levels that facilitate or impede the acceptability of bNAbs among susceptible communities in India.

The SBE will mirror the sampling frame and the broad respondent profiles from the FGDs and IDIs. Keeping in mind that Ethnolab elicits the most useful insights in small and intimate settings, the sample would include 6 participants for each end-user group (distinct and different from the participants in the FGD or IDIs) across each site. Thus, the total sample size would be 90. Each instance of Ethnolab will have 6 respondents, and a total of 20 Ethnolab-based SBEs will be conducted across all 3 sites.

In addition, 5 KIIs will be conducted with health care service providers and policy makers in each region, amounting to a total of 15 KIIs. Thus, the total sample size of the qualitative component of the study is expected to be approximately 300 (FGD: 30×8=240, IDI=45, and KII=15).

Implementing Partners

The implementing partners for the study are YR Gaitonde Centre for AIDS Research and Education (YRGCARE), Centre for Sexuality and Health Research and Policy (C-SHaRP), and The Humsafar Trust (HST), who will be responsible for conducting the FGDs, IDIs, and KIIs. The designing of the Ethnolab game–based data collection method will be done by Final Mile and IAVI. Final Mile, in working with other study partners (YRGCARE, C-SHaRP, and HST), will be responsible for the implementation and conduct of the SBE sessions across all study sites.

Data Collection

Overview

Data from FGDs, IDIs, and KIIs will be collected using semistructured interview topic guides. Trained research staff will conduct the FGDs, IDIs, and KIIs. The research staff will receive additional training specific to the content of this study and research ethics. SBEs will be conducted by partner consultants and will also include a round of initial meetings with the other study clinical research center partners to ensure alignment with the findings from the FGDs and IDIs.

Lines of Enquiry for FGDs and IDIs

For the FGDs and IDIs among end-users, the following broad areas will be covered in the lines of inquiry:

1. Preference elicitation questions: Under this process, the group will be asked about individual product attributes and their preference for different features under that attribute. The process will aim to understand which attributes matter most to the populations and the preferences for different

subgroups under that population to gain an overall community-level perspective. Efforts will also be made to understand the reasons for these preferred options. This section would also cover the individual, interpersonal, and social concerns that might drive end-user decision-making.

2. Relative desirability of predetermined product profiles (attribute bundles): As a next step, participants within each focus group will be presented with 4 product profiles comprising 5 to 6 attributes in different combinations (bundles) through a mixture of visual methods and information, education, and communication tools. These are modeled after various HIV prevention products, including the current bNAb product under investigation. Participants will be requested to choose their "most/least preferred" profiles, rank the remaining 2, and explain the reasons behind their choice. In addition to enabling a deeper understanding of preferences and trade-offs, this would also aid in understanding the most critical attributes informing decision-making on product use among prospective end-users.

The topic guide will be translated into native languages (Hindi, Tamil, Telugu, or Marathi), back-translated into English, and then revised in the original language. All discussions will be audio-recorded, transcribed, and translated. They will be deidentified before proceeding for further data analysis. Each FGD and each IDI will span over 60 to 90 minutes.

Data Collection Process for SBE

The SBE sessions will consist of three parts:

1. *Ethnolab Conundrum game*: The Conundrum game will expose participants to multiple scenarios, each ending with a decision conundrum having different possible outcomes. Each scenario will simulate the real-world context of participants by representing a protagonist of the same age, gender, and socioeconomic level in a relevant health-related situation. The scenarios will be constructed using preliminary insights generated from the FGDs and IDIs, with decision points informed by heuristics and behavior science principles. The research is gamified: participants will be asked to respond quickly in real time and choose the option they think will coincide with most respondents in the group and will win points if it does. The game will thus generate responses representative of mental models, emotions, and biases rather than deliberate and rational analysis [48]. Preference reversal will be tested through tweaks in the context simulation and the framing of attributes.
2. *Ideal product profile exercise*: The participants will go through a series of prompts to design the ideal prevention product suited to their needs. This activity will be an adapted version of the product profile ranking exercise used in the first round of qualitative research. It will be designed to give participants an expanded choice set to clearly articulate their trade-offs and allow for tracing certain preference reversal patterns. This will enable an overall high engagement and easy and detailed discussion on product attributes.
3. *Group conversations*: Once the games are over, participants will be split into multiple groups of dyads and triads for group conversations (where scenarios and reactions are still fresh in their minds) regarding the experience, decisions, and preferences in the game [50]. The conversations on the scenarios provide opportunities for improved contextualization of the responses, understanding emotions and other causative factors behind preferences, and tracing decision pathways.

The data generated from the games, along with the ensuing conversations, will help elicit behavioral insights and identify intrinsic drivers and extrinsic factors influencing the preferences and decisions of prospective end-users. The Ethnolab play will last for approximately 60 minutes, and the subsequent group discussions will last for 45 minutes. The overall activity will not exceed 2 hours. The session will involve engaging games to maintain a playful environment, and adequate breaks will also be incorporated to ensure that the time of engagement does not become burdensome for the participants.

Lines of Enquiry for KIIs

Semistructured interview guides will consist of 10 to 12 open-ended questions and scripted probes. The interview guides will be translated into native languages (Hindi, Tamil, or Marathi), back-translated into English, and then revised in the original language. Key informants for each study population will be asked questions for the need perception of a prevention product, preference and importance of product attributes, social and cultural acceptability, risk compensation, health systems readiness, and alignment with the policy environment in India. Each KII will be conducted for approximately 90 minutes.

Data Analysis and Validation

Analysis

The qualitative approach will use triangulation to strengthen and ensure the accuracy of data [65]. According to Denzin and Lincoln [66], triangulation is a process in which several methods are used in the study and might be used in four basic ways: (1) data triangulation, (2) methods triangulation, (3) theory triangulation, and (4) researcher triangulation. In this study, data triangulation, methods triangulation, and researcher triangulation will be used. All transcripts will be redacted (to remove any personally identifying information that might inadvertently have been recorded) and uploaded into NVivo (Lumivero) or Dedoose (University of California). First, a line-by-line review of the transcripts will be performed, and first-level codes will be identified to create a common a priori codebook (based on the adapted conceptual or theoretical framework and topic guides). All codes will be then entered and tagged to associated chunks of text. Texts corresponding to each of the first-level codes will be coded by at least 2 independent analysts and reviewed by senior investigators. Explanatory or theoretical or etic (researcher generated) codes will be arrived at using a constant comparative method [67].

The SBE results will be analyzed using the cognitive and emotional appraisal framework [68] as a base. Appraisal theories are componential theories that view an emotional episode as involving changes in a number of organismic subsystems and

components. The components could include an appraisal, a motivational, a somatic, and a motor component. The framework will be used to generate the codebook and will then feed into the 4 major categories of context, emotions, mental models, and decision levers. This will be done along with the ranking of preferences drawn from the experiential game data. The SBEs will be analyzed to gain an in-depth understanding of (1) preference construction and (2) preference reversal.

Validation

Data source triangulation and researcher triangulation will enhance the reliability and trustworthiness of the findings [69]. Thus, study implementation and data analysis will also incorporate researcher reflexivity and researcher triangulation by maintaining "quicknotes" (a brief summary of every interview or focus group by the interviewers or moderators that will be shared with the analysts and investigators for feedback), writing memos, and engaging in peer debriefing to maintain ongoing awareness of our social location and how it may influence the research process and interpretation. A maximum of 2 interviewers or moderators will be used for every population of interest to ensure that there is minimum bias in the way questions are asked or follow-up probes are used.

Data Security for Storage and Transmission

Names or other personal identifiers will not be collected from the participants. Only the investigators and key research staff at the participating research sites will have access to the transcripts or translated text and digital recordings. As soon as an interview is completed, the audio file will be transferred from the digital recorder to password-protected computers. Subsequently, the file will be deleted from the digital recorder. The transcriptionist and translator will sign a confidentiality pledge stating that they will not reveal any information from the interviews to anyone else. The digital copies of transcripts and translated text will also be stored on password-protected computers.

Only this study's research staff at the participating research site will have access to the audio files, transcripts, and translated text. All digital recordings will be redacted, and any personal identifying information will be removed. Digital recordings will be deleted after 1 year (the 1-year delay is to ensure that there are no gaps in the transcripts). Redacted transcripts will be maintained for 2 years and then destroyed. Informed consent forms will be separately stored and will include signs, initials, or "X" marks rather than names. Unique identification codes will be assigned to all individual records, including digital recordings and transcripts. Hard copies of the data and related documents will be stored in a secure location in locked cabinets in the offices of study and will be accessed only by the research staff.

Ethical Considerations

Institutional Review Board Review and Approvals

The study was presented to the institutional review boards (IRBs) of all 3 implementing partners (HST, C-SHaRP, and YRGCARE), and all comments received were adequately addressed in the protocol. The approved protocol (HST-IRB-50-01/2021; C-SHaRP/0007327/220; YRGCARE-359) will be implemented for data collection and analysis.

Informed Consent Process

Participants for IDIs, KIIs, FGDs, and SBEs will be presented with an information sheet that outlines the scope of the study and a consent form that provides options to sign or put initials or put an "X" mark. This approach has been accepted by the IRB for other previous studies. Given the potentially low literacy levels of some participants, the research assistants will offer to read and explain the information sheet and consent form to the participants. As part of the informed consent process, all potential participants will be informed that their decision to participate or not in interviews or games will not affect the services they currently receive or may receive in the future from their respective community agencies.

Compensation

Participants in the FGDs, IDIs, and SBEs will receive an honorarium of INR 500 (US $6.25) for participating in the study. This amount is based on input from the community advisory boards of the study partners in India. This covers the costs incurred for roundtrip transportation. If the focus group or IDI participants elect to withdraw from the study during data collection, they will still receive compensation. Key informants will receive INR 1500 (US $18.75) (wherever applicable), and this is proposed from previous learning wherein key informants reported loss of wages owing to their participation and suggested that an honorarium should be instituted for KIIs to minimize such experiences. All interviews will be conducted in person, and honorariums will be in cash.

Privacy and Confidentiality Protection of Participants and Do-No-Harm Measures

Overview

Being a qualitative study, with no biological samples collection, there is no medical risk to a research participant of this study. The study also does not pose any financial risk to the participants. However, participants' confidentiality could be compromised through engagement in the study, and participants might feel uncomfortable answering questions about sexual behaviors. Recognizing these possibilities, some mitigation measures that will be adopted are as follows:

1. Unique identity number and no names: No participant names will be collected. Participants will be asked to mark only their initials or put an "X" mark on the consent form. Participants will be identified only by a unique numerical identifier. Individuals will be instructed not to use their surnames but to use a nickname or pseudonym. In addition, all transcripts will be anonymized so that any identifying information that is inadvertently mentioned will be removed from the written transcript.
2. Training for research interviewers or FGD moderators: Interviewers or moderators will be well trained in research ethics and interviewing techniques. They will be trained to be sensitive to the needs of the participants to stop, rest, skip particular questions, or discontinue their involvement

in the study at any time. Interviewers will be clearly instructed that participants are allowed not to answer any question and continue with the interview or to stop the interview at any time. In addition, research interviewers and field research staff will be trained in research ethics and confidentiality and will all be required to sign confidentiality agreements.

3. Explicit information on potential social risks to participants of focus groups: For focus groups, social risks include unwanted disclosure of one's sexual orientation or sexual behaviors and facing possible stigma or discrimination if a member of the larger community discovered the participant's orientation or drug use or sex work status. Furthermore, confidentiality will be maintained by holding interviews and focus groups at discreet locations that many of the participants already frequently visit (eg, local CBO or NGO office). In addition, facilitators and interviewers will be trained in research ethics and there is already a list of transcribers or translators who possess sufficient experience in transcribing research interviews. They are also well versed in the significance of upholding confidentiality and anonymity.
4. Transcription and translation of FGD, IDI, KII, and behavioral experiments: Professional transcribers will be hired for the transcription or translation of audio-recorded interviews (FGDs, IDIs, KIIs, and behavioral experiment discussions). There already exists a list of transcribers or translators with adequate experience in transcribing research interviews and who know about the importance of maintaining confidentiality and anonymity. They (new or experienced) will be oriented about the importance of maintaining the confidentiality of the audio files and transcripts and will be asked to keep all the research information confidential by not discussing or sharing the content of the interviews in any form or format with anyone other than the designated research contact persons. The transcriber or translator will be asked to sign a confidentiality pledge before transcription or translation.

Do-No-Harm Measures

In addition to the mentioned measures, all study staff will be trained in guidelines and policies related to human participant research ethics to ensure no unintended harm to the participants. This will be applicable for all participants, keeping in mind their vulnerabilities, but especially noteworthy for engagement with adolescent populations. The study teams will adhere to the National Youth Policy and also be trained in the guidelines stated by the Rashtriya Kishore Swasthya Karyakram [70].

Plan for Reporting Unanticipated Problems or Study Deviations

The study investigators will report unanticipated problems and study deviations to the local IRB. Such events will also be communicated to International AIDS Vaccine Initiative for further review or escalation, if required. Minor problems and protocol deviations, if any, (which pose no risk to participants or others) will be reported in the annual protocol continuing review.

COVID-19–Related Guidelines

All study data collection–related activities will be conducted by adhering to the state or national guidelines in view of COVID-19.

Possible Benefits to Participants

There are no direct benefits to participants for taking part in this study. However, the participants will be better informed about the various HIV prevention options currently available across the globe and the options under development. The study has the potential to benefit the society and the participant's communities if the data collected are found effective and are adopted in routine service delivery or for further informing bNAb research.

Results

The study is being implemented across 3 sites in India among 5 different populations and key informants. The data collection will be followed by data analysis workshops to enable standardization of analysis across all sites and partners. Extensive analysis based on the analytical frameworks will lead to the expected outcomes of the study.

Discussion

Principal Findings

The study will provide critical insights into factors driving the end-user decision-making with regard to prevention product choices and assess the acceptability of bNAbs in the Indian context. It will also help understand the health system and programmatic factors that would influence product introduction and uptake among target populations in India. The specific anticipated outcomes from the study can be highlighted as follows:

1. *Product preferences*: Insights from the FGDs, IDIs, and SBEs will aid in identifying specific product attributes that matter the most to the end-users and why some attributes have less preference. Within each attribute, it will be possible to identify the options that the respondents feel are more significant to their individual context. Insights will also be generated on end-user preferences that are stable across all contexts and preferences that are dynamic and may vary with changing circumstances. Finally, it will also be possible to outline the acceptability and unique value proposition of bNAb products in the Indian context.
2. *Behavioral factors*: Another outcome of the study will be identification of the most relevant target populations in India for HIV bNAb products and user segmentation of the target population based on key behavioral determinants, including an interplay between user profiles and preferences. The study will also help understand the contextual drivers of preferences and choices at individual, interpersonal, social, and structural levels and aid in delineating the key decision levers and pathways that lead to a preference or reversal of the same. These decision levers could be understood in the form of norms, values, goals, mental models, and emotions and would be critical

to decipher to understand acceptability of a product. In addition, often, the stated preferences are different from the observed choices when they are simulated through real-life situations. Thus, the gamified components will also provide a chance to highlight the say-do gap to inform product development.

3. *Health systems and programmatic readiness*: Insights from the health service providers and policy makers will provide a critical understanding of the needs perception of the potential product in the existing product landscape, understanding of the cultural and social acceptability, and risk compensation. Their views will also provide critical insights into the additional efforts and resources required for potential introduction, delivery, and implementation of bNAb products in the Indian context. This will include program integration perspectives and other structural factors such as workforce availability and supply chain integration. The study will also enable an understanding of the existing policy landscape and alignment of the potential product with the same toward informing the feasibility of introduction.

Insights generated from all the abovementioned outcome domains will represent perspectives of populations of interest across geographies in India and will be collated into management presentations to provide an overview of the acceptability and feasibility of bNAb products in this region toward informing product development strategies.

Limitations of the Study

We anticipate some limitations. First, being a qualitative study, an inherent limitation of the study is that the findings may not be generalizable (in a statistical sense) as purposive sampling, a nonprobability sampling widely used in qualitative research, was used. However, we will try to ensure diversity when recruiting potential participants from various study subgroups, that is, by using maximum variation or diversity sampling, a type of purposive sampling. Such a strategy, along with a detailed description of the settings and participant characteristics, will increase the chances of the transferability of the findings to similar contexts and populations. Second, the study is being implemented by 3 study partners in different settings. Although all interviewers used standardized data collection tools and underwent common trainings, personal differences in interviewing styles may result in varied elicitation of responses from end-users. We will try to reduce this bias by having periodic debriefing sessions with the research team, especially data collectors, which will help the team to reflect on how one's values and beliefs might influence the way we ask questions in the interviews or FGDs or in arriving at inferences when analyzing the data [71].

Conclusions

With the evolution in the HIV prevention research field and the expansion of the prevention toolbox, end-users have a wide spectrum of choices. It is important for product developers to understand the drivers of these choices to clearly articulate the unique value proposition of each product to define their positioning in the choice spectrum. It is also critical to generate timely evidence on target populations, facilitators and barriers of use, relative importance of products, and communication needs to facilitate, plan, and enable policy decisions for the introduction of newer products. Thus, this study will aid in generating insights that will be critical for product developers and policy makers.

Acknowledgments

This study is made possible by the support of the American people through the United States Agency for International Development (USAID) and the US President's Emergency Plan for AIDS Relief (PEPFAR). The contents of this protocol are the sole responsibility of International AIDS Vaccine Initiative and do not necessarily reflect the views of USAID, PEPFAR, or the US Government. The authors acknowledge all end-users, nongovernmental organizations, and community-based organizations who facilitated the data collection process, enabled adequate outreach, and participated in the study.

Data Availability

The data sets generated during the study will be used to analyze the final findings from the study. The analyzed data sets will be available in the main manuscript that will be published highlighting the findings from this study. For data sharing, national policies applicable to Indian research data [72] will be adhered to.

Conflicts of Interest

Some of the authors (JM, SuH, PA, SM, MK) are affiliated with the International AIDS Vaccine Initiative, which is a not-for-profit organization that is involved in the development of broadly neutralizing antibodies. All other authors declare no other conflicts of interest.

References

1. Global HIV and AIDS fact sheet. Joint United Nations Programme on HIV/Aids. URL: https://www.unaids.org/en/resources/fact-sheet [accessed 2023-05-23]
2. Seyler L, Lacor P, Allard SD. Current challenges in the treatment of HIV. Pol Arch Intern Med 2018 Oct 31;128(10):609-616 [FREE Full text] [doi: 10.20452/pamw.4357] [Medline: 30387448]

3. Cohen J. Long-acting injectable drug prevents HIV infections. Science 2020 May 19 [FREE Full text] [doi: 10.1126/science.abc8634]
4. Cairns G. The vaginal ring against HIV: regulatory approval for a new prevention choice for women. aidsmap. 2020 Jul 30. URL: https://www.aidsmap.com/news/jul-2020/vaginal-ring-against-hiv-regulatory-approval-new-prevention-choice-women; [accessed 2023-05-20]
5. Walker LM, Phogat SK, Chan-Hui PY, Wagner D, Phung P, Goss JL, Protocol G Principal Investigators, et al. Broad and potent neutralizing antibodies from an African donor reveal a new HIV-1 vaccine target. Science 2009 Oct 09;326(5950):285-289 [FREE Full text] [doi: 10.1126/science.1178746] [Medline: 19729618]
6. Wu X, Yang ZY, Li Y, Hogerkorp CM, Schief WR, Seaman MS, et al. Rational design of envelope identifies broadly neutralizing human monoclonal antibodies to HIV-1. Science 2010 Aug 13;329(5993):856-861 [FREE Full text] [doi: 10.1126/science.1187659] [Medline: 20616233]
7. Huang J, Ofek G, Laub L, Louder MK, Doria-Rose NA, Longo NS, et al. Broad and potent neutralization of HIV-1 by a gp41-specific human antibody. Nature 2012 Nov 15;491(7424):406-412 [FREE Full text] [doi: 10.1038/nature11544] [Medline: 23151583]
8. Shingai M, Nishimura Y, Klein F, Mouquet H, Donau OK, Plishka R, et al. Antibody-mediated immunotherapy of macaques chronically infected with SHIV suppresses viraemia. Nature 2013 Nov 14;503(7475):277-280 [FREE Full text] [doi: 10.1038/nature12746] [Medline: 24172896]
9. Sok D, van Gils MJ, Pauthner M, Julien JP, Saye-Francisco KL, Hsueh J, et al. Recombinant HIV envelope trimer selects for quaternary-dependent antibodies targeting the trimer apex. Proc Natl Acad Sci U S A 2014 Dec 09;111(49):17624-17629 [FREE Full text] [doi: 10.1073/pnas.1415789111] [Medline: 25422458]
10. Mendoza P, Gruell H, Nogueira L, Pai JA, Butler AL, Millard K, et al. Combination therapy with anti-HIV-1 antibodies maintains viral suppression. Nature 2018 Sep 26;561(7724):479-484 [FREE Full text] [doi: 10.1038/s41586-018-0531-2] [Medline: 30258136]
11. Schommers P, Gruell H, Abernathy ME, Tran MK, Dingens AS, Gristick HB, et al. Restriction of HIV-1 escape by a highly broad and potent neutralizing antibody. Cell 2020 Feb 06;180(3):471-89.e22 [FREE Full text] [doi: 10.1016/j.cell.2020.01.010] [Medline: 32004464]
12. Chang LW, Serwadda D, Quinn TC, Wawer MJ, Gray RH, Reynolds SJ. Combination implementation for HIV prevention: moving from clinical trial evidence to population-level effects. Lancet Infect Dis 2013 Jan;13(1):65-76 [FREE Full text] [doi: 10.1016/S1473-3099(12)70273-6] [Medline: 23257232]
13. Laher F, Salami T, Hornschuh S, Makhale LM, Khunwane M, Andrasik MP, et al. Willingness to use HIV prevention methods among vaccine efficacy trial participants in Soweto, South Africa: discretion is important. BMC Public Health 2020 Nov 07;20(1):1669 [FREE Full text] [doi: 10.1186/s12889-020-09785-0] [Medline: 33160341]
14. Godfrey-Faussett P, Frescura L, Abdool Karim Q, Clayton M, Ghys PD, (on behalf of the 2025 prevention targets working group). HIV prevention for the next decade: Appropriate, person-centred, prioritised, effective, combination prevention. PLoS Med 2022 Sep;19(9):e1004102 [FREE Full text] [doi: 10.1371/journal.pmed.1004102] [Medline: 36156593]
15. Horwitz JA, Halper-Stromberg A, Mouquet H, Gitlin AD, Tretiakova A, Eisenreich TR, et al. HIV-1 suppression and durable control by combining single broadly neutralizing antibodies and antiretroviral drugs in humanized mice. Proc Natl Acad Sci U S A 2013 Oct 08;110(41):16538-16543 [FREE Full text] [doi: 10.1073/pnas.1315295110] [Medline: 24043801]
16. Barouch DH, Whitney JB, Moldt B, Klein F, Oliveira TY, Liu J, et al. Therapeutic efficacy of potent neutralizing HIV-1-specific monoclonal antibodies in SHIV-infected rhesus monkeys. Nature 2013 Nov 14;503(7475):224-228 [FREE Full text] [doi: 10.1038/nature12744] [Medline: 24172905]
17. Scheid JF, Horwitz JA, Bar-On Y, Kreider EF, Lu CL, Lorenzi JC, et al. HIV-1 antibody 3BNC117 suppresses viral rebound in humans during treatment interruption. Nature 2016 Jul 28;535(7613):556-560 [FREE Full text] [doi: 10.1038/nature18929] [Medline: 27338952]
18. Caskey M, Schoofs T, Gruell H, Settler A, Karagounis T, Kreider EF, et al. Antibody 10-1074 suppresses viremia in HIV-1-infected individuals. Nat Med 2017 Feb 16;23(2):185-191 [FREE Full text] [doi: 10.1038/nm.4268] [Medline: 28092665]
19. Bar KJ, Sneller MC, Harrison LJ, Justement JS, Overton ET, Petrone ME, et al. Effect of HIV antibody VRC01 on viral rebound after treatment interruption. N Engl J Med 2016 Nov 24;375(21):2037-2050 [FREE Full text] [doi: 10.1056/NEJMoa1608243] [Medline: 27959728]
20. Corey L, Gilbert PB, Juraska M, Montefiori DC, Morris L, Karuna ST, et al. Two randomized trials of neutralizing antibodies to prevent HIV-1 acquisition. N Engl J Med 2021 Mar 18;384(11):1003-1014. [doi: 10.1056/nejmoa2031738]
21. WHO preferred product characteristics for monoclonal antibodies for HIV prevention. World Health Organization. URL: https://iris.who.int/bitstream/handle/10665/360491/9789240045729-eng.pdf?sequence=1 [accessed 2023-11-01]
22. Griffin JB, Ridgeway K, Montgomery E, Torjesen K, Clark R, Peterson J, et al. Vaginal ring acceptability and related preferences among women in low- and middle-income countries: a systematic review and narrative synthesis. PLoS One 2019 Nov 8;14(11):e0224898 [FREE Full text] [doi: 10.1371/journal.pone.0224898] [Medline: 31703094]

23. Kennedy C, Fonner V. Pre-exposure prophylaxis for people who inject drugs: a systematic review. In: Kennedy C, Fonner V, editors. Consolidated Guidelines on HIV Prevention, Diagnosis, Treatment and Care for Key Populations – 2016 Update. Geneva, Switzerland: World Health Organization; 2016.
24. Quaife M, Eakle R, Cabrera Escobar MA, Vickerman P, Kilbourne-Brook M, Mvundura M, et al. Divergent preferences for HIV prevention: a discrete choice experiment for multipurpose HIV prevention products in South Africa. Med Decis Making 2018 Jan;38(1):120-133. [doi: 10.1177/0272989X17729376] [Medline: 28863752]
25. Atujuna M, Newman PA, Wallace M, Eluhu M, Rubincam C, Brown B, et al. Contexts of vulnerability and the acceptability of new biomedical HIV prevention technologies among key populations in South Africa: a qualitative study. PLoS One 2018 Feb 8;13(2):e0191251 [FREE Full text] [doi: 10.1371/journal.pone.0191251] [Medline: 29420549]
26. Bauermeister JA, Downs JS, Krakower DS. PrEP product acceptability and dual process decision-making among men who have sex with men. Curr HIV/AIDS Rep 2020 Jun 16;17(3):161-170 [FREE Full text] [doi: 10.1007/s11904-020-00497-z] [Medline: 32297220]
27. Koechlin FM, Fonner VA, Dalglish SL, O'Reilly KR, Baggaley R, Grant RM, et al. Values and preferences on the use of oral pre-exposure prophylaxis (PrEP) for HIV prevention among multiple populations: a systematic review of the literature. AIDS Behav 2017 May 29;21(5):1325-1335 [FREE Full text] [doi: 10.1007/s10461-016-1627-z] [Medline: 27900502]
28. Patel SK, Rohan LC. On-demand microbicide products: design matters. Drug Deliv Transl Res 2017 Dec 6;7(6):775-795 [FREE Full text] [doi: 10.1007/s13346-017-0385-4] [Medline: 28589452]
29. Eakle R, Weatherburn P, Bourne A. Understanding user perspectives of and preferences for oral PrEP for HIV prevention in the context of intervention scale-up: a synthesis of evidence from sub-Saharan Africa. J Int AIDS Soc 2019 Jul 22;22 Suppl 4(Suppl Suppl 4):e25306 [FREE Full text] [doi: 10.1002/jia2.25306] [Medline: 31328429]
30. Humphrey JM, Naanyu V, MacDonald KR, Wools-Kaloustian K, Zimet GD. Stated-preference research in HIV: a scoping review. PLoS One 2019 Oct 30;14(10):e0224566 [FREE Full text] [doi: 10.1371/journal.pone.0224566] [Medline: 31665153]
31. Eakle R, Bourne A, Jarrett C, Stadler J, Larson H. Motivations and barriers to uptake and use of female-initiated, biomedical HIV prevention products in sub-Saharan Africa: an adapted meta-ethnography. BMC Public Health 2017 Dec 19;17(1):968 [FREE Full text] [doi: 10.1186/s12889-017-4959-3] [Medline: 29258455]
32. Eisingerich AB, Wheelock A, Gomez GB, Garnett GP, Dybul MR, Piot PK. Attitudes and acceptance of oral and parenteral HIV pre-exposure prophylaxis among potential user groups: a multinational study. PLoS One 2012 Jan 11;7(1):e28238. [doi: 10.1371/journal.pone.0028238] [Medline: 22247757]
33. Krakower DS, Mayer KH. The role of healthcare providers in the roll out of pre-exposure prophylaxis. Curr Opin HIV AIDS 2016 Jan;11(1):41-48 [FREE Full text] [doi: 10.1097/COH.0000000000000206] [Medline: 26417953]
34. Venter WD. Pre-exposure prophylaxis: the delivery challenge. Front Public Health 2018 Jul 6;6:188 [FREE Full text] [doi: 10.3389/fpubh.2018.00188] [Medline: 30035106]
35. Joglekar NS, Joshi SN, Deshpande SS, Parkhe AN, Katti UR, Mehendale SM. Acceptability and adherence: findings from a Phase II study of a candidate vaginal microbicide, 'Praneem polyherbal tablet', in Pune, India. Trans R Soc Trop Med Hyg 2010 Jun;104(6):412-415. [doi: 10.1016/j.trstmh.2009.12.007] [Medline: 20096909]
36. Tolley EE, Tsui S, Mehendale S, Weaver MA, Kohli R. Predicting product adherence in a topical microbicide safety trial in Pune, India. AIDS Behav 2012 Oct 30;16(7):1808-1815 [FREE Full text] [doi: 10.1007/s10461-011-0036-6] [Medline: 21877203]
37. Mehendale S, Deshpande S, Kohli R, Tsui S, Tolley E. Acceptability of coitally-associated versus daily use of 1% tenofovir vaginal gel among women in Pune, India. Int Health 2012 Mar;4(1):63-69. [doi: 10.1016/j.inhe.2011.11.003] [Medline: 24030882]
38. Prabhughate A, Sarna A, Brady M. Tenofovir gel for HIV prevention for women: perspectives of key opinion leaders from India. Health Policy Technol 2014 Mar;3(1):59-65 [FREE Full text] [doi: 10.1016/j.hlpt.2013.11.002]
39. Chandhiok N, Joshi SN, Gangakhedkar R. Acceptability of oral and topical HIV chemoprophylaxis in India: implications for at-risk women and men who have sex with men. Sex Health 2014 Jul;11(2):171-179. [doi: 10.1071/SH13067] [Medline: 24119324]
40. Chakrapani V, Newman PA, Shunmugam M, Mengle S, Varghese J, Nelson R, et al. Acceptability of HIV pre-exposure prophylaxis (PrEP) and implementation challenges among men who have sex with men in India: a qualitative investigation. AIDS Patient Care STDS 2015 Oct;29(10):569-577. [doi: 10.1089/apc.2015.0143] [Medline: 26348459]
41. Chakrapani V, Newman PA, Shunmugam M, Mengle S, Nelson R, Rubincam C, et al. "Like holding an umbrella before it rains": acceptability of future rectal microbicides among men who have sex with men in India-a modified technology acceptance model. Qual Health Res 2017 Jul 20;27(8):1236-1248. [doi: 10.1177/1049732317697947] [Medline: 28682740]
42. Chakrapani V, Shunmugam M, Rawat S, Baruah D, Nelson R, Newman PA. Acceptability of HIV pre-exposure prophylaxis among transgender women in India: a qualitative investigation. AIDS Patient Care STDS 2020 Feb 01;34(2):92-98 [FREE Full text] [doi: 10.1089/apc.2019.0237] [Medline: 31951490]
43. Lambooij MS, Harmsen IA, Veldwijk J, de Melker H, Mollema L, van Weert YW, et al. Consistency between stated and revealed preferences: a discrete choice experiment and a behavioural experiment on vaccination behaviour compared. BMC Med Res Methodol 2015 Mar 12;15(1):19 [FREE Full text] [doi: 10.1186/s12874-015-0010-5] [Medline: 25887890]

44. Nyasani DK, Mutua GN, Sajabi RM, Ng'ang'a JW, Gachie JN, Maina AM, et al. Reported willingness to participate in a hypothetical HIV vaccine trial and its translation to actual participation among healthy adults-experience from Kenya. PLoS One 2018 Nov 2;13(11):e0206656 [FREE Full text] [doi: 10.1371/journal.pone.0206656] [Medline: 30388145]
45. Strauss M, George G, Mantell JE, Romo ML, Mwai E, Nyaga EN, et al. Stated and revealed preferences for HIV testing: can oral self-testing help to increase uptake amongst truck drivers in Kenya? BMC Public Health 2018 Nov 06;18(1):1231 [FREE Full text] [doi: 10.1186/s12889-018-6122-1] [Medline: 30400898]
46. Tversky A, Kahneman D. Judgment under uncertainty: heuristics and biases. Science 1974 Sep 27;185(4157):1124-1131. [doi: 10.1126/science.185.4157.1124] [Medline: 17835457]
47. Kanhemann D. Thinking Fast and Slow. New York, NY: Farrar, Straus and Giroux; 2011.
48. Sgaier SK, Sharma S, Eletskaya M, Prasad R, Mugurungi O, Tambatamba B, et al. Attitudes and decision-making about early-infant versus early-adolescent male circumcision: demand-side insights for sustainable HIV prevention strategies in Zambia and Zimbabwe. PLoS One 2017 Jul 27;12(7):e0181411 [FREE Full text] [doi: 10.1371/journal.pone.0181411] [Medline: 28749979]
49. Gomez A, Malone S, Prasad R, Gangaramany A, Croucamp Y, Mulhausen J, et al. Understanding HIV prevention in high-risk adolescent girls and young women in two South African provinces. S Afr Health Rev 2019;2019(1):167-171 [FREE Full text]
50. Engl E, Kretschmer S, Jain M, Sharma S, Prasad R, Ramesh BM, et al. Categorizing and assessing comprehensive drivers of provider behavior for optimizing quality of health care. PLoS One 2019 Apr 17;14(4):e0214922 [FREE Full text] [doi: 10.1371/journal.pone.0214922] [Medline: 30995274]
51. HIV Sentinel Surveillance (HSS): technical brief. National AIDS Control Organization (NACO). 2017. URL: https://naco.gov.in/sites/default/files/HIV%20SENTINEL%20SURVEILLANCE_06_12_2017_0.pdf [accessed 2024-01-03]
52. Beattie TS, Bhattacharjee P, Suresh M, Isac S, Ramesh BM, Moses S. Personal, interpersonal and structural challenges to accessing HIV testing, treatment and care services among female sex workers, men who have sex with men and transgenders in Karnataka state, South India. J Epidemiol Community Health 2012 Oct 11;66 Suppl 2(Suppl 2):ii42-ii48 [FREE Full text] [doi: 10.1136/jech-2011-200475] [Medline: 22495772]
53. Chakrapani V, Velayudham J, Shunmugam M, Newman PA, Dubrow R. Barriers to antiretroviral treatment access for injecting drug users living with HIV in Chennai, South India. AIDS Care 2014 Nov 28;26(7):835-841 [FREE Full text] [doi: 10.1080/09540121.2013.861573] [Medline: 24283220]
54. National family health survey (2015-16). Ministry of Health and Family Welfare. 2017. URL: http://rchiips.org/nfhs/nfhs-4Reports/India.pdf [accessed 2024-01-03]
55. Sekhon M, Cartwright M, Francis JJ. Acceptability of healthcare interventions: an overview of reviews and development of a theoretical framework. BMC Health Serv Res 2017 Jan 26;17(1):88 [FREE Full text] [doi: 10.1186/s12913-017-2031-8] [Medline: 28126032]
56. Mensch BS, van der Straten A, Katzen LL. Acceptability in microbicide and PrEP trials. Current Opinion in HIV and AIDS 2012 Nov;7(6):534-541. [doi: 10.1097/coh.0b013e3283590632]
57. Campbell JI, Aturinda I, Mwesigwa E, Burns B, Santorino D, Haberer JE, et al. The Technology Acceptance Model for Resource-Limited Settings (TAM-RLS): a novel framework for mobile health interventions targeted to low-literacy end-users in resource-limited settings. AIDS Behav 2017 Nov;21(11):3129-3140 [FREE Full text] [doi: 10.1007/s10461-017-1765-y] [Medline: 28421356]
58. WHO-framework on health systems. World Health Organization. URL: http://www.who.int/healthsystems/strategy/everybodys_business.pdf [accessed 2024-01-03]
59. Hunter A, Brewer JD. Designing multi-method research. In: Hesse-Biber SN, Johnson RB, editors. The Oxford Handbook of Multimethod and Mixed Methods Research Inquiry. Oxford, UK: Oxford University Press; 2015.
60. Mukherjee N, Zabala A, Huge J, Nyumba TO, Adem Esmail B, Sutherland WJ. Comparison of techniques for eliciting views and judgements in decision‐making. Methods Ecol Evol 2018 Jan 11;9(1):54-63 [FREE Full text] [doi: 10.1111/2041-210x.12940]
61. Sussman S, Burton D, Dent CW, Stacy AW, Flay BR. Use of focus groups in developing an adolescent tobacco use cessation program: collective norm effects. J Applied Social Pyschol 2006 Jul 31;21(21):1772-1782 [FREE Full text] [doi: 10.1111/j.1559-1816.1991.tb00503.x]
62. Moris A. The what and why of in-depth interviewing. In: Morris A, editor. A Practical Introduction to In-Depth Interviewing. Thousand Oaks, CA: Sage Publications; 2015.
63. HIV prevention among adolescent girls and young women. Joint United Nations Programme on HIV/Aids. URL: https://www.unaids.org/sites/default/files/media_asset/UNAIDS_HIV_prevention_among_adolescent_girls_and_young_women.pdf [accessed 2024-01-03]
64. Crossman A. Understanding purposive sampling: an overview of the methods and its applications. ThoughtCo. 2020 Mar 19. URL: https://www.thoughtco.com/purposive-sampling-3026727 [accessed 2024-01-03]
65. Lincoln YS, Guba EG. Naturalistic Inquiry. Thousand Oaks, CA: Sage Publications; 1985.
66. Denzin NK, Lincoln YS. The Sage Handbook of Qualitative Research. Los Angeles, CA: Sage Publications; 2015.

67. Strauss A, Corbin J. Basics of Qualitative Research: Techniques and Procedures for Developing Grounded Theory. Thousand Oaks, CA: Sage Publications; 1998.
68. Frijda NH, Mesquita B. The analysis of emotions. In: Mascolo MF, Griffin S, editors. What Develops in Emotional Development?. Cham, Switzerland: Springer; 1998:273-295.
69. Pope C, Ziebland S, Mays N. Qualitative research in health care. Analysing qualitative data. BMJ 2000 Jan 08;320(7227):114-116 [FREE Full text] [doi: 10.1136/bmj.320.7227.114] [Medline: 10625273]
70. Rashtriya Kishor Swasthya Karyakram (RKSK). National Health Mission. URL: https://nhm.gov.in/index4.php?lang=1&level=0&linkid=152&lid=173 [accessed 2023-11-03]
71. Rankl F, Johnson GA, Vindrola-Padros C. Examining what we know in relation to how we know it: a team-based reflexivity model for rapid qualitative health research. Qual Health Res 2021 Jun;31(7):1358-1370 [FREE Full text] [doi: 10.1177/1049732321998062] [Medline: 33745367]
72. Data Protection guideline of the National AIDS Control Organization. National AIDS Control Organization. URL: https://www.naco.gov.in/sites/default/files/Data%20Protection%20Guideline%20of%20National%20AIDS%20Control%20Programme.pdf [accessed 2024-01-03]

Abbreviations

AGYW: adolescent girls and young women
ARV: antiretroviral
bNAb: broadly neutralizing antibody
CBO: community-based organization
C-SHaRP: Centre for Sexuality and Health Research and Policy
FGD: focus group discussion
FSW: female sex worker
HST: Humsafar Trust
IDI: in-depth interview
IRB: institutional review board
KII: key informant interview
MSM: men who have sex with men
NGO: nongovernmental organization
PrEP: preexposure prophylaxis
PWID: people who inject drugs
SBE: simulated behavioral experiment
TFA: Theoretical Framework of Acceptability
TGW: transgender women
WHO: World Health Organization
YRGCARE: YR Gaitonde Centre for AIDS Research and Education

Edited by A Mavragani; submitted 29.05.23; peer-reviewed by J Andriesen, R Golwalkar; comments to author 13.10.23; revised version received 03.11.23; accepted 13.12.23; published 07.02.24.

Please cite as:
Mukherjee J, Rawat S, ul Hadi S, Aggarwal P, Chakrapani V, Rath P, Manchi P, Aylur S, Malhotra S, Keane M, Gangaramany A Understanding the Acceptability of Broadly Neutralizing Antibodies for HIV Prevention Among At-Risk Populations and Feasibility Considerations for Product Introduction in India: Protocol for a Qualitative Study
JMIR Res Protoc 2024;13:e47700
URL: https://www.researchprotocols.org/2024/1/e47700
doi:10.2196/47700
PMID:38324364

Protocol

Lifestyle Medicine Implementation in 8 Health Systems: Protocol for a Multiple Case Study Investigation

Meghan L Ames[1], RDN, MSPH; Micaela C Karlsen[2], MSPH, PhD; Samantha M Sundermeir[1], RDN, MS; Neve Durrwachter[1], MSPH; Tyler A Hemmingson[2], MPH; Melissa M Reznar[3], MPH, PhD; Kara Livingston Staffier[2], MPH; Bruce Weeks[2], MD; Joel Gittelsohn[1], PhD

[1]Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, United States

[2]American College of Lifestyle Medicine, Chesterfield, MO, United States

[3]School of Health Sciences, Oakland University, Rochester, MI, United States

Corresponding Author:
Meghan L Ames, RDN, MSPH
Bloomberg School of Public Health, Johns Hopkins University
615 N. Wolfe Street
Baltimore, MD, 21205
United States
Phone: 1 4105168000
Email: meghan.ames@jhu.edu

Abstract

Background: Lifestyle medicine (LM) is the use of therapeutic lifestyle changes (including a whole-food, plant-predominant eating pattern; regular physical activity; restorative sleep; stress management; avoidance of risky substances; and positive social connection) to prevent and treat chronic illness. Despite growing evidence, LM is still not widely implemented in health care settings. Potential challenges to LM implementation include lack of clinician training, staffing concerns, and misalignment of LM services with fee-for-service reimbursement, but the full range of factors facilitating or obstructing its implementation and long-term success are not yet understood. To learn important lessons for success and failure, it is crucial to understand the experiences of different LM programs.

Objective: This study aims to describe in depth the protocol used to identify barriers and facilitators impacting the implementation of LM in health systems.

Methods: The study team comprises team members at the American College of Lifestyle Medicine (ACLM), including staff and researchers with expertise in public health, LM, and qualitative research. We recruited health systems that were members of the ACLM Health Systems Council. From among 15 self-nominating health systems, we selected 7 to represent a diversity of geographic location, type, size, expertise, funding, patients, and LM services. Partway through the study, we recruited 1 additional contrasting health system to serve as a negative case. For each case, we conducted in-depth interviews, document reviews, site visits (limited due to the COVID-19 pandemic), and study team debriefs. Interviews lasted 45-90 minutes and followed a semistructured interview guide, loosely based on the Consolidated Framework for Implementation Research (CFIR) model. We are constructing detailed case narrative reports for each health system that are subsequently used in cross-case analyses to develop a contextually rich and detailed understanding of various predetermined and emergent topics. Cross-case analyses will draw on a variety of methodologies, including in-depth case familiarization, inductive or deductive coding, and thematic analysis, to identify cross-cutting themes.

Results: The study team has completed data collection for all 8 participating health systems, including 68 interviews and 1 site visit. We are currently drafting descriptive case narratives, which will be disseminated to participating health systems for member checking and shared broadly as applied vignettes. We are also conducting cross-case analyses to identify critical facilitators and barriers, explore clinician training strategies to facilitate LM implementation, and develop an explanatory model connecting practitioner adoption of LM and experiences of burnout.

Conclusions: This protocol paper offers real-world insights into research methods and practices to identify barriers and facilitators to the implementation of LM in health systems. Findings can advise LM implementation across various health system contexts. Methodological limitations and lessons learned can guide the execution of other studies with similar methodologies.

International Registered Report Identifier (IRRID): DERR1-10.2196/51562

(JMIR Res Protoc 2024;13:e51562) doi:10.2196/51562

KEYWORDS

healthy lifestyle; implementation science; lifestyle medicine; multiple case study; noncommunicable diseases; prevention; qualitative methods

Introduction

Cardiovascular disease, diabetes, and other chronic illnesses (including mood disorders) continue to be the leading causes of morbidity and mortality in the United States [1,2]. An estimated US $4.1 trillion is spent annually on health care for individuals with chronic physical and mental health conditions [2]. Poor health behaviors, such as a less healthy diet, physical inactivity, and substance use, exacerbate these conditions and cost the United States an estimated US $1.3 trillion per year [3]. An estimated 75%-90% of chronic illnesses could be prevented by lifestyle modification [4].

Lifestyle medicine (LM) is a "medical specialty that uses therapeutic lifestyle interventions as a primary modality" to prevent, treat, and reverse chronic conditions [5]. This "evidence-based, whole-person, prescriptive lifestyle change" is built around 6 pillars: a whole-food, plant-predominant eating pattern; regular physical activity; restorative sleep; stress management; avoidance of risky substances; and positive social connection [5]. These innovative and comprehensive approaches, especially those related to diet, have been shown to promote healthy weight, decrease the risk of type 2 diabetes, reduce cardiovascular risk factors, and improve quality of life [6-15]. Experts estimate US $116 billion could be saved annually through modest changes in health behavior and care delivery that result in improved treatment rates, increased physical activity, reduced smoking, and reduced obesity [16].

Interest in LM is growing, as evidenced by the rising membership of the American College of Lifestyle Medicine (ACLM), which increased by approximately 300% between 2018 and 2021 [17]. In 2017, the American Medical Association House of Delegates emphasized the importance of LM treatment by passing a resolution supporting providers to prescribe healthy lifestyle behaviors [18]. Despite these advances, adoption in clinical practice is slow [12,13,19-21], and additional research is needed to better understand the barriers and facilitators to implement this approach in health care settings [20].

The Consolidated Framework for Implementation Research (CFIR) is commonly referenced in the implementation science field to characterize factors that can influence the successful implementation of health services [22]. It includes 5 domains: intervention, inner setting, outer setting, individuals involved, and the implementation process. About 13% of the estimated 625 health systems across the United States are members of the ACLM Health Systems Council and are at varying stages of LM implementation [23,24]. Commonly, the inner setting of LM takes place within primary care and the general internal medicine environment, as well as medical specialties such as diabetes and oncology. Implementation processes and strategies can often extend across disciplines, such as the case with the modification of electronic medical records to prompt behavioral screening and referrals. Systematic implementation of LM faces various challenges, including inadequate leadership support and clinician training in the inner setting and patient preferences and reimbursement complexities in the outer setting [19,20,22,25]. A 2019 survey of ACLM members assessed respondents' current practice of LM, including reimbursement, quality measures, and patient outcomes [26]. In reviewing findings (published elsewhere), ACLM leadership and consultants determined that greater critical richness and additional details could be achieved through a qualitative examination of a subset of US health care systems with LM programs.

ACLM's mission calls for additional high-quality research, education, and advocacy to continue building evidence that LM should be more comprehensively implemented by US health care systems [27]. However, the current literature lacks documentation of the most effective implementation strategies to support LM practice. To address this gap, we are conducting a multi–health system case study to understand the factors that led to the development, growth, and maintenance of successful LM programs within health systems. Specific aims of *Lifestyle Medicine Integration in Health Systems: A Case Study Project* include: (1) examining in-depth 8 LM programs and constructing a detailed case narrative report for each system; (2) identifying factors influencing the initiation and growth of LM practices; and (3) describing common facilitators and barriers across health systems to the continued implementation of LM.

This paper outlines the study protocol, including case selection, data analysis, and dissemination of research findings. It will aid in interpreting study findings and advise the research execution of other studies that incorporate similar methodologies across various settings.

Methods

Overview

In response to a gap in the rich understanding of barriers and facilitators to implementing LM in health systems, the research team selected a qualitative research approach investigating multiple health systems as individual case studies. This multiple case study approach incorporates insights from multiple instances of the phenomenon of interest [28,29].

This paper describes the 8 steps used to conduct this research, as outlined in Table 1. At the time of this writing, steps 1-5 have been completed and steps 6-8 are in progress.

Table 1. Protocol steps for the Lifestyle Medicine Integration in Health Systems study.

Step	Activity	Status[a]
1	Formation of the study team	Complete
2	Selection of methods	Complete
3	Recruitment and training of the study team	Complete
4	Case study nomination and selection	Complete
5	Iterative data collection	Complete
6	Iterative preparation of case study narratives	In progress
7	Preparation of cross-case reports	In progress
8	Dissemination of findings	In progress

[a]As of February 1, 2024.

Step 1: Formation of Study Team (Completed)

The study team comprises team members at ACLM staff and researchers with expertise in public health, LM (including behavior change), and qualitative research. As the national medical professional organization representing physicians and other health professionals practicing LM, ACLM is uniquely positioned to form and coordinate this study team. In addition to representing individual practitioners, ACLM also coordinates a network of health systems, the Health Systems Council (HSC). This group comprises integrated health systems around the United States committed to growing their LM service offerings and sharing their experiences and learnings with other council members [24]. In July 2021, the study team initiated regular (weekly or biweekly) meetings to discuss research aims and methods. The study team has continued to meet throughout the duration of the project.

Step 2: Selection of Methods (Completed)

Through discussion at regular meetings and review of qualitative literature, the study team identified the methods that would be used for this project. We selected a qualitative case study approach, embracing constructivist epistemology (the belief that there is no one truth and that findings are created by the interaction between the patients or informants and the observer or data collector) [30]. Case studies are a qualitative methodology that facilitates the exploration of a specific topic through the development of complex narratives, promoting rich insights from multiple sources within single and multiple cases [28,31,32]. Although findings are heavily influenced by contextual factors, the cross-case reports (described later) provide insights that can be transferred to other settings. This need for transferability suggests a multiple case (rather than single-case) design would be appropriate for the identified research questions [32].

We selected case studies to allow for contextual diversity and triangulation, or the gathering of evidence from multiple data sources, to yield convergent findings [28,33]. To facilitate triangulation, the study methodologies included data collection from multiple stakeholders and source types (in-depth interviews, document review, survey responses, and direct observation). Further, document review allows for the gathering of evidence by interviewers ahead of interviews and reduces the burden on informants [32]. We selected in-depth interviews instead of focus groups to allow for triangulation from different perspectives (both individual experiences and professional roles) and reduce social desirability bias and fear of disclosure among informants [34]. Finally, direct observation (in the form of in-person site visits) yields insights that interviewees may have accidentally omitted due to their own familiarity with their particular context.

Step 3: Recruitment and Training of Study Team (Completed)

The study team is coled by the principal investigator (MCK) and a senior investigator with expertise in qualitative research and case study methods (JG). Additional expert advisors representing ACLM (TAH and KLS) and academic institutions (MLA, SMS, ND, and MMR) offer critical insights and guidance to protocol development and implementation. All data collection was completed by researchers who are external to ACLM, apart from 2 students who were previously involved as members of ACLM. ACLM staff advise on study design or implementation, participate in team meetings, and are part of the iterative review process, but do not conduct data collection.

There were 8 data collectors, who primarily comprised graduate-level students trained in the fields of public health and medicine. Data collectors were hired as research assistants and recruited through study team networks. All data collectors completed data collection training designed and delivered by the academic consultant. The training included general principles of qualitative research, qualitative interviewing techniques, and a review of the study protocol.

Step 4: Case Study Nomination and Selection (Completed)

Multiple case studies are recommended to contain 4-10 cases to achieve sufficient variability while providing a manageable amount of transferrable insights [28]. Stake [28] identifies 3 criteria that should be present when selecting cases: (1) the case must be relevant to the quintain (or phenomenon of interest, which is LM implementation); (2) the cases must provide contextual diversity; and (3) the cases must allow researchers to observe and explore complexities and contexts.

We followed a purposive sampling approach that leveraged the preexisting ACLM HSC network, which is uniquely positioned

to access health systems with LM programs. From March 21-April 1, 2022, recruitment emails were disseminated through ACLM HSC email communications. During the recruitment period, 15 health systems were self-nominated by an employee representative from each interested health system. The self-nomination form captured data on the health system's geographic location, patient demographics, payer types, LM practitioners, programs available, and the estimated reach of the LM program.

Table 2 includes selected self-reported data for the participating health systems and describes geographic location by census-based US regions to preserve health system anonymity [35]. Data reported through the nomination form were not corroborated and should be interpreted conservatively. One health system (site code H) did not complete the nomination form and was recruited through a different mechanism, described below.

Table 2. Summary of self-reported characteristics of participating health systems.

Site code	Region	Level of focus[a]	Reach[b]
A	South	Subspecialty	Small
B	West	Specialty	Large
C	Midwest	Subspecialty	Medium
D	West	Specialty	Medium
E	South	Specialty	Medium
F	Midwest	Subspecialty	Small
G	West	Specialty	Large
H	South	—[c]	—

[a]"Specialty" indicates lifestyle medicine is a stand-alone area of treatment programming; "subspecialty" indicates lifestyle medicine is an adjunct approach embedded in other treatment specialties.

[b]Reported estimated number of patients receiving care at the time of nomination, where "large" is >5000, "medium" is 1000-5000, and "small" is <1000.

[c]Not available.

Study team members reviewed all self-nomination forms and came to a consensus through discussion about which cases to include to achieve contextual diversity, including variability in program size, age, geographic location, payer model, and population served. We selected 4 instrumental cases that were generally representative of the "typical" nominees seen but varied in the aforementioned characteristics [28]. We also selected 2 intrinsic cases that offered a unique context due to their stage (either very early or relatively mature in development), size, and extent of LM practice integration [28]. Selected cases were invited to confirm participation through a health system representative authority.

Partway through case recruitment and data collection, the study team determined that a contrasting case was needed to demonstrate the experiences of a health system that had initiated and then aborted an LM program. The study team agreed that this perspective would yield unique insights about implementation barriers to LM. This iterative approach is an accepted multiple case study procedure, through which redesign can emerge partway through case selection [32]. Original recruitment strategies did not satisfy this need, and the study team used an additional recruitment strategy that built upon individual communications rather than wide-reaching HSC communications channels. One case (site code H) was recruited using this approach and varied slightly in the data collection methods described below.

Step 5: Iterative Data Collection (Completed)

Overview

Each participating health system was assigned a single data collector as a site lead, whose responsibilities included coordinating data collection and drafting the case narrative. The site lead managed a team of 1-2 other data collectors, who conducted individual interviews with different members of the health system's LM team. Overall, 4 types of data were collected: in-depth interviews, site visits, existing documents, and study team notes.

In-Depth Interviews

The study team conducted at least 6-8 in-depth interviews with individuals identified in each participating health system. Health system liaisons were asked to identify employees who were integral to the implementation of the LM programming. They were provided a list of potential types of roles sought for interviews and asked to prioritize individuals who served as health system leaders or administrators (including billing professionals) and physicians. Other health care professionals delivering LM were also requested and included nurse practitioners, registered dietitians, behavioral health specialists, health coaches, exercise physiologists, physical therapists, kinesiologists, and mental health professionals. Only in the instance of the contrasting case were former employees also invited to participate in interviews.

Interviews lasted 45-90 minutes and were conducted through video call (typically), telephone (rarely), or in-person (rarely). When using video call, interviewees had the option of

participating with their camera on (typically) or off (rarely). Interviews were open-ended and exploratory and followed a semistructured interview guide designed to achieve the study aims and allow for adaptability based on the interviewee or health system context. The interview guide was iteratively designed by study team members and loosely structured on the CFIR model [22]. Minor updates to the interview guide were made as emergent topics were identified.

In alignment with the CFIR, interviewees were asked about the inner (structural characteristics, culture, and available resources) and outer (patient population, billing, or payer practices) settings of their health system in addition to individual factors (their specific role and the roles of others) [22]. They were also asked to describe their understanding of the intervention (LM), how it differs from other types of medicine within their setting, and how it was adapted for their specific setting. The interview also included questions about barriers, facilitators, and processes related to program launch and growth. Interviewers were trained to probe topics particularly relevant to the interviewee or health system context. If warranted, the interviewer requested a follow-up interview with an interviewee. These follow-up interviews were intended to answer specific questions, provide missing details, or explore a topic not previously discussed. The most recent version of the interview guide at the time of publication is available in Multimedia Appendix 1.

The 2 study team members assigned to each participating health system were responsible for participating in each associated interview, either as a primary interviewer or as an interview reviewer, which involves reviewing the transcript. Interviews were recorded using the video meeting software (Zoom; Zoom Video Communications [36]) or a recording device (or sometimes both for redundancy) and stored in a secure location on the cloud. Recordings were transcribed using the Microsoft One Drive (Microsoft Corporation) transcription and then manually reviewed and edited for accuracy by study team members. Additionally, interviewers documented emerging themes or other contextual factors following each interview.

Document Review

Interviews were supplemented by the review of available health system documentation. The study team collected and reviewed publicly available annual reports, websites, program promotional materials, strategic plans, and relevant community health needs assessments. Interviewees were asked about additional materials they thought were relevant to the interview themes, and such materials (which may include organizational charts, internal planning documents, and patient education materials) were also reviewed. The study team maintained a database of all reviewed documents to aid in identifying additional documents for review. Interviewers referenced documents if and as needed when reflecting on and taking notes about past interviews, preparing for upcoming interviews, and sharing updates during study team discussions. For example, if an interviewee mentions an LM program that is referenced by multiple names, the interviewer can reference the health system website and patient recruitment materials to confirm the official name of the program. Additionally, documents are referenced during the preparation of the case study narratives and cross-case analysis to corroborate findings, fill in missing details, and provide illustrative examples. For example, if a health system reported promoting referrals by sending email communications to physicians, the language from the communication may be included in the case study narrative as an example of that recruitment strategy.

Site Visits

An in-person site visit occurred for 1 site and included unstructured observations of the settings and conversations with health system employees, which mirrored themes included in the in-depth interview guide. Photos from the site visit (including patient waiting areas, exam rooms, dining and exercise facilities, offices, and other available areas) are referenced in the qualitative data analysis. Otherwise, site visits were not conducted. This decision was made due to the restrictions of the COVID-19 pandemic.

Weekly Study Team Discussions and Iterative Review (Currently in Progress)

Following the principle of emergent design [37], the study team meets 2-4 times per month to debrief from interviews and discuss emerging themes. During team meetings, data collectors report on themes from recent interviews, and the study team discusses how findings enhance the understanding of health system LM implementation and identifies areas to probe further in future interviews. This is also when the study team discusses similarities and differences among health systems and determines the need for potential changes to the study protocol, case selection, interview guide, case narrative outline, and cross-case analysis. Additionally, study team members report on current events and publications that are relevant to research aims. Meeting recordings and minutes are available for study team members to reference during data analysis.

Step 6: Preparation of Case Study Narratives (Currently in Progress)

In collective case study analysis, it is prudent to conduct individual analysis initially (described below) and follow with cross-case analysis (described in step 7) [38]. Through an iterative and collaborative process, the study team developed a case report format that is followed for the preparation of each case narrative to facilitate intercase comparison. This requires that case narratives open with a presentation of objective data, including name, location, size, payer model, etc. The following sections align with the overall study aims and include potential barriers and facilitators to initiation and sustainment. After completing 2 of the case study narratives, the study team decided to add 2 additional sections focused on clinician training and provider burnout to capture emergent themes. All case reports will follow the same report template (the original 2 case study narratives were revised to align with the updated structure) but vary in length and subtopics covered specific to each health system. The case narrative template is included in Multimedia Appendix 2.

The site's lead data collector is primarily responsible for writing the case study narrative. Other study team members review and comment on case narrative drafts until a consensus is reached. As appropriate and necessary, study team members may conduct

additional follow-up interviews or share versions of the case narratives with interviewees (with individual identifiers removed) to facilitate member checking. Additionally, 1 team member is responsible for reviewing all reports for consistency in form, content, and style.

Step 7: Cross-Case Analysis (Currently in Progress)

Following the completion of case study narratives, the study team completes cross-case analyses focused on topics of interest. Specific analysis topics are not yet final but will likely include billing, care delivery models, clinician training, leadership support, buy-in, intervention content, workplace culture, and burnout. Each cross-case analysis will yield a manuscript to be submitted for peer-reviewed publication. Because the cross-case analyses are not yet complete, the following methods offer a high-level overview of the procedures planned for each analysis report.

Some cross-case analyses will follow the multiple case study methodology reported by Stake [28], which includes the following steps: (1) plan the cross-case analysis and identify themes relevant to research questions; (2) become familiar with individual cases; (3) assess case utility for each cross-case theme; and (4) sort and merge findings relevant to themes. In the Stake [28] approach, a series of interactive worksheets are completed to identify emergent themes, guide analysts through their review of case narratives, and plan and execute a cross-case report. This case study analysis methodology was selected as it preserves contextual information to a large degree. Other cross-case analyses may leverage a coding approach, which uses search queries to identify relevant segments of transcripts or documents and then applies an inductive coding schema to the resulting data.

Step 8: Dissemination of Findings (Currently in Progress)

The study team plans to disseminate a series of manuscripts. This paper offers an overview of the methods conducted and planned for data collection, analysis, and reporting. We also plan to disseminate shortened, deidentified versions of the case study narratives to serve as vignettes for consideration by other practitioners. Additional papers will provide insights for each of the cross-case analyses by comparing and contrasting specific findings for each case study site and highlighting common practices seen in instrumental cases and unusual situations seen in intrinsic cases [28]. These can advise on the implementation and integration of LM programs into health systems that can be applied in other settings to initiate or scale current LM offerings.

Additionally, we plan to share deidentified case narratives with the respective participating health systems. This serves the dual purpose of (1) facilitating member checking and (2) offering the benefit of an external perspective to participating health systems.

Ethical Considerations

The University of New England's institutional review board (IRB) reviewed the study protocol and determined it was exempt from IRB review and oversight (project number 1221-21). Before the interview, all participating individuals completed a written informed consent, which included an overview of the study purpose, a request for participation, a description of privacy protection efforts, and a review of potential risks and benefits. Participants were not compensated for their time.

Results

At the time of this writing (February 1, 2024), the study team has completed all the interviews at 8 health systems. The team interviewed 63 individuals, 5 of whom participated in a follow-up interview, resulting in 68 total interviews. Every site included an interview with at least 1 administrator and physician. Across all sites, interviews were conducted with 25 health system leaders or administrators; 16 physicians; 7 registered dietitians; 6 behavioral health specialists or health coaches; 4 nurse practitioners; 2 exercise physiologists, physical therapists, or kinesiologists; 2 mental health professionals; and 1 individual with an unclassified role.

The study team has completed initial drafts of all 8 case study narratives and is abridging and deidentifying them for member checking and broader dissemination. Cross-case analysis is underway to identify critical facilitators and barriers, explore clinician training strategies to facilitate LM implementation and develop an explanatory model connecting practitioner adoption of LM and experiences of burnout. Additional analyses may investigate how billing strategies, care delivery models, leadership support or buy-in, and intervention content can impact LM implementation in health systems.

Discussion

Overview

This research is the first multiple case study examining facilitators and barriers to LM implementation in health system settings. It will address a gap in the literature by providing insight into the barriers and facilitators to adopting LM practice in health systems. Below is a discussion of limitations, strengths, and opportunities for further research.

Limitations

ACLM serves as the primary funder for this work, potentially introducing a pro-LM bias. To reduce the influence of this bias, the study team was intentionally designed to be diverse and include experts who are external to ACLM and thus not biased in the same way that ACLM affiliates are. Additionally, all methodological and analysis decisions are made during study team meetings, which include multiple perspectives, including 1 senior advisor, in addition to ACLM.

In some cases, the study team was challenged to identify interviewees who comprehensively represented the breadth of LM activities in a single health system. This is partly due to the size and complexity of participating health systems. Individual interviewees were identified by 1 or 2 liaisons at each health system and sometimes did not include groups or types of individuals who would have offered valuable insights. For example, 1 site provided names of individuals who were involved in implementing one specific LM program but were

not familiar with the LM residency program that was offered by a different unit of the health system. This resulted in in-depth data about the specific LM program but fewer insights into the LM residency offerings. Additionally, some health systems were unable to allow nonexempt employees to participate in in-depth interviews because the study was not compensating interviewees for their participation. This resulted in an overrepresentation of leadership and an underrepresentation of front-line workers and intervention delivery personnel. To address these challenges, the study team circled back to health system liaisons to request interviews with additional individuals whose perspectives were not initially included, although the requests were not always met. Data collection methods did not directly include patients or community members, resulting in a gap in these perspectives. Interviewees were asked to speak about the experiences of these individuals, but future research should also investigate these perspectives, specifically.

Finally, site visits and in-person interviews were limited due to restrictions associated with the COVID-19 pandemic. We were only able to conduct 1 site visit, which was conducted in person. To adapt, we revised our methods to prioritize internet-based interviews. Through this process, we learned that internet-based interviews facilitated easier scheduling and access to individuals and often yielded high-quality interviews that were thought to be comparable to in-person interviews. Considering the added logistical benefits, the study team determined the internet-based interview approach to be preferable to in-person site visits. No interviews were conducted in person.

Strengths

This multiple case study methodology and our iterative team-based approach are strengths of this research. By preserving the context of each case, researchers can gain a rich understanding of the many factors impacting the phenomenon of interest [28,31]. Although the selection of ACLM HSC members allows for insights into the experiences of early adopters, the findings may not be translatable to relatively more nascent programs. Throughout the early stages of case selection, our team reviewed health system components to ensure variability in program maturation. We intentionally selected health systems with more recently established LM programs and also sought out and recruited a contrasting case that had initiated and then greatly reduced LM programming. However, the study would have been further strengthened by the inclusion of additional negative cases. The heterogeneity of participating health systems will contribute to the transportability of the study findings. Future research should investigate if and how barriers and facilitators are different among health systems that are not currently aligned with LM.

A strength of this study is that the cases and analyses take place at the health system level, allowing a more comprehensive perspective that incorporates all CFIR domains [22]. Health systems are complex systems of hospitals, clinics, and individuals connected through joint ownership or management [38]. Within these systems are varying cultures (“individuals involved” domain), policies, and processes (“inner setting” domain), which can impact practices (“process domain”). Examination at the health system organization level offers insights into the macrolevel factors (“inner” and “outer setting” domains) that impact LM implementation. Gaining permission to work with such large and complex organizations can be challenging, however, and in some instances, investigation was delayed and even prohibited due to the inability or unwillingness of health system leadership to provide permission for participation. Some health system leaders expressed confidentiality concerns, noting that patient perspectives of the organization and their practices were a critical consideration.

Conclusions

This protocol paper offers real-world examples of research methodologies used to gather data on a series of health systems. Additionally, the study findings will yield practical insights into strategies to effectively implement LM in health systems. Health system leaders and administrators can draw on these findings to establish and grow their own LM programs and integrate LM practices into existing services. Expanded access to LM treatment may result in improved morbidity and mortality outcomes related to chronic diseases [1,6,12].

Acknowledgments

The authors would like to thank the participating health systems and staff for their support of this project, as well as American College of Lifestyle Medicine employees, including Kaitlyn Pauly, who advised on this work.

Data Availability

The data presented in this study cannot be shared due to privacy concerns and the inability to adequately secure the identity of the participants.

Authors' Contributions

MCK and JG are co–principal investigators. MLA, JG, MCK, and SMS contributed to the methodology. MLA was involved in writing and preparing the original draft of the manuscript. MLA, ND, JG, TAH, MCK, MMR, KLS, SMS, and BW contributed to the writing, reviewing, and editing of the manuscript. MCK and SMS were responsible for project administration. MCK was responsible for funding acquisition. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

MCK, TAH, and KLS are employed by the American College of Lifestyle Medicine. The other coauthors receive consulting payments from the American College of Lifestyle Medicine.

Multimedia Appendix 1
In-depth interview guide.
[DOCX File , 42 KB - resprot_v13i1e51562_app1.docx]

Multimedia Appendix 2
Case study narrative outline.
[DOCX File , 37 KB - resprot_v13i1e51562_app2.docx]

References

1. Leading causes of death. Centers for Disease Control and Prevention. 2022. URL: https://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm [accessed 2022-01-19]
2. Buttorff C, Ruder T, Bauman M. Multiple Chronic Conditions in the United States. Santa Monica, CA: RAND; 2017.
3. Pronovost PJ, Urwin JW, Beck E, Coran JJ, Sundaramoorthy A, Schario ME, et al. Making a dent in the trillion-dollar problem: toward zero defects. NEJM Catalyst 2021;2(1). [doi: 10.1056/cat.19.1064]
4. Willett WC. Balancing life-style and genomics research for disease prevention. Science 2002;296(5568):695-698. [doi: 10.1126/science.1071055] [Medline: 11976443]
5. About us. American College of Lifestyle Medicine. URL: https://lifestylemedicine.org/about-us/ [accessed 2023-03-25]
6. Rippe JM. Lifestyle medicine: the health promoting power of daily habits and practices. Am J Lifestyle Med 2018;12(6):499-512 [FREE Full text] [doi: 10.1177/1559827618785554] [Medline: 30783405]
7. Turner-McGrievy GM, Davidson CR, Wingard EE, Wilcox S, Frongillo EA. Comparative effectiveness of plant-based diets for weight loss: a randomized controlled trial of five different diets. Nutrition 2015;31(2):350-358. [doi: 10.1016/j.nut.2014.09.002] [Medline: 25592014]
8. Jakše B, Pinter S, Jakše B, Pajek MB, Pajek J. Effects of an ad libitum consumed low-fat plant-based diet supplemented with plant-based meal replacements on body composition indices. Biomed Res Int 2017;2017:9626390 [FREE Full text] [doi: 10.1155/2017/9626390] [Medline: 28459071]
9. Tonstad S, Butler T, Yan R, Fraser GE. Type of vegetarian diet, body weight, and prevalence of type 2 diabetes. Diabetes Care 2009;32(5):791-796 [FREE Full text] [doi: 10.2337/dc08-1886] [Medline: 19351712]
10. Wright N, Wilson L, Smith M, Duncan B, McHugh P. The BROAD study: a randomised controlled trial using a whole food plant-based diet in the community for obesity, ischaemic heart disease or diabetes. Nutr Diabetes 2017;7(3):e256 [FREE Full text] [doi: 10.1038/nutd.2017.3] [Medline: 28319109]
11. Livingston KA, Freeman KJ, Friedman SM, Stout RW, Lianov LS, Drozek D, et al. Lifestyle medicine and economics: a proposal for research priorities informed by a case series of disease reversal. Int J Environ Res Public Health 2021;18(21):11364 [FREE Full text] [doi: 10.3390/ijerph182111364] [Medline: 34769879]
12. Guo XY, Shu J, Fu XH, Chen XP, Zhang L, Ji MX, et al. Improving the effectiveness of lifestyle interventions for gestational diabetes prevention: a meta-analysis and meta-regression. BJOG 2019;126(3):311-320. [doi: 10.1111/1471-0528.15467] [Medline: 30216635]
13. Wong VWH, Ho FYY, Shi NK, Sarris J, Ng CH, Tam OKY. Lifestyle medicine for anxiety symptoms: a meta-analysis of randomized controlled trials. J Affect Disord 2022;310:354-368. [doi: 10.1016/j.jad.2022.04.151] [Medline: 35523299]
14. Katz DL, Karlsen MC, Chung M, Shams-White MM, Green LW, Fielding J, et al. Hierarchies of Evidence Applied to Lifestyle Medicine (HEALM): introduction of a strength-of-evidence approach based on a methodological systematic review. BMC Med Res Methodol 2019;19(1):178 [FREE Full text] [doi: 10.1186/s12874-019-0811-z] [Medline: 31429718]
15. Satija A, Bhupathiraju SN, Rimm EB, Spiegelman D, Chiuve SE, Borgi L, et al. Plant-based dietary patterns and incidence of type 2 diabetes in US men and women: results from three prospective cohort studies. PLoS Med 2016;13(6):e1002039 [FREE Full text] [doi: 10.1371/journal.pmed.1002039] [Medline: 27299701]
16. The costly chronic disease epidemic. Partnership to Fight Chronic Disease. 2016. URL: https://www.fightchronicdisease.org/ [accessed 2024-02-08]
17. Follefson M. American college of lifestyle medicine: 2021 annual member report. American College of Lifestyle Medicine. 2021. URL: https://lifestylemedicine.org/ [accessed 2024-02-08]
18. Healthy lifestyles H-425. American Medical Association. 2017. URL: https://policysearch.ama-assn.org/policyfinder/detail/Healthy%20Lifestyles%20H-425.972?uri=%2FAMADoc%2FHOD.xml-0-3746.xml [accessed 2022-01-19]
19. Patel P, Madrid M. Successfully integrating lifestyle medicine into health systems. Am J Lifestyle Med 2021;15(5):510-513 [FREE Full text] [doi: 10.1177/15598276211008397] [Medline: 34646099]
20. Petersen MR, Freeman AM, Madrid M, Aggarwal M. Strategies for incorporating lifestyle medicine in everyday hospital practice. Am J Lifestyle Med 2021;15(5):531-537 [FREE Full text] [doi: 10.1177/15598276211006664] [Medline: 34646102]

21. Katz DL. How to improve clinical practice and medical education about nutrition. AMA J Ethics 2018;20(10):E994-E1000 [FREE Full text] [doi: 10.1001/amajethics.2018.994] [Medline: 30346928]
22. Damschroder LJ, Aron DC, Keith RE, Kirsh SR, Alexander JA, Lowery JC. Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. Implement Sci 2009;4:50 [FREE Full text] [doi: 10.1186/1748-5908-4-50] [Medline: 19664226]
23. Furukawa MF, Machta RM, Barrett KA, Jones DJ, Shortell SM, Scanlon DP, et al. Landscape of health systems in the United States. Med Care Res Rev 2020;77(4):357-366 [FREE Full text] [doi: 10.1177/1077558718823130] [Medline: 30674227]
24. Health systems council. American College of Lifestyle Medicine. 2021. URL: https://lifestylemedicine.org/health-systems-council/ [accessed 2024-02-13]
25. Freeman KJ, Grega ML, Friedman SM, Patel PM, Stout RW, Campbell TM, et al. Lifestyle medicine reimbursement: a proposal for policy priorities informed by a cross-sectional survey of lifestyle medicine practitioners. Int J Environ Res Public Health 2021;18(21):11632 [FREE Full text] [doi: 10.3390/ijerph182111632] [Medline: 34770148]
26. Pollard KJ, Gittelsohn J, Patel P, Lianov L, Freeman K, Staffier KL, et al. Lifestyle medicine practitioners implementing a greater proportion of lifestyle medicine experience less burnout. Am J Health Promot 2023;37(8):1121-1132 [FREE Full text] [doi: 10.1177/08901171231182875] [Medline: 37368959]
27. Mission/Vision. American College of Lifestyle Medicine. 2021. URL: https://lifestylemedicine.org/about-us/ [accessed 2024-02-13]
28. Stake RE. Multiple Case Study Analysis. New York, NY: The Guilford Press; 2006.
29. Stake RE. The Art of Case Study Research. London: Sage Publications; 1995.
30. Crabtree B, Miller W. In: Miller BCW, editor. Doing Qualitative Research. London: Sage Publications; 2012.
31. Creswell JW. Qualitative Inquiry and Research Design: Choosing among Five Approaches. Thousand Oaks, CA: Sage Publications; 2007.
32. Yin RK. Case Study Research: Design and Methods. 5th Edition. Los Angeles: Sage; 2014.
33. Mason J. Qualitative Researching. 2nd Edition. London: Sage Publishing; 2002.
34. Hollander JA. The social contexts of focus groups. J Contemp Ethnogr 2016;33(5):602-637. [doi: 10.1177/0891241604266988]
35. Census regions and divisions of the United States. US Census Bureau. URL: https://www2.census.gov/geo/pdfs/maps-data/maps/reference/us_regdiv.pdf [accessed 2024-02-08]
36. Zoom. 5.13.11 ed2023. Zoom Video Communications I. URL: https://community.zoom.com/t5/Meetings/Updating-to-Version-5-13-11-13434-from-Version-5-9-7-3931-so-I/m-p/106842 [accessed 2024-02-08]
37. Creswell JW. Research Design: Qualitative, Quantitative, and Mixed Methods Approaches. 4th Edition. Thousand Oaks, CA: Sage Publications, Inc; 2014.
38. Crowe S, Cresswell K, Robertson A, Huby G, Avery A, Sheikh A. The case study approach. BMC Med Res Methodol 2011;11:100 [FREE Full text] [doi: 10.1186/1471-2288-11-100] [Medline: 21707982]

Abbreviations

ACLM: American College of Lifestyle Medicine
CFIR: Consolidated Framework For Implementation Research
HSC: Health Systems Council
IRB: institutional review board
LM: lifestyle medicine

Edited by A Mavragani; submitted 03.08.23; peer-reviewed by B Bode, D Ruijter; comments to author 28.01.24; revised version received 04.02.24; accepted 06.02.24; published 13.03.24.

Please cite as:
Ames ML, Karlsen MC, Sundermeir SM, Durrwachter N, Hemmingson TA, Reznar MM, Staffier KL, Weeks B, Gittelsohn J
Lifestyle Medicine Implementation in 8 Health Systems: Protocol for a Multiple Case Study Investigation
JMIR Res Protoc 2024;13:e51562
URL: https://www.researchprotocols.org/2024/1/e51562
doi:10.2196/51562
PMID:38320320

Protocol

Target Product Profile for a Machine Learning–Automated Retinal Imaging Analysis Software for Use in English Diabetic Eye Screening: Protocol for a Mixed Methods Study

Trystan Macdonald[1,2,3], MBChB; Jacqueline Dinnes[3], MSc, PhD; Gregory Maniatopoulos[4], PhD; Sian Taylor-Phillips[5], PhD; Bethany Shinkins[5], PhD; Jeffry Hogg[6], MBBS, MRes; John Kevin Dunbar[7], MBChB; Ameenat Lola Solebo[8,9], PhD; Hannah Sutton[10], BA; John Attwood[11], MA; Michael Pogose[12], MSc; Rosalind Given-Wilson[13], MBBS; Felix Greaves[14,15], PhD; Carl Macrae[16], PhD; Russell Pearson[17], PhD; Daniel Bamford[7], MA; Adnan Tufail[9,18], MD; Xiaoxuan Liu[1,2,3*], PhD; Alastair K Denniston[1,2,3,19,20*], PhD

[1]Ophthalmology Department, Queen Elizabeth Hospital Birmingham, University Hospitals Birmingham National Health Service Foundation Trust, Birmingham, United Kingdom

[2]Academic Unit of Ophthalmology, Institute of Inflammation and Aging, College of Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom

[3]National Institute for Health and Care Research Birmingham Biomedical Research Centre, Birmingham, United Kingdom

[4]School of Business, University of Leicester, Leicester, United Kingdom

[5]Warwick Medical School, University of Warwick, Coventry, United Kingdom

[6]Population Health Sciences Institute, Faculty of Medical Sciences, The University of Newcastle upon Tyne, Newcastle, United Kingdom

[7]NHS England, Leeds, United Kingdom

[8]Population Policy and Practice, University College London Great Ormond Street Institute of Child Health, London, United Kingdom

[9]Moorfields Eye Hospital NHS Foundation Trust, London, United Kingdom

[10]Lay member, Oxford, United Kingdom

[11]Alder Hey Children's Hospital, Alder Hey Children's Hospital NHS Foundation Trust, Liverpool, United Kingdom

[12]Hardian Health, London, United Kingdom

[13]St. George's University Hospitals National Health Service Foundation Trust, London, United Kingdom

[14]National Institute for Health and Care Excellence, London, United Kingdom

[15]Faculty of Medicine, School of Public Health, Imperial College London, London, United Kingdom

[16]Nottingham University Business School, University of Nottingham, Nottingham, United Kingdom

[17]Medicines and Healthcare Products Regulatory Agency, London, United Kingdom

[18]Institute of Ophthalmology, University College London, London, United Kingdom

[19]Centre for Regulatory Science and Innovation, Birmingham Health Partners, Birmingham, United Kingdom

[20]National Institute for Health and Care Research Biomedical Research Centre at Moorfields and University College London Institute of Ophthalmology, London, United Kingdom

[*]these authors contributed equally

Corresponding Author:
Alastair K Denniston, PhD
Ophthalmology Department
Queen Elizabeth Hospital Birmingham
University Hospitals Birmingham National Health Service Foundation Trust
Mindelsohn Way
Edgbaston
Birmingham, B15 2TH
United Kingdom
Phone: 44 1213716905
Email: a.denniston@bham.ac.uk

Abstract

Background: Diabetic eye screening (DES) represents a significant opportunity for the application of machine learning (ML) technologies, which may improve clinical and service outcomes. However, successful integration of ML into DES requires careful product development, evaluation, and implementation. Target product profiles (TPPs) summarize the requirements necessary for successful implementation so these can guide product development and evaluation.

Objective: This study aims to produce a TPP for an ML-automated retinal imaging analysis software (ML-ARIAS) system for use in DES in England.

Methods: This work will consist of 3 phases. Phase 1 will establish the characteristics to be addressed in the TPP. A list of candidate characteristics will be generated from the following sources: an overview of systematic reviews of diagnostic test TPPs; a systematic review of digital health TPPs; and the National Institute for Health and Care Excellence's Evidence Standards Framework for Digital Health Technologies. The list of characteristics will be refined and validated by a study advisory group (SAG) made up of representatives from key stakeholders in DES. This includes people with diabetes; health care professionals; health care managers and leaders; and regulators and policy makers. In phase 2, specifications for these characteristics will be drafted following a series of semistructured interviews with participants from these stakeholder groups. Data collected from these interviews will be analyzed using the shortlist of characteristics as a framework, after which specifications will be drafted to create a draft TPP. Following approval by the SAG, in phase 3, the draft will enter an internet-based Delphi consensus study with participants sought from the groups previously identified, as well as ML-ARIAS developers, to ensure feasibility. Participants will be invited to score characteristic and specification pairs on a scale from "definitely exclude" to "definitely include," and suggest edits. The document will be iterated between rounds based on participants' feedback. Feedback on the draft document will be sought from a group of ML-ARIAS developers before its final contents are agreed upon in an in-person consensus meeting. At this meeting, representatives from the stakeholder groups previously identified (minus ML-ARIAS developers, to avoid bias) will be presented with the Delphi results and feedback of the user group and asked to agree on the final contents by vote.

Results: Phase 1 was completed in November 2023. Phase 2 is underway and expected to finish in March 2024. Phase 3 is expected to be complete in July 2024.

Conclusions: The multistakeholder development of a TPP for an ML-ARIAS for use in DES in England will help developers produce tools that serve the needs of patients, health care providers, and their staff. The TPP development process will also provide methods and a template to produce similar documents in other disease areas.

International Registered Report Identifier (IRRID): DERR1-10.2196/50568

(JMIR Res Protoc 2024;13:e50568) doi:10.2196/50568

KEYWORDS

artificial intelligence; design; developers; diabetes mellitus; diabetic eye screening; diabetic retinopathy; diabetic; DM; England; eye screening; imaging analysis software; implementation; machine learning; retinal imaging; study protocol; target product profile

Introduction

Diabetic Eye Screening and Its Delivery in the United Kingdom

Diabetic eye screening (DES) aims to prevent vision loss from diabetic retinopathy (DR), a sight-threatening microvascular complication of diabetes [1]. In the United Kingdom, people with diabetes aged 12 years or older undergo yearly fundus photography with images interpreted by human graders to detect and assess the severity of DR. This allows detection of DR in its early asymptomatic stages, facilitating early referral to hospital eye services where treatment is more effective [2,3]. DES is associated with improved clinical [4] and economic [5] outcomes and a reduction in blindness from DR since its introduction in 2003 [6]. However, DES is both labor and resource intensive [7], and costs are expected to increase with a projected rise in diabetes prevalence [8]. In the United Kingdom, grading is undertaken by experienced professionals in a quality-assured and controlled multilevel system [9] with a high sensitivity for sight-threatening diseases [10]. However, grading represents a significant cost despite the fact that the majority of people with diabetes have no evidence of DR or only mild disease [11] and are at low risk of visual loss in the near term [12].

Automated Retinal Imaging Analysis Software

DES grading is considered a promising use case for automation, and indeed, DES in Scotland has used automated retinal imaging analysis software (ARIAS) since 2012 [13,14]. This software uses "symbolic" artificial intelligence (AI) with grading "rules" programmed by humans [15] and is used in a primary grader role. The Scottish "autograder" has demonstrated a sensitivity of 90.5% (95% CI 89.3%-91.6%) and specificity of 67.4% (95% CI 66%-68.8%) for referable disease or ungradable images [13], with 50% of images it graded in 2018 requiring no further human review [16]. It is, however, unable to process the optic disc–centered images acquired in screening protocols elsewhere in the United Kingdom and has not been adopted outside Scotland [17].

Subsequent advances in AI, most notably in machine learning (ML), where AI "learns" patterns from data it is presented as opposed to being programmed by humans, have given rise to a newer generation of machine learning–automated retinal imaging analysis software (ML-ARIAS). These have demonstrated better performance than symbolic tools on

routinely collected UK screening images, including disc-centered photos. Heydon et al [18] found ML-ARIAS was able to achieve sensitivity and specificity of 95.7% (95% CI 94.8%-96.5%) and 54% (95% CI 53.4%-54.5%), respectively, for referable disease or ungradable images in a large sample taken from routine screening in 3 UK programs. A health technology assessment has also estimated that ML-ARIAS in a triage or primary grader role could be cost-effective and cost-saving compared to purely manual grading [17]. Consequently, there have been calls for ML-ARIAS's adoption into DES in the United Kingdom [19].

Bridging the Implementation Gap

In response to these calls, the UK National Screening Committee (NSC), an independent scientific advisory group that advises UK governments on screening programs, commissioned a review to ascertain whether ARIAS should be more widely adopted in 2021 [19]. While the review found evidence suggesting ML-ARIAS to be safe, accurate, and cost-effective, it also highlighted evidence gaps that prevented a recommendation for their use. The review highlighted that the acceptability of ML-ARIAS with patients and health care professionals was unknown, as was their real-world performance post implementation, recognizing that this may be affected by a range of clinical and technical factors. While research to address these evidence gaps is currently ongoing [20], the review's conclusions reflect an awareness in the wider field of health care AI that evidence of good diagnostic accuracy cannot predict the impact tools will have post deployment. This awareness contributes toward a growing "implementation gap" [21,22] or "chasm" [23] in health care AI, with increasing numbers of tools failing to be adopted into clinical use following promising research. This situation has a number of negative consequences, such as significant opportunity cost, with tools' development requiring significant public [24] or private investment [25], as well as a failure for patients, health care professionals, or systems to realize the benefits tools may offer for a lack of appropriate evidence generation.

A similar situation has existed in the pharmaceutical and medical device industries for decades. Despite significant investment in research and development, few biomarkers, drugs, or devices are ever adopted into routine clinical care, often failing to achieve regulatory approval or demonstrate sufficient clinical or economic benefits to health care providers [26,27]. To combat this situation, pharmaceutical companies began to outline the characteristics necessary for a successful product in the earliest stages of development, summarizing these in "target product profiles" (TPPs). These documents often incorporate considerations essential to successful clinical use but not covered in traditional research, such as interaction with existing care pathways and resource constraints. TPPs are used to guide research development as part of a broader "quality by design" approach that has been encouraged by regulatory agencies [28,29] and widely adopted in industry with notable successes [30,31]. TPPs have since been used by governments [32], health care providers [33], and nonprofit organizations [34] for drugs [35,36] and medical devices [37], particularly in the context of infectious diseases [38,39] and the developing world [40,41].

Aim

This study aims to produce a TPP for an ML-ARIAS for use in English DES (E-DES), enabling the development of ML tools that match the needs of people with diabetes, health care professionals, regulators, and providers. This work will focus on the English context, as variations in the commissioning and organization of DES between UK nations may affect the stakeholders needed as well as the TPP's final contents. However, we hope this work will be valuable for screening programs in other nations in the United Kingdom and beyond.

Objectives

The objectives of this study are to (1) identify which characteristics should be addressed in a TPP for an ML-ARIAS (this will be achieved through an overview of systematic reviews of TPPs, a systematic review of digital health TPPs, and by extracting standard's from the National Institute of Health and Care Excellence's (NICE) Evidence Standards Framework for Digital Health Technologies (ESF); (2) draft specifications for an ML-ARIAS TPP through semistructured interviews with members of key stakeholder groups; and (3) validate the contents of a TPP for an ML-ARIAS through a modified Delphi consensus study.

Methods

Ethical Considerations

Ethical approval for this study has been granted by the University of Birmingham Institutional Research Board (ERN_2023-0620). The study will be undertaken in accordance with the Helsinki Declaration of 1975, as revised in 2000. Informed consent will be sought from participants. The interviews and consensus meeting will be recorded and transcribed, with participants given the opportunity to opt out with deletion of their responses up to a week after their interview or meeting date, after which their responses will be anonymized and therefore no longer attributable to them. Recordings of the interview and consensus meeting will be deleted following transcription, with the anonymized transcripts stored on secure institutional research servers for up to 10 years. Delphi participants will be informed that their responses are anonymized and therefore cannot be deleted following submission. Contact details they provide in order to be able to participate in the consensus meeting will be stored on secure servers until the end of the study, after which they will be deleted.

People with diabetes participating in the study advisory group (SAG) and consensus meeting will have their travel costs reimbursed as well as their time reviewing documents or attending meetings at £25 (US $31.57) per hour in line with National Institute for Health and Care Research (NIHR) guidance [42,43].

Identifying Key Stakeholder Groups

The successful use of ML-ARIAS in E-DES will require the approval, collaboration, and consent of a diverse range of stakeholder groups. To ensure our TPP is both comprehensive

and authoritative it is therefore important to incorporate the knowledge and opinions of all these groups in its development.

A recent qualitative systematic review on stakeholder perspectives of clinical AI implementation identified the following key stakeholder groups influencing implementation: patients, carers, and the public; health care professionals; health care managers and leaders; regulators and policy makers; and developers [44]. Mapped to our use case and context, these broad stakeholder groups can be further divided as follows: people with diabetes, carers, and the public; E-DES technicians and graders, as well as ophthalmologists (health care professionals); managers of E-DES services provided by either the NHS or independent providers (health care managers and leaders); the Medicines and Healthcare Products Regulatory Agency (MHRA), NICE, the Care Quality Commission (CQC), and NSC (regulators and policy makers); and ML-ARIAS developers. Our study will aim to encompass the opinions of all these groups as outlined below.

Study Delivery and Oversight

Study Management Group

A study management group (SMG) led by the chief investigator AKD will be responsible for the design and delivery of the study.

Recruitment

SMG members will be recruited from the host institution to facilitate ease of communication and regular meetings.

Sampling

The SMG will include experts in the relevant clinical, scientific, and methodological domains, project management support, and a person with diabetes.

Study Advisory Group

The SMG will be supported by a SAG, which will bring additional breadth of expertise from a range of key stakeholder groups. The SAG will provide critical feedback and advice throughout the project in quarterly project review meetings and at specific junctures outlined in the protocol and ad hoc.

Recruitment

SAG recruitment strategies will be tailored to individual stakeholder groups. People with diabetes will be recruited through diabetes charities. Clinical and methodological experts with previous experience developing TPPs will be identified through their publications in the field. Representatives of relevant regulatory and policy bodies will be recruited through their organizations (NSC, MHRA, NICE, and CQC).

Sampling

The SAG will aim to recruit at least 2 representatives from each of the broad stakeholder groups previously identified, with the exception of ML-ARIAS developers, omitted to avoid bias arising from conflict of interest. Experts in TPP development and health economics will also be invited to the SAG to add a greater breadth of expertise.

User Group

A TPP user group (UG) consisting of ML-ARIAS developers will be assembled to provide feedback on the TPP as outlined below to ensure feasibility is factored into the development process.

Sampling

The UG will consist of only ML-ARIAS developers.

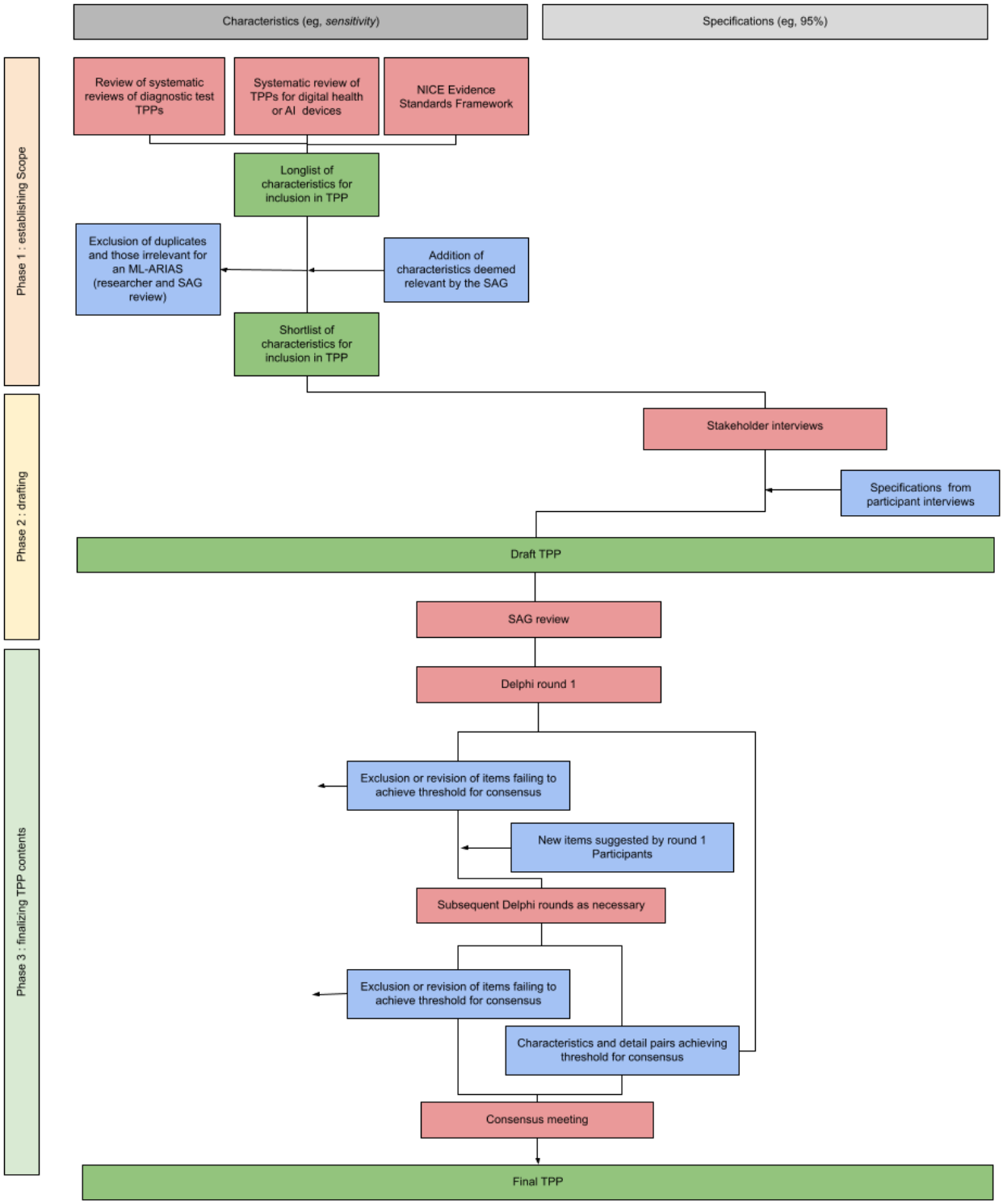
Recruitment

Developers with ML-ARIAS approved by British, European, Australian, or US medical device regulators will be invited to participate, along with those with technologies included in the UK NSC's 2021 review.

Phase 1: Literature Reviews to Establish the Scope of an ML-ARIAS TPP

See Figure 1 for an overview of the ML-ARIAS TPP development process.

Figure 1. Diagram of the machine learning–automated retinal imaging analysis software (ML-ARIAS) target product profile (TPP) development process. AI: artificial intelligence; NICE: National Institute for Health and Care Excellence; SAG: study advisory group.



Rationale

This phase will seek to establish what characteristics a TPP for an ML-ARIAS should address in order to be both relevant and comprehensive. A long list of potential characteristics for inclusion in an ML-ARIAS TPP will be generated through 2 reviews. These will be built on the work of Cocco et al [45], who published a list of all characteristics previously reported in diagnostic test TPPs in a 2020 systematic review.

Overview of Systematic Reviews of Target Product Profiles for Diagnostic Tests

This will seek to identify all systematic reviews of diagnostic test TPPs with the aim of extracting the characteristics reported in each review or the TPPs they capture. Based on a scoping search, we anticipate this review will include the systematic review by Cocco et al [45] and any new resources published since.

Systematic Review of TPPs for Digital Health Tools

As Cocco et al's [45] review did not include any TPPs for digital health tools, our long list of potential characteristics may therefore omit characteristics unique to these tests. The purpose of this review is to identify all TPPs published for digital health tools (including AI) and extract the characteristics they report. This will include TPPs for therapeutic as well as diagnostic devices.

Multimedia Appendix 1 includes MEDLINE search strategies for both reviews, developed in consultation with an information specialist and using validated search filters where possible [45-47]. Strategies for other bibliographic databases will be adapted from these, as will a web search strategy using a systematic method previously reported [48]. The 2 reviewers (TM and JH) will perform a title and abstract screening, then a full-text review to assess eligibility. Disagreements will be arbitrated by the senior investigator (AKD).

Generating AI-Specific Characteristics from NICE's Evidence Standards Framework for Digital Health Technologies

Rationale

As scoping searches for digital health TPPs have returned very few TPPs for AI and specifically ML tools, relying on the above reviews alone to determine the scope of our TPP may risk omitting characteristics unique to these devices and essential for their successful deployment. To generate AI-specific characteristics, we will therefore adapt standards from NICE's ESF for digital health technologies, a gold standard tool designed to evaluate digital health technologies for UK commissioning decisions. This was revised in 2022 to encompass AI devices, with the new AI standards being generated through a multistakeholder Delphi consensus process [49,50]. The 2 reviewers (TM and JH) will review the ESF, extracting relevant standards, with disagreements resolved by discussion or arbitration by the senior investigator (AKD). The extracted standards will be adapted into characteristics and added to the long list from the earlier reviews.

Shortlisting Characteristics for Inclusion in a Draft TPP

The list of candidate characteristics will be reviewed by the SMG to remove any irrelevant to the use case or proposed technology and consolidate the remainder, removing any duplicates. Disagreements between SMG members will be resolved through discussion and arbitration by the senior investigator (AKD) if necessary.

The remaining characteristics will then be mapped to the nonadoption, abandonment, scale-up, spread, and sustainability (NASSS) framework [51], a tool outlining the interacting complexity of factors at the policy, organizational, and practice level that may influence the successful implementation of digital health technology [52]. The NASSS will help group the characteristics into broader themes and help identify factors affecting successful implementation that they do not cover.

The included characteristics will then be presented to the SAG, along with those excluded and the NASSS domains not covered by the shortlist. SAG members will be asked to identify any characteristics incorrectly excluded and approve a final shortlist of characteristics for subsequent research phases through discussion or vote.

Phase 2: Drafting the TPP

Scoping Interviews

A TPP typically includes a table of characteristics and their specifications. Characteristics might include "target population" with "people with diabetes aged 12 years or older" as its associated specification. The drafting of specifications for each of the characteristics shortlisted in phase 1 will be informed by semistructured interviews with participants from each key stakeholder group previously identified. The final output of phase 2 will be a full draft TPP for entry into a modified Delphi consensus study in phase 3.

Sampling

Purposive sampling will initially be used with the aim of interviewing at least 1 individual from all the stakeholder groups relevant to the use case previously identified, with the exception of ML-ARIAS developers. As the interviews progress, theoretical sampling will be used to better explore areas of disagreement or characteristics that have not been addressed in previous interviews. Snowball sampling will also be used, with participants invited to suggest potential interviewees. An approximate target of 20 participants has been set; however, the scale of recruitment will be refined by the SMG as the interviews progress.

Recruitment

People with diabetes will be recruited through diabetes charities and offered compensation for their time in accordance with NIHR guidelines [42,43]. Clinical and methodological experts, as well as industry representatives with previous knowledge or experience of AI in DES or TPPs, will be identified through their publications in the field. Representatives of relevant regulatory and policy bodies will be recruited by contacting their organizations (NSC, MHRA, and NICE). It is anticipated that members of the SAG will facilitate the recruitment of key stakeholders in their respective stakeholder groups.

Data Collection

Ahead of the interviews, participants will be sent information in plain English on E-DES, AI, and TPPs.

The interviews will be conducted over video teleconferencing software (Zoom; Zoom Video Communications, Inc). Interview participants will initially be asked to provide demographic data, including stakeholder groups, location, age, sex, gender, and ethnicity. A preprepared topic guide informed by the shortlist of characteristics produced in phase 1 will be developed and used to encourage a free-flowing conversation between interviewer and interviewee focused on the latter's opinions, priorities, and concerns regarding the adoption of ML-ARIAS in E-DES. The topic guide will be iterated as the interviews progress to ensure all implementation considerations are covered and adapted to different stakeholder groups to facilitate meaningful participation.

All the interviews will be conducted by 2 clinicians (TM and JH) with previous training and experience in qualitative interviewing. They will present themselves as researchers during the interviews so as not to introduce bias to the data collected [53]; however, as their status may become apparent during the interview and can be discovered on the internet, they will use reflective journaling to identify and mitigate against any effects this may have on data collection [54]. Both interviewers will take field notes during and after the interviews to provide context for the data analysis.

Data Analysis

All the interviews will be digitally recorded and transcribed verbatim. Data analysis will begin after the first interview and proceed in parallel with the remainder. One researcher (TM) will code the interview transcripts using qualitative analysis software (NVivo, Lumivero). The coded data will then be mapped to the shortlist of characteristics produced from phase 1, using this as a framework to aid analysis [55].

The data collected will be reviewed throughout the collection period by the SMG to identify and manage biases in sampling, data collection, analysis, and interpretation. The data will be used to iterate the topic guide, recruitment, and sampling strategies to allow the exploration of problematic issues, divergent views between or within stakeholder groups, and implementation considerations not previously explored.

On completion of the data analysis, the SMG will draft characteristics' specifications based on the analyzed data. An initial draft TPP will be presented to the SAG for review and approval before entry into phase 3.

Phase 3: Finalizing the TPP

Internet-Based Delphi Consensus Rounds

The draft TPP will be entered into an internet-based Delphi study using purpose-made software (Qualtrics XM; Qualtrics). The contents and form of the Delphi survey will be coproduced by the SMG and SAG with the close involvement of both groups' patient representatives. It will also be piloted to ensure it is broadly comprehensible and accessible.

At the start of each Delphi round, participants will be presented with information in plain English on E-DES, AI, and TPPs. In subsequent rounds after round 1, participants will also be provided with a report of the previous round (see Data Analysis section below). Each round will remain open for a minimum of 2-4 weeks, and it is expected that at least 2 rounds will be conducted. Extensions to rounds' time frames and further rounds may be considered in consultation with the SAG.

Sampling

In line with similar studies successfully conducted in other contexts [56-58], we aim to recruit more than 100 respondents overall, with at least 10 from each broader stakeholder group previously outlined, including ML-ARIAS developers. Completed returns will be monitored by the stakeholder group, and further measures taken targeted at individual groups to boost recruitment if necessary. These may include targeted email or newsletter reminders.

Recruitment

People with diabetes will be recruited by asking diabetes charities to disseminate a link to the Delphi survey among their members. Similarly, the British Association of Retinal Screeners will be asked to disseminate a link among their members to recruit DES professionals. The SMG and SAG will be asked to disseminate a survey link to their wider networks to recruit regulators, clinicians, and academics. ARIAS developers with technologies previously identified by the UK NSC's Rapid Review will be invited to participate, as will those receiving funding from the NHS AI Health and Care Award.

Data Collection

Participants will be asked which stakeholder groups they belong to, their geographic location, age, sex, gender, and ethnicity. In each round, participants will be asked to score each characteristic and specification on a Likert scale ranging from 1 to 5, with 1 being "definitely exclude" and 5 being "definitely include." Recognizing that some stakeholder groups may not have the expertise to confidently score characteristic and specification pairs in some areas, participants will be given the option to omit pairs or identify other stakeholder groups they would be comfortable making this decision on their behalf. Free-text boxes will be provided to comment on characteristic and specification pairs or suggest edits. Another box at the end of the survey will provide an opportunity for participants to suggest entirely new characteristic and specification pairs.

Data Analysis

After each round, the responses will be aggregated and analyzed. A report will be produced summarizing response rates and characteristic and specification pairs scores descriptively, with scores broken down by subgroup. Free-text responses will be imported into qualitative analysis software and coded.

Consensus will be defined as >70% of respondents scoring a characteristic and specification pair 4-5 and <15% 1 in any stakeholder group. Characteristic and specification pairs exceeding this threshold will exit the survey process and proceed to the consensus meeting for discussion. Those not meeting this threshold will be revised by the SMG, taking into account their scores in previous rounds by different stakeholder groups and their coded free-text responses. The revised characteristic and specification pairs will then enter subsequent rounds, along with any new items suggested by participants in the previous round.

Consensus Meeting

The Delphi results will be reviewed, and the final TPP contents will be agreed upon at an in-person consensus meeting.

Before the consensus meeting, feedback will be sought from members of the UG. This feedback, along with the Delphi round results broken down by stakeholder group, will be sent to consensus meeting participants ahead of the meeting.

The consensus meeting itself will be led by an experienced facilitator. At the meeting, participants will be presented with each characteristic and specification pair in turn, and an opportunity will be provided for discussion and edits. The Delphi round results broken down by stakeholder group as well as the UG's feedback on the characteristic and specification

pairs will be made available to aid discussion. Meeting participants will be asked to vote on the inclusion of each characteristic and specification pair, with a supermajority of >70% among voting participants needed for inclusion in the final TPP. An abstention will be permitted.

Recruitment

Participants in the Delphi study will be asked whether they wish to be considered for participation. Meeting attendees will be agreed upon with the SAG and invited to the meeting by email.

Sampling

Purposive sampling will be used to ensure there are at least 2 members from all the key stakeholder groups previously identified, with the exception of ML-ARIAS developers, to avoid conflicts of interest. Travel expenses will be offered to all attendees.

Results

This project has received funding from the NIHR Birmingham Biomedical Research Centre since February 2022 and an NIHR incubator grant for regulatory science awarded to the University Hospitals Birmingham NHS Foundation Trust in June 2023.

Both the SMG and SAG have been assembled and have convened their first meetings. Phase 1 began in April 2023; database searches were performed in May 2023 and the phase was completed in November 2023. Phase 2 began in November 2023 and is expected to be completed in March 2024. As of March 2024, 21 interviews have been performed. Phase 3 is expected to begin in April 2024 and be completed in July 2024. The final TPP and its methods will be submitted to a peer-reviewed journal for publication and reported using the Consolidated Criteria for Reporting Qualitative Research (COREQ) criteria [59].

Discussion

Benefits of Establishing a TPP for an ML-ARIAS for Use in E-DES

ML-ARIAS offer an innovative approach for E-DES to meet rising demand and improve clinical, economic, or service outcomes. However, there is a risk that any or all of these could be negatively impacted by the introduction of an ML-ARIAS due to failures to design, evaluate, or deploy such tools appropriately. For example, placing an ML-ARIAS designed to be highly sensitive but poorly specific as a primary grader may necessitate additional decision arbitration in the screening service, or risk increasing unnecessary referrals to hospital eye services. Either eventuality may significantly reduce (or even negate) any cost benefits, or negatively impact the experience of people with diabetes or E-DES professionals. Alternatively, an ML-ARIAS's economic value could be significantly reduced by any requirement to update existing IT infrastructure, making it economically unviable.

While it is impossible to forecast all such potential pitfalls, some are predictable and could be avoided by outlining the NHS' requirements with regard to an ML-ARIAS within a TPP. This can then be used to guide product development and evaluation. Depending on who is involved in TPP development, these documents can also reflect the priorities of all stakeholder groups, including those often neglected in traditional procurement processes, such as patients and delivery staff.

The knowledge of what should go into a TPP for an ML-ARIAS likely already exists, albeit spread over members of different stakeholder groups and sometimes not formally recorded. Where desired characteristics are not clearly understood, for example, when trade-offs exist between competing priorities, our proposed consensus methodology provides a means to better establish requirements or areas where future research is needed.

Given that product requirements can be hard to identify, it is unsurprising that innovation frequently aligns poorly with the actual needs of health care professionals, health services, and their users. Creating a TPP to gather this knowledge in a concise format can accelerate the development of products that meet these stakeholders' needs at a cost much less than that of late-stage product failures or unsuccessful deployments. As well as improving developers' efficiency in product development or testing, other stakeholders stand to gain from TPPs' development. Knowing the essential characteristics of a tool, commissioners can make more assured commissioning decisions, drawing on the collective knowledge of all stakeholders contributing to the TPP. In an ML-ARIAS context, people with diabetes will also have a unique opportunity to influence product design and implementation strategies, increasing the likelihood that tools are acceptable to them and good DES uptake is maintained.

Comparison to Previous Work

To our knowledge, this project represents the first public use of TPPs for an AI health care technology. Our final TPP and the learning accrued through its development will provide a strong basis for the development of TPPs for other disease areas. As no best practice currently exists on TPP development [45], we will use a 3-phase multistakeholder-modified Delphi-consensus method similar to that used to develop reporting guidelines [56,60], core outcome sets [57,61] and previous TPPs [35,40,62]. This method aims to foster values such as inclusivity, patient empowerment, and consensus, and we intend to transfer these values into best practices in a new field.

Limitations

This project has a number of potential risks that we have sought to mitigate, most notably a failure to recruit and retain participants in the Delphi process, the omission of critical characteristics, and a failure to adequately represent and balance the needs of stakeholder groups.

With regard to securing good recruitment and retention for the Delphi process, we have secured the strong engagement of all relevant stakeholder groups with representatives of each on the SAG. Their involvement in the design of the Delphi survey aims to ensure it is broadly acceptable and achievable by all, as well as mitigate against a significant "drop-off" between Delphi rounds, a common issue that can introduce bias. To further mitigate this, we will also monitor returns collectively and at a

stakeholder group level during each round, allowing interventions such as reminders, further engagement activities, or the extension of round durations, if necessary.

The risk of omitting an essential characteristic in our TPP is increased as this will be the first developed for an AI diagnostic test, and characteristics cannot simply be copied from those previously published in the field. Additionally, some characteristics may only be identified and prioritized by single stakeholder groups. It is therefore important that the TPP development process provide sufficient opportunity for these novel or underappreciated characteristics to be identified. To do this, our reviews will specifically target resources in the field of digital and AI health care to establish which characteristics to report, and our method will provide opportunities for members of all stakeholder groups to put forward additional requirements at multiple stages.

There is also the risk that our methods may generate characteristics that put undue emphasis on the priorities of 1 stakeholder group over another. One may hypothesize that a developer might wish to set TPP requirements at a low, easily achievable level that would be unacceptable to patients and health service providers on the grounds of safety or quality. Conversely, patients and health professionals may have an unrealistic idea of what is possible and argue for TPP requirements to be set near or at perfection (eg, "must not miss any cases"). Our TPP development process seeks to both surface and balance competing priorities to produce a common, achievable target where possible, including being open regarding which stakeholder groups hold different views, potential conflicts of interest, and the actual consequences of decisions and compromises. To ensure that the requirements of the TPP remain achievable, ML-ARIAS developers will be invited to participate in the internet-based Delphi rounds as well as the UG, feedback from which will be presented at the meeting where the final TPP will be agreed. Bidirectional thresholds will also be used in the Delphi phase, such that characteristic and specification pairs must have a minimum level of support as well as a maximum level of dissent allowed to progress, increasing the likelihood that these are achievable as well as acceptable to all.

Conclusions

In developing a TPP for an ML-ARIAS, we will for the first time bring patients, health care professionals, commissioners, methodologists, clinical AI experts, and developers together to provide a target for AI developers to work toward. It is our aim that this will increase the likelihood of the development of ML-ARIAS that are fit-for-purpose for the NHS, improve screening outcomes and of benefit all stakeholders. In addition, we hope that this first public use of TPPs in health care AI and our open sharing of our methods will enable others to develop TPPs for a range of unmet needs, providing clarity to developers and accelerating innovation toward products that will be welcomed by patients and providers alike.

Acknowledgments

All authors were involved in the conception and design of the work. TM, XL, AKD, JD, JH, ST-P, GM, and BS drafted the manuscript. All authors reviewed the manuscript and approved the final version. TM is a doctoral fellow funded by the University Hospitals Birmingham NHS Foundation Trust.

Data Availability

Data sharing is not applicable to this article, as no data sets were generated or analyzed during this study.

Conflicts of Interest

CM acts as the national professional advisor for patient safety at the Care Quality Commission. RGW is a member of the UK National Screening Committee and a nonexecutive director of Moorfields Eye Hospital. FG is employed by NICE and the Department of Health and Social Care in England.

Multimedia Appendix 1
Review search strategies.
[DOCX File , 19 KB - resprot_v13i1e50568_app1.docx]

References

1. Diabetic eye screening: programme overview. Gov.UK. URL: https://www.gov.uk/guidance/diabetic-eye-screening-programme-overview [accessed 2022-11-15]
2. Photocoagulation treatment of proliferative diabetic retinopathy. Clinical Application of Diabetic Retinopathy Study (DRS) findings, DRS Report Number 8. The Diabetic Retinopathy Study Research Group. Ophthalmology 1981;88(7):583-600. [Medline: 7196564]
3. Savolainen EA, Lee QP. Diabetic retinopathy—need and demand for photocoagulation and its cost-effectiveness: evaluation based on services in the United Kingdom. Diabetologia 1982;23(2):138-140. [doi: 10.1007/BF01271176] [Medline: 6813169]

4. Fendrick AM, Javitt JC, Chiang YP. Cost-effectiveness of the screening and treatment of diabetic retinopathy. What are the costs of underutilization? Int J Technol Assess Health Care 1992;8(4):694-707. [doi: 10.1017/s0266462300002385] [Medline: 1464489]
5. Javitt JC, Aiello LP. Cost-effectiveness of detecting and treating diabetic retinopathy. Ann Intern Med 1996;124(1 Pt 2):164-169. [doi: 10.7326/0003-4819-124-1_part_2-199601011-00017] [Medline: 8554212]
6. Liew G, Michaelides M, Bunce C. A comparison of the causes of blindness certifications in England and Wales in working age adults (16-64 years), 1999-2000 with 2009-2010. BMJ Open 2014;4(2):e004015 [FREE Full text] [doi: 10.1136/bmjopen-2013-004015] [Medline: 24525390]
7. Hex N, Bartlett C, Wright D, Taylor M, Varley D. Estimating the current and future costs of type 1 and type 2 diabetes in the UK, including direct health costs and indirect societal and productivity costs. Diabet Med 2012;29(7):855-862. [doi: 10.1111/j.1464-5491.2012.03698.x] [Medline: 22537247]
8. Haider S, Thayakaran R, Subramanian A, Toulis KA, Moore D, Price MJ, et al. Disease burden of diabetes, diabetic retinopathy and their future projections in the UK: cross-sectional analyses of a primary care database. BMJ Open 2021;11(7):e050058 [FREE Full text] [doi: 10.1136/bmjopen-2021-050058] [Medline: 34253675]
9. Scanlon PH. The English national screening programme for diabetic retinopathy 2003-2016. Acta Diabetol 2017;54(6):515-525 [FREE Full text] [doi: 10.1007/s00592-017-0974-1] [Medline: 28224275]
10. Oke JL, Stratton IM, Aldington SJ, Stevens RJ, Scanlon PH. The use of statistical methodology to determine the accuracy of grading within a diabetic retinopathy screening programme. Diabet Med 2016;33(7):896-903 [FREE Full text] [doi: 10.1111/dme.13053] [Medline: 26666463]
11. Scanlon PH, Nevill CR, Stratton IM, Maruti SS, Massó-González EL, Sivaprasad S, et al. Prevalence and incidence of diabetic retinopathy (DR) in the UK population of Gloucestershire. Acta Ophthalmol 2022;100(2):e560-e570 [FREE Full text] [doi: 10.1111/aos.14927] [Medline: 34180581]
12. Scanlon PH, Aldington SJ, Leal J, Luengo-Fernandez R, Oke J, Sivaprasad S, et al. Development of a cost-effectiveness model for optimisation of the screening interval in diabetic retinopathy screening. Health Technol Assess 2015;19(74):1-116 [FREE Full text] [doi: 10.3310/hta19740] [Medline: 26384314]
13. Philip S, Fleming AD, Goatman KA, Fonseca S, McNamee P, Scotland GS, et al. The efficacy of automated "disease/no disease" grading for diabetic retinopathy in a systematic screening programme. Br J Ophthalmol 2007;91(11):1512-1517 [FREE Full text] [doi: 10.1136/bjo.2007.119453] [Medline: 17504851]
14. Fleming AD, Goatman KA, Philip S, Prescott GJ, Sharp PF, Olson JA. Automated grading for diabetic retinopathy: a large-scale audit using arbitration by clinical experts. Br J Ophthalmol 2010;94(12):1606-1610. [doi: 10.1136/bjo.2009.176784] [Medline: 20858722]
15. Confalonieri R, Coba L, Wagner B, Besold TR. A historical perspective of explainable artificial intelligence. Wiley Interdiscip Rev Data Min Knowl Discov Wiley 2021;11(1):e1391 [FREE Full text] [doi: 10.1002/widm.1391]
16. Styles CJ. Introducing automated diabetic retinopathy systems: it's not just about sensitivity and specificity. Eye (Lond) 2019;33(9):1357-1358 [FREE Full text] [doi: 10.1038/s41433-019-0535-7] [Medline: 31358924]
17. Tufail A, Kapetanakis VV, Salas-Vega S, Egan C, Rudisill C, Owen CG, et al. An observational study to assess if automated diabetic retinopathy image assessment software can replace one or more steps of manual imaging grading and to determine their cost-effectiveness. Health Technol Assess 2016;20(92):1-72 [FREE Full text] [doi: 10.3310/hta20920] [Medline: 27981917]
18. Heydon P, Egan C, Bolter L, Chambers R, Anderson J, Aldington S, et al. Prospective evaluation of an artificial intelligence-enabled algorithm for automated diabetic retinopathy screening of 30000 patients. Br J Ophthalmol 2021;105(5):723-728 [FREE Full text] [doi: 10.1136/bjophthalmol-2020-316594] [Medline: 32606081]
19. Zhivko Z, Jaime P, Morwenna R, Michael A, Jenny L, Goda K, et al. Automated grading in the diabetic eye screening programme. UK National Screening Committee. 2021. URL: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1035903/Evidence_summary_AI_in_DESP_2021.pdf [accessed 2024-02-27]
20. Ethnic differences in performance and perceptions of artificial intelligence retinal image analysis systems for the detection of diabetic retinopathy in the NHS Diabetic Eye Screening Programme. National Institute for Health and Care Research. URL: https://fundingawards.nihr.ac.uk/award/AI_HI200008 [accessed 2023-08-16]
21. DECIDE-AI Steering Group. DECIDE-AI: new reporting guidelines to bridge the development-to-implementation gap in clinical artificial intelligence. Nat Med 2021;27(2):186-187. [doi: 10.1038/s41591-021-01229-5] [Medline: 33526932]
22. Seneviratne MG, Shah NH, Chu L. Bridging the implementation gap of machine learning in healthcare. BMJ Innov 2019;6(2):45-47 [FREE Full text] [doi: 10.1136/bmjinnov-2019-000359]
23. Aristidou A, Jena R, Topol EJ. Bridging the chasm between AI and clinical implementation. Lancet 2022;399(10325):620. [doi: 10.1016/S0140-6736(22)00235-5] [Medline: 35151388]
24. Artificial intelligence funding. National Institute for Health and Care Research. URL: https://www.nihr.ac.uk/explore-nihr/funding-programmes/ai-award.htm [accessed 2023-02-22]
25. Krasniansky A, Evans B, Zweig M, from: W, Shah P, Hawks C, et al. 2021 year-end digital health funding: seismic shifts beneath the surface. Rock Health. 2022. URL: https://rockhealth.com/insights/2021-year-end-digital-health-funding-seismic-shifts-beneath-the-surface/ [accessed 2023-02-22]

26. Ioannidis JPA, Bossuyt PMM. Waste, leaks, and failures in the biomarker pipeline. Clin Chem 2017;63(5):963-972 [FREE Full text] [doi: 10.1373/clinchem.2016.254649] [Medline: 28270433]
27. Wouters OJ, McKee M, Luyten J. Estimated research and development investment needed to bring a new medicine to market, 2009-2018. JAMA 2020;323(9):844-853 [FREE Full text] [doi: 10.1001/jama.2020.1166] [Medline: 32125404]
28. Guidance for industry Q8(R2) pharmaceutical development. Federal Drug Administration. 2009. URL: https://www.fda.gov/media/71535/download [accessed 2024-02-27]
29. Quality by design. European Medicines Agency. 2018. URL: https://www.ema.europa.eu/en/human-regulatory/research-development/quality-design [accessed 2023-02-24]
30. U.S. Food and Drug Administration, Centre for Drug Evaluation and Research. Januvia NDA 21-995. U.S. Food and Drug Administration. 2006. URL: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021995s000_ChemR.pdf [accessed 2024-02-27]
31. Gavyzia NDA 125486Orig1s000. U.S. Food and Drug Administration. 2013. URL: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/125486Orig1s000ChemR.pdf [accessed 2024-02-27]
32. Target product profile: point of care SARS-CoV-2 detection tests. Gov.UK. URL: https://www.gov.uk/government/publications/how-tests-and-testing-kits-for-coronavirus-covid-19-work/target-product-profile-point-of-care-sars-cov -2-detection-tests [accessed 2022-11-15]
33. Woodhall SC, Gorwitz RJ, Migchelsen SJ, Gottlieb SL, Horner PJ, Geisler WM, et al. Advancing the public health applications of chlamydia trachomatis serology. Lancet Infect Dis 2018;18(12):e399-e407 [FREE Full text] [doi: 10.1016/S1473-3099(18)30159-2] [Medline: 29983342]
34. About us. FIND. 2016. URL: https://www.finddx.org/about/ [accessed 2022-11-24]
35. Lewin SR, Attoye T, Bansbach C, Doehle B, Dubé K, Dybul M, et al. Multi-stakeholder consensus on a target product profile for an HIV cure. Lancet HIV 2021;8(1):e42-e50 [FREE Full text] [doi: 10.1016/S2352-3018(20)30234-4] [Medline: 33271125]
36. Target product profile for sleeping sickness. Drugs for Neglected Diseases initiative (DNDi). 2020. URL: https://dndi.org/diseases/sleeping-sickness/target-product-profile/ [accessed 2022-11-15]
37. Preferred Product Characteristics for Personal Protective Equipment for the Health Worker on the Frontline Responding to Viral Hemorrhagic Fevers in Tropical Climates. Geneva, Switzerland: World Health Organisation; 2018.
38. Malaria Vaccines: Preferred Product Characteristics and Clinical Development Considerations. Geneva, Switzerland: World Health Organization; 2022.
39. Measles-Rubella Microarray Patch (MR-MAP) target product profile. In: World Health Organization. Geneva, Switzerland: World Health Organization; 2020.
40. Pellé KG, Rambaud-Althaus C, D'Acremont V, Moran G, Sampath R, Katz Z, et al. Electronic clinical decision support algorithms incorporating point-of-care diagnostic tests in low-resource settings: a target product profile. BMJ Glob Health 2020;5(2):e002067 [FREE Full text] [doi: 10.1136/bmjgh-2019-002067] [Medline: 32181003]
41. High-priority target product profile for hepatitis C diagnosis in decentralized settings: report of a consensus meeting. FIND. 2015. URL: https://forumresearch.org/projects/hcv-drug-development-advisory-group/additional-projects-of-the-hcv-drag/1167-high-priority-tpp-for-hepatitis-c-diagnosis-in-decentralized-settings-report-of-a-consensus-meeting [accessed 2024-02-27]
42. Payment guidance for researchers and professionals, version 1.4. National Institute for Health and Care Research. 2023. URL: https://www.nihr.ac.uk/documents/payment-guidance-for-researchers-and-professionals/27392 [accessed 2023-02-22]
43. UK standards for public involvement. National Institute for Health Research. 2019. URL: https://www.invo.org.uk/wp-content/uploads/2019/11/UK-standards-for-public-involvement-v6.pdf [accessed 2024-02-27]
44. Hogg HDJ, Al-Zubaidy M, Talks J, Denniston AK, Kelly CJ, Malawana J, et al. Stakeholder perspectives of clinical artificial intelligence implementation: systematic review of qualitative evidence. J Med Internet Res 2023;25:e39742 [FREE Full text] [doi: 10.2196/39742] [Medline: 36626192]
45. Cocco P, Ayaz-Shah A, Messenger MP, West RM, Shinkins B. Target product profiles for medical tests: a systematic review of current methods. BMC Med 2020;18(1):119 [FREE Full text] [doi: 10.1186/s12916-020-01582-1] [Medline: 32389127]
46. Search strategies. BMJ. 2017. URL: https://bestpractice.bmj.com/info/toolkit/learn-ebm/study-design-search-filters/ [accessed 2023-05-12]
47. Wu L. Research guides: electronic health records: EHR literature. University of Tennessee Health Science Center. 2017. URL: https://libguides.uthsc.edu/c.php?g=657371&p=4615105 [accessed 2023-05-12]
48. Godin K, Stapleton J, Kirkpatrick SI, Hanning RM, Leatherdale ST. Applying systematic review search methods to the grey literature: a case study examining guidelines for school-based breakfast programs in Canada. Syst Rev 2015;4:138 [FREE Full text] [doi: 10.1186/s13643-015-0125-0] [Medline: 26494010]
49. Unsworth H, Wolfram V, Dillon B, Salmon M, Greaves F, Liu X, et al. Building an evidence standards framework for artificial intelligence-enabled digital health technologies. Lancet Digit Health 2022;4(4):e216-e217 [FREE Full text] [doi: 10.1016/S2589-7500(22)00030-9] [Medline: 35337640]

50. Evidence standards framework for digital health technologies. National Institute of Health and Care Excellence. 2022. URL: https://www.nice.org.uk/corporate/ecd7 [accessed 2024-02-27]
51. Greenhalgh T, Wherton J, Papoutsi C, Lynch J, Hughes G, A'Court C, et al. Beyond adoption: a new framework for theorizing and evaluating nonadoption, abandonment, and challenges to the scale-up, spread, and sustainability of health and care technologies. J Med Internet Res 2017;19(11):e367 [FREE Full text] [doi: 10.2196/jmir.8775] [Medline: 29092808]
52. Maniatopoulos G, Procter R, Llewellyn S, Harvey G, Boyd A. Moving beyond local practice: reconfiguring the adoption of a breast cancer diagnostic technology. Soc Sci Med 2015;131:98-106 [FREE Full text] [doi: 10.1016/j.socscimed.2015.02.036] [Medline: 25769108]
53. Richards H, Emslie C. The 'doctor' or the 'girl from the university'? Considering the influence of professional roles on qualitative interviewing. Fam Pract 2000;17(1):71-75 [FREE Full text] [doi: 10.1093/fampra/17.1.71] [Medline: 10673494]
54. Ortlipp M. Keeping and using reflective journals in the qualitative research process. TQR 2008;13(4):695-705 [FREE Full text] [doi: 10.46743/2160-3715/2008.1579]
55. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol 2006;3(2):77-101. [doi: 10.1191/1478088706qp063oa] [Medline: 32100154]
56. Liu X, Rivera SC, Moher D, Calvert MJ, Denniston AK, SPIRIT-AI and CONSORT-AI Working Group. Reporting guidelines for clinical trial reports for interventions involving artificial intelligence: the CONSORT-AI extension. BMJ 2020;370:m3164 [FREE Full text] [doi: 10.1136/bmj.m3164] [Medline: 32909959]
57. Tallouzi MO, Mathers JM, Moore DJ, Bucknall N, Calvert MJ, Murray PI, COSUMO Working Group. Development of a core outcome set for clinical trials in non-infectious uveitis of the posterior segment. Ophthalmology 2021;128(8):1209-1221 [FREE Full text] [doi: 10.1016/j.ophtha.2021.01.022] [Medline: 33515595]
58. Denkinger CM, Dolinger D, Schito M, Wells W, Cobelens F, Pai M, et al. Target product profile of a molecular drug-susceptibility test for use in microscopy centers. J Infect Dis 2015;211(Suppl 2):S39-S49 [FREE Full text] [doi: 10.1093/infdis/jiu682] [Medline: 25765105]
59. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. Int J Qual Health Care 2007;19(6):349-357 [FREE Full text] [doi: 10.1093/intqhc/mzm042] [Medline: 17872937]
60. Moher D, Schulz KF, Simera I, Altman DG. Guidance for developers of health research reporting guidelines. PLoS Med 2010;7(2):e1000217 [FREE Full text] [doi: 10.1371/journal.pmed.1000217] [Medline: 20169112]
61. Williamson PR, Altman DG, Bagley H, Barnes KL, Blazeby JM, Brookes ST, et al. The COMET handbook: version 1.0. Trials 2017;18(Suppl 3):280 [FREE Full text] [doi: 10.1186/s13063-017-1978-4] [Medline: 28681707]
62. Kadam R, White W, Banks N, Katz Z, Dittrich S, Kelly-Cirino C. Target product profile for a mobile app to read rapid diagnostic tests to strengthen infectious disease surveillance. PLoS One 2020;15(1):e0228311 [FREE Full text] [doi: 10.1371/journal.pone.0228311] [Medline: 31995628]

Abbreviations

AI: artificial intelligence
ARIAS: automated retinal imaging analysis software
COREQ: Consolidated Criteria for Reporting Qualitative Research
CQC: Care Quality Commission
DES: diabetic eye screening
DR: diabetic retinopathy
E-DES: English diabetic eye screening
ESF: Evidence Standards Framework
MHRA: Medicines and Healthcare Products Regulatory Agency
ML: machine learning
ML-ARIAS: machine learning–automated retinal imaging analysis software
NASSS: nonadoption, abandonment, scale-up, spread, and sustainability
NICE: National Institute for Health and Care Excellence
NIHR: National Institute for Health and Care Research
NSC: National Screening Committee
SAG: study advisory group
SMG: study management group
TPP: target product profile
UG: user group

Edited by A Mavragani; submitted 14.09.23; peer-reviewed by G Lim, A Hidki; comments to author 26.12.23; revised version received 02.02.24; accepted 13.02.24; published 27.03.24.

Please cite as:
Macdonald T, Dinnes J, Maniatopoulos G, Taylor-Phillips S, Shinkins B, Hogg J, Dunbar JK, Solebo AL, Sutton H, Attwood J, Pogose M, Given-Wilson R, Greaves F, Macrae C, Pearson R, Bamford D, Tufail A, Liu X, Denniston AK
Target Product Profile for a Machine Learning–Automated Retinal Imaging Analysis Software for Use in English Diabetic Eye Screening: Protocol for a Mixed Methods Study
JMIR Res Protoc 2024;13:e50568
URL: https://www.researchprotocols.org/2024/1/e50568
doi:10.2196/50568
PMID:38536234

Protocol

How a National Organization Works in Partnership With People Who Have Lived Experience in Mental Health Improvement Programs: Protocol for an Exploratory Case Study

Ciara Robertson[1], BSc, MEd; Carina Hibberd[1], BSc, PhD; Ashley Shepherd[1], BA, PhD; Gordon Johnston, BSc

[1]Faculty of Health Sciences and Sport, University of Stirling, Stirling, United Kingdom

Corresponding Author:
Carina Hibberd, BSc, PhD
Faculty of Health Sciences and Sport
University of Stirling
Pathfoot building
Stirling, FK9 4LA
United Kingdom
Phone: 44 1786 466334
Email: carina.hibberd@stir.ac.uk

Abstract

Background: This is a research proposal for a case study to explore how a national organization works in partnership with people with lived experience in national mental health improvement programs. Quality improvement is considered a key solution to addressing challenges within health care, and in Scotland, there are significant efforts to use quality improvement as a means of improving health and social care delivery. In 2016, Healthcare Improvement Scotland (HIS) established the improvement hub, whose purpose is to lead national improvement programs that use a range of approaches to support teams and services. Working in partnership with people with lived experience is recognized as a key component of such improvement work. There is, however, little understanding of how this is manifested in practice in national organizations. To address gaps in evidence and strengthen a consistent approach, a greater understanding is required to improve partnership working.

Objective: The aim of this study is to better understand how a national organization works in partnership with people who have lived experience with improvement programs in mental health services, exploring people's experiences of partnership working in a national organization. An exploratory case study approach will be used to address the research questions in relation to the Personality Disorder (PD) Improvement Programme: (1) How is partnership working described in the PD Improvement Programme? (2) How is partnership working manifested in practice in the PD Improvement Programme? and (3) What factors influence partnership working in the PD Improvement Programme?

Methods: An exploratory case study approach will be used in relation to the PD Improvement Programme, led by HIS. This research will explore how partnership working with people with lived experience is described and manifested in practice, outlining factors influencing partnership working. Data will be gathered from various qualitative sources, and analysis will deepen an understanding of partnership working.

Results: This study is part of a clinical doctorate program at the University of Stirling and is unfunded. Data collection was completed in October 2023; analysis is expected to be completed and results will be published in January 2025.

Conclusions: This study will produce new knowledge on ways of working with people with lived experience and will have practical implications for all improvement-focused interventions. Although the main focus of the study is on national improvement programs, it is anticipated that this study will contribute to the understanding of how all national public service organizations work in partnership with people with lived experience of mental health care.

International Registered Report Identifier (IRRID): DERR1-10.2196/51779

(JMIR Res Protoc 2024;13:e51779) doi:10.2196/51779

KEYWORDS

partnership; engagement; case study; mental health; improvement; national program; quality improvement

Introduction

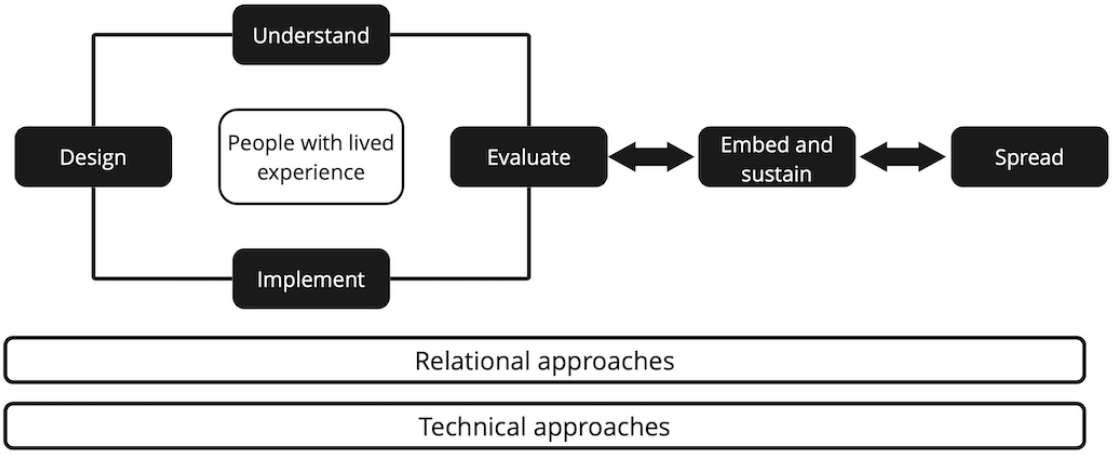
Overview

The need to improve quality in mental health (MH) care is widely recognized, in response to both long-standing problems and more contemporary pressures [1,2]. For several years, quality improvement (QI) has been considered a key solution to many health care challenges, supporting the design and delivery of services. Over the last decade, there has been a significant effort to use QI within health care settings, including the introduction of national organizations to lead improvement programs.

There are several national organizations in Scotland with an improvement focus, including the Centre for Sustainable Delivery, the Health and Social Care Alliance Scotland, the Improvement Service, and Healthcare Improvement Scotland (HIS). In 2016, HIS established the improvement hub (ihub), whose purpose is to enable health and care systems to apply improvement methodologies to the design and implementation of changes that deliver sustainable improvements in the health and well-being outcomes of people in Scotland [3]. The ihub within HIS is uniquely placed with a focus on improvement support for those delivering health and social care across Scotland, including MH services.

Work within the ihub is delivered through improvement programs that use a range of theories and techniques to support teams and services through an improvement journey. National improvement programs have an important role to play in health care. However, there are challenges within centrally led programs that require sensitive understanding and management [4]. The development of improvement programs recognizes growing evidence that the impact of QI in health care is mixed and of poor quality [5], and there is a need to reconceptualize improvement efforts in response to the evidence base [6]. In order to address some concerns within the literature, the ihub has outlined a broad approach to improvement that forms the basis of their improvement programs. The core components of improvement programs within the ihub are described in the framework for planned improvement (Figure 1 [3]), which outlines the stages of improvement work. In the Framework for Planned Improvement, the initial focus is on understanding the system and designing, implementing, and evaluating changes, with people with lived experience at the center of this work. People with lived experience include people who have lived or living experience, their families, caregivers, and supporters. Improvement programs then aim to embed and sustain successful change within practice and spread the learning to other areas. Underpinning the framework is the recognition of the importance of the relational aspect of change and the use of technical QI approaches, including the model for improvement.

Figure 1. Components of improvement programmes, adapted from Healthcare Improvement Scotland's Framework for Planned Improvement.



A key principle to improvement is working in partnership with others in the system, including other agencies, people with lived experience, and frontline staff. In Scotland, a seminal paper by Christie [7] recommended that there should be a stronger partnership working with people and communities in the design and delivery of services they use, including those involved in health care improvement. There is a growing evidence base supporting the need to work with people with lived experience in health care improvement. People with lived experience have a key role to play in understanding problems and identifying solutions to ensure change delivers outcomes that make a difference to patients [8]. Working with people with lived experience in improvement initiatives can strengthen and enrich the organizational agenda for improvement in health care [9] and should be seen as a core component of all improvement programs. Within MH services, people with lived experience should be able to participate in the development of policies to improve MH systems [10] and should therefore be involved in health care improvement initiatives. Working with people with lived experience should be based on authentic, interdependent partnership work [6], which will improve the quality and value of services.

Despite the recognition that working with people with lived experience is central to improvement-focused work, there are a number of challenges and a lack of critical examination of partnership working within the health care improvement literature [11]. There is a lack of understanding of the phenomenon of partnership working, including the mechanisms of partnership working, organizational features supporting partnership working (eg, leadership), and the impact and outcomes achieved from working with people with lived experience [11,12]. There is also little understanding in the

literature of how working with people with lived experience is manifested in practice in national organizations [13].

This research will explore how a national organization works in partnership with people with lived experience in a MH improvement program. This research will focus on one improvement program—the Personality Disorder (PD) Improvement Programme within HIS' ihub. The PD Improvement Programme is a commissioned piece of work funded by the Scottish Government to understand the current service provision in Scotland for people with a diagnosis of PD and identify the key opportunities for improvement. This research will use a case study approach to explore how partnership working is planned, conceptualized, and manifested in practice within the PD Improvement Programme.

Objectives

The aim of this study is to better understand how a national organization works in partnership with people who have lived experience with improvement programs in MH services, exploring people's experiences of partnership working in a national organization. An exploratory case study approach will be used to address the research questions in relation to the PD Improvement Programme:

1. How is partnership working described in the PD Improvement Programme?
2. How is partnership working manifested in practice in the PD Improvement Programme?
3. What factors influence partnership working in the PD Improvement Programme?

This research will consist of 2 phases. The first phase will address the first 2 research questions through document analysis and observations of meetings within the early stages of the PD Improvement Programme. Semistructured interviews will be carried out in the second phase of this research to explore participants' experiences of partnership working, addressing the third research question.

Benefits of This Research

It is anticipated that the findings of this research will contribute to an understanding of partnership working in national organizations and will be used to identify a framework for partnership working so that partnership working can be improved across the organization and other national organizations.

Methods

Overview

In order to address the research aim, it is appropriate to use case study methodology. A case study approach is appropriate when the focus of the study is on how and why questions; the behavior of participants will not be changed; the context is relevant to the phenomenon studied; and when there are unclear boundaries between phenomenon and context [14]. Partnership working sits within the wider context, and case study methodology is well placed to understand relationships between context and intervention [15], with partnership working conceptualized as the intervention in this research. A case study approach will enable a holistic exploration of the complex social processes and mechanisms underpinning partnership working within QI [16]. Data will be collected from a wide range of qualitative sources, including document data, participant observations, and semistructured interviews.

Case Study Design

The DESCARTE model [17] will be used in this research to inform the design, conduct, and reporting of the case study. There are 3 stages to this model: the situation of the research and the researcher, determining the components of the case study design, and data analysis.

Situation of the Research and the Researcher

In designing case study research, it has been recommended that the researcher state explicitly their informing philosophical approach, situation of "Self" within the research, and any ethical considerations to outline the position of research and the researcher [17].

The lead researcher is currently working as part of the improvement team within HIS and therefore will be considered an insider researcher. Although this position may support access to naturalistic data and respondents, there is a risk that there may be conflict between the researcher and participants who have professional relationships, and a risk that respondents may change their behavior or responses due to this relationship [18]. This will increase the risk of bias within the research, and strategies should be used throughout the different stages of the research process to reduce these risks [19]. For this study, strategies will include planning the interview process, using research diaries, reflection, and ongoing monitoring with the supervisory team. The lead researcher will also work closely with a public partner at key stages of this research. Public partners are volunteers who HIS trains and supports to provide a public perspective to their work, and a public partner with lived experience of mental illness will be involved at several stages of this research.

Components of the Case Study

Although case study research can have a level of creativity and flexibility—where the researcher may choose epistemologies and theories suited to their preferences and the nature of the inquiry, clear descriptions of paradigms, theories, and methods should be provided to demonstrate rigor [20]. These will be described to outline the main components of the case study.

Binding the Case

First, it is important to identify what the case will be and set clear parameters or boundaries to ensure the study has a clear and reasonable scope—a process referred to as binding [21]. The parameters of this study will be determined by definition and context; for this research, the case will consist of the PD Improvement Programme within HIS. Early involvement of people with lived experience in the conceptual stages of improvement work has been highlighted to ensure meaningful involvement with influence and impact [22]. The PD Improvement Programme is the first commissioned work for HIS to improve the understanding of the context of service provision for people with a diagnosis of PD across Scotland.

The program will include working with people with lived experience and frontline staff working in clinical roles. The commission is from the Scottish Government and will run between June 2021 and March 2023. This case study will follow the PD Improvement Programme during the current stage of the program: creating the conditions and understanding the system. This stage will involve establishing the program and working practices for working in partnership during the PD Improvement Programme. The parameter for this case is to explore working in partnership with people with lived experience and will not include exploration of wider partnerships working in this program.

Type of Case Study

Exploratory case studies can be used to explore situations in which the intervention being researched does not have a clear, single set of outcomes [21]. Given the diversity within QI and the complexity of partnership work, an exploratory approach is considered appropriate.

Design

In phase 1 of this case study, data will be collected from organizational documents, followed by nonparticipant observations of key program meetings. This data will help explore how partnership working is described, defined, and manifested in practice. This will be followed in phase 2 by semistructured interviews with key participants to explore their experiences of partnership working in the program.

Phase 1: Document Data

In the first phase of data collection, analysis of organizational documents will be used to provide an understanding of plans, infrastructure, and frameworks used to support partnerships working with people with lived experience. It is anticipated that documents may include commission agreements, planning papers, minutes of key meetings, presentations or diagrams describing the program infrastructure, and partnerships working in the program. Further documents relevant to the study may emerge and will be included as appropriate. Access to these documents will be through the program lead within HIS.

As there is no agreed definition of partnership working, documents will be analyzed for any description of partnership, which may include terms such as involvement, participation, engagement, and empowerment. The content of documents will be analyzed, including the document, author, date, description of partnership working, and any actions taken or recommendations. Meetings with the public partner will be agreed upon to discuss the data analysis and the identification of themes at each stage of the data analysis.

Themes developed from the document review will be included in the structure of observations and used to develop the interview proforma in the following phases of the research.

Phase 1: Nonparticipant Observations

Following document analysis, nonparticipant observations of PD Improvement Programme meetings will be used to gather data on how partnership working with people with lived experience in the program is manifested in practice. Meetings observed will be chosen based on a purposive sample, and there will be between 3 and 6 observations completed. The portfolio lead will be asked to provide a list of all meetings taking place in the early stages of the program, which is likely to be within the first 6-9 months of the program. A sample of meetings most likely to demonstrate partnership working in practice [23] will be selected to be observed, such as planning meetings and advisory group meetings. The meetings will be chosen by the researcher to address any potential bias and ensure the appropriate independence of the research.

A framework for partnership working will be used to guide observations (Textbox 1 [24]). This model describes 4 key dimensions of partnership: process, actors (identity and position), decisions, and power relationships. Although the use of this framework provides some structure to the observations, a form of semistructured observation will be adopted to allow for some naturalistic observations [23] and include themes identified in the document analysis.

Nonparticipant observation will allow observation of the environment, language, nonverbal data, and interaction in partnership. General context will be noted for each observation, including location, time, duration, meeting roles, and purpose of the event or meeting.

There is a possibility that the presence of a researcher will increase the risk bias by changing the behavior of participants, and strategies will be used to reduce this risk. Strategies will include giving a clear explanation of the plan for observation and being aware of the position of the researcher to be as unobtrusive as possible [25]. Observations will be primarily descriptive and will provide the basis for the interpretation of data obtained by semistructured interviews in the final stage of data collection. Meetings will be held with the public partner to discuss themes developed at this stage of data collection and to agree on the format of semistructured interviews in phase 2.

Textbox 1. Framework for partnership working observation guide used in an exploratory case study, adapted from Carpentier.

Dimension of partnership working and observation guide

- Process
  - How is partnership working planned for and what preparations are in place to support partnership working?
  - How many events or meetings involve people with lived experience?
  - Who is involved in setting the agenda and context for meetings?
- Actors: identity and position
  - Who attends meetings?
  - What are people's positions within the organization or program?
- Decisions
  - How are decisions in the program made?
  - How are people with lived experience involved in decision-making in the program?
- Power relationships
  - Who contributes to the event or meeting?
  - What is the response to people with lived experience's contribution?
  - What efforts are made to support contributions from people with lived experience?

Phase 2: Semistructured Interviews

The final stage of data gathering will be semistructured interviews with participants from the PD Improvement Programme, including people across disciplines and people with lived experience. Interviews will be used to gain an understanding of participants' experiences and perceptions of partnership working with people with lived experience. A schedule for interviews will be prepared based on themes developed from the document review and observations. The interview proforma will be developed with people with lived experience working as a public partner in HIS to ensure questions are relevant and likely to receive meaningful responses [22]. All interviews will follow the schedule developed as an aide memoire; however, it is important to allow flexibility to adapt to each participant's response to allow exploration of emerging and reported experiences [26]. Interviews will be held at a location agreed upon the researcher and participant and may be face-to-face, remote through Teams (Microsoft Corporation), or by telephone. All interviews will be recorded and transcribed.

The population within this case will include a purposive sample of staff and people with lived experience who are involved in and contribute to the work of the PD Improvement Programme. It is anticipated that this will be between 6 and 8 interviews. Participants will include clinical and improvement staff working directly on the PD Improvement Programme operating at different levels of the organization and people with lived experience working with the PD Improvement Programme. This should ensure diversity within the perspectives gained from the interviews.

Recruitment Strategy and Informed Consent

Participants will be recruited through the PD Improvement Programme and will include a purposive sample of people involved in the program based on their role. All people involved in the program will be offered the opportunity to participate in this study and will be asked to sign a consent form and return it to the researcher at the start of each stage of the research.

There will be a process of ongoing consent for each phase of this research. In phase 1, each participant in the meetings observed will be asked to consent to the observation and recording during selected meetings and consent to being contacted for an interview at the second phase of research if appropriate. This will ensure each participant has a full understanding of the research, their role within it, the benefits and risks, and their right to withdraw from the research. Each participant's consent will be documented in a written form they will be invited to sign before the meeting. Consent will be reviewed at the start of the meeting as a process of ongoing informed consent. If there are participants in the meeting who do not consent, their contribution to the meeting will be omitted during transcription. For meetings held online, participants who do not consent will be offered the chance to turn their camera off during the meeting and use the chat box for contributions if required. This may affect the understanding of the wider context of discussions, and therefore, efforts will be made to observe meetings with full consent.

In phase 2, people will be asked to consent to participate in semistructured interviews. Consent will be documented for each participant; they will be asked to sign a written consent form, and consent will be confirmed verbally at the start of each interview. Once consent is documented, the researcher will select a purposive sample of people who will participate in interviews based on their role in the program. All people who have given consent will be contacted to discuss the next steps, and interviews will be arranged with participants to ensure they take place at a suitable time and setting.

Data Analysis

Data analysis will organize, find patterns, and elicit themes in the data to help deepen an understanding of partnership working within the national PD Improvement Programme. There are various mechanisms for quality assurance within this research, including the use of a reflexive field diary, discussions with supervisors, and member checking where participants can check transcriptions following observations and interviews. During analysis, there will also be regular meetings with a public partner working in HIS to review and discuss themes to check emerging findings and the researcher's interpretation, as a form of participant validation to improve scientific rigor. A framework for data analysis is outlined in Table 1 [27].

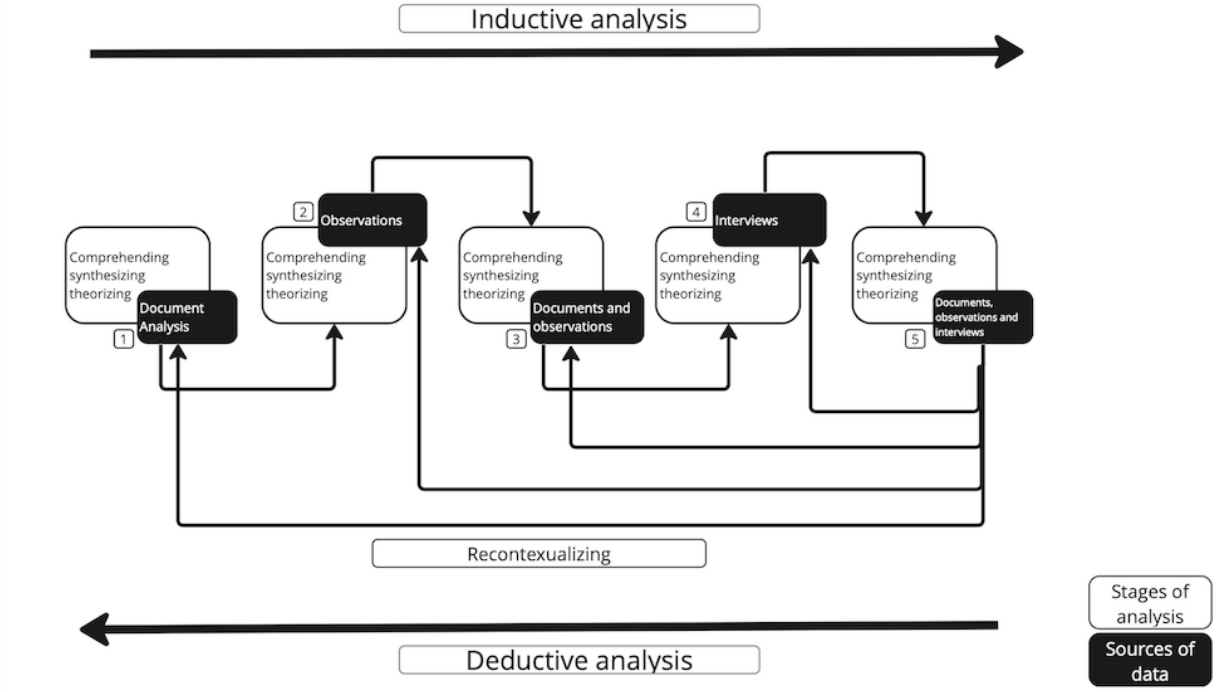
In order to develop convergent evidence, the structure outlined in Figure 2 will be applied to data analysis.

Effective organization of data will be important to this case study to enable the tracking of data sources, notes, documents, narratives, and other data [14]. NVivo (version 12; QSR International) will be used to support the management of data and to assist within and across case study analysis, appropriate to case study research [27]. Data collection and analysis will occur concurrently, as is practiced in qualitative studies [14].

Table 1. Thematic data analysis plan for an exploratory case study adapted from Houghton et al.

Stage of data analysis	Analysis strategy	Application for this research
Comprehending	Broad coding	This stage will analyze data to generate and develop codes. In this stage, enough data will be gathered to write a detailed, coherent, and rich description of partnership working.
Synthesizing	Pattern coding memoing	This stage will review codes identified at the broad coding stage and identify patterns within the data. Memos will provide summaries of key information for each theme, which will be used in further development of propositions of the data.
Theorizing	Distilling and ordering and testing executive summary statements	Relationships between categories of data will be examined, building a more integrated understanding of partnership working from all perspectives and data sources.
Recontextualizing	Developing propositions	Concepts identified will be synthesized to consider how the understanding of partnership working may be applied in different settings.

Figure 2. Data analysis plan for thematic analysis in an exploratory case study.



Patient Involvement

The objective of this research is to deepen an understanding of how national improvement programs work in partnership with people with lived experience. This focus was developed through a review of current literature and organizational objectives [28] and has been highlighted by people with lived experience who have worked with HIS in other national MH improvement programs [29].

Patient involvement has been central to the development and design of this research, and a public partner has been involved in the design and will be involved in the analysis of this research. In phase 1, this included involvement in the review and analysis of themes as a form of participant validation to improve scientific rigor [30]. The public partner advised on the burden of intervention for people with lived experience in this study and has been involved in the design of phase 2, including the

design of interviews, the development of the distress response policy, and advising on participant recruitment. The public partner will continue to be involved during the data analysis of phase 2, reviewing and discussing themes developed at this phase, and will be invited to advise on plans for dissemination of the study results to participants and linked communities.

Ethical Considerations

Ethical approval has been granted from HIS' research oversight group, the University of Stirling Research Ethics Committee, and the Integrated Research Application System through the Queen Square Research Ethics Committee (for phase 1; 318323) and the Black Country Research Ethics Committee (for phase 2; 309926). This study is part of a clinical doctorate program at the University of Stirling and is unfunded.

Results

Data collection was completed in October 2023; analysis is expected to be completed and results published in January 2025.

Discussion

This study will produce new knowledge on ways of working with people with lived experience and will have practical implications for all improvement focused interventions. Though the main focus of the study is on national improvement programs, it is anticipated that this study will contribute to the understanding of how all national public service organizations work in partnership with people with lived experience of MH care. The anticipated time for completion and write-up is 24 months. Information will be shared with key stakeholders on the progress of this research, including HIS and the University of Stirling, and opportunities for presentation of this research will be sought. These may include QI conferences and communities—including the Q Community (The Health Foundation), MH organization events, and NHS Scotland events. The findings will be completed with a thesis submitted to the University of Stirling and will be reported in an appropriate journal, such as *BMJ Open Quality* or the *Journal for Healthcare Quality*.

Acknowledgments

The authors thank Healthcare Improvement Scotland's Mental Health Improvement Portfolio Team. This research has received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data Availability

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

Authors' Contributions

CR is a student in the clinical doctorate program at the University of Stirling. CH is the lead supervisor and researcher. AS is the supervisor for this research. Both supervisors contributed to the design of the research protocol, advising on analysis, and developing the manuscript for this research. GJ is the public partner advising on the design, analysis, and dissemination of this research.

Conflicts of Interest

None declared.

References

1. The state of health care and adult social care in England 2015/16. Care Quality Commission. 2016 Oct 12. URL: https://www.cqc.org.uk/sites/default/files/20161019_stateofcare1516_web.pdf [accessed 2023-01-28]
2. Gilburt H. Mental health under pressure. The King's Fund. London; 2015. URL: https://assets.kingsfund.org.uk/f/256914/x/78db101b90/mental_health_under_pressure_2015.pdf [accessed 2023-01-28]
3. Our approach to supporting improvement. Healthcare Improvement Scotland. 2016. URL: https://ihub.scot/media/1870/improvement-hub-our-approach-to-supporting-improvement-v6-27092016.pdf [accessed 2023-01-28]
4. Lining up: how do improvement programmes work? The Health Foundation. 2013. URL: https://www.health.org.uk/publications/lining-up-how-do-improvement-programmes-work [accessed 2024-03-28]
5. Dixon-Woods M. How to improve healthcare improvement-an essay by Mary Dixon-Woods. BMJ 2019;367:l5514 [FREE Full text] [doi: 10.1136/bmj.l5514] [Medline: 31575526]
6. Batalden P, Foster T. From assurance to coproduction: a century of improving the quality of health-care service. Int J Qual Health Care 2021;33(Supplement_2):ii10-ii14 [FREE Full text] [doi: 10.1093/intqhc/mzab059] [Medline: 34849968]
7. Christie C. Christie Commission on the future delivery of public services. Scottish Government. 2011 Jun 29. URL: https://www.gov.scot/publications/commission-future-delivery-public-services/documents/ [accessed 2022-01-04]
8. Alderwick H, Jones B, Charles A, Warburton W. Making the case for quality improvement: lessons for NHS boards and leaders. The King's Fund. 2017. URL: https://www.kingsfund.org.uk/publications/making-case-quality-improvement [accessed 2021-05-25]

9. Fitzsimons B. Voices and stories are central to improving healthcare. BMJ 2022;376:o114 [FREE Full text] [doi: 10.1136/bmj.o114] [Medline: 35039314]
10. Carbonell Á, Navarro-Pérez JJ, Mestre MV. Challenges and barriers in mental healthcare systems and their impact on the family: a systematic integrative review. Health Soc Care Community 2020;28(5):1366-1379 [FREE Full text] [doi: 10.1111/hsc.12968] [Medline: 32115797]
11. Palmer VJ. The participatory zeitgeist in health care: it is time for a science of participation. J Particip Med 2020;12(1):e15101-e15106 [FREE Full text] [doi: 10.2196/15101] [Medline: 33064092]
12. Kjellström S, Areskoug-Josefsson K, Gäre BA, Andersson AC, Ockander M, Käll J, et al. Exploring, measuring and enhancing the coproduction of health and well-being at the national, regional and local levels through comparative case studies in Sweden and England: the 'Samskapa' research programme protocol. BMJ Open 2019;9(7):e029723 [FREE Full text] [doi: 10.1136/bmjopen-2019-029723] [Medline: 31350253]
13. Connolly J, McGillivray S, Munro A, Mulherin T, Anderson J, Gray N, et al. How co-production and co-creation is understood, implemented and sustained as part of improvement programme delivery within the health and social care context in Scotland. University of the West of Scotland. 2020. URL: https://researchonline.gcu.ac.uk/en/publications/how-co-production-and-co-creation-is-understood-implemented-and-s [accessed 2024-03-28]
14. Baxter P, Jack S. Qualitative case study methodology: study design and implementation for novice researchers. TQR 2015;13(4):544-559 [FREE Full text] [doi: 10.46743/2160-3715/2008.1573]
15. Grant A, Bugge C, Wells M. Designing process evaluations using case study to explore the context of complex interventions evaluated in trials. Trials 2020;21(1):982 [FREE Full text] [doi: 10.1186/s13063-020-04880-4] [Medline: 33246496]
16. Yin RK. Case Study Research: Design and Methods. London: Sage Publications, Inc; 2011:221-222.
17. Carolan CM, Forbat L, Smith A. Developing the DESCARTE model: the design of case study research in health care. Qual Health Res 2016;26(5):626-639. [doi: 10.1177/1049732315602488] [Medline: 26336896]
18. Caruana C. Ethical considerations when carrying out research in one's own academic institution. Symposia Melitensia 2015;10(10):61-71 [FREE Full text]
19. Fleming J. Recognizing and resolving the challenges of being an insider researcher in work-integrated learning. Int J Work-Integr Learn 2018;19(3):311-320 [FREE Full text]
20. Hyett N, Kenny A, Dickson-Swift V. Methodology or method? A critical review of qualitative case study reports. Int J Qual Stud Health Well-being 2014;9:23606 [FREE Full text] [doi: 10.3402/qhw.v9.23606] [Medline: 24809980]
21. Yin RK. Case Study Research: Design and Methods. Thousand Oaks: SAGE Publications; 2003.
22. Byrne L, Wykes T. A role for lived experience mental health leadership in the age of Covid-19. J Ment Health 2020;29(3):243-246 [FREE Full text] [doi: 10.1080/09638237.2020.1766002] [Medline: 32449392]
23. Simons H. Case Study Research in Practice. Los Angeles: SAGE Publications, Ltd; 2009.
24. Carpentier N. Beyond the ladder of participation: an analytical toolkit for the critical analysis of participatory media processes. Javnost 2016;23(1):70-88 [FREE Full text] [doi: 10.1080/13183222.2016.1149760]
25. Creswell JW, Creswell JD. Research Design: Qualitative, Quantitative and Mixed Methods Approaches, Fifth Edition. Thousand Oaks, CA: Sage Publications, Inc; 2018.
26. Smith JA, Flowers P, Larkin M. Interpretative Phenomenology Analysis: Theory, Method and Research. London: Sage Publications; 2009.
27. Houghton C, Murphy K, Shaw D, Casey D. Qualitative case study data analysis: an example from practice. Nurse Res 2015;22(5):8-12. [doi: 10.7748/nr.22.5.8.e1307] [Medline: 25976531]
28. Our strategy 2022—27 draft for consultation. Healthcare Improvement Scotland. 2022. URL: https://www.healthcareimprovementscotland.org/news_and_events/news/news_draft_strategy.aspx [accessed 2023-04-04]
29. Lindsay A. Sharing recent lived experience to help improve services. Healthcare Improvement Scotland. 2021. URL: https://ihub.scot/improvement-programmes/mental-health-portfolio/early-intervention-in-psychosis/personal-reflections/sharing-recent-lived-experience-to-help-improve-services/ [accessed 2023-04-04]
30. Crowe S, Cresswell K, Robertson A, Huby G, Avery A, Sheikh A. The case study approach. BMC Med Res Methodol 2011;11:100 [FREE Full text] [doi: 10.1186/1471-2288-11-100] [Medline: 21707982]

Abbreviations

HIS: Healthcare Improvement Scotland
ihub: improvement hub
MH: mental health
PD: personality disorder
QI: quality improvement

Edited by A Mavragani; submitted 12.08.23; peer-reviewed by J Abbas, D Bradford; comments to author 21.02.24; revised version received 13.03.24; accepted 14.03.24; published 19.04.24.

Please cite as:
Robertson C, Hibberd C, Shepherd A, Johnston G
How a National Organization Works in Partnership With People Who Have Lived Experience in Mental Health Improvement Programs: Protocol for an Exploratory Case Study
JMIR Res Protoc 2024;13:e51779
URL: https://www.researchprotocols.org/2024/1/e51779
doi:10.2196/51779
PMID:38640479

Protocol

Mapping Respiratory Health Digital Interventions in South and Southeast Asia: Protocol for a Scoping Review

Laura Evans[1], MSc; Jay Evans[1], MSc; Monica Fletcher[1], MSc; Adina Abdullah[2], PhD; Zakiuddin Ahmed[3], MD

[1]Usher Institute, University of Edinburgh, Edinburgh, United Kingdom

[2]Department of Primary Care Medicine, Faculty of Medicine, Universiti Malaya, Kuala Lumpur, Malaysia

[3]Riphah Institute of Healthcare Improvement and Safety, Islamabad, Pakistan

Corresponding Author:
Laura Evans, MSc
Usher Institute
University of Edinburgh
Medical School
Teviot Place
Edinburgh, EH8 9AG
United Kingdom
Phone: 44 (0)131 651 4138
Email: v1levan6@exseed.ed.ac.uk

Abstract

Background: The last 2 decades have been a time of exponential growth and maturation for digital health, while the global burden of respiratory disease continues to grow worldwide. Leveraging digital health interventions (DHIs) to manage and mitigate respiratory disease and its adverse health effects presents itself as an obvious path forward.

Objective: We aimed to understand the current digital landscape and enabling environment around respiratory health to reduce costs, avoid duplication, and understand the comprehensiveness of DHIs.

Methods: This study will follow a scoping review methodology as outlined by Arksey and O'Malley, the Joanna Briggs Institute, and the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) checklist. MEDLINE, Embase, CINAHL, PsycINFO, Cochrane Library, Web of Science, PakiMedNet, and MyMedR databases will be searched along with key websites, repositories, and gray literature databases. The terms "respiratory health," "digital health," "South Asia," and "Southeast Asia," as well as related terms will be searched. The results will be screened for duplicates and then against the inclusion and exclusion criteria. For the studies included, data will be extracted, collated, and analyzed.

Results: The scoping review was started in July 2023 and will be finalized by February 2024. Results will be presented following the World Health Organization's classification of DHIs to categorize interventions in a standardized format and the mobile health evidence reporting and assessment checklist to report on the effectiveness of interventions. Further exposition of the evidence extracted will be presented through narrative synthesis.

Conclusions: As DHIs continue to proliferate, the need to understand the current landscape becomes more pertinent. In this scoping review, we will seek to more clearly understand what digital health tools and technologies are being used in the current landscape of digital health in South and Southeast Asia for respiratory health and to what extent they are addressing the respiratory health needs of the region. The results will inform recommendations on digital health tools for respiratory health in South and Southeast Asia will help funders and implementers of DHIs leverage existing technologies and accelerate innovations that address documented gaps in the studied countries.

International Registered Report Identifier (IRRID): DERR1-10.2196/52517

(JMIR Res Protoc 2024;13:e52517) doi:10.2196/52517

KEYWORDS

digital health; respiratory health; Asia; scoping review; landscape mapping; digital health intervention; digital health environment; mobile health; mHealth

Introduction

Digital health and care refer to the use of information communication technologies, commonly known as digital health interventions (DHIs), by health and care professionals, patients, carers, or health managers to manage illnesses and wellness [1-4]. The last 2 decades have been a time of exponential growth and maturation for digital health [4] due to the promises of improved health for all and personal health empowerment [5]. Concurrently, the global burden of respiratory disease continues to grow worldwide, with infectious and noncommunicable respiratory diseases being among the top 10 medical conditions (out of 369 diseases and injuries measured) in terms of years of life lost due to premature death and years lived with a disability (measured by disability-adjusted life years) [6,7]. This increased burden of respiratory disease is more acutely felt in Asia, where mortality rates are higher and public awareness and government engagement are lower than in other regions of the world [8,9]. Leveraging DHIs to manage and mitigate respiratory disease and its adverse health effects presents itself as an obvious path forward. However, the first step to harnessing the power of digital health must be understanding the current digital landscape and enabling the environment to reduce costs, avoid duplication, and increase the efficiency, accessibility, and sustainability of such interventions [10-13].

The National Institute for Health Research (NIHR)–funded Global Health Research Unit on Respiratory Health (RESPIRE) is a collaboration between several Asian organizations and universities in Bangladesh, Bhutan, India, Malaysia, Pakistan, Indonesia, and Sri Lanka and the University of Edinburgh in Scotland, United Kingdom [9,14,15]. RESPIRE aims to achieve the following:

> *develop into a world-leading Unit that will: (i) map and collate continuing and emerging respiratory challenges; (ii) prioritise existing evidence-based interventions that have the potential to be adapted to reduce mortality and morbidity in low- and middle-income countries (LMICs); (iii) support local adaptation and tailoring of interventions for deployment in low-resource environments and catalyse developmental work in areas of unmet need; (iv) support local implementation efforts and evaluation of programmes of work; and (v) identify the best delivery mechanisms for long-term delivery and scaling-up.*

This is done through 4 different translational platforms, of which 1 platform focuses on Digital Health and Innovation and aims to provide holistic support to partner countries on the design, funding, deployment, and sustainability of new and existing digital health interventions for respiratory health. This scoping review will contribute to advancing the aims and work of Digital Health and Innovations.

Understanding the current landscape of DHIs that target respiratory diseases will (1) uncover existing gaps, (2) highlight potential opportunities, (3) suggest research and program priorities most needed in the field of digital health to address current respiratory health diseases in South and Southeast Asia, and (4) further advance RESPIRE's overall aims. Therefore, we aim to undertake a scoping review to map respiratory disease DHIs in South and Southeast Asia to identify existing technologies, opportunities, and gaps, and to put forward pertinent recommendations from the insights gained.

Methods

Scoping Review Methodology

The scoping review methodology, as outlined by Arksey and O'Malley and the Joanna Briggs Institute (JBI) [16,17], is an appropriate approach for mapping DHIs. Scoping reviews allow flexibility when exploring the diverse and heterogenous field of digital health, are appropriate when using different sources of data (eg, peer-reviewed journals, gray literature, and expert opinions), and permit inclusion and exclusion criteria to be iteratively refined as more evidence is uncovered [16-19]. Additionally, the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) [20] will be followed to ensure adherence to methodological standards.

Identifying the Research Question

This scoping review will seek to answer the following research questions:

1. What digital health tools and technologies are being used in South and Southeast Asia for respiratory health?
2. How are these addressing (or not) the respiratory health needs of the region?
3. What recommendations can be made from the literature?

Identifying Relevant Studies

To identify relevant literature, academic databases will be searched along with key websites, repositories, and gray literature databases that may contain relevant information for our scoping review. Textbox 1 shows the proposed databases.

The search strategy has been initially drafted for MEDLINE in the Ovid platform (Textbox 2) and will be adapted for the remaining databases. The search strategy has been iteratively developed and refined by the authors' input and the librarian at the University of Edinburgh. The terms "respiratory health," "digital health," "South Asia," and "Southeast Asia," as well as all relevant variations of these terms have been included in the search strategy to gather as much pertinent literature and information as possible.

Textbox 1. Proposed database and key websites.

Databases

- MEDLINE
- Embase
- CINAHL
- PsycINFO
- Cochrane Library
- Web of Science
- PakMediNet
- MyMedR

Other sources

- ProQuest Thesis and Dissertations
- Digital Health Atlas
- Global Digital Health Index
- Digital Square's Map and Match
- United Nations Children's Emergency Fund's Mapping of Digital Health Tools and Technologies
- World Health Organization's Global Index Medicus

Textbox 2. Search strategy.

Search terms

1. occupational diseases/ or Asthma/ or Air Pollution/ or Respiratory Tract Diseases/ or Occupational Exposure/ or Air Pollutants/ or Tuberculosis/ or Tuberculosis, Pulmonary/ or "Tobacco Use"/ or Tobacco/ or "Tobacco Use Cessation"/ or "Tobacco Use Cessation Devices"/ or Pulmonary Disease, Chronic Obstructive/ or Pneumonia/ or COVID-19/
2. (respiratory health or tuberculosis or tobacco or pneumonia).mp
3. 1 or 2
4. telemedicine/ or telehealth/ or artificial intelligence/ or machine learning/ or medical informatics/ or electronic health records/ or mobile applications/ or exp Informatics/
5. (artificial intelligence or digital health or e-health or ehealth or m-health or mhealth or (digital adj2 (health or solution* or system*)) or (health adj2 (electronic or record* or tele*)) or ict4d or (information adj5 development) or machine learning or mobile health or telecare or telehealth or telemedicine or tele-health or teleconsultation or tele-consultation or tele-care or tele-medicine or (tele adj1 (medicine or care or health or consultation)) or ((virtual* or remote*) adj4 (visit* or consult* or meet* or appoint* or communicat*)) or (Health* adj4 tech*) or e-portal* or eportal* or (Patient* adj2 portal*) or (medical adj2 informatic*)).mp.
6. 4 or 5
7. Asia/ or Asia, Southern/ or Asia, Southeastern/
8. (Asia or Brunei Darussalam or Cambodia or Indonesia or Lao People's Democratic Republic or Malaysia or Myanmar or Philippines or Singapore or Thailand or Timor-Leste or Viet Nam or Vietnam or Afghanistan or Bangladesh or Bhutan or India or Iran or Islamic Republic of Iran or Maldives or Nepal or Pakistan or Sri Lanka).mp
9. 7 or 8
10. 3, 6, and 9

Study Selection

Exclusion and inclusion criteria have been developed according to the domains of population, concept, context, and type of evidence, suggested by the JBI [17,18]. Additionally, an "other variables" category has been created to include year, language, and format criteria (Table 1). The regions of South and Southeast Asia include 19 countries as established by the United Nations Statistics Division [21]. These 2 regions have been chosen because they contain all the RESPIRE2 countries. Multicountry studies containing countries from the selected regions and other regions of the world will be included in the initial screening and only excluded if they do not provide the data of interest separate for each country. Only studies in English and those published in the last 10 years (since 2013) will be included to keep the scope of this review within manageable boundaries.

Table 1. Inclusion and exclusion criteria.

Domain	Inclusion criteria	Exclusion criteria
Population	• Any population	• N/A[a]
Concept	• Technological interventions for respiratory health that fall under any of the categories of the World Health Organization's classification of digital health interventions • Respiratory health includes respiratory infections, noncommunicable respiratory diseases, and preventable risk factors for respiratory conditions, as defined by RESPIRE[b]	• Other nontechnological interventions used for respiratory health • Not a respiratory health focus
Context	• South and Southeast Asia	• The rest of the world
Types of evidence sources	• Any study design	• Books • Abstracts only • Posters • Protocols
Other variables	• Published in English • Studies or data published in the last 10 years (2013-2023) • Full article or data are available digitally	• Published in any other language • Studies or data published before 2013 • Full article or data are not available digitally

[a]N/A: not applicable.

[b]RESPIRE: The National Institute for Health Research–funded Global Health Research Unit on Respiratory Health.

For information found in a scientific study format, Covidence software [22] will be used to eliminate duplicates and carry out screening and extraction. After deduplication, title, abstract, and full-text screening will be done by 2 authors according to the inclusion and exclusion criteria. Discrepancies will be first addressed by consensus between those 2 authors. If there is a lack of consensus, a third reviewer will decide.

For all other types of information or data found from searches, manual screening by 1 reviewer will happen first. Relevant data will be entered into a spreadsheet, and a second reviewer will assess it. Discrepancies will first be addressed between both reviewers, and if there is no consensus, a third reviewer will make the final decision. We will not contact authors directly to further understand whether a study should be included since it would most likely significantly lengthen the timeline for this scoping review.

Scoping reviews use secondary data and do not require ethics approval under RESPIRE rules. However, the authors will adhere to the highest ethical standards when carrying out the review. This protocol establishes a transparent and reproducible study design, which limits the potential for personal bias [23].

Charting the Data

After selection, relevant data will be extracted to a spreadsheet using Covidence. The extraction form will be first piloted in 3-5 studies to assess if it is fit for purpose as recommended by the JBI. Data selected from a nonscientific study format will be entered into the extraction spreadsheet as accurately as possible. However, it is acknowledged that not all fields may contain relevant information, and some fields may need to be modified (eg, data from the Digital Health Atlas will have a "source of information" field instead of an "author" field).

When 2 or more articles refer to the same overall study, those articles will be grouped as one before data extraction.

Collating, Summarizing, and Reporting the Results

After data analysis, the data will be collated and analyzed as follows:

- Quantitative data (ie, the number of studies, type of study, and year) will be presented.
- Qualitative data will be presented following the World Health Organization's classification of digital health interventions [24] to categorize interventions in a standardized format and the mobile health evidence reporting and assessment checklist [25] to report on the comprehensiveness of the interventions.
- Narrative synthesis will be used to answer the research questions and to present further data extracted.

Consultation

Consultation with stakeholders will be ongoing throughout the scoping review process. We will disseminate early findings among partners so that they can provide feedback on findings and that feedback can be incorporated into the discussion.

Results

This scoping review was started in July 2023 and will be finalized by February 2024. Preliminary findings will be shared with stakeholders and a final write-up of the scoping review is projected to be finalized by the end of March 2024. To date, 10,469 studies have been screened. The screening of abstracts is underway.

Discussion

Expected Outcomes

Through this scoping review, we will seek to better understand what digital health tools and technologies are being used in South and Southeast Asia for respiratory health and to what extent they are addressing the respiratory health needs of the region. The results will inform recommendations on digital health tools for respiratory health in South and Southeast Asia and will help funders and implementers of DHIs leverage existing technologies and accelerate innovations that address documented gaps in the studied countries. The results of this review will be limited by the fact that only studies in English and studies published in the last 10 years will be included. This review will enhance the knowledge of digital health tools and technologies in the region, which is paramount before undertaking any new initiative, as it helps prevent redundant work and investment by building on existing systems and lessons learned.

Conclusions

As DHIs, in general and in respiratory health in particular, continue to proliferate, the need to understand the current landscape becomes more pertinent. Through this scoping review, we will systematically map out DHIs, which serves as the required first step in any well-informed and thought-out design and deployment of DHIs.

Acknowledgments

We would like to thank Marshall Dozier, the librarian at the University of Edinburgh, who provided feedback on the protocol's search strategy and overall design.

Generative artificial intelligence was not used at any time during the research and writing of this protocol.

This research was funded by the UK National Institute for Health and Care Research (NIHR)— Global Health Research Unit on Respiratory Health (RESPIRE; NIHR132826)—using UK aid from the UK Government to support global health research. The views expressed in this publication are those of the authors and not necessarily those of the NIHR or the United Kingdom Government.

Data Availability

The data resulting from this scoping review will be made available as supplementary materials at the time of publication.

Authors' Contributions

JE and LE conceptualized the idea. LE drafted the manuscript and search strategy. JE, MF, AA, and ZA provided feedback on the draft.

Conflicts of Interest

AA is a shareholder of a digital health company in Malaysia (UMCH Technology Sdn Bhd).

Multimedia Appendix 1
Peer-review reports from the National Institute for Health and Care Research (NIHR).
[PDF File (Adobe PDF File), 741 KB - resprot_v13i1e52517_app1.pdf]

References

1. Australian Government Department of Health and Aged Care. About health technologies and digital health. Australian Government Department of Health and Aged Care. 2021. URL: https://www.health.gov.au/topics/health-technologies-and-digital-health/about [accessed 2023-04-04]
2. Ronquillo Y, Meyers A, Korvek SJ. Digital Health. Treasure Island, FL: StatPearls Publishing; 2023.
3. European Commission. eHealth: digital health and care. European Commission. 2023. URL: https://health.ec.europa.eu/ehealth-digital-health-and-care/overview_en [accessed 2023-04-04]
4. Mahya FZ. A brief history of digital health. Medium. 2021. URL: https://medium.com/that-medic-network/a-brief-history-of-digital-health-b238f1f5883c [accessed 2023-03-15]
5. Maaß L, Pan C, Freye M. Mapping digital public health interventions among existing digital technologies and internet-based interventions to maintain and improve population health in practice: protocol for a scoping review. JMIR Res Protoc 2022 Mar 31;11(3):e33404 [FREE Full text] [doi: 10.2196/33404] [Medline: 35357321]
6. Roser M, Ritchie H, Spooner F. Burden of disease. Our World in Data. 2021. URL: https://ourworldindata.org/burden-of-disease [accessed 2023-03-15]
7. Vos T, Lim SS, Abbafati C, et al.. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 2020 Oct 17;396(10258):1204-1222 [FREE Full text] [doi: 10.1016/S0140-6736(20)30925-9] [Medline: 33069326]

8. Soriano JB, Kendrick PJ, Paulson KR, Gupta V, Abrams EM, Adedoyin RA, et al. Prevalence and attributable health burden of chronic respiratory diseases, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet Respiratory Medicine 2020 Jun;8(6):585-596. [doi: 10.1016/s2213-2600(20)30105-3]
9. Sheikh A, Campbell H, Balharry D, Baqui AH, Bogaert D, Cresswell K, et al. RESPIRE: The National Institute for Health Research's (NIHR) Global Respiratory Health Unit. J Glob Health 2018 Dec;8(2):020101 [FREE Full text] [doi: 10.7189/jogh.08.020101] [Medline: 30603074]
10. Hui CY, Abdulla A, Ahmed Z, Goel H, Monsur Habib GM, Teck Hock T, RESPIRE Group. Mapping national information and communication technology (ICT) infrastructure to the requirements of potential digital health interventions in low- and middle-income countries. J Glob Health 2022 Dec 29;12:04094 [FREE Full text] [doi: 10.7189/jogh.12.04094] [Medline: 36579436]
11. Evans J, Bhatt S, Sharma R. The path to scale: navigating design, policy, and infrastructure. mHealth Innovation in Asia 2018:31-48. [doi: 10.1007/978-94-024-1251-2_3]
12. Cresswell K, Williams R, Sheikh A. Developing and applying a formative evaluation framework for health information technology implementations: qualitative investigation. J Med Internet Res 2020 Jun 10;22(6):e15068 [FREE Full text] [doi: 10.2196/15068] [Medline: 32519968]
13. Protocol: an evidence gap map for digital health interventions. World Bank. URL: https://documents1.worldbank.org/curated/en/211341591931421760/pdf/Study-Protocol-An-Evidence-Gap-Map-for-Digital-Health-Interventions.pdf [accessed 2023-03-15]
14. NIHR RESPIRE. IPCRG. URL: https://www.ipcrg.org/projects/research/nihr-respire [accessed 2023-03-16]
15. What is RESPIRE? University of Edinburgh. URL: https://www.ed.ac.uk/usher/respire/about/what-is-respire [accessed 2023-03-16]
16. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. Int J Soc Res Methodol 2005 Feb;8(1):19-32. [doi: 10.1080/1364557032000119616]
17. Peters MDJ, Godfrey C, McInerney P, Munn Z, Tricco AC, Khalil H. Chapter 11: Scoping Reviews. JBI Reviewer's Manual. 2020. URL: https://jbi-global-wiki.refined.site/space/MANUAL/4685848/Previous+versions?attachment=/rest/api/content/4685848/child/attachment/att4698146/download&type=application/pdf&filename=JBI_Reviewers_Manual_2020March [accessed 2023-01-06]
18. The Joanna Briggs Institute Reviewers' Manual: 2015 edition. The Joanna Briggs Institute. 2015. URL: https://www.researchgate.net/publication/294736492_Methodology_for_JBI_Scoping_Reviews/link/56c39d7108aee3dcd41667f5/download?_tp=eyJjb250ZXh0Ijp7ImZpcnN0UGFnZSI6InB1YmxpY2F0aW9uIiwicGFnZSI6InB1YmxpY2F0aW9uIn19 [accessed 2020-08-25]
19. Evans L, Evans J, Pagliari C, Källander K. Exploring the equity impact of current digital health design practices: protocol for a scoping review. JMIR Res Protoc 2022 May 17;11(5):e34013 [FREE Full text] [doi: 10.2196/34013] [Medline: 35579918]
20. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. Ann Intern Med 2018 Oct 02;169(7):467-473 [FREE Full text] [doi: 10.7326/M18-0850] [Medline: 30178033]
21. Statistics division. United Nations Stats. URL: https://unstats.un.org/unsd/methodology/m49/ [accessed 2023-07-05]
22. Covidence - Better systematic review management. Covidence. URL: https://www.covidence.org/ [accessed 2021-02-24]
23. Suri H. Ethical Considerations of Conducting Systematic Reviews in Educational Research. Zawacki-Richter O, Kerres M, Bedenlier S. eds. Systematic Reviews in Educational Research: Methodology, Perspectives and Application. Wiesbaden: : Springer Fachmedien 2020:41-54. [doi: 10.1007/978-3-658-27602-7_3]
24. Classification of Digital Health Interventions V1.10. URL: https://apps.who.int/iris/bitstream/handle/10665/260480/WHO-RHR-18.06-eng.pdf [accessed 2022-10-11]
25. Agarwal S, LeFevre AE, Lee J, L'Engle K, Mehl G, Sinha C, et al. Guidelines for reporting of health interventions using mobile phones: mobile health (mHealth) evidence reporting and assessment (mERA) checklist. BMJ 2016 Mar 17;352:i1174. [doi: 10.1136/bmj.i1174] [Medline: 26988021]

Abbreviations

DHI: digital health intervention
JBI: Joanna Briggs Institute
NIHR: National Institute for Health Research
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
RESPIRE: National Institute for Health Research–funded Global Health Research Unit on Respiratory Health

Edited by A Mavragani; submitted 06.09.23; this is a non–peer-reviewed article;accepted 21.09.23; published 12.01.24.

Please cite as:
Evans L, Evans J, Fletcher M, Abdullah A, Ahmed Z
Mapping Respiratory Health Digital Interventions in South and Southeast Asia: Protocol for a Scoping Review
JMIR Res Protoc 2024;13:e52517
URL: https://www.researchprotocols.org/2024/1/e52517
doi:10.2196/52517
PMID:38214954

Protocol

Homestay Hosting Dynamics and Refugee Well-Being: Protocol for a Scoping Review

Areej Al-Hamad[1], PhD; Yasin M Yasin[2], PhD; Kateryna Metersky[1], PhD; Sepali Guruge[1], PhD; Khadija Mahsud[2], MLiS

[1]Toronto Metropolitan University, Toronto, ON, Canada

[2]University of Doha for Science and Technology, Doha, Qatar

Corresponding Author:
Areej Al-Hamad, PhD
Toronto Metropolitan University
DCC544- 288 Church St.
Toronto, ON, M5B 1Z5
Canada
Phone: 1 416 979 5044 ext 554727
Email: areej.hamad@torontomu.ca

Abstract

Background: The process of refugee resettlement and integration into new communities is a complex and multifaceted challenge, not only for the refugees themselves but also for the host families involved in homestay housing arrangements. While these homestay arrangements are designed to facilitate smoother transitions and enhance the well-being of refugees, the nuanced dynamics of these interactions and their overall impact on both refugees and their host families remain underexplored. Understanding the experiences of refugees and their host families is vital for effective refugee settlement, integration, and well-being. However, the intricacies of homestay refugee hosting, their interactions with host families, and the impact on their well-being are still unclear and ambiguous.

Objective: The aim of this scoping review is to examine the breadth of literature on the experiences of refugees living in homestay arrangements with their host families. This review seeks to understand how these dynamics influence refugee well-being, including their integration, social connections, and mental health. Additionally, this scoping review aims to synthesize existing literature on homestay hosting dynamics, focusing on the experiences of refugees and their host families, to identify gaps in knowledge and suggest areas for future research.

Methods: This scoping review follows Joanna Briggs Institute methodology and will search databases such as CINAHL, SOCIndex, MEDLINE through EBSCO; APA PsycInfo, Scopus through OVID; and Web of Science Core Collection, ProQuest Dissertations, and Theses, and SciELO Citation Index, focusing on literature from 2011 onward, in English, in relation to refugee groups in different host countries, including all types of literature. Literature will be screened by 2 independent reviewers, with disagreements resolved by consensus or a third reviewer. A custom data extraction tool will be created by the research team.

Results: The results will be organized in tables or diagrams, accompanied by a narrative overview, emphasizing the main synthesized findings related to the dynamics of homestay hosting with host families and refugee well-being. No critical appraisal will be conducted. This scoping review is expected to identify research gaps that will inform the development of homestay refugee hosting models, policies, and practices. It will also offer insights into best practices and policy recommendations to improve homestay hosting programs, ultimately contributing to more effective refugee settlement and integration strategies.

Conclusions: Understanding the intricate dynamics of homestay hosting arrangements is crucial for developing policies and programs that support the well-being of refugees and the families that host them. This scoping review will shed light on the current knowledge landscape, identify research gaps, and suggest ways to enhance the homestay hosting experience for all parties involved. Through this work, we aim to contribute to the development of more inclusive, supportive, and effective approaches to refugee hosting, resettlement, and integration.

International Registered Report Identifier (IRRID): DERR1-10.2196/56242

(JMIR Res Protoc 2024;13:e56242) doi:10.2196/56242

KEYWORDS

cohabitation; homestay; hospitality; host family; host-guest relationship; refugee; well-being

Introduction

Overview

The global displacement of refugees amounted to 35.3 million individuals, with a majority comprising female individuals [1]. However, as the number of individuals seeking refuge in host countries grows, the housing needs of such people beckon resolution. One prosperous solution that has arisen from housing needs is refugee hosting [2]. Within the purview of refugee studies, the term "hosting" signifies the established societies or communities that undertake the resettlement of refugees [3]. Hosting communities are often credited with the expectation to foster welcoming and accepting environments for refugee women and their families to settle after escaping conflict [4].

Families seeking support may be placed, by publicly or privately funded organizations, into the homes of host families. Such homes are volunteered by willing families or individuals, many of whom are refugees or immigrants [4]. Hosting communities and their members often play a crucial role in extending hospitality and support to refugee women and their families to facilitate integration [5]. This culture of hospitality is also observed at the individual level notably within urban communities, where there is a rising trend of individuals and families hosting refugees in their private residences [6]. The role of these host families typically involves temporarily sharing their homes and resources with newly arrived refugees, all with the aim of enhancing the settlement process [6]. However, the use of the terms "host" and "hosting" illustrates a host-guest relationship, positioning refugees within the domain of the hosts. This conveys an underlying power imbalance between the hosts and the refugees [4,7]. This dynamic can also cultivate certain expectations imposed on refugees, dictating their behavior according to the host's perceived standards of being worthy of hospitality [7]. For example, in a study by Monforte et al [7], exploring the responsibility of hosting, private hosts expressed emotional connection and mutual affection as a jointly shared responsibility with refugees, placing expectations on refugees to reciprocate. When refugees did not meet their expectations due to language barriers or unwillingness to discuss their past, hosts' perception of the refugee's value altered [7].

The expectation of the refugee to be a "good guest" highlights the conditional nature of private hosting, therefore requiring refugees to prove they are deserving of being hosted [4,5,7]. When refugees do not match the expectations or ideas of hosts, this can create an uncomfortable environment for refugees [5]. Furthermore, hosting arrangements and expectations can limit refugees' control over their surroundings, as they are essentially guests in someone else's domain [4,6,7]. This lack of control over their living situation can potentially hinder their ability to rebuild their lives autonomously, trigger power differences, and add an extra layer of vulnerability [8,9]. This power difference is even more pronounced for refugee women due to the intersection of gender-related disparities [10]. In addition, refugees' lack of host country citizenship further positions them as guests and makes them vulnerable to various abuses of power [11]. Viewing refugees women as mere guests within host homes and communities increases their social and economic vulnerabilities, especially without sufficient system-level policies and safeguards in place to protect their welfare [12].

Dağtaş [13] argues that refugee lived experience is heavily influenced by the host country's political conditions and social welfare policies (for refugees). In addition, current literature has revealed that hosting frameworks have created a racialized discourse of nonbelonging [14]. Furthermore, reviews of the literature on current homestay or family hosting practices and regulations for refugee groups highlight an enormous gap [6]. Although communities and host families play an immense role in refugee settlement, refugee well-being relies heavily on standards being shaped by inclusive and informed social welfare policies and practices [15]. Host families and the communities in which refugees are hosted are pivotal in their successful settlement and success [7,15]. They may provide crucial aid to refugees, including more tangible forms of support, such as housing or financial aid, in addition to more abstract forms of assistance, such as cultural orientation, emotional support, and social comfort [7]. However, as generally unregulated social groups, the success of such support provided to refugees can vary largely based on cultural competency, empathetic disposition and understanding, and the attitudes and perspectives of communities and host families [4,15]. For a meaningful exploration of the hosting practices and dynamics implemented by the host families, it is imperative to understand the discourse these practices bring forth and their implications on refugees' well-being.

A preliminary search of the literature through review registries (Open Science Framework and Joanna Briggs Institute (JBI) Evidence Synthesis) was conducted. No current or in-progress scoping reviews on this topic were identified. Existing reviews do not study the specific relationship between refugees and host families; reviews on the topic of refugee integration, in general, tend to be focused on a particular geography in terms of the host country or on a particular subset of refugees (eg, by gender, host country, or accommodations practices). The aim of this scoping review is to explore the experiences of refugees with their host families and understand the dynamics of homestay hosting on refugee well-being. A scoping review is an appropriate method to gather, organize, and chart the evidence [16] related to refugees living with host families. It aims to pinpoint variances and parallels in homestay hosting approaches and practices, enhancing our comprehension of their effects on refugee well-being. This review is intended to inform future research that could guide evolving practices or models for refugee hosting.

Review Question

What is known from the existing literature about the experiences of refugees with homestay hosting?

Methods

Overview

The proposed scoping review will be conducted in accordance with the JBI methodology for scoping review [16] and the PRISMA-ScR (Preferred Reporting Items for Systematic and Meta-Analyses extension for Scoping Reviews) [16,17]. The

protocol of this review has been registered with the Open Science Framework [18].

Eligibility Criteria

Participants

This review will consider studies involving participants who identify as refugees, displaced persons, or asylum seekers. There will be no restrictions based on age or gender.

Concept

This review will consider literature that pertains to refugee hosting experience, hosting practices, homestay, host-guest relationship, cohabitation, and refugee well-being.

Context

This review will consider literature specific to refugee accommodation, hosting family, and homestay hosting practices in different host countries and different geographical settings.

Types of Sources

This review will consider all types of study designs. Database searches will not be limited to a particular evidence source type. Primary research articles, review articles, editorials, theses, dissertations, reports, publications after 2011, and other gray literature in English will be included. This scoping review will also include theses and conference proceedings. Opinion papers will also be considered for inclusion in this scoping review, depending on the focus and context.

Search Strategy

In collaboration with a research librarian, the search strategy was built using some seed articles supplied to the librarian by the lead researcher as well as an initial search of several databases using basic terms. The search strategy, encompassing all identified keywords and index terms, will be tailored to suit each database and information source included. These searches were built up and used to develop a full search strategy for CINAHL (Multimedia Appendix 1). For other interfaces, the search will be modified as per the accepted Booleans, etc. The final scoping review will include all searches as appendices. The search strategy was also peer-reviewed by a fellow librarian using the PRESS Peer Review Strategy [19]. Studies published in English since 2011 will be included. The reference list of all included sources will be screened for additional studies. The databases to be searched include CINAHL, SOCIndex, MEDLINE, and Academic Search Complete through the EBSCO interface; APA PsycInfo and Scopus through the OVID interface; and Web of Science Core Collection, ProQuest Dissertations and Theses, SciELO Citation Index, and ProQuest through the Web of Science interface. As no source filters will be used, gray literature on these databases, such as conference proceedings and theses, will also be captured.

Study Selection

Following the search, all identified citations will be collated and uploaded into EndNote (version 21; Clarivate) and duplicates will be removed. Following a pilot test, titles and abstracts will then be screened by 2 or more independent reviewers for assessment against the inclusion criteria for the review. Potentially relevant studies will be retrieved in full and their citation details imported into the JBI System for the Unified Management of the Assessment and Review of Information (SUMARI) for the unified management, assessment, and review of information [20]. The full text of selected citations will be assessed in detail against the inclusion criteria by 2 or more independent reviewers. Reasons for the exclusion of papers in full text that do not meet the inclusion criteria will be recorded and reported in an appendix to the full review. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussion or with an additional reviewer. The results of the search and the study inclusion process will be reported in full in the final scoping review and presented in a PRISMA (Preferred Reporting Items for Systematic and Meta-Analyses) flow diagram [16,17].

Data Extraction

Data will be extracted from studies included in the review by 2 independent reviewers using a data extraction tool developed by the reviewers based on content relevant to the review question (Multimedia Appendix 2). The data extracted will include specific details about the participants, concept, context, study methods, and key findings relevant to the review question. The initial data extraction tool will undergo adjustments and updates as needed throughout the data extraction phase from each selected source of evidence. These changes will be thoroughly documented in the scoping review. Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer. We will reach out to the authors for further details or clarifications when necessary. Should we encounter missing, unclear, or ambiguous data crucial for our analysis, we will contact the respective authors.

Results

To address this scoping review's objective of identifying, collating, and mapping the evidence about the term homestay hosting in relation to refugee groups with their host families in different host countries, we will undertake a comprehensive and thorough analytical process. This will involve synthesizing information from the selected studies into a cohesive framework. The key outcomes of this process will be systematically documented in a detailed table, which will encapsulate the diverse definitions, interpretations, and implementations of "homestay hosting" encountered in the literature (Multimedia Appendix 3). This will serve as a crucial reference point, offering a consolidated view of how "homestay hosting" is understood and applied by different researchers and practitioners in the field. Beyond merely summarizing these findings, the review will extend its analysis to include the development of diagrams. These visual aids, to be included in Multimedia Appendix 4 are designed to visually represent the relationships and connections between the various elements of refugee homestay hosting.

The diagramming effort aims to clarify how the specific aspects of homestay hosting interact with the broader concept of family hosting and with each other. This visual mapping will not only make the complex interrelations more accessible but also highlight potential areas for further research or intervention.

Complementing the tables and diagrams, a narrative summary will be provided to weave together the review's findings in a coherent format. This narrative will contextualize the evidence within the scope of the review's objectives, offering insights into how the concept of homestay hosting contributes to our understanding of refugee support mechanisms. It will explore the implications of the findings for policy, practice, and future research, particularly emphasizing the nuances of refugee experiences in homestay settings and the roles of host families. Through this multifaceted approach—combining tabular summaries, visual diagrams, and narrative synthesis—the scoping review will offer a comprehensive and nuanced exploration of refugee homestay hosting, thereby enriching the discourse on refugee accommodation and support strategies.

Discussion

Overview

This scoping review will shed light on the intricate relationship between homestay hosting environments and refugee well-being, offering new perspectives on how these arrangements affect refugees' lives. By dissecting the dynamics within homestay settings, our analysis will bring to the forefront the multifaceted ways in which these hosting arrangements influence refugee well-being. Such insights are invaluable for policy makers and practitioners tasked with crafting and executing refugee hosting programs and models, providing them with a deeper understanding of the elements that contribute to successful refugees' integration and support. Our findings will highlight critical areas ripe for further exploration, suggesting that while this review lays the groundwork, it also underscores the necessity for more focused research. Detailed investigations, particularly longitudinal studies, could elucidate the evolving nature of refugee well-being within homestay contexts, offering a clearer picture of long-term outcomes. Similarly, comparative analyses of various hosting models could reveal best practices, guiding the development of more effective and supportive hosting frameworks. While this scoping review opens the door to a better understanding of the complex interplay between homestay hosting and refugee well-being, it also highlights the critical need for ongoing research. Future studies, armed with the foundational knowledge provided by this review, have the potential to further dissect and enhance the nuances of the homestay-refugee relationship. Such research is crucial for refining hosting practices and policies, aiming for a more empathetic and effective approach to supporting refugees worldwide, ultimately contributing to their well-being and successful integration into host communities.

Implications

The implications of our review extend beyond academic discourse, offering actionable insights for policy makers, practitioners, and researchers alike. By advocating for tailored support mechanisms, clear policy guidelines, and further research into the long-term effects of homestay arrangements, this review sets the stage for future studies that can build on our findings. Ultimately, we hope that our work will pave the way for more empathetic, effective, and sustainable refugee support practices worldwide, ensuring that both refugees and their host families can thrive together in their shared communities.

Limitations

This review protocol is not without limitations. One significant constraint is the scope of the literature reviewed, which may not encompass all existing studies on homestay hosting and refugee well-being due to language and publication date restrictions. Additionally, the inherent nature of scoping reviews to broadly map a field of study implies that the depth of analysis on specific topics might be limited and there will be no quality assessment of the selected resources. This limitation points to the necessity for targeted, in-depth studies that can build on the preliminary insights offered here. Furthermore, the diversity of homestay arrangements and refugee experiences across different cultural and geographical contexts may not be fully captured, highlighting the need for context-specific research to fully understand the nuances of homestay hosting and its impact on refugee well-being.

Conclusion

This scoping review will highlight the complex relationship between homestay hosting and refugee well-being, revealing both the potential and challenges of such arrangements. By examining the current state of research, the multifaceted nature of these hosting arrangements and their effects on both refugees and their host families will be illuminated. Our findings can highlight the critical need for policies and practices that are deeply informed by an understanding of these intricate dynamics to support the well-being of refugees and their hosts effectively. Understanding the intricate dynamics of homestay hosting arrangements is crucial for developing policies and programs that support the well-being of refugees and the families that host them. This review will shed light on the current knowledge landscape, identifying research gaps and suggesting ways to enhance the homestay hosting experience for all parties involved. This review's findings will inform the development of more inclusive, supportive, and effective approaches to refugee hosting, resettlement, and integration. To the best of our knowledge, this review represents the inaugural scoping review designed to explore the dynamic of homestay hosting and refugee well-being and the benefits such exploration brings to inform the development of refugee hosting models and practices.

Acknowledgments

We would like to thank all authors who contributed to this protocol. Their expertise, unique insights, and commitment have been crucial in shaping and enriching this work. Each author's distinct knowledge and dedication have significantly enhanced the quality and depth of our discussion. We are grateful for their valuable contributions and the collaborative effort that made this

protocol both informative and comprehensive. We affirm that ChatGPT was used solely for the purpose of language enhancement in the preparation of this protocol. It did not generate content for the study protocol, contribute to ideation, or provide any statements or references used herein. ChatGPT is not listed as an author, and its use was strictly limited to linguistic improvements. We adhered to all applicable artificial intelligence–related policies, regulations, and best practices in the use of this tool, ensuring that its application was in compliance with ethical standards for academic publication.

This review was supported by the Social Sciences and Humanities Research Council's (SSHRC) Insight Development Grant (grant 430-2023-00080). SSHRC had no role in the design, execution, interpretation, or writing of the manuscript.

Data Availability

This review protocol's supporting data are shared in the manuscript appendices, enhancing transparency and understanding. These appendices include the search strategy, data extraction tool or instrument, table of key findings, and term map diagram, offering insights into our methodology, data analysis, findings, and conceptual framework. For further details or clarifications, readers are encouraged to contact the corresponding author.

Declaration

AAH, YMY, K Metersky, and SG are registered nurses and researchers deeply committed to issues of equity and social justice in practice and inquiry and situate themselves as immigrants working to support the health and well-being of refugee groups. The work of this scoping review represents a continuation of a program of research dedicated to supporting meaningful hosting, settlement, and integration of refugee groups as a fundamental aspect of promoting and protecting their health and well-being.

Authors' Contributions

AAH contributed to the conceptualization of the review topic. K Mahsud contributed to developing and running the search strategies. AAH, YMY, K Metersky, and SG contributed to developing the review methods and criteria, providing feedback for the search strategies, and drafting and critically reviewing the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[DOCX File , 15 KB - resprot_v13i1e56242_app1.docx]

Multimedia Appendix 2
Data extraction tool.
[DOCX File , 13 KB - resprot_v13i1e56242_app2.docx]

Multimedia Appendix 3
Table of key findings.
[DOCX File , 12 KB - resprot_v13i1e56242_app3.docx]

Multimedia Appendix 4
Term map diagram.
[DOCX File , 69 KB - resprot_v13i1e56242_app4.docx]

Multimedia Appendix 5
Peer-review report from the Social Sciences and Humanities Research Council (SSHRC).
[PDF File (Adobe PDF File), 21 KB - resprot_v13i1e56242_app5.pdf]

References

1. Refugee statistics. United Nations High Commissioner for Refugees (UNHCR). URL: https://www.unhcr.org/refugee-statistics/ [accessed 2024-02-24]
2. Caron CM. Hosting as shelter during displacement: considerations for research and practice. J Int Humanitarian Action 2019;4:5 [FREE Full text] [doi: 10.1186/s41018-019-0052-0]
3. Yassine B, Al-Harithy H, Boano C. Refugees hosting other refugees: endurance and maintenance of care in Ouzaii (Lebanon). J Refug Stud 2021;34(3):2871-2890. [doi: 10.1093/jrs/fez098]

4. Gardner J, Lenette C, Al Kalmashi R. Who is the host? Interrogating hosting from refugee-background women's perspectives. J Intercultural Stud 2022;43(5):621-638. [doi: 10.1080/07256868.2022.2063819]
5. Boccagni P, Giudici D. Entering into domestic hospitality for refugees: a critical inquiry through a multi-scalar view of home. Identities 2021;29(6):787-806. [doi: 10.1080/1070289x.2021.1909359]
6. Ran GJ, Join-Lambert H. Influence of family hosting on refugee integration and its implication on social work practice: the French case. Eur J Soc Work 2019;23(3):461-474. [doi: 10.1080/13691457.2019.1706450]
7. Monforte P, Maestri G, d'Halluin E. 'It's like having one more family member': private hospitality, affective responsibility and intimate boundaries within refugee hosting networks. J Sociol 2021;57(3):674-689. [doi: 10.1177/1440783321991679]
8. Farahani F. Hospitality and hostility: the dilemmas of intimate life and refugee hosting. J Sociol 2021;57(3):664-673 [FREE Full text] [doi: 10.1177/14407833211018511]
9. Zhou YY, Grossman G, Ge S. Inclusive refugee-hosting can improve local development and prevent public backlash. World Dev 2023;166:106203 [FREE Full text] [doi: 10.1016/j.worlddev.2023.106203]
10. Al-Hamad A, Forchuk C, Oudshoorn A, McKinley GP. The potential of merging intersectionality and critical ethnography for advancing refugee women's health research. ANS Adv Nurs Sci 2022;45(2):143-154. [doi: 10.1097/ANS.0000000000000404] [Medline: 34879023]
11. de Simone S. Beyond normativity and benchmarking: applying a human security approach to refugee-hosting areas in Africa. Third World Q 2019;41(1):168-183. [doi: 10.1080/01436597.2019.1660635]
12. Senthanar S, MacEachen E. Disentangling assumptions: refugee women's access to and use of social assistance in Canada. J Ethn Migr Stud 2022;49(9):2213-2228. [doi: 10.1080/1369183x.2022.2134096]
13. Dağtaş S. Inhabiting difference across religion and gender: displaced women's experiences at Turkey's border with Syria. Refuge 2018;34(1):50-59 [FREE Full text] [doi: 10.7202/1050854ar]
14. Rottmann SB, Nimer M. 'We always open our doors for visitors'—hospitality as homemaking strategy for refugee women in Istanbul. Migr Stud 2021;9(3):1380-1398. [doi: 10.1093/migration/mnab005]
15. Hebbani A, Khawaja NG, Famularo J. Hosting an asylum seeker in Australia: a nationwide exploratory study. Aust Psychol 2020;51(2):154-163. [doi: 10.1111/ap.12123]
16. Peters MDJ, Marnie C, Tricco AC, Pollock D, Munn Z, Alexander L, et al. Updated methodological guidance for the conduct of scoping reviews. JBI Evid Implement 2021;19(1):3-10. [doi: 10.1097/XEB.0000000000000277] [Medline: 33570328]
17. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med 2018;169(7):467-473 [FREE Full text] [doi: 10.7326/M18-0850] [Medline: 30178033]
18. Yasin YM, Al-Hamad A, Metersky K, Guruge S, Mahsud K. Homestay hosting dynamics and refugee wellbeing: a scoping review protocol. OSF Registries. 2024. URL: https://osf.io/wfsjr [accessed 2024-02-27]
19. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS peer review of electronic search strategies: 2015 guideline statement. J Clin Epidemiol 2016;75:40-46 [FREE Full text] [doi: 10.1016/j.jclinepi.2016.01.021] [Medline: 27005575]
20. Munn Z, Aromataris E, Tufanaru C, Stern C, Porritt K, Farrow J, et al. The development of software to support multiple systematic review types: the Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information (JBI SUMARI). Int J Evid Based Healthc 2019;17(1):36-43. [doi: 10.1097/XEB.0000000000000152] [Medline: 30239357]

Abbreviations

JBI: Joanna Briggs Institute
PRISMA: Preferred Reporting Items for Systematic and Meta-Analyses
PRISMA-ScR: Preferred Reporting Items for Systematic and Meta-Analyses extension for Scoping Reviews
SUMARI: System for the Unified Management of the Assessment and Review of Information

Edited by A Mavragani; submitted 10.01.24; this is a non–peer-reviewed article;accepted 08.02.24; published 19.03.24.

Please cite as:
Al-Hamad A, Yasin YM, Metersky K, Guruge S, Mahsud K
Homestay Hosting Dynamics and Refugee Well-Being: Protocol for a Scoping Review
JMIR Res Protoc 2024;13:e56242
URL: https://www.researchprotocols.org/2024/1/e56242
doi:10.2196/56242
PMID:38502182

Protocol

Monitoring and Evaluation of Dementia-Friendly Neighborhoods Using a Walkshed Approach: Protocol for a Scoping Review

Mark Groulx[1], PhD; Shannon Freeman[2], PhD; Keone Gourlay[3], BPl; Dawn Hemingway[4], PhD; Emma Rossnagel[1], MPH; Habib Chaudhury[5], PhD; Mohammadjavad Nouri[5], PhD

[1]University of Northern British Columbia, Prince George, BC, Canada

[2]School of Nursing, University of Northern British Columbia, Prince George, BC, Canada

[3]School of Planning and Sustainability, University of Northern British Columbia, Prince George, BC, Canada

[4]School of Social Work, University of Northern British Columbia, Prince George, BC, Canada

[5]Department of Gerontology, Simon Fraser University, Vancouver, BC, Canada

Corresponding Author:
Mark Groulx, PhD
University of Northern British Columbia
3333 University Way
Prince George, BC, V2N 4Z9
Canada
Phone: 1 250 960 5837
Email: mark.groulx@unbc.ca

Abstract

Background: The number of people in society living with dementia is growing. In Canada, most people who live with dementia live at home, often in a neighborhood setting. Neighborhood environments can be a source of independence, social engagement, and well-being. They can also contain barriers that limit physical activity, social engagement, and well-being. A dementia-friendly neighborhood includes assets that support persons living with dementia and their caregivers in multiple life domains, including those that support walking within the neighborhood environment.

Objective: The objectives for this scoping review are twofold. First, focusing on walkshed analysis, we aim to extend scholarly understandings of methodological practices used in the monitoring and evaluation of dementia-friendly neighborhoods. Second, we aim to provide clear and practical guidance for those working in planning, design, and public health fields to assess the neighborhood context in support of evidence-based action to improve the lives of persons living with dementia.

Methods: The study design follows Arksey and O'Malley's scoping review framework and PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) guidelines. We will conduct a search of peer-reviewed studies in 6 electronic databases to identify the use of Geographic Information System analysis to measure the walkshed of persons living with dementia in a community setting. As age is a primary risk factor associated with dementia, we will also include studies that focus more broadly on community-dwelling older adults aged 65 years and older. Data will be extracted, analyzed, and represented according to 3 domains. This includes study details, walkshed analysis methods, and criteria and indicators used to measure dementia-friendly neighborhoods.

Results: The results of the study and the submission of a manuscript for peer review are expected in June 2024. The results of the review are expected to contribute to an understanding of methods for monitoring and evaluating dementia-friendly neighborhoods. Expected findings will include a detailed breakdown of current parameters and routines used to conduct walkshed analysis. Findings will also convey criteria that can be operationalized in a Geographic Information System as indicators to assess barriers and facilitators to walking in a neighborhood setting.

Conclusions: As far as we are aware, the proposed scoping review will be the first to provide comprehensive methodological or technical guidance for conducting walkshed analysis specific to persons living with dementia. Both the scalability and objective nature of walkshed analysis are likely to be of direct interest to public health practitioners, planners, and allied professionals. Clearly documenting methods used in walkshed analysis can spur increased collaboration across these disciplines to enable an evidence-informed approach to improving neighborhood environments for persons living with dementia.

International Registered Report Identifier (IRRID): PRR1-10.2196/50548

(JMIR Res Protoc 2024;13:e50548) doi:10.2196/50548

KEYWORDS

dementia-friendly; neighborhood; persons living with dementia; walkability; walkshed

Introduction

Overview

Walkshed analysis identifies the extent of the community environment surrounding a central location that is accessible at a scale where walking is a competitive mode of mobility [1]. Once a walkshed is delineated in a Geographic Information System (GIS), criteria and indicators can identify barriers and enablers to walking [2]. Walkshed analysis is relevant to planning and public-health partnerships that seek to support persons living with dementia. More than 55 million people are currently living with dementia across the world. The global prevalence of dementia is projected to continue to rise by approximately 10 million new cases per year [3]. In Canada, most people experiencing dementia live at home. As of 2016, around 69% of those aged 80 years or younger were living outside of the long-term care system [4]. As an umbrella term, dementia captures the experience of progressive cognitive decline. It can impact an individual's mood, behavior, and actions, including the performance of key activities of daily living [5]. There are many types of dementia, including Alzheimer dementia, vascular dementia, frontotemporal dementia, lewy body dementia, mixed dementia, and young-onset dementia. Alzheimer disease is the most common cause, contributing to 60% to 70% of cases of dementia [6].

Literature on dementia-friendly communities (and neighborhoods) takes a relational view [7,8]. This view acknowledges that well-being is conditioned by interrelated aspects of a person's social, built, and ecological surroundings [8-10]. Accordingly, scholars identify dementia-friendly environments as the arrangement of supportive assets into a community fabric that promotes meaningful societal engagement for persons living with dementia and their caregivers [11]. This includes the complex social relations that persons living with dementia experience in a community setting, making the physical neighborhood part of a relational and moral context [12,13].

Scholarship on dementia-friendly communities and neighborhoods stems from calls to better support persons who are living with dementia outside of an institutional setting [11]. These calls reflect the fact that scholars have long viewed neighborhoods as a central relational context shaping individual behavior and life quality [14]. As early as the turn of the 20th century, ideas about neighborhood planning in North America drew on sociological concepts such as Charles H Cooley's primary group. The primary group and similar concepts asserted that the neighborhood was the main setting for the social relations that informed one's perspectives and ideals [15].

A long fascination with neighborhood environments helps explain the growing effort to understand how the neighborhood can enable or hinder self-determination for persons living with dementia. This includes aspects of identity development and one's ability to shape life balance [10,12,16]. Remaining close to the home, or aging in place, is also "closely intertwined with (a person's) sense of self and identity" [17]. By contrast, moving away from familiar areas can have negative effects on persons living with dementia [18]. To remain active and engaged within their environments while aging in place, persons living with dementia need special considerations and support in their neighborhoods [17].

The influence of the built environment on a sense of community and one's place therein remains up for debate in an increasingly mobile and digital society [19,20]. At the same time, there is a convincing body of evidence demonstrating that planning and design can impact behavior. The extent to which a neighborhood setting encourages or discourages important social and health behaviors such as walking is a particular focus for planning-health partnerships [21-23]. There is also a growing body of evidence illustrating that walking outdoors boosts quality of life for those living with dementia, contributing to improved mood, quality of sleep, and sense of freedom [17,24,25].

Urban planning scholar Lawrence Frank significantly advanced the conception and measurement of walkability. He describes walkability as the extent to which an environment's social and physical characteristics promote walking as a competitive and desirable form of mobility [26,27]. Recent work has extended the idea of walkability to a more encompassing notion of "active living environments." Active living environments are defined as "the emergent natural, built, and social properties of neighborhoods that promote physical activity and health and allow for equitable access to health-enhancing resources" [28].

Scholars have used a wide variety of methods to study walkability and its relation to walking behavior. These include phenomenological interviews [29], cross-sectional community surveys [30], observational techniques [31], surveys [32,33], photovoice [34,35], and in-situ walking interviews [12]. Scholars have also deployed criteria and indicators that enable monitoring and evaluation of the social, built, and ecological environments that make up a city [36]. In some cases, criteria and indicators are operationalized using a geospatial approach that assesses barriers and facilitators to walking in a small area (eg, 1 km) surrounding a central location such as a residence. This approach is often referred to as walkshed analysis.

In North America, walkability is now well researched within urban settings in the context of the "general population." By comparison, factors that shape walkability for members of equity-deserving groups, particularly persons living with dementia, are comparatively understudied. There is a need to better document (1) what walkability criteria and indicators are relevant to the lived experience of persons living with dementia, (2) how methods are operationalized to examine barriers and facilitators using a walkshed approach, and (3) where barriers and facilitators of walkability for persons living with dementia

may align or conflict with those of other populations. Given these needs, the objectives for this scoping review are twofold:

1. Focusing on walkshed analysis, extend scholarly understandings of methodological practices used in the monitoring and evaluation of dementia-friendly neighborhoods.
2. Provide clear and practical guidance for those working in planning, design, and public health fields to assess the neighborhood context in support of evidence-based action to improve the lives of persons living with dementia.

To achieve the preceding objectives, this scoping review will address the following research question: What dimensions, criteria, and indicators can be recognized within the academic literature for measuring neighborhood walkability for persons living with dementia based on a walkshed methodology?

Existing Reviews

This protocol was informed by an initial review of existing peer-reviewed literature. The purpose of this review was to identify possible knowledge syntheses on the use of walkshed methodology to document barriers and facilitators faced by persons living with dementia. Table 1 summarizes key aspects of 6 related knowledge syntheses. All but 1 of the identified studies were published within the past 5 years [36]. A total of 2 of the studies directly focused on persons living with dementia. Other studies focused on dementia risk factors among older adults (see Table 1).

Table 1. Summary of comparable existing knowledge syntheses as they relate to the proposed scoping review.

Reference	Title	Objective	Population focus	Addresses aspects of walkshed methods	Addresses objective criteria
Akinci et al [21], 2022	How different are objective operationalizations of walkability for older adults compared to the general population? a systematic review	Summarize and compare methods used to operationalize objective walkability for older adults and the general population	Older adults or general population	Yes	Yes
Cerin et al [36], 2017	The neighbourhood physical environment and active travel in older adults: a systematic review and meta-analysis	Identify correlates of neighborhood physical features and active travel in older adults and quantify the strength of associations	Older adults	No	Yes
Sturge et al [37], 2021	Features of the social and built environment that contribute to the well-being of persons with dementia who live at home: a scoping review	Summarize evidence from qualitative studies about how social and built environment features influence well-being for persons living with dementia	Persons living with dementia	No	Yes
Gan et al [25], 2022	Dementia-friendly neighbourhood and the built environment: a scoping review	Synthesize knowledge and support policy direction related to dementia-friendly neighborhood environments and attendant psychosocial outcomes	Persons living with dementia	No	Yes
Peters et al [2], 2020	Measuring the association of objective and perceived neighborhood environment with physical activity in older adults: challenges and implications from a systematic review	Assess the correlates of neighborhood characteristics and physical activity in older adults to provide a body of evidence to support neighborhood environmental interventions	Older adults	Yes	Yes
Chen et al [38], 2022	Neighbourhood-built environment associated with cognition and dementia risk among older adults: a systematic literature review	Assess the state of current knowledge on the links between neighborhood environments and cognitive health in older adults	Older adults at risk of dementia	No	Yes

Gan and colleagues [25] reviewed 29 studies and documented methodologies ranging from applications of virtual reality to measurements of statistical association. No use of walkshed methods was reported. The authors also assessed the psychosocial outcomes of outdoor use (eg, increased social agency, anxiety, and promotion of personhood) and built environment characteristics that facilitate use and participation (eg, land use diversity, presence of landmarks, and irregular street grids).

By contrast, Sturge and colleagues [37] focused solely on qualitative studies exploring how social and built environments contribute to the well-being of persons living with dementia at home. Under a theme examining "connection to society and supportive relationships," the authors review 4 key areas of support. These include contact with friends and family, social networks afforded by formal events and professional services, connections available across a host of neighborhood settings (eg, pubs and cafés), and the mixed reactions persons living with dementia can experience when disclosing their diagnosis. A second theme titled "interaction with natural environments and public space" examines supports (eg, parks and sounds of children playing) and barriers (eg, complex street environments and noise from traffic).

Both Peters and colleagues [2] and Akinci and colleagues [21] review (respectively) aspects of walkshed methodology in the context of older adults or older adults and the general public. Neither focused specifically on persons living with dementia. Peters and colleagues [2] distinguish between subjective and

objective measures and discuss the use of accelerometers, GIS, and field-based audit approaches. They document key aspects related to the use of walkshed methods with older adults. Elements include operational definitions of a neighborhood, walking times or distances used to define a walkshed, and neighborhood attributes associated with walking and other physical activity. Akinci and colleagues [21] similarly report on GIS-based methods for spatial analysis. They report on walkshed buffer types and sizes and 167 different walkability variables across 24 studies of older adults.

The identified 6 studies are each related to the aim of this proposed scoping review. None directly cover the realm we seek to document. In 4 cases, the studies do not review objective walkshed methods. The remaining 2 cases do not focus on persons living with dementia.

Methods

Study Eligibility

The primary objective of this study is to report on research relevant to the use of walkshed methodology. We are specifically interested in walkshed analysis which involves the monitoring and evaluation of barriers and facilitators to walking in a neighborhood setting. Eligible studies will include those that reveal details about how to define a walkshed in a manner that is appropriate to the walking experience of persons living with dementia (eg, walking distance used to define a walkshed). We anticipate that this group of studies may largely involve quantitative, GIS-based case studies. Studies that document criteria and indicators that can be used to identify and track barriers to and facilitators of walking will also be included. We anticipate that the methodologies of these studies will be more diverse, including qualitative, quantitative, mixed methods and review articles.

We will include publications from any date in our initial pool. This may influence the variability of results, such as key definitions. A start date is not included because we anticipate that there will be a limited number of available studies related to walkshed analysis for our focus population. An open-ended start date may also allow us to identify when walkshed analysis emerged in various literatures.

We will not limit eligibility by geographic scope and will include studies from any country or region. Studies from a diverse range of geographic settings will also be eligible. This will include various community environments (eg, urban, suburban, exurban, and rural), but we anticipate that urban and suburban settings will predominate. Due to the composition of the team, eligibility will be limited to studies available in English. Our primary goal is the transfer of knowledge about rigorous methodological techniques within and beyond the academic sphere. As such, only peer-reviewed journal articles will be eligible. For additional details on study inclusion or exclusion, see Textbox 1.

Textbox 1. Summary of the inclusion and exclusion process and the criteria (framed as prompts) used to exclude studies.

Review level

- Level 1: title, abstract, and keyword review
  - Does the study include a focus on geographic areas within a community setting?
  - Does the study include a focus on outdoor spaces?
  - Does the study include a focus on people's use of the community environment by walking or other forms of non-motorized mobility?
- Level 2: full text article review
  - Did the study collect and analyze primary or secondary data following a structured methodological approach?
  - Does the study identify measurable criteria and indicators related to walkability or report on the use of walkshed methods?
  - Does the study specifically focus on environmental use by persons living with dementia or older adults?

Population and Setting

This review will be guided by Arskey and O'Malley's [39] 6-step scoping review process. It will include studies that involve participants recognized to be living with dementia or mild cognitive impairment and who reside in a community setting. Studies that focus on persons living in congregate care-based facilities such as assisted living homes and long-term care homes will be excluded. We expect to find few published studies that explicitly focus on this population in the context of operational aspects of walkshed methodology. As age is the primary risk factor associated with dementia, we will also include studies that focus more broadly on community-dwelling older adults aged 65 years and older [6]. We will track differences in existing evidence between these population groups.

Search Strategy

Our search strategy was developed by a project manager with experience conducting scoping reviews. It involved consultation with a research librarian and the broader research team. The latter consultation involved a workshop that iteratively identified, tested, and respecified search domains and terms. Our search strategy includes a combination of subject headings and title or abstract-focused keyword searching (Textbox 2). These strategies target the intersection of an activity or policy domain (walking), an environmental setting domain (outdoor neighborhood setting), and a population focus domain (persons living with dementia and older adults). We will apply search

strings to 6 electronic databases known to publish high-quality research around our focus domains (PubMed, Medline, CINAHL, APA PsycINFO, Business Source, and Web of Science). Endnote will be used to manage citations, and DistillerSR (DistilerSR Inc) and Excel (Microsoft Corporation) will be used to manage the inclusion, data extraction, and charting stages of this review.

Textbox 2. Domain areas and search terms to be used in search strings for database searches.

Domain areas and search terms

- Activity or policy - walking, walkshed, walkability, walk, wayfinding, way finding, indicator, criteria, dimension, requirement, experience, audit, measure
- Environmental setting - footpath, greenspace, green space, population density, rural population, neighbourhood characteristics, city planning, communit*, neighbo*rhood*, built environment, urban design*, urban planning, town planning, city planning, building densit*, social densit*, population densit*
- Population focus - dementia, alzheimer*, aged

Article Selection Process

After removing duplicate sources from our initial study pool using DistillerSR, we will use DistillerSR to complete screening at 2 levels. At level 1, we will assess the title, abstract, and keywords of each potential source. This assessment will include 2 independent reviewers using the level 1 inclusion criteria in Textbox 1. Studies will be excluded if both reviewers definitively identify relevant content and answer no to any of the criteria prompts. Studies will be moved to level 2 screening if a prompt cannot be answered definitively. To promote consistency at level 2 article screening, 2 reviewers will assess the full text of all remaining sources. Studies will only be included if reviewers can definitively answer yes to all inclusion prompts. We will address discrepancies at each level at a team meeting that involves a reassessment of the source and a consensus decision made by the team.

Data Charting and Representation

Data charting and representation will follow 2 interrelated steps outlined by Arksey and O'Malley [39]. Common practices in scoping review methodology and existing knowledge syntheses documented above informed the creation of the data charting schema listed below. Using this schema, we will develop a data matrix in Excel. This matrix will organize data and allow for the analysis of key items of information. Following guidance from Levac and colleagues [40], we will review and iteratively update the initial schema shown in Table 2 as the final study pool is examined. A total of 2 reviewers will extract data for a subset of papers (n=5). They will compare and update the schema as they reflect on processes and outcomes. Final data extraction will be completed by a single reviewer.

Table 2. Initial data charting schema for creation of data charting matrix.

Study details	Walkshed methods	Criteria and indicators
Title	Definition of walkability	Measurement domains reported
Lead author	GIS[a] operationalization of walkshed	Measurement criteria reported
Year of publication	Distance or time parameter	Criteria used with persons living with dementia
Journal name	Data sources and types	Criteria used with older adults
Journal discipline (if applicable)	GIS routines (if reported)	Measurement indicators reported
Country of lead author's institution	Population focus	GIS based indicators
Study method	N/A[b]	Data sources for indicator calculation
N/A	N/A	Method for indicator measurement or representation

[a]GIS: Geographic Information System.

[b]N/A: not applicable.

Beyond tracking the breadth (eg, diversity of methods) and location (eg, countries of origin) of literature, descriptive numerical summaries will examine 2 key topics. First, we will document the tools, data, and parameters used to define a walkshed. The review will make a contribution to the existing literature by documenting implementation approaches specific to the context of persons living with dementia. We will also compare these approaches to those used in studies of an older adult population. Second, we will chart criteria and indicators used to measure aspects of dementia-friendly neighborhood and community environments. By documenting indicators that scholars have operationalized using GIS-based analyses, we will make a key contribution to the transfer of the methodology.

The final scoping review will use descriptive results (eg, diversity of methods) represented using a combination of summary tables and figures (eg, Sankey diagrams). Limited textual information will support these visual elements. We will represent comparative results related to criteria and indicators as a larger data matrix. This matrix will visualize how

researchers have operationalized indicators in GIS for the 2 populations of interest. A longer textual description will contextualize these results. Finally, using thematic analysis, we will convey synthesized themes that capture nuance lacking in the descriptive and comparative results [41-43]. We expect to highlight considerations for the use of walkshed methodology not yet documented in recent studies focused on older adults [2,21]. We also expect to identify where criteria used to assess walkability for persons living with dementia and older adults converge and diverge. The risk of bias will not be assessed. This is consistent with the broad nature of our review question and the norms identified in the development of the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) [44,45].

Results

The results of the study and the submission of a manuscript for peer review are expected in June 2024.

Discussion

Overview

Scholars from the fields of planning, public health, urban design, gerontology, and architecture have produced a wealth of evidence and guidance related to walkability. Branching out from the "general population," studies increasingly focus on targeted population groups. These foci better recognize the social, cultural, and demographic barriers and enablers to walking that shape one's experience of the neighborhood. The proposed scoping review will synthesize the growing evidence base with specific reference to persons living with dementia. By including relevant studies focused on an older adult population, the review will also identify where current best practice for monitoring and evaluation diverges and converges for these populations. Expected findings include a detailed breakdown of current parameters and routines used to conduct walkshed analysis. Findings will also convey criteria that can be operationalized in GIS as indicators to assess barriers and facilitators to walking in a neighborhood setting.

Studies already identified here have documented monitoring and evaluation methods relevant to walkability for persons living with dementia. Methods include interviews, community survey techniques, and field audits of the neighborhood environment. Our planned focus on GIS-based walkshed analysis will further document a highly scalable monitoring and evaluation tool and technique.

Limitations

The final scoping review will be subject to limitations, despite following accepted methodological practice [39,40]. First, as a scoping review, there will not be a quality assessment of studies, which presents a risk of bias. Second, only English studies will be included, which will overemphasize evidence and practice from western countries. Third, we expect that the use of walkshed analysis for persons living with dementia will be an offshoot of techniques and literature focused on older adults. There may therefore be limited literature specific to persons living with dementia. To mitigate the risk of making assumptions about the transfer of methodological guidance from one population to another, we will explicitly track and compare findings across groups.

Conclusions

As far as we are aware, the proposed scoping review will be the first to provide comprehensive methodological or technical guidance for conducting walkshed analysis specific to persons living with dementia. There are 3 target audiences for this scoping review. These include applied academic researchers in the field of public health, applied academic researchers in the fields of urban planning and design, and evidence-based practitioners across these fields. Scholars identify neighborhood environments as an upstream source of barriers and enablers that shape walking behavior and associated health and well-being cobenefits [12,17,25]. Understanding the individual and population health impacts of neighborhood environments requires the expertise of health researchers and practitioners. Understanding how neighborhood environments came to be and how to reshape them through land-use and built-form interventions requires the expertise of planners and designers. By clearly documenting methods used in walkshed analysis, our goal is to spur increased collaboration across these disciplines to enable an evidence-informed approach to improving neighborhood environments for persons living with dementia.

Acknowledgments

The authors would like to thank the DemSCAPE team for their efforts.

Data Availability

The data generated and analyzed during this study will include content extracted from published, peer-reviewed journal articles. Full details about parameters, data sets, and Geographic Information System routines used in walkshed analysis, as well as a full list of associated indicators, will be reported in the scoping review publication. Additional data generated and analyzed during the study will be available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

References

1. Sandalack BA, Uribe FGA, Zanjani AE, Shiell A, McCormack GR, Doyle-Baker PK. Neighbourhood type and walkshed size. Journal of Urbanism: International Research on Placemaking and Urban Sustainability 2013;6(3):236-255 [FREE Full text] [doi: 10.1080/17549175.2013.771694]
2. Peters M, Muellmann S, Christianson L, Stalling I, Bammann K, Drell C, et al. Measuring the association of objective and perceived neighborhood environment with physical activity in older adults: challenges and implications from a systematic review. Int J Health Geogr 2020;19(1):47 [FREE Full text] [doi: 10.1186/s12942-020-00243-z] [Medline: 33168094]
3. Dementia: key facts. World Health Organization. 2023. URL: https://www.who.int/news-room/fact-sheets/detail/dementia [accessed 2023-12-07]
4. Dementia in home and community care. Canadian Institute for Health Information. 2018. URL: https://www.cihi.ca/en/dementia-in-canada/dementia-care-across-the-health-system/dementia-in-home-and-community-care [accessed 2023-12-07]
5. Freeman S, Pelletier C, Ward K, Bechard L, Regan K, Somani S, et al. Factors influencing participation in physical activity for persons living with dementia in rural and northern communities in Canada: a qualitative study. BMJ Open 2022;12(6):e060860 [FREE Full text] [doi: 10.1136/bmjopen-2022-060860] [Medline: 35710242]
6. Navigating the path forward for dementia in Canada: the landmark study—report 1. Alzheimer Society of Canada. 2022. URL: https://alzheimer.ca/en/research/reports-dementia/landmark-study-report-1-path-forward [accessed 2023-12-07]
7. Oliver M. The social model of disability: thirty years on. Disabil Soc 2013;28(7):1024-1026 [FREE Full text] [doi: 10.1080/09687599.2013.818773]
8. Biglieri S. Implementing dementia-friendly land use planning: an evaluation of current literature and financial implications for greenfield development in suburban Canada. Plan Pract Res 2018;33(3):264-290 [FREE Full text] [doi: 10.1080/02697459.2017.1379336]
9. Luo Y, Zhang L, Pan X. Neighborhood environments and cognitive decline among middle-aged and older people in China. J Gerontol B Psychol Sci Soc Sci 2019;74(7):e60-e71 [FREE Full text] [doi: 10.1093/geronb/gbz016] [Medline: 30726959]
10. Mmako NJ, Courtney-Pratt H, Marsh P. Green spaces, dementia and a meaningful life in the community: a mixed studies review. Health Place 2020;63:102344 [FREE Full text] [doi: 10.1016/j.healthplace.2020.102344] [Medline: 32543430]
11. Finlay J, Meltzer G. Dementia-friendly neighborhoods: methodological challenges and research opportunities. J Urban Des Ment Health 2021;7:2 [FREE Full text]
12. Biglieri S, Dean J. Everyday built environments of care: examining the socio-spatial relationalities of suburban neighbourhoods for people living with dementia. Wellbeing Space Soc 2021;2:100058 [FREE Full text] [doi: 10.1016/j.wss.2021.100058]
13. Clark A, Campbell S, Keady J, Kullberg A, Manji K, Odzakovic E, et al. Understanding the meaning of neighbourhoods for people living with dementia: the value of a relational lens. In: Ward R, Clark A, Phillipson L, editors. Dementia and Place: Practices, Experiences, and Connections. Bristol, UK: Bristol University Press; 2021:23-43.
14. Talen E. Social science and the planned neighbourhood. Town Plan Rev 2017;88(3):349-373 [FREE Full text] [doi: 10.3828/tpr.2017.22]
15. Banerjee T, Baer WC. Beyond the Neighborhood Unit: Residential Environments and Public Policy. Berlin, Germany: Springer Science & Business Media; 2013.
16. Helvik S. Coping and health promotion in persons with dementia. In: Haugen G, Eriksson M, editors. Health Promotion in Health Care—Vital Theories and Research. Berlin, Germany: Springer; 2021.
17. Odzakovic E, Hellström I, Ward R, Kullberg A. 'Overjoyed that I can go outside': using walking interviews to learn about the lived experience and meaning of neighbourhood for people living with dementia. Dementia 2020;19(7):2199-2219. [doi: 10.1177/1471301218817453] [Medline: 30541394]
18. Sheehan B, Burton E, Mitchell L. Outdoor wayfinding in dementia. Dementia 2006;5(2):271-281 [FREE Full text] [doi: 10.1177/1471301206062254]
19. Calhoun C. Community without propinquity revisited: communications technology and the transformation of the urban public sphere. Sociol Inq 1998;68(3):373-397 [FREE Full text] [doi: 10.1111/j.1475-682x.1998.tb00474.x]
20. Goodspeed R. Community and urban places in a digital world. City and Community 2017;16(1):9-15 [FREE Full text] [doi: 10.1111/cico.12218]
21. Akinci ZS, Delclòs-Alió X, Vich G, Salvo D, Ibarluzea J, Miralles-Guasch C. How different are objective operationalizations of walkability for older adults compared to the general population? a systematic review. BMC Geriatr 2022;22(1):673 [FREE Full text] [doi: 10.1186/s12877-022-03233-x] [Medline: 35971086]
22. Frank LD, Mayaud J, Hong A, Fisher P, Kershaw S. Unmet demand for walkable transit-oriented neighborhoods in a midsized Canadian community: market and planning implications. J Plan Educ Res 2019;42(4):568-584 [FREE Full text] [doi: 10.1177/0739456x19831064]
23. Talen E, Koschinsky J. The walkable neighborhood: a literature review. Int J Sustainable Land Use Urban Panning 2013;1(1):42-63.
24. White EB, Montgomery P. Dementia, walking outdoors and getting lost: incidence, risk factors and consequences from dementia-related police missing-person reports. Aging Ment Health 2015;19(3):224-230. [doi: 10.1080/13607863.2014.924091] [Medline: 24912376]

25. Gan DRY, Chaudhury H, Mann J, Wister AV. Dementia-friendly neighborhood and the built environment: a scoping review. Gerontologist 2022;62(6):e340-e356 [FREE Full text] [doi: 10.1093/geront/gnab019] [Medline: 33564829]
26. Frank LD, Pivo G. Impacts of mixed use and density on utilization of three modes of travel: single-occupant vehicle, transit, and walking. Transp Res Rec 1994;1466:44-52 [FREE Full text]
27. Frank LD, Sallis JF, Conway TL, Chapman JE, Saelens BE, Bachman W. Many pathways from land use to health: associations between neighborhood walkability and active transportation, body mass index, and air quality. J Am Plann Assoc 2006;72(1):75-87 [FREE Full text] [doi: 10.1080/01944360608976725]
28. Tobin M, Hajna S, Orychock K, Ross N, DeVries M, Villeneuve PJ, et al. Rethinking walkability and developing a conceptual definition of active living environments to guide research and practice. BMC Public Health 2022;22(1):450 [FREE Full text] [doi: 10.1186/s12889-022-12747-3]
29. Crust L, Keegan R, Piggott D, Swann C. Walking the walk: a phenomenological study of long-distance walking. J Appl Sport Psychol 2011;23(3):243-262 [FREE Full text] [doi: 10.1080/10413200.2010.548848]
30. Chudyk AM, McKay HA, Winters M, Sims-Gould J, Ashe MC. Neighborhood walkability, physical activity, and walking for transportation: a cross-sectional study of older adults living on low income. BMC Geriatr 2017;17(1):82 [FREE Full text] [doi: 10.1186/s12877-017-0469-5] [Medline: 28395672]
31. Girling C, Zheng K, Monti A, Ebneshahidi M. Walkability vs. walking: assessing outcomes of walkability at Southeast False Creek, Vancouver, Canada. Journal of Urbanism: International Research on Placemaking and Urban Sustainability 2019;12(4):456-475 [FREE Full text] [doi: 10.1080/17549175.2019.1626269]
32. Chaudhury H, Campo M, Michael Y, Mahmood A. Neighbourhood environment and physical activity in older adults. Soc Sci Med 2016;149:104-113 [FREE Full text] [doi: 10.1016/j.socscimed.2015.12.011] [Medline: 26708246]
33. Herbolsheimer F, Mahmood A, Ungar N, Michael YL, Oswald F, Chaudhury H. Perceptions of the neighborhood built environment for walking behavior in older adults living in close proximity. J Appl Gerontol 2021;40(12):1697-1705. [doi: 10.1177/0733464820979258] [Medline: 33353472]
34. Chaudhury H, Mahmood A, Michael YL, Campo M, Hay K. The influence of neighborhood residential density, physical and social environments on older adults' physical activity: an exploratory study in two metropolitan areas. J Aging Stud 2012;26(1):35-43 [FREE Full text] [doi: 10.1016/j.jaging.2011.07.001] [Medline: 37841338]
35. Mahmood A, Chaudhury H, Hay K, Michael Y, Campo M, Sarte A. A photovoice documentation of the role of neighborhood physical and social environments in older adults' physical activity in two metropolitan areas in North America. Soc Sci Med 2012;74(8):1180-1192 [FREE Full text] [doi: 10.1016/j.socscimed.2011.12.039]
36. Cerin E, Nathan A, van Cauwenberg J, Barnett DW, Barnett A. The neighbourhood physical environment and active travel in older adults: a systematic review and meta-analysis. Int J Behav Nutr Phys Act 2017;14(1):15 [FREE Full text] [doi: 10.1186/s12966-017-0471-5] [Medline: 28166790]
37. Sturge J, Nordin S, Patil DS, Jones A, Légaré F, Elf M, et al. Features of the social and built environment that contribute to the well-being of people with dementia who live at home: a scoping review. Health Place 2021;67:102483 [FREE Full text] [doi: 10.1016/j.healthplace.2020.102483] [Medline: 33254054]
38. Chen X, Lee C, Huang H. Neighborhood built environment associated with cognition and dementia risk among older adults: a systematic literature review. Soc Sci Med 2022;292:114560 [FREE Full text] [doi: 10.1016/j.socscimed.2021.114560] [Medline: 34776284]
39. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. Int J Soc Res Methodol 2005;8(1):19-32 [FREE Full text] [doi: 10.1080/1364557032000119616]
40. Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. Implement Sci 2010;5(1):69 [FREE Full text] [doi: 10.1186/1748-5908-5-69] [Medline: 20854677]
41. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol 2006;3(2):77101 [FREE Full text] [doi: 10.1191/1478088706qp063oa]
42. Braun V, Clarke V. What can "thematic analysis" offer health and wellbeing researchers? Int J Qual Stud Health Well-being 2014;9:26152 [FREE Full text] [doi: 10.3402/qhw.v9.26152] [Medline: 25326092]
43. Charmaz K. Constructing Grounded Theory—2nd Edition. Thousand Oaks, California, United States: Sage Publications, Inc; 2014.
44. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med 2018;169(7):467-473 [FREE Full text] [doi: 10.7326/M18-0850] [Medline: 30178033]
45. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015;350:g7647 [FREE Full text] [doi: 10.1136/bmj.g7647] [Medline: 25555855]

Abbreviations

GIS: Geographic Information System
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols

PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

Edited by A Mavragani; submitted 04.07.23; peer-reviewed by JD Bacsu, G Chelberg; comments to author 17.08.23; revised version received 31.10.23; accepted 01.11.23; published 03.01.24.

Please cite as:
Groulx M, Freeman S, Gourlay K, Hemingway D, Rossnagel E, Chaudhury H, Nouri M
Monitoring and Evaluation of Dementia-Friendly Neighborhoods Using a Walkshed Approach: Protocol for a Scoping Review
JMIR Res Protoc 2024;13:e50548
URL: https://www.researchprotocols.org/2024/1/e50548
doi:10.2196/50548
PMID:38170573

Protocol

Overview of Retention Strategies for Medical Doctors in Low- and Middle-Income Countries and Their Effectiveness: Protocol for a Scoping Review

Norehan Jinah[1*], MD; Ili Abdullah Sharin[1*], MD; Pangie Bakit[1*], MBBS; Izzuan Khirman Adnan[1*], MBBS; Kun Yun Lee[1*], MBBChBAO, MPH, DrPH

Centre of Leadership & Professional Development, Institute for Health Management, National Institutes of Health Malaysia, Shah Alam, Malaysia
[*]all authors contributed equally

Corresponding Author:
Norehan Jinah, MD
Centre of Leadership & Professional Development
Institute for Health Management
National Institutes of Health Malaysia
Blok B1, Kompleks NIH, Jalan Setia Murni U13/52
Seksyen U13, Setia Alam
Shah Alam, 40170
Malaysia
Phone: 60 33627400 ext 8306
Fax: 60 33627401
Email: norehan.j@moh.gov.my

Abstract

Background: The global shortage and maldistribution of health care workers, especially medical doctors, pose a significant threat to achieving the United Nations' sustainable development goal 3 of ensuring well-being and healthy lives for all. Low- and middle-income countries (LMICs) are disproportionately affected by this crisis, with a high rate of brain drain from rural to urban areas, as well as to high-income countries. Various retention strategies have been implemented in different settings and organizations. However, their effectiveness remains underexplored, particularly in LMICs.

Objective: We aim to review the available retention strategies for medical doctors in LMICs and to determine the effectiveness of the various strategies. This review aims to compile relevant research findings on this issue to generate a thorough summary of all the retention strategies practiced in LMICs and, more importantly, to provide the current state of evidence of the effectiveness of these strategies in retaining medical doctors in countries with limited resources and high disease burden.

Methods: The structured framework given by Arksey and O'Malley will serve as the basis for conducting this scoping review. A comprehensive search strategy will be conducted across 4 electronic databases (PubMed, EBSCOHost, Scopus, and ScienceDirect). A systematic approach following the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines will be executed to search, screen, review, and extract data from studies that meet predefined inclusion criteria. Data encompassing bibliographical information, study location, retention strategies, influencing factors, and outcomes (effectiveness) will be obtained from the selected studies using standardized data extraction. Endnote and Microsoft Excel will be used for reference management and removal of duplicate studies. A narrative synthesis will be performed after categorizing and analyzing all the extracted data to identify recurrent themes.

Results: This ongoing review will generate a comprehensive compilation of retention strategies implemented in LMICs to prevent brain drain among medical doctors. Data extraction is currently in progress, and completion is expected by early 2024. Themes regarding the types of strategies, influencing factors, and outcomes will be synthesized. The findings will highlight effective retention strategies, gaps, and challenges in implementation for the benefits of future research. By identifying common barriers and facilitators, this review will provide insights into enhancing the policies and initiatives for doctor retention in LMICs.

Conclusions: This scoping review explores the retention strategies practiced in LMICs and attempts to identify effective strategies from existing research. By evaluating the barriers and challenges that influence the effectiveness of these strategies, policymakers and health care leaders can strive to obtain balanced and optimal health human resources in their respective organizations and countries.

Trial Registration: Malaysian National Medical Research Register (NMRR) ID-23-01994-OGW; https://nmrr.gov.my/research-directory/ac4f5b88-8619-4b2b-b6c7-9abcef65fdcd

International Registered Report Identifier (IRRID): DERR1-10.2196/52938

(JMIR Res Protoc 2024;13:e52938) doi:10.2196/52938

KEYWORDS

health care workforce; retention strategies; medical doctors; low-income and middle-income countries; scoping review

Introduction

Overview

Optimal functioning of the health care system relies heavily on the quantity and quality of health care workers (HCWs). The ability to enhance health service coverage and ensure that everyone in the population has access to the highest possible level of health relies on the availability, accessibility, acceptability, and quality of the health care workforce [1]. However, in recent years, a critical global challenge has emerged: a crisis characterized by a shortage and maldistribution of HCWs including doctors, nurses, and other professionals. This crisis poses a significant threat to achieving the United Nations Sustainable Development Goal 3 (promoting well-being and ensuring healthy lives for people of all ages) [2]. Nowhere is the impact of this challenge more acute than in low- and middle-income countries (LMICs), where limited financial and human resources compound the challenge of providing essential health care services. LMICs represent various nations in a diverse economic spectrum, encompassing low-income, lower-middle-income, and upper-middle-income countries. On the basis of the World Bank classification [3], low-income economies are defined as those with a gross national income (GNI) per capita of ≤US $1135 in 2022; lower middle-income economies are those with a GNI per capita between US $1136 and US $4465; upper middle-income economies are those with a GNI per capita between US $4466 and US $13,845. In contrast, high-income economies are those with a GNI per capita of ≥US $13,846. Remarkably, this classification encompasses 137 countries, constituting 63% of all nations worldwide [4].

The World Health Organization projected that by 2030, countries, predominantly LMICs, will face a substantial deficit of approximately 18 million health workers [5]. This significant shortage will greatly hamper the capacity to deliver vital health care services to those populations in most significant need. Simultaneously, countries with varied levels of socioeconomic development encounter different challenges in health human resource planning related to employment, deployment, and retention of their workforce [6]. Medical doctors are vital to the health care system because of their expertise, care, and impact. They play a crucial role in ensuring optimal health care delivery within health care institutions [7]. However, many parts of the world are grappling with a shortage of doctors, which stems from various factors such as emigration, imbalanced distribution between rural and urban areas, and shifts in population demographics [5]. There is a global shortage of approximately 2.8 million doctors [5], with LMICs bearing the brunt of this burden [8]. This scarcity is further exacerbated by the phenomenon of brain drain, with doctors from LMICs emigrating to high-income countries (HICs) due to better job offers and career progress. In some HICs, foreign-trained physicians sometimes amount to one-fifth of the total number of doctors in the workforce [9]. The movement of doctors from lower-to higher-income settings has resulted in substantial economic consequences, not solely due to the transfer of human capital, but more importantly, indirect impacts, such as increased morbidity and mortality associated with the loss of doctors [10].

Apart from brain drain to other countries, there is also a high rate of doctors' resignations from the public health care system to join the more lucrative private sector, especially in countries with dual health care financing systems. Job dissatisfaction, including unsatisfactory work environment (lack of facilities, inflexible working hours, poor career progression, lack of professional autonomy, and ineffective management style) and unfavorable service conditions (poor salaries and funding, duplication of activities), are closely associated with high mobility, especially from the public to private sectors [11-13]. The phenomenon of HCWs resigning poses a significant obstacle to the advancement of the health care system in any given country, making it a topic of widespread concern [14]. The increasing number of resignations among HCWs, particularly in the Asia Pacific region, has been reported as the greatest threat to the development and sustainability of a resilient health care system in a recent study [15]. Despite efforts to increase supply and retain them, the workforce is still struggling to meet public health demands, as demonstrated in Spain and Brazil [16]. The same issue was also reported in India, where the vacancy rates were nearly 21% and 42% for medical officers and specialists at health centers, respectively [17].

Addressing the global health workforce crisis requires comprehensive strategies at both national and international levels. Retaining HCWs is a challenge in almost every country, be it HICs such as Canada, Australia, and Scotland or LMICs in Africa and Asia, especially in rural and remote areas [18,19]. Retention encompasses the duration between the initial engagement with a service and the eventual separation or departure from that service. It serves as a metric to gauge the length of time an individual stays within the service [20]. Retention strategies in the context of doctors encompass a range of interventions designed to attract and keep doctors in particular settings, such as remote or rural areas, with a specific focus on LMICs [21-23]. These strategies are aimed at mitigating doctor shortages and ensuring equitable health care access for underserved populations. Policy makers and health care managers must comprehend the factors that influence doctor retention and formulate targeted measures to address these factors [24,25]. Effective retention strategies contribute to the

stability and continuity of health care delivery, especially in regions with limited accessibility [21,23].

The significance of retention strategies lies in their capacity to yield various benefits, including cost savings, employee engagement, productivity, knowledge retention, competitive advantage, and organizational stability [26]. Addressing doctor shortages requires tailoring retention strategies to the unique challenges and requirements of health care professionals in each country. This is particularly critical in LMICs, where health care systems often contend with fragility, staffing shortages, limited resources, and a higher disease burden [27-29]. Furthermore, these countries grapple with brain drain challenges, issues of health care accessibility, weakened political will, and unstable governmental systems [30-33].

There are many known impediments to the retention of doctors, the most common being unfavorable working conditions, limited opportunities for career advancement, nonappealing financial incentive structures, unsupportive community environments, and the restriction of financial resources [34,35]. Other barriers include inadequate living standards, excessive workloads, insufficient equipment, lack of opportunities for skill enhancement and private practice, and unfair promotion practices [36]. In addition, stress, burnout, and insufficient work-life balance also play a role in doctors' decision to leave [37]. Strategies aimed at addressing these barriers have been proposed and implemented at various levels and organizations, such as providing career development plans, ensuring minimum financial incentives, establishing avenues for private practice, enhancing work conditions, providing opportunities for skill improvement, and implementing transparent and equitable promotion systems.

Objective of Conducting the Scoping Review

Numerous publications have discussed the factors influencing the retention of doctors in LMICs [38-41], providing suggestions for various strategies and initiatives. However, there is limited research evaluating and summarizing the effectiveness of these strategies, particularly in LMICs. Therefore, the objective of this scoping review is to identify and delineate the available retention strategies for medical doctors in LMICs and to determine the effectiveness of these strategies.

To determine if prior research has addressed the same subject, we performed an initial exploratory literature review. Our search revealed the absence of existing or ongoing systematic reviews and scoping reviews related to our specific topic. McClain et al [42] primarily explored retention strategies and barriers concerning nurses, while Noya et al [43] concentrated on the rural and remote medical workforce, and Verma et al [22] focused on primary care doctors in general.

Conversely, our review aims to synthesize research evidence to generate an all-encompassing perspective on the effectiveness of retention strategies for doctors in LMICs. This synthesis will identify gaps in existing literature, pinpointing areas that require additional investigation within the context of doctor retention in resource-constrained countries with high disease burden. Our inclusive methodology considers a broad spectrum of studies and settings and delivers a comprehensive evaluation of these strategies.

Methods

Ethical Considerations

As the methodology for this scoping review solely entails reviewing and collecting data from existing literature without involving human participants, ethical clearance was waived by the Medical Research and Review Committee Malaysia.

Protocol Design

Overview

For this scoping review, we will use the methodological framework introduced by Arksey and O'Malley [44], who structured the review process into 5 stages. In addition, we enhanced the quality and rigor of our review based on the guidelines from the Joanna Briggs Institute Manual [45]. We will also incorporate the recommendations provided by Levac et al [46] to ensure consistency in assessing the studies during this scoping review. Transparent reporting will be ensured by using the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines [47]. We describe the protocol for this scoping review in five stages:

1. Formulating research questions
2. Identifying relevant studies
3. Selecting eligible studies
4. Charting the data
5. Collating, summarizing, and reporting the results

Stage 1: Formulating Research Questions

Following the recommendations given by Levac et al [46], we set our objective to explore strategies or interventions available for retaining doctors within health care institutions in LMICs and to identify effective measures to prevent doctor attrition. Therefore, we formulated two specific research questions for this review:

1. What are the retention strategies currently being implemented for doctors in LMICs?
2. Which strategies have been identified and evaluated as effective in retaining doctors in LMICs?

Stage 2: Identifying Relevant Studies

A meticulous search strategy plays a vital role in ensuring the inclusion of pertinent studies in scoping reviews. The research team has developed a comprehensive search strategy that encompasses various keywords and their synonyms related to the topic of interest. We selected search terms based on the research questions, including terms such as "retention," "retain," "maintain," "doctor," "physician," and "general practitioner." These terms has been used both individually and in combination following the iterative process inherent in the scoping review methodology.

The final search string, adhering to Boolean logic, takes the following form: *(retention OR retain OR intention to leave OR intention to stay OR motivation to stay OR willingness to work) AND (doctor OR physician OR specialist OR general practitioner OR medical practitioner) AND (low- and middle-income countries OR LMIC)*. This meticulously designed search string aimed to gather all pertinent materials aligned with the objectives of this scoping review.

Various types of documents were screened during this stage, including journal articles, documents, or regulatory reviews, sourced from each of the 4 databases: PubMed, EBSCOHost, Scopus, and ScienceDirect. These databases were selected for their relevance to health and human resource services. During the screening process, if the available information in the title and abstract is insufficient to make an informed decision, the articles will be included for full-text screening. Adhering to the standard approach for conducting scoping reviews, we will not conduct quality appraisal of the included studies. An example of a preliminary MEDLINE (PubMed) search strategy is presented in Textbox 1.

Textbox 1. Example of MEDLINE (PubMed) search strategy.

- (retention[Title/Abstract] OR retain[Title/Abstract] OR intention to stay[Title/Abstract] OR intention to leave[Title/Abstract] OR motivation to stay[Title/Abstract] OR willingness to work[Title/Abstract]) AND (doctor*[Title/Abstract] OR physician*[Title/Abstract] OR specialist*[Title/Abstract] OR general practitioner*[Title/Abstract] OR general physician*[Title/Abstract] OR medical practitioner*[Title/Abstract]) AND (low- and middle-income country[Title/Abstract] OR low- and middle-income countries[Title/Abstract] OR low-income country[Title/Abstract] OR low-income countries[Title/Abstract] OR lower middle-income country[Title/Abstract] OR lower middle-income countries[Title/Abstract] OR upper middle-income country[Title/Abstract] OR upper middle-income countries[Title/Abstract] OR Afghanistan[Title/Abstract] OR Albania[Title/Abstract] OR Algeria[Title/Abstract] OR American Samoa[Title/Abstract] OR Angola[Title/Abstract] OR Armenia[Title/Abstract] OR Azerbaijan[Title/Abstract] OR Bangladesh[Title/Abstract] OR Belarus[Title/Abstract] OR Byelarus[Title/Abstract] OR Belorussia[Title/Abstract] OR Belize[Title/Abstract] OR Benin[Title/Abstract] OR Bhutan[Title/Abstract] OR Bolivia[Title/Abstract] OR Bosnia[Title/Abstract] OR Botswana[Title/Abstract] OR Brazil[Title/Abstract] OR Bulgaria[Title/Abstract] OR Burma[Title/Abstract] OR Burkina Faso[Title/Abstract] OR Burundi[Title/Abstract] OR Cabo[Title/Abstract] Verde[Title/Abstract] OR Cape Verde[Title/Abstract] OR Cambodia[Title/Abstract] OR Cameroon[Title/Abstract] OR Central African Republic[Title/Abstract] OR Chad[Title/Abstract] OR China[Title/Abstract] OR Colombia[Title/Abstract] OR Comoros[Title/Abstract] OR Comoros[Title/Abstract] OR Comoro[Title/Abstract] OR Congo[Title/Abstract] OR Costa Rica[Title/Abstract] OR Côte d'Ivoire[Title/Abstract] OR Cuba[Title/Abstract] OR Djibouti[Title/Abstract] OR Dominica[Title/Abstract] OR Dominican Republic[Title/Abstract] OR Ecuador[Title/Abstract] OR Egypt[Title/Abstract] OR El Salvador[Title/Abstract] OR Equatorial Guinea[Title/Abstract] OR Eritrea [Title/Abstract]OR Ethiopia[Title/Abstract] OR Fiji[Title/Abstract] OR Gabon[Title/Abstract] OR Gambia[Title/Abstract] OR Gaza[Title/Abstract] OR Georgia[Title/Abstract] OR Georgia Republic[Title/Abstract] OR Ghana[Title/Abstract] OR Grenada[Title/Abstract] OR Grenadines[Title/Abstract] OR Guatemala[Title/Abstract] OR Guinea[Title/Abstract] OR Guinea[Title/Abstract]-Bissau[Title/Abstract] OR Guyana[Title/Abstract] OR Haiti[Title/Abstract] OR Herzegovina[Title/Abstract] OR Hercegovina[Title/Abstract] OR Honduras[Title/Abstract] OR India[Title/Abstract] OR Indonesia[Title/Abstract] OR Iran[Title/Abstract] OR Iraq[Title/Abstract] OR Ivory Coast[Title/Abstract] OR Jamaica[Title/Abstract] OR Jordan[Title/Abstract] OR Kazakhstan[Title/Abstract] OR Kenya[Title/Abstract] OR Kiribati[Title/Abstract] OR Democratic People's Republic of Korea[Title/Abstract] OR Kosovo[Title/Abstract] OR Kyrgyz[Title/Abstract] OR Kirghizia[Title/Abstract] OR Kirghiz[Title/Abstract] OR Kyrgyzstan[Title/Abstract] OR Lao PDR[Title/Abstract] OR Laos[Title/Abstract] OR Lebanon[Title/Abstract] OR Lesotho[Title/Abstract] OR Liberia[Title/Abstract] OR Libya[Title/Abstract] OR Macedonia[Title/Abstract] OR Madagascar[Title/Abstract] OR Malawi[Title/Abstract] OR Malay[Title/Abstract] OR Malaya[Title/Abstract] OR Malaysia[Title/Abstract] OR Maldives[Title/Abstract] OR Mali[Title/Abstract] OR Marshall Islands[Title/Abstract] OR Mauritania[Title/Abstract] OR Mauritius[Title/Abstract] OR Mexico[Title/Abstract] OR Micronesia[Title/Abstract] OR Moldova[Title/Abstract] OR Mongolia[Title/Abstract] OR Montenegro[Title/Abstract] OR Morocco[Title/Abstract] OR Mozambique[Title/Abstract] OR Myanmar[Title/Abstract] OR Namibia[Title/Abstract] OR Nepal[Title/Abstract] OR Nicaragua[Title/Abstract] OR Niger[Title/Abstract] OR Nigeria[Title/Abstract] OR Pakistan[Title/Abstract] OR Palau[Title/Abstract] OR Papua New Guinea[Title/Abstract] OR Paraguay[Title/Abstract] OR Peru[Title/Abstract] OR Philippines[Title/Abstract] OR Principe[Title/Abstract] OR Romania[Title/Abstract] OR Ruanda[Title/Abstract] OR Rwanda[Title/Abstract] OR Samoa[Title/Abstract] OR Sao Tome[Title/Abstract] OR Senegal[Title/Abstract] OR Serbia[Title/Abstract] OR Sierra Leone[Title/Abstract] OR Solomon Islands[Title/Abstract] OR Somalia[Title/Abstract] OR South Africa[Title/Abstract] OR South Sudan[Title/Abstract] OR Sri Lanka[Title/Abstract] OR St Lucia[Title/Abstract] OR St Vincent[Title/Abstract] OR Sudan[Title/Abstract] OR Surinam[Title/Abstract] OR Suriname[Title/Abstract] OR Swaziland[Title/Abstract] OR Syria[Title/Abstract] OR Syrian Arab Republic[Title/Abstract] OR Tajikistan[Title/Abstract] OR Tadzhikistan[Title/Abstract] OR Tajikistan[Title/Abstract] OR Tadzhik[Title/Abstract] OR Tanzania[Title/Abstract] OR Thailand[Title/Abstract] OR Timor[Title/Abstract] OR Togo[Title/Abstract] OR Tonga[Title/Abstract] OR Tunisia[Title/Abstract] OR Turkey[Title/Abstract] OR Turkmen[Title/Abstract] OR Turkmenistan[Title/Abstract] OR Tuvalu[Title/Abstract] OR Uganda[Title/Abstract] OR Ukraine[Title/Abstract] OR Uzbek[Title/Abstract] OR Uzbekistan[Title/Abstract] OR Vanuatu[Title/Abstract] OR Venezuela[Title/Abstract] OR Vietnam[Title/Abstract] OR West Bank OR Yemen[Title/Abstract] OR Zambia[Title/Abstract] OR Zimbabwe[Title/Abstract])

Stage 3: Selecting Eligible Studies

The review process begins with the team convening to discuss decisions related to study inclusion and exclusion based on the principles of transparency, reproducibility, and rigor. This practice further advances a systematic and unbiased approach throughout the review process. The inclusion and exclusion criteria are presented in Textbox 2. We chose to focus primarily on studies published in English language due to their global prevalence, ensuring a comprehensive analysis, increased accessibility, and reduced language-related biases due to limited translation resources. Furthermore, the focus on studies published in English language streamlines the accessibility and application of research findings, making them readily available and applicable to a broader audience.

To maintain the scientific rigor of this review, we made a deliberate choice to exclude gray literature from our review, such as dissertations, essays, consensus, reports, theses, and government documents. However, while gray literature may provide valuable insights that supplement traditional academic

literature [48], it presents challenges in terms of systematic search and quality verification [49].

Following the PRISMA-ScR guidelines [47], the first step begins with identifying articles from various databases. Duplicates and irrelevant studies will then be removed. Abstracts or full texts will be evaluated based on predetermined inclusion and exclusion criteria to determine eligible studies. This screening process involves careful examination of both the retrieved search results and their reference lists. To ensure the most relevant search results, we will refine the literature search throughout the review process. At least 2 investigators will independently assess the eligibility of publications by reviewing their titles and abstracts. Publications deemed relevant to this scoping review are obtained in full text and reviewed against the same inclusion criteria.

In cases of disagreement during publication selection, both reviewers will revisit the full-text articles to reach a consensus. If consensus cannot be reached, an impartial third reviewer will be consulted to resolve the disagreement. Consistent meetings and discussions at different stages of the article review process are essential to maintain alignment, address challenges, refine search strategies, ensure consistency, and foster a collaborative and efficient approach. The scoping review will record and report reasons for excluding sources of evidence in the full text that do not meet the inclusion criteria. The reporting of the review will incorporate a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram (Figure 1), which visually presents the screening and selection process [50].

Textbox 2. Inclusion and exclusion criteria of the study selection process.

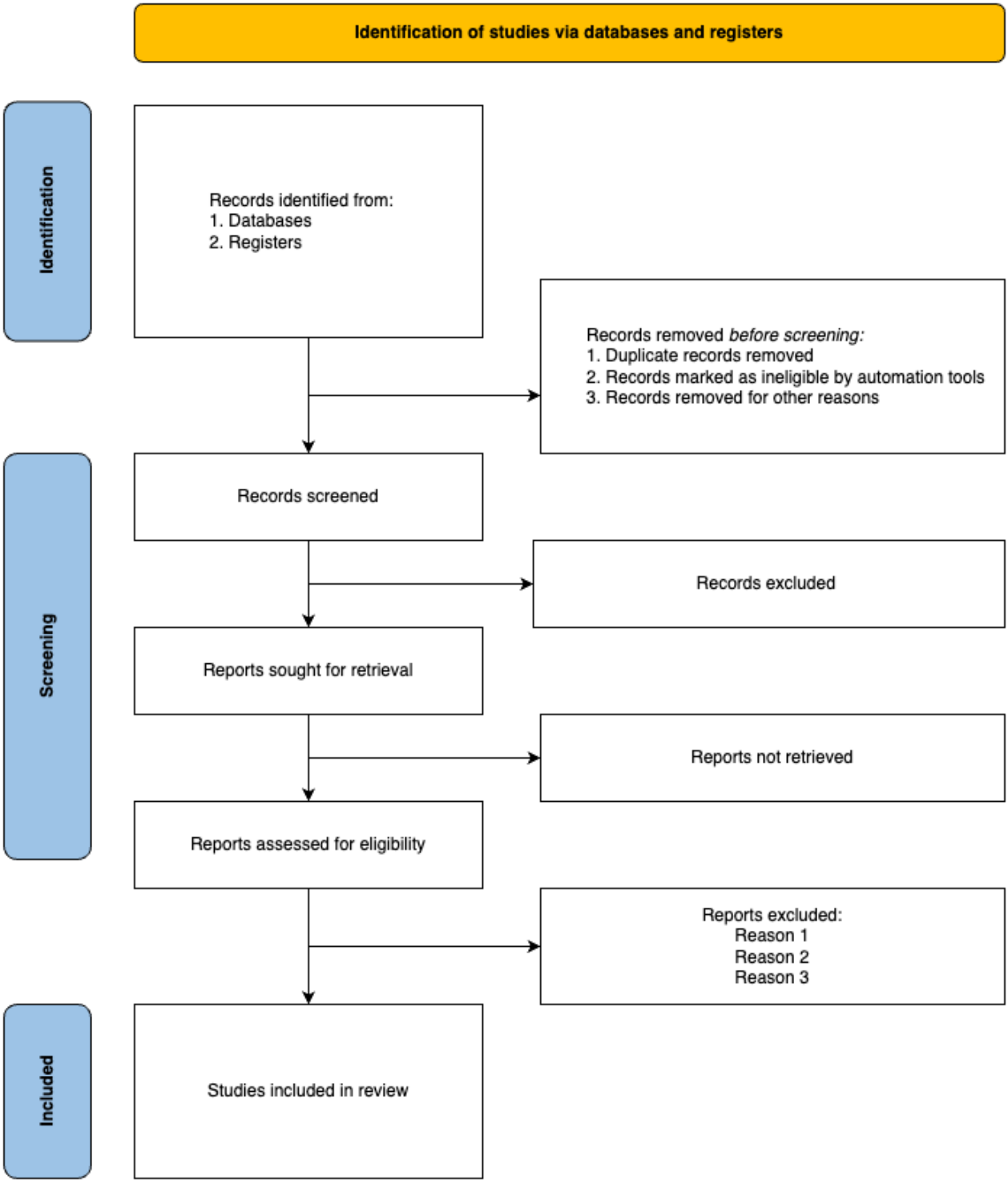
Inclusion criteria

- Publication year: January 2013 to February 2023
- Language in publication: English
- Research location: low- and middle-income countries (LMICs)
- Target population: medical doctors
- Types of documents: journal articles, documents, or regulatory reviews with proper references

Exclusion criteria

- Publication year: before January 2013 and after February 2023
- Language in publication: other languages
- Research location: other than LMICs
- Target population: other health care professionals
- Types of documents: dissertations, essays, consensus, government documents, reports, and theses that do not have any proper references

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for the scoping review process.



Stage 4: Charting the Data

The data extracted from the full-text articles will be organized into a data extraction table using Microsoft Excel (Microsoft Corporation). The data table will be structured to accommodate the characteristics of the data. The aim of charting the data is to create a descriptive summary of the results to address the objectives of the scoping review and to answer the research questions. This process facilitates the categorization of information before proceeding with further tabulation. For reference, Textbox 3 presents the categories corresponding to each characteristic in the data extraction table. In an iterative process, investigators will continually gather data and keep the data extraction table up-to-date. If significant data are found in records initially not designated for extraction, the data extraction form will be revised, and these additional data will be retrieved from the records already reviewed.

Textbox 3. Preliminary data extraction table.

Basic characteristics and description

- Bibliographical data
  - First author and year of publication of the article
- Article title
  - A succinct description of the content of the article
- Country
  - Name of the low- and middle-income countries
- Aims or purpose of the study
  - Expresses the intention or aspiration of the research
- Type of study
  - Study design or methodology
  - Which type of study was conducted?
- Study population
  - Physician—specialty or department
  - Number of people involved
  - Inclusion and exclusion criteria of the study
  - Demographic characteristics
  - Other characteristics
- Study location
  - Location characteristics (urban, rural, or remote or hospital or district, state, or area)
  - Institution (name)
- Factors influencing retention
  - Financial or career and professional or working conditions, personal, cultural, or living conditions factors
- Retention strategy
  - Strategy type or focus (education and regulatory or ii. monetary compensation or iii. management, and environment and social support)
  - Strategy name
  - Strategy characteristics, content, and description
  - Strategy implementation (levels, duration, and date)
- Outcomes measure
  - Description of the result (effective or successful to retain)
  - How were the turnover and results assessed?
- Barriers and challenges
  - Barriers and challenges in implementing the strategies
- Study limitations
  - Weaknesses within the research design that may influence the outcomes and conclusions of the research

Stage 5: Collating, Summarizing, and Reporting the Results

The primary goal of the scoping review is to present the narrative findings of existing literature through an analytical framework or thematic construction, without the requirement to assess the quality or significance of each study. We will use a traditional integrative review approach to compile all the identified materials. Our objective is to identify recurring themes across research and synthesize data from the selected studies. Using these themes as guidelines, we will create a literature map and present it in the form of a table, summarizing the publications and their respective characteristics.

The results of the scoping review will be organized into tables that categorize the characteristics of each publication. Accompanying these results will be narrative summaries that describe how each result relates to our research questions, including any unexpected or particularly notable findings. We will also address any gaps observed in the literature, research needs, and implications for practice. Subsequently, the outcomes of this review will be shared with relevant stakeholders, and their expertise and perspectives will be incorporated.

Results

This review will provide a comprehensive mapping of existing research and literature pertaining to the retention of medical doctors in LMICs to enhance the understanding of the complex dynamics of doctor retention. It will also assess the current knowledge and pinpoint any gaps in the literature, focusing on factors influencing doctor retention and effective retention strategies such as financial incentives, working conditions, career advancement opportunities, and personal motivations.

Furthermore, this review can offer insights into best practices and approaches for retaining doctors in LMICs to guide policy makers and health care administrators who struggle with retention challenges. They can customize the best policy recommendations based on specific needs and obstacles in local settings to improve doctor retention rates in their respective organizations and governments.

The review was initiated in May 2023, and the research protocol was finalized in July 2023. We registered the review with the Malaysian National Medical Research Register (NMRR ID-23-01994-OGW). The search, which was concluded in August 2023, yielded 9141 articles. The PRISMA flow diagram will be used to illustrate the flow of the literature search in this review [50]. The results will be presented using charts and tables, supplemented by a narrative description. Any existing literature gaps will be identified, and the significance of our findings will be emphasized in the subsequent discussion section. The review is expected to be concluded in January 2024, with the outcomes published in a journal for wider dissemination.

Discussion

Overview

Adequate investment in health care capacity is imperative to move toward the United Nations' sustainable development goals, specifically goal 3 (ensuring good health and well-being) and goal 10 (reducing inequalities), and to achieve various global development objectives, with a robust health care workforce being the top priority. Therefore, establishing a comprehensive plan that encompasses effective retention strategies to complement medical education reforms is vital to cultivating a health care environment that is equitable and resilient at both regional and global levels. Our focus on retention strategies for medical doctors is driven by their unique challenges and critical roles in health care. Doctors hold central positions in health care delivery, not only providing medical expertise but also taking a leadership role in influencing critical patient care decision-making, and their turnover can have significant negative impacts on patient care and quality of health care services [51]. Furthermore, doctors are the most affected by the brain drain crisis, especially in LMICs, leading to a significant financial burden and experience loss. Therefore, prioritizing doctor retention is vital for mitigating brain drain, reducing productivity and financial loss, and sustaining effective health care service delivery.

The shortage of doctors in LMICs represents a pressing concern that demands immediate attention and concerted efforts on a global scale, in view of its significant impact on public health. This predicament has a direct adverse effect on the health and welfare of populations residing in LMICs, as doctor shortages can impede access to crucial medical services, ultimately resulting in preventable illnesses and higher mortality rates. Moreover, cross-border brain drain exacerbates existing health care inequalities both within and between countries. Persistent disparities in the accessibility of health care services, if they continue to exist, will disproportionately affect rural and underserved areas with limited resources, thereby perpetuating social and economic inequalities and impeding advancements toward achieving universal health care coverage.

Expected Outcomes

This scoping review will present a comprehensive overview of retention strategies that have been proposed, practiced, and evaluated in LMICs as a response to overcome the challenges faced in retaining medical doctors and preventing brain drain. These strategies may encompass a wide array of approaches, including financial incentives, opportunities for professional development, initiatives to promote work-life balance, and support for career advancement. Moreover, the focus on LMICs may shed light on distinct regional or country-specific challenges and variations in customized strategies. It may also highlight the varied effectiveness of different strategies, depending on the contextual factors at play. It is unlikely to be a one-size-fits-all solution, as certain strategies may exhibit promising outcomes in bolstering medical doctor retention, while others may demonstrate limited impact depending on the local settings.

In short, this review will present common barriers and facilitators that significantly influence the successful implementation of retention strategies for doctors in LMICs. By exploring the challenges encountered during strategy implementation, we also aim to offer a more comprehensive and nuanced understanding of the factors influencing the effectiveness of doctor retention strategies in LMICs. This, in turn, can contribute to improving the retention of medical doctors in LMICs, aligning with the Sustainable Development Goal 3 goal of promoting well-being and ensuring healthy lives for everyone. Comprehension of these elements has the potential to aid policy makers and health care administrators in developing more relevant interventions and prioritizing effective strategies.

Since it is likely that different contexts play a critical role in the outcomes of various retention strategies, we will also attempt to address this connection in our review. Certain strategies, if proven successful, can also be modified and embedded within a broader health care ecosystem to benefit a wider group of health care professionals. Common factors contributing to brain drain among HCWs include financial rewards, career development, hospital infrastructure, political issues, and family issues [52]. While we focus on the dynamics surrounding medical doctors and the customized retention approach for them in this review, as the challenges faced by doctors may be unique and differ significantly from those of other groups, the comparison and extrapolation of various retention strategies for different health care professionals is a worthy topic for future research or review.

Review Limitations

This review has several limitations that deserve further discussion. First, the language restriction used in the search strategy may have unintentionally excluded relevant studies published in languages other than English. This is a significant concern because many LMICs have diverse linguistic landscapes with numerous languages. The decision to focus primarily on English was necessitated by practical considerations, such as the broader availability and accessibility of English-language research. Furthermore, we believe that the exclusion of non–English-language studies would minimize language-related biases in the review process, given the limited access to translation resources in our setting.

Another limitation of this review is the exclusion of gray literature. This decision is influenced by the difficulties associated with accessing gray literature, which encompasses issues of limited availability, inconsistent indexing, variable accessibility, and challenges in assessing the quality and reliability of information. By excluding gray literature, there is a risk of missing important findings and diverse perspectives not found in peer-reviewed academic sources. Nevertheless, although gray literature can offer valuable insights as a complement to conventional academic literature [48], it introduces difficulties in systematic retrieval and quality assessment [49], thus making it difficult to maintain the scientific rigor of this review.

In addition, this review is likely to include studies with different levels of methodological rigor and quality, and this could potentially affect the overall reliability of its conclusions and may introduce heterogeneity into our analysis. Moreover, this review aims to provide a comprehensive overview of existing literature regarding effective retention strategies for doctors in LMICs; thus, the analysis results are likely to be less in depth compared with systematic reviews that follow a more rigorous and narrowly focused methodology. Nonetheless, this broad approach is valuable for summarizing the diversity of strategies and findings in the field of doctor retention in LMICs, allowing for a holistic understanding of the subject.

Conclusions

This scoping review is fundamental in providing a better understanding of the practical implications of various retention strategies for doctors in LMICs and in drawing valuable lessons from effective strategies in existing literature. Furthermore, by highlighting emerging trends and identifying implementation challenges within LMICs, this review will pave the way for more precisely targeted policies and interventions to strengthen doctor retention in the most needed regions. It also offers valuable guidance to policy makers and health care administrators by showcasing best practices with positive outcomes, thereby refining their approach to addressing attrition and brain drain.

Acknowledgments

The authors would like to thank the Director General of Health, Malaysia for the permission to publish this paper.

Data Availability

Data sharing is not applicable to this paper, as no data sets were generated or analyzed in this review.

Conflicts of Interest

None declared.

References

1. UN Economic and Social Council. General comment no. 14: the right to the highest attainable standard of health (art. 12 of the covenant). UN Committee on Economic, Social and Cultural Rights (CESCR). 2000 Aug 11. URL: https://www.refworld.org/docid/4538838d0.html [accessed 2023-08-10]

2. Seifman R. Global health workforce crisis: what to do. Impakter. 2019 Jul 11. URL: https://impakter.com/global-health-workforce-crisis-what/ [accessed 2023-08-10]
3. World bank country and lending groups. The World Bank. URL: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups [accessed 2023-08-12]
4. Lencucha R, Neupane S. The use, misuse and overuse of the 'low-income and middle-income countries' category. BMJ Glob Health 2022 Jun;7(6):e009067 [FREE Full text] [doi: 10.1136/bmjgh-2022-009067] [Medline: 35672116]
5. The world health report : 2006 : working together for health. World Health Organization. 2006. URL: https://iris.who.int/handle/10665/43432 [accessed 2023-08-12]
6. Health workforce. World Health Organization. URL: https://www.who.int/health-topics/health-workforce#tab=tab_1 [accessed 2023-08-12]
7. Williams SJ, Nightingale EO, Filner B. The physician's role in a changing health care system. In: Medical Education and Societal Needs: A Planning Report for the Health Professions. Washington, DC: National Academies Press; 1983.
8. A universal truth: no health without a workforce. World Health Organization. 2013. URL: https://cdn.who.int/media/docs/default-source/health-workforce/ghwn/ghwa/ghwa_auniversaltruthreport.pdf?sfvrsn=966aa7ab_7&download=true [accessed 2023-08-10]
9. Mullan F. The metrics of the physician brain drain. N Engl J Med 2005 Oct 27;353(17):1810-1818. [doi: 10.1056/NEJMsa050004] [Medline: 16251537]
10. Saluja S, Rudolfson N, Massenburg BB, Meara JG, Shrime MG. The impact of physician migration on mortality in low and middle-income countries: an economic modelling study. BMJ Glob Health 2020 Jan 07;5(1):e001535 [FREE Full text] [doi: 10.1136/bmjgh-2019-001535] [Medline: 32133161]
11. Ali Jadoo SA, Aljunid SM, Dastan I, Tawfeeq RS, Mustafa MA, Ganasegeran K, et al. Job satisfaction and turnover intention among Iraqi doctors--a descriptive cross-sectional multicentre study. Hum Resour Health 2015 Apr 19;13:21 [FREE Full text] [doi: 10.1186/s12960-015-0014-6] [Medline: 25903757]
12. Kanchanachitra C, Lindelow M, Johnston T, Hanvoravongchai P, Lorenzo FM, Huong NL, et al. Human resources for health in southeast Asia: shortages, distributional challenges, and international trade in health services. Lancet 2011 Feb 26;377(9767):769-781. [doi: 10.1016/S0140-6736(10)62035-1] [Medline: 21269674]
13. Aidalina M, Aniza I. Factors associated with the brain-drain phenomenon of doctors from the public sector to the private sector in Selangor and Kuala Lumpur. Int J Public Health Clin Sci 2015;2(1) [FREE Full text]
14. Mbindyo PM, Blaauw D, Gilson L, English M. Developing a tool to measure health worker motivation in district hospitals in Kenya. Hum Resour Health 2009 May 20;7:40 [FREE Full text] [doi: 10.1186/1478-4491-7-40] [Medline: 19457237]
15. Bin Abdul Rassip MN, Puteh SE. Physicians intention to leave from Malaysia government hospitals with existing retention strategy. J Public Health Policy Plan 2020;4(3):30-37. [doi: 10.35841/public-health-policy.4.3.30-37]
16. Scheffer MC, Pastor-Valero M, Cassenote AJ, Compañ Rosique AF. How many and which physicians? A comparative study of the evolution of the supply of physicians and specialist training in Brazil and Spain. Hum Resour Health 2020 Apr 21;18(1):30 [FREE Full text] [doi: 10.1186/s12960-020-00472-0] [Medline: 32316989]
17. Purohit B, Martineau T. Issues and challenges in recruitment for government doctors in Gujarat, India. Hum Resour Health 2016 Jul 19;14(1):43 [FREE Full text] [doi: 10.1186/s12960-016-0140-9] [Medline: 27431766]
18. Increasing access to health workers in remote and rural areas through improved retention: global policy recommendations. World Health Organization. 2010. URL: https://iris.who.int/handle/10665/44369 [accessed 2023-08-12]
19. Khalil M, Alameddine M. Recruitment and retention strategies, policies, and their barriers: a narrative review in the Eastern Mediterranean region. Health Sci Rep 2020 Oct 05;3(4):e192 [FREE Full text] [doi: 10.1002/hsr2.192] [Medline: 33033753]
20. Waldman JD. Change your metrics: if you get what you measure, then measure what you want--retention. J Med Pract Manage 2006;22(1):13-19. [Medline: 16986634]
21. Lehmann U, Dieleman M, Martineau T. Staffing remote rural areas in middle- and low-income countries: a literature review of attraction and retention. BMC Health Serv Res 2008 Jan 23;8:19 [FREE Full text] [doi: 10.1186/1472-6963-8-19] [Medline: 18215313]
22. Verma P, Ford JA, Stuart A, Howe A, Everington S, Steel N. A systematic review of strategies to recruit and retain primary care doctors. BMC Health Serv Res 2016 Apr 12;16:126 [FREE Full text] [doi: 10.1186/s12913-016-1370-1] [Medline: 27067255]
23. Frehywot S, Mullan F, Payne PW, Ross H. Compulsory service programmes for recruiting health workers in remote and rural areas: do they work? Bull World Health Organ 2010 May;88(5):364-370 [FREE Full text] [doi: 10.2471/BLT.09.071605] [Medline: 20461136]
24. Brugha R, Clarke N, Hendrick L, Sweeney J. Doctor retention: a cross-sectional study of how Ireland has been losing the battle. Int J Health Policy Manag 2021 Jun 01;10(6):299-309 [FREE Full text] [doi: 10.34172/ijhpm.2020.54] [Medline: 32610753]
25. Yan W, Sun G. Income, workload, and any other factors associated with anticipated retention of rural doctors? Prim Health Care Res Dev 2022 Mar 02;23:e12 [FREE Full text] [doi: 10.1017/S1463423621000839] [Medline: 35232522]
26. Al-Suraihi WA, Samikon SA, Al-Suraihi AH, Ibrahim I. Employee turnover: causes, importance and retention strategies. Eur J Bus Manag Res 2021 Jun 09;6(3):1-10. [doi: 10.24018/ejbmr.2021.6.3.893]

27. Zurn P, Vujicic M, Lemière C, Juquois M, Stormont L, Campbell J, et al. A technical framework for costing health workforce retention schemes in remote and rural areas. Hum Resour Health 2011 Apr 06;9:8 [FREE Full text] [doi: 10.1186/1478-4491-9-8] [Medline: 21470420]
28. Henderson LN, Tulloch J. Incentives for retaining and motivating health workers in Pacific and Asian countries. Hum Resour Health 2008 Sep 15;6:18 [FREE Full text] [doi: 10.1186/1478-4491-6-18] [Medline: 18793436]
29. Mbemba GI, Gagnon MP, Hamelin-Brabant L. Factors influencing recruitment and retention of healthcare workers in rural and remote areas in developed and developing countries: an overview. J Public Health Afr 2016 Dec 31;7(2):565 [FREE Full text] [doi: 10.4081/jphia.2016.565] [Medline: 28299160]
30. Haileamlak A. The triple challenges of low and middle-income countries. Ethiop J Health Sci 2018 Jan;28(1):1-2 [FREE Full text] [doi: 10.4314/ejhs.v28i1.1] [Medline: 29622901]
31. Kruk ME, Gage AD, Joseph NT, Danaei G, García-Saisó S, Salomon JA. Mortality due to low-quality health systems in the universal health coverage era: a systematic analysis of amenable deaths in 137 countries. Lancet 2018 Nov 17;392(10160):2203-2212 [FREE Full text] [doi: 10.1016/S0140-6736(18)31668-4] [Medline: 30195398]
32. Ngoc Dinh M, Nygate J, Hoang Minh Tu V, Thwaites CL, Global Grand Challenges Event Vietnam Group. New technologies to improve healthcare in low- and middle-income countries: global grand challenges satellite event, Oxford University clinical research unit, Ho Chi Minh City, 17th-18th September 2019. Wellcome Open Res 2020 Aug 13;5:142 [FREE Full text] [doi: 10.12688/wellcomeopenres.16008.2] [Medline: 32864470]
33. Haniffa R, Pubudu De Silva A, de Azevedo L, Baranage D, Rashan A, Baelani I, et al. Improving ICU services in resource-limited settings: perceptions of ICU workers from low-middle-, and high-income countries. J Crit Care 2018 Apr;44:352-356. [doi: 10.1016/j.jcrc.2017.12.007] [Medline: 29275269]
34. Sirili N, Frumence G, Kiwara A, Mwangu M, Anaeli A, Nyamhanga T, et al. Retention of medical doctors at the district level: a qualitative study of experiences from Tanzania. BMC Health Serv Res 2018 Apr 10;18(1):260 [FREE Full text] [doi: 10.1186/s12913-018-3059-0] [Medline: 29631589]
35. Darkwa EK, Newman MS, Kawkab M, Chowdhury ME. A qualitative study of factors influencing retention of doctors and nurses at rural healthcare facilities in Bangladesh. BMC Health Serv Res 2015 Aug 27;15:344 [FREE Full text] [doi: 10.1186/s12913-015-1012-z] [Medline: 26307265]
36. Darbyshire D, Brewster L, Isba R, Body R, Basit U, Goodwin D. Retention of doctors in emergency medicine: a scoping review of the academic literature. Emerg Med J 2021 Sep 03;38(9):663-672 [FREE Full text] [doi: 10.1136/emermed-2020-210450] [Medline: 34083428]
37. Ayobami RB, Wallis M, Karodia AM. Exploring the factors that affect retention of medical doctors: a case study of Jane Furse Hospital, Limpopo Province, South Africa. Eur J Manag Bus Econ 2016 Jul;1(2016) [FREE Full text]
38. Shah SM, Zaidi S, Ahmed J, Rehman SU. Motivation and retention of physicians in primary healthcare facilities: a qualitative study from Abbottabad, Pakistan. Int J Health Policy Manag 2016 Aug 01;5(8):467-475 [FREE Full text] [doi: 10.15171/ijhpm.2016.38] [Medline: 27694660]
39. Mdegela MS. Factors affecting health workforce retention following an in-service training programme in Malawi and Tanzania. University of Liverpool. 2020 Nov. URL: https://livrepository.liverpool.ac.uk/3128281/1/200867950_Nov2020.pdf.pdf [accessed 2023-08-12]
40. Putri LP, O'Sullivan BG, Russell DJ, Kippen R. Factors associated with increasing rural doctor supply in Asia-Pacific LMICs: a scoping review. Hum Resour Health 2020 Dec 01;18(1):93 [FREE Full text] [doi: 10.1186/s12960-020-00533-4] [Medline: 33261631]
41. Daneshkohan A, Zarei E, Mansouri T, Maajani K, Ghasemi MS, Rezaeian M. Factors affecting job motivation among health workers: a study from Iran. Glob J Health Sci 2014 Nov 26;7(3):153-160 [FREE Full text] [doi: 10.5539/gjhs.v7n3p153] [Medline: 25948438]
42. McClain AR, Palokas M, Christian R, Arnold A. Retention strategies and barriers for millennial nurses: a scoping review. JBI Evid Synth 2022 Jan 01;20(1):121-157. [doi: 10.11124/JBIES-20-00577] [Medline: 35039468]
43. Noya F, Carr S, Freeman K, Thompson S, Clifford R, Playford D. Strategies to facilitate improved recruitment, development, and retention of the rural and remote medical workforce: a scoping review. Int J Health Policy Manag 2022 Oct 19;11(10):2022-2037 [FREE Full text] [doi: 10.34172/ijhpm.2021.160] [Medline: 34973053]
44. Westphaln KK, Regoeczi W, Masotya M, Vazquez-Westphaln B, Lounsbury K, McDavid L, et al. From Arksey and O'Malley and beyond: customizations to enhance a team-based, mixed approach to scoping review methodology. MethodsX 2021 May 7;8:101375 [FREE Full text] [doi: 10.1016/j.mex.2021.101375] [Medline: 34430271]
45. Peters MD, Godfrey C, McInerney P, Munn Z, Trico AC, Khalil H. Chapter 11: scoping reviews (2020 version). In: Aromataris E, Munn Z, editors. JBI Manual for Evidence Synthesis. Adelaide, Australia: Joanna Briggs Institute; 2020.
46. Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. Implement Sci 2010 Sep 20;5:69 [FREE Full text] [doi: 10.1186/1748-5908-5-69] [Medline: 20854677]
47. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med 2018 Oct 02;169(7):467-473 [FREE Full text] [doi: 10.7326/M18-0850] [Medline: 30178033]

48. Adams J, Hillier-Brown FC, Moore HJ, Lake AA, Araujo-Soares V, White M, et al. Searching and synthesising 'grey literature' and 'grey information' in public health: critical reflections on three case studies. Syst Rev 2016 Sep 29;5(1):164 [FREE Full text] [doi: 10.1186/s13643-016-0337-y] [Medline: 27686611]
49. Godin K, Stapleton J, Kirkpatrick SI, Hanning RM, Leatherdale ST. Applying systematic review search methods to the grey literature: a case study examining guidelines for school-based breakfast programs in Canada. Syst Rev 2015 Oct 22;4(1):138 [FREE Full text] [doi: 10.1186/s13643-015-0125-0] [Medline: 26494010]
50. PRISMA flow diagram. PRISMA. URL: http://prisma-statement.org/prismastatement/flowdiagram.aspx [accessed 2023-08-12]
51. Schaefer R, Jenkins LS, North Z. Retaining doctors and reducing burnout through a flexible work initiative in a rural South African training hospital. Afr J Prim Health Care Fam Med 2021 Mar 23;13(1):e1-e5 [FREE Full text] [doi: 10.4102/phcfm.v13i1.2799] [Medline: 33764133]
52. Najib M, Juni MH, Salloum A. Brain-drain phenomenon among healthcare workers. Int J Public Health Clin Sci 2019 May;6(3):90-103. [doi: 10.32827/ijphcs.6.3.90]

Abbreviations

GNI: gross national income
HCW: health care worker
HICs: high-income countries
LMICs: low- and middle-income countries
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews

Edited by A Mavragani; submitted 21.09.23; peer-reviewed by T Ramesh, C Normand, E Kawamoto; comments to author 16.10.23; revised version received 06.11.23; accepted 09.11.23; published 08.01.24.

Please cite as:
Jinah N, Abdullah Sharin I, Bakit P, Adnan IK, Lee KY
Overview of Retention Strategies for Medical Doctors in Low- and Middle-Income Countries and Their Effectiveness: Protocol for a Scoping Review
JMIR Res Protoc 2024;13:e52938
URL: https://www.researchprotocols.org/2024/1/e52938
doi:10.2196/52938
PMID:38190235

Protocol

Virtual Reality for Developing Patient-Facing Communication Skills in Medical and Graduate Education: Protocol for a Scoping Review

Nairy Khodabakhshian[1,2*], BSc; Kyla Gaeul Lee[1,3*], MSc; Tulip Marawi[1,4*], MSc; Maryam Sorkhou[1,5], BSc; Sobiga Vyravanathan[1], MEd; Nicole Harnett[1,6], MEd

[1]Institute of Medical Science, University of Toronto, Toronto, ON, Canada
[2]Labatt Family Heart Centre, The Hospital for Sick Children, Toronto, ON, Canada
[3]Department of Psychiatry, Sinai Health, Toronto, ON, Canada
[4]Sunnybrook Research Institute, Toronto, ON, Canada
[5]Addictions Division, Centre for Addiction and Mental Health, Toronto, ON, Canada
[6]Department of Radiation Oncology, University of Toronto, Toronto, ON, Canada
[*]these authors contributed equally

Corresponding Author:
Nicole Harnett, MEd
Department of Radiation Oncology
University of Toronto
610 University Avenue
Toronto, ON
Canada
Phone: 1 416 946 4501
Email: nicole.harnett@rmp.uhn.ca

Abstract

Background: Clinician-patient communication is an integral component in providing quality medical care. However, research on clinician-patient communication has shown overall patient discontent with provider communication skills. While virtual reality (VR) is readily used for procedural-based learning in medical education, its potential for teaching patient-facing communication skills remains unexplored. This scoping review aims to evaluate the effectiveness and feasibility of VR applications used for patient-facing communication skills development in medical education.

Objective: The primary objective is to synthesize and evaluate the effectiveness of available VR tools and applications used for patient-facing communication skills development in medical education. The secondary objectives are to (1) assess the feasibility of adapting VR applications to develop patient-facing communication skills in medical education and (2) provide an overview of the challenges associated with adapting VR applications to develop patient-facing communication skills in medical education.

Methods: A total of 4 electronic databases (ERIC, Embase, PubMed, and MEDLINE) were searched for primary peer-reviewed articles published through April 11, 2023. Articles evaluating the implementation of non-, semi-, and fully immersive VR training for patient- or caregiver-facing communication skills training provided to graduate, medical, or other allied health care professions students were included. Studies that assessed augmented reality, mixed reality, artificial intelligence, or VR for non–communication-based training were excluded. Study selection will include a title, abstract, and full-text screening by 4 authors. Data from eligible studies will be extracted and entered into a database and presented in tabular format. Findings will be reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for scoping reviews.

Results: As of April 11, 2023, the search strategy has been confirmed and the search has been completed. We are currently at the title and abstract screening stage. Once complete, the articles will undergo full-text screening according to eligibility criteria as described in the methods.

Conclusions: The findings of this review will inform the development of a graduate-level clinical skills research course within the Institute of Medical Science graduate department at the University of Toronto. It is also expected that these findings will be of interest to other health care–specific faculties inside and beyond our institution. Further, our scoping review will summarize the limited field of literature on VR use in medical communications training and identify areas for future inquiry.

International Registered Report Identifier (IRRID): DERR1-10.2196/53901

(JMIR Res Protoc 2024;13:e53901) doi:10.2196/53901

KEYWORDS

communication; medical education; patient-facing; scoping review; technology; virtual reality

Introduction

Effective communication skills are crucial for health care professionals to establish trust and build rapport with their patients, facilitate shared decision-making, and deliver high-quality care. Poor communication between clinicians and patients has been associated with decreased health care quality, increased human and economic cost of care, disenrollment from health care plans, poor adherence to recommended treatments, and propensity to sue for medical malpractice [1-4]. Accordingly, American medical colleges [5] and Canadian medical schools [6] have stated that clinician-patient communication is an integral component of quality medical care and highlighted the need for formal training programs at the undergraduate, postgraduate, and continuing education levels. However, research on clinician-patient communication has shown overall patient discontent even when clinicians indicate their own communication to be good or excellent [7]. Although there has been increasing emphasis placed on communication skills training in most health care curricula, significant challenges remain in their implementation and evaluation. These training approaches are often limited in time, resources, personnel, contextualization, unclear frameworks, and teaching strategies [8]. Incorporating educational tools that promote and develop patient-focused communication skills is imperative for the delivery of comprehensive care by health care professionals.

Virtual reality (VR) has emerged as a promising tool that addresses the challenges associated with limited access to health care institutions, personnel, contextualization, and feedback to evaluate frameworks and teaching outcomes. VR is defined as an educational tool that uses computer technology to generate a 3D image or environment with which a user can interact in a seemingly real or physical manner [9]. Presently, VR has been mainly used for training in procedural skills, typically for surgical training, but has been expanding to other applications as well [10]. There are currently 3 main categories of VR: nonimmersive, semi-immersive, and fully immersive. Nonimmersive VR is typically a screen-based display that is connected to handheld mechanical or haptic units [11]. Nonimmersive VR is commonly used to develop technical psychomotor skills, such as those needed in endoscopic surgery [12]. In semi-immersive VR, users use a VR headset and dedicated controllers to interact with a 3D VR, usually spanning 180° [13]. The addition of body sensors provides a fully immersive experience in which a user is placed entirely in a virtual environment, and their awareness of the real world is disconnected [9]. Semi- and fully immersive VR is particularly useful for teaching appropriate responses to stressful scenarios such as mass casualties, emergency surgical procedures, and cardiopulmonary resuscitation [14,15].

VR offers a simulated environment for diverse applications that enable learners to practice various skills with patients and caregivers in a safe and controlled setting without relying on health care facilities or personnel [10]. For example, Izard et al [16] demonstrated the effective use of VR in teaching surgical trainees detailed practical knowledge about surgical procedures. Another study by Birrenbach et al [17] leveraged VR during the COVID-19 pandemic to explore the short- and long-term effectiveness of VR simulation versus traditional learning methods for training health care professionals in hand disinfection, nasopharyngeal swab-taking, and donning or doffing of personal protective equipment [17]. VR technology can also provide learners with immediate feedback on their communication skills, tangible learning outcomes for educators, and allow for the repeated practice of challenging scenarios that may not be possible in real-life clinical settings [11,12]. Zackoff et al [14] used VR to train medical students in managing respiratory distress. The participants reported the VR environment as equal or superior to the perceived effectiveness of other training modalities such as standardized patients and high-fidelity mannequins. The learners also perceived VR as equally effective to standardized patients for communication training [14].

While less researched compared to technical medical skills, the rapid progression of technology has expanded the possibilities of using VR as a training tool targeting communication skills. Immersive first-person VR was found to be successful in teaching effective health dialogues and communication skills. For example, clinicians and postgraduate medical residents who used VR were more confident in and more capable of communicating difficult medical information to patients [18]. Furthermore, undergraduate research students who were trained with VR were better prepared for real-world patient interactions that involved obtaining consent [19]. Overall, VR was able to improve the dialogue performance of students with little to no previous communication training, with students posttraining being able to respond to patient questions in a more accurate and timely manner [19]. In another study, VR allowed participants to replay their experiences to help them recognize and analyze their interactions and emotions to help inform their future communications with patients [20]. Altogether, VR delivers immersion and realism, reflecting real-world scenarios that increase empathetic communication with patients [21-23]. Despite the strong evidence presented in these studies, there is still a lack of consensus on the most effective VR tools and applications for patient-facing communication skills development in medical or health care professional education (referred to as “medical education” hereafter).

Effective communication skills are crucial for health care professionals to deliver high-quality care and establish positive patient-clinician relationships, ultimately improving patient outcomes. The use of VR technology for communication skills training in medical education has the potential to provide learners with a safe and controlled environment to practice challenging scenarios and receive immediate feedback on their

communication skills. The majority of VR participants agreed that the technology was reflective of real life, strongly suggesting VR as a capable educational tool [21,23]. VR was also a highly rated learning experience and preferred over standard didactic lectures [24,25]. However, the applications of VR for communication skills development in health care professionals remain limited. This scoping review aims to synthesize and evaluate the available evidence on the effectiveness of VR tools and applications for patient-facing communication skills development in medical education and inform educators and health care professionals on the potential benefits and limitations of this technology.

Methods

Approach

To inform our objectives, we will conduct a scoping review following the methodology described by Arksey and O'Malley [26] and Levac and colleagues [27]. As our research aims to describe the application of an emerging tool (VR) in medical education and we intend on applying the findings of the scoping review to the development of a new clinical research skills course, a scoping review is an appropriate approach. While similar in rigor to systematic reviews, a scoping review allows for a preliminary assessment of the size of existing evidence to inform future directions for research priorities by identifying knowledge gaps, usually in an area of ongoing research and knowledge synthesis [28,29].

The scoping review approach encompasses the following six stages: (1) identifying the research question; (2) identifying relevant studies; (3) selecting studies; (4) charting the data; (5) collating, summarizing, and reporting the results; and (6) engaging in knowledge translation and stakeholder discussions. We will adhere to the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) [30].

Stage 1: Identifying the Research Question

The objective of this scoping review is to outline and assess the available VR tools and applications used for patient-facing communication skills development within the context of medical education. To meet this objective, we have developed the following research questions:

1. How is VR implemented in a medical education setting to develop patient-facing communication skills?
2. Is VR an effective tool to develop patient-facing communication skills in a medical education context?
3. Is adapting VR tools to develop patient-facing communication skills in medical education feasible?
4. What are the challenges associated with adapting VR tools and applications to develop patient-facing communication skills in medical education?

Stage 2: Identifying Relevant Studies

To inform our study selection, we developed an operational definition of VR, communication, and medical education students.

Operational Definition of VR

We defined VR as a computer-based tool that generates a 3D image or environment that allows the participant to look about and navigate within a seemingly real or physical world [21,31,32]. Key attributes of VR in our definition included the use of (1) 3D imaging, (2) the ability to actively interact with the virtual environment, and (3) visual and auditory feedback that allows the user to feel immersed in the virtual environment [33]. In order to capture the full breadth of VR, our operational definition included nonimmersive (eg, screen-based VR simulators), semi-immersive (ie, immersive VR without physical movement), and fully immersive VR (usually using head-mounted displays and hand-held equipment) [31].

Operational Definition of Communication

We define communication as effectively engaging in conversation and exchanging information with patients, caregivers, or decision-makers regarding a medical condition in simple, clear, and plain language. Within the context of trainees in a medical education setting, effective communication skills include, but are not limited to (1) obtaining informed consent to perform a procedure; (2) engaging in difficult conversations (eg, breaking bad news); (3) collecting personal, sensitive, and confidential patient information in an ethical manner; (4) listening attentively to patient or caregiver concerns to assess the patient's health and condition; (5) maintaining professional relationships with patients and caregivers; and (6) validating and addressing patient or caregiver emotions and concerns [34,35].

Operational Definition of Medical Education Students

For our scoping review, we identified medical education students as any student in a medical or health care profession field. These students included but were not limited to, graduate, medical, nursing, physical therapy, physiotherapy, occupational therapy, or other allied health care professions students that are required to interact directly with patient populations in the delivery of their care and would thus benefit in communications training in their work. All students and trainees that may be included in the circle of care, either directly or indirectly, that communicated with patients were included in our definition of medical education students.

Search Strategy

In collaboration with a health sciences research librarian at the University of Toronto, a member of our team (MS) developed the search strategy to locate published and unpublished studies on PubMed, ERIC, Embase, and MEDLINE databases on April 11, 2023. The search was limited to data that were published from January 2000 to April 2023.

The search strategy explores specific search terms within subject headings, titles, abstracts, and keywords (Textbox 1). The search strategy, including all identified keywords and index terms, was adapted for each database to account for appropriate MeSH (Medical Subject Headings) terms. Textbox 1 shows the search strategy used for each database, with concepts combined with Boolean operators AND and OR. Further potentially relevant studies will be identified by conducting a search of the

references of included articles and relevant systematic reviews and meta-analyses.

Textbox 1. The search strategy used to obtain studies.

1. computer simulation/ or augmented reality/ or virtual reality/
2. computer-assisted instruction/ or simulation training/ or high fidelity simulation training/ or patient simulation/
3. ((virtual or mixed or augment*) adj3 (realit* or simulation*)).tw,kf.
4. (simulation* adj3 (train or trained or training* or patient* or instruction*)).tw,kf.
5. ((computer* or computational) adj3 (model* or simulation* or assisted instruction)).tw,kf.
6. 1 or 2 or 3 or 4 or 5
7. (class* or postsecondary or educat* or instruct*).tw,kf.
8. 6 and 7
9. ((clinic* or patient or medic* or communicat*) adj2 (skill* or interact* or instruct*)).tw,kf.
10. 8 and 9

Stage 3: Study Selection

Overview

The study selection phase will include the following two screening phases: (1) title and abstract screening and (2) full-text screening. First, 4 authors (NK, KGL, TM, and MS) will screen the titles and abstracts of all eligible studies identified through searching the electronic databases for relevance according to the inclusion and exclusion criteria outlined in Textbox 2. Each title and abstract will be screened by 2 of 4 authors (NK, KGL, TM, and MS), and in order for an article to move past the first screening phase, it must be accepted for inclusion by 2 authors. Disagreements will be resolved through a discussion among at least 3 of the following 4 authors: NK, KGL, TM, and MS. Second, these 4 authors (NK, KGL, TM, and MS) will download and review the full text of all articles passing the first screening phase. Similar to the first screening phase, each article will be reviewed by 2 of 4 authors (NK, KGL, TM, and MS), and in order for an article to move past this screening phase, it must also be accepted for inclusion by 2 authors. Disagreements will be resolved through a discussion among all authors. Screening and study selection will be conducted using the Covidence reference management system.

Textbox 2. Study inclusion and exclusion criteria used during screening.

Inclusion criteria

- Published in a peer-reviewed journal in the English language.
- Participants are graduate medical, nursing, physical therapy, physiotherapy, occupational therapy, or other allied health care professions students receiving patient-facing communication skills training.
- Study evaluates the implementation of nonimmersive, semi-immersive, or fully immersive virtual reality training for patient- or caregiver-facing communication skills training.
- Study reports (quantitatively or qualitatively) the learning outcomes of students, the teaching outcomes of educators, or educators' and learners' perspectives on virtual reality content and delivery.
- Published after 2000.

Exclusion criteria

- Commentaries, editorial notes, systematic reviews, meta-analyses, opinion articles, protocols, dissertations, or book chapters.
- Studies using any form of virtual reality for non–communication-based clinical skills (eg, surgical planning and therapeutic or treatment applications).
- Studies using augmented reality, mixed reality, artificial intelligence, or robotics.
- Studies using manikins for simulation training.

Inclusion Criteria

Only articles published in the English language will be considered for this scoping review. Only articles that are peer-reviewed will be considered in order to ensure that the quality of the articles reviewed is of the highest standard. Articles published only after the year 2000 will be included, as the use of technology in education only became more widespread in the early 2000s. Although most of the literature on VR in medical education was published after 2010, there are relevant articles that were published between 2000 and 2009, as 3 of the 9 studies included in the systematic review by Rourke [36] were published between 2000 and 2009. Similarly, 2 other systematic reviews [37,38] included studies published between

2000 and 2009. We adhered to the PICO framework to define the populations, interventions, comparisons, outcomes, and study designs eligible for our review. Studies were included if they met the following criteria: studies including undergraduate, graduate, medical students, medical residents, and any health care professional (ie, population); studies assessing either asynchronous or synchronous VR training methodologies specifically designed for the cultivation of clinical skills in medical education (ie, intervention); studies may or may not comprise of a control group of learners who do not receive VR training (ie, comparison); and studies that assess either the learning outcomes, feasibility, efficacy, and impact of the VR technology in relation to clinical skills teaching methodologies (ie, outcomes).

Exclusion Criteria

We aim to further develop a clinical research skills graduate-level course focused on patient-facing communication skills. Therefore, we excluded articles that outline the utility of VR for non–communication-based clinical skills, such as studies using VR to teach surgical procedures, other field-specific medical interventions, combining and administering pharmacotherapy, pain management, and other noncommunication skills or practices. We additionally excluded commentaries, editorials, other reviews and meta-analyses, opinion articles, protocols, dissertations, conference abstracts, and book chapters. Studies in a language other than English were excluded, in addition to studies using non-VR tools to teach clinical communication skills, such as manikins, CD-ROMs, or roleplaying actors. As our aim is to inform the development of a graduate-level clinical research skills course using VR, we restricted our search to only capture VR applications and excluded other forms of experiences, including augmented reality (AR) and mixed reality (MR). While VR allows the user to be fully immersed in the virtual environment, AR and MR supplement and integrate VR with the user's reality [39,40]. As our course intends to use technology to simulate patient-facing scenarios to teach medical communications skills to students, AR and MR were not considered due to the low fidelity of these technologies. Textbox 2 presents a comprehensive overview of our review's inclusion and exclusion criteria.

Stage 4: Charting the Data

Data from studies meeting the inclusion criteria will be extracted and entered into a database created by the study team. Proposed data fields for extraction include: bibliographic information (ie, author, year of publication, and study's PubMed ID), location of publication, reported time frame, type of study, participant population (ie, student field of study, student year of study, and affiliated institution), description of the VR tool (eg, nonimmersive, semi-immersive, and fully immersive), technology used to deliver the VR (eg, computer screen and head-mounted device), reported student experience (eg, satisfaction and ease of use), developer and instructor experience (eg, lessons learned), reported barriers and facilitators to the use of VR (if available), and communication-related outcomes. This developed database will be revised upon piloting the data extraction of 25 articles to ensure that the data relevant to the aforementioned aims are satisfied.

Stage 5: Collating, Summarizing, and Reporting Results

The aim of our scoping review is to synthesize the evidence describing the effectiveness and impact of and lessons learned in the feasibility and implementation of VR applications and tools used for patient-facing communication skills. Accordingly, we will use a narrative-qualitative approach to synthesis. Descriptive data about the included studies (ie, location of study, type of study, and participant population) will be reported. Collated data pertaining to effectiveness, impact, lessons learned, and facilitators and barriers to implementation and use of VR will be organized into key themes, then presented through narratives and tables. The results of the search will be included in the final scoping review and presented as a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram. Data will be charted using a structured form and narratively summarized. Additionally, we will identify and report gaps in the available literature. Lastly, the review's findings will be considered within a broader context of research, practice, and educational design implications.

Stage 6: Stakeholder Discussions

The findings from this scoping review will help modify the clinical research skills graduate course that is being developed by the authors for the Institute of Medical Science (IMS) graduate program. The findings will be shared with the IMS Curriculum Committee, and the recommendations from this committee will be reviewed to further develop the course, which will undergo the governance process at the University of Toronto. The IMS would like to offer this course to students from different clinical departments in the future, and having this review include participants who are graduate medical, nursing, physical therapy, physiotherapy, occupational therapy, or other allied health care professions students will help inform course development.

Ethical Considerations

No protocol was registered, and research ethics approval was not sought as all data are publicly available.

Results

As of April 11, 2023, the search strategy has been confirmed, and the search has been completed. After removing duplicates, our search identified 4141 studies eligible for title and abstract screening. Of these studies, 89 were included for full-text screening. Currently, 4 authors (NK, TM, KGL, and MS) are completing the full-text screening. We anticipate that full-text screening will be completed by February 2024. Following this stage, the results of the review will be tabulated, visualized, and summarized descriptively. The target date for manuscript submission is June 2024.

Discussion

Principal Results

VR is emerging as a promising educational tool in medical education that can address the challenges associated with limited resources, cost, and the provision of immediate feedback. This scoping review aims to synthesize and assess the effectiveness of available VR tools and applications to teach patient-facing communication skills in medical education. In addition, this review will assess the feasibility of implementing VR applications and provide an overview of the challenges and lessons learned in VR application implementation and use in medical education.

Implications and Conclusions

Immediately, the findings of this review will inform the development of a graduate-level VR-based clinical skills research course within the IMS at the University of Toronto, but it is expected that these findings will be of interest to other health care–specific departments within and beyond our institution and will guide future research questions. For example, VR use in medical education has largely focused on technical skills in, for example, anatomy or surgery to date [41,42], with limited literature on VR use in medical communications or professional skills training [10]. Nevertheless, of the scarce literature available on communications and professional skills training in medical education, VR has been shown to foster the development of various competencies, including interprofessional collaboration [43,44], empathy and compassion [45,46], and confidence [47]. Moreover, given the significance of communication as a crucial skill in various medical education specialties, our scoping review holds relevance for educational settings across all medical specialties wherein clinicians and researchers engage with patients and caregivers. Therefore, our scoping review will contribute to this growing field by summarizing the limited field of literature on VR use in medical communications training, informing educators and health care professionals of the potential benefits and limitations of this technology, and identifying areas for future inquiry.

Limitations

Our proposed protocol has potential methodological limitations and limitations related to the current use of VR in medical education. We restricted our search to only include VR applications and excluded AR or MR applications; therefore, our review is not equipped to draw any conclusions regarding AR or MR use in medical communication skills training. Moreover, we only included studies reported in the English language, and therefore we may potentially not entirely capture findings reported in other languages. Additionally, we recognize the current technological and accessibility limitations in the utility of VR within medical education. For example, implementing VR applications requires costly resources, including specialized hardware of high quality and the expertise of trained personnel, which could present technological barriers and create disparities in accessing the technology among academic institutions [48]. From a pedagogical perspective, previous authors have outlined limitations, including decreased face-to-face communication, the need for robust and adequate evaluation procedures that assess real-life skills, and the importance of more research establishing VR as an effective education for clinical and communication skills [49]. However, a comprehensive overview of the limitations of VR is beyond the scope of this protocol and has been the focus of other reviews [48,49].

Conflicts of Interest

None declared.

References

1. Kohn LT, Corrigan JM, Donaldson MS, Committee on Quality of Health Care in America. To Err is Human: Building a Safer Health System. Washington, DC: National Academies Press; 2000.
2. Levinson W, Roter DL, Mullooly JP, Dull VT, Frankel RM. Physician-patient communication. The relationship with malpractice claims among primary care physicians and surgeons. JAMA 1997;277(7):553-559. [doi: 10.1001/jama.277.7.553] [Medline: 9032162]
3. Roter DL, Hall JA, Katz NR. Relations between physicians' behaviors and analogue patients' satisfaction, recall, and impressions. Med Care 1987;25(5):437-451. [doi: 10.1097/00005650-198705000-00007] [Medline: 3695654]
4. Safran DG, Montgomery JE, Chang H, Murphy J, Rogers WH. Switching doctors: predictors of voluntary disenrollment from a primary physician's practice. J Fam Pract 2001;50(2):130-136. [Medline: 11219560]
5. Medical School Objectives Writing Group. Learning objectives for medical student education--guidelines for medical schools: report I of the medical school objectives project. Acad Med 1999;74(1):13-18 [FREE Full text] [doi: 10.1097/00001888-199901000-00010] [Medline: 9934288]
6. Canadian Medical Association. Consensus statement from the workshop on the teaching and assessment of communication skills in Canadian medical schools. Can Med Assoc J 1992;147(8):1149-1150. [Medline: 1393928]
7. Hitawala A, Flores M, Alomari M, Kumar S, Padbidri V, Muthukuru S, et al. Improving physician-patient and physician-nurse communication and overall satisfaction rates: a quality improvement project. Cureus 2020;12(4):e7776 [FREE Full text] [doi: 10.7759/cureus.7776] [Medline: 32461851]
8. Deveugele M. Communication training: skills and beyond. Patient Educ Couns 2015;98(10):1287-1291. [doi: 10.1016/j.pec.2015.08.011] [Medline: 26298220]

9. Ahmadpour N, Randall H, Choksi H, Gao A, Vaughan C, Poronnik P. Virtual reality interventions for acute and chronic pain management. Int J Biochem Cell Biol 2019;114:105568. [doi: 10.1016/j.biocel.2019.105568] [Medline: 31306747]
10. Mergen M, Meyerheim M, Graf N. Reviewing the current state of virtual reality integration in medical education—a scoping review protocol. Syst Rev 2023;12(1):97 [FREE Full text] [doi: 10.1186/s13643-023-02266-6] [Medline: 37337293]
11. Wong MAME, Chue S, Jong M, Benny HWK, Zary N. Clinical instructors' perceptions of virtual reality in health professionals' cardiopulmonary resuscitation education. SAGE Open Med 2018;6:1-8 [FREE Full text] [doi: 10.1177/2050312118799602] [Medline: 30245815]
12. Van Herzeele I, Aggarwal R, Neequaye S, Darzi A, Vermassen F, Cheshire NJ. Cognitive training improves clinically relevant outcomes during simulated endovascular procedures. J Vasc Surg 2008;48(5):1223-1230, 1230.e1 [FREE Full text] [doi: 10.1016/j.jvs.2008.06.034] [Medline: 18771880]
13. Blackburn SC, Griffin SJ. Role of simulation in training the next generation of endoscopists. World J Gastrointest Endosc 2014;6(6):234-239 [FREE Full text] [doi: 10.4253/wjge.v6.i6.234] [Medline: 24932375]
14. Zackoff MW, Real FJ, Cruse B, Davis D, Klein M. Medical student perspectives on the use of immersive virtual reality for clinical assessment training. Acad Pediatr 2019;19(7):849-851. [doi: 10.1016/j.acap.2019.06.008] [Medline: 31201953]
15. Heinrichs WL, Youngblood P, Harter P, Kusumoto L, Dev P. Training healthcare personnel for mass-casualty incidents in a virtual emergency department: VED II. Prehosp Disaster Med 2010;25(5):424-432. [doi: 10.1017/s1049023x00008505] [Medline: 21053190]
16. Izard SG, Juanes JA, Peñalvo FJG, Estella JMG, Ledesma MJS, Ruisoto P. Virtual reality as an educational and training tool for medicine. J Med Syst 2018;42(3):50. [doi: 10.1007/s10916-018-0900-2] [Medline: 29392522]
17. Birrenbach T, Zbinden J, Papagiannakis G, Exadaktylos AK, Müller M, Hautz WE, et al. Effectiveness and utility of virtual reality simulation as an educational tool for safe performance of COVID-19 diagnostics: prospective, randomized pilot trial. JMIR Serious Games 2021;9(4):e29586 [FREE Full text] [doi: 10.2196/29586] [Medline: 34623315]
18. Omlor AJ, Schwärzel LS, Bewarder M, Casper M, Damm E, Danziger G, et al. Comparison of immersive and non-immersive virtual reality videos as substitute for in-hospital teaching during coronavirus lockdown: a survey with graduate medical students in Germany. Med Educ Online 2022;27(1):2101417 [FREE Full text] [doi: 10.1080/10872981.2022.2101417] [Medline: 35850619]
19. Pan X, Slater M, Beacco A, Navarro X, Rivas AIB, Swapp D, et al. The responses of medical general practitioners to unreasonable patient demand for antibiotics--a study of medical ethics using immersive virtual reality. PLoS One 2016;11(2):e0146837 [FREE Full text] [doi: 10.1371/journal.pone.0146837] [Medline: 26889676]
20. Hubal RC, Day RS. Informed consent procedures: an experimental test using a virtual character in a dialog systems training application. J Biomed Inform 2006;39(5):532-540 [FREE Full text] [doi: 10.1016/j.jbi.2005.12.006] [Medline: 16464644]
21. Haowen J, Vimalesvaran S, Kyaw BM, Car LT. Virtual reality in medical students' education: a scoping review protocol. BMJ Open 2021;11(5):e046986 [FREE Full text] [doi: 10.1136/bmjopen-2020-046986] [Medline: 34039577]
22. Fertleman C, Aubugeau-Williams P, Sher C, Lim AN, Lumley S, Delacroix S, et al. A discussion of virtual reality as a new tool for training healthcare professionals. Front Public Health 2018;6:44 [FREE Full text] [doi: 10.3389/fpubh.2018.00044] [Medline: 29535997]
23. Chang CC, Hwang GJ. An experiential learning-based virtual reality approach to fostering problem-resolving competence in professional training. Interact Learn Environ 2021;31(8):4713-4728. [doi: 10.1080/10494820.2021.1979049]
24. Real FJ, DeBlasio D, Beck AF, Ollberding NJ, Davis D, Cruse B, et al. A virtual reality curriculum for pediatric residents decreases rates of influenza vaccine refusal. Acad Pediatr 2017;17(4):431-435. [doi: 10.1016/j.acap.2017.01.010] [Medline: 28126612]
25. Riesen E, Morley M, Clendinneng D, Ogilvie S, Murray MA. Improving interprofessional competence in undergraduate students using a novel blended learning approach. J Interprof Care 2012;26(4):312-318. [doi: 10.3109/13561820.2012.660286] [Medline: 22559163]
26. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. Int J Soc Res Methodol 2005;8(1):19-32. [doi: 10.1080/1364557032000119616]
27. Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. Implement Sci 2010;5:69 [FREE Full text] [doi: 10.1186/1748-5908-5-69] [Medline: 20854677]
28. Grant MJ, Booth A. A typology of reviews: an analysis of 14 review types and associated methodologies. Health Info Libr J 2009;26(2):91-108 [FREE Full text] [doi: 10.1111/j.1471-1842.2009.00848.x] [Medline: 19490148]
29. Munn Z, Peters MDJ, Stern C, Tufanaru C, McArthur A, Aromataris E. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. BMC Med Res Methodol 2018;18(1):143 [FREE Full text] [doi: 10.1186/s12874-018-0611-x] [Medline: 30453902]
30. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med 2018;169(7):467-473 [FREE Full text] [doi: 10.7326/M18-0850] [Medline: 30178033]
31. Bracq MS, Michinov E, Jannin P. Virtual reality simulation in nontechnical skills training for healthcare professionals: a systematic review. Simul Healthc 2019;14(3):188-194 [FREE Full text] [doi: 10.1097/SIH.0000000000000347] [Medline: 30601464]

32. Lopreiato JO. Healthcare Simulation Dictionary. Rockville, MD: Agency for Healthcare Research and Quality; 2016.
33. Mantovani F, Castelnuovo G, Gaggioli A, Riva G. Virtual reality training for health-care professionals. Cyberpsychol Behav 2003;6(4):389-395. [doi: 10.1089/109493103322278772] [Medline: 14511451]
34. Bearman M, Cesnik B, Liddell M. Random comparison of 'virtual patient' models in the context of teaching clinical communication skills. Med Educ 2001;35(9):824-832. [doi: 10.1046/j.1365-2923.2001.00999.x] [Medline: 11555219]
35. Hamdy H, Sreedharan J, Rotgans JI, Zary N, Bahous SA, Venkatramana M, et al. Virtual Clinical Encounter Examination (VICEE): a novel approach for assessing medical students' non-psychomotor clinical competency. Med Teach 2021;43(10):1203-1209. [doi: 10.1080/0142159X.2021.1935828] [Medline: 34130589]
36. Rourke S. How does virtual reality simulation compare to simulated practice in the acquisition of clinical psychomotor skills for pre-registration student nurses? A systematic review. Int J Nurs Stud 2020;102:103466. [doi: 10.1016/j.ijnurstu.2019.103466] [Medline: 31783192]
37. Kyaw BM, Saxena N, Posadzki P, Vseteckova J, Nikolaou CK, George PP, et al. Virtual reality for health professions education: systematic review and meta-analysis by the digital health education collaboration. J Med Internet Res 2019;21(1):e12959 [FREE Full text] [doi: 10.2196/12959] [Medline: 30668519]
38. Kim HY, Kim EY. Effects of medical education program using virtual reality: a systematic review and meta-analysis. Int J Environ Res Public Health 2023;20(5):3895 [FREE Full text] [doi: 10.3390/ijerph20053895] [Medline: 36900904]
39. Carmigniani J, Furht B. Augmented reality: an overview. In: Furht B, editor. Handbook of Augmented Reality. New York, NY: Springer; 2011:3-46.
40. Rokhsaritalemi S, Sadeghi-Niaraki A, Choi SM. A review on mixed reality: current trends, challenges and prospects. Appl Sci 2020;10(2):636 [FREE Full text] [doi: 10.3390/app10020636]
41. Jiang H, Vimalesvaran S, Wang JK, Lim KB, Mogali SR, Car LT. Virtual reality in medical students' education: scoping review. JMIR Med Educ 2022;8(1):e34860 [FREE Full text] [doi: 10.2196/34860] [Medline: 35107421]
42. Bric JD, Lumbard DC, Frelich MJ, Gould JC. Current state of virtual reality simulation in robotic surgery training: a review. Surg Endosc 2016;30(6):2169-2178. [doi: 10.1007/s00464-015-4517-y] [Medline: 26304107]
43. Liaw SY, Wu LT, Soh SLH, Ringsted C, Lau TC, Lim WS. Virtual reality simulation in interprofessional round training for health care students: a qualitative evaluation study. Clin Simul Nurs 2020;45:42-46. [doi: 10.1016/j.ecns.2020.03.013]
44. Qiao J, Xu J, Li L, Ouyang YQ. The integration of immersive virtual reality simulation in interprofessional education: a scoping review. Nurse Educ Today 2021;98:104773. [doi: 10.1016/j.nedt.2021.104773] [Medline: 33497990]
45. Stargatt J, Bhar S, Petrovich T, Bhowmik J, Sykes D, Burns K. The effects of virtual reality-based education on empathy and understanding of the physical environment for dementia care workers in Australia: a controlled study. J Alzheimers Dis 2021;84(3):1247-1257. [doi: 10.3233/JAD-210723] [Medline: 34633323]
46. Dyer E, Swartzlander BJ, Gugliucci MR. Using virtual reality in medical education to teach empathy. J Med Libr Assoc 2018;106(4):498-500 [FREE Full text] [doi: 10.5195/jmla.2018.518] [Medline: 30271295]
47. Lesch H, Johnson E, Peters J, Cendán JC. VR simulation leads to enhanced procedural confidence for surgical trainees. J Surg Educ 2020;77(1):213-218 [FREE Full text] [doi: 10.1016/j.jsurg.2019.08.008] [Medline: 31466895]
48. Baniasadi T, Ayyoubzadeh SM, Mohammadzadeh N. Challenges and practical considerations in applying virtual reality in medical education and treatment. Oman Med J 2020;35(3):e125 [FREE Full text] [doi: 10.5001/omj.2020.43] [Medline: 32489677]
49. Cook DA, Hatala R, Brydges R, Zendejas B, Szostek JH, Wang AT, et al. Technology-enhanced simulation for health professions education: a systematic review and meta-analysis. JAMA 2011;306(9):978-988. [doi: 10.1001/jama.2011.1234] [Medline: 21900138]

Abbreviations

AR: augmented reality
IMS: Institute of Medical Science
MeSH: Medical Subject Headings
MR: mixed reality
PICO: populations, interventions, comparisons, and outcomes
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Review
VR: virtual reality

Edited by A Mavragani; submitted 23.10.23; peer-reviewed by F Albalwy; comments to author 03.01.24; revised version received 09.01.24; accepted 11.01.24; published 01.02.24.

Please cite as:
Khodabakhshian N, Gaeul Lee K, Marawi T, Sorkhou M, Vyravanathan S, Harnett N
Virtual Reality for Developing Patient-Facing Communication Skills in Medical and Graduate Education: Protocol for a Scoping Review
JMIR Res Protoc 2024;13:e53901
URL: https://www.researchprotocols.org/2024/1/e53901
doi:10.2196/53901
PMID:38300671

Protocol

Interactive Narrative–Based Digital Health Interventions for Vaccine Communication: Protocol for a Scoping Review

Ahmed Haji Said[1], MBBS, MPH; Kate Winskell[1], PhD; Robert A Bednarczyk[1], PhD; Erin E Reardon[2], MFA, MLIS; Lavanya Vasudevan[1], MPH, CPH, PhD

[1]Hubert Department of Global Health, Rollins School of Public Health, Emory University, Atlanta, GA, United States

[2]Woodruff Health Sciences Center Library, Emory University, Atlanta, GA, United States

Corresponding Author:
Ahmed Haji Said, MBBS, MPH
Hubert Department of Global Health
Rollins School of Public Health
Emory University
1518 Clifton Rd
Atlanta, GA, 30322
United States
Phone: 1 404 727 3956
Email: ahmed.haji.said@emory.edu

Abstract

Background: Interactive narrative–based digital health interventions hold promise for effectively addressing the complex determinants of vaccine hesitancy and promoting effective communication across a wide range of settings and vaccine types. Synthesizing evidence related to the implementation and evaluation of these interventions could offer valuable perspectives for shaping future strategies in vaccine communication. Prior systematic and scoping reviews have examined narrative-based vaccine communication interventions but not the inclusion of interactivity in such interventions.

Objective: The overall objective of the scoping review is to summarize the evidence on the use of interactive narrative–based digital health interventions for vaccine communication. Specific research questions focus on describing the use of interactive narrative–based digital health interventions (RQ1), describing evaluations of the impact of interactive narrative–based digital health interventions on promoting vaccine uptake (RQ2), and factors associated with their implementation (RQ3).

Methods: A detailed search string will be used to search the following databases for records that are relevant to the review questions: PubMed, Embase, Scopus, Web of Science, CINAHL, and PsycINFO. Two reviewers will independently screen the titles and abstracts of identified records against the predefined eligibility criteria. Subsequently, eligible records will undergo comprehensive full-text screening by 2 independent reviewers to assess their relevance to review questions. A data charting tool will be developed and used to extract relevant information from the included articles. The extracted information will be analyzed following the review questions and presented as a narrative summary. Tabular or graphical representations will be used to display review findings, as relevant.

Results: Public health informationists were consulted to develop the detailed search strategy. The final search string comprised terms related to narrative communication, digital health, and vaccines. The search string was customized to each proposed publication database and implemented on April 18, 2023. A total of 4474 unique records were identified using the search strategy and imported into the Covidence (Veritas Health Innovation Ltd) review management software for title and abstract screening. Title and abstract screening of identified records are ongoing as of December 29, 2023.

Conclusions: To our knowledge, this will be the first scoping review to investigate the features of interactive narrative–based digital health interventions and their role in vaccine communication. The goal of this study is to provide a comprehensive overview of the current research landscape and identify prevailing gaps in knowledge. The findings will provide insights for future research and development of novel applications of interactive narrative–based digital health vaccine communication interventions.

International Registered Report Identifier (IRRID): DERR1-10.2196/51137

(JMIR Res Protoc 2024;13:e51137) doi:10.2196/51137

KEYWORDS

narrative; storytelling; digital health; social media; interactive; vaccine; vaccination; vaccine hesitancy; vaccine communication

Introduction

Background

Vaccinations prevent more than 20 infectious diseases and avert 4-5 million deaths across the lifespan globally each year [1]. Yet, global progress on vaccinations has stalled in the last decade because of factors associated with vaccine complacency, convenience, or confidence [2]. These factors can result in vaccine hesitancy, a state of decisional ambivalence that manifests as a "delay in acceptance or refusal of vaccination despite availability of vaccination services" [2]. Vaccine hesitancy is blamed for backslides in vaccination coverage in high-income countries (eg, in Europe and the Americas), where issues with vaccine availability are less of a factor in suboptimal vaccine uptake [3]. Even in non–high-income settings, vaccine hesitancy may be present because of vaccination service interruptions and barriers to vaccine access [4]. The World Health Organization Strategic Advisory Group of Experts on Immunization noted that "vaccine hesitancy is complex and context-specific, varying with time, population, geographical location, and vaccine type" [2]. Passive or sloganized approaches frequently used by vaccination programs are insufficient to address the complexity and variability of the factors underlying vaccine hesitancy [5]. In a systematic review, Jarrett et al [6] found that dialogue-based communication strategies such as those leveraging mass media, social mobilization, and community influencers were effective in addressing vaccine hesitancy, whereas passive strategies such as those using posters and websites had a lower impact. One way to incorporate dialogue-based content may be through the use of narratives. The growth in the use of narratives for vaccine communication in recent years presents an opportunity to further study and innovate on its use to support vaccination uptake.

Narratives are ubiquitous in human society and have been used for persuasive health communication for decades [7,8]. Narrative-based communication strategies may be effective for understanding and addressing the complex determinants of vaccine hesitancy and enabling dialogue-based vaccine communication across varied settings and types of vaccines. The proliferation of digital technologies such as mobile phones has led to rapid and widespread sharing of health-related narratives via digital media (eg, social media platforms). These digital modalities of information communication may permit new ways for individuals to interact with narratives. For instance, interactive narrative–based digital health interventions, such as choose-your-own-adventure games, may offer individuals the chance to make decisions for their characters, influencing the unfolding of divergent paths and outcomes of their journeys [9]. Such interventions show a promising approach to storytelling by fostering self-efficacy that could be leveraged for vaccination promotion [10].

While prior systematic and scoping reviews have examined narrative-based communication for health [11,12], or specifically vaccines [13], the interactivity of narrative-based digital health interventions was not the focus. A synthesis of ways in which interactive narrative–based digital health interventions have been used for vaccine communication can facilitate the development and adaptation of novel applications to support vaccination. The goal of this scoping review is to summarize the evidence on the use of interactive narrative–based digital health interventions for vaccine communication.

Concepts Included in This Review

Overview

The 4 key concepts included in this review are narrative communication, digital health, interactivity, and vaccine communication.

Narrative Communication

For the purposes of this review, we follow Hinyard and Kreuter [7] definition of narratives as: "any cohesive and coherent story with an identifiable beginning, middle, and end that provides information about scene, characters, and conflict; raises unanswered questions or unresolved conflict; and provides resolution."

Narratives may be presented in different ways (eg, entertainment education, case histories, and testimonials) or delivered through different modalities (eg, social media, comics, and plays) [7,8]. The content of narratives may include "official stories that are constructed to tell an innocuous version of events or the position of a group, invented stories that are made up or fictional, firsthand experiential stories, secondhand stories (ie, retelling of someone else's story), and culturally common stories that are generalized and pervasive in a cultural context" [7,14]. For this review, we are interested in describing all elements of narratives used in vaccine communication, including the use of characters, settings, plots, points of view, features, and themes.

Digital Health

Digital health is defined as "the use of information and communications technology in support of health and health-related fields" [15]. The phrase digital health encompasses computer-based (electronic health or "eHealth") and mobile phone–based approaches for communicating health information and delivering health services. It also includes newer information and communication technology domains such as artificial intelligence [15]. Individuals may leverage digital technologies to cultivate social connections and access medical advice, including information on vaccines [10,16]. For this review, we are interested in describing all elements of digital health interventions that deliver narratives on vaccines, including the types of devices, modalities, and specific digital strategies as defined in the World Health Organization classification of digital health interventions [17].

Interactivity

For the purpose of this review, we define the term "interactive" as the active engagement of individuals with the narrative via digital health, aiming to raise awareness, empower behavior

change, and ultimately lead to improved vaccination outcomes. Interactivity in narrative-based digital health interventions may allow individuals to make sense of stories related to vaccines and vaccination. Interactivity may take various forms depending on the specific narrative, digital medium, or platform being used. For instance, interactive narratives may transcend the boundaries of passive information consumption, empowering individuals to actively shape the narrative's trajectory through decision-making processes (eg, games for health) [9], or individuals may respond to actions and outcomes of the narrative's characters (eg, via likes or comments on posts), or feature in the narratives themselves (eg, as avatars). For this review, we are interested in describing ways in which interaction with narratives has been incorporated via digital health in vaccination communication interventions.

Vaccine Communication

For this review, we describe vaccine communication very broadly as any communication related to vaccines. The purpose of the communication could vary (eg, for mass communication to promote new vaccines, provider-patient communication, to reduce misinformation, counter vaccine hesitancy, or train health workers). Communication about vaccines can involve a wide range of mechanisms including improving knowledge or awareness, shaping attitudes and beliefs, and so forth. We are interested in describing different vaccine communication use cases where interactive narrative–based digital health interventions have been used. We will include all vaccine types and populations targeted for communication. The communication process will be examined for 5 key components: sender, channel, message, receiver, and feedback [18].

Description of the Intervention

We are interested in any digital health interventions that incorporate narratives and interactivity for vaccine communication. We are interested in all types of narrative communication including games for health, entertainment education, storytelling, testimonials, and case histories. The entities delivering the narratives (ie, the messengers) may be formally trained (eg, doctors, public health experts, and researchers), laypersons (eg, community health workers, and peers), organizations, or health systems. The recipients may be persons receiving information on vaccinations or persons providing vaccination services.

The narrative vaccination communication process can take place entirely through a digital medium or via hybrid approaches that have at least 1 digital health component. For instance, in a hybrid approach, a provider may use a digital health aid to communicate vaccination narratives (eg, a narrative vaccination video on a tablet device) but follow up with a discussion (ie, interaction) about the video.

Research Objectives

This scoping review aims to answer the following specific research questions (RQs):

RQ1: How have interactive narrative–based digital health interventions been used for vaccine communication?

RQ2: How have interactive narrative–based digital health interventions been evaluated for promoting vaccine uptake?

RQ3: What implementation factors are associated with the use of interactive narrative–based digital health interventions for vaccine communication?

Methods

Overview

The methods of this scoping review are reported in accordance with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) checklist (Multimedia Appendix 1) [19].

Inclusion Criteria

Due to the hierarchical nature of the research questions, all included articles need to fulfill the inclusion criteria for RQ1. Within this subset of research articles, a subset of articles will also satisfy the inclusion criteria for RQ2 and RQ3.

RQ1: How have interactive narrative–based digital health interventions been used for vaccine communication?

- Studies encompassing any form of vaccine communication irrespective of vaccine type. We will consider studies incorporating vaccine communication alongside other interventions (eg, nutrition)
- Studies using narrative communication where the target audience can engage with the narrative
- Studies where the narrative is delivered via digital health devices (eg, via mobile phones and tablets) and modalities (eg, SMS text messages, applications, and games for health), including hybrid approaches where at least 1 component is delivered digitally
- Studies published as original research articles, presenting empirical findings obtained from data collection efforts.

RQ2: How have interactive narrative–based digital health interventions been evaluated for promoting vaccine uptake?

- Studies that meet the criteria for RQ1
- Studies that have been evaluated for vaccine uptake (eg, whether individuals received a vaccination or not after exposure to the narrative intervention) or vaccination intention.

RQ3: What implementation factors are associated with the use of narrative-based digital health interventions for vaccine communication?

- Studies meeting the criteria for RQ1
- Studies reporting implementation factors (ie, barriers and facilitators) related to the implementation of interactive narrative–based digital health interventions for vaccine communication
- Studies reporting implementation outcomes (eg, feasibility, acceptability, adoption, cost, reach, usability, and sustainability) derived from the evaluation of interactive narrative–based digital health interventions for vaccine communication.

Exclusion Criteria

We will exclude (1) publications classified as gray literature, protocols, trial registries, editorials, opinion pieces, and systematic and scoping reviews (ie, not an original research article); (2) original research articles for which full text are not available; (3) studies published in languages other than English for which certified translations in English are not available from the original source; (4) for RQ2, studies solely reporting intermediate outcomes related to vaccination knowledge, attitudes, or beliefs without data on vaccination intention or uptake; and (5) for RQ3 specifically, studies lacking empirical data on implementation factors or outcomes.

Search Strategy and Data Extraction

Two public health informationists (ER and HR) were consulted to develop the search strategy. A detailed search string was formulated in PubMed (Textbox 1) using a combination of MeSH (Medical Subject Headings) terms and relevant keywords to cover the domains of narratives, digital health, and vaccine communication.

The following other databases were searched using customized versions of the search string presented in Textbox 1: PubMed, Embase, Scopus, Web of Science, CINAHL, and PsycINFO. Studies that were published since 2010 will be included in the review due to the proliferation of digital storytelling as a tool for health care delivery around that time [20]. The research articles will be limited to English only. Screening and data extraction will be conducted using Covidence review management software as follows:

- Titles and abstracts will be independently reviewed by 2 researchers and records will be sorted as included or excluded for the next stage of review based on consensus voting. Full-text screening of included abstracts and titles will be completed by 2 reviewers, and a similar consensus voting approach will be followed. A third independent researcher will be consulted if the reviewers do not reach a consensus, and the majority vote will apply.
- We will develop and implement a data extraction template in Covidence based on the inclusion criteria, research objective, and RQs. Characteristics of the studies (eg, date, author, research question, and study findings) will be documented using the template by 2 researchers for each included study.

During the data extraction process (Textbox 2), we will focus on gathering the following information from included studies.

Textbox 1. Search string used for identifying relevant records in PubMed.

((“Narration”[Mesh] or Communication[Mesh]) or (narrat*[tw] or storytell*[tw] or story-tell*[tw] or “story telling”[tw] or storyline*[tw] or story[tw] or stories[tw] or conversation*[tw] or testimoni*[tw])) AND ((“Social Media”[Mesh] or “Mobile Applications”[Mesh] or “Smartphone”[Mesh] or “Telemedicine”[Mesh] or “Artificial Intelligence”[Mesh] or “Digital Technology”[Mesh] or “Computers”[Mesh]) or (digital[tw] or app[tw] or apps[tw] or “social media”[tw] or twitter[tw] or facebook[tw] or tiktok[tw] or instagram[tw] or Weibo[tw] or youtube[tw] or telegram[tw] or Whatsapp[tw] or Tumblr[tw] or Pinterest[tw] or snapchat[tw] or wechat[tw] or reddit[tw] or myspace[tw] or computer*[tw] or smartphone*[tw] or chat[tw] or blog*[tw] or game[tw] or gaming[tw] or games[tw] or gamification[tw] or weblog*[tw] or online[tw] or web-based[tw] or electronic[tw] or ehealth[tw] or e-health[tw] or “electronic health”[tw] or mhealth[tw] or m-health[tw] or “mobile health”[tw] or “artificial intelligence”[tw] or ai[tw] or “machine learning”[tw] or “deep learning”[tw] or chatbot[tw] or “chat bot”[tw] or chatgpt[tw])) AND ((“Vaccines”[Mesh] or “Vaccination”[Mesh]) or (vaccin*[tw] or immuniz*[tw] or immunis*[tw] or anti-vax*[tw] or antivax*[tw] or “anti vax”[tw] or anti-vaccin*[tw])) AND (English[Filter]

Textbox 2. Proposed elements of data extraction by review question.

Study information: In a table of included studies, we will summarize study dates, publication information, study setting, participants, study designs, and objectives.

RQ1: We will summarize different elements involved in narrative communication across a range of contexts. Our analysis will include how individuals engage with interactive digital health interventions or modalities, examining the various modes of interaction and their impact on the overall narrative experience. The outcome of the narratives, examining factors such as their congruence with individuals’ personal values, their memorability, perceived realism, and other relevant elements will be described. Theories and frameworks used in the included studies such as Schank and Berman categorization of narratives (official, invented, first-hand experiential, second-hand, and culturally common), or other pertinent theoretical frameworks will be analyzed [14]. Furthermore, we will provide insights into the available evidence by vaccine type, whether the emphasis is solely on vaccination, and whether the vaccines are integrated with other health interventions.

RQ2: All elements described for RQ1, and evidence of impact on the uptake of vaccines, specifically examining whether individuals were vaccinated or not after being exposed to interactive narrative-based digital health interventions for vaccine communication. We will also review studies that have evaluated vaccination intention, which relates to individuals’ expressed willingness or plans to get vaccinated.

RQ3: We will include all elements described in RQ1, along with the implementation outcomes related to the use of narrative-based digital health interventions for vaccine communication. These implementation outcomes include outcomes such as acceptability, adoption, cost, reach, usability, sustainability, and others. Additionally, we aim to identify studies that report on the barriers and facilitators associated with implementing interactive narrative-based digital health interventions for vaccine communication. By examining these factors, we seek to gain a comprehensive understanding of the feasibility and implementation of utilizing such interventions for vaccine communication efforts.

Data Analysis

Review findings will be communicated through a PRISMA (Preferred Reporting Items for Systematic Reviews) flowchart, tables, figures containing descriptive statistics, and narrative summaries corresponding to our research questions. Research findings will be published in a peer-reviewed academic journal and presented in scientific conference presentations in the forthcoming months.

Ethical Considerations

Since the review used published journal articles exclusively, an ethical board review board was not necessary to conduct this review.

Results

The detailed search string was implemented in the proposed databases searching for publications from inception until April 18, 2023. The search results (n=6836 records) were imported into EndNote Software (version 20; Clarivate) for the removal of duplicate records, and deduplicated records (n=4676) were uploaded to Covidence review management software for eligibility screening. Title and abstract screening is ongoing as of December 29, 2023. We anticipate the scoping review findings to be published in 2024.

Discussion

Principal Findings

Prior systematic and scoping reviews in the realm of vaccine communication have evaluated various interventions such as behavioral nudges [13] and dialogue-based communication interventions [21]. However, none of these reviews have specifically evaluated the effects of interactive narrative–based digital health interventions for vaccine communication. This scoping review aims to identify and synthesize relevant studies that describe interactive narrative–based digital health interventions tailored specifically for vaccine communication. Our primary goal is to synthesize empirical evidence on the ways these interventions are used, implemented, and evaluated and highlight gaps to inform future research and implementation.

Implications for Research and Practice

The study findings may help researchers and public health practitioners understand how interactive narrative–based digital health interventions have been used to promote vaccinations and add context or perspective that may be missing from traditional messaging campaigns [2,5]. The findings from the scoping review may guide the future development of interactive narrative–based digital health interventions for vaccine communication and identify interventions for further evidence synthesis. Additionally, the review may highlight implementation outcomes linked to these interventions or successful components within them. Through a comprehensive synthesis of existing literature, the review may reveal effective strategies, challenges, and gaps in previously developed interventions. Furthermore, the review has the potential to stimulate new research questions or hypotheses aimed at addressing these gaps, thereby contributing to the dynamic landscape of vaccine communication.

Narratives are often exploited in the spread of vaccine misinformation. While the proliferation of digital devices such as mobile phones and tablets has enabled widespread reach of information through communication channels such as social media, they have also helped the spread of misinformation, thereby affecting the public's confidence around vaccination [22]. Hence, review findings may also inform the use of interactive digital health interventions to combat vaccine misinformation.

Strengths and Limitations

The strength of our study lies in its inclusive research approach, encompassing all populations, vaccine types, narratives, and digital health interventions, potentially capturing a diverse array of use cases for interactive narrative–based digital health interventions. However, several potential limitations exist with our approach. First, our reliance on peer-reviewed journal articles might lead us to overlook relevant interventions described in the gray literature. Second, our search strategy does not include the term "interaction," which necessitates researchers' interpretation of interactivity during title and abstract screening. Finally, this being a scoping review, we do not plan to appraise the studies for risk of bias, and our conclusions may have limitations as we are not accounting for potential biases in the included studies.

Conclusions

In this scoping review, we will summarize the use of interactive narrative–based digital health interventions for vaccine communication. To our knowledge, this study will be the first to investigate the interactive features of these interventions and their impact on vaccine communication. Our study aims to illuminate the prevailing gaps in knowledge and provide an overview of the present research landscape. Furthermore, review findings may provide insights for public health practitioners and researchers, laying the groundwork for future studies and applications using interactive narratives for vaccine communication. Review findings may also be of relevance to vaccine communication researchers and global vaccination programs, enabling them to consider novel applications of interactive narrative–based digital health interventions in future initiatives for vaccine communication.

Acknowledgments

The authors extend their gratitude to Hannah Rogers, MLS (Public Health Informationist, Woodruff Health Sciences Center Library, Emory University) for her invaluable assistance in crafting the search strategy and identifying relevant databases relevant to the review objective.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist.
[PDF File (Adobe PDF File), 94 KB - resprot_v13i1e51137_app1.pdf]

References

1. Immunization. World Health Organization. 2019. URL: https://www.who.int/news-room/facts-in-pictures/detail/immunization [accessed 2023-05-12]
2. MacDonald NE, SAGE Working Group on Vaccine Hesitancy. Vaccine hesitancy: definition, scope and determinants. Vaccine 2015;33(34):4161-4164 [FREE Full text] [doi: 10.1016/j.vaccine.2015.04.036] [Medline: 25896383]
3. de Figueiredo A, Simas C, Karafillakis E, Paterson P, Larson HJ. Mapping global trends in vaccine confidence and investigating barriers to vaccine uptake: a large-scale retrospective temporal modelling study. Lancet 2020;396(10255):898-908 [FREE Full text] [doi: 10.1016/S0140-6736(20)31558-0] [Medline: 32919524]
4. Vasudevan L, Baumgartner JN, Moses S, Ngadaya E, Mfinanga SG, Ostermann J. Parental concerns and uptake of childhood vaccines in rural Tanzania—a mixed methods study. BMC Public Health 2020;20(1):1573 [FREE Full text] [doi: 10.1186/s12889-020-09598-1] [Medline: 33081744]
5. Goldstein S, MacDonald NE, Guirguis S, SAGE Working Group on Vaccine Hesitancy. Health communication and vaccine hesitancy. Vaccine 2015;33(34):4212-4214 [FREE Full text] [doi: 10.1016/j.vaccine.2015.04.042] [Medline: 25896382]
6. Jarrett C, Wilson R, O'Leary M, Eckersberger E, Larson HJ, SAGE Working Group on Vaccine Hesitancy. Strategies for addressing vaccine hesitancy—a systematic review. Vaccine 2015;33(34):4180-4190 [FREE Full text] [doi: 10.1016/j.vaccine.2015.04.040] [Medline: 25896377]
7. Hinyard LJ, Kreuter MW. Using narrative communication as a tool for health behavior change: a conceptual, theoretical, and empirical overview. Health Educ Behav 2007;34(5):777-792. [doi: 10.1177/1090198106291963] [Medline: 17200094]
8. Bekalu MA, Bigman CA, McCloud RF, Lin LK, Viswanath K. The relative persuasiveness of narrative versus non-narrative health messages in public health emergency communication: evidence from a field experiment. Prev Med 2018;111:284-290 [FREE Full text] [doi: 10.1016/j.ypmed.2017.11.014] [Medline: 29154794]
9. Winskell K, Sabben G, Obong'o C. Interactive narrative in a mobile health behavioral intervention (Tumaini): theoretical grounding and structure of a smartphone game to prevent HIV among young Africans. JMIR Serious Games 2019;7(2):e13037 [FREE Full text] [doi: 10.2196/13037] [Medline: 31066692]
10. Stoner MCD, Tweedy D, Comello MGL, Toval C, Pettifor AE, Larsen MA, et al. Using narratives to inform the development of a digital health intervention related to COVID-19 vaccination in Black young adults in Georgia, North Carolina and Alabama. Vaccine 2022;40(48):6908-6916 [FREE Full text] [doi: 10.1016/j.vaccine.2022.10.027] [Medline: 36280559]
11. Dudley MZ, Squires GK, Petroske TM, Dawson S, Brewer J. The use of narrative in science and health communication: a scoping review. Patient Educ Couns 2023;112:107752. [doi: 10.1016/j.pec.2023.107752] [Medline: 37068426]
12. McCall B, Shallcross L, Wilson M, Fuller C, Hayward A. Storytelling as a research tool used to explore insights and as an intervention in public health: a systematic narrative review. Int J Public Health 2021;66:1604262 [FREE Full text] [doi: 10.3389/ijph.2021.1604262] [Medline: 34795554]
13. Reñosa MDC, Landicho J, Wachinger J, Dalglish SL, Bärnighausen K, Bärnighausen T, et al. Nudging toward vaccination: a systematic review. BMJ Glob Health 2021;6(9):e006237 [FREE Full text] [doi: 10.1136/bmjgh-2021-006237] [Medline: 34593513]
14. Schank RC, Berman TR. The pervasive role of stories in knowledge and action. In: Green MC, Strange JJ, Brock TC, editors. Narrative Impact: Social and Cognitive Foundations. New Jersey: Lawrence Erlbaum Associates Publishers; 2002:287-313.
15. WHO guideline: recommendations on digital interventions for health system strengthening. World Health Organization. 2019. URL: https://www.who.int/publications/i/item/9789241550505 [accessed 2024-01-12]
16. Cascini F, Pantovic A, Al-Ajlouni YA, Failla G, Puleo V, Melnyk A, et al. Social media and attitudes towards a COVID-19 vaccination: a systematic review of the literature. EClinicalMedicine 2022;48:101454 [FREE Full text] [doi: 10.1016/j.eclinm.2022.101454] [Medline: 35611343]
17. Classification of digital health interventions v1.0. World Health Organization. 2018. URL: https://apps.who.int/iris/bitstream/handle/10665/260480/WHO-RHR-18.06-eng.pdf [accessed 2024-01-12]
18. Sheehan J, Laver K, Bhopti A, Rahja M, Usherwood T, Clemson L, et al. Methods and effectiveness of communication between hospital allied health and primary care practitioners: a systematic narrative review. J Multidiscip Healthc 2021;14:493-511 [FREE Full text] [doi: 10.2147/JMDH.S295549] [Medline: 33654406]
19. PRISMA for systematic review protocols (PRISMA-P). PRISMA. 2015. URL: http://www.prisma-statement.org/Extensions/ScopingReviews [accessed 2024-01-12]
20. Park E, Forhan M, Jones CA. The use of digital storytelling of patients' stories as an approach to translating knowledge: a scoping review. Res Involv Engagem 2021;7(1):58 [FREE Full text] [doi: 10.1186/s40900-021-00305-x] [Medline: 34454604]

21. Karras J, Dubé E, Danchin M, Kaufman J, Seale H. A scoping review examining the availability of dialogue-based resources to support healthcare providers engagement with vaccine hesitant individuals. Vaccine 2019;37(44):6594-6600. [doi: 10.1016/j.vaccine.2019.09.039] [Medline: 31540811]
22. Wilson SL, Wiysonge C. Social media and vaccine hesitancy. BMJ Glob Health 2020;5(10):e004206 [FREE Full text] [doi: 10.1136/bmjgh-2020-004206] [Medline: 33097547]

Abbreviations

MeSH: Medical Subject Headings
PRISMA: Preferred Reporting Items for Systematic Reviews
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
RQ: research question

Edited by A Mavragani; submitted 22.07.23; peer-reviewed by W Evans, I Ballalai, A Ahmed; comments to author 22.11.23; revised version received 29.12.23; accepted 02.01.24; published 09.02.24.

Please cite as:
Haji Said A, Winskell K, Bednarczyk RA, Reardon EE, Vasudevan L
Interactive Narrative–Based Digital Health Interventions for Vaccine Communication: Protocol for a Scoping Review
JMIR Res Protoc 2024;13:e51137
URL: https://www.researchprotocols.org/2024/1/e51137
doi:10.2196/51137
PMID:38335024

Protocol

Simultaneous Cardiopulmonary Exercise Testing and Echocardiography for Investigation of Cardiopulmonary Dysfunction in Outpatients: Protocol for a Scoping Review

Benjamin Gerhardy[1,2,3], MBBS, MPHTM, FRACP, DDU; Shanthosh Sivapathan[2,3], MBBS, FRACP, MPH; Sam Orde[2,3], MBBS, FCICM, DDU, FASE, PhD; Lucy Morgan[1,3,4], MBBS, FRACP, PhD

[1]Department of Respiratory Medicine, Nepean Hospital, Kingswood, Australia

[2]Department of Intensive Care Medicine, Nepean Hospital, Kingswood, Australia

[3]Faculty of Medicine and Health Sciences, University of Sydney, Kingswood, Australia

[4]Department of Respiratory Medicine, Concord Repatriation General Hospital, Concord, Australia

Corresponding Author:
Benjamin Gerhardy, MBBS, MPHTM, FRACP, DDU
Department of Respiratory Medicine
Nepean Hospital
Derby Street
Kingswood
Australia
Phone: 61 47342000
Email: benjamin.gerhardy@health.nsw.gov.au

Abstract

Background: Cardiopulmonary dysfunction is a complex process with a broad range of etiologies. Investigations performed either at rest or those that only assess the function of a single organ (heart or lungs) are often insufficient. A simultaneous cardiopulmonary exercise test with stress echocardiography is a new approach to assessing cardiopulmonary dysfunction as it provides anatomical and functional imaging simultaneously while under increasing stress. To date, the application of cardiopulmonary exercise test-stress echocardiography (CPET-SE) has been broad and without structure, and its effect on patient outcomes is unclear.

Objective: The objective of this scoping review is to explore and analyze the evidence regarding the role of simultaneous CPET-SE in investigating cardiopulmonary dysfunction in outpatients. It will include any published study in which adult (older than or equal to 18 years of age) patients have completed a CPET-SE for the investigation of cardiopulmonary dysfunction.

Methods: This review will follow the Arksey and O'Malley framework, supported by the Joanna Briggs Institute methodology for scoping reviews. It will use the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) checklist. Data sources will include MEDLINE, Scopus, Embase, and Cochrane (including reviews, trials, and protocols) electronic databases, with no date range defined. The search will be limited to the English language with no restrictions regarding pathology. Secondary references of the included sources will also be assessed by a hand search for suitability. A 2-person title-abstract screen and data charting process will be used. Independent experts will be used for consultation including an academic librarian and clinicians. The Covidence software will be used for article screening.

Results: This scoping review will provide a unified and detailed description of the applications of CPET-SE in investigating cardiopulmonary dysfunction. This will provide a platform for future research harnessing this investigatory method. The results will be presented in both tabular and graphical formats to ensure clarity. The results of this scoping review will be submitted to a relevant peer-reviewed academic journal for publication.

Conclusions: The CPET-SE is a powerful tool for investigating cardiopulmonary dysfunction but remains in its infancy with a patchwork approach to indications, data reporting, and interpretation. This scoping review will unify the literature and provide a platform for future researchers and the development of a comprehensive application guideline.

Trial Registration: Open Science Framework; https://osf.io/98r3e

International Registered Report Identifier (IRRID): PRR1-10.2196/52076

(JMIR Res Protoc 2024;13:e52076) doi:10.2196/52076

KEYWORDS

cardiopulmonary; echocardiography; exercise; cardiopulmonary exercise test

Introduction

Cardiopulmonary dysfunction is the loss of the normal bidirectional functional relationship that exists between the heart and the lungs [1,2]. It can range in severity from subclinical (and only manifesting under stress) to fatal, with a timeline that can be acute, chronic, or acute on chronic. Cardiopulmonary dysfunction can be the consequence of single-organ (heart or lung) disease, systemic disease (eg, sepsis) [3,4], or iatrogenic (eg, medications or mechanical ventilation) [5,6].

The investigation of cardiopulmonary dysfunction requires an assessment of the complex heart-lung relationship. The 2 primary interfaces where these organs interact are the right heart-pulmonary circulation relationship (often referred to as "coupling") and the alveolus-pulmonary capillary relationship [7]. Coupling denotes the relationship between the pulsatile pump of the right ventricle and its opposing arterial vascular load (ie, pulmonary arterial circulation) [8]. As one component of this relationship changes (eg, the increase in arterial stiffness seen in aging due to loss of vessel elasticity) [9], the other responds (eg, with ventricular remodeling) to maintain normal coupling, giving optimal cardiac mechanics and cardiopulmonary efficiency at rest [10].

The alveolus-pulmonary capillary relationship has pressure as its currency. In the healthy upright lung, the majority of ventilation and perfusion occurs at the lung base, where both the pulmonary arterial and pulmonary venous pressures exceed the alveolar gas pressure (West zone 3) [11]. This facilitates constant blood flow past the alveolus giving uninterrupted gas exchange—in normal physiological conditions the alveolar pressure does not affect blood flow through the pulmonary circulation [11,12]. Lung hyperinflation can cause compression of the alveolar vessels leading to raised pulmonary vascular pressures, an increase in pulmonary blood transit time, myocardial hypoperfusion, and biventricular systolic dysfunction [13-16]. If there is concurrent right heart dysfunction, there may also be reduced pulmonary vascular blood flow, further worsening this process [15]. Patients with airway disease have a predilection for progressive (dynamic) hyperinflation during exercise, a condition characterized by increasing end-expiratory lung volume. This increase in volume within the fixed thoracic cage leads to an increase in the intra-alveolar pressure, with higher degrees of dynamic hyperinflation related to a poorer cardiac output during the activity [17].

In the outpatient setting, the investigation of cardiopulmonary dysfunction often involves a series of single-organ assessment tools such as computed tomography imaging of the lung, complex lung function testing, and transthoracic echocardiography. These single-organ, static investigations provide little insight into cardiopulmonary performance when under physiological (eg, exercise) or pathological (eg, sepsis) stress [18,19]. Current commonly used functional testing modalities such as stress echocardiography can provide additional information and have a role in the investigation of specific conditions in patients with the appropriate pretest probability—for example, assessing for coronary artery disease in patients with anginal symptoms [5]. However, this test is not capable of assessing the intricacies of cardiopulmonary dysfunction. A cardiopulmonary exercise test (CPET) provides integrative information about cardiac, respiratory, and metabolic responses to exercise and is considered the gold standard in the integrative assessment of cardiorespiratory function [20]. Peak oxygen consumption (VO2peak) measured by CPET is the key measure of cardiopulmonary fitness [21], has a stronger relationship with all-cause mortality than many common chronic diseases [22], and can be improved with low-burden lifestyle interventions [23]. Despite this, CPET also has limitations, most notably that it provides no anatomical information about cardiac function under an increasing workload. As a result, conditions with significant prognostic implications including exercise-induced pulmonary hypertension [24] or exercise-induced diastolic function [25] may go unnoticed.

Recently the combination of cardiopulmonary exercise test-stress echocardiography (CPET-SE) has been used to explore cardiopulmonary dysfunction. Studies have explored the role of CPET-SE in exploring conditions such as dyspnea [26], heart failure [27,28], contractile reserve [29], and left atrial dysfunction [30]. While the application is broad, the indications for this test combination remain undefined, and there is no consensus regarding the optimal protocol for the exercise and imaging components. Similarly, any additional prognostic benefits over traditional testing are undefined.

Given the complexity involved in investigating cardiopulmonary dysfunction, the breadth of applications for CPET-SE, and the lack of standardization for the test, we propose a scoping review to assess the literature surrounding the use of CPET-SE in investigating cardiopulmonary dysfunction in the outpatient setting. This will include an exploration of its impact on shaping the diagnostic and management processes of cardiopulmonary dysfunction. This scoping review will provide shape to the literature regarding this combined testing modality and provide an evidence base for future research.

A preliminary search of MEDLINE, the Cochrane Database of Systematic Reviews, and Joanna Briggs Institute (JBI) Evidence Synthesis was conducted and no current or underway systematic reviews or scoping reviews on the topic were identified.

Methods

Overview

This scoping review will be conducted in accordance with the JBI methodology for scoping reviews [31], based on earlier work from Arksey and O'Malley [32]. It will follow the process of (1) identifying the research question; (2) identifying the

relevant studies; (3) defining criteria for study inclusion; (4) data charting; (5) collation, summarizing, and reporting of results; and (6) peer feedback [29]. The PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) [33] checklist will be followed.

Identification of the Research Question

The primary question of this scoping review is "What is the role of simultaneous cardiopulmonary exercise testing and echocardiography in investigating adult outpatients with symptoms of cardiopulmonary dysfunction?" Associated subquestions for this review are "What are the primary pathologies in which simultaneous cardiopulmonary exercise testing and echocardiography has been used?" and "Is there any evidence that CPET-SE provides additional diagnostic benefit over traditional testing?"

Identification of the Relevant Studies

Overview

The Population, Concept, Context (PCC) framework was used to scaffold the main components of the research question.

Population, Concept, and Context

Population and concept have been combined in this scoping review as they are interlinked, that is, it is inclusive of all patients undergoing this particular combined investigatory modality.

All studies involving patients aged 18 years or older with either known cardiopulmonary disease or symptoms suggestive of cardiopulmonary dysfunction who underwent a simultaneous transthoracic echocardiogram and CPET will be included. There will be no limitations regarding specific disease states or symptom burden.

To best capture the potential breadth of the literature, all studies involving simultaneous echocardiography and cardiopulmonary exercise testing will be included. The minimum data set required for the CPET is continuous gas exchange data, continuous cardiac monitoring, and either a stationary bike or treadmill ergometer. This is in line with accepted clinical practice [34].

The outcomes of interest are the range of contexts in which the combined investigation technique has been applied and the overall assessment of its use in providing clinically relevant information.

Sources

This scoping review will consider the following study designs: randomized and nonrandomized controlled trials, observational studies (retrospective and prospective), and descriptive studies including case series and reports. Systematic reviews that meet the inclusion criteria will also be included.

A hand search of all studies included in the final review will be performed to identify additional literature that may not have been uncovered in the initial database search. Published abstracts and conference proceedings will be considered if they meet the inclusion criteria. Consideration will also be given to grey literature (including expert opinion pieces) if they contain sufficient detail to meet the inclusion criteria. Such data will be identified through discussion with an existing local and international network of experts in the field.

Study or Source of Evidence Selection

All identified citations will be collated via the online software Covidence [35]. EndNote (version 20.3; Clarivate Analytics) will be used as the reference management software. The title and abstract screening will be performed by 2 independent reviewers to determine relevance and suitability using the inclusion criteria.

Studies identified as relevant will undergo full-text assessment by 2 independent reviewers. Appropriate studies will undergo data extraction. Studies deemed inappropriate will have the rationale for such recorded and reported in the scoping review.

Disagreements at either title-abstract or full-text screening will be resolved through the use of a third independent reviewer. The results of the search and the study inclusion process will be reported in full in the final scoping review and presented in a PRISMA-ScR flow diagram [33].

Study Inclusion Criteria

The search strategy will be constructed with assistance from an experienced academic librarian. An initial limited search of MEDLINE and Scopus was performed to identify relevant keywords from titles and abstracts. These index terms were used to develop the complete search strategy for MEDLINE, Scopus, Embase, and the Cochrane Library (including reviews, protocols, and trials; see Multimedia Appendix 1). The search strategy, including all identified keywords and index terms, will be adapted for each included database and information source. The search strategy deliberately does not reference inpatient or outpatient to ensure that the search results have an appropriate breadth. Only studies published in English will be included. No date restrictions are in place, that is, the databases will be searched from inception to the search date.

Data Charting

Data extraction will be performed by 2 independent reviewers using a customized data extraction tool based on the JBI template [31] (see Multimedia Appendix 2 for the draft data extraction tool). This tool will be piloted using the first 10% of the included full-text studies. After this period the tool will be reevaluated and modified as appropriate to ensure collection of all relevant data. If necessary, this modified (final) data extraction tool will be used for all included full-text studies including the cohort used in the pilot.

Any disagreements with the data charting process will be resolved through discussion, or where necessary, by a third independent reviewer. Where there is missing data, the authors of the original manuscripts will be contacted for additional data or clarification. A critical appraisal of the articles included in the full-text analysis will not be performed.

Result in Collation, Summary, and Reporting

The PRISMA-ScR [33] checklist will be used to guide collation and reporting. The extracted data will be presented predominately in tabular format, in line with the data extraction tool and the review questions of this scoping review (Multimedia

Appendix 3). It is expected that some data (specifically diagnostic categories and symptom burden) will also be presented diagrammatically to aid clarity. A narrative summary will accompany the tabulated results and will describe how the results relate to the objective and research questions of this scoping review.

Validation, Consultation, and Feedback

Local experts on echocardiography, cardiopulmonary disease, and exercise testing not involved in the authorship of this protocol will be consulted at specific points in this process, including during stages 3 and 5. An academic librarian will be used during stage 2 to ensure the search is thorough and relevant.

Ethical Considerations

Ethics approval has not been sought for this review as data are being collected from published literature.

Results

This scoping review is expected to yield results by late 2023 or early 2024. These results will be presented within the local hospital network by the authorship group to inform current clinical practice and provide an evidence base for future studies using this combined modality. The results of this scoping review will also be presented in article format and submitted for publication in a relevant peer-reviewed journal.

Discussion

Principal Findings

We seek to explore the application and outcomes of a combination of CPET-SE in clinical practice. To the best of our knowledge, this is the first exploratory review on this subject and will be a comprehensive description of the literature.

Advanced functional testing (including CPET) provides data that are more representative of an individual's ability to tolerate a stressor (eg, surgery) or it can induce the symptom (eg, exercise intolerance) of a patient while simultaneously capturing a comprehensive data set for thorough investigation. Combining this with real-time imaging such as echocardiography adds another layer of information [26,27]. Individually there are international guidelines for these tests [20,36,37], but how to best combine them is not clear.

There are significant potential advantages with the CPET-SE; however, the literature appears heterogeneous across testing or acquisition protocols and inconsistent in reporting results making interpretation challenging for clinicians. This scoping review can serve as part of the groundwork required for future guidelines regarding simultaneous CPET-SE.

Strengths of this protocol include the use of a structured, multi-database literature search with few constraints; the use of an established scoping review framework; and the use of independent expert consultation throughout the process.

Limitations

There are 2 primary limitations to this scoping review. The first is the risk of missing relevant studies in the search steps. Multiple databases relevant to medical literature are being included, and the search terms include both whole words and conventional acronyms for CPET, there is a risk that there are additional acronyms or abbreviations used internationally that are unknown to the authors of the scoping review and therefore the literature may be missed. Limiting search results to articles published in English is the second limitation.

Conclusions

The role of exercise testing in clinical practice is expanding, and with this expansion comes novel testing regimens such as CPET-SE. By providing a summary of the application of combined CPET and echocardiography in current practice we will have the base from which a unified, comprehensive, and standardized testing approach can be proposed including indications, testing procedures, and reporting protocols. This will benefit clinicians (by providing an evidence base on which they can structure their testing), researchers (by giving a degree of data homogeneity and allowing more rigorous statistical analysis), and ultimately patients.

Acknowledgments

The authors acknowledge the University of Sydney library staff (Tess Aitken) for their assistance in search planning and preparation. The authors acknowledge the Nepean and Blue Mountains Local Health District, and Nepean Hospital for their support of the project.

Data Availability

Data sharing is not applicable to this study as no data sets were generated or analyzed during this study.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[DOCX File , 13 KB - resprot_v13i1e52076_app1.docx]

Multimedia Appendix 2
Data extraction instrument.
[DOCX File , 15 KB - resprot_v13i1e52076_app2.docx]

Multimedia Appendix 3
Data presentation instrument.
[DOCX File , 14 KB - resprot_v13i1e52076_app3.docx]

References

1. Sunagawa K, Sagawa K, Maughan WL. Ventricular interaction with the loading system. Ann Biomed Eng 1984;12(2):163-189. [doi: 10.1007/BF02584229] [Medline: 6507965]
2. Pinsky MR. Cardiopulmonary interactions: physiologic basis and clinical applications. Ann Am Thorac Soc 2018 Feb;15(Suppl 1):S45-S48 [FREE Full text] [doi: 10.1513/AnnalsATS.201704-339FR] [Medline: 28820609]
3. Hollenberg SM, Singer M. Pathophysiology of sepsis-induced cardiomyopathy. Nat Rev Cardiol 2021 Jun;18(6):424-434. [doi: 10.1038/s41569-020-00492-2] [Medline: 33473203]
4. Jarczak D, Kluge S, Nierhaus A. Sepsis-pathophysiology and therapeutic concepts. Front Med (Lausanne) 2021;8:628302 [FREE Full text] [doi: 10.3389/fmed.2021.628302] [Medline: 34055825]
5. Pellikka PA, Arruda-Olson A, Chaudhry FA, Chen MH, Marshall JE, Porter TR, et al. Guidelines for performance, interpretation, and application of stress echocardiography in ischemic heart disease: from the American Society of Echocardiography. J Am Soc Echocardiogr 2020 Jan;33(1):1-41.e8 [FREE Full text] [doi: 10.1016/j.echo.2019.07.001] [Medline: 31740370]
6. Bistola V, Arfaras-Melainis A, Polyzogopoulou E, Ikonomidis I, Parissis J. Inotropes in acute heart failure: from guidelines to practical use: therapeutic options and clinical practice. Card Fail Rev 2019 Nov;5(3):133-139 [FREE Full text] [doi: 10.15420/cfr.2019.11.2] [Medline: 31768269]
7. Forfia PR, Vaidya A, Wiegers SE. Pulmonary heart disease: the heart-lung interaction and its impact on patient phenotypes. Pulm Circ 2013 Jan;3(1):5-19 [FREE Full text] [doi: 10.4103/2045-8932.109910] [Medline: 23662171]
8. Monge García MI, Santos A. Understanding ventriculo-arterial coupling. Ann Transl Med 2020 Jun;8(12):795 [FREE Full text] [doi: 10.21037/atm.2020.04.10] [Medline: 32647720]
9. Sun Z. Aging, arterial stiffness, and hypertension. Hypertension 2015 Feb;65(2):252-256 [FREE Full text] [doi: 10.1161/HYPERTENSIONAHA.114.03617] [Medline: 25368028]
10. Chantler PD, Lakatta EG. Arterial-ventricular coupling with aging and disease. Front Physiol 2012;3:90 [FREE Full text] [doi: 10.3389/fphys.2012.00090] [Medline: 22586401]
11. West JB, Dollery CT, Naimark A. Distribution of blood flow in isolated lung; relation to vascular and alveolar pressures. J Appl Physiol 1964;19(4):713-724 [FREE Full text] [doi: 10.1152/jappl.1964.19.4.713] [Medline: 14195584]
12. Hughes JM, Glazier JB, Maloney JE, West JB. Effect of lung volume on the distribution of pulmonary blood flow in man. Respir Physiol 1968;4(1):58-72. [doi: 10.1016/0034-5687(68)90007-8] [Medline: 5639524]
13. Kyhl K, Drvis I, Barak O, Mijacika T, Engstrøm T, Secher NH, et al. Organ perfusion during voluntary pulmonary hyperinflation; a magnetic resonance imaging study. Am J Physiol Heart Circ Physiol 2016;310(3):H444-H451 [FREE Full text] [doi: 10.1152/ajpheart.00739.2015] [Medline: 26589331]
14. Eichinger M, Walterspacher S, Scholz T, Tetzlaff R, Puderbach M, Tetzlaff K, et al. Glossopharyngeal insufflation and pulmonary hemodynamics in elite breath hold divers. Med Sci Sports Exerc 2010;42(9):1688-1695 [FREE Full text] [doi: 10.1249/MSS.0b013e3181d85dc3] [Medline: 20195178]
15. Mijacika T, Kyhl K, Frestad D, Barak FO, Drvis I, Secher NH, et al. Effect of pulmonary hyperinflation on central blood volume: an MRI study. Respir Physiol Neurobiol 2017;243:92-96. [doi: 10.1016/j.resp.2017.05.012] [Medline: 28583413]
16. Jörgensen K, Müller MF, Nel J, Upton RN, Houltz E, Ricksten SE. Reduced intrathoracic blood volume and left and right ventricular dimensions in patients with severe emphysema: an MRI study. Chest 2007;131(4):1050-1057. [doi: 10.1378/chest.06-2245] [Medline: 17426209]
17. Galera R, Casitas R, Martínez-Cerón E, Rodríguez-Fraga O, Utrilla C, Torres I, et al. Effect of dynamic hyperinflation on cardiac response to exercise of patients with chronic obstructive pulmonary disease. Arch Bronconeumol (Engl Ed) 2021;57(6):406-414 [FREE Full text] [doi: 10.1016/j.arbr.2020.09.008] [Medline: 34088392]
18. Franciosa JA, Park M, Levine TB. Lack of correlation between exercise capacity and indexes of resting left ventricular performance in heart failure. Am J Cardiol 1981;47(1):33-39. [doi: 10.1016/0002-9149(81)90286-1] [Medline: 7457405]
19. Lipkin DP. The role of exercise testing in chronic heart failure. Br Heart J 1987;58(6):559-566 [FREE Full text] [doi: 10.1136/hrt.58.6.559] [Medline: 3322350]
20. American Thoracic Society, American College of Chest Physicians. ATS/ACCP statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med 2003;167(2):211-277 [FREE Full text] [doi: 10.1164/rccm.167.2.211] [Medline: 12524257]

21. Balady GJ, Arena R, Sietsema K, Myers J, Coke L, Fletcher GF, et al. Clinician's guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. Circulation 2010;122(2):191-225 [FREE Full text] [doi: 10.1161/CIR.0b013e3181e52e69] [Medline: 20585013]
22. Kokkinos P, Faselis C, Samuel IBH, Pittaras A, Doumas M, Murphy R, et al. Cardiorespiratory fitness and mortality risk across the spectra of age, race, and sex. J Am Coll Cardiol 2022;80(6):598-609 [FREE Full text] [doi: 10.1016/j.jacc.2022.05.031] [Medline: 35926933]
23. Hayıroğlu MI, Çınar T, Hayıroğlu SC, Şaylık F, Uzun M, Tekkeşin AI. The role of smart devices and mobile application on the change in peak VO2 in patients with high cardiovascular risk: a sub-study of the LIGHT randomised clinical trial. Acta Cardiol 2023;78(9):1000-1005. [doi: 10.1080/00015385.2023.2223005] [Medline: 37318090]
24. Ho JE, Zern EK, Lau ES, Wooster L, Bailey CS, Cunningham T, et al. Exercise pulmonary hypertension predicts clinical outcomes in patients with dyspnea on effort. J Am Coll Cardiol 2020;75(1):17-26 [FREE Full text] [doi: 10.1016/j.jacc.2019.10.048] [Medline: 31918830]
25. Sud K, Bhatia KS, Vogel B, Bohra C, Argulian E. Prognostic significance of exercise-induced diastolic dysfunction: a systematic review. Echocardiography 2020;37(10):1594-1602. [doi: 10.1111/echo.14841] [Medline: 32892393]
26. Verwerft J, Bertrand PB, Claessen G, Herbots L, Verbrugge FH. Cardiopulmonary exercise testing with simultaneous echocardiography: blueprints of a dyspnea clinic for suspected HFpEF. JACC Heart Fail 2023;11(2):243-249. [doi: 10.1016/j.jchf.2022.11.004] [Medline: 36754531]
27. Pugliese NR, Fabiani I, Santini C, Rovai I, Pedrinelli R, Natali A, et al. Value of combined cardiopulmonary and echocardiography stress test to characterize the haemodynamic and metabolic responses of patients with heart failure and mid-range ejection fraction. Eur Heart J Cardiovasc Imaging 2019;20(7):828-836 [FREE Full text] [doi: 10.1093/ehjci/jez014] [Medline: 30753369]
28. Borghi-Silva A, Labate V, Arena R, Bandera F, Generati G, Pellegrino M, et al. Exercise ventilatory power in heart failure patients: functional phenotypes definition by combining cardiopulmonary exercise testing with stress echocardiography. Int J Cardiol 2014;176(3):1348-1349. [doi: 10.1016/j.ijcard.2014.07.268] [Medline: 25135333]
29. Moneghetti KJ, Kobayashi Y, Christle JW, Ariyama M, Vrtovec B, Kouznetsova T, et al. Contractile reserve and cardiopulmonary exercise parameters in patients with dilated cardiomyopathy, the two dimensions of exercise testing. Echocardiography 2017;34(8):1179-1186. [doi: 10.1111/echo.13623] [Medline: 28681553]
30. Sugimoto T, Bandera F, Generati G, Alfonzetti E, Barletta M, Losito M, et al. Left atrial dynamics during exercise in mitral regurgitation of primary and secondary origin: pathophysiological insights by exercise echocardiography combined with gas exchange analysis. JACC Cardiovasc Imaging 2020;13(1 Pt 1):25-40 [FREE Full text] [doi: 10.1016/j.jcmg.2018.12.031] [Medline: 30878440]
31. Peters MDJ, Godfrey C, McInerney P, Munn Z, Tricco AC, Khalil H. Chapter 11: scoping reviews (2020 version). In: Aromataris E, Munn Z, editors. JBI Manual for Evidence Synthesis. Adelaide, Australia: Joanna Briggs Institute; 2020.
32. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. Int J Soc Res Methodol 2005;8(1):19-32. [doi: 10.1080/1364557032000119616]
33. McGowan J, Straus S, Moher D, Langlois EV, O'Brien KK, Horsley T, et al. Reporting scoping reviews-PRISMA ScR extension. J Clin Epidemiol 2020;123:177-179. [doi: 10.1016/j.jclinepi.2020.03.016] [Medline: 32229248]
34. Sietsema KE, Stringer WW, Sue DY, Ward S. In: Sietsema KE, Stringer WW, Sue DY, Ward S, Rossiter HB, Porszasz J, editors. Wasserman & Whipp's: Principles of Exercise Testing and Interpretation: Including Pathophysiology and Clinical Applications, 6th Edition. Alphen aan den Rijn, Netherlands: Wolters Kluwer Health; 2020.
35. Covidence Systematic Review Software. Melbourne, Australia: Veritas Health Innovation; 2023.
36. Mitchell C, Rahko PS, Blauwet LA, Canaday B, Finstuen JA, Foster MC, et al. Guidelines for performing a comprehensive transthoracic echocardiographic examination in adults: recommendations from the American Society of Echocardiography. J Am Soc Echocardiogr 2019;32(1):1-64 [FREE Full text] [doi: 10.1016/j.echo.2018.06.004] [Medline: 30282592]
37. Glaab T, Taube C. Practical guide to cardiopulmonary exercise testing in adults. Respir Res 2022;23(1):9 [FREE Full text] [doi: 10.1186/s12931-021-01895-6] [Medline: 35022059]

Abbreviations

CPET: cardiopulmonary exercise test
CPET-SE: cardiopulmonary exercise test-stress echocardiography
JBI: Joanna Briggs Institute
PCC: Population, Concept, Context
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

Edited by A Mavragani; submitted 22.08.23; peer-reviewed by C Asuzu, M Hayıroğlu, E Mekhael; comments to author 04.12.23; revised version received 27.12.23; accepted 28.12.23; published 12.02.24.

Please cite as:
Gerhardy B, Sivapathan S, Orde S, Morgan L
Simultaneous Cardiopulmonary Exercise Testing and Echocardiography for Investigation of Cardiopulmonary Dysfunction in Outpatients: Protocol for a Scoping Review
JMIR Res Protoc 2024;13:e52076
URL: https://www.researchprotocols.org/2024/1/e52076
doi:10.2196/52076
PMID:38345834

Protocol

Ethical and Quality of Care-Related Challenges of Digital Health Twins in Older Care Settings: Protocol for a Scoping Review

Md Shafiqur Rahman Jabin[1,2], PhD; Emillia Vann Yaroson[3], PhD; Adaobi Ilodibe[4], MSc; Tillal Eldabi[5], PhD

[1]Department of Medicine and Optometry, Linnaeus University, Kalmar, Sweden

[2]Faculty of Health Studies, University of Bradford, Bradford, United Kingdom

[3]Department of Operations and Analytics, University of Huddersfield, Huddersfield, United Kingdom

[4]Department of Applied Artificial Intelligence and Data Analytics, University of Bradford, Bradford, United Kingdom

[5]Faculty of Management, Law & Social Sciences, University of Bradford, Bradford, United Kingdom

Corresponding Author:
Md Shafiqur Rahman Jabin, PhD
Faculty of Health Studies
University of Bradford
Horton A, Room: 2.10
Richmond Road
Bradford, BD7 1DP
United Kingdom
Phone: 44 7915673612
Email: mjabin@bradford.ac.uk

Abstract

Background: Digital health twins (DHTs) have been evolving with their diverse applications in medicine, specifically in older care settings, with the increasing demands of older adults. DHTs have already contributed to improving the quality of dementia and trauma care, cardiac treatment, and health care services for older individuals. Despite its many benefits, the optimum implementation of DHTs has faced several challenges associated with ethical issues, quality of care, management and leadership, and design considerations in older care settings. Since the need for such care is continuously rising and there is evident potential for DHTs to meet those needs, this review aims to map key concepts to address the gaps in the research knowledge to improve DHT implementation.

Objective: The review aims to compile and synthesize the best available evidence regarding the problems encountered by older adults and care providers associated with the application of DHTs. The synthesis will collate the evidence of the issues associated with quality of care, the ethical implications of DHTs, and the strategies undertaken to overcome those challenges in older care settings.

Methods: The review will follow the Joanna Briggs Institute (JBI) methodology. The published studies will be searched through CINAHL, MEDLINE, JBI, and Web of Science, and the unpublished studies through Mednar, Trove, OCLC WorldCat, and Dissertations and Theses. Studies published in English from 2002 will be considered. This review will include studies of older individuals (aged 65 years or older) undergoing care delivery associated with DHTs and their respective care providers. The concept will include the application of the technology, and the context will involve studies based on the older care setting. A broad scope of evidence, including quantitative, qualitative, text and opinion studies, will be considered. A total of 2 independent reviewers will screen the titles and abstracts and then review the full text. Data will be extracted from the included studies using a data extraction tool developed for this study.

Results: The results will be presented in a PRISMA-ScR (Preferred Reporting Items for Systematic Review and Meta-Analysis extension for Scoping Reviews) flow diagram. A draft charting table will be developed as a data extraction tool. The results will be presented as a “map” of the data in a logical, diagrammatic, or tabular form in a descriptive format.

Conclusions: The evidence synthesis is expected to uncover the shreds of evidence required to address the ethical and care quality-related challenges associated with applying DHTs. A synthesis of various strategies used to overcome identified challenges will provide more prospects for adopting them elsewhere and create a resource allocation model for older individuals.

International Registered Report Identifier (IRRID): DERR1-10.2196/51153

(JMIR Res Protoc 2024;13:e51153) doi:10.2196/51153

KEYWORDS

accessibility; data security; effectiveness; equality; health equity; patient safety; right to privacy; social care

Introduction

Overview

Digital health twins (DHTs), defined as digital representations (digital twins) of patients (physical twins), are an emerging technology aimed at meeting some of the above challenges. DHTs are generated from multimodal patient data, population data, and real-time updates on patient and environmental variables [1]. The field of a digital twin, particularly in health care, has been evolving by using machine learning data aggregated from various patients through modeling the conditions and attributes of a particular patient [2].

The application of digital twins in health and medicine is diverse; for example, DHTs have been used in intensive care units for critical care [3], treatment of patients with trauma [4], and cardiac treatment [5]. Precision health or personalized care for primary prevention with DHTs for older adults has emerged to address the need to mitigate these significant resources and reinforcements. This can allow for collecting data that enables more individually tailored interventions, both to promote and prevent, diagnose, and treat—interventions with greater precision [6].

Moreover, digital twins have widely been used in older care settings, for example, care homes [7] or for older individuals in different settings, such as hospitals [8]. The evidence suggests that the application of DHTs in dementia is broad, such as detecting the signs of dementia [8], assessing the risks associated with Alzheimer disease–related dementia [9], and supporting better dementia care [10]. DHTs have also been found to improve health care services for older individuals by providing real-time supervision and accurate crisis warning [11] and to improve the efficiency and accessibility of medical services for older individuals [12].

With the increase in life expectancy, older adults are growing in the United Kingdom and around the world and are expected to live longer with multiple disabilities and diseases [13]. Around 19% of the population in the United Kingdom is aged 65 years or older, many of whom require health and social care services to enable them to live longer and have a better quality of life [14]. This number is expected to grow by a further 77% (from 1.4 million to 2.4 million) for older adults by 2040 [15]. While this demographic shift makes older adults the major users of health and care resources [16], it places an unprecedented strain on the workforce of the social care sector [17].

Health and social care for older adults is a complex sociotechnical system that undergoes continuous change [18]. Over the last 3 decades, quality of care has progressively been on the agenda because the care delivery can itself harm patients [19,20], either by providing less than optimal care [21] or by things going wrong with its delivery [22,23]. Whenever a new technology or technological innovation is introduced to improve the quality of care, such as efficiency and effectiveness, new and often unforeseen issues emerge that require attention and awareness [18,21,24]. Thus, new challenges arise continuously, which need resetting priorities for other dimensions of quality of care [18], such as patient safety [25] and health equity [26]. This new technology, that is, the implementation of DHT, is no exception, which can even cause technical [27], ethical [26,27], legal [27,28], and societal challenges [27].

The challenges associated with management and leadership include a lack of discussions, cooperation, negotiations, and agreement among various health and social care providers while new routines are being adopted [6,29]. Design considerations concerning big data-related problems involve data visualization, data availability and accessibility, data integration and interoperability into clinical workflow [10], and privacy and security across the entire system [6,10]. Issues involving the quality of care in terms of DHT implementation are safety, equity, and appropriateness [10,26,28]. Some of the ethical challenges regarding the application of DHTs include autonomy, informed consent, the right to privacy, and surveillance health care [26].

The UK Government's Plan for Tech and Digital Economy desires an expansion of the United Kingdom's existing expertise in deep foundational technologies, including digital twins and artificial intelligence [30]. This has been supported by the Government's Plan for Digital Health and Social Care to expedite technology adoption [31], while the UK Research and Innovation (UKRI) inaugurated a funding scheme to establish a multidisciplinary research community in digital twinning [32]. The UKRI's initiative focuses on addressing aspects of ethics, human interaction, environmental sustainability and security, and resilience [32], while NHS (National Health Service) England emphasizes the digital transformation of adult social care—the need for personalized care [33].

In order to shape this review, we will focus on older individuals and consider the following dimensions for the quality of care: safety, equity, effectiveness, and accessibility. Conducting a scoping review for the care of older adults is the most ideal and reliable approach to illuminate the current issues associated with DHTs. There is a need for mapping the key concepts to address questions beyond those associated with the experience and effectiveness of this intervention due to DHT's evolving applications in older care settings [34]. Our proposed review is in line with the vision of the NHS and the UKRI to understand the challenges faced by health and social care professionals, older adults, and their relatives concerning DHT used in personalized care for older adults. Therefore, the review results can readily be accepted, with more prospects of being adopted elsewhere and meeting today's societal challenges—creating a model for gathering individualized data, disease prevention, monitoring, and resource allocation for older adults.

A preliminary search of Campbell systematic reviews, the Cochrane Database of Systematic Reviews, PROSPERO

(International Prospective Register of Systematic Reviews), and Joanna Briggs Institute (JBI) Evidence Synthesis was conducted; however, no current or underway systematic reviews or scoping reviews on the topic were identified.

Aim and Review Questions

The primary purpose of this scoping review is to compile and synthesize the best available evidence regarding the challenges of DHT encountered in older care settings. This review is believed to uncover the shreds of evidence that will require diligent attention to address the ethical challenges and the challenges concerning the quality of care associated with the application of DHT. Moreover, this study will identify the strategies that have been used to overcome those challenges in older care settings. Therefore, there is a need for new knowledge through evidence synthesis using existing knowledge to be put to good use.

Specifically, the review questions are as follows:

1. What problems are faced by older individuals (their family and relatives) and health and social care providers associated with the application of DHTs in older care settings?
2. What are the documented issues related to the quality of care for older adults, such as safety, equity, effectiveness, and accessibility, concerning DHTs?
3. What are the ethical challenges concerning the application of DHTs in older care settings?
4. What strategies have been evaluated and implemented in older care settings that address the challenges associated with DHTs?

Methods

The proposed scoping review will be conducted in accordance with the JBI methodology for scoping reviews [35].

Search Strategy

Databases will be searched for both published and unpublished studies. The approach to searching for studies for a scoping review will follow the standard 3-step method (Table 1). The first step will be an initial limited search of a selection of relevant databases, followed by an analysis of text words in the title and abstract and the index terms used to describe the article. The search for published studies will include a 2-way search strategy. One is to search the journal and reference databases, such as CINAHL, MEDLINE, JBI, and Web of Science. Another is to search article-based (journal) databases, such as the ACM digital library, IEEE Xplore, and BMJ Journals. The search for unpublished studies will include Mednar, Trove, OCLC WorldCat, and Dissertations and Theses. A second search using all identified keywords and index terms will then be undertaken across all included databases. Additional search strategies, that is, citation search—specific researcher or article (eg, gold-standard article), and chain search—review reference list of the systematically selected articles will be included to complement the search for published and unpublished papers. Studies, such as reviews (systematic, scoping, and umbrella) and letters to editors, will be excluded. Any studies that lack ethical concerns will also be excluded. Studies published in English will be considered. Studies published from 2002 (when the concept of “digital twin” was first coined by Dr Michael in 2002) [36] onward will be considered for inclusion in this review.

Table 1. Search strategy on databases.

Participant, concept, and context scheme	#	Search string	Hits on MEDLINE (July 18)	Hits on CINAHL (July 18), n	Hits on APA PsycInfo (July 18), n	Hits on Web of Science (July 18), n	Hits on Scopus (July 19), n	Hits on WorldCat (July 20), n	Hits on JBI[a] (July 20), n
Digital health twin in older care settings	1	"digital health twin*" OR "digital twin*" OR "digital phenotype" OR "digital shadow" OR "virtual patient*" OR "personalised health model*" OR "digital patient model" OR "in silico patient*"	6,404,833	639	2982	11,763	17,051	36,108	2
Digital health twin in older care settings	2	older OR aged OR elderly OR senior* OR elder OR "old person*" OR "older person*" OR "old people" OR "older adult*" OR "older people" OR geriatric*	2457	1,251,839	829,113	5,690,683	6,817,585	31,208,688	1773
	3	# 1 AND #2	204	46	21	449	327	1682	0
Health care setting	4	health* OR hospital* OR care* OR caring OR nursing OR treatment OR aid OR management OR therapy	18,297,577	5,152,991	2,786,771	21,428,220	23,457,440	5180	2837
Combined	5	#3 AND #4	189	43	19	308	250	1384	0
Filters	6	#3 + English, from 2002 onward (exc meeting abstract, editorial material and book chapters.	197	45	21	428	309	8	0
Filters	7	#5 + English, from 2002 onward (exc meeting abstract, editorial material and book chapters.	184	43	19	300	237	4	0

[a]JBI: Joanna Briggs Institute.

Eligibility Criteria

Overview

This scoping review will include the following PCC mnemonics—population, concept, and context. These mnemonics will be used as a guide (not a policy); therefore, the inclusion criteria of this systematic review will include a detailed description of types of participants, concepts, and context, as well as search strategies, data extraction, charting, analysis, and presenting the results. The eligibility criteria are listed in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Review articles
- Conference paper
- Gray literature
- Early access
- English
- Studies involving older individuals associated with a digital health twin (DHT), regardless of gender, age, ethnicity, socioeconomic status, disorders, or disability.
- Studies that include paid or unpaid carers, whether they are family members or friends.
- Studies that include care providers involved in older care settings and DHTs, whether they are licensed or unlicensed.
- Studies that evaluate and discuss the process and application of DHTs involving caregivers, older individuals, or family, friends, or relatives.
- Studies from 2002 through 2023.
- Studies that specifically evaluate and discuss the process and application of DHTs in settings such as geriatric wards of primary health care, hospitals or clinics, nursing homes, care homes, and home care facilities for older individuals.

Exclusion criteria

- Meeting abstracts
- Editorial materials
- Book chapters
- All other languages
- Studies that do not involve older individuals or care providers associated with DHTs in older care settings.
- Studies that do not focus on the application of DHTs or are not directly related to older care settings.
- Studies from 2001 and earlier.
- Studies not in the context of older care settings.
- Studies where DHTs are not used.

Participants

This review will include studies of older individuals (aged 65 years or older) undergoing care delivery associated with DHTs, irrespective of gender and diversity, including age, ethnicity, socioeconomic status, disorders, and disability. Studies that focus on caregivers (family and friends—paid or unpaid) and care providers (licensed or unlicensed) involved in the care of older adults in relation to DHTs will also be included.

Concept

In this scoping review, the key concept is the process and application of DHTs. Studies that evaluate the application of DHTs involving older care providers, older individuals, family, friends, or relatives will be considered.

Context

The systematic review will consider studies that are based in the older care settings associated with DHTs, such as geriatric wards of primary health care, hospitals or clinics, old-age homes, nursing homes, care homes, and home care facilities for older individuals.

Types of Sources

This scoping review will consider both experimental and quasi-experimental study designs, including randomized controlled trials, nonrandomized controlled trials, before and after studies, and interrupted time-series studies. In addition, analytical observational studies, including prospective and retrospective cohort studies, case-control studies, and analytical cross-sectional studies, will be considered for inclusion. This review will also consider descriptive observational study designs, including case series, individual case reports, and descriptive cross-sectional studies, for inclusion.

Qualitative studies that focus on qualitative data, including but not limited to designs such as phenomenology, grounded theory, ethnography, qualitative description, and action research, will also be considered.

Text and opinion papers regarding the benefits and challenges of DHT and strategies to overcome the challenges posed by DHTs will also be considered as a scoping review that includes a broad scope of evidence.

Study or Source of Evidence Selection

Following the search, all identified citations will be collated and uploaded into EndNote (version 20; Clarivate Analytics),

and duplicates will be removed. Following a pilot test, titles and abstracts will then be screened by 2 or more independent reviewers for assessment against the inclusion criteria for the review. Potentially relevant sources will be retrieved in full, and their citation details will be imported into the JBI System for the Unified Management, Assessment and Review of Information [37]. The full text of selected citations will be assessed in detail against the inclusion criteria by 2 or more independent reviewers. Reasons for the exclusion of sources of evidence in full text that do not meet the inclusion criteria will be recorded and reported in the scoping review. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussion or with an additional reviewer or reviewers. The results of the search and the study inclusion process will be reported in full in the final scoping review and presented in a PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) flow diagram [38].

Data Extraction

Data will be extracted from papers included in the scoping review by 2 or more independent reviewers using a data extraction tool developed by the reviewers. The data extracted will include specific details about the participants, concept, context, study methods, and key findings relevant to the review questions.

A draft charting table will be developed as a data extraction tool. The charting table will be modified and revised as necessary during the process of extracting data from each included evidence source. Modifications will be detailed in the scoping review. Any disagreements that arise between the reviewers will be resolved through discussion or with an additional reviewer or reviewers. If appropriate, authors of papers will be contacted to request missing or additional data, where required.

Results

The results will be presented as a “map” of the data extracted from the included papers in a logical, diagrammatic, or tabular (as necessary) form and in a descriptive format that aligns with the objective and scope of the review. Some critical information that the charting table will include is (but is not limited to): year of publication, country of origin for the study, aims, study population and sample size, methodology or methods, type of intervention or comparator, duration of the intervention, and type of outcomes and how they were measured (if applicable). A clear explanation for each category will be provided, accompanied by a narrative summary describing how the results relate to the review objective and questions.

This scoping review protocol was first developed by the principal author as part of a postdoctoral fellowship at Linnaeus University in February 2022. Later, the protocol was refined and continued as part of research development at the University of Bradford by the lead author, who has been undertaking a full search since July 2023. We expect the analysis to be completed by January 2024 and the final scoping review manuscript to be submitted by April 2024.

Discussion

Overview

The world’s population is getting older—aging brings with it complicated and multiple challenges such as poorer mobility, balance, sight or hearing, dementia, diabetes, and an increased risk of injuries [39]. With the trend of increasing older adults, it is estimated that almost 1 in 6 adults must work in care by 2038 to meet the demand for older adults in home care alone. This is a hard target to meet, given the current shortfalls in the workforce available in social care sectors, which became more apparent during the COVID-19 pandemic [17]. Not to mention the lack of incentive in many countries to take such jobs. Since technology is seen as a means to address the shortage of care workers by health and social care policy makers [13], we believe that DHTs have the capability of addressing the demand for the care of older adults and compensating for the shortage of care workers.

A recent rapid literature review of studies of DHT for managing health care systems identified 17 studies, concluding that DHT can contribute to safety management, information management, health management and well-being promotion, and health care operational control [40]. With appropriate implementation, DHT helps treat patients as virtualized standalone assets [41], improve patient treatment and diagnostics [6], and improve the quality of life overall [42].

The current concept of DHT is diverse as it is still a new and emerging domain, particularly in older care settings [7-10,34], with the aim of improving the quality of care by increasing efficiency [43]. New definitions, concepts, and dimensions in regard to DHT may be identified in this review that may have the potential to help in furthering the design, development, implementation, and evaluation process of DHT. We believe that the evidence synthesis will help us design a larger implementation project, that is, assembling unique and existing technologies to create a new digital twin platform for older care settings.

Since DHTs are expensive and sometimes may not be readily available to older adults to a large extent [44], this study will assess the different circumstances and needs of older adults. This study will ensure appropriate resources and solutions are allocated to needy individuals, covering aspects of equity, and closing the gap in health inequality. The benefits of DHT will help us understand informed decision-making in older care settings.

Limitations

The findings of the review need to be treated with caution since our search is restricted in terms of language and publication period. To overcome these limitations, a comprehensive strategy, that is, a standard 3-step method, will be followed, such as the inclusion of gray literature, which may provide additional insights into the review findings. There may also be a possibility pertaining to the findings in terms of the limited number of included studies, which may further add a layer of bias to the

selected studies. The evidence-based practice center methods guide proposed by the Agency for Healthcare Research and Quality will be followed to minimize the risk of bias in individual studies [45].

To ensure the systematic scoping review generates generalizable findings, discussions with older adults, their relatives, and the relevant public will be held to support the interpretation of the findings and dissemination of the review.

Conclusions

No current or ongoing systematic reviews or scoping reviews on the topic were identified. This review will uncover the shreds of evidence requiring diligent attention to address the ethical challenges and the challenges concerning the quality of care associated with the application of DHT. Additionally, this study will identify the strategies that have been used to overcome those identified challenges in older care settings, providing more prospects for adopting them elsewhere and creating a model of resource allocation for older individuals.

Acknowledgments

The authors would like to thank Evalill Nilsson and the librarians from Linnaeus University and the University of Bradford for their guidance and assistance in this research. This study is being undertaken without external funding. A publishing grant has been received from Linnaeus University as part of the University Library's research support.

Data Availability

All data generated during this study will be included in the original review article (and its supplementary information files).

Conflicts of Interest

None declared.

References

1. Venkatesh KP, Raza MM, Kvedar JC. Health digital twins as tools for precision medicine: considerations for computation, implementation, and regulation. NPJ Digit Med 2022;5(1):150 [FREE Full text] [doi: 10.1038/s41746-022-00694-7] [Medline: 36138125]
2. Chakshu NK, Sazonov I, Nithiarasu P. Towards enabling a cardiovascular digital twin for human systemic circulation using inverse analysis. Biomech Model Mechanobiol 2021;20(2):449-465 [FREE Full text] [doi: 10.1007/s10237-020-01393-6] [Medline: 33064221]
3. Chase JG, Zhou C, Knopp JL, Shaw GM, Näswall K, Wong JHK, et al. Digital twins in critical care: what, when, how, where, why? IFAC-PapersOnLine 2021;54(15):310-315 [FREE Full text] [doi: 10.1016/j.ifacol.2021.10.274]
4. Croatti A, Gabellini M, Montagna S, Ricci A. On the integration of agents and digital twins in healthcare. J Med Syst 2020;44(9):161 [FREE Full text] [doi: 10.1007/s10916-020-01623-5] [Medline: 32748066]
5. Prakosa A, Arevalo HJ, Deng D, Boyle PM, Nikolov PP, Ashikaga H, et al. Personalized virtual-heart technology for guiding the ablation of infarct-related ventricular tachycardia. Nat Biomed Eng 2018;2(10):732-740 [FREE Full text] [doi: 10.1038/s41551-018-0282-2] [Medline: 30847259]
6. Boulos MNK, Zhang P. Digital twins: from personalised medicine to precision public health. J Pers Med 2021;11(8):745 [FREE Full text] [doi: 10.3390/jpm11080745] [Medline: 34442389]
7. Khan S, Saied IM, Ratnarajah T, Arslan T. Evaluation of unobtrusive microwave sensors in healthcare 4.0-toward the creation of digital-twin model. Sensors (Basel) 2022;22(21):8519 [FREE Full text] [doi: 10.3390/s22218519] [Medline: 36366218]
8. Kobayashi T, Fukae K, Imai T, Arai K. Digital twin agent for super-aged society. 2022 Presented at: IEEE International Conference on Consumer Electronics (ICCE); January 07-09, 2022; Las Vegas, NV, USA. [doi: 10.1109/icce53296.2022.9730230]
9. Cai F, Patharkar A, Wu T, Lure FYM, Chen H, Chen VC. STRIDE: systematic radar intelligence analysis for ADRD risk evaluation with gait signature simulation and deep learning. IEEE Sens J 2023;23(10):10998-11006 [FREE Full text] [doi: 10.1109/jsen.2023.3263071] [Medline: 37547101]
10. Wickramasinghe N, Ulapane N, Andargoli A, Ossai C, Shuakat N, Nguyen T, et al. Digital twins to enable better precision and personalized dementia care. JAMIA Open 2022;5(3):ooac072 [FREE Full text] [doi: 10.1093/jamiaopen/ooac072] [Medline: 35992534]
11. Bruynseels K, de Sio FS, van den Hoven J. Digital twins in health care: ethical implications of an emerging engineering paradigm. Front Genet 2018;9:31 [FREE Full text] [doi: 10.3389/fgene.2018.00031] [Medline: 29487613]
12. Liu Y, Zhang L, Yang Y, Zhou L, Ren L, Wang F, et al. A novel cloud-based framework for the elderly healthcare services using digital twin. IEEE Access 2019;7:49088-49101 [FREE Full text] [doi: 10.1109/access.2019.2909828]
13. Help at home: use of assistive technologies for older people. National Institute for Health and Care Research. 2018. URL: https://evidence.nihr.ac.uk/collection/help-at-home-use-of-assistive-technology-for-older-people/ [accessed 2024-01-19]

14. Ageing and older population UK statistics for 2022. Age UK. 2022. URL: https://www.ageukmobility.co.uk/mobility-news/article/ageing-and-older-population-uk-statistics-for-2022 [accessed 2024-12-25]
15. National population projections: 2018-based. Office for National Statistics. 2019. URL: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationprojections/bulletins/nationalpopulationprojections/2018based [accessed 2024-01-19]
16. Shuvo SS, Symum H, Ahmed MR, Yilmaz Y, Zayas-Castro JL. Multi-objective reinforcement learning based healthcare expansion planning considering pandemic events. IEEE J Biomed Health Inform 2023;27(6):2760-2770 [FREE Full text] [doi: 10.1109/JBHI.2022.3187950] [Medline: 35776827]
17. Ferguson I, Lavalette M. Adult social care - technology enabled care strategy. In: Critical and Radical Debates in Social Work. Bristol UK: Policy Press; 2013.
18. Taylor BJ. Developing an integrated assessment tool for the health and social care of older people. Br J Soc Work 2011;42(7):1293-1314 [FREE Full text] [doi: 10.1093/bjsw/bcr133]
19. Jabin MSR, Magrabi F, Hibbert P, Schultz T, Bessen T, Runciman W. Identifying and characterizing system issues of health information technology in medical imaging as a basis for recommendations. 2019 Presented at: IEEE International Conference on Imaging Systems and Techniques (IST); December 09-10, 2019; Abu Dhabi, United Arab Emirates. [doi: 10.1109/ist48021.2019.9010426]
20. Jabin MSR, Magrabi F, Hibbert P, Schultz T, Runciman W. Identifying clusters and themes from incidents related to health information technology in medical imaging as a basis for improvements in practice. 2019 Presented at: IEEE International Conference on Imaging Systems and Techniques (IST); December 09-10, 2019; Abu Dhabi, United Arab Emirates. [doi: 10.1109/ist48021.2019.9010280]
21. Jabin MSR, Pan D, Nilsson E. Characterizing healthcare incidents in Sweden related to health information technology affecting care management of multiple patients. Health Informatics J 2022;28(2):14604582221105440 [FREE Full text] [doi: 10.1177/14604582221105440] [Medline: 35762538]
22. Jabin MSR, Steen M, Wepa D, Bergman P. Assessing the healthcare quality issues for digital incident reporting in Sweden: incident reports analysis. Digit Health 2023;9:20552076231174307 [FREE Full text] [doi: 10.1177/20552076231174307] [Medline: 37188073]
23. Jabin MSR, Pan D. Software-related challenges in Swedish healthcare through the lens of incident reports: a desktop study. Digit Health 2023;9:20552076231203600 [FREE Full text] [doi: 10.1177/20552076231203600] [Medline: 37744748]
24. Jabin M, Magrabi F, Hibbert P, Schultz T, Runciman W. Identifying and classifying incidents related to health information technology in medical imaging as a basis for improvements in practice. 2020 Presented at: IEEE International Conference on Imaging Systems and Techniques (IST); December 09-10, 2019; Abu Dhabi, United Arab Emirates. [doi: 10.1109/ist48021.2019.9010109]
25. Ahmadi-Assalemi G, Al-Khateeb H, Maple C, Epiphaniou G, Alhaboby ZA, Alkaabi S, et al. Digital twins for precision healthcare. In: Jahankhani H, Kendzierskyj S, Chelvachandran N, Ibarra J, editors. Cyber Defence in the Age of AI, Smart Societies and Augmented Humanity. Cham: Springer International Publishing; 2020:133-158.
26. Huang PH, Kim KH, Schermer M. Ethical issues of digital twins for personalized health care service: preliminary mapping study. J Med Internet Res 2022;24(1):e33081 [FREE Full text] [doi: 10.2196/33081] [Medline: 35099399]
27. Drummond D, Coulet A. Technical, ethical, legal, and societal challenges with digital twin systems for the management of chronic diseases in children and young people. J Med Internet Res 2022;24(10):e39698 [FREE Full text] [doi: 10.2196/39698] [Medline: 36315239]
28. Okegbile SD, Cai J, Niyato D, Yi C. Human digital twin for personalized healthcare: vision, architecture and future directions. IEEE Network 2023;37(2):262-269 [FREE Full text] [doi: 10.1109/mnet.118.2200071]
29. Hofflander M. Implementing Video Conferencing in Discharge Planning Sessions: Leadership and Organizational Culture when Designing IT Support for Everyday Work in Nursing Practice. Sweden: Department of Health, Blekinge Institute of Technology; 2015.
30. Policy paper: UK digital strategy. Department for Digital, Culture., Media, and Sport. 2022. URL: https://www.gov.uk/government/publications/uks-digital-strategy/uk-digital-strategy [accessed 2023-04-04]
31. Department of Health and Social Care, NHS England. Policy paper: a plan for digital health and social care. Gov.UK. 2022. URL: https://www.gov.uk/government/publications/a-plan-for-digital-health-and-social-care [accessed 2024-01-19]
32. Develop a UK digital twinning research community with a NetworkPlus. UK Research and Innovation. 2023. URL: https://www.ukri.org/opportunity/develop-a-uk-digital-twinning-research-community-with-a-networkplus/ [accessed 2024-04-03]
33. Policy paper: next steps to put people at the heart of Care. Department of Health & Social Care. 2023. URL: https://www.gov.uk/government/publications/adult-social-care-system-reform-next-steps-to-put-people-at-the-heart-of-care/next-steps-to-put-people-at-the-heart-of-care [accessed 2024-01-19]
34. Sahal R, Alsamhi SH, Brown KN. Personal digital twin: a close look into the present and a step towards the future of personalised healthcare industry. Sensors (Basel) 2022;22(15):5918 [FREE Full text] [doi: 10.3390/s22155918] [Medline: 35957477]

35. Peters MDJ, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. Int J Evid Based Healthc 2015;13(3):141-146 [FREE Full text] [doi: 10.1097/XEB.0000000000000050] [Medline: 26134548]
36. Grieves M. In: Mavris D, Schwartz KG, Flumerfelt S, Briceno S, editors. Complex Systems Engineering: Theory and Practice. Reston, VA: American Institute of Aeronautics and Astronautics; 2019:175-200.
37. Munn Z, Aromataris E, Tufanaru C, Stern C, Porritt K, Farrow J, et al. The development of software to support multiple systematic review types: the Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information (JBI SUMARI). Int J Evid Based Healthc 2019;17(1):36-43 [FREE Full text] [doi: 10.1097/XEB.0000000000000152] [Medline: 30239357]
38. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6(7):e1000097 [FREE Full text] [doi: 10.1371/journal.pmed.1000097] [Medline: 19621072]
39. Fjell A. Preventive Home Visits Among Older People: Risk Assessment, Self-rated Health and Experiences of Healthy Ageing. Sweden: Karolinska Institutet; 2021.
40. Elkefi S, Asan O. Digital twins for managing health care systems: rapid literature review. J Med Internet Res 2022;24(8):e37641 [FREE Full text] [doi: 10.2196/37641] [Medline: 35972776]
41. Ricci A, Croatti A, Montagna S. Pervasive and connected digital twins—a vision for digital health. IEEE Internet Comput 2022;26(5):26-32. [doi: 10.1109/mic.2021.3052039]
42. El Saddik A, Badawi H, Velazquez RAM, Laamarti F, Diaz RG, Bagaria N, et al. Dtwins: a digital twins ecosystem for health and well-being. IEEE COMSOC MMTC Commun Front 2019;14(2):39-43 [FREE Full text]
43. Sun T, He X, Li Z. Digital twin in healthcare: recent updates and challenges. Digit Health 2023;9:20552076221149651 [FREE Full text] [doi: 10.1177/20552076221149651] [Medline: 36636729]
44. Friebe MH. Healthcare in need of innovation: exponential technology and biomedical entrepreneurship as solution providers (keynote paper). 2020 Presented at: Proceedings Volume 11315, Medical Imaging 2020: Image-Guided Procedures, Robotic Interventions, and Modeling; February 15-20, 2020; Houston, Texas, United States URL: https://www.spiedigitallibrary.org/conference-proceedings-of-spie/11315.toc#_=_ [doi: 10.1117/12.2556776]
45. Viswanathan M, Ansari MT, Berkman ND, Chang S, Hartling L, McPheeters M, et al. Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions. In: Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville, MD: Agency for Healthcare Research and Quality; 2008.

Abbreviations

DHT: digital health twin
JBI: Joanna Briggs Institute
NHS: National Health Service
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
PROSPERO: International Prospective Register of Systematic Reviews
UKRI: UK Research and Innovation

Edited by A Mavragani; submitted 22.07.23; peer-reviewed by D Verran, K Fuji; comments to author 13.10.23; revised version received 19.11.23; accepted 13.12.23; published 23.02.24.

Please cite as:
Jabin MSR, Yaroson EV, Ilodibe A, Eldabi T
Ethical and Quality of Care-Related Challenges of Digital Health Twins in Older Care Settings: Protocol for a Scoping Review
JMIR Res Protoc 2024;13:e51153
URL: https://www.researchprotocols.org/2024/1/e51153
doi:10.2196/51153
PMID:38393771

Protocol

Professional-Facing Digital Health Solutions for the Care of Patients With Chronic Pain: Protocol for a Systematic Scoping Review

Haruno McCartney[1], BSc; Ashleigh Main[1], MSc; Maryam Ibrar[1], MA, MSc; Harleen Kaur Rai[1], PhD; Natalie McFayden Weir[2], PhD; Roma Maguire[1], PhD

[1]Department of Computer and Information Sciences, University of Strathclyde, Glasgow, United Kingdom

[2]Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, United Kingdom

Corresponding Author:
Haruno McCartney, BSc
Department of Computer and Information Sciences
University of Strathclyde
16 Richmond St
Glasgow, G1 1XH
United Kingdom
Phone: 44 (0) 141 548 318
Email: haruno.mccartney@strath.ac.uk

Abstract

Background: Chronic pain is a highly prevalent condition and one of the most common reasons why people seek health care. As a result, chronic pain has a significant personal and economic burden. The COVID-19 pandemic has aggravated the situation for patients with chronic pain through increased risk factors (eg, anxiety or depression) as well as decreased access to health care. Digital health solutions to support people with chronic pain are becoming increasingly popular. Most of the research has focused on patient-facing digital health solutions, although it is clear that the involvement of health and care professionals is crucial in chronic pain care. Certainly, digital health solutions intended for the use of health and care professionals in the care of patients with chronic pain (ie, professional facing) exist, for example, for clinical decision support; however, no review has investigated the studies reporting these interventions.

Objective: The overall aim of this scoping review is to identify the available professional-facing digital health solutions for the purpose of chronic pain management. The objectives of this review are to investigate the components, target populations, and user settings of the available professional-facing digital solutions; health and care professionals' perspectives on using digital health solutions (if reported); the methods in which the digital health solutions are developed; and the outcomes of using professional-facing digital health solutions.

Methods: Databases including MEDLINE, Embase, CINAHL, PsycInfo, and Inspec will be searched for studies reporting professional-facing digital health solutions for chronic pain care, using a comprehensive search strategy developed for each of the specific databases. A total of 2 independent reviewers will screen the titles and abstracts for review inclusion and then conduct full-text screening. Any conflicts in study inclusion will be resolved by a third reviewer at each stage of the screening process. Following data extraction and quality assessment, a qualitative content analysis of the results will be conducted. This review will identify the available professional-facing digital health solutions for chronic pain management. The results of this review are likely to be heterogeneous in terms of content (ie, the digital solutions will serve a variety of purposes, settings, target populations, etc) and methods (ie, experimental and nonexperimental designs).

Results: The review is expected to finish in March 2024 and published in the summer of 2024.

Conclusions: This protocol outlines the need for a scoping review to identify professional-facing digital health solutions for the management of chronic pain. Results from this review will contribute to the growing field of research into the utility of digital health for chronic pain management.

International Registered Report Identifier (IRRID): DERR1-10.2196/51311

(JMIR Res Protoc 2024;13:e51311) doi:10.2196/51311

KEYWORDS

burden; chronic pain; clinician; digital health solution; digital health; digital solutions; eHealth; healthcare professional; mHealth; pain management; patient-facing; risk factor

Introduction

Overview

Chronic pain is a highly prevalent condition, estimated to be affecting 20% to 30% of people worldwide [1,2]. Pain is defined by the International Association for the Study of Pain as an "unpleasant sensory and emotional experience associated with actual or potential tissue damage" [2]. Although there is some debate on the length of time an individual must experience pain for it to transition from "acute" to "chronic," the *International Classification of Diseases, 11th Revision* defines chronic pain as pain lasting ≥3 months [3]. Chronic pain can also be further categorized into primary (no evident cause); secondary (as a result of an underlying condition); or in some cases, both [4,5].

Various approaches to chronic pain treatment exist, including pharmacological interventions (ie, analgesic medication from paracetamol to opioids) and nonpharmacological interventions (eg, physical therapy and psychological therapy such as cognitive behavioral therapy) [6]. The treatment of chronic pain can be extremely complex; mismanagement can lead to significant issues, for example, opioid dependency [7]. Working toward providing appropriate and effective treatment for patients with chronic pain is crucial to reducing the issues surrounding the mismanagement of chronic pain.

Pain is one of the most common reasons why people seek health care [1]. Due to the prevalence of the condition and its consequent impact on health care, chronic pain has a significant economic burden [1,8] with the estimated costs to the economy reaching billions in the United Kingdom [9,10] and other countries within Europe [11]. Furthermore, during the COVID-19 pandemic, health care resources were diverted from chronic pain management toward more emergency, COVID-19–related conditions [12]. The pandemic has exacerbated the challenges that patients with chronic pain may face; for example, social isolation and lockdown have led to reduced access to health care as well as increased anxiety or depression and reduced mobility, all of which are factors that may aggravate chronic pain symptoms [13-15]. Certainly, the pandemic has led to a reconsideration of traditional health care methods and has highlighted the importance of being flexible with novel methods of health care delivery [13,16]. There is a clear need for new innovations in chronic pain management [17] as a result of its economic burden, which has been further aggravated by the issues presented by the pandemic.

Digital health solutions may provide a unique opportunity to mitigate these challenges to chronic pain management cost-effectively [8,12]. There has been a recent rise in the number of digital solutions available for chronic pain management [14], such as applications for patient self-management [18] and digitally delivered physical therapy [19]. There is variation in the nomenclature of "digital health," with definitions continuing to evolve [20]. Although there is no universally accepted definition for "digital health," digital health refers to all digital, electronic, and computer technologies to improve health [21]; it is used synonymously with "eHealth" in much of the literature [21]. Indeed, terms such as "digital health," "eHealth," "mobile health (mHealth)," and "telemedicine or telehealth" have been used interchangeably [21]. The components of digital health are broad and may include mobile apps (mHealth), web applications, wearable technology, artificial intelligence, analytics, and telemedicine [20]. Digital solutions within health care provide many benefits, specifically to chronic pain management; they offer access to remote care and reduce the impact in some areas of health care service provision, for example, staff shortages and lack of resources [22]. It may also help in reducing waiting lists for care [23]. Now more than ever, this is important due to the challenges that health care systems face.

Previous reviews have focused on digital solutions for chronic pain [24-26] and for specific chronic pain conditions such as osteoarthritis and lower back pain [22,27]. Such reviews have focused particularly on the effect of digital solutions on patient outcomes, with many of the included interventions being patient-facing for the purpose of self-management. The results of these reviews show that digital solutions have a positive impact on patients with chronic pain, on outcomes such as pain intensity, quality of life, coping skills, and adherence to exercise [22,24-27].

There has been an emphasis on health and care professional involvement and contact as an important facilitator in the adoption of digital health solutions, as collaboration with key stakeholders and end-user groups is essential for the development of sustainable and usable systems [28]. Despite this, many digital solutions are developed and implemented without the involvement of health and care professionals [27]. Much of the literature also highlights the importance of multidisciplinary professional involvement in general chronic pain care [2,29,30]. Primary care clinicians are particularly essential in the process of chronic pain management [5,30]. Chronic pain management must go beyond self-management alone (through purely patient-facing solutions) and also involve multidisciplinary health and care professionals [2,5,29,30].

Previous studies on the perspectives of health and care professionals have also highlighted the potential of digital solutions as a useful tool for health and care professionals, that is, for education, patient-follow ups, etc [23]. Digital solutions targeting education for professionals may be particularly useful for chronic pain management, as negative attitudes and a lack of clinician knowledge are significant barriers to chronic pain care [31]. National guidelines state that it is essential for health and care professionals to have the best possible resources and support to manage patients with chronic pain [5], which could be facilitated by digital health solutions. Indeed, there are existing professional-facing digital solutions for the management of chronic pain, such as clinical decision support tools [32]. It is clear that there is a utility to digital health solutions for health

and care professionals (ie, to provide education and other resources that adhere to guidelines for care) and that such applications exist; however, to our knowledge, no previous reviews have investigated the available professional-facing digital solutions for chronic pain.

Thus, the objective of this scoping review is to investigate the professional-facing digital solutions available for the management of chronic pain conditions.

Review Question

This scoping review aims to answer the question: What research-based digital health solutions, specifically designed for the use of health and care professionals, are available for the management of chronic pain?

Therefore, the objectives of this scoping review are to investigate the following:

1. The components of existing professional-facing digital solutions for the management of chronic pain: (1) what are the user features, (2) what data do they collect, (3) are they integrated into larger systems or stand-alone (eg, within a system involving a patient-facing application), (4) security or privacy considerations, (5) target populations, and (6) settings (eg, pharmacy, hospital, or multisite adoption)
2. The frameworks and methods with which the digital solutions were designed and developed.
3. The outcomes measured and the effectiveness of the digital solutions, that is, implementation success and clinical effectiveness
4. Health and care professionals' perceptions of the usability and usefulness of digital solutions in the management of chronic pain (if reported)

Methods

The proposed scoping review will be conducted in accordance with the Joanna Briggs Institute methodology for scoping reviews [33] and will be reported according to the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) [34].

Eligibility Criteria

The population, concept, and context (PCC) will be used to guide the assessment of studies for review inclusion.

Inclusion Criteria

Population

Studies will be included if the reported digital health solutions' intended user demographic is health and care professionals directly involved in the care of patients (aged 18 years or older) with chronic pain. "Health and care professional" will refer to any professional who provides a health and care service, including, but not limited to, nurses, pharmacists, general practitioners, physiotherapists, other therapists, psychologists, and social care professionals. There will be no restrictions on the type of health and care profession of the participants.

Concept

The concept of interest for this review is digital health solutions (including, but not limited to, eHealth, mHealth, telehealth, web-based interventions, etc) intended to assist health and care professionals in the diagnosis and management of chronic pain. Any chronic pain-specific digital health solutions that are specifically designed for the end user to be health and care professionals will be considered in this review; therefore, the included solutions are likely to be heterogeneous in aim, user features, and functionality. This may include those intended for clinical decision support, education, remote patient monitoring, etc. Solutions may include mobile apps, web-based applications, or any other tools provided digitally.

Digital health solutions for the management of all types of chronic pain conditions will be considered, including chronic primary pain (eg, fibromyalgia, complex regional pain syndrome, and chronic primary headache), chronic secondary pain (eg, osteoarthritis and chronic pain secondary to cancer), or both [4,5]. Digital health solutions must be chronic pain specific, that is, for the management of a diagnosed chronic pain condition, with pain defined as "chronic" and lasting 3 or more months.

Context

There will be no restrictions on the context of this review. Contexts may include research and clinical settings, that is, any environment in which health and care professionals may be involved in the management of patients with chronic pain. Settings will likely include primary, secondary, and tertiary care settings (eg, pharmacies, general practitioners, and hospitals) and community settings (eg, residential facilities and the patient's home).

Exclusion Criteria

Studies reporting digital health solutions intended for use by patients only (eg, for self-management purposes) without a professional-facing component will be excluded. Studies will also be excluded if the digital health solution is not specifically intended for the management of a chronic pain condition (eg, studies reporting communication between health care professionals and patients through telephone or videoconferencing [Zoom, Zoom Video Communications; Microsoft Teams, Microsoft Corporation; etc] only, without specific digital chronic pain support, or studies reporting management of chronic pain using a digital health solution designed for general health care, that is, electronic health records). Digital health solutions will not be considered if they support the care of acute or nonchronic pain, for example, nonspecific low back pain. Studies reporting digital health solutions for nonadult patients (<18 years old) with chronic pain will also be excluded. Other exclusion criteria include gray literature and studies not written in the English language.

Types of Sources

This scoping review will consider all types of study designs. This may include experimental studies on the effectiveness of professional-facing digital solutions for the management of chronic pain (eg, randomized controlled trials, before and after sequential design, etc) or nonexperimental studies on the

development of digital solutions (eg, qualitative studies involving interviews). If only the abstract is available for a relevant study, the author will be contacted for further study information.

Search Strategy

A comprehensive search strategy will be developed using subject headings specific to databases MEDLINE, Embase, CINAHL, PsycInfo, and Inspec (Multimedia Appendix 1). The search strategy will comprise three categories relevant to the PCC inclusion criteria: terms relating to (1) chronic pain (concept of interest), (2) digital health (concept of interest), and (3) health and care professionals (population). There will be no terms in the search strategy limiting the context, as there will be no restrictions on setting. Search terms used for chronic pain will be developed using terms used in the National Institute for Health and Care Excellence guidelines for the management of chronic pain [4]. Keywords and index terms from previous relevant literature will be used to form search terms for all categories within the search strategy. The search strategies will be reviewed by an academic librarian to gain assistance on database-specific guidelines and to ensure the searches capture as many papers fitting the eligibility criteria as possible. Backward-citation searches will also be conducted by reviewing the references of the included studies for relevant articles. Researchers and experts in the field will be contacted to inquire about studies that fit the inclusion criteria.

Study or Source of Evidence Selection

Following the search and after removing duplicates, titles and abstracts will be screened by 2 independent reviewers against the inclusion criteria, with any disagreements resolved through discussion with a third independent reviewer. Full texts of potential studies fitting the inclusion criteria will then be reviewed again, in detail, by 2 independent reviewers. Reasons for exclusion will be recorded at the full-text reviewing stage and reported in the scoping review. Any disagreements that may arise at this stage will be resolved through discussion with a third independent reviewer. Screening and full-text review will be conducted on Covidence (Veritas Health Innovation Ltd).

Data Extraction

Data will be extracted from the studies fitting the inclusion criteria by 2 independent reviewers using a data extraction tool developed for the purpose of this review (Multimedia Appendix 2). The data extraction tool will be developed from the Template for Intervention Description and Replication checklist [35], which focuses on the digital solution components, that is, the rationale of the intervention, user features, procedures, etc. Additional information specific to the review aims will also be collected, for example, participant demographic information and perspectives of health and care professional users (if reported). Data extraction will first be piloted by the 2 reviewers by extracting the data from 10% of the studies fitting the inclusion criteria together through discussion.

As the included studies are likely to be diverse in design (due to no restrictions being imposed on the type of source), quality assessment will be conducted using Quality Assessment for Diverse Studies [36]. Although it is not essential to conduct a quality assessment in a scoping review [33], ascertaining the overall quality of the studies included in this review will be beneficial, as the literature suggests research in digital health for chronic pain is of low quality [37].

Data Analysis and Presentation

This scoping review will aim to conduct a qualitative content analysis of the results, that is, code the features of the digital health solutions used by the included studies into overall categories using NVivo (Lumivero, QSR International). If the results of the review are too heterogeneous for this, a narrative synthesis of the features of the digital health tools will be conducted. No analyses will be conducted to ascertain the overall effectiveness of professional-facing digital health solutions (as this is out of the scope of a scoping review). However, we will report the effectiveness of the individual digital health solutions as reported by each of the included studies in a narrative summary.

Expected Results

This scoping review will identify the available professional-facing digital health solutions for the management of chronic pain, their components, user settings, and target populations; professionals' perspectives on the use of digital health solutions; the methods in which the professional-facing digital health solutions are developed (ie, co-design framework used); and the outcomes of professional-facing digital health solutions. It is expected that the included studies will report on a variety of professional-facing digital health solutions. This may include systems for clinical decision support, symptom management, patient follow up, and educational tools. The outcomes of individual professional-facing digital solutions are also expected to be varied; they will likely have differing measures of effectiveness.

The types of studies fitting the inclusion criteria will most likely be heterogeneous in their methodology, as no restrictions have been imposed on design. Some included studies may report the early stages of developing the professional-facing digital solution (eg, nonexperimental studies such as those using interviews, surveys, and focus groups), while others may report on the effectiveness of the professional-facing digital solution (eg, experimental studies like randomized controlled trials). It is difficult to predict the quality assessment of these studies, at this stage.

The qualitative content analysis of the results will help to answer the review questions, that is, what are the user features, what data do they collect, are they integrated into larger systems or stand-alone, and what are their target population and user settings? If the included studies report on health and care professionals' perspectives, for example, through interviews or surveys, qualitative analysis will also provide information on the health and care professionals' perspectives on using professional-facing digital solutions.

Results

The scoping review is expected to be finished by March 2024 and the first search will be implemented in July 2023. The

results of the scoping review are expected to be published by the summer of 2024.

Discussion

Overview

To the best of our knowledge, this will be the first scoping review of professional-facing digital health solutions for the management of chronic pain. As we move further into a more digital age, there is a growing need for research into digital health and chronic pain care. This has been further emphasized by the challenges to care presented by the pandemic.

This scoping review will provide a foundation for further research into digital health solutions to make chronic pain care more efficient and innovative, from a health and care professional perspective. Results from this review will contribute to knowledge on the available professional-facing digital health solutions (including their components, user settings, target populations, development, and the perspectives of professionals on the use of such systems), as well as the gaps in the research on digital health solutions targeted toward health and care professionals (for example, areas of care that are not covered). As this is a scoping review, no conclusions can be drawn on the overall effectiveness of the professional-facing digital solutions, only the outcomes of the individual digital solutions as reported by the included studies.

We intend to conduct a qualitative content analysis to synthesize the results of this review. However, it is difficult to ascertain the method by which the included studies will report their findings (most likely extremely heterogeneous, given the broad inclusion criteria). Therefore, it may only be possible to conduct a narrative synthesis of the features of the professional-facing digital health solutions for chronic pain management. Either method of synthesizing the results of this review will produce valuable information on practices in chronic pain care and contribute knowledge to the field of digital health research.

Patient-Facing Versus Professional-Facing Digital Health Solutions for Chronic Pain Management

Although previous reviews have not focused on digital health solutions intended for use by health and care professionals, the literature supports the effectiveness of digital health solutions for the management of chronic pain. Recent systematic reviews suggest that mHealth interventions for chronic pain have a positive effect on patient outcomes (eg, pain intensity, quality of life, and functional ability) [25,26]. However, the literature also suggests that the quality of studies on digital health solutions for chronic pain is subpar, with Moreno-Ligero and colleagues [25] reporting “medium” quality for the majority of their included studies. This further highlights the need for a quality assessment to be conducted in this scoping review, to ascertain the quality of the studies on professional-facing digital solutions for chronic pain management.

Similarly, previous studies reporting on health and care professionals’ perspectives have focused on patient-facing digital health solutions for chronic pain management, that is, self-management interventions. Varsi and colleagues [23] emphasized the need for a comprehensive treatment approach to chronic pain care of which digital health solutions could provide if factors such as health care provider involvement, timely support, and follow up are also considered. Professional-facing digital health solutions may be one of the ways in which the latter factors could be incorporated into a more comprehensive system for managing chronic pain. Additionally, health and care professional involvement is required, not only in the use of digital health solutions but also in their development; many studies reporting digital health solutions for chronic pain management were designed without stakeholder involvement [23] and developed without using co-design methods or any form of user evaluation. This is also particularly essential for professional-facing digital health solutions and will be addressed in this review.

Strengths and Limitations

A significant strength of this scoping review is the systematic method of conducting the searches. A specialized academic librarian will aid in the development of comprehensive and individualized search strategies (Multimedia Appendix 1). Search terms will be formulated using specific subject headings for each database (eg, Medical Subject Headings for MEDLINE) as well as keywords taken from previous similar reviews. Search terms to describe chronic pain will be developed from terms used in the National Institute for Health and Care Excellence guidelines for the management of chronic pain [4]. A total of 2 blinded reviewers will independently complete all steps of the reviewing process, and a third reviewer will resolve any disagreements. Due to this systematic process, this review is likely to include most of the relevant studies that fit the inclusion criteria. Furthermore, this scoping review will follow the Joanna Briggs Institute scoping review manual as well as the PRISMA-ScR checklist.

The findings of this review will be limited to those published in the English language; therefore, there is a possibility that some professional-facing digital health solutions developed and reported in non-English–speaking countries will be missed by this review. It is important to consider that, as guidelines for chronic pain care and digital health differ between countries, jurisdiction of development and implementation may be a significant factor in the type of digital health solutions reported in this review. Furthermore, as some digital health solutions are developed commercially and do not have an academic foundation, the search of academic databases (without a market review, eg, app store search) may not have captured all professional-facing digital health solutions for chronic pain management. However, the quality of digital health solutions is largely dependent on their scientific foundation, which is facilitated by academic development, and nonevidence-based professional digital health solutions are not likely to be useful or realistically implemented in clinical chronic pain care settings. In order to find all available digital health solutions, it would be useful to communicate with health and care professionals currently involved in chronic pain care. Future studies may benefit from conducting interviews with health and care professionals to ascertain what digital health solutions are currently implemented in clinical settings and the benefits or

drawbacks of such systems in the care of patients with chronic pain.

Conclusion

This protocol outlines the need for a scoping review to identify professional-facing digital health solutions for the management of chronic pain. The results of this review will highlight the available digital health solutions available for health and care professionals to use specifically for chronic pain care and provide information regarding the system's components, user settings, specific target populations, and development. This scoping review will be systematically conducted to ensure most of the relevant literature is included; however, some professional-facing digital health solutions may be missed if they are developed commercially (without academic publication) or not reported in the English language. Findings from this review will contribute to the ever-growing field of digital health research and provide further information on how digital health can improve chronic pain care.

Acknowledgments

Special thanks to Dr David Stirling for funding the PhD project that this scoping review forms a part of, as well as to the academic support librarian, Elaine Blair, who helped in developing the search strategies.

Data Availability

Data sharing is not applicable to this article as it is a protocol and no data sets have been generated or analyzed yet.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategies.
[DOCX File , 24 KB - resprot_v13i1e51311_app1.docx]

Multimedia Appendix 2
Data extraction template.
[DOCX File , 26 KB - resprot_v13i1e51311_app2.docx]

References

1. Cohen SP, Vase L, Hooten WM. Chronic pain: an update on burden, best practices, and new advances. Lancet 2021;397(10289):2082-2097. [doi: 10.1016/S0140-6736(21)00393-7] [Medline: 34062143]
2. Multidisciplinary pain centre development manual. International Association for the Study of Pain. URL: https://www.iasp-pain.org/resources/toolkits/pain-management-center/ [accessed 2023-04-03]
3. International Classification of Diseases 11th Revision. World Health Organization. 2022. URL: https://icd.who.int/en [accessed 2023-05-02]
4. Chronic pain (primary and secondary) in over 16s: assessment of all chronic pain and management of chronic primary pain. The National Institute for Health and Care Excellence (NICE). URL: https://www.nice.org.uk/guidance/ng193 [accessed 2023-04-03]
5. Management of Chronic Pain. Scottish Intercollegiate Guidelines Network (SIGN). URL: https://www.sign.ac.uk/our-guidelines/management-of-chronic-pain/ [accessed 2023-04-03]
6. Hylands-White N, Duarte RV, Raphael JH. An overview of treatment approaches for chronic pain management. Rheumatol Int 2017;37(1):29-42. [doi: 10.1007/s00296-016-3481-8] [Medline: 27107994]
7. Salduker S, Allers E, Bechan S, Hodgson RE, Meyer F, Meyer H, et al. Practical approach to a patient with chronic pain of uncertain etiology in primary care. J Pain Res 2019;12:2651-2662 [FREE Full text] [doi: 10.2147/JPR.S205570] [Medline: 31564957]
8. Dear BF, Karin E, Fogliati R, Dudeney J, Nielssen O, Scott AJ, et al. A cost-effectiveness analysis of an internet-delivered pain management program delivered with different levels of clinician support: results from a randomised controlled trial. J Pain 2021;22(3):344-358 [FREE Full text] [doi: 10.1016/j.jpain.2020.11.003] [Medline: 33227510]
9. Maniadakis N, Gray A. The economic burden of back pain in the UK. Pain 2000;84(1):95-103. [doi: 10.1016/S0304-3959(99)00187-6] [Medline: 10601677]
10. British Pain Society press release: chronic pain costs the UK £billions but research funding is inadequate. British Pain Society. URL: https://www.britishpainsociety.org/mediacentre/news/british-pain-society-press-release-chronic-pain-costs-the-uk-billions-but-research-funding-is-inadequate/#_ftn3 [accessed 2023-05-30]

11. Breivik H, Eisenberg E, O'Brien T, OPENMinds. The individual and societal burden of chronic pain in Europe: the case for strategic prioritisation and action to improve knowledge and availability of appropriate care. BMC Public Health 2013;13:1229 [FREE Full text] [doi: 10.1186/1471-2458-13-1229] [Medline: 24365383]
12. Puntillo F, Giglio M, Brienza N, Viswanath O, Urits I, Kaye AD, et al. Impact of COVID-19 pandemic on chronic pain management: looking for the best way to deliver care. Best Pract Res Clin Anaesthesiol 2020;34(3):529-537 [FREE Full text] [doi: 10.1016/j.bpa.2020.07.001] [Medline: 33004164]
13. Clauw DJ, Häuser W, Cohen SP, Fitzcharles MA. Considering the potential for an increase in chronic pain after the COVID-19 pandemic. Pain 2020;161(8):1694-1697 [FREE Full text] [doi: 10.1097/j.pain.0000000000001950] [Medline: 32701829]
14. Tous NC, Santos Martín L, Corral CS, Cutillas AMR, Alfonsel BN, Moyano MR, et al. Development of an integrated solution for patients with neurostimulator for chronic pain in times of COVID-19: a mobile application with a support center. Neurocirugia (Astur : Engl Ed) 2022;33(6):318-327 [FREE Full text] [doi: 10.1016/j.neucie.2021.12.001] [Medline: 34961726]
15. Solé E, Racine M, Tomé-Pires C, Galán S, Jensen M, Miró J. Social factors, disability, and depressive symptoms in adults with chronic pain. Clin J Pain 2020;36(5):371-378. [doi: 10.1097/AJP.0000000000000815] [Medline: 32040011]
16. Akkemik Ü, Onay M. Telemedicine in patients with chronic pain in COVID-19 pandemic. Agri 2023;35(1):48-49 [FREE Full text] [doi: 10.14744/agri.2022.06937] [Medline: 36625185]
17. Ahmadpour N, Randall H, Choksi H, Gao A, Vaughan C, Poronnik P. Virtual reality interventions for acute and chronic pain management. Int J Biochem Cell Biol 2019;114:105568. [doi: 10.1016/j.biocel.2019.105568] [Medline: 31306747]
18. Devan H, Farmery D, Peebles L, Grainger R. Evaluation of self-management support functions in apps for people with persistent pain: systematic review. JMIR Mhealth Uhealth 2019;7(2):e13080 [FREE Full text] [doi: 10.2196/13080] [Medline: 30747715]
19. Grona SL, Bath B, Busch A, Rotter T, Trask C, Harrison E. Use of videoconferencing for physical therapy in people with musculoskeletal conditions: a systematic review. J Telemed Telecare 2018;24(5):341-355. [doi: 10.1177/1357633X17700781] [Medline: 28403669]
20. Mathews SC, McShea MJ, Hanley CL, Ravitz A, Labrique AB, Cohen AB. Digital health: a path to validation. NPJ Digit Med 2019;2:38 [FREE Full text] [doi: 10.1038/s41746-019-0111-3] [Medline: 31304384]
21. Burrell A, Zrubka Z, Champion A, Zah V, Vinuesa L, Holtorf AP, et al. How useful are digital health terms for outcomes research? An ISPOR special interest group report. Value Health 2022;25(9):1469-1479 [FREE Full text] [doi: 10.1016/j.jval.2022.04.1730] [Medline: 36049797]
22. Lara-Palomo IC, Gil-Martínez E, Ramírez-García JD, Capel-Alcaraz AM, García-López H, Castro-Sánchez AM, et al. Efficacy of e-Health interventions in patients with chronic low-back pain: a systematic review with meta-analysis. Telemed J E Health 2022;28(12):1734-1752. [doi: 10.1089/tmj.2021.0599] [Medline: 35532971]
23. Varsi C, Solem IKL, Eide H, Børøsund E, Kristjansdottir OB, Heldal K, et al. Health care providers' experiences of pain management and attitudes towards digitally supported self-management interventions for chronic pain: a qualitative study. BMC Health Serv Res 2021;21(1):275 [FREE Full text] [doi: 10.1186/s12913-021-06278-7] [Medline: 33766028]
24. Hussain A, Haroon H, Ahmed A, Gilani SA. Digital technologies in management of chronic pain—a systematic review. J Pak Med Assoc 2022;72(6):1158-1165 [FREE Full text] [doi: 10.47391/JPMA.3885] [Medline: 35751328]
25. Moreno-Ligero M, Moral-Munoz JA, Salazar A, Failde I. mHealth intervention for improving pain, quality of life, and functional disability in patients with chronic pain: systematic review. JMIR Mhealth Uhealth 2023;11:e40844 [FREE Full text] [doi: 10.2196/40844] [Medline: 36729570]
26. Pfeifer AC, Uddin R, Schröder-Pfeifer P, Holl F, Swoboda W, Schiltenwolf M. Mobile application-based interventions for chronic pain patients: a systematic review and meta-analysis of effectiveness. J Clin Med 2020;9(11):3557 [FREE Full text] [doi: 10.3390/jcm9113557] [Medline: 33167300]
27. Sulaiman SK, Wong AYL, Li LL, Antwi-Afari MF, Ou H, Wh Tsang H. The use of mobile health technology in the management of osteoarthritis: a scoping review with scientometric analyses. Int J Med Inform 2023;170:104937. [doi: 10.1016/j.ijmedinf.2022.104937] [Medline: 36493537]
28. Bhattarai P, Phillips JL. The role of digital health technologies in management of pain in older people: an integrative review. Arch Gerontol Geriatr 2017;68:14-24. [doi: 10.1016/j.archger.2016.08.008] [Medline: 27584871]
29. Gatchel RJ, McGeary DD, McGeary CA, Lippe B. Interdisciplinary chronic pain management: past, present, and future. Am Psychol 2014;69(2):119-130. [doi: 10.1037/a0035514] [Medline: 24547798]
30. Mills S, Torrance N, Smith BH. Identification and management of chronic pain in primary care: a review. Curr Psychiatry Rep 2016;18(2):22 [FREE Full text] [doi: 10.1007/s11920-015-0659-9] [Medline: 26820898]
31. Glajchen M. Chronic pain: treatment barriers and strategies for clinical practice. J Am Board Fam Pract 2001;14(3):211-218 [FREE Full text] [Medline: 11355054]
32. Downie AS, Hancock M, Shaheed CA, McLachlan AJ, Kocaballi AB, Williams CM, et al. An electronic clinical decision support system for the management of low back pain in community pharmacy: development and mixed methods feasibility study. JMIR Med Inform 2020;8(5):e17203 [FREE Full text] [doi: 10.2196/17203] [Medline: 32390593]

33. Aromataris E, Munn Z. Scoping reviews. In: JBI Manual for Evidence Synthesis. Adelaide, Australia: Joanna Briggs Institute (JBI); 2020.
34. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med 2018;169(7):467-473 [FREE Full text] [doi: 10.7326/M18-0850] [Medline: 30178033]
35. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ 2014;348(mar07 3):-g1687 [FREE Full text] [doi: 10.1136/bmj.g1687] [Medline: 24609605]
36. Harrison R, Jones B, Gardner P, Lawton R. Quality Assessment with Diverse Studies (QuADS): an appraisal tool for methodological and reporting quality in systematic reviews of mixed- or multi-method studies. BMC Health Serv Res 2021;21(1):144 [FREE Full text] [doi: 10.1186/s12913-021-06122-y] [Medline: 33588842]
37. Portelli P, Eldred C. A quality review of smartphone applications for the management of pain. Br J Pain 2016;10(3):135-140 [FREE Full text] [doi: 10.1177/2049463716638700] [Medline: 27583140]

Abbreviations

mHealth: mobile health
PCC: population, concept, and context
PRISMA-ScR: Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews

Edited by A Mavragani; submitted 27.07.23; peer-reviewed by T Janmohamed, KL Mauco, M Muldoon; comments to author 02.12.23; revised version received 22.12.23; accepted 13.02.24; published 05.03.24.

Please cite as:
McCartney H, Main A, Ibrar M, Rai HK, Weir NM, Maguire R
Professional-Facing Digital Health Solutions for the Care of Patients With Chronic Pain: Protocol for a Systematic Scoping Review
JMIR Res Protoc 2024;13:e51311
URL: https://www.researchprotocols.org/2024/1/e51311
doi:10.2196/51311
PMID:38441946

Protocol

Data Visualization Support for Tumor Boards and Clinical Oncology: Protocol for a Scoping Review

Dominik Boehm[1,2*], MSc; Cosima Strantz[3*], MSc; Jan Christoph[3,4], Dr rer biol hum; Hauke Busch[5], Dr rer nat; Thomas Ganslandt[3], Dr med; Philipp Unberath[1,6], Dr rer biol hum

[1]Medical Center for Information and Communication Technology, Universitätsklinikum Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany

[2]Bavarian Cancer Research Center (Bayerisches Zentrum für Krebsforschung), Erlangen, Germany

[3]Chair of Medical Informatics, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany

[4]Junior Research Group (Bio-)medical Data Science, Faculty of Medicine, Martin-Luther-University Halle-Wittenberg, Halle, Germany

[5]Group for Medical Systems Biology, Lübeck Institute of Experimental Dermatology, University of Lübeck, Lübeck, Germany

[6]SRH Fürth University of Applied Sciences, Fürth, Germany

[*]these authors contributed equally

Corresponding Author:
Dominik Boehm, MSc
Medical Center for Information and Communication Technology
Universitätsklinikum Erlangen
Friedrich-Alexander-Universität Erlangen-Nürnberg
Glückstraße 11
Erlangen, 91054
Germany
Phone: 49 91318546478
Email: dominik.boehm@uk-erlangen.de

Abstract

Background: Complex and expanding data sets in clinical oncology applications require flexible and interactive visualization of patient data to provide the maximum amount of information to physicians and other medical practitioners. Interdisciplinary tumor conferences in particular profit from customized tools to integrate, link, and visualize relevant data from all professions involved.

Objective: The scoping review proposed in this protocol aims to identify and present currently available data visualization tools for tumor boards and related areas. The objective of the review will be to provide not only an overview of digital tools currently used in tumor board settings, but also the data included, the respective visualization solutions, and their integration into hospital processes.

Methods: The planned scoping review process is based on the Arksey and O'Malley scoping study framework. The following electronic databases will be searched for articles published in English: PubMed, Web of Knowledge, and SCOPUS. Eligible articles will first undergo a deduplication step, followed by the screening of titles and abstracts. Second, a full-text screening will be used to reach the final decision about article selection. At least 2 reviewers will independently screen titles, abstracts, and full-text reports. Conflicting inclusion decisions will be resolved by a third reviewer. The remaining literature will be analyzed using a data extraction template proposed in this protocol. The template includes a variety of meta information as well as specific questions aiming to answer the research question: "What are the key features of data visualization solutions used in molecular and organ tumor boards, and how are these elements integrated and used within the clinical setting?" The findings will be compiled, charted, and presented as specified in the scoping study framework. Data for included tools may be supplemented with additional manual literature searches. The entire review process will be documented in alignment with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) flowchart.

Results: The results of this scoping review will be reported per the expanded PRISMA-ScR guidelines. A preliminary search using PubMed, Web of Knowledge, and Scopus resulted in 1320 articles after deduplication that will be included in the further review process. We expect the results to be published during the second quarter of 2024.

Conclusions: Visualization is a key process in leveraging a data set's potentially available information and enabling its use in an interdisciplinary setting. The scoping review described in this protocol aims to present the status quo of visualization solutions for tumor board and clinical oncology applications and their integration into hospital processes.

International Registered Report Identifier (IRRID): DERR1-10.2196/53627

(JMIR Res Protoc 2024;13:e53627) doi:10.2196/53627

KEYWORDS

clinical oncology; tumor board; cancer conference; multidisciplinary; visualization; software; tool; scoping review; tumor; malignant; benign; data sets; oncology; interactive visualization; data; patient; patients; physicians; medical practitioners; medical practitioner; conference

Introduction

Multidisciplinary team interventions, and especially tumor boards (or multidisciplinary cancer conferences [MCCs]) have been shown to significantly improve the quality of cancer care [1-3]. Complex, multimodal, and ever-growing data sets in multidisciplinary settings present special challenges when it comes to data visualization [4]. These data sets can include anything from demographic information and laboratory results to tumor imaging, pharmacotherapeutic timelines, and genomics data, providing limitless opportunities for aggregation and joint visualization. The need for digital support and customized visualization solutions becomes especially apparent when discussing the time constraints often found in clinical oncology settings. Available time frames for treatment decisions might range between 10 and 20 minutes per patient [5], highlighting the importance of aggregated and annotated data to enable participating health care professionals to include all relevant information in the decision-making process. However, even without taking limited time into account, the growing complexity of patient data makes it difficult to fully understand a patient's health status without the support of visualization, even more so when multiple points of data on the patient journey are available [6,7]. While tools for the visualization of multimodal data in the described settings exist [8-10], there is no current overview of actively used and established visualization tools and their key differences, especially on an international level.

The rise of molecular tumor boards (MTBs) has been an additional driving factor in the development of digital support applications for interdisciplinary settings and the incorporation of multimodal data. Combining ordinary clinical information with the complexity of genomics data required special tooling to enable oncologists to make fully informed treatment decisions and limit the time necessary for the MTBs' preparation [11,12]. Virtual MTBs and rising numbers of outpatient referrals lead to a heterogeneous pool of tumor board participants and increase the need for intuitive visualization. Complex patient journeys have to be presented in a condensed and clear manner, sometimes crossing language barriers, without prior knowledge of the patient or their history [12,13]. This led to the emergence of software solutions such as cBioPortal (Memorial Sloan Kettering Cancer Center) [14-16], The Cancer Core Europe Molecular Tumor Board Portal [17], and AMBAR [18], offering complex visualization of genomic variants found in cancer samples.

Additionally, knowledge bases such as OncoKB [19] or CIViC [20] have been created, providing access to annotations with aggregated and structured information on available targeted therapies. The usage of these established tools not only supports the preparation and execution of MTBs but also increases the consistency of therapy recommendations between molecular tumor conferences, even for patients with rare cancers and mutation patterns [21]. Research indicates that differing processes and tools may lead to inconsistent therapy recommendations [22].

To enable the visualization of data for the preparation and execution of MCCs, patient and supplementary data must be made available to the tools used. This is challenging as the availability of interfaces or APIs for the import of data sets can vary greatly and is often only possible through the use of proprietary data formats, which may require the development of extract, transform, and load processes to automate data import and export [23]. Additionally, data privacy regulations and ethical concerns may limit the usage of external services. Several German initiatives and consortiums (eg, Medical Informatic Initiative [24], Bavarian Center for Cancer Research [25], and German Network for Personalized Medicine [26]) are working on standardized data sets and processes related to the cancer patient journey in German hospitals. This includes software extensions for established tools such as cBioPortal, for example, covering the documentation and visualization of therapy decisions in MTBs [27,28].

In summary, there is an increasing need for additional visualization in the context of tumor board settings to leverage the full potential of growing data sets for patient care and therapy decisions. Integrating these software solutions into clinical processes is a challenging task, requiring data from a variety of sources to be readily available to facilitate their use in the preparation and execution of tumor boards. With this in mind, the objective of the proposed scoping review is to identify available software support for MCCs described in scientific literature, gather key aspects of applied visualization strategies as well as their integration into existing processes, and present them in a comprehensive overview.

Methods

Design

For conducting this scoping review study, we will use the scoping study framework of Arksey and O'Malley [29] as a methodological blueprint for this review.

Arksey and O'Malley describe a five-stage model for scoping study design: (1) identification of the research questions; (2) identification of relevant studies; (3) study selection; (4) data extraction and charting; and (5) collating, summarizing, and reporting the results. Any subsequent deviations of the final report from the scoping review protocol will be highlighted and explained in the scoping review report.

Stage 1: Identification of the Research Questions

While there has been a continuous development of digital support tools for clinical oncology settings over the last few years, currently no structured overview of the visualization tools and techniques used in these applications exists. The core research question driving the scoping review was proposed based on these circumstances, and further developed through multiple iterations of discussion in the research team:

> *Research question: What are the key features of data visualization solutions used in molecular and organ tumor boards, and how are these elements integrated and used within the clinical setting?*

Starting from this overarching research question, specific questions we wanted to answer while extracting data from relevant literature were developed. These were used at a later step to design the data extraction template. They were the following: (1) What data visualization solution is being used? (2) What kind of data are being visualized? (3) How do they visualize the available data? (4) How are these elements integrated and used within the clinical setting? (5) How accessible are the solutions? (6) Are the solutions already being used in hospitals? (7) Have the proposed or implemented solutions been evaluated?

Stage 2: Identification of Relevant Studies

Core Concepts and Keywords

To find relevant studies and gain an insight into the search domain an initial manual literature search was executed. In total, 19 key papers were identified and used to extract concepts for the development of a search strategy. All in all, we were able to identify 3 core concepts that relevant literature would have to encompass. First, tumor boards or similar settings as the target domain. Second, software or some other form of digitalized support. Lastly, the described mode of support delivered by the software, for example, visualization, usage as a decision support system, or personalized medicine.

In the following process, these concepts were used to define keywords for the development of individual search strategies for the chosen databases (Textbox 1). The initial manual literature search showed that relevant literature can be found in a variety of different contexts. Supporting applications for tumor boards may be described in publications covering the development of those tools, their integration into hospital processes, evaluations of their efficacy, or even as a sidenote in the medical literature. As such some of the keywords may seem out of scope at first glance but lead to the inclusion of additional relevant results. MTBs present one of the driving institutions for the development of multimodal and interactive visualization solutions for clinical oncology settings and as such provide a variety of keywords to the search strategy.

Textbox 1. Concepts and corresponding keywords.

Target domain

- Tumor board, tumor conference, molecular tumor board, mutation database, and cancer genomics.

Software

- Virtual, digital, software, tool, platform, and portal.

Mode of support

- Visualization, interactive, preparation, usability, clinical decision support system, personalized medicine, and precision medicine.

Query Construction

Using the defined concepts and corresponding keywords, search strategies for the different databases were built. The general strategy for this process was connecting concepts through "AND" operators, while keywords were connected by "OR" operators. The search was limited to title and abstract where possible since this proved to consistently recall key literature and articles of interest while greatly reducing the amount of out-of-scope search results. The queries were adapted to the specific database needs, for example, the usage of Medical Subject Heading Terms for PubMed. The resulting queries were tested on their recall of key literature and accuracy. They underwent an iterative optimization process based on their performance and in a last step were validated by a librarian. The proposed queries can be found in Multimedia Appendix 1. All future deviations will be documented and discussed in the final publication.

Stage 3: Study Selection

Inclusion and Exclusion Criteria

Only articles published in English during the last 10 years will be included. Since our initial search showed a very broad range of target literature types, we decided not to use further inclusion or exclusion criteria to include all potentially relevant articles.

Selection Process

All literature found by applying the search strategies to PubMed [30], Web of Knowledge [31], and SCOPUS [32] will be exported into a compatible format and uploaded to Rayyan (Rayyan) [33], which will be used for the 2-step study selection process. In the first step, title-abstract screening will be

performed to quickly exclude out-of-scope literature, reducing the workload for the full-text screening stage. Each paper will be screened by at least 2 reviewers. An additional reviewer will solve conflicting inclusion decisions. During the second screening phase, full-text screening will be performed to exclude results that will not assist in answering the research question described in Stage 1. To increase consistency, criteria for the inclusion and exclusion of literature during the screening process will be supplied to all participating researchers and discussed in a meeting before the start of the screening. The study selection process will be documented using Rayyan. The results of this process will be compiled into a PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) [34] flowchart.

Stage 4: Data Extraction and Charting

All selected literature will be searched for metadata and information relevant to answering the proposed research question. For a standardized approach between reviewing parties, a data extraction template (Table 1) was developed, encompassing all required metadata, as well as specifics regarding each aspect of the overarching research question. The data extraction template was designed in a close fashion to templates from similar review projects [35,36] as their authors were consulted during the development process of this protocol. Potential modifications to the template will be documented, properly highlighted, and discussed in the final publication.

Table 1. The data extraction tool template.

Data and item	Description
Metadata	
Title[a]	Title
Citation details[a]	Author (first), journal, and DOI
Year of publication[a]	Year of publication
Publication type[a]	Type of publication
Institute[a]	Corresponding institute
Funding source	Funding source of the publication
Objective[a]	Publication objective
Methods[a]	Short description of the methodology used
Summary result[a]	Short description of the results
Conclusion	Short description of the conclusion
Keywords	Keywords
Citations	List of articles citing this paper
Results related to the research question	
What data visualization solutions are being used?	Name and description of the applications or tools that are being used
What kind of data are being visualized?	List and description of the data that is being visualized. Name and a short description of the corresponding standardized or harmonized data set if applicable
How do they visualize the available data?	List and description of the modes of visualization applied, including interactive features such as filtering or customization
How are these elements integrated and used within the clinical setting?	Description of the integration into the clinical setting if available, covering the process integration as well as software interfaces and capabilities for the documentation of tumor boards, if available
How accessible are the solutions?	Accessibility of the software, for example, open source or commercial product, and licensing information
Are the solutions already being used in hospitals?	List of hospitals that are already using the software
Has there been a methodical evaluation of the proposed or implemented solution?	Description of the evaluation methodology and the corresponding results, if available

[a]Mandatory field.

Stage 5: Collating, Summarizing, and Reporting the Results

After data extraction and charting, the results will be analyzed in a 2-step process per Arksey and O'Malley's framework [29]. First, the findings will be analyzed numerically, comparing the extent, nature, and distribution of the literature found. Following that we will prepare a thematic overview on visualization solutions for tumor boards and clinical oncology. The visualized data per tool, as well as the respective visualization strategies

used and remaining elements of the data extraction template, will be charted and appropriate graphics will be created. The findings will be presented following the PRISMA-ScR reporting guidelines [34].

Ethical Considerations

Since our review will not involve human participants, this study does not require ethics approval.

Results

The scoping review started with a tentative search beginning in September 2023 leading to 2057 results with a suspected 1227 duplicates. In the next step titles and abstracts will be iteratively screened by reviewers to decide on the paper's inclusion in the further review process (see stage 3). This will be based on the criteria described in the Methods section. Included articles will be analyzed by applying the appended data extraction tool (see stage 4). This step is expected to be finished by December 2023. Lastly, the results will be summarized and compiled (see stage 5) up until the beginning of 2024. We expect them to be published during the second quarter of 2024.

Discussion

We designed a scoping review, aiming to present the current state of software support for clinical oncology settings, focusing on visualization solutions used in MCCs and their integration into hospital processes. The initial search, executed using the methods and queries described in this protocol, was able to show that a significant amount of potentially relevant literature can be found in the selected electronic databases. By asserting that manually identified key papers are included in the results, we are confident that the results produced by the search queries include the target domains.

However, a potential limitation of the completeness of the scoping review might be its focus on scientific literature. While tumor boards are often actively part of research projects and publicize their findings including used software solutions, commercial visualization tools and supporting software are being used as well. These might present new and interesting approaches but would not be necessarily found during a literature search. However, limited access to these applications would make their analysis difficult, and closed-source solutions often present limited possibilities for extensions and follow-up work. Additionally, available literature on supporting software might focus on features apart from visualization and offer limited insight into the questions posed. We aim to mitigate this by supplementing the findings through additional manual searches for included software.

We expect the scoping review's findings to show the current state of data visualization in clinical oncology settings. By comparing these results with the data most commonly available in the context of tumor boards and upcoming data sets we aim to anticipate visualization needs and provide starting points for more focused requirement analysis. Lastly, we hope to inform the future development of flexible visualization solutions for expanding oncology data sets.

Acknowledgments

This work was funded by the German Federal Ministry for Education and Research through the PM4Onco project (01ZZ2322S, 01ZZ2322N, and 01ZZ2322R), and by the Bavarian Cancer Research Center (BZKF). This work was performed in (partial) fulfillment of the requirements for obtaining the degree "Dr. rer. biol. hum." at the Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU).

Conflicts of Interest

None declared.

Multimedia Appendix 1
Proposed search queries for PubMed, Web of Knowledge, and SCOPUS.
[DOCX File , 14 KB - resprot_v13i1e53627_app1.docx]

References

1. Specchia ML, Frisicale EM, Carini E, Di Pilla A, Cappa D, Barbara A, et al. The impact of tumor board on cancer care: evidence from an umbrella review. BMC Health Serv Res 2020;20(1):73 [FREE Full text] [doi: 10.1186/s12913-020-4930-3] [Medline: 32005232]
2. Di Pilla A, Cozzolino MR, Mannocci A, Carini E, Spina F, Castrini F, et al. The impact of tumor boards on breast cancer care: evidence from a systematic literature review and meta-analysis. Int J Environ Res Public Health 2022;19(22):14990 [FREE Full text] [doi: 10.3390/ijerph192214990] [Medline: 36429708]
3. Lamb BW, Green JSA, Benn J, Brown KF, Vincent CA, Sevdalis N. Improving decision making in multidisciplinary tumor boards: prospective longitudinal evaluation of a multicomponent intervention for 1,421 patients. J Am Coll Surg 2013;217(3):412-420. [doi: 10.1016/j.jamcollsurg.2013.04.035] [Medline: 23891067]
4. Luchini C, Lawlor RT, Milella M, Scarpa A. Molecular tumor boards in clinical practice. Trends Cancer 2020;6(9):738-744 [FREE Full text] [doi: 10.1016/j.trecan.2020.05.008] [Medline: 32517959]

5. Larburu N, Muro N, Arrue M, Álvarez R, Kerexeta J. DESIREE—a web-based software ecosystem for the personalized, collaborative and multidisciplinary management of primary breast cancer. : IEEE; 2018 Presented at: 2018 IEEE 20th International Conference on e-Health Networking, Applications and Services (Healthcom); September 17-20, 2018; Ostrava, Czech Republic. [doi: 10.1109/healthcom.2018.8531099]
6. Wanderer JP, Nelson SE, Ehrenfeld JM, Monahan S, Park S. Clinical data visualization: the current state and future needs. J Med Syst 2016;40(12):275 [FREE Full text] [doi: 10.1007/s10916-016-0643-x] [Medline: 27787779]
7. Ledesma A, Bidargaddi N, Strobel J, Schrader G, Nieminen H, Korhonen I, et al. Health timeline: an insight-based study of a timeline visualization of clinical data. BMC Med Inform Decis Mak 2019;19(1):170 [FREE Full text] [doi: 10.1186/s12911-019-0885-x] [Medline: 31438942]
8. Lawonn K, Smit NN, Bühler K, Preim B. A survey on multimodal medical data visualization. Comput Graph Forum 2018;37(1):413-438. [doi: 10.1111/cgf.13306]
9. Kahraman A, Arnold FM, Hanimann J, Nowak M, Pauli C, Britschgi C, et al. MTPpilot: an interactive software for visualization of next-generation sequencing results in molecular tumor boards. JCO Clin Cancer Inform 2022(6):e2200032 [FREE Full text] [doi: 10.1200/cci.22.00032]
10. Canuel V, Rance B, Avillach P, Degoulet P, Burgun A. Translational research platforms integrating clinical and omics data: a review of publicly available solutions. Brief Bioinform 2015;16(2):280-290 [FREE Full text] [doi: 10.1093/bib/bbu006] [Medline: 24608524]
11. O'Donoghue SI, Baldi BF, Clark SJ, Darling AE, Hogan JM, Kaur S, et al. Visualization of biomedical data. Annu Rev Biomed Data Sci 2018;1(1):275-304 [FREE Full text] [doi: 10.1146/annurev-biodatasci-080917-013424]
12. Schapranow MP, Borchert F, Bougatf N, Hund H, Eils R. Software-tool support for collaborative, virtual, multi-site molecular tumor boards. SN Comput Sci 2023;4(4):358 [FREE Full text] [doi: 10.1007/s42979-023-01771-8] [Medline: 37131499]
13. Pishvaian MJ, Blais EM, Bender RJ, Rao S, Boca SM, Chung V, et al. A virtual molecular tumor board to improve efficiency and scalability of delivering precision oncology to physicians and their patients. JAMIA Open 2019;2(4):505-515 [FREE Full text] [doi: 10.1093/jamiaopen/ooz045] [Medline: 32025647]
14. de Bruijn I, Kundra R, Mastrogiacomo B, Tran TN, Sikina L, Mazor T, et al. Analysis and visualization of longitudinal genomic and clinical data from the AACR Project GENIE Biopharma Collaborative in cBioPortal. Cancer Res 2023;83(23):3861-3867 [FREE Full text] [doi: 10.1158/0008-5472.CAN-23-0816] [Medline: 37668528]
15. Cerami E, Gao J, Dogrusoz U, Gross BE, Sumer SO, Aksoy BA, et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discov 2012;2(5):401-404 [FREE Full text] [doi: 10.1158/2159-8290.CD-12-0095] [Medline: 22588877]
16. Gao J, Aksoy BA, Dogrusoz U, Dresdner G, Gross B, Sumer SO, et al. Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. Sci Signal 2013;6(269):pl1 [FREE Full text] [doi: 10.1126/scisignal.2004088] [Medline: 23550210]
17. Tamborero D, Dienstmann R, Rachid MH, Boekel J, Baird R, Braña I, et al. Support systems to guide clinical decision-making in precision oncology: The Cancer Core Europe Molecular Tumor Board Portal. Nat Med 2020;26(7):992-994. [doi: 10.1038/s41591-020-0969-2] [Medline: 32632195]
18. Fürstberger A, Ikonomi N, Kestler AMR, Marienfeld R, Schwab JD, Kuhn P, et al. AMBAR—interactive alteration annotations for molecular tumor boards. Comput Methods Programs Biomed 2023;240:107697 [FREE Full text] [doi: 10.1016/j.cmpb.2023.107697] [Medline: 37441893]
19. Chakravarty D, Gao J, Phillips S, Kundra R, Zhang H, Wang J, et al. OncoKB: a precision oncology knowledge base. JCO Precision Oncology 2017;1(1):1-16 [FREE Full text] [doi: 10.1200/po.17.00011] [Medline: 28890946]
20. Griffith M, Spies NC, Krysiak K, McMichael JF, Coffman AC, Danos AM, et al. CIViC is a community knowledgebase for expert crowdsourcing the clinical interpretation of variants in cancer. Nat Genet 2017;49(2):170-174 [FREE Full text] [doi: 10.1038/ng.3774] [Medline: 28138153]
21. Koopman B, Groen HJM, Ligtenberg MJL, Grünberg K, Monkhorst K, de Langen AJ, et al. Multicenter comparison of molecular tumor boards in The Netherlands: definition, composition, methods, and targeted therapy recommendations. Oncologist 2021;26(8):e1347-e1358 [FREE Full text] [doi: 10.1002/onco.13580] [Medline: 33111480]
22. Rieke DT, Lamping M, Schuh M, Le Tourneau C, Basté N, Burkard ME, et al. Comparison of treatment recommendations by molecular tumor boards worldwide. JCO Precis Oncol 2018;2:1-14 [FREE Full text] [doi: 10.1200/PO.18.00098] [Medline: 35135153]
23. Cheng KY, Pazmino S, Schreiweis B. ETL processes for integrating healthcare data—tools and architecture patterns. Stud Health Technol Inform 2022;299:151-156. [doi: 10.3233/SHTI220974] [Medline: 36325856]
24. Semler SC, Wissing F, Heyder R. German medical informatics initiative: a national approach to integrating health data from patient care and medical research. Methods Inf Med 2018;57(S 01):e50-e56 [FREE Full text] [doi: 10.3414/ME18-03-0003] [Medline: 30016818]
25. Arbeitsgruppe Molekulares Tumorboard / Molekulare Medizin (MOLTB). Bayerisches Zentrum für Krebsforschung. URL: https://bzkf.de/arbeitsgruppe-molekulares-tumorboard-molekulare-medizin-moltb/ [accessed 2023-03-27]

26. Illert AL, Stenzinger A, Bitzer M, Horak P, Gaidzik VI, Möller Y, et al. The German network for personalized medicine to enhance patient care and translational research. Nat Med 2023;29(6):1298-1301. [doi: 10.1038/s41591-023-02354-z] [Medline: 37280276]
27. Reimer N, Unberath P, Busch H, Börries M, Metzger P, Ustjanzew A, et al. Challenges and experiences extending the cBioPortal for cancer genomics to a molecular tumor board platform. Stud Health Technol Inform 2021;287:139-143. [doi: 10.3233/SHTI210833] [Medline: 34795098]
28. Reimer N, Unberath P, Busch H, Ingenerf J. FhirSpark—implementing a mediation layer to bring FHIR to the cBioPortal for cancer genomics. Stud Health Technol Inform 2021;281:303-307. [doi: 10.3233/SHTI210169] [Medline: 34042754]
29. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. Int J Soc Res Methodol 2005;8(1):19-32. [doi: 10.1080/1364557032000119616]
30. PubMed. URL: https://pubmed.ncbi.nlm.nih.gov/ [accessed 2023-10-11]
31. WebOfKnowledge.: Clarivate URL: https://WebofKnowledge.com [accessed 2023-10-11]
32. About Scopus—abstract and citation database. Elsevier. URL: https://www.elsevier.com/solutions/scopus [accessed 2023-10-11]
33. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev 2016;5(1):210 [FREE Full text] [doi: 10.1186/s13643-016-0384-4] [Medline: 27919275]
34. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med 2018;169(7):467-473 [FREE Full text] [doi: 10.7326/M18-0850] [Medline: 30178033]
35. Gierend K, Krüger F, Waltemath D, Fünfgeld M, Ganslandt T, Zeleke AA. Approaches and criteria for provenance in biomedical data sets and workflows: protocol for a scoping review. JMIR Res Protoc 2021;10(11):e31750 [FREE Full text] [doi: 10.2196/31750] [Medline: 34813494]
36. Wabo GK, Prasser F, Gierend K, Siegel F, Ganslandt T. Data quality- and utility-compliant anonymization of common data model-harmonized electronic health record data: protocol for a scoping review. JMIR Res Protoc 2023;12:e46471 [FREE Full text] [doi: 10.2196/46471] [Medline: 37566443]

Abbreviations

MCC: multidisciplinary cancer conference
MTB: molecular tumor board
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

Edited by A Mavragani; submitted 13.10.23; peer-reviewed by N Ikonomi, J Dönitz; comments to author 02.12.23; revised version received 17.12.23; accepted 19.12.23; published 05.03.24.

Please cite as:
Boehm D, Strantz C, Christoph J, Busch H, Ganslandt T, Unberath P
Data Visualization Support for Tumor Boards and Clinical Oncology: Protocol for a Scoping Review
JMIR Res Protoc 2024;13:e53627
URL: https://www.researchprotocols.org/2024/1/e53627
doi:10.2196/53627
PMID:38441925

Protocol

Innovative Solutions for Patients Who Undergo Craniectomy: Protocol for a Scoping Review

Laura L Fernandez[1*], MD, MSci; Dylan Griswold[2,3*], BA; Isla Khun[4*], MA, MSc; Diana Victoria Rodriguez De Francisco[5,6*], BSME

[1]Clinical & Translational Science Institute and Center for Global Surgery, University of Utah, Salt Lake City, UT, United States
[2]NIHR Global Health Research Group on Neurotrauma, University of Cambridge, Cambridge, United Kingdom
[3]Division of Neurosurgery, Department of Clinical Neurosciences, University of Cambridge, Cambridge, United Kingdom
[4]University of Cambridge, Cambridge, United Kingdom
[5]University of Central Florida, Orlando, FL, United States
[6]Universidad Metropolitana, Caracas, Venezuela
[*]all authors contributed equally

Corresponding Author:
Laura L Fernandez, MD, MSci
Clinical & Translational Science Institute and Center for Global Surgery
University of Utah
27 S Mario Capecci Dr, Bldg 379
Salt Lake City, UT, 84133
United States
Phone: 1 3186234080
Email: laura.fernandez.9802@gmail.com

Abstract

Background: Decompressive craniectomy (DC) is a widely used procedure to alleviate high intracranial pressure. Multidisciplinary teams have designed and implemented external medical prototypes to improve patient life quality and avoid complications following DC in patients awaiting cranioplasty (CP), including 3D printing and plaster prototypes when available.

Objective: This scoping review aims to understand the extent and type of evidence about innovative external prototypes for patients who undergo DC while awaiting CP.

Methods: This scoping review will use the Joanna Briggs Institute methodology for scoping reviews. This scoping review will include noninvasive medical devices for adult patients who undergo DC while waiting for CP. The search strategy will be implemented in MEDLINE, Embase, Web of Science, Scielo, Scopus, and the World Health Organization (WHO) Global Health Index Medicus. Patent documents were also allocated in Espacenet, Google Patents, and the World Intellectual Property Organization (WIPO) database.

Results: This scoping review is not subject to ethical approval as there will be no involvement of patients. The dissemination plan includes publishing the review findings in a peer-reviewed journal and presenting results at conferences that engage the most pertinent stakeholders in innovation and neurosurgery.

Conclusions: This scoping review will serve as a baseline to provide evidence for multidisciplinary teams currently designing these noninvasive innovations to reduce the risk of associated complications after DC, hoping that more cost-effective models can be implemented, especially in low- and middle-income countries.

International Registered Report Identifier (IRRID): DERR1-10.2196/50647

(JMIR Res Protoc 2024;13:e50647) doi:10.2196/50647

KEYWORDS

cranioplasty; decompressive craniectomy; global neurosurgery; intellectual property; stroke; traumatic brain injury; innovative; innovative solutions; craniectomy; increased intracranial pressure; intracranial pressure; prototypes; medical devices; middle-income countries; low-income countries; noninvasive

Introduction

Traumatic brain injuries (TBIs) remain a significant global health challenge affecting more than 69 million people annually [1]. The incidence of TBIs in low- and middle-income countries is disproportionate, 3 times greater than in high-income countries [1]. Severe forms of TBI (5.58 million people each year or 73 cases per 100,000 people) and other critical pathologies such as strokes and brain tumors often require a life-saving neurosurgical procedure called decompressive craniectomy (DC) [1]. DC is an essential surgical procedure that alleviates intracranial pressure, which consists of removing a section of the skull to avoid inward brain constriction due to brain parenchyma and cranial rigidity [2]. However, this intervention leaves patients vulnerable and at risk of neurological impairment, further traumas, and self-esteem difficulties while waiting for cranioplasty (CP) [3].

The overall complication rate after DC has been reported to be as high as 50% [3]. These complications include (1) the syndrome of the trephined, in which the atmospheric pressure compresses the brain parenchyma and the neurological status of the patient deteriorates after the removal of a skull bone flap, in 13% of patients who undergo DC; (2) hemorrhage, in 58%; (3) external herniation, in 25%; (4) wound complications (such as ulceration or necrosis) or surgical site infection, in up to 9%; (5) cerebral spinal fluid leakage, in 6.3%; and (6) increased risk of severe injuries from falling, among others [4-6].

A critical challenge post-DC patients face is the need for protective measures for the craniectomy site. A study described that at least 88.9% of patients have reported needing a device to prevent contact with the craniectomy site [7]. In response to this challenge, external protective devices have emerged as a potential solution to replicate the protective effects of CP and minimize postoperative complications.

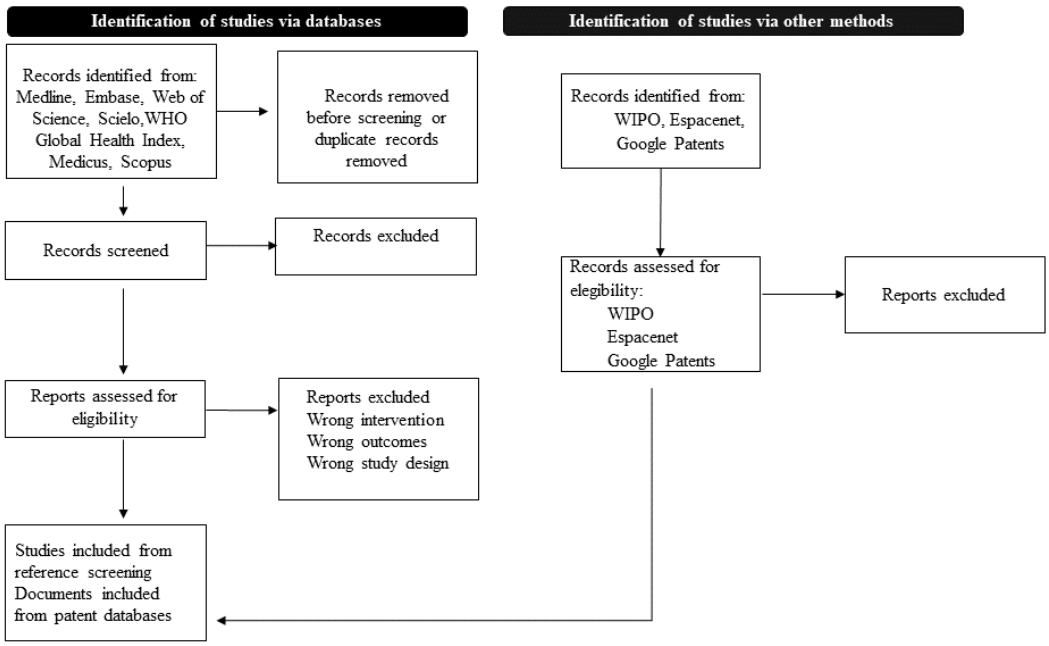
Nowadays, technological innovation in medicine drives care improvements, surgical techniques, and preventative medicine. This is especially true in neurosurgery, as shown by neurostimulation in functional neurosurgery, microneurosurgery, and the merging of computed tomography and magnetic resonance imaging intraoperatively, always possible because of the multidisciplinary teams [7,8]. The global medical device industry is highly competitive, with many countries contributing to its development and growth worldwide. Interdisciplinary teams have designed and implemented external medical prototypes in response to the need to improve patient's quality of life and avoid complications following DC in patients awaiting CP, including 3D printing and plaster prototypes, when available. Therefore, the objective of this scoping review is to develop a better understanding of available innovations in technology for patients with DC who are awaiting CP worldwide.

Methods

Overview

The proposed scoping review will use and follow the Joanna Briggs Institute methodology for scoping reviews [9]. The proposed methodology is presented in Figure 1.

Figure 1. Summary of the search strategy process. WHO: World Health Organization; WIPO: World Intellectual Property Organization.



Review Question

What is the current landscape of external medical devices replicating the effects of CP worldwide?

Eligibility Criteria

Participants

This scoping review will include prototypes for adult patients who undergo DC while waiting for CP.

Concept

External medical devices that replicate the effects of CP.

Context

This scoping review will not exclude documents based on geographic areas as it is intended to identify and locate where they have been designed and implemented.

Types of Sources

This scoping review will consider experimental and quasi-experimental study designs, including randomized controlled trials, non-randomized controlled trials, before and after studies, and interrupted time-series studies. Consideration will be given to the inclusion of analytical observational studies, which may include prospective and retrospective cohort studies, case-control, or analytical cross-sectional studies. This review will consider descriptive observational study designs, including case series, individual case reports, and descriptive cross-sectional studies for inclusion. Qualitative studies that focus on qualitative data will also be included, but are not limited to, designs such as phenomenology, grounded theory, ethnography, qualitative description, and action research.

In addition, systematic reviews that meet the inclusion criteria will also be considered, depending on the research question. Text and opinion papers will also be considered for inclusion in this scoping review. Worldwide patents will be allocated in the central databases Espacenet, Google Patents, and World Intellectual Property Organization (WIPO).

Search Strategy

The search strategy will be carried out by an experienced librarian (IK) to locate both published and unpublished documents. An initial limited search of MEDLINE was undertaken to identify studies on the topic. The text words in the titles and abstracts of relevant studies and the index terms used to describe the studies were used to develop a complete search strategy for PubMed, Scopus, Web of Science, Scielo (see Multimedia Appendix 1), and the World Health Organization (WHO) international database. Patents will also be allocated in Espacenet, Google Patents, and WIPO. The search strategy, including all identified keywords and index terms, will be adapted for each included database and information source. The reference list of all included sources of evidence will be screened for additional studies. Studies published in any language will be included, and translation services will be used if necessary. No time limit has been established.

Study or Source of Evidence Selection

All identified citations will be collated and uploaded to EndNoteX9 (Clarivate Analytics) after the search. The citations will then be imported into Covidence software (Veritas Health Innovation) for screening. A total of 2 independent researchers will examine titles and abstracts for inclusion. The full text of selected studies will be retrieved and assessed. Full-text studies that do not meet the inclusion criteria will be excluded, and the reasons for exclusion will be provided in the final scoping review. Any disagreements between the researchers during either title and abstract screening or full-text screening will be resolved through discussion or with a third reviewer. All included studies will undergo a process of data extraction using a standardized data extraction tool. The final study will report the search results in complete and present using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist.

Data Extraction

Data will be extracted from papers and patent documents included in the scoping review by 2 or more independent reviewers using a data extraction tool developed by the reviewers. The data extracted will include specific details about the participants, concept, context, study methods, and critical findings relevant to the review questions.

A draft extraction is provided in Multimedia Appendix 2. It will be modified as necessary while extracting data from each included evidence source. Modifications will be detailed in the scoping review. Any reviewer disagreements will be resolved through discussion or with additional reviewers. If appropriate, authors of studies could be contacted to request missing or other data, where required.

Data Analysis and Presentation

The extracted data will be presented in tabular form and as a narrative summary that aligns with the aim of this scoping review. The table will report (1) the distribution of medical devices by countries of origin or study design, (2) functional claims or features, (3) implementation strategies, (4) patient outcomes, (5) costs, and (6) strengths and weaknesses. This table may be further refined at the review stage. Graphical representations may be used, including bar charts, line charts, pie charts, and diagrams. A narrative summary will accompany the tabulated or charted results and describe how the results relate to the review's objectives.

Ethical Considerations

No ethics approval will be required, as this review is based on already published data and does not involve interaction with human participants.

Results

The research for this systematic review commenced in February 2023, and we expect to publish the findings in 2024. The plan for dissemination, however, is to publish the review results in a peer-reviewed journal and present findings at high-level conferences that engage the most pertinent stakeholders involved in innovation and neurosurgery.

Discussion

Cumulatively, 6838 studies were identified from the database searches and 1652 from patent searches, after which 64 scientific papers and 4 patent documents were left for full-text review. Of these, 9 documents met the inclusion criteria and will be used in the final synthesis. Three categories of study design were identified: case reports (n=6), cohort studies (n=1), and exploratory clinical trials (n=1). One of the documents was not a scientific report and was categorized as a patent document. The complete data analysis and discussion will be published in an indexed journal once it is finished in an indexed journal upon completion.

This protocol has been rigorously developed and explicitly designed to illustrate and summarize the evidence regarding innovative external devices for patients with DC awaiting CP worldwide. This scoping review will serve as a baseline to provide evidence for multidisciplinary teams currently designing these noninvasive innovations to reduce the risk of associated complications after DC, hoping that more cost-effective models can be implemented, especially in middle-income and low-income countries. The principal limitation of this and any scoping review is the quality of the included studies leaving the included literature with a higher risk of bias.

Although most of these devices were developed in middle- and high-income countries, they serve as a starting point for implementation and future development in lower-income countries where no current solutions exist.

Acknowledgments

The Educational Resource Development Council and the Center for Global Surgery of the University of Utah supported LF. The Gates Cambridge Trust supported DG. DG was funded by the Gates Cambridge Trust (OPP1144).

Data Availability

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

Authors' Contributions

LLF, DG, and IK designed the review. LLF and DG refined the review design. All authors were involved in subsequent draft study reviews and updates and approved the final version of this protocol.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Pubmed and Scopus Search strategy.
[DOCX File , 16 KB - resprot_v13i1e50647_app1.docx]

Multimedia Appendix 2
Data extraction instrument.
[DOCX File , 32 KB - resprot_v13i1e50647_app2.docx]

References

1. Dewan MC, Rattani A, Gupta S, Baticulon RE, Hung YC, Punchak M, et al. Estimating the global incidence of traumatic brain injury. J Neurosurg 2018;130(4):1080-1097 [FREE Full text] [doi: 10.3171/2017.10.JNS17352] [Medline: 29701556]
2. Mee H, Anwar F, Timofeev I, Owens N, Grieve K, Whiting G, et al. Cranioplasty: a multidisciplinary approach. Front Surg 2022;9:864385 [FREE Full text] [doi: 10.3389/fsurg.2022.864385] [Medline: 35656088]
3. Yang XF, Wen L, Shen F, Li G, Lou R, Liu WG, et al. Surgical complications secondary to decompressive craniectomy in patients with a head injury: a series of 108 consecutive cases. Acta Neurochir (Wien) 2008 Dec;150(12):1241-7; discussion 1248 [FREE Full text] [doi: 10.1007/s00701-008-0145-9] [Medline: 19005615]
4. Gopalakrishnan MS, Shanbhag NC, Shukla DP, Konar SK, Bhat DI, Devi BI. Complications of decompressive craniectomy. Front Neurol 2018;9:977 [FREE Full text] [doi: 10.3389/fneur.2018.00977] [Medline: 30524359]
5. Kurland DB, Khaladj-Ghom A, Stokum JA, Carusillo B, Karimy JK, Gerzanich V, et al. Complications associated with decompressive craniectomy: a systematic review. Neurocrit Care 2015;23(2):292-304 [FREE Full text] [doi: 10.1007/s12028-015-0144-7] [Medline: 26032808]
6. Livesay S, Moser H. Evidence-based nursing review of craniectomy care. Stroke 2014;45(11):e217-e219 [FREE Full text] [doi: 10.1161/STROKEAHA.114.006355] [Medline: 25316281]

7. Marcus HJ, Hughes-Hallett A, Kwasnicki RM, Darzi A, Yang GZ, Nandi D. Technological innovation in neurosurgery: a quantitative study. J Neurosurg 2015;123(1):174-181 [FREE Full text] [doi: 10.3171/2014.12.JNS141422] [Medline: 25699414]
8. Zusman EE. Restructuring of multidisciplinary scientific meetings improves valuable exchange of information. Neurosurgery 2011;69(4):N16-N18 [FREE Full text] [doi: 10.1227/01.neu.0000405594.01331.c2] [Medline: 21900803]
9. Aromataris E, Munn Z, Tufanaru C, Campbell J, Hopp L. JBI Reviewer's Manual. The Joanna Briggs Institute. 2019. URL: https://jbi-global-wiki.refined.site/space/MANUAL/4685848/Previous+versions?attachment=/rest/api/content/4685848/child/attachment/att4698146/download&type=application/pdf&filename=JBI_Reviewers_Manual_2020March [accessed 2024-02-14]

Abbreviations

CP: cranioplasty
DC: decompressive craniectomy
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
TBI: traumatic brain injury
WHO: World Health Organization
WIPO: World Intellectual Property Organization

Edited by A Mavragani; submitted 15.12.23; peer-reviewed by DM Sanchez Parra, S Li; comments to author 25.01.24; revised version received 30.01.24; accepted 31.01.24; published 07.03.24.

Please cite as:
Fernandez LL, Griswold D, Khun I, Rodriguez De Francisco DV
Innovative Solutions for Patients Who Undergo Craniectomy: Protocol for a Scoping Review
JMIR Res Protoc 2024;13:e50647
URL: https://www.researchprotocols.org/2024/1/e50647
doi:10.2196/50647
PMID:38451601

Protocol

Characteristics of Occupational Therapy Interventions to Promote Healthy Aging: Protocol for a Scoping Review

Katrina Bannigan[1], BD, BSc, PhD; Nicole Jade Larkan[1], BA, PGDip; Emmanuelle Renee Rogelia Meurgue[1], BSc; Jason Chun Hin Sze[1], BSc

School of Health and Life Sciences, Glasgow Caledonian University, Glasgow, United Kingdom

Corresponding Author:
Katrina Bannigan, BD, BSc, PhD
School of Health and Life Sciences
Glasgow Caledonian University
Cowcaddens Road
Glasgow, G4 0BA
United Kingdom
Phone: 44 01413313608
Email: katrina.bannigan@gcu.ac.uk

Abstract

Background: Healthy aging is a pressing public health priority. Focusing on what people do every day may be a meaningful approach to lifestyle change, suggesting a need for occupation therapy interventions to promote healthy aging. A preliminary database search was conducted, and no current or underway systematic or scoping reviews on the topic were identified. Developing an overview of studies of occupational therapy interventions to promote healthy aging is a necessary first step to understanding the existing knowledge and increasing the impact of future interventions. This scoping review will build on previously conducted reviews.

Objective: This scoping review will identify the following: (1) what occupational therapy interventions exist for promoting healthy aging in community-dwelling adults? and (2) what are the intervention characteristics, their evaluated outcome, and the impact observed?

Methods: This protocol was reviewed by 2 occupational therapists as part of a patient and public involvement consultation. The review will consider all studies and publications of occupational therapy focused on promoting healthy aging in community-dwelling adults who are aged 18 years and older. Databases to be searched are AMED, CINAHL, Cochrane Library, Embase, JBI EBP database, MEDLINE, OAlster, PsycINFO, PsycArticles, ProQuest Dissertations & Theses, ProQuest nursing and allied health source, PubMed, and Science Direct. Studies published in any language will be included. Titles and abstracts will be screened against the inclusion criteria using Covidence (Veritas Health Innovation). Potentially relevant studies will be retrieved in full and assessed against the inclusion criteria. No date limiters will be used. Study selection will be completed by 2 independent reviewers. Data will be extracted using a data extraction tool, including descriptive characteristics of the participants including age, sex, and socioeconomic status. Data will be charted using the TIDieR (Template for Intervention Description and Replication) checklist in alignment with the review objectives. The scoping review will be reported in accordance with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) statement.

Results: The research began in October 2023, and the results are expected to be published in 2024.

Conclusions: This scoping review will produce valuable information about occupation-based interventions to promote healthy aging to support the development of an occupational therapy intervention.

Trial Registration: Open Science Framework 5k36d; https://osf.io/5k36d/

International Registered Report Identifier (IRRID): DERR1-10.2196/55198

(JMIR Res Protoc 2024;13:e55198) doi:10.2196/55198

KEYWORDS

healthy aging; interventions; occupational therapy; public health; scoping review; intervention; aging; lifestyle change; aging population; well-being; occupation-based approach; occupational therapists; older people

Introduction

Overview

The proportion of older people in society will double to 22% between 2015 and 2050 [1]. To this end, the United Nations has instituted a *decade of healthy aging 2021-2030* aimed at promoting healthy aging and addressing the challenges associated with an aging population across the life course [2]. This means active aging and healthy lifestyles have become priorities for public health internationally [3]. Healthy aging is "the process of developing and maintaining the functional ability that enables well-being in older age" [4]. It comprises the intrinsic capacity of the individual—their physical and mental capacities, environmental characteristics, and the interactions between them [2]. It is not necessary to be completely free from illness or disability to achieve healthy aging [2]. A meaningful life, such as a life filled with worthwhile activities [5] or being able to remain living in the community, may help promote successful and healthy aging [6]. This suggests an occupation-based approach centered on what people do every day could be a key to unlocking the 5 pillars to aging well, namely, healthy eating, hydration, exercise, social connections, and cognitive health [7]. Occupational therapists provide opportunities for individuals to engage in activities and live how they wish at every stage of life, and this may offer a meaningful approach to healthy aging [8]. It has been suggested that "The occupational therapy profession has an essential role to play in healthy aging that includes enabling participation" [9].

Occupational therapists already work in this field and occupation-based health promotion interventions exist [10]. However, some of the existing reviews are no longer current; for example, Gustafsson et al [11], Arbesman and Mosley [12], and Stav et al [13] have not been updated. A review of older people's lived experience of occupation and well-being, based on 3 studies of moderate quality, suggests there is a relationship between well-being and occupation for older people. This is shaped by 2 factors: "first, variation and independence in undertaking activities; second, having a choice between the occupations and a structure of activities that make up daily life. The two factors are influenced by a balance between having activities alone and with others." [14]. A review of economic evaluations of occupational therapy for people with cognitive or functional decline, or both, found that evidence was scarce, with few comprehensive high-quality economic evaluations having been conducted, but those that have been conducted suggest the interventions are effective and have economic benefits [15].

The literature focuses on older people, rather than other points in the life span, despite the life course approach endorsed by the United Nations' *decade of healthy aging 2021-2030* [2]. Nonetheless, the population of older adults has been variously defined as 60 years old [13], over 65 years of age or older [9], or 80 years of age or older [12]. Interventions have targeted people living in nursing homes [16], Australian residential aged care facilities [17], and community-dwelling older people [10,17,18]. The focus has tended to be on secondary prevention, within the context of disease management, rather than primary prevention with community-dwelling adults [10]. No study was identified that delineated the characteristics of the interventions reviewed, which is a necessary first step to understanding the existing knowledge and supporting the design, evaluation, and impact of future interventions [19]. Intervention development should be explicit about the content of the intervention, its theoretical foundation, and the context in which the intervention is delivered [11]. Therefore, to further understand how occupational therapy can contribute to promoting healthy aging, it is important to understand the interventions available, their characteristics, and the impact observed [20].

A scoping review is a first step toward identifying what occupational therapy interventions exist to promote healthy aging for community-dwelling adults. A preliminary search of Cochrane Library, figshare, JBI Evidence Synthesis MEDLINE, Open Science Framework, PROSPERO, and PubMed was conducted. The search identified 11 recent reviews. While the reviews identified had a bearing on the topic, most were not specifically about the topic. A total of 7 of the 11 reviews were about discrete topics, that is, older adults' occupations in heatwaves [21], joy among older people [22], quality of life [16,23], e-tools for transportation planning [24], occupational therapy in residential aged care [17], and instruments to support occupational therapy practice [9]. A review by Kim et al [18] focused on daily functioning and included occupational therapy, but its focus was on activities of daily living and instrumental activities of daily living rather than the broader concept of healthy aging. A scoping review by Mehrotra et al [20] about healthy aging and occupational therapy in South Asian countries was potentially replicable for a wider population, but the full report is not available and the authors of the protocol have not responded to requests for the full report. The rapid review by Owusu-Addo et al [25] was about implementation approaches rather than interventions. Occupational therapy was included in the review of the theory-based specification of nonpharmacological treatments in aging and dementia by Sikkes et al [26], but it did not cover specific interventions and its focus was dementia—secondary prevention—rather than healthy aging more generally. This means that no existing or contemporary review was identified, but these reviews provide valuable insights into how to conduct a review in this field. For example, keywords for searching should include productive aging [10], aging well, healthy aging, positive aging, and successful aging [20]. Thus, a scoping review will be conducted to provide an overview of occupational therapy in relation to promoting healthy aging and discover gaps in knowledge. This will provide up-to-date evidence about occupational therapy interventions to promote healthy aging and its characteristics [19].

Review Questions

This scoping review will identify the following: (1) what occupational therapy interventions exist for promoting healthy aging in community-dwelling adults? and (2) what are the intervention characteristics, their evaluated outcome, and the impact observed?

Methods

Study Design

The proposed scoping review will be conducted in accordance with the Joanna Briggs Institute (JBI) methodology for scoping reviews [27]. This scoping review protocol is registered on the Open Science Framework [28] and will be reported in accordance with the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) statement [29]. This scoping review protocol will be conducted using the JBI guidelines for scoping reviews to ensure a systematic methodology that can be replicated and reported in line with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) [30].

Eligibility Criteria

Participants

This review will consider studies of occupational therapy focused on promoting healthy aging in adults living in the community—community-dwelling—aged 18 years or older. This may include adults living in their own homes or a care setting. Studies will be excluded if they focus on children.

Concept

The concept being mapped in this scoping review will be occupational therapy interventions to promote healthy aging in the context of the life course approach. The life course approach acknowledges that health and well-being are influenced by social, economic, and environmental factors throughout a person's life, as well as personal characteristics [31]. The terms active aging and healthy aging, although subtlety different, are often used interchangeably, that is, active aging refers to "optimizing opportunities for health, participation and security in order to enhance the quality of life as people age" [32], and healthy aging is defined as "developing and maintaining the functional ability that enables well-being in older age" [4], where functional ability includes people's ability to meet their basic needs to ensure an adequate standard of living, learning, growing and making decisions, being mobile, building and maintaining relationships, and contributing to society [2]. Therefore, this scoping review will consider studies with interventions that focus on active aging or healthy aging as part of health promotion, that is, primary prevention. Studies will be excluded if they address secondary prevention, that is, interventions that focus on the early stages of disease, such as fall prevention for older adults following a fall, or tertiary prevention, that is, interventions during the symptomatic phase of a disease to minimize disability and maximize quality of life, such as foot care for people living with diabetes.

The word "occupation," in the context of occupational therapy, refers to the everyday activities that humans engage in as part of their daily routine to occupy time, providing purpose and meaning to their lives [33,34]. Occupations are the activities people want to do, need to do, or are expected to do [34]. Examples of these meaningful activities can include social interaction with peers, cooking, different forms of exercise, and working [35]. Occupation-based interventions aim to enhance the performance of an individual when undertaking meaningful activities of daily living by increasing their social and community interaction [36]. Occupation-focused interventions encapsulate the rapid improvement of an individual's performance through compensatory methods by implementing adaptive measures to be tailored to their current performance level [37]. Interventions are implemented to increase the performance of the individual in the desired or necessary tasks [38].

Context

This review will consider studies from any setting, in any country. As a global perspective will be considered, it means no limit on language will be made in the search strategy. This will ensure valuable insights are not lost because they were published in a language other than English [39]. As no language limits will be imposed, relevant papers that are not published in the English language will be translated using Google Translate. Jackson et al [40] have revisited the work by Balk et al [41], who recommended that Google Translate can be used with caution because Google has updated its translation engine. Jackson et al [40] concluded that it is a viable, accurate tool for translating non-English language trials for the purpose of conducting systematic reviews, which is why we will use it for our review. We appreciate that a scoping review is more narrative based than a systematic review; therefore, if we have access to a native speaker, the translation will be checked by them. If it is not possible to verify the translation, this will be reported within the review report. The number and sources of non-English language literature will be reported in the review report.

Types of Sources

This scoping review will consider both experimental and quasi-experimental study designs, including randomized controlled trials, nonrandomized controlled trials, before and after studies, and interrupted time-series studies. In addition, analytical observational studies, including prospective and retrospective cohort studies, case-control studies, and analytical cross-sectional studies will be considered for inclusion. This review will also consider descriptive observational study designs, including case studies, individual case reports, and descriptive cross-sectional studies for inclusion. Qualitative studies will also be considered that focus on qualitative data including, but not limited to, designs such as phenomenology, grounded theory, ethnography, qualitative description, action research, and feminist research. In addition, systematic reviews that meet the inclusion criteria will also be considered depending on the research question. Text and opinion papers will also be considered for inclusion in this scoping review.

Review Team

The review is being conducted by a team comprised of an academic (KB) and 3 postgraduate researchers (JCHS, NJL, and ERRM).

Patient and Public Involvement

The scoping review protocol has been reviewed by 2 occupational therapists working in the field of healthy aging or with older people.

Search Strategy

The search strategy will aim to locate both published and unpublished studies. An initial limited search of AMED, CINAHL, Cochrane Library, MEDLINE PsycINFO, and PubMed was undertaken to identify if a review of this topic has previously been conducted. The text words contained in the titles and abstracts of relevant studies, and the index terms used to describe the studies were used to develop a full search strategy for AMED, CINAHL, Cochrane Library, Embase, JBI EBP database, MEDLINE, OAlster, PsycINFO, PsycArticles, ProQuest nursing and allied health source, ProQuest Dissertations & Theses, PubMed, and Science Direct (see Multimedia Appendix 1 for an example search strategy). The search strategy, including all identified keywords and index terms, will be adapted for each included database and information source. The reference list of all included sources of evidence will be screened for additional studies. The searches will be conducted by KB, NJL, JCHS, and ERRM. No date or language limiters will be used.

Study or Source of Evidence Selection

Following the search, all identified citations will be collated and uploaded into Covidence [42] and duplicates will be removed. Following a pilot test, titles and abstracts will then be screened by 2 or more independent reviewers for assessment against the inclusion criteria for the review. Potentially relevant sources will be retrieved in full, and their citation details imported into Covidence [42]. The full text of selected citations will be assessed in detail against the inclusion criteria by 2 or more independent reviewers. Reasons for the exclusion of sources of evidence that do not meet the inclusion criteria during full-text screening will be recorded and reported in the scoping review. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussion or with additional reviewers. The results of the search and the study inclusion process will be reported in full in the final scoping review and presented in a PRISMA-ScR flow diagram [30].

Data Extraction

A draft extraction form is provided (see Multimedia Appendix 2). The draft data extraction tool may be modified and revised as necessary during the process of extracting data from each included evidence source. Modifications will be detailed in the scoping review. Any disagreements that arise between the reviewers will be resolved through discussion or with additional reviewers. If appropriate, authors of papers will be contacted to request missing or additional data, where required.

Ethical Considerations

As this scoping review covers reviewing and extracting data from publicly available materials, this study does not require ethics approval.

Data Analysis

The TIDieR (Template for Intervention Description and Replication) checklist will be used in this review to ensure completeness in the reporting of the characteristics of interventions [43]. The extracted data will be charted in tabular form using the TIDieR checklist. The charted results will be accompanied by a narrative summary and will describe the relationship between the result and the review's objectives and questions. The results will be presented in accordance with the TIDieR format and the main conceptual categories used in the extraction too, as well as gaps in the existing literature. These results will be presented in relation to the question of this scoping review. The narrative will be guided by the Patterns, Advances, Gaps, Evidence for practice and Research recommendations (PAGER) framework [44]—a structured approach to the analysis and reporting of scoping reviews.

Results

The research began in October 2023, and the results are expected to be published in 2024.

Discussion

Findings

This scoping review will produce a map of the current body of research about occupational therapy interventions to promote healthy aging among community-dwelling adults. As far as we know, this is the first scoping review that maps the occupational therapy interventions that exist to promote healthy aging for community-dwelling adults, the intervention characteristics, and their evaluated outcome and impact that is not limited to any country. Similar to any review, there exist limitations when conducting a scoping review. Although a rigorous identification and inclusion strategy has been delineated, there is still a risk that some valuable information, which could have enhanced our comprehension, might be inadvertently excluded. This is particularly prevalent in the case of grey literature, which may not always come up in academic searches. As the aim and nature of a scoping review are to explore the breadth of a topic to see what has been done, but not the depth, the reviewers are not able to evaluate the quality of the studies that are incorporated within the scoping review. Although scoping reviews can be helpful in generating hypotheses and identifying research gaps, they may not offer the same degree of thoroughness or meticulousness as a systematic review that involves a more rigorous and comprehensive methodology for data collection and analysis and, consequently, may offer a higher level of evidence than scoping reviews [45]. A methodological appraisal of the included studies will not be performed. It is important to note that the limitations and results presented in the suggested review may not be all-encompassing or investigated beyond the peer-review stage of the published paper.

Conclusions

The review authors will use the findings of this scoping review to support the development of a manualized occupational therapy intervention [46] to promote healthy aging within the EmpowerAge program being developed at Glasgow Caledonian University.

Acknowledgments

The authors would like to thank Laura Hall and Rowena Harrison for their contribution to the development of this protocol.

Data Availability

Data sharing is not applicable to this study as no data sets were generated or analyzed during protocol development.

Authors' Contributions

The design of the protocol was conducted by KB. The drafting of the study was done by KB, JCHS, NJL, and ERRM. All authors approved the final study.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[DOCX File , 30 KB - resprot_v13i1e55198_app1.docx]

Multimedia Appendix 2
Data extraction instrument.
[DOCX File , 33 KB - resprot_v13i1e55198_app2.docx]

References

1. World Health Organization. Ageing and health. World Health Organization. Geneva, Switzerland: World Health Organization; 2022. URL: https://www.who.int/news-room/fact-sheets/detail/ageing-and-health [accessed 2023-09-28]
2. World Health Organization. Decade of Healthy Ageing: Baseline Report. Geneva: World Health Organization; 2021.
3. Rodríguez-Monforte M, Fernández-Jané C, Martin-Arribas A, Costa-Tutusaus L, Sitjà-Rabert M, Ramírez-García I, et al. Interventions across the retirement transition for improving well-being: a scoping review. Int J Environ Res Public Health 2020;17(12):4341 [FREE Full text] [doi: 10.3390/ijerph17124341] [Medline: 32560506]
4. World Health Organization. World Report on Ageing and Health. Geneva: World Health Organization; 2015. URL: https://www.who.int/publications/i/item/9789241565042 [accessed 2024-03-05]
5. Steptoe A, Fancourt D. Leading a meaningful life at older ages and its relationship with social engagement, prosperity, health, biology, and time use. Proc Natl Acad Sci U S A 2019;116(4):1207-1212 [FREE Full text] [doi: 10.1073/pnas.1814723116] [Medline: 30617082]
6. Mack R, Salmoni A, Viverais-Dressler G, Porter E, Garg R. Perceived risks to independent living: the views of older, community-dwelling adults. Gerontologist 1997;37(6):729-736 [FREE Full text] [doi: 10.1093/geront/37.6.729] [Medline: 9432989]
7. Vseteckova J. Five pillars of ageing well. The Open University. 2023. URL: https://www.open.edu/openlearn/health-sports-psychology/mental-health/five-pillars-ageing-well [accessed 2024-02-23]
8. Moll SE, Gewurtz RE, Krupa TM, Law MC, Larivière N, Levasseur M. "Do-live-well": a Canadian framework for promoting occupation, health, and well-being. Can J Occup Ther 2015;82(1):9-23. [doi: 10.1177/0008417414545981] [Medline: 25803944]
9. Knightbridge L, Bourke-Taylor HM, Hill KD. Healthy ageing through participation in community situated activities: a scoping review of assessment instruments to support occupational therapy practice. Aust Occup Ther J 2022;69(4):493-509 [FREE Full text] [doi: 10.1111/1440-1630.12802] [Medline: 35445413]
10. Smallfield S, Elliott SJ. Occupational therapy interventions for productive aging among community-dwelling older adults. Am J Occup Ther 2020;74(1):7401390010p1-7401390010p5 [FREE Full text] [doi: 10.5014/ajot.2020.741003] [Medline: 32078523]
11. Gustafsson S, Edberg AK, Johansson B, Dahlin-Ivanoff S. Multi-component health promotion and disease prevention for community-dwelling frail elderly persons: a systematic review. Eur J Ageing 2009;6(4):315 [FREE Full text] [doi: 10.1007/s10433-009-0132-x] [Medline: 28798613]
12. Arbesman M, Mosley LJ. Systematic review of occupation- and activity-based health management and maintenance interventions for community-dwelling older adults. Am J Occup Ther 2012;66(3):277-283. [doi: 10.5014/ajot.2012.003327] [Medline: 22549592]
13. Stav WB, Hallenen T, Lane J, Arbesman M. Systematic review of occupational engagement and health outcomes among community-dwelling older adults. Am J Occup Ther 2012;66(3):301-310. [doi: 10.5014/ajot.2012.003707] [Medline: 22549595]

14. Jessen-Winge C, Petersen MN, Morville AL. The influence of occupation on wellbeing, as experienced by the elderly: a systematic review. JBI Database System Rev Implement Rep 2018;16(5):1174-1189. [doi: 10.11124/JBISRIR-2016-003123] [Medline: 29762312]
15. Rahja M, Comans T, Clemson L, Crotty M, Laver K. Economic evaluations of occupational therapy approaches for people with cognitive and/or functional decline: a systematic review. Health Soc Care Community 2018;26:635-653 [FREE Full text] [doi: 10.1111/hsc.12553] [Medline: 29532555]
16. Portillo CU, Arenillas JIC, Miralles PM. Occupational therapy interventions for the improvement of the quality of life of healthy older adults living in nursing homes: a systematic review. Am J Health Promot 2023;37(5):698-704. [doi: 10.1177/08901171221145159] [Medline: 36503271]
17. Calderone L, Bissett M, Molineux M. Occupational therapy in Australian residential aged care facilities: a systematic mapping review. Aust Occup Ther J 2022;69(5):625-636 [FREE Full text] [doi: 10.1111/1440-1630.12824] [Medline: 35715976]
18. Kim M, Shin E, Kim S, Sok S. The effectiveness of multicomponent intervention on daily functioning among the community-dwelling elderly: a systematic review. Int J Environ Res Public Health 2022;19(12):7483 [FREE Full text] [doi: 10.3390/ijerph19127483] [Medline: 35742730]
19. O'Cathain A, Croot L, Duncan E, Rousseau N, Sworn K, Turner KM, et al. Guidance on how to develop complex interventions to improve health and healthcare. BMJ Open 2019;9(8):e029954 [FREE Full text] [doi: 10.1136/bmjopen-2019-029954] [Medline: 31420394]
20. Mehrotra S, Pundir P, Shetty RS. Healthy ageing and occupational therapy in South Asian countries: a scoping review protocol. BMJ Open 2021;11(5):e044657 [FREE Full text] [doi: 10.1136/bmjopen-2020-044657] [Medline: 33952545]
21. Fransson A, Carlstedt AB, Gustafsson S. Older adults' occupations in heat waves: a scoping review. Scand J Occup Ther 2023;30(7):1000-1015 [FREE Full text] [doi: 10.1080/11038128.2023.2231165] [Medline: 37402383]
22. Goodwin VA, Hall AJ, Bethel A, Taylor E, Tatnell L, Turner M, et al. Understanding joy amongst older people: a scoping review. Arch Gerontol Geriatr 2023;115:105118 [FREE Full text] [doi: 10.1016/j.archger.2023.105118] [Medline: 37516061]
23. Frías-Luque MD, Toledano-González A. Determinants of quality of life and well-being in cognitively unimpaired older adults: a systematic review. PeerJ 2022;10:e12900 [FREE Full text] [doi: 10.7717/peerj.12900] [Medline: 35186486]
24. Tahir S, Abdulrazak B, Baillargeon D, Girard C, Provencher V. Adapting transportation planning e-tools to older adults' needs: scoping review. JMIR Aging 2023;6:e41938 [FREE Full text] [doi: 10.2196/41938] [Medline: 37191985]
25. Owusu-Addo E, Ofori-Asenso R, Batchelor F, Mahtani K, Brijnath B. Effective implementation approaches for healthy ageing interventions for older people: a rapid review. Arch Gerontol Geriatr 2021;92:104263. [doi: 10.1016/j.archger.2020.104263] [Medline: 33010790]
26. Sikkes SAM, Tang Y, Jutten RJ, Wesselman LMP, Turkstra LS, Brodaty H, et al. Toward a theory-based specification of non-pharmacological treatments in aging and dementia: focused reviews and methodological recommendations. Alzheimers Dement 2021;17(2):255-270 [FREE Full text] [doi: 10.1002/alz.12188] [Medline: 33215876]
27. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015;350:g7647 [FREE Full text] [doi: 10.1136/bmj.g7647] [Medline: 25555855]
28. Bannigan K, Sze JCH, Larkan N, Mergue E. Characteristics of occupational therapy interventions to promote healthy ageing: a scoping review. Center for Open Science. 2023. URL: https://osf.io/5k36d/ [accessed 2024-02-28]
29. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4(1):1 [FREE Full text] [doi: 10.1186/2046-4053-4-1] [Medline: 25554246]
30. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med 2018;169(7):467-473 [FREE Full text] [doi: 10.7326/M18-0850] [Medline: 30178033]
31. The Minsk declaration: the life-course approach in the context of health 2020. World Health Organization. 2015. URL: https://apps.who.int/iris/handle/10665/349095 [accessed 2023-09-28]
32. Active ageing: a policy framework. World Health Organization. 2002. URL: https://apps.who.int/iris/handle/10665/67215 [accessed 2023-09-28]
33. Christiansen C, Baum CM, Bass JD. A welcome to occupational therapy: performance, participation, and well-being. In: Occupational Therapy: Performance, Participation, and Well-Being, 4th Edition. Thorofare, NJ: SLACK Incorporated; 2015.
34. American Occupational Therapy Association. Occupational therapy practice framework: domain and process-fourth edition. Am J Occup Ther 2020;74(Suppl 2):7412410010p1-7412410010p87. [doi: 10.5014/ajot.2020.74S2001] [Medline: 34780625]
35. Legg LA, Lewis SR, Schofield-Robinson OJ, Drummond A, Langhorne P. Occupational therapy for adults with problems in activities of daily living after stroke. Cochrane Database Syst Rev 2017;7(7):CD003585 [FREE Full text] [doi: 10.1002/14651858.CD003585.pub3] [Medline: 28721691]
36. Fisher AG. Occupation-centred, occupation-based, occupation-focused: same, same or different? Scand J Occup Ther 2013;20(3):162-173. [doi: 10.3109/11038128.2012.754492] [Medline: 23311311]

37. Ford E, Di Tommaso A, Molineux M, Gustafsson L. Identifying the characteristics of occupation-centred practice: a Delphi study. Aust Occup Ther J 2022;69(1):25-37 [FREE Full text] [doi: 10.1111/1440-1630.12765] [Medline: 34490901]
38. Ikiugu MN, Lucas-Molitor W, Feldhacker D, Gebhart C, Spier M, Kapels L, et al. Guidelines for occupational therapy interventions based on meaningful and psychologically rewarding occupations. J Happiness Stud 2018;20(7):2027-2053. [doi: 10.1007/s10902-018-0030-z]
39. Rasmussen LN, Montgomery P. The prevalence of and factors associated with inclusion of non-english language studies in Campbell systematic reviews: a survey and meta-epidemiological study. Syst Rev 2018;7(1):129 [FREE Full text] [doi: 10.1186/s13643-018-0786-6] [Medline: 30139391]
40. Jackson JL, Kuriyama A, Anton A, Choi A, Fournier JP, Geier AK, et al. The accuracy of Google Translate for abstracting data from non-English-language trials for systematic reviews. Ann Intern Med 2019;171(9):677-679. [doi: 10.7326/M19-0891] [Medline: 31357212]
41. Balk EM, Chung M, Hadar N, Patel K, Yu WW, Trikalinos TA, et al. Accuracy of Data Extraction of Non-English Language Trials with Google Translate. Rockville, Maryland: Agency for Healthcare Research and Quality (US); 2012.
42. The world's #1 systematic review tool. Covidence. Melbourne, Australia: Veritas Health Innovation URL: https://www.covidence.org/ [accessed 2024-02-28]
43. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: Template for Intervention Description and Replication (TIDieR) checklist and guide. BMJ 2014;348:g1687 [FREE Full text] [doi: 10.1136/bmj.g1687] [Medline: 24609605]
44. Bradbury-Jones C, Aveyard H, Herber OR, Isham L, Taylor J, O'Malley L. Scoping reviews: the PAGER framework for improving the quality of reporting. Int J Soc Res Methodol 2021;25(4):457-470. [doi: 10.1080/13645579.2021.1899596]
45. Munn Z, Peters MDJ, Stern C, Tufanaru C, McArthur A, Aromataris E. Systematic review or scoping review? guidance for authors when choosing between a systematic or scoping review approach. BMC Med Res Methodol 2018;18(1):143 [FREE Full text] [doi: 10.1186/s12874-018-0611-x] [Medline: 30453902]
46. Blanche EI, Fogelberg D, Diaz J, Carlson M, Clark F. Manualization of occupational therapy interventions: illustrations from the pressure ulcer prevention research program. Am J Occup Ther 2011;65(6):711-719 [FREE Full text] [doi: 10.5014/ajot.2011.001172] [Medline: 22214116]

Abbreviations

JBI: Joanna Briggs Institute
PAGER: Patterns, Advances, Gaps, Evidence for practice and Research recommendations
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
TIDieR: Template for Intervention Description and Replication

Edited by A Mavragani; submitted 05.12.23; peer-reviewed by K Laver, A Batrakoulis; comments to author 22.02.24; revised version received 23.02.24; accepted 26.02.24; published 18.03.24.

Please cite as:
Bannigan K, Larkan NJ, Meurgue ERR, Sze JCH
Characteristics of Occupational Therapy Interventions to Promote Healthy Aging: Protocol for a Scoping Review
JMIR Res Protoc 2024;13:e55198
URL: https://www.researchprotocols.org/2024/1/e55198
doi:10.2196/55198
PMID:38498043

Protocol

Analysis of Self-Care Activities in Type 2 Diabetes in Brazil: Protocol for a Scoping Review

Marileila Marques Toledo[1*], MSc; Edson da Silva[2*], PhD; Elizabethe Adriana Esteves[1,3*], PhD

[1]Graduate Program in Health Sciences, Universidade Federal dos Vales do Jequitinhonha e Mucuri (UFVJM), Diamantina, Brazil

[2]Department of Basic Sciences, Universidade Federal dos Vales do Jequitinhonha e Mucuri (UFVJM), Diamantina, Brazil

[3]Graduate Program in Nutrition Sciences, Universidade Federal dos Vales do Jequitinhonha e Mucuri (UFVJM), Diamantina, Brazil

[*]all authors contributed equally

Corresponding Author:
Edson da Silva, PhD
Department of Basic Sciences
Universidade Federal dos Vales do Jequitinhonha e Mucuri (UFVJM)
Edifício DCB-DCBIO, Campus JK, Rodovia MGT 367, Alto da Jacuba, 5000
Diamantina, 39100-000
Brazil
Phone: 55 38 3532 1200
Email: edson.silva@ufvjm.edu.br

Abstract

Background: Diabetes mellitus is a chronic disease that is growing worldwide. It is estimated that 15.7 million people aged between 20 and 79 years live with diabetes in Brazil, and the majority of cases are type 2 diabetes (T2D). To successfully manage diabetes, the patient needs to develop self-care activities. However, there is limited understanding of what self-care activities are performed by people with T2D in Brazil.

Objective: This study aims to identify and map studies that evaluate self-care activities in T2D in Brazil.

Methods: This is a scoping review protocol structured according to the methodological guidelines of the Joanna Briggs Institute. Six databases and gray literature were used. The process of searching, identifying, and evaluating the papers was carried out by 2 independent reviewers, guided by the assumptions established by the Joanna Briggs Institute. We sought to answer the following guiding question: How are self-care activities for people with T2D evaluated in Brazil? We included papers and publications in any language, from public and private domains, and with different methodological approaches.

Results: Initial database searches produced a total of 681 results. These papers will be critically analyzed, and relevant information will be extracted. Quantitative and qualitative results of the papers reviewed will be presented to respond to the study's objective. We intend to publish the scoping review in the first half of 2024.

Conclusions: The protocol for this scoping review will evaluate the main self-care activities carried out by adults and older people with T2D in Brazil. The results may help identify knowledge gaps and contribute to future research and diabetes education interventions.

International Registered Report Identifier (IRRID): DERR1-10.2196/49105

(JMIR Res Protoc 2024;13:e49105) doi:10.2196/49105

KEYWORDS

type 2 diabetes mellitus; self-care; self-care activities; Brazil; diabetes mellitus; T2D; chronic disease; self-care activity; aging; ageing; methodological guidelines; knowledge; gaps; diabetes education; hyperglycemia; insulin resistance; health education

Introduction

Diabetes mellitus (DM) is a significant and growing health problem worldwide. In 2021, the International Diabetes Federation estimated that 8.8% (537 million) of the world's population aged 20 to 79 years had diabetes. If current trends persist, the number of people with diabetes is projected to exceed 783 million by 2045. Brazil ranks sixth in the number of cases, with 15.7 million people diagnosed in the 20-79 years age group, which is projected to increase to 23.2 million cases in 2045 [1].

DM can be classified into 4 main types, based on its etiology: type 1 diabetes (T1D), type 2 diabetes (T2D), gestational DM,

and other types of diabetes. T2D is the most prevalent form, accounting for approximately 90% to 95% of diabetes cases worldwide [2].

The causes of T2D are still poorly understood, but there is a strong link with excess weight, obesity, lack of physical activity, aging, ethnicity, and family history. T2D has an insidious onset and is characterized by insulin resistance, partial deficiency of insulin secretion by pancreatic β cells, and changes in incretin secretion [2,3].

There is evidence that T2D can be prevented or delayed [1]. However, the patient often remains undiagnosed with T2D for several years. T2D occurs when hyperglycemia is the result of insulin resistance that has been established gradually over many years until diagnosis [1,2]. In this case, the person does not present the classic signs of diabetes, such as dehydration or involuntary weight loss, and the diagnosis comes with acute or chronic complications of diabetes [2].

Diabetes complications are categorized as microvascular and macrovascular disorders. Thus, diabetes and its complications can lead to disability and constitute one of the main causes of early mortality in most countries [1,4].

For satisfactory management of diabetes and effective adjustment in lifestyle, it is necessary to develop self-care activities, which include adherence to a healthy diet, regular physical activity, blood glucose monitoring, foot care, medication use, and smoking cessation [5].

Self-care is defined as the ability of individuals, their families, and the community to promote and maintain their health, prevent disease, and manage their illness and disability with or without the support of a health professional [6].

The Association of Diabetes Care & Education Specialists (ADCES) emphasizes that diabetes self-care can be effective through 7 important behaviors (ADCES7 self-care behaviors [7]): (1) ensuring variety and balance between quality, quantity, and food safety (healthy eating)—fresh or minimally processed foods should be prioritized and thus form the basis of the diet, and ultraprocessed foods should be avoided; (2) engaging in physical activity and regular training with aerobic and resistance exercises (being active); (3) blood glucose monitoring, using reagent strips and glucometers or glucose monitoring with interstitial glucose sensors (controlling blood glucose values); (4) understanding and managing the use of medications at the correct times every day, according to medical prescription (taking medication); (5) being prepared to face unexpected complications, such as hyperglycemia or hypoglycemia, resulting from an error in carbohydrate counting, physical activity, use of alcoholic beverages, excess medication, or change in medication schedule (solving problems); (6) practicing behaviors that prevent or minimize chronic complications and adverse outcomes related to diabetes (reducing risks)—examples of these behaviors include making positive lifestyle changes and participating in a diabetes education program, and it is recommended to be up to date with laboratory and complementary tests (glycated hemoglobin, cholesterol levels, assessment of renal function, and fundus examination), clinical assessment, and emotional aspects; and (7) developing personalized strategies to face daily stress and know how to act in special situations such as travel, parties, and intercurrent illnesses (eg, infections and other clinical situations that impact blood glucose, etc). Seeking information and alternatives to adapt to different situations, thus benefiting glycemic control and self-efficacy, favors patients to face the challenges of diabetes (adapting healthily) [7].

There is vast scientific literature on diabetes and many self-care–related studies. However, to the best of our knowledge, no previous attempt to establish an analysis of different self-care activities in T2D focused on Brazilians. Thus, this protocol will guide a scoping review to identify and map studies evaluating self-care activities in T2D in Brazil. Scoping reviews are considered a type of literature review that maps and identifies the nature and extent of relevant evidence in a given field of research. It also seeks to identify gaps in evidence, clarify key concepts, and report on the types of evidence that address and inform practice in a thematic area [8].

This protocol will guide a scoping review to identify and map studies that evaluate self-care activities in T2D in Brazil.

Methods

Scoping Review

To maintain rigor, the scoping review methodology used for this protocol will be that of the *Joanna Briggs Institute (JBI) Reviewer's Manual 2020* [9], which establishes five steps: (1) identification of research question; (2) identification of relevant studies; (3) selection of studies; (4) data analysis; and (5) grouping, synthesis, and presentation of data. The authors also followed the recommendations of the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews), according to the JBI Manual [9].

This study also followed all procedures standard to systematic reviews (search tests during elaboration of the protocol, data collection, data extraction, synthesis, analysis, and discussion of results and conclusions), as recommended by Cochrane (*Cochrane Handbook for Systematic Reviews of Interventions* [10]). A preliminary search of the PROSPERO Cochrane Database of Systematic Reviews and JBI Evidence Synthesis was performed. No existing or ongoing scoping reviews or systematic reviews were identified on this topic.

After completing the scoping review, the results will be submitted for publication in a peer-reviewed scientific journal. The research project for this scoping review protocol was previously registered in the Open Science Framework [11].

Stage 1: Identifying the Research Question

The first step comprises the elaboration of a research question. This review followed the *Population*, *Concept*, and *Context* strategy for a scoping review [9]. The following were defined: people diagnosed with T2D (*Population*); actions or strategies to evaluate self-care, self-management, or self-efficacy of people with T2D (*Concept*); and studies developed in Brazil (*Context*). Thus, the guiding question of this study is as follows: How are self-care activities for people with T2D evaluated in Brazil?

Stage 2: Identifying Relevant Studies

We performed a database search: (1) MEDLINE, (2) Web of Science - Core Collection, (3) Scopus, (4) Embase, (5) LILACS, and (6) SCIELO. In addition, a search was carried out for unpublished and possibly eligible studies in the gray literature, retrieved from 3 sources: the Brazilian Digital Library of Theses and Dissertations, Google Scholar (limited to the first 10 pages, in order of relevance), and the website of the Brazilian Diabetes Society. For the search strategy, terms were extracted from recognized thesauruses in the health area: Health Sciences Descriptors, Medical Subject Headings, and Embase Subject Headings. Thus, it started with the following terms: type 2 DM, self-management, self-efficacy, self-care, and Brazil. In order to broaden the search and better direct the findings, synonymous terms and the Boolean operators OR and AND were used according to the needs of each database (Multimedia Appendix 1).

As eligibility criteria, we included (1) Brazilian studies that were conducted with people diagnosed with T2D, older than 18 years, of both genders, and with or without comorbidities; (2) studies that focus on self-care activities for people with T2D; (3) studies that describe the evaluation process of these activities; and (4) studies that evaluate 2 or more self-care activities. The time frame used was the period from 2011 to 2023. The year 2011 is marked by the elaboration of the Strategic Action Plan for Combating Chronic Noncommunicable Diseases in Brazil 2011-2022 [12] and the Model of Attention to Chronic Conditions [13]. Original studies, dissertations, and theses were considered without language restriction, with quantitative, qualitative, or mixed design. Duplicate studies; studies on T1D, gestational diabetes, or prediabetes; studies that associate T2D with other types of diabetes; research protocols; editorials; reviews; letters; and Brazilian studies carried out in partnership with other countries were excluded.

Stage 3: Study Selection

The identified literature was exported to the Mendeley reference manager (Elsevier), via the web version, to remove duplicates. It was then imported into the Rayyan (Qatar Computing Research Institute) systematic review management software, online version [14], for screening and selection of studies. The studies were selected independently by 2 previously trained researchers from the team, and a third researcher resolved conflicts in the absence of consensus. All identified studies' titles and abstracts were evaluated based on the established inclusion and exclusion criteria. After the assessment of a study's pertinence to the review question, it was selected for reading in full for later data extraction. Its references were analyzed in search of additional studies. This stage was developed based on the recommendations of the international guide PRISMA-ScR, with the presentation of a flowchart on the process of the search and selection of studies, quantitative results of each database, included or excluded studies, and the total number of works selected for evaluation and synthesis [15].

Stage 4: Charting the Data

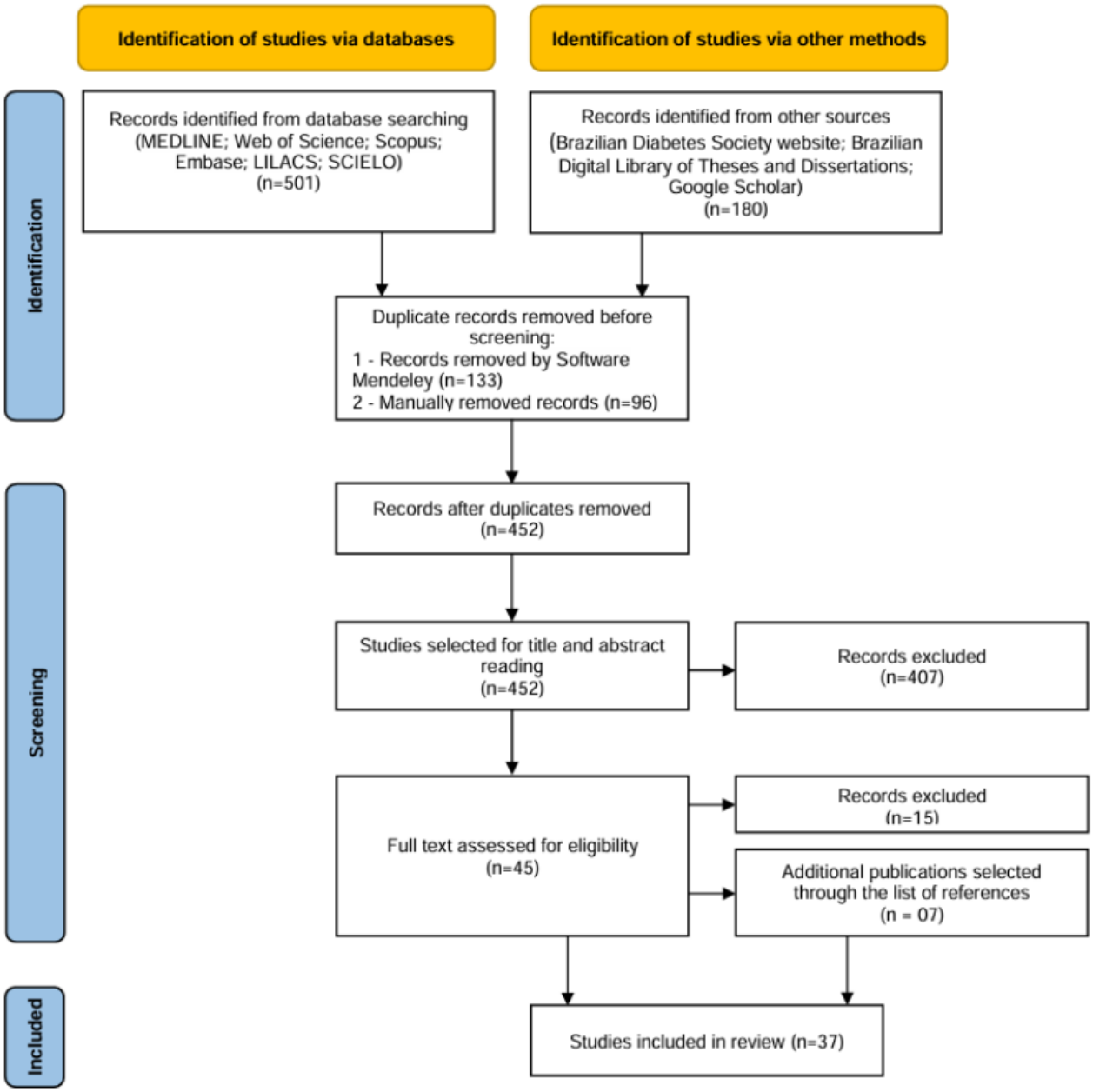
For the data extraction, a standardized data extraction tool was created in a Microsoft Office Excel Online spreadsheet, developed by the reviewers, and tested for this study in a pilot test based on the JBI tool [9] to characterize the studies. The instrument was independently used by 2 researchers to capture information to describe the extent and nature of the studies (authorship, year of publication, study typology, objectives primary results, and authors' recommendations). Information was also collected, such as characteristics of the population, specific self-care activities (general food, specific food, physical activity, blood glucose monitoring, foot care, medication use, and smoking), and identification of diabetes self-care behaviors. If there was any disagreement between the data extracted by the 2 reviewers, it was resolved by dialogue between both reviewers or, if necessary, with a third reviewer. The studies were coded with letters and numbers following a logical sequence. Tables S1-3 in Multimedia Appendix 2 [7,16] are examples of the data extraction tools created for this study.

Stage 5: Collating, Summarizing, and Reporting the Data

Qualitative data will be analyzed using the Bardin content analysis technique [17] and descriptively by 2 authors and validated by the entire research team. As for quantitative data, Table S1 in Multimedia Appendix 2 will verify which self-care activities were carried out in each study and classify each activity as favorable or unfavorable. Table S3 in Multimedia Appendix 2 will verify which of the 7 self-care behaviors are addressed in the studies. The results will be presented in tables, graphs, and images, along with the construction of narratives to clarify the information and discuss it in light of relevant and updated literature. The scoping review will record and report reasons for excluding sources of evidence in the full text that do not meet the inclusion criteria. The review report will incorporate a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram (Figure 1), visually presenting the screening and selection process.

The assessment of methodological quality and risk of bias is optional [8] and will not be performed in our study.

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for the scoping review process.



Ethical Considerations

This scoping review does not require ethical approval from the institutional review board.

Results

In August 2023, our initial database searches identified 681 papers. Duplicates were removed, and screening of extracted titles and abstracts resulted in 37 papers. A critical evaluation analysis of the collected papers was carried out to extract relevant information. The screening was carried out in September 2023. Similarities and differences contained in various data from the papers are being analyzed and compared between September and November 2023. We estimate the publication of the scoping review will be in the first half of 2024.

Discussion

Principal Findings

Reviews that focus on self-care for adults and older people with T2D have been specific to educational interventions for self-care. To the best of our knowledge, this will be the first scoping review to understand how self-care activities carried out by people with T2D in Brazil are evaluated.

This scoping review will identify gaps in the literature and provide information on future research needs related to self-care assessment and its relationship to the 7 ADCES self-care behaviors [7] of adults and older adults with diabetes.

The method of this scoping review complies with the JBI recommendations [9] and the most recent guidelines for using the PRISMA-ScR tool [15], adapted for the study context. One of the benefits of using PRISMA is that it makes it possible to

guide the writing of the research so that it reflects the investigative activities that will be carried out without losing details, in addition to guaranteeing methodological rigor [18]. Another advantage of a scoping review is the possibility of obtaining an overview of the scientific evidence about a given phenomenon in a structured, systematized, impartial, and transparent way [8].

The results of the scoping review will be discussed thoroughly based on the research question and will be discussed with the evidence reported in the literature on the research topic. We believe that our results will support the development of guidelines, thereby overcoming identified challenges and revealing new opportunities for assessing self-care behaviors in diabetes.

Limitations

This scoping review will follow well-established methods, yet limitations will exist. First, most of the studies included are cross-sectional, which does not allow for long-term conclusions. Second, the noninclusion of texts published in other indexing databases and the choice to select studies only on the first 10 pages of Google Scholar may result in omitting potentially relevant research.

Conclusions

This review will map and compare how the main self-care activities carried out by people with T2D in Brazil are evaluated. Our study will help identify existing knowledge gaps and how research on the topic is conducted. This knowledge will enable researchers and health care professionals to understand self-care activities in T2D better. Consequently, the results of our scoping review may contribute to future research and health education programs focusing on T2D.

Acknowledgments

The authors deeply thank the Universidade Federal dos Vales do Jequitinhonha e Mucuri (UFVJM) for institutional support and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) for financial support and scholarship. The authors declare that they did not use generative artificial intelligence to write the manuscript. However, they did use Grammarly [19] in some parts to spell-check the writing.

Data Availability

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

Authors' Contributions

The study was designed by MMT, ES, and EAE. MMT and ES contributed to data collection. MMT wrote the manuscript, and ES and EAE contributed to the final draft of the manuscript. All authors approved the final article.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy outlining concepts and alternative search terms.
[PDF File (Adobe PDF File), 116 KB - resprot_v13i1e49105_app1.pdf]

Multimedia Appendix 2
Information about the following instruments: Data extraction instrument; Measurement of each self-care activity seven days a week; and Diabetes self-care behaviors.
[PDF File (Adobe PDF File), 302 KB - resprot_v13i1e49105_app2.pdf]

References

1. International Diabetes Federation. IDF Diabetes Atlas, 10th edition. International Diabetes Federation. Brussels, Belgium: Boyko EJ, Karuranga S, Magliano DJ, Saeedi P, Sun H; 2021 Nov 01. URL: https://diabetesatlas.org/atlas/tenth-edition/ [accessed 2024-02-24]
2. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 2. Classification and diagnosis of diabetes: standards of care in diabetes-2023. Diabetes Care 2022 Dec 12;46(Suppl 1):S19-S40 [FREE Full text] [doi: 10.2337/dc23-S002] [Medline: 36507649]
3. Rodacki M, Teles M, Gabbay M, Montenegro R, Bertoluci M. Classificação do diabetes. Diretriz Oficial da Sociedade Brasileira de Diabetes, Conectando Pessoas. São Paulo: Bertoluci, M; 2023 Dec 14. URL: https://doi.org/10.29327/557753.2022-1 [accessed 2024-02-24]

4. Sociedade Brasileira de Diabetes. Diretrizes da sociedade Brasileira de diabetes 2019-2020. In: Forti AC, Pires AC, Pittito BA, Gerchman B, Oliveira JEP, Zajdenverg L, et al, editors. Sociedade Brasileira de Diabetes. São Paulo: Clannad Editora Científica; Nov 01, 2019:1-491.
5. American Diabetes Association. Standards of medical care in diabetes-2021 abridged for primary care providers. Clin Diabetes 2021 Jan 01;39(1):14-43 [FREE Full text] [doi: 10.2337/cd21-as01] [Medline: 33551551]
6. World Health Organization. WHO Guideline on Self-Care Interventions for Health and Well-Being, 2022 Revision. Geneva: World Health Organization; Jun 27, 2022:1-186.
7. Kolb L. An effective model of diabetes care and education: the ADCES7 self-care behaviors™. Sci Diabetes Self Manag Care 2021 Feb 11;47(1):30-53 [FREE Full text] [doi: 10.1177/0145721720978154] [Medline: 34078208]
8. Peters MDJ, Godfrey C, McInerney P, Munn Z, Tricco AC, Khalil H. Chapter 11: scoping reviews (2020 version). In: Aromataris E, Munn Z, editors. JBI Manual for Evidence Synthesis. Adelaide, Australia: JBI; Oct 05, 2022:1-46.
9. Aromataris E, Munn Z. JBI Manual for Evidence Synthesis. Adelaide, Australia: JBI; Jun 12, 2020.
10. Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editors. Cochrane Handbook for Systematic Reviews of Interventions. 2nd ed. Chichester, United Kingdom: The Cochrane Collaboration and John Wiley & Sons Ltd; 2019.
11. Toledo MM, Silva E, Esteves EA. Analysis of self-care activities in type 2 diabetes in Brazil: protocol for a scoping review. Preprint posted online 2023 Aug 15 [FREE Full text] [doi: 10.17605/OSF.IO/ZK4HY]
12. Ministério da Saúde (BR). Secretaria de Vigilância em Saúde. Plano de ações estratégicas para o enfrentamento das doenças crônicas não transmissíveis (DCNT) no Brasil 2011-2022, 1st Edition. In: Plano de ações estratégicas para o enfrentamento das doenças crônicas não transmissíveis (DCNT) no Brasil 2011-2022, 1st Edition. Brasília: Ministério da Saúde: Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Análise de Situação de Saúde; Jun 02, 2011.
13. Mendes EV. O cuidado das condições crônicas na atenção primária à saúde: o imperativo da consolidação da estratégia da saúde da família. In: O cuidado das condições crônicas na atenção primária à saúde: o imperativo da consolidação da estratégia da saúde da família. Brasília: Pan American Health Organization; 2012:1-512.
14. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev 2016 Dec 05;5(1):210 [FREE Full text] [doi: 10.1186/s13643-016-0384-4] [Medline: 27919275]
15. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med 2018 Sep 04;169(7):467-473 [FREE Full text] [doi: 10.7326/M18-0850] [Medline: 30178033]
16. Michels MH, Coral MHC, Sakae TM, Damas TB, Furlanetto LM. Questionnaire of Diabetes Self-Care Activities: translation, cross-cultural adaptation and evaluation of psychometric properties [Article in Portuguese]. Arq Bras Endocrinol Metabol 2010 Oct;54(7):644-651. [doi: 10.1590/s0004-27302010000700009] [Medline: 21085770]
17. Bardin L. In: Reto LA, Pinheiro A, editors. Análise de Conteúdo, 6th Edition. São Paulo: Edições 70 Ltda; 2016.
18. Araújo WCO. Recuperação da informação em saúde [Article in Portuguese]. Convergências em Ciência da Informação 2020 Oct 07;3(2):100-134 [FREE Full text] [doi: 10.33467/conci.v3i2.13447]
19. Araújo WCO. Recuperação da informação em saúde [Article in Portuguese]. Convergências em Ciência da Informação 2020 Oct 07;3(2):100-134 [FREE Full text] [doi: 10.33467/conci.v3i2.13447]

Abbreviations

ADCES: Association of Diabetes Care & Education Specialists
DM: diabetes mellitus
JBI: Joanna Briggs Institute
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
T1D: type 1 diabetes
T2D: type 2 diabetes

Edited by A Mavragani; submitted 29.11.23; peer-reviewed by L Powell, J Malavar; comments to author 03.01.24; revised version received 26.01.24; accepted 19.02.24; published 20.03.24.

Please cite as:
Toledo MM, da Silva E, Esteves EA
Analysis of Self-Care Activities in Type 2 Diabetes in Brazil: Protocol for a Scoping Review
JMIR Res Protoc 2024;13:e49105
URL: https://www.researchprotocols.org/2024/1/e49105
doi:10.2196/49105
PMID:38506891

Protocol

Definitions and Measurements for Atypical Presentations at Risk for Diagnostic Errors in Internal Medicine: Protocol for a Scoping Review

Yukinori Harada[1], MD, PhD; Ren Kawamura[1], MD, PhD; Masashi Yokose[1], MD, PhD; Taro Shimizu[1], MD, MSc, MPH, MBA, PhD; Hardeep Singh[2,3], MD, MPH

[1]Department of Diagnostic and Generalist Medicine, Dokkyo Medical University, Mibu, Japan

[2]Center for Innovations in Quality, Effectiveness and Safety, Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX, United States

[3]Health Services Research Section, Department of Medicine, Baylor College of Medicine, Houston, TX, United States

Corresponding Author:
Yukinori Harada, MD, PhD
Department of Diagnostic and Generalist Medicine
Dokkyo Medical University
880 Kitakobayashi
Mibu, 321-0293
Japan
Phone: 81 282 86 1111
Email: yharada@dokkyomed.ac.jp

Abstract

Background: Atypical presentations have been increasingly recognized as a significant contributing factor to diagnostic errors in internal medicine. However, research to address associations between atypical presentations and diagnostic errors has not been evaluated due to the lack of widely applicable definitions and criteria for what is considered an atypical presentation.

Objective: The aim of the study is to describe how atypical presentations are defined and measured in studies of diagnostic errors in internal medicine and use this new information to develop new criteria to identify atypical presentations at high risk for diagnostic errors.

Methods: This study will follow an established framework for conducting scoping reviews. Inclusion criteria are developed according to the participants, concept, and context framework. This review will consider studies that fulfill all of the following criteria: include adult patients (participants); explore the association between atypical presentations and diagnostic errors using any definition, criteria, or measurement to identify atypical presentations and diagnostic errors (concept); and focus on internal medicine (context). Regarding the type of sources, this scoping review will consider quantitative, qualitative, and mixed methods study designs; systematic reviews; and opinion papers for inclusion. Case reports, case series, and conference abstracts will be excluded. The data will be extracted through MEDLINE, Web of Science, CINAHL, Embase, Cochrane Library, and Google Scholar searches. No limits will be applied to language, and papers indexed from database inception to December 31, 2023, will be included. Two independent reviewers (YH and RK) will conduct study selection and data extraction. The data extracted will include specific details about the patient characteristics (eg, age, sex, and disease), the definitions and measuring methods for atypical presentations and diagnostic errors, clinical settings (eg, department and outpatient or inpatient), type of evidence source, and the association between atypical presentations and diagnostic errors relevant to the review question. The extracted data will be presented in tabular format with descriptive statistics, allowing us to identify the key components or types of atypical presentations and develop new criteria to identify atypical presentations for future studies of diagnostic errors. Developing the new criteria will follow guidance for a basic qualitative content analysis with an inductive approach.

Results: As of January 2024, a literature search through multiple databases is ongoing. We will complete this study by December 2024.

Conclusions: This scoping review aims to provide rigorous evidence to develop new criteria to identify atypical presentations at high risk for diagnostic errors in internal medicine. Such criteria could facilitate the development of a comprehensive conceptual model to understand the associations between atypical presentations and diagnostic errors in internal medicine.

Trial Registration: Open Science Framework; www.osf.io/27d5m

International Registered Report Identifier (IRRID): DERR1-10.2196/56933

(JMIR Res Protoc 2024;13:e56933) doi:10.2196/56933

KEYWORDS

atypical presentations; diagnostic errors; internal medicine; scoping review protocol; atypical presentation; high risk; data extraction; descriptive statistics; criteria; qualitative; content analysis; inductive approach; clinical informatics; clinical decision support

Introduction

Diagnostic errors, defined as "the failure to (a) establish an accurate and timely explanation of the patient's health problem(s) or (b) communicate that explanation to the patient" [1], is an important concern in improving patient safety and diagnostic excellence. According to a recent report, approximately 0.8 million people may become permanently disabled or die annually due to diagnostic errors in the United States [2]. While diagnostic errors can occur across care settings, internal medicine is one of the highest-risk care settings for diagnostic errors [3,4]. Internal medicine physicians, as well as surgery and emergency medicine physicians, also frequently confront malpractice claims related to diagnostic errors [5,6]. Internal medicine covers a broad spectrum of complaints and diseases, which can contribute to higher diagnostic uncertainty in patients presenting to internal medicine with undiagnosed conditions [3,7]. Therefore, more complex and difficult diagnostic decisions are required in internal medicine, which can result in higher susceptibility to diagnostic errors [3].

Diagnostic errors are usually related to multifactorial causes such as system-related errors; cognitive errors; and patient factors, including challenging disease presentations [8-10]. To date, while many studies have been conducted to address major system-related and cognitive errors using common measurements, patient factors, including challenging disease presentations, have not been investigated as much. However, among challenging disease presentations, atypical presentations have been increasingly recognized for their significant impact on diagnostic errors [11-15]. Atypical presentations are described as "a shortage of prototypical features that are most frequently encountered in patients with the disease, features encountered in advanced presentations of the disease or simply features of the disease commonly listed in medical textbooks" [16], which can make diagnosis more challenging and distract the diagnostic process. Indeed, atypical presentations were reported to be associated with a higher prevalence of diagnostic errors compared to typical presentations [12-14], and a pilot systematic review of case reports of diagnostic errors suggested that higher numbers of contributing factors were detected in the cases with atypical presentations compared to the cases without atypical presentations [15]. Moreover, a previous study showed that the prevalence of diagnostic errors in patients with atypical presentations of stroke was smaller when cared for by health care providers who are familiar with atypical presentations of stroke [17]. Although the results cannot be easily generalized to other conditions, developing strategies to prevent progression from an atypical presentation to diagnostic error seems to be a promising approach to improving patient safety [11,12].

Atypical presentations seem to be especially an important issue for diagnostic errors in internal medicine: first, atypical presentations may be commonly observed (up to approximately 30%) in the internal medicine department [13]; second, internal medicine physicians consider atypical presentations to be the most important contributor to diagnostic errors in their clinical practice [18]; and third, atypical presentations can be an important contributing factor to a higher prevalence of diagnostic errors in internal medicine [10,13]. Therefore, a comprehensive understanding of the association between atypical presentations and diagnostic errors is required. Knowledge gaps in this area persist possibly due to the lack of consensus on the definition and measurement of atypical presentations and because a comprehensive conceptual model to understand how atypical presentations progress to diagnostic errors is still lacking.

A scoping review is more appropriate than a systematic review when the review aims to identify knowledge gaps, scope a body of literature, and clarify concepts. A scoping review is also more appropriate than a narrative review when clarification around a concept or theory is required [19]. From this perspective, a scoping review is more ideally suited to determine the body of literature on atypical presentation and diagnostic errors and identify any gaps in knowledge [20]. Moreover, without a universal definition for atypical presentations, future studies about diagnostic errors may have systematic biases by excluding patients with atypical presentations at high risk for missed diagnostic opportunities [21]. Therefore, this scoping review will also facilitate future studies by developing practical criteria and measurements for atypical presentations.

Throughout this scoping review, the key terms such as diagnostic errors, atypical presentations, and internal medicine are defined as follows:

- Diagnostic errors—defined as the failure to (1) establish an accurate and timely explanation of the patient's health problems or (2) communicate that explanation to the patient [1], which also include delayed, wrong, and missed diagnosis [10].
- Atypical presentations—defined as patient demographics (eg, age, sex, and race); symptoms and signs; test results; or clinical course, including the response to treatment, deviated from the prototypical patterns for the final diagnosis.
- Internal medicine—defined as a medical specialty concerned with the diagnosis and treatment of diseases of the internal organ systems of adults.

To develop a new definition and useful criteria to identify atypical presentations that are at high risk of diagnostic errors,

this scoping review aims to identify and present the available information regarding the definitions and measurements for atypical presentations in the evidence sources about diagnostic errors in internal medicine.

The primary review question is "What definitions and measurements have been used to identify atypical presentations in the studies investigating diagnostic errors in adult patients in internal medicine?" The subquestions are "What specific diseases have been targeted by the studies investigating the association between atypical presentations and diagnostic errors in adult patients in internal medicine?" and "What specific types of atypical presentations have been reported as relevant to diagnostic errors in adult patients in internal medicine?"

Methods

Study Design

The proposed scoping review will be conducted in accordance with the Joanna Briggs Institute methodology for scoping reviews [22,23] and in line with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) [24].

Inclusion Criteria

Participants

This review will consider studies that include adult patients. We will exclude studies that focus on children.

Concept

This review will consider studies that explore the association between atypical presentations and diagnostic errors (using any clear definition or criteria or measurement to identify atypical presentations and diagnostic errors). We will exclude studies that investigate only atypical presentations or diagnostic errors.

Context

This review will consider studies that focus on the setting of internal medicine.

Types of Sources

This scoping review will consider quantitative, qualitative, and mixed methods study designs for inclusion. In addition, systematic reviews and text and opinion papers will be considered for inclusion in the proposed scoping review. Case reports, case series, and conference abstracts will be excluded.

Search Strategy

The search strategy will aim to locate both published and unpublished primary studies, reviews, and text and opinion papers. An initial limited search of MEDLINE (PubMed) and Science Citation Index Expanded (Web of Science) was undertaken to identify papers on the topic. The text words contained in the titles and abstracts of relevant papers, and the index terms used to describe the papers, were used to develop a full search strategy for MEDLINE (PubMed; Multimedia Appendix 1). The search strategy, including all identified keywords and index terms, will be adapted for each included information source. The reference lists of papers included in the review will be screened for additional papers. Papers published in all languages will be included. Papers indexed from database inception to December 31, 2023, will be included. The databases to be searched include MEDLINE (PubMed), Science Citation Index Expanded (Web of Science), CINAHL, Embase, Google Scholar, and Cochrane Library. Sources of unpublished studies and gray literature to be searched include medRxiv.

Study or Source of Evidence Selection

Following the search, all identified records will be collated and uploaded into Covidence (Covidence), and duplicates will be removed. Following a pilot test, titles and abstracts will then be screened by 2 independent reviewers (YH and RK) for assessment against the inclusion criteria for the review. Potentially relevant papers will be retrieved in full, and their citation details imported into Covidence. The full text of selected citations will be assessed in detail against the inclusion criteria by 2 independent reviewers (YH and RK). Reasons for exclusion of full-text papers that do not meet the inclusion criteria will be recorded and reported in the scoping review. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussion or with a third reviewer (MY). Interrater reliability will be monitored and reported. The results of the search will be reported in full in the final scoping review and presented in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram [25].

Data Extraction

Data will be extracted from papers included in the scoping review by 2 independent reviewers (YH and RK) using a data extraction tool developed by the reviewers. The data extracted will include specific details about the patient characteristics (eg, age, sex, and disease), the definitions and measuring methods for atypical presentations and diagnostic errors, clinical settings (eg, department and outpatient or inpatient), type of evidence source, and the association between atypical presentations and diagnostic errors relevant to the review question. A draft extraction tool is provided in Table 1. The draft data extraction tool will be modified and revised as necessary during the process of extracting data from each included paper. Modifications will be detailed in the full scoping review. Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer (MY). Authors of papers will be contacted to request missing or additional data, where required.

Table 1. Data extraction instrument for the scoping review. The scoping review will include published or unpublished studies indexed in databases until December 2023; the scoping review will include quantitative, qualitative, and mixed methods study designs; systematic reviews; and opinion papers. The target population is adult patients cared for in internal medicine settings without restriction on disease, location, or time frame.

	Data extraction
Evidence source information	
Author	✓
Year	✓
Country	✓
Aim	✓
Study type or source	✓
Population	
Participants	✓
Age (years)	✓
Sex	✓
Target disease	✓
Context	
Setting	✓
Concept	
Details of the definitions and measurements to identify atypical presentations	✓
Details of the definitions and measurements to identify diagnostic errors	✓
Description or statistical results about the association between atypical presentations and diagnostic errors	✓
Details of the characteristics related to atypical presentations	✓

Data Analysis and Presentation

The extracted data will be presented in tabular format with descriptive statistics, and from this, the key components or types of atypical presentations—the purpose of this scoping review—will be identified to develop new criteria to identify atypical presentations for future studies of diagnostic errors. Developing the new criteria will follow the Joanna Briggs Institute guidance for a basic qualitative content analysis approach (following an inductive approach) [26]. In addition, we will classify the sources of evidence into 2 categories: disease-specific or generic studies to identify diseases and settings where the current evidence is lacking. Finally, we will list the specific types of atypical presentations highly associated with diagnostic errors.

Results

As of January 2024, a literature search through multiple databases is ongoing. We will complete this study by December 2024.

Discussion

Expected Findings

This scoping review aims to identify and present the available information regarding the definitions and measurements for atypical presentations to inform a new definition and criteria to identify atypical presentations at high risk of diagnostic errors. To maximize the quality of this scoping review, we will follow the updated scoping review guidelines, use multiple databases, and develop search strategies in consultation with experienced and skilled librarians. In addition, our review group includes expertise in diagnostic error research and has experience in developing new theories and concepts related to the diagnostic process. This scoping review aims to provide a rigorous evidence summary to describe how atypical presentations have been defined and measured in prior literature and use these findings to develop new criteria to identify atypical presentations at high risk for diagnostic errors. Findings will also inform the development of a comprehensive conceptual model to understand the associations between atypical presentations and diagnostic errors in internal medicine.

Comparison With Prior Work

In a systematic review focused on diagnostic errors in primary care, Kostopoulou et al [16] defined atypical presentations as "a shortage of prototypical features that are most frequently encountered in patients with the disease, features encountered in advanced presentations of the disease or simply features of the disease commonly listed in medical textbooks"; however, this definition has not been applied in subsequent research investigating the association between atypical presentations and diagnostic errors due to several limitations. For instance, the difficulty in defining the gold standard classic textbook disease descriptions may be one of the possible reasons that the definition has not been used. Current studies use disease-specific criteria for atypical presentations to detect and measure atypical presentations at high risk of diagnostic errors [12]. However, such an approach also has limitations: understanding of certain

atypical presentation features of a disease evolves over time, and these features might not stand the test of time. An example of this is the loss of taste, which was recognized as an atypical symptom of COVID-19 during the early stages of the pandemic; however, as we learn more about the disease, the loss of taste is no more considered atypical for COVID-19. This scoping review will clarify the gaps and complexity in each disease's diagnostic criteria to diagnose atypical presentations and suggest a more refined approach that accounts for the limitations of prior definitions. The implications of our findings will be significant, indicating the potential for improving diagnostic processes and diagnostic accuracy by applying our new criteria.

Limitations

This scoping review will have several limitations. First, this scoping review will not include studies outside of internal medicine, and findings may not generalize to specialties outside of internal medicine. Furthermore, the evolving nature of diagnostic criteria and practices in internal medicine necessitates ongoing revision and validation of our proposed definitions and criteria. Second, although we will search for unpublished studies and gray literature, we may overlook some, potentially bringing bias to our understanding and conclusions. Third, confirmation bias can distort the findings in this scoping review because each study related to diagnostic errors may have overlooked atypical presentations. However, the upcoming new criteria from this scoping review can be expected to increase sensitivity to detect atypical presentations and reduce confirmation bias in future studies. Fourth, defining "atypical presentation" itself may present challenges, as evidenced by the difficulty in clearly distinguishing between concepts such as atypical presentations, phenotype, and nonspecific symptoms, as well as the challenge in defining the degree of atypicality and the boundary between typical and atypical. However, this is precisely the reason this research needs to be done because these issues need further clarification. Definitions and distinctions of these concepts will become clearer as a result of this exploration.

Conclusions

This scoping review can provide a rigorous evidence summary to describe how atypical presentations have thus far been defined and measured and help develop new criteria to identify atypical presentations at high risk for diagnostic errors in internal medicine. Developing the new criteria is expected to facilitate the development of a comprehensive conceptual model to understand the associations between atypical presentations and diagnostic errors in internal medicine. Additionally, such criteria can reduce the systematic selection biases in future diagnostic error studies that evaluate patients with atypical presentations. Review findings will highlight the need for further research to validate and refine these criteria, aiming to improve diagnostic processes and outcomes for patients with atypical presentations.

Acknowledgments

The authors acknowledge Ms Tomoko Nagaoka and Mr Shunya Suzuki (Reference Service Unit, Dokkyo Medical University Library, Tochigi, Japan) for their insightful suggestions as specialist librarians for creating search strategies. HS is funded in part by the Houston Veterans Administration (VA) Health Services Research and Development (HSR&D) Center for Innovations in Quality, Effectiveness and Safety (CIN13–413), the VA National Center for Patient Safety, and the Agency for Healthcare Research and Quality (R01HS028595 and R18HS029347). The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the US government.

Data Availability

Data sharing is not applicable to this paper as no data sets were generated or analyzed during this study.

Authors' Contributions

YH conceptualized the study and conducted an initial limited search; YH wrote the draft and RK, MY, TS, and HS provided critical revisions to it; all authors contributed to the final revision of this paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[DOCX File , 17 KB - resprot_v13i1e56933_app1.docx]

References

1. National Academies of Sciences, Engineering, and Medicine, Institute of Medicine, Board on Health Care Services, Committee on Diagnostic Error in Health Care. In: Miller BT, Balogh EP, Ball JR, editors. Improving Diagnosis in Health Care. Washington, DC: The National Academies Press; 2015.
2. Newman-Toker DE, Nassery N, Schaffer AC, Yu-Moe CW, Clemens GD, Wang Z, et al. Burden of serious harms from diagnostic error in the USA. BMJ Qual Saf 2024;33(2):109-120 [FREE Full text] [doi: 10.1136/bmjqs-2021-014130] [Medline: 37460118]

3. van den Berge K, Mamede S. Cognitive diagnostic error in internal medicine. Eur J Intern Med 2013;24(6):525-529. [doi: 10.1016/j.ejim.2013.03.006] [Medline: 23566942]
4. Regina ML, Vecchié A, Bonaventura A, Prisco D. Patient safety in internal medicine. In: Donaldson L, Ricciardi W, Sheridan S, Tartaglia R, editors. Textbook of Patient Safety and Clinical Risk Management. Cham: Springer; 2021:213-252.
5. Watari T. Malpractice claims of internal medicine involving diagnostic and system errors in Japan. Intern Med 2021;60(18):2919-2925 [FREE Full text] [doi: 10.2169/internalmedicine.6652-20] [Medline: 33776001]
6. Watari T, Tokuda Y, Mitsuhashi S, Otuki K, Kono K, Nagai N, et al. Factors and impact of physicians' diagnostic errors in malpractice claims in Japan. PLoS One 2020;15(8):e0237145 [FREE Full text] [doi: 10.1371/journal.pone.0237145] [Medline: 32745150]
7. Wijesekera TP, Sanders L, Windish DM. Reflections on diagnosis and diagnostic errors: a survey of internal medicine resident and attending physicians. J Gen Intern Med 2020;35(2):614-615 [FREE Full text] [doi: 10.1007/s11606-019-05045-z] [Medline: 31093840]
8. Schiff GD. Finding and fixing diagnosis errors: can triggers help? BMJ Qual Saf 2012;21(2):89-92 [FREE Full text] [doi: 10.1136/bmjqs-2011-000590] [Medline: 22129932]
9. Schiff GD, Hasan O, Kim S, Abrams R, Cosby K, Lambert BL, et al. Diagnostic error in medicine: analysis of 583 physician-reported errors. Arch Intern Med 2009;169(20):1881-1887 [FREE Full text] [doi: 10.1001/archinternmed.2009.333] [Medline: 19901140]
10. Graber ML, Franklin N, Gordon R. Diagnostic error in internal medicine. Arch Intern Med 2005;165(13):1493-1499 [FREE Full text] [doi: 10.1001/archinte.165.13.1493] [Medline: 16009864]
11. Schiff GD, Volodarskaya M, Ruan E, Lim A, Wright A, Singh H, et al. Characteristics of disease-specific and generic diagnostic pitfalls: a qualitative study. JAMA Netw Open 2022;5(1):e2144531 [FREE Full text] [doi: 10.1001/jamanetworkopen.2021.44531] [Medline: 35061037]
12. Newman-Toker DE, Peterson SM, Badihian S, Hassoon A, Nassery N, Parizadeh D, et al. Diagnostic errors in the emergency department: a systematic review. Agency for Healthcare Research and Quality. 2022. URL: https://effectivehealthcare.ahrq.gov/products/diagnostic-errors-emergency-updated/research [accessed 2024-03-02]
13. Harada Y, Otaka Y, Katsukura S, Shimizu T. Prevalence of atypical presentations among outpatients and associations with diagnostic error. Diagnosis (Berl) 2024;11(1):40-48. [doi: 10.1515/dx-2023-0060] [Medline: 38059495]
14. Cifra CL, Eyck PT, Dawson JD, Reisinger HS, Singh H, Herwaldt LA. Factors associated with diagnostic error on admission to a PICU: a pilot study. Pediatr Crit Care Med 2020;21(5):e311-e315 [FREE Full text] [doi: 10.1097/PCC.0000000000002257] [Medline: 32097247]
15. Harada Y, Watari T, Nagano H, Suzuki T, Kunitomo K, Miyagami T, et al. Diagnostic errors in uncommon conditions: a systematic review of case reports of diagnostic errors. Diagnosis (Berl) 2023;10(4):329-336. [doi: 10.1515/dx-2023-0030] [Medline: 37561056]
16. Kostopoulou O, Delaney BC, Munro CW. Diagnostic difficulty and error in primary care—a systematic review. Fam Pract 2008;25(6):400-413 [FREE Full text] [doi: 10.1093/fampra/cmn071] [Medline: 18842618]
17. Chang TP, Bery AK, Wang Z, Sebestyen K, Ko YH, Liberman AL, et al. Stroke hospitalization after misdiagnosis of "benign dizziness" is lower in specialty care than general practice: a population-based cohort analysis of missed stroke using SPADE methods. Diagnosis (Berl) 2021;9(1):96-106. [doi: 10.1515/dx-2020-0124] [Medline: 34147048]
18. Matulis JC, Kok SN, Dankbar EC, Majka AJ. A survey of outpatient internal medicine clinician perceptions of diagnostic error. Diagnosis (Berl) 2020;7(2):107-114. [doi: 10.1515/dx-2019-0070] [Medline: 31913847]
19. Munn Z, Peters MDJ, Stern C, Tufanaru C, McArthur A, Aromataris E. Systematic review or scoping review? guidance for authors when choosing between a systematic or scoping review approach. BMC Med Res Methodol 2018;18(1):143 [FREE Full text] [doi: 10.1186/s12874-018-0611-x] [Medline: 30453902]
20. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. Int J Soc Res Methodol 2005;8(1):19-32. [doi: 10.1080/1364557032000119616]
21. Miller AC, Arakkal AT, Koeneman SH, Cavanaugh JE, Polgreen PM. A clinically-guided unsupervised clustering approach to recommend symptoms of disease associated with diagnostic opportunities. Diagnosis (Berl) 2023;10(1):43-53 [FREE Full text] [doi: 10.1515/dx-2022-0044] [Medline: 36127310]
22. Peters MDJ, Marnie C, Tricco AC, Pollock D, Munn Z, Alexander L, et al. Updated methodological guidance for the conduct of scoping reviews. JBI Evid Synth 2020;18(10):2119-2126 [FREE Full text] [doi: 10.11124/JBIES-20-00167] [Medline: 33038124]
23. Peters MDJ, Godfrey C, McInerney P, Munn Z, Tricco AC, Khalil H. Chapter 11: Scoping reviews (2020 version). In: Aromataris E, Munn Z, editors. JBI Manual for Evidence Synthesis. Adelaide: Joanna Briggs Institute; 2020.
24. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med 2018;169(7):467-473 [FREE Full text] [doi: 10.7326/M18-0850] [Medline: 30178033]
25. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71 [FREE Full text] [doi: 10.1136/bmj.n71] [Medline: 33782057]

26. Pollock D, Peters MDJ, Khalil H, McInerney P, Alexander L, Tricco AC, et al. Recommendations for the extraction, analysis, and presentation of results in scoping reviews. JBI Evid Synth 2023;21(3):520-532 [FREE Full text] [doi: 10.11124/JBIES-22-00123] [Medline: 36081365]

Abbreviations

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

Edited by A Mavragani; submitted 30.01.24; peer-reviewed by G Schiff, K Ishizuka; comments to author 22.02.24; accepted 26.02.24; published 25.03.24.

Please cite as:
Harada Y, Kawamura R, Yokose M, Shimizu T, Singh H
Definitions and Measurements for Atypical Presentations at Risk for Diagnostic Errors in Internal Medicine: Protocol for a Scoping Review
JMIR Res Protoc 2024;13:e56933
URL: https://www.researchprotocols.org/2024/1/e56933
doi:10.2196/56933
PMID:38526541

Protocol

Telehealth Evaluation in the United States: Protocol for a Scoping Review

Yunxi Zhang[1,2], PhD; Yueh-Yun Lin[2], PhD; Lincy S Lal[3], PharmD, PhD; Jennifer C Reneker[4], PT, MSPT, PhD; Elizabeth G Hinton[5], MSIS, AHIP; Saurabh Chandra[2,6], MBBS, PhD; J Michael Swint[3,7], PhD

[1]Department of Data Science, John D Bower School of Population Health, University of Mississippi Medical Center, Jackson, MS, United States

[2]Center for Telehealth, University of Mississippi Medical Center, Jackson, MS, United States

[3]Department of Management, Policy and Community Health, The University of Texas School of Public Health, Houston, TX, United States

[4]Department of Population Health Sciences, John D Bower School of Population Health, University of Mississippi Medical Center, Jackson, MS, United States

[5]Rowland Medical Library, University of Mississippi Medical Center, Jackson, MS, United States

[6]Department of Medicine, University of Mississippi Medical Center, Jackson, MS, United States

[7]Institute for Clinical Research and Learning Healthcare, John P and Katherine G McGovern Medical School, The University of Texas Health Science Center at Houston, Houston, TX, United States

Corresponding Author:
Yunxi Zhang, PhD
Department of Data Science
John D Bower School of Population Health
University of Mississippi Medical Center
2500 North State Street
Jackson, MS, 39216-4505
United States
Phone: 1 6018153477
Email: yzhang4@umc.edu

Abstract

Background: The rapid expansion of telehealth services, driven by the COVID-19 pandemic, necessitates systematic evaluation to guarantee the quality, effectiveness, and cost-effectiveness of telehealth services and programs in the United States. While numerous evaluation frameworks have emerged, crafted by various stakeholders, their comprehensiveness is limited, and the overall state of telehealth evaluation remains unclear.

Objective: The overarching goal of this scoping review is to create a comprehensive overview of telehealth evaluation, incorporating perspectives from multiple stakeholder categories. Specifically, we aim to (1) map the existing landscape of telehealth evaluation, (2) identify key concepts for evaluation, (3) synthesize existing evaluation frameworks, and (4) identify measurements and assessments considered in the United States.

Methods: We will conduct this scoping review in accordance with the Joanna Briggs Institute (JBI) methodology for scoping reviews and in line with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews). This scoping review will consider documents, including reviews, reports, and white papers, published since January 1, 2019. It will focus on evaluation frameworks and associated measurements of telehealth services and programs in the US health care system, developed by telehealth stakeholders, professional organizations, and authoritative sources, excluding those developed by individual researchers, to collect data that reflect the collective expertise and consensus of experts within the respective professional group.

Results: The data extracted from selected documents will be synthesized using tools such as tables and figures. Visual aids like Venn diagrams will be used to illustrate the relationships between the evaluation frameworks from various sources. A narrative summary will be crafted to further describe how the results align with the review objectives, facilitating a comprehensive overview of the findings. This scoping review is expected to conclude by August 2024.

Conclusions: By addressing critical gaps in telehealth evaluation, this scoping review protocol lays the foundation for a comprehensive and multistakeholder assessment of telehealth services and programs. Its findings will inform policy makers,

health care providers, researchers, and other stakeholders in advancing the quality, effectiveness, and cost-effectiveness of telehealth in the US health care system.

Trial Registration: OSF Registries osf.io/aytus; https://osf.io/aytus

International Registered Report Identifier (IRRID): DERR1-10.2196/55209

(JMIR Res Protoc 2024;13:e55209) doi:10.2196/55209

KEYWORDS

cost; effectiveness; evaluation; framework; healthcare delivery; measurement; quality; scoping review; telehealth; United States

Introduction

Overview

Telehealth has witnessed a remarkable transformation in recent years, propelled by the COVID-19 pandemic, which has greatly accelerated its adoption and expansion. The imperative for social distancing and the need to minimize in-person contact have made telehealth a pivotal tool at the forefront of health care delivery, helping to ensure accessibility and continuity of health care. This transformation has been further facilitated by significant expansions in telehealth service coverage, as well as regulatory requirements for telehealth visits, by the Centers for Medicare and Medicaid Services (CMS) and other payers, enhancing accessibility and affordability for patients across the nation [1-5].

The rapid expansion of telehealth services underscores the necessity for comprehensive guidance and evaluation of telehealth programs to guarantee the quality and effectiveness of health care delivery. The World Health Organization (WHO) has published a series of operational guidelines and evaluation frameworks to facilitate its global strategy on digital health development [6-9].

Recognizing the importance of maintaining service quality in practice, professional groups and telehealth stakeholders across the United States have actively contributed to the development of clinical guidelines. For instance, the American Telemedicine Association (ATA) published practice guidelines to enhance the technical quality and reliability of telemental health services for children and adolescents [10]. The ATA's practice guidelines for ocular telehealth-diabetic retinopathy were updated to their third edition in 2020 to incorporate new evidence and technologies [11]. Furthermore, the American Heart Association (AHA) has advocated using remote patient monitoring technologies to improve cardiovascular disease outcomes [12], highlighting the ever-expanding role of telehealth in quality health care. The American Nurses Association (ANA) updated its core principles on telehealth in 2019 to provide guidance for health care professionals in delivering quality care using health technologies [13]. Similarly, the National Association of Social Workers (NASW) published guidance on legal considerations for telemental health, promoting adherence to state and federal practice guidelines and payer contract agreements among social workers [14].

Concurrently, in response to the rapidly evolving landscape of telehealth services, researchers, professional groups, and organizations have crafted telehealth evaluation frameworks. These frameworks have been designed to guide and facilitate the assessment of specific dimensions of telehealth programs. For example, Zhang et al [15] designed a framework to guide the development and evaluation of sustainable telehealth programs. Curfman et al [16] developed an economic framework focusing on measuring the value of pediatric telehealth. Moreover, a consortium of experts from the Kaiser Permanente (KP) Institute for Health Policy, AcademyHealth, the ATA, and the Physician Insurers Association of America (PIAA) collaborated on a telehealth research and policy framework, facilitating the assessment of health services and the quality of health care [17]. During the COVID-19 pandemic, the National Quality Forum (NQF) updated its telehealth measurement development framework, initially created in 2017, through an environmental scan conducted in 2021 [18-20].

Despite the wealth of telehealth evaluation frameworks available, several critical questions remain unanswered. First, the rapidly evolving state of telehealth programs, along with the emergence of innovative telehealth tools, has underscored the pressing need for a comprehensive grasp of the essential concepts that should be considered in their evaluation. For instance, the growing use of artificial intelligence in clinical assessments and the application of virtual reality among pediatric patients with autism spectrum disorder have garnered broad attention [21,22]. It is imperative to acquire a broader evaluation framework that accommodates these emerging technologies and provides a comprehensive understanding of integrating state-of-the-art technologies on telehealth platforms. As such, a scoping review that systematically identifies what telehealth services and programs are evaluated and how they are assessed is needed.

Additionally, while numerous frameworks have been proposed, many of them have been developed primarily from a narrow perspective or to address a specific need, potentially limiting their broader applicability and the comprehensiveness of the evaluation. For example, the framework developed by Zhang et al [15] focused on the sustainability of single telehealth programs, encompassing domains of program implementation, clinical effectiveness, and economic analysis. In contrast, the framework developed by KP, AcademyHealth, the ATA, and the PIAA considered five domains, including (1) policy context, (2) payment policy, (3) delivery, (4) modality, and (5) outcomes [17]. In the case of the NQF telehealth measurement development framework, it emphasizes assessing the impact of telehealth on health care system readiness and health outcomes in rural areas, spanning across another five domains: (1) access to care and technology; (2) costs, business model, and logistics; (3) experience; (4) effectiveness; and (5) equity [15,18,19]. Given the diverse array of telehealth stakeholders in the United

States, including patients, providers, hospitals, payers, professional associations, federal agencies, policy makers, and legislators, it is necessary to consider the perspectives of multiple stakeholders and comprehensively evaluate telehealth services and programs.

Moreover, the measurements and assessments associated with telehealth evaluation domains and frameworks remain unclear, raising questions about how to effectively gauge the impact and outcomes of telehealth services and programs. While the frameworks developed by the WHO, Zhang et al [15], and NQF outline the measurements to be considered, this clarity is absent in the frameworks developed by KP, AcademyHealth, the ATA, and the PIAA [6-9,17,18].

Objective and Review Question

The broad objective of this scoping review is to answer the question of what is known about telehealth services and program evaluation in the United States. Specifically, this scoping review will be conducted to (1) map the existing landscape of telehealth evaluation, (2) identify key concepts for evaluation, (3) synthesize existing frameworks, and (4) identify measurements and assessments that have been considered.

A preliminary search of PROSPERO, MEDLINE, the Cochrane Database of Systematic Reviews, the Open Science Framework, and JBI Evidence Synthesis was conducted, and no current or in-progress scoping reviews or systematic reviews on the topic were identified.

Methods

Study Design

The scoping review will be conducted in accordance with the Joanna Briggs Institute (JBI) methodology for scoping reviews and in line with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) [23-25].

Protocol and Registration

The protocol for this scoping review is registered on the Open Science Framework (osf.io/aytus) [26]. The scoping review is expected to be completed in 6 months.

Eligibility Criteria

The eligibility for this scoping review is elaborated following the Population, Concept, and Context (PCC) framework.

Participants

This scoping review will consider a range of document types, including reviews, reports, and white papers, specifically related to telehealth evaluation frameworks and associated measurements. The evaluation frameworks to be included will focus on telehealth services and programs used for the provision of health services through well-established modalities, such as store-and-forward telemedicine, remote monitoring, real-time counseling, audio and video conferencing, and videotelephony, as well as emerging innovations integrated with telehealth platforms, such as virtual realities and artificial intelligence [27]. We will exclude manuscripts with data analyses only, case studies, project intervention reports (including scale-up and scale-down studies), and commentaries.

Concept

This review will examine concepts pertaining to the evaluation frameworks of telehealth services and programs. The concepts to be examined will encompass existing evaluation frameworks and associated measurements developed by telehealth stakeholders, professional organizations, and authoritative sources, excluding those developed by individual researchers. This approach will allow us to collect data that reflect the collective expertise and consensus of experts within the respective professional group. The aim is to create a comprehensive overview of telehealth evaluation, incorporating perspectives from multiple stakeholder categories, including but not limited to public and private payers, providers, and policy makers.

Context

This review will consider documents published in English for various health care settings, for example, primary care, specialty care, and rural health care for adult and pediatric patients. Considering the diversity of the contexts of telehealth services and programs across different health care systems and the unique nature of the US health care system, publications reporting on evaluation frameworks developed for regions that do not include the United States will be excluded. Documents published by worldwide health organizations will be included, given their relevance and influence in US health care.

Search Strategy

As many evaluation frameworks are likely to be published on stakeholders' websites, we will source data from peer-reviewed journals and gray literature, such as reports, white papers, policy documents, and guidelines.

The search strategy will aim to locate published reviews, reports, and white papers. An initial PubMed search was undertaken to identify articles on the topic. The text words contained in the titles and abstracts of relevant articles and the index terms used to describe the articles were used to develop a full search strategy for PubMed (Multimedia Appendix 1). The search strategy, including all identified keywords and index terms, will be adapted for each included database and information source. The reference lists of all included studies will be screened for additional titles. The databases to be searched include PubMed (US National Library of Medicine), Health Technology Assessments (International Network of Agencies for Health Technology Assessment), and Web of Science Core Collection (Clarivate Analytics). The websites of telehealth stakeholders, professional organizations, and authoritative sources mentioned in the included articles will be screened for additional documents.

Documents published from January 1, 2019, to the present will be considered for inclusion. While we recognize the relevance of earlier publications, the rapid expansion of telehealth, particularly accelerated by the COVID-19 pandemic, has led to significant changes in telehealth services and programs. During and after the pandemic, not only did the volume of telehealth

services increase, but there was also a diversification in the types of modalities considered under the telehealth umbrella. For example, before the pandemic, audio-only interactions were not widely regarded as telehealth, and various modalities like e-consults and e-visits were not as commonly used as they are now. Therefore, the inclusion of documents published from January 1, 2019 onward will allow us to focus on the most recent and relevant telehealth service and program evaluations.

Source of Evidence Selection

Following the search, all identified records will be collated and uploaded into EndNote (V21; Clarivate Analytics), with duplicates removed. A total of 2 reviewers will independently screen titles and abstracts against the inclusion criteria. Following a pilot test, titles and abstracts will then be screened by 2 independent reviewers for assessment against the inclusion criteria for the review. All screening will be completed through Rayyan, a web-based tool for evidence synthesis projects [28]. The full text of selected citations will be assessed in detail against the inclusion criteria by 2 or more independent reviewers. Reasons for the exclusion of full-text documents that do not meet the inclusion criteria will be recorded and reported in the scoping review. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussion. The results of the search will be reported in full in the final scoping review and presented in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram [29].

Data Extraction

Data will be extracted from documents selected for inclusion in the scoping review by 2 independent reviewers using a data extraction tool developed by the reviewers based on the JBI data extraction template for scoping review [24]. The data extracted will include specific details about the PCC methods and key findings relevant to the review question. A draft extraction tool is provided in Multimedia Appendix 2. The draft data extraction tool will be modified and revised as necessary during the process of extracting data from each included document. Modifications will be detailed in the full scoping review. Any disagreements that arise between the reviewers will be resolved through discussion.

Results

Reviewers will synthesize data across selected documents using tools such as tables and figures. Frequency counts of domains and measurements considered in frameworks and guidelines will be presented when applicable to highlight key patterns. Visual aids like Venn diagrams will be used to illustrate the relationships between the evaluation frameworks from various sources. Additionally, a narrative summary will be crafted to further describe how the results align with the review objectives, facilitating a comprehensive overview of the findings. This scoping review is expected to conclude by August 2024.

Discussion

Implications

In light of the rapid expansion of telehealth services, this scoping review seeks to address critical gaps in the current understanding of telehealth evaluation. The urgency of this endeavor is underscored by the need to ensure the quality, effectiveness, and cost-effectiveness of telehealth programs, with their increasing significance to the US health care system.

This scoping review will be the first to synthesize existing evidence of telehealth services and program evaluation in the United States and to facilitate the future development of telehealth in the postpandemic era. It will provide insights into the evaluation of state-of-the-art technology integration into telehealth.

In addition, the synthesized evaluation concepts and frameworks crafted by multiple telehealth stakeholders will guide the development of a multistakeholder evaluation framework that allows the comprehensive assessment of telehealth services and programs. Specifically, a multistakeholder framework will offer an inclusive and adaptable approach to telehealth evaluation, making it relevant and valuable to a wide range of users. By accommodating the diversity of telehealth initiatives, technologies, and objectives that exist within the US health care system, it will provide flexibility for stakeholders to tailor their evaluations for specific needs and objectives. In the evolving landscape of telehealth, where innovations and changes occur regularly, new technologies, practices, and policies would also be considered in the multistakeholder framework. The consideration of measurements and assessments will further illuminate the path toward actionable telehealth evaluation by providing more context and details.

Limitations

While we aim to conduct a comprehensive scoping review, some limitations should be considered. First, to ensure the comprehensiveness and relevance of this study's findings, we only consider frameworks developed for regions that encompass the United States. For instance, frameworks from organizations like the WHO are considered if they pertain to the US context. However, given the unique and complex nature of the US health care system, the results from this scoping review might not be directly applicable to other countries. In addition, given that the scoping review aims to provide a comprehensive overview of telehealth evaluation from a multistakeholder perspective, the scoping review will exclude documents carried out by individual researchers. Therefore, when evaluating local telehealth programs, it is advisable to include specific local considerations in addition to the results of this scoping review.

Conclusions

This scoping review will serve as a critical initial step in advancing the understanding of telehealth evaluation, given the current role of telehealth in the US health care system. Its findings will inform policy makers, health care providers, researchers, and other stakeholders involved in the rapidly evolving field of telehealth. By addressing these fundamental questions, this protocol lays the foundation for the scoping

review for comprehensive telehealth evaluation and future telehealth advancement.

Acknowledgments

This work is supported by the Office for the Advancement of Telehealth, Health Resources and Services Administration, US Department of Health and Human Services, under a cooperative agreement award (2 U66RH31459 - 04 - 00). The information, conclusions, and opinions expressed are those of the authors, and no endorsement is intended or should be inferred.

Authors' Contributions

YZ, YYL, LSL, JCR, EGH, and JMS undertook the conceptualization and methodology of this study. YZ drafted the initial version of the manuscript, with all authors contributing to the investigation and subsequent review and editing. YZ and EGH managed the resources for the study, while YZ and SC handled project administration. SC secured the funding for the project. SC and JMS provided additional supervision.

Conflicts of Interest

LSL is an employee of ConcertAI. All other authors have no conflicts of interest to declare.

Multimedia Appendix 1
Search strategy.
[DOCX File , 21 KB - resprot_v13i1e55209_app1.docx]

Multimedia Appendix 2
Data extraction instrument.
[DOCX File , 22 KB - resprot_v13i1e55209_app2.docx]

References

1. Mehrotra A, Jena AB, Busch AB, Souza J, Uscher-Pines L, Landon BE. Utilization of telemedicine among rural medicare beneficiaries. JAMA 2016;315(18):2015-2016 [FREE Full text] [doi: 10.1001/jama.2016.2186] [Medline: 27163991]
2. Thomas KC, Ellis AR, Konrad TR, Holzer CE, Morrissey JP. County-level estimates of mental health professional shortage in the United States. Psychiatr Serv 2009;60(10):1323-1328 [FREE Full text] [doi: 10.1176/ps.2009.60.10.1323] [Medline: 19797371]
3. Wang PS, Lane M, Olfson M, Pincus HA, Wells KB, Kessler RC. Twelve-month use of mental health services in the United States: results from the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005;62(6):629-640 [FREE Full text] [doi: 10.1001/archpsyc.62.6.629] [Medline: 15939840]
4. McClellan M, Rajkumar R, Couch M, Holder D, Pham M, Long P, et al. Health care payers COVID-19 impact assessment: lessons learned and compelling needs. NAM Perspect 2021;2021:10.31478/202105a [FREE Full text] [doi: 10.31478/202105a] [Medline: 34532685]
5. Arora P, Mehta D, Ha J. Impact of telehealth on health care resource utilization during the COVID-19 pandemic. J Comp Eff Res 2022;11(5):301-309 [FREE Full text] [doi: 10.2217/cer-2021-0242] [Medline: 35040354]
6. Defining Evaluation Indicators for Telemedicine as a Tool for Reducing Health Inequities: Study and Results of a Community of Practice. Washinton, DC: World Health Organization; 2016.
7. Digital Implementation Investment Guide (DIIG): Integrating Digital Interventions into Health Programmes. Geneva, Switzerland: World Health Organization; 2020.
8. Global health strategy on digital health. World Health Organization. 2022. URL: https://cdn.who.int/media/docs/default-source/digital-health-documents/en_who_digitalhealth_summary-(1).pdf?sfvrsn=e491ac50_5 [accessed 2024-02-28]
9. WHO Guideline: Recommendations on Digital Interventions for Health System Strengthening: Web Supplement 2: Summary of Findings and GRADE Tables. Geneva, Switzerland: World Health Organization; 2019.
10. Myers K, Nelson EL, Rabinowitz T, Hilty D, Baker D, Barnwell SS, et al. American telemedicine association practice guidelines for telemental health with children and adolescents. Telemed J E Health 2017;23(10):779-804. [doi: 10.1089/tmj.2017.0177] [Medline: 28930496]
11. Horton MB, Brady CJ, Cavallerano J, Abramoff M, Barker G, Chiang MF, et al. Practice guidelines for ocular telehealth-diabetic retinopathy, third edition. Telemed J E Health 2020;26(4):495-543 [FREE Full text] [doi: 10.1089/tmj.2020.0006] [Medline: 32209018]
12. Using remote patient monitoring technologies for better cardiovascular disease outcomes guidance. American Heart Association. 2019. URL: https://www.heart.org/-/media/files/about-us/policy-research/policy-positions/clinical-care/remote-patient-monitoring-guidance-2019.pdf?la=en [accessed 2024-02-28]

13. ANA core principles on connected health. American Nurses Association. 2019. URL: https://www.nursingworld.org/~4a9307/globalassets/docs/ana/practice/ana-core-principles-on-connected-health.pdf [accessed 2024-02-28]
14. Felton E. Telemental health. National Association of Social Workers. 2020. URL: https://www.socialworkers.org/LinkClick.aspx?fileticket=xmfNHyy8i8M%3D&portalid=0 [accessed 2024-02-28]
15. Zhang Y, Chandra S, Peña MT, Lal L, Summers RL, Swint JM. Framework for evaluating and developing sustainable telehealth programs. Telemed J E Health 2023;29(9):1421-1425. [doi: 10.1089/tmj.2022.0407] [Medline: 36716266]
16. Curfman A, McSwain SD, Chuo J, Olson CA, Simpson K. An economic framework to measure value of pediatric telehealth. Telemed J E Health 2021;27(12):1440-1442 [FREE Full text] [doi: 10.1089/tmj.2020.0520] [Medline: 33891500]
17. Edmunds M, Tuckson R, Lewis J, Atchinson B, Rheuban K, Fanberg H, et al. An emergent research and policy framework for telehealth. eGEMS 2017;5(2):1 [FREE Full text] [doi: 10.13063/2327-9214.1303] [Medline: 28459085]
18. Rural telehealth and healthcare system readiness measurement framework—final report. National Quality Forum. 2021. URL: https://www.qualityforum.org/Publications/2021/11/Rural_Telehealth_and_Healthcare_System_Readiness_Measurement_Framework_-_Final_Report.aspx [accessed 2024-02-28]
19. Leveraging quality measurement to improve rural health, telehealth, and healthcare system readiness—final environmental scan report. National Quality Forum. 2021. URL: https://tinyurl.com/4nubb2sw [accessed 2024-02-24]
20. Creating a framework to support measure development for telehealth. National Quality Forum. 2017. URL: https://www.qualityforum.org/Publications/2017/08/Creating_a_Framework_to_Support_Measure_Development_for_Telehealth.aspx [accessed 2024-02-28]
21. Tsoi KKF. Application of artificial intelligence on a symptom diagnostic platform for telemedicine a pilot case study. : IEEE; 2019 Presented at: 2019 IEEE International Conference on Systems, Man and Cybernetics (SMC); October 6-9, 2019; Bari, Italy. [doi: 10.1109/smc.2019.8914229]
22. Elkin TD, Zhang Y, Reneker JC. Gaze fixation and visual searching behaviors during an immersive virtual reality social skills training experience for children and youth with autism spectrum disorder: a pilot study. Brain Sci 2022;12(11):1568 [FREE Full text] [doi: 10.3390/brainsci12111568] [Medline: 36421892]
23. Peters MDJ, Marnie C, Tricco AC, Pollock D, Munn Z, Alexander L, et al. Updated methodological guidance for the conduct of scoping reviews. JBI Evid Implement 2021;19(1):3-10. [doi: 10.1097/XEB.0000000000000277] [Medline: 33570328]
24. Peters MDJ, Godfrey C, McInerney P, Munn Z, Tricco AC, Khalil H. Chapter 11: Scoping reviews. In: JBI Manual for Evidence Synthesis. Adelaide, Australia: Joanna Briggs Institute; 2020.
25. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med 2018;169(7):467-473 [FREE Full text] [doi: 10.7326/M18-0850] [Medline: 30178033]
26. Zhang Y, Lin YY, Lal LS, Reneker JC, Hinton EG, Chandra S, et al. Framework for telehealth evaluation: a scoping review protocol. OSF. 2023. URL: https://doi.org/10.17605/OSF.IO/AYTUS [accessed 2024-02-28]
27. Eswaran H, Dawson L. Telehealth: current definitions and future trends. The Rural Telehealth Evaluation Center (RTEC). 2022. URL: https://idhi.uams.edu/rtec/wp-content/uploads/sites/4/2022/05/Telehealth-Definitions-Paper-06MAY2022-1.pdf [accessed 2024-02-28]
28. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev 2016;5(1):210 [FREE Full text] [doi: 10.1186/s13643-016-0384-4] [Medline: 27919275]
29. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Int Surg J 2021;88:105906 [FREE Full text] [doi: 10.31222/osf.io/jb4dx]

Abbreviations

AHA: American Heart Association
ANA: American Nurses Association
ATA: American Telemedicine Association
CMS: Centers for Medicare and Medicaid Services
JBI: Joanna Briggs Institute
KP: Kaiser Permanente Institute for Health Policy
NASW: National Association of Social Workers
NQF: National Quality Forum
PCC: Population, Concept, and Context
PIAA: Physician Insurers Association of America
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
WHO: World Health Organization

Edited by A Mavragani; submitted 05.12.23; peer-reviewed by M Pena, K Drude; comments to author 01.02.24; revised version received 06.02.24; accepted 07.02.24; published 28.03.24.

Please cite as:
Zhang Y, Lin YY, Lal LS, Reneker JC, Hinton EG, Chandra S, Swint JM
Telehealth Evaluation in the United States: Protocol for a Scoping Review
JMIR Res Protoc 2024;13:e55209
URL: https://www.researchprotocols.org/2024/1/e55209
doi:10.2196/55209
PMID:38546709

Protocol

Digital Health Interventions in Older Adult Populations Living With Chronic Disease in High-Income Countries: Protocol for a Scoping Review

Mir Nabila Ashraf[1], MSc; Natasha L Gallant[2], PhD; Cara Bradley[3], MLiS

[1]Centre on Aging and Health, University of Regina, Regina, SK, Canada

[2]Department of Psychology and Centre on Aging and Health, University of Regina, Regina, SK, Canada

[3]Dr John Archer Library and Archives, University of Regina, Regina, SK, Canada

Corresponding Author:
Natasha L Gallant, PhD
Department of Psychology and Centre on Aging and Health
University of Regina
3737 Wascana Parkway
Regina, SK, S4S 0A2
Canada
Phone: 1 306 585 4219
Email: Natasha.Gallant@uregina.ca

Abstract

Background: Globally, around 80% percent of adults aged 65 years or older are living with at least 1 chronic disease, and 68% percent have 2 or more chronic diseases. Older adults living with chronic diseases require greater health care services, but these health care services are not always easily accessible. Furthermore, the COVID-19 pandemic has resulted in unprecedented changes in the provision of health care services for older adults. During the COVID-19 pandemic, digital health interventions for chronic disease management were developed out of necessity, but the evidence regarding these and developed interventions is lacking.

Objective: In this scoping review, we aim to identify available digital health interventions such as emails, text messages, voice messages, telephone calls, video calls, mobile apps, and web-based platforms for chronic disease management for older adults in high-income countries.

Methods: We will follow the Arksey and O'Malley framework to conduct the scoping review. Our full search strategy was developed following a preliminary search on MEDLINE. We will include studies where older adults are at least 65 years of age, living with at least 1 chronic disease (eg, cancer, cardiovascular disease, chronic obstructive pulmonary disease, and diabetes), and residing in high-income countries. Digital health interventions will be broadly defined to include emails, text messages, voice messages, telephone calls, video calls, mobile apps, and web-based platforms.

Results: This scoping review is currently ongoing. As of March 2023, our full search strategy has resulted in a total of 9901 records. We completed the screening of titles and abstracts and obtained 442 abstracts for full-text review. We are aiming to complete our full-text review in October 2024, data extraction in November 2024, and data synthesis in December 2024.

Conclusions: This scoping review will generate evidence that will contribute to the further development of digital health interventions for future chronic disease management among older adults in high-income countries. More evidence-based research is needed to better understand the feasibility and limitations associated with the use of digital health interventions for this population. These evidence-based findings can then be disseminated to decision-makers and policy makers in other high-income countries.

International Registered Report Identifier (IRRID): DERR1-10.2196/49130

(JMIR Res Protoc 2024;13:e49130) doi:10.2196/49130

KEYWORDS

chronic disease; high-income countries; digital health; interventions; older adults; quality of life

Introduction

Globally, according to the World Health Organization (WHO), 41 million people die from chronic diseases each year [1]. Four chronic diseases, including cancer, cardiovascular diseases, chronic respiratory diseases, and diabetes, are responsible for over 80% of all premature mortality worldwide [1]. Chronic disease outcomes are worse for older adults compared to their younger counterparts [2]. For instance, according to the US Centers for Disease Control and Prevention (CDC), around 85% of older adults in the United States endure at least 1 chronic disease and approximately 60% have at least 2 chronic diseases [3,4]. In Canada, approximately 70% of people aged at least 65 years are living with at least 1 of 10 common chronic diseases [4]. Life expectancy continues to increase, especially in high-income countries [5], and, given that age increases the risk of developing chronic diseases [6], the prevalence of chronic disease is also expected to grow. Thus, it is crucial to identify potential strategies for older adults with chronic diseases in high-income countries. Furthermore, while older adults living with chronic diseases require a greater amount of health care services, these health care services are not always easily accessible for this population [7].

The COVID-19 pandemic has had and continues to have a detrimental impact on the global health systems [8]. During the initial stages of the COVID-19 pandemic, older adults were often unable to access health care services due to public health mandates [9]. In the later stages of the COVID-19 pandemic, access to health care services was still limited due to lengthened waitlists and increased staff shortages [10]. Older adults living with chronic diseases and their caregivers experienced increased levels of stress and worse chronic disease outcomes due to this lack of access [11,12]. It is therefore essential that alternatives to in-person interventions be developed to ensure accessible health care services during public health emergencies such as the COVID-19 pandemic.

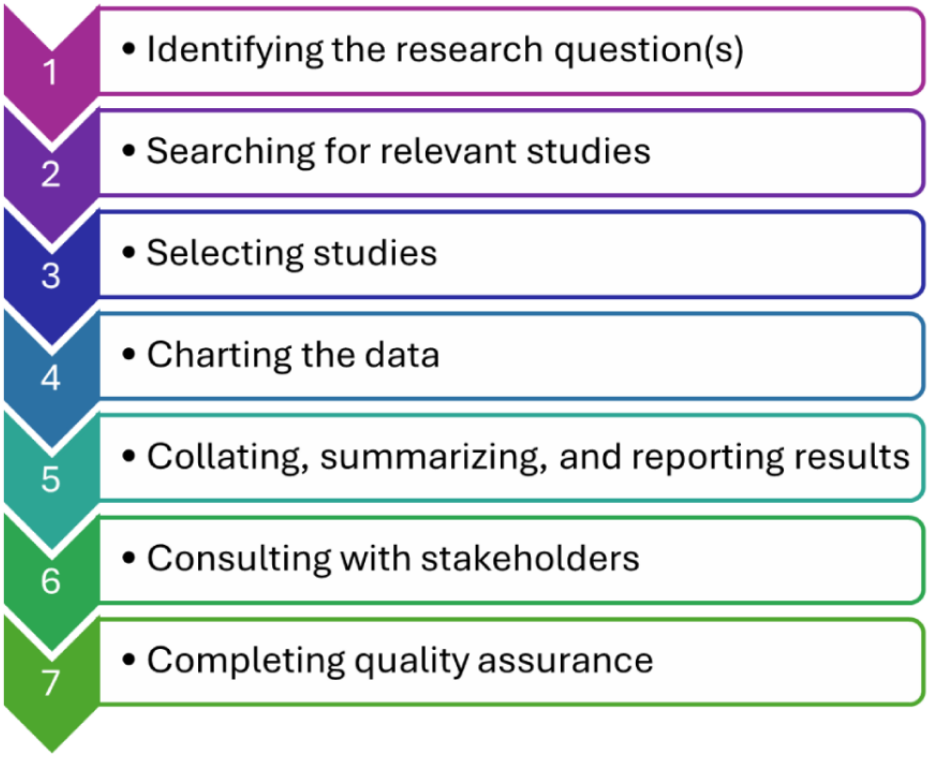
Amid the emergent COVID-19 pandemic, digital health interventions such as telehealth and app-based health care were developed in response to limitations to in-person interventions [13]. There are few evidence-based guidelines on digital health intervention for chronic disease management. Thus, this review is essential to identify available digital health interventions to manage chronic diseases among older adults. So, the primary aim of this scoping review is to identify available digital health interventions for chronic disease management among older adults in high-income countries. The secondary aim of this scoping review will be to identify potential outcomes associated with these digital health interventions such as early diagnosis, increasing health literacy for chronic disease management, or improving quality of life. Findings from this scoping review will further support the development and evaluation of future digital health interventions.

Methods

Overview

The 6 steps of the Arksey and O'Malley [14] framework will be used to conduct a scoping review to investigate digital health interventions to manage chronic disease among older adults in high-income countries. Given the possibility of a high risk of bias when conducting reviews [15], we will include a quality assessment as an additional step in our scoping review as recommended by Levac et al [16]. Thus, the scoping review will be completed in the 7 steps illustrated in Figure 1.

Figure 1. Arksey and O'Malley's methodological framework with the additional step of quality assurance.



Step 1: Identifying the Research Questions

For this scoping review, the research questions that have been identified are as follows: What are the digital health interventions aimed at improving outcomes associated with chronic disease management for older adults? (2) With regards to the identified digital health interventions, what are the associated outcomes (such as early diagnosis, prevention, or treatment for chronic disease or increasing health literacy on chronic disease management) for (1) older adults, (2) their caregivers, and (3) the health system?

Step 2: Searching for Relevant Studies

A preliminary search was conducted in the Cochrane Database of Systematic Reviews, Joanna Briggs Institute (JBI) Evidence Synthesis, Open Science Framework, and International Prospective Register of Systematic Reviews (PROSPERO) to identify other similar scoping reviews. Following this preliminary search, the full search strategy was conducted by an academic librarian. An initial MEDLINE search was undertaken in February 2023 to identify papers on the topic by focusing on the concepts of older adults, caregivers, the health care system, digital interventions, and chronic disease. The text words contained in the titles and abstracts of relevant papers, as well as the index terms used to describe the papers were used to develop a full search strategy for Ovid MEDLINE(R) and In-Process, In-Data-Review and Other Non-Indexed Citations and Daily (1946-2023; Multimedia Appendix 1). Papers published in any language from database inception to the present were included. The search strategy, including all identified text words and index terms, was translated to CINAHL Plus (Ebsco; 1966-2023), JBI EBP Database (Ovid; 2012-2023), PsycINFO (Ovid; 1806-2023), and Web of Science (1966-2023) by the academic librarian that can be accessed upon request. Finally, using similar text words and index terms, sources of grey literature searched included Google Advanced, Grey Literature Report, and ProQuest Dissertations & Theses: Global (1861-2022). The full search strategy was undertaken on April 3, 2023.

Step 3: Selecting Studies

Following a pilot test, titles and abstracts of studies including methodology of randomized controlled trials, nonrandomized controlled trials, pre-post studies, interrupted time-series studies, prospective cohort studies, retrospective cohort studies, case-control studies, and cross-sectional studies will be imported into Covidence (Veritas Health Innovation). The titles and abstract will be screened by 2 independent reviewers for assessment against the inclusion criteria for the scoping review as outlined below for full-text review. The selected papers will be downloaded for full-text review in detail against the inclusion criteria by 2 independent reviewers. Reasons for exclusion of full-text studies that do not meet the inclusion criteria will be recorded and reported in the scoping review. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussion or with a third reviewer.

Inclusion Criteria

Population

The population of interest includes adults who are aged at least 65 years and living with chronic disease. For a study to be included in this review, at least 50% of the sample must be aged at least 65 years or the mean age of the sample needs to be at least 65 years. Chronic diseases considered eligible for this review include cancer, cardiovascular diseases, chronic obstructive pulmonary disease, and diabetes. Finally, studies will be included if they are with populations residing in 1 of the selected countries with a high or very high Human Development Index [17]—Australia, Canada, and the United States.

Interventions

Studies examining digital health interventions for chronic disease management will be included. Digital health interventions will be broadly defined to include emails, text messages, voice messages, telephone calls, video calls, mobile apps, and web-based platforms. Chronic disease management will be defined as the management of at least one of the following chronic diseases: cancer, cardiovascular diseases, chronic obstructive pulmonary disease, and diabetes.

Comparisons

Studies with comparisons to digital health interventions (such as placebo or health service delivery as usual) or without comparison (no comparative intervention), will be considered.

Outcomes

Following the initial screening of papers, we have identified a few potential outcomes such as studies that include outcomes related to physical health (eg, blood pressure and blood sugars) and mental health (eg, anxiety and depression) assessed with validated tools or approaches will be considered for this scoping review. Improvements in health education or health literacy as well as quality of life will also be considered as appropriate. However, we are open to adding other outcomes following full-text review after iterative discussion with research team members.

Exclusion Criteria

The exclusion criteria for this study are (1) studies published in a form other than a peer-reviewed journal paper; (2) studies written in a language other than English; (3) studies with less than 50% of the sample aged at least 65 years or the mean age of the sample less than 65 years; (4) studies focused solely on chronic diseases other than cancer, cardiovascular diseases, chronic obstructive pulmonary disease, and diabetes; (5) studies published in a country other than Australia, Canada, or the United States; and (6) studies examining health interventions that are not digital (eg, in-person counseling) or digital interventions that are not focused on health (eg, general time management skills).

Step 4: Charting the Data

Data will be extracted from studies included in the scoping review by 2 independent reviewers using a data extraction tool developed by the reviewers. Any disagreements that arise between the reviewers will be resolved through discussion or

with a third reviewer. The data extracted will include the following details: authors, year of publication, objectives, type of study, population, intervention, comparisons, and outcomes. Where required, authors of papers will be contacted to request missing or additional data. A draft of our data extraction tool is provided (Multimedia Appendix 2). The draft data extraction tool will be modified and revised as necessary during the process of extracting data from each included paper. Modifications will be detailed in the full scoping review.

Step 5: Collating, Summarizing, and Reporting the Results

The results will be reported in full in the final scoping review and presented in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram [18,19]. When summarizing, we will list the type and format of interventions included in eligible studies. We will also organize similar outcomes together to determine the direction of outcomes included in the interventions. We will use descriptive numerical summary analysis for the results. The data will be mapped and presented in tabular format to make it easier to answer our research questions. A narrative summary will accompany the results and will describe how the results relate to the research questions.

Step 6: Consultation With Stakeholders

For this step, we will consult with researchers from high-income countries with expertise in older adults, chronic disease management, and digital interventions to provide any relevant studies aligned with our research questions. We will also consult with a group of patient partners living with chronic disease to validate the study findings.

Step 7: Quality Assessment

We will assess the quality of the studies included in this scoping review using JBI's Critical Appraisal Checklist for Systematic Reviews and Research Syntheses [20]. Prior to critical appraisal, 2 independent reviewers will meet to determine the criteria for indicating a "yes," "no," "unclear," or "not applicable" response in the context of this scoping review for each of the 11 items. For items that are deemed "unclear," authors of the reviews will be contacted to request missing or additional data for clarification. Each study will be ranked according to findings from the critical appraisal as low quality (ie, "yes" for 0%-33% of critical appraisal items with a "yes" or "no"), medium quality (ie, "yes" for 34%-66% of critical appraisal items with a "yes" or "no"), and high quality (ie, "yes" for 67%-100% of critical appraisal items with a "yes" or "no"). The results of critical appraisal will be reported in a critical appraisal table.

Results

Screening of titles and abstracts has been completed. The full-text review is expected to be complete by the end of October 2024, followed by data extraction in November 2024, and data synthesis in December 2024. We will disseminate the findings of the scoping review at the national and international scientific conference proceedings and by publishing the paper in a peer-reviewed journal.

Discussion

Principal Findings

With our rapidly aging population, digital health interventions may play a crucial role, especially for the management of chronic diseases among older adults. To our knowledge, our research will be one of the first that will highlight the available digital health interventions for the management of chronic disease which leads to major issues such as disability and interruption in the activities of daily living among older adults [7]. This scoping review will provide a comprehensive synthesis of existing digital interventions that will contribute to designing a feasible intervention model that can be customized by communities that need to manage chronic disease and improve the quality of life among older adults.

Though we will conduct a comprehensive scoping review, there may be some limitations that we will not be able to address. In this scoping review, we will only include peer-reviewed journal papers, so we may miss and exclude some of the evidence-based unpublished data from our findings. Another important limitation is that papers written in a language other than English will be excluded from our scoping review. Thus, additional research focusing on the available unpublished data findings and non-English papers would be helpful for generating evidence to gather available digital health interventions for chronic disease management.

The findings of the scoping review will assist researchers in the further establishment of digital health interventions for chronic disease management among older adults. More evidence-based research is crucial to understanding the potential barriers and enablers of digital health for older adults and, especially, older adults with chronic diseases.

Conclusions

Digital health interventions have become a prevalent form of health care services since the COVID-19 pandemic, but more evidence-based research is needed to assess the outcomes associated with digital health interventions. Findings from this scoping review will provide an overview of empirical evidence regarding digital health interventions and provide a stepping stone for the development and evaluation of future digital health interventions for older adults living with chronic disease.

Acknowledgments

This scoping review was supported by a grant awarded to NLG from the Saskatchewan Health Research Foundation (6127) along with President's Publication Fund and Arts Publication Fund awards from the University of Regina. MNA was supported by scholarships from the University of Regina's Faculty of Arts and Faculty of Graduate Studies & Research.

Authors' Contributions

All authors contributed to the paper writing, revision, and identifying the search strategy. NLG and MNA conceptualized the study. CB formulated and modified the search strategy.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Database and search strategy.
[DOCX File , 16 KB - resprot_v13i1e49130_app1.docx]

Multimedia Appendix 2
Data extraction instrument.
[DOC File , 25 KB - resprot_v13i1e49130_app2.doc]

References

1. Noncommunicable diseases. World Health Organization. 2022. URL: https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases#:~:text=Key%20facts,%2D%20and%20middle%2Dincome%20countries [accessed 2022-09-16]
2. Allen JO. Ageism as a risk factor for chronic disease. Gerontologist 2016 Aug;56(4):610-614 [FREE Full text] [doi: 10.1093/geront/gnu158] [Medline: 25618315]
3. Talking with your older patient: supporting older patients with chronic conditions. National Institutes of Health. 2017. URL: https://www.nia.nih.gov/health/supporting-older-patients-chronic-conditions [accessed 2023-01-24]
4. About chronic diseases. Centers for Disease Control and Prevention. 2017. URL: https://www.cdc.gov/chronicdisease/about/index.htm [accessed 2019-01-11]
5. Average life expectancy in industrial and developing countries for those born in 2023, by gender. Statista. 2022. URL: https://www.statista.com/statistics/274507/life-expectancy-in-industrial-and-developing-countries/#:~:text=More%20developed%20countries%20tend%20to,had%20the%20highest%20for%20females [accessed 2024-03-12]
6. Tam T. Aging and chronic diseases: a profile of Canadian seniors. Government of Canada. 2020. URL: https://www.canada.ca/en/public-health/services/publications/diseases-conditions/aging-chronic-diseases-profile-canadian-seniors-report.html [accessed 2024-03-12]
7. Maresova P, Javanmardi E, Barakovic S, Barakovic Husic J, Tomsone S, Krejcar O, et al. Consequences of chronic diseases and other limitations associated with old age - a scoping review. BMC Public Health 2019 Nov 01;19(1):1431 [FREE Full text] [doi: 10.1186/s12889-019-7762-5] [Medline: 31675997]
8. Impact of COVID-19 on people's livelihoods, their health and our food systems. World Health Organization. 2020. URL: https://www.who.int/news/item/13-10-2020-impact-of-covid-19-on-people's-livelihoods-their-health-and-our-food-systems [accessed 2020-10-13]
9. Lebrasseur A, Fortin-Bédard N, Lettre J, Raymond E, Bussières E, Lapierre N, et al. Impact of the COVID-19 pandemic on older adults: rapid review. JMIR Aging 2021 Apr 12;4(2):e26474 [FREE Full text] [doi: 10.2196/26474] [Medline: 33720839]
10. COVID-19 has caused major disruptions and backlogs in health care, new WHO study finds. World Health Organization. 2022. URL: https://www.who.int/europe/news/item/20-07-2022-covid-19-has-caused-major-disruptions-and-backlogs-in-health-care--new-who-study-finds [accessed 2022-07-20]
11. Faronbi JO, Faronbi GO, Ayamolowo SJ, Olaogun AA. Caring for the seniors with chronic illness: the lived experience of caregivers of older adults. Arch Gerontol Geriatr 2019;82:8-14 [FREE Full text] [doi: 10.1016/j.archger.2019.01.013] [Medline: 30710847]
12. Bosetti C, Rognoni M, Ciampichini R, Paroni L, Scala M, d'Oro LC, et al. A real world analysis of COVID-19 impact on hospitalizations in older adults with chronic conditions from an Italian region. Sci Rep 2022 Aug 12;12(1):13704 [FREE Full text] [doi: 10.1038/s41598-022-17941-2] [Medline: 35962037]
13. Purnamayanti NKD, Wicaksana AL. Digital health services among patients with diabetes during the COVID-19 pandemic: a scoping review. Indian J Endocrinol Metab 2021;25(2):86-92 [FREE Full text] [doi: 10.4103/ijem.ijem_153_21] [Medline: 34660235]

14. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. Int J Soc Res Methodol 2005 Feb;8(1):19-32. [doi: 10.1080/1364557032000119616]
15. Glasziou P, Vandenbroucke JP, Chalmers I. Assessing the quality of research. BMJ 2004 Jan 03;328(7430):39-41 [FREE Full text] [doi: 10.1136/bmj.328.7430.39] [Medline: 14703546]
16. Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. Implement Sci 2010 Sep 20;5:69 [FREE Full text] [doi: 10.1186/1748-5908-5-69] [Medline: 20854677]
17. Human development report. United Nations Development Programme. 2022. URL: https://www.undp.org/arab-states/publications/human-development-report-2021-22 [accessed 2024-03-12]
18. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med 2018 Oct 02;169(7):467-473 [FREE Full text] [doi: 10.7326/M18-0850] [Medline: 30178033]
19. Knobloch K, Yoon U, Vogt PM. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement and publication bias. J Craniomaxillofac Surg 2011 Mar;39(2):91-92. [doi: 10.1016/j.jcms.2010.11.001] [Medline: 21145753]
20. Munn Z, Barker TH, Moola S, Tufanaru C, Stern C, McArthur A, et al. Methodological quality of case series studies: an introduction to the JBI critical appraisal tool. JBI Evid Synth 2020 Oct;18(10):2127-2133 [FREE Full text] [doi: 10.11124/JBISRIR-D-19-00099] [Medline: 33038125]

Abbreviations

CDC: US Centers for Disease Control and Prevention
JBI: Joanna Briggs Institute
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO: International Prospective Register of Systematic Reviews
WHO: World Health Organization

Edited by A Mavragani; submitted 18.05.23; peer-reviewed by A Nguyen, SQ Yoong; comments to author 28.06.23; revised version received 02.10.23; accepted 06.10.23; published 28.03.24.

Please cite as:
Ashraf MN, Gallant NL, Bradley C
Digital Health Interventions in Older Adult Populations Living With Chronic Disease in High-Income Countries: Protocol for a Scoping Review
JMIR Res Protoc 2024;13:e49130
URL: https://www.researchprotocols.org/2024/1/e49130
doi:10.2196/49130
PMID:38546710

Protocol

Holistic Person-Centered Care in Radiotherapy: Protocol for a Scoping Review

Fatima Bhyat[1], MTech; Andrew Makkink[2], PhD; Karien Henrico[2], PhD

[1]Department of Medical Imaging and Radiation Sciences, University of Johannesburg, Johannesburg, South Africa

[2]Department of Emergency Medical Care, University of Johannesburg, Johannesburg, South Africa

Corresponding Author:
Andrew Makkink, PhD
Department of Emergency Medical Care
University of Johannesburg
John Orr Building
Cnr Siemert and Beit Street
Johannesburg, 2091
South Africa
Phone: 27 11 5596236
Email: amakkink@uj.ac.za

Abstract

Background: Several types of health care professionals are responsible for the care of patients with cancer throughout their engagement with the health care system. One such type is the radiotherapist. The radiotherapist not only administers treatment but is also directly involved with the patient during treatment. Despite this direct contact with the patient, the narrative tends to focus more on technical tasks than the actual patient. This task-focused interaction is often due to the highly sophisticated equipment and complex radiotherapy treatment processes involved. This often results in not meeting the psychosocial needs of the patient, and patients have acknowledged noncompliance and delayed treatment as a result.

Objective: The scoping review aims to explore, chart, and map the available literature on holistic person-centered care in radiotherapy and to identify and present key concepts, definitions, methodologies, knowledge gaps, and evidence related to holistic person-centered care in radiotherapy.

Methods: This protocol was developed using previously described methodological frameworks for scoping studies. The review will include both peer-reviewed and gray literature regarding holistic, person-centered care in radiotherapy. A comprehensive search strategy has been developed for MEDLINE (Ovid), which will be translated into the other included databases: Scopus, CINAHL (EBSCO), MEDLINE (PubMed), Embase (Elsevier), Cochrane Library, and the Directory of Open Access Journals. Gray literature searching will include Google (Google Books and Google Scholar), ProQuest, the WorldWideScience website, the OpenGrey website, and various university dissertation and thesis repositories. The title and abstract screening, full-text review, and relevant data extraction will be performed independently by all 3 reviewers using the Covidence (Veritas Health Innovation) software, which will also be used to guide the resolution of conflicts. Sources selected will be imported into ATLAS.ti (ATLAS.ti Scientific Software Development GmbH) for analysis, which will consist of content analysis, narrative analysis, and descriptive synthesis. Results will be presented using narrative, diagrammatic, and tabular formats.

Results: The review is expected to identify research gaps that will inform current and future holistic, person-centered care in radiotherapy. The review commenced in November 2023, and the formal literature search was completed by the end of February 2024. Final results are expected to be published in a peer-reviewed journal by 2025.

Conclusions: The findings of this review are expected to provide a wide variety of strategies aimed at providing holistic, person-centered care in radiotherapy, as well as to identify some gaps in the literature. These findings will be used to inform future studies aimed at designing, developing, evaluating, and implementing strategies toward improved holistic, person-centered care in radiotherapy.

International Registered Report Identifier (IRRID): DERR1-10.2196/51338

(JMIR Res Protoc 2024;13:e51338) doi:10.2196/51338

KEYWORDS

cancer patient; cancer; cancer care; holistic care; person-centered care; person-centered; radiologist; radiology; radiotherapist; radiotherapy; scoping review; holistic care

Introduction

Radiotherapy, also referred to as radiation therapy, is a treatment modality that uses high-energy radiation or radioactive substances to destroy cancer cells or prevent their growth [1]. The clinical usefulness of ionizing radiation was discovered after the discovery of X-rays and has since developed into a medical specialty. Ionizing radiation damages the genetic material of cancer cells, blocking the cells' ability to proliferate, thus destroying the cancer cells [2]. Radiotherapy has become a highly cost-effective, leading modality in cancer treatment, as it can be used as a primary form of treatment or in combination with other modalities for curative or palliative purposes within cancer treatment [3]. Radiotherapy has an approximate 40% cure rate when used as a single modality of treatment compared to only 11% achieved by chemotherapy when used as a single modality of treatment [4]. Chemoradiotherapy use has experienced substantial growth and is now established as the standard treatment for various types of tumors, such as cervical, non–small cell lung cancer, and bladder cancer, as elaborated in this discussion. It provides considerable advantages in patient survival and local disease control while not significantly increasing long-term toxicities [5]. Radiotherapy is considered a conservative form of treatment with reduced adverse effects, unlike other treatments such as surgery, which can have mutilating and other long-term adverse effects, thus maintaining a good quality of life [6].

Evidence-based practice shows that more than 50% of patients with cancer will undergo a course of radiotherapy as part of their treatment, and despite this, patients appear to lack knowledge of the importance of radiotherapy treatment and its effects [7,8]. Negative perceptions toward receiving radiotherapy treatment have been expressed, as some patients with cancer consider it to be a form of poison, while others fear the effects of radiation as they believe it would cause another cancer, thus delaying seeking care [6,9]. Despite the vast improvement in radiotherapy technology, in addition to dealing with treatment-related toxicities [10], many patients also experience emotional challenges such as fear, anger, depression, stress, and anxiety [7,11]. Almost a third of patients with cancer acknowledge not having their psychosocial needs taken care of during treatment, resulting in a decrease in compliance, delayed treatment, and a decrease in quality of life, thus negatively impacting tumor control [7,12,13]. These perceptions, therefore, present an urgent need for a person-centered care approach to enhance the experience and well-being of the patient with cancer [14]. A person-centered care approach considers the needs and preferences of patients and thus allows patients to be actively involved in any treatment and decision-making [15]. Although patients with cancer come across many health professionals along their journey, radiotherapists have a key role in the experience of the patient with cancer as they find themselves in direct contact with the patient throughout the course of their radiotherapy treatment [12,16].

Radiotherapists are experts in the technical and clinical planning and delivery of radiotherapy treatment. They are equally responsible for providing care and support, monitoring and managing treatment-related toxicities, and coordinating supportive care, which can be last up to 6 weeks [8]. This places the radiotherapist in a unique position to engage with patients concerning their diagnosis and treatment [16,17]. However, despite the radiotherapist's direct contact with the patient, the narrative tends to focus more on technical tasks and other barriers, often at the cost of important psychosocial needs not being met [18]. Radiotherapists' disregard for patient care has also been influenced by the stressful nature of the workplace environment and the time pressures they face [17]. Nonetheless, the consequences of providing support in the form of empathy, compassion, and reassurance must be understood by radiotherapists, as it can result in alleviating their patients' anxiety and fear before the treatment [19]. Empathy is of particular importance in cancer delivery, as patients acknowledge having greater satisfaction and self-awareness when treated with empathy [20,21]. The length of time that a patient with cancer spends interacting with a radiotherapist has been shown to have a considerable impact on their overall experience [17]. Radiotherapists' daily direct contact with patients with cancer, therefore, not only enables them to prioritize their unique needs and values but also allows them to be involved in their care, creating a person-centered approach to treatment.

Radiotherapists can facilitate person-centered care by ensuring patients have their undivided attention [22]. This process can be initiated by building a rapport with each patient, communicating effectively, answering their questions, discussing their preferences, listening actively, addressing their physical and emotional needs, providing them with dignity, and collaborating with other health care professionals to ensure the patient's needs are met. Patients stated that they felt more included and positive about their radiotherapy treatment when these aspects were addressed [8,17,22]. Person-centered care is also considered to be synonymous with "wholism," or, as some may prefer, "holism." Holistic care considers the body, mind, soul, and spirit as interrelated and acknowledges the whole experience [23]. Holistic, person-centered care is, therefore, becoming increasingly important in cancer treatment, including radiotherapy [24]. Holistic care in radiotherapy allows for a personalized approach to patient care, which includes addressing the physical, emotional, social, and spiritual needs of the patient, empowering the patient, and promoting healing and well-being, thus improving the overall quality of life of the patient.

There is a paucity of literature related to holistic, person-centered care in radiotherapy. A search of the Open Science Framework, the Cochrane Database of Systematic Reviews, and Johanna Briggs Institute (JBI) Evidence Synthesis was conducted, and no published or in progress scoping or

systematic reviews were identified relating to holistic person-centered care in radiotherapy.

The proposed scoping review will explore, map, and summarize the nature, range, and extent of published literature available that relates to holistic person-centered care in radiotherapy. Identified sources will be described in terms of population, purpose, and setting, as well as theoretical underpinnings, outcome measures, and key findings. The proposed scoping review will assist in identifying common practices, knowledge gaps in the literature, and potential areas for future research and development.

Methods

Protocol Design

The proposed scoping review was developed using the methodological framework for scoping reviews developed by Arksey and O'Malley [25] and incorporates the updated frameworks suggested by Levac et al [26] and Peters et al [27], as well as the updated JBI methodology for scoping reviews [28]. The "population, concept, and context" (PCC) framework will guide the review, which will follow the following stages: (1) identification of the review question or questions and (2) identification of relevant studies. This will assist with the development of specific inclusion criteria to facilitate a comprehensive search of the literature. A comprehensive search for relevant studies will then be conducted, followed by the screening of those studies. The PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) will guide the reporting process [29].

Step 1: Identification of the Review Question or Questions

The research questions that will guide this scoping review are as follows: (1) What sources are available that relate to holistic, patient-centered care in radiotherapy? (2) What types of studies have been conducted on holistic, patient-centered care in radiotherapy? (3) In what settings have these studies been conducted? (4) What health care professionals and patients have been included in the studies? (5) What has the key approach been to the studies? (6) What theories have underpinned the studies? and (7) Were there any identified measures or outcomes from the studies?

Step 2: Identification of Relevant Studies

A comprehensive search strategy has been developed by the 3 members of the research team and an experienced librarian and information specialist. An exploratory search in MEDLINE (PubMed) and CINAHL (EBSCO) was performed to identify relevant articles on the topic (Multimedia Appendix 1). Once the scoping review commences, identified keywords in the titles and abstracts of articles related to the review question will be used to complement the search strategy, thus allowing for a more comprehensive search. The search strategy will also be adapted as required by scrutinizing the reference lists of articles that meet the inclusion criteria to find additional papers. Literature published in English and studies that can be translated will be considered. The search will commence in August 2023 and will not have a date limit to ensure that all studies that meet the inclusion criteria are considered. Once the search for each database has been completed, the results will be imported into Covidence (Veritas Health Innovation) for storage, organization, removal of duplicates, screening, and mapping of the data [30].

Step 3: Selection of Studies for Inclusion

The preliminary inclusion criteria will be defined using the PCC format. Details for each aspect of this format are described in the following sections.

Population

The population for this scoping review will be radiotherapists and patients involved in radiotherapy. Given that the scoping review aims to explore holistic person-centered care in radiotherapy, there will be no limitations placed relating to cancer or radiotherapy type, duration of treatment, or final outcome, nor will there be age, geographical, or time-based limitations placed on sources.

Concept

This review will consider studies that focus on person-centered care within radiotherapy to identify key concepts, definitions, methodologies used, existing models of care, and knowledge gaps in the literature. Any studies that included an intervention to improve person-centered care in radiotherapy and sources of evidence that informed practice will also be included.

Context

The scoping review will consider literature that is relevant to the radiotherapy context. The review will include the experiences of patients receiving radiotherapy treatment and evidence on the role of radiotherapists in providing any form of care or support to patients with cancer during radiotherapy treatment. in both private and public settings.

Types of Sources

In view of the fact that patient-centered care has been and is still a key issue in health care, the scoping review will aim to explore and integrate qualitative, quantitative, and mixed methods research data concerning person-centered care. Literature will be sourced from databases that will include Scopus, CINAHL (EBSCO), PubMed, the Education Resources Information Centre, the Cochrane Library, Sabinet, and the Directory of Open Access Journals. Any systematic reviews that meet the inclusion criteria will also be taken into account. Secondary sources that will be used in the search include Google (Google Books and Scholar), ProQuest, the WorldWideScience website, the OpenGrey website, and various university dissertations and thesis repositories.

Study Selection

Studies identified in the initial database search will be collated and then transferred into Covidence, which allows for duplicates to be removed and for appropriate studies to be sorted and selected based on the inclusion criteria [30]. The first stage, which involves the screening of titles and abstracts, will be performed independently by all 3 members of the research team, who will vote in Covidence to determine primary inclusion. Any disagreements will be resolved through discussion among

the team members, and in the event of an impasse, the decision will be by majority vote. The second stage of article selection will involve the downloading of identified sources from the first stage and then a screening of these articles in Covidence. Full-text sources that do not meet the inclusion criteria will be recorded, and reasons for exclusion will be reported in the scoping review. Any disagreements between the research team members at any stage of the selection process will be resolved through discussion. The PRISMA-ScR checklist and flow diagram will be used to report and present in full the results of the search and study inclusion selection in the final scoping review [28,29].

Step 4: Charting and Extraction of the Data

The extraction tool will be developed by the research team (Multimedia Appendices 2 and 3) in accordance with the JBI methodology for scoping reviews [29] and will be piloted in Excel (Microsoft Corporation) for relevance and ease of use. With the aid of an extraction tool, data will be independently extracted from the selected studies by the 3 members of the research team. Covidence has the advantage that changes can be made to the data extraction form at any time, even while extraction is in progress [30]. The data extracted will include study-specific details regarding article title, authors, geographic area, journal or other source, year of publication, aim or purpose, study population and sample size, context, methodology, intervention, outcomes, and key findings related to the scoping review questions. Data must be compared, and a consensus must be reached before the data can be exported. After completing the literature search and collecting all related evidence regarding person-centered care in radiotherapy, the next step will be to chart the data. This step involves synthesizing and interpreting the data, which allows key issues and themes to be highlighted. Sources will be imported into ATLAS.ti (ATLAS.ti Scientific Software Development GmbH), and thematic analysis will be used to identify themes that will then be summarized and discussed in relation to the study aims and objectives [31]. The identified codes and themes will be used to map the different aspects of person-centered care in radiotherapy as well as any evidence gaps. Should any missing data be noted in the data extraction table, it will be noted as “missing.” The data will be collated from ATLAS.ti and presented in a narrative summary and table format.

Step 5: Collation, Synthesis, and Reporting of the Results

The results will allow the researchers to better understand the delivery of holistic, person-centered care in radiotherapy. In addition, the role of the radiotherapist will be analyzed, as will what is required of them to enhance this phenomenon. The results may also raise awareness of important issues in the radiotherapy profession that should be included in the education of future radiotherapists. The results will be reported in accordance with the PRISMA-ScR reporting guidelines.

Results

The scoping review commenced in November 2023, and the formal literature search was completed by the end of February 2024. We are currently in the process of screening articles. A preliminary search of the literature was conducted using the Scopus database in November 2023, revealing 37,345 results using the initial search terms. We intend to publish the manuscript in an appropriate, peer-reviewed, and open-access health care journal to describe our findings and conclusions to the academic audience in 2025.

Discussion

Overview

There are several aspects related to patient-centered care within radiotherapy where gaps exist, but these are not well described. This scoping review intends to provide an overview of the current knowledge related to patient-centered care in radiotherapy, the effects that patient-centered care in radiotherapy has on both patients and radiotherapists, and to highlight existing gaps in the literature. The use of gray literature may also supplement the search to find pertinent information that cannot be found in the databases. Finally, this strategy will provide an important lens for understanding the value of delivering holistic, person-centered care in radiotherapy. The scoping review method complies with the JBI recommendations [28] and will use the most recent reporting guidelines [29] to ensure that a comprehensive process that can be tracked is used.

The findings will assist radiotherapists and radiotherapy departments, as well as educational institutions, in identifying elements that are vital for the delivery of holistic, person-centered care in radiotherapy. The study may also determine the need for additional curriculum content or additional courses for radiotherapists to fulfill their role as holistic care providers.

Limitations

The scoping review has some limitations. First, the search terms are variable due to the differing terminology used to describe radiotherapy and patients with cancer. Also, the research team will only consider sources available in English, meaning that sources not written in English will be missed, limiting generalizability. The quality of the studies included will not be evaluated for quality or methodological rigor; however, this is acceptable within the context of a scoping review and the aims of this review.

Conclusion

The scoping review will assist in providing information that will be indispensable in the development of a conceptual framework to guide holistic, person-centered care in radiotherapy. The results will be disseminated at a national radiotherapy conference, including publishing a paper in a radiotherapy journal. This scoping review strategy hopes to address a gap in the literature and create awareness for radiotherapists about the importance of delivering holistic, person-centered care.

Acknowledgments

The researchers would like to express their gratitude to their library consultant, Ms Dorcas Rathaba, at the University of Johannesburg, for her assistance in developing the search strategy for this protocol.

The review will contribute to the completion of a doctoral degree from the Faculty of Health Sciences, University of Johannesburg, for the author FB.

Authors' Contributions

All authors contributed to the manuscript. AWM led the development of the methods and search strings. FB and KH contributed to the contextualization of the protocol and reviewed the Methods section. AWM is the primary supervisor, and KH is the co-supervisor of FB.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search terms and results from an initial search conducted in Scopus.
[DOCX File , 155 KB - resprot_v13i1e51338_app1.docx]

Multimedia Appendix 2
JBI template source of evidence details, characteristics, and results extraction instrument.
[DOCX File , 154 KB - resprot_v13i1e51338_app2.docx]

Multimedia Appendix 3
Data extraction sheet developed by researchers for data extraction.
[DOCX File , 154 KB - resprot_v13i1e51338_app3.docx]

References

1. Gianfaldoni S, Gianfaldoni R, Wollina U, Lotti J, Tchernev G, Lotti T. An overview on radiotherapy: from its history to its current applications in dermatology. Open Access Maced J Med Sci 2017;5(4):521-525 [FREE Full text] [doi: 10.3889/oamjms.2017.122] [Medline: 28785349]
2. Mohan G, T P A, A J J, K M S, Narayanasamy A, Vellingiri B. Recent advances in radiotherapy and its associated side effects in cancer—a review. JoBAZ 2019 Feb 27;80(1):1-10 [FREE Full text] [doi: 10.1186/s41936-019-0083-5]
3. Samant R, Cisa-Paré E, Balchin K, Renaud J, Bunch L, Wheatley-Price P, et al. Assessment of patient satisfaction among cancer patients undergoing radiotherapy. J Cancer Educ 2022;37(5):1296-1303 [FREE Full text] [doi: 10.1007/s13187-020-01950-8] [Medline: 33432468]
4. Ndlovu N. Radiotherapy treatment in cancer control and its important role in Africa. Ecancermedicalscience 2019;13:942 [FREE Full text] [doi: 10.3332/ecancer.2019.942] [Medline: 31552115]
5. Rallis K, Lai Yau TH, Sideris M. Chemoradiotherapy in Cancer Treatment: Rationale and Clinical Applications. Anticancer Res 2021 Jan;41(1):1-7. [doi: 10.21873/anticanres.14746] [Medline: 33419794]
6. Soko GF, Burambo AB, Mngoya MM, Abdul BA. Public Awareness and Perceptions of Radiotherapy and Their Influence on the Use of Radiotherapy in Dar es Salaam, Tanzania. J Glob Oncol 2019 Nov;5:1-10 [FREE Full text] [doi: 10.1200/JGO.19.00175] [Medline: 31702947]
7. Mattarozzi K, Fino E, Panni V, Agostini A, Morganti A, Russo PM. The Role Of Effective Radiation Therapist-Patient Communication In Alleviating Treatment-Related Pain And Procedural Discomfort During Radiotherapy. Patient Prefer Adherence 2019;13:1861-1865 [FREE Full text] [doi: 10.2147/PPA.S214375] [Medline: 31802855]
8. O'Neill AGM, Hughes CM, McClure P, Barbosa B, Muscat K, Oliveira C, et al. Patient-reported perspectives of therapeutic radiographers when undergoing radiotherapy: A European multi-centre study. Radiography (Lond) 2023 May;29 Suppl 1:S32-S39. [doi: 10.1016/j.radi.2023.01.027] [Medline: 36889995]
9. Merchant S, O'Connor M, Halkett G. Time, space and technology in radiotherapy departments: how do these factors impact on patients' experiences of radiotherapy? Eur J Cancer Care (Engl) 2017 Mar;26(2):1-9. [doi: 10.1111/ecc.12354] [Medline: 26179657]
10. Dilalla V, Chaput G, Williams T, Sultanem K. Radiotherapy side effects: integrating a survivorship clinical lens to better serve patients. Curr Oncol 2020 Apr;27(2):107-112 [FREE Full text] [doi: 10.3747/co.27.6233] [Medline: 32489253]

11. Edwards LB, Greeff LE. Exploring grassroots feedback about cancer challenges in South Africa: a discussion of themes derived from content thematic analysis of 316 photo-narratives. Pan Afr Med J 2017;28:173 [FREE Full text] [doi: 10.11604/pamj.2017.28.173.11894] [Medline: 29541319]
12. Elsner K, Naehrig D, Halkett GKB, Dhillon HM. Reduced patient anxiety as a result of radiation therapist-led psychosocial support: a systematic review. J Med Radiat Sci 2017 Sep;64(3):220-231 [FREE Full text] [doi: 10.1002/jmrs.208] [Medline: 28160448]
13. Halkett G, O'Connor M, Jefford M, Aranda S, Merchant S, Spry N, et al. RT prepare: a radiation therapist-delivered intervention reduces psychological distress in women with breast cancer referred for radiotherapy. Br J Cancer 2018;118(12):1549-1558 [FREE Full text] [doi: 10.1038/s41416-018-0112-z] [Medline: 29855611]
14. Famiglietti RM, Neal EC, Edwards TJ, Allen PK, Buchholz TA. Determinants of patient satisfaction during receipt of radiation therapy. Int J Radiat Oncol Biol Phys 2013 Sep 01;87(1):148-152. [doi: 10.1016/j.ijrobp.2013.05.020] [Medline: 23920394]
15. Durnin R, Shepherd P, Gilleece T. An evaluation of the information needs of radiotherapy patients and their families. J Radiother Pract 2020 Jul 09;20(4):473-479 [FREE Full text] [doi: 10.1017/s1460396920000497]
16. Arnold BL, Halkett G, Dhillon H, Girgis A. Do radiation therapists feel able to routinely screen for symptoms and distress in people with cancer: barriers impacting practice. J Med Radiat Sci 2021;68:149-156 [FREE Full text] [doi: 10.1002/jmrs.465] [Medline: 33729701]
17. Flood T, O Neill A, Oliveira CM, Barbosa B, Soares AL, Muscat K, et al. Patients' perspectives of the skills and competencies of therapy radiographers/radiation therapists (TRs/RTTs) in the UK, Portugal and Malta; a qualitative study from the SAFE Europe project. Radiography (Lond) 2023 May;29 Suppl 1:S117-S127 [FREE Full text] [doi: 10.1016/j.radi.2023.03.002] [Medline: 36959043]
18. Azzopardi J, Mercieca S, Portelli JL. Radiographers' perception on the provision of psychosocial support for cancer patients. J Radiother Pract 2022 Jul 22;22:e52 [FREE Full text] [doi: 10.1017/s1460396922000218]
19. Malenfant S, Jaggi P, Hayden K, Sinclair S. Compassion in healthcare: an updated scoping review of the literature. BMC Palliat Care 2022 May 18;21(1):80 [FREE Full text] [doi: 10.1186/s12904-022-00942-3] [Medline: 35585622]
20. Sanders JJ, Dubey M, Hall JA, Catzen HZ, Blanch-Hartigan D, Schwartz R. What is empathy? Oncology patient perspectives on empathic clinician behaviors. Cancer 2021 Nov 15;127(22):4258-4265 [FREE Full text] [doi: 10.1002/cncr.33834] [Medline: 34351620]
21. Wong E, Mavondo F, Horvat L, McKinlay L, Fisher J. Healthcare professionals' perspective on delivering personalised and holistic care: using the Theoretical Domains Framework. BMC Health Serv Res 2022 Mar 01;22(1):281 [FREE Full text] [doi: 10.1186/s12913-022-07630-1] [Medline: 35232432]
22. Harman C, Khine R, Sarchosoglou A, Bajinskis A, Brusadin G, Cornacchione P, et al. Guest editorial - Patient engagement and inclusion in radiotherapy. Radiography (Lond) 2022 May;28(2):255-257. [doi: 10.1016/j.radi.2022.03.012] [Medline: 35428448]
23. Chinn PL, Kramer MK, Sitzman K. Knowledge Development in Nursing: Theory and Process, 11th Edition. St. Louis, MO: Elsevier; 2022.
24. Grilo AM, Santos B, Baptista I, Monsanto F. Exploring the cancer patients' experiences during external radiotherapy: A systematic review and thematic synthesis of qualitative and quantitative evidence. Eur J Oncol Nurs 2021 Jun;52:101965. [doi: 10.1016/j.ejon.2021.101965] [Medline: 34023669]
25. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. Int J Soc Res Methodol 2005 Feb;8(1):19-32 [FREE Full text] [doi: 10.1080/1364557032000119616]
26. Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. Implement Sci 2010 Sep 20;5:69 [FREE Full text] [doi: 10.1186/1748-5908-5-69] [Medline: 20854677]
27. Peters MDJ, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. Int J Evid Based Healthc 2015 Sep;13(3):141-146. [doi: 10.1097/xeb.0000000000000050] [Medline: 26134548]
28. Peters MDJ, Marnie C, Tricco AC, Pollock D, Munn Z, Alexander L, et al. Updated methodological guidance for the conduct of scoping reviews. JBI Evid Synth 2020 Oct;18(10):2119-2126. [doi: 10.11124/JBIES-20-00167] [Medline: 33038124]
29. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. Ann Intern Med 2018 Oct 02;169(7):467-473 [FREE Full text] [doi: 10.7326/M18-0850] [Medline: 30178033]
30. Kellermeyer L, Harnke B, Knight S. Covidence and Rayyan. J Med Libr Assoc 2018 Oct 04;106(4):580-583 [FREE Full text] [doi: 10.5195/jmla.2018.513]
31. Braun V, Clarke V. One size fits all? What counts as quality practice in (reflexive) thematic analysis? Qualitative Research in Psychology 2020 Aug 12;18(3):328-352 [FREE Full text] [doi: 10.1080/14780887.2020.1769238]

Abbreviations

JBI: Johanna Briggs Institute

PCC: population, concept, and context
PRISMA-ScR: Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews

Edited by A Mavragani; submitted 28.07.23; peer-reviewed by C Berterö, S Gorthy; comments to author 06.12.23; revised version received 11.12.23; accepted 17.12.23; published 03.04.24.

Please cite as:
Bhyat F, Makkink A, Henrico K
Holistic Person-Centered Care in Radiotherapy: Protocol for a Scoping Review
JMIR Res Protoc 2024;13:e51338
URL: https://www.researchprotocols.org/2024/1/e51338
doi:10.2196/51338
PMID:38569177

Protocol

Exploring the Use and Implications of AI in Sexual and Reproductive Health and Rights: Protocol for a Scoping Review

Tigest Tamrat[1], MPH; Yu Zhao[2], MSc; Denise Schalet[2], MHP, LLM; Shada AlSalamah[2,3], MSc, PhD; Sameer Pujari[2], MS; Lale Say[1], MSc, MD

[1]UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction, Department of Sexual and Reproductive Health and Research, World Health Organization, Geneva, Switzerland

[2]Department of Digital Health and Innovations, Science Division, World Health Organization, Geneva, Switzerland

[3]Information Systems Department, College of Computer and Information Sciences, King Saud University, Riyadh, Saudi Arabia

Corresponding Author:
Tigest Tamrat, MPH
UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction
Department of Sexual and Reproductive Health and Research
World Health Organization
20 Avenue Appia
Geneva, 1218
Switzerland
Phone: 41 22 791 4417
Email: tamratt@who.int

Abstract

Background: Artificial intelligence (AI) has emerged as a transformative force across the health sector and has garnered significant attention within sexual and reproductive health and rights (SRHR) due to polarizing views on its opportunities to advance care and the heightened risks and implications it brings to people's well-being and bodily autonomy. As the fields of AI and SRHR evolve, clarity is needed to bridge our understanding of how AI is being used within this historically politicized health area and raise visibility on the critical issues that can facilitate its responsible and meaningful use.

Objective: This paper presents the protocol for a scoping review to synthesize empirical studies that focus on the intersection of AI and SRHR. The review aims to identify the characteristics of AI systems and tools applied within SRHR, regarding health domains, intended purpose, target users, AI data life cycle, and evidence on benefits and harms.

Methods: The scoping review follows the standard methodology developed by Arksey and O'Malley. We will search the following electronic databases: MEDLINE (PubMed), Scopus, Web of Science, and CINAHL. Inclusion criteria comprise the use of AI systems and tools in sexual and reproductive health and clear methodology describing either quantitative or qualitative approaches, including program descriptions. Studies will be excluded if they focus entirely on digital interventions that do not explicitly use AI systems and tools, are about robotics or nonhuman subjects, or are commentaries. We will not exclude articles based on geographic location, language, or publication date. The study will present the uses of AI across sexual and reproductive health domains, the intended purpose of the AI system and tools, and maturity within the AI life cycle. Outcome measures will be reported on the effect, accuracy, acceptability, resource use, and feasibility of studies that have deployed and evaluated AI systems and tools. Ethical and legal considerations, as well as findings from qualitative studies, will be synthesized through a narrative thematic analysis. We will use the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) format for the publication of the findings.

Results: The database searches resulted in 12,793 records when the searches were conducted in October 2023. Screening is underway, and the analysis is expected to be completed by July 2024.

Conclusions: The findings will provide key insights on usage patterns and evidence on the use of AI in SRHR, as well as convey key ethical, safety, and legal considerations. The outcomes of this scoping review are contributing to a technical brief developed by the World Health Organization and will guide future research and practice in this highly charged area of work.

Trial Registration: OSF Registries osf.io/ma4d9; https://osf.io/ma4d9

International Registered Report Identifier (IRRID): PRR1-10.2196/53888

(JMIR Res Protoc 2024;13:e53888) doi:10.2196/53888

KEYWORDS

artificial intelligence; AI; sexual health; reproductive health; maternal health; gender; machine learning; natural language processing; review; systematic documentation; protocol; scoping review; electronic database; technical consultation; intervention; methodology; qualitative; World Health Organization; WHO; decision-making

Introduction

Artificial intelligence (AI) refers to the development of algorithms, processes, machines, and computer programs capable of performing automated tasks, without the programming of each step explicitly by a human [1,2]. Advances in computing processing combined with the amassing of data through digital tools, particularly with increases in the penetration of mobile devices, have propelled the field of AI within health [3-6]. AI includes approaches such as machine learning, in which statistical and mathematical modeling techniques are used to define and analyze data. This can also be applied through natural language processing to analyze text-based data and signal processing for audio, images, and videos [6,7]. The use of AI varies across health fields, with radiology and pathology being the dominant areas where machine learning has been leveraged to optimize the processing of large volumes of medical imaging data [6,7]. Recent advancements in AI, particularly generative AI and large language models, have expanded the ability to address a diverse set of health needs.

The field of sexual and reproductive health encompasses health domains, such as family planning and fertility care, maternal health, sexually transmitted infections (STIs), safe abortion care, sexual health and well-being, and gender-based violence [8,9]. It is underpinned by broader principles of bodily autonomy, human rights, women's empowerment, and gender equality, encapsulated as sexual and reproductive health and rights (SRHR) [10]. Considering the perceived sensitivity and often politicization of these health topics beyond the influence of technology, the use of AI in SRHR is an emerging area with both great potential and justifiable concerns. Individuals' desires for anonymity in seeking sexual and reproductive health services positions AI systems and tools, such as conversational agents, as critical conduits for expanding access to information and care [11-13]. Furthermore, shortfalls in human resources and the need for targeted health interventions, such as in the areas of maternal health care and management of STIs, serve as key issues that have the potential to be addressed through the predictive capabilities offered by AI [14]. In addition, the use of AI to power "software as a medical device" [15] presents an opportunity to leapfrog access to diagnostic devices, such as ultrasounds [16] and blood pressure equipment [17]. This has also been seen with the emergence of contraceptive and fertility software applications [18,19], which are increasingly securing regulatory approvals from national authorities [20,21].

The convergence of AI in SRHR also presents heightened risks and implications. This is especially evident as the use of underlying health data raises concerns about infringements on women's health and bodily autonomy, as well as the potential misuse of this technology for surveillance of populations in vulnerable situations. Furthermore, existing challenges in digital health implementation [22], including biases, limited inclusivity, and gender disparities, could be exacerbated with the introduction of AI [6,23-25]. As such, the intersection of AI and SRHR raises nuanced implications and warrants close examination of the current landscape to highlight the evidence base and document the ethical, regulatory, and human rights considerations. This scoping review will build on the general literature of AI in health and focus specifically on how AI is being used within SRHR, including evidence on effect and related considerations to inform a comprehensive understanding of the state of the field.

Methods

Overview

We will conduct a scoping review using the established methodological framework of Arksey and O'Malley [26] that includes (1) identifying the research question; (2) identifying relevant studies; (3) study selection; (4) charting the data; and (5) collating, summarizing, and reporting the results. Considering this is an emerging area of research, we will also include a stakeholder consultation to inform the discussion. We will follow the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) format for the publication of the findings [27].

Stage 1: Identifying Research Questions

This scoping review aims to explore the range of ways in which AI is being applied in SRHR and synthesize the key considerations to ensure its effective, safe, and ethical use. The research questions for this review include the following:

- Patterns and characteristics of use: How are AI systems and tools being applied to SRHR, in terms of health domains, intended purpose (eg, screening, counseling, forecasting), target users, and AI data life cycle?
- Evidence on harms and benefits: What are the effect, acceptability, feasibility, resource use, and implications on gender, equity, and rights of AI systems and tools used in SRHR?
- Ethical, legal, and safety implications: What are the ethical, legal, and safety considerations specific to the use of AI systems and tools in SRHR?

Stage 2: Identifying Relevant Studies

To identify relevant studies for inclusion, we will search the following electronic databases: MEDLINE (PubMed), Scopus, Web of Science, and CINAHL. In addition, we will use citation searching from relevant articles to identify sources that may not have been retrieved in our original search.

The search strategy will be a combination of constructs related to AI and SRHR. An overview of search terms is presented in Multimedia Appendix 1. We will leverage search strategies and Medical Subject Headings (MeSH) terms used in other scoping reviews focused on AI in health care [28-32]. Considering this is an emerging topic, we will not set a start date for the search.

Stage 3: Study Selection

We will conduct a 2-step abstract and title screening following the eligibility criteria in Textbox 1. We will use Covidence, a standard web-based screening and extraction tool, to manage the screening process.

We will not exclude manuscripts based on geographic location, language, or publication date. Commentaries, opinions, and editorials that do not have an underlying empirical basis will be excluded to adjust for potential subjectivity and bias. In addition to using Covidence, we will search the citations of included studies to identify relevant articles that may have been overlooked in our initial search.

All references will be collated into a single reference manager (EndNote), where duplicate entries will be removed. Articles will be screened independently by 2 coauthors. Identified discrepancies will be resolved through discussion, and, if needed, escalated to a coauthor for arbitration.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Studies reporting on artificial intelligence (AI) applications to aspects of sexual and reproductive health and rights
- Clearly described methodology; we will include quantitative studies, qualitative studies, and program evaluations and descriptions

Exclusion criteria

- Focus exclusively on digital interventions (eg, traditional text messaging or targeted client communication) that do not explicitly use AI systems and tools
- Focus on health care robotics or nonhuman studies
- Commentaries, opinion pieces, and editorials

Stage 4: Charting the Data

We will develop a data extraction sheet to standardize the retrieval of information in alignment with the research questions (Table 1). The data extraction form will be developed by adapting common themes from other scoping reviews on AI [31,33], as well as reviewing requirements from digital health reporting checklists [34,35], information on the intervention, including how AI was applied to SRHR, the specific SRHR domains of interest, population, geographic coverage, implementation challenges, outcomes, and ethical and legal considerations.

Table 1. Categories for data extraction.

Category	Illustrative information to be extracted	Relevant research questions
Article information	• Article title • Author(s) • Year • Country • Setting or context (facility, community, home or self, research) • Aim or objectives • Study design or methodology	• Patterns of use
SRHR[a] health domain	• To be selected from a predefined list of common SRHR areas and expanded on accordingly • Examples include family planning or contraception counseling and provision, fertility care, safe abortion, sexually transmitted infections, antenatal care, post-natal care, etc	• Patterns of use
Targeted population	• Will be selected from a predefined list and expanded accordingly. Examples include health workers, health system managers, individuals or health service users	• Patterns of use
Intended purpose of AI[b]	The intended purposes for using AI: • Health information, education, and promotion • Screening and diagnostics • Clinical care and management • Personal health monitoring • Forecasting health trends • Health systems management • Research and drug development	• Patterns of use
AI life cycle	Stages of AI development and evaluation [36]: • Data creation • Data acquisition • Model development • Model evaluation • Model deployment	• Patterns of use
Algorithm development and models	• Predictive or generative models • Documentation of algorithm development and training process • Presence of regulatory approval	• Patterns of use
Outcomes and findings	• Outcomes based on the Evidence to Decision framework [37], which includes effect, accuracy, acceptability, feasibility, equity, resource considerations, gender, equity, and rights • Key themes and findings • Implementation challenges • Lessons learned • Unintended consequences, risks, and implications • Approaches used to mitigate unintended consequences	• Evidence on harms and benefits
Implications	• Legal implications • Ethical implications	• Ethical and legal implications

[a]SRHR: sexual and reproductive health and rights.

[b]AI: artificial intelligence.

Stage 5: Collating, Summarizing, and Reporting the Results

We will collate and summarize information from the data extraction sheets. The results will present the general patterns of use of AI in SRHR, including the specific health domains for which AI is being applied, the intended purpose of the AI system and tools, and maturity within the AI life cycle. We will use established frameworks, including the continuum of care and SRHR conceptual model for categorizing health domains [8,9] and the AI life cycle to map the maturity of AI systems and tools in use [36].

To assess evidence on harms and benefits, studies will first be tagged based on their AI life cycle [36] to distinguish between interventions that are in the early stages of model development and validation versus those that have been implemented and evaluated. We will extract outcomes on the subset of studies identified as being in the model deployment and evaluation phases of the AI life cycle [36]. The type of outcome data to be extracted will be guided by the domains of the Evidence to

Decision framework, including accuracy, effect, acceptability, feasibility, resource use, and gender equity and rights [37]. Where possible, we will pool findings across similar outcome measures and present a summary of findings on outcomes related to accuracy and effect. We will conduct a thematic analysis on ethical, legal, and safety considerations, as well as on findings from qualitative studies.

Results

The database searches described above resulted in 12,793 records when the searches were conducted in October 2023. Screening is underway, and the analysis is expected to be completed by July 2024.

Discussion

Building on the broader literature on AI and health, findings from this review will provide fundamental insights into the usage patterns, implications, and evidence related to AI in SRHR, as well as highlight key considerations and risks. A key strength of this review is the composition of a multidisciplinary authorship team to ensure both the technological and SRHR perspectives are appropriately reflected. Moreover, this scoping review serves as a foundational resource to inform a technical brief developed by the World Health Organization [38] and to guide future research and practice. One limitation of this review is its focus on empirical studies, in which insights from the gray literature and AI consumer products may be overlooked if they are not reflected in the peer-reviewed literature. However, due to the high number of records in the search, we believe this scoping review can reliably provide a comprehensive overview of usage patterns and key implications.

The intersection of AI and SRHR has been fraught with concerns, particularly related to infringements on women's reproductive health choices and the exacerbation of gender biases and inequity [39]. Meanwhile, technological advances hold great promise for overcoming longstanding challenges in access to and provision of SRHR services. This systematic analysis of AI in SRHR seeks to facilitate clarity and nuanced discussion in this highly charged field and direct efforts toward responsibly and meaningfully harnessing of AI to address SRHR needs and the broader goals of universal health coverage.

Acknowledgments

We acknowledge Rebecca Carlson and Kavita Kothari for serving as the information specialists in developing and conducting the search strategy. We thank Ana Pilar Betran and Agata Ferretti for their guidance in discussing the eligibility criteria. We are grateful to the participants from the World Health Organization technical consultation on artificial intelligence and sexual and reproductive health and rights for their insights and expertise in refining the taxonomies underpinning the extraction of studies. This work is funded by the UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction, a cosponsored program executed by the World Health Organization.

Data Availability

Access to the Covidence database can be made available after the publication of findings by emailing srhhrp@who.int and through a mutually signed agreement.

Authors' Contributions

TT developed the protocol and manuscript with input from YZ, DS, SA, SP, and LS. All authors have made substantial intellectual contributions in developing the manuscript and have reviewed and approved it for submission and publication.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[DOCX File , 30 KB - resprot_v13i1e53888_app1.docx]

References

1. Russell SJ. Artificial Intelligence: A Modern Approach, 3rd Ed. Upper Saddle River, NJ: Prentice Hall; 2010.
2. Regulatory considerations on artificial intelligence for health. World Health Organization. 2023. URL: https://iris.who.int/handle/10665/373421 [accessed 2024-03-22]
3. Benke K, Benke G. Artificial intelligence and big data in public health. Int J Environ Res Public Health 2018 Dec 10;15(12):2796 [FREE Full text] [doi: 10.3390/ijerph15122796] [Medline: 30544648]
4. Schwalbe N, Wahl B. Artificial intelligence and the future of global health. Lancet 2020 May;395(10236):1579-1586. [doi: 10.1016/s0140-6736(20)30226-9]
5. Haug CJ, Drazen JM. Artificial intelligence and machine learning in clinical medicine, 2023. N Engl J Med 2023 Mar 30;388(13):1201-1208. [doi: 10.1056/nejmra2302038]

6. Ethics and governance of artificial intelligence for health: WHO guidance. World Health Organization. 2021 Jun 28. URL: https://www.who.int/publications/i/item/9789240029200 [accessed 2024-03-22]
7. Okeibunor JC, Jaca A, Iwu-Jaja CJ, Idemili-Aronu N, Ba H, Zantsi ZP, et al. The use of artificial intelligence for delivery of essential health services across WHO regions: a scoping review. Front Public Health 2023 Jul 4;11:1102185 [FREE Full text] [doi: 10.3389/fpubh.2023.1102185] [Medline: 37469694]
8. Sexual health and its linkages to reproductive health: an operational approach. World Health Organization. 2017 Sep 20. URL: https://www.who.int/publications/i/item/978924151288 [accessed 2024-03-22]
9. Sexual and reproductive health interventions in the WHO UHC Compendium. World Health Organization. 2021 Apr 05. URL: https://who.int/publications/i/item/9789240022867 [accessed 2024-03-28]
10. Coates A, Allotey P. Global health, sexual and reproductive health and rights, and gender: square pegs, round holes. BMJ Glob Health 2023 Jan 18;8(1):e011710 [FREE Full text] [doi: 10.1136/bmjgh-2023-011710] [Medline: 36653069]
11. Nadarzynski T, Bayley J, Llewellyn C, Kidsley S, Graham CA. Acceptability of artificial intelligence (AI)-enabled chatbots, video consultations and live webchats as online platforms for sexual health advice. BMJ Sex Reprod Health 2020 Jul 21;46(3):210-217 [FREE Full text] [doi: 10.1136/bmjsrh-2018-200271] [Medline: 31964779]
12. Wang H, Gupta S, Singhal A, Muttreja P, Singh S, Sharma P, et al. An artificial intelligence chatbot for young people's sexual and reproductive health in India (SnehAI): instrumental case study. J Med Internet Res 2022 Jan 03;24(1):e29969 [FREE Full text] [doi: 10.2196/29969] [Medline: 34982034]
13. Mills R, Mangone ER, Lesh N, Mohan D, Baraitser P. Chatbots to improve sexual and reproductive health: realist synthesis. J Med Internet Res 2023 Aug 09;25:e46761 [FREE Full text] [doi: 10.2196/46761] [Medline: 37556194]
14. Young SD, Crowley JS, Vermund SH. Artificial intelligence and sexual health in the USA. Lancet Digit Health 2021 Aug;3(8):e467-e468. [doi: 10.1016/s2589-7500(21)00117-5]
15. Angehrn Z, Haldna L, Zandvliet AS, Gil Berglund E, Zeeuw J, Amzal B, et al. Artificial intelligence and machine learning applied at the point of care. Front Pharmacol 2020 Jun 18;11:759 [FREE Full text] [doi: 10.3389/fphar.2020.00759] [Medline: 32625083]
16. Shen Y, Chen L, Yue W, Xu H. Artificial intelligence in ultrasound. Eur J Radiol 2021 Jun;139:109717. [doi: 10.1016/j.ejrad.2021.109717] [Medline: 33962110]
17. Festo C, Vannevel V, Ali H, Tamrat T, Mollel GJ, Hlongwane T, et al. Accuracy of a smartphone application for blood pressure estimation in Bangladesh, South Africa, and Tanzania. NPJ Digit Med 2023 Apr 17;6(1):69 [FREE Full text] [doi: 10.1038/s41746-023-00804-z] [Medline: 37069209]
18. Karakoyun T, Podhaisky H, Frenz A, Schuhmann-Giampieri G, Ushikusa T, Schröder D, et al. Digital medical device companion (MyIUS) for new users of intrauterine systems: app development study. JMIR Med Inform 2021 Jul 13;9(7):e24633 [FREE Full text] [doi: 10.2196/24633] [Medline: 34255688]
19. McMillan C. Rethinking the regulation of digital contraception under the medical devices regime. Medical Law International 2023 Feb 11;23(1):3-25. [doi: 10.1177/09685332231154581]
20. Fertility awareness method. Family Planning Australia. 2021 Jan 28. URL: https://www.fpnsw.org.au/media-news/blog/2021-01-28-fertility-awareness-method [accessed 2024-03-22]
21. FDA allows marketing of first direct-to-consumer app for contraceptive use to prevent pregnancy. US Food & Drug Administration. 2018 Aug 10. URL: https://www.fda.gov/news-events/press-announcements/fda-allows-marketing-first-direct-consumer-app-contraceptive-use-prevent-pregnancy [accessed 2024-03-22]
22. Bacchus LJ, Reiss K, Church K, Colombini M, Pearson E, Naved R, et al. Using digital technology for sexual and reproductive health: are programs adequately considering risk? Glob Health Sci Pract 2019 Dec 23;7(4):507-514. [doi: 10.9745/ghsp-d-19-00239]
23. Bauer GR, Lizotte DJ. Artificial intelligence, intersectionality, and the future of public health. Am J Public Health 2021 Jan;111(1):98-100. [doi: 10.2105/ajph.2020.306006]
24. Safdar NM, Banja JD, Meltzer CC. Ethical considerations in artificial intelligence. Eur J Radiol 2020 Jan;122:108768. [doi: 10.1016/j.ejrad.2019.108768] [Medline: 31786504]
25. Buolamwini J, Gebru T. Gender shades: intersectional accuracy disparities in commercial gender classification. 2018 Presented at: Proceedings of the 1st Conference on Fairness, Accountability and Transparency; February 23-24; New York, NY p. 77-91 URL: https://proceedings.mlr.press/v81/buolamwini18a.html
26. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. Int J Soc Res Methodol 2005 Feb;8(1):19-32. [doi: 10.1080/1364557032000119616]
27. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, Tunçalp, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med 2018 Oct 02;169(7):467-473. [doi: 10.7326/m18-0850]
28. von Gerich H, Moen H, Block LJ, Chu CH, DeForest H, Hobensack M, et al. Artificial intelligence-based technologies in nursing: a scoping literature review of the evidence. Int J Nurs Stud 2022 Mar;127:104153 [FREE Full text] [doi: 10.1016/j.ijnurstu.2021.104153] [Medline: 35092870]
29. Sharma M, Savage C, Nair M, Larsson I, Svedberg P, Nygren JM. Artificial intelligence applications in health care practice: scoping review. J Med Internet Res 2022 Oct 05;24(10):e40238 [FREE Full text] [doi: 10.2196/40238] [Medline: 36197712]

30. Bhatt P, Liu J, Gong Y, Wang J, Guo Y. Emerging artificial intelligence-empowered mhealth: scoping review. JMIR Mhealth Uhealth 2022 Jun 09;10(6):e35053 [FREE Full text] [doi: 10.2196/35053] [Medline: 35679107]
31. Takiddin A, Schneider J, Yang Y, Abd-Alrazaq A, Househ M. Artificial intelligence for skin cancer detection: scoping review. J Med Internet Res 2021 Nov 24;23(11):e22934 [FREE Full text] [doi: 10.2196/22934] [Medline: 34821566]
32. Mörch CM, Atsu S, Cai W, Li X, Madathil S, Liu X, et al. Artificial intelligence and ethics in dentistry: a scoping review. J Dent Res 2021 Dec 01;100(13):1452-1460. [doi: 10.1177/00220345211013808] [Medline: 34060359]
33. Chu CH, Leslie K, Shi J, Nyrup R, Bianchi A, Khan SS, et al. Ageism and artificial intelligence: protocol for a scoping review. JMIR Res Protoc 2022 Jun 09;11(6):e33211 [FREE Full text] [doi: 10.2196/33211] [Medline: 35679118]
34. Perrin Franck C, Babington-Ashaye A, Dietrich D, Bediang G, Veltsos P, Gupta PP, et al. iCHECK-DH: guidelines and checklist for the reporting on digital health implementations. J Med Internet Res 2023 May 10;25:e46694 [FREE Full text] [doi: 10.2196/46694] [Medline: 37163336]
35. Agarwal S, LeFevre AE, Lee J, L'Engle K, Mehl G, Sinha C, WHO mHealth Technical Evidence Review Group. Guidelines for reporting of health interventions using mobile phones: mobile health (mHealth) evidence reporting and assessment (mERA) checklist. BMJ 2016 Mar 17;352:i1174. [doi: 10.1136/bmj.i1174] [Medline: 26988021]
36. Ng MY, Kapur S, Blizinsky KD, Hernandez-Boussard T. The AI life cycle: a holistic approach to creating ethical AI for health decisions. Nat Med 2022 Nov 26;28(11):2247-2249 [FREE Full text] [doi: 10.1038/s41591-022-01993-y] [Medline: 36163298]
37. Moberg J, Oxman AD, Rosenbaum S, Schünemann HJ, Guyatt G, Flottorp S, et al. The GRADE Evidence to Decision (EtD) framework for health system and public health decisions. Health Res Policy Syst 2018 May 29;16(1):45 [FREE Full text] [doi: 10.1186/s12961-018-0320-2] [Medline: 29843743]
38. The role of artificial intelligence in sexual and reproductive health and rights: technical brief. World Health Organization. 2024. URL: https://iris.who.int/bitstream/handle/10665/376294/9789240090705-eng.pdf?sequence=1, [accessed 2024-03-25]
39. Khosla R, Mishra V, Singh S. Sexual and reproductive health and rights and bodily autonomy in a digital world. Sex Reprod Health Matters 2023 Dec 10;31(4):2269003 [FREE Full text] [doi: 10.1080/26410397.2023.2269003] [Medline: 37930349]

Abbreviations

AI: artificial intelligence
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
MeSH: Medical Subject Headings
SRHR: sexual and reproductive health and rights
STI: sexually transmitted infection

Edited by A Mavragani; submitted 23.10.23; peer-reviewed by F Yu, A Hidki; comments to author 02.01.24; revised version received 23.01.24; accepted 09.02.24; published 09.04.24.

Please cite as:
Tamrat T, Zhao Y, Schalet D, AlSalamah S, Pujari S, Say L
Exploring the Use and Implications of AI in Sexual and Reproductive Health and Rights: Protocol for a Scoping Review
JMIR Res Protoc 2024;13:e53888
URL: https://www.researchprotocols.org/2024/1/e53888
doi:10.2196/53888
PMID:38593433

Protocol

The Conceptualization and Measurement of Research Impact in Primary Health Care: Protocol for a Rapid Scoping Review

Monica Aggarwal[1], PhD; Brian G Hutchison[2,3], MSc, MD; Kristina M Kokorelias[4,5], PhD; Vivian R Ramsden[6], RN, PhD; Noah M Ivers[7,8], MD, PhD; Andrew Pinto[7,9,10], MSc, MD; Ross E G Uphsur[1,7], MSc, MA, MD; Sabrina T Wong[11], RN, PhD; Nick Pimlott[7], MD, PhD; Steve Slade[12], BA

[1]Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada
[2]Department of Family Medicine, McMaster University, Hamilton, ON, Canada
[3]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada
[4]Rehabilitation Sciences Institute, University of Toronto, Toronto, ON, Canada
[5]Section of Geriatrics, Sinai Health, Toronto, ON, Canada
[6]Department of Academic Family Medicine, University of Saskatchewan, Saskatoon, SK, Canada
[7]Department of Family and Community Medicine, Faculty of Medicine, University of Toronto, Toronto, ON, Canada
[8]Women's College Hospital, Toronto, ON, Canada
[9]Upstream Lab, MAP Centre for Urban Health Solutions, Li Ka Shing Knowledge Institute, Unity Health Toronto, Toronto, ON, Canada
[10]Department of Family and Community Medicine, St. Michael's Hospital, Toronto, ON, Canada
[11]School of Nursing and Centre for Health Services and Policy Research, University of British Columbia, Vancouver, BC, Canada
[12]Research Department, College of Family Physicians of Canada, Mississuaga, ON, Canada

Corresponding Author:
Monica Aggarwal, PhD
Dalla Lana School of Public Health
University of Toronto
155 College Street
Toronto, ON, M5T 3M7
Canada
Phone: 1 6473815534
Email: monica.aggarwal@utoronto.ca

Abstract

Background: The generation of research evidence and knowledge in primary health care (PHC) is crucial for informing the development and implementation of interventions and innovations and driving health policy, health service improvements, and potential societal changes. PHC research has broad effects on patients, practices, services, population health, community, and policy formulation. The in-depth exploration of the definition and measures of research impact within PHC is essential for broadening our understanding of research impact in the discipline and how it compares to other health services research.

Objective: The objectives of the study are (1) to understand the conceptualizations and measures of research impact within the realm of PHC and (2) to identify methodological frameworks for evaluation and research impact and the benefits and challenges of using these approaches. The forthcoming review seeks to guide future research endeavors and enhance methodologies used in assessing research impact within PHC.

Methods: The protocol outlines the rapid review and environmental scan approach that will be used to explore research impact in PHC and will be guided by established frameworks such as the Canadian Academy of Health Sciences Impact Framework and the Canadian Health Services and Policy Research Alliance. The rapid review follows scoping review guidelines (PRISMA-ScR; Preferred Reporting Items for Systematic Review and Meta-Analysis Extension for Scoping Reviews). The environmental scan will be done by consulting with professional organizations, academic institutions, information science, and PHC experts. The search strategy will involve multiple databases, citation and forward citation searching, and manual searches of gray literature databases, think tank websites, and relevant catalogs. We will include gray and scientific literature focusing explicitly on research impact in PHC from high-income countries using the World Bank classification. Publications published in English from 1978 will be considered. The collected papers will undergo a 2-stage independent review process based on predetermined inclusion criteria. The research team will extract data from selected studies based on the research questions and the CRISP (Consensus

Reporting Items for Studies in Primary Care) protocol statement. The team will discuss the extracted data, enabling the identification and categorization of key themes regarding research impact conceptualization and measurement in PHC. The narrative synthesis will evolve iteratively based on the identified literature.

Results: The results of this study are expected at the end of 2024.

Conclusions: The forthcoming review will explore the conceptualization and measurement of research impact in PHC. The synthesis will offer crucial insights that will guide subsequent research, emphasizing the need for a standardized approach that incorporates diverse perspectives to comprehensively gauge the true impact of PHC research. Furthermore, trends and gaps in current methodologies will set the stage for future studies aimed at enhancing our understanding and measurement of research impact in PHC.

International Registered Report Identifier (IRRID): PRR1-10.2196/55860

(JMIR Res Protoc 2024;13:e55860) doi:10.2196/55860

KEYWORDS

research impact; primary health care; measurement; definition; concept; development; implementation; health policy; policy; health service; rapid review; review; research; policies; societal; productivity; literature database

Introduction

High-performing primary health care (PHC) is recognized as the cornerstone of robust health care systems [1,2]. High-income countries often possess robust health care systems with well-established PHC organizations and research institutions, making them pivotal in shaping global health policies and practices [3,4]. High-quality research identifying what is needed to strengthen the performance of PHC organizations and their integration with each other and the broader health system is essential to inform the sustainable development of health care [5]. A PHC orientation to health service research strives to understand the influence of health's socioeconomic, physical, biological, and cultural determinants within the relevant broader political, sociohistorical, and economic contexts. PHC services can improve health and health services delivery, which could result in improved individual, community, and population health outcomes.

The need for PHC research to determine the efficacy of treatment and test theories and develop new models of care has been documented [6]. PHC encompasses primary care, disease prevention, health promotion, population health, and community development within a holistic framework to provide essential community-focused health care [7,8]. We operationalize "PHC research" to refer to studies that investigate a broad range of topics related to preventive care, health promotion, diagnosis, treatment, ongoing management of common illnesses and chronic conditions, and the social determinants of health within the context of PHC settings [9].

There are several conceptual frameworks and approaches that have been developed for research impact assessment [10]. In Canada, the Canadian Academy of Health Sciences (CAHS) Impact Framework has been adapted to examine the impact of investments in health research. The CAHS Impact Framework uses 5 impact categories: advancing knowledge, capacity building, informing decision-making, health impacts, and socioeconomic impacts and provides a menu of nearly 70 indicators that map onto these domains [11]. In 2018, the Canadian Health Services and Policy Research Alliance (CHSaPRA) was developed by the Canadian health research community based on CAHS to guide the assessment of the impact of research on decision-making [12].

Despite the development of these frameworks, little is known about how research impact is conceptualized in PHC [13]. Globally, PHC research is a small proportion of research output [14]. While existing reviews address research impact within the health care and health service research context [15,16], these reviews are not tailored to consider the unique functions of PHC. As noted by the Council of Academic Family Medicine, PHC research is unique since it involves the delivery of care to patients across the care life cycle, which includes disease prevention, health promotion, and chronic care management [17-20]. It also provides evidence that is unique for the organization and delivery of care, evaluation of innovations, translation of research into practice, and participatory action and community-based approaches [17]. Due to the broader effects of research on patients, practices, services, population health, community, and policy formulation, a dedicated review in PHC is essential to broaden our understanding of research impact, including nuances of how it may or may not be different than other health services research. To establish directions to evolve definitions of research productivity in the context of PHC, funders, academic institutions, researchers, and the public need a better understanding of "research impact" in PHC.

Several scoping reviews, such as those conducted by Murphy et al [21] on measurement in rural PHC, Noorihekmat et al [22] on performance measurement frameworks in public health and primary care systems, and Akl et al [23] on faculty productivity in academic medical centers, have explored aspects of research productivity and measurement within health care. However, to the best of our knowledge, there is no existing review that has offered a focused exploration of the specific conceptualizations and measures of research impact within the context of PHC. Such a review would offer a unique and detailed analysis that aims to elucidate the nuances and intricacies of research productivity, thereby contributing a distinct perspective to the existing literature.

This review protocol aims to fill a gap in knowledge by examining the scientific literature on research impact in the context of PHC. Drawing from established frameworks like the

CAHS Impact Framework [24] and CHSaPRA [25], we will aim to (1) elucidate the various conceptualizations of research impact within the context of PHC and (2) identify measures of research impact used in the PHC literature by PHC researchers. The study will contribute to understanding and identifying trends in how the impact is understood and measured, highlighting existing gaps or areas needing further investigation within this domain. The findings of the study will be leveraged to inform a future study that will explore the perspectives of patients, citizens, community groups representing equity-deserving groups, PHC leaders, researchers, and policy makers on the definition and measurement of research impact in PHC.

Methods

Study Design

A rapid scoping review [26] and environmental scan [27] will be conducted. A rapid scoping review methodology is suitable for this investigation, as it allows for a comprehensive but expedited exploration of the existing literature surrounding research impact within PHC. Given the breadth of the topic and the need to capture a wide array of literature quickly, the rapid scoping review methodology aligns with the urgency to understand conceptualizations and measurements of research impact in PHC [26]. This approach permits the incorporation of diverse study designs, including gray literature and various publication types, facilitating a thorough investigation of research impact concepts within a condensed timeframe [26]. However, the rapid review will be informed by existing guidelines for scoping reviews [28] and the Arksey and O'Malley [29] methodological steps (stages 1 to 5 described below), aiming for standardized execution and reporting and enhancing the credibility of the findings. Scoping reviews aim to map fundamental concepts in a research area, define key terms, and delineate conceptual limits, making it suitable for our purposes [29,30]. The CRISP (Consensus Reporting Items for Studies in Primary Care) statement proposed by Sturgiss et al [31] will be used for the comprehensive extraction and reporting in PHC research to enable the analysis of practices and policies across a diverse range of countries and territories.

Similar to a rapid review, an environmental scan is often used by institutions to collect information [27]. An environmental scan is a systematic approach to gathering and analyzing information from various sources beyond traditional academic literature, including publicly available data, unpublished reports, and consultations with experts [32]. It aims to comprehensively identify relevant information, trends, and developments within a specific field or context [32]. Researchers can also use an environmental scan to identify current and potential research needs and trends to enhance decision-making [27]. While there are various methodologies and sources for collecting and analyzing information for an environmental scan [32], our environmental scan will be conducted by identifying professional organizations, academic institutions, and experts in the fields of information science and PHC to begin our search.

We will adhere the reporting of our review to the PRISMA-ScR (Preferred Reporting Items for Systematic Review and Meta-Analysis Extension for Scoping Reviews) reporting guidelines [33], as there are currently no existing guidelines for rapid reviews. The study will be conducted in 2024 with results anticipated by the end of the year. The research team is comprised of PHC researchers (clinicians, PhD trained) or leaders in the field.

Stage 1: Identifying the Research Questions

We intend to address the following research questions: (1) How is research impact conceptualized in PHC? (2) How is research impact measured in PHC? (3) What methodological or conceptual frameworks are used to evaluate PHC research impact? What are the benefits and challenges of assessing PHC research impact?

Stage 2: Identifying Relevant Studies

We will work with an information specialist to develop a search strategy for the following academic databases: PsycINFO, MEDLINE, Embase, and CINAHL Plus. These databases were intentionally selected for their inclusion of PHC literature and thus are likely to capture relevant scholarly material. The strategy will initially be applied in MEDLINE before being adapted for other databases. We will also search for literature in Google Scholar to "the wide range of resources including papers from academic journals, conference papers, theses, and dissertations" [34]. The peer-reviewed search strategy will also be used in Google Scholar. A citation search of the reference lists of selected papers will be conducted to ensure that a wider scope of papers is included. Forward citation searching will also be done for literature that cites eligible studies included in the review [35]. Scopus, Web of Science, and Google Scholar will be used for forward citation tracking to ensure a comprehensive search.

To ensure a comprehensive review of relevant sources and databases, relevant gray literature databases, catalogs, and search engines (eg, Google, OpenGrey, and TripPro) will be hand searched across high-income countries. White papers will also be explored through health care–focused think-tank websites. We will also contact librarians in the field of PHC and information specialists through several mailing lists (including Canadian Medical Libraries and expert searching through the College of Family Physicians of Canada) to ask for further studies or gray literature. We define gray literature as "that which is produced on all levels of government, academics, business and industry in print and electronic formats, but which is not controlled by commercial publishers" [36].

An environmental scan of institutes and initiatives that follow their strategic funding to understand research impacts, such as the Canadian Institute for Health Research's Community-Based Primary Health Care reports and the SPOR Evidence Alliance [37] will also be conducted. We also aim to examine metrics used by funding agencies within jurisdictions. We will contact each one individually for any published or unpublished evaluations of these PHC activities and ask for any other organizations or experts, who may help us to find as many materials as possible.

The search strategies for the databases were devised in collaboration with the 2 information specialists (Multimedia Appendix 1). Before the literature search and screening process,

reviewers will receive training from the principal investigator (MA) to ensure a foundational grasp of the field's background and the review's objectives.

Stage 3: Study Selection

Two research assistants (one of whom is KMK) will perform all searches in the databases, citation searching, as well as the environmental scan. Findings from all databases will be amalgamated and imported into Covidence (Veritas Health Innovation) for streamlined documentation and management of studies throughout the review process [38]. Additionally, any duplicate publications will be eliminated.

For the gray literature and environmental scan, the research assistants will independently conduct searches across the sources. The research assistants will document the sources and databases accessed for gray literature, specifying the search terms, strategies, and any limitations applied. Any date range, filters, and criteria used to identify relevant gray literature sources will be noted. The research assistants will document the results obtained, including the number of documents retrieved, and provide a clear account of any exclusions made along with justifications. During frequent team meetings, the research team will discuss how duplicates were managed. This documentation should ensure transparency and reproducibility, allowing others to follow and validate the search methodology [39,40]. Gray literature will be organized and managed in a structured Microsoft Excel (Microsoft Corp) spreadsheet. Microsoft Excel will also be used to organize details of the environmental scan, such as the institute or initiative names, contact information, links to relevant reports or evaluations, dates of contact, and any additional notes or follow-up actions required.

We will include gray and scientific literature of any study design that (1) have an explicit focus on the research impact, (2) explicitly focus on PHC research, and (3) are published from a high-income country (defined as per the World Bank classification [41], ie, Andorra, Antigua and Barbuda, Aruba, Australia, Austria, Bahamas, Bahrain, Barbados, Belgium, Bermuda, British Virgin Islands, Brunei Darussalam, Canada, Cayman Islands, Channel Islands, Chile, Croatia, Curaçao, Cyprus, Czech Republic, Denmark, Estonia, Faroe Islands, Finland, France, French Polynesia, Germany, Gibraltar, Greece, Greenland, Guam, Hong Kong SAR China, Hungary, Iceland, Ireland, Isle of Man, Israel, Italy, Japan, Republic of Korea, Kuwait, Latvia, Liechtenstein, Lithuania, Luxembourg, Macao SAR China, Malta, Monaco, Nauru, Netherlands, New Caledonia, New Zealand, Northern Mariana Islands, Norway, Oman, Palau, Poland, Portugal, Puerto Rico, Qatar, San Marino, Saudi Arabia, Seychelles, Singapore, Sint Maarten (Dutch part), Slovakia, Slovenia, Spain, St Kitts and Nevis, St Martin (French part), Sweden, Switzerland, Taiwan China, Trinidad and Tobago, Turks and Caicos Islands, the United Kingdom, United Arab Emirates, Uruguay, the United States, and Virgin Islands (United States).

We define an "explicit focus on the research impact" as studies or papers where the primary or significant emphasis is placed on evaluating, measuring, or discussing the effects, outcomes, influence, or implications of research activities or interventions in the field of PHC or by PHC providers. This includes studies using both formal methodological frameworks, such as the CAHS Impact Framework, and ad hoc approaches using single or limited metrics. This could involve investigations into the tangible outcomes or effects of research endeavors such as changes in health care practices, policy implications, patient outcomes, health system improvements, or societal impacts resulting from PHC research initiatives [42]. Additionally, studies proposing frameworks for evaluating PHC research impact, regardless of whether they are empirically trialed or piloted, are considered, recognizing the value of theoretical advancements in this domain. However, studies predominantly focused on assessing the impact of health care interventions themselves, rather than the research process or outcomes, are excluded to ensure a manageable scope and relevance to the review objectives.

Limiting inclusion to studies published from high-income countries aligns with the rapid nature of this review while ensuring a focus on PHC research that reflects contexts, systems, and health care settings that share similar socioeconomic and health care infrastructure characteristics.

Only literature from 1978 (signing of the Alma-Ata Declaration [43]) to the present day and published in English will be considered. Research conducted within this timeframe ensures relevance to contemporary PHC practices and current understanding but also allows for the inclusion of recent advancements, methodologies, and perspectives in the field. Setting a specific timeframe and language criteria can help manage the volume of literature to be reviewed, which is key in a rapid review [26,44].

The results from all databases will be imported into EndNote (Clarivate Analytics), and all duplicates will be removed [45]. The unique papers will then be added to Covidence software to help facilitate screening, study selection, and extraction [38]. After generating a list of papers from our search strategy, we will engage in a 2-stage screening process with at least 1 independent reviewer at each stage. In the first stage, 2 trained, independent reviewers will screen papers for suitability based on their titles and abstracts in duplicate. We will report on the calculation of interrater reliability using Cohen κ coefficient [46] to assess the consistency of screening decisions between reviewers and ensure the reliability of the study selection process. A third reviewer will review 25% of the excluded papers to ensure no papers were inadvertently excluded. If there is ambiguity on whether specific papers fit the scope of this protocol, the principal investigator (MA) will be consulted. In the second stage, single reviewer (KMK) will conduct full-text reviews of the potentially eligible studies using the inclusion criteria aforementioned [47]. Again, a third reviewer will review 25% of the excluded papers to ensure no papers were inadvertently excluded. Throughout the process, disagreements between reviewers regarding the inclusion or exclusion of papers will be resolved via discussion with the principal investigator (MA), who will advise the reviewers of the outcome (ie, include or exclude). Given the iterative nature of scoping reviews, the inclusion and exclusion criteria will be refined (eg, added specificity), if needed, after increased familiarity with the data.

The comprehensive outcomes of both the searches (ie, databases and gray literature, including the environmental scan) and the study inclusion procedure will be thoroughly detailed in the final report of the review. These will be articulated using a PRISMA-ScR flow diagram, ensuring a clear and structured presentation of the search process and the selection of studies for the review [33].

Stage 4: Charting the Data

The research team will develop initial charting variables based on the research questions and the CRISP statement [48]. The preliminary variables that will be extracted from the studies will include (1) authors, (2) year, (3) country where the study was conducted or country of first author's affiliation, (4) journal, (5) methodology of paper (including whether a framework or ad hoc approach is used for measuring impact), (6) definition or conceptualization of impact (including how the impact is measured), (7) notice of research team's primary care experience and collaboration, (8) description of the study participants and populations in the context of primary care, (9) description of the primary care team, (10) description of the conditions under study in the context of primary care outcome measures (primary and secondary), (11) units of analysis, (12) findings, and (13) recommendations or discussion (eg, gaps, challenges or barriers, recommendations, and evidence-based or best practices).

Two team members will independently chart the first 5 papers that meet our inclusion criteria and refine the definitions for the variables or charting categories if necessary. The research team will discuss the extracted data. If consensus is reached, 1 researcher (KMK) will extract data from the remaining papers. If consensus is not reached, the 2 individuals will continue to extract 1 paper in duplicate until consensus is reached. All discrepancies between reviewers will be addressed through discussion and by involving additional individuals. The charted data will be organized and presented in a Microsoft Excel spreadsheet.

Stage 5: Collating, Summarizing, and Reporting the Results

To achieve our aims, we will adopt 3 distinct strategies for reporting and presentation. Initially, the research team will use a PRISMA-ScR checklist to ensure systematic reporting of our methods and screening processes [33]. Additionally, the charted data will be reviewed, synthesized, and analyzed through a numerical summary analysis that will include an overview of study characteristics and help to identify predominant conceptualizations and measurement frameworks used for research impact in PHC [29]. A directed content analysis will be carried out on the extracted data [49]. This method entails identifying specific concepts, definitions, methodological approaches, recommendations, benefits, and challenges associated with research impact in PHC. A coding framework will be developed based on established theories and frameworks relevant to PHC research impact, ensuring that the analysis remains focused and aligned with the study objectives. Each piece of extracted data will be systematically coded according to predefined categories, allowing for consistent and structured analysis. Through the directed content analysis, key themes extracted from the selected papers will be categorized, summarized, and presented using a narrative synthesis [47] that describes how research impact is conceptualized and measured in PHC. This analysis will also encompass definitions of research impacts, methodological techniques to measure research impact, and recommendations for improving PHC research impact and identify benefits or challenges of measurements of research impact in the context of PHC.

Finally, the synthesis will address strengths, study limitations, existing knowledge gaps, and potential avenues for future research pertinent to research impact in the realm of PHC. This is aligned with the goals of scoping reviews, which aims to comprehensively outline the scope and characteristics of existing literature [29]. However, as consistent with the scoping review methodology, we anticipate that the narrative synthesis will be an iterative process and dependent on the literature found [47].

Results

The results of this study are expected in December 2024. The dissemination of findings from this rapid scoping review on the conceptualization and measurement of research impact in PHC will ensure that the insights generated are shared with relevant stakeholders and contribute to informed decision-making and further research efforts.

The findings of this scoping review will be disseminated through various channels to reach a wide audience. A paper detailing the methodology, findings, and implications of the rapid review and environmental scan will be submitted to a relevant peer-reviewed journal in the field of PHC, family medicine, health services research, or impact assessment (eg, *Journal of Primary Care & Community Health*, *BMC Family Practice*, *Health Services Research*, *Journal of Health Services Research & Policy*, and *The Annals of Family Medicine*). A concise and accessible policy brief summarizing the key findings and their implications for policy makers, stakeholders, and PHC leaders will be developed and distributed through appropriate channels (eg, College of Family Physicians of Canada, Canadian Institute for Health Information, Canadian Foundation for Healthcare Improvement, Canadian Institutes of Health Research, Canadian Primary Care Sentinel Surveillance Network, and Canadian Primary Care Research Network). The research team will present the findings at relevant academic conferences, seminars, and workshops attended by researchers, practitioners, and policy makers in the fields of PHC and health services research (eg, North American Primary Care Research Group, Canadian Association of Health Services and Policy Research, Society for Academic Primary Care, and International Conference on Primary Health Care). Collaboration with existing networks and initiatives in PHC research and impact assessment will be sought to integrate the findings into ongoing discussions and efforts. The dissemination materials will be tailored to the needs and interests of different stakeholders. For example, academic publications will provide detailed methodology and findings for researchers, while policy briefs will focus on practical implications for decision makers. We will also create 1-page infographics for patient and public communities (eg, National Association of Community Health Centers). Presentations and

webinars will be customized to engage different audiences effectively.

Discussion

Preliminary Findings

The preliminary findings from this study have yet to be compiled and analyzed as the review is ongoing. The forthcoming rapid review and environmental scan on research impact in PHC will help to elucidate conceptualizations and measurement methodologies of impact, shaping the understanding of research impact within this domain. By rigorously and systematically reviewing a breadth of literature sources, this study aspires to unravel the diverse perspectives and approaches used to gauge the impact of research activities in PHC. This review will be able to discern trends, illuminate potential gaps, and outline areas necessitating further exploration or refinement in the assessment of research impact. Such delineations are envisioned to inform future research, policy considerations, and practice innovations in medicine and academia, ultimately contributing to the continuous enhancement of PHC services and policies in PHC settings.

Limitations

The methodology and methods outlined for the scoping review and environmental scan present several potential limitations. First, the selection process might carry biases due to restrictions such as language and publication date, possibly excluding valuable insights from diverse settings or languages. We acknowledge that relying solely on the World Bank's classification system for high-income countries may oversimplify the diversity of socioeconomic and health care infrastructure characteristics among nations and may not consider the varied health care contexts, systems, and priorities among high-income countries that could in turn influence research impact.

Additionally, researcher biases might influence study interpretation or selection, potentially affecting the review's credibility. Second, while the rapid review approach aids efficiency, it may compromise a comprehensive understanding of nuanced concepts related to research impact in PHC. Third, accessing relevant unpublished materials in gray literature might pose challenges, potentially affecting the credibility or reliability of findings.

Conclusions

This protocol outlines a rapid scoping review and environmental scan for exploring research impact in PHC, which will provide critical insights for advancing PHC systems. Recognizing PHC's pivotal role in health care, this study underscores the need for comprehensive research to bolster PHC organizations' performance and integration within broader health systems. Drawing from established frameworks such as CAHS and CHSaPRA, the forthcoming review will examine how research impact is conceptualized and measured in PHC, addressing an existing gap in knowledge. Emphasizing the scarcity of recent reviews specifically focused on this domain, this upcoming study pioneers a comprehensive analysis, shedding light on the nuances of research impact. By delineating varied conceptualizations of research impact and measures used in PHC, this review charts a pathway for future research, potentially refining measurement methodologies and informing decision-making for stakeholders in the PHC landscape.

While findings are pending, the study aspires to inform future research endeavors, policy formulations, and practice enhancements in the realm of PHC, which has a pivotal role within health care systems both provincially and federally, for example, Indigenous people living on reserve and people living in prisons.

Data Availability

The data sets generated and analyzed during this study will be made available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[DOCX File , 26 KB - resprot_v13i1e55860_app1.docx]

References

1. Aggarwal M, Hutchison BG. Toward a primary care strategy for Canada. Canadian Foundation for Healthcare Improvement. 2012. URL: https://tinyurl.com/yspbwyxj [accessed 2024-03-25]
2. Aggarwal M, Hutchison B, Abdelhalim R, Baker GR. Building high-performing primary care systems: after a decade of policy change, is Canada "walking the talk?". Milbank Q 2023;101(4):1139-1190 [FREE Full text] [doi: 10.1111/1468-0009.12674] [Medline: 37743824]
3. Doty MM, Tikkanen RS, FitzGerald M, Fields K, Williams RD. Income-related inequality in affordability and access to primary care in eleven high-income countries. Health Affairs 2021;40(1):113-120 [FREE Full text] [doi: 10.1377/hlthaff.2020.01566]

4. Griffiths UK, Legood R, Pitt C. Comparison of economic evaluation methods across low-income, middle-income and high-income countries: what are the differences and why? Health Econ 2016;25(Suppl 1):29-41 [FREE Full text] [doi: 10.1002/hec.3312] [Medline: 26775571]
5. van Lerberghe W. Primary health care—now more than ever. World Health Organization. 2008. URL: https://www.who.int/director-general/speeches/detail/primary-health-care---now-more-than-ever [accessed 2024-03-25]
6. Nass SJ, Levit LA, Gostin LO, Institute of Medicine (U.S.). Committee on Health Research and the Privacy of Health Information, the HIPAA Privacy Rule. The value, importance, and oversight of health research. In: Beyond the HIPAA Privacy Rule: Enhancing Privacy, Improving Health Through Research. Washington, DC: National Academies Press; 2009.
7. Shoultz J, Hatcher PA. Looking beyond primary care to primary health care: an approach to community-based action. Nurs Outlook 1997;45(1):23-26. [doi: 10.1016/s0029-6554(97)90054-3] [Medline: 9139259]
8. Primary health care: report of the international conference on primary health sare, Alma-Ata, USSR, 6-12 September, 1978. World Health Organization. 1978. URL: https://www.who.int/publications/i/item/9241800011 [accessed 2024-03-25]
9. Miller WL, Crabtree BF. Primary care research: a multimethod typology and qualitative road map. In: Doing Qualitative Research. Thousand Oaks, CA: Sage Publications; 1992:3-28.
10. Greenhalgh T, Raftery J, Hanney S, Glover M. Research impact: a narrative review. BMC Med 2016;14:78 [FREE Full text] [doi: 10.1186/s12916-016-0620-8] [Medline: 27211576]
11. Making an impact: a preferred framework and indicators to measure returns on investment in health research. Report of the panel on the return on investments in health research january 2009. Canadian Academy of Health Sciences. 2009. URL: https://www.cahs-acss.ca/wp-content/uploads/2011/09/ROI_FullReport.pdf [accessed 2024-03-20]
12. Making an impact: a shared framework for assessing the impact of health services and policy research on decision-making. Canadian Health Services and Policy Research Alliance (CHSaPRA). 2018. URL: https://researchimpact.ca/archived/making-an-impact-a-shared-framework-for-assessing-the-impact-of-health-services-and-policy-research-on-decision-making/ [accessed 2024-03-20]
13. Fernández-Ramos A, Romero-Rodríguez E. Thematic analysis of primary care journals indexed in journal citation reports: 2015-2019. Semergen 2021;47(6):394-403. [doi: 10.1016/j.semerg.2021.07.007] [Medline: 34456128]
14. Hajjar F, Saint-Lary O, Cadwallader JS, Chauvin P, Boutet A, Steinecker M, et al. Development of primary care research in North America, Europe, and Australia from 1974 to 2017. Ann Fam Med 2019;17(1):49-51 [FREE Full text] [doi: 10.1370/afm.2328] [Medline: 30670396]
15. Rivera SC, Kyte DG, Aiyegbusi OL, Keeley TJ, Calvert MJ. Assessing the impact of healthcare research: a systematic review of methodological frameworks. PLoS Med 2017;14(8):e1002370 [FREE Full text] [doi: 10.1371/journal.pmed.1002370] [Medline: 28792957]
16. Banzi R, Moja L, Pistotti V, Facchini A, Liberati A. Conceptual frameworks and empirical approaches used to assess the impact of health research: an overview of reviews. Health Res Policy Syst 2011;9:26 [FREE Full text] [doi: 10.1186/1478-4505-9-26] [Medline: 21702930]
17. Primary care research: its unique role in health care. Association of the Departments of Family Medicine. URL: https://www.stfm.org/media/1664/cafm-primary-care-research-unique-role.pdf [accessed 2024-03-20]
18. Goodyear-Smith F, Bazemore A, Coffman M, Fortier R, Howe A, Kidd M, et al. Primary care research priorities in low-and middle-income countries. Ann Fam Med 2019;17(1):31-35 [FREE Full text] [doi: 10.1370/afm.2329] [Medline: 30670392]
19. O'Neill B, Aversa V, Rouleau K, Lazare K, Sullivan F, Persaud N. Identifying top 10 primary care research priorities from international stakeholders using a modified Delphi method. PLoS One 2018;13(10):e0206096 [FREE Full text] [doi: 10.1371/journal.pone.0206096] [Medline: 30359391]
20. Goodyear-Smith F, Bazemore A, Coffman M, Fortier R, Howe A, Kidd M, et al. Primary care financing: a systematic assessment of research priorities in low- and middle-income countries. BMJ Glob Health 2019;4(Suppl 8):e001483 [FREE Full text] [doi: 10.1136/bmjgh-2019-001483] [Medline: 31478025]
21. Murphy P, Burge F, Wong ST. Measurement and rural primary health care: a scoping review. Rural Remote Health 2019;19(3):4911 [FREE Full text] [doi: 10.22605/RRH4911] [Medline: 31365828]
22. Noorihekmat S, Rahimi H, Mehrolhassani MH, Chashmyazdan M, Haghdoost AA, Tabatabaei SVA, et al. Frameworks of performance measurement in public health and primary care system: a scoping review and meta-synthesis. Int J Prev Med 2020;11:165 [FREE Full text] [doi: 10.4103/ijpvm.IJPVM_34_19] [Medline: 33312474]
23. Akl EA, Meerpohl JJ, Raad D, Piaggio G, Mattioni M, Paggi MG, et al. Effects of assessing the productivity of faculty in academic medical centres: a systematic review. CMAJ 2012;184(11):E602-E612 [FREE Full text] [doi: 10.1503/cmaj.111123] [Medline: 22641686]
24. Graham KER, Langlois-Klassen D, Adam SAM, Chan L, Chorzempa HL. Assessing health research and innovation impact: evolution of a framework and tools in Alberta, Canada. Front Res Metr Anal 2018;3:25 [FREE Full text] [doi: 10.3389/frma.2018.00025]
25. Assessing the impact of health services and policy research: a guide to implementing the CHSPRA informing decision-making impact framework. Canadian Health Services and Policy Research Alliance (CHSaPRA). 2022. URL: https://tinyurl.com/y4wp43vx [accessed 2024-03-20]

26. Tricco AC, Antony J, Zarin W, Strifler L, Ghassemi M, Ivory J, et al. A scoping review of rapid review methods. BMC Med 2015;13:224 [FREE Full text] [doi: 10.1186/s12916-015-0465-6] [Medline: 26377409]
27. Pashiardis P. Environmental scanning in educational organizations: uses, approaches, sources and methodologies. Int J Educ Manag 1996;10(3):5-9. [doi: 10.1108/09513549610115055]
28. Macdonald M, Misener RM, Weeks L, Helwig M. Covidence vs Excel for the title and abstract review stage of a systematic review. JBI Evid Implement 2016;14(4):200-201. [doi: 10.1097/01.xeb.0000511346.12446.f2]
29. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. Int J Soc Res Methodol 2005;8(1):19-32. [doi: 10.1080/1364557032000119616]
30. Tricco AC, Lillie E, Zarin W, O'Brien K, Colquhoun H, Kastner M, et al. A scoping review on the conduct and reporting of scoping reviews. BMC Med Res Methodol 2016;16:15 [FREE Full text] [doi: 10.1186/s12874-016-0116-4] [Medline: 26857112]
31. Sturgiss JC L, Phillips WR, Moriarty F, Orkin A, Lucassen P, van der Wouden JC. Consensus Reporting Items for Studies in Primary Care (CRISP): an international Delphi survey of researchers and end-users. Aust J Prim Health 2021;27(4):XLVII.
32. Thomas PS. Environmental scanning—the state of the art. Long Range Plan 1980;13(1):20-28. [doi: 10.1016/0024-6301(80)90051-5]
33. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA extension for Scoping Reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med 2018;169(7):467-473 [FREE Full text] [doi: 10.7326/M18-0850] [Medline: 30178033]
34. Burget M, Bardone E, Pedaste M. Definitions and conceptual dimensions of responsible research and innovation: a literature review. Sci Eng Ethics 2017;23(1):1-19. [doi: 10.1007/s11948-016-9782-1] [Medline: 27090147]
35. Hinde S, Spackman E. Bidirectional citation searching to completion: an exploration of literature searching methods. Pharmacoeconomics 2015;33(1):5-11. [doi: 10.1007/s40273-014-0205-3] [Medline: 25145803]
36. Schöpfel J, Farace DJ. Grey literature. In: Encyclopedia of Library and Information Sciences, 3rd Edition. Boca Raton, FL: CRC Press; 2010:2029-2039.
37. Dahl LT, Katz A, McGrail K, Diverty B, Ethier JF, Gavin F, et al. The SPOR-Canadian data platform: a national initiative to facilitate data rich multi-jurisdictional research. Int J Popul Data Sci 2020;5(1):1374 [FREE Full text] [doi: 10.23889/ijpds.v5i1.1374] [Medline: 34007883]
38. Babineau J. Product review: Covidence (systematic review software). J Can Health Libr Assoc 2014;35(2):68 [FREE Full text] [doi: 10.5596/c14-016]
39. Mahood Q, Van Eerd D, Irvin E. Searching for grey literature for systematic reviews: challenges and benefits. Res Synth Methods 2014;5(3):221-234. [doi: 10.1002/jrsm.1106] [Medline: 26052848]
40. Godin K, Stapleton J, Kirkpatrick SI, Hanning RM, Leatherdale ST. Applying systematic review search methods to the grey literature: a case study examining guidelines for school-based breakfast programs in Canada. Syst Rev 2015;4:138 [FREE Full text] [doi: 10.1186/s13643-015-0125-0] [Medline: 26494010]
41. World Bank country and lending groups. The World Bank. 2022. URL: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups [accessed 2024-03-20]
42. Mant D, Del Mar C, Glasziou P, Knottnerus A, Wallace P, van Weel C. The state of primary-care research. Lancet 2004;364(9438):1004-1006. [doi: 10.1016/s0140-6736(04)17027-x]
43. Declaration of Alma-Ata. World Health Organization. 1978. URL: https://www.who.int/publications/i/item/WHO-EURO-1978-3938-43697-61471 [accessed 2024-03-20]
44. Khangura S, Konnyu K, Cushman R, Grimshaw J, Moher D. Evidence summaries: the evolution of a rapid review approach. Syst Rev 2012;1:10 [FREE Full text] [doi: 10.1186/2046-4053-1-10] [Medline: 22587960]
45. Bramer WM, Giustini D, de Jonge GB, Holland L, Bekhuis T. De-duplication of database search results for systematic reviews in EndNote. J Med Libr Assoc 2016;104(3):240-243 [FREE Full text] [doi: 10.3163/1536-5050.104.3.014] [Medline: 27366130]
46. Park CU, Kim HJ. Measurement of inter-rater reliability in systematic review. Hanyang Med Rev 2015;35(1):44 [FREE Full text] [doi: 10.7599/hmr.2015.35.1.44]
47. Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. Implement Sci 2010;5:69 [FREE Full text] [doi: 10.1186/1748-5908-5-69] [Medline: 20854677]
48. Phillips WR, Sturgiss E, Glasziou P, Hartman TCO, Orkin AM, Prathivadi P, et al. Improving the reporting of primary care research: consensus reporting items for studies in primary care—the CRISP statement. Ann Fam Med 2023;21(6):549-555 [FREE Full text] [doi: 10.1370/afm.3029] [Medline: 37788942]
49. Assarroudi A, Nabavi FH, Armat MR, Ebadi A, Vaismoradi M. Directed qualitative content analysis: the description and elaboration of its underpinning methods and data analysis process. J Res Nurs 2018;23(1):42-55 [FREE Full text] [doi: 10.1177/1744987117741667] [Medline: 34394406]

Abbreviations

CAHS: Canadian Academy of Health Sciences

CHSaPRA: Canadian Health Services and Policy Research Alliance
CRISP: Consensus Reporting Items for Studies in Primary Care
PHC: primary health care
PRISMA-ScR: Preferred Reporting Items for Systematic Review and Meta-Analysis Extension for Scoping Reviews

Edited by A Mavragani; submitted 27.12.23; peer-reviewed by K Garzon Diaz, D Hua, J Job; comments to author 06.02.24; revised version received 27.02.24; accepted 04.03.24; published 23.04.24.

Please cite as:
Aggarwal M, Hutchison BG, Kokorelias KM, Ramsden VR, Ivers NM, Pinto A, Uphsur REG, Wong ST, Pimlott N, Slade S
The Conceptualization and Measurement of Research Impact in Primary Health Care: Protocol for a Rapid Scoping Review
JMIR Res Protoc 2024;13:e55860
URL: https://www.researchprotocols.org/2024/1/e55860
doi:10.2196/55860
PMID:38652900

Protocol

Seasonal Malaria Chemoprevention Therapy in Children Up To 9 Years of Age: Protocol for a Cluster-Randomized Trial Study

Mahamoudou Toure[1], MSPH, MD, PhD; Jeffrey G Shaffer[2], PhD; Daouda Sanogo[1], MPH, MD; Soumba Keita[1], MSc, PharmD; Moussa Keita[1], MSc, PhD; Fousseyni Kane[1], MSc, MD; Bourama Traore[1], PharmD, MSc; Djeneba Dabitao[1], PharmD, PhD; Aissata Kone[3], MPH, MD; Cheick Oumar Doumbia[1], MPH, MD; Joseph Keating[2], PhD; Joshua Yukich[2], PhD; Helle H Hansson[4], PhD; Alyssa E Barry[5,6], PhD; Mahamadou Diakité[1], PharmD, DPhil; Michael Alifrangis[4], PhD; Seydou Doumbia[1], MD, PhD

[1]University Clinical Research Center, Universite des Sciences, des Techniques et des Technologies, Bamako, Mali

[2]Tulane University School of Public Health and Tropical Medicine, New Orleans, LA, United States

[3]Mali National Malaria Control Program, Bamako, Mali

[4]Center for Medical Parasitology, Department of Immunology and Microbiology, University of Copenhagen, Copenhagen, Denmark

[5]Institute for Mental and Physical Health and Clinical Translation (IMPACT) and School of Medicine, Deakin University, Geelong, Melbourne, Australia

[6]Life Sciences Discipline, Burnet Institute, Melbourne, Australia

Corresponding Author:
Mahamoudou Toure, MSPH, MD, PhD
University Clinical Research Center
Universite des Sciences, des Techniques et des Technologies
Point G
Bamako
Mali
Phone: 223 66778912
Email: mah.toure@gmail.com

Abstract

Background: Seasonal malaria chemoprevention (SMC) is recommended by the World Health Organization for the sub-Sahel region in sub-Saharan Africa for preventing malaria in children 3 months old to younger than 5 years. Since 2016, the Malian National Malaria Control Program has deployed SMC countrywide during its high malaria transmission season at a rate of 4 monthly cycles annually. The standard SMC regimen includes sulfadoxine-pyrimethamine (SP) plus amodiaquine (AQ). Resistance against SP is suspected to be rising across West Africa; therefore, assessing the effectiveness of an alternative antimalarial drug for SMC is needed to provide a second-line regimen when it is ultimately needed. It is not well understood whether SMC effectively prevents malaria in children aged 5 years or older.

Objective: The primary goal of the study is to compare 2 SMC regimens (SP-AQ and dihydroartemisinin-piperaquine [DHA-PQ]) in preventing uncomplicated *Plasmodium falciparum* malaria in children 3 months to 9 years old. Secondly, we will assess the possible use of DHA-PQ as an alternative SMC drug in areas where resistance to SP or AQ may increase following intensive use.

Methods: The study design is a 3-arm cluster-randomized design comparing the SP-AQ and DHA-PQ arms in 2 age groups (younger than 5 years and 5-9 years) and a control group for children aged 5-9 years. Standard SMC (SP-AQ) for children younger than 5 years was provided to the control arm, while SMC with SP-AQ was delivered to children aged 3 months to 9 years (arm 2), and SMC with DHA-PQ will be implemented in study arm 3 for children up to 9 years of age. The study was performed in Mali's Koulikoro District, a rural area in southwest Mali with historically high malaria transmission rates. The study's primary outcome is *P falciparum* incidence for 2 SMC regimens in children up to 9 years of age. Should DHA-PQ provide an acceptable alternative to SP-AQ, a plausible second-line prevention option would be available in the event of SP resistance or drug supply shortages. A significant byproduct of this effort included bolstering district health information systems for rapid identification of severe malaria cases.

Results: The study began on July 1, 2019. Through November 2022, a total of 4556 children 3 months old to younger than 5 years were enrolled. Data collection ended in spring 2023, and the findings are expected to be published later in early 2024.

Conclusions: Routine evaluation of antimalarial drugs is needed to establish appropriate SMC age targets. The study goals here may impact public health policy and provide alternative therapies in the event of drug shortages or resistance.

Trial Registration: ClinicalTrials.gov NCT04149106, https://clinicaltrials.gov/ct2/show/NCT04149106

International Registered Report Identifier (IRRID): DERR1-10.2196/51660

(JMIR Res Protoc 2024;13:e51660) doi:10.2196/51660

KEYWORDS

malaria; seasonal malaria chemoprevention; RCT; randomized; controlled trial; controlled trials; parasite; parasites; mosquito; mosquitoes; vector-borne; malarial; antimalarial; age; Plasmodium falciparum, protocol, cluster-randomized trial; child; children; infant; infants; pediatric; pediatrics; clinical trial; clinical trials; drug; drugs; pharmacy; pharmacology; pharmaceutic; pharmaceutics; pharmaceuticals; pharmaceutical; medication; medications

Introduction

Malaria is endemic to south and central Mali, where over 90% of its approximately 17.6 million population is at risk for infection [1]. The disease primarily burdens rural areas that maintain suitable larval habitats and lack access to adequate health care [1]. Malaria transmission is highly seasonal in Mali (length of the transmission periods varies from 3 to 6 months), with a peak of malaria cases at the end of the rainy season (October through November), though it may be affected by irrigation schemes [2,3]. Deaths due to malaria registered at health centers totaled 1050 in 2017, with 669 (63.7%) occurring among children younger than 5 years. However, these results are likely substantially underreported. For instance, in 2015, health facilities in Mali reported over 2.3 million confirmed malaria cases and 1544 malaria deaths, but actual estimates were 7.5 million and 21,000, respectively [1].

Since 2007, support from the US Presidential Malaria Initiative program and other sponsors resulted in a 50% reduction in Mali's malaria burden. These efforts have been carried out through increased preventive and treatment measures such as long-lasting insecticide-treated mosquito nets (LLINs), indoor residual spraying, artemisinin-based combination therapies (ACTs), and intermittent preventive treatment of pregnant women (IPTp); and more recently, seasonal malaria chemoprevention (SMC). The most widely implemented malaria control interventions are the joint use of LLINs and rapid treatment of malaria cases with ACTs, IPTp, and SMC. Indoor residual spraying was previously implemented on a small scale in several Malian districts but is currently implemented in only a single district in central Mali.

Despite the broad deployment of these interventions, malaria prevalence and incidence rates remain high in Mali according to the routine Malaria Indicators Surveys [4]. Since 2010, the International Centers of Excellence in Malaria Research (ICEMR), in collaboration with Mali's National Malaria Control Program (NMCP), has identified significant constraints to malaria control implementation strategies in Mali, including the upward shift of the prevalence of infection and incidence of disease in children younger than 5 years to children aged 5-9 and 10-14 years [5,6]. These findings are particularly significant as the World Health Organization (WHO) guidelines recommend SMC only for children 3 months old to younger than 5 years. Therefore, the Mali NMCP and its partners have expressed SMC effectiveness and intervention strategies as key research priorities.

While the sulfadoxin and pyrimethamine regimen (SP) remains effective in West Africa, resistance to this regimen has been observed in East African regions where *Plasmodium falciparum* is highly prevalent. SMC is not currently recommended for countries in southern and eastern Africa due to widespread resistance, although there are some locations where transmission patterns suggest potential suitability [7,8]. In western parts of Africa, higher frequencies of the triple dihydrofolate reductase mutants and the quadruple mutant (triple dihydrofolate reductase plus dihydropteroate synthetase 437) associated with significant resistance to SP have been observed in children receiving SMC in both Mali and Senegal [9,10]. Recent studies have also reported SP resistance in several parts of Mali [11,12]. The wide-scale deployment of SMC in sub-Saharan African countries required increased focus on *P falciparum* resistance as well as ongoing assessments of new alternative drug combinations for SMC as this strategy has proven to be effective in reducing the impact on severe malaria and mortality in children 3 months old to younger than 5 years [13]. A recent study in Burkina Faso suggests that higher dosages and extended dosing of dihydroartemisinin-piperaquine (DHA-PQ) to 4 monthly doses (and cover the entire high malaria transmission period) could reduce malaria incidence up to 58% during the peak transmission season [14,15]. DHA-PQ has demonstrated excellent efficacy for chemoprevention and benefits from the long half-life of piperaquine and offers a protective efficacy of 98% against malaria in Thai adults when administered monthly [7]. In Senegalese children, similar monthly malaria incidence was observed among children receiving monthly DHA-PQ vs SP+amodiaquine (AQ) as SMC regimen [8].

A study in Uganda reported a 58% greater protective efficacy for DHA-PQ over SP-AQ based on monthly administration among children younger than 5 years [9]. This study aims to determine whether SMC effectively prevents malaria in children aged 5-9 years. The evidence-based approaches used will guide policy in Mali and other countries in West Africa using SMC.

Methods

Ethical Considerations

The study was approved by the University of Sciences, Techniques and Technologies Ethics Board under the following reference (N°2019/04/CE/FMPOS). The trial will report the

efficacy of 2 SMC subtypes (SP-AQ and DHA-PQ) for preventing *P falciparum* malaria in children aged 5-9 years in Mali. Should the findings show that SMC is efficacious for children in this age group, it may impact policy SMC delivery in Mali.

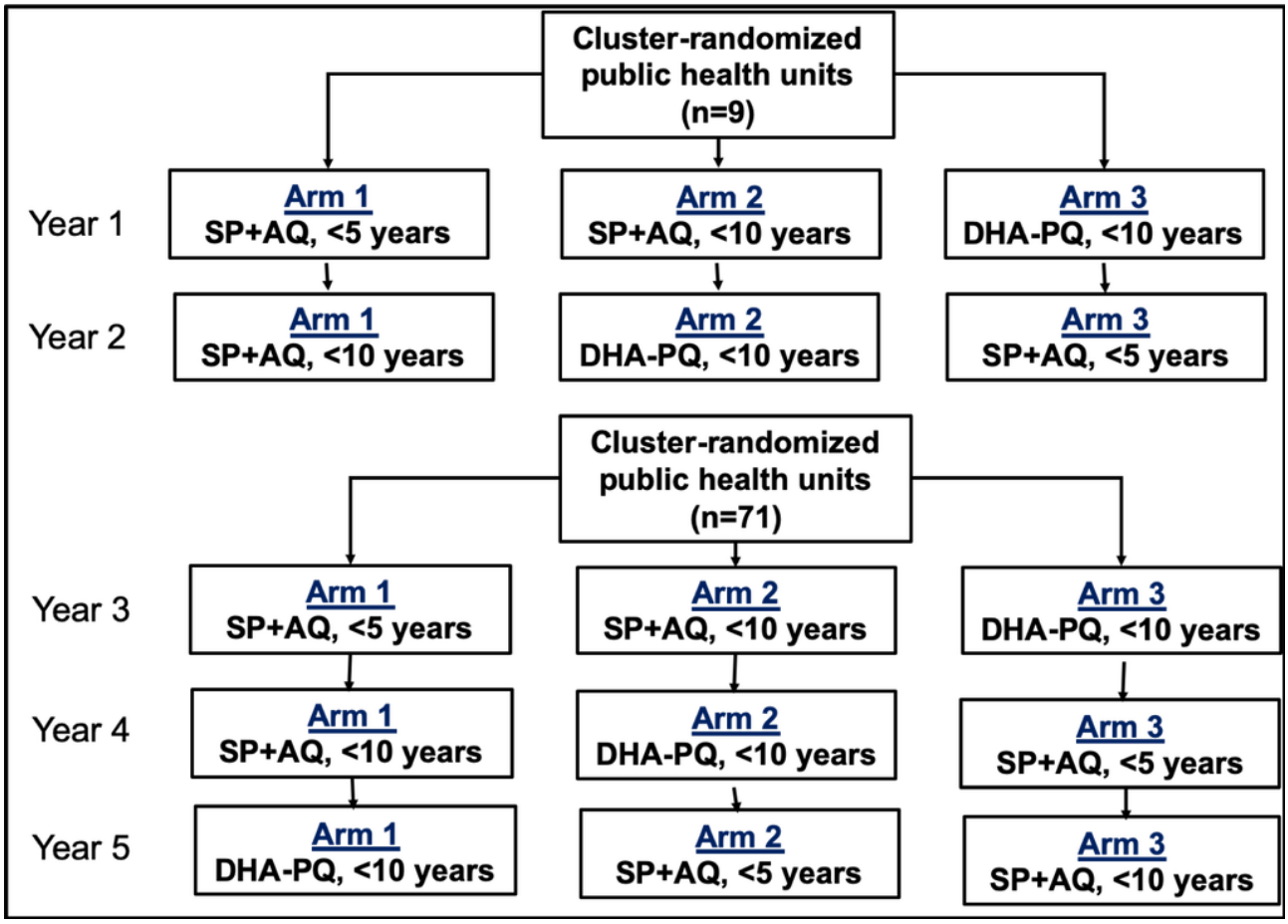
Study Site

Mali's Koulikoro District is situated in its southern region, approximately 50 miles (18 km) north of Bamako and 255 miles (410 km) from the Guinea border [11]. The district maintains 21 health zones and 71 community health posts. The current population in the district is 282,570, with approximately 4% of its population <1 year of age and 18% between 1 and 4 years of age. The total number of villages a community health center covers ranges from 8 to 31. The most populous village is Kolebougou, with 34,712 persons; the least populated is Souban Village, with 5085 persons. Ongoing malaria control activities include case management (rapid diagnostic tests and ACTs), IPTp, SMC, and LLIN use. District health centers maintain clinical and laboratory research capacity and full-time staff and clinicians for malaria screening and patient care. The site was chosen for the proposed research because of its diverse range of malaria control interventions, collaborative research agreements with the University of Sciences, Techniques and Technologies of Bamako, Mali (USTTB), high malaria transmission rates, and rural location.

Study Design and Population

The study was as a 3-arm cluster-randomized design, as illustrated in Figure 1.

Figure 1. Study design of a 3-arm cluster-randomized trial on age targets for season malaria chemoprevention. The study was performed from July 2019 to March 2023. AQ: amodiaquine; DHA: dihydroartemisinin; PQ: piperaquine; SP: sulfadoxine-pyrimethamine.

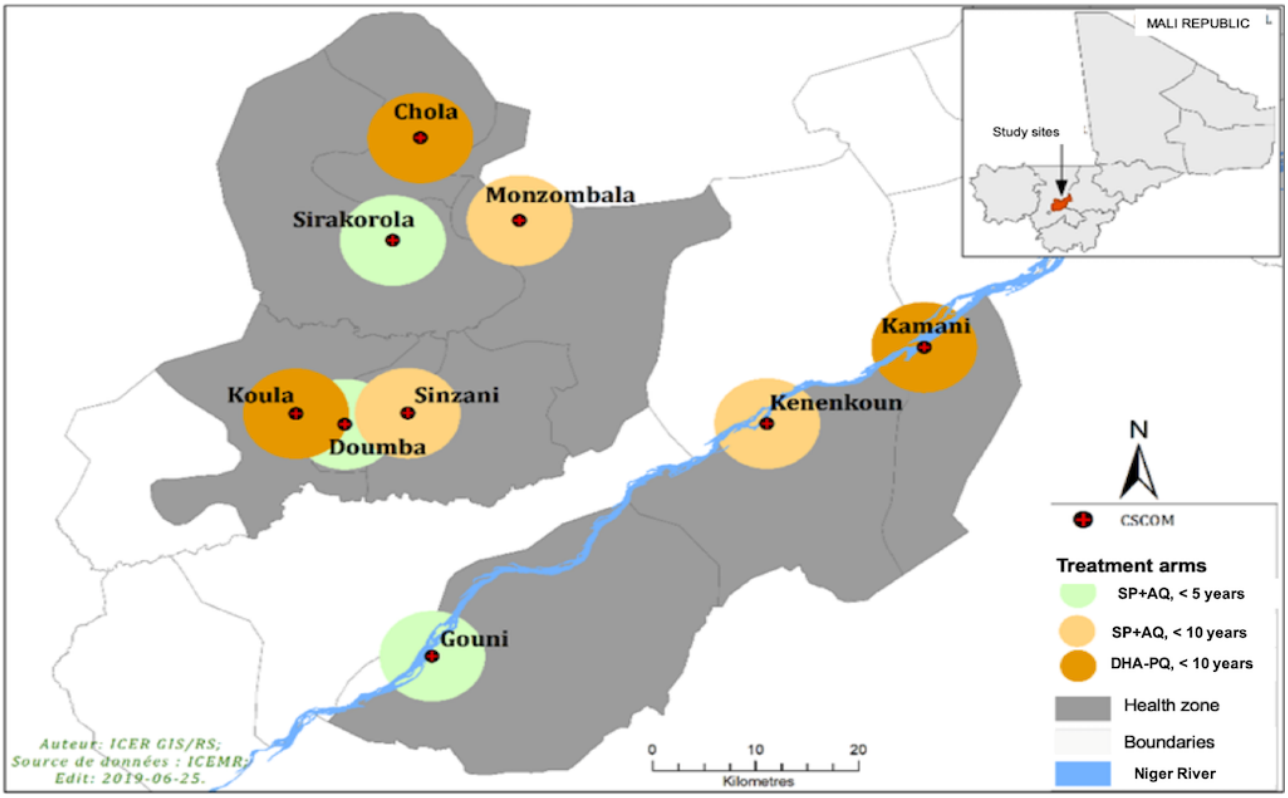


The study population includes children aged 3 months to 9 years in each village. Each study arm includes 3 corresponding public health units (PHUs) that differ with respect to their ecology, proximity to the Niger River, and region in the context of Koulikoro District (northern, central, and southern).

Cluster Selection

A total of 9 villages were randomly selected from Mali's Koulikoro District for participation. The selection strategy focused on 3 aspects: proximity to the Niger River (which lies in the southern part of the region) and the central and northern parts of the sampling region. Within these strata, villages were rank-ordered according to their populations. Random selection was carried out such that villages of high, medium, and low populations were sampled from each of these strata. A total of 3 villages (1 village per stratum with different ranking in terms of population size) were assigned to a single treatment arm (Figure 2).

Figure 2. Map of the 9 study sites in Mali's Koulikoro District. The 9 study sites are near the central part of Mali's Koulikoro District. Study sites were selected as 3 villages near the Niger River, 3 villages in the northern part of Koulikoro District, and 3 villages in the central part of Koulikoro. AQ: amodiaquine; DHA: dihydroartemisinin; PQ: piperaquine; SP: sulfadoxine-pyrimethamine.



The southernmost villages (Gouni, Kenenkoun, Kamani) are situated near the Niger River, while the remaining villages (Doumba, Sinzani, Koula; and Sirakorola, Monzombala, and Chola) lie in the northern and southern parts of the region above the Niger River, respectively.

Randomization

Probability proportional to population size sampling was used for allocating villages to the study arm. Random treatment assignment was balanced according to population size in each stratum (low, medium, and high), resulting in a 3 by 3 Latin square arrangement (Table 1).

Table 1. Study site classification per sampling region within the Koulikoro District, Mali.

Region	Population size		
	Small	Medium	Large
South	Gouni (A)[a]	Kamani (C)	Kenenkoun (B)
Central	Sinzani (B)	Doumba (A)	Koula (C)
North	Chola (C)	Monzombala (B)	Sirakorola (A)

[a]A, B, and C denote the 3 study arms.

Specifically, PHUs were rank-ordered according to their total populations, and the top 3 PHUs (in terms of their populations) were chosen to represent Koulikoro's southern, central, and northern regions. The PHUs were then randomized to treatment according to the Latin square arrangement shown in Table 1.

Eligibility and Enrollment

Participants were eligible to participate if they were residents of the sampled village, aged 3 months to 9 years of age at enrollment, were asymptomatic of current chronic diseases, and did not have a history of allergies to SP, AQ, or DHA-PQ therapies. Informed, written consent is required for all study participants annually. Consent was administered in oral or written formats and included a full description of voluntary participation, the right to withdraw from the study at any time, and the right to refuse to answer any question or participate in any research component.

Study Outcomes

The primary study outcome is the incidence of severe or uncomplicated *P falciparum* malaria. The population denominator for incidence calculations was derived from the house-to-house enumeration with household member listing. Secondary outcomes were abstracted from censuses and enumeration lists for selected villages, including village-level distributions on populations, age, gender, residential status, and LLIN use. Exhaustive selection was carried out in villages for selected PHUs for those children who met the eligibility criteria

and for whom consent of parents or tutors for enrollment was obtained. A baseline malaria infection prevalence survey was carried out before the initial SMC campaign. Follow-up surveys at community health centers were also carried out to assess malaria incidence among study participants. Monthly SMC administration and compliance with treatment assessment were captured via reports by caregivers and measurement of AQ metabolite by enzyme-linked immunosorbent assays. Demographic data, including age, sex, and clinical parameters (including temperature, pulse, and respiration rate), were recorded at a community health center visit. Malaria cases were defined as fever or a history of fever within the past 48 hours associated with either positive malaria rapid diagnostic test or a positive blood smear prepared during that visit.

Hypotheses and Rationale

The primary hypotheses were as follows:

1. Malaria incidence in children was at least 10% higher in the 5- to 9-year age group without SP-AQ than in children in the 5- to 9-year age group with SP-AQ.
2. Malaria incidence in children 3 months old to younger than 5 years receiving DHA-PQ was not statistically different from children in the same age group receiving SP-AQ.

Data Collection and Management

Confirmed malaria case incidence data will be collected from public health facilities through electronic data capture. A REDCap (Research Electronic Data Capture; Vanderbilt University) database and mobile app were used for this study, and data synchronization will be performed daily for quality checking complemented with data queries distributed to the centralized data center at USTTB.

A Priori Sample Size and Statistical Power

The power and sample size assessment is based on the ability to detect a clinically significant difference in malaria incidence proportions between the 3 comparison groups in year 1. The minimum clinically meaningful differences between the comparison groups was set at 10%. The sample sizes were calculated assuming a design effect of 2 with a 2-sided type I error set at 0.05 and power set at 80%. The number of required subjects per study arm for detecting at least 10% differences in malaria incidence proportions was 1552 in year 1. This result was inflated by 233 subjects in year 2 to account for new subjects due to increased child ages, yielding 1785 participants per arm total or 5355 participants overall.

Phase 2 (Years 3-5, 2021-2023)

This phase involved expansion to 71 public health posts in years 3-5 (Figure 3). The district-wide data collection plan will build on the efforts for years 1-2 and focus on (1) cluster-randomized health posts to the 3 treatment arms and (2) semiannual community cross-sectional surveys. More specifically, the 71 health posts over the entire district were divided into 4 regions (Table 2).

Figure 3. Map of the selection approach for 71 public health posts in Mali's Koulikoro District.

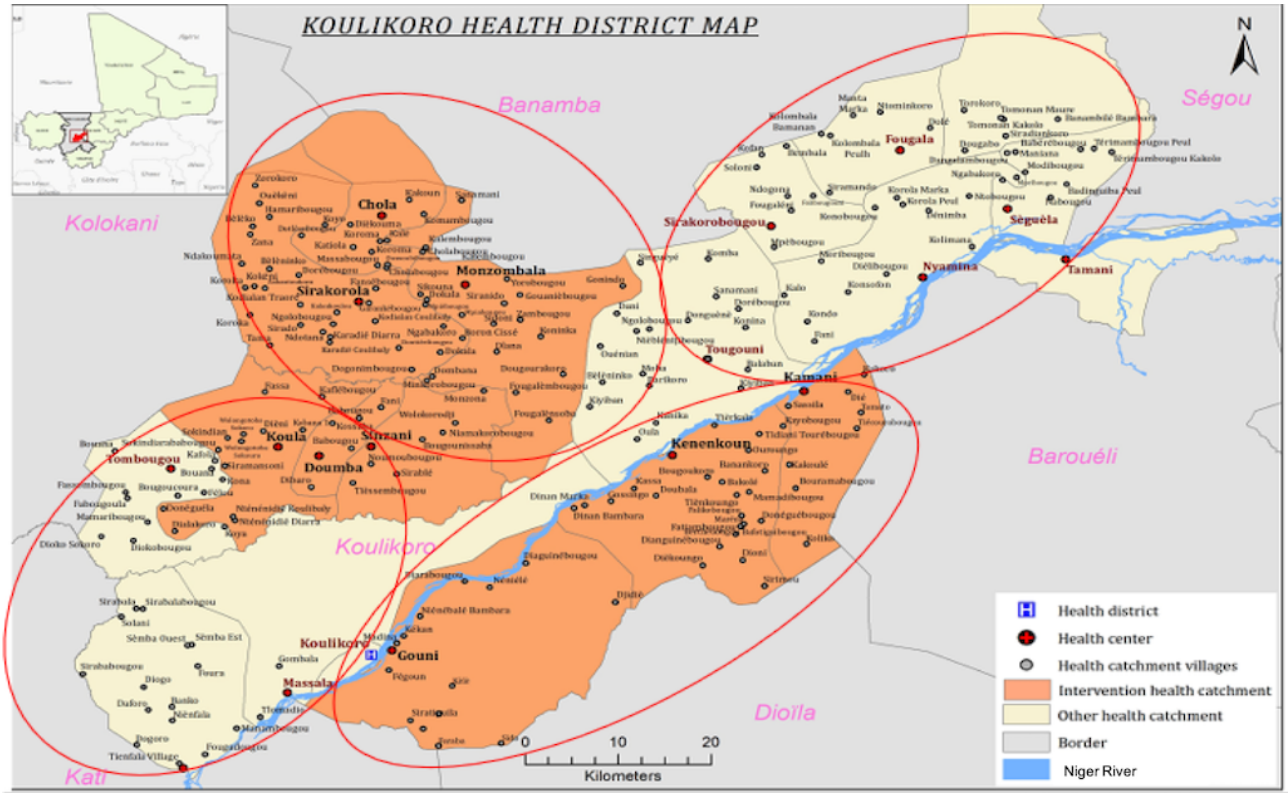


Table 2. Stratum matched by the year of the study.

Stratum (region), years 3-5 sampling approach	Stratum (region), years 1-2 sampling approach
Northeast	Not done
Northwest	North
Southwest	Central
Southeast	South

Within the stratum, health posts will be randomized to 1 of 3 treatment arms (SP-AQ <5 years, SP-AQ <10 years, and DHA-PQ <10 years). Allocation was proportional to population size based on census populations up to 9 years of age while balancing on population sizes across the 3 study arms. For regions maintaining a total number of health posts that were not divisible by 3, 1 or 2 adjacent health posts were considered as a single unit to ensure divisibility (Figure 3).

The health facilities selected in years 1 and 2 were also be selected in years 3-5 and will leverage the process and training already in place in 9 health centers. Patterns over the entire 5-year study period will be analyzed for these 9 villages. Semiannual cross-sectional household surveys will permit assessment of community-level effects over the entire 5-year period.

Results

The study began on July 1, 2019. Through November 2022, a total of 4556 children were enrolled during the pilot phase (2019-2020) in 9 villages across the Koulikoro Health District. In 2022, preliminary findings have been presented at the American Society of Tropical Medicine Conference [16] and published in the *American Journal of Tropical Medicine and Hygiene* [17]. SP-AQ and DHA-PQ were highly effective in reducing *P falciparum* malaria in children 5-9 years in Koulikoro, Mali, at both the pilot and district-wide study phases. Data collection ended in spring 2023, and the findings are expected to be published later in early 2024. Results will be summarized and reported using both intention-to-treat and per-protocol analyses.

Discussion

This study was designed to assess the effectiveness and efficacy of SP-AQ in children aged up to 9 years and of DHA-PQ as an alternative in the event of drug resistance to AQ or SP in West Africa and, more broadly, across Africa. The trial included 2 SMC regimens to provide a viable alternative therapy in the event of drug resistance or shortages in drug supply. The study enrolled over 5000 subjects in 9 villages in Mali's Koulikoro District. The expanded phase of the study covered the entire Koulikoro District. The initial phase of the study covered 9 villages, which may be considered as a pilot for the larger district-wide trial.

This study provides an opportunity to directly measure the effect of the 2 drugs while extending SMC to older children in response to recent reports showing an age shift in malaria incidence and prevalence among older children. The study site here comprised different ecological settings represented countrywide with differential malaria transmission intensities. For instance, each study arm was composed of a village located along the Niger River where longer transmission seasons have historically occurred, a village located in the central part of Koulikoro District where malaria transmission peaks between July and October, and a village in the southern part of Koulikoro District where malaria transmission season has been historically shorter (August to November) than the other 2 locations. Also, all selected villages maintain community health facilities where malaria case management is done routinely. Additionally, a routine assessment of treatment compliance by measuring amodiaquine metabolite in the veinous blood of children after treatment will be performed for the first time to determine SMC compliance across all 4 dosing periods. While the number of villages was initially restricted to 3 per study arm, all 71 PHUs in Koulikoro will be covered across the 3 study arms should the study meet the go/no go criteria for continued funding.

Particular challenges at the outset of the study planning involved garnering support from regional health administrators about using DHA-PQ instead of SMC and extending SMC use to children aged 5-9 years. Since the inception of Mali's NMCP, a key partner in this effort made apparent the study's rationale in terms of its implications on potential drug resistance with health agents, community leaders, and health workers before the SMC campaign was launched in Mali. Determining the appropriate age target for preventive therapies remains challenging for developing countries like Mali. The age captured during the most recent census was used to estimate the number of children failing in the <5 and 5-9-year age groups, which was usually reported by the participants' parents or guardians. However, approximately 2% of subjects were misclassified during the SMC administration due to erroneous reporting during the census. Therefore, more accurate estimations of participant age (which was used to define the comparison groups) were captured for the study here at baseline.

SMC covers the rainy season that coincidentally occurs during school vacations and agricultural activities in rural Mali. Therefore, a child's movement during that period is often a cause for losses to follow-up as children frequently might travel to Mali's capital city of Bamako from July to September, while others will move with their family to the farms (hamlets) until October when school commences.

We believe that this study provides a somewhat novel study design that will aid researchers in assessing age targets in locations where controlled studies are not feasible.

Acknowledgments

We are grateful to the National Institutes of Health for funding this study. We also thank the kind community leaders and residents in Koulikoro District for their guidance, support, and participation. We thank Dr Donald J. Krogstad for his lifelong mission for improving health outcomes in West Africa and whose efforts laid the groundwork for this study. We dedicate the study to those impacted by malaria and hope the study contributes to reducing the burden of malaria in Koulikoro and across Mali. This work was supported by Cooperative Agreements from the National Institutes of Allergy and Infectious Diseases (NIAID) for the West African International Center of Excellence for Malaria Research (ICEMR): U19AI089696 and U19AI129387 (from 2010 to 2017, 2017 to 2024, and 2016 to 2021, respectively). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Data Availability

Data will be archived on the ClinEpiDB institutional repository [18] to ensure long-term availability, preservation, and access. The data sets generated during this study are available from the corresponding author on reasonable request as well as from the West Africa International Centers of Excellence in Malaria Research (ICEMR) Program Director by e-mail (sdoumbi@icermali.org or sdoumbia@gmail.com)

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the National Institute of Allergy and Infectious Diseases Special Emphasis Panel Limited Competition: Revision Applications for International Centers of Excellence for Malaria Research (NIH, USA).
[PDF File (Adobe PDF File), 421 KB - resprot_v13i1e51660_app1.pdf]

References

1. President's Malaria Initiative: Mali Country Profile. OCHA. 2019 Feb 15. URL: https://reliefweb.int/report/mali/presidents-malaria-initiative-mali-country-profile [accessed 2023-10-31]
2. Ceesay SJ, Casals-Pascual C, Erskine J, Anya SE, Duah NO, Fulford AJC, et al. Changes in malaria indices between 1999 and 2007 in the Gambia: a retrospective analysis. Lancet 2008;372(9649):1545-1554 [FREE Full text] [doi: 10.1016/S0140-6736(08)61654-2] [Medline: 18984187]
3. Sogoba N, Doumbia S, Vounatsou P, Bagayoko MM, Dolo G, Traoré SF, et al. Malaria transmission dynamics in Niono, Mali: the effect of the irrigation systems. Acta Trop 2007;101(3):232-240. [doi: 10.1016/j.actatropica.2007.02.005] [Medline: 17362859]
4. Mali MIS, 2015—MIS final report (French). USAID. 2015. URL: https://dhsprogram.com/publications/publication-mis24-mis-final-reports.cfm [accessed 2023-10-31]
5. Carneiro I, Roca-Feltrer A, Griffin JT, Smith L, Tanner M, Schellenberg JA, et al. Age-patterns of malaria vary with severity, transmission intensity and seasonality in Sub-Saharan Africa: a systematic review and pooled analysis. PLoS One 2010;5(2):e8988 [FREE Full text] [doi: 10.1371/journal.pone.0008988] [Medline: 20126547]
6. Nkumama IN, O'Meara WP, Osier FHA. Changes in Malaria epidemiology in Africa and new challenges for elimination. Trends Parasitol 2017;33(2):128-140 [FREE Full text] [doi: 10.1016/j.pt.2016.11.006] [Medline: 27939610]
7. Somé AF, Zongo I, Compaoré YD, Sakandé S, Nosten F, Ouédraogo JB, et al. Selection of drug resistance-mediating Plasmodium falciparum genetic polymorphisms by seasonal malaria chemoprevention in Burkina Faso. Antimicrob Agents Chemother 2014;58(7):3660-3665 [FREE Full text] [doi: 10.1128/AAC.02406-14] [Medline: 24733476]
8. WHO policy recommendation: Seasonal Malaria Chemoprevention (SMC) for Plasmodium falciparum malaria control in highly seasonal transmission areas of the Sahel sub-region in Africa. WHO. 2012. URL: https://iris.who.int/bitstream/handle/10665/337978/WHO-HTM-GMP-2012.02-eng.pdf [accessed 2023-10-31]
9. Maiga H, Lasry E, Diarra M, Sagara I, Bamadio A, Traore A, et al. Seasonal malaria chemoprevention with sulphadoxine-pyrimethamine and amodiaquine selects Pfdhfr-dhps quintuple mutant genotype in Mali. PLoS One 2016;11(9):e0162718 [FREE Full text] [doi: 10.1371/journal.pone.0162718] [Medline: 27662368]
10. Venkatesan M, Alifrangis M, Roper C, Plowe CV. Monitoring antifolate resistance in intermittent preventive therapy for malaria. Trends Parasitol 2013;29(10):497-504 [FREE Full text] [doi: 10.1016/j.pt.2013.07.008] [Medline: 23948432]
11. Diakité SAS, Traoré K, Sanogo I, Clark TG, Campino S, Sangaré M, et al. A comprehensive analysis of drug resistance molecular markers and Plasmodium falciparum genetic diversity in two malaria endemic sites in Mali. Malar J 2019;18(1):361 [FREE Full text] [doi: 10.1186/s12936-019-2986-5] [Medline: 31718631]
12. Niaré K, Dara A, Sagara I, Sissoko MS, Guindo CO, Cissé NH, et al. In vivo efficacy and parasite clearance of artesunate + sulfadoxine-pyrimethamine versus artemether-lumefantrine in Mali. Am J Trop Med Hyg 2016;94(3):634-639 [FREE Full text] [doi: 10.4269/ajtmh.15-0503] [Medline: 26811430]

13. Apinjoh TO, Ouattara A, Titanji VPK, Djimde A, Amambua-Ngwa A. Genetic diversity and drug resistance surveillance of Plasmodium falciparum for malaria elimination: is there an ideal tool for resource-limited Sub-Saharan Africa? Malar J 2019;18(1):217 [FREE Full text] [doi: 10.1186/s12936-019-2844-5] [Medline: 31242921]
14. Chotsiri P, Zongo I, Milligan P, Compaore YD, Somé AF, Chandramohan D, et al. Optimal dosing of dihydroartemisinin-piperaquine for seasonal malaria chemoprevention in young children. Nat Commun 2019;10(1):480 [FREE Full text] [doi: 10.1038/s41467-019-08297-9] [Medline: 30696903]
15. Zongo I, Milligan P, Compaore YD, Some AF, Greenwood B, Tarning J, et al. Randomized noninferiority trial of dihydroartemisinin-piperaquine compared with sulfadoxine-pyrimethamine plus amodiaquine for seasonal malaria chemoprevention in Burkina Faso. Antimicrob Agents Chemother 2015;59(8):4387-4396 [FREE Full text] [doi: 10.1128/AAC.04923-14] [Medline: 25918149]
16. Toure M, Kané F, Keita S, Sanogo D, Keita M, Traoré B. Effectiveness of dihydroartemisinin-piperaquine (DHAPQ) for seasonal malaria chemoprevention (SMC) among children under ten years of age in Koulikoro, Mali: a cluster-randomized trial. 2022 Presented at: 71st American Society of Tropical Medicine and Hygiene (ASTMH) Annual Meeting; October 30-November 3, 2022; Seattle, WA United States URL: https://www.astmh.org/annual-meeting [doi: 10.2196/preprints.51660]
17. Doumbia S, Sogoba N, Diakite M, Toure M, Keita M, Konaté D, et al. A decade of progress accelerating malaria control in Mali: evidence from the West Africa International Center of Excellence for Malaria Research. Am J Trop Med Hyg 2022;107(4_Suppl):75-83 [FREE Full text] [doi: 10.4269/ajtmh.21-1309] [Medline: 36228923]
18. Explore the Studies. ClinEpiDB. URL: https://clinepidb.org/ce/app [accessed 2023-11-14]

Abbreviations

ACT: artemisinin-based combination therapy
AQ: amodiaquine
DHA: dihydroartemisinin
ICEMR: International Centers of Excellence in Malaria Research
IPTp: intermittent preventive treatment of pregnant women
LLIN: long-lasting insecticide-treated mosquito net
NMCP: National Malaria Control Program
PHU: public health unit
PQ: piperaquine
REDCap: Research Electronic Data Capture
SMC: seasonal malaria chemoprevention
SP: sulfadoxine-pyrimethamine
USTTB: University of Sciences, Techniques and Technologies of Bamako, Mali
WHO: World Health Organization

Edited by A Mavragani; submitted 07.08.23; this is a non–peer-reviewed article;accepted 26.10.23; published 22.01.24.

Please cite as:
Toure M, Shaffer JG, Sanogo D, Keita S, Keita M, Kane F, Traore B, Dabitao D, Kone A, Doumbia CO, Keating J, Yukich J, Hansson HH, Barry AE, Diakité M, Alifrangis M, Doumbia S
Seasonal Malaria Chemoprevention Therapy in Children Up To 9 Years of Age: Protocol for a Cluster-Randomized Trial Study
JMIR Res Protoc 2024;13:e51660
URL: https://www.researchprotocols.org/2024/1/e51660
doi:10.2196/51660
PMID:38252481

Publisher:
JMIR Publications
130 Queens Quay East.
Toronto, ON, M5A 3Y5
Phone: (+1) 416-583-2040
Email: support@jmir.org